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Transition-metal and organocatalysis in natural product synthesis

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Editorial

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This article is part of the Thematic Series "Transition-metal and organocatalysis in natural product synthesis".

Guest Editors: D. Y.-K. Chen and D. Ma

The total synthesis of natural products, a field of organic chemistry that is both historical and contemporary, has undoubtedly entered a new paradigm over the past decade with the advent of revolutionary new synthetic methods and innovative synthetic concepts. Putting aside the downstream applications of natural-product synthesis in the interrogation of biological processes, elucidation of biogenetic origins, structural assignments and many others, its fundamental and indispensable value as a vehicle for the discovery of new synthetic transformations is well-testified and unparalleled by any other research discipline over the history of chemical science. These transformations, largely concerning carbon–carbon/carbon–heteroatom bond formations, asymmetric induction, and catalysis, constantly expand the repertoire of powerful tools available at the organic chemist's disposal, and enable more challenging synthetic problems to be investigated. As such, this catalytic cycle of discovery fueled by natural-product synthesis continues to capture and captivate the imagination of both practitioners and students of organic chemistry around the world and will do so far beyond the foreseeable future. In particular, the recent discovery of novel transitional-metal complexes and their associated chemical transformations, and rediscovery of the unprecedented reactivity of previously documented transition-metal complexes with subtle changes in the reaction conditions and the reacting substrate have been extremely fruitful since the turn of the millennium, most notably in promoting reactions of unfunctionalized and unactivated chemical bonds. Furthermore, the application of organic compounds as promoters of chemical transformations has also witnessed increasing sophistication, substrate scope, and efficiency together with new modes of activation, which rival or at times surpass those exhibited by transition metals. Last but not least, the judiciary combination of transition-metal and organic mediators, together with tandem processes encompassing multiple reaction cycles in a programmed sequence, represents a new horizon with vast potentials that have yet to be fully understood and exploited.

In this Thematic Series, selected examples of metal- and organic-compound-promoted chemical processes that render the preparation of architecturally complex natural products, natural-product subdomains, or natural-product-like scaffolds, are presented. These illustrative synthetic studies are intended to showcase the most recent developments, at the same time highlight the state-of-the-art and current limitations, and in doing so set the path for the future. It is our great anticipation that this Thematic Series will instigate and inspire further investigations in this field, and challenge the existing technologies and our current mindset in target-oriented synthetic design. Ultimately, we wish that the newly acquired knowledge will translate to further advances in synthetic organic chemistry and provide more enabling tools for synthetic-chemistry-dependent research fields and beyond.

David Yu-Kai Chen and Dawei Ma

Seoul, Shanghai, June 2013

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Asymmetric synthesis of a highly functionalized bicyclo[3.2.2]nonene derivative

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Full Research Paper

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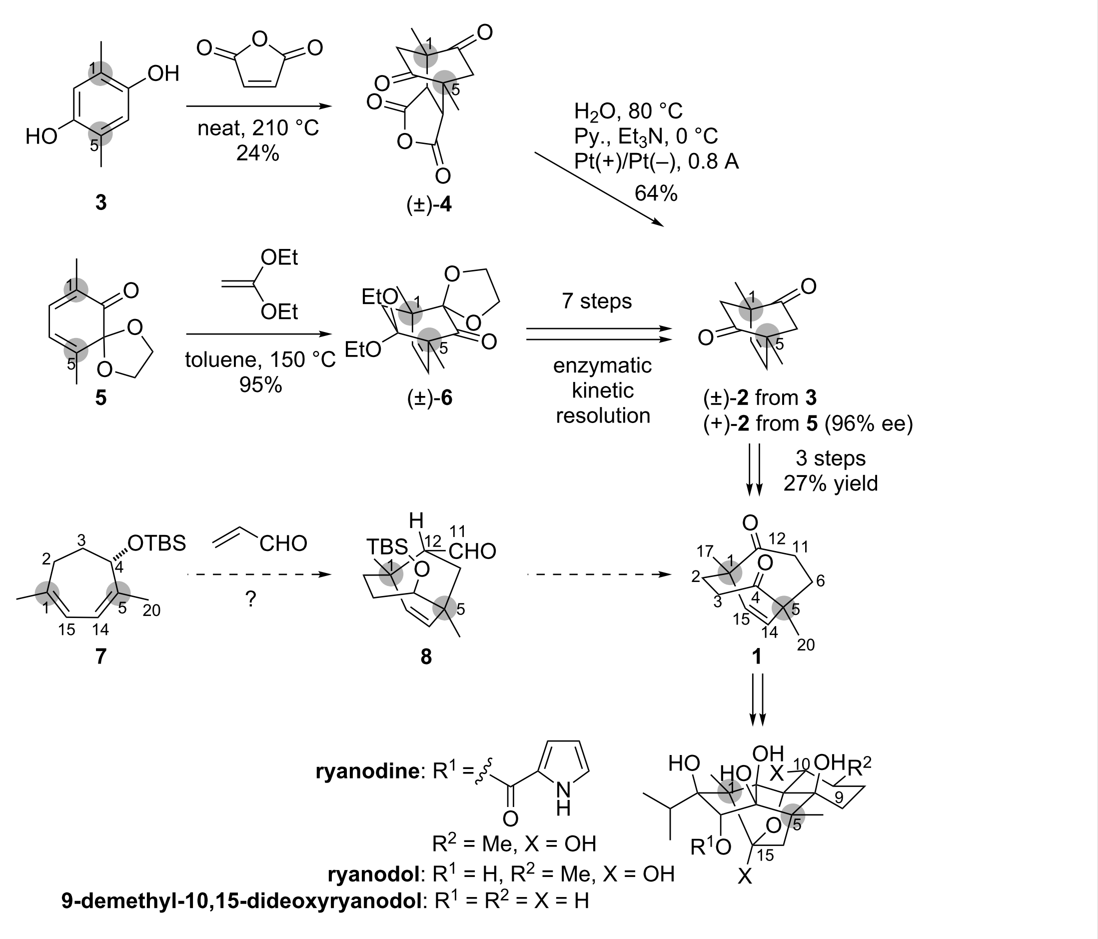
Abstract

The stereoselective Diels–Alder reaction between an optically active 1,4-dimethylcycloheptadiene and acrolein was effectively promoted by TBSOTf to produce a bicyclo[3.2.2]nonene derivative bearing two quaternary carbons. Seven additional transformations from the obtained bicycle delivered the C_2-symmetric bicyclo[3.3.2]decene derivative, a key intermediate in our synthetic study of ryanodine.

Introduction

Ryanodine (Scheme 1) [1-3] is a potent modulator of the intracellular calcium release channels, known as ryanodine receptors [4,5]. Its complex architecture, including eight contiguous tetrasubstituted carbons on the pentacyclic ABCDE-ring system, has posed a formidable synthetic challenge. To date, the only total synthesis of a compound in this class of natural products was reported by Deslongchamps, who constructed ryanodol in 1979 [6-9]. Most recently, we reported the synthesis of 9-demethyl-10,15-dideoxyryanodol [10] by taking advantage of the intrinsic C_2-symmetry of the target molecule. In this synthesis, C_2-symmetric compounds such as bicyclo[3.3.2]decene **1** were strategically designed, and application of pairwise functionalizations of these molecules minimized the total number of steps.

Bicyclo[3.3.2]decene **1** was prepared from C_2-symmetric bicyclo[2.2.2]octene **2** through a ring-expansion reaction (Scheme 1) [11]. We reported the synthetic routes to racemic **2** and enantiomerically pure **2** from **3** and **5**, respectively. Specifically, the dearomatizing Diels–Alder reaction between 2,5-dimethylbenzene-1,4-diol (**3**) and maleic anhydride lead to the construction of bicyclo[2.2.2]octene **4**, which was then transformed into racemic **2** through electrolysis [11]. Alternatively, the Diels–Alder reaction between 3,6-dimethyl-*o*-quinone



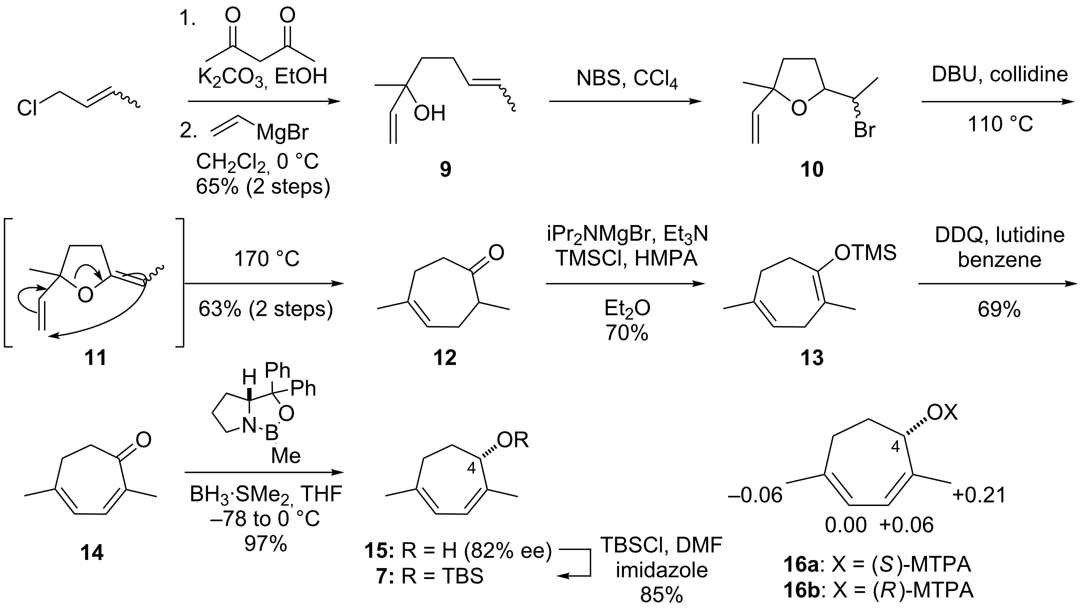
Scheme 1: Structure of ryanodine and the Diels–Alder reactions for construction of the potential intermediates of ryanodine.

monoacetal **5** and 1,1-diethoxyethylene provided bicyclo[2.2.2]octene **6**, which was then converted to enantiopure **2** via an enzymatic kinetic resolution [12]. The Diels–Alder reaction was effectively employed in both of these syntheses for construction of the two quaternary carbons at the C1 and C5 positions of ryanodine (highlighted in gray). However, the current route to (+)-**2** from racemic **6** generated the unnecessary antipode. Therefore, development of an alternative asymmetric route to **1** was planned to further improve the overall practicality. Here we report an asymmetric Diels–Alder reaction for simultaneous installation of the C1- and C5-stereocenters using the optically active cycloheptadiene derivative **7**, and its derivatization into bicyclo[3.3.2]decene **1**.

We assumed that the C4-stereocenter of optically active seven-membered diene **7** would permit the requisite stereoselective Diels–Alder reaction (Scheme 1). Namely, the reaction between **7** and acrolein was expected to stereoselectively introduce the C1, C5 and C12 stereocenters to afford bicyclo[3.2.2]nonene **8**. The C11-aldehyde of **8** was then to be utilized as a handle for the ring expansion to access **1**. To the best of our knowledge, construction of the two quaternary carbons by the intermolecular Diels–Alder reaction of 1,4-disubstituted cycloheptadiene derivatives has not been reported [13,14].

Results and Discussion

The synthesis of optically active **7** began from crotyl chloride (Scheme 2). The carbon chain extension of crotyl chloride by treatment with acetylacetone and K_2CO_3 [15], followed by the addition of vinylmagnesium bromide [16], provided **9**. The bromoetherification of tertiary alcohol **9** by using NBS led to tetrahydrofuran **10** as a diastereomeric mixture. Next, the base-induced elimination of HBr converted **10** to diene **11**, which underwent the Claisen rearrangement at 170 °C to give rise to heptenone **12** [17-21]. The more thermodynamically stable silyl enol ether **13** was regioselectively formed from **12** under Holton's conditions [22], and DDQ-mediated oxidation of **13** resulted in the formation of α,β-unsaturated ketone **14**. Asymmetric reduction of ketone **14** was in turn realized by applying a stoichiometric amount of (*R*)-CBS and $BH_3 \cdot SMe_2$ to produce **15** (82% ee) [23]. The absolute configuration of C4 was determined as *S* by the modified Mosher method after acylation of

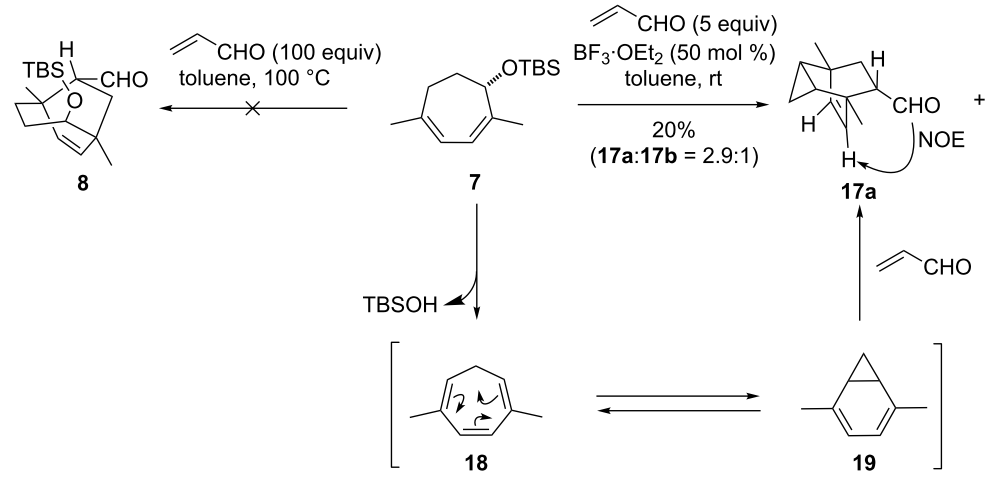


Scheme 2: Asymmetric synthesis of **7** and determination of the absolute configuration at C4 of **15** by the modified Mosher method. The numbers are differences in ^{1}H chemical shifts between **16a** and **16b** ($\Delta\delta = \delta$**16a** − δ**16b**).

15 using (*R*)- and (*S*)-MTPACl [24]. Finally, the hydroxy group of **15** was protected as its TBS ether to afford **7**.

We then explored the Diels–Alder reaction between **7** and acrolein to construct the bicyclo[3.2.2]nonene structure (Scheme 3). The Diels–Alder reaction under thermal conditions (100 °C) induced the decomposition of diene **7**, and only the starting material was recovered after 10 h (26%). Because of the low reactivity of **7**, we applied a Lewis acid to facilitate the reaction. However, the reaction of **7** and acrolein in the presence of BF_3·OEt_2 (50 mol %) led to formation of the unexpected bicyclo[2.2.2]octene skeletons **17a** and **17b** as a 2.9:1 mixture. Under these conditions, BF_3·OEt_2-promoted elimination of the allylic siloxy group in **7** generated triene **18**, which then isomerized into **19** via a 6π-electrocyclic reaction. Diene **19**, which appeared to be more reactive than the original diene **7**, then underwent the Diels–Alder reaction to provide **17a** and **17b**.

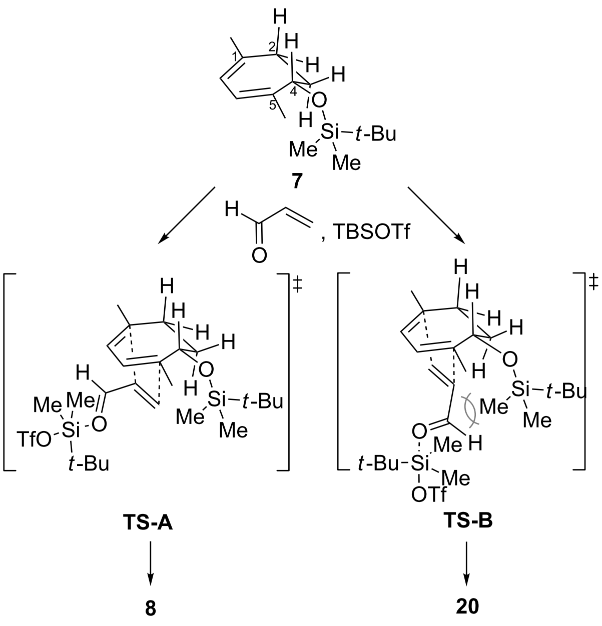
Formation of **17a** and **17b** in Scheme 3 confirmed that selective activation of acrolein in the presence of the Lewis-basic allylic oxygen was a prerequisite to the successful formation



Scheme 3: Generation of **17** through the 6π-electrocyclic reaction and the Diels–Alder reaction.

of **8**. We anticipated that bulky trialkylsilyl triflates would function as such chemoselective Lewis acids, because the activation of the TBS-connected oxygen of **7** by the silyl triflate would cause highly unfavorable steric interactions. Indeed, the cycloaddition between **7** and acrolein proceeded even at −78 °C by the action of TMSOTf (50 mol %) in toluene to afford the bicyclo[3.2.2]nonene **8** and **20** along with a small amount of two other isomers **21ab** (Table 1, entry 1). Among the various silyl triflates used (Table 1, entries 1–3), TBSOTf was found to be superior to TMSOTf or TIPSOTf in terms of the combined yield. Alteration of the amount of TBSOTf from 50 mol % (Table 1, entry 2) to 200 mol % (Table 1, entry 4) and change of the solvent from toluene (Table 1, entry 4) to CH_2Cl_2 (Table 1, entry 5) increased the yield of the adducts. It is particularly worthy of note that the use of 2,6-di-*tert*-butylpyridine in combination with 200 mol % of TBSOTf effectively inhibited the Lewis-acid-promoted elimination of the C4-oxy group, and that the ratio of **8** to **20** was improved from 1.6:1 to 3.4:1 by replacement of the solvent (Table 1, entries 4 and 5). Thus, we developed an effective method for synthesis of the requisite stereoisomer **8** by applying a TBSOTf-promoted Diels–Alder reaction [25,26]. Most importantly, the C4-stereocenter behaved as the control element to introduce the two quaternary carbons (C1 and 5) and the C12-stereocenter.

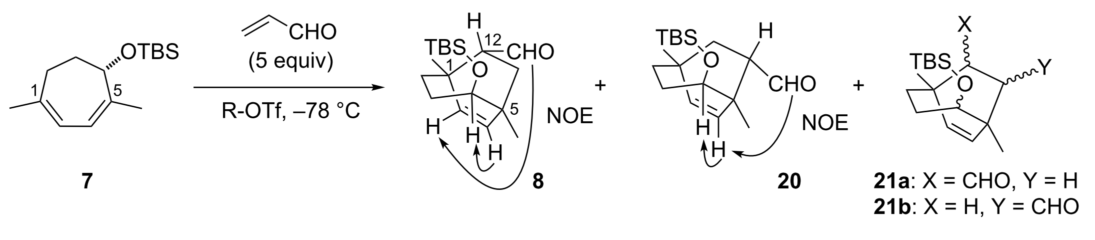
The selective formation of **8** out of eight possible isomers is rationalized in Scheme 4. The *endo*-type transition states would be favored over their *exo*-type counterparts, and acrolein would approach from the bottom face of **7** to avoid steric interactions with the axially oriented C2- and C4-hydrogen atoms on the top face [27]. These considerations eliminate six out of the eight stereoisomeric transition states, and leave only **TS-A** and **TS-B**, which in fact correspond to the generated adducts **8** and **20**, respectively. **TS-A** would be preferred over **TS-B** due to the unfavorable interaction of the two proximal TBS groups in **TS-B**, allowing formation of **8** as the major compound.



Scheme 4: Rationale of the stereoselectivity of the Diels–Alder reaction.

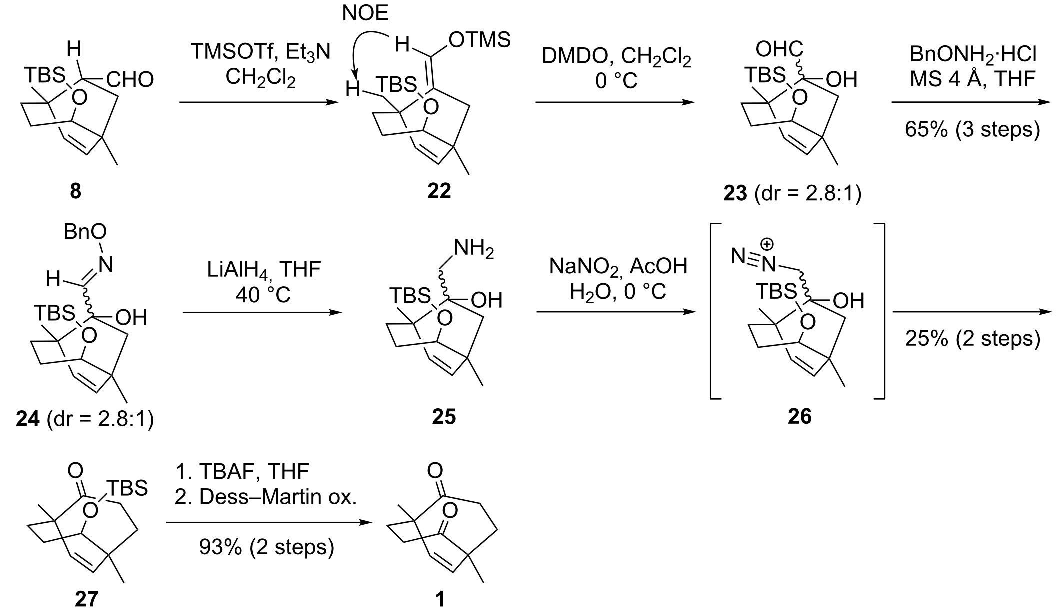
Having synthesized the optically active **8**, the next task was the preparation of C_2-symmetric bicyclo[3.3.2]decene **1** from **8** (Scheme 5). The silyl enol ether formation of aldehyde **8**

Table 1: Optimization of the Diels–Alder reaction.[a]



entry	silyl triflate (R)	solvent	yield[b]	ratio[c] (**8**/**20**/**21ab**)
1	TMS (50 mol %)	toluene	31%	1.9:1:0.6
2	TBS (50 mol %)	toluene	59%	1.8:1:0.5
3	TIPS (50 mol %)	toluene	47%	1.9:1:0.4
4[d]	TBS (200 mol %)	toluene	69%	1.6:1:0.4
5[d]	TBS (200 mol %)	CH_2Cl_2	88%	3.4:1:0.5

[a] Reaction was performed at 0.5 M. [b] Combined yield of **8**, **20** and two other isomers **21a**/**21b**. [c] Ratio was determined by ^1H NMR analysis. [d] 2,6-Di-*tert*-butylpyridine (200 mol %) was added as a buffer.



Scheme 5: Synthesis of C_2-symmetric **1**.

afforded **22** as a single stereoisomer, and the obtained **22** was oxidized with DMDO to provide α-hydroxy aldehyde **23** as a diastereomeric mixture (dr = 2.8:1). Compound **23** then reacted with benzyl hydroxylamine to produce oxime **24**, $LiAlH_4$-treatment of which led to **25**. The regioselective ring expansion of seven-membered **25** was induced by treatment with $NaNO_2$ in acetic acid [28,29], resulting in the formation of eight-membered **27** through the intermediary of **26**. Finally, the desilylation of **27** with TBAF and the subsequent oxidation of the resultant hydroxy group delivered the symmetric diketone **1** in optically active form.

Conclusion

In summary, we developed a synthetic route to the optically active seven-membered **7** and established the TBSOTf-promoted stereoselective Diels–Alder reaction between **7** and acrolein to construct highly functionalized bicyclo[3.2.2]nonene **8** bearing two quaternary carbons. Seven additional transformations of **8**, including the ring expansion of the seven-membered ring to an eight-membered ring, delivered C_2-symmetric bicyclo[3.3.2]decene **1**, which is the key intermediate in our synthetic studies of ryanodine.

Experimental

General: All reactions sensitive to air or moisture were carried out under argon or nitrogen atmosphere in dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. All other reagents were used as supplied unless otherwise stated. Analytical thin-layer chromatography (TLC) was performed by using E. Merck Silica gel 60 F254 precoated plates. Flash column chromatography was performed by using 40–50 μm Silica Gel 60N (Kanto Chemical Co., Inc.), 40–63 μm Silicagel 60 (Merck) or 32–53 μm Silica-gel BW-300 (Fuji Silysia Chemical Ltd.). Melting points were measured on a Yanaco MP-J3 micro melting-point apparatus and are uncorrected. Optical rotations were recorded on a JASCO DIP-1000 Digital Polarimeter. Infrared (IR) spectra were recorded on a JASCO FT/IR-4100 spectrometer. ^1H and ^{13}C NMR spectra were recorded on JEOL JNM-ECX-500, JNM-ECA-500, or JNM-ECS-400 spectrometers. Chemical shifts were reported in parts per million (ppm) on the δ scale relative to $CHCl_3$ (δ 7.26 for ^1H NMR), $CDCl_3$ (δ 77.0 for ^{13}C NMR), C_6D_5H (δ 7.16 for ^1H NMR), C_6D_6 (δ 128.0 for ^{13}C NMR), $CO(CD_3)(CD_2H)$ (δ 2.05 for ^1H NMR) as internal references. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet, m, multiplet. The numbering of the compounds corresponds to that of the natural products. High-resolution mass spectra were measured on Bruker microTOFII.

TMS-enol ether 13: Methylmagnesium bromide (3.0 M in Et_2O, 8.5 mL, 26 mmol) was added to a solution of iPr_2NH (3.9 mL, 28 mmol) in Et_2O (170 mL) at 0 °C. The mixture was stirred at room temperature for 19 h, and cooled to −78 °C. Then, a solution of **12** [3.5 g as a 5.7:1 mixture of **12** (23 mmol) and Et_2O] in Et_2O (60 mL), TMSCl (9.1 mL, 72 mmol), Et_3N (11.3 mL, 81 mmol), and HMPA (2.0 mL, 11 mmol) were successively added to the mixture. The reaction mixture was stirred at room temperature for 18 h and cooled to 0 °C. Phosphate buffer (pH 7, 100 mL) was added, and the resultant solution was extracted with Et$_2$O (150 mL × 3). The combined organic layers were washed with H$_2$O (30 mL) and brine (200 mL), dried over Na$_2$SO$_4$, filtered, and concentrated. The residue was purified by flash column chromatography (silica gel 200 g, pentane only) to afford silyl enol ether **13** (3.3 g, 16 mmol) and its regioisomer (344 mg, 1.64 mmol) in 70% and 7% yield, respectively. The synthesized silyl enol ether **13** was immediately subjected to the next reaction: colorless oil; ^{1}H NMR (500 MHz, C$_6$D$_6$) δ 0.17 (9H, s, C*H*$_3$ of TMS), 1.61 (3H, d, *J* = 1.2 Hz, H17), 1.73 (3H, s, H20), 2.05 (2H, t, *J* = 6.3 Hz, H2ab), 2.31–2.35 (2H, m, H3ab), 2.60 (2H, d, *J* = 5.7 Hz, H14ab), 5.53 (1H, tq, *J* = 5.7, 1.2 Hz, H15); ^{13}C NMR (125 MHz, C$_6$D$_6$) δ 1.2, 19.3, 25.8, 30.9, 31.7, 32.8, 114.7, 123.3, 137.4, 146.4. The regioisomer of **13**: colorless oil; ^{1}H NMR (400 MHz, C$_6$D$_6$) δ 0.18 (9H, s, C*H*$_3$ of TMS), 1.19 (3H, d, *J* = 6.9 Hz, H20), 1.67 (3H, br s, H17), 2.00 (1H, ddd, *J* = 14.6, 7.3, 7.3 Hz, H14a), 2.23–2.27 (1H, m, H14b), 2.32–2.40 (1H, m, H5), 2.46 (1H, dd, *J* = 17.9, 6.4 Hz, H2a), 2.62 (1H, dd, *J* = 17.9, 5.5 Hz, H2b), 4.95 (1H, dd, *J* = 6.4, 5.5 Hz, H3), 5.49 (1H, br ddq, *J* = 7.3, 7.3, 1.4 Hz, H15).

Diene 14: DDQ (7.1 g, 31 mmol) was added to a solution of **13** (3.3 g 16 mmol) and 2,6-lutidine (5.4 mL, 46 mmol) in benzene (30 mL) at 0 °C. The reaction mixture was stirred at room temperature for 20 min and filtered through a short column of Al$_2$O$_3$ with Et$_2$O. The filtrate was concentrated. The residue was purified by flash column chromatography (silica gel 120 g, pentane/Et$_2$O 10:1 to 5:1) to afford diene **14** (1.5 g, 11 mmol) in 69% yield: yellow oil; IR (neat) ν_{max}: 2949, 1656, 1595, 1431, 1377 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.92 (3H, s, H20), 1.98 (3H, s, H17), 2.29 (2H, t, *J* = 6.3 Hz, H2ab), 2.64 (2H, t, *J* = 6.3 Hz, H3ab), 5.80 (1H, d, *J* = 8.0 Hz, H15), 6.51 (1H, d, *J* = 8.0 Hz, H14); ^{13}C NMR (100 MHz, CDCl$_3$) δ 20.4, 26.5, 28.1, 41.7, 122.4, 136.0, 137.0, 150.0, 201.3; HRMS–ESI (*m/z*): [M + Na]$^+$ calcd for C$_9$H$_{12}$ONa, 159.0780; found, 159.0778.

Diene 15: BH$_3$·SMe$_2$ (220 μL, 2.3 mmol) was added to a solution of (*R*)-2-Me-CBS-oxazaborolidine (1.0 M in toluene, 2.3 mL, 2.3 mmol) in THF (6 mL) at 0 °C. The solution was stirred for 30 min at 0 °C and cooled to −78 °C. Then a solution of diene **14** (265 mg, 1.94 mmol) in THF (3 mL) was added at −78 °C. The reaction mixture was warmed to 0 °C over 15 min, and H$_2$O (10 mL) was added. The resultant solution was extracted with Et$_2$O (6 mL × 3). The combined organic layers were washed with brine (5 mL), dried over Na$_2$SO$_4$, filtered and concentrated. The residue was purified by flash column chromatography (silica gel 5 g, pentane/Et$_2$O 20:1 to 5:1) to afford **15** (261 mg**,** 1.89 mmol) in 97% yield. The enantiopurity of **15** was determined as 82% ee by comparison of the integrations of the H14 peak at 5.78 and 5.72 ppm on ^{1}H NMR after the esterification with (*S*)-MTPACl; yellow oil; $[\alpha]_D^{20}$ −402 (*c* 0.995, CHCl$_3$); IR (neat) ν_{max}: 3336, 2965, 2920, 2880, 1434, 1056, 1013 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.54 (1H, br s, O*H*), 1.75 (1H, dddd, *J* = 13.7, 11.9, 2.8, 2.8 Hz, H3a), 1.85 (3H, s, H17 or 20), 1.95 (3H, s, H17 or 20), 2.00–2.15 (2H, m, H2a and 3b), 2.32–2.39 (1H, br dd, *J* = 16.5, 11.9 Hz, H2b), 4.20 (1H, m, H4), 5.52 (1H, br d, *J* = 7.8 Hz, H14 or 15), 5.61 (1H, d, *J* = 7.8 Hz, H14 or 15); ^{13}C NMR (125 MHz, C$_6$D$_6$) δ 24.0, 26.6, 29.2, 33.2, 72.4, 120.7, 122.6, 140.2, 142.9; HRMS–ESI (*m/z*): [M + Na]$^+$ calcd for C$_9$H$_{14}$ONa, 161.0937; found, 161.0934.

Diene 7: The mixture of **15** (259 mg, 1.88 mmol), imidazole (300 mg, 4.41 mmol) and TBSCl (330 mg, 2.19 mmol) in DMF (6.0 mL) was stirred for 8.5 h at room temperature and cooled to 0 °C. H$_2$O (10 mL) was added to the reaction mixture, and the resultant solution was stirred for 30 min. The mixture was extracted with EtOAc (6 mL × 3). The combined organic layers were dried over Na$_2$SO$_4$, filtered and concentrated. The residue was purified by flash column chromatography (silica gel 5 g, hexane/EtOAc 1:0 to 100:1) to afford **7** (404 mg, 1.60 mmol) in 85% yield; colorless oil; $[\alpha]_D^{20}$ −247 (*c* 1.04, CHCl$_3$); IR (neat) ν_{max}: 2956, 2928, 2856, 1472, 1436, 1253 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.085 (3H, s, C*H*$_3$ of TBS), 0.093 (3H, s, C*H*$_3$ of TBS), 0.91 (9H, s, *t*-Bu of TBS), 1.75 (1H, dddd, *J* = 13.3, 10.5, 2.3, 2.3 Hz, H3a), 1.83 (3H, s, H17), 1.85 (3H, s, H20), 1.92–2.00 (1H, dddd, *J* = 13.3, 8.7, 6.4, 2.3 Hz, H3b), 2.04 (1H, ddd, *J* = 16.5, 8.7, 2.3 Hz, H2a), 2.40 (1H, br dd, *J* = 16.5, 10.5 Hz, H2b), 4.22 (1H, br d, *J* = 6.4 Hz, H4), 5.50 (1H, d, *J* = 7.8 Hz, H15), 5.54, (1H, d, *J* = 7.8 Hz, H14); ^{13}C NMR (100 MHz, CDCl$_3$) δ −4.3, −4.1, 18.5, 24.0, 26.2, 26.9, 30.0, 34.9, 73.4, 120.5, 121.5, 141.4, 143.2; HRMS–ESI (*m/z*): [M + Na]$^+$ calcd for C$_{15}$H$_{28}$OSiNa, 275.1802; found, 275.1801.

Cycloadduct 8 and 20: TBSOTf (530 μL, 2.3 mmol) was added to a solution of **7** (297 mg, 1.18 mmol), acrolein (390 μL, 5.8 mmol) and 2,6-di-*tert*-butylpyridine (530 μL, 2.3 mmol) in CH$_2$Cl$_2$ (2.4 mL) at −78 °C. The reaction mixture was stirred for 15 min at −78 °C, and then saturated aqueous NaHCO$_3$ (3 mL) was added. The resultant mixture was extracted with EtOAc (5 mL × 3). The combined organic layers were dried over Na$_2$SO$_4$, filtered and concentrated. The residue was purified by flash column chromatography (silica gel 12 g, hexane/CH$_2$Cl$_2$ 4:1 to 3:1) to afford pure **20** (23 mg, 75 μmol), a mixture of **20**, **21a**, **21b** and **8** (215 mg, 0.67 mmol), and pure **8** (87 mg, 0.29 mmol) in 88% combined yield. **8**: colorless oil; $[\alpha]_D^{20}$ +25.6 (*c* 1.13, CHCl$_3$); IR (neat) ν_{max}: 2954, 2930, 1724, 1253, 1070 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.02 (6H, s, C*H*$_3$ of TBS × 2), 0.88 (9H, s, *t*-Bu of TBS), 1.02 (3H, s, H17 or 20), 1.03 (3H, s, H17 or 20), 1.21 (1H, dd, *J* = 14.6, 4.1 Hz, H6a), 1.42 (1H, ddd, *J* = 13.7, 5.5, 5.0 Hz, H2a), 1.56 (1H, ddd,

J = 13.7, 11.5, 5.0 Hz, H2b), 1.72 (1H, dddd, J = 14.6, 11.5, 9.2, 5.5 Hz, H3a), 1.84 (1H, dddd, J = 14.6, 5.0, 5.0, 5.0 Hz, H3b), 2.34 (1H, dd, J = 14.6, 9.6 Hz, H6b), 2.57 (1H, ddd, J = 9.6, 5.5, 4.1 Hz, H12), 3.38 (1H, dd, J = 9.2, 5.0 Hz, H4), 5.76 (1H, d, J = 9.2 Hz, H14), 5.81 (1H, d, J = 9.2 Hz, H15), 9.29 (1H, d, J = 5.5 Hz, C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.2, 18.1, 25.9, 26.7, 27.0, 29.2, 34.5, 35.3, 40.2, 40.4, 56.5, 71.7, 138.1, 138.3, 204.4; HRMS–ESI (m/z): $[M + Na]^+$ calcd for $C_{18}H_{32}O_2SiNa$, 331.2064; found, 331.2063. **20**: IR (neat) ν_{max}: 2954, 2930, 2856, 1724, 1253, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.02 (6H, s, CH_3 of TBS × 2), 0.88 (9H, s, *t*-Bu of TBS), 1.02 (3H, s, CH_3CCHCHO), 1.06 (3H, s, CH_3CCH_2), 1.34 (1H, ddd, J = 13.7, 6.0, 3.7 Hz, $CCH_AH_BCH_2$), 1.52–1.59 (2H, m, $CCH_AH_BCH_2$ and CCH_AH_BCHCHO), 1.70–1.87 (2H, m, CCH_2CH_2CH(OTBS)), 1.91 (1H, dd, J = 14.7, 10.1 Hz, CCH_AH_BCHCHO), 2.97 (1H, ddd, J = 10.1, 5.0, 5.0 Hz, C*H*CHO), 3.32 (1H, dd, J = 9.2, 5.5 Hz, C*H*(OTBS)), 5.55 (1H, d, J = 9.2 Hz, CC*H*=$CHCCH_2$), 5.97 (1H, d, J = 9.2 Hz, CCH=C*H*CCH_2), 9.37 (1H, d, J = 5.0 Hz, C*H*O); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.8, −4.2, 18.1, 24.1, 25.9, 29.7, 33.8, 34.1, 34.6, 38.0, 41.8, 50.6, 73.5, 134.1, 142.4, 204.3; HRMS–ESI (m/z): $[M + Na]^+$ calcd for $C_{18}H_{32}O_2SiNa$, 331.2064; found, 331.2057.

Oxime 24: TMSOTf (220 μL, 1.2 mmol) was added to a solution of **8** (122 mg, 0.395 mmol) and Et_3N (330 μL, 2.4 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C. The reaction mixture was stirred at room temperature for 15 h and cooled to 0 °C. Phosphate buffer (pH 7, 5 mL) was added, and the resultant mixture was extracted with EtOAc (6 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was passed through a short column (silica gel 100 mg, hexane/EtOAc 2:1) to afford the crude TMS enol ether **22**, which was used in the next reaction without further purification. DMDO (58 mM in acetone, 6.8 mL, 0.39 mmol) was added to a solution of the above crude TMS enol ether **22** in CH_2Cl_2 (1.0 mL). The reaction mixture was stirred for 10 min at 0 °C, and then isoprene (39 μL, 0.39 mmol) was added. The resultant solution was concentrated. The residue was roughly purified by flash column chromatography (silica gel 24 g, hexane/EtOAc 1:0 to 10:1) to afford hydroxy aldehyde **23** (93 mg) as a diastereomixture (2.8:1), which was used in the next reaction without further purification. A mixture of the above crude **23**, $BnONH_2$·HCl (135 mg, 0.846 mmol), and MS4Å (93 mg) in THF (3.0 mL) was stirred at room temperature for 22 h. The reaction mixture was filtered through a pad of Celite with EtOAc (15 mL), and the filtrate was concentrated. The residue was purified by flash column chromatography (silica gel 15g, hexane/toluene 2:1 to 0:1 then hexane/CH_2Cl_2 1:1 to 1:3) to afford oxime **24a** (81 mg, 0.19 mmol) and **24b** (29 mg, 67 μmol) in 48% and 17% yield, respectively, over three steps. **24a**: colorless oil: $[\alpha]_D^{20}$ +60 (c 0.73, $CHCl_3$); IR (neat) ν_{max}: 3522, 2954, 2929, 2856, 1455, 1363, 1254, 1067 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.006 (3H, s, CH_3 of TBS), 0.012 (3H, s, CH_3 of TBS), 0.88 (9H, s, *t*-Bu of TBS), 0.98 (3H, s, H17 or 20), 1.02 (3H, s, H17 or 20), 1.33 (1H, d, J = 16.1 Hz, H6a), 1.36–1.57 (3H, m, H2ab and 3a), 1.85 (1H, dddd, J = 14.9, 5.8, 5.8, 5.8 Hz, H3b), 2.81 (1H, d, J = 16.1 Hz, H6b), 2.94 (1H, s, O*H*), 3.40 (1H, dd, J = 6.3, 5.8 Hz, H4), 5.13 (2H, s, OCH_2Ph), 5.73 (1H, d, J = 9.2 Hz, H14 or 15), 5.79 (1H, d, J = 9.2 Hz, H14 or 15), 7.30–7.39 (5H, m, aromatic), 7.71 (1H, s, C*H*NOBn); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.8, −4.3, 18.1, 23.3, 25.9, 27.0, 32.6, 33.9, 39.7, 42.6, 42.9, 71.0, 76.3, 78.0, 128.0, 128.42, 128.44, 137.1, 137.3, 138.4, 152.8; HRMS–ESI (m/z): $[M + Na]^+$ calcd for $C_{25}H_{39}NO_3SiNa$, 452.2591; found, 452.2589. **24b**: IR (neat) ν_{max}: 3525, 3025, 2955, 2928, 2856 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.01 (3H, s, CH_3 of TBS), 0.02 (3H, s, CH_3 of TBS), 0.83 (3H, s, H17), 0.88 (9H, s, *t*-Bu of TBS), 0.95 (3H, s, H20), 1.33–1.42 (1H, m, H2a), 1.50 (1H, d, J = 15.1 Hz, H6a), 1.80–1.88 (2H, m, H2b and 3a), 1.96–2.07 (1H, m, H3b), 2.44 (1H, d, J = 15.1 Hz, H6b), 3.42 (1H, dd, J = 8.2, 6.0 Hz, H4), 3.48 (1H, s, O*H*), 5.06 (2H, s, OCH_2Ph), 5.62 (1H, d, J = 9.6 Hz, H14), 5.65 (1H, d, J = 9.6 Hz, H15), 7.27–7.35 (5H, m, aromatic), 7.39 (1H, s, C*H*NOBn); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.1, 18.1, 23.5, 25.9, 26.7, 34.3, 34.9, 41.4, 41.5, 42.3, 71.6, 76.2, 78.1, 127.9, 128.3, 128.4, 137.2, 137.6, 138.3, 156.2; HRMS–ESI (m/z): $[M + Na]^+$ calcd for $C_{25}H_{39}NO_3SiNa$, 452.2591; found, 452.2580.

Ketone 27: $LiAlH_4$ (2.0 M in THF, 380 μL, 0.76 mmol) was added to a solution of oxime **24** (110 mg, 0.256 mmol, a 2.8:1 diastereomixture of **24a** and **24b**) in THF at 0 °C. The reaction mixture was stirred at 0 °C for 10 min, at room temperature for 2.5 h, and at 40 °C for 2 h. After additional $LiAlH_4$ (2.0 M in THF, 380 μL, 0.76 mmol) was added, the reaction mixture was stirred at 50 °C for a further 3.5 h. $LiAlH_4$ (2.0 M in THF, 380 μL, 0.76 mmol) was added again, and the reaction mixture was stirred for a further 1 h. After the reaction mixture was cooled to 0 °C, H_2O (87 μL) was added. The resultant solution was stirred for 1 h at room temperature, and then 15% aqueous NaOH (87 μL) and H_2O (260 μL) were added. The solution was stirred for 9 h. The resultant mixture was filtered through a pad of Celite with THF (30 mL), and the filtrate was concentrated to afford amino alcohol **25**, which was used in the next reaction without further purification. A solution of $NaNO_2$ (141 mg, 2.04 mmol) in H_2O (1.3 mL) was added to a solution of the above crude amino alcohol **25** in H_2O (3.8 mL) and AcOH (1.0 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 3 h, and then saturated aqueous $NaHCO_3$ (30 mL) was added. The resultant mixture was extracted with EtOAc (8 mL × 4). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (silica gel 18 g, hexane/CH_2Cl_2 3:1 to 0:1) to afford ketone **27** (20 mg, 65 μmol) in 25% yield over two steps: colorless oil; $[\alpha]_D^{20}$ +134 (*c* 0.165, $CHCl_3$); IR (neat) ν_{max}: 2954, 2929, 2856, 1703, 1462, 1063 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.01 (6H, s, CH_3 of TBS × 2), 0.86 (9H, s, *t*-Bu of TBS), 1.11 (3H, s, H17 or 20), 1.12 (3H, s, H17 or 20), 1.41 (1H, ddd, *J* = 14.9, 8.1, 2.3 Hz, H6a), 1.52–1.72 (3H, m, H2ab and 3a), 1.75–1.81 (1H, m, H3b), 2.25 (1H, ddd, *J* = 12.6, 5.2, 2.3 Hz, H11a), 2.34 (1H, ddd, *J* = 14.9, 12.6, 5.2 Hz, H6b), 2.93 (1H, ddd, *J* = 12.6, 12.6, 8.1 Hz, H11b), 3.40 (1H, dd, *J* = 10.3, 4.6 Hz, H4), 5.56 (1H, d, *J* = 10.9 Hz, H14), 5.73 (1H, d, *J* = 10.9 Hz, H15); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.7, −4.2, 18.0, 25.9, 26.4, 29.0, 31.2, 34.6, 40.0, 42.2, 42.4, 50.3, 73.7, 137.6, 139.4, 218.5; HRMS–ESI (*m/z*): $[M + Na]^+$ calcd for $C_{18}H_{32}O_2SiNa$, 331.2064; found, 331.2078.

***C_2*-symmetric diketone 1:** TBAF (1.0 M in THF, 130 μL, 0.13 mmol) was added to a solution of **27** (13 mg, 42 μmol) in THF (0.9 mL) at room temperature. The reaction mixture was stirred for 1.5 h at room temperature and at 40 °C for 1.5 h. TBAF (1.0 M in THF, 83 μL, 83 μmol) was added again to the reaction mixture, and the reaction mixture was stirred at 40 °C for a further 16.5 h. The reaction mixture was cooled to room temperature, and passed through a short column of silica gel with Et_2O. The filtrate was concentrated to afford crude alcohol, which was used in the next reaction without further purification. A mixture of the above crude alcohol, $NaHCO_3$ (33 mg, 0.39 mmol), and Dess–Martin periodinane (53 mg, 0.13 mmol) in CH_2Cl_2 (0.8 mL) was stirred at room temperature for 2.5 h, and then saturated aqueous $Na_2S_2O_3$ (3 mL) was added. The resultant mixture was extracted with Et_2O (4 mL × 3). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (silica gel 1 g, pentane/Et_2O 5:1 to 2:1) to afford C_2-symmetric diketone **1** (7.5 mg, 39 μmol) in 93% yield over two steps: crystal; m.p. 55 °C; $[\alpha]_D^{20}$ +260 (*c* 0.37, $CHCl_3$). Other analytical data of **1** were identical to those reported by our group previously [11].

Supporting Information

Supporting Information File 1

Experimental procedures and NMR spectra of all newly synthesized compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-74-S1.pdf]

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Synthesis of phenanthridines via palladium-catalyzed picolinamide-directed sequential C–H functionalization

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Letter

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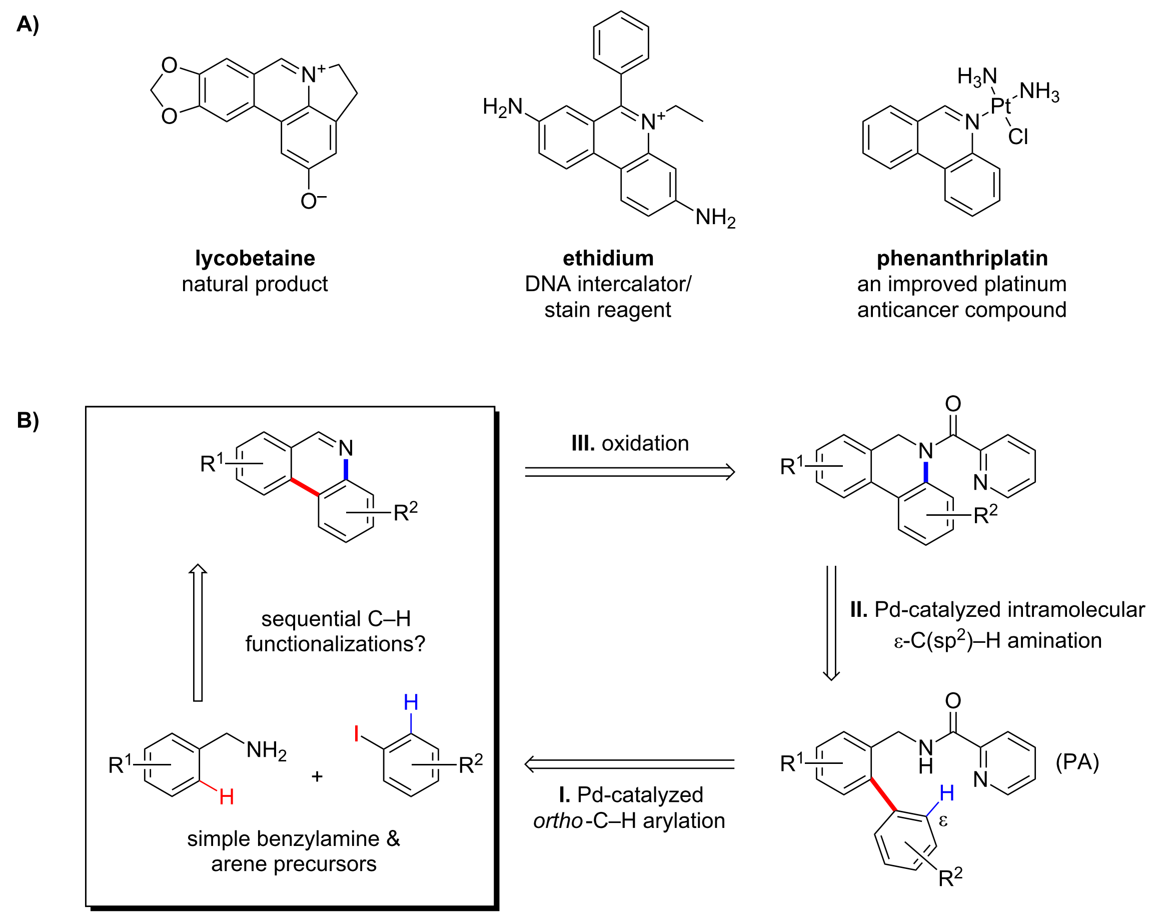
Abstract

We report a new synthesis of phenanthridines based on palladium-catalyzed picolinamide-directed sequential C–H functionalization reactions starting from readily available benzylamine and aryl iodide precursors. Under the catalysis of $Pd(OAc)_2$, the *ortho*-C–H bond of benzylpicolinamides is first arylated with an aryl iodide. The resulting biaryl compound is then subjected to palladium-catalyzed picolinamide-directed intramolecular dehydrogenative C–H amination with $PhI(OAc)_2$ oxidant to form the corresponding cyclized dihydrophenanthridines. The benzylic position of these dihydrophenanthridines could be further oxidized with $Cu(OAc)_2$, removing the picolinamide group and providing phenathridine products. The cyclization and oxidation could be carried out in a single step and afford phenathridines in moderate to good yields.

Introduction

Phenanthridines and 5,6-dihydro-phenanthridines are important core structures found in a variety of natural products and functional molecules (Scheme 1A) [1-8]. Synthetic methods for their preparation include the classical Pictet–Hubert condensation [9], radical-mediated reactions [10-13], metal-catalyzed cross-couplings [14-18], cycloadditions [19], and others [20-22]. More recently, methods based on the metal-catalyzed functionalization of carbon–hydrogen (C–H) bonds have also emerged as viable strategies for synthesizing phenanthridines [23-25]. Despite these advances, construction of phenanthridines with complex substitution patterns remains difficult and often requires lengthy and inefficient synthetic sequences. Herein, we report a novel method for phenanthridine synthesis based on sequential palladium-catalyzed picolinamide



Scheme 1: Representative phenanthridine compounds and our synthetic strategy based on Pd-catalyzed sequential C–H functionalizations.

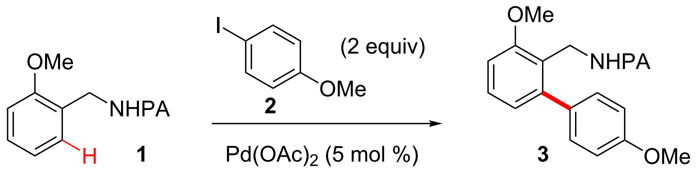
(PA)-directed C–H functionalization reactions beginning from easily accessible PA-protected benzylamine and aryl iodide precursors.

Results and Discussion

New synthetic strategy for phenanthridine compounds. The picolinamide (PA) group has been shown to be an excellent directing group for a range of Pd-catalyzed C–H functionalization reactions [26-35]. In 2005, the Daugulis laboratory first reported that the *ortho*-C(sp^2)−H bond of benzylpicolinamides could be arylated with aryl iodides under Ag-promoted Pd-catalyzed conditions [26]. In 2012, our laboratory [28] as well as that of Daugulis [27] independently reported that picolinamide substrates can undergo intramolecular dehydrogenative C–H amination reactions to afford medium-sized *N*-heterocycles under the catalysis of Pd(OAc)$_2$ with PhI(OAc)$_2$ oxidant. These discoveries led us to explore whether we could develop a new strategy for synthesizing phenanthridines. As outlined in Scheme 1B, we envisioned that *ortho*-arylated benzylamine picolinamides could undergo an intramolecular amination at the *ortho* ε-C–H position of the newly installed arene group to form cyclized dihydrophenanthridines, which could be further converted to phenanthridine products under oxidative conditions. Ideally, we hoped to perform both the intramolecular C–H amination and subsequent oxidation in a single step [36].

Arylation of 2-methoxybenzyl picolinamide 1 with 4-iodoanisole (2) under various conditions. We commenced the study by investigating the arylation of 2-methoxybenzyl picolinamide **1** with 4-iodoanisole (**2**) under various conditions (Table 1) to form our desired arylated product **3**. Our initial attempt under the original Pd(OAc)$_2$-catalyzed AgOAc-promoted solvent-free condition afforded the desired arylated product **3** in good yield (Table 1, entry 1). This method, however, required the use of expensive silver salt as an additive and high reaction temperature (150 °C). We next sought to replace the silver salts with cheaper reagents and lower the reaction temperature [12]. Not surprisingly, the arylation yield dropped significantly when the reaction was performed in toluene solvent at 120 °C (Table 1, entry 2). Addition of PivOH (0.3 equiv) gave little improvement (Table 1, entries 3 and 4).

Table 1: Optimization of the Pd-catalyzed *ortho*-C–H arylation of benzylpicolinamide. All screening reactions were carried out in a 10 mL glass vial on a 0.2 mmol scale.



entry	additives (equiv)	temperature (°C)	solvent	yield of **3** (%)[a]
1	AgOAc (1.5)	150	no solvent	76
2	AgOAc (1.5)	120	toluene	6
3	AgOAc (1.5), PivOH (0.3)	120	toluene	3
4	PivOH (0.3)	120	toluene	5
5	K_2CO_3 (2)	120	toluene	57
6	PivOH (0.3), K_2CO_3 (2)	120	toluene	90
7	PivOH (0.3), $KHCO_3$ (2)	120	toluene	95 (91)[b]
8	AcOH (0.3), $KHCO_3$ (2)	120	toluene	78
9	*o*PBA[c] (0.3), $KHCO_3$ (2)	120	toluene	84
10	PivOH (0.3), $KHCO_3$ (2)	90	toluene	29

[a]Yields are based on ^{1}H NMR analysis of the reaction mixture after workup; [b]Isolated yield; [c]oPBA: *ortho*-phenylbenzoic acid.

To our delight, the desired arylation reaction was largely restored with the application of 2 equiv of K_2CO_3 at 120 °C for 24 h (Table 1, entry 5). Furthermore, an excellent yield was obtained when K_2CO_3 was replaced with $KHCO_3$ and 0.3 equiv of PivOH was applied (Table 1, entry 7). The most effective carboxylate ligand and solvent was found to be PivOH and toluene, respectively.

The determination of the scope of this reaction with benzylpicolinamide and aryl iodide substrates. With the optimized conditions in hand, we next explored the scope of benzylpicolinamide and aryl iodide substrates (Figure 1). The electronic properties of benzylpicolinamide and aryl iodides had little influence on the reactivity, as benzylpicolinamide and aryl iodide substrates bearing electron-donating and withdrawing substituents react in good yields (**3**, **8**, and **12**). Significantly decreased arylation yield was observed for *ortho*-substituted aryl iodides (e.g., **9**). The sterics of the benzylpicolinamides is also important for the regioselectivity of the arylation reaction. For instance, the less hindered *ortho* position is preferentially arylated (e.g., **14**) when a *meta* substitutent is present on the benzylpicolinamide. Aryl bromides are much less reactive compared with aryl iodide substrates **4**. This is in accordance with results on the Pd-catalyzed PA-directed arylation of more inert C(sp^3)–H bonds [29].

Cyclization of biaryl compounds to form dihydrophenanthridines. Next, we investigated the cyclization of biaryl compounds to form dihydrophenanthridines via Pd-catalyzed intramolecular dehydrogenative amination of ε-C(sp^2)–H bonds [37-45]. To our delight, treatment of **3** in the presence of 5 mol % of Pd(OAc)$_2$ and 2 equiv of PhI(OAc)$_2$ in toluene at 120 °C for 24 h gave the desired dihydrophenanthridine **16** in good yield (Table 2, entry 1). In addition, a further oxidized phenanthridine **17** was obtained as a side product. Compound **17** is presumably generated through the PhI(OAc)$_2$-mediated oxidation of the benzylic C–H bond to form a phenanthridinium intermediate **18**, which then undergoes a removal of the PA group. Encouraged by these observations, we proceeded to explore whether the cyclization and oxidation steps can be performed in one step to give the phenanthridines in a shorter procedure. A variety of oxidants, such as 1,4-benzoquinone (BQ), $KMnO_4$, ceric ammonium nitrate (CAN), and copper salts were examined [46]. The combination of PhI(OAc)$_2$ (2 equiv) and Cu(OAc)$_2$ (2 equiv) afforded the phenanthridine product **17** in highest yield (Table 2, entry 7). The yield can be further improved using 10 mol % of Pd(OAc)$_2$ catalyst (Table 2, entry 8). In a control experiment, dihydrophenanthridine **16** was oxidized with the application of Cu(OAc)$_2$ (2 equiv) in toluene at 120 °C for 24 h, forming **17** in excellent yield. We believe that PhI(OAc)$_2$ serves as the oxidant for the initial Pd-catalyzed intramolecular C–H amination step, in which a Pd$^{II/IV}$ catalytic manifold might be operative. Cu(OAc)$_2$ is responsible for the subsequent oxidation of the benzylic C–H bond of dihydrophenanthridine.

Extension of the cyclization–oxidation step to other arylated picolinamide substrates. The coupled cyclization–oxidation

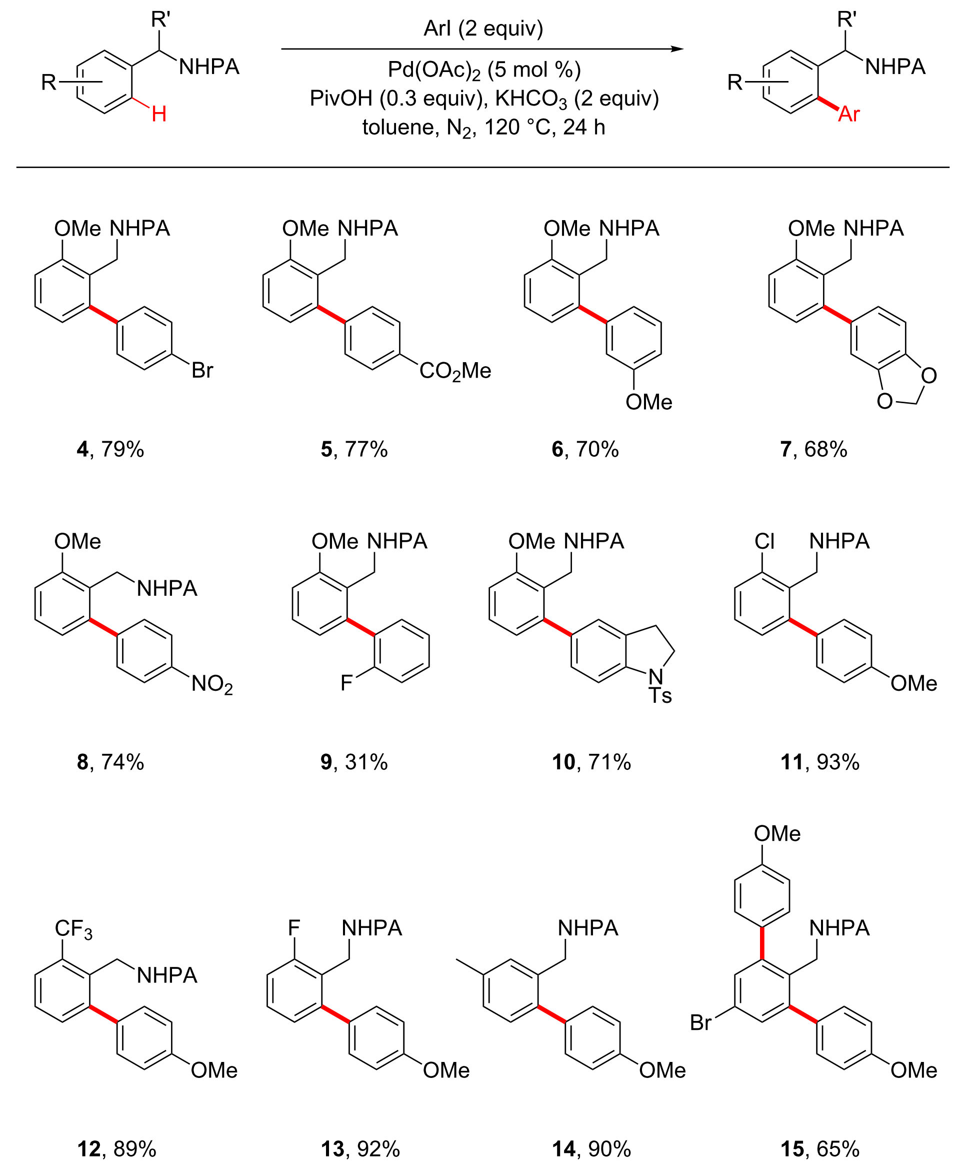


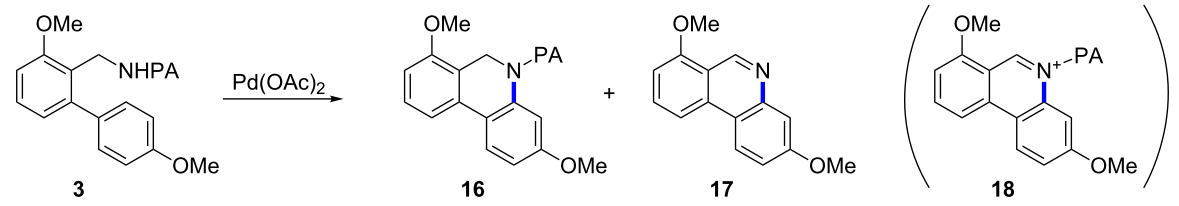
Figure 1: Substrate scope of the Pd-catalyzed PA-directed C–H arylation reaction. All reactions were carried out in a 10 mL glass vial on a 0.2 mmol scale; yields are based on the isolated product.

step detailed above was then used to synthesize phenanthridines from other arylated picolinamide substrates (Figure 2). In general, electron-rich arene motifs, installed by C–H arylation, gave a higher yield of phenanthridine products; electron-deficient substrates provide a lower yield. For instance, substrate **8** with a *para*-nitro group failed to give any cyclized product under the standard conditions. Substrates with moderately electron-withdrawing groups, such as **20** bearing a *para*-ester group, reacted in moderate yield. The electronic properties of the benzylpicolinamide scaffold had much less influence on the reaction. For example, product **22** bearing an *ortho*-CF_3 substituent was obtained in 51% yield. Finally, it is noteworthy that all of the above phenanthridine products show intense blue fluorescence. We expect our synthetic strategy will afford access to phenanthridines bearing varied substitution patterns, enabling applications in biology and materials science.

Conclusion

In summary, we have developed a readily applicable two-step method for the synthesis of phenanthridines from easily accessible benzylamine picolinamides and aryl iodides. In the first step, an improved protocol allows us to carry out the Pd-catalyzed PA-directed C–H arylation reaction without the use of expensive silver additives. In the second step, application of $PhI(OAc)_2$ and $Cu(OAc)_2$ oxidant under the catalysis of

Table 2: Formation of phenanthridine **17** in a single step by Pd-catalyzed intramolecular C–H amination followed by oxidation. All screening reactions were carried out in a 10 mL glass vial on a 0.2 mmol scale.



entry	$Pd(OAc)_2$ (mol %)	additives (equiv)	yield (%)^a	
			16	**17**
1	5	$PhI(OAc)_2$ (2)	40	5
2	5	$PhI(OAc)_2$ (2), AcOH (2)	23	8
3	5	$PhI(OAc)_2$ (2), BQ (2)	35	10
4	5	$PhI(OAc)_2$ (2), $KMnO_4$ (2)	56	3
5	5	$PhI(OAc)_2$ (2), CAN (2)	37	25
6	5	$PhI(OAc)_2$ (2), $CuCl_2$ (2)	29	34
7	5	$PhI(OAc)_2$ (2), $Cu(OAc)_2$ (2)	17	51
8	10	$PhI(OAc)_2$ (2), $Cu(OAc)_2$ (2)	15	62 (58)^b

^{a}Yields are based on ^{1}H NMR analysis of the reaction mixture after workup; ^{b}Isolated yield.

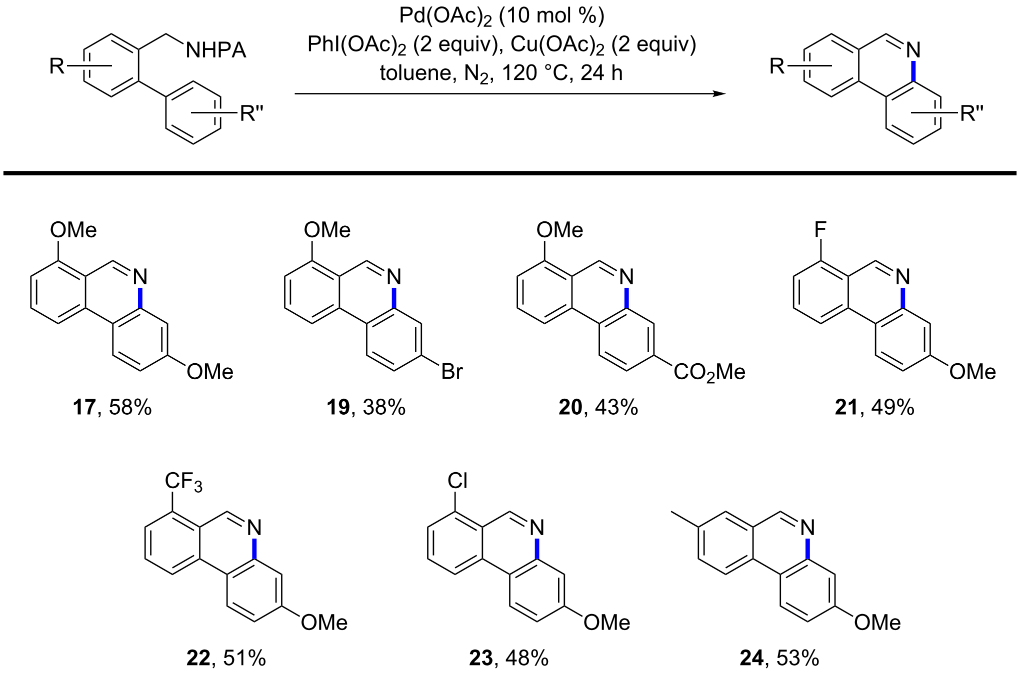


Figure 2: Substrate scope of this phenanthridine synthesis. All reactions were carried out in a 10 mL glass vial on a 0.2 mmol scale; yields are based on isolated product.

$Pd(OAc)_2$ affords phenanthridines in moderate to good yields. Applications of this method to the synthesis of more complex phenanthridines with novel photophysical properties are currently underway.

Experimental

General conditions: All commercial materials were used as received unless otherwise noted. All solvents were obtained from a JC Meyer solvent dispensing system and used without further purification. Flash chromatography was performed using 230–400 mesh SiliaFlash 60® silica gel (Silicycle Inc.). $PhI(OAc)_2$ (98%, Aldrich), $Pd(OAc)_2$ (98%, Aldrich) were used in the Pd-catalyzed reactions. NMR spectra were recorded on Bruker CDPX-300, DPX-300, DPX-400 instruments and calibrated by using residual solvent peaks as the internal reference. Multiplicities are recorded as: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, m = multiplet. High-resolution ESI mass experiments were operated on a Waters LCT Premier instrument.

Standard procedure for the Pd-catalyzed *ortho* C–H arylation reaction: A mixture of picolinamide **1** [30] (48 mg, 0.2 mmol, 1 equiv), aryl iodide **2** (94 mg, 0.4 mmol, 2 equiv), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 0.05 equiv), $KHCO_3$ (40 mg, 0.4 mmol, 2.0 equiv), and PivOH (6 mg, 0.06 mmol, 0.3 equiv) in anhydrous toluene (4 mL) in a 10 mL glass vial (purged with N_2, sealed with PTFE cap) was heated at 120 °C for 24 h. The reaction mixture was filtered through a short pad of celite and concentrated in vacuo. The resulting residue was purified by silica-gel flash chromatography (hexanes/EtOAc 3:1) to give the product **3** as a pale white solid (64 mg, 91%). Compounds **4–15** were prepared from the known precursors [30] by using the standard C–H arylation procedure.

Standard procedure for the Pd-catalyzed cyclization and oxidation reaction to form phenanthridines: A mixture of picolinamide **3** (70 mg, 0.2 mmol, 1 equiv), $Pd(OAc)_2$ (4.4 mg, 0.02 mmol, 0.1 equiv), $PhI(OAc)_2$ (129 mg, 0.4 mmol, 2.0 equiv), and $Cu(OAc)_2$ (72 mg, 0.4 mmol, 2 equiv) in anhydrous toluene (4 mL) in a 10 mL glass vial (purged with N_2, sealed with PTFE cap) was heated at 120 °C for 24 h. The reaction mixture was filtered through a short pad of celite and concentrated in vacuo. The resulting residue was purified by silica gel flash chromatography (hexanes/EtOAc 4:1) to give the product **17** as a pale white solid (28 mg, 58%). Compounds **19–24** were prepared by using the standard cyclization–oxidation procedure.

Compound 3. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.53 (d, *J* = 4.2 Hz, 1H), 8.40 (s, 1H), 8.21 (d, *J* = 7.5 Hz, 1H), 7.85–7.80 (m, 1H), 7.42–7.30 (m, 3H), 6.99–6.93 (m, 4H), 4.65 (d, *J* = 5.4 Hz, 2H), 3.95 (s, 3H), 3.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.3, 158.8, 158.6, 150.2, 147.9, 143.6, 137.1, 132.7, 130.3, 128.3, 125.8, 123.4, 122.7, 122.1, 113.6, 109.1, 55.7, 55.2, 36.8; HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{21}H_{21}N_2O_3$, 349.1552; found, 349.1546.

Compound 4. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.52 (d, *J* = 4.5 Hz, 1H), 8.36 (s, 1H), 8.19 (d, *J* = 7.8 Hz, 1H), 7.84 (td, *J* = 7.8, 1.4 Hz, 1H), 7.55 (d, *J* = 8.3 Hz, 2H), 7.41 (dd, *J* = 5.0, 6.8 Hz, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 8.3 Hz, 2H), 6.97 (d, *J* = 8.2 Hz, 1H), 6.89 (d, *J* = 7.7 Hz, 1H), 4.59 (d, *J* = 5.5 Hz, 2H), 3.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 163.3, 158.7, 150.1, 148.0, 142.5, 139.4, 137.1, 131.3, 130.9, 128.6, 125.9, 123.5, 122.4, 122.1, 121.6, 109.9, 55.8, 36.7; HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{20}H_{18}BrN_2O_2$, 397.0552; found, 397.0561.

Compound 5. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.51 (d, *J* = 4.0 Hz, 1H), 8.33 (s, 1H), 8.15 (d, *J* = 7.6 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.80 (t, *J* = 7.6 Hz, 1H), 7.44–7.34 (m, 4H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 4.58 (d, *J* = 5.2 Hz, 2H), 3.95 (s, 3H), 3.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.9, 163.3, 158.7, 150.2, 148.0, 145.2, 142.9, 137.2, 129.5, 129.3, 129.0, 128.6, 125.9, 123.5, 122.3, 122.2, 110.0, 55.8, 52.1, 36.6; HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{22}H_{21}N_2O_4$, 377.1501; found, 377.1509.

Compound 6. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.51 (d, *J* = 4.2 Hz, 1H), 8.34 (s, 1H), 8.19 (d, *J* = 7.8 Hz, 1H), 7.40–7.31 (m, 1H), 6.98–6.91 (m, 5H), 4.66 (d, *J* = 5.4 Hz, 2H), 3.94 (s, 3H), 3.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.8, 159.7, 159.0, 150.7, 148.4, 144.4, 142.3, 137.6, 129.7, 128.9, 126.3, 124.0, 123.0, 122.6, 122.1, 114.9, 113.8, 110.1, 55.3, 55.6, 37.2; HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{21}H_{21}N_2O_3$, 349.1552; found, 349.1564.

Compound 7. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.53 (d, *J* = 4.2 Hz, 1H), 8.34 (s, 1H), 8.19 (d, *J* = 7.8 Hz, 1H), 7.84–7.80 (m, 1H), 7.40–7.29 (m, 2H), 6.96–6.80 (m, 5H), 6.00 (s, 2H), 4.64 (d, *J* = 5.4 Hz, 1H), 3.96 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.4, 158.7, 150.3, 148.0, 147.4, 146.9, 143.7, 137.1, 134.4, 128.4, 125.8, 123.7, 122.8, 122.7, 122.2, 109.9, 109.5, 108.1, 101.0, 55.8, 36.8; HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{21}H_{20}N_2O_4$, 363.1345; found, 363.1355.

Compound 8. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.53 (d, *J* = 4.1 Hz, 1H), 8.41 (s, 1H), 8.29 (d, *J* = 8.8 Hz, 2H), 8.16 (d, *J* = 7.8 Hz, 1H), 7.85 (td, *J* = 7.7, 1.6 Hz, 1H), 7.55 (d, *J* = 8.7 Hz, 2H), 7.42–7.34 (m, 2H), 7.03 (d, *J* = 8.2 Hz, 1H), 6.89 (d, *J* = 7.7 Hz, 1H), 4.58 (d, *J* = 5.7 Hz, 2H), 3.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 163.4, 158.8, 150.0, 148.1, 147.4, 147.1, 141.4, 137.3, 130.4, 128.9, 126.1, 123.7, 123.5, 122.2, 122.2, 110.7, 56.0, 36.6; HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{20}H_{18}N_3O_4$, 364.1297; found, 364.1292.

Compound 9. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.53 (d, *J* = 4.2 Hz, 1H), 8.32 (s, 1H), 8.18–8.16 (m, 1H), 7.85–7.80 (m, 1H), 7.38–7.30 (m, 4H), 7.25–7.13 (m, 2H), 7.02–6.92 (m, 2H), 4.64–4.90 (m, 2H), 3.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ

163.8, 161.2, 158.9, 150.7, 148.4, 137.8, 137.6, 132.0, 129.9, 128.9, 126.2, 125.2, 124.5, 123.3, 122.6, 115.9, 115.8, 110.7, 56.22, 37.2; HRMS (*m/z*): $[M + H]^+$ calcd for $C_{20}H_{18}FN_2O_2$, 337.1352; found, 337.1364.

Compound 10. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.51 (d, *J* = 4.0 Hz, 1H), 8.25 (s, 1H), 8.17 (d, *J* = 7.8 Hz, 1H), 7.84 (td, *J* = 7.7, 1.7 Hz, 1H), 7.73 (d, *J* = 8.3 Hz, 2H), 7.66 (d, *J* = 8.3 Hz, 1H), 7.41–7.36 (m, 1H), 7.32–7.24 (m, 3H), 7.17 (d, *J* = 8.3 Hz, 1H), 7.06 (s, 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 6.88 (d, *J* = 7.4 Hz, 1H), 4.57 (d, *J* = 5.4 Hz, 2H), 3.95 (t, *J* = 8.8 Hz, 2H), 3.92 (s, 3H), 2.93 (t, *J* = 8.4 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 163.3, 158.7, 150.2, 148.1, 144.1, 143.4, 141.3, 137.2, 136.1, 133.9, 131.8, 129.8, 128.7, 128.5, 127.3, 126.2, 125.9, 123.5, 122.6, 122.1, 114.5, 109.5, 55.8, 50.1, 36.7, 27.8, 21.5; HRMS (*m/z*): $[M + H]^+$ calcd for $C_{29}H_{18}N_3O_4S$, 514.1801; found: 514.1813.

Compound 11. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.54 (d, *J* = 3.9 Hz, 1H), 8.21 (d, *J* = 7.5 Hz, 2H), 7.88–7.83 (m, 1H), 7.46–7.41 (m, 2 H), 7.34–7.23 (m, 4 H), 6.96 (d, *J* = 8.7 Hz, 1H), 4.72 (d, *J* = 5.4 Hz, 1H), 8.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.5, 159.1, 149.8, 148.0, 144.9, 137.2, 135.8, 132.9, 132.4, 130.1, 129.2, 128.7, 128.6, 126.0, 122.2, 113.8, 55.2, 39.6; HRMS (*m/z*): $[M + H]^+$ calcd for $C_{20}H_{18}ClN_2O_2$, 353.1057; found, 353.1067.

Compound 12. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.50 (d, *J* = 4.8 Hz, 1H), 8.14 (d, *J* = 7.8 Hz, 1H), 7.93 (s, 1H), 7.83–7.74 (m, 2H), 7.50–7.39 (m, 3H), 7.28–7.22 (m, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 4.71 (d, *J* = 4.5 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.0, 159.1, 149.6, 148.0, 145.6, 137.1, 134.6, 133.5, 131.9, 130.1, 129.9, 127.8, 126.0, 125.4, 122.1, 113.8, 55.2, 38.2; HRMS (*m/z*): $[M + H]^+$ calcd for $C_{21}H_{18}F_3N_2O_2$, 387.1320; found, 387.1328.

Compound 13. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.51 (d, *J* = 4.2 Hz, 1H), 8.18 (d, *J* = 7.8 Hz, 2H), 7.83–7.79 (m, 1H), 7.42–7.38 (m, 1H), 7.33–7.30 (m, 3H), 7.11 (d, *J* = 7.5 Hz, 2H), 6.97 (d, *J* = 8.7 Hz, 2H), 4.68 (d, *J* = 5.4 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.7, 160.4, 159.1, 149.7, 147.9, 144.4, 137.1, 131.6, 130.1, 128.9, 128.7, 126.0, 122.6, 122.1, 114.3, 113.8, 55.2, 35.6; HRMS (*m/z*): $[M + H]^+$ calcd for $C_{20}H_{18}FN_2O_2$, 337.1352; found, 337.1357.

Compound 14. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.50 (d, *J* = 4.5 Hz, 1H), 8.27–8.21 (m, 2H), 7.82 (t, *J* = 7.5 Hz, 1H), 7.41–7.29 (m, 4H), 7.19 (dd, *J* = 14.1 and 7.8 Hz, 2H), 6.98 (d, *J* = 8.4 Hz, 2H), 4.64 (d, *J* = 6.0 Hz, 2H), 3.84 (s, 3H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.8, 158.5, 149.6, 147.8, 138.4, 137.0, 136.9, 135.2, 132.8, 130.0, 129.1, 127.9, 125.9, 122.0, 113.5, 55.0, 41.1, 20.9; HRMS (*m/z*): $[M + H]^+$ calcd for $C_{21}H_{21}N_2O_2$, 333.1603; found, 333.1609.

Compound 15. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.45 (d, *J* = 4.7 Hz, 1H), 8.01 (d, *J* = 7.8 Hz, 1H), 7.78 (m, 2H), 7.42 (s, 2H), 7.37 (m, 1H), 7.30 (d, *J* = 8.7 Hz, 4H), 6.90 (d, *J* = 8.7 Hz, 4H), 4.47 (d, *J* = 5.1 Hz, 2H), 3.79 (s, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 162.9, 159.1, 149.5, 147.8, 145.2, 137.0, 132.3, 132.2, 132.1, 129.9, 125.9, 121.8, 121.0, 113.8, 55.2, 39.0; HRMS (*m/z*): $[M + H]^+$ calcd for $C_{27}H_{24}Br_3N_2O_3$, 503.0970; found, 503.0975.

Compound 17. ^1H NMR ($CDCl_3$, 300 MHz) δ 9.72 (s, 1H), 8.45 (d, *J* = 9.0 Hz, 1H), 8.08 (d, *J* = 8.2 Hz, 1H), 7.75 (t, *J* = 8.1 Hz, 1H), 7.61 (d, *J* = 2.6 Hz, 1H), 7.33–7.29 (m, 1H), 6.99 (d, *J* = 7.8 Hz, 1H), 4.09 (s, 3H), 4.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 160.5, 157.5, 149.1, 147.2, 134.6, 132.1, 124.3, 118.5, 117.1, 113.8, 110.1, 105.9, 56.2, 56.0; HRMS (*m/z*): $[M + H]^+$ calcd for $C_{15}H_{14}NO_2$, 240.1025; found, 240.1030.

Compound 19. ^1H NMR ($CDCl_3$, 400 MHz) δ 9.68 (s, 1H), 8.33 (m, 2H), 8.04 (d, *J* = 8.3 Hz, 1H), 7.75 (m, 2H), 7.04 (d, *J* = 7.9 Hz, 1H), 4.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 157.6, 149.5, 145.7, 133.8, 132.5, 132.2, 130.1, 124.3, 122.5, 117.4, 113.7, 107.2, 55.9; HRMS (*m/z*): $[M + H]^+$ calcd for $C_{14}H_{11}BrNO$, 228.0024; found, 228.0032.

Compound 20. ^1H NMR ($CDCl_3$, 300 MHz) δ 9.75 (s, 1H), 8.84 (s, 1H), 8.54 (d, *J* = 8.7 Hz, 1H), 8.24 (d, *J* = 7.5 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.09 (d, *J* = 8.1 Hz, 1H), 4.06 (s, 3H), 4.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.8, 157.4, 149.2, 144.0, 133.2, 132.1, 132.0, 130.1, 127.0, 126.7, 122.9, 117.9, 114.2, 107.8, 55.8, 52.4; HRMS (*m/z*): $[M + H]^+$ calcd for $C_{16}H_{13}NO_3$, 268.0974, found, 268.0970.

Compound 21. ^1H NMR ($CDCl_3$, 300 MHz) δ 9.59 (s, 1H), 8.46 (d, *J* = 9.0 Hz, 1H), 8.29 (d, *J* = 8.4 Hz, 1H), 7.82–7.74 (m, 1H), 7.64 (s, 1H), 7.37–7.26 (m, 2H), 4.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.6, 147.4, 146.6, 134.6, 131.7, 131.6, 123.8, 118.7, 117.4, 117.3, 111.1, 110.8, 110.1, 55.7; HRMS (*m/z*): $[M + H]^+$ calcd for $C_{14}H_{10}FNO$, 228.0825; found, 228.0830.

Compound 22. ^1H NMR ($CDCl_3$, 300 MHz) δ 9.62 (s, 1H), 8.72 (d, *J* = 8.4 Hz, 1H), 8.47 (d, *J* = 9.0 Hz, 1H), 7.95 (d, *J* = 7.2 Hz, 1H), 7.85 (t, *J* = 8.1 Hz, 1H), 7.62 (d, *J* = 2.4 Hz, 1H), 7.36 (dd, *J* = 9.0 Hz and 2.7 Hz, 1H), 4.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.7, 149.3, 145.8, 133.8, 129.5, 125.8, 124.4, 124.3, 123.4, 122.2, 119.1, 117.6, 109.8, 55.6; HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{15}H_{12}F_3NO$, 278.0793; found, 278.0797.

Compound 23. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.72 (s, 1H), 8.46–8.42 (m, 2H), 7.72–7.62 (m, 3H), 7.35 (dd, *J* = 9.0 and 2.4 Hz, 1H), 4.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 160.5, 150.1, 146.1, 134.5, 133.9, 131.0, 126.9, 123.6, 122.3, 120.4, 118.8, 117.1, 109.9, 55.6; HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{14}H_{11}ClNO$, 244.0529; found, 244.0534.

Compound 24. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.23 (s, 1H), 8.48–8.42 (m, 2H), 7.82 (s, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.62 (s, 1H), 7.34–7.30 (m, 1H), 4.02 (s, 3H), 2.62 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.2, 154.2, 146.3, 137.4, 136.7, 133.4, 131.1, 128.5, 123.6, 121.7, 118.2, 118.4, 110.3, 56.0, 21.9; HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{15}H_{13}NO$, 244.1075; found, 244.1079.

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Study on the total synthesis of velbanamine: Chemoselective dioxygenation of alkenes with PIFA via a stop-and-flow strategy

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Full Research Paper

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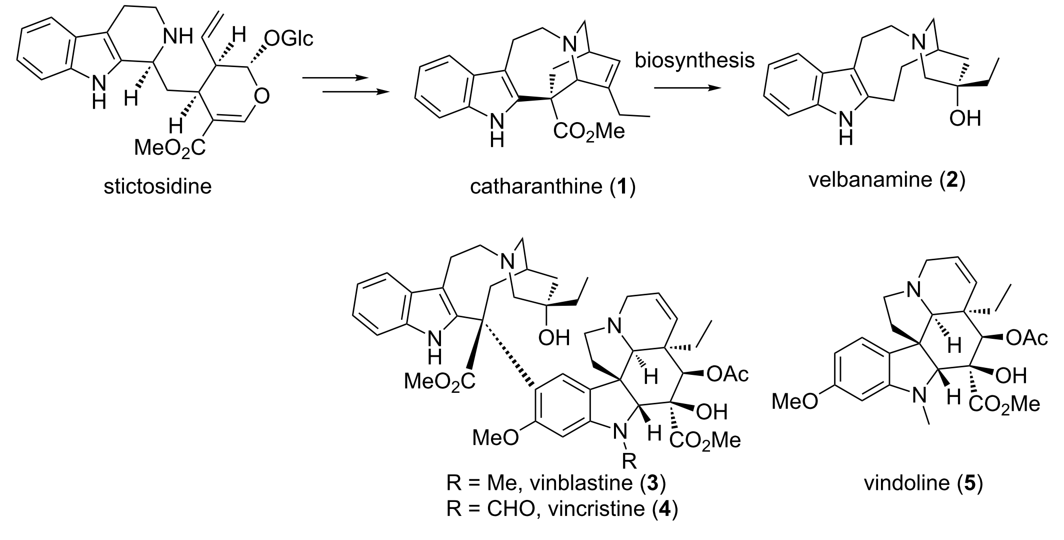
Abstract

A “stop-and-flow” strategy was developed for the chemoselective dioxygenation of alkenes with a PIFA-initiated cyclization. This method is conceived for the desymmetrization of seco-diene, and a series of substituted 5-hydroxymethyl-γ-lactones were constructed after hydrolysis. This strategy also differentiates terminally substituted alkenes and constitutes a potentially novel synthetic approach for the efficient synthesis toward velbanamine.

Introduction

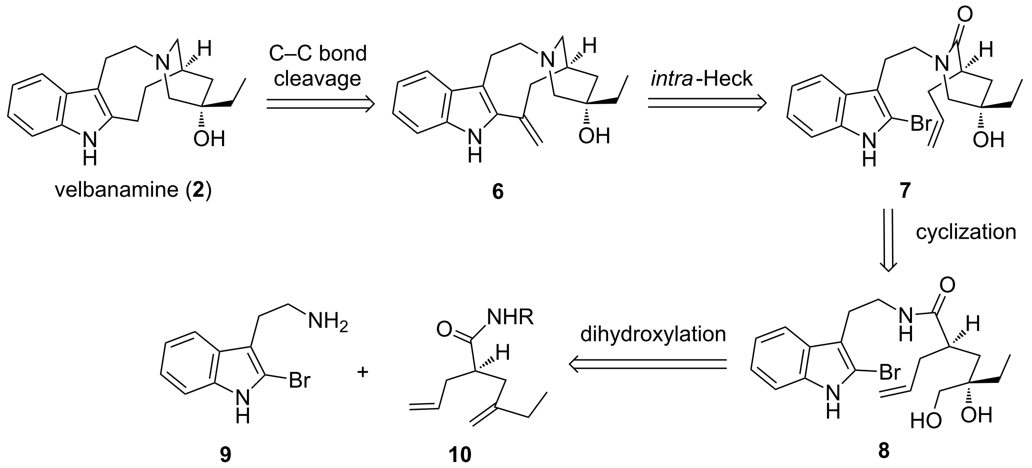
Stictosidine-derived indole alkaloids comprise a large category of alkaloids with diverse biological activities [1]. Their complex chemical structures and applications in pharmaceuticals have sparked numerous synthetic efforts in the past few decades. Dimeric indole alkaloids such as vinblastine (**3**) (Scheme 1) still inspire synthetic chemists to develop novel strategies for their efficient synthesis [2-11]. Isolated from the pantropical plant *Catharanthus roseus*, vinblastine (**3**) and vincristine (**4**) have potent antitumor activity and are clinically utilized in the treatment of Hodgkin’s disease and leukemia [12-14]. Fragmentation of **3** under acidic conditions delivers two structural units, desacetylvindoline and velbanamine (**2**) [15]. The reassembling of catharanthine (**1**) and vindoline (**5**) into the parent alkaloids **3** and **4** by using $FeCl_3$-promoted oxidative coupling supports the biogenesis of heterodimeric indole alkaloids [11]. Interestingly, velbanamine (**2**) was later identified in leaves and twigs of *Tabernaemontana eglandulosa* in 1984 [16]. Therefore, the syntheses of velbanamine (**2**) and structurally closely related alkaloids may be important for the syntheses of their dimeric alkaloids. The modification of these alkaloids in the context of clinical drug development still poses a challenge to synthetic and medicinal chemists.



Scheme 1: Biogenetic origin of *Vinca* alkaloids.

Since the first racemic synthesis of velbanamine (**2**) was disclosed by Büchi and co-workers in 1968, four racemic syntheses and two enantioselective syntheses have been reported in spite of several synthetic efforts toward the core structure [17-24]. The practical synthesis of velbanamine (**2**) and a general approach toward structurally related alkaloids remain an intriguing task in the synthetic community. Here, we would like to disclose our recent efforts on method development toward the efficient construction of velbanamine-type indole alkaloids. As shown in Scheme 2, an intramolecular Heck reaction (*via* 9-*exo* manner) would finalize the 9-membered ring, which was biogenetically derived from a retro-Mannich reaction from catharanthine (Scheme 1) [25]. The terminal alkene **6** can be disconnected to give amide **7**, which may be derived from 2-bromotryptamine **9** and seco-diene **10**. Clearly, the chemoselective dioxygenation of **10** is the main theme in our synthetic endeavor. From here, we expect that current synthetic methods may provide a general basis for similar important structures, such as isovelbanamine and cleavamine.

Dioxygenation has been adopted as a powerful method to transform an alkene into vicinal functional groups in the synthesis of natural products and pharmaceuticals. Numerous synthetic methods have been developed for this purpose, mediated by metals such as Os, Mn, Pd, Ru, Fe, and Ag [26-37]. On the other hand, the metal-free hypervalent iodine(III)-mediated reactions have recently enjoyed a renaissance attracting exten-



Scheme 2: Synthetic strategy for velbanamine based on chemoselective dioxygenation.

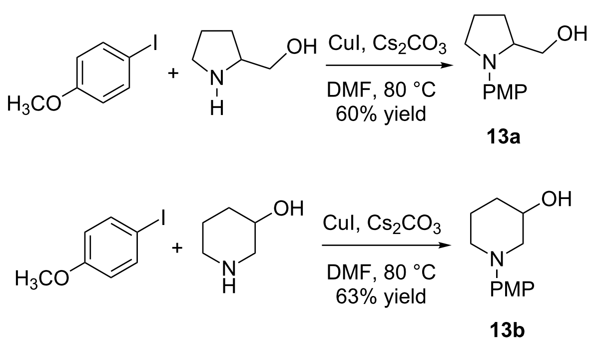
sive investigations [38,39]. It is particularly interesting in the case where iodolactones, obtained from the iodolactonization of alkenes in the presence of iodine, can be converted into hydroxylactone upon saponification [40,41]. This appealing metal-free protocol evolved into enantioselective iodolactonization by using chiral amides or esters. The catalytic asymmetric halogen lactonization, as an emerging area, also attracted a lot of attention in recent years [42-44].

The two terminal alkenes in compound **10** pose a challenge for chemoselective dioxygenation or iodolactonization. To address this problem, we turn our attention to differentiating the two types of terminal alkenes. Although iodolactonization as exemplified in Kita's elegant synthesis of rubrenolide resulted in a practical approach on desymmetrization [45], the subsequent hydrolysis still required an extra step to reveal the proper hydroxy group.

Results and Discussion

The pathway of cyclization

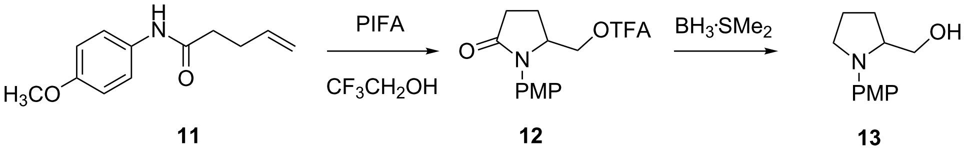
Recently, Tellitu, Dominguez, and co-workers reported an intramolecular oxyamidation of alkene **11** with phenyliodine(III)-bis(trifluoroacetate) (PIFA) (Scheme 3) [46]. The lactam **12** was originally assigned as an unstable intermediate, which should be subsequently reduced to pyrrolidine **13**. It was particularly striking to us that the arene unprecedentedly stabilizes the primary carbon cation through a neighboring participation in the mechanism proposed by Tellitu et al. To resolve the confusion, we synthesized the corresponding pyrrolidine through an alternative approach (Scheme 4). The amination of *para*-methoxyaryliodide with 2-hydroxymethylpyrrolidine in the presence of Cs_2CO_3 and a catalytic amount of copper iodide in DMF afforded **13a** in 60% isolated yield [47]. To our surprise, the proton NMR of **13a** was distinct from that of the originally proposed **13** by Tellitu et al. [46]. Based on the Baldwin rule, both 5-*exo-trig* and 6-*endo-trig* are favorable in the cyclization. Meanwhile, the ring expansion may occur to constitute the functionalized piperidine ring, resembling Cossy's endeavor to synthesize velbanamine [48]. In this regard, the same coupling condition was applied for the reaction of 3-hydroxypiperidine with *para*-methoxyaryliodide. Unexpectedly, the spectrum of the resulting amine **13b** was not consistent with that of **13**.



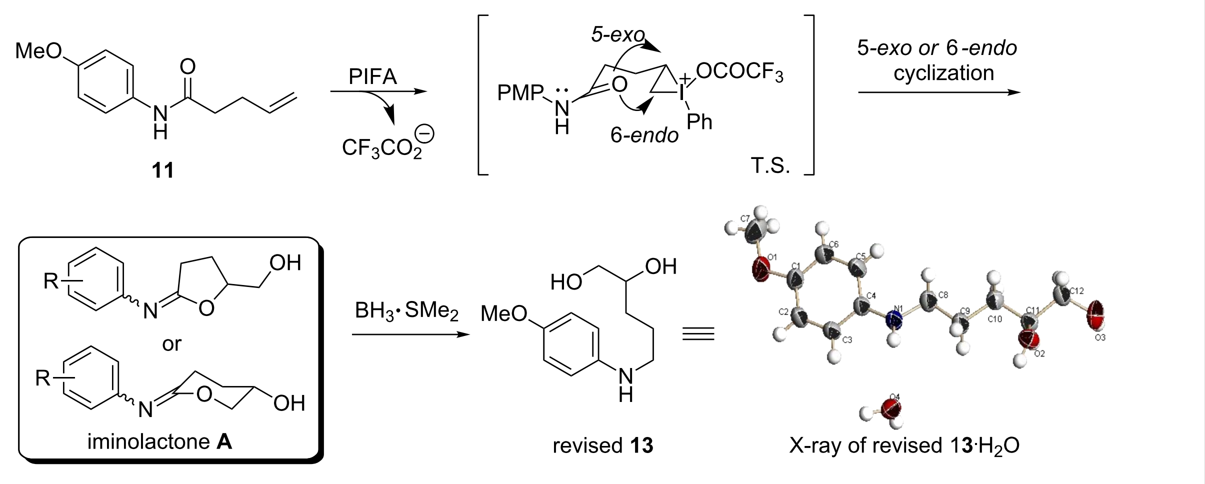
Scheme 4: Copper-catalyzed amination of aryliodide.

Based on the general iodolactonization principle, the C–O dipole in an amide is aligned for a favorable nucleophilic addition due to the "double-bond character" in a planar amide [41]. In the PIFA-promoted cyclization, lactonization was more likely to be a prominent process than lactamization. Following Tellitu's procedure [46], we re-synthesized **13** and subjected it to the proton NMR in the presence of D_2O. Three proton signals were exchanged with deuterium. X-ray analysis further contributed to the elucidation of the linear structure of **13** as shown in Scheme 5 [49]. The revised structure **13** implies that the amide **11** did not undergo the oxyamidation under the previously defined reaction conditions. Alternatively, it appears that iodolactonization of the amide dominated when compound **11** was subjected to the oxidation conditions of PIFA in CF_3CH_2OH. Mechanistically, the terminal double bond is activated by hyperiodine or via a halogenium-like intermediate [50-52]. The subsequent intramolecular ring-closing reaction in a 5-*exo* or 6-*endo* manner delivers iminolactones **A**. The reduction with borane gives hydroxyamine **13**. In this new proposal, the iminolactone **A** could be unstable and difficult to purify according to Tellitu's findings [46]. Similar stability of iminolactone is documented in the literature [53-55].

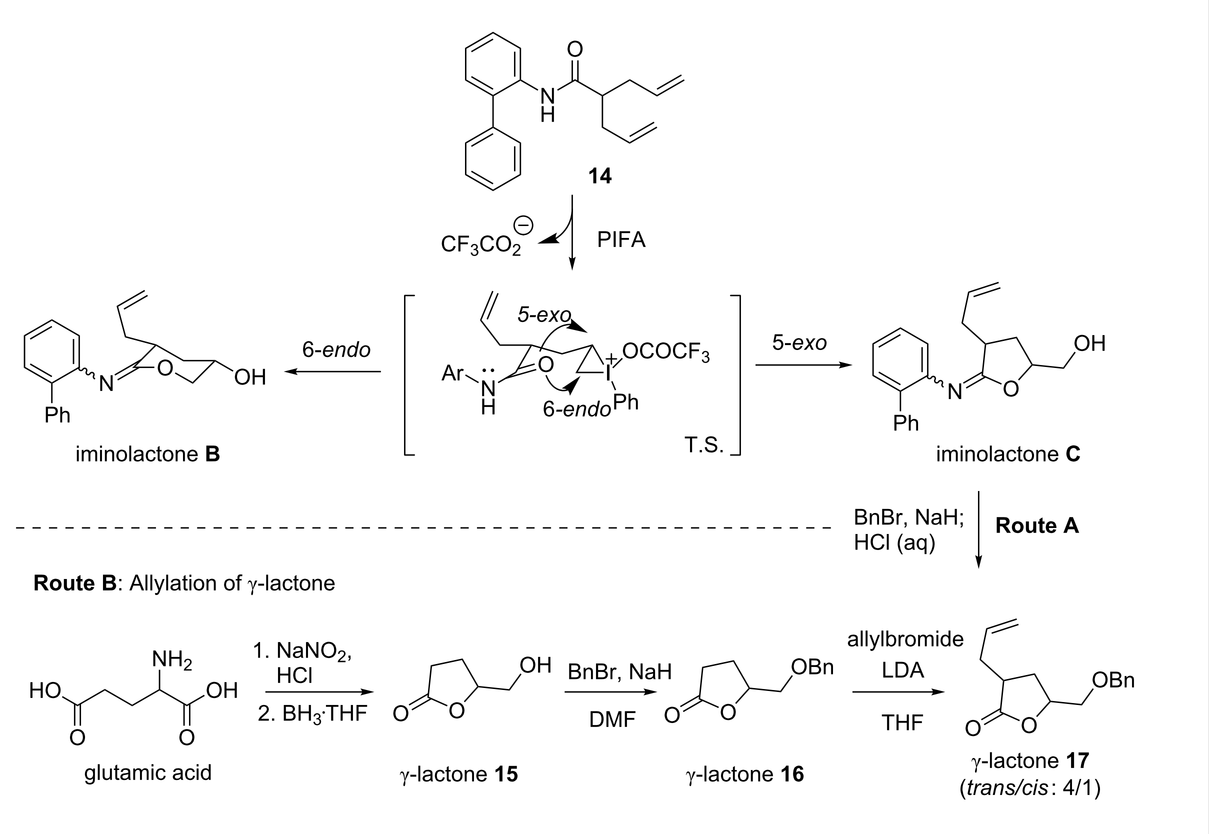
Although we have established the amide-assisted dioxygenation of an alkene, the structure of the iminolatone **A** is still a mystery. In principle, both 5-*exo-trig* and 6-*endo-trig* are favorable during the cyclization (Scheme 6). However, the instability of the iminolactone **A** impedes further characterization, and consequently, the possible cyclization mode is difficult to



Scheme 3: Intramolecular oxyamidation of alkene **11** with phenyliodine(III)-bis(trifluoroacetate) (PIFA) by Tellitu, Dominguez and co-workers [46].



Scheme 5: Revised PIFA-promoted cyclization of amide **11**.



Scheme 6: PIFA-promoted cyclization to synthesize lactone.

clarify. We envisioned that the steric hindrance of the amide would prevent the hydrolysis of the iminolactone during the work-up stage. After several experiments, *ortho*-biphenylamide **14** was chosen as a starting point. To our delight, two isomers of iminolactone were separated on a silica-gel column. After the treatment of benzyl bromide in the presence of NaH, the acidic work-up delivered two diastereoisomers of lactone **17** (Route A). This was further confirmed by an alternative synthesis based on a known procedure [56], in which 3-substituted-γ-lactone **17** was derived from the stereoselective alkylation of Bn-protected 5-hydroxymethyl-γ-lactone **16** (Route B). Two diastereoisomers of the *trans*-isomer of **17** (ratio 4/1) were identical with compounds from the PIFA-promoted cyclization (Scheme 6, Route A). Based on these conclusive experiments, we believe that the 5-*exo-trig* cyclization is the favorable pathway during the PIFA-mediated amide-cyclization of alkene. Two isomers after cyclization were then attributed to the stereoisomers of the C=N double bond in the iminolactone **C**. This notion is also consistent with numerous reports on the iodocyclization with amide [41].

Chemoselective dioxygenation

The structural assignment of **13** and the verification of the reaction pathway encouraged us to explore the synthetic potential of the dioxygenation of alkene with the assistance of an amide. The dioxygenation can be "*stopped*" after the first PIFA-promoted cyclization to form an iminolactone (such as the intermediate **C** in Scheme 6). Thus, if the original amide group could be recovered, it may "*flow*" into the second round of alkene dioxygenation. This "stop-and-flow" approach easily differentiates two alkene groups during the synthetic endeavor. In our experiment, after cyclization of amide **18a**, the corresponding iminolactone was hydrolyzed under Mukaiyama's conditions (sat. $Na_2B_4O_7$ buffer in CH_3CN) [53] to give amide **19a** in 72% yield [57]. The different substituents on aniline (Figure 1) slightly deteriorated the isolated yield. The geminal bis-substituted alkene gave a moderate yield of the corresponding dihydroxyamide **19d**. The α-methylated substrate was also dioxygenated albeit in a low diastereoselectivity (dr 1:1).

When two alkene groups co-existed as in compound **20**, desymmetrization delivered the mono-dioxygenated product **21** in a dr ratio of 1:1 (Scheme 7). The less polar **22a** was confirmed by X-ray diffraction [58]. The second alkene was further dioxygenated by repeating the previous protocol to deliver **23** with a 3/1 diastereoselectivity from **22b**. The encountered poor chemoselectivity under conventional metal-mediated conditions for the dioxygenation of seco-dienes such as **20** implies that this iterative method may find usage in organic synthesis. In this mode, we can install four hydroxy groups on a seco-diene with different protecting groups. Although several research groups have investigated the desymmetrization of seco-diene by using iodolactonization [59-64], our strategy here proves the concept of "stop-and-flow" to functionalize alkenes step-by-step with a simple hydrolysis in between.

Synthetic applications

After a simple acidic work-up, the established desymmetrization process can also be applied to prepare 3-alkyl-5-hydroxymethyl-γ-lactone, which has been widely found in natural products and compounds of pharmaceutical interest [65-68]. The usual methods including the alkylation at C-3 or the iodolactonization of amides or esters comprises multiple production steps, such as the hydrolysis of the halogen compounds and the protecting groups. However, the direct dioxygenation can easily construct γ-lactones by a simple acidic work-up as shown in Scheme 8. For example, when **24a** (R = Bn) was subjected to the PIFA-mediated cyclization, the desired γ-lactone **25a** was isolated after hydrolysis in 94% yield with a ratio of trans/cis of 1.9:1. Compound **25a** can be easily converted into the key intermediate in the synthesis of indinavir, a protease inhibitor used as a component of a highly active antiretroviral therapy to treat HIV infection and AIDS [69]. When two alkene groups exist in **24b–d**, the terminal alkene preferentially underwent cyclization to deliver a variety of 3-susbtituted-γ-lactones (**25b–d**). For comparison, the *m*CPBA-epoxidation approach in literature always demonstrated that electron-rich alkenes are more reac-

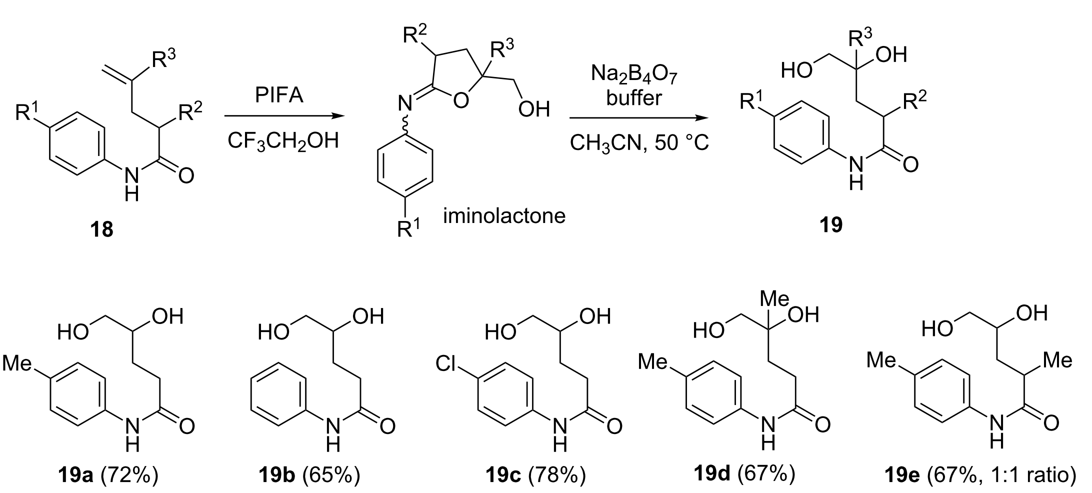
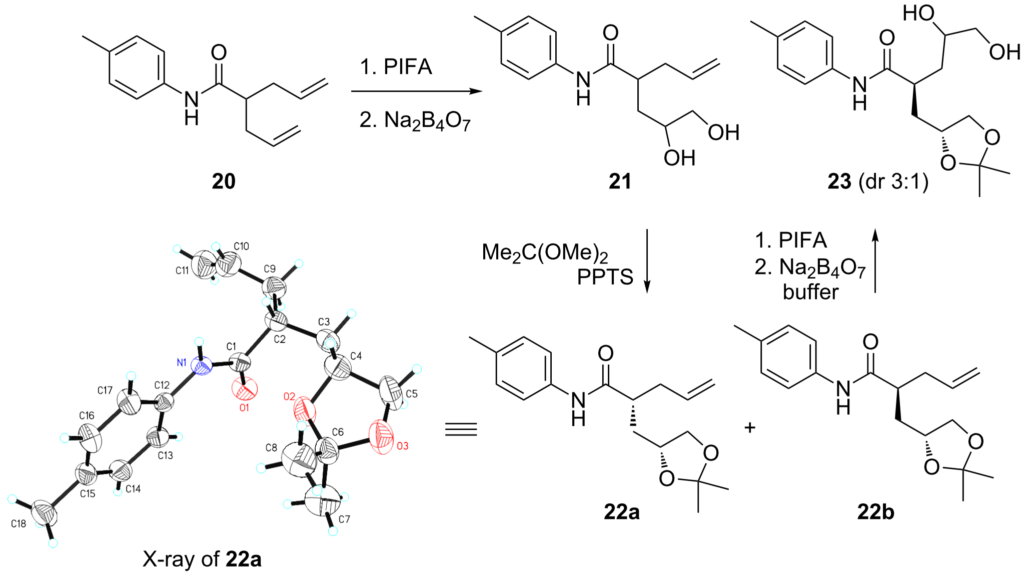
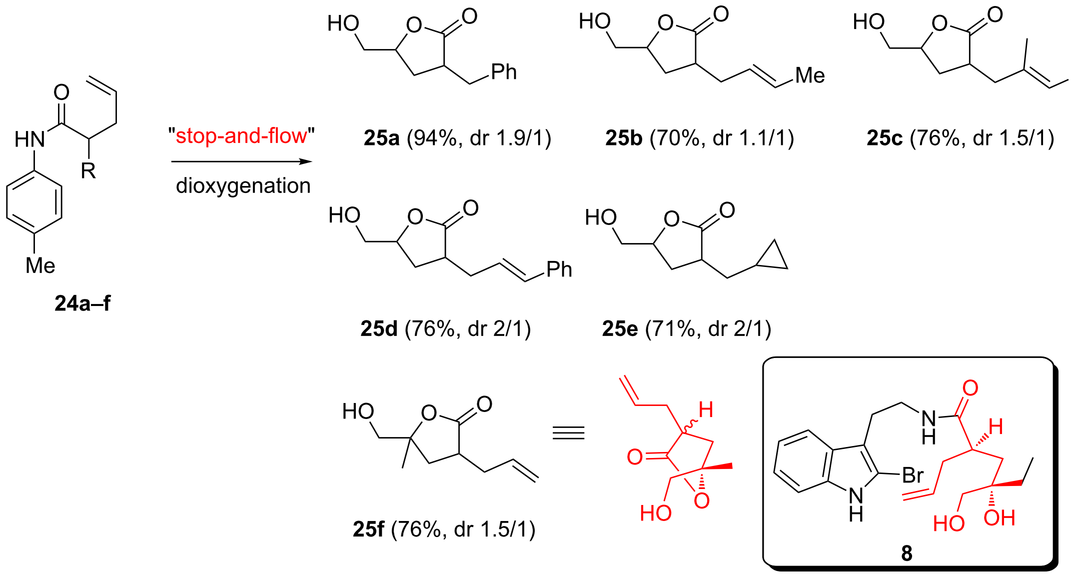


Figure 1: Hydrolysis of iminolactone **18** under basic conditions.



Scheme 7: "Stop-and-flow" strategy for the stepwise dioxygenation of alkenes.



Scheme 8: "Stop-and-flow" strategy for the construction of γ-lactone derivatives.

tive leading to the reversal of chemoselectivity [70,71]. A cyclopropane group was also tolerated during this operation and lactone **25e** was obtained in 71% yield with a dr ratio of 2:1.

Product **25f** was particularly interesting since the "stop-and-flow" strategy can differentiate two terminal alkenes. The more reactive geminally substituted alkene was dioxygenized to deliver all functional groups required in **8**, which was designed as a key intermediate in our synthetic plan toward velbanamine (Scheme 2). The stereoselectivity still awaits further improvement. Nevertheless, as a proof of concept, the current approach allows us to develop an efficient synthetic route to access challenging synthetic targets.

Conclusion

In summary, with a comprehensive validation of PIFA-promoted cyclization of alkenes, a synthetically useful desymmetrization approach via the dioxygenation of alkenes was developed. The "stop-and-flow" strategy allows us to easily functionalize seco-dienes step-by-step. Moreover, this approach also chemoselectively functionalizes terminal alkenes instead of internal ones. Substituted 5-hydroxymethyl-γ-lactones have been constructed in a protecting-group-free manner. The synthetic application in the efficient synthesis of velbanamine-type indole alkaloids as well as the enantioselective desymmetrization are currently pursued in our laboratory and will be reported in due course.

Supporting Information

Supporting Information File 1

Experimental descriptions, analytical and X-ray data.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-113-S1.pdf]

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Synthesis of the tetracyclic core of *Illicium* sesquiterpenes using an organocatalyzed asymmetric Robinson annulation

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Full Research Paper

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Abstract

An enantioselective synthesis of the core framework of neurotrophic *Illicium* majucin-type sesquiterpenes is described here. This strategy is based on an organocatalyzed asymmetric Robinson annulation and provides an efficient approach for a diversity-oriented synthesis of *Illicium* natural products that holds remarkable therapeutic potential for neurodegenerative diseases.

Introduction

Neurotrophins are a family of endogenous proteins that are vital for neuron function, survival, and regeneration [1-3]. As such, they have prompted intense studies toward the treatment of various neurodegenerative diseases including Alzheimer's disease [4] and Parkinson's disease [5]. Despite their unambiguous importance, approaches to neurotrophin-based drug development have encountered problems associated with their limited oral availability, insufficient delivery to the central neural system and considerable manufacturing cost [6,7]. These limitations have stimulated the search for small molecules that can enhance or mimic neurotrophin activity as potential drug leads [8-12].

Majucin-type *Illicium* sesquiterpenes (Figure 1) [13], such as majucin (**1**) [14,15], jiadifenolide (**2**) [16], jiadifenin (**3**) [17], jiadifenoxolane A (**4**) [16] and (2*R*)-hydroxynorneomajucin (**5**) [18], share a caged tetracyclic scaffold (**6**). These compounds (**2**–**5**) have shown a great potential in enhancing neurite outgrowth in primary cultured rat cortical neurons at low nanomolar to low micromolar concentrations. Thus, to develop an efficient synthetic approach toward the complex core skeleton of these natural products is of paramount importance. Consequently, this family of neurotrophic sesquiterpenes has been the focus of extensive synthetic studies in which asymmetric and efficient

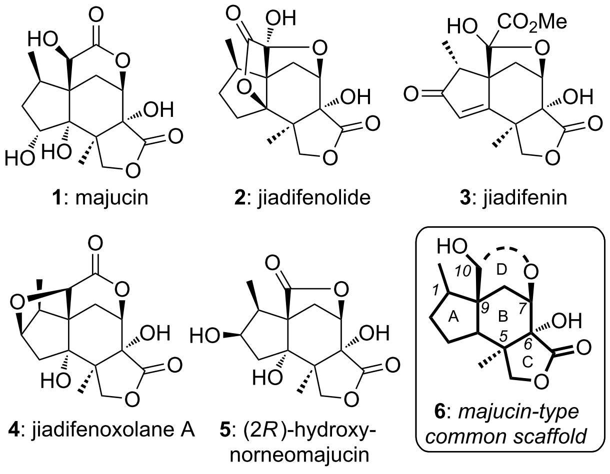


Figure 1: Representative majucin-type *Illicium* sesquiterpenes.

construction of the tetracyclic core presents the principal challenge [19-23].

We have recently reported a unified synthetic strategy of **2**, **3** and designed analogues using scaffold **7** as the key intermediate (Figure 2) [24-26]. A potential drawback of this strategy is the late-stage modification of the A ring motif of **7** that requires additional steps for the synthesis of the target molecules. In an effort to overcome this issue, we describe here a second-generation strategy of framework **9** in which the C-1 center has been methylated early in the synthesis. As such, it represents an efficient route toward a diversity-oriented synthesis of several *Illicium* sesquiterpenes. The enantioselective entry to these molecules is based on an organocatalyzed asymmetric Robinson annulation that allows access to the enantiomerically enriched bicyclic motif **8** from achiral diketone **11** (Figure 2).

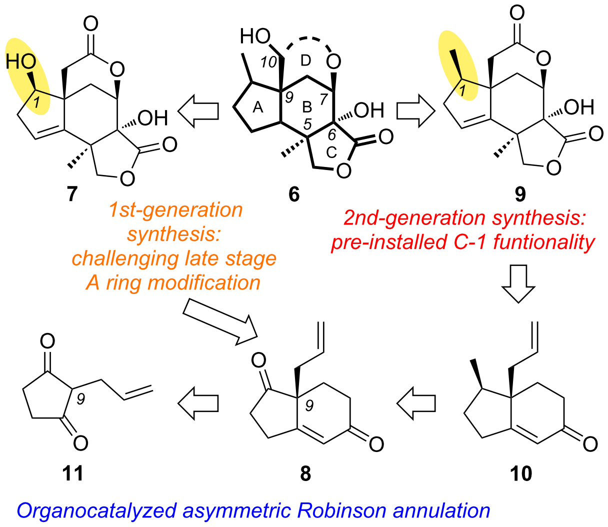
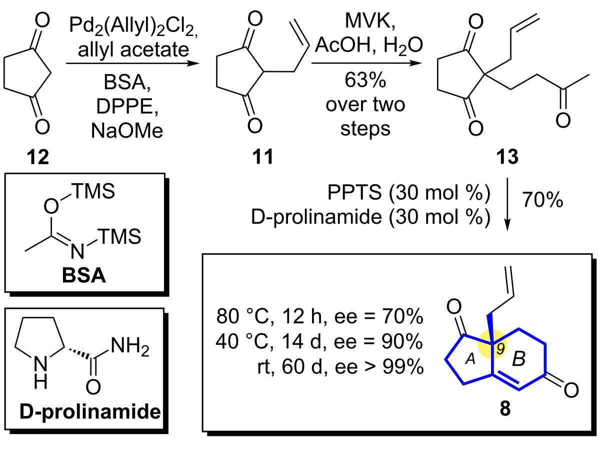


Figure 2: Comparison of core skeleton synthetic strategies.

Results and Discussion

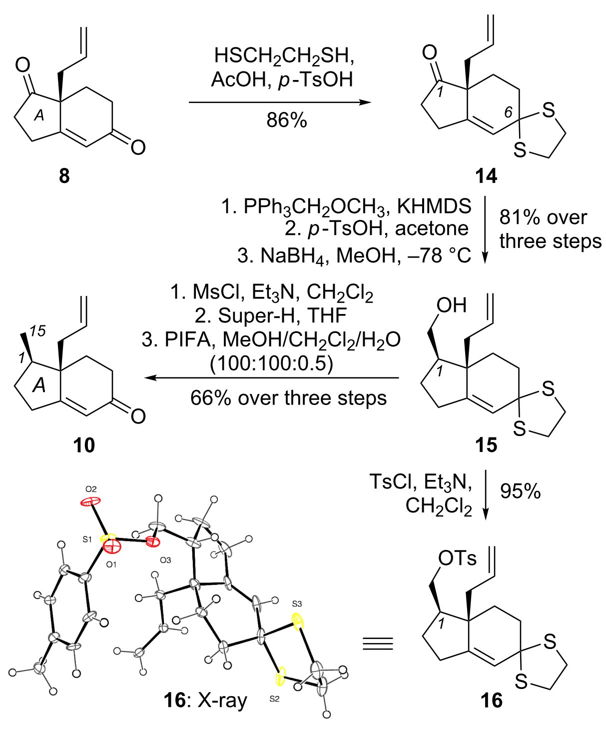
During the past 20 years, organocatalysis has emerged as an important field in asymmetric stereoselective synthesis due to its advantages, which include high enantioselectivity, environmental friendliness and ease of handling [27-50]. Organocatalyzed asymmetric Robinson annulation has long been proven to be one of the most powerful strategies to construct bicyclic systems with a chiral quaternary center [51-58]. Among them, the Hajos–Wiechert and Wieland–Miescher ketones represent two of the most famous examples [59-65]. With this background information in mind, we devised an enantioselective synthesis of **8** starting from commercially available dione **12**, and the synthesis of **8** was previously published [25,26]. Tsuji–Trost allylation [66-68] of **12** produced compound **11**, which was readily converted to **13** by an acid-catalyzed Michael addition with methyl vinyl ketone (MVK) (two steps, 63% overall yield) [69-71]. The organocatalyzed cyclization of **13** was achieved by optimizing the previously reported Tu/Zhang conditions [71] using D-prolinamide as the organocatalyst (Scheme 1). Performing this reaction at 80 °C gave rise to bicyclic motif **8** in about 70% ee (70 % yield after 12 h), while decreasing the temperature to 25 °C increased the enantioselectivity to over 99% (70% yield after 60 days). To compromise between high enantioselectivity and short reaction time, we decided to pursue this conversion at 40 °C where we obtained an enantiomeric excess of 90% (70% yield after 14 days).

The enantiomerically enriched Hajos–Wiechert-like diketone **8** (ee > 90%) was then subjected to a selective protection of the C-6 enone motif to yield dithioketal **14** (86% yield) [72-74].



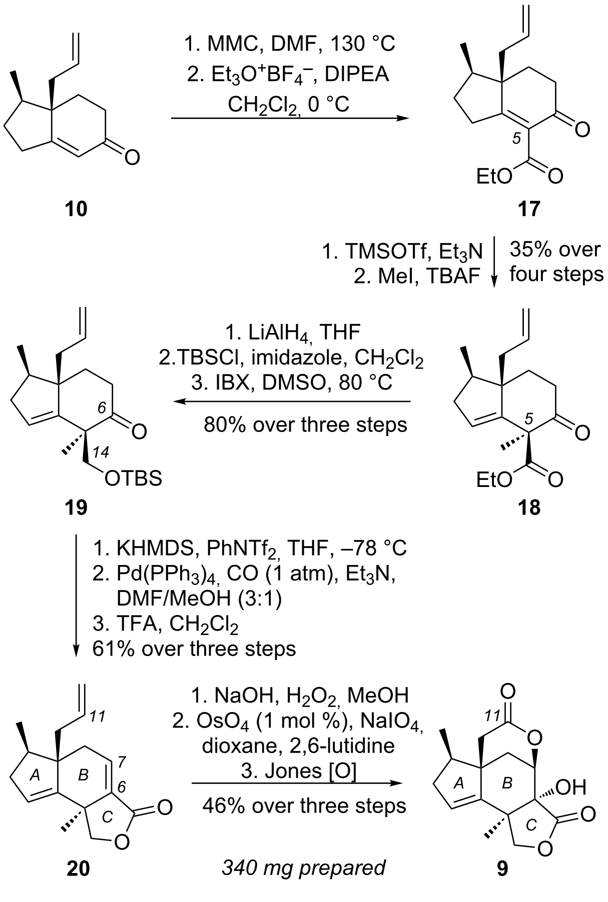
Scheme 1: Organocatalyzed asymmetric Robinson annulation.

Wittig olefination of the C-1 ketone with methoxymethylenetriphenylphosphine [75] yielded the corresponding enol methyl ether, which was hydrolyzed to the aldehyde under acidic conditions and reduced with $NaBH_4$ to form alcohol **15** with desired diastereoselectivity at the C-1 center (dr = 9:1) in 81% yield (over three steps) [76]. The stereochemistry of **15** was unambiguously confirmed by single-crystal X-ray analysis of the related tosylate derivative **16** [77]. Deoxygenation of the C-15 primary alcohol was performed by: (a) mesylation of the alcohol with MsCl; and (b) reductive deoxygenation with $LiEt_3BH$ (super hydride). The thioketal protecting group was then removed under oxidative conditions with [bis(trifluoroacetoxy)iodo]benzene (PIFA) to yield ketone **10** in good yield (66% over three steps, Scheme 2) [78]. This approach allowed us to produce a sufficient amount of enone **10** (>10 grams) for further functionalization.



Scheme 2: Early stage A-ring functionalization.

Conversion of **10** to **9** was accomplished based on our previously reported strategy (Scheme 3) [25]. Treatment of **10** with magnesium methyl carbonate (MMC) [79-81] yielded the C-5 carboxylic acid that, without further purification, was esterified under Meerwein's conditions to afford β-ketoester **17**. Treatment of **17** with TMSOTf/Et_3N followed by enolate alkylation [82] under TBAF/MeI conditions afforded the desired C-5 quaternary center of **18** as a single isomer (35% over four steps). Global reduction of **18** with lithium aluminium hydride produced the corresponding C-6/C-14 diol motif. Selective TBS protection of the C-14 primary alcohol followed by an IBX oxidation of the C-6 secondary alcohol yielded ketone **19** in 80% combined yield over three steps. Triflation of the C-6 ketone with McMurry's reagent ($PhNTf_2$) [83-86] followed by a Pd(0)-catalyzed carbomethoxylation [87-90] produced the desired C-ring lactone **20** in 61% yield. Epoxidation of the C-6/C-7 enone with NaOH/H_2O_2 followed by oxidative cleavage of the C-11 terminal alkene under OsO_4/$NaIO_4$ conditions [91,92] afforded the corresponding C-11 aldehyde. Exposure of this intermediate to Jones oxidation triggered a highly efficient oxidation–epoxide opening [93-98] reaction cascade [99,100] to construct the critical D-ring of **9** (46% yield, over 3 steps). Notably, this scalable approach rendered us several hundred milligrams of compound **9**, paving the way for a diversity-oriented synthesis. For example, a Mn(III) promoted C-2 allylic oxidation [24,101,102] would provide a C-2 oxygenated functionality. Similarly, C-10 α-substitution would provide a large diversity of neurotrophic analogues based on our recent findings [26].



Scheme 3: Synthesis of core scaffold **9**.

Conclusion

We describe here an efficient and enantioselective approach to tetracyclic lactone **9** representing a key motif toward the synthesis of various neurotrophic [103-110] *Illicium* sesquiterpenes. Key to the strategy was a highly enantioselective Robinson annulation reaction that proceeded under organocatalytic conditions to form the Hajos–Wiechert-like enone **8**. The overall strategy highlights the importance of organocatalytic approaches in the modern synthesis of bioactive natural products [111-116].

Supporting Information

Supporting Information File 1

Experimental procedures for the syntheses of all new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-126-S1.pdf]

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Establishing the concept of aza-[3 + 3] annulations using enones as a key expansion of this unified strategy in alkaloid synthesis

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Full Research Paper

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Abstract

A successful enone version of an intramolecular aza-[3 + 3] annulation reaction is described here. Use of piperidinium trifluoroacetate salt as the catalyst and toluene as the solvent appears to be critical for a successful annulation. We also demonstrated for the first time that microwave irradiation can accelerate aza-[3 + 3] annulation reactions. An attempt to expand the scope of the enone aza-[3 + 3] annulation was made in the form of propyleine synthesis as a proof of concept. While synthesis of the enone annulation precursor was successfully accomplished, the annulation proved to be challenging and was only modestly successful.

Introduction

Throughout the past decade, we have been developing an aza-[3 + 3] annulation reaction as a general and unified strategy in alkaloid synthesis [1-32]. Our aza-[3 + 3] annulation, which has been classified as Type-II [1], with Type-I aza-[3 + 3] annulation being reserved for Robinson's double Mannich-type process [33], utilizes readily accessible and easily handled vinylogous amides and vinyl iminium salts. It provides a significant complementary, if not superior, approach to aza-[4 + 2] cycloadditions in constructing piperidines, because the azadienes and imines required are not always the most accessible and/or easily handled substrates given the problems of isomerization and hydrolysis (Figure 1) [34-37].

The prevalence of six-membered nitrogen heterocyclic motifs in alkaloids renders the development of this aza-[3 + 3] annulation into a powerful strategy a unique opportunity in the field of

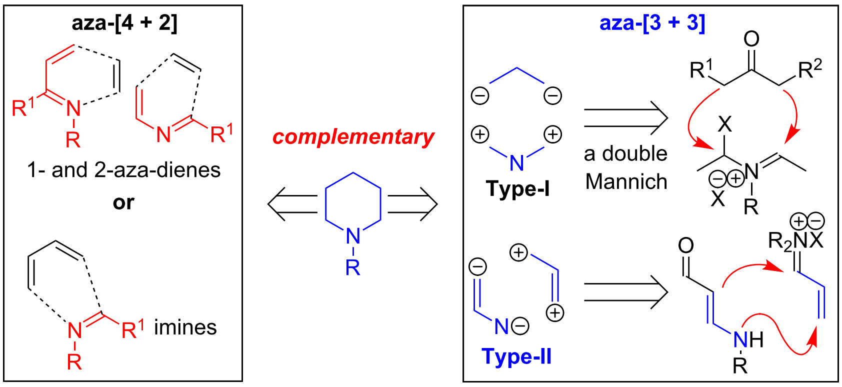
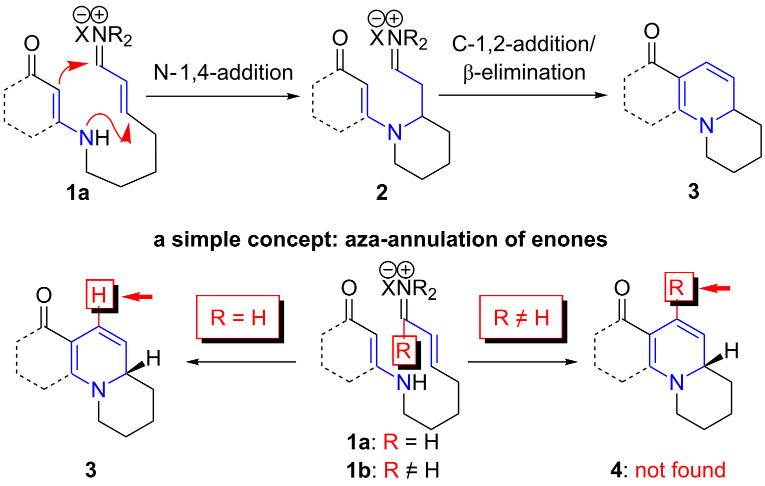


Figure 1: An aza-[3 + 3] annulation.

alkaloid synthesis [1-4,8-15]. The intramolecular variant of this annulation has proven to be particularly valuable for total synthesis [16,26-32]. Specifically, the intramolecular aza-[3 + 3] annulation of vinylogous amides tethered to a vinyl iminium motif **1a** proceeds through a tandem sequence of N-1,4-addition and C-1,2-addition/β-elimination [16,17], effectively leading to a variety of nitrogen heterocyclic motifs, such as **3**, which are prevalent among alkaloids (Scheme 1) [16,26-32]. However, there was a significant deficiency in this annulation: the inability to employ vinylogous amides tethered to α,β-unsaturated ketones, or enones **1b** (R ≠ H) (Scheme 1).

Conceptually, employing enals or enones in an aza-[3 + 3] annulation appears to constitute very little difference, with the major difference lying in the R group in their respective products **3** and **4**. While seemingly an insignificant perturbation, the ability to employ enones in aza-[3 + 3] annulations can generate a vast array of opportunities, including the case where R is as small and simple as a Me group, which would already represent a facile entry to aza-phenylene alkaloids [30,31,38-45], such as propyleine [46-48], as well as lycopodium alkaloids that are rich in bioactivities [49-51] (Figure 2). In addition, the importance of these ventures into an aza-[3 + 3] annulation with enones can also be further demonstrated through syntheses of tetrahydroisoquinolines and indole alkaloids [52-55] in which the R group can constitute a larger functionality of the alkaloids, such as that seen in geissoschizine [52-57], and ipecac alkaloids such as protoemetine [48,52-55,58-61], emetine [52-55,58-63], and tubulosine [64]. With the appropriate choice of an R group in the synthetic design, a highly convergent and expedient strategy can come forth for constructing these alkaloids. We report herein our success in achieving intramolecular aza-[3 + 3] annulations of an enone.



Scheme 1: Aza-[3 + 3] annulations with enones.

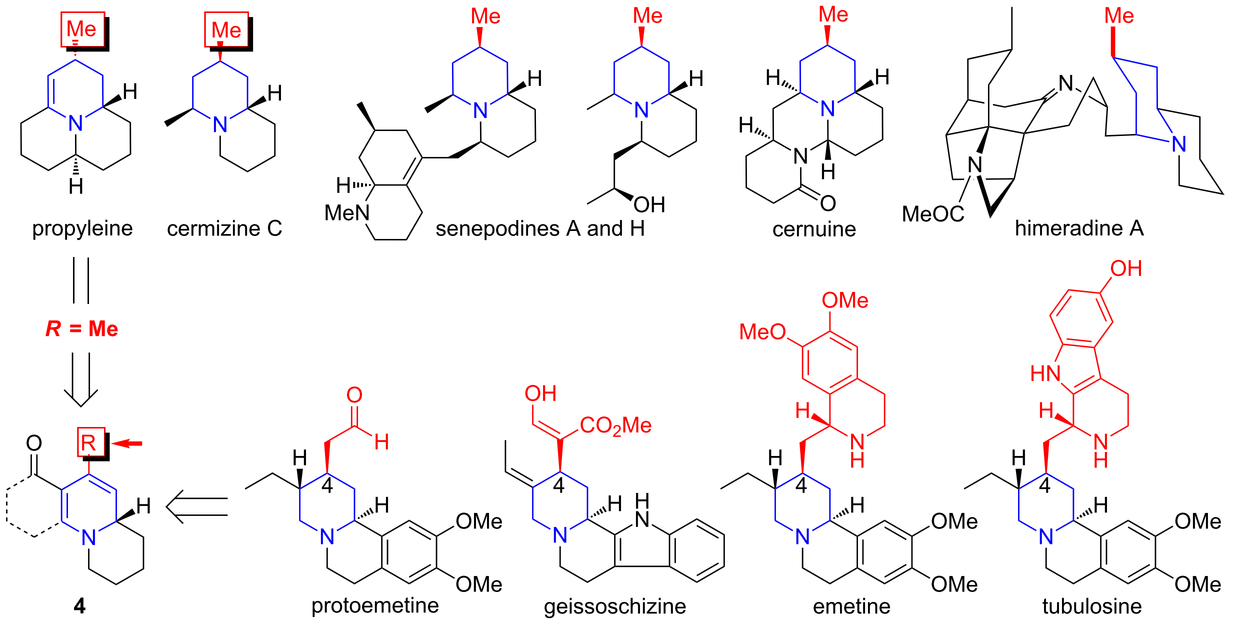


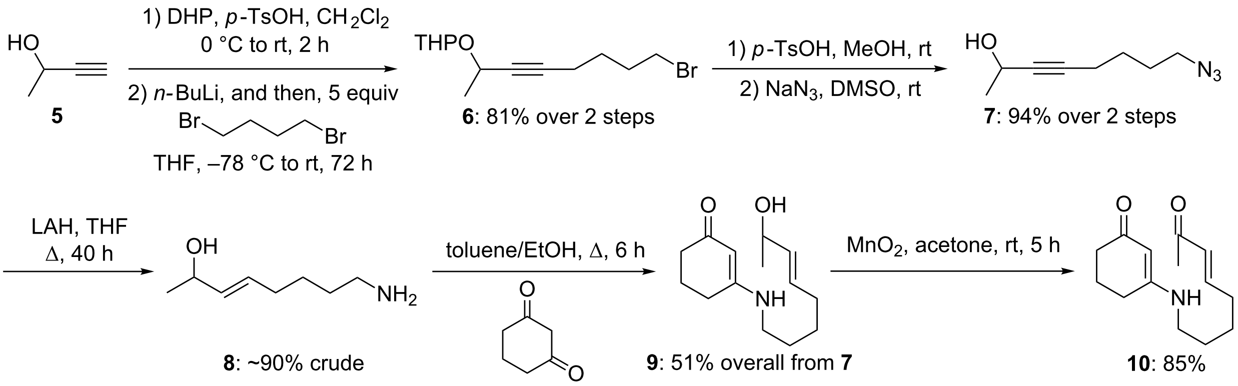
Figure 2: Possible natural-product targets.

Results and Discussion

To examine the feasibility of an enone intramolecular aza-[3 + 3] annulation, a seven-step synthesis of the annulation substrate **10** commencing from 3-butyn-2-ol (**5**) was carried out (Scheme 2). Protection of secondary propargyl alcohol **5** as the THP-ether followed by alkylation of a lithium acetylide onto 1,4-dibromobutane afforded bromide **6** in 81% overall yield. Acid-mediated removal of THP followed by azide formation using NaN_3 afforded alkyl azide **7** in 94% overall yield.

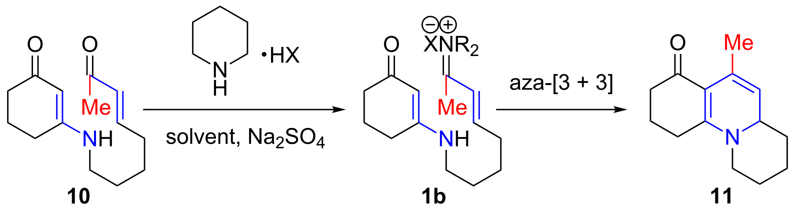
Preparation of vinylogous amide **9** was then achieved by a two-step sequence: (a) LAH-mediated azide reduction to give a primary amine with concomitant reduction of the alkyne revealing the olefin functionality; and (b) dehydrative condensation of this primary amine with 1,3-cyclohexanedione. Oxidation of the secondary allylic alcohol in **9** with MnO_2 at ambient temperature provided enone **10** in 85% yield. We were poised to investigate the viability of the enone aza-[3 + 3] annulation.

Our initial efforts to employ enone substrate **10** met with failure when using up to 500 mol % of piperidinium chloride [65] (Table 1, entry 1) or 100 mol % piperidinium acetate salts (Table 1, entry 2); even at higher temperatures of 120 °C, these chloride and acetate salts proved to be ineffective (Table 1, entry 3). We then explored salts prepared from stronger acids such as (+)-camphorsulfonic acid (CSA) and trifluoroacetic acid, which should tend to dissociate easier in the reaction medium and lead to a more reactive vinyl iminium salt intermediate **1b**. We were



Scheme 2: Synthesis of the annulation precursor enone **10**.

Table 1: Catalyst screening and optimization.



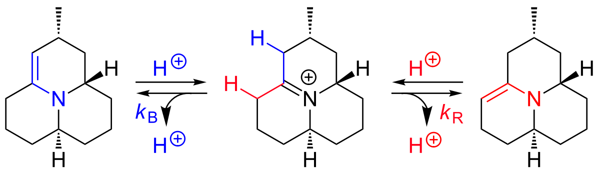
entry[a]	HX (mol %)	solvent	temp (°C)	time (h)	conv. (%)	yield (%)[b]
1	HCl (500)	EtOAc/toluene	100	16	0	–
2	HOAc (100)	EtOAc	85	12	0	–
3	HOAc (500)	toluene	120	16	0	–
4	(+)-CSA[c] (100)	toluene	120	12	100	60
5	HO_2CCF_3 (500)	toluene	85	7	79	39
6	HO_2CCF_3 (100)	toluene	85	5	100	50
7	HO_2CCF_3 (100)	EtOAc/toluene	110	4	92	41
8	HO_2CCF_3 (50)	toluene	150	3	100	87
9	HO_2CCF_3 (90)	toluene	MW[d]	1.5	94	65

[a]All reactions run in a sealed tube. Concn = 0.03–0.04 M; 5.0 equiv Na_2SO_4. [b]Isolated yields. [c](+)-Camphorusulfonic acid. [d]450-W Microwave.

elated to observe that the use of 100 mol % of piperidinium CSA salt in toluene at 120 °C provided 100% conversion with 60% yield of cycloadduct **11** (Table 1, entry 4). Further optimizations using trifluoroacetate salt (Table 1, entries 5–8) revealed that the yield could be improved to 87%, while lowering the catalyst loading from 500 mol % to 50 mol %, although the reaction temperature was raised to 150 °C. Lastly, we also examined the use of microwave irradiation [66,67] and observed a distinct rate enhancement (Table 1, entry 9).

The observed reactivity difference of the trifluoroacetate and camphorsulfonic acid salts, as compared to the chloride and acetate salts, can be attributed to the rate at which they promote vinyl iminium ion formation through a "balanced act" [12]. The difference in reactivity is related to the dissociation capacity of the respective amine salts. Since both "free amine" and "free acid" are needed in a synergistic manner to generate the vinyl iminium ion from the corresponding enone, the ability of the amine salt to dissociate to its "free amine" and "free acid" can exert an impact on the rate of the iminium formation. The low reactivity of the chloride salt can be attributed to its higher resistance toward dissociation, or is simply a tighter ion-pair compared to the CSA and the trifluoroacetate salt. At the same time, the formation of vinyl iminium ion from carbonyl systems and the "free amine" is also promoted by protonation of the carbonyl group via the "free acid". Consequently, the increased reactivity of the CSA and trifluoroacetate salt from the acetate salt can be attributed to a higher acidity of the acids.

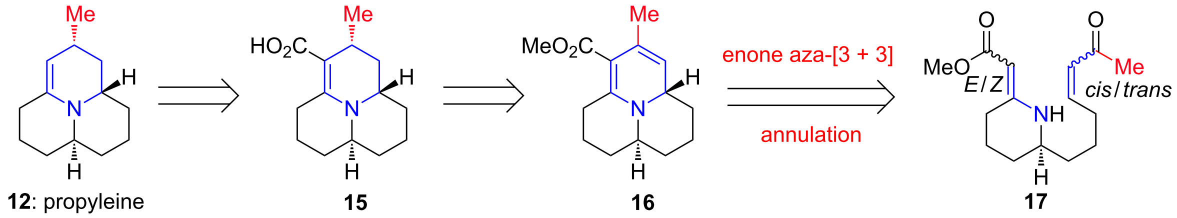
After establishing the feasibility of the enone version of the intramolecular aza-[3 + 3] annulation we turned our attention to propyleine (**12**) (see Figure 2 and Scheme 3) as a possible target to showcase the new enone aza-[3 + 3] annulation. Propyleine (**12**) was isolated in 1972 from *Propylaea quatuordecimpunctata* in a continued effort by Tursch and co-workers [46,47] in their isolation of the azaphenalene family of defensive alkaloids from various ladybug beetles [38-45]. Mueller and Thompson [48] in 1980 found it interesting that the isomeric enamine named isopropyleine (**14**) was not reported in the original paper [46,47] taking into account that the isolation conditions involved acid–base extractions. It is conceivable that propyleine (**12**) and isopropyleine (**14**) could be interconvertable under acidic conditions via intermediate iminium salt **13**.



12: propyleine **13** **14**: isopropyleine

Scheme 3: Propyleine-isopropeleine interconversion.

To investigate this matter, Mueller and Thompson carried out the first and the only synthesis of propyleine known to date



Scheme 4: Retrosynthesis of propyleine (**12**).

[48]. They were able to take a mixture of propyleine and isopropyleine with 1:3 ratio as determined by ^{1}H NMR and watch two sets of proton resonances collapse into one that corresponds to the iminium salt **13** after addition of TFA. This experiment strongly suggested that propyleine (**12**) and isopropyleine (**14**) could equilibrate under acidic conditions, thereby implying that the observed ratio of **12** and **14** represents a thermodynamic one in favor of the more stable isopropyleine [48]. With these experimental findings, Mueller and Thompson concluded that the alkaloid isolated by Tursch and co-workers [46,47] was in fact a mixture of readily interconvertable **12** and **14**.

We found this controversy in the isolation and total synthesis papers an interesting one that deserves further investigations. Consequently, we performed ab initio calculations on **12** and **14** to gain insight into their relative thermodynamic stability. Models of the most stable conformers and their corresponding energies are shown in Figure 3. To our surprise, propyleine (**12**) is 2.59 kcal mol^{-1} more stable than isopropyleine (**14**), which is the opposite of the Mueller–Thompson postulation [48]. Our calculations suggest that the ratio obtained from the Mueller–Thompson study was likely determined by the kinetics (k_B versus k_R) in the deprotonation step or the tautormerization process from the iminium salt **13**, and not by thermodynamics as originally proposed. Resolving this interesting literature controversy added extra incentive for us to pursue propyleine.

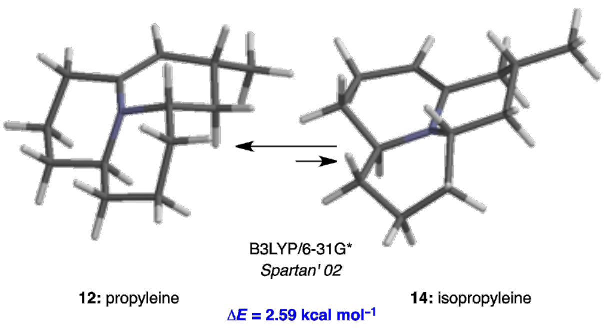


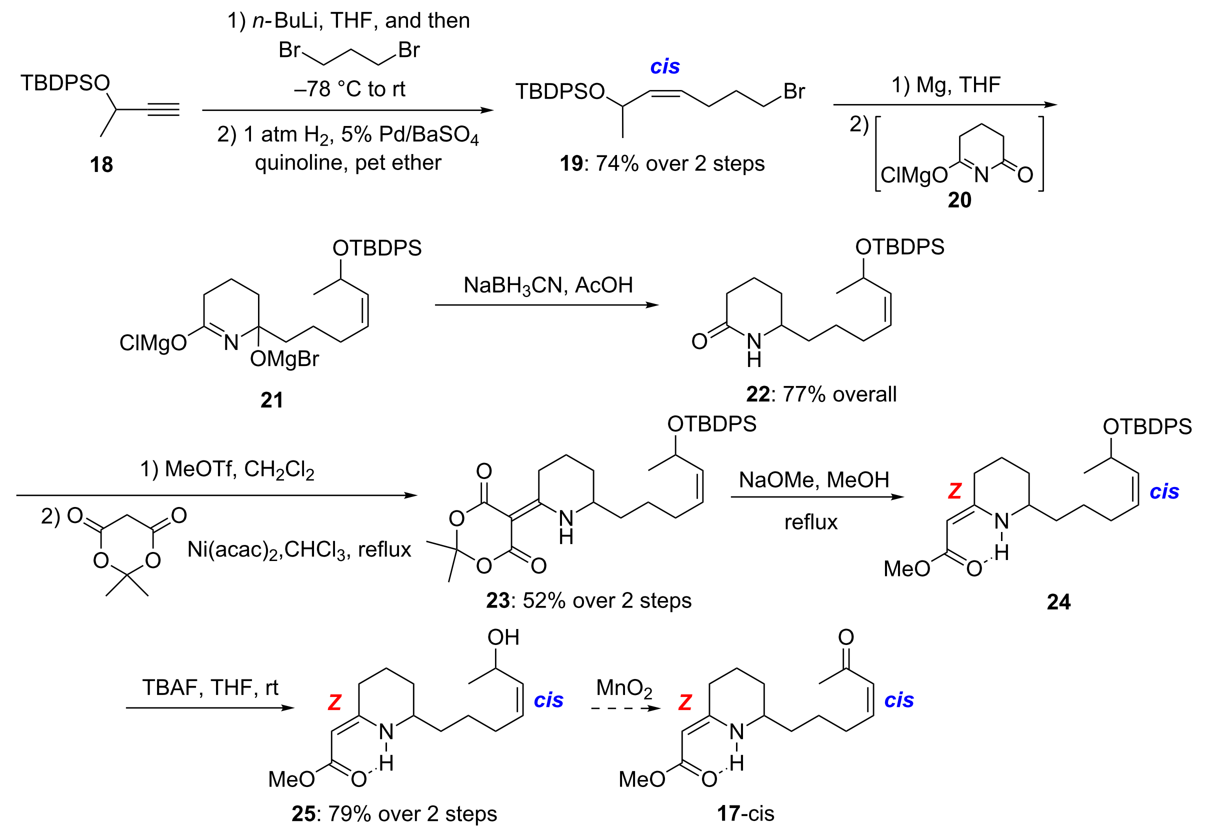
Figure 3: Relative stabilities of propyleine and isopropyleine.

Retrosynthetically, we envisioned propyleine (**12**) to come from the decarboxylation reaction of vinylogous carbamic acid **15** [10,28], which could be derived from stereoselective hydrogenation of the endocyclic olefin in tricycle **16** (Scheme 4). Vinylogous urethane **16** should be accessible via our intramolecular aza-[3 + 3] annulation of enone **17**. Enone **17** could be *E* or *Z* with respect to the vinylogous urethane olefin, and *cis* or *trans* with respect to the enone double bond. Thus, from the spectroscopic analysis stand point, synthesis of **17** could be messy.

In the forward direction to synthesize **17**, we used the approach developed in our model study for the synthesis of precoccinelline, hippodamine and myrrhine alkaloids [30,31]. Specifically, TBDPS-protected 3-butyne-2-ol **18** was converted to bromoalkene **19** in two steps involving alkylation with an excess of dibromopropane and subsequent Lindlar's hydrogenation (Scheme 5). Grignard addition to the glutarimide Mg-salt **20** followed by reduction of the Mg salt **21** afforded lactam **22** as an inseparable 1:1 mixture of two diastereomers in 77% overall yield [68-70].

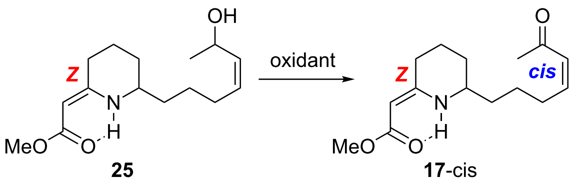
Vinylogous amide **23** was prepared by *O*-methylation of lactam **22** with freshly distilled MeOTf followed by condensation with Meldrum's acid in the presence of Ni(acac)$_2$. Treatment of **23** with MeONa in MeOH under reflux gave vinylogous urethane **24**. It is noteworthy that the geometry of the vinylogous urethane double bond exclusively favored *Z*, presumably due to the internal hydrogen bonding. Cleavage of the TBDPS group with TBAF provided allylic alcohol **25** in 79% from **23**. However, submission of **25** to the standard MnO$_2$ oxidation procedure did not lead to enone **17**, with only the starting material being recovered (Table 2). After extensive screening of various oxidation protocols, we succeeded with the Doering–Parikh conditions [71], and the *cis* geometry of the enone olefin was preserved under these conditions.

With enone **17**-*cis* in hand, we studied its intramolecular aza-[3 + 3] annulation reaction utilizing piperidinium salts (Table 3). When compound **17**-*cis* was treated with the acetate salt in EtOAc at rt, no reaction was observed after 18 h



Scheme 5: Synthesis of allyl alcohol **25**.

Table 2: Synthesis of the annulation precursor **17**.

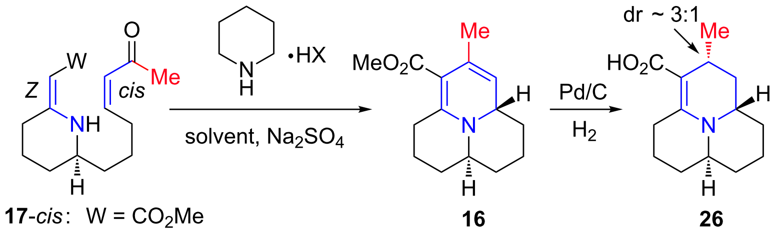


entry	oxidants	solvent	yield (%)
1	MnO_2	CH_2Cl_2	no rxn (rt)
2	MnO_2	CH_2Cl_2	decomp (40 °C)
3	$BaMnO_4$	CH_2Cl_2	no rxn
4	DMP	CH_2Cl_2	slow decomp
5	PCC	CH_2Cl_2	decomp
6	TEMPO/oxone	toluene	no rxn
7	TPAP/NMO	CH_2Cl_2	decomp
8	Pyr-SO_3/DMSO	CH_2Cl_2	85%

(Table 3, entry 1). Heating this reaction mixture at 85 °C for 12 h only led to slow isomerization of *cis*-enone **17** to the thermodynamically more stable *trans*-isomer again with no formation of the desired annulation product **16** (Table 3, entry 2). The inefficiency of the piperidinium acetate salt in the intramolecular *aza*-[3 + 3] annulation of enones was consistent with our previous findings (see Table 1). We were also not successful in converting enone **17**-*cis* to the desired tricycle **16** using the more reactive trifluoroacetate salt and EtOAc as the solvent. In this case also only isomerization to *trans*-enone was detected (Table 3, entry 3). Heating this reaction to 130 °C led to eventual decomposition of the starting material (Table 3, entry 4).

However, when enone **17**-*cis* was heated in toluene at 100 °C, complete consumption of starting material was observed after 5 h (Table 3, entry 5). Even though the reaction was relatively messy, the formation of the desired cycloadduct **16** was confirmed by the presence of characteristic signals in the ^1H NMR spectra of the crude mixture. Unfortunately, attempts to isolate the annulation product in pure form were not successful, probably due to the high instability of the electron-rich dihydropyridine moiety in **16**. Based on our previous experience with precarious annulation products, in situ hydrogenation was then carried out, and we managed to track down ~30% of the desired reduced aza-annulation product **26**, although stereoselectivity for the reduction was modest. We ultimately elected

Table 3: Aza-[3 + 3] annulations of **17**-*cis*.



entry[a]	HX (1.0 equiv)	solvent	temp (°C)	time (h)	yield (%)[b]
1	HOAc	EtOAc	25	18	–
2	HOAc	EtOAc	85	12	**17**-*trans*
3	HO_2CCF_3	EtOAc	55	12	**17**-*trans*
4	HO_2CCF_3	EtOAc	130	12	decomp
5	HO_2CCF_3	toluene	100	5	30% of **26**

[a] All reactions run in a sealed tube. Concn = 0.03–0.04 M; 5.0 equiv Na_2SO_4. [b] Isolated yields.

not to force our way toward propyleine using the enone aza-[3 + 3] annulation, as we succeeded in total syntheses of other members of the azaphenalene alkaloid family through annulations with enals [30,31]. While it is disappointing that this particular system may have lacked sufficient stability for this to be a suitable synthetic approach, success in an enone version of intramolecular aza-[3 + 3] annulation will allow us to find future applications.

Conclusion

Herein, we have described a successful enone version of intramolecular aza-[3 + 3] annulation reaction. Use of piperidinium trifluoroacetate salt as the catalyst and toluene as the solvent appears to be critical for a successful annulation. We also demonstrated for the first time that microwave irradiation can accelerate aza-[3 + 3] annulation reactions. An attempt to expand the scope of enone aza-[3 + 3] annulation was made in the form of propyleine synthesis as a proof of concept. While the synthesis of an enone annulation precursor was successfully accomplished, the annulation itself proved to be challenging and was only modestly successful. Future investigations are underway to pursue alkaloid synthesis via enone aza-[3 + 3] annulation.

Supporting Information

Supporting Information File 1

Experimental section.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-131-S1.pdf]

Acknowledgements

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Exploration of an epoxidation–ring-opening strategy for the synthesis of lyconadin A and discovery of an unexpected Payne rearrangement

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Full Research Paper

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Abstract

In the context of synthetic efforts targeting the alkaloid lyconadin A, scalemic epoxide **25** was prepared by a highly stereoselective sequence involving a Myers alkylation and a Shi epoxidation. Ring-opening of this epoxide with a vinylcopper complex afforded alcohol **26** instead of the expected product **27**. An unusual Lewis acid promoted Payne rearrangement of an α-trityloxy epoxide is proposed to account for this outcome.

Introduction

Lyconadin A (**1**, Figure 1) was isolated from the club moss *Lycopodium complanatum* in 2001 by Kobayashi and co-workers [1]. Subsequent to this discovery, lyconadins B–F were isolated and characterized [2-4]. Biological assays revealed that **1** exhibits cytotoxicity against murine lymphoma L1210 and human epidermoid carcinoma KB cells (IC_{50} = 0.46 μg/mL and 1.7 μg/mL, respectively) [1]. Moreover, **1** has been shown to promote nerve growth factor biosynthesis in 1321N1 human astrocytoma cells [2]. In addition to its interesting bioactivity, lyconadin A presents a significant synthetic challenge by virtue of its unique pentacyclic skeleton, which contains six stereocenters and a pyridone ring. It is therefore not surprising that **1** has attracted the attention of the organic synthesis community. The first total synthesis of lyconadin A was reported in 2007 by Smith and Beshore [5,6], and efforts from

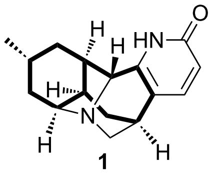

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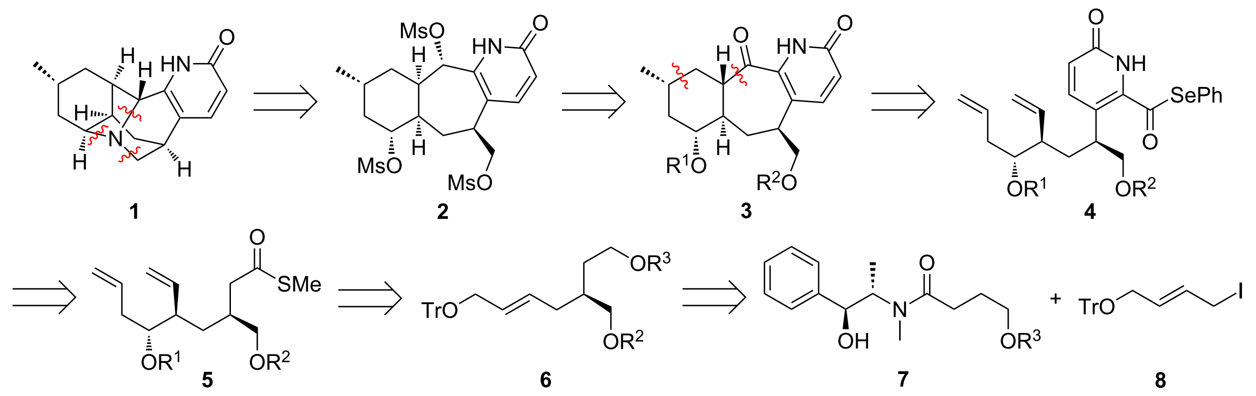
Figure 1: Lyconadin A.



Scheme 1: Retrosynthetic analysis of **1**.

the Sarpong [7,8] and Fukuyama [9,10] groups have also culminated in the construction of **1**.

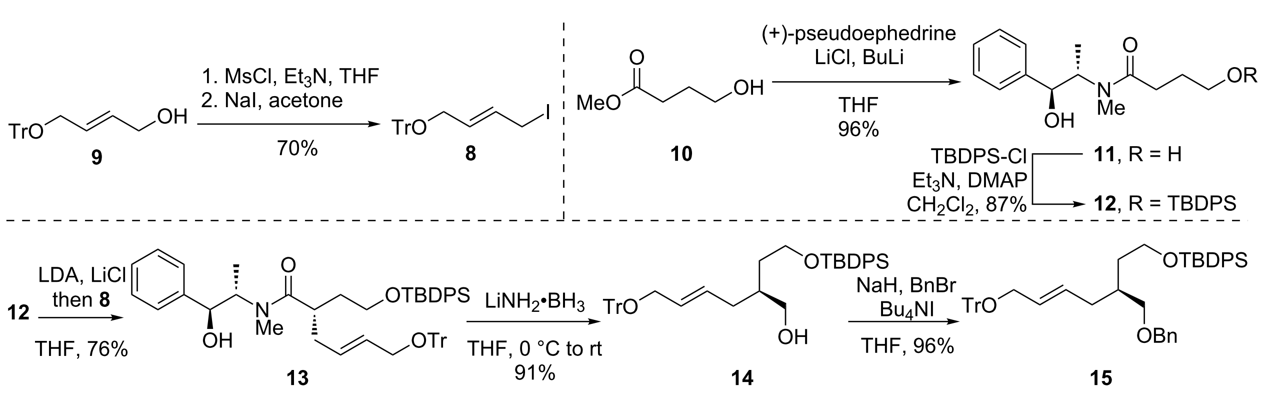
Our initial interest in lyconadin A was sparked by recognition that a 7-*exo*–6-*exo* cyclization cascade would efficiently furnish its bicyclo[5.4.0]undecane system, which is shown in bold in Figure 1. Subsequent to this observation, we performed model studies that demonstrated the viability of highly stereoselective 7-*exo-trig* acyl radical–6-*exo-trig* alkyl radical cyclizations as a means of preparing bicyclo[5.4.0]undecanes fused to aromatic rings [11]. Then, we devised an annulation protocol inspired by the work of Donohoe and co-workers [12,13] that provided access to substituted pyridones of the type found in **1** from thioester precursors [14]. Based on these encouraging results, we decided to target lyconadin A for synthesis. Herein, we provide an account of our studies directed toward the construction of this alkaloid. Specifically, we describe our efforts to prepare advanced intermediates that could be employed in the aforementioned pyridone annulation and tandem radical cyclization processes. In the course of this work, we discovered an unusual Payne-like rearrangement process that occurred in preference to the ring-opening of a hindered epoxide.

Results and Discussion

Our retrosynthetic analysis of lyconadin A is shown in Scheme 1. We reasoned that **1** could be formed by an alkylation cascade triggered by exposure of trimesylate **2** or a related electrophile to ammonia. A sequential alkylation process would serve as a viable alternative in the event of problems with this approach. In turn, *cis*-fused trimesylate **2** could be derived from *trans*-fused tricyclic ketone **3** by epimerization and standard functional-group manipulations. Based on the aforementioned model study [11], 7-*exo*–6-*exo* tandem radical cyclization of phenyl selenoester **4** was expected to produce ketone **3**. Disassembly of the pyridone moiety of **4** according to our annulation protocol [14] revealed thioester **5** as a suitable precursor. We believed that this compound could be prepared from alkene **6** in two consecutive epoxidation–ring-opening sequences involving vinyl nucleophiles. We anticipated that a chiral catalyst such as one of the ketones developed by Shi and co-workers [15-18] would control the stereochemistry of the epoxidation of **6**. Presumably, the identity of the protecting groups on this substrate (i.e., R^2 and R^3) would be critical to the success of the reaction. After formation of the epoxide, the bulky trityl ether was envisioned to direct the subsequent ring-opening to the distal carbon [19-22]. Alkene **6** would ultimately be formed by a Myers alkylation [23] of (+)-pseudoephedrine derived amide **7** with allylic iodide **8**.

The initial epoxidation substrate of type **6** that we targeted possessed benzyl and TBDPS ethers as the protecting groups. First, allylic iodide **8** was synthesized by iodination of the mesylate derived from known alcohol **9** [24] (Scheme 2). Then, coupling of methyl γ-hydroxybutyrate (**10**) [25] with lithiated (+)-pseudoephedrine afforded amide **11** in excellent yield. Selective silylation of the primary alcohol of **11** delivered substrate **12**. Alkylation of the enolate derived from **12** with **8** according to the Myers protocol [23] furnished adduct **13** in very high yield. Although not measured directly, the dr of this compound was assumed to be very high (i.e., ≥95:5) based on the results of an alkylation conducted on a very similar substrate (see below). The configuration of the newly formed stereocenter of **13** was assigned based on the established stereochemical course of the Myers alkylation [23]. Finally, reductive removal of the chiral auxiliary with lithium amidotrihydroborate [26] produced alcohol **14**, and benzylation yielded triether **15**.

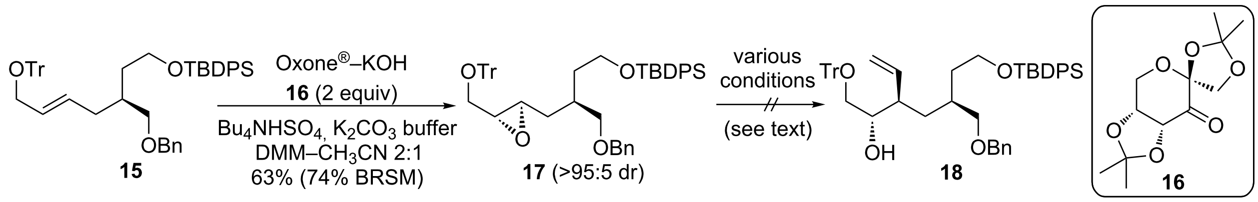
Asymmetric epoxidation of alkene **15** was somewhat sluggish and required superstoichiometric amounts of Shi's fructose-derived ketone **16** [27]. The resulting epoxide **17** was produced in moderate yield but excellent (<95:5) diastereomeric ratio



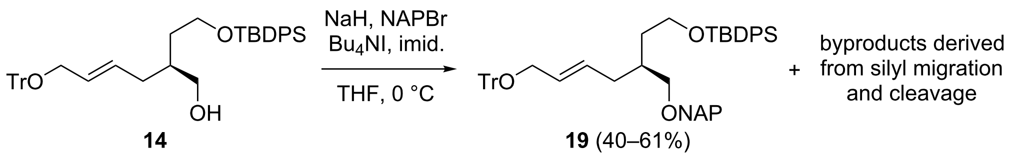
Scheme 2: Synthesis of triether **15**.

(Scheme 3). The epoxide stereochemistry was assigned based on the reported outcomes of epoxidations mediated by **16** [27]. Epoxide **17** was then subjected to ring-opening reactions with vinyl Grignard reagents in the presence of various copper salts. Surprisingly, only trace amounts of the desired product were detected, with recovered starting material and multiple byproducts typically comprising the majority of the mass balance. Although not investigated in detail, analysis of these reactions by ^{1}H NMR and mass spectrometry indicated that partial debenzylation was occurring. Accordingly, we decided to replace the benzyl ether with a 2-naphthylmethyl (NAP) ether [28]. Unfortunately, attempted protection of alcohol **14** produced varying yields of triether **19** along with byproducts derived from migration and/or scission of the TBDPS ether (Scheme 4). Modification of the reaction conditions failed to suppress the deleterious silyl migration and cleavage.

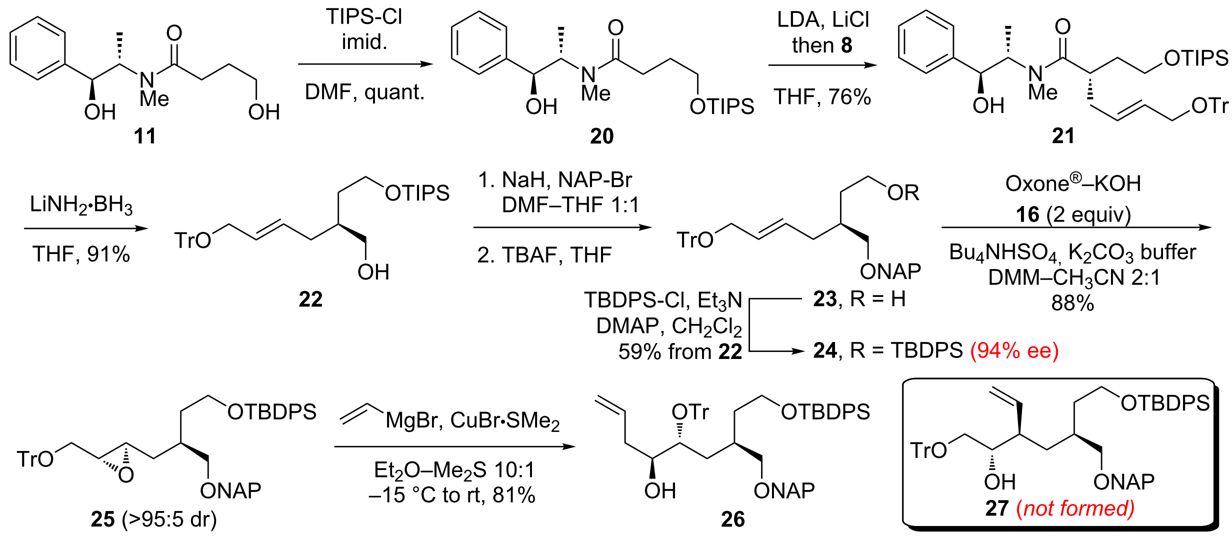
With the hope that a more robust silyl ether would not migrate, we installed a TIPS group on alcohol **11** (Scheme 5). Gratifyingly, TIPS-protected amide **20** was alkylated by **8** in the same yield as TBDPS-protected amide **12**. Reductive removal of the chiral auxiliary furnished alcohol **22** in 91% yield. Fortunately, naphthylmethylation of **22** was achieved without migration of the TIPS group. Surprisingly, Shi epoxidation of the NAP ether derivative of **22** was low-yielding (<10%), and ring-opening of the resulting epoxide did not proceed. These results prompted us to swap the bulky TIPS moiety for a smaller TBDPS group, and triether **24** was obtained uneventfully in 77% overall yield from **22**. Notably, the high (94%) ee of **24** as established by chiral HPLC analysis demonstrated that the Myers alkylation of **20** had proceeded with excellent diastereoselectivity. Then, we were pleased to find that Shi epoxidation of **24** provided **25** in reasonable (72%) yield and high (>95:5) dr. After considerable



Scheme 3: Synthesis and attempted ring-opening of epoxide **17**.



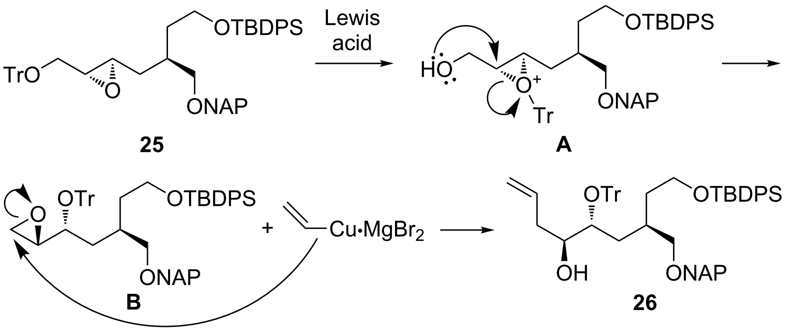
Scheme 4: Attempted protection of **14** and silyl migration.



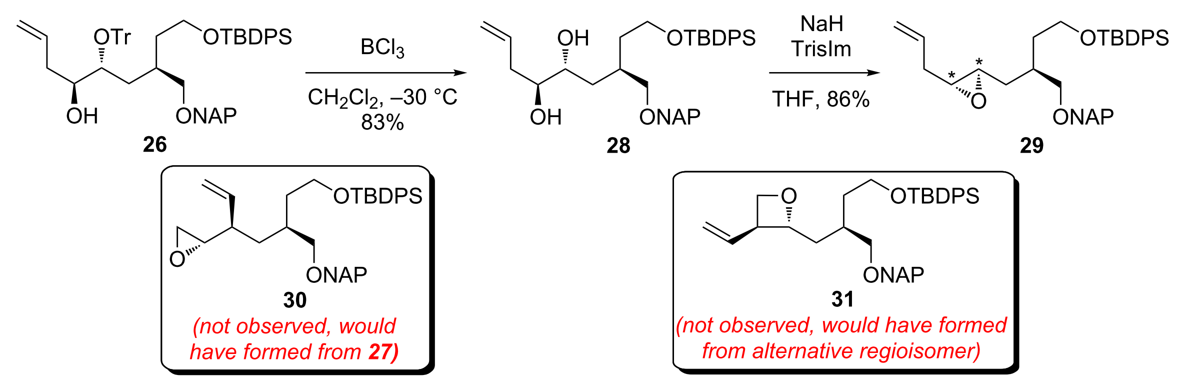
Scheme 5: Synthesis and ring-opening rearrangement of epoxide **25**.

experimentation, we discovered that CuBr•Me$_2$S [29] in conjunction with vinylmagnesium bromide was uniquely effective at facilitating the ring-opening of **25**. However, careful inspection of the ^{1}H NMR spectrum revealed the presence of one less hydrogen atom than expected in the 3–4 ppm region and one more hydrogen atom than expected in the 1–2 ppm region. Clearly, neither the anticipated product **27** nor the regioisomer derived from attack at the more hindered epoxide carbon had been generated. Instead, the NMR data were consistent with the formation of a different regioisomer, tentatively identified as alcohol **26**, which had been produced in good yield.

Presumably, the extremely hindered nature of internal epoxide **25** precluded its direct ring-opening, allowing alcohol **26** to form by means of a Payne rearrangement [30]. A possible mechanistic pathway for this transformation is given in Scheme 6. Coordination of a Lewis acid (likely a copper or magnesium species) to the trityl ether moiety of **25** could promote migration of the trityl group [31,32] to the epoxide, generating intermediate **A**. Payne rearrangement of **A** would then furnish epoxide **B**. Finally, attack of the vinylcopper complex [29] at the less-hindered carbon of the epoxide would provide **26**. Acid- and Lewis acid promoted Payne rearrangements of epoxy alcohols [33,34] and epoxy methyl ethers [35] have been described, but we are unaware of any prior reports of Payne rearrangements of the bulkier epoxy trityl ethers. However, previous observations of trityl migration [31,32], although rare, do lend support to our mechanistic proposal. The NMR data for **26**, while strongly supportive of the carbon backbone as drawn, do not permit an unambiguous assignment of the trityl ether to the C4 or C5 oxygen atom. An alternative



Scheme 6: Proposed mechanism for generation of alcohol **26**.



Scheme 7: Synthesis of epoxide **29** from alcohol **26** (asterisks indicate relative but not absolute stereochemistry).

pathway to this carbon skeleton involving a Payne rearrangement without trityl migration can also be envisioned, and under this scenario, the trityl ether would be located at C4 rather than C5. This possibility cannot be ruled out, but it would require opening of an activated epoxonium species at the less-substituted carbon instead of the more-substituted carbon as is typically observed. Thus, we favor the mechanism shown in Scheme 6.

To provide additional evidence for the structure of **26**, this compound was converted into epoxide **29** as outlined in Scheme 7. Selective detritylation was accomplished by exposure to BCl_3 at low temperature [36]. Camphorsulfonic acid was also effective for this transformation, although lengthy reaction times were required. Treatment of the resulting diol **28** with 2,4,6-triisopropylbenzenesulfonyl imidazole (TrisIm) effected regioselective sulfonylation (presumably of the less-hindered homoallylic alcohol, although this cannot be known for sure) followed by cyclization [37], delivering a single *trans*-disubstituted epoxide **29** of uncertain absolute stereochemistry in good yield. Examination of the ^{1}H NMR spectrum of **29** clearly demonstrated that a disubstituted epoxide had been generated. Alcohol **27**, or the aforementioned regioisomer that would have resulted from ring-opening of epoxide **25** at the more hindered carbon, would have afforded terminal epoxide **30** or oxetane **31**, respectively, when subjected to this two-step sequence. While these observations do not shed light on the location of the trityl ether in **26**, they do provide compelling evidence that the carbon backbone of this compound is correct as drawn and is produced by a Payne rearrangement of some type.

Conclusion

In the context of synthetic efforts targeting the polycyclic alkaloid lyconadin A, we prepared scalemic epoxide **25**. A Myers alkylation and a reagent-controlled Shi epoxidation were used to construct this compound in a highly stereoselective fashion. The bulky trityl group of **25** was intended to serve as a means of directing a ring-opening reaction to the distal carbon of the epoxide [19-22]. However, an unanticipated Lewis acid promoted Payne rearrangement intervened, producing alcohol **26** instead of the expected regioisomer **27**. We believe that the extremely hindered nature of epoxide **25** prevented the desired ring-opening process, thereby enabling the unusual rearrangement to proceed. Conceivably, future studies of the scope and limitations of Lewis acid promoted Payne rearrangement–ring-opening cascades could establish their utility in organic synthesis.

Supporting Information

Supporting Information File 1

Name: Experimental procedures and characterization data for all new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-132-S1.pdf]

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Selective copper(II) acetate and potassium iodide catalyzed oxidation of aminals to dihydroquinazoline and quinazolinone alkaloids

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Full Research Paper

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Abstract

Copper(II) acetate/acetic acid/O_2 and potassium iodide/*tert*-butylhydroperoxide systems are shown to affect the selective oxidation of ring-fused aminals to dihydroquinazolines and quinazolinones, respectively. These methods enable the facile preparation of a number of quinazoline alkaloid natural products and their analogues.

Introduction

Quinazoline alkaloids are a class of naturally occurring compounds with a range of medicinal properties and have been indicated for use as bronchodilators, vasodilators, anti-inflammatory agents and acetylcholinesterase inhibitors [1-5]. Many of the plants these products have been isolated from, such as *Adhatoda vasica, Peganum harmala* and *Evodia rutaecarpa*, have been used in folk medicine for centuries [6-9]. Since the original isolation of vasicine (**1**, Figure 1) in 1888 [10], the biological properties of this class of alkaloids have been extensively studied.

A number of synthetic strategies have been employed to gain access to quinazoline alkaloids [5,11-26]. Perhaps the most common method involves the condensation of an *ortho*-aminobenzoic ester with a lactam promoted by phosphoryl chloride, known as the Niementowski reaction [3,27-30] (Figure 2). The availability, or lack thereof, of the corresponding lactam can determine the length and efficiency of the route. Access to the sometimes more biologically active dihydroquinazolines, such as deoxyvasicine (**2**), from quinazolinones requires a subsequent reduction of the amide. In 2008, our group reported the syntheses of deoxyvasicinone (**4**) and rutaecarpine (**6**) by the potassium permanganate promoted oxidation of aminals, which in turn were obtained from the condensation of *ortho*-aminobenzaldehydes and simple secondary amines [31,32]. A number of these aminal precursors were

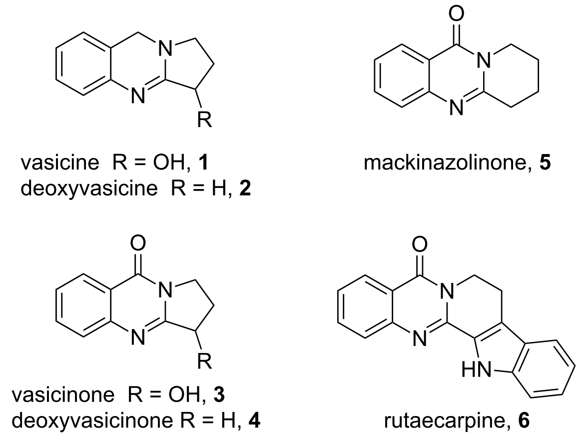


Figure 1: Examples of naturally occurring quinazoline alkaloids.

prepared in generally good to excellent yields with the scope encompassing various cyclic amines and substituents on the aminobenzaldehyde aryl ring. Since then, we have demonstrated that the reaction can be run on a multigram scale [33] and have shown that dihydroquinazolines vasicine (**1**) and deoxyvasicine (**2**) can be synthesized from their corresponding aminals by using an iodine-promoted oxidation [34]. While resulting in good yields, these oxidations have the drawback of requiring large amounts of a strong oxidant for the permanganate oxidation and the necessity of stoichiometric *n*-butyllithium for the iodine reaction.

The conversion of the aminals formed from the condensation of aminobenzaldehydes and secondary amines to the corresponding dihydroquinazoline and quinazolinone structures under mild and catalytic conditions would be preferable to using harsh oxidants and strong bases. Han et al. have recently shown the ability of copper salts, in conjunction with oxygen, to catalyze oxidations of 2-substituted tetrahydroquinazoline aminals to quinazolines [35] (Figure 2). In addition, Reddy and co-workers have developed a catalytic system in which 2,3-substituted tetrahydroquinazoline aminals are converted to quinazolinones using *tert*-butylhydroperoxide (TBHP) and catalytic potassium iodide [36,37]. While these examples deal with the oxidation of bicyclic aminals, we were interested in developing methods to create dihydroquinazoline and quinazolinone alkaloids from ring-fused aminals. Here we present catalytic methods for the synthesis of both these compound classes from aminals using $Cu(OAc)_2/O_2/AcOH$ and KI/TBHP systems, respectively.

Results and Discussion

Copper-catalyzed oxidations of aminals to dihydroquinazolines

Copper-catalyzed oxidation reactions have received a great deal of interest in recent years [38-44]. Han's copper-catalyzed method for the synthesis of aminals to quinazolines results in high yields [35], but the process is not applicable to mono-oxidation as dihydroquinazolines are not isolated as products in these reactions. We set out to develop a method for the syn-

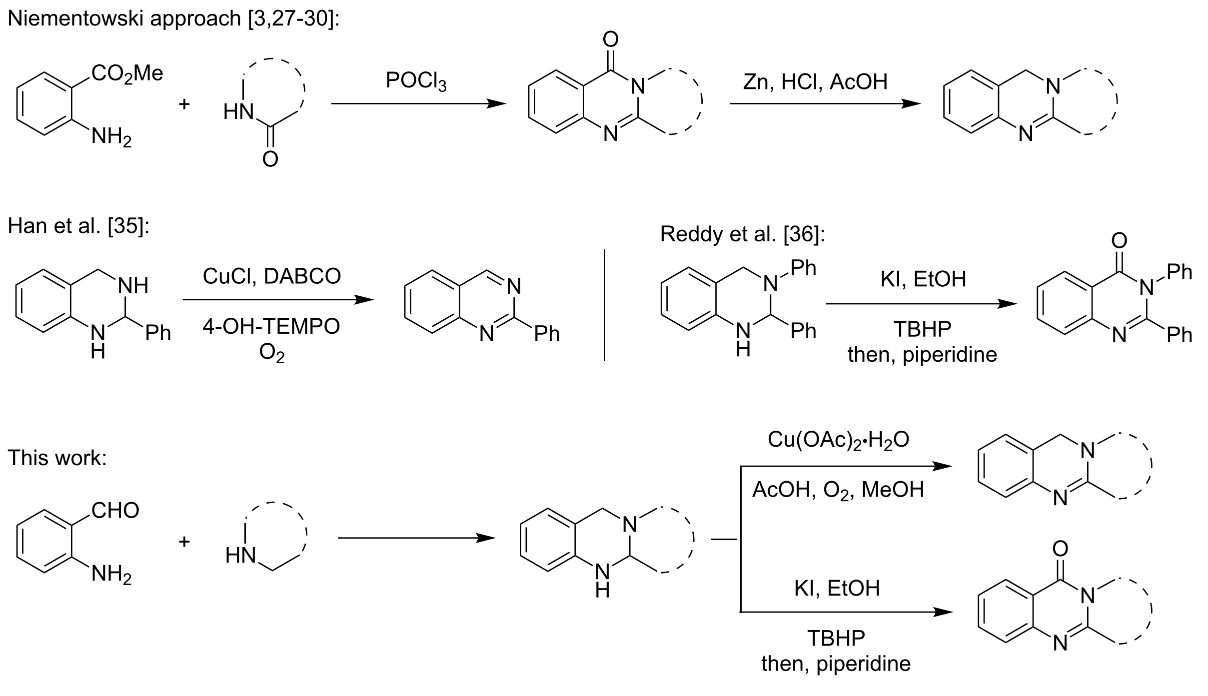
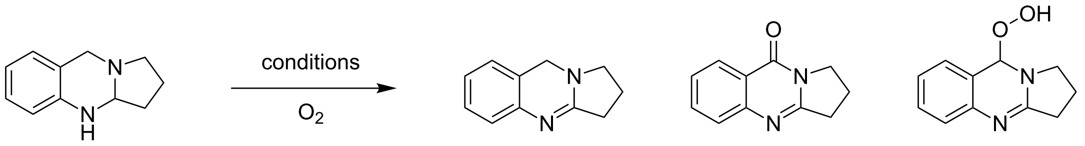


Figure 2: Different approaches to the synthesis of quinazoline alkaloid structures.

thesis of dihydroquinazolines that would prevent further oxidation at the benzylic position. A factor complicating this effort was that dihydroquinazolines like deoxyvasicine (**2**) are known to auto-oxidize to their quinazolinone counterparts by exposure to air [3,45-47]. We initiated our efforts by exposing aminal **7** to stoichiometric amounts of $CuCl_2$ in acetonitrile under a nitrogen atmosphere, which led to the formation of **2** in 81% yield (Table 1, entry 1). To improve the efficiency of the process, catalytic conditions were subsequently evaluated. When aminal **7** was heated under reflux in an oxygen atmosphere and in the presence of 20 mol % of $CuCl_2$, **2** was only observed in trace amounts; deoxyvasicinone (**4**) and peroxide **8** were also formed as products. Switching the catalyst to $Cu(OAc)_2$ led to a 15% yield of the desired product **2**, but the process was still unselective.

It appears that the first oxidation occurs exclusively at the aminal site to form deoxyvasicine (**2**). The presence of the amidine moiety apparently activates the molecule for oxidation at the benzylic position; we have observed that samples of aminal **7** can remain stable in the freezer for years, whereas **2** begins to convert to **4** within a day when exposed to atmospheric oxygen. Considering this, we reasoned that addition of a weak acid to protonate the relatively basic amidine moiety of **2** might deactivate the benzylic position toward oxidation while not interfering with the initial aminal oxidation. Indeed, using 1.1 equivalents of acetic acid as an additive with catalytic $Cu(OAc)_2$ in acetonitrile led to the formation of **2** in 53% yield without formation of **4** and **8** (Table 1, entry 4). A simple change of the solvent from acetonitrile to methanol drastically improved the yield of **2** to 81% (Table 1, entry 5). A number of different copper salts, solvents and acids were then evaluated, but none of the changes led to a further improvement in yield. It appears that under certain conditions catalyst deactivation via copper oxide formation decreased the catalyst turnover and consequently product yields.

Table 1: Optimization of conditions for deoxyvasicine (**2**) formation.[a]



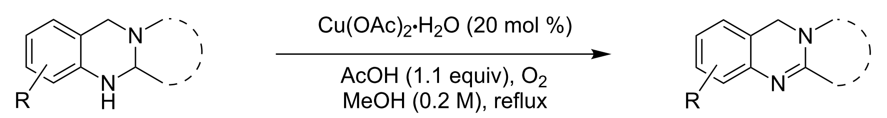
7 **2** **4** **8**

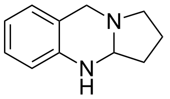
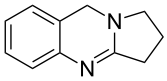
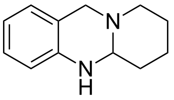
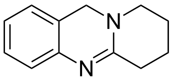
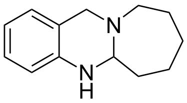
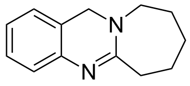
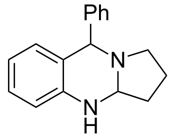
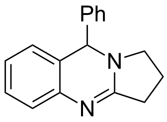
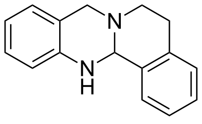
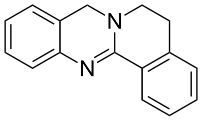
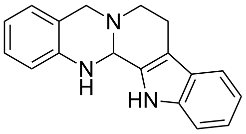
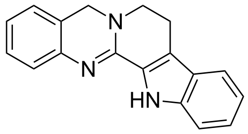
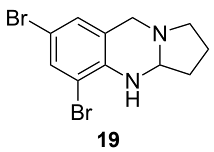
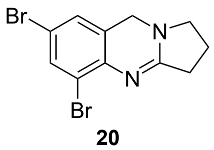
Entry	Solvent (0.2 M)	Catalyst (mol %)	Acid (equiv)	Temp. (°C)	Time (h)	Yield of **2** (%)	Yield of **4** (%)	Yield of **8** (%)
1[b]	MeCN	$CuCl_2·2H_2O$ (100)	–	rt	6	81	–	–
2	MeCN	$CuCl_2·2H_2O$ (20)	–	81	2	trace	14	10
3	MeCN	$Cu(OAc)_2·H_2O$ (20)	–	81	3	15	17	trace
4	MeCN	$Cu(OAc)_2·H_2O$ (20)	AcOH (1.1)	81	3	53	–	–
5	MeOH	$Cu(OAc)_2·H_2O$ (20)	AcOH (1.1)	65	4	81	–	–
6	MeOH	$Cu(OAc)_2·H_2O$ (20)	–	65	4	33	6	24
7	AcOH	$Cu(OAc)_2·H_2O$ (20)	–	80	24	18[c]	–	–
8	DMF	$Cu(OAc)_2·H_2O$ (20)	AcOH (1.1)	80	4	17	20	–
9	MeOH	$Cu(2\text{-}EH)_2$ (20)	2-EHA (1.1)	65	12	71	–	–
10	MeOH	CuBr (20)	AcOH (1.1)	65	8	72	–	–
11	EtOH[d]	$Cu(OAc)_2·H_2O$ (20)	AcOH (1.1)	78	1.5	73	–	trace
12	MeOH	$Cu(OAc)_2·H_2O$ (10)	AcOH (1.1)	65	18	67	–	trace
13	MeOH	$Cu(OAc)_2·H_2O$ (20)	AcOH (1.1)	40	24	61	trace	trace
14	MeOH	$Cu(acac)_2$ (10)	AcOH (1.1)	65	24	68[c]	trace	trace

[a] Reactions were performed on a 0.25 mmol scale. $Cu(2\text{-}EH)_2$ = copper(II) 2-ethylhexanoate. 2-EHA = 2-ethylhexanoic acid. [b] Nitrogen atmosphere. [c] The reaction was incomplete. [d] 95% Solution.

Using the optimized reaction conditions, a range of different aminals were selectively oxidized to the corresponding dihydroquinazolines (Table 2). In general, these products were obtained in moderate to good yields. Product **10**, containing a piperidine ring, required a higher reaction temperature and resulted in a lower yield than the corresponding pyrrolidine and azepane products (**2** and **12**, respectively). While differences in conformation may in part account for the observed differences in reactivity (X-ray crystal structures of aminals containing pyrrolidine and piperidine revealed that the pyrrolidine-containing aminal adopts a bent structure, whereas the piperidine aminal appears relatively strain-free [34]), this finding likely relates to the reduced propensity of six-membered rings to engage in reactions that form exocyclic double bonds. The isolation of azepinoquinazoline **12** in 73% yield was gratifying but somewhat unexpected since Decker reported that samples of the compound completely oxidized to quinazolinone **23** when exposed to air for 24 h [3]. This demonstrates the need for

Table 2: Scope of the copper-catalyzed conversion of aminals to dihydroquinazolines.[a]



Entry	Starting material	Product	Time (h)	Yield (%)
1	 **7**	 **2**	7	86
2[b,c]	 **9**	 **10**	8	57
3[c]	 **11**	 **12**	7	73
4	 **13**	 **14**	24	72
5	 **15**	 **16**	8	82
6	 **17**	 **18**	4	47
7[b,d]	 **19**	 **20**	72	18

[a]Reactions run on a 1 mmol scale. [b]EtOH used as solvent. [c]0.5 mmol scale. [d]Reaction incomplete.

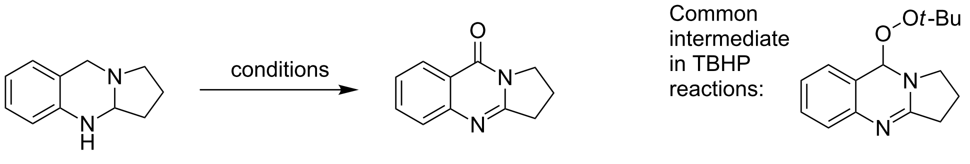
acetic acid to protonate the amidine, preventing further oxidation. While product **16** was obtained in good yields from tetrahydroisoquinoline-aminal **15**, rutaecarpane-derived product **18** was formed in only 47% yield, apparently due to unidentified side-reactions. The reaction leading to the synthesis of the dibromo- analogue of deoxyvasicine **20**, even under elevated temperature and extended reaction time, still did not reach completion after 3 days. The attenuated reactivity of aminal **19** is most likely the result of the decreased electron density on the anilinic nitrogen.

KI-catalyzed oxidations of aminals to quinazolinones

Different conditions for the direct catalytic oxidation of aminals to quinazolinones were also explored. The use of $Cu(OAc)_2$ and methanol, while appropriate for furnishing deoxyvasicine (**2**) from aminal **7**, did not result in satisfactory yields of deoxyvasicinone (**4**, Table 1). Attempts to use other copper(I) or copper(II) salts and solvents under oxygen without the addition of acid to promote the full oxidation of aminal **21** to deoxyvasicinone (**4**) were met with disappointment, with yields of **4** for these conditions reaching a maximum of around 40% (Table 3). In most cases, peroxide **8** was observed as a major side product. The Cu/TEMPO/DABCO catalyst system employed by Han et al. [35] for the oxidation of aminals to quinazolines provided an increased yield of 50% (Table 3, entry 9). The best yields were obtained by using the conditions developed by Reddy and co-workers [36], namely the combined use of catalytic amounts of potassium iodide (20 mol %) and excess TBHP (5 equiv), followed by the addition of piperidine. In this instance, deoxyvasicinone was isolated in 80% yield (Table 3, entry 12). In the course of this reaction, the TBHP adduct **22** is formed as an intermediate that is subsequently converted to the quinazolinone upon addition of piperidine. A slight modification of Reddy's conditions, in which piperidine was added directly to the solution after 36 hours instead of the removal of solvent from the intermediate peroxide beforehand, resulted in identical yields.

Using the optimized conditions, a range of different quinazolinones were synthesized (Table 4). In general, yields were moderate to good for substrates with varying ring sizes. In this manner the natural products deoxyvasicine (**4**), mackinazolinone (**5**) and rutaecarpine (**6**) were prepared, in addition to the azepinoquinazolone **23**, which has been demonstrated to be a more effective antitussive agent than codeine [48]. Dibromo-

Table 3: Optimization of conditions for deoxyvasicinone (**4**) formation.[a]

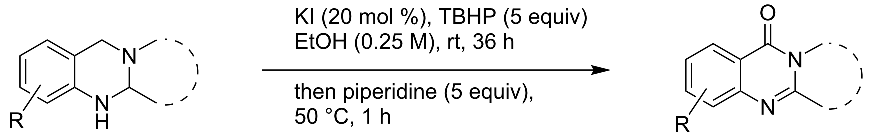


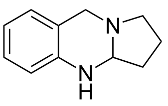
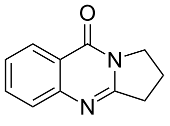
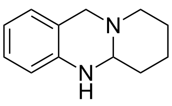
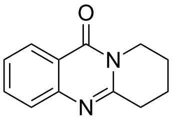
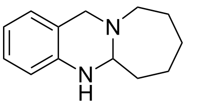
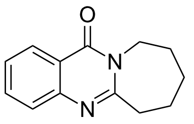
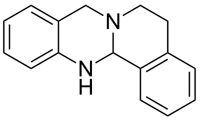
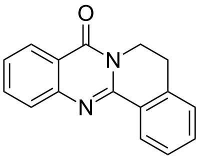
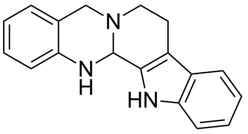
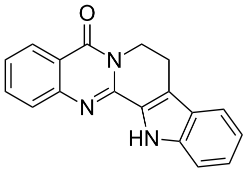
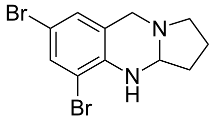
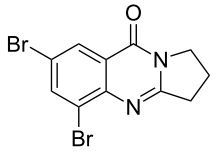
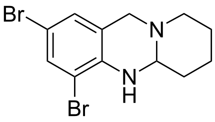
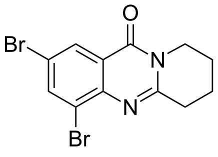
21 **4** **22**

Entry	Solvent (0.2 M)	Catalyst (mol %)	Oxidant (equiv)	Additive (equiv)	Temp. (°C)	Time (h)	Yield of **4** (%)
1	DMSO	CuBr (20)	O_2	–	100	2	21
2	DMSO	CuBr (20)	O_2	DBU (0.4)	100	17	25
3	DMSO	CuBr (20)	O_2	DBU (2)	100	3	22
4	DMSO	CuBr (20)	O_2	–	60	3	28
5	MeCN	CuBr(10)	O_2	–	80	24	43
6	DMF	CuBr(10)	O_2	–	80	24	42
7	DMSO	CuI (20)	O_2	–	60	3	29
8	MeCN	$CuCl_2 \cdot 2H_2O$ (20)	O_2	–	50	5	19
9	MeCN	CuCl (10)	O_2	DABCO (0.1), TEMPO (0.05)	80	12	50
10	DMSO	CuCl (10)	O_2	DABCO (0.1), TEMPO (0.05)	100	3	38
11	PhMe	CuBr (20)	TBHP (5)	piperidine[b] (5)	rt	0.5	61
12	EtOH	KI (20)	TBHP (5)	piperidine[b] (5)	rt	36	80

[a]Reactions run on a 0.25 mmol scale. DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene. DABCO = 1,4-Diazabicyclo[2.2.2]octane. TEMPO = 2,2,6,6-Tetramethylpiperidine-1-oxy radical. [b]Piperidine was added at the end of the reaction and the reaction mixture was heated at 50 °C for 1 h.

Table 4: Scope of KI-catalyzed conversion of aminals to quinazolinones.[a]



Entry	Starting material	Product	Yield [%]
1	 **7**	 **4**	84
2[b]	 **9**	 **5**	59
3[b]	 **11**	 **23**	69
4	 **15**	 **24**	60
5	 **17**	 **6**	58
6	 **19**	 **25**	88
7	 **26**	 **27**	50

[a]Reactions run on a 1 mmol scale. [b]0.5 mmol scale.

deoxyvasicinone analogue **25** was obtained in relatively high yield (88%) whereas the corresponding analogue of mackinazolinone (**27**) was obtained in only 50% yield.

Interestingly, when quaternary aminal **28** was subjected to oxidative conditions in an attempt to prepare compound **29**, deoxyvasicinone (**4**) was obtained as the major product in a process that involved demethylation (Scheme 1, reaction 1). The demethylation of aminals has been previously reported in cases where the product achieves aromaticity [49-51], which is presumably the driving force for this transformation. Aminal **30**, which contains two tertiary amines and is readily obtainable by an acid-promoted hydride shift process [52-54], was also exposed to oxidative conditions (Scheme 1, reaction 2). We had hypothesized that quinazolinone **32** might be formed in this reaction by the debenzylation of an intermediate iminium ion. However, the major product from this reaction was identified to be **31**, the apparent product of iminium hydrolysis.

Conclusion

We have demonstrated that quinazoline alkaloids and their analogues can be synthesized from aminals by using $Cu(OAc)_2$/O_2/AcOH and KI/TBHP catalyst systems. The use of acetic acid in addition to oxygen and catalytic copper(II) salts was determined to prevent overoxidation of dihydroquinazolines, allowing access to these structures under mild conditions. A number of natural products and their analogues were obtainable by these methods, which should facilitate the preparation of novel materials for biological studies.

Supporting Information

Supporting Information File 1

Experimental details, characterization data and ^1H and ^{13}C NMR spectra for all new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-135-S1.pdf]

Acknowledgements

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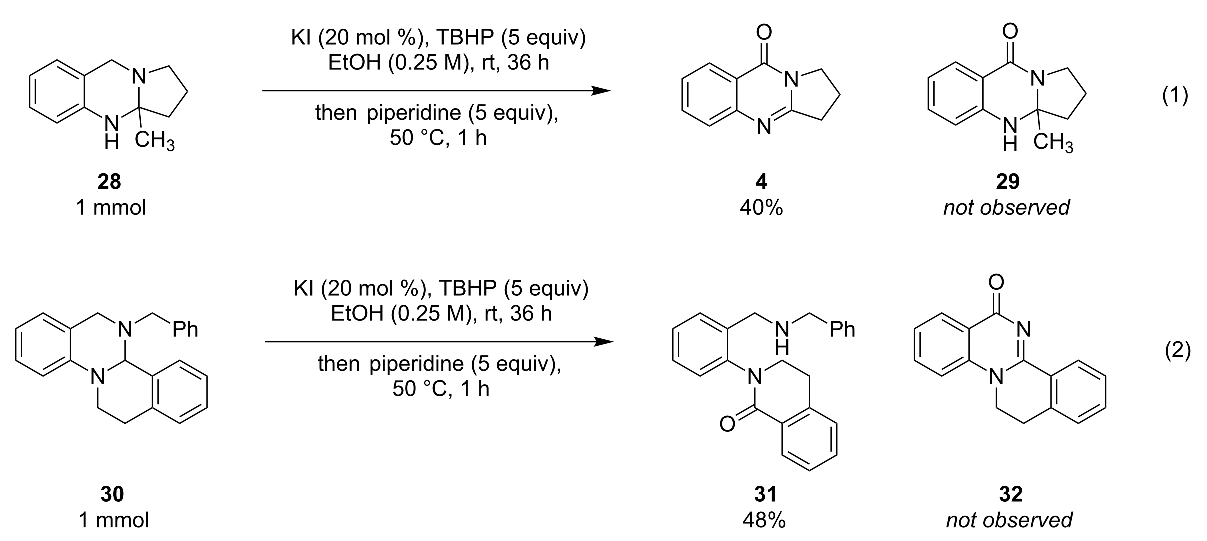

Scheme 1: Oxidation of other aminal systems.

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An organocatalytic route to 2-heteroarylmethylene decorated *N*-arylpyrroles

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Full Research Paper

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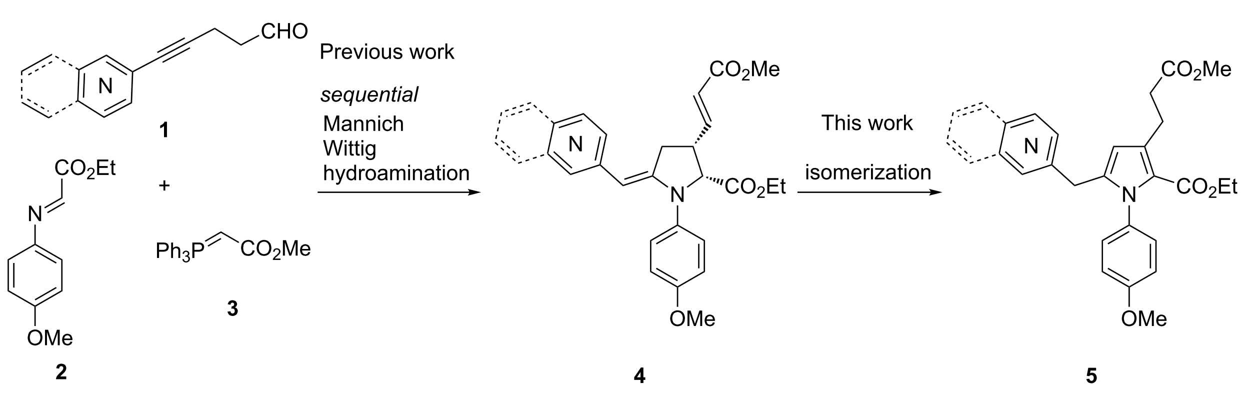
Abstract

A concise and regioselective preparation of 2-heteroarylmethylene decorated *N*-arylpyrroles is described through a metal-free Mannich/Wittig/hydroamination sequence followed by isomerization of the *N*-arylpyrrolidine adducts. Furthermore, the C–H regioselective oxidation of these substrates is demonstrated, extending the molecular diversity and versatility of these scaffolds.

Introduction

Due to their presence in some natural products [1] and pharmaceuticals [2-4], the preparation of *N*-arylpyrroles is an active field of investigation [5]. Depending on their substituents, *N*-arylpyrroles could also be electron donor/acceptor molecules with a dual fluorescence ability suggesting attractive optoelectronic applications [6,7]. If the *N*-arylation of pyrroles is possible by Ullmann-type condensation [8-10], the regioselective functionalization of pyrroles is less trivial when asymmetric substrates are targeted. An indirect solution, based on the construction of substituted pyrrolidines that oxidize into elaborated pyrroles, can be employed fruitfully [11,12]. We recently described a one-pot organo-catalyzed synthesis of *N*-heteroarylmethylene pyrrolidines **4** [13] from readily available aldehydes **1** and imine **2** by a sequence of Mannich coupling [14-24], Wittig olefination with phosphonium **3**, and proton-mediated hydroamination (Scheme 1). In the course of our investigations, we observed that pyrrolidine **4** could be converted into the corresponding pyrrole **5** by a simple isomerization, avoiding the use of oxidants. We describe herein the details of these observations and the scope of this methodology for the concise preparation of substituted 2-heteroaromatic decorated *N*-arylpyrroles.



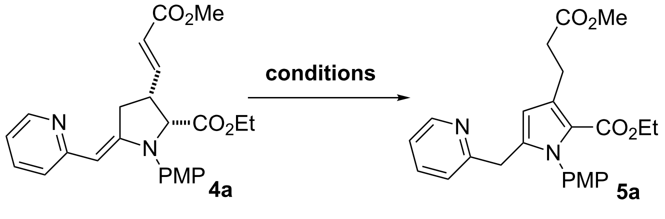
Scheme 1: Synthetic approach toward *N*-arylpyrroles.

Results and Discussion

We first observed the unexpected formation of pyrrole **5a** in 50% yield after treatment of pyrrolidine **4a** with KCN in DMF (Scheme 2, conditions a). Although obtained in modest yield, we found the original and unique structure of the substituted pyrrole **5a** interesting, especially with the 2-pyridylmethylene decoration. In an attempt to rationalize the formation of **5a**, we hypothesized that KCN acted as a nucleophilic and weak base since the level of oxidation of **4a** and **5a** was the same. To improve the efficiency of the transformation, a stronger nucleophilic base such as DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) was tested [25]. Pleasingly, when pyrrolidine **4a** was exposed to DBU in CH_2Cl_2, **5a** was obtained in excellent yield (98%, 1 h, conditions b; Scheme 2). The reaction can also be promoted by a catalytic amount of DBU (0.2 equiv) delivering **5a** (96%) after prolonged reaction time (22 h, conditions c, Scheme 2). Interestingly and despite its strong nucleophilic character, DABCO (1,4-diazabicyclo[2.2.2]octane) was unable to promote the isomerization (conditions d, Scheme 2) and the starting material was recovered.

As presented in Scheme 3, the methodology was next attempted in a one-pot process. Hence, the transformation of aldehyde **1a** and imine **2a** into pyrrolidine **4a** was followed by the introduction of DBU leading to pyrrole **5a** in 26% yield. However, proceeding stepwise and isolating the pyrrolidine **4a** by a simple filtration on silica gel before isomerization is more rewarding: following this route, the global yield for the whole process reaches 59% yield. Applying this procedure, various 2-heteroarylmethylenepyrrolidines **4b–h** prepared from aldehydes **1b–h** and imine **2a** were exposed to DBU (1.1 equiv). Pleasingly, pyrrolidines **4b–h** were transformed into the corresponding pyrroles **5b–i** with homogeneous efficiency. Hence, the chemistry proved to be compatible with substrates containing *meta*-, *para*-pyridyl and quinolinyl substituents, allowing the preparation of **5b** (81%), **5c** (78%) and **5d** (98%). Pyrrolidine **4e** containing an electronically deficient pyridyl residue was also converted into **5e** (80%) while pyrrolidine **4f** bearing a pyrazine core underwent aromatization with high efficiency to give **5f** (97%). The C_2-symmetric scaffold **4g** was efficiently converted into **5g** (86%) and similar treatment of pyrimidine **4h** provided pyrrole **5h** in high yield (91%).

The Mannich coupling was next attempted with different imines **2b–e** in order to modulate the nature of the aryl moiety (Scheme 4). The electronic nature of the aniline being crucial



conditions

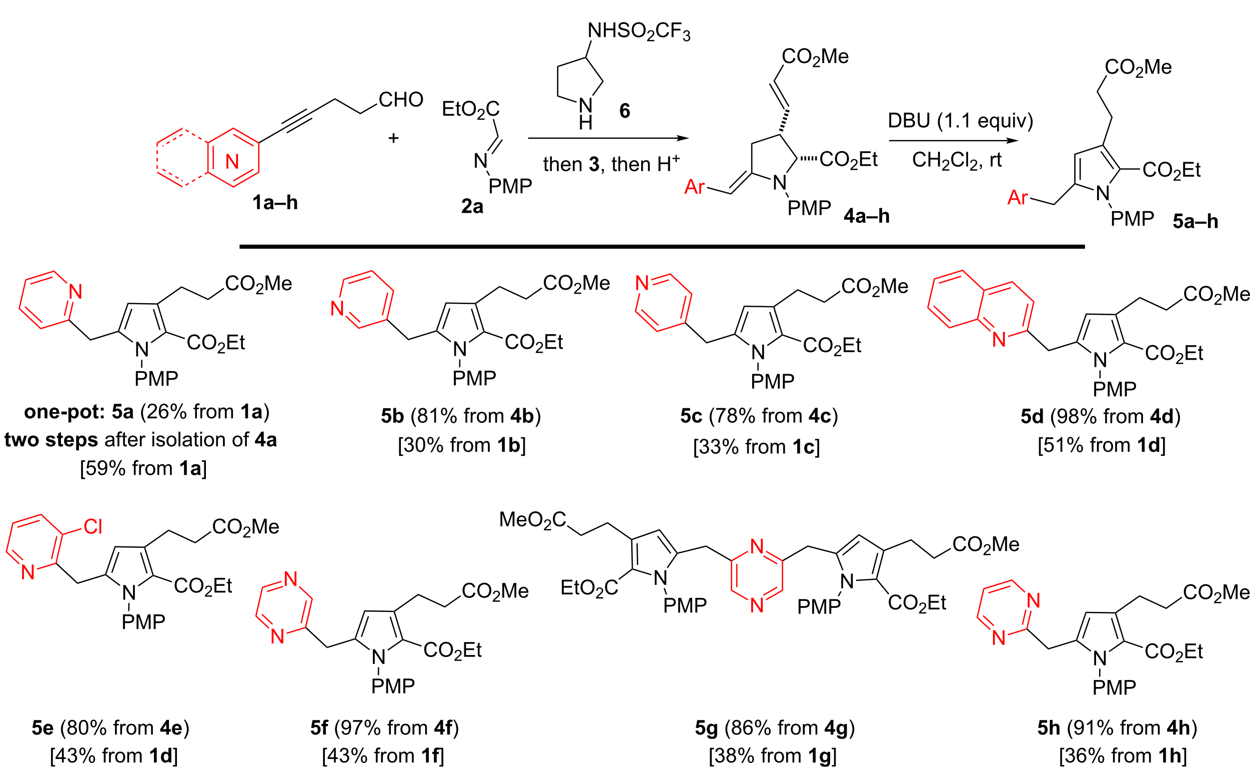
a. KCN (1.1 equiv), DMF, rt, 90 min, 50%

b. DBU (1.1 equiv), CH_2Cl_2, rt, 1 h, >98%

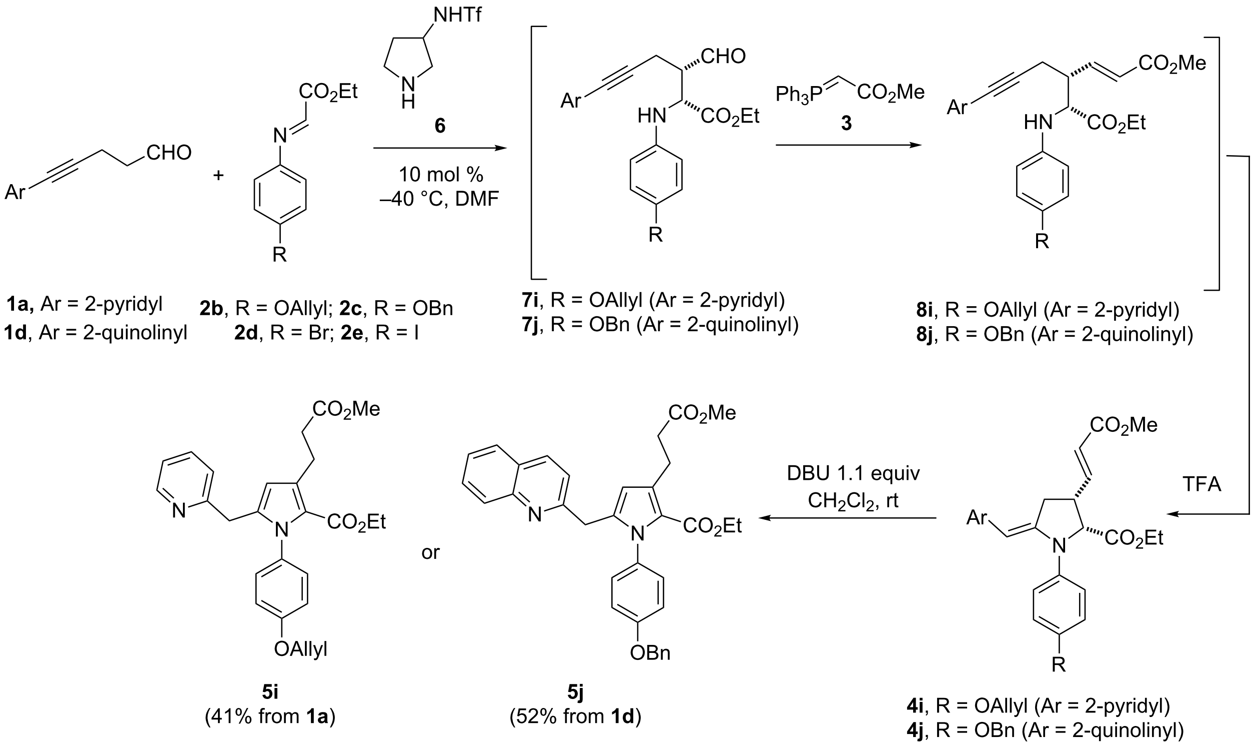
c. DBU (0.2 equiv), CH_2Cl_2, rt, 22 h, 96%

d. DABCO (1.1 equiv), CH_2Cl_2, rt, 0%

Scheme 2: Isomerization of pyrrolidine **4a** (PMP: 4-methoxyphenyl).



Scheme 3: Preparation of *N*-arylpyrroles **5a–h** (unless otherwise specified, yields in brackets refer to the isomerization step while yields in square brackets refer to the two-step procedure from the corresponding aldehyde).



Scheme 4: Variation of imines.

for the stability of the imine and the hydroamination step, electronically rich anilines were selected to form imines **2b**,**c**. Hence, when imines **2b**,**c** were exposed to aldehyde **1a** in the presence of catalyst **6** (available in racemic form), the Mannich adducts **7i**,**j** were obtained and directly reacted with phosphonium salt **3**. In line with our procedure, the resulting acyclic anilines **8i**,**j** were then exposed to TFA to promote the cyclization into pyrrolidines **4i**,**j** which upon treatment with DBU were converted into pyrroles **5i**,**j** in 41% and 52% overall yields. While *p*-alkoxy substituted (R = OAllyl, OBn) anilines are compatible, the methodology proved troublesome with *o*-alkoxy substituted anilines, the main limitation being the formation of the corresponding imines. Similarly, imine **2d** prepared from *para*-bromoaniline was found to be unstable and only degradation was observed during the Mannich reaction. When imine **2e**, derived from the *para*-iodoaniline, was engaged in the process, the hydroamination step turned out to be problematic, which prevented the isolation of the corresponding pyrrolidine.

Even if not completely elucidated, a mechanism of the isomerization can be suggested in which the acrylate moiety is crucial. Indeed, without this unsaturation, it was not possible to observe the isomerization of the *exo*-enamine into the *endo* compound under basic treatment [26]. These observations suggest that DBU or KCN behave as base to promote the deconjugation of the acrylate moiety of **4a** [27]. The resulting product **4a'** would lead under basic treatment to pyrroline **4a"** from which aromatization to **5a** would be expected to follow (Scheme 5).

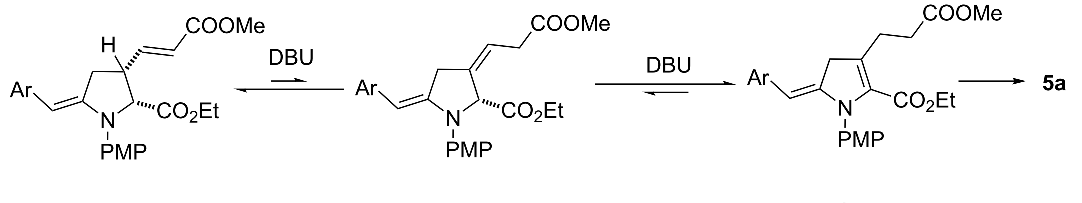
Having established a practical methodology for the preparation of substituted *N*-arylpyrroles, we next undertook synthetic transformations to extend the molecular diversity of the substrates. While attempts to perform an oxidation of the bis(heteroaryl)methylene position with elemental sulfur [28] or SeO_2 failed, the oxidation of this methylene position was regioselectively carried out by treatment of **5a**–**e** with $(NH_4)_2Ce(NO_3)_6$ (CAN), delivering the alcohols **9a**–**e** (Scheme 6). The methylene oxidation was especially efficient with substrates containing mononitrogenated heteroaryl substituents, with yields ranging from 64–87%. Oxidation under the same conditions was found to be more troublesome with pyrazine **5f** since alcohol **9f** was isolated in only 20% yield. Similar treatment of pyrazine **5g** and pyrimidine **5h** gave a complex mixture of products. While the oxidation of the bis(aryl)methylene position with CAN has been reported [29], this is the first example of bis(heteroaryl)methylene oxidation employing this reagent [30]. In order to increase the local electron deficiency of the scaffold, **9a** was oxidized with 2-iodoxybenzoic acid (IBX) into ketone **10a** (98%), which presents an ideal push–pull configuration tunable with the pH by protonation of the pyridine ring. This is likely to lead to applications of **10a** such as for new water-soluble molecular probes.

Conclusion

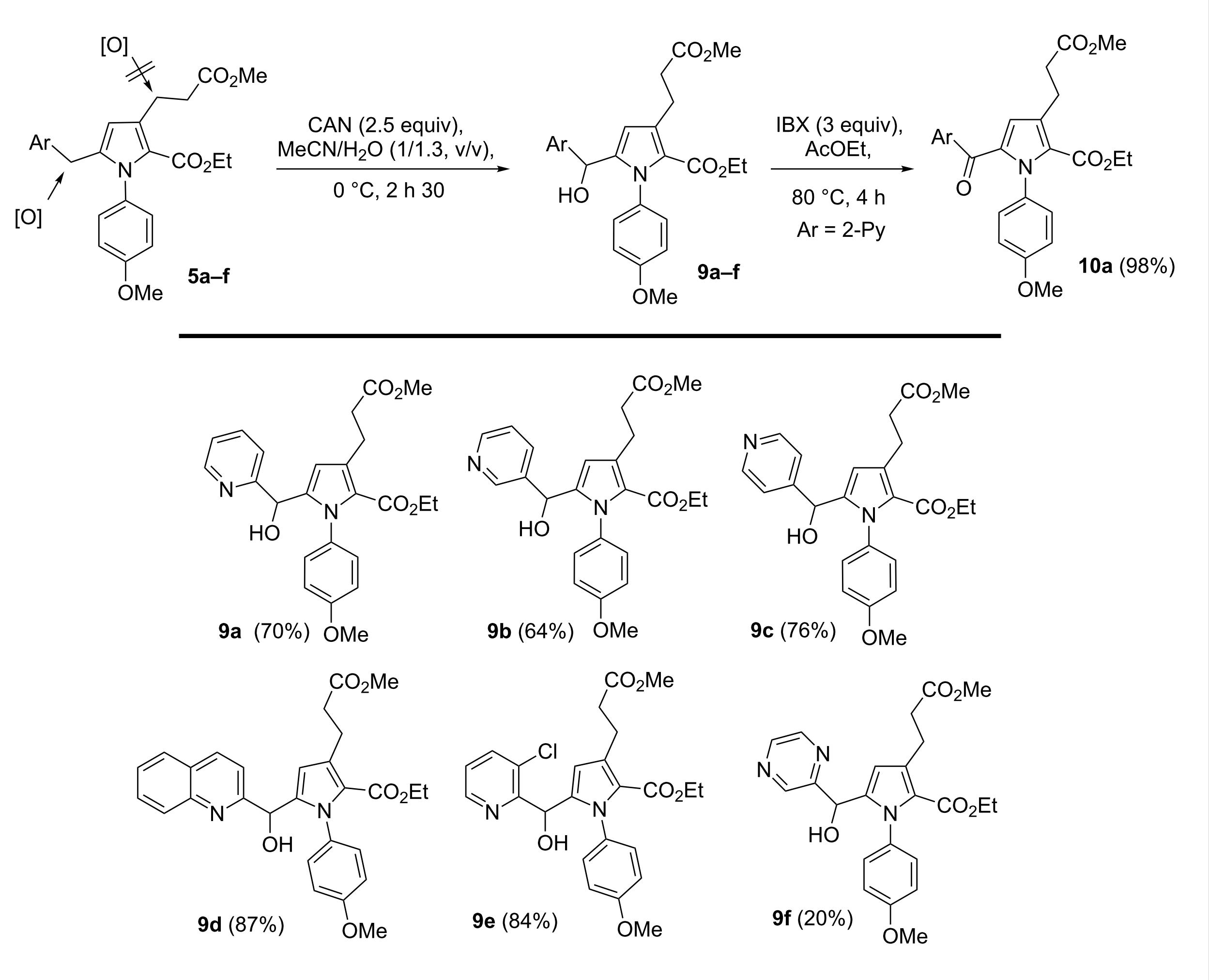
A new catalytic and regioselective preparation of substituted *N*-arylpyrroles decorated with various 2-heteroaromatic scaffolds is reported. Based on the isomerization of pyrrolidines prepared by a simple and efficient sequence of Mannich/Wittig olefination/hydroamination reactions, no oxidant or metallic salts were employed [31]. This study also led us to investigate the feasibility of this process with different anilines and enlarge the molecular diversity of the scaffold. So far the methodology is limited to electron-rich anilines due to the formation and reactivity of the corresponding imines and the stability of the Mannich adduct for the hydroamination step. However, this electronic configuration is ideal for the preparation of electron donor/acceptor *N*-arylpyrroles as demonstrated in this study. In addition, we documented an efficient C–H oxidation of the bis(heteroaryl)methylene position promoted by CAN.

Experimental

General: ^1H and ^{13}C NMR spectra were recorded in deuterated chloroform on Bruker Avance DPX 400 or 300 spectrometers and were referenced to residual chloroform (7.26 ppm, ^1H; 77.00 ppm, ^{13}C). Chemical shifts are expressed in parts per million (ppm). Data for ^1H are reported as follows: chemical



Scheme 5: Possible mechanism.



Scheme 6: Bis(heteroaryl)methylene oxidation of **5a–f**.

shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, sept = septuplet, m = multiplet), coupling constant (Hz), integration. Mass spectra and high-resolution mass spectra (HRMS) were obtained on a Waters-Micromass Q-Tof micro instrument. IR data were obtained on a PerkinElmer Spectrum 100 FTIR-spectrometer with only major peaks being reported. Thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} plates (0.1 mm, Merck). Visualization was accomplished with UV (254 nm) or $KMnO_4$ staining solutions. Chromatographic separations were achieved on silica-gel columns (Kieselgel 60, 40–63 µm, Merck).

Technical grade *N*,*N*-dimethylformamide and dichloromethane were used for this work. Following our procedure [13], catalyst **6** was prepared from (±)-1-benzyl-3-aminopyrrolidine [18471-40-4]. *N*-Arylimino ethyl glyoxylates **2a–c** were prepared by a condensation of ethyl glyoxylate and arylamines in toluene (*c* = 1 M) with $MgSO_4$ at room temperature. IBX (2-iodoxybenzoic acid) was prepared according to standard procedures.

Ethyl 3-(3-methoxy-3-oxopropyl)-1-(4-methoxyphenyl)-5-(pyridin-2-ylmethyl)-1*H*-pyrrole-2-carboxylate (5a): Representative procedure: In a flask containing a stirred solution of **4a** (432 mg, 1.02 mmol, 1.0 equiv) in CH_2Cl_2 (10.2 mL) at room temperature was introduced DBU (168 µL, 1.12 mmol). The mixture was allowed to react at this temperature for 1 h. Then, the volatiles were removed under reduced pressure and the crude was purified by flash column chromatography (CH_2Cl_2/MeOH 99:1) on silica gel to yield **5a** (432 mg, 99%) as an orange oil. ^1H NMR (300 MHz, $CDCl_3$) 1.08 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 2.65 (br t, *J* = 7.9 Hz, 2H), 3.11 (br t, *J* = 7.9 Hz, 2H), 3.67 (s, 3H), 3.81 (s, 3H), 3.83 (s, 2H), 4.06 (q, *J* = 7.1 Hz, 2H), 5.92 (s, 1H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 7.8 Hz, 1H), 6.98 (d, *J* = 8.8 Hz, 2H), 7.06 (m, 1H), 7.52 (td, *J* = 1.5, 7.8 Hz, 1H), 8.45 (d, *J* = 4.3 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 173.7, 160.8, 158.9, 158.4, 149.1, 137.6, 136.3, 132.4, 132.1, 128.8 (2*CH), 122.8, 121.3, 120.7, 113.5 (2*CH), 110.4, 59.3, 55.2, 51.3, 35.8, 34.9, 23.5, 13.9 ppm; IR: 2920, 1690, 1512, 1438, 1245, 1169, 1080, 910, 727

cm^{-1}; HRMS (ESI^+): $(M + H)^+$ calcd for $C_{24}H_{27}N_2O_5$, 423.1920; found, 423.1926; R_f 0.15 (CH_2Cl_2/MeOH 99:1).

Ethyl 5-(hydroxy(pyridin-2-yl)methyl)-3-(3-methoxy-3-oxopropyl)-1-(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (9a): Representative procedure: In a flask containing a well stirred solution of CAN (269 mg, 0.490 mmol, 3.0 equiv) in H_2O (3.1 mL) at 0 °C was introduced dropwise a solution of **5a** (69 mg, 0.164 mmol in 2.4 mL of CH_3CN) over 10 min. Then, the mixture was allowed to react at this temperature for 3 h and was quenched by the addition of an aqueous solution of $Na_2S_2O_3$ (1 M). The resulting mixture was extracted with AcOEt (3×), and the combined organic layers were washed with brine, dried over $MgSO_4$, and filtered. The volatiles were removed under reduced pressure to give 58 mg of the crude product, which was purified by flash column chromatography (CH_2Cl_2/MeOH 99:1) on silica gel to yield **9a** (49 mg, 71%) as an orange oil. ^1H NMR (300 MHz, $CDCl_3$) 1.08 (t, J = 7.1 Hz, 3H, $OCH_2\mathit{CH_3}$), 2.60 (br t, J = 7.9 Hz, 2H), 3.06 (m, 2H), 3.64 (s, 3H), 3.82 (s, 3H), 4.06 (q, J = 7.1 Hz, 2H), 5.43 (s, 1H), 5.85 (s, 1H), 6.87 (ddd, J = 2.8, 8.6, 11.4 Hz, 2H), 7.05 (d, J = 7.8 Hz, 1H), 7.08–7.22 (m, 3H), 7.61 (dt, J = 1.6, 7.8 Hz, 1H), 8.45 (d, J = 4.8 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 173.7 (Cq), 160.9 (Cq), 159.1 (Cq), 158.9 (Cq), 147.7 (CH), 141.0 (Cq), 136.6 (CH), 132.0 (Cq), 131.7 (Cq), 129.4 (2*CH), 122.6 (CH), 121.7 (Cq), 121.3 (CH), 113.6 (CH), 113.4 (CH), 110.1 (CH), 67.1 (CH), 59.6 (CH_2), 55.4 (CH_3), 51.4 (CH_3), 35.0 (CH_2), 23.5 (CH_2), 13.9 (CH_3) ppm; IR: 3375, 2927, 1733, 1688, 1512, 1436, 1368, 1295, 1081, 1030, 999, 834, 753 cm^{-1}; HRMS (ESI^+): $(M + H)^+$ calcd for $C_{24}H_{27}N_2O_6$, 439.1869; found, 439.1886; R_f 0.1 (CH_2Cl_2/MeOH 9:1).

Ethyl 3-(3-methoxy-3-oxopropyl)-1-(4-methoxyphenyl)-5-picolinoyl-1*H*-pyrrole-2-carboxylate (10a): A solution of **9a** (26 mg, 0.0593 mmol) in AcOEt (0.6 mL) was treated with IBX (50 mg, 0.178 mmol, 3 equiv). The suspension was stirred at 80 °C for 4 h before being brought to rt and filtered. Evaporation of the volatile led to analytically pure **10a** which can be further purified by flash chromatography (CH_2Cl_2/MeOH 99.3:0.7) to yield 24 mg of **10a**. ^1H NMR (400 MHz, $CDCl_3$) 1.10 (t, J = 7.1 Hz, 3H), 2.69 (br t, J = 7.8 Hz, 2H), 3.14 (br t, J = 7.8 Hz, 2H), 3.67 (s, 3H), 3.82 (s, 3H), 4.11 (q, J = 7.1 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 8.8 Hz, 2H), 7.21 (s, 1H), 7.41–7.46 (ddd, J = 1.3, 4.7, 6.1 Hz, 1H), 7.80 (dt, J = 1.6, 7.7 Hz, 1H), 7.86 (br d, J = 7.7 Hz, 1H), 8.68 (d, J = 4.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 182.9 (Cq), 173.5 (Cq), 160.7 (Cq), 159.1 (Cq), 155.4 (Cq), 148.3 (CH), 136.9 (CH), 133.3 (Cq), 133.0 (Cq), 130.6 (Cq), 128.5 (2*CH), 127.8 (Cq), 126.2 (CH), 124.0 (CH), 123.0 (CH), 113.3 (2*CH), 60.5 (CH_2), 55.3 (CH_3), 51.5 (CH_3), 34.9 (CH_2), 23.2 (CH_2), 13.8 (CH_3) ppm; IR: 2952, 1716, 1647, 1511, 1437, 1335, 1230, 1164, 1085, 831, 746, 689 cm^{-1}; HRMS (ESI^+): $(M + H)^+$ calcd for $C_{24}H_{25}N_2O_6$; 437.1713; found, 437.1700; R_f 0.25 (CH_2Cl_2/MeOH 99:1).

Supporting Information

Supporting Information File 1

Physical and spectroscopic data of **5b–j**, **9b–e** and ^1H and ^{13}C spectra of all new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-168-S1.pdf]

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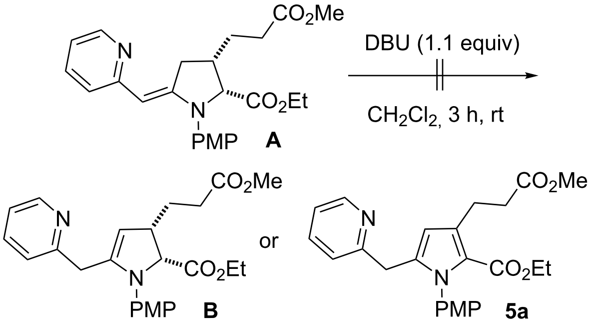
26. No reaction occurred when **A** was exposed to DBU under an argon atmosphere. When the experiment was conducted under an air atmosphere, pyrroline **B** or pyrrole **5a** were not observed but degradation occurred after 24 h. These experiments point to the deconjugation of the acrylate moiety as the first step.



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Beilstein Journal of Organic Chemistry

A reductive coupling strategy towards ripostatin A

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Full Research Paper

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Guest Editors: D. Y.-K. Chen and D. Ma

Abstract

Synthetic studies on the antibiotic natural product ripostatin A have been carried out with the aim to construct the C9−C10 bond by a nickel(0)-catalyzed coupling reaction of an enyne and an epoxide, followed by rearrangement of the resulting dienylcyclopropane intermediate to afford the skipped 1,4,7-triene. A cyclopropyl enyne fragment corresponding to C1−C9 has been synthesized in high yield and demonstrated to be a competent substrate for the nickel(0)-catalyzed coupling with a model epoxide. Several synthetic approaches toward the C10−C26 epoxide have been pursued. The C13 stereocenter can be set by allylation and reductive decyanation of a cyanohydrin acetonide. A mild, fluoride-promoted decarboxylation enables construction of the C15−C16 bond by an aldol reaction. The product of this transformation is of the correct oxidation state and potentially three steps removed from the targeted epoxide fragment.

Introduction

The ripostatins (A, B, and C) are a family of antibiotic natural products, isolated in 1995 by Höfle and colleagues from cultures of the myxobacterium *Sorangium cellulosum* (Figure 1) [1,2]. Ripostatins A and B are active against Gram-positive bacteria due to their inhibition of bacterial ribonucleic acid polymerase. These compounds inhibit chain initiation of RNA synthesis in *Staphylococcus aureus,* a particularly infectious bacterial strain with reported drug resistance to the antibiotics vancomycin and methicillin [3]. Ripostatin A exists as an equilibrium mixture of ketone and hemiketal forms, the ratio of which is reported to be 55:45 in methanolic solution. In the hemiketal form, the bicyclic framework of ripostatin A features an unusual *in*/*out* connectivity. The 14-membered macrocyclic core of ripostatin A contains three double bonds, arranged in a rare 1,4,7-skipped triene. The alkene geometry was determined to be (2*E*,5*E*,8*E*) by measurement of NOE enhancements [4].

Ripostatin B and its C15 epimer can be obtained from ripostatin A by reduction with sodium borohydride, while ripostatin C can be formed from ripostatin A by a mild base-mediated elimination. Consequently, ripostatin A was selected as the primary target for synthesis.

At the outset of our efforts, the only published synthetic study on the ripostatins was Kirschning's synthesis of C1−C5 and C6−C24 fragments of ripostatin B [5]. However, these fragments could not be connected by esterification due to steric hindrance from bulky protecting groups, as well as susceptibility of the skipped dienes therein to double bond isomerization and migration under basic conditions. However, the ripostatins intrigued others, and three total syntheses of ripostatin B were published in succession in 2012 [6-8]. Tang and Prusov extended their synthetic method to syntheses of 15-deoxyripostatin A, and later ripostatin A itself [9]. All of these approaches to the ripostatins share several key features: use of ring-closing metathesis to form the 14-membered macrocycle, preceded by one or more Stille couplings to generate the double 1,4-diene (Figure 2).

Notwithstanding the successful syntheses of ripostatins, preparation of configurationally defined skipped polyenes (1,4-dienes and higher homologues) remains a significant challenge in organic chemistry. The doubly allylic protons found in these structures may be sensitive to strong base as well as hydrogen abstraction [10,11]. While classical methods for the preparation of 1,4-dienes include partial reduction of alkynes and carbonyl olefination, a variety of transition-metal-mediated processes have been developed for the synthesis of skipped dienes of varied substitution patterns [12-15]. Most recently, Sigman and colleagues have reported a palladium-catalyzed 1,4-difunctionalization of 1,4-butadiene with vinylboronic acid and vinyl triflate that can be used to rapidly access the skipped triene of ripostatin A [16].

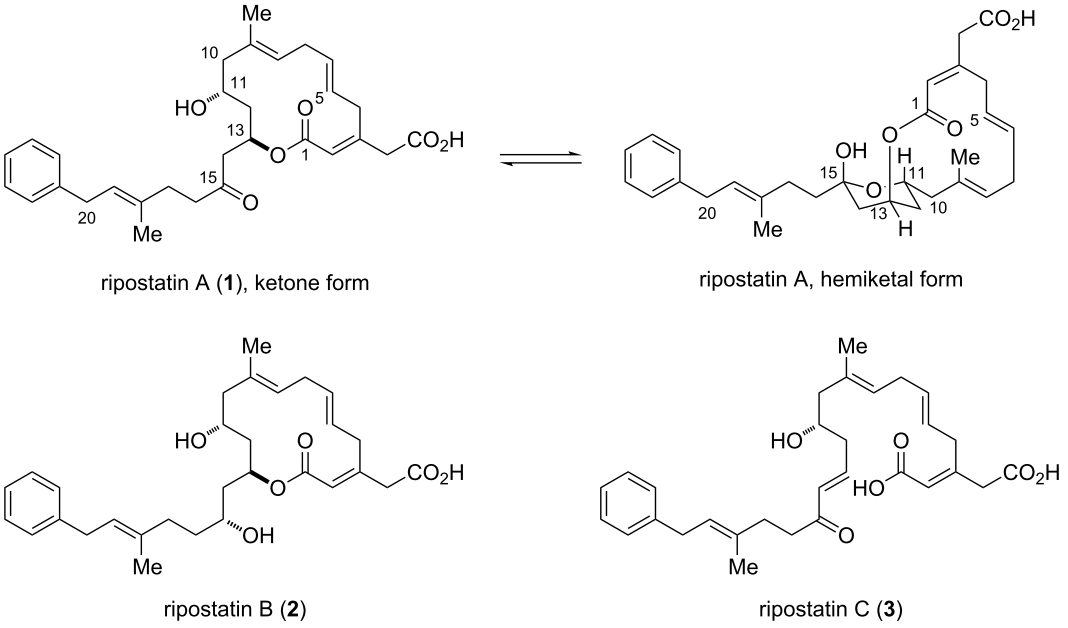


Figure 1: Structures of the ripostatins.

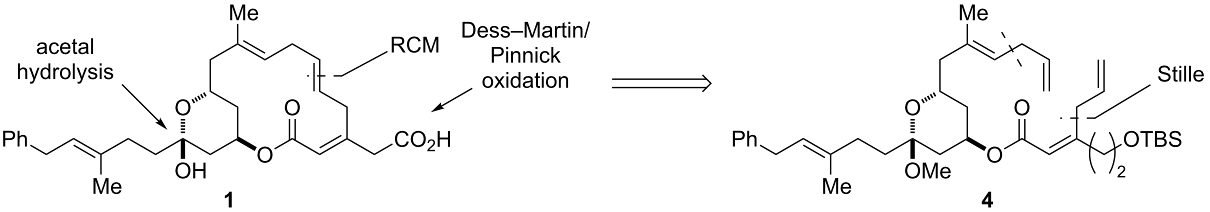
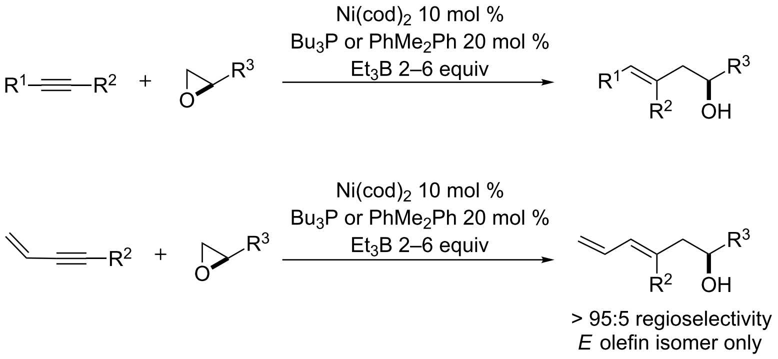


Figure 2: Retrosynthesis of ripostatin A.

We recognized that the C11 stereocenter and the C8–C9 trisubstituted olefin of ripostatin A mapped onto a nickel-catalyzed coupling reaction of alkynes and epoxides developed in our laboratory (Scheme 1) [17]. In the intermolecular reaction, stereospecific *cis* addition across the alkyne is observed, and the stereochemistry at the epoxide is preserved in the transformation. Aliphatic epoxides are opened selectively (>95:5) at the terminal position. Although very high regioselectivity with respect to the alkyne is observed when R^1 = Ph and R^2 = Me, attempts to differentiate between aliphatic alkyne substituents lead to mixture of regioisomers. When a 1,3-enyne is coupled with simple epoxides, however, >95:5 regioselectivity is observed for C–C bond formation distal to the pendant alkene [18].

In conjunction with the nickel-catalyzed fragment coupling, we wished to investigate whether it would be possible to delay introduction of the potentially sensitive 1,4,7-triene by masking it as a cyclopropyldiene, then unveiling the skipped triene portion via a 1,5-hydrogen rearrangement (Figure 3). This strategy would allow us to take advantage of the high regioselectivity in enyne–epoxide reductive coupling reactions. Furthermore, the proposed rearrangement would serve to differentiate the ester groups, as hydrogen would migrate from adjacent to the ester *cis* to the dienyl chain only.

While offering a unique approach to the skipped triene portion of ripostatin, this route was not without significant uncertainty. First, substrates containing a vinyl cyclopropane unit had not been previously tested under nickel-catalyzed reductive coupling conditions. Nickel(0) is known to catalyze the rearrangement of vinylcyclopropanes to cyclopentenes; however, activating substituents are commonly required [19-21]. Furthermore, application of a proposed 1,5-hydrogen rearrangement to ripostatin A would require that the reaction proceed to give the triene with *E,E,E* configuration selectively out of four possible configurational outcomes (Scheme 2).



Scheme 1: Nickel-catalyzed reductive coupling of alkynes and epoxides.

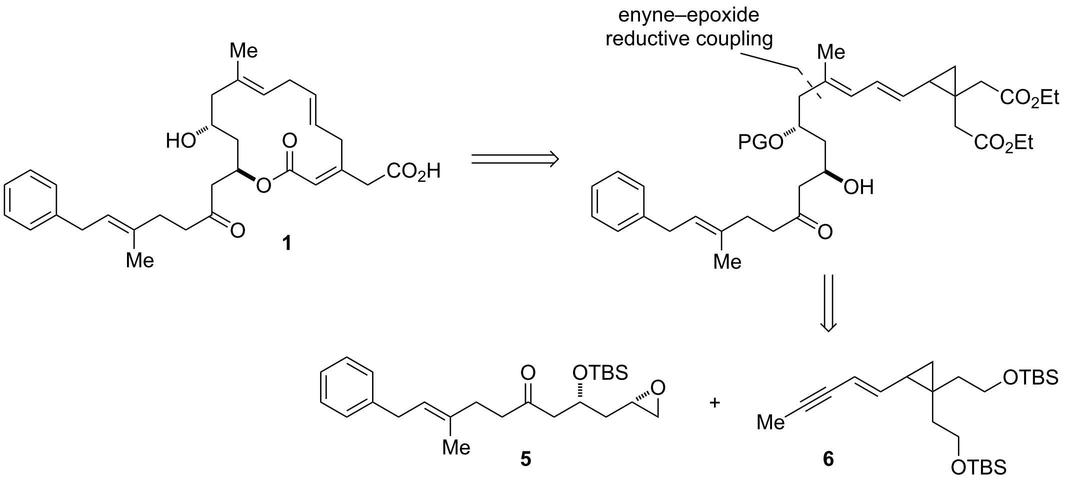
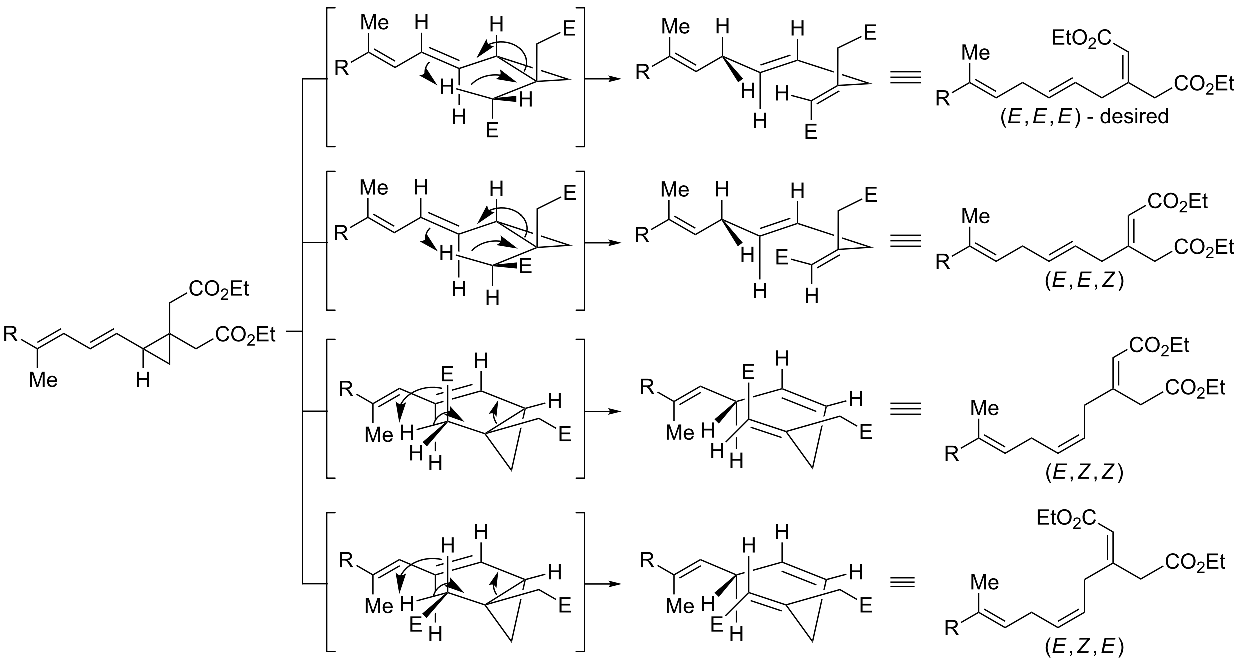


Figure 3: Proposed retrosynthesis of ripostatin A featuring enyne–epoxide reductive coupling and rearrangement.



Scheme 2: Potential transition states and stereochemical outcomes for a concerted 1,5-hydrogen rearrangement.

Rearrangement of vinylcyclopropanes has been used to prepare 1,4-skipped dienes of varying geometry (Scheme 3). It has long been known that *cis*-disubstituted vinylcyclopropanes can undergo 1,5-hydrogen migration under thermal conditions to deliver acyclic 1,4-dienes [22]. In this reaction manifold, the new "acceptor-derived" double bond is formed via an endo transition state, leading to a *cis* olefinic configuration in the product (Scheme 3, reaction 1). Berson has quantified the energetic preference in this transformation, while Turos has shown that the presence of a silicon substituent on the "donor carbon" facilitates the hydrogen migration [23-26].

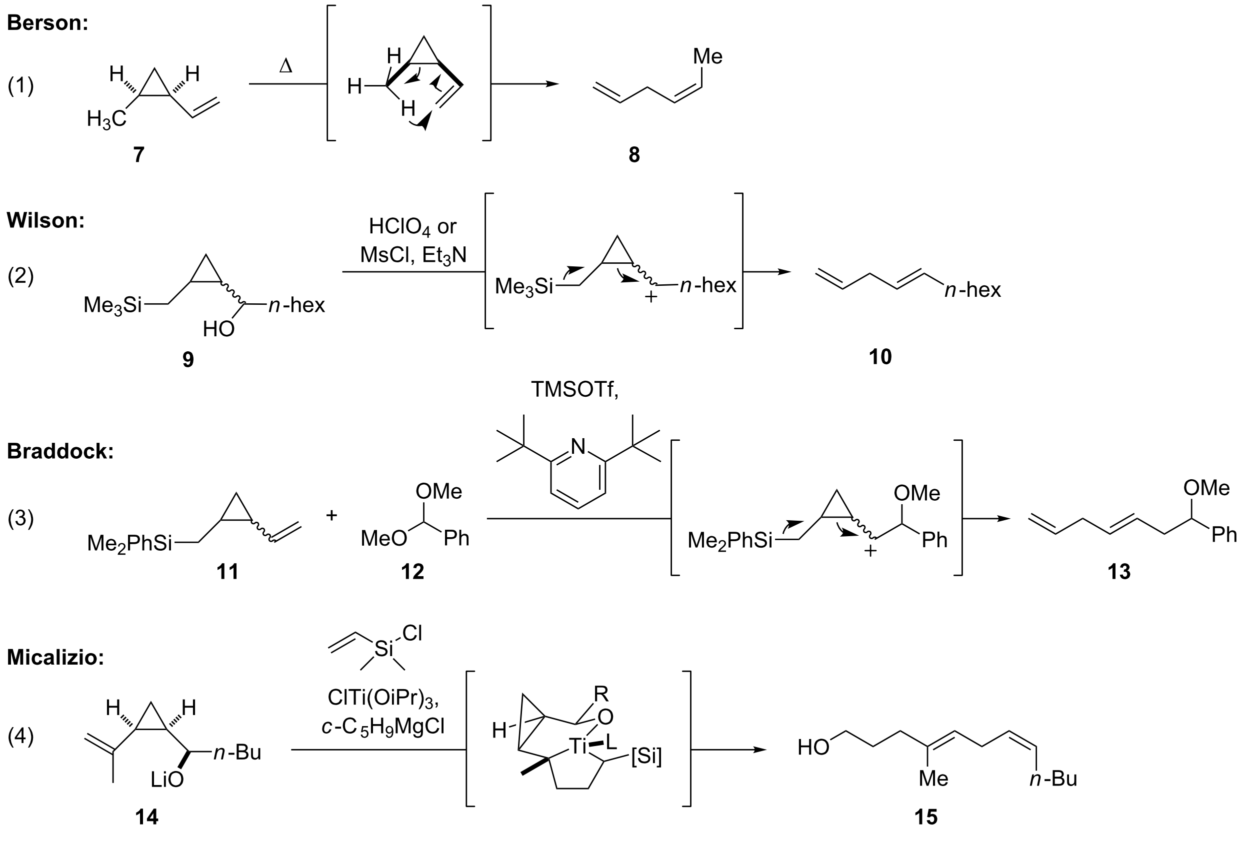
In contrast, Wilson has reported formation of the *trans* double bond in the opening of a cyclopropane with an adjacent hydroxy or mesylate leaving group, regardless of the initial configuration of the cyclopropane (Scheme 3, reaction 2) [27]. Braddock has demonstrated that the internal 3,4-*E* olefin is obtained exclusively in Prins reactions terminated by cyclopropylmethylsilane (Scheme 3, reaction 3), which may be explained by the participation of a carbocation that is stabilized by the adjacent cyclopropane ring in the bisected conformation where (CHOR)R′ is oriented *anti* to the cyclopropane [28-30]. Finally, Micalizio has described a titanium-mediated, alkoxide-directed fragment coupling reaction between vinylcylopropanes and vinyldimethylchlorosilane (Scheme 3, reaction 4) in which the stereochemical outcome of the rearrangement is orchestrated by the adjacent alkoxide, which is believed to direct formation of a tricyclic titanacyclopentane that subsequently fragments in a stereospecific manner [31].

We were intrigued by the apparent difference in selectivity observed in cyclopropane rearrangements proceeding via a neutral pathway versus those proceeding by more polar or directed mechanisms. Although the *E* geometry of the central olefin in the ripostatin A triene is more consistent with a polar mode of reactivity than a neutral 1,5-hydrogen migration, we still wished to investigate the outcome of rearrangement under thermal conditions. To the best of our knowledge, such a rearrangement has not been explored for structures containing an additional alkenyl substituent in conjugation, or with electron-withdrawing groups adjacent to the site of hydrogen migration. In particular, the latter's ability to facilitate the buildup of negative charge at an adjacent carbon might play an important role in the stereoelectronic course of the reaction.

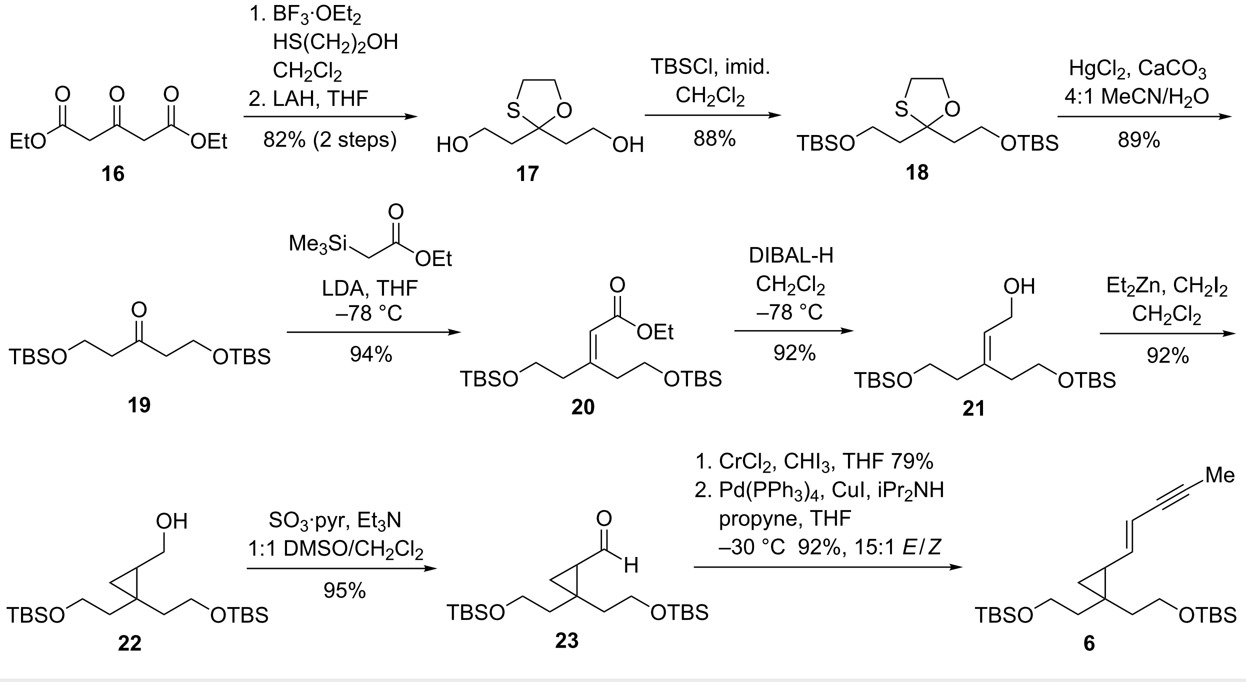
Results and Discussion

Synthesis of cyclopropylenyne and reductive coupling with model epoxide

Diethyl 1,3-acetonedicarboxylate (Scheme 4, **16**) was rapidly identified as an inexpensive five-carbon fragment possessing the appropriate oxygenation pattern for preparation of the C1–C9 enyne fragment. However, due to keto–enol tautomer-



Scheme 3: Rearrangements of vinylcyclopropanes to acylic 1,4-dienes.



Scheme 4: Synthesis of cyclopropyl enyne.

ization, carbonyl olefination methods are of limited utility for this substrate. Instead, the ketone was protected as the mixed *S*,*O*-ketal and reduced to the diol **17**. Protection of the hydroxy groups and removal of the ketal afforded ketone **19**. A number of alternative promoters were investigated to avoid the use of mercury(II) salts in the ketal deprotection (including MeI, H_2O_2, $AgClO_4/I_2$); however, these generally led to concomitant removal of the TBS groups.

Ketone **19** was converted to the α,β-unsaturated ester **20** using the Peterson olefination [32]. Treatment of **20** with the sulfur ylide derived from trimethylsulfoxonium iodide [33,34] led to recovery of starting material at room temperature, but decomposition at elevated temperatures. Instead, the enone was smoothly reduced to the allylic alcohol, and a Furukawa-modified Simmons–Smith reaction [35] afforded the cyclopropyl alcohol **22** in high yield.

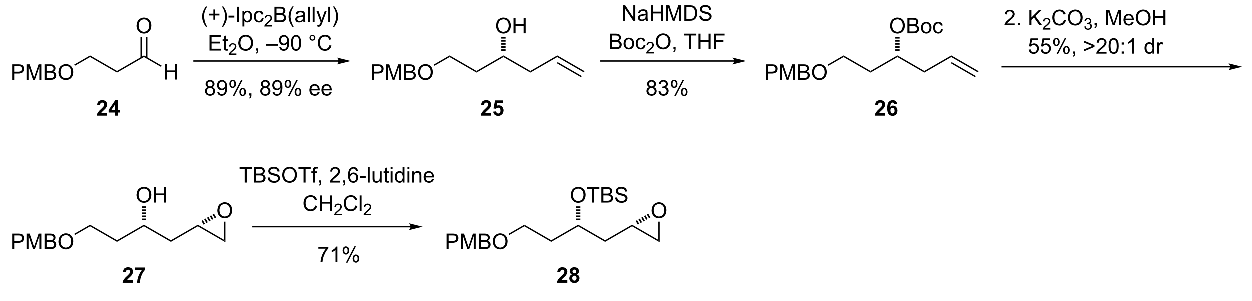
Oxidation to the cyclopropyl aldehyde **23** offered a branching point from which either the *E*- or *Z*-substituted enyne could be synthesized, should we wish to study the rearrangement of both diene geometries. To access our initial target, the *E*-enyne **6**, a Takai olefination [36] was used to generate the *E*-vinyl iodide. The vinyl iodide was sufficiently stable for purification by silica gel chromatography but, following purification, was immediately carried forward to a Sonogashira reaction with propyne [37]. The enyne could be obtained in 15:1 *E*/*Z* selectivity, in 10 steps and 35% overall yield. It was found that the use of freshly distilled THF in the Takai olefination and careful temperature control in the subsequent cross coupling were critical to the preservation of high *E*/*Z* selectivity over the course of these transformations. Once isolated, however, enyne **6** proved to be quite stable and could be stored for extended periods at 0–5 °C without appreciable isomerization or decomposition.

With a suitable cyclopropylenyne in hand, a model epoxide substrate containing the 1,3-oxygenation pattern found in ripostatin A (Scheme 5) was prepared by using a route analogous to one reported by Smith [38]. Allylation of **24** with (+)-*B*-allyldiisopinocampheylborane generated the alcohol **25** in high yield and enantioselectivity. Directed epoxidation using $VO(acac)_2$ and *tert*-butyl hydroperoxide was initially performed in order to furnish **27** directly; however, this proceeded in only modest yield and diastereoselectivity (53%, 2.8:1 *syn*/*anti*). Although the ratio of *syn*/*anti* epoxide diastereomers could be enhanced by subjecting the mixture to hydrolytic kinetic resolution [39], greater throughput could be obtained by converting **25** to the *tert*-butyl carbonate, performing an iodocyclization, then cleaving the iodocarbonate and closing the epoxide under basic conditions. Silyl protection of the secondary alcohol afforded the desired model compound **28**.

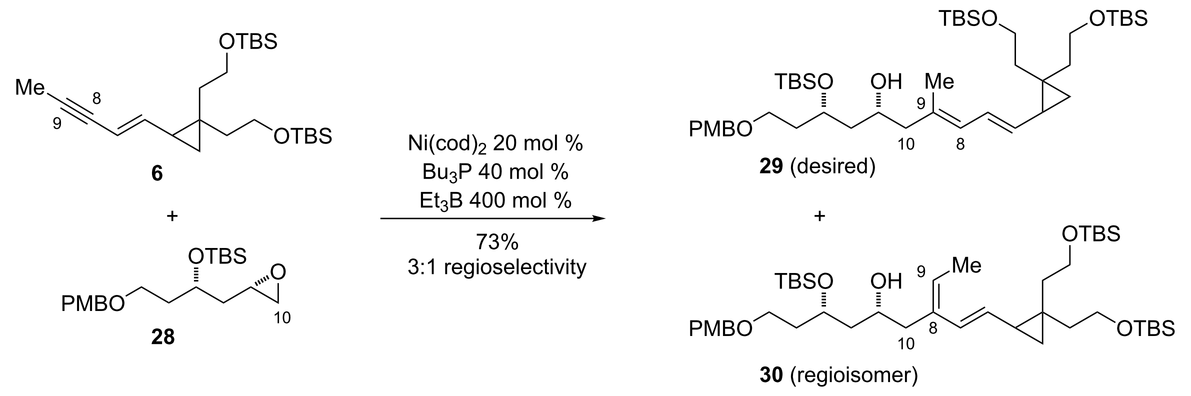
Enyne **6** and epoxide **28** were subjected to standard nickel-catalyzed reductive coupling conditions, and reductive coupling proceeded in good yield, leaving the cyclopropane ring intact (Scheme 6). However, the desired diene **29** was isolated along with the regioisomeric product **30** in approximately a 3:1 ratio. The desired product could be partially separated from the regioisomer by careful silica gel chromatography.

It may be instructive at this stage to consider the proposed mechanism of the nickel-catalyzed alkyne or enyne–epoxide reductive coupling reaction (Scheme 7). In contrast to the mechanistic framework proposed [40,41] for reductive coupling reactions of alkynes and aldehydes developed in our laboratory [42,43], it is believed that epoxide oxidative addition precedes alkyne addition, as opposed to concerted oxidative coupling. At least when dimethylphenylphosphine is used as ligand, this may proceed via the intermediacy of a betaine species. In the reductive coupling reaction of enynes and epoxides, the olefin coordinates to nickel and directs alkyne insertion.

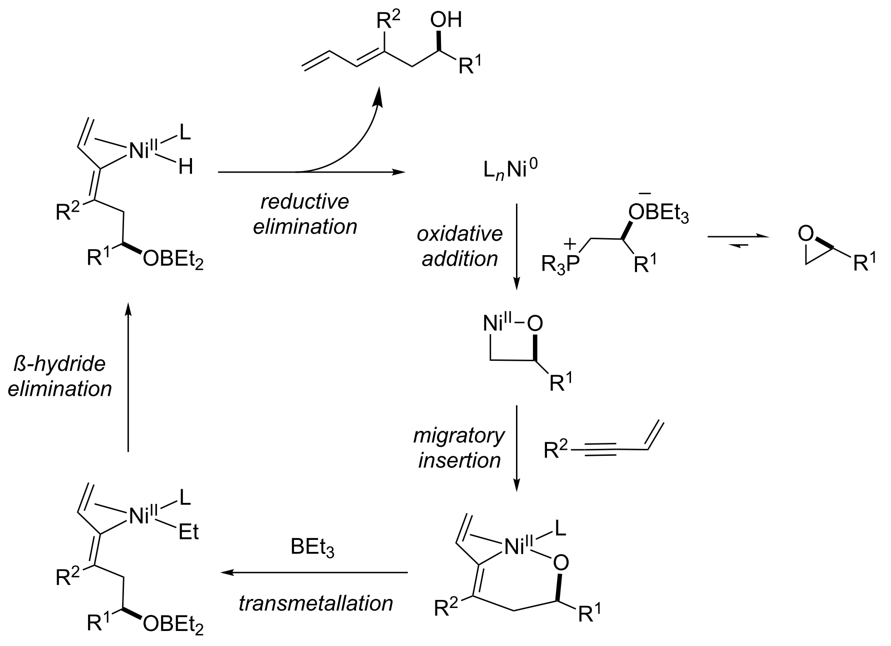
Because of this directing effect, formation of the regioisomeric diene product is atypical for reductive coupling reactions of enynes and epoxides. However, in reactions of 1-phenyl-1-propyne and epoxides with oxygenation in the 3-position



Scheme 5: Synthesis of model epoxide for investigation of the nickel-catalyzed coupling reaction.



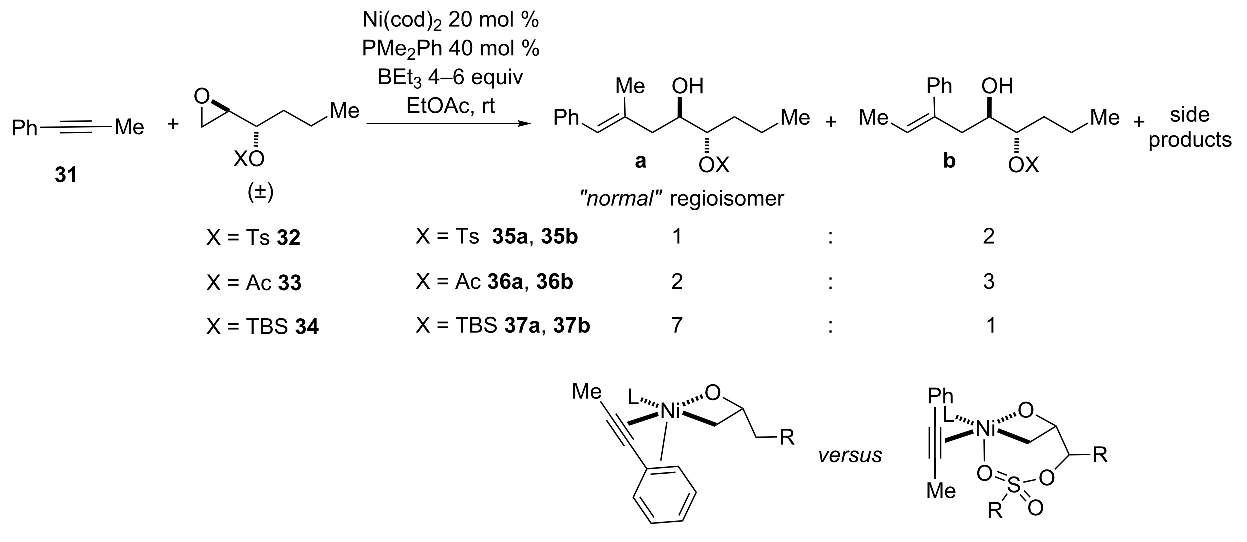
Scheme 6: Nickel-catalyzed enyne–epoxide reductive coupling reaction.



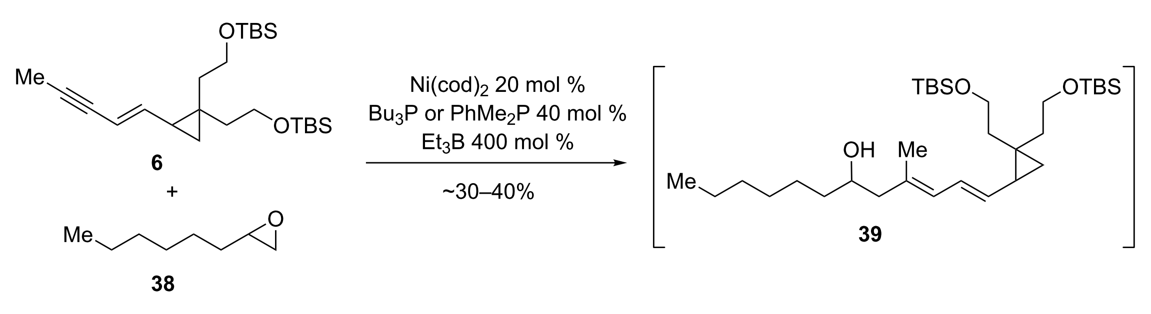
Scheme 7: Proposed mechanism for the nickel-catalyzed coupling reaction of alkynes or enynes with epoxides.

(Scheme 8), it was found that while epoxides containing adjacent silyl ethers afforded mainly the expected regioisomer (7:1 **37a**/**37b**), epoxides with sulfonate esters (e.g., tosyl, **32**) and esters (e.g., acetyl, **33**) afforded a regioisomeric mixture of opposite (albeit poor) selectivity relative to that normally observed for unfunctionalized epoxides [44]. This is proposed to be an effect of the coordinating ability of Lewis basic oxygen atoms in tosylates and esters, which may disrupt the binding and directing effect of phenyl or alkenyl groups.

In the case of the ripostatin A model system, the most likely candidate for chelation is the oxygen protected as the PMB ether. Although an eight-membered chelate might seem too large to play an important role in directing regioselectivity, the 3:1 regioselectivity observed in the "normal" direction is consistent with chelation playing a diminished role relative to the seven-membered chelates invoked for coupling of 3-oxygenated epoxides. We attempted to discern whether this interaction was the reason for the observed regioselectivity by performing the nickel-catalyzed coupling reaction with 1,2-epoxyoctane, which lacks potentially chelating functional groups (Scheme 9). Although the coupling product **39** appears to be formed in the reaction with either Bu_3P or $PhMe_2P$ as ligand, the non-polar nature of this molecule complicates chromatographic purification, and mixtures of what appears to be **39** along with one or more other products were obtained. Based on these results, regioisomer formation cannot be excluded.



Scheme 8: Regioselectivity changes in reductive couplings of alkynes and 3-oxygenated epoxides.



Scheme 9: Enyne reductive coupling with 1,2-epoxyoctane.

Several aspects of the enyne synthesis and the nickel-catalyzed coupling reaction require further investigation. As **6** does not itself appear to undergo thermal rearrangement, it seems advantageous to convert this compound to the corresponding diester. Preliminary investigation indicates that oxidation of the diol derived from **6** is complicated by the 1,5-relationship of the alcohols. Despite the greater complexity inherent to this alternative, differentiation of the alcohols allowing for sequential oxidation may be necessary.

Dithiane approach to epoxide

With respect to the synthesis of the proposed epoxide fragment **5**, we initially envisioned using the reaction of lithiated dithianes with epoxides (Figure 4) [45-49]. We reasoned that **41**

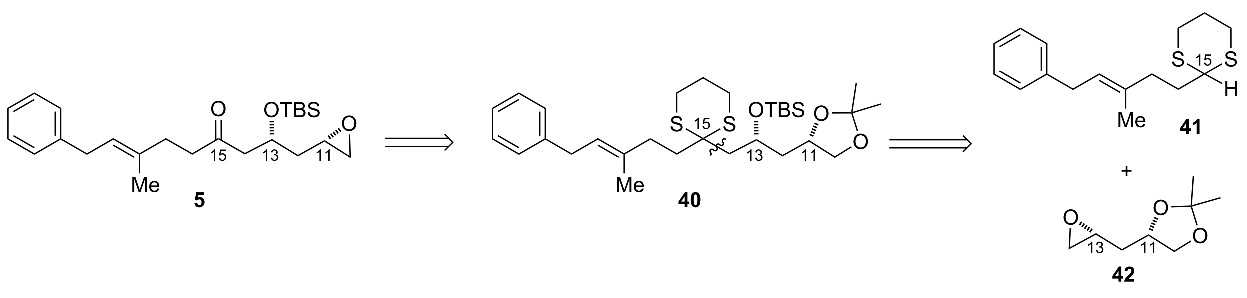


Figure 4: Initial retrosynthesis of the epoxide fragment by using dithiane coupling.

could be expediently accessed from the corresponding aldehyde by making use of a Claisen rearrangement to set the geometry of the γ,δ-unsaturated double bond.

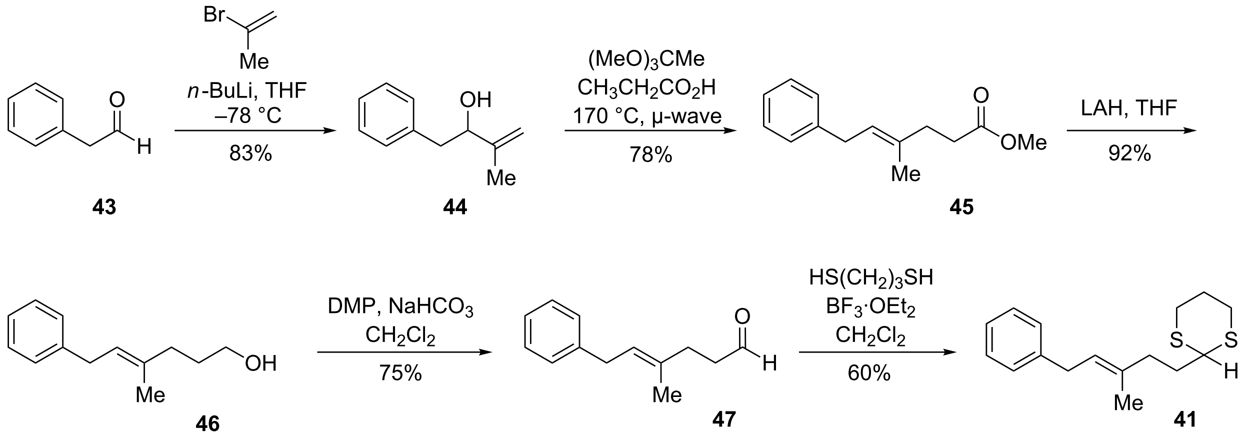
In the forward direction, the allylic alcohol **44** was obtained from reaction of the alkenyllithium reagent derived from 2-bromopropene with phenylacetaldehyde (Scheme 10). In our hands, the organolithium afforded significantly higher and more reproducible yields than either the commercially available Grignard reagent or the organocerium. Johnson–Claisen rearrangement [50] of **44** proceeded smoothly to give the γ,δ-unsaturated ester **45**. Conducting the reaction without added solvent in a microwave reactor at 170 °C allowed the reaction to proceed in just 30 minutes; a significant improvement over heating the reaction mixture in toluene under reflux, which typically required 48 hours to obtain a comparable yield. Reduction and oxidation afforded the aldehyde **47**, which could then be converted to dithiane **41**.

Unfortunately, attempts to couple **41** with an oxygenated epoxide fragment under a variety of conditions reported by Smith for lithiation and electrophilic trapping [51] were unsuccessful. We suspected that the lithiated dithiane was not being generated and decided to investigate this step of the reaction independently of reaction with the epoxide electrophile. To this end, **41** was treated with *tert*-butyllithium at –78 °C in a 90:10 THF/HMPA mixture, referred to as the method of first choice for lithiation of complex dithianes (Scheme 11). Following warming to –42 °C, the reaction was quenched with deuterated methanol. Analysis of the product by ^{1}H NMR revealed that no deuterium incorporation (to the sensitivity of integration) had occurred at the desired dithiane site, while approximately 80% deuterium incorporation had occurred at the allylic/benzylic site.

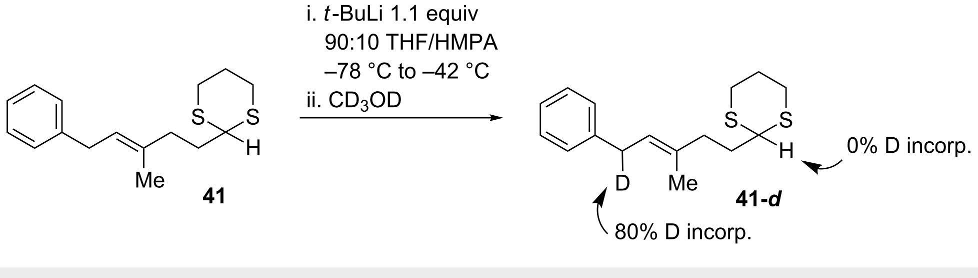
These results indicated that the presence of the trisubstituted C18–C19 olefin would interfere with dithiane coupling. However, given the suitability of the Claisen rearrangement for formation of this bond, we wished to preserve that transformation. Accordingly, an alternate route that would capitalize on the electrophilic nature of aldehyde **47** to form the bond corresponding to C14–C15 of ripostatin A instead was sought.

Oxy-Michael approach to epoxide

We were intrigued by a recent report by Falck describing an organocatalytic oxy-Michael addition to achiral δ-hydroxy-α,β-



Scheme 10: Synthesis of dithiane by Claisen rearrangement.



Scheme 11: Deuterium labeling reveals that the allylic/benzylic site is most acidic.

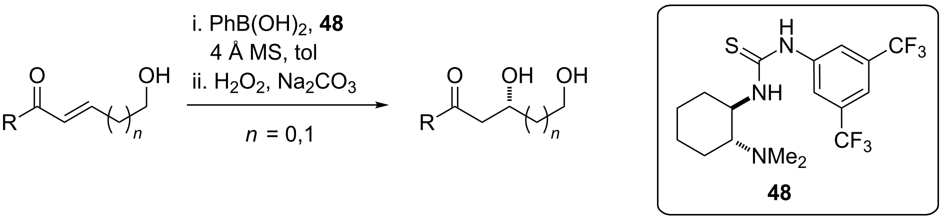
enones (Scheme 12) [52]. The hydroxy group is delivered in a directed fashion from the boronic acid hemiester generated in situ from the substrate and phenylboronic acid. It is proposed that complexation of the tertiary nitrogen to boron and coordination of the carbonyl act in a push/pull fashion, simultaneously enhancing the nucleophilicity of the boronate oxygen as well as imposing a chiral environment around the enone. Aliphatic enones react more sluggishly in this transformation; however, 3,4,5-trimethoxyphenylboronic acid may be used as a more efficient nucleophilic partner to circumvent this limitation.

Application of this transformation to the ripostatin A epoxide fragment **5** allows installation of the C13 hydroxy group via conjugate addition to the δ-hydroxy-α,β-enone **49** (Figure 5). Although the diastereoselectivity of this reaction using substrates with a chiral center at the hydroxy group had not been investigated in the published study, substitution at the carbinol position was reportedly well tolerated for the reaction using γ-hydroxy-α,β-enones. Although the presence of chirality at the δ-position allows for diastereoselective intramolecular oxy-Michael addition of hemiacetal-derived alkoxides into α,β-unsaturated esters, the extension of this reaction to ketones was not successful [53]. In turn, we intended to prepare **49** by hydrometalation of **50** and addition into aldehyde **47**.

To this end, (*R*)-glycidol was protected as the *para*-methoxybenzoate ether to give the PMB glycidol **52** (Scheme 13), in which the configuration is now assigned as (*S*). Opening the epoxide of **52** with the ethylenediamine complex of lithium acetylide in a 1:1 THF/DMSO solvent mixture at 0 °C allowed the terminal alkyne to be accessed in 84% yield without rearrangement to the internal alkyne. Silyl protection afforded alkyne **50**, which was prone to decomposition upon extended storage, even at −20 °C.

Hydrozirconation of alkyne **50** with Schwartz's reagent [54,55] was followed by transmetallation to zinc and nonselective addition into aldehyde **47**. Oxidation of the resulting allylic alcohol mixture afforded the enone **53**. Prior to the key oxy-Michael addition, it was necessary to remove the *tert*-butyldimethylsilyl protecting group. Use of TBAF under buffered (acetic acid) or unbuffered conditions proved sluggish and somewhat low-yielding, typically ~50%. Various other promoters led to decomposition ($BF_3{\cdot}OEt_2$) or low conversion (CsF); however, a modest improvement in yield was noted with the use of 1% HCl in MeOH (with a small amount of THF to dissolve the starting material).

The oxy-Michael addition with chiral thiourea and phenylboronic acid proceeded to give a single diastereomer; however, after 48 h at 50 °C, only 17% of the *syn* diol was formed, and 56% of the starting material was re-isolated. Under the modified conditions for less reactive aliphatic aldehydes using 3,4,5-trimethoxyphenylboronic acid, we were unable to isolate the desired diol from the reaction mixture. Since the oxy-Michael substrate derived from **53** contains an existing stereocenter at the directing hydroxy group, we also attempted to carry out the



Scheme 12: Oxy-Michael addition to δ-hydroxy-α,β-enones.

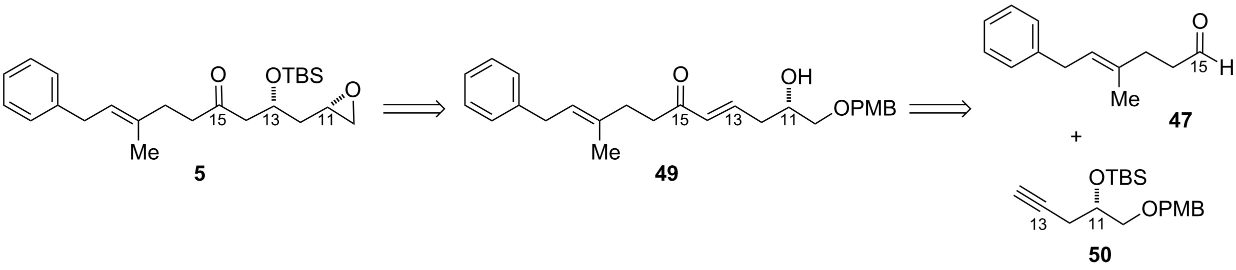
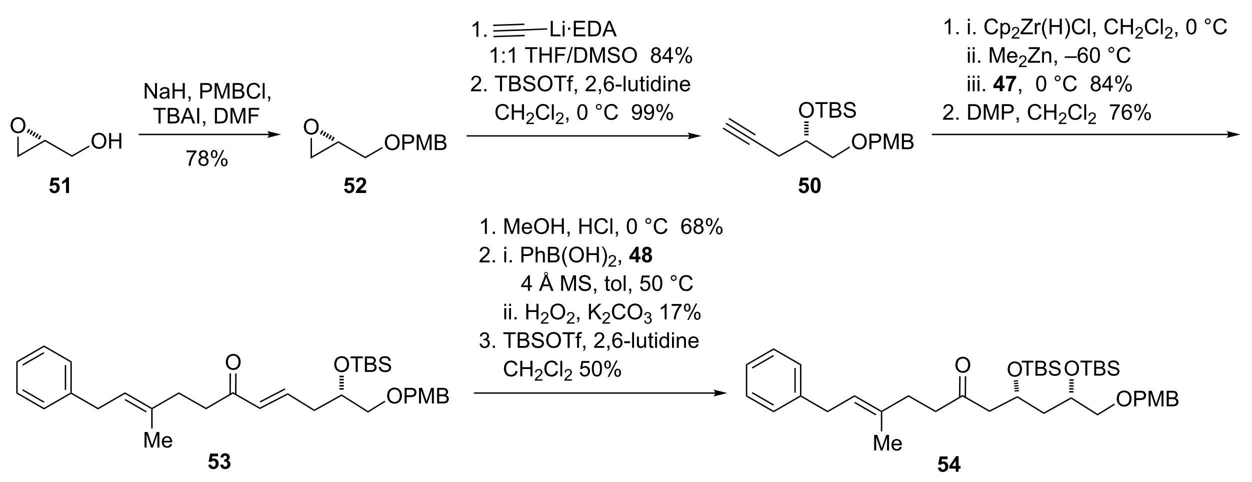


Figure 5: Revised retrosynthesis of epoxide **5**.



Scheme 13: Synthesis of functionalized ketone by oxy-Michael addition.

reaction with diisopropylamine as a substitute for the thiourea catalyst. This modification afforded both the *syn* and *anti* diols in roughly a 1:1 ratio and a combined yield of 40–45%, albeit without recovery of starting material. The *syn* and *anti* diastereomers could be separated by repeated silica gel chromatography, and the desired *syn* diol was converted to the bis-silylated compound **54**.

However, attempted oxidative deprotection of the PMB ether of **54** with DDQ led to destruction of the material. It seems likely that this is again due to the presence of the allylic/benzylic site in the molecule, although no individual decomposition products could be identified. Although it is possible that further screening of deprotection conditions might have allowed us to move forward with this route, the modest yields and long reaction time of the oxy-Michael addition severely limited material throughput. In order to proceed with the synthesis, we needed a more robust route, with the following criteria: (1) no protecting groups requiring oxidative cleavage, and (2) introduction of the C13 hydroxy group at an early stage.

Iodocyclization approaches to epoxide

In the preparation of model epoxide **28**, iodocyclization was used to introduce oxygenation in a stereoselective fashion from a chiral homoallylic alcohol. Applying this disconnection, we hypothesized that we might be able to introduce the epoxide functional group of **5** by iodocyclization of the *tert*-butyl carbonate **55** (Figure 6). Although the additional double bond in this substrate presents a potential site for competing reaction pathways, we were encouraged by a report by Bartlett in which the iodocyclization of the *tert*-butyl carbonate derivative of 1,7-octadien-4-ol afforded exclusively the 6-membered carbonate derivative, with product arising from cyclization onto the more distant double bond not detected [56]. We set out to access **55** from deprotonation of methyl ketone **57** on the less hindered side and alkylation with bromide **56**.

The *E*-allylic bromide was prepared rapidly, albeit in modest yield, with an Appel reaction [57] of the known allylic alcohol [58]. To synthesize ketone **57**, we opted to utilize an asymmetric aldol reaction to set the stereochemistry of the β-hydroxy

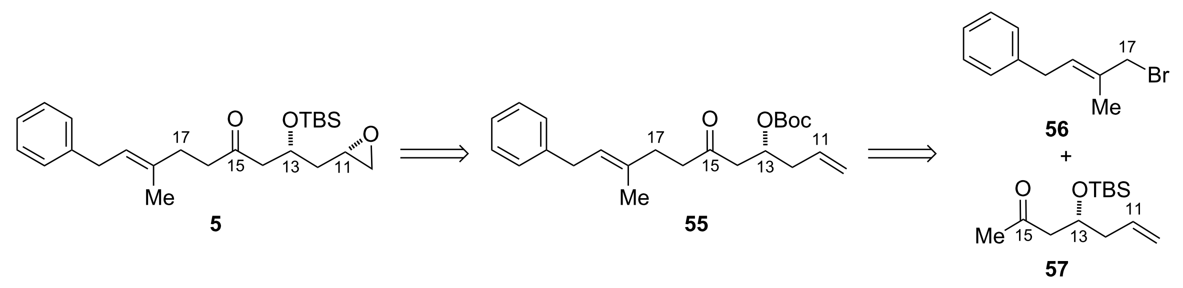


Figure 6: Retrosynthesis by using iodocylization to introduce the epoxide.

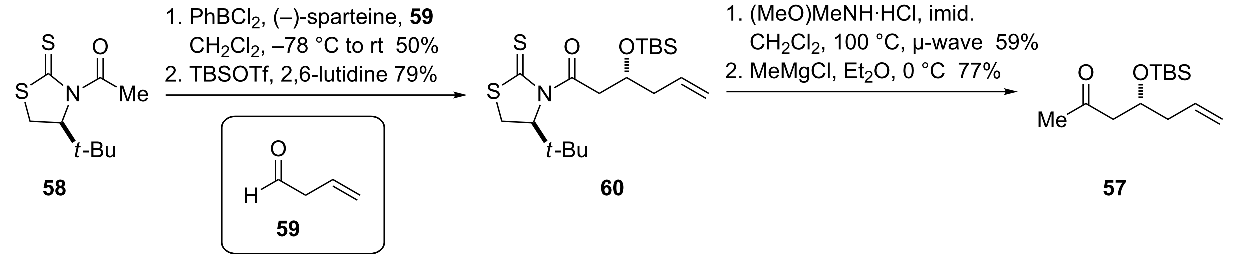
group. Since the report of Evans's diastereoselective asymmetric aldol reaction using the boron enolates of *N*-acyloxazolidinones [59], numerous chiral-auxiliary-based methods have been developed for the synthesis of *syn*- or *anti*-propionate aldol units. However, many of these auxiliaries, including the Evans oxazolidinones, fail to give high stereoselectivities when employed in acetate aldol reactions [60]. Of the methods available, we selected Sammakia's boron enolate-based strategy using the *N*-acetylthiazolidinethione **58** (Scheme 14) for its high reported diastereoselectivity with aliphatic aldehydes and its avoidance of toxic tin reagents [61].

The reaction of the brightly colored **58** with but-3-enal proceeded in moderate yield, with an initial diastereoselectivity around 10:1, with further enhancement following silyl protection and purification. Although the silylated compound **60** proved to be reluctant to form the Weinreb amide, microwave irradiation allowed this process to proceed on a reasonable time scale. Grignard addition to the Weinreb amide afforded ketone **57**.

Unfortunately, attempts to unite ketone **57** and bromide **56** via alkylation were unsuccessful. Although deprotection at the less-substituted site of the methyl ketone using LDA was verified in a deuterium quench experiment, the alkylation did not proceed at temperatures from −78 °C to 0 °C. While the ketone was re-isolated cleanly following the reaction, the bromide was converted to a mixture of olefinic compounds. Faced with the difficulty of forming the C16−C17 bond by alkylation, we considered potential routes arising from retrosynthetic disconnection of the C15−C16 bond (Figure 7). It was recognized that reaction of the enolate of ester **45**, a compound previously synthesized in just two steps, and subsequent oxidation could give the β-ketoester **61**. Decarboxylation of this compound would provide rapid access to the key iodocyclization substrate **55**.

Aldehyde **62** was prepared by reduction of the thiazolidinethione **60** with DIBAL-H (Scheme 15). Treatment of the ester with LDA, followed by trapping with the aldehyde, afforded the aldol adduct as a mixture of up to four possible diastereomers. This was then oxidized under Ley's conditions [62] to the β-ketoester **61**, itself a mixture of two diastereomers.

Initially, we attempted to induce decarboxylation of **61** by treatment with LiOH in a 1:1 water/THF mixture. No reaction was observed at room temperature, but heating to 70 °C resulted in elimination of the β-siloxy group. The Krapcho reaction offers an essentially neutral method for the decarboxylation of base- and acid-sensitive substrates [63]. Under these conditions (sodium chloride in wet DMSO at elevated temperatures) the desired decarboxylation reaction proceeded, although only in modest yield (Scheme 16). Reduction of the temperature from 180 °C to 120 °C led to much lower conversion, as expected, but did not improve mass recovery in the reaction. Somewhat more surprisingly, silyl deprotection with TBAF was also low yielding. Interestingly, when the order of these operations was reversed, the Krapcho conditions led to a complex product mix-



Scheme 14: Synthesis of ketone **57** using thiazolidinethione chiral auxiliary.

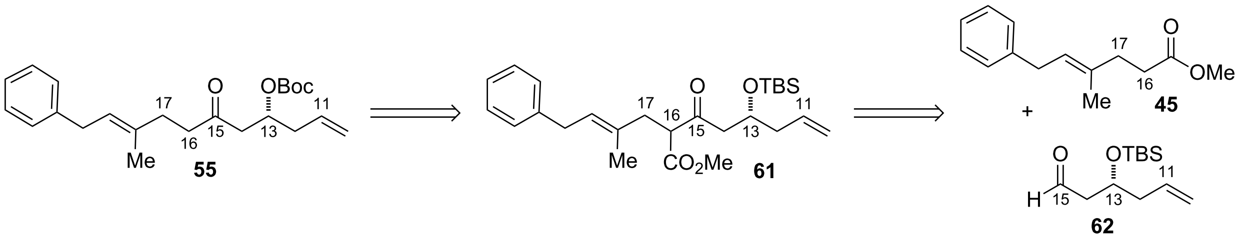
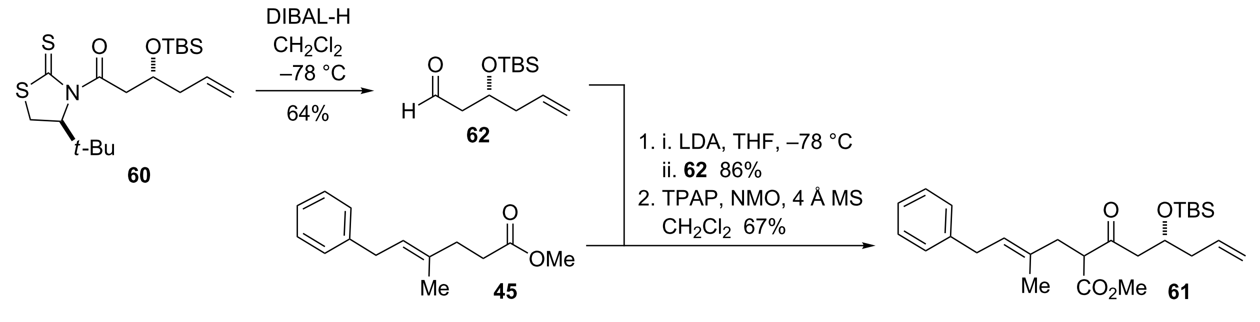
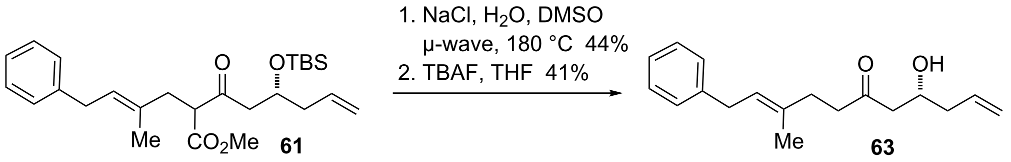


Figure 7: Retrosynthesis involving decarboxylation of a β-ketoester.



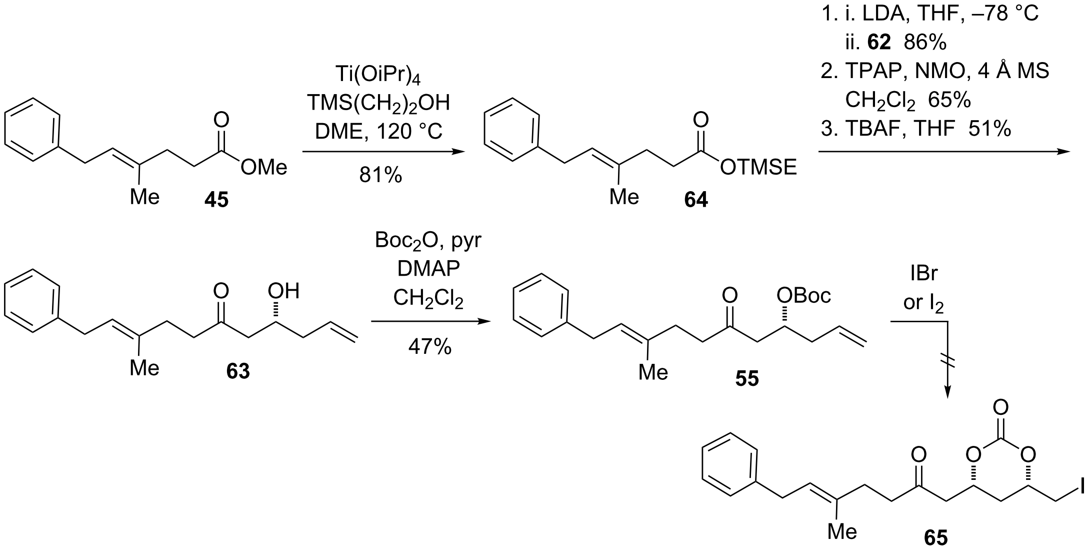
Scheme 15: Synthesis of β-ketoester **61**.



Scheme 16: Decarboxylation of **61** under Krapcho conditions.

ture, the major component of which appeared to be the dienone, formed by elimination and isomerization of the terminal olefin into conjugation.

We reasoned that the decarboxylation and silyl deprotection steps could be coupled into one operation by switching from the methyl ester to the 2-trimethylsilylethyl (TMSE) ester. Although there was concern that if the TBS group were removed first, the free hydroxy group would undergo elimination, it seemed likely that both deprotections would proceed at ambient temperature, which might circumvent this issue. Transesterification of methyl ester **45** to TMSE ester **64** proceeded in good yield, and following an analogous procedure for aldol reaction and oxidation the TMSE β-ketoester was obtained (Scheme 17). Treatment with an excess of TBAF in THF at room temperature overnight resulted in formation of the



Scheme 17: Improved synthesis of **63** and attempted iodocyclization.

β-hydroxyketone **63**. Although the yield for this transformation remained moderate, it was higher than that obtained for either of the individual steps from the methyl series that it replaced.

The cleavage of TMSE β-ketoesters with TBAF·3H_2O has been described in the literature as a chemoselective method for decarboxylation in the presence of other types of β-ketoesters [64]. Comparable yields for the decarboxylation to form **63** were obtained with this reagent as with the anhydrous solution, or when the reaction was run in DMF instead of THF. The use of TAS-F (tris(dimethylamino)sulfonium trifluoromethylsilicate) was clearly inferior, leading to incomplete conversion and elimination. With TBAF, partial elimination could sometimes be observed; however, this typically occurred in less than 10%. Given these results, it seems that the fluoride-mediated deprotection of TMSE β-ketoesters is deserving of further exploration and utilization as a method for the decarboxylation of sensitive synthetic intermediates.

Alcohol **63** was derivatized as the Boc carbonate, a reaction plagued by the formation of the carbonate arising from two molecules of **63**. The ratio of Boc derivative to symmetrical carbonates is dependent on the acidity of the alcohol and not necessarily improved by increasing the stoichiometry of Boc_2O [65]. Disappointingly, treatment of **55** with IBr or I_2 led to exhaustive decomposition of the material. Similarly, attempts to convert the homoallylic olefin of **55** into the epoxide via directed oxidation with VO(acac)$_2$ and TBHP again resulted in an intractable mixture of products.

While investigations into installing the epoxide via iodocyclization were ultimately not fruitful, in the course of this route an expeditious and perhaps underappreciated disconnection was identified in the construction of the C15−C16 bond via a simple aldol reaction, followed by TBAF-promoted decarboxylation to remove the ester. We concluded that selective reaction of the terminal olefin in the presence of the trisubstituted olefin was not a feasible proposition. Therefore, a substrate with oxygenation present at C10 and C11 from an early stage was needed as well.

Acetonide approach to epoxide

To obtain the key C10−C11 epoxide in **5** in stereoselective fashion from displacement of a leaving group at C10, a means for the selective formation of a *syn*-1,3-diol at C11 and C13 is required. Rychnovsky has demonstrated that alkylation of 4-cyano-1,3-dioxanes (cyanohydrin acetonides) constitutes a practical and valuable approach to *syn*-1,3-diol synthesis [66]. The lithiated cyanohydrin acetonides react as nucleophiles with alkyl, allyl, and propargyl halides, as well as with epoxides. Although the alkylation itself is highly stereoselective in favor of the axial nitrile, the *syn*-1,3-diol stereochemistry is ultimately set in a subsequent reductive decyanation step. We planned to synthesize **5** by reaction of the cyanohydrin acetonide **67** with the epoxide electrophile **66** (Figure 8) [67].

The dimethyl derivative of L-malic acid was chemoselectively reduced with borane-dimethylsulfide and sodium borohydride to afford diol **69** (Scheme 18) [68]. The primary alcohol was protected as the TIPS ether, and the secondary alcohol subsequently converted to the TMS ether. Reduction with DIBAL-H afforded the aldehyde **71** without over-reduction to the alcohol. Acetonide formation proceeded smoothly to give **67** as an inconsequential mixture of diastereomers. However, attemps to alkylate the lithiated anion of **67** with epoxide **66** led only to recovery of starting material. Interestingly, although alkylations of the acetonide are known to be stereoselective, protonation does not appear to be, as a *cis* and *trans* mixture was obtained from the attempted reaction of a single acetonide diastereomer.

In the course of investigating why **66** and **67** failed to react, attempts were made to trap the anion of **67** with a more reactive electrophile. Allyl bromide reacted rapidly, affording the product **73** as a single diastereomer (Scheme 19). The configuration of this compound, as well as subsequent compounds along this route, could be assigned as the 1,3-*syn* acetonide by analysis of the ^{13}C chemical shifts of the acetonide methyl groups [69]. It was recognized that conversion of this olefin to the aldehyde would provide an ideal electrophile for a revised β-ketoester decarboxylation strategy. To this end, reduction of the nitrile proceeded with the expected selectivity; this arises

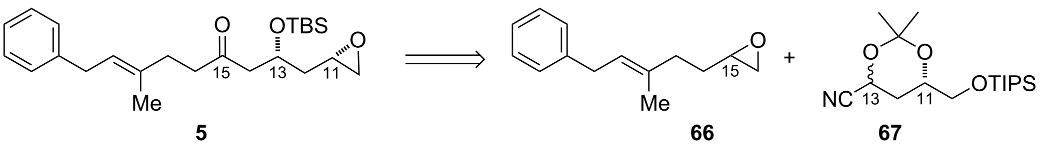
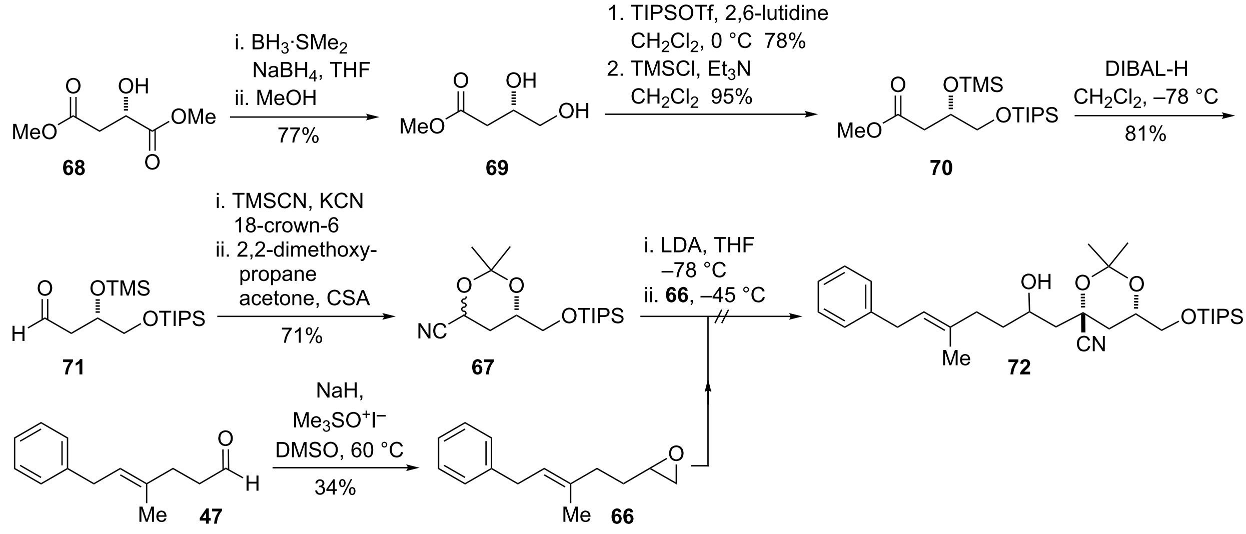
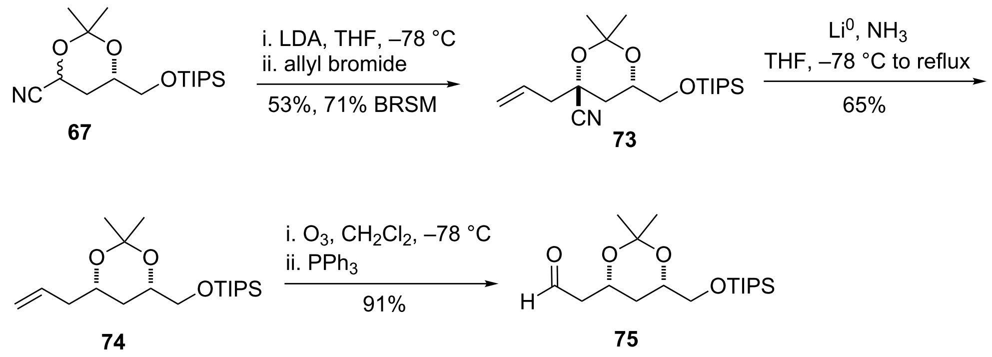


Figure 8: Retrosynthesis utilizing Rychnovsky's cyanohydrin acetonide methodology.



Scheme 18: Synthesis of cyanohydrin acetonide and attempted alkylation with epoxide.



Scheme 19: Allylation of acetonide and conversion to aldehyde.

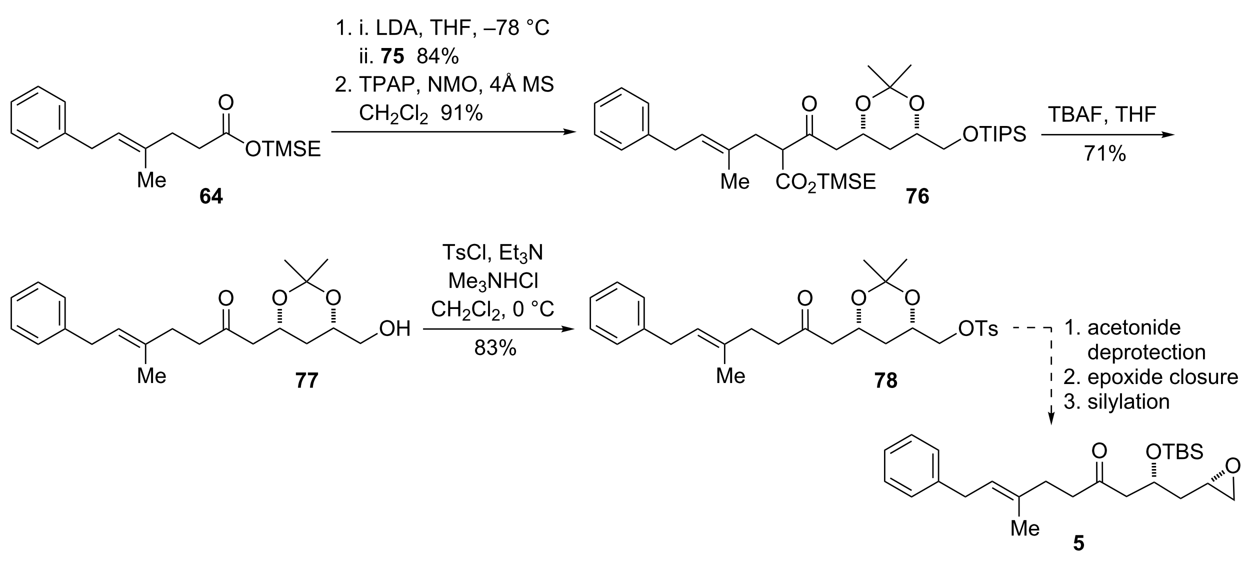
from equilibration of the intermediate radical to the more stable axial radical. It was essential to allow the reaction to warm under reflux due to the insolubility of the starting material in liquid ammonia. Ozonolysis of the pendant olefin afforded aldehyde **75** in high yield.

Following the prior procedure, the lithium enolate of TMS ester **64** was reacted with aldehyde **75**, and the mixture of diastereomeric alcohols was oxidized to the β-ketoester **76** (Scheme 20). This substrate did not appear to be prone to elimination, and treatment of the β-ketoester with TBAF in THF provided the decarboxylated and deprotected alcohol **77**. The primary alcohol could be converted to the tosylate **78** in good yield with tosyl chloride, triethylamine, and trimethylamine hydrochloride as the catalyst.

The alcohol **77** and tosylate **78** contain all of the carbon atoms of epoxide fragment **5** in the correct oxidation state. The remaining steps required to access the epoxide consist of acetonide deprotection, displacement of the tosylate or another appropriate leaving group to obtain the terminal epoxide, and silyl protection.

Conclusion

Nickel-catalyzed reductive coupling methodologies are an attractive fragment coupling strategy for the synthesis of complex natural products. The formation of sensitive skipped diene units in this context remains largely an unsolved problem for organic chemistry, but reactions for the rearrangement of vinylcyclopropanes present an intriguing avenue for exploration. To facilitate future studies in this vein, a cyclopropylenyne corres-



Scheme 20: Synthesis of the epoxide precursor by an aldol−decarboxylation sequence.

ponding to the C1−C9 carbons of ripostatin A was synthesized in ten steps and up to 35% yield, and was shown to be a viable substrate in a nickel-catalyzed coupling reaction. The lack of complete regioselectivity in this transformation highlights that the factors governing selectivity in this reaction are more complex and more substrate dependent than initially anticipated.

Several strategies for synthesis of the C10−C26 epoxide fragment were examined, including dithiane linchpin coupling, oxy-Michael addition to an enone, and iodocyclization methods. Fluoride-promoted decarboxylation of TMSE esters was identified as a mild strategy enabling simple aldol reactions for the construction of the C15−C16 bond. Allylation and reductive decyanation of a lithiated cyanohydrin acetonide was used to set the C13 stereocenter. Additional efforts are needed to convert a fully oxygenated, ketone-containing triol into the critical epoxide fragment and to investigate the rearrangement of reductive coupling products.

Supporting Information

Supporting Information File 1

Experimental procedures and characterization data for newly synthesized compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-175-S1.pdf]

Acknowledgements

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The small A value of a nitrile means that it behaves as a hydrogen in ^{13}C acetonide analysis. The observed ^{13}C acetonide chemical shifts of 30.8 and 21.6 ppm are consistent with the *syn* acetonide.

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Organocatalytic asymmetric selenofunctionalization of tryptamine for the synthesis of hexahydropyrrolo[2,3-*b*]indole derivatives

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Full Research Paper

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Abstract

A chiral phosphoric acid-catalyzed selenofunctionalization of tryptamine derivatives provides access to 3a-(phenylselenyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole derivatives in high yields and with synthetically useful levels of enantioselectivity (up to 89% ee).

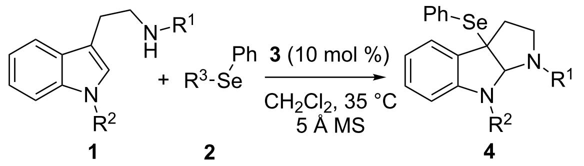
Introduction

Selenofunctionalization of carbon–carbon double bonds provides practicable opportunities for rapid construction of molecule complexity [1-8], because the versatile carbon–selenium bond could either stabilize carbanions [9,10], serve as a radical precursor [11-13], or undergo a *syn*-selective oxidative elimination via the selenoxide [14,15]. A widely accepted mechanism suggests that a key discrete seleniranium ion intermediate is initially formed, and then trapped by internal amine through nucleophilic attack to furnish the product. So far, in addition to the chiral-substrate-induced strategy [16], chiral selenylating agents [17-24] are commonly designed for asymmetric selenofunctionalization of carbon–carbon double bonds. In 2010, Denmark and co-workers reported a Lewis base catalyzed asymmetric selenoetherification of olefins, whereas the enantioselectivity was not quite synthetically attractive (up to 70% ee) [25]. As chiral 3-substituted hexahydropyrroloindoline is a key structural moiety prevalent in a large number of bioactive indole alkaloids [26,27], direct access to which by selenofunctionalization has been considered to be promising but challenging. Danishefsky found that the treatment of bis(Cbz)tryptamine with *N*-phenylselenophthalimide (*N*-PSP) in the presence of a catalytic amount of p-toluenesulfonic acid (PTSA) was able to afford a racemic selenofunctionalization product in 84% yield [28]. These leading findings indicate that either Lewis base or Brønsted acid shows catalytic activity for the selenofunctionalization reaction. Since chiral phosphoric acids have been shown to be Brønsted acid/Lewis base bifunctional organocatalysts [29-33], we ask whether the chiral BINOL-based phosphoric acids are able to catalyze the selenofunctionalization of tryptamine derivatives.

Results and Discussion

Initially, we investigated a reaction of bis(Cbz)tryptamine reagent **1a** with *N*-phenylselenophthalimide (*N*-PSP) (**2a**) by using phosphoric acids **3** (Table 1, Figure 1) as catalysts for the validation of our hypothesis. Encouragingly, the reaction proceeded smoothly in the presence of 10 mol % of the phosphoric acids evaluated under the assistance of 5 Å molecular sieves. Apparently, the stereoselectivity depended on the N-protecting group of tryptamine **1**. When nitrogen atoms of the tryptamine were both protected with Cbz, a very poor enantioselectivity was observed regardless of the catalysts used (Table 1, entries 1–3). Notably, only the substrate bearing an electron-withdrawing N-protecting group at the indole nitrogen (R^2) underwent a smooth reaction to afford the desired product. When the R^2 was replaced with a methyl group, the *N*-PSP directly underwent a coupling reaction with tryptamine derivatives **1** at the 2-position in 76% yield [34], indicating that the electronically rich substitution inhibited the desired selenofunctionalization reaction. Other selenofunctionalization reagents, such as **2b** and **2c** could also participate in the reaction under similar conditions, but both showed lower reactivity than **2a**. Interestingly, the selenofunctionalization reagent **2d**, which was the best substrate in the reaction developed by Denmark [25], however, was completely unreactive in our case. After the optimal R^2 protecting group and the phenylseleno reagent were determined, we focused on the evaluation of the N-protecting group of the tryptamine (R^1) to improve the enantioselectivity. The Fmoc group was found to be better than any other substituents that were screened (Table 1, entries 10 and 11 versus 12). The optimization of reaction parameters including solvents and temperature found dichloroethane (DCE) to be the best solvent in terms of enantioselectivity, and the best results could be accessed by conducting at 0 °C (Table 1, entries 13 and 14).

Table 1: Optimization of reaction conditions.[a]



entry	3	R^1	R^2	2	yield (%)[b]	ee (%)[c]
1	**3a**	Cbz	Cbz	**2a**	56	10
2	**3b**	Cbz	Cbz	**2a**	46	6
3	**3c**	Cbz	Cbz	**2a**	36	0
4	**3a**	Cbz	Boc	**2a**	49	6
5	**3a**	Cbz	Me	**2a**	–	–
6	**3a**	Cbz	Ac	**2a**	67	24
7	**3a**	Cbz	Ac	**2b**	63	25
8	**3a**	Cbz	Ac	**2c**	37	5
9	**3b**	Cbz	Ac	**2d**	–	–
10	**3b**	Cbz	Ac	**2a**	65	48
11	**3b**	CO_2Et	Ac	**2a**	61	27
12	**3b**	Fmoc	Ac	**2a**	60	63
13[d]	**3b**	Fmoc	Ac	**2a**	75	77
14[d,e]	**3b**	Fmoc	Ac	**2a**	78	86

[a]The reaction was performed in 0.1 mmol scale in DCM (1 mL) with 5 Å MS (100 mg). [b]Isolated yield. [c]The ee was determined by HPLC. [d]In DCE. [e]The temperature was 0 °C.

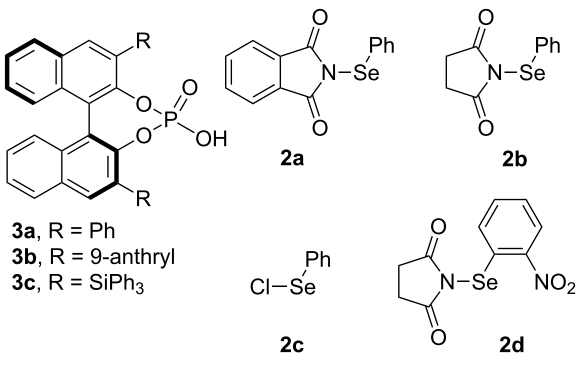


Figure 1: Catalysts and seleno reagents evaluated in this study.

After optimizing the reaction conditions, a variety of tryptamine analogues were synthesized for this chiral phosphoric acid-catalyzed asymmetric selenofunctionalization. As shown in Figure 2, no matter what the chemical and electronic feature of the substituents on the benzene moiety of either substrates or *N*-PSP, various tryptamine analogues could be smoothly transformed into the corresponding products in satisfactory yields (65–85%) and with good enantioselectivities (71–89%; Figure 2, **4b**–**4i**). In addition, the products were solid and easy to recrystallize to enhance the optical purity. After a single recrystallization from methanol, the optical purity of some products, such as **4e**, was enhanced to >99% ee. Importantly, the configuration could be assigned by X-ray crystallography. The crystal structure of **4a** (>99%) indicated that the configuration of the stereogenic centers was assigned to be (3a*R*,8a*S*) (Figure 3) [35].

On the basis of experimental observations, we proposed a reaction mechanism (Scheme 1). The phosphoric acid acts as a bifunctional catalyst and simultaneously activates both the tryptamine derivative and *N*-PSP by hydrogen-bonding inter-

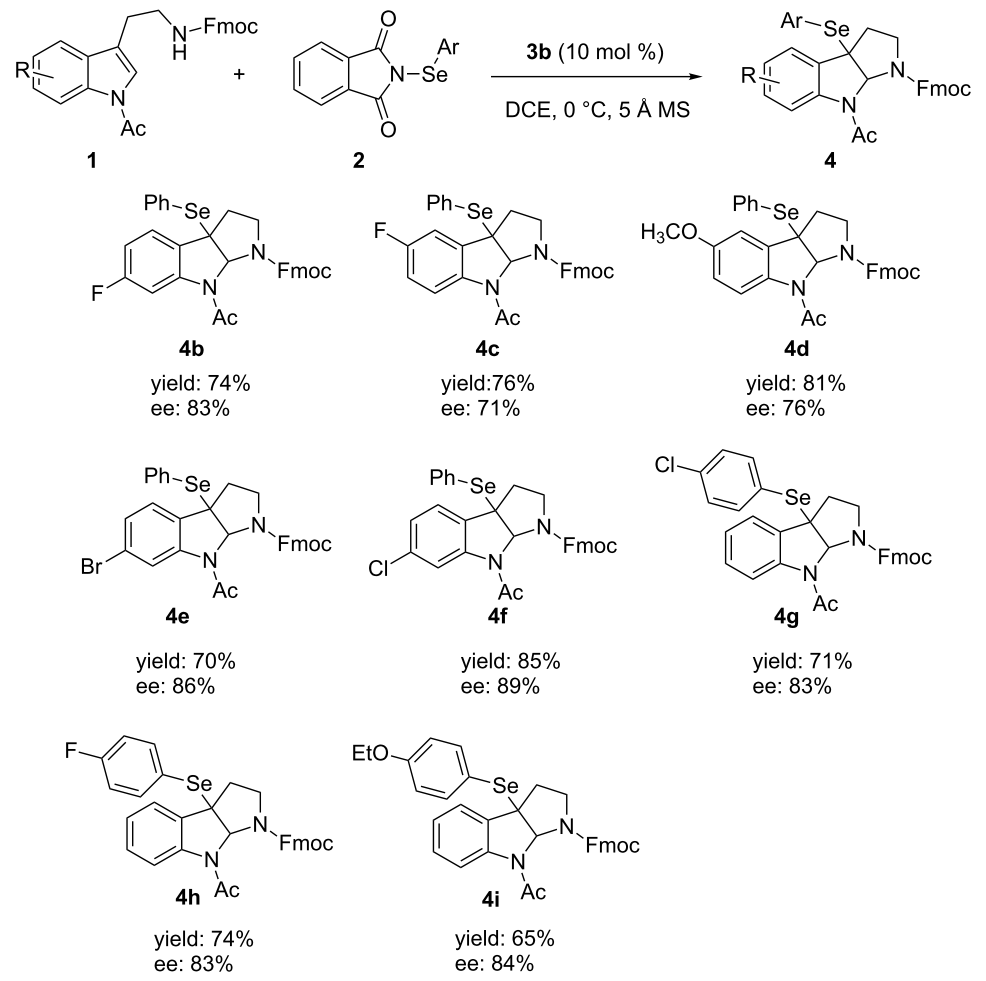


Figure 2: Generality for substitution at the indoline moiety. The reaction was performed in 0.1 mmol scale in DCE (1 mL) with 5 Å MS (100 mg) in 0 °C and the ratio of **2**/**1** is 3:1. The reaction was performed for 1–3 days. The given yields are isolated yields, and the ee's were determined by HPLC.

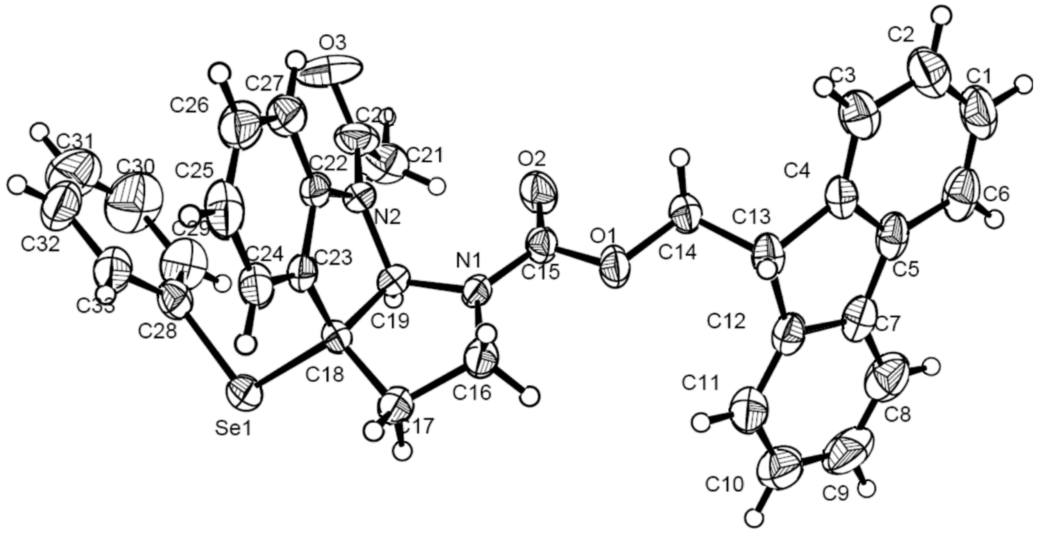
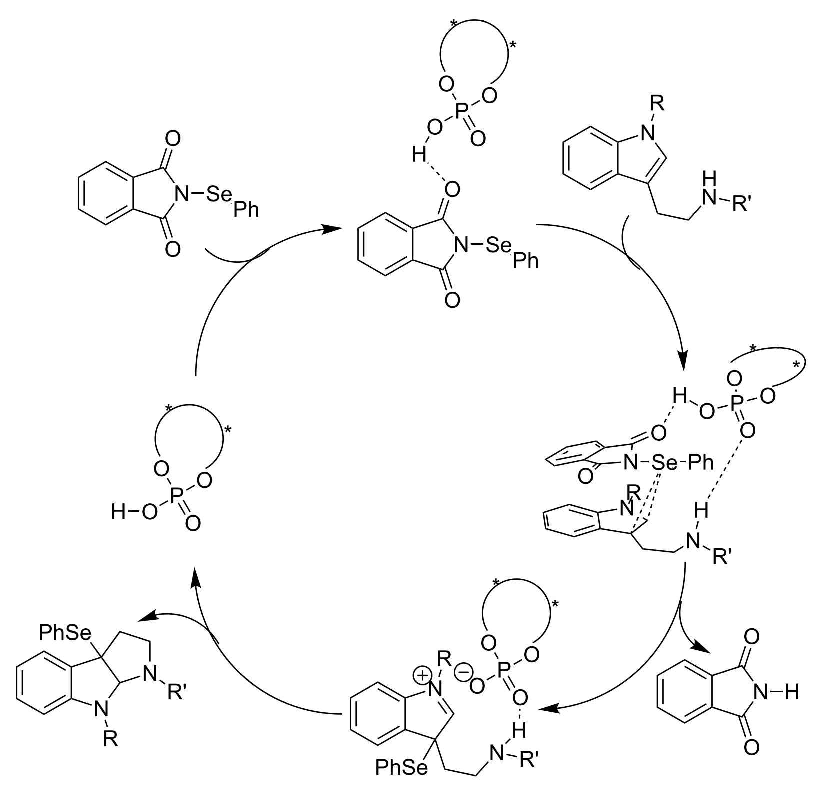


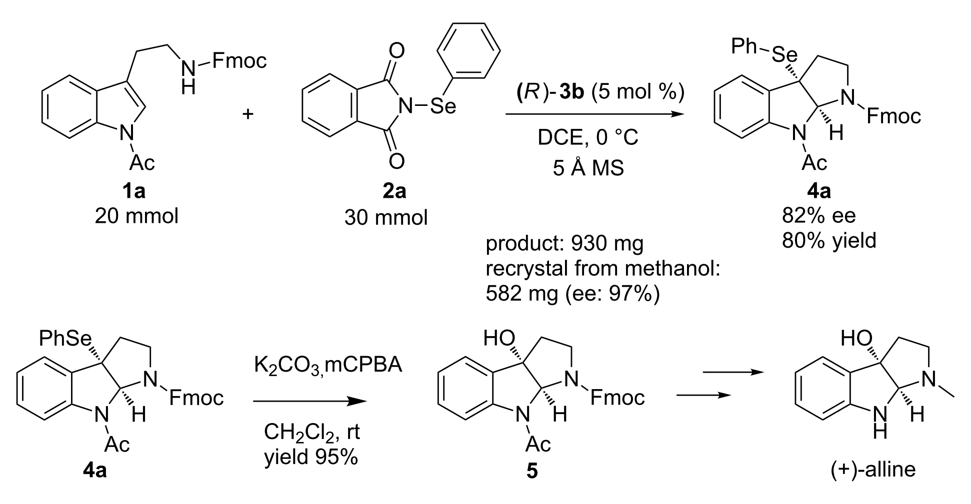
Figure 3: X-ray crystallography of **4a** catalyzed by (*S*)-**3b**.



Scheme 1: The plausible reaction mechanism.

action. Then, the asymmetric selenofunctionalization occurred at the 3-substituted tryptamine and subsequently the proton of the phosphoric acid protonates the phthalimide anion to release phthalimide. Finally, the amide on the side chain of the tryptamine derivatives attacks the resultant iminium cation leading to the formation of the product in an enantioselective manner.

Finally, we demonstrate the synthetic application of this reaction in the construction of the 3a-(phenylselenyl)bispyrrolidino[2,3-*b*]indoline core structure (Scheme 2). Under the optimized reaction conditions, the enantioselective substitution reaction gave **4a** in 78% yield and 86% ee. However, when the reaction was scaled up to 20 mmol, both the yield and the stereoselectivity were significantly sacrificed. To our delight,



Scheme 2: Scale up of the protocol and synthetic application.

the reaction running on a similar scale could give **4a** in 80% yield and 82% ee by tuning the stoichiometry of the phenylseleno reagent (**2a**) to 1.5 equiv by using 5 mol % of catalyst (*R*)-**3b**. After a single recrystallization from methanol, the product **4a** was obtained in 50% yield and with 97% ee. The oxidative deselenation of **4a** with MCPBA afforded the corresponding alcohol **5** in 95% yield. The stereochemistry of the alcohol was found to be identical to that of the parent selenide, as demonstrated previously [36].

Conclusion

In summary, we have developed a reaction for the enantioselective selenofunctionalization of tryptamine derivatives with *N*-phenylselenophthalimide (*N*-PSP) catalyzed by chiral phosphoric acids (up to 89% ee). In this context, we used this protocol to prepare the key chiral precursor of the (+)-alline.

Supporting Information

Supporting Information File 1

Experimental procedures and characterization data for new compounds. In addition, confirmatory crystallographic data are included.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-177-S1.pdf]

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Bioinspired total synthesis of katsumadain A by organocatalytic enantioselective 1,4-conjugate addition

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Letter

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Abstract

Katsumadain A, a naturally occurring influenza virus neuraminidase (NA) inhibitor, was synthesized by using a bioinspired, organocatalytic enantioselective 1,4-conjugate addition of styryl-2-pyranone with cinnamaldehyde, followed by a tandem Horner–Wadsworth–Emmons/oxa Michael addition.

Introduction

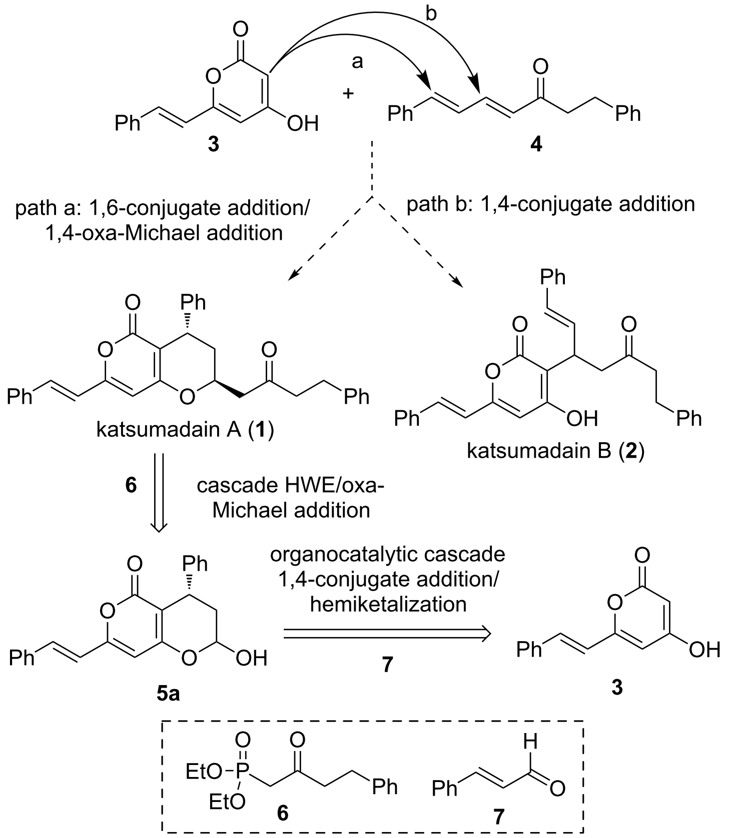
2-Pyranone is a privilege structure that is often present in natural products and pharmaceuticals, many of which exhibit diverse molecular architectures and biological profiles [1,2]. For example, katsumadain A (**1**) and B (**2**), which were isolated from *Alpinia katsumadai Hayata* (Zingiberaceae), a chinese herbal drug used as an anti-emetic and stomachic agent, are two natural products bearing a diarylheptanoid scaffold that is incorporated into the styryl-2-pyranone moiety [3]. Preliminary biological evaluations showed that **1** and **2** feature anti-emetic activities on copper sulfate-induced emesis in young chicks. More recently, Rollinger et al. disclosed that katsumadain A (**1**) exhibited prominent in vitro inhibitory activity against the human influenza virus A/PR/8/34 of the subtype H1N1 (IC_{50} 1.05–0.42 μM) by targeting the enzyme neuraminidase (NA) [4,5]. Moreover, it also inhibited the NA of four H1N1 swine influenza viruses with IC_{50} values between 0.59 and 1.64 μM. Therefore, katsumadain A represents an attractive lead structure for the anti-flu drug discovery [6].

We recently reported the biomimetic total synthesis of katsumadain C [7], a natural product isolated from the same resource as katsumadain A and B [8]. As part of our continuous interest in the synthesis of bioactive 2-pyranone-derived natural products, we launched a project aiming to develop a highly efficient route for the synthesis of katasumadain A as well as its analogues, which would pave the way for their application in further biomedical investigations.

Biosynthetically, katsumadain A is assumed to be derived from styryl-2-pyranone **3** and alnustone (**4**) [9] through a 1,6-conjugate addition/oxa-Michael addition cascade reaction (path a, Scheme 1). Indeed, both **3** and **4** are known natural substances. Apparently, the biosynthetic pathway represents the most straightforward and convergent approach to synthesize katsumadain A. However, its efficiency might be limited to some extent, given that α,β,γ,δ-unsaturated ketone **4** could undergo a competitive 1,4-conjugate addition to provide the other natural product katsumadain B (path b, Scheme 1). Actually, the regioselectivity of a conjugate addition with α,β,γ,δ-unsaturated Michael acceptors remains a considerable challenge, as it is heavily dependent on the steric and electronic nature of the substrates [10,11]. Moreover, the enantioselective 1,6-conjugate addition to acyclic dienones or dienoates monosubstituted at the β- and δ-position has rarely been investigated [12-15], thus leaving open the question of whether or not a biomimetic approach towards katsumadain A might succeed. Keeping these concerns in mind, an alternative strategy was designed as a fallback, in which katsumadain A could be accessed from the lactol **5a** and phosphonate **6** via a tandem Horner–Wadsworth–Emmons (HWE)/oxa-Michael addition reaction [16]. In turn, **5a** could be derived from **3** and cinnamaldehyde (**7**) by an organocatalytic enantioselective 1,4-conjugate addition followed by the hemiketal formation.

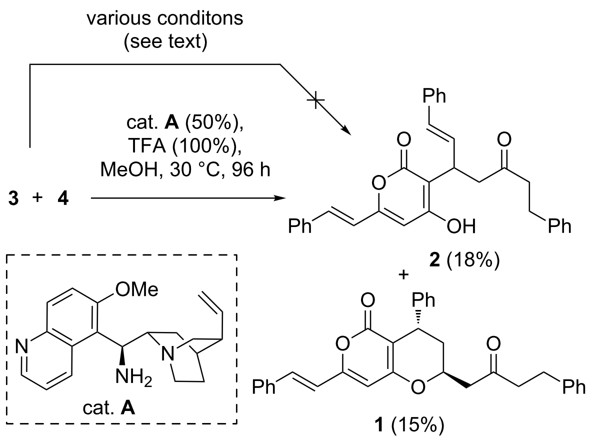
Results and Discussion

Our investigation was initiated by an investigation of the conditions that could effect the proposed biomimetic approach towards katsumadain A and katsumadain B. Both styryl-2-pyranone **3** [17] and alnustone (**4**) [18] were synthesized according to the literature methods. First of all, the 1,6-conjugate addition of **3** towards **4** was attempted by employing various conditions, including different basic conditions (NaH, DBU, KHMDS) by activation of the nucleophile **3** or acidic conditions (AcOH, TMSOTf, Sc(OTf)$_3$ and In(OTf)$_3$) by activation of the electrophile **4**. However, all of these reactions failed to provide satisfactory results and only lead to the recovery or the substantial decomposition of the starting material. We then turned our attention to the organocatalytic conjugated addition reaction. Among the various documented conditions [19-23], the 9-amino-9-deoxyepicinchona alkaloid-promoted Michael addi-



Scheme 1: Proposed biosynthetic pathway and strategic analysis for synthesis of katsumadain A.

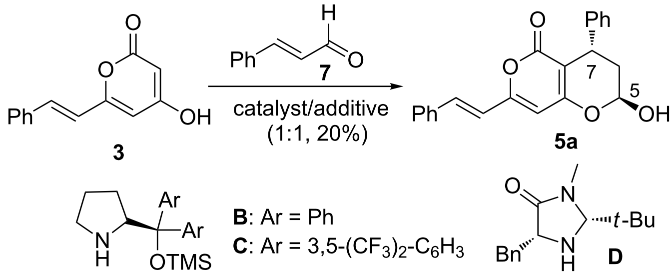
tion is particularly attractive, mainly due to the availability of the catalyst and its superior reactivity towards the activation of the unsaturated ketone substrates through formation of the corresponding iminium intermediate [22]. To our delight, when we tried the standard conditions (30% catalyst **A**, 60% TFA, DCM, 96 h) in our case, we isolated a product in 25% isolated yield, which was proved to be the 1,4-adduct katsumadain B (**2**). Encouraged by this result, we further optimized the reaction by screening different solvents (CH_3CN, THF, DMSO and MeOH) and additives (HCl, TFA and DMAP), aiming to improve the efficiency and selectivity (1,4- or 1,6-adduct) of the reaction. In most of the cases the 1,4-conjugate addition proceeded dominantly, while no or only trace amounts of the 1,6-adduct katsumadain A (**1**) was observed. The best result was obtained when the reaction was performed with a substoichiometric amount of catalyst **A** with MeOH as a solvent, in which katsumadain A and B were isolated in a 5:6 ratio with a combined yield of 33% (Scheme 2).



Scheme 2: Preliminary results of the biomimetic synthesis of katsumadain A.

With limited success regarding the the biomimetic synthesis of katsumadain A, we then moved towards the alternative approach as described in Scheme 1. We envisioned that in this scenario an organocatalytic 1,4-conjugate addition [24-27] between **3** and **7** would circumvent both the reactivity and selectivity issues, which we have struggled with in the aforementioned studies. To validate this hypothesis, we performed a systematic investigation of the organocatalytic 1,4-conjugate addition by examining various reaction parameters, including organocatalyst, acid additive, solvent temperature, and reaction temperature (Table 1). The first reaction was performed by stirring a mixture of **3** and **7** in DCM at room temperature for 12 h

Table 1: Condition screening of organocatalytic 1,4-conjugate addition/hemiketalization of styryl-2-pyranone with α,β-unsaturated aldehydes.



Entry[a]	Catalyst	Additive	Solvent	*T* (°C)	Yield (%)	ee (%)[b]
1	**B**	none	DCM	23	41	78
2	**B**	BA	DCM	23	78	91
3	**C**	BA	DCM	23	41	−81
4	**D**	BA	DCM	23	10	nd
5	**B**	PNBA	DCM	23	94	80
6	**B**	BA	MeOH	23	80	91
7	**B**	BA	CH_3CN	23	78	75
8	**B**	BA	DMSO	23	79	93
9	**B**	BA	Toluene	23	66	91
10	**B**	BA	MeOH	0	78	92
11	**B**	BA	DCM	0	82	92
12	**B**	BA	DCM	−20	45	93

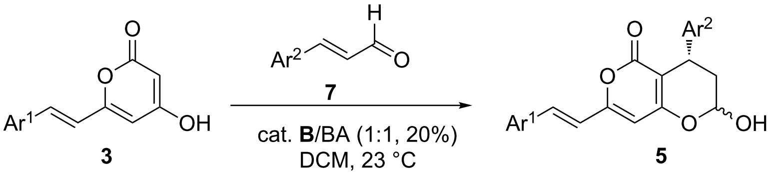
[a]Each reaction was run with **3** (0.5 mmol) and **7** (0.6 mmol) in 2.0 mL solvent as shown above. [b]The ee value was measured with the corresponding lactone product of **5a** using chiral HPLC.

in the presence of Hayashi catalyst **B** [28]. It was found that the desired product **5a** was obtained, albeit in moderate yield and enantioselectivity (Table 1, entry 1). To our delight, the usage of benzoic acid (BA) as an additive could dramatically improve the reaction by affording **5a** in a good yield (78%) and a good ee value (91%, Table 1, entry 2). Besides the catalyst **B**, both Jørgensen catalyst **C** [29] and MacMillan catalyst **D** [30] were also tested in this reaction, but gave inferior results (Table 1, entries 3 and 4). As to the acid additive, *p*-nitrobenzoic acid (PNBA) was found to afford **5a** in an excellent yield, but with a decreased ee value (80%). Furthermore, the solvent effect was also examined. Among the several solvents examined, both MeOH and DMSO proved to be suitable solvent systems (Table 1, entries 6 and 8) by furnishing comparable results with DCM, while MeCN and toluene led to modest results (Table 1, entry 7 and 9). Finally, we found that the reaction temperature has some influence on the outcomes, with a slightly improved enantioselectivity (92% ee) obtained at 0 °C (Table 1, entry 10 and 11). Although the best ee value (93%) was achieved at −20 °C, the reaction became sluggish and the yield dropped to 45% (Table 1, entry 12). It is noteworthy that **5a** was isolated as a mixture of C-5 diastereoisomers (β-isomer/α-isomer = 5:1 to 7:1) in all of the above cases. For convenience, the ee value of **5a** was determined with the corresponding lactone derivative. Furthermore, the absolute stereochemistry of **5a** (β-isomer) was assigned as (7*S*,5*R*) by using the Mosher ester method (see Supporting Information File 1 for details).

To evaluate the substrate scope of the reaction, we then examined different substituted styryl-2-pyranone and cinnamaldehyde derivatives as Michael addtion donors and acceptors (Table 2). When styryl-2-pyranone **3a** remained unchanged, a variety of cinnamaldehyde derivatives (**7a**–**f**) bearing either electron-withdrawing groups (4-Cl, 4-CF_3 and 4-NO_2, Table 2, entries 2-4) or electron-donating groups (4-MeO or 3,5-MeO, Table 2, entries 5 and 6) on the phenyl ring proved to be suitable substrates, affording the corresponding products (**5b**–**f**) in good yields and enantioselectivities. Besides **3a**, the Michael addition donors could also be extended to other substituted styryl-2-pyranone derivatives (e.g., **3b** and **3c**, Table 2, entries 7–11), all of which gave acceptable results. As proof-of-concept cases, the above outcomes indicate that the developed organocatalytic enantioselective 1,4-conjugate addition could be potentially applied to the synthesis of various bicyclic compounds bearing different aromatic moieties (Ar^1 and Ar^2), which paves the way to access katsumadain A and its analogues for further biomedical studies.

Having achieved the bicyclic core of katsumadain A in an efficient and enantioselective manner, we then moved towards its total synthesis through the proposed tandem Horner–Wadsworth–Emmons/oxa-Michael addition. As expected, deprotonation of **6** [31] with KHMDS at −40 °C for 0.5 h followed by the addition of the lactol **5a** led to the formation of katsumadain A as the only diastereoisomer in 52% yield,

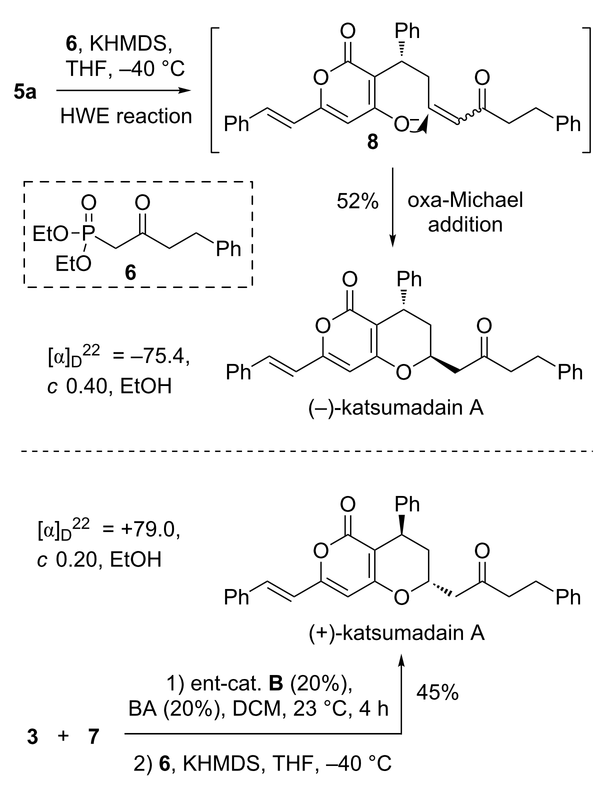
Table 2: Substrate scope of organocatalytic 1,4-conjugate addition/hemiketalization of styryl-2-pyranones with α,β-unsaturated aldehydes.



Entry[a]	Substrate (**3** and **7**)	Yield of **5** (%)[b]	ee value of **5** (%)[c]
1	**3a**: Ar^1 = Ph; **7a**: Ar^2 = Ph	82 (**5a**)	92
2	**3a**: Ar^1 = Ph; **7b**: Ar^2 = 4-Cl-Ph	59 (**5b**)	83
3	**3a**: Ar^1 = Ph; **7c**: Ar^2 = 4-CF_3-Ph	77 (**5c**)	82
4	**3a**: Ar^1 = Ph; **7d:** Ar^2 = 4-NO_2-Ph	79 (**5d**)	88
5	**3a**: Ar^1 = Ph; **7e:** Ar^2 = 4-MeO-Ph	78 (**5e**)	87
6	**3a**: Ar^1 = Ph; **7f:** Ar^2 = 3,5-MeO-Ph	70 (**5f**)	92
7	**3b**: Ar^1 = 4-MeO-Ph; **7a**: Ar^2 = Ph	84 (**5g**)	82
8	**3c:** Ar^1 = Furan; **7b**: Ar^2 = 4-Cl-Ph	88 (**5h**)	84
9	**3c:** Ar^1 = Furan; **7d**: Ar^2 = 4-NO_2-Ph	76 (**5i**)	91
10	**3c:** Ar^1 = Furan; **7e**: Ar^2 = 4-MeO-Ph	75 (**5j**)	80
11	**3c:** Ar^1 = Furan; **7g**: Ar^2 = Naphthyl	79 (**5k**)	90

[a]Each reaction was run with **3** (0.5 mmol) and **7** (0.6 mmol) in 2.0 mL solvent as shown above. [b]Each of **5a–k** was obtained as a mixture of C-5 diastereoisomers (the ratio of α-isomer:β-isomer varied from 1:5 to 1:7. [c]The ee value of **5a–k** was measured with the corresponding lactone product using chiral HPLC.

apparently via the in situ generated intermediate **8**. The spectroscopic data of the synthetic katsumadain A were in accordance with those of the natural one [32]. However, we found that its optical rotation ($[a]_D^{25}$ = −75.4, *c* 0.40, EtOH) was quite different from the reported one ($[a]_D^{25}$ +3.7, *c* 0.40, EtOH), indicating that the naturally occurring **1** might exist as a racemic substance. Given that the two enantiomers of katsumadain A might show different behaviors in the biological studies from each other as well as from the racemic compounds, we also synthesized (+)-katsumadain A in a similar way by simply replacing the catatalyst **B** with its enantiomer in the organocatalytic 1,4-conjugate addition (Scheme 3).



Scheme 3: Total synthesis of both enantiomers of katsumadain A.

Conclusion

We accomplished the first enantioselective total synthesis of katsumadain A, a naturally occurring influenza virus neuraminidase (NA) inhibitor. The key elements of the synthesis featured a bioinspired, organocatalytic enantioselective 1,4-conjuate addition and a tandem HWE/oxa-Michael addition. Due to the high efficiency and flexibility of the synthetic route it is applicable to the syntheses of both enantiomers of katsumadain A as well as their analogues. Applications of these compounds in relevant biomedical studies are ongoing in this laboratory, and the progress will be reported in due course.

Experimental

Representative procedure for the organocatalytic 1,4-conjugate addition: To a mixture of **3a** (214 mg, 1.0 mmol) and **7a** (163 mg, 1.2 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C was added PhCOOH (24 mg, 0.2 mmol) and catalyst **B** (50 mg, 0.2 equiv). The mixture was stirred at 0 °C for 10 h before being quenched by saturated aqueous NH_4Cl. The mixture was extracted with DCM (3 × 10 mL), and the organic layers were washed with brine and dried over $MgSO_4$. The organic solvent was removed under vacuum, and the residue was purified by column chromatography (CH_2Cl_2:ethyl acetate = 20:1) to give **5a** (284 mg, 82% yield) as a light yellow solid.

Supporting Information

Supporting Information File 1

Experimental procedures and characterization data for synthetic **1**, **3a**–**c**, **5a**–**k** and **9a**–**k**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-182-S1.pdf]

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32. The ee value of the synthetic (+)-**1**and (−)-**1** was determined to be 80% and 81%, respectively, suggesting that partial racemization occurred in the HWE reaction, presumably via the intermediate **8**.

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Asymmetric allylic alkylation of Morita–Baylis–Hillman carbonates with α-fluoro-β-keto esters

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Full Research Paper

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Guest Editors: D. Y.-K. Chen and D. Ma

Abstract

In the presence of a commercially available *Cinchona* alkaloid as catalyst, the asymmetric allylic alkylation of Morita–Baylis–Hillman carbonates, with α-fluoro-β-keto esters as nucleophiles, have been successfully developed. A series of important fluorinated adducts, with chiral quaternary carbon centres containing a fluorine atom, was achieved in good yields (up to 93%), with good to excellent enantioselectivities (up to 96% ee) and moderate diastereoselectivities (up to 4:1 dr).

Introduction

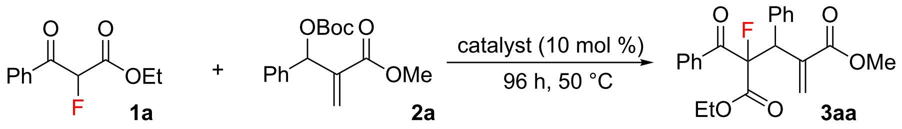
Fluorine is the most electronegative element in the periodic table, resulting in a highly polar C–F bond. This gives fluoroorganic compounds unique properties, compared with their parent compounds [1]. Due to the rareness of organofluorine compounds in nature, synthetic fluorinated compounds have been widely applied in numerous areas, including materials, agrochemicals, pharmaceuticals and fine chemicals [2-4]. In this context, the stereoselective introduction of fluorine atoms in molecules has become one of the most exciting and intense research areas in the recent years.

Lewis base-catalyzed asymmetric allylic alkylations (AAA) of Morita–Baylis–Hillman (MBH) adducts [5,6], such as acetates and carbonates, have become an attractive option to access various chiral *C*- [7-19], *N*- [20-25], *O*- [26-30], *P*- [31-33] and *S*-allylic [34] and spirocyclic compounds [35-37]. Several protocols have been established to introduce fluorine atoms in AAA of MBH adducts. For example, to introduce a CF_3 group, Shibata and co-workers [13] and Jiang and co-workers [14] successively reported the asymmetric allylic trifluoromethylation of MBH adducts with Ruppert's reagent [(trifluoromethyl)trimethylsilane, Me_3SiCF_3] in the presence of $(DHQD)_2PHAL$ as catalyst. In 2011, our research group [15], Shibata and co-workers [16] and Rios and co-workers [17] reported the addition of fluoromethyl(bisphenylsulfones) to MBH carbonates to access chiral monofluoromethyl derivatives. Furthermore, Rios and co-workers presented an asymmetric substitution of MBH carbonates with 2-fluoromalonates in good enantioselectivities [38]. Notably, the reaction between an achiral fluorocarbon nucleophile with MBH carbonates, to afford compounds with chiral quaternary carbon centres bearing a fluorine atom, remains a formidable task. Since 2009, we developed a highly enantioselective and diastereoselective guanidine-catalyzed conjugate addition and Mannich reaction of α-fluoro-β-ketoesters with excellent results [38-40]. Herein, we wish to report the first allylic alkylation of MBH carbonates with α-fluoro-β-ketoesters in excellent enantioselectivities and moderate diastereoselectivities, furnishing enantiopure fluorinated compounds with chiral quaternary carbon centres containing a fluorine atom.

Results and Discussion

In the preliminary experiments, we investigated the reaction of α-fluoro-β-ketoester **1a** with MBH carbonate **2a** as the model substrate, in the presence of several commercially available *Cinchona* alkaloids as Lewis base catalysts (Table 1). First, the reaction was conducted in the presence of quinine at 50 °C in dichloroethane (DCE) as the solvent (Table 1, entry 1). The desired adduct **3aa** was obtained in 53% yield with poor enantio- and diastereoselectivity. Cinchonine provided similarly poor results (Table 1, entry 2). Next, we screened a series of C_2-symmetric bis-*Cinchona* alkaloids as catalysts under the same conditions (Table 1, entries 3–7). $(DHQD)_2PHAL$ showed moderate catalytic activity; **3aa** was obtained in 67% yield with

Table 1: Catalyst screening[a].



Entry	Catalyst	Solvent	Yield (%)[b]	ee (%)[c]	dr[c]
1	quinine	DCE	53	32 (27)	55:45
2	cinchonine	DCE	59	21 (10)	55:45
3	$(DHQD)_2PHAL$	DCE	67	71 (57)	60:40
4	$(DHQD)_2AQN$	DCE	53	–5 (–5)	56:44
5	$(DHQ)_2PHAL$	DCE	64	–35 (–1)	52:48
6	$(DHQ)_2PYR$	DCE	60	–25 (–1)	59:41
7	$(DHQ)_2AQN$	DCE	47	–11 (–10)	55:45
8	$(DHQD)_2PHAL$	DCM	56	69 (55)	58:42
9	$(DHQD)_2PHAL$	toluene	78	85 (65)	67:33
10	$(DHQD)_2PHAL$	Et_2O	59	45 (30)	55:45
11	$(DHQD)_2PHAL$	EA	58	55 (30)	55:45
12	$(DHQD)_2PHAL$	THF	61	31 (49)	63:37
13	$(DHQD)_2PHAL$	MeCN	57	49 (19)	65:35
14	$(DHQD)_2PHAL$	MeOH	63	35 (20)	60:40
15	$(DHQD)_2PHAL$	*o*-xylene	74	85 (65)	72:28
16	$(DHQD)_2PHAL$	*m*-xylene	65	87 (74)	70:30
17	$(DHQD)_2PHAL$	*p*-xylene	72	85 (55)	68:32
18	$(DHQD)_2PHAL$	mesitylene	78	89 (72)	71:29
19[d]	$(DHQD)_2PHAL$	mesitylene	67	92 (69)	74:26
20[e]	$(DHQD)_2PHAL$	mesitylene	45	94 (55)	75:25

[a]Unless otherwise noted, reactions were performed with 0.05 mmol of **1a**, 0.15 of **2a**, and 0.005 mmol of catalyst in 0.5 mL solvent. [b]Yield of isolated product. [c]Determined by HPLC methods. The data in parenthesis is the ee value of the minor diastereoisomer [d]The reaction was conducted at 25 °C, 1.0 mmol scale in 1.0 mL of mesitylene. [e]The reaction was conducted at 10 °C, 1.0 mmol scale in 1.0 mL of mesitylene.

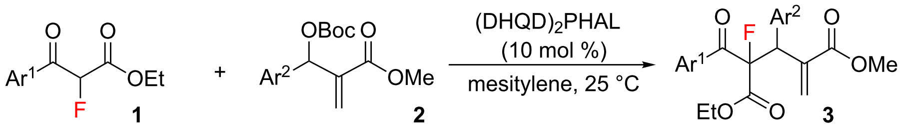
71% ee and 60:40 dr (entry 3). The effects of solvent were then investigated (Table 1, entries 8–18). The best-performing solvent was mesitylene with respect to enantio- and diastereoselectivity; providing **3aa** in 78% yield with 89% ee and 71:29 dr (entry 18). The reaction temperature can be decreased to 25 °C and 67% yield of **3aa** with 92% ee and 74:26 dr was obtained (entry 19). A slight increase in enantio- and diastereoselectivity could be obtained when the reaction temperature was decreased to 10 °C, but the reaction rate became too sluggish to be useful (Table 1, entry 20).

Using the established conditions, allylic alkylations of α-fluoro-β-ketoesters **1b–g** with MBH carbonate **2a** were found to afford the products **3ba–ga** in 67–79% yield with 88–96% ee and 3:1 to 4:1 dr (Table 2, entries 1–6). The results showed that the introduction of various aryl substituents in α-fluoro-β-ketoesters did not affect the reactivity and stereoselectivity. Subsequently, the scope of the allylic alkylation with respect to various MBH carbonates **2** and α-fluoro-β-ketoester **1a** was investigated (Table 2, entries 7–20). The desired allylic alkylation adducts **3ab–o** were achieved in moderate to good yields with good to excellent enantioselectivities and moderate diastereoselectivities. MBH carbonates (Table 2, **2b**–**k**) with electron-withdrawing groups appended on the aromatic rings were more active than those (Table 2, **2l**–**m**) with electron-neutral and donating groups. Excellent ee values with moderate dr values were obtained when the phenyl groups of MBH carbonates were replaced with hetereoaromatic groups, such as thiophene and furan (Table 2, **2n**–**o**).

Conclusion

We have developed an asymmetric allylic alkylation of MBH carbonates with α-fluoro-β-ketoesters, catalyzed by a commercially available *Cinchona* alkaloid. Several fluorinated adducts, with chiral quaternary carbon centres containing a fluorine atom, were successfully prepared in 50–93% yields with 84–96% ee and a dr of 3:1 to 4:1. The absolute configurations of adducts still have to be determined and will be reported in due course.

Table 2: Allylic alkylation of α-fluoro-β-ketoesters **1** with MBH carbonates **2**[a].



Entry	Ar^1, **1**	Ar^2, **2**	Time (h)	**3**	Yield (%)[b]	ee (%)[c]	dr[d]
1	*p*-FPh, **1b**	Ph, **2a**	40	**3ba**	71	88	3:1
2	*p*-ClPh, **1c**	Ph, **2a**	70	**3ca**	79	93	3:1
3	*p*-BrPh, **1d**	Ph, **2a**	70	**3da**	75	96	3:1
4	*m*-BrPh, **1e**	Ph, **2a**	70	**3ea**	72	90	3:1
5	3,5-Cl_2Ph, **1f**	Ph, **2a**	70	**3fa**	69	88	3:1
6	*p*-MePh, **1g**	Ph, **2a**	50	**3ga**	67	94	4:1
7	Ph, **1a**	*p*-NO_2Ph, **2b**	70	**3ab**	91	95	3:1
8	Ph, **1a**	*p*-CF_3Ph, **2c**	70	**3ac**	65	87	4:1
9	Ph, **1a**	*p*-FPh, **2d**	70	**3ad**	71	90	3:1
10	Ph, **1a**	*p*-ClPh, **2e**	70	**3ae**	73	93	4:1
11	Ph, **1a**	*p*-BrPh, **2f**	96	**3af**	64	91	4:1
12	Ph, **1a**	*m*-NO_2Ph, **2g**	96	**3ag**	93	95	3:1
13	Ph, **1a**	*m*-ClPh, **2h**	70	**3ah**	81	91	3:1
14	Ph, **1a**	*m*-BrPh, **2i**	70	**3ai**	78	90	4:1
15	Ph, **1a**	*o*-FPh, **2j**	96	**3aj**	73	86	4:1
16	Ph, **1a**	*o*-ClPh, **2k**	70	**3ak**	84	86	4:1
17	Ph, **1a**	*p*-MePh, **2l**	70	**3al**	53	91	4:1
18	Ph, **1a**	*p*-MeOPh, **2m**	70	**3am**	50	91	3:1
19	Ph, **1a**	2-thienyl, **2n**	90	**3an**	78	92	4:1
20	Ph, **1a**	2-furyl, **2o**	96	**3ao**	73	84	3:1

[a] Reactions were performed with 0.1 mmol of **1**, 0.3 mmol of **2**, and 0.005 mmol of $(DHQD)_2$PHAL in 1.0 mL mesitylene. [b] Yield of isolated product. [c] Determined by chiral HPLC on the major diastereoisomer. [d] Determined by ^{1}H NMR analysis.

Experimental

Representative procedure for the synthesis of 3aa: α-Fluoro-β-ketoester **1a** (21.0 mg, 1.0 equiv, 0.1 mmol) and $(DHQD)_2PHAL$ (7.8 mg, 0.1 equiv, 0.01 mmol) were dissolved in mesitylene (1.0 mL) at 25 °C. After the addition of MBH carbonate **2a** (3.0 equiv, 0.3 mmol) the reaction mixture was stirred at 25 °C. The reaction was monitored by TLC. After 96 hours, flash chromatography affords product **3aa** (25.7 mg, 67% yield) as colorless oil.

Supporting Information

Supporting Information File 1

Experimental details and spectroscopic data.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-216-S1.pdf]

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Total synthesis of the endogenous inflammation resolving lipid resolvin D2 using a common lynchpin

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Full Research Paper

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Abstract

The total synthesis of the endogenous inflammation resolving eicosanoid resolvin D2 (**1**) is described. The key steps involved a Wittig reaction between aldehyde **5** and the ylide derived from phosphonium salt **6** to give enyne **17** and condensation of the same ylide with aldehyde **7** to afford enyne **11**. Desilylation of **11** followed by hydrozirconation and iodination gave the vinyl iodide **4** and Sonogashira coupling between this compound and enyne **3** provided alkyne **18**. Acetonide deprotection, partial reduction and ester hydrolysis then gave resolvin D2 (**1**).

Introduction

The resolution of inflammation is a tightly governed active process effectively mediated by a range of bioactive polyunsaturated fatty acids, peptides and proteins. In 2002, a new family of endogenously generated lipid mediators involved in the resolution of inflammation named the resolvins (resolution phase interaction products) were identified by Serhan and co-workers in the inflammatory exudates of aspirin treated mice [1-3]. The resolvins are divided into 2 groups, the D-series resolvins D2 (**1**) and D1 (**2**) [3], which are derivatives of docosahexaenoic acid (DHA) (Figure 1) and the E-series [4] derived from eicosapentaenoic acid. Structural analysis by mass spectrometry (MS) showed that resolvin D2 (RvD2, **1**) was a 17-hydroxy derivative of DHA (17HDHA) [1]. However, no NMR experiments were performed due to nanogram quantities isolated and the stereochemistry was tentatively assigned based on the proposed biosynthesis via lipoxygenase modification of DHA.

RvD2 (**1**) prevents the adherence of polymorphonuclear leukocytes (PMN) to the blood vessel wall by promoting the shedding of L-selectin from PMNs thus preventing binding to E selectin on the endothelial cell lining of the blood vessel [5]. Furthermore, RvD2 (**1**) promotes the influx and phagocytic activity of macrophages, facilitating clearance of dead cells and microbial pathogens, allowing resolution of inflammation and

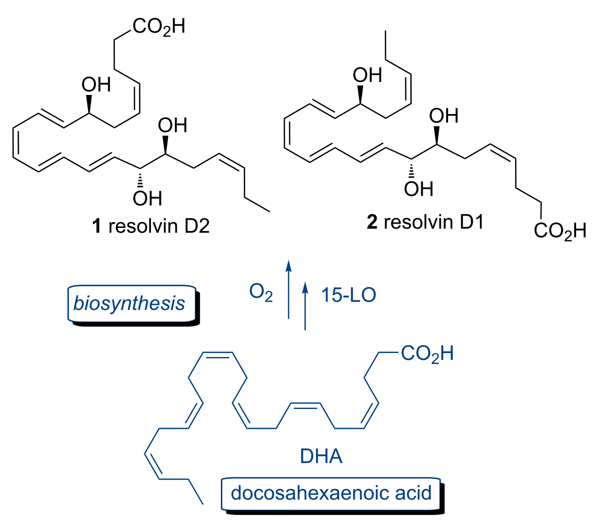


Figure 1: Structures of resolvins D1 (**1**) and D2 (**2**).

infection [5]. This successful evaluation of the resolvin series in preclinical models of bacterial sepsis has stimulated strong interest in their therapeutic potential, as RvD2 appears to express the unusual combination of anti-inflammatory and antimicrobial activity. Further interest in inflammation-resolving lipids is stimulated by their inhibitory effects on inflammatory pain, which are mediated via inhibition of the activity of TRPV1 and TRPA1 calcium channels on sensory nerves [6]. Resolvin D1 (**2**) [7] has been shown to act directly on human PMNs and also regulates actin polymerization [8]. Whilst RvD1 has been shown to act on the FPR2 and GPR32 types of G-Protein-coupled receptors, the receptor(s) for RvD2 remain to be identified. Identification of the receptors mediating the combined anti-inflammatory and antimicrobial actions would facilitate efforts to identify ligands that have better drug-like properties than RvD2 or its analogues. However, such efforts have been limited by the lack of availability of suitable amounts of RvD2.

The first total synthesis of (7*S*,16*R*,17*S*)-RvD2 (**1**) was communicated by Spur in 2004 [9] but this report did not include an experimental section although physical data for some compounds was provided. A similar synthesis of RvD2 was utilized by others for the production of **1** for a biological study [5] but again, there was no experimental provided. The total synthesis of resolvin D1 has also been reported [10] along with resolvins D3 [11], D5 [12], D6 [13] and resolvins E1 [4,14,15], E2 [16,17] and E3 [18] with full experimental details included for resolvins D3 [11], E2 [16] and E3 [18]. An improved synthesis of the C16–C20 fragment of resolvin E1 has also been reported [19]. We were interested in accessing amounts of RvD2 (**1**) for biological evaluation but without detailed synthetic sequence to follow and given the very high cost [20] of commercial **1** we elected to develop an alternative route to provide this important compound and analogues for further biological evaluation. Herein we describe a synthesis of RvD2 (**1**) which includes full experimental details so that other researchers can produce useful amounts of this important compound as well as novel isomers.

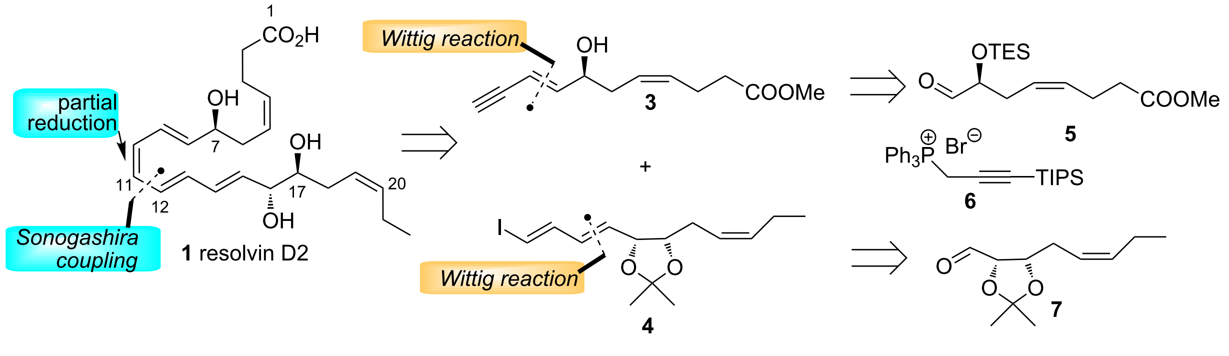
Results and Discussion

Retrosynthetic analysis

A retrosynthetic analysis of RvD2 (**1**) is shown in Scheme 1. It was envisaged that the target compound **1** could be secured via a Sonogashira coupling to form the C11–C12 bond followed by partial reduction. This is similar to the endgame of the reported syntheses of **1** [5,9] but both of these approaches involved formation of the C9–C10 bond as the convergent step. In our approach, **1** could arise from enyne **3** and vinyl iodide **4** which could both be obtained by Wittig extension using the common linchpin phosphorus ylide derived from phosphonium salt **6** [21,22] and each of the homochiral aldehydes **5** and **7** [9].

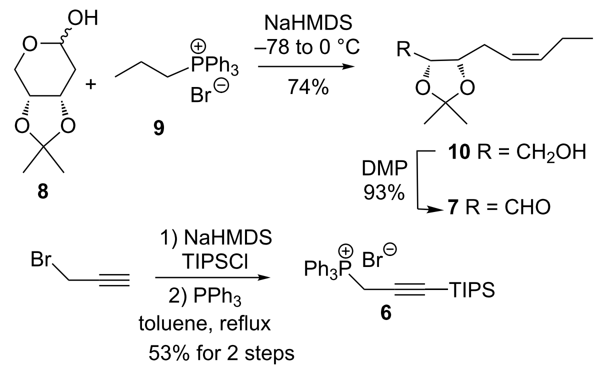
Synthesis of vinyl iodide 4

The synthesis of fragment **4** began with the production of the aldehyde **7** as shown in Scheme 2. A Wittig reaction between



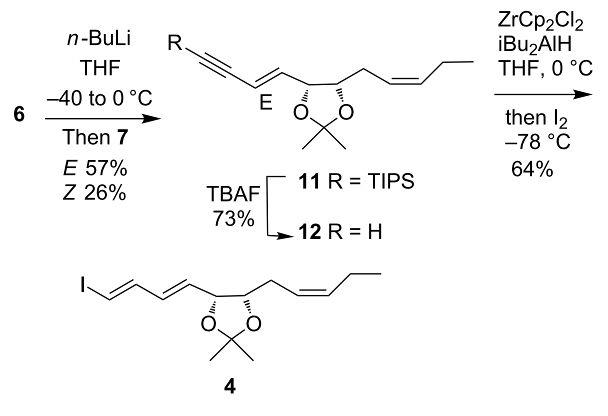
Scheme 1: Retrosynthetic analysis of RvD2 (**1**).

hemiacetal **8** [23] and the ylide derived from **9** provided the alkene **10** [9] with excellent stereoselectivity. Oxidation of **10** with Dess–Martin periodinane then afforded aldehyde **7**. The phosphonium salt **6** [21,22] was produced from propargyl bromide via silylation of the derived sodium salt with TIPSCl followed by reaction with triphenylphosphine.



Scheme 2: Synthesis of aldehyde **7** and phosphonium salt **6**.

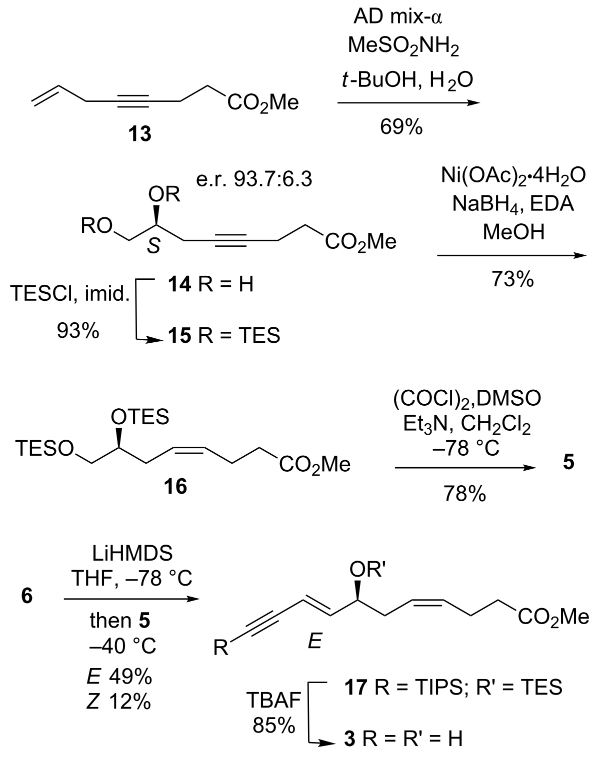
Treatment of the salt **6** with *n*-BuLi gave the ylide and condensation with the aldehyde **7** afforded the desired *E*-enyne **11** along with the *Z*-isomer in a ratio of 2.2:1 which were easily separated by flash chromatography (Scheme 3). The minor *Z*-isomer could also provide novel stereoisomer analogues of RvD2 (**1**). Removal of the TIPS group with TBAF gave terminal alkyne **12**. Alkyne **12** then underwent smooth hydrozirconation utilizing the procedure reported by Negishi [24] were $ZrCp_2HCl$ is generated in situ by reduction of $ZrCp_2Cl_2$ with DIBALH in THF. Iodinolysis of the zirconium species then gave the diene iodide **4** in good yield. Selectivity for this process was excellent with only a trace of the regioisomer formed.



Scheme 3: Synthesis of vinyl iodide **4**.

Synthesis of dienyne 3

Our approach to the aldehyde **5** began with the production of the known bis-TES ether [9] produced by an alternative procedure (Scheme 4) in which the C7 stereochemistry was introduced via asymmetric dihydroxylation [25,26]. Thus, ester **13** [27] was treated with AD-mix-α in *t*-BuOH/H_2O to give diol **14** in reasonable yield. The enantioselectivity and absolute configuration of the secondary alcohol was determined by conversion of diol into the bis-(*S*)-Mosher ester [28,29]. Integration of the ^1H MMR spectrum indicated the e.r. was 93.7:6.3 and Mosher analysis (See Supporting Information File 2 for details) confirmed the stereochemistry of the new asymmetric center of the major enantiomer as *S* in accord with the predicted outcome [25]. Silylation gave bis-TES ether **15** and partial reduction of the alkyne using P2-Ni as catalyst [30] afforded the alkene **16**. Desilylation of the primary TES group in **16** and concomitant oxidation to aldehyde **5** was achieved under Swern conditions as reported by Spur [31].

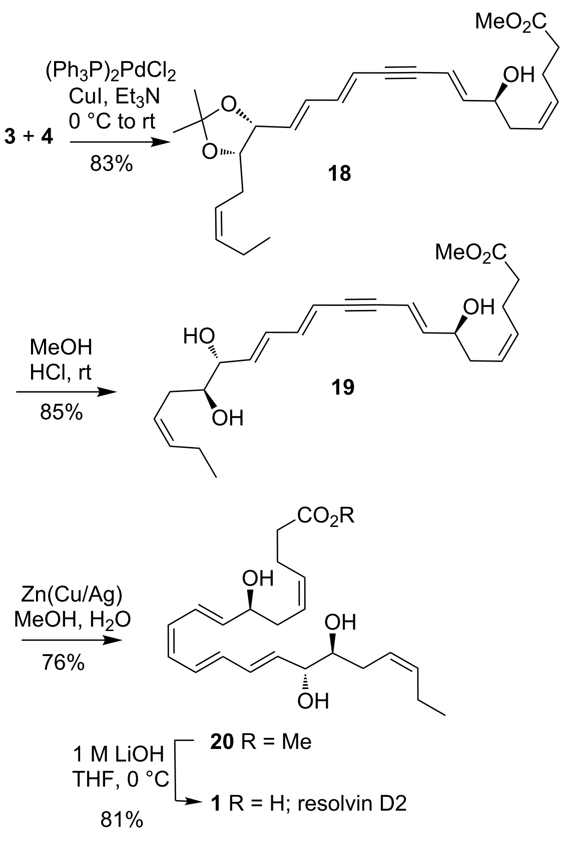


Scheme 4: Synthesis of enyne **3**.

Deprotonation of salt **6** with LiHMDS followed by condensation with aldehyde **5** gave the *E*-enyne and the corresponding *Z*-isomer in a 4:1 ratio. The use of LiHMDS as base was critical for reasonable yields and stereoselectivity in this case. Global deprotection of **17** with TBAF gave the enyne **3** in good yield.

Total synthesis of resolvin D2 (**1**)

The completion of the synthesis of RvD2 (**1**) is shown in Scheme 5. Sonogashira coupling [32,33] between **3** and **4** was very efficient giving the alkyne **18** in good yield. Removal of the acetonide was effected by treatment with HCl in MeOH to give the known triol **19** [9]. The final steps to **1** were similar with those previously reported [5,9]. Thus, partial reduction of the triple bond using Zn(Cu/Ag) [34] to afforded RvD2 methyl ester **20** in 76% yield. A large excess of the Zn reagent was required to obtain a good conversion of **19** into **20**. The ^{1}H NMR spectrum ($CDCl_3$ solvent) of RvD2 methyl ester (**20**) compared well to that reported [5]. Final ester hydrolysis and mild acid work-up then gave RvD2 (**1**).



Scheme 5: Completion of the synthesis of RvD2 (**1**).

The synthetic RvD2 (**1**) had physical data identical to that reported [9,35] and we measured the specific rotation of this material for the first time ($[\alpha]_D$ −17.5° (*c* 0.075, CH_2Cl_2)). In our hands, both RvD2 methyl ester (**20**) and RvD2 (**1**) itself were highly unstable, especially to acid. Prolonged standing in $CDCl_3$ or CD_3CN solution or exposure to light caused rapid decomposition and so NMR spectra were obtained quickly. We found that RvD2 methyl ester (**20**) was not very soluble in CD_3CN so spectra were best run in $CDCl_3$ that was filtered through basic alumina immediately prior to use. Spectra for RvD2 (**1**) were always measured for CD_3CN. Even with short exposure to the solvent, we still observed degradation to unidentified compounds. Samples of RvD2 (**1**) can be stored in EtOH or frozen in DMSO solution but should be used immediately upon thawing. Alternatively, the triol **19** proved more stable than both RvD2 methyl ester (**20**) and RvD2 (**1**) and can be stored for longer periods prior to conversion to **1** which should be used rapidly for biological assessment to avoid degradation.

Conclusion

The total synthesis of RvD2 (**1**) has been completed using a common linchpin Wittig reaction. Using this approach, we were able to prepare sufficient quantities of this important inflammation resolving compound for further biological evaluation.

Supporting Information

Supporting Information File 1

Experimental.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-310-S1.pdf]

Supporting Information File 2

^{1}H and ^{13}C NMR spectra of all intermediates and the mass spectrum of RvD2 (**1**).
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-310-S2.pdf]

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35. One ^{13}C NMR chemical shift (CD_3CN solvent) was different to that reported. (34.6 ppm quoted as 31.2 ppm in [9]).

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