First Total Synthesis of the Marine Alkaloids (±)-Fasicularin and (±)-Lepadiformine Based on Stereocontrolled Intramolecular Acylnitroso-Diels−Alder Reaction

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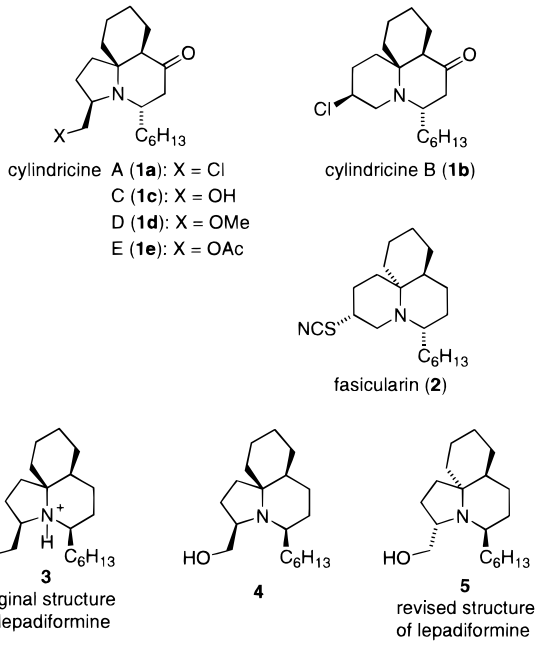
Abstract: The first total synthesis of tricyclic marine alkaloids (±)-fasicularin (**2**) and (±)-lepadiformine (**5**) was accomplished. The key common strategic element for the synthesis is the stereocontrolled intramolecular hetero-Diels−Alder reaction of an *N*-acylnitroso moiety to an exocyclic diene with or without bromine substitution to control the syn-facial or anti-facial selectivity, respectively, leading to the trans- or cis-fused decahydroquinoline ring systems **21** or **39** involving the simultaneous introduction of the nitrogenated quaternary center in a single step. On further elaboration of the six-membered or five-membered ring A, the trans-fused adduct **21** provided either (±)-fasicularin (**2**) or (±)-lepadiformine (**5**). The hydrochloride salt of synthetic (±)-**5** was found to be identical with the isolated natural sample of lepadiformine; however, the tricyclic amino alcohol **4** having the proposed structure of lepadiformine in a nonzwitterionic form, derived from the cis-fused adduct **39**, was found to be different from lepadiformine by spectral comparison. These results thus unambiguously established the relative stereochemistry of lepadiformine, formerly assigned incorrectly, to be 3*R**,5*S**,7a*R**,11a*R** shown by **5**.

Introduction

Tunicates (ascidians) have been proven to be a particularly rich source of a variety of structurally fascinating and bioactive nitrogen compounds.[1] Since the first members were reported in 1993, 11 cylindricines A−K have been identified from the Tasmanian ascidians *Clavelina cylindrica* as new marine alkaloids[2] with a tricyclic ring system unprecedented among natural products, consisting of the perhydropyrrolo[2,1-*j*]quinoline or the perhydropyrido[2,1-*j*]quinoline. Shortly after the first isolation of cylindricines A (**1a**) and B (**1b**)[2a] the isolation and structure elucidation of a closely related marine alkaloid, named lepadiformine, from the ascidian *Clavelina lepadiformis* collected in Tunisia was reported by Biard and co-workers in 1994.[3] It was found to be moderately cytotoxic toward various tumor cell lines in vitro. On the basis of extensive NMR studies, this alkaloid was given structure **3** including a unique zwitterionic form. Although its observed specific rotation value (in a $CHCl_3$ solution) is zero, and the absolute stereochemistry is still unknown, it is believed that lepadiformine is not racemic.

In addition to these tricyclic alkaloids, fasicularin (**2**) was recently discovered by Patil and co-workers[4] from the Micronesian ascidian *Nephteis fasicularis*, which has selective activity against a DNA repair-deficient organism and is cytotoxic to Vero cells with an IC_{50} of 14 μg/mL. The structure and relative stereochemistry of **2** were deduced on the basis of extensive NMR studies, though the absolute configuration is still unknown. The novel structural features and biological significance of these tricyclic alkaloids represent a promising new class of nitrogen heterocycles biosynthesized by ascidians (such as indolizidines, quinolizidines, and decahydroquinolines), and have attracted the increasing attention of organic chemists during the past few years. Thus, several approaches involving construction of the



(1) For recent reviews on marine natural products, see: (a) Davidson, B. S. *Chem. Rev.* **1993**, *93*, 1771−1791. (b) Faulkner, D. J. *Nat. Prod. Rep.* **1994**, *11*, 355−394. (c) Faulkner, D. J. *Nat. Prod. Rep.* **1995**, *12*, 223−269. (d) Faulkner, D. J. *Nat. Prod. Rep.* **1996**, *13*, 75−125. (e) Faulkner, D. J. *Nat. Prod. Rep.* **1998**, *15*, 113−158. (f) Faulkner, D. J. *Nat. Prod. Rep.* **1999**, *16*, 155−198.

(2) (a) Blackman, A. J.; Li, C.; Hockless, D. C. R.; Skelton, B. W.; White, A. H. *Tetrahedron* **1993**, *49*, 8645−8656. (b) Li, C.; Blackman, A. J. *Aust. J. Chem.* **1994**, *47*, 1355−1361. (c) Li, C.; Blackman, A. J. *Aust. J. Chem.* **1995**, *48*, 955−965.

(3) Biard, J. F.; Guyot, S.; Roussakis, C.; Verbist, J. F.; Vercauteren, J.; Weber, J. F.; Boukef, K. *Tetrahedron Lett.* **1994**, *35*, 2691−2694.

(4) Patil, A. D.; Freyer, A. J.; Reichwein, R.; Carte, B.; Killmer, L. B.; Faucette, L.; Johnson, R. K.; Faulkner, D. J. *Tetrahedron Lett.* **1997**, *38*, 363−364.

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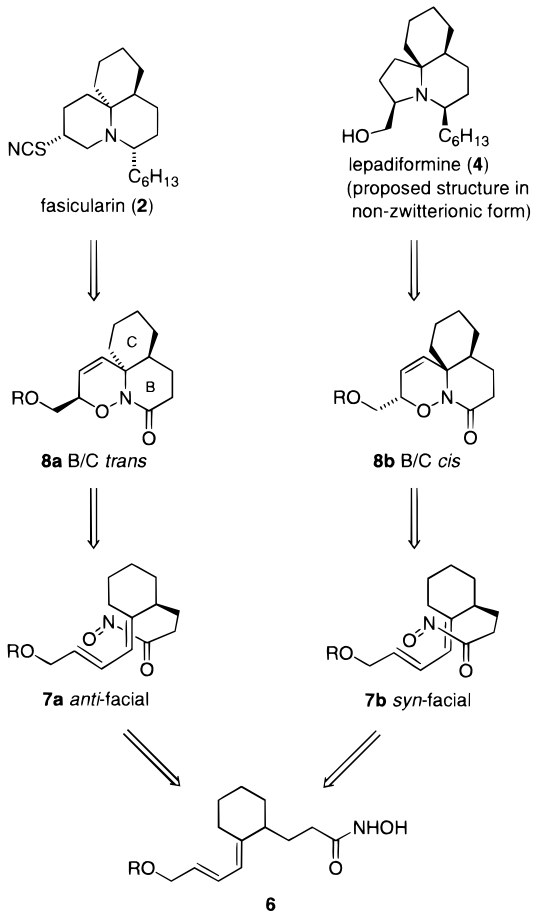
azatricyclic ring systems have been developed, which led to the total syntheses of cylindricines A−E (**1a**−**e**).[5] In another approach, Weinreb and co-workers[6] reported the synthesis of the putative structure **4** of lepadiformine, and they found that the synthetic material is clearly different from natural lepadiformine and exists in a nonzwitterionic form as **4** instead of **3**. In addition, Pearson et al.[7] have synthesized the three other possible diastereomers of **4** at C(3) and C(5) and have found that none of these stereoisomers correspond to lepadiformine.[8] These results called into question the validity of the published structure of lepadiformine. However, at the outset of our project, since these arguments pertaining to the lepadiformine structure were not published, we planned to synthesize lepadiformine based on structure **4** having the stereochemistry originally assigned. Also, we became interested in fasicularin (**2**) as a target for synthesis. Since these compounds **2** and **4** comprise a perhydroquinoline ring system, which is a common core unit present in this class of alkaloids, with trans and cis ring fusions, respectively, it presented an opportunity for the diastereoselective construction of the perhydroquinoline skeleton. Accordingly, the route for the synthesis of **2** and **4** we have envisaged is shown in Scheme 1. Conceptually, this approach involves as the key feature an intramolecular hetero-Diels−Alder reaction using an *N*-acylnitroso compound **7**, generated from a hydroxamic acid **6**, wherein anti and syn facial additions are formally possible through endo transition states **7a** and **7b** to form B/C trans- and B/C cis-fused cycloadducts **8a** and **8b**, respectively, which correspond to fasicularin (**2**) and compound **4**.

In this paper, we report the synthesis of (±)-fasicularin (**2**) and the tricyclic compound **4**[9] having the stereochemistry originally proposed for lepadiformine via diastereocontrolled routes by employing an intramolecular hetero-Diels−Alder methodology. Furthermore, we describe the application of this methodology to the synthesis of (±)-lepadiformine (**5**), which led to revision of the proposed structure **3** for the natural product, thus achieving the first total synthesis of lepadiformine (**5**) as well as fasicularin (**2**).

Results and Discussion

Diastereofacial Intramolecular Hetero-Diels−Alder Reaction of Acylnitroso Compounds. The hetero-Diels−Alder reaction of *N*-acylnitroso compounds has been widely investigated and proved to be useful for natural products synthesis because of its potential for further structural elaboration.[10,11] However, there was only one example of the use of an exocyclic diene as a diene component in the intramolecular acylnitroso-Diels−Alder reaction for the formation of a fused 7/6 ring system.[12] In this case, syn-facial stereochemistry was predominant as a result of the approach of the acylnitroso moiety to the exocyclic diene moiety from the same face to the anchor position of the tether, though in low selectivity. These findings suggest that the nitroso-diene intermediate generated from **6** prefers a syn-facial approach via **7b** to form the B/C cis-fused adduct **8b** rather than the B/C trans-fused adduct **8a**. Inspection of molecular models, however, suggests that the anti-facial transition state conformation **7a** leading to trans selectivity is energetically most favorable among the possible conformations (vide infra).

Scheme 1



We thus began our investigation by preparing the hydroxamic acid **19** needed for the cycloaddition to examine the facial selectivity. As shown in Scheme 2, the Horner−Emmons reaction of ketone **9**[13] was carried out to give the unsaturated nitrile **10** in 97% yield as a 13:1 inseparable mixture of the *E* and *Z* isomers, which was without separation subjected to DIBALH reduction to form the unsaturated aldehyde **11** (77%).

(5) (a) For synthesis of (±)-cylindricines A, D, and E, see: Snider, B. B.; Liu, T. *J. Org. Chem*. **1997**, *62*, 5630−5633. (b) For synthesis of (−)-cylindricine C, see: Molander, G. A.; Rönn, M. *J. Org. Chem.* **1999**, *64*, 5183−5187. (c) For synthesis of (±)-cylindricines A and B, see: Liu, J. F.; Heathcock, C. H. *J. Org. Chem*. **1999**, *64*, 8263−8266.

(6) (a) Werner, K. M.; De los Santos, J. M.; Weinreb, S. M.; Shang, M. *J. Org. Chem*. **1999**, *64*, 686−687. (b) Werner, K. M.; De los Santos, J. M.; Weinreb, S. M.; Shang, M. *J. Org. Chem*. **1999**, *64*, 4865−4873.

(7) (a) Pearson, W. H.; Barta, N. S.; Kampf, J. W. *Tetrahedron Lett*. **1997**, *38*, 3369−3372. (b) Pearson, W. H.; Ren, Y. *J. Org. Chem*. **1999**, *64*, 688−689.

(8) For other approaches to the perhydropyrrolo[2,1-*j*]quinoline ring system, see: (a) Aubé, J.; Millligan, G. L. *J. Am. Chem. Soc*. **1991**, *113*, 8965−8966. (b) Ollero, L.; Mentink, G.; Rutjes, F. P. J. T.; Speckamp, W. N.; Hiemstra, H. *Org. Lett*. **1999**, *1*, 1331−1334.

(9) For part of a preliminary account of this work on the synthesis of compound **4**, see: Abe, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett*. **2000**, *41*, 1205−1208.

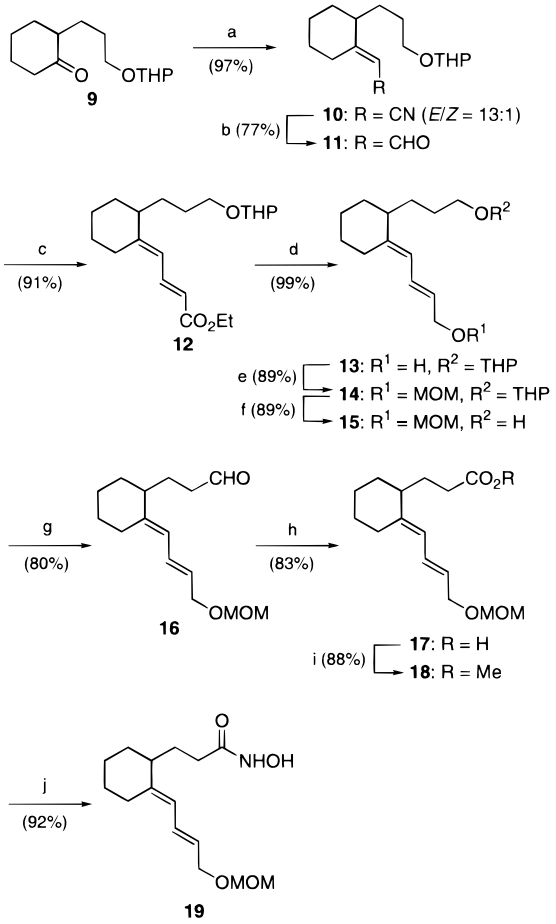
(10) For our own achievements in the development of the intramolecular acylnitroso-Diels−Alder approach for the synthesis of nitrogen-containing natural products, see: Kibayashi, C.; Aoyagi, S. *Synlett* **1995**, 873−879.

(11) For reviews on the acylnitroso-Diels−Alder reaction, see: (a) Kirby, G. W. *Chem. Soc. Rev*. **1977**, *6*, 1−24. (b) Weinreb, S. M.; Staib, R. P. *Tetrahedron* **1982**, *38*, 3087−3128. (c) Boger, D. L.; Weinreb, S. M. *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987. (d) Weinreb, S. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pp 401−449. (e) Streith, J.; Defoin, A. *Synthesis* **1994**, 1107−1117. (f) Orena, M. In *Methods of Organic Chemistry (Houben-Weyl)*, 4th ed.; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1995; Vol. E21e, pp 5547−5587.

(12) (a) Burkholder, T. P.; Fuchs, P. L. *J. Am. Chem. Soc.* **1988**, *110*, 2341−2342. (b) Burkholder, T. P.; Fuchs, P. L. *J. Am. Chem. Soc.* **1990**, *112*, 9601−9613.

(13) Prepared according to: Corey, E. J.; Boger, D. L. *Tetrahedron Lett*. **1978**, 2461−2464.

Scheme 2[a]



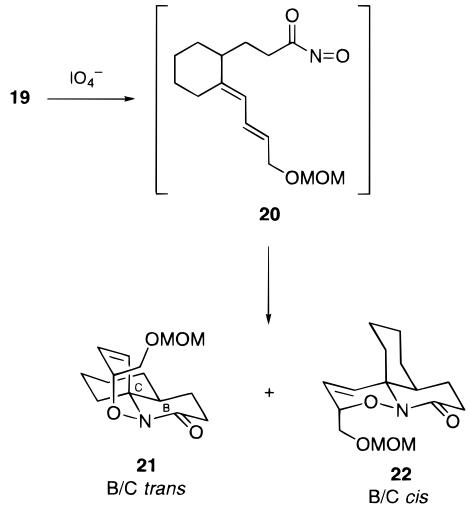
[a] Reagents and conditions: (a) $(EtO)_2P(O)CH_2CN$, BuLi, THF, −50 °C; (b) DIBALH, CH_2Cl_2, −30 °C; (c) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C; (d) DIBALH, CH_2Cl_2; (e) MOMCl, *i*-Pr_2NEt, CH_2Cl_2; (f) TsOH, MeOH, room temperature, then separation of the geometric isomers; (g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78→0 °C; (h) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*-BuOH−H_2O; (i) CH_2N_2, Et_2O; (j) NH_2OH·HCl, KOH, MeOH.

Horner−Emmons olefination of **11** yielded the (*E*,*E*)-ester **12** along with a small amount of a (*Z*,*E*)-isomer (combined yield: 91%), which underwent sequentially DIBALH reduction, MOM protection of the hydroxyl group, deprotection of the THP ether, and then separation of the geometric isomers, affording the (*E*,*E*)-alcohol **15** in 78% overall yield. Compound **15** was converted by Swern oxidation and subsequent oxidation with sodium chlorite to the corresponding carboxylic acid **17** (66%), which was transformed into the hydroxamic acid **19** (81%) by diazomethane esterification followed by treatment with hydroxylamine under alkaline conditions.

Upon oxidation of **19** with Pr_4NIO_4 under the conventional nonaqueous conditions using $CHCl_3$ at 0 °C, the in situ generated acylnitroso compound **20** was subjected to intramolecular [4 + 2] cycloaddition to yield the B/C trans-fused and cis-fused tricyclic lactams, **21** and **22**, with low diastereoselection of 2.1:1 in 58% combined yield (see Table 1, entry 1).

It has been demonstrated that the use of water as the solvent for Diels−Alder reaction improves rate, yield, and selectivity owing to the hydrophobic effect on a reactant encapsulated in a cavity surrounded by a hydrogen-bonding network of water molecules.[14] Indeed, our previous studies revealed[15] that the use of aqueous conditions for the intramolecular acylnitroso-Diels−Alder reaction effects significant enhancement of the diastereoselectivity due to the hydrophobic effect. Accordingly, the

Table 1. Intramolecular Diels−Alder Reaction of the *N*-Acylnitroso Compound[a]



entry	periodate	solvent	**21:22**[b]	yield (%)[c]
1	Pr_4NIO_4	$CHCl_3$	2.1:1	58
2	Pr_4NIO_4	H_2O−MeOH (5:1)	4.5:1	80
3	Bu_4NIO_4	H_2O−MeOH (5:1)	4.5:1	84
4	Bu_4NIO_4	H_2O−DMF (5:1)	4.7:1	75
5	Bu_4NIO_4	H_2O−DMSO (5:1)	4.8:1	77

[a] All reactions were carried out by treatment of the hydroxamic acid **19** with the periodate at 0 °C for 30−45 min. [b] The ratios were determined by HPLC analysis. [c] Isolated combined yield.

cycloaddition of **19** was carried out in aqueous media; the results obtained are collected in Table 1 (entries 2−5). As can be seen, employing these aqueous conditions significantly enhanced the desired trans selectivity (4.5:1 to 4.8:1) as well as yields (75−84%). These isomers **21** and **22** could be separated chromatographically. The minor isomer **22**, which is crystalline, was subjected to X-ray crystallographic analysis,[16] unequivocally confirming its relative stereochemistry as shown.

The trans facial preference observed in the cycloaddition of **19** can be rationalized in terms of endo transition states **20**. The syn-facial transition state conformer **20B** leading to the cis-fused adduct **22** would produce repulsive interactions between the ring methylene group at C(3) and the nitroso-containing tethering side chain and also between the C(5)-methylene group and the nitrogen atom. The other possible syn-facial conformer **20C** leading to the cis-fused adduct **22** would be disfavored due to the tethering side chain placed into an axial position. Thus, avoidance of these unfavorable steric interactions should lead to the most favored anti-facial conformer **20A**, in which the tethering side chain is equatorially disposed, affording the trans-fused adduct **21**. The hydrophobic effect in this case may have contributed to stabilize the more compact endo transition state conformer **20A** rather than **20B** and **20C** on enhancement of the trans selectivity as well as the yield.

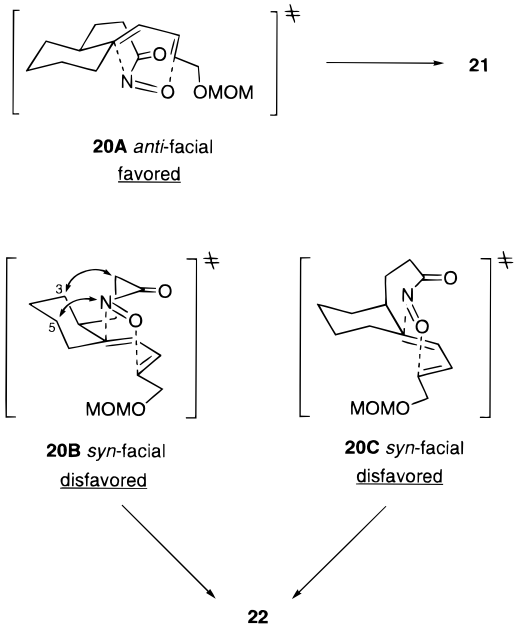
To the best of our knowledge, the predominant formation of the trans-adduct via such an anti-facial transition state with the dienophile approaching from the face opposite to the anchor position of the tether has not been previously recognized in an intramolecular Diels−Alder reaction.[17]

From these results, we expected that the cycloaddition using the nitroso-diene compound with bromine substitution at the

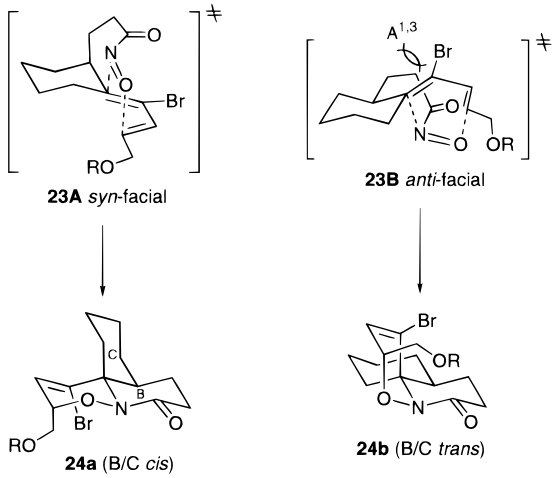
(14) For a recent review, see: Lubineau, A.; Augé, J.; Queneau, Y. *Synthesis* **1994**, 741−760.

(15) Naruse, M.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **1994**, *35*, 595−598.

(16) See Supporting Information.

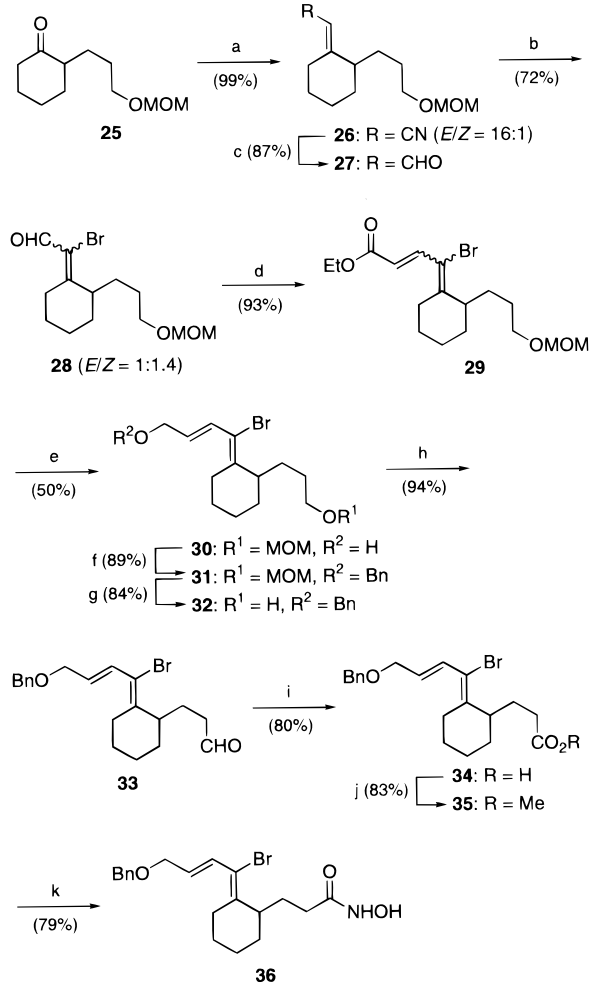


diene tether would lead to the preferential formation of the B/C cis-fused adduct **24a**, since a syn-facial transition state **23A** with the tethering 2-alkyl side chain adopting an axial position to avoid the 1,3-allylic strain[18] with the bromine atom is predicted to be energetically more favorable than an anti-facial one **23B** leading to a B/C trans-fused adduct **24b**. We thus next turned our attention to the cycloaddition using the bromine-substituted nitroso-diene compound.



The ketone **25**[13] was subjected to Horner−Emmons olefination to give the unsaturated nitrile **26** in 99% yield as a 16:1 *E*/*Z* mixture, which was converted in 87% yield to the unsaturated aldehyde **27** by DIBALH reduction (Scheme 3). Bromination of **27** led to a 1:1.4 *E*/*Z* mixture of the bromide **28** (72%), which was subjected sequentially to Horner−Emmons

Scheme 3[a]



[a] Reagents and conditions: (a) $(EtO)_2P(O)CH_2CN$, BuLi, THF, −50 °C; (b) DIBALH, CH_2Cl_2, −30 °C; (c) (i) Br_2·dioxane, −50 °C; (ii) pyridine, room temperature; (d) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, (e) DIBALH, CH_2Cl_2, 0 °C, then separation of the geometric isomers; (f) BnCl, $Bu_4N{\cdot}HSO_4$, NaOH, benzene; (g) PPTS, *t*-BuOH; (h) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (i) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*-BuOH−H_2O; (j) CH_2N_2, Et_2O; (k) $NH_2OH{\cdot}HCl$, KOH.

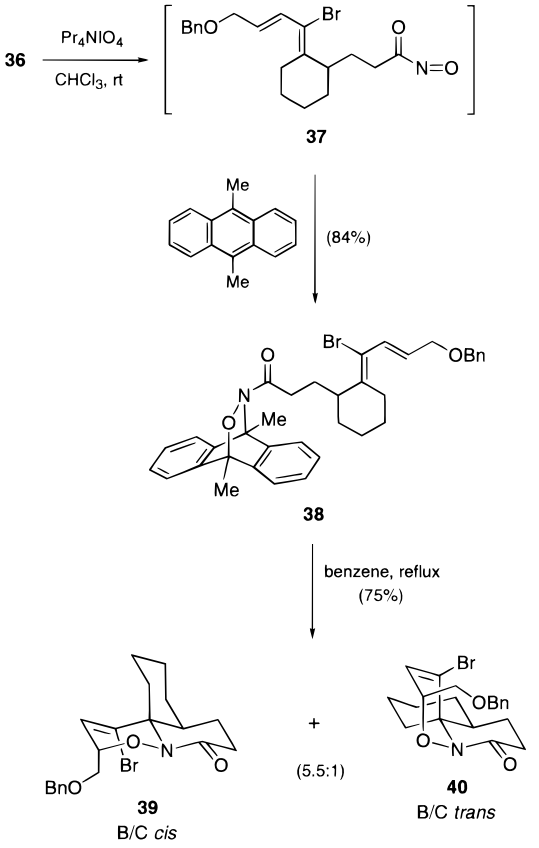
condensation, DIBALH reduction, and then separation of the mixture of the geometric isomers to provide the (*Z*,*E*)-alcohol **30** as a single isomer in 47% overall yield. After O-benzylation followed by removal of the MOM protecting group, the resulting alcohol **32** was converted to the carboxylic acid **34** via two-step oxidation (Swern oxidation followed by $NaClO_2$ oxidation) in 56% overall yield for four steps from **30**. Esterification followed by treatment with hydroxylamine provided the hydroxamic acid **36** (66%).

Treatment of **36** with Pr_4NIO_4 in a $CHCl_3$ solution at room temperature allowed the acylnitroso-diene **37** generated in situ to undergo intramolecular cycloaddition; however, although the TLC analysis revealed that the starting material disappeared within 20 min, the reaction produced only a poor yield (8%) of the cycloadducts **39** and **40** in a 2.6:1 ratio, though the desired cis-fused cycloadduct **39** was predominantly formed as expected. Neither prolonging the reaction time at room temperature nor heating at reflux temperature improved the yield of the cycloadducts; in the latter case, rapid decomposition of the substrate resulted. The poor yield in this cyclization would be attributed to a significant decrease of the reactivity of the acylnitroso compound **37** due to the attachment of an electron-

(17) For reviews on intramolecular Diels−Alder reaction, see: (a) Oppolzer, W. *Angew. Chem., Int. Ed. Engl*. **1977**, *16*, 10−23. (b) Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63−97. (c) Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183. (d) Ciganek, E. *Org. React.* **1984**, *32*, 1−374. (e) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187−238. (f) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pp 513−550. (g) Craig, D. In *Methods of Organic Chemistry (Houben-Weyl)*, 4th ed.; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1995; Vol. E21c, pp 2872−2904.

(18) (a) Johnson, F. *Chem. Rev*. **1968**, *68*, 375−413. (b) Hoffmann, R. W. *Chem. Rev*. **1989**, *89*, 1841−1860.

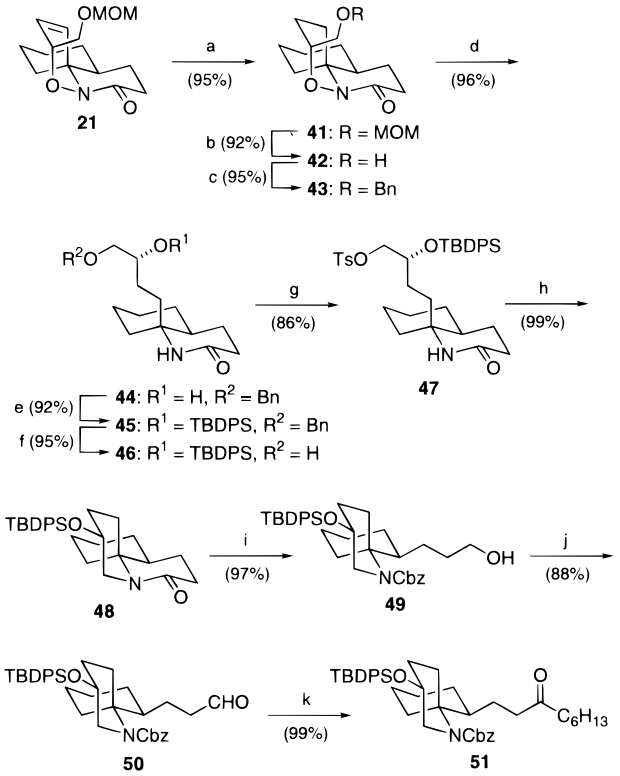
Scheme 4



withdrawing bromine atom to the diene moiety, which would lead to decomposition of the in situ generated **37** with properties associated with the RCO−N═O species, namely, they are extremely labile and short-lived.[11a] To overcome these problems including the inherent disadvantage of the acylnitroso compound, we sought to utilize the 9,10-dimethylanthracene adduct **38** which was considered to be a stable acylnitroso equivalent.[19] Thus, upon exposure of **36** to the same oxidation conditions (Pr_4NIO_4, $CHCl_3$, room temperature) in the presence of 9,10-dimethylanthracene, intermolecular cycloaddition reaction smoothly proceeded to form the adduct **38** in 84% yield (Scheme 4). Thermolysis of **38** in refluxing benzene caused a retro-Diels−Alder reaction to regenerate the intermediate acylnitroso diene **37**, which immediately underwent intramolecular cycloaddition under the reaction conditions, affording the cycloadducts **39** and **40** in 75% yield and in a 5.5:1 ratio favoring the B/C cis-fused adducts **39** in contrast to the facial selectivity (anti) observed in the cycloaddition with the nonbrominated acylnitroso-dine **20** described above.

Synthesis of (±)-Fasicularin. Having obtained the desired trans-fused cycloadduct **21** through the face-selective anti-addition described above, we initially focused our efforts on the total synthesis of fasicularin (**2**). Catalytic hydrogenation of the double bond of **21** and removal of the MOM protecting group produced **42** (87%), the stereochemistry of which was confirmed by X-ray crystallography.[16] After protection of the hydroxyl group as the benzyl ether, the N−O bond of **43** was cleaved by treatment with sodium amalgam and the resulting secondary alcohol **44** was protected as the *tert*-butyldiphenylsilyl (TBDPS) ether to afford **45** in 84% overall yield from **42**. Compound **45** was converted to the tosylate **47** in 82% yield by hydrogenolytic removal of the benzyl group followed by tosylation. Cyclization of **47** to the tricyclic lactam **48** was accomplished using sodium hydride in THF at reflux to give a

Scheme 5[a]



[a] Reagents and conditions: (a) H_2, Pd−C, MeOH; (b) concentrated, HCl, MeOH, reflux; (c) BnBr, NaH, Bu_4NI, DMF, room temperature; (d) Na(Hg), Na_2HPO_4, EtOH; (e) TBDPSCl, imidazole, DMF; (f) H_2, Pd−C, MeOH; (g) TsCl, Et_3N, DMAP, CH_2Cl_2; (h) NaH, THF, reflux; (i) (i) $LiNH_2BH_3$, THF; (ii) CbzCl, Na_2CO_3, $CHCl_3-H_2O$; (j) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78→ 0 °C; (k) $C_6H_{13}MgBr$, Et_2O, 0 °C, then PCC, CH_2Cl_2.

virtually quantitative yield. Since attempts to introduce the hexyl side chain into the lactam ring in **48** were unsuccessful, ring-opening of the lactone ring was deemed necessary for the attachment of the hexyl side chain. Thus, **48** was exposed to $LiNH_2BH_3$, prepared from $BH_3{\cdot}NH_3$ and BuLi,[20] at room temperature, leading to reductive ring-opening,[21] and it underwent subsequent N-protection to give the azaspiro[5,5]undecane derivative **49** in 97% yield. Swern oxidation of **49** and subsequent addition of the hexyl Grignard reagent followed by PCC oxidation provided the ketone **51** in 87% overall yield.

Palladium-catalyzed hydrogenation of **51** resulted in ring closing via hydrogenolytic cleavage of the Cbz group followed by hydrogenation of the in situ generated iminium ion **52** to form the tricyclic products **53** and **54** in slight preference for undesired **53** (1.3:1, 86% combined yield) with the configuration at the hexyl group inconsistent with that of fasicularin (Scheme 6).

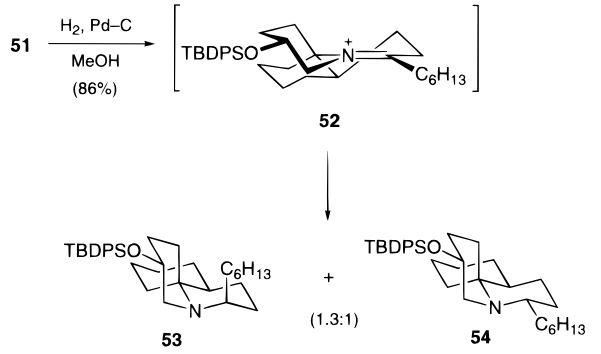
The formation of desired **54** was thus found to be less favored probably due to the steric hindrance in an intermediary iminium ion **52** that disturbs hydrogen delivery from the sterically congested β face. To circumvent this problem associated with the face selectivity of the hydrogenation, we envisaged the use

(19) (a) Kirby, G. W.; Sweeny, J. G. *J. Chem. Soc., Chem. Commun.* **1973**, 704−705. (b) Corrie, J. E. T.; Kirby, G. W.; Sharma, R. P. *J. Chem. Soc., Chem. Commun.* **1975**, 915−916. (c) Keck, G. E. *Tetrahedron Lett.* **1978**, 4767−4770

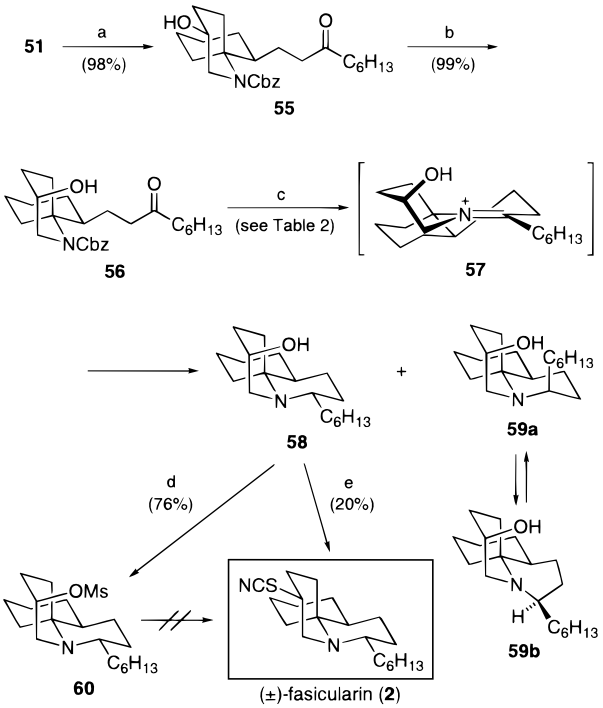
(20) Myers, A. G.; Yang, B. H.; Kopecky, D. J. *Tetrahedron Lett.* **1996**, *37*, 3623−3626.

(21) For recent application of this reaction to lactam ring-opening, see: Aoyagi, S.; Tanaka, R.; Naruse, M.; Kibayashi, C. *J. Org. Chem.* **1998**, *63*, 8397−8406.

Scheme 6



Scheme 7[a]



[a] Reagents and conditions: (a) Bu_4NF, THF; (b) (i) DEAD, Ph_3P, *p*-$NO_2C_6H_4CO_2H$; (ii) 5% NaOH, THF, (c) H_2, Pd−C, for the solvent, see Table 2; (d) MsCl, Et_3N, DMAP; (e) HSCN, Ph_3P, DEAD, benzene.

of a substrate bearing a hydroxyl group to be bound to the catalytic surface during hydrogenation so as to enforce addition of hydrogen from the sterically hindered β face.[22] For this purpose, the silyl protecting group in **51** was removed and subsequent inversion of configuration at the secondary alcohol center in **55** using the Mitsunobu procedure[23] led to the epimerized alcohol **56** in very high yield. We first examined the reductive cyclization of **56** in ethanol, which proceeded under the hydrogenolytic conditions with palladium on carbon to provide a 1:1.7 mixture of the tricyclic products **58** and **59** in 63% combined yield favoring the undesired 6β-hexyl isomer **59** (Table 2, entry 1). The use of ethyl acetate as a solvent resulted in the preferential formation of **59** as well with a slight decrease of the **58**/**59** ratio (1:1.3) (entry 2). The results indicate that the use of a polar solvent does not lead to the face selectivity of the hydrogenation in the desired sense, presumably due to the competitive association of the solvent molecule with the

(22) For a comprehensive review on heteroatom-directed organic reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370.

(23) Mitsunobu, O. *Synthesis* **1981**, 1−28.

Table 2. Cyclization of **56** via Intramolecular Reductive Amination

entry	solvent	**58**:**59**[a]	yield (%)[b]
1	EtOH	1:1.7	63
2	AcOEt	1:1.3	66
3	benzene	3.4:1	65
4	cyclohexane	5.2:1	62

[a] The ratios were based on the isolated products. [b] Isolated combined yield.

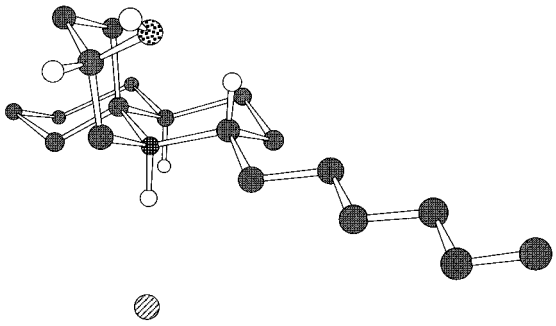


Figure 1. The X-ray structure (Chem3D representation) of **58**·HCl.

metal surface, which diminishes the directing effect of the hydroxyl group in the iminium intermediate **57**. We envisaged the hydrocarbons as nonpolar solvents, which do not compete for binding sites of the catalytic surface, thus enforcing the hydroxyl group-catalyst association and thereby favoring formation of the desired 6α-hexyl isomer **58**.[24] Therefore, the catalytic hydrogenation of **56** was carried out using benzene and cyclohexane, whereby the stereochemical outcome of the cyclization was found to be reversed as expected, affording the desired 6α-hexyl isomer **58** which predominated with ratios of 3.4:1 and 5.2:1, respectively, over its 6-epi isomer **59** (entries 3 and 4).

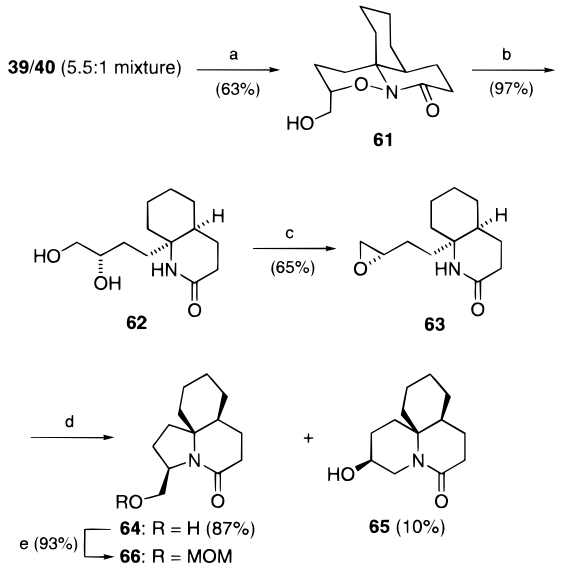
The 6α-hexyl side chain occupying the equatorial position postulated for **58** was irrevocably confirmed by the X-ray crystal structure analysis (Figure 1). We expected that the 6β-hexyl isomer **59** would adopt the conformation **59b** in a twist-boat form for ring B leaving the hexyl group in the equatorial position to avoid severe steric interaction between the β-hexyl group and ring A bearing the β-hydroxyl group present in the chair conformation **59a**. This is in agreement with molecular mechanics (MM3) calculations (Molecular Mechanics, Version 4.0, CAChe system, Oxford Molecular Group, Inc.), which show that the twist-boat conformation **59b** is ca. 2.0 kcal/mol more stable than the chair conformation **59a**.

For the final thiocyanation step, transformation of the hydroxyl group in **58** into an adequate leaving group in an S_N2 fashion was carried out. Although triflation was difficult, probably due to the sterically hindered nature of the hydroxyl group function, the mesylate **60** was obtained in 76% yield, and we expected to introduce the thiocyanyl group with the correct stereochemistry via a nucleophilic displacement reaction. However, all attempts using KSCN under various conditions gave only elimination and decomposition products. To circumvent this problem in this thiocyanation strategy, an alternative route to convert **58** directly into (±)-fasicularin (**2**) was next sought. Treatment of **58** with the isothiocyanatophosphonium salt[25] resulted in no reaction (at −45 °C to room temperature)

(24) For a discussion of the solvent effect on the stereochemical outcome of directed catalytic hydrogenation, see: Thompson, H. W.; McPherson, E.; Lences, B. L. *J. Org. Chem.* **1976**, *41*, 2903−2906.

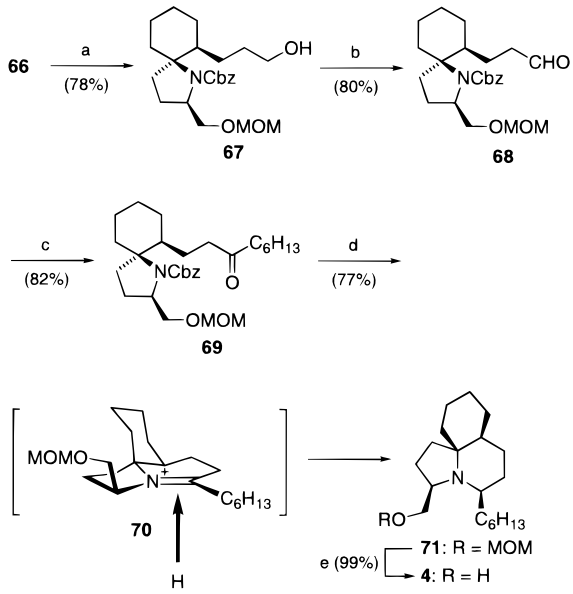
(25) (a) Tamura, Y.; Kawasaki, T.; Adachi, M.; Tanio, M.; Kita, Y. *Tetrahedron Lett.* **1977**, 4417−4420. (b) Burski, J.; Kieszkowski, J.; Michalski, J.; Pakulski, M.; Skowronska, A. *Tetrahedron* **1983**, *39*, 4175−4181.

Scheme 8[a]



[a] Reagents and conditions: (a) H_2, Pd−C, Et_3N, MeOH, then separation of the cis/trans isomers; (b) Na(Hg), $NaHPO_4$, EtOH; (c) (i) MsCl, collidine; (ii) NaOH, THF−MeOH; (d) NaH, THF; (e) MOMCl, *i*-Pr_2NEt.

Scheme 9[a]



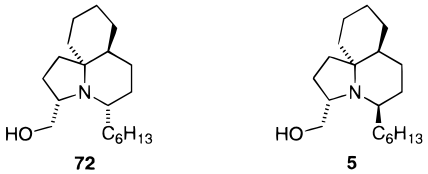
[a] Reagents and conditions: (a) (i) $LiNH_2BH_3$, THF; (ii) CbzCl, Na_2CO_3, benzene−H_2O; (iii) K_2CO_3, MeOH−H_2O; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (c) (i) $C_6H_{13}MgBr$, Et_2O; (ii) PCC, CH_2Cl_2; (d) H_2, Pd−C, EtOH; (e) concentrated HCl, MeOH.

or formation of a small amount of the isothiocyanate (at 60 °C); however, a Mitsunobu condensation (Ph_3P, DEAD, benzene)[26] with thiocyano acid proceeded with complete inversion of configuration at the reaction center to provide (±)-fasicularin (**2**), albeit in low yield (20%) and with concomitant formation of an elimination product (54%) and an isothiocyanate (2%). The synthetic material of (±)-**2** so obtained showed ^1H and ^{13}C NMR spectra in full agreement with those of natural fasicularin, which verified the structure and relative stereochemistry proposed in the literature[4] for the natural product.

Synthesis of the Putative Structure of Lepadiformine. The next object of our research was the synthesis of the putative structure **4** of lepadiformine in the nonzwitterionic form utilizing the above-described B/C cis-fused cycloadduct **39** including a small amount of the trans-fused isomer **40** which were obtained as an inseparable 5.5:1 diastereomeric mixture (Scheme 8). Reduction of the double bond, debenzylation, and debromination of this mixture were accomplished by hydrogenation over palladium on carbon in the presence of Et_3N in a single operation, affording the cis-fused isomer **61** in 63% yield after chromatographic separation. Reductive N−O bond cleavage of **61** using sodium amalgam gave the 1,2-diol **62** in excellent yield, which was converted to the epoxide **63** in 65% yield via selective mesylation of the primary alcohol function followed by alkaline treatment. Treatment of **63** with NaH in refluxing THF caused selective intramolecular 5-exo-epoxy ring-opening to form the tricyclic lactam **64** in 87% yield in preference to the 6-endo-epoxy ring-opening (leading to **65** in 10% yield).

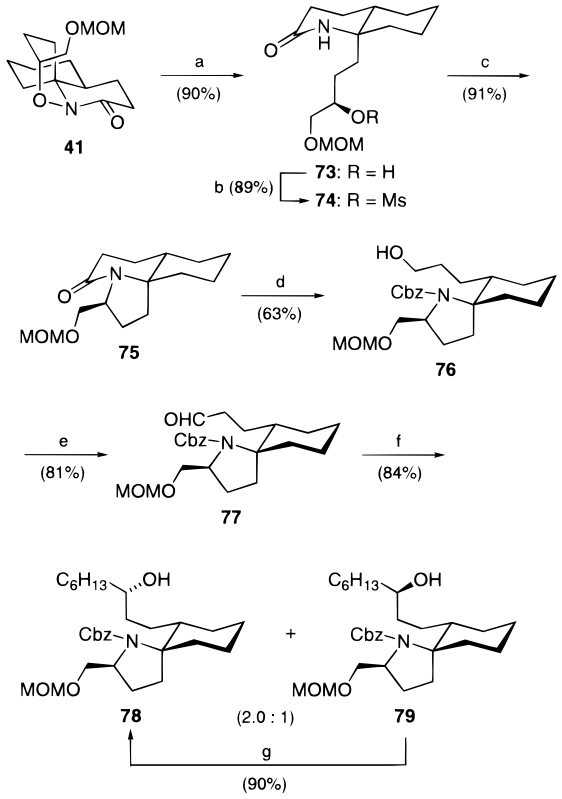
After protection of the hydroxyl group as the MOM ether, reductive lactam ring-opening of **66** was effected using $LiNH_2BH_3$, leading to the azaspiro alcohol which underwent N-protection to give **67** in 78% overall yield (Scheme 9). Swern oxidation of **67** and subsequent addition of hexylmagnesium bromide followed by PCC oxidation afforded the ketone **69** in 66% overall yield. Cyclization of **69** could be successfully performed via intramolecular reductive amination under catalytic hydrogenation conditions to produce **71** as a single isomer in 77% yield. The preferential formation of this diastereomer can be explained by invoking an iminium intermediate **70** in which hydrogenation should occur on the less hindered α face. Finally, removal of the MOM protecting group from **71** under methanolic HCl conditions provided in 95% yield the tricyclic amino alcohol **4**, possessing the stereostructure proposed for lepadiformine, which was found to exist in a nonzwitterionic form as shown rather than the proposed zwitterionic structure **3**. The spectral properties (^1H and ^{13}C NMR) for both the free base and the hydrochloride salt of the synthetic material, however, were clearly different from those reported[3] for natural lepadiformine.

Total Synthesis of Lepadiformine. While our work was in progress, Weinreb et al.[6] reported the synthesis of the putative structure **4** of lepadiformine and found their synthetic material to be different from natural lepadiformine. At the same time, Pearson et al.[7] described the syntheses of the remaining three of the four diastereoisomers of **4** at C(3) and C(5); however, none of these compounds was found to be compatible with lepadiformine. From these results, they suggested that the originally proposed structure **3** (or **4** in a nonzwitterionic form) of lepadiformine must be revised to be epimeric at C(11a), thus constituting the trans-fused perhydroquinoline ring system as in fasicularin. Furthermore, the cis relationship between the hydroxymethyl group of the pyrrolidine ring and the C(11) methylene group has previously been defined by NOESY correlation.[3] Considering these findings and the NMR spectral evidence, two structures **72** and **5** both constituting the trans-fused decahydroquinoline framework can be reasonably proposed for lepadiformine. It was envisioned that these compounds **72** and **5** could be constructed by utilizing the above-described



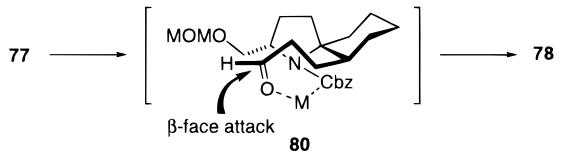
(26) This procedure was based upon the following: Sliwska, H.-R.; Liaaen-Jensen, S. *Tetrahedron: Asymmetry* **1993**, *4*, 361−368.

Scheme 10[a]



[a] Reagents and conditions: (a) Na(Hg), Na_2HPO_4, EtOH; (b) MsCl, Et_3N, DMAP; (c) *t*-BuOK, THF, room temperature; (d) (i) $LiNH_2BH_3$, THF, room temperature; (ii) CbzCl, Na_2CO_3; (e) $(COCl)_2$, DMSO, Et_3N, −78→ 0 °C; (f) $C_6H_{13}MgBr$, Et_2O, 0 °C; (g) (i) *p*-$NO_2C_6H_4CO_2H$, Ph_3P, DEAD; (ii) 10% NaOH, THF−MeOH.

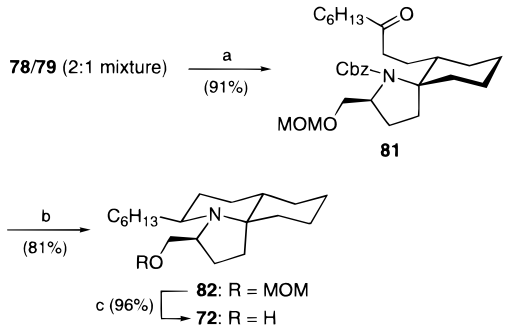
tricyclic lactam **41**, the intermediate for the synthesis of fasicularin, as the starting material having the trans-fused octahydroquinolinone unit. To investigate this approach, **41** was subjected to reductive cleavage of the N−O bond to give the alcohol **73**, which was converted to the tricyclic lactam **75** via mesylation followed by base treatment (Scheme 10). Reductive lactam ring-opening of **75** using $LiNH_2BH_3$ followed by N-protection provided the azaspiro compound **76** in 63% yield. Swern oxidation of **76** and subsequent addition of the hexyl Grignard reagent to the aldehyde **77** afforded the epimeric secondary alcohols **78** and **79** with a 2.0:1 ratio favoring the α-isomer **78** in 68% combined yield from **76**. The stereochemical outcome of the preferential formation of **78** could be accounted for by a transition-state model **80** involving the chelation[27] of the carbonyl groups of the formyl and *N*-Cbz functions with Mg. The minor *β*-isomer **79** could be converted to the α-isomer **78** by inversion of the hydroxyl configuration using the Mitsunobu procedure in 90% yield; thus, the total yield of **78** from the aldehyde **77** was 81%.



The 2.0:1 epimeric mixture of the alcohols **78** and **79** described above was converted to the ketone **81** that underwent

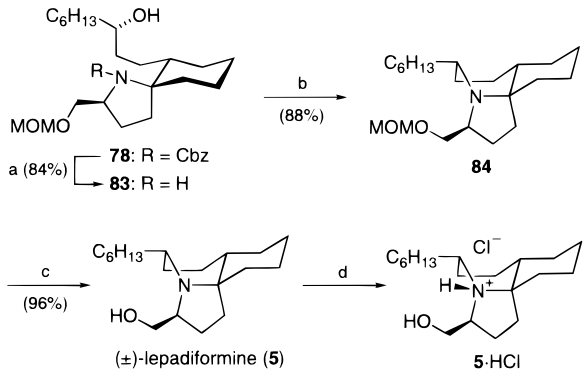
(27) Garner, P.; Ramakanth, S. *J. Org. Chem.* **1986**, *51*, 2609−2611.

Scheme 11[a]



[a] Reagents and conditions: (a) PCC, CH_2Cl_2; (b) H_2, Pd−C, MeOH; (c) concentrated HCl, MeOH.

Scheme 12[a]



[a] Reagents and conditions: (a) H_2, Pd−C, MeOH; (b) Ph_3P, CBr_4, Et_3N, room temperature; (c) concentrated HCl, MeOH, room temperature, then 5% K_2CO_3; (d) 1 N HCl−MeOH.

ring closure upon catalytic hydrogenation to form the tricyclic compound **82** as a single isomer in 74% overall yield (Scheme 11). Removal of the MOM protecting group under the standard acidic conditions afforded the tricyclic amino alcohol **72** in 96% yield. The spectra (^1H and ^{13}C NMR) of both the free base and the hydrochloride salt of **72** were found to be different from those reported[3] for natural lepadiformine.

Our next concern was the synthesis of another target **5** by utilizing the α-alcohol **78**. Thus, after hydrogenolytic removal of the Cbz group, the resulting amino alcohol **83** was exposed to CBr_4 and Ph_3P, which led to smooth dehydrocyclization[28] with complete inversion of the configuration at C(3′) to form **84** in 74% yield from **78** (Scheme 12). Deprotection of the MOM protecting group with concentrated HCl in methanol and subsequent basic treatment provided **5** as an oil in 96% yield. Further treatment of this material with methanolic HCl followed by evaporation of the solvent resulted in the hydrochloride salt of **5** as a solid. This provided single crystals from recrystallization in ether, thus allowing structural assignment to be unambiguously secured by X-ray analysis,[29] which revealed the stereochemistry of **5**·HCl with the B ring in a somewhat unusual boat (twist-boat) form with the preferred adoption of an equatorial orientation of the hexyl side chain (Figure 2). Although both ^1H and ^{13}C NMR spectral data for synthetic **5** as the free base were distinctly different from those published[3] for natural lepadiformine, measurement of the ^1H and ^{13}C NMR spectra of the synthetic hydrochloride salt **5**·HCl allowed direct

(28) Shishido, Y.; Kibayashi, C. *J. Org. Chem.* **1992**, *57*, 2876−2883.

(29) Many attempts at obtaining a crystalline derivative of natural lepadiformine (provided by Professor Biard as an oil) suitable for X-ray crystallography were unsuccessful (W. Pearson, personal communication).

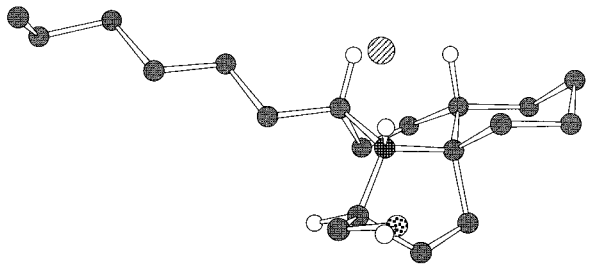


Figure 2. The X-ray structure (Chem3D representation) of synthetic (±)-lepadiformine hydrochloride [**5**·HCl].

comparison with the spectra on natural lepadiformine kindly provided by Professor Biard, revealing an exact match. This finding strongly implies that the structure of natural lepadiformine reported in the literature[3] was actually that of the hydrochloride salt; this is understandable because the isolation of the natural alkaloid was made by evaporation of an acidic solution (MeOH−1 N HCl, 99:1) of the chromatography fractions. These results therefore clearly indicate that structural formula **3** involving the zwitterionic form originally assigned to natural lepadiformine should be revised to **5** as shown.

In summary, the first total synthesis of tricyclic marine alkaloids (±)-fasicularin (**2**) and (±)-lepadiformine (**5**) was accomplished. The key common strategic element for the synthesis is the stereocontrolled intramolecular hetero-Diels−Alder reaction of an *N*-acylnitroso moiety to an exocyclic diene with or without bromine substitution to control the syn-facial or anti-facial selectivity, respectively, leading to the cis- or trans-fused decahydroquinoline ring systems involving the simultaneous introduction of the nitrogenated quaternary center in a single step. On further elaboration of the six-membered or five-membered ring A, the trans-fused adduct provided either (±)-fasicularin (**2**) or (±)-lepadiformine (**5**), and the cis-fused adduct was converted into the originally proposed structure **4** of lepadiformine in the nonzwitterionic form. The present investigation thus unambiguously established the relative stereochemistry of lepadiformine, formerly assigned incorrectly, to be 3*R**,5*S**,7a*R**,11a*R**.

Experimental Section[30]

Preparation of (3*R,8a*S**,12a*R**)- and (3*R**,8a*R**,12*R**)-2-[(Methoxymethoxy)methyl]-8,8a,9,10,11,12-hexahydro-3*H*-[1,2]oxazino[3,2-*j*]quinolin-6(7*H*)-one (21 and 22): Typical Procedure.** To an ice-cooled, vigorously stirred emulsion of **19** (824 mg, 2.91 mmol) dispersed in a 5:1 mixture (13 mL) of water and MeOH was added solid tetrabutylammonium periodate (2.52 g, 5.11 mmol). After being stirred at 0 °C for 20 min, the mixture was quenched with 10% aqueous $Na_2S_2O_3$ (50 mL) and extracted with $CHCl_3$ (2 × 500 mL). The combined organic extracts were washed with water, dried ($MgSO_4$), and concentrated in vacuo to give an oil. HPLC analysis (hexane−2-propanol, 5:1) of the crude product showed the formation of a 4.5:1 mixture of the cycloadducts **21** and **22**, which was separated by chromatography ($CHCl_3$−acetone, 9:1). The first fractions afforded **21** (565 mg, 69%) as a colorless oil, which solidified on storage in a refrigerator. Recrystallization from hexane afforded colorless needles: mp 28−29 °C; IR (KBr) 3445, 1679 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23−1.88 (m, 10H), 2.41 (dt, J = 12.9, 3.1 Hz, 1H), 2.45−2.51 (m, 2H), 3.39 (s, 3H), 3.58 (dd, J = 10.6, 6.1 Hz, 1H), 3.89 (m, 1H), 4.62 (tt, J = 6.6, 2.7 Hz, 1H), 4.68 and 4.74 (ABq, J = 6.4 Hz, 2H), 5.88 (A part of ABX, J = 10.6, 2.4 Hz, 1H), 6.36 (B part of ABX, J = 10.6, 2.5 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 22.1, 24.7, 25.6, 27.1, 34.3, 38.2, 43.7, 55.4, 62.4, 69.9, 79.3, 97.0, 125.8, 130.6, 168.3; EIMS *m*/*z* (relative intensity) 281 (M^+, 0.4), 45 (100); HRMS calcd for $C_{15}H_{23}NO_4$ (M^+) 281.1627, found 281.1617.

(30) See Supporting Information for General Procedures.

The second fractions afforded **22** (126 mg, 15%) as a white solid, which was recrystallized from AcOEt−hexane to give colorless needles: mp 101−102 °C; IR (KBr) 3319, 1732, 1669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.18−1.97 (m, 9H), 2.12 (qd, J = 12.9, 5.6 Hz, 1H), 2.26 (br d, J = 13.2 Hz, 1H), 2.42 (A part of ABX, J = 17.2, 12.5, 6.5 Hz, 1H), 2.54 (B part of ABX, J = 17.2, 5.7, 1.7 Hz, 1H), 3.37 (s, 3H), 3.56 (A′ part of A′B′X, J = 10.9, 4.5 Hz, 1H), 3.68 (B′ part of A′B′X, J = 10.9, 7.3 Hz, 1H), 4.58 (m, 1H), 4.68 and 4.69 (ABq, J = 6.5 Hz, 2H), 5.82 (A″ part of A″B″X, J = 10.4, 3.6 Hz, 1H), 6.35 (B″ part of A″B″X, J = 10.4, 1.8 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 20.6, 22.3, 22.5, 27.4, 32.1, 32.6, 38.3, 55.4, 61.5, 68.3, 78.3, 97.2, 123.6, 131.1, 164.7; EIMS *m*/*z* (relative intensity) 281 (M^+, 1), 221 (12), 45 (100). Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.04; H, 8.24; N, 4.98. Found: C, 64.07; H, 7.96; N, 4.99.

Benzyl (2*E*,4*Z*)-4-Bromo-4-{2-[3-(1,8-dimethyl-15-oxa-16-szatetracyclo[6.6.2.0^{2,7}.0^{9,14}]hexadeca-2,4,6,9,11,13-hexaen-16-yl)-3-oxopropyl]cyclohexylidene}-2-butenyl Ether (38). A solution of **36** (696 mg, 1.70 mmol) in $CHCl_3$ (10 mL) was added dropwise to a solution of 9,10-dimethylanthracene (897 mg, 4.26 mmol) and tetrapropylammonium periodate (moistened with 10% water; 788 mg, 1.70 mmol) in $CHCl_3$ (10 mL). The mixture was stirred for 1 h at room temperature, quenched with 5% aqueous $Na_2S_2O_3$ (5 mL), and extracted with $CHCl_3$ (2 × 50 mL). The organic phase was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by chromatography (hexane−AcOEt, 25:1) gave **38** (883 mg, 84%) as a white solid, which was recrystallized from Et_2O−hexane to give colorless needles: mp 41−42 °C; IR (KBr) 1678 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36−1.80 (m, 9H), 1.88 (td, J = 14.2, 4.4 Hz, 1H), 2.04 (ddd, J = 16.3, 10.8, 4.9 Hz, 1H), 2.20 (s, 3H), 2.21 (m, 1H), 2.69 (s, 3H), 3.10 (m, 1H), 4.15 (dd, J = 5.7, 1.3 Hz, 2H), 4.55 (s, 2H), 6.16 (dt, J = 14.6, 5.7 Hz, 1H), 6.61 (d, J = 14.6 Hz, 1H), 7.18−7.50 (m, 13H).

(3*R,8a*R**,12a*R**)- and (3*R**,8a*S**,12a*R**)-3-[(Benzyloxy)methyl]-1-bromo-8,8a,9,10,11,12-hexahydro-3*H*-[1,2]oxazino[3,2-*j*]quinolin-6(7*H*)-one (39 and 40).** A solution of **38** (876 mg, 1.43 mmol) in benzene (450 mL) was heated at reflux with stirring for 3 h. After being cooled to room temperature, the solution was concentrated in vacuo and subjected to chromatography eluting with hexane−AcOEt (25:1) to give 437 mg (75%) of an inseparable 5.5:1 mixture (based on ^1H NMR analysis) of **39** and **40** as a colorless oil: IR (neat) 1790, 1683 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.16−1.66 (m, 6H), 1.78 (br d, J = 10.4 Hz, 1H), 1.87 (tdd, J = 13.6, 6.2, 3.5 Hz, 2H), 2.29−2.39 and 2.41 (m, and, d, J = 6.1 Hz, respectively, total 2H in 5.5:1 ratio), 2.50 (m, 1H), 2.57 and 2.62 (dd, J = 13.5, 6.8 Hz, each, total 1H in 5.5:1 ratio), 3.60 and 3.58 (A part of ABX, J = 9.9, 7.0 Hz, and A′ part of A′B′X, J = 9.8, 7.8 Hz, respectively, total 1H in 5.5:1 ratio), 3.84 and 3.90 (B part of ABX, J = 9.9, 5.8 Hz, and B′ part of A′B′X, J = 9.7, 5.8 Hz, respectively, total 1H in 5.5:1 ratio), 4.54 and 4.56 ($^1/_2$ABq, J = 11.8 Hz, each, total 1H in 5.5:1 ratio), 4.60 and 4.62 ($^1/_2$ABq, J = 11.8 Hz, each, total 1H in 5.5:1 ratio), 4.61 (m, 1H), 6.18 and 6.32 (d, J = 3.2 Hz, and, d, J = 2.6 Hz, respectively, total 1H in 5.5:1 ratio), 7.27−7.35 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.4 and 21.3 (1 carbon in 5.5:1 ratio), 22.5 and 24.5 (1 carbon in 5.5:1 ratio), 25.0 and 25.2 (1 carbon in 5.5:1 ratio), 25.8 and 27.9 (1 carbon in 5.5:1 ratio), 29.9 and 33.9 (1 carbon in 5.5:1 ratio), 32.3 and 38.9 (1 carbon in 5.5:1 ratio), 37.2 and 44.7 (1 carbon in 5.5:1 ratio), 66.8 and 64.9 (1 carbon in 5.5:1 ratio), 71.7 and 69.5 (1 carbon in 5.5:1 ratio), 73.4 and 72.0 (1 carbon in 5.5:1 ratio), 81.7 and 80.9 (1 carbon in 5.5:1 ratio), 127.7, 127.8 (2C), 128.4 (2C), 129.5, 130.5, 138.0, 169.0 and 169.2 (1 carbon in 5.5:1 ratio); EIMS *m*/*z* (relative intensity) 408 (M^+ + 3, 6), 406 (M^+ + 1, 6), 326 (M^+ − Br, 11), 268 (12), 205 (10), 176 (13), 91 (100). Anal. Calcd for $C_{20}H_{24}NO_3Br$: C, 59.12; H, 5.95; N, 3.45. Found: C, 59.09; H, 6.08; N, 3.33.

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Supporting Information Available: Detailed experimental procedures and spectral data for **2**, **4**, **5**, **10**−**19**, **26**−**36**, **41**−**51**, **53**−**56**, **58**−**69**, **71**−**79**, and **81**−**84**; X-ray data and ORTEP diagrams of **5**·HCl, **23**, **41**, and **58**·HCl (/PDF). This material is available free of charge via Internet at http://pubs.acs.org.

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