Pergamon

Tetrahedron Letters 41 (2000) 1205–1208

TETRAHEDRON
LETTERS

Total synthesis of the proposed structure of lepadiformine via intramolecular *N*-acylnitroso Diels–Alder reaction

Hideki Abe, Sakae Aoyagi and Chihiro Kibayashi *

School of Pharmacy, Tokyo University of Pharmacy and Life Science, Horinouchi, Hachioji, Tokyo 192-0392, Japan

Received 21 October 1999; revised 11 November 1999; accepted 12 November 1999

Abstract

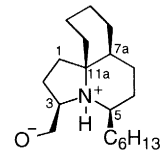
A stereocontrolled approach to the proposed structure of lepadiformine has been achieved employing an intramolecular hetero Diels–Alder reaction of an *N*-acylnitroso compound, in which *syn*-face selectivity was controlled. The NMR data of the product synthesized based on this approach is not identical with those reported for natural lepadiformine. Thus, the proposed structure for natural lepadiformine must be revised.

Keywords: alkaloids; cytotoxines; nitroso compounds; cycloaddition.

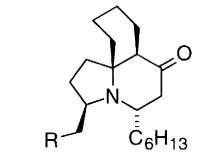
In 1994, Biard and co-workers[1] published a report on the isolation and structure elucidation of lepadiformine (**1**), a new marine alkaloid from the ascidian *Clavelina lepadiformis* collected in Tunisia. It was found to be moderately cytotoxic toward various tumor cell lines in vitro. Its structure including a unique zwitterionic form was assigned based on spectral analysis, though the absolute configuration was still unknown. Lepadiformine and related marine alkaloids cylindricines (**2**–**9**),[2] also isolated from the ascidians, are azatricyclic compounds possessing a perhydropyrrolo[2,1-*j*]quinoline skeleton as a common structural feature unprecedented among natural products. These alkaloids have attracted considerable synthetic attention, and the development of new ring-forming reactions aimed at constructing the pyrroloquinoline framework has been the major subject of recent synthetic efforts.[3] In view of this, we envisioned the stereoselective construction of the azatricyclic structure **1** proposed for lepadiformine by employing the strategy involving an intramolecular hetero Diels–Alder cycloaddition of an *N*-acylnitroso compound.[4,5]

* Corresponding author. Fax: +0081-426-764475; e-mail: kibayasi@ps.toyaku.ac.jp (C. Kibayashi)

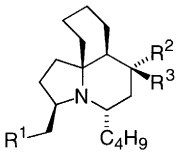
0040-4039/00/$ - see front matter
PII: S0040-4039(99)02172-3



lepadiformine (**1**)

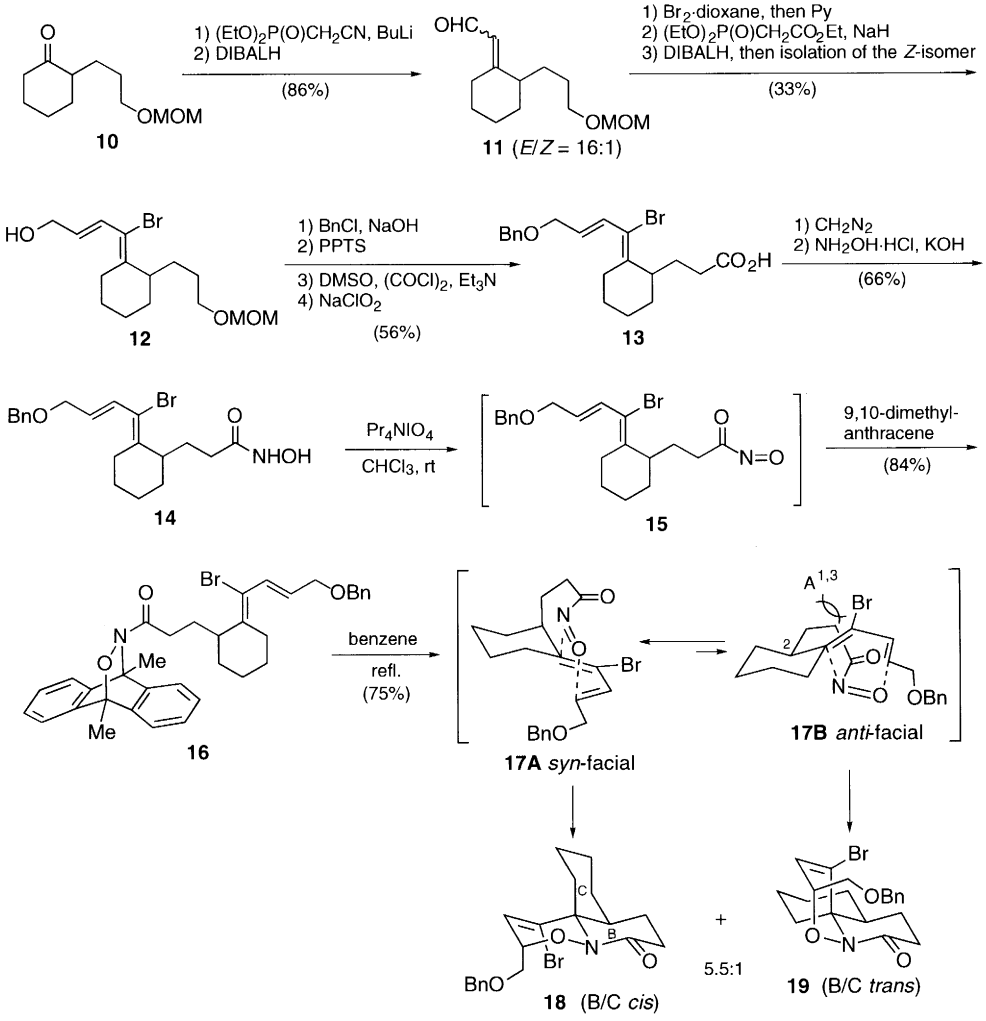


cylindricine A (**2**) R = Cl
C (**3**) R = OH
D (**4**) R = OMe
E (**5**) R = OAc
F (**6**) R = SCN



cylindricine G (**7**) R_1 = SCN; R_2 = R_3 = O
H (**8**) R_1 = SCN; R_2 = OAc; R_3 = H
I (**9**) R_1 = NCS; R_2 = OAc; R_3 = H

The ketone **10** was subjected to Horner–Emmons olefination followed by DIBALH reduction of the cyano group to give the α,β-unsaturated aldehyde **11** in 86% yield as a 16:1 *E*/*Z* mixture favoring the *E*-isomer (Scheme 1). Addition of bromine to this mixture and subsequent regioselective dehydrobromination led to the α-bromo-α,β-unsaturated aldehyde, which underwent Horner–Emmons olefination followed by DIBALH reduction and chromatographic separation to afford the (*Z*)-bromodiene **12** in 33% overall yield. Conversion of **12** to the carboxylic acid **13** was carried out in 56% overall yield by the

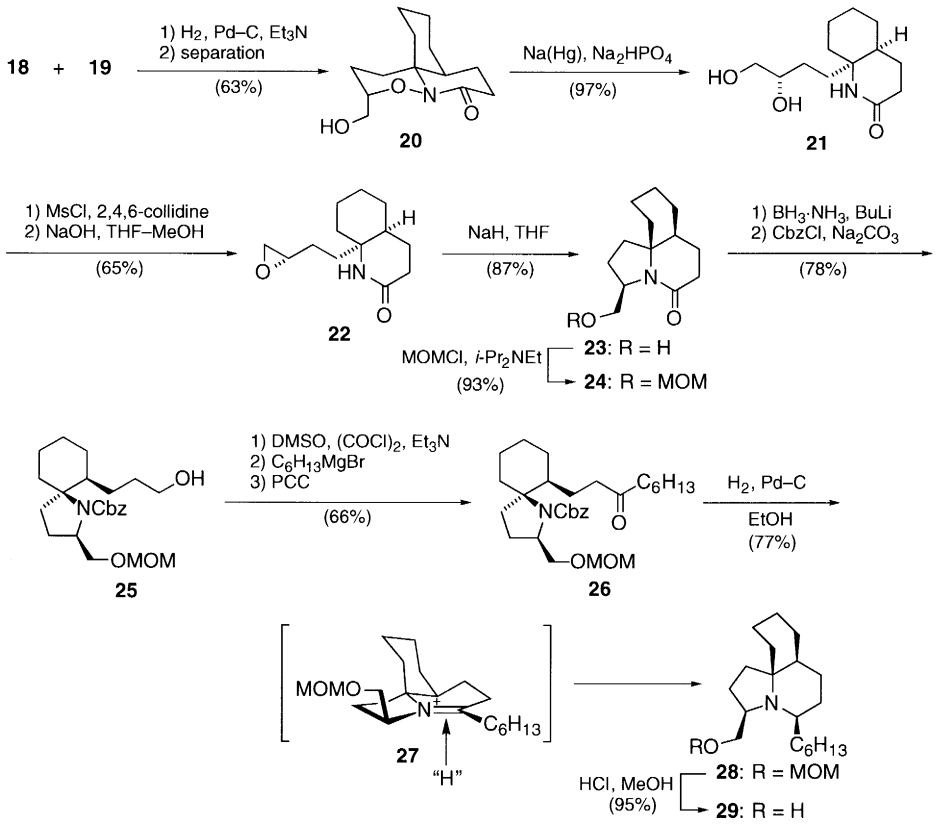


Scheme 1.

following four-step sequence: *O*-benzylation, removal of the MOM protective group, Swern oxidation, and oxidation of the resulting aldehyde with sodium chlorite. Esterification of **13** with diazomethane followed by treatment with hydroxylamine provided the hydroxamic acid **14** (66% yield), which was treated with Pr_4NIO_4 in a $CHCl_3$ solution at room temperature in order to allow the acylnitroso diene **15** 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 **18** and **19** in a 2.6:1 ratio, although the desired *cis*-fused cycloadduct **18** was predominantly formed (Scheme 1). 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 **15** due to the attachment of an electron-withdrawing bromine atom to the diene moiety. The sluggish nature of the cycloaddition reaction in this case would lead to decomposition of the in situ generated **15** with properties associated with the RCO–N=O species, namely, they are extremely labile and short-lived.[5a] To overcome these problems, including the inherent disadvantage of the acylnitroso compounds, we sought to utilize the 9,10-dimethylanthracene adduct **16** which was considered to be a stable acylnitroso equivalent.[5a,6] Thus, upon exposure of **14** to the same oxidation conditions in the presence of 9,10-dimethylanthracene, intermolecular cycloaddition reaction smoothly proceeded to form the adduct **16** in 84% yield. Thermolysis of **16** in refluxing benzene caused a retro Diels–Alder reaction to regenerate the intermediate acylnitroso diene **15**, which immediately underwent intramolecular cycloaddition under the reaction conditions, affording the cycloadducts **18** and **19** in 75% yield and in a 5.5:1 ratio. The preference for the formation of the desired B/C *cis*-fused adduct **18** can be rationalized on the basis of a *syn*-facial transition state **17A** with a preferred adoption of an axial position of the tethering 2-alkyl side chain, which avoids the 1,3-allylic strain with the bromine atom.[7]

After catalytic hydrogenation of the diastereomeric mixture of the cycloadducts **18** and **19** in the presence of Et_3N, the B/C *cis*-fused isomer **20** was chromatographically separated in 63% yield (Scheme 2). Reductive N–O bond cleavage of **20** using sodium amalgam to give the 1,2-diol **21** in excellent yield, which was converted to the epoxide **22** in 65% yield via selective mesylation of the primary hydroxyl group was followed by alkaline treatment. Treatment of **22** with NaH in refluxing THF caused intramolecular epoxide opening, producing the perhydropyrroloquinolone **23** in 87% yield. After protection of the hydroxyl group as a MOM ether, **24** underwent reductive ring-opening of the lactam using LiH_2NBH_3,[8] followed by *N*-protection to provide the azaspiro compound **25** in 78% yield from **24**. Swern oxidation of **25** and subsequent addition of hexylmagnesium bromide followed by PCC oxidation afforded the ketone **26** in 66% overall yield. Cyclization of **26** could be successfully performed under catalytic hydrogenation conditions (H_2, Pd–C, EtOH) to produce **28**[9] as a single isomer in 77% yield. The preferential formation of this diastereomer can be explained by invoking an iminium intermediate **27** in which hydrogenation should occur on the less hindered α face.

Finally, removal of the MOM protecting group from **28** under methanolic HCl conditions provided the aminoalcohol in 95% yield, possessing the stereostructure proposed for lepadiformine, which was found to exist in a non-zwitterionic form as **29**. The spectral properties (^1H and ^{13}C NMR) for both the free base and hydrochloride salt of the synthetic material, however, were not identical with those reported[1] for natural lepadiformine. While our work was in progress, Weinreb et al.[10] reported the synthesis of the putative structure **29** of lepadiformine and found their synthetic material to be different from natural lepadiformine. At the same time, Pearson and Ren[11] described the syntheses of the remaining three of the four diastereoisomers of **29** at C-3 and C-5; however, none of these four compounds was found to be compatible with lepadiformine. These findings as well as our result clearly suggest that the originally proposed structure of natural lepadiformine requires revision.



Scheme 2.

References

1. Biard, J. F.; Guyot, S.; Roussakis, C.; Verbist, J. F.; Vercauteren, J.; Weber, J. F.; Boukef, K. *Tetrahedron Lett.* **1994**, *35*, 2691–2694.
2. (a) Blackman, A. J.; Li, C.; Hockless, D. C. R.; Skelton, B. W.; White, A. H. *Tetrahedron* **1993**, *38*, 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. (a) Pearson, W. H.; Barta, N. S.; Kampf, J. W. *Tetrahedron Lett.* **1997**, *38*, 3369–3372. (b) Snider, B. B.; Liu, T. *J. Org. Chem.* **1997**, *62*, 5630–5633. (c) Molander, G. A.; Rönn, M. *J. Org. Chem.* **1999**, *64*, 5183–5187.
4. 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.
5. For reviews on acylnitroso-Diels–Alder reaction, see: (a) Kirby, G. W. *Chem. Soc. Rev.* **1977**, *6*, 1–24. (b) Boger, D. L.; Weinreb, S. M. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987. (c) Streith, J.; Defoin, A. *Synthesis* **1994**, 1107–1117. (d) 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.
6. (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. *Tetrahedron Lett.* **1978**, 4767–4770.
7. When the cycloaddition was performed using the hydroxamic acid lacking a bromine atom, the preferential formation of the B/C *trans*-fused adduct via an *anti*-facial transition state was observed (unpublished result).
8. Myers, A. G.; Yang, B. H.; Kopecky, D. J. *Tetrahedron Lett.* **1996**, *37*, 3623–3626.
9. The stereostructure of **28** was verified by NOE study.
10. (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.
11. Pearson, W. H.; Ren, Y. *J. Org. Chem.* **1999**, *64*, 688–689.