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Application of Chiral 2-Isoxazoline for the Synthesis of *syn*-1,3-Diol Analogues

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Abstract

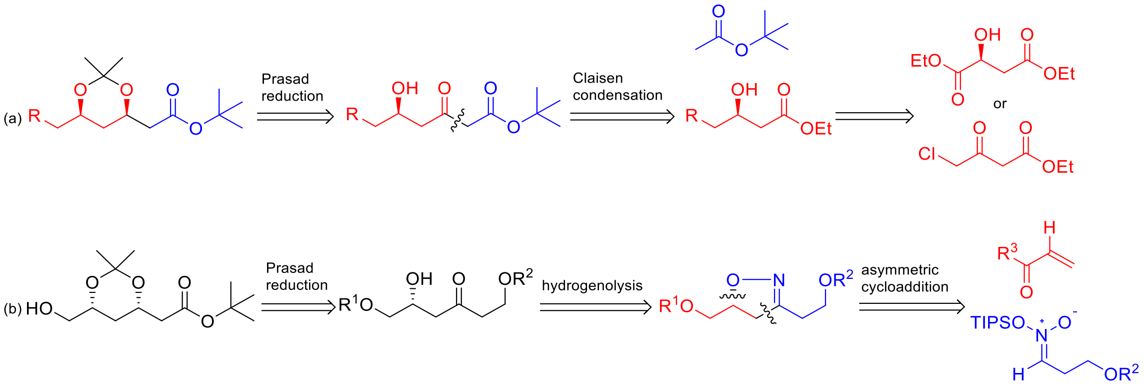
Asymmetric cycloaddition of TIPS nitronate catalyzed by “Cu(II)-bisoxazoline” gave the 2-isoxazoline product in 85% yield, which was converted into *t*-butyl (3*S*,5*R*)-6-hydroxy-3,5-*O*-isopropylidene-3,5-dihydroxyhexanoate in 11 steps via a *β*-hydroxy ketone.

Keywords

cycloaddition; silyl nitronate; isoxazoline; *β*-hydroxy ketone; 1,3-diol

Introduction

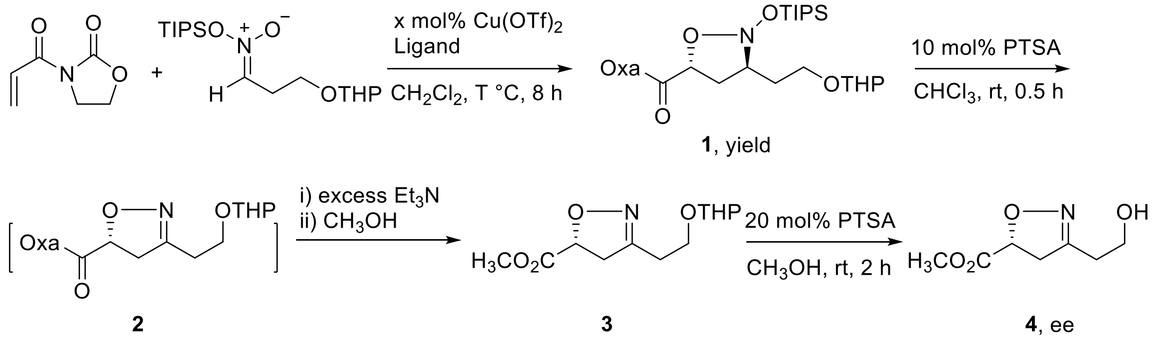
Chiral 1,3-diol structure is common in a broad spectrum of natural products.[1,2] (3*R*)-*β*-Hydroxy-*δ*-lactone or its open-ring equivalent (3*R*)-*syn*-3,5-dihydroxypentanoic acid, is a common structure in naturally occurring mevastatin (or compactin), lovastatin or closely related statins, and synthetic statins. Either *syn*- or *anti*- 1,3-diol could be prepared from enantiomerically pure *β*-hydroxy ketone via *β*-hydroxy directed carbonyl reduction in Evans' [3] or Prasad's[4–11] method. Narasaka–Prasad reduction of the *δ*-hydroxy-*β*-keto-ester derived from a *β*-hydroxy ester[12–23] is widely used to prepare *t*-butyl (3*R*)-3,5-*O*-isopropylidene-3,5-dihydroxyhexanoate (Scheme 1a)[24–37], which is a building block for synthetic statins,[38–41] though enzymatic synthesis[42–48] of chiral *β*-hydroxy-*δ*-lactone moiety or its equivalents, pioneered by Wong,[42] is equally competitive. Here, we report the preparations of *t*-butyl (3*S*,5*R*)-6-hydroxy-3,5-*O*-isopropylidene-3,5-dihydroxyhexanoate and related *syn*-1,3-diol analogues from a chiral 2-isoxazoline (Scheme 1b). This work is a continuous part of our effort in the asymmetric synthesis and applications of chiral 2-isoxazolines.[49–51]



Scheme 1: Access to *t*-butyl 3,5-*O*-isopropylidene-3,5-dihydroxyhexanoates: (a) Previous methods using Claisen condensation. (b) Our new method using cycloaddition.

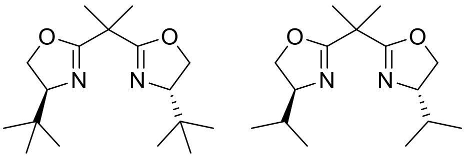
Results and Discussion

Our syntheses commenced with a chiral 3,5-disubstituted-2-isoxazoline **3** or **4**, which was prepared from silyl nitronate via asymmetric 1,3-dipolar cycloaddition developed in our lab (Scheme 2).[49] 3-Nitropropionic acid methyl ester was first tried to prepare the corresponding triisopropylsilyl nitronate but no desired product was observed. 3-Nitropropanol, protected as the THP ether, was used to prepare the triisopropylsilyl nitronate. Catalytic asymmetric cycloaddition gave the 2-isoxazolidine cycloadduct **1** in a high yield. In the light of our previous ligand screening results,[49] two bisoxazolines with an isopropyl or *t*-butyl group were tested. Optimization of the conditions established that 26 mol% ligand B together with 20 mol% Cu(OTf)$_2$ in anhydrous CH_2Cl_2 catalyzed the cycloaddition between *N*-acryloyl-1,3-oxazolidin-2-one and the silyl nitronate at –50 °C to give **1** in 95% isolated yield, which subsequently generated **4** in 80% ee. Decreasing the amount of the chiral Lewis acid catalyst led to the decrease of both the ee and the yield. Desilylation of the 2-isoxazolidine **1** was effected in $CHCl_3$ using catalytic amount of *p*-toluenesulfonic acid (PTSA). Though the yield of the *in situ* generated 2-isoxazoline **2** bearing the 1,3-oxazolidin-2-one auxiliary was perfect, purification of **2** by silica gel chromatography was problematic due to decomposition. No pure product was isolated from crude **2** by chromatography on silica gel. Decomposition happened to a compound similar to **2**, in which the 3-substituent was CH_2OH.[49] To overcome this problem, the crude reaction mixture containing **2** and PTSA was concentrated before excess Et_3N was added followed by CH_3OH as the solvent. These operations removed the 1,3-oxazolidin-2-one auxiliary while reserving the THP group, and obtained the corresponding methyl ester **3** (Scheme 2), which was stable and could be subjected to silica gel chromatography. Compound **4** was used to determine the stereoselectivity of the cycloaddition step as well as for oxidation.



Entry	Ligand	x mol% Cu	T (°C)	Yield (%)	ee (%)
1	**A**	10	−50	25	18
2	**A**	20	−50	75	72

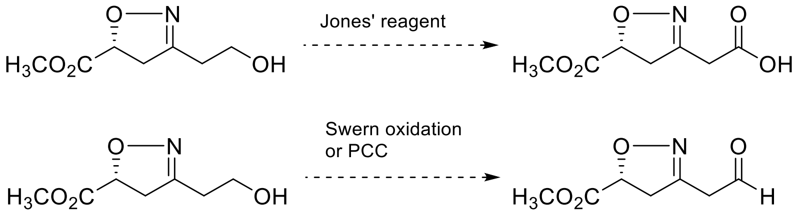
3	**B**	10	−50	70	66
4	**B**	20	−50	95	80
5	**B**	20	−40	78	78
6	**B**	20	−60	84	80



Ligand A Ligand B

Scheme 2: Optimization of the conditions for the asymmetric cycloaddition.

Oxidation of the 2-isoxazoline **4** with Jones' reagent gave a complicated mixture, in which the desired carboxylic acid was not observed (Scheme 3). Stepwise oxidation of the free hydroxy group to carboxy via intermediary of the aldehyde was then examined. Swern or pyridinium chlorochromate (PCC) oxidation of **4** also gave a complicated mixture without the desired aldehyde detected. These failed reactions indicated that the 2-isoxazoline moiety could not survive under oxidation conditions. Based on this assumption, the corresponding silyl nitronate from 3-nitropropanal or its acetal was not tried for cycloaddition.



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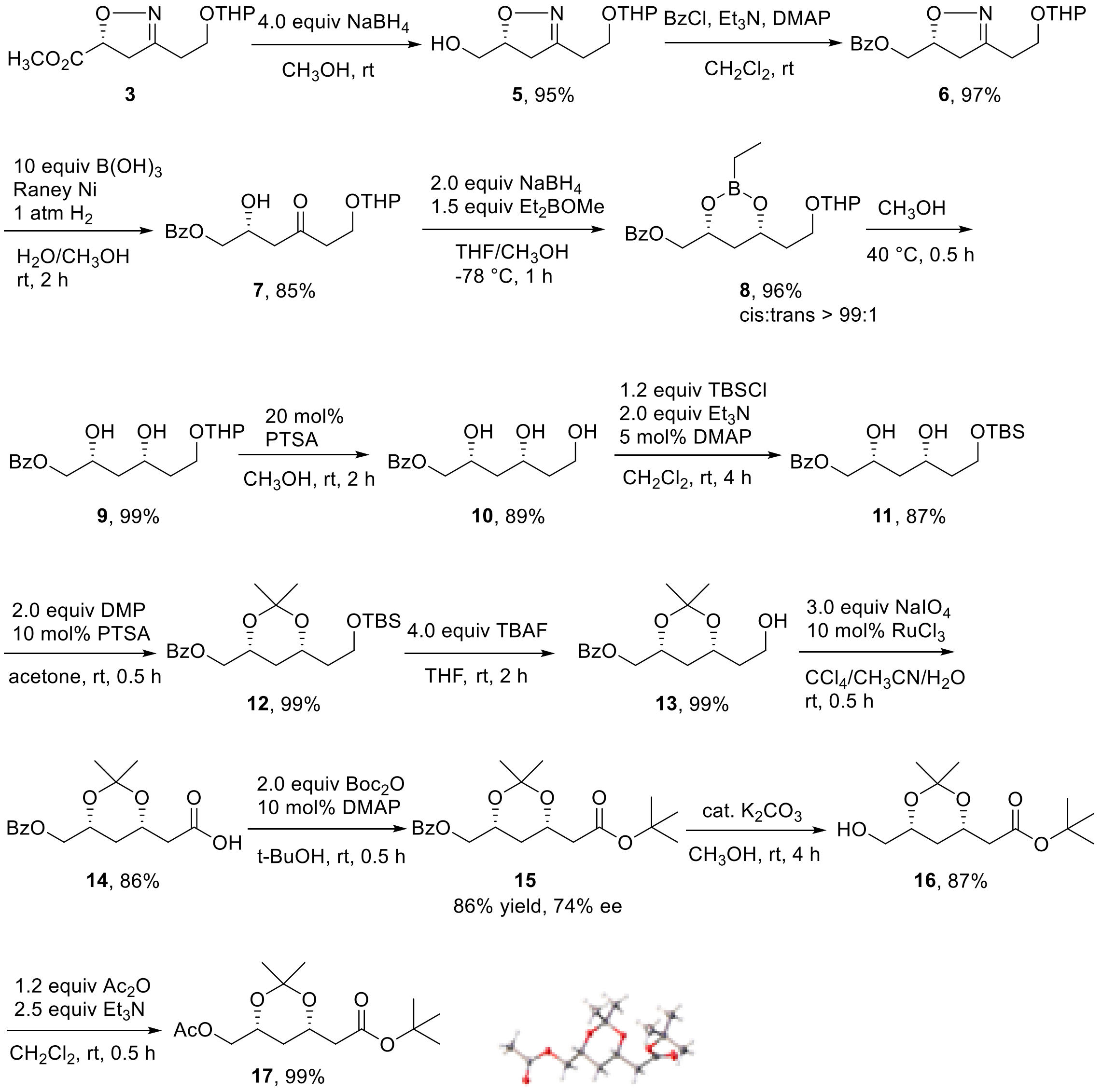
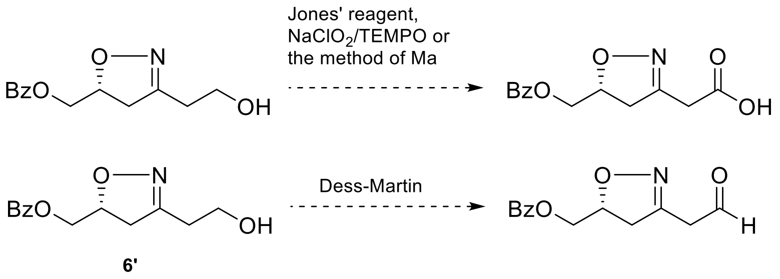
Scheme 3: Attempted oxidations of **4**.

We then set to liberate the *β*-hydroxy ketone synthon by ring-opening of the isoxazoline **3** (Scheme 4). Raney Ni catalyzed hydrogenolysis in the presence of boronic acid had been widely utilized to disconnect the N–O bond as well as to hydrolyze the resulting imine into a ketone.[52] We applied this method to **3**. However, the desired *β*-hydroxy ketone was never obtained. In one instance, the methyl ketone from retro-aldol reaction of the desired *β*-hydroxy ketone was observed. In our experience, hydrogenolysis of 2-isoxazoline having a 5-ester group was troublesome. Thus, the 5-ester group was reduced with $NaBH_4$ to give **5**. The hydroxy was subsequently protected with benzoyl (Scheme 4), which also worked as a chromophore facilitating HPLC analysis. Here, we tried oxidations once again. After removal of THP from **6**, the resulting compound **6'** was subjected to oxidation with various reagents (Scheme 5).[53–55] The expected carboxylic acid or aldehyde was not observed, which further verified the intolerance exemplified in Scheme 4. These results prompted us to try the oxidation in a later stage.



Scheme 4: Preparations of **16** and related *syn*-1,3-diol compounds.

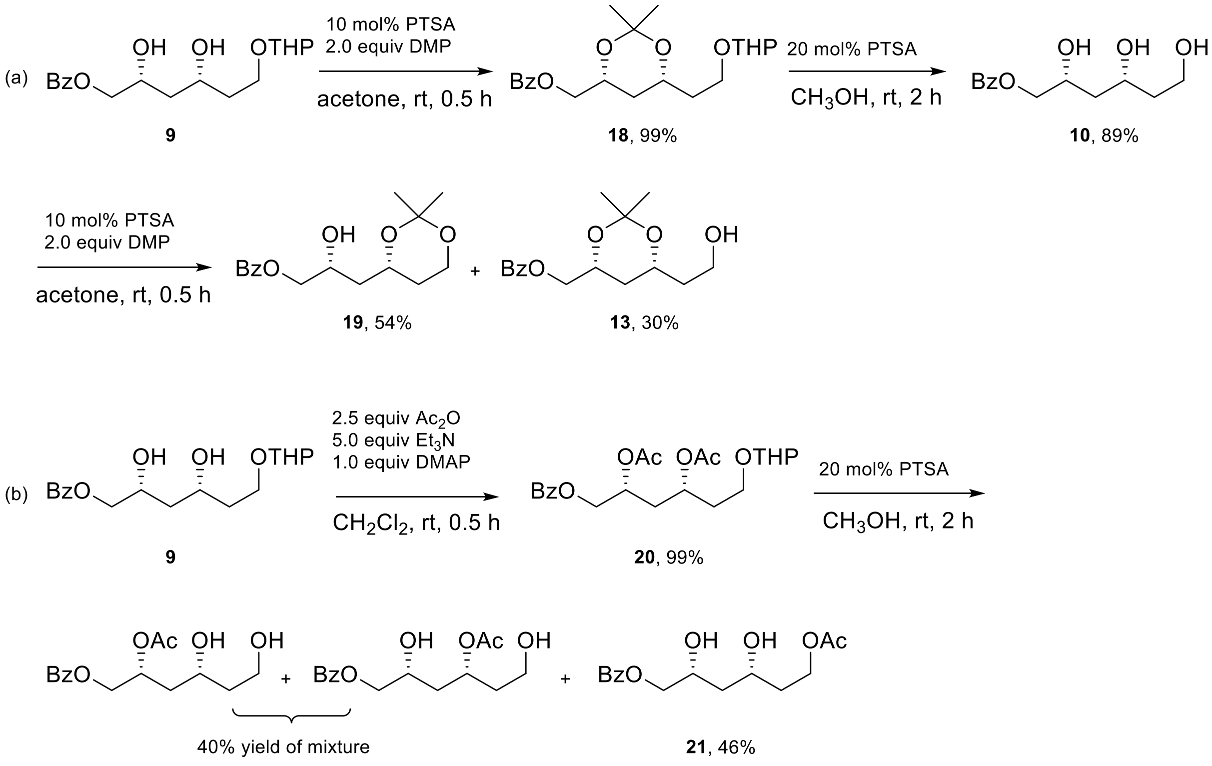


Scheme 5: Attempted oxidations of **6'**.

When **6** was subjected to Raney Ni catalyzed hydrogenolysis, the desired *β*-hydroxy ketone **7** was obtained in 85% yield (Scheme 4). Under the weak acidic conditions, the THP group survived. Next, Narasaka–Prasad reduction[4–11] of **7** using Et_2BOMe and $NaBH_4$ at −78 °C gave stable ethylboronate **8** in 96% yield. Several ethylboronate compounds have been reported.[9–11, 56–62] From **8** to **9**, no H_2O_2 treatment was necessary. Rotary evaporation of **8** with CH_3OH at ca. 40 °C easily removed the ethylborane group. Removal of THP in **9** delivered a 1,3,5-trihydroxy compound **10**. In another way, **10** could be prepared by treating **8** with PTSA in CH_3OH at rt. NMR spectra of **8–10** exhibited only one set of signals corresponding to the *syn*-dihydroxy products, indicating an extra high diastereoselectivity (*syn*:*anti* > 99:1) during the reduction. To unambiguously determine the diastereo ratio, the *anti*-1,3-diol corresponding to **10** was prepared from **7** by $RuCl_3$-PPh_3 catalyzed hydrogenation.[63,64] However, the two diastereomers had completely same proton NMR spectra.

The terminal hydroxy group of **10** was protected with TBS[65–69] and the *syn*-hydroxy groups subjected to acetonization using PTSA and dimethoxypropane (DMP) to give **12** in 86% total yield.[70] Treatment of **12** with TBAF again liberated the terminal hydroxy group for further oxidation. $RuCl_3$ catalyzed oxidation of **13** with $NaIO_4$ yielded the carboxylic acid **14** in 86% yield,[70] which was reacted with Boc_2O to get the *tert*-butyl ester **15**. [26,43,71] The ee of **15** was determined as 74%. The racemic sample of **15** was prepared from racemic diethyl malate in known methods.[26,27] Finally, K_2CO_3 catalyzed methanolysis gave **16** in 87% yield.[26,27] The absolute stereochemistry of **16** was confirmed by the crystal structure[72] and the specific rotation[28] of **17**. Centimeter-long prismatic single crystals of **17** were obtained by slowly evaporating the solvent of a petroleum solution.

Starting from **9**, we tested several reactions in order to selectively protect the internal hydroxy groups (Scheme 6). Though not fruitful, these results deserve some comments. PTSA catalyzed acetonization of **9** using 2.0 equiv DMP gave the acetonide **18** in a quantitative yield. Treating **18** with catalytic amount of PTSA in methanol gave **10**, with the protection groups removed except benzoyl. PTSA catalyzed acetonization of **10** using 2.0 equiv DMP gave a mixture of two acetonides **19** and **13**, which are separable over silica gel chromatography (Scheme 6a). In another trial (Scheme 6b), acylation of the two hydroxy groups in **9** yielded **20** in a quantitative yield. PTSA catalyzed removal of THP in **20** in methanol did occur. However, concomitant monodeacylation as well as further acyl-transfer reaction also took place, resulting in a mixture. These results indicated THP, isopropylidene or Ac protection to primary or secondary hydroxy group did not well tolerate PTSA catalyzed methanolysis.



Scheme 6: Attempted selective protections of internal 1,3-hydroxy groups: (a) Acetonizations of 1,3-diols; (b) Removal of co-existing Ac and THP on hydroxy groups.

Conclusion

In conclusion, we synthesized *t*-butyl (3*S*,5*R*)-6-hydroxy-3,5-*O*-isopropylidene-3,5-dihydroxyhexanoate (**16**), which is enantiomeric to a key intermediate for atorvastatin, from a chiral 2-isoxazoline (**3**). The *β*-hydroxy ketone **7** obtained from **3** could be easily converted into several *syn*-1,3-diol analogues, demonstrating the usefulness of chiral 2-isoxazoline.

Experimental

1: To a dry Schlenk tube were added $Cu(OTf)_2$ (144 mg, 0.4 mmol), chiral bisoxazoline **B** (139 mg, 0.52 mmol) and anhydrous CH_2Cl_2 (4 mL) under N_2. After stirring at room temperature for 2 h, a clear solution was formed, which was cooled to −50 °C and *N*-acryloyl-1,3-oxazolidin-2-one (282 mg, 2 mmol) was added. After stirring for 30 min, a solution of the silyl nitronate (3.0 mmol) in anhydrous CH_2Cl_2 (6 mL) was added. The mixture was stirred for 8 h at −50 °C and monitored by TLC. After the reaction was completed, the product was purified by silica gel chromatography.

Yellow oil (923 mg, 95 % yield), R_f = 0.40 (1:1 hexanes/AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.77–5.74 (m, 1H, $CH_2C\mathbf{H}O$), 4.53 (s, 1H, $OC\mathbf{H}O$), 4.44 (t, *J* = 8.0 Hz, 2H, $C\mathbf{H}_2O$), 4.03–3.99 (m, 2H, $C\mathbf{H}_2O$), 3.79–3.74 (m, 2H, $OC\mathbf{H}_2CH_2$), 3.47–3.37 (m, 3H, $NC\mathbf{H}$ and $NC\mathbf{H}_2$), 2.75–2.66 (m, 1H, $CHC\mathbf{H}_2CH$), 2.31–2.27 (m, 1H, $CHC\mathbf{H}_2CH$), 2.17–2.12 (m, 1H, $C\mathbf{H}_2CH_2$), 1.84–1.79 (m, 2H, $CH_2C\mathbf{H}_2$ and $CH_2CH_2C\mathbf{H}_2$), 1.68–1.49 (m, 6H, $C\mathbf{H}_2C\mathbf{H}_2C\mathbf{H}_2$), 1.24–1.15 (m, 3H, SiCH), 1.07–1.01 (m, 18H, $SiCH(C\mathbf{H}_3)_2$);

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ: 170.8, 153.1, 98.9, 98.9, 77.4, 77.2, 69.9, 69.8, 65.2, 62.8, 62.5, 62.3, 42.6, 35.6, 35.5, 30.7, 30.6, 29.9, 29.8, 25.5, 19.6, 19.5, 18.1, 18.0, 12.2; IR (cm^{-1}): 3544, 2942, 2867, 2725, 2249, 1780, 1704, 1464, 1386, 1275, 1133, 1035, 883, 806, 677; MS (ESI): calculated for $C_{23}H_{42}N_2O_7Si$ $[M+Na]^+$ 509.2659, found 509.2659.

3: To a solution of **1** (0.86 g, 1.78 mmol) in $CHCl_3$ (15 mL) was added PTSA (31 mg, 0.178 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred until complete consumption of the starting material (0.5 h). Vacuum was applied to remove the solvent before Et_3N (5 mL) was added. After stirring for 5 min, methanol (30 mL) was added and the mixture stirred overnight at room temperature. The crude product was purified by column chromatography.

Yellow oil (0.41 g, 89% yield), R_f = 0.42 (1:1 hexanes/ AcOEt). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.92–4.87 (m, 1H, OC**H**CO), 4.51–4.50 (m, 1H, OC**H**O), 3.88–3.82 (m, 1H, C$\mathbf{H}_2$O), 3.75–3.71 (m, 1H, C$\mathbf{H}_2$O), 3.68 (s, 3H, C$\mathbf{H}_3$), 3.56–3.50 (m, 1H, C$\mathbf{H}_2$O), 3.42–3.39 (m, 1H, C$\mathbf{H}_2$O), 3.24–3.31 (m, 1H, CHC$\mathbf{H}_2$CH), 2.62–2.54 (m, 1H, CH_2C$\mathbf{H}_2$CH), 1.74–1.44 (m, 6H, C$\mathbf{H}_2$C$\mathbf{H}_2$C$\mathbf{H}_2$); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ: 171.0, 156.9, 99.0, 98.9, 64.4, 64.3,62.5, 62.4, 52.6, 41.6, 30.6, 27.9, 25.4, 19.6, 19.5; IR (cm^{-1}): 3481, 2950, 2873, 2852, 2657, 1756, 1738, 1734, 1628, 1456, 1436, 1367, 1354, 1201, 1134, 1034, 869, 814, 752, 740; MS (ESI): calculated for $C_{12}H_{19}NO_5$ $[M+H]^+$ 258.1341, found 258.1340.

Supporting Information

Electronic supplementary information (ESI) available: Complete experimental procedures and some of the spectroscopic techniques.

Acknowledgements

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