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Total synthesis of Helioxanthin, Retrohelioxanthin, and analogs via Photo-Dehydro-Diels-Alder reaction as key step

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Abstract

With the aim to develop efficient synthetic routes to 7,8-substituted aryl-naphthalene lignans and structural analogs via a Photo-Dehydro-DIELS-ALDER reaction as key step, three different approaches were investigated. The first strategy is based on the presence of electron-withdrawing groups (EWG) as placeholder for alkoxy groups (EWG strategy). Although two lignan analogs (**19**, **20**) could be prepared the EWG strategy was not an optimum solution. The second strategy takes advantage of different sizes of *meta*-substituents to force the formation of 7,8-substituted products (*meta*-directing strategy). Here, a sufficient large size difference is mandatory. While the combination TMS/OMe works very well and provided the access to natural product analogs **29** and **30**, the combination TMS/OBn completely failed. The third and most successful approach is based on blocking *ortho*-positions with the bulky

TMS group (*ortho*-blocking strategy). By using this method, the natural products helioxanthin **1** and retrohelioxanthin **2** could be successfully synthesized.

Keywords

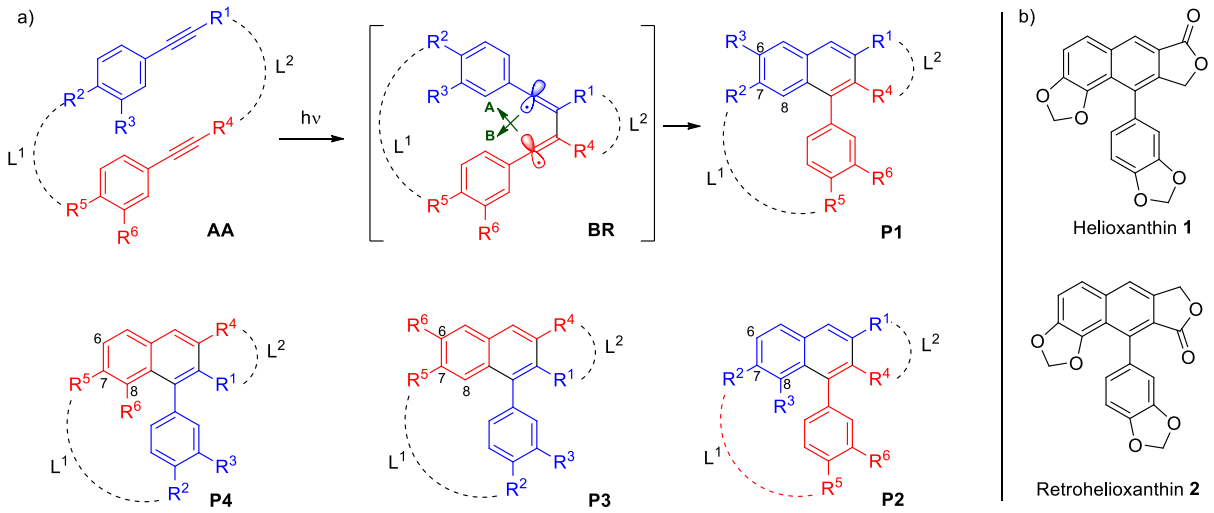
Lignans; Natural products; Total synthesis; Photochemistry; Naphthalenes

Introduction

The lignans represent a large class of structurally divers natural products. isolated from plants having in common that their basic molecular framework consists of two C_6C_3 building blocks [1]. Therefore, the lignans belong to the phenylpropanoides [2]. Cinnamic acid derivatives, *e.g.* caffeic acid, are key intermediates of the biosynthetic pathway to lignans. Depending on the kind of linkage between the C_6C_3 units and the presence of additional oxygen atoms, different types of lignans may be distinguished: dibenzylbutyrolactons and -furans, dibenzylbutans, furo[3,4-c]furans, dibenzocyclo-octadienes, and arylnaphthalenes [3]. Many lignans exhibit interesting biological activities such as antiviral [4], antibacterial [5], anti-oxidant [6], antihypertensive [7], cytotoxic [8], and antineoplastic [9] activity. Because lignans are secondary metabolites, plants contain only minute amounts in most cases. Consequently, there is still a great demand for efficient total syntheses of lignans.

For several years we are investigating the synthetic potential of the Photo-Dehydro-DIELS-ALDER (PDDA) reaction [10], especially for the total synthesis of arylnaphthalen lignans (ANL) [11,12]. The simplified mechanism of the PDDA reaction is summarized in Scheme 1 (for the sake of simplicity the intermediate cycloallenes and aspects of the spin state were omitted). Two arylacetylenes **AA** (red/blue) serve as reactants of the DDA reaction. Because the *inter*molecular PDDA

reaction is less efficient, a linker unit (L^1 or L^2) is necessary in most cases. In contrast to the classic DIELS-ALDER reaction [13] the PDDA reaction is a stepwise process. Butadien-1,4-diyl diradicals **BR** are assumed to be the first intermediates after the initial C-C bond formation. At this stage two different subsequent steps are possible, if the substituents (R^1-R^3 *vs.* R^4-R^6) of the aryl acetylenes are not identical (**A** or **B**, green). Moreover, if the substituents R^3 and/or R^5 are not hydrogen two different *o*-positions may be attacked. If the lower radical center attacks the upper arene (path **A**) products **P1** and **P2** are expected, whereas **P3** and **P4** result from path **B**. The exploration of the factors (substituents, linkers, reaction conditions) influencing the selectivity toward these four isomeric products is the key objective of our investigations. A particular challenge is the selective synthesis of products with substituents in positions 7,8 (**P2**, **P4**). A series arylnaphthalen lignans exhibits this substituent pattern. Helioxanthin **1**, a potent antiviral agent, which was first isolated from *Heliopsis scabra* [14], and its isomer retrohelioxanthin **2**, isolated from *Justicia neesii* [15] and *Linum perenne* [16], are two prominent examples of 7,8-substituted ANL. In this work, we compare three different strategies to selectively synthesize 7,8-substituted ANL and use the findings for the total synthesis of helioxanthin **1**, retrohelioxanthin **2**, and structural analogs.



Scheme 1: a) Simplified mechanism of the (Photo)-Dehydro-DIELS-ALDER reaction. b) Structures of helioxanthin **1** and retrohelioxanthin **2**.

A few total syntheses of **1** and **2** were published in the literature. As early as 1971 STEVENSON and HOLMES reported on the DDA reaction of 2-bromo-3,4-methylendioxy phenylpropiolic acid and obtained **1** with low yields and low 6,7/7,8-selecticity [17]. Later this approach was improved but the "**P1-P4**"-selectivity (see Scheme 1) was still low [18]. In 1996 CHARLTON and co-workers developed a route to helioxanthin **1** with a DIELS-ALDER reaction of *in situ* generated benzo[c]furanes with maleic anhydride [19]. Some years later MIZUFUNE and co-workers developed a total synthesis of **1** with a Pd-catalyzed benzoannulation of benzyliden butyrolactons as key step [20]. The latest method to prepare helioxanthin **1** is based on an oxidative cyclization of radicals generated from arylpropargyl cyanoacetates [21].

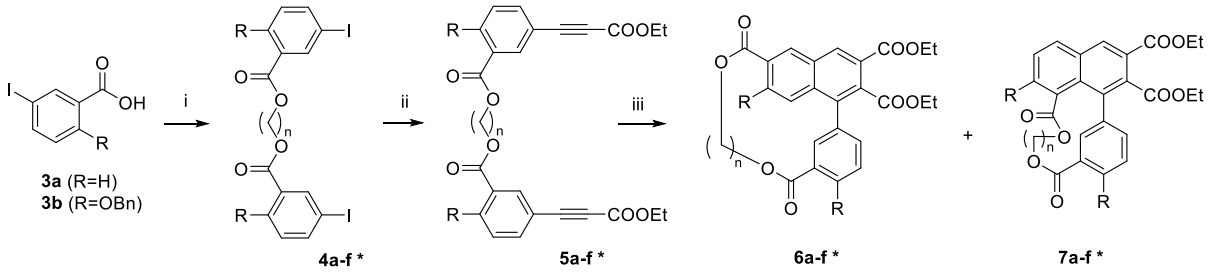
BRUMMOND and KOKSIS investigated the oxidative DIELS-ALDER reaction of cinnamyl arylpropiolates and obtained retrohelioxanthin **2** in a mixture with the 6,7-substituted isomer, whereby the latter was the main product [22]. A modification of the above-

mentioned method by CHARLTON [19] was used to prepare a mixture of **1** and **2**. [23]. Such mixtures were also obtained in the early works by STEVENSON [17,18].

Results and Discussion

The EWG strategy

In connection with earlier studies towards synthesis and properties of 1,6- and 1,8-naphthalenophanes we observed that electron-withdrawing groups (EWG) prefer the 8-position in the resulting arylnaphthalenes [24]. Esters or ketones as EWG could be converted into phenols in few steps and function as directing placeholders. Because ester groups in *m*-position regarding the alkyne moiety served as EWG at the time, we first investigated comparable systems. Thus, six PDDA reactants **5** were prepared from *m*-iodobenzoic acids **3**. While **3a** is commercially available, **3b** with an additional BnO-substituent was prepared according to the literature [25]. Using three ω,ω'-diols with different length the diesters **4a-f** were prepared (linker L^1, see Scheme 1), which were converted to **5a-f** by a SONOGASHIRA coupling [26] with triethyl orthopropiolate. The irradiation of compounds **5** with UVB light gave almost always mixtures of naphthalenophanes **6** and **7** (Scheme 2). Only in one case (entry 2, R = H, n = 4) the desired 8-substituted naphthalenophane (**7b**) was formed as main product, while elsewhere the preferred formation of 6-substituted products **6** was observed. The yields of compounds **4** – **7** are summarized in Table 1.

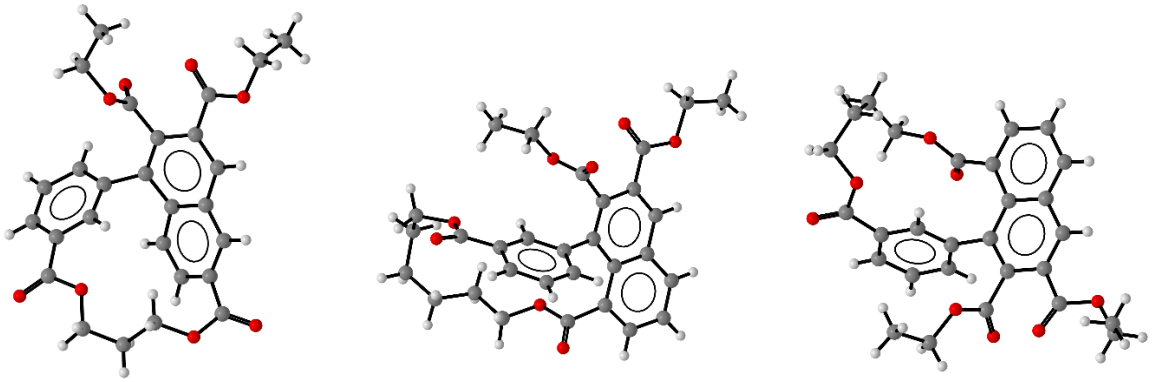


Scheme 2: Preparation of napthalenophanes **6** and **7** (i $HO(CH_2)_nOH$, DIC, DMAP, DCM, r.t., ii triethyl orthopropiolate, $PdCl_2(PPh_3)_2$, TEA, r.t., iii UVB, DCM, * see table 1).

Table 1: Yields of compounds **4** - **7**.

Entry	No.	n	R	yield of **4** (%)	yield of **5** (%)	yield of **6** (%)	yield of **7** (%)
1	**a**	6	H	67	89	35	32
2	**b**	4	H	52	78	**20**	**40**
3	**c**	3	H	62	99	55	0
4	**d**	6	OBn	70	71	56	33
5	**e**	4	OBn	75	99	15	12
6	**f**	3	OBn	54	78	79	2

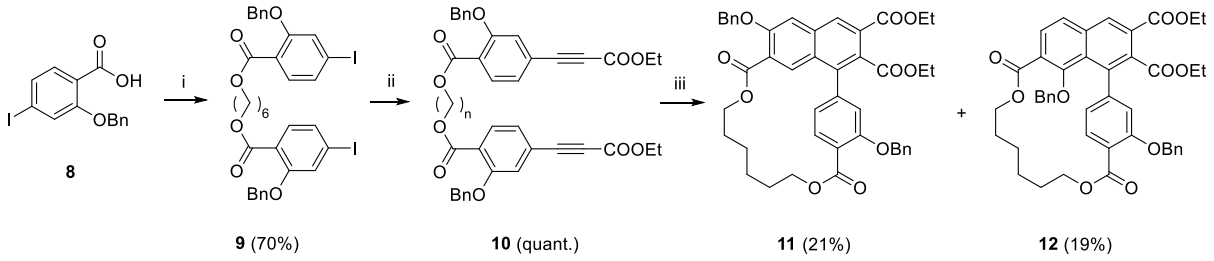
The X-ray structures of **6c**, **7a**, and **7b** are depicted in Figure 1 (For details see the Supporting information).



6c **7a** **7b**

Figure 1. X-Ray structures of **6c**, **7a**, and **7b**.

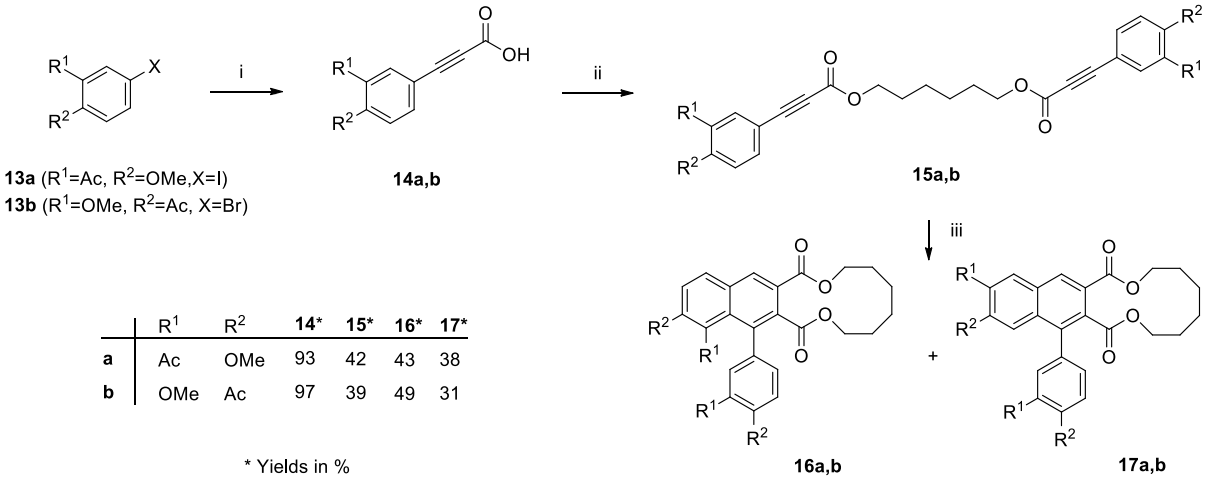
To find out whether an ester group in *p*-position is better suited to direct a group in 8-position we prepared diester **10** from O-benzyl-5-iodo-salicylic acid **8** [27] in a similar way as described above for **5**. The irradiation of **10** provided the 8- and 6-substituted products **11**, **12** without significant selectivity (Scheme 3). Bearing in mind that the conversion of ester groups to phenols requires several synthetic steps, we no longer pursued this approach.



Scheme 3: Preparation of napthalenophanes **11** and **12** (i hexan-1,6-diol, DIC, DMAP, DCM, r.t., ii triethyl orthopropiolate, $PdCl_2(PPh_3)_2$, TEA, r.t., iii UVB, DCM).

Next we investigated systems bearing a linker L^2 instead of L^1 (see Scheme 1). This opens up the possibility to use acetyl groups as EWG, which can be more easily converted to phenols. Starting with acetophenones **13a** [28] and **13b** [29] the

arylpropiolic acids were prepared in the usual manner. An esterification with hexan-1,6-diol provided the diester with Ac as EWG in *m*- (**15a**) or *p*-position (**15b**). The UVB irradiation gave the arylnaphthalenes **16** and **17** with a significant preference of 8-subsituted compounds **16** (Scheme 4).

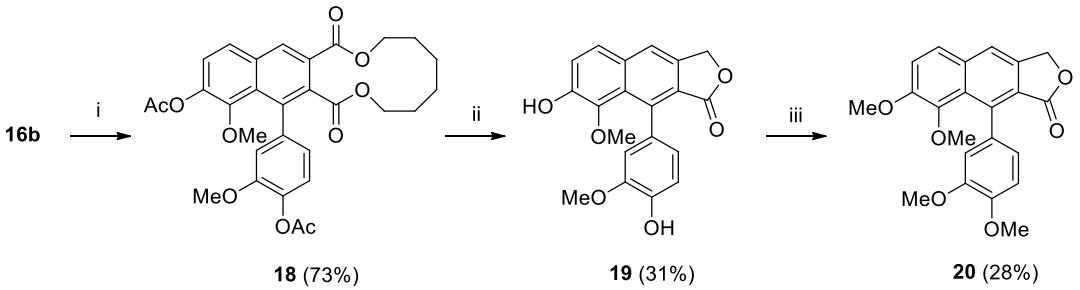


	R¹	R²	14*	15*	16*	17*
a	Ac	OMe	93	42	43	38
b	OMe	Ac	97	39	49	31

* Yields in %

Scheme 4: Preparation and PDDA reaction of diester **15** (i 1. triethyl orthopropiolate, $PdCl_2(PPh_3)_2$, TEA, 2. NaOH,H_2O/MeOH, ii i hexan-1,6-diol, DIC, DMAP, DCM, r.t., iii UVB, DCM).

16b, the main product from the irradiation of **15b**, was used for the preparation of two retrohelioxanthin analogs (**19**, **20**). Thus, the acetyl groups could be successfully converted to phenol esters by a BAEYER-VILLIGER oxidation [30]. The resulting compound **18** was reduced to **19** by treatment with $LiAlH_4$ and methylated to **20** in the end (Scheme 5).

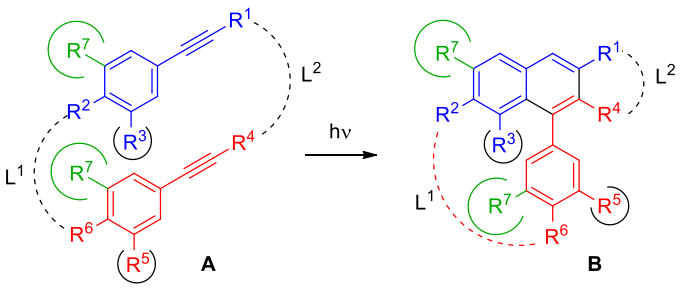


Scheme 5: Preparation of retrohelioxanthin analogs **19** and **20** (i MCPBA, DCM, rfx., ii $LiAlH_4$, THF, r.t., iii MeI, K_2CO_3, acetone, rfx.)

In summary, the EWG approach actually leads to the preference of the 8-position. In no case, however, these products were exclusively formed. Therefore, we not yet consider the EWG strategy as an optimal solution for the 6,7-*vs*-7,8 problem.

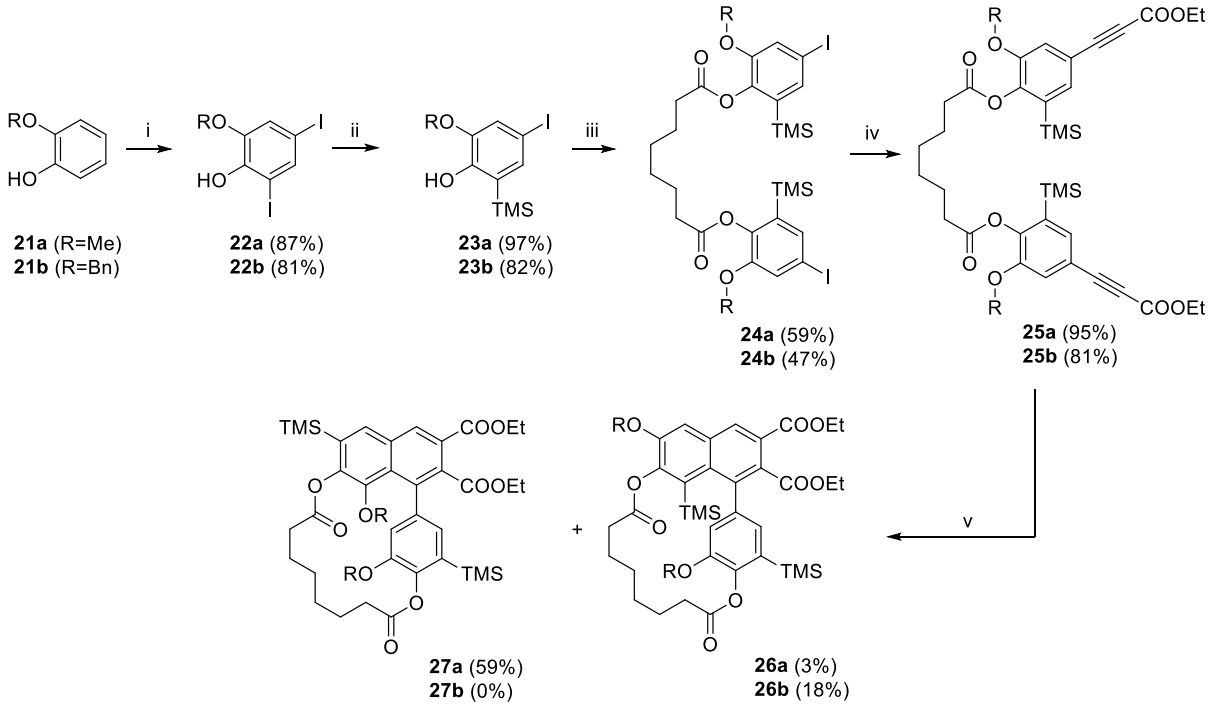
The *meta*-directing strategy

This approach is based on the hypothesis that the presence of an additional bulky substituent R^7 (green) in the reactant **A** competes with the smaller substituents R^3, R^5 and forces the formation of products with R^3 in 8-position (Scheme 6). This implies that the removal of R^7 in the product **B** is possible under mild conditions. Moreover, we were aware of the danger of "steric overkill". Bearing in mind these boundary conditions we chose trimethylsilyl as directing groups.



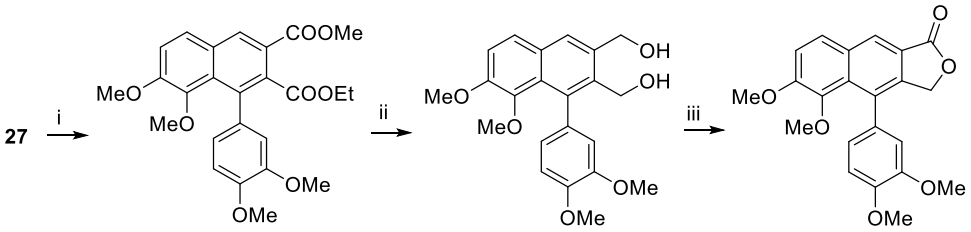
Scheme 6: The *meta*-directing strategy.

Starting with commercially available guaiacol **21a** and 2-(benzyloxy)phenol **21b** the diiodo derivatives **22** were prepared [31]. After silylation of the hydroxyl group and treatment with n-BuLi an 1,3-O→C silyl migration took place giving phenols **23** [32]. A suberic diester was then installed as linker of type L^1 based on previous experience [11, 12]. The resulting diesters **24** was subjected to a SONOGASHIRA coupling [26] and gave the PDDA reactant **25**. By irradiation of **25a** with UVB light the naphthalenophane **27a** with the OMe group in 8-position was obtained as main product (59%) while only minute amounts of product **26** with the TMS group in 8-position were formed. In contrast, the irradiation of **25b** provided only the naphthalenophane **26b** with low yields and the formation of the desired compound **27b** was not observed. Obviously, the size difference between OBn and TMS is not large enough to cause the directing effect (Scheme 7).



Scheme 7: i NaI, NaOH, NaOCl, MeOH, 0°C, ii 1. HMDS, THF, rfx. 2. BuLi, THF, -78°C, iii suberic acid, DIC, DMAP, DCM, r.t., iv triethyl orthopropiolate, $PdCl_2(PPh_3)_2$, TEA, v UVB, DCM

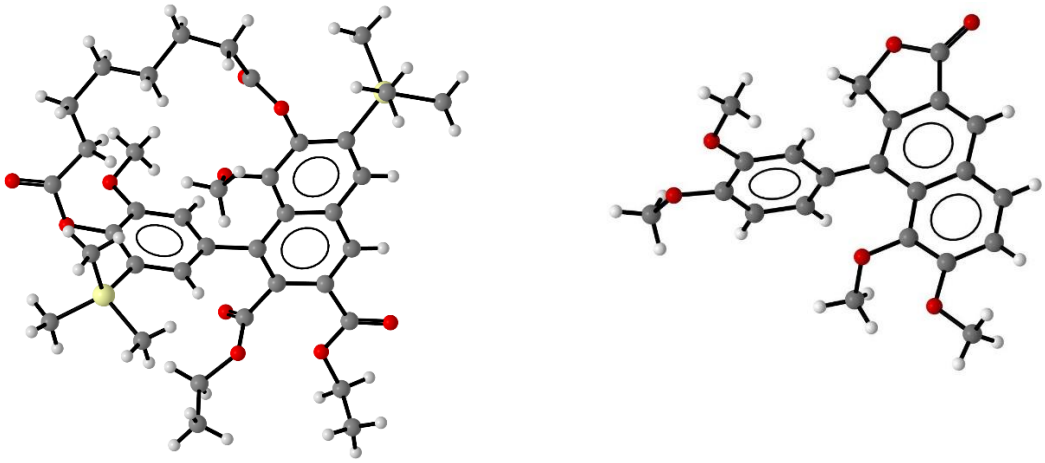
The naphthalenophane **27a** was used to prepare two new lignan analogs **29**, **30**. First the silyl groups and the linker unit were removed simultaneously and the resulting phenols and the carboxylic group in 3-position (the upper ester group was also saponified under these conditions) were methylated to compound **28**. The reduction of **28** with $LiAlH_4$ provided **29**, an analog of Alashinol D [12], and the subsequent selective oxidation with MnO_2 gave the helioxanthin analog **30** (Scheme 8).



28 (20%) **29** (32%) **30** (76%)

Scheme 8: Synthesis of compounds **29** and **30** (i NaOH, KF, MeI, EtOH, rfx., ii $LiAlH_4$, THF, r.t., iii MnO_2, DCM, r.t.)

The X-ray structures of **27a** and **30** are depicted in Figure 2 (For details see the Supporting information).



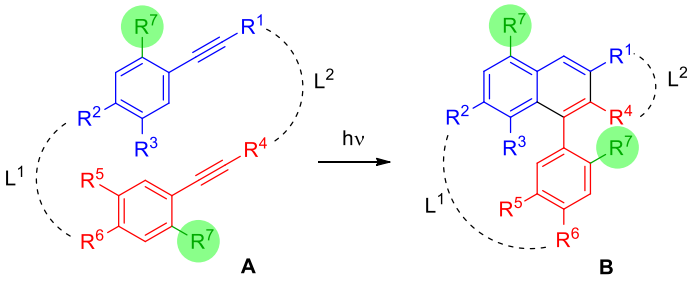
27a **30**

Figure 2. X-Ray structures of **27a** and **30**.

While the *meta*-directing strategy is a good option for the synthesis of tetramethoxy lignan analogs (cf. **28**-**30**) the implementation is difficult for bis-methylendioxy structures such as **1,2** because free phenolic OH groups are needed for the installation of linker L^1.

The *ortho*-blocking strategy

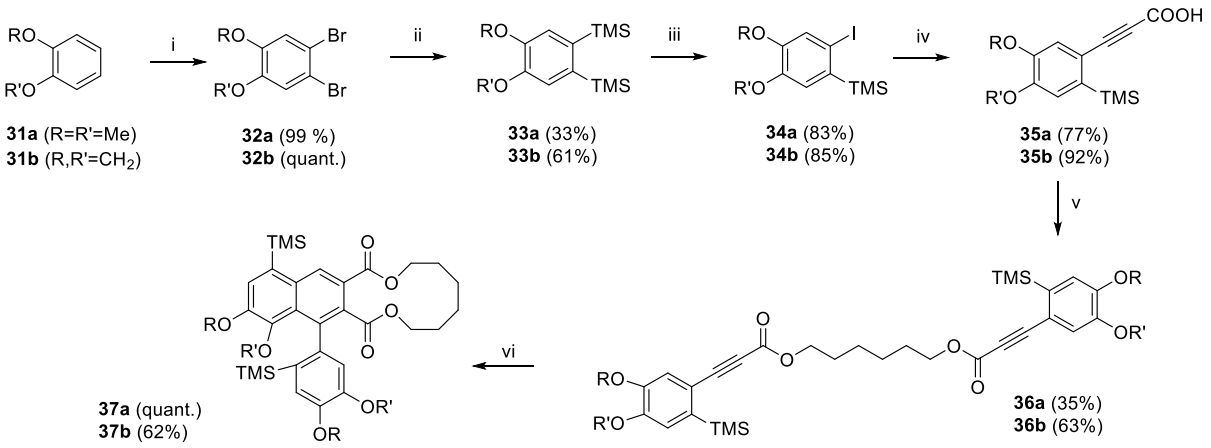
As discussed above two different *ortho*-positions may be attacked at the stage of the diradicals **BR** (see Scheme 1), if substitutents R^3 and R^6 are present. The selectivity of this radical attack determines whether 6,7- or 7,8-substituted arylnaphthalenes are formed. Bearing in mind that the last step of the PDDA reaction comprises of a migration of a hydrogen atom from the attacked position (usually an intermolecular process) [10], it seems reasonable to force the attack at the desired *o*-position by blocking of the other *o*-position with a suitable atom or group R^7 (green) in the reactants **A** (Scheme 9). Here too, the easy removability of R^7 in the products **B** is an important prerequisite for the success of this approach.



Scheme 9: The *ortho*-blocking strategy.

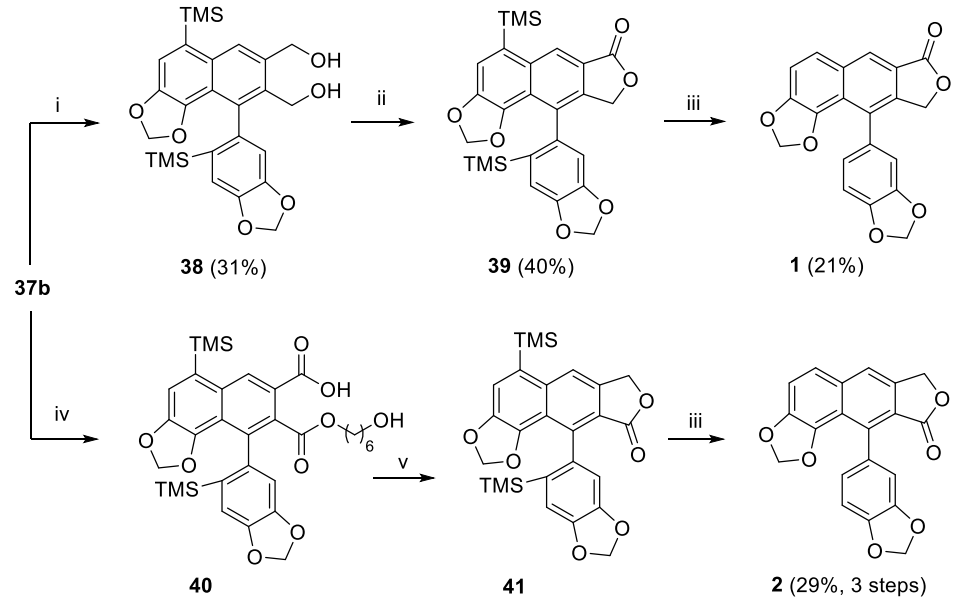
Recently we investigated the influence of fluorine as *o*-substituent. In contrast to the expectation that the fluorine atom blocks the respective position, a preferred attack on the F-*ipso*-position was observed. This phenomenon could be successfully exploited for the total synthesis of the lignan Comfreyn A [33].

In view of the positive experience in the *m*-directing strategy (see previous section) we chose the TMS group in the *o*-blocking strategy as well. Starting with catechol ethers **31a,b** a regioselective double-bromination to compounds **32** [34] and an exchange of Br to TMS gave ethers **33** [35]. By treatment of these compounds with NIS in acetic acid [36] one of the TMS groups was selectively exchanged to iodine (**34**). The arylpropiolic acids **35** were prepared from **34** in the usual manner. Once again, we used hexan-1,6-diol as L^2 type linker in the PDDA reactants **36**. The irradiation of compounds **36** provided the arylnaphthalenes **37** bearing the alkoxy substituents in 7,8-position as the only product (Scheme 10).



Scheme 10: Synthesis of arylnaphthalenes **37** (I Br_2, DCM, ii Mg, CuCl, LiCl, TMSCl, THF, r.t. iii NIS, AcOH, r.t., iv 1. triethyl orthopropiolate, $PdCl_2(PPh_3)_2$, TEA, 2. NaOH,H_2O/MeOH, v hexan-1,6-diol, DIC, DMAP, DCM r.t., vi UVB, DCM.

The remaining steps towards the natural products **1** and **2** involved the conversion of the diester moiety to butyrolactons and the removal of the TMS groups. The procedures starting with **37a** are summarized in Scheme 11. The first steps of the route to **1** corresponds to the method described above for the conversion of **28** to **30** (see Scheme 8, reduction with $LiAlH_4$ → **38**, cyclization with MnO_2 → **39**). The TMS groups could be smoothly removed in the final step by treatment with TFA and helioxanthin **1** was obtained. The route to **2** used an approach originally described by PADWA [37]. The first step is based on the selective saponification of the ester group in 3-position using potassium trimethylsilylanolate. The resulting mono-ester **40** underwent spontaneous cyclization to **41** upon treatment with BH_3Me_2S. Retrohelioxanthin **2** was formed once more by the removal of the TMS groups with TFA (Scheme 11).



Scheme 11: Synthesis of Helioxanthin **1** and Retrohelioxanthin **2**. (i $LiAlH_4$, THF, r.t., ii MnO_2, DCM, r.t., iii TFA, $CHCl_3$, r.t., iv TMSO-K, THF, r.t., v BH_3Me_2S, THF, r.t.)

Conclusion

The objective of the present study was the development of an effective synthetic strategy toward 7,8-substituted aryl-naphthalenes, which are present in several naturally occurring lignans, such as helioxanthin **1** or retrohelioxanthin **2**. In this respect, we pursued three different strategies: the EWG strategy, the *meta*-directing strategy, and the *ortho*-blocking strategy. The aim was to favor the formation of the thermodynamically less stable 7,8-substituted isomers in the PDDA reaction and repress the formation of 6,7-substituted products. The EWG strategy provided the access to two retrohelioxanthin analogs (**19**, **20**) but proved not to be an optimum solution for the 6,7/7,8-problem. The *meta*-directing strategy, which is based on the difference in size of two *meta*-substituents works very well for OMe groups and enabled the synthesis of two lignan analogs (**29**, **30**), but completely failed with larger OBn groups. The most powerful strategy was found to be the *ortho*-blocking strategy. The formation of 7,8-substituted isomers is forced by blocking one *ortho*-position by a

TMS group. In this way, the target compounds helioxanthin **1** and retrohelioxanthin **2** could be successfully prepared.

In summary, we investigated three different approaches to force the formation of 7,8-substituted aryl-naphthalenes in PDDA reactions. All three approaches were successful, whereby the *ortho*-blocking strategy has proven to be the most efficient method.

Supporting Information

Experimental procedures, details of X-ray structure analysis and copies of ^{1}H, ^{13}C NMR spectra.

Supporting Information File 1:

File Name: Helioxanthin_BJOC_SI.pdf

File Format: pdf

Acknowledgements

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