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Asymmetric Synthesis of Alkannin and Shikonin.

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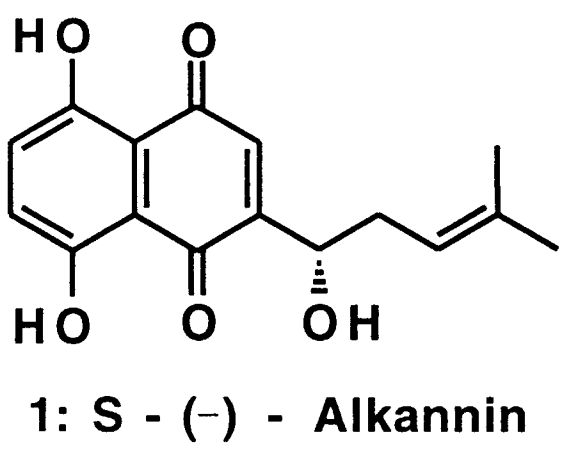
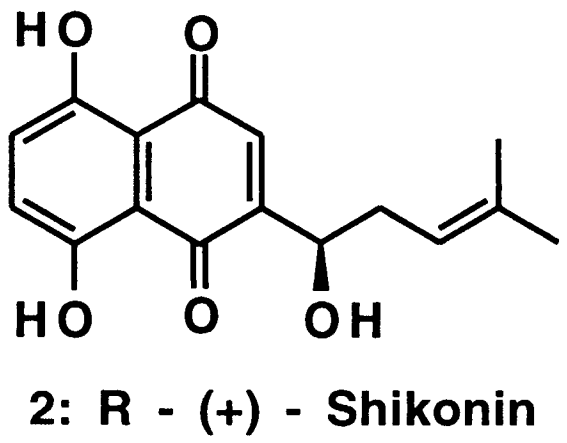
Abstract: A new general and convergent route for the synthesis of the title compounds is presented. The polyoxygenated aromatic ring system is annulated in one operation by the condensation of a Michael type acceptor with an 1,4 dipole equivalent. The chiral center of the target is introduced via an asymmetric allyl boration in high ee. Overall, the fully protected natural product is constructed within 8 steps in 35% total yield.

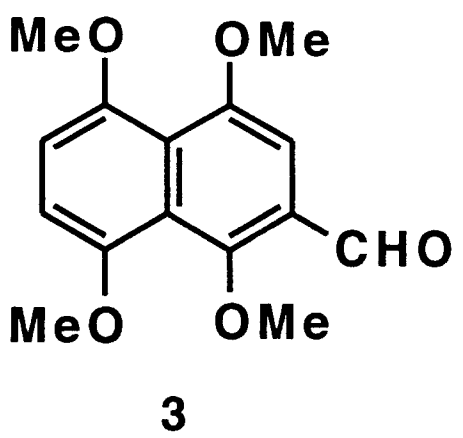
Alkannin, **1**, Shikonin, **2**, and their derivatives are naturally occurring dyes found in the outer surface of the roots of many traditional medicinal plants of the Boraginaceae family[1] (mainly in the genus of *Alkanna*, *Lithospermum*, *Arnebia* and *Echium*). They show a broad spectrum of significant biological activities including antiinflammatory,[2] antibacterial and antifungal,[3] immunostimulating,[4] anticancer,[5] as well as strong inhibition of topoisomerase I.[6] The most prominent and unique feature is their wound healing properties,[7] known from the ancient times.[8] In the last two decades, research pertaining to their chemical and biological properties and transformations, as well as pharmacology and formulation has been increased dramatically.[9] On the contrary, there are but a few reports on their total synthesis,[10, 11] out of which only one is asymmetric.[11] Tetramethoxyformyl naphthalene **3**, prepared either from the expensive 5,8-dihydroxy-1,4-naphthoquinone (naphthazarin) in two steps or from 1,8-dihydroxynaphthalene in a multistep sequence,[12] is the common synthon in all synthetic routes. An aldol type condensation with Braun's chiral auxiliary, was employed for the preparation of the asymmetric center, however the obtained enantiomeric excess was moderate (44-65% ee) and this was attributed to the presence of the methoxy groups.[11]



1: S - (–) - Alkannin



2: R - (+) - Shikonin



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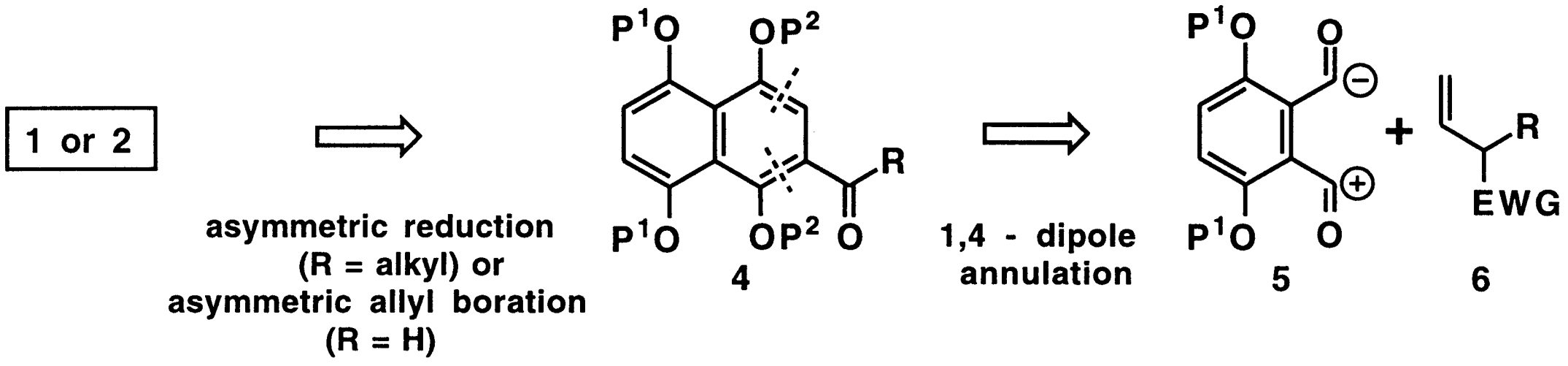
We would like to report a different approach towards the title compounds, the key disconnections of which are depicted on Scheme 1. According to this retrosynthetic scheme, the chiral center of the target molecules may be established by employing a borane asymmetric reduction (R = alkyl) or asymmetric allylation (R= H) on intermediate **4**. Analogous substrates have been reported to afford high ee's under both

operations.[13] Moreover, key intermediate **4**, may be effectively annulated from a synthetic equivalent of 1,4 dipole **5** and a Michael acceptor of the general type **6**. This operation is quite common for the construction of anthracycline type molecules whereas the Michael acceptor is a cyclic enone.[14]



Scheme 1: Key disconnections for the construction of compounds of the general type **1** or **2**. (P^1, P^2 = protective groups; EWG = electron withdrawing group)

In order to exploit our methodology, the well known synthon **7**[15] was subjected to condensation with acrylonitrile **8**, affording after protection of the resulted phenol, aromatic nitriles **10** or **11** in 68% or 73% overall yields, respectively (Scheme 2).[16] Nitrile **11**, was smoothly converted to the respective formyl derivative using DIBAL, which was subsequently subjected to an asymmetric allyl boration with (+)-allyldiisopinocamphenyl borane at -78 ^oC. Allyldiisopinocamphenyl borane was prepared from commercially available diisopinocamphenyl chloride (Aldrich) according to H. C. Brown's procedure[17] and its optical purity was measured to be 80%.[13b] The resulting alcohol **12** was isolated in 78% chemical yield and a calculated optical purity of 82%.[18] According to literature precedents the R configuration should be expected for the prepared alcohol. Application of the advanced Mosher's ester method,[19] on (*S*)-MTPA ester of alcohol **12** indicated also the R configuration.

Having established the chiral center of our target, we then proceeded to the completion of the side chain construction. Thus, after protection of the hydroxyl group with TBSCl, imidazole and a catalytic amount of DMAP, the terminal double bond was cleaved to the corresponding aldehyde using a two step protocol in almost quantitative yield. Wittig type elongation of the resulting aldehyde using the ylide of 2-iodopropane, afforded fully protected (*R*)- (+)-Shikonin **14** in high overall yield (8 steps, 35% total yield). Since the deprotection of intermediate **14** has already been published,[11] the formal asymmetric synthesis of the title compounds has been completed. The same route was followed using the other antipode of diisopinocamphenyl borane reagent, leading to the formation of S - (−) - Alkannnin. In this sequence the ee of the asymmetric operation was calculated to be 78%.

In conclusion, we have developed an effective design for the synthesis of the title compounds and a concise synthetic plan which can be utilized to rapidly prepare a variety of related analogs. The versatility and applicability of our methodology for the construction of related compounds is currently under investigation.

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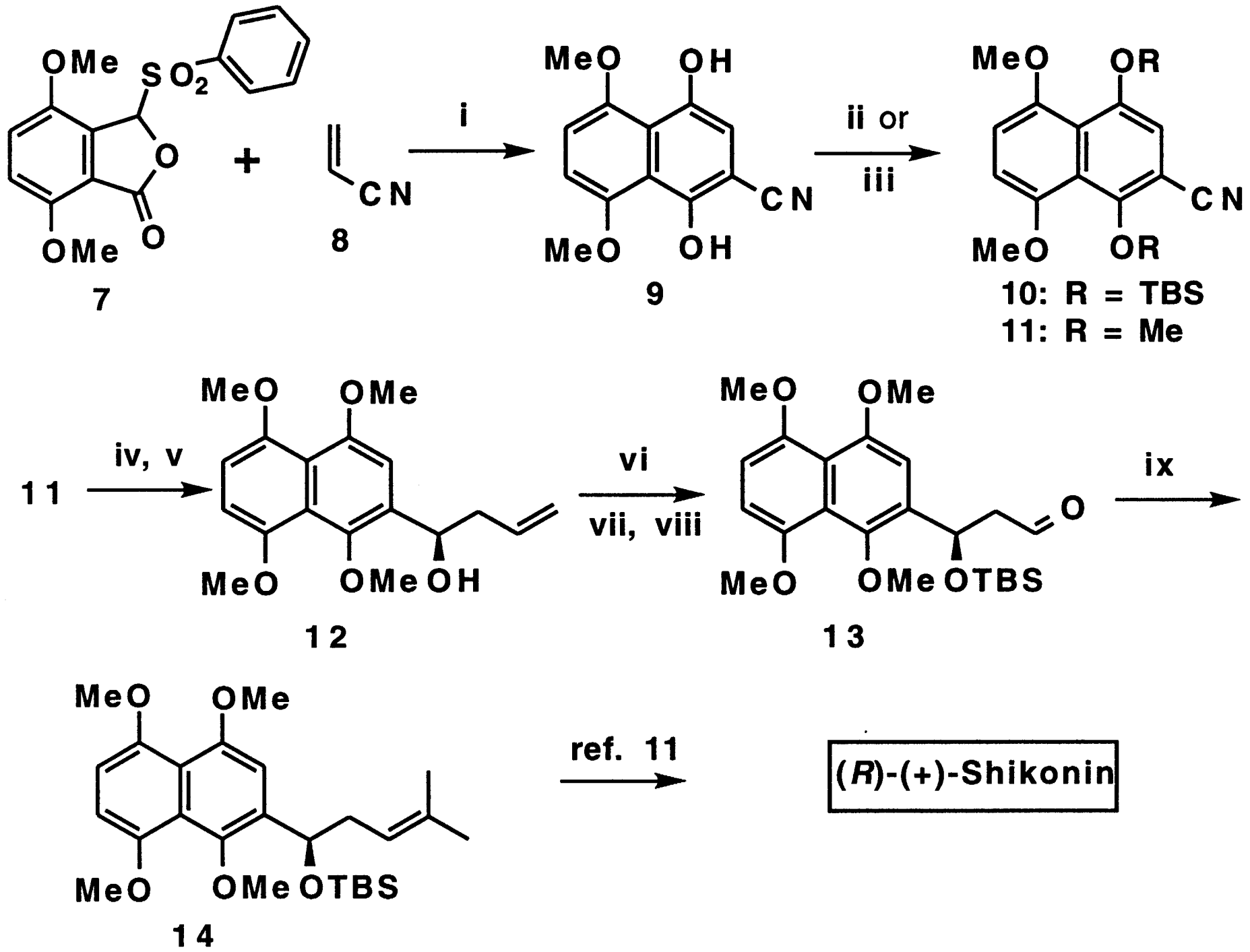

Scheme 2. Synthesis of *R*-(+)- Shikonin. Reagents and conditions :

(i) 2.2. eq. diisopropylamine, 2.2 eq. n-BuLi, THF, 0 °C, 5 min; then -78 °C, **7** in THF (1 eq., 6 mM), 0.5 h then 3 eq. **8**, -78 °C, 30 min; (ii) 4.4 eq. K_2CO_3, 3 eq. $(MeO)_2SO_2$, acetone, 65 °C, 6h, 73% yield based on **7**; (iii) 3.5 eq. TBSCl, 3.5 eq. DMAP, CH_2Cl_2, 25 °C, 12h, 68% yield based on **7**; (iv) CH_2Cl_2, 1.6 eq. DIBAL, -78 °C, 2 h, 88%; (v) 1.01 eq. (+)-DIPCl, 1.00 eq AllylMgBr, Et_2O, -78 °C, 1.5 h then 1.00 eq. aldehyde, 0.5 h, then ethanolamine -78 to 25 °C, 1 h, 78%; (vi) 1.5 eq. TBSCl, 2 eq. imidazole, 0.2 eq. DMAP, DMF, 25 °C, 3 h, 97%; (vii) 3 eq. $K_3Fe(CN)_6$, 3 eq. K_2CO_3, 0.02 eq. $K_2OsO_2(OH)_4$, 0.1 eq. $(DHQ)_2PHAL$, 2.2 eq. $CH_3SO_2NH_2$, *t*-BuOH:acetone:H_2O 3:1:3, 0 to 25 °C, 3h, quench with Na_2SO_3; (viii) 1.1 eq. $NaIO_4$, H_2O:EtOH 5:1, 0 to 25 °C, 1.5 h, 98% for two steps; (ix) 1.7 eq. nBuLi, 2.5 eq. $Ph_3PCHIMe_2$, Et_2O, 0 °C, 1.5 h, then 1 eq. **13**, 0 to 25 °C, 2.5h, 74% based on **13**

TBS = ^{t}Butyldimethylsilyl, DIP = diisopinocamphenyl borane, DMAP = N,N-dimethylaminopyridine

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