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Total Synthesis of the Marine Alkaloid (−)-Lepadin B

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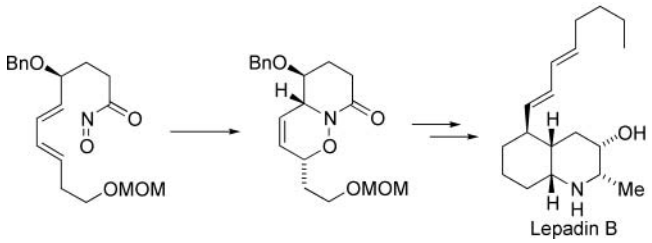
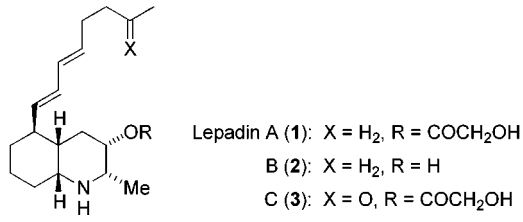
ABSTRACT



An enantioselective total synthesis of (−)-lepadin B has been developed starting from (2*S*,4*S*)-2,4-*O*-benzylidene-2,4-dihydroxybutanal. The key steps in the synthesis include the use of an aqueous intramolecular acylnitroso Diels−Alder reaction to afford the *trans*-1,2-oxazinolactam and Suzuki cross-coupling reaction to elaborate the (*E*,*E*)-octadienyl unit.

Lepadin A (**1**) was first isolated in 1991 from the tunicate *Clavelina lepadiformis* collected in the North Sea[1] and represents the first example of a decahydroquinoline alkaloid from a marine natural source. Subsequently, the very closely related compounds, lepadins B (**2**) and C (**3**), along with



Lepadin A (**1**): X = H_2, R = $COCH_2OH$
B (**2**): X = H_2, R = H
C (**3**): X = O, R = $COCH_2OH$

lepadin A, have been found in the flatworm *Prosthecerаeus villatus* and its tunicate prey *C. lepadiformis*.[2] Both lepadins A (**1**) and B (**2**) have been shown to exhibit significant in vitro cytotoxicity against human cancer cell lines.[2] Quite recently, the first total synthesis of **2** has been reported, which confirmed its absolute configuration as shown.[3] Herein, we report an enantioselective strategy for the total synthesis of (−)-lepadin B that features the use of an intramolecular hetero-Diels−Alder reaction of an *N*-acylnitroso compound.[4]

We have recently demonstrated[5] the utility of enantiopure 2,4-*O*-benzylidene-2,4-dihydroxybutanal (**4**) as a C_4 chiral synthon for the total synthesis of several natural products based on the acylnitroso Diels−Alder approach. We thus planned to employ (2*S*)-configured **4**, conveniently available on a large scale from L-malic acid,[6] as the simple starting material for the synthesis of the natural enantiomer of lepadin B (**2**). Thus, the synthesis began with a Horner−Emmons reaction of **4** to give a 20:1 *E*/*Z* mixture of the corresponding unsaturated esters (86% combined yield), wherein no epimerization at the C2 chiral center was detected (Scheme 1).[7] The major *E*-isomer **5** was subjected to DIBALH reduction

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(2) Kubanek, J.; Williams, D. E.; de Silva. E. D.; Allen, T.; Andersen, R. J. *Tetrahedron Lett.* **1995**, *36*, 6189−6192.
(3) (a) Toyooka, N.; Okumura, M.; Takahata, H. *J. Org. Chem.* **1999**, *64*, 2182−2183. (b) Toyooka, N.; Okumura, M.; Takahata, H.; Nemoto, H, *Tetrahedron* **1999**, *55*, 10673−10684.
(4) For applications of intramolecular acylnitroso-Diels−Alder reaction to natural products synthesis from our laboratory, see: Kibayashi, C.; Aoyagi, S. *Synlett* **1995**, 873−879.
(5) (a) Naruse, M.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **1994**, *59*, 1358−1364. (b) Naruse, M.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **1994**, *35*, 9213−9216. (c) Naruse, M.; Aoyagi, S.; Kibayashi, C. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1113−1124.
(6) Corcoran, R. C. *Tetrahedron Lett.* **1990**, *31*, 2101−2104. (b) Thiam, M.; Slassi, A.; Chastrette, F.; Amouroux, R. *Synth. Commun.* **1992**, *22*, 83−95.

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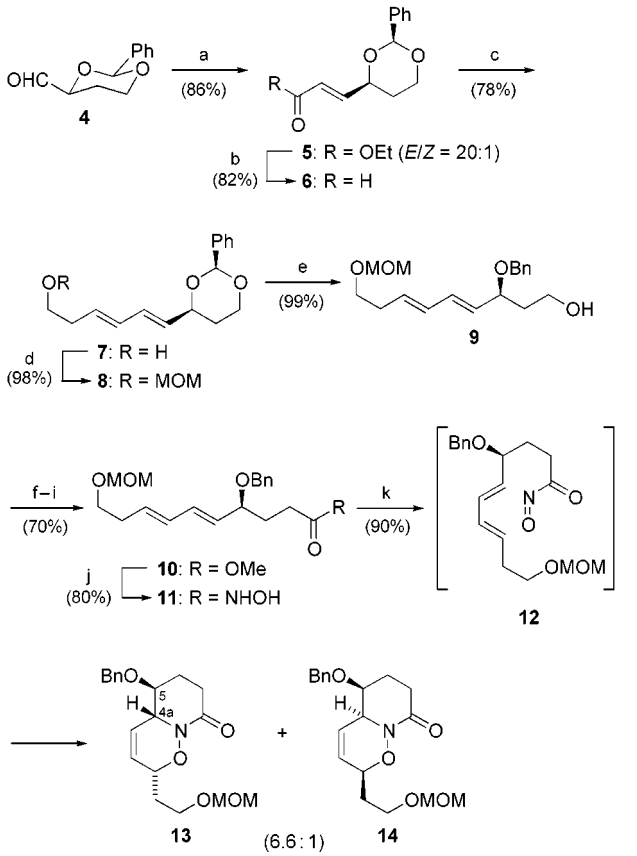
Scheme 1[a]

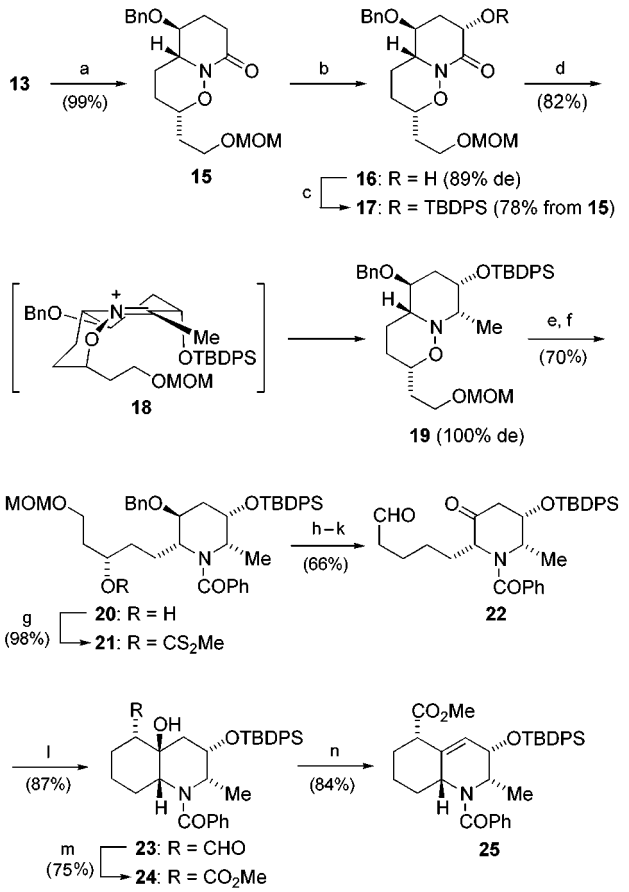


[a] Reagents and conditions: (a) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, −20 °C to rt; (b) (i) DIBALH, THF, rt; (ii) MnO_2, CH_2Cl_2; (c) $Ph_3P^+(CH_2)_3OHI^-$, LiHMDS, THF, 0 °C to rt; (d) MOMCl, *i*-Pr_2NEt, CH_2Cl_2; (e) DIBALH, CH_2Cl_2; (f) TsCl, DMAP, Et_3N, CH_2Cl_2; (g) NaCN, DMSO, 50 °C; (h) NaOH, MeOH−H_2O, reflux; (i) CH_2N_2, Et_2O; (j) NH_2OH·HCl, KOH, MeOH, 0 °C; (k) Pr_4NIO_4, H_2O-DMF (50:1), 0 °C.

followed by MnO_2 oxidation of the resultant alcohol to afford the aldehyde **6** in 82% overall yield. Subsequent Wittig olefination of **6** with $Ph_3P{=}CH(CH_2)_2OLi$[8] yielded the desired (3*E*,5*E*)-diene **7** in 69% yield along with a small amount (9%) of the (3*Z*,5*E*)-isomer. Protection of **7** as its MOM ether followed by reductive ring opening of the benzylidene acetal with DIBALH produced the (*E*,*E*)-4,6-nonadienol **9**. Conversion of **9** to **10** was straightforward. Thus, tosylation, displacement by cyanide, alkaline hydrolysis, and then diazomethane esterification afforded **10** in 70% overall yield (four steps). Compound **10** was then transformed to the hydroxamic acid **11** (80%) by treatment with hydroxylamine under alkaline conditions. In our earlier study, use of aqueous media for intramolecular Diels−Alder reaction of the acylnitroso compounds effected significant enhancement of the trans selectivity compared with the reaction under nonaqueous conditions.[9] Consistent with these observations, on the treatment with Pr_4NIO_4 at 0 °C in water−DMF (50:1) the hydroxamic acid **11** underwent cycloaddition via the in situ generated acylnitroso compound **12**, yielding the trans (with respect to C4a and C5) cycloadduct **13** as a major isomer with a significantly increased diastereoselectivity of 6.6:1 compared with the reaction conducted in a chloroform solution which afforded a 1.7:1 trans/cis ratio.

Catalytic hydrogenation (Pd−C, THF) of the olefin moiety of the trans-cycloadduct **13** gave **15** (Scheme 2). The Davis

Scheme 2[a]



[a] Reagents and conditions: (a) H_2, Pd−C, THF; (b) LiHMDS, (+)-[(8,8-dichlorocamphoryl)sulfonyl]oxaziridine, THF, −78 °C; (c) TBDPSCl, imidazole, DMF; (d) MeMgBr, THF, 0 °C, then $NaBH_3CN$, AcOH, THF, 0 °C; (e) Zn, 90% AcOH, 60 °C; (f) PhCOCl, then 5% KOH; (g) CS_2, NaH, imidazole, then MeI, THF; (h) Bu_3SnH, AIBN, benzene, reflux; (i) PPTS, *t*-BuOH, reflux; (j) H_2, $Pd(OH)_2$, MeOH; (k) $(COCl)_2$, DMSO, Et_3N, −78 → 0 °C; (l) piperidine (0.2 equiv), AcOH (0.2 equiv), benzene, reflux; (m) (i) PDC, DMF; (ii) CH_2N_2, Et_2O; (n) $SOCl_2$, Et_3N.

methodology[10] was then exploited to introduce a hydroxyl group into the C7 position of **15** to form **16**. Oxidation of the sodium enolate (NaHMDS, THF, −78 °C) of **15** with (±)-2-(phenylsulfonyl)-3-phenyloxaziridine[11] followed by protection of the resultant hydroxyl group as the *tert*-butyldiphenylsilyl (TBDPS) ether afforded the oxygenated product in 86% yield but with a very low diastereoselectivity of 1.1:1 in favor of the requisite (7*S*)-isomer **17**. With the

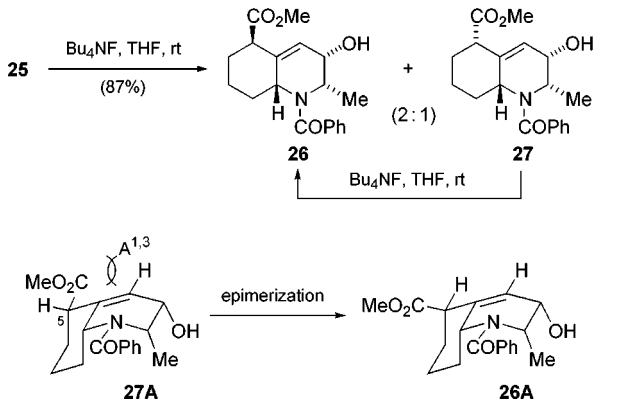
(7) The reason no epimerization occurs in the Wittig reaction of the (2*R*)-enantiomer of **4** has been discussed in a previous publication (ref 5a).

(8) Maryanoff, B. E.; Reitz, A. B.; Duhl-Emswiler, B. A. *J. Am. Chem. Soc.* **1985**, *107*, 217−226.

oxidation of the lithium enolate (LiHMDS, THF, −78 °C) of **15** using (+)-[(8,8-dichlorocamphoryl)sulfonyl]oxaziridine,[12] constituting a matched pair, subsequent silyl protection gave rise to **17** (78%) with remarkable increase in the diastereoselectivity (17:1). The next step required a stereoselective introduction of the methyl group into C8. This was smoothly accomplished by the tandem Grignard reaction−reduction procedure developed earlier in these laboratories.[13] Thus, when **17** was allowed to react with methylmagnesium bromide followed by $NaBH_3CN$ in acidic medium (AcOH), reduction of the intermediary iminium ion **18** proceeded with steric and stereoelectronic controls to afford **19** as a single diastereomer (82% overall yield from **17**). Reductive cleavage of the N−O bond of **19** (Zn, AcOH) followed by N-benzoylation of the resulting amino alcohol gave **20**, which was converted to the *S*-methyl dithiocarbonate **21** and subjected to a four-step sequence of reactions, involving deoxygenation with tributyltin hydride,[14] acidic removal of the methoxymethyl group, hydrogenolysis of the benzyl group, and Swern oxidation, to provide the keto aldehyde **22** (66% overall yield from **21**). Intramolecular aldol reaction conditions (KOH, MeOH, 0 °C) led to the desired product **23** but in very low yield (10%) accompanied by complex side reactions. However, the use of a catalytic amount of piperidine and acetic acid in refluxing benzene resulted in a clear reaction to form **23** in much improved yield (87%) as a single diastereomer. After several failed attempts at dehydration of the aldehyde **23**, **23** was converted to the ester **24** (PDC, then CH_2N_2), which smoothly underwent dehydration with $SOCl_2$ and Et_3N to form the octahydroquinoline **25** (84%).

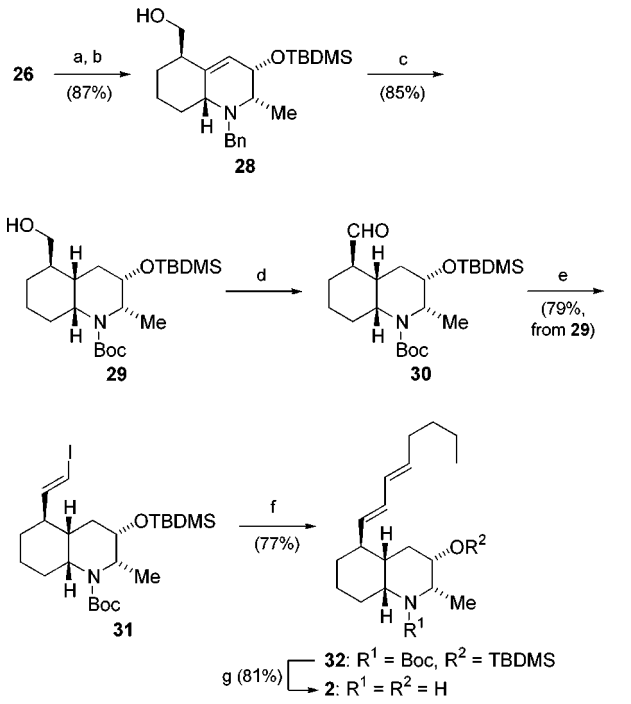
Exposure of **25** to Bu_4NF at room temperature caused cleavage of the TBDPS ether and epimerization at the labile C5 stereocenter under the reaction conditions to give a 2:1 chromatographically separable mixture of the 5β- and the 5α-esters **26** and **27** in favor of **26** in 87% total yield (Scheme 3). The 5α-isomer **27** with undesired C5 chirality could be converted to a 2:1 equilibrium mixture of **26** and **27** by treatment under the same conditions (Bu_4NF, THF, rt, 5 d); in this manner, the conversion of **25** into required **26** could be increased to 75% yield. The observed epimerization of **27** to **26** can be interpreted in terms of more thermodynamically stable **26A**, in which the methoxycarbonyl group orients axial to avoid an allylic strain.

Scheme 3



With compound **26** in hand, it was converted to the amino alcohol **28** (87%) through silylation followed by $LiAlH_4$ reduction of the methoxycarbonyl and *N*-benzoyl groups (Scheme 4). Catalytic hydrogenation of **28** (5 atm H_2, Pd−C, THF) resulted in exclusive formation of the decahydroquinoline **29** with the cis ring juncture in 85% yield after N-Boc protection. The stereochemical outcome in this case implies hydroxyl-directed hydrogenation[15] wherein the substrate is bound to the catalyst surface on the same side as

Scheme 4[a]



[a] Reagents and conditions: (a) TBDMSCl, imidazole, DMF; (b) $LiAlH_4$, THF, reflux; (c) (i) H_2 (5 atm), Pd−C, THF; (ii) $(Boc)_2O$, CH_2Cl_2; (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 → 0 °C; (e) CHI_3, $CrCl_2$, THF; (f) (*E*)-1-hexenyldihydroxyborane, $Pd(PPh_3)_4$ (5 mol %), 2 M aqueous KOH, THF, 50 °C; (g) Bu_4NF, THF, then CF_3CO_2H, CH_2Cl_2.

(9) Naruse, M.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **1994**, *35*, 595−598. See also refs 5b and 5c.

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the hydroxyl group, resulting in the addition of hydrogen syn to the coordinating moiety. After Swern oxidation, the resultant aldehyde **30** was subjected to Takai olefination[16] with CHI_3 and $CrCl_2$ in THF as a single geometric isomer to form the (*E*)-alkenyl iodide **31** (79% yield from **29**). Subsequent elaboration of the octadienyl side chain was achieved by palladium-catalyzed Suzuki cross-coupling[17] with (*E*)-hexenyldihydroxyborane ($Pd(PPh_3)_4$, aqueous KOH, THF, 50 °C), affording **32** in 77% yield. The final deprotection of the silyl and N-Boc groups provided (−)-lepadin B (**2**), whose trifluoroacetate salt was obtained in a crystalline form,[18] mp 212−214 °C ($CHCl_3$-hexane); $[\alpha]^{28}_D$ −67.4 (*c* 0.25, MeOH). This showed spectral properties (^1H and ^{13}C NMR) in full agreement with those of the trifluoroacetate of natural **2**.

In summary, the enantioselective synthesis of (−)-lepadin B has been achieved through the exploitation of an intramolecular acylnitroso Diels−Alder reaction. Application of this methodology to the synthesis of other members of this family of natural alkaloids is underway and will be reported in due course.

Acknowledgment. We are grateful to Professor R. J. Andersen for providing authentic spectra of ^1H and ^{13}C NMR of the trifluoroacetate salt of natural lepadin B.

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(17) For a recent review, see: Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.

(18) The trifluoroacetate salt of **2** has been reported[2] as an oil having $[\alpha]_D$ −96 (MeOH).