ORGANIC LETTERS

2003
Vol. 5, No. 18
3249−3252

Efficient Synthesis of the Azaspirocyclic Core Structure of Halichlorine and Pinnaic Acid by Intramolecular Acylnitroso Ene Reaction

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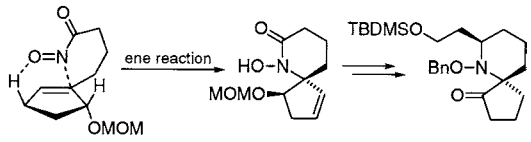
Received June 6, 2003

ABSTRACT



A new efficient strategy for the construction of the 6-azaspiro[4.5]decane ring system was developed using intramolecular ene reaction of the acylnitroso compound. The spirocyclic ene product obtained as a single diastereomer was subsequently subjected to highly stereoselective ethynylation, leading to the azaspirodecane core of halichlorine and the pinnaic acids.

Halichlorine (**1**) is a novel marine alkaloid isolated in 1996 by Uemura and co-workers from the Japanese sponge *Halichondria okadai* Kadota.[1] The structurally related natural products, pinnaic acid (**2**) and tauropinnaic acid (**3**), were isolated by the same research group from the Okinawan bivalve *Pinna muricata*.[2] The absolute configuration of halichlorine (**1**) was determined by chemical correlation of a degradation product.[1b] This group of natural products share in common a 6-azaspiro[4.5]decane ring system. The unique structures and potentially valuable biological activities of these alkaloids have prompted intense synthetic interest culminating in several routes to the core azaspirodecane system.[3] The total syntheses of halichlorine (**1**) and pinnaic acid (**2**) were recently achieved by Danishefsky's group,[4,5] leading to revision of the structure originally proposed for pinnaic acid and establishment of the relative and absolute stereochemistry of these alkaloids **1** and **2**.

In our synthetic approach, we designed a strategy that could be utilized in the synthesis of halichlorine and the pinnaic acids. Disconnection of the C2−C3 and C13−C14 bonds in these molecules and the N−C23 bond in halichlorine produces an adequately functionalized common fragment **4** valuable for these syntheses as shown in Figure 1. We envisioned that synthesis of this azaspirodecane core **4** would be accessible by utilizing methodology based on intramolecular ene reactions[6] of acylnitroso compounds, although

(1) (a) Kuramoto, M.; Tong, C.; Yamada, K.; Chiba, T.; Hayashi, Y.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3867−3870. (b) Arimoto, H.; Hayakawa, I.; Kuramoto, M.; Uemura, D. *Tetrahedron Lett.* **1998**, *39*, 861−862.

(2) Chou, T.; Kuramoto, M.; Otani, Y.; Shikano, M.; Yazawa, K.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3871−3874.

(3) (a) Lee, S.; Zhao, Z. *Org. Lett.* **1999**, *1*, 681−683. (b) Arimoto, H.; Asano, S.; Uemura, D. *Tetrahedron Lett.* **1999**, *40*, 3583−3586. (c) Lee, S.; Zhao, Z. *Tetrahedron Lett.* **1999**, *40*, 7921−7924. (d) Clive, D. L. J.; Yeh, V. S. C. *Tetrahedron Lett.* **1999**, *40*, 8503−8507. (e) Koviach, J. L.; Forsyth, C. J. *Tetrahedron Lett.* **1999**, *40*, 8529−8532. (f) Shindo, M.; Fukuda, Y.; Shishido, K. *Tetrahedron Lett.* **2000**, *41*, 929−932. (g) Wright, D. L.; Schulte, J. P., II; Page, M. A. *Org. Lett.* **2000**, *2*, 1847−1850. (h) White, J. D.; Blakemore, P. R.; Korf, E. A.; Yokochi, A. F. T. *Org. Lett.* **2001**, *3*, 413−415. (i) Fenster, M. D. B.; Patrick, B. O.; Dake, G. R. *Org. Lett.* **2001**, *3*, 2109−2112.

(4) For the synthesis of halichlorine, see: (a) Trauner, D.; Danishefsky, S J. *Tetrahedron Lett.* **1999**, *40*, 6513−6516. (b) Trauner, D.; Schwarz, J. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3542−3545. (c) Trauner, D.; Churchill, D. G.; Danishefsky, S. J. *Helv. Chim. Acta* **2000**, *83*, 2344−2351.

(5) For the synthesis of pinnaic acid, see: (a) Carson, M. W.; Kim, G.; Hentemann, M. F.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4450−4452. (b) Carson, M. W.; Kim, G.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4453−4456.

10.1021/ol030073y CCC: $25.00
Published on Web 08/08/2003

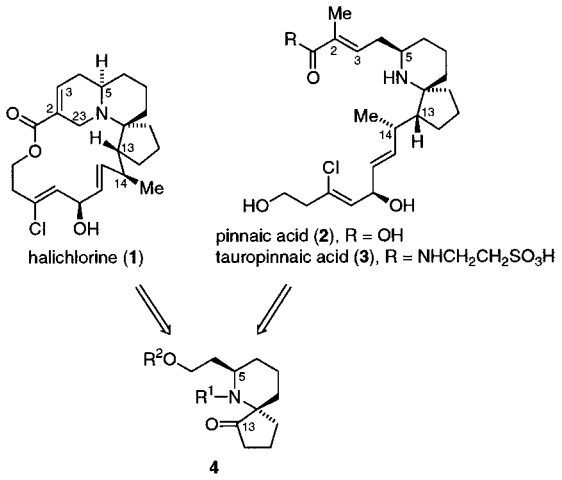
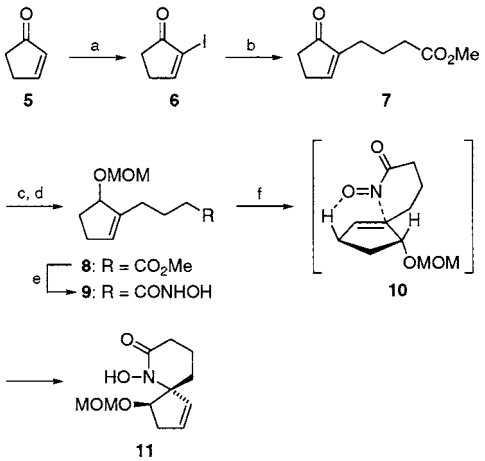


Figure 1.

these interesting reactions have found limited application in natural products synthesis compared with the corresponding Diels−Alder cycloadditions.[7] Herein we would like to present an efficient stereoselective synthesis of the azaspiro[4.5]-decane intermediate **4** via an intramolecular acylnitroso ene reaction as a key transformation.

The assembly of the 6-azaspiro[4.5]decane core began with the preparation of the hydroxamic acid **9**, the precursor of the acylnitroso compound (Scheme 1). The iodoenone **6**,

Scheme 1[a]



[a] Reagents and conditions: (a) I_2, CCl_4-pyridine; (b) 9-[MeO_2C-$(CH_2)_3$]-9-BBN, Cs_2CO_3, $PdCl_2$(dppf), Ph_3As, DMF−THF−H_2O, rt, 70%; (c) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C, 94%; (d) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, rt, 99%; (e) $NH_2OH \cdot HCl$, KOH, MeOH, 0 °C, 82%; (f) Pr_4NIO_4, $CHCl_3$, 0 °C, 82%.

prepared from 2-cyclopentene-1-one (**5**) by a literature procedure,[8] was subjected to the Suzuki−Miyaura coupling[9] with the alkylborane, affording the enone ester **7** in 70% yield. Enone reduction with $NaBH_4/CeCl_3$ followed by MOM protection of the resultant cyclopentenol led to **8**, which was converted into the hydroxamic acid **9** by treatment with hydroxylamine under the alkaline conditions. With the hydroxamic acid **9** in hand, we next explored the viability of an intramolecular ene reaction. Upon oxidation of **9** with tetrapropylammonium periodate in $CHCl_3$ at 0 °C, intramolecular ene reaction of the in situ-generated acylnitroso compound **10** proceeded smoothly to yield the spirocyclic lactam **11** in 82% yield as a single diastereomer. The structure assignment of **11** was confirmed by X-ray crystallographic analysis (Figure 2). Remarkable facial stereo-

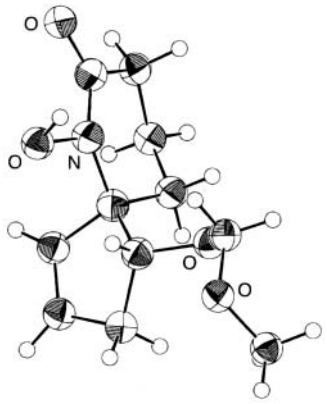


Figure 2. ORTEP drawing of the X-ray crystal structure of **11**.

selectivity in this reaction is consistent with predominant approach of the nitroso moiety in **10** to the less hindered β-face of the cyclopentene ring opposite the MOM-oxy group. It is noteworthy that oxidation of the hydroxamic acid **9** gave rise to a one-pot acylnitroso ene reaction at low temperature to generate the ene product in high yield, although, in general, intramolecular ene reaction of acylnitroso compounds has been conducted under the conditions by thermal dissociation at 80−110 °C of acylnitroso Diels−Alder adducts with 9,10-dimethylanthracene[10] or cyclopentadiene.[11]

(6) For application of acynitroso-ene reactons to natural products synthesis, see: (a) Keck, G. E.; Webb, R. R., II. *J. Am. Chem. Soc.* **1981**, *103*, 3173−3177. (b) Keck, G. E.; Webb, R. R., II. *J. Org. Chem.* **1982**, *47*, 1302−1309. (c) Keck, G. E.; Yates, J. B. *J. Org. Chem.* **1982**, *47*, 3590−3591.

(7) For reviews concerning Diels−Alder reaction of acylnitroso cpompounds, see: (a) Kirby, G. W. *Chem. Soc. Rev.* **1977**, *6*, 1−24. (b) Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087−3128. (c) Boger, D. L.; Weinreb, S. M. *Hetereo Diels−Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987. (d) Streith, J.; Defoin, A. *Synthesis* **1994**, 1107−1117. (e) Kibayashi, C.; Aoyagi, S. *Synlett* **1995**, 873−879. (f) Vogt, P. F.; Miller, M. J. *Tetrahedron* **1998**, *54*, 1317−1348.

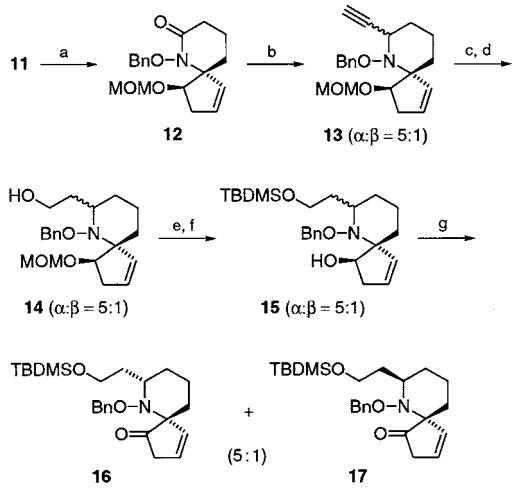
(8) Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W.; Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron Lett.* **1992**, *33*, 917−918.

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

(10) (a) Keck, G. E.; Webb, R. *Tetrahedron Lett.* **1979**, 1185−1186. (b) Keck, G. E.; Webb, R. R.; Yates, J. B. *Tetrahedron* **1981**, *37*, 4007−4016.

(11) (a) Kirby, G. W.; McGuigan, H.; McLean, D. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1961−1966. (b) Christie, C. C.; Kirby, G. W.; McGuigan, H.; Mackinnon, J. W. M. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2469−2473.

Scheme 2[a]



[a] Reagents and conditions: (a) BnBr, NaH, Bu_4NIO_4, DMF, rt 98%; (b) HC≡CLi·$H_2NCH_2CH_2NH_2$, THF, 5 °C, then, $NaBH_3CN$, AcOH, rt, 74%; (c) disiamylborane, Et_2O, rt, then H_2O_2, NaOH, rt, 94%; (d) $NaBH_4$, 2-propanol, 0 °C, 90%; (e) $LiBF_4$, MeCN−H_2O, 72 °C, 72%; (f) TBDMSCl, Et_3N, DMAP, CH_2Cl_2, rt, 99%; (g) Dess−Martin periodinane, CH_2Cl_2, rt, 87%, 5:1 ratio (**16**/**17**).

With a viable approach to the spirocyclic lactam **11** assured, we turned our attention to the stereoselective introduction of the O-protected hydroxyethyl unit into the C5 position of the azaspirocyclic core system. After protection of the *N*-hydroxyl group of **11** with the benzyl group, treatment of **12** with lithium acetylide ethylenediamine complex at 5 °C followed by $NaBH_3CN$ reduction in acidic medium (AcOH) furnished the 5-ethynyl product **13** as a 5:1 epimeric mixture, favoring the α-epimer, although the stereochemical assignment of these isomers was made at a later stage (Scheme 2). Hydroboration of the ethynyl group in **13** was effectively accomplished by treatment with disiamylborane to form the aldehyde, which was reduced with $NaBH_4$ to give the epimeric alcohols **14** in 85% yield from **13**. In the deprotection of the MOM group in **14**, acidic treatment was unsuccessful, possibly due to the formation of an aziridinium ion during the reaction. Cleavage of the MOM ether was thus performed using lithium tetrafluoroborate in MeCN−H_2O, and then the primary hydroxyl group in the resulting diol was selectively protected as the TBDMS ether to give **15**. After Dess−Martin oxidation[12] of **15**, the resulting epimeric ketones **16** and **17** were separated using silica gel chromatography, and NOESY experiments (Figure 3) revealed that the dominant product was the undesired (5*S**)-isomer **16**. The stereoselectivity in the ethynylation of **12** can be rationalized by invoking the intermediary iminium ion **18** (Figure 4), wherein the axial attack of hydride

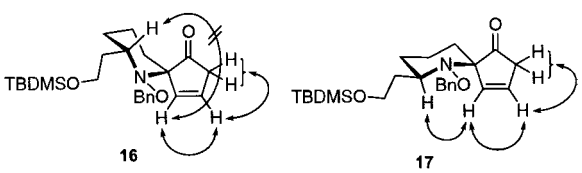


Figure 3. Selected NOESY for **16** and **17**.

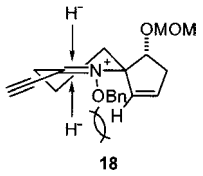
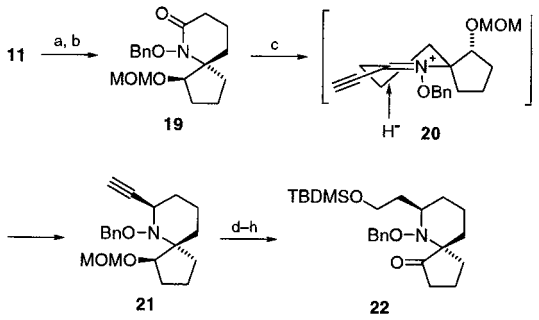


Figure 4.

from the α-face of the iminium ion double bond is hindered by the C10 alkenic hydrogen in the cyclopentene ring, and therefore, the hydride attack may preferentially occur from the *β*-face, thus leading to the (5*S**)-isomer of **13**.

We anticipated that this steric constraint might be overcome by reducing the C10−C11 double bond. Thus, the spirocyclic lactam **11** was subjected to catalytic hydrogenation (5 atm H_2, Pd−C) followed by benzyl protection to give **19** (Scheme 3). For the ethynylation of **19**, the same

Scheme 3[a]



[a] Reagents and conditions: (a) H_2 (5 atm), Pd−C, MeOH, 99%; (b) BnBr, NaH, Bu_4NIO_4, DMF, rt, 98%; (c) HC≡CLi·$H_2NCH_2CH_2NH_2$, THF, 5 °C, then $NaBH_3CN$, AcOH, MeOH, rt, 67%; (d) disiamylborane, Et_2O, rt, then H_2O_2, NaOH, rt, 96%; (e) $NaBH_4$, 2-propanol, 0 °C, 91%; (f) $LiBF_4$, MeCN−H_2O, 72 °C, 83%; (g) TBDMSCl, Et_3N, DMAP, CH_2Cl_2, rt, 97%; (h) Dess−Martin periodinane, CH_2Cl_2, rt, 75%.

conditions using lithium acetylide ethylenediamine complex and $NaBH_3CN$ as before were employed. After workup, the desired (5*R**)-ethynyl azaspirodecane **21** was obtained (67% yield) as a single diastereomer. The result obtained for the formation of **21** confirmed that the stereoelectronically preferred axial addition[13] of hydride took place almost

(12) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287. (c) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

(13) (a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Oxford, 1983; Chapter 6. (b) Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289−296.

exclusively from the desired α-face of the π-plane of the iminium ion **20**. Conversion of **21** into the keto-azaspirocycle **22** was achieved in a five-step sequence involving hydroboration, $NaBH_4$ reduction, deprotection, and Dess−Martin oxidation, in 53% overall yield. Confirmation of the stereochemical assignment of **22** was ascertained by direct comparison with an authentic sample obtained from the above-described compound **17** by catalytic hydrogenation (H_2, Pd−C, THF, 86% yield).

In summary, we have developed a new efficient strategy for the preparation of the 6-azaspiro[4.5]decane core of halichlorine and the pinnaic acids utilizing as a key step an intramolecular ene reaction of the acylnitroso compound in a one-pot procedure. The approach results in excellent control of the relative stereochemistry at the nitrogeneous quaternary stereogenic center in the azaspirocyclic ring system, which allows the enantioselective preparation of the azaspirocyclic intermediate (5*S*,7*R*)-**22** required for the enantioselective synthesis of the natural alkaloids starting from the chiral hydroxamic acid (*R*)-**9**. Extension of this methodology to the total synthesis of halichlorine and pinnaic acid is now underway.

Supporting Information Available: Characterization data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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