Natural Products Synthesis

Total Synthesis of Lepadins B, D, E, and H; Determination of the Configuration of the Latter Three Alkaloids**

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Lepadins are a growing family of alkaloids with a *cis*-fused decahydroquinoline ring. Its first member, lepadin A (**1a**, Scheme 1), was isolated in 1991 by Steffan from the tunicate *Clavelina lepadiformis* in the North Sea.[1] Two other members, lepadins B (**1b**) and C, were isolated from the same

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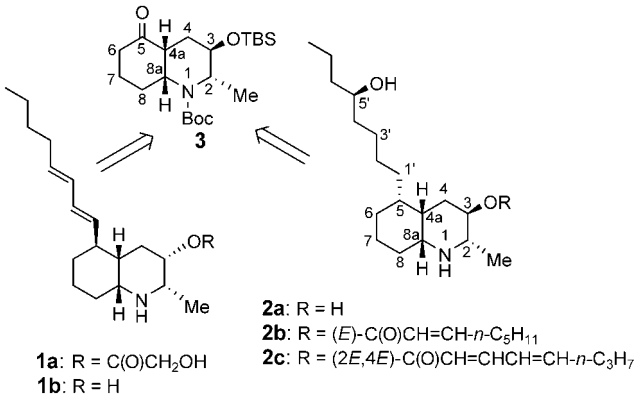
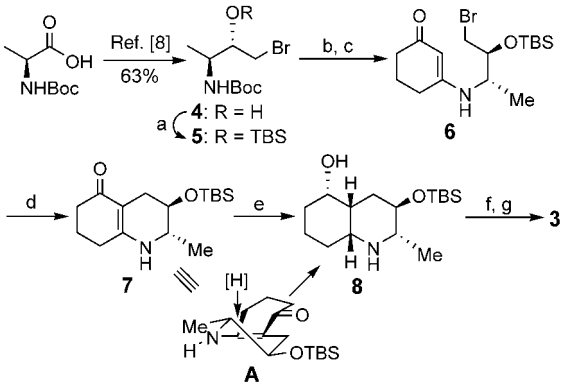


Scheme 1. Structures and retrosynthetic analysis of lepadins A (**1a**), B (**1b**), D (**2a**), E (**2b**), and H (**2c**). Boc = *tert*-butoxycarbonyl, TBS = *tert*-butyldimethylsilyl.



Scheme 2. a) TBSCl, imidazole, DMF; b) HCO_2H/CH_2Cl_2, then aqueous $NaHCO_3$, 80% from **4**; c) 1,3-cyclohexandione, benzene, reflux, 65%; d) NEt_3, NaI, DMF, 110°C, 98%; e) Pt/C, 80 atm H_2, dry AcOH, 50°C, 85%; f) $(Boc)_2O$, benzene, 90%; g) Dess–Martin oxidation, 92%. DMF = *N*,*N*-dimethylformamide.

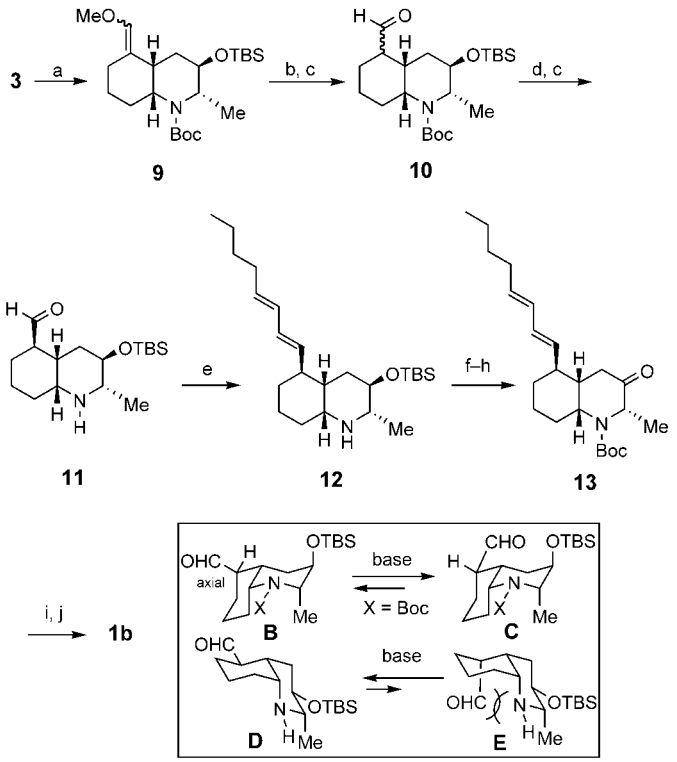
species and other sources four years later.[2] These compounds have been found to possess significant in vitro cytotoxicity against several human cancer cell lines.[2] Very recently, Wright et al. reported the isolation of lepadins D–F from a new *Didemnum* species collected from the Great Barrier Reef,[3] whereas Carroll and co-workers described their discovery of lepadins F–H in *Aplidium tabascum* Kott.[4] Interestingly, lepadins D–F showed low cytotoxicity but significant and selective antiplasmodinium and antitrypanosomal activity and therefore may serve as lead structures for the development of novel antimalarial drugs.[3]

During the past five years, considerable effort has been directed towards the total synthesis of lepadins, and two successful protocols have resulted.[5,6] However, the requirement by both routes of lengthy reaction sequences to construct the left cyclohexane ring greatly diminished their synthetic efficiency. In 2002 Zard and co-workers described a short formal synthesis of racemic lepadin B,[7] but many more steps would evidently be necessary if this strategy was applied in an enantioselective synthesis. Herein we wish to describe a very efficient and general entry into the lepadin family. The key elements include a concise synthesis of the bicyclic ketone **3** (Scheme 1) and subsequent stereoselective introduction of both α- and β-oriented side chains at C5 of this intermediate. Furthermore, the configuration of lepadins D (**2a**), E (**2b**), and H (**2c**) was established fully through this study; in previous reports the absolute configuration of these three compounds and their configuration at C5′ were undefined.

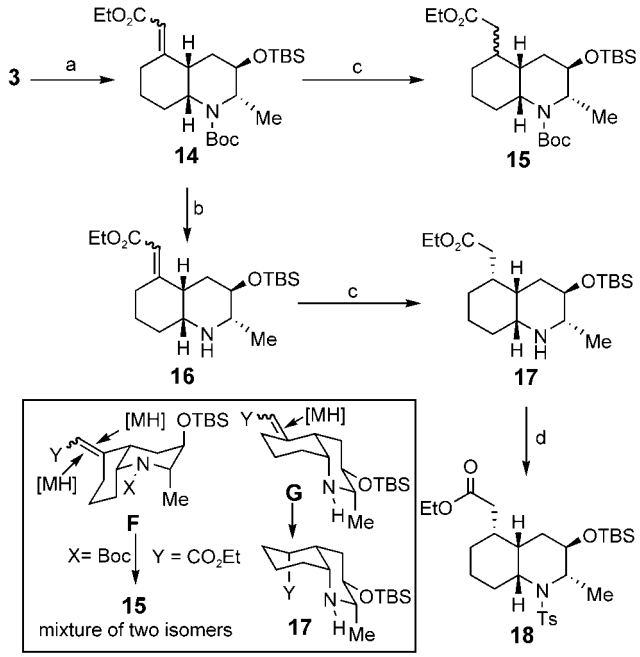
The assembly of the bicyclic ketone **3** from *N*-Boc-L-alanine is outlined in Scheme 2. *N*-Boc-L-alanine was converted in three steps by a literature procedure into the α-amino alcohol **4** (63% overall yield),[8] which was protected as the silyl ether **5**. After selective cleavage of the Boc group of **5** with formic acid, the resulting amine was condensed with 1,3-cyclohexandione in benzene at reflux to give the enamine **6.** Subsequent alkylative cyclization of **6** mediated by Et_3N at 110°C in DMF produced the enone **7**. The next planned step was the diastereoselective hydrogenation of the C–C double bond in **7**. Based on a previous observation,[9] we envisaged that a stereoelectronically controlled axial addition of hydrogen would occur at the *Re* face of the more stable conformation **A**, thus leading to the desired configuration at C4a and C8a for the synthesis of lepadins A, B, D, E, and H. As expected, this reaction worked well under the catalysis of Pt/C in dry acetic acid at 80 atm and 50°C to afford **8** as a single isomer with the 4a*R*,8a*R* configuration, as established by NOESY studies. Other catalysts, such as Raney-Ni, Pd/C, and $Pd(OH)_2/C$, failed to promote the reaction. Finally, the protection of **8** with a Boc group followed by a Dess–Martin oxidation provided **3**.

The stage was now set for the installation of the β-oriented side chain at C5 of the ketone **3** to complete the synthesis of lepadin B. Accordingly, **3** was successfully transformed into the olefin **9** through a Wittig reaction (Scheme 3). Selective hydrolysis of the enol ether moiety of **9** with trichloroacetic acid in dichloromethane containing a trace of water gave the aldehyde **10**.[10] By ^{1}H NMR spectroscopic analysis it was found that an inseparable mixture of diastereomers were present in a ratio of 1:1.3. After failure to enhance the ratio by treatment of this mixture with K_2CO_3 in methanol, we realized that the two isomers might have similar stability and occupy the favored conformations **B** and **C**, respectively. Further conformational analysis based on the studies of Booth and co-workers[11] showed that if the *N*-Boc group was removed, the favored conformations would be **D** and **E** for the two possible aldehydes. The more pronounced 1,5-strain in **E** would make conformer **D** more stable, and thus compound **11** with the aldehyde substituent in the β orientation would be afforded exclusively. Indeed, after selective cleavage of the Boc group in **10** with trifluoroacetic acid (TFA) and subsequent treatment with K_2CO_3 in methanol, the aldehyde **11** was isolated as a single isomer.

The C1′–C8′ side chain was installed by a Horner–Wadsworth–Emmons reaction,[12] and the desired *E*,*E* diene **12** was obtained with greater than 95% selectivity. (Several methods for a modified Julia olefination gave a mixture in favor of the *E*,*Z* diene.[13]) The remaining task for completion of the synthesis was the inversion of the C3 stereocenter, for which we employed an oxidation/reduction strategy. Thus, after protection of the N atom with a Boc group, desilyation with TBAF and a subsequent Dess–Martin oxidation pro-



Scheme 3. a) $Ph_3P{=}CHOMe$, −40 °C→RT, 75 %; b) CCl_3CO_2H, CH_2Cl_2, H_2O (trace); c) K_2CO_3, MeOH, 79 % for **10** and 76 % for **11** from **9**; d) CF_3CO_2H, CH_2Cl_2; e) diethyl (2*E*)-heptenylphosphonate, KHMDS, THF, 95 %; f) $(Boc)_2O$, benzene, reflux; g) TBAF, THF; h) Dess–Martin oxidation, 60 % for 3 steps; i) $NaBH_4$, MeOH, −78 °C, 90 %; j) CF_3CO_2H (5 %), CH_2Cl_2, 80 %. HMDS = hexamethyldisilazide, TBAF = tetrabutylammonium fluoride.

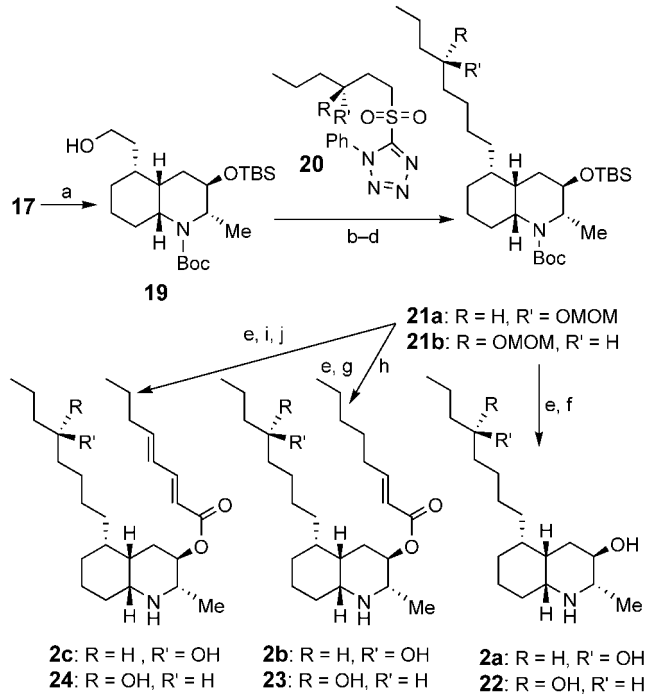


Scheme 4. a) $TMSCH_2CO_2Et$, LDA, −78 °C→RT, 98 %; b) CF_3CO_2H, CH_2Cl_2, 100 %; c) Pt/C, H_2 (1 atm), dry AcOH, 50 °C, 95 %; d) TsCl, Et_3N, CH_2Cl_2, 80 %. LDA = lithium diisopropylamide, TMS = trimethylsilyl, Ts = *p*-toluenesulfonyl.

vided the ketone **13**. The reduction of **13** with $NaBH_4$ gave a single diastereomer, which was treated with TFA to furnish lepadin B as its TFA salt, whose analytical data were identical to those reported.[2] The overall yield was about 5.3 % over 20 linear steps from *N*-Boc-L-alanine.

To introduce the α-oriented side chain at C5 of the ketone **3**, a Peterson reaction[14] was employed to provide the olefin **14** (Scheme 4). Direct Pt/C-catalyzed hydrogenation of **14** in dry acetic acid gave **15** with a diastereomeric ratio of 3:1. However, we were pleased to observe that the hydrogenation of **16**, a derivative of **14** without the *N*-Boc group, produced **17** in a highly diastereoselective manner (d.r. > 97:3). X-ray crystal-structure analysis of **18**, a tosylation product of **17**, confirmed that the side chain at C5 was in the α orientation. These two stereochemical courses might be rationalized by the difference in steric hindrance towards hydrogen attack in the two favored conformations **F** and **G**, as depicted in Scheme 4.

The completion of lepadins D, E, and H is depicted in Scheme 5. The protection of **17** by treatment with $(Boc)_2O$, followed by reduction with DIBAL, afforded the alcohol **19**, which was oxidized to the aldehyde, coupled with the sulfone **20**, and hydrogenated over Pd/C to produce **21**. Since the sulfones **20** could be constructed by a Sharpless epoxidation/reductive ring opening sequence and subsequent transforma-



Scheme 5. a) $(Boc)_2O$, DMAP, then DIBAL, −40 °C, 95 %; b) Swern oxidation; c) **20**, NaHMDS, THF; d) Pd/C, H_2, 90 %; e) TBAF, THF, room temperature, 100 %; f) HCl, *i*PrOH/MeOH, 85 %; g) (2*E*)-octenoic acid, $Cl_3C_6H_2COCl$, iPr_2NEt, DMAP, 64 %; h) CF_3CO_2H, CH_2Cl_2, 87 %; i) (2*E*,4*E*)-octadienoic acid, EDCI, DMAP, CH_2Cl_2, 73 %; j) CF_3CO_2H, CH_2Cl_2, 90 %. DIBAL = diisobutylaluminum hydride, DMAP = 4-dimethylaminopyridine, EDCI = 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, MOM = methoxymethyl.

tions,[15] both (*R*)-**20** and (*S*)-**20** were readily accessible by tuning the ligands in the Sharpless epoxidation, thus providing a chance to establish the configuration at C5′. The complete deprotection of **21** led to both **2a** and its C5′ epimer **22**. The cleavage of just the silyl ether in **21** yielded two alcohols, which were acylated with (2*E*)-octenoic acid ($Cl_3C_6H_2COCl/i$PrNEt$_2$)[16] or (2*E*,4*E*)-octadienoic acid (EDCI/DMAP),[17] and then deprotected to furnish **2b** and **23**, and **2c** and **24**, respectively. Although both the NMR spectra and the optical rotation for **2a** and **22**, **2b** and **23**, and **2c** and **24** were very similar, a marked difference in the ^{1}H NMR spectra of **2c** and **24** at $\delta = 1.2$–1.5 ppm clearly showed that the data for **2c**, but not for **24**, were identical to those reported for lepadin H. Furthermore, the value $[\alpha]_D^{20} = -12$ ($c = 1.0$ MeOH) observed for the hydrochloride salt of **2a** is close to that reported for the hydrochloride salt of lepadin D ($[\alpha]_D^{20} = -14$ ($c = 0.2$ MeOH)[3]), whereas the value for the optical rotation of the hydrochloride salt of **22** was significantly lower ($[\alpha]_D^{20} = -5.7$ ($c = 0.9$ MeOH)). Therefore, we concluded that lepadins D, E, and H have the absolute configuration 2*S*,3*R*,4a*S*,5*S*,8a*R*,5′*R*.

In summary, we have developed an efficient and divergent strategy towards the lepadins, including a concise synthesis of lepadin B, as well as the first total synthesis of lepadins D, E, and H, which enabled us to fully determine their configuration. These results should prompt further studies on the synthesis and biological activity of these compounds and their analogues.

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Keywords: alkaloids · configuration determination · hydrogenation · olefination · total synthesis

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