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Published on Web 07/17/2003

Construction of Eight-Membered Ether Rings by Olefin Geometry-Dependent Internal Alkylation: First Asymmetric Total Syntheses of (+)-3-(*E*)- and (+)-3-(*Z*)-Pinnatifidenyne

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Abstract: The first and highly stereoselective asymmetric total syntheses of eight-membered ring ether marine natural products (+)-3-(*E*)-pinnatifidenyne and (+)-3-(*Z*)-pinnatifidenyne have been accomplished. Notable features of our syntheses include a novel and efficient construction of oxocene **5** by a highly stereo- and regioselective internal alkylation and direct ketone synthesis of ketone **16** from the α-alkyloxy amide moiety in oxocene **5**.

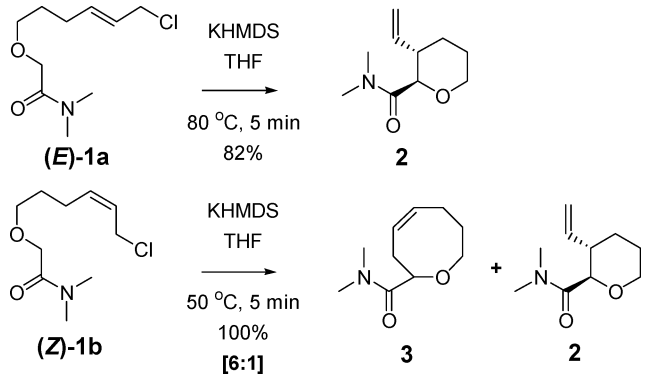
Introduction

Medium-ring ethers constitute important structural features present in a number of biologically active marine natural products.[1] Because of the well-known difficulty of their construction by standard cyclization methods due to unfavorable entropic and enthalpic factors,[2] the development of efficient approaches to these medium-sized rings,[3a−c] particularly eight-membered ones,[3d−f] has been an important challenge to synthetic organic chemists. Although many unique and interesting methods have been designed for this purpose, there still remains a need for efficient and general approaches to the construction of medium-ring ethers.

During our studies directed toward the total syntheses of natural products based upon intramolecular S_N2' alkylations,[4] we accidentally discovered "olefin geometry-dependent" internal alkylation (vide infra), which led us to develop an efficient and unprecedented method for eight-membered ring formation as shown in Scheme 1.

Thus, intramolecular amide enolate alkylation of a readily available *trans*-allylic chloride **1a**[5] with KHMDS in THF at 80 °C, as anticipated, provided exclusively *trans*-disubstituted S_N2' product **2** in 82% yield. On the other hand, the treatment of the corresponding *cis*-allylic chloride **1b**[5] with KHMDS in THF at 50 °C afforded a 6:1 mixture of eight-membered ring ether **3** and tetrahydropyran **2** in quantitative yield. Although more studies are needed to explain a striking difference in regiochemical behavior (S_N2 vs S_N2') observed during the above "olefin geometry-dependent" intramolecular alkylations, it is probable that the geometrically restricted cis configuration of the olefin might decrease the entropic and enthalpic barriers associated with formation of the eight-membered ring.

Scheme 1. Olefin Geometry-Dependent Internal Alkylation



Results and Discussion

To illustrate the potential of the present methodology, we set out to synthesize (+)-3-(*E*)-pinnatifidenyne (**4a**) and (+)-3-(*Z*)-pinnatifidenyne (**4b**),[6] which were isolated from the red

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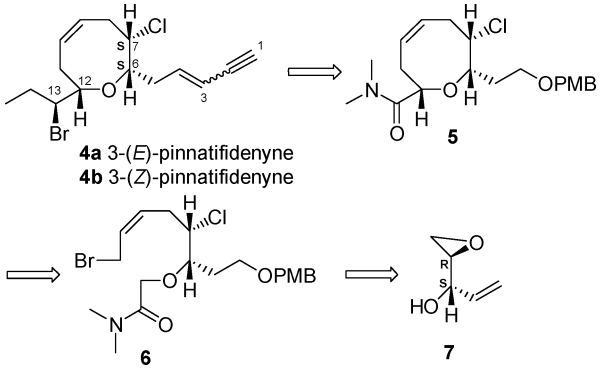
(5) Prepared in three steps from the known *cis*- and *trans*-6-(tetrahydropyran-2-yloxy)hex-4-en-1-ol as follows: (1) 2-bromo-*N*,*N*-dimethylacetamide, NaH, THF; (2) PTSA, EtOH; (3) CCl_4, Ph_3P.

10.1021/ja035538u CCC: $25.00

Scheme 2. Retrosynthetic Analysis of Pinnatifidenynes



seaweed *Laurencia pinnatifida* in 1982. The structures of these eight-membered ring ether marine natural products were assigned on the basis of spectral, chemical, and X-ray diffraction analyses. In our retrosynthetic analysis for 3-(*E*)- and 3-(*Z*)-pinnatifidenyne, as summarized in Scheme 2, we envisioned that key oxocene **5** could be stereoselectively synthesized from cyclization substrate **6** by our intramolecular amide enolate alkylation strategy. Further analysis indicated known (2*R*,3*S*)-1,2-epoxy-4-penten-3-ol **7**[7a] should be an ideal synthetic precursor for asymmetric synthesis of acyclic substrate **6**.

Our total syntheses of the pinnatifidenynes are depicted in Scheme 3. Protection of the secondary hydroxy group of epoxy alcohol **7**[7b] (>98% ee)[8] as a 2-(trimethylsilyl)ethoxymethyl (SEM)[9a] ether **8**, followed by regioselective opening with propargyl tetrahydropyranyl ether under Yamaguchi conditions,[10] afforded homopropargylic alcohol **9** in 81% overall yield. After protection of the hydroxy group of alcohol **9** with 3,4-dimethoxybenzyl bromide (DMB−Br), the resulting acetylene **10** was semihydrogenated using Lindlar catalyst to produce *cis*-olefin **11** in 92% yield from alcohol **9**. Regioselective hydroboration of the terminal olefin moiety of bis-alkene **11** with 9-BBN (83%) and subsequent PMB protection[11a] of the resulting primary alcohol **12** afforded suitably protected ether **13** in 94% yield. Removal of the SEM protecting group of **13** with TBAF,[9b] followed by O-alkylation with 2-bromo-*N*,*N*-dimethylacetamide of the resulting alcohol, led to amide **14** in 75% overall yield.

Crucial chlorination[12] of the C(7) hydroxy group with inversion of configuration was successfully accomplished by selective removal of the DMB protecting group of **14** with DDQ[11b,c] and subsequent treatment of the resulting alcohol with CCl_4 and trioctylphosphine in the presence of pyridine (74%). Thus obtained chloride **15** was converted to the internal alkylation substrate **6** by removal of the THP protecting group under acidic conditions followed by bromination of the resulting allylic alcohol with CBr_4 and PPh_3 in 88% overall yield for the two steps.

With the requisite cyclization substrate **6** in hand, we then addressed the key intramolecular amide enolate alkylation to construct the oxocene skeleton. To our satisfaction, bromoamide **6** underwent a smooth cyclization to furnish the desired oxocene **5** in 86% yield without a detectable amount of the corresponding S_N2' product upon treatment with 1.1 equiv of LiHMDS in THF at room temperature. The relative stereochemistry of the newly generated C(12) stereocenter of the oxocene **5** was assigned as cis to C(6) by NOESY studies. This stereochemical outcome can be rationalized by invoking a transition state geometry as shown in **A**.

For reasons of brevity and efficiency, direct conversion[13] of the α-alkyloxy amide moiety in oxocene **5** to the ketone group of **16** would be more desirable than the more cumbersome conventional sequence involving nonstereoselective addition[14] of EtMgBr to the corresponding aldehyde and reoxidation. To our delight, this direct ketone synthesis could be cleanly performed by treatment of α-alkyloxy amide **5** with EtMgBr in THF at 0 °C for 1 h to furnish ketone **16** in 92% yield. Ketone **16** was reduced diastereoselectively with L-Selectride in a Felkin−Ahn sense[14] to provide exclusively alcohol **17** in quantitative yield. Mitsunobu inversion of the secondary alcohol **17** with *p*-nitrobenzoic acid in the presence of DIAD/PPh_3, followed by reductive removal of the *p*-nitrobenzoate group with LAH, afforded epimeric alcohol **18** in 79% overall yield. Introduction of the bromine functionality at C(13) with inversion of configuration was carried out by a slight modification of the conventional method (CBr_4, Oct_3P, 1-methylcyclohexene)[15] to provide the desired bromide **19** (83%) along with its $\Delta^{13,14}$ elimination product (~3%).[16]

After completion of the C(12) side chain, we turned our attention to assembly of the unsaturated C(6) appendage. Removal of the PMB group of bromide **19** with DDQ afforded alcohol **20** in 97% yield. Dess−Martin periodinane oxidation[17]

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(16) Alcohol **18** was stereoselectively transformed in a sequence identical to that of 3-(*E*)-13-epipinnatifidenyne[16a] and 3-(*Z*)-13-epipinnatifidenyne,[16b] recently isolated marine natural products. However, the spectral data of our synthetic material are distinctively different from those of the natural products. Professsor V. Roussis (University of Athens, Greece) is currently reinvestigating their structural assignment. See the Supporting Information. (a) Iliopoulou, D.; Vagias, C.; Harvala, C.; Roussis, V. *Phytochemistry* **2002**, *59*, 111−116. (b) San-Martin, A.; Darias, J.; Soto, H.; Contreras, J. S.; Rovirosa, J. *Nat. Prod. Lett*. **1997**, *10*, 303−311.
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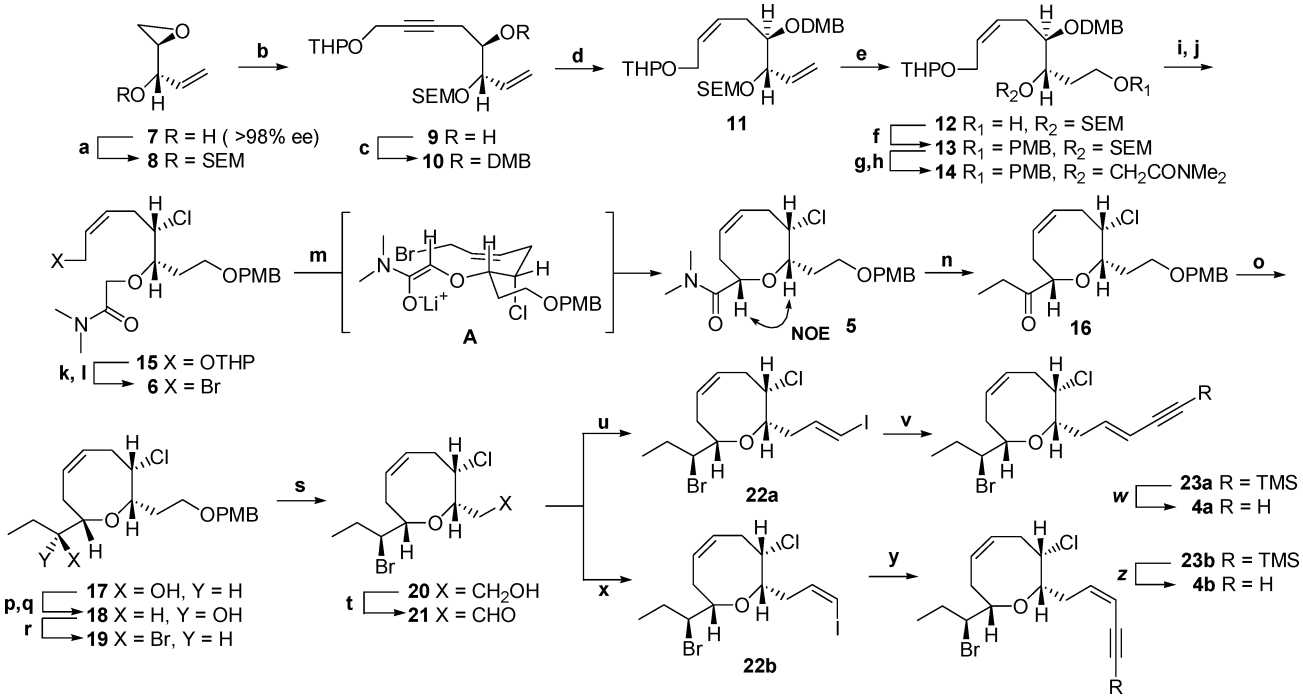
Scheme 3. Total Syntheses of Pinnatifidenynes[a]



[a] Reagents and conditions: (a) SEMCl, NaH, THF, 0 °C to room temperature, 3 h, 90%; (b) $HCCCH_2OTHP$, *n*-BuLi, $BF_3{\cdot}Et_2O$, THF, −78 °C, 1 h, 90%; (c) DMBBr, NaH, THF/DMF, 0 °C to room temperature, 2 h, 92%; (d) H_2, Lindlar cat., pyridine, EtOAc, room temperature, 3 h, 100%; (e) 9-BBN, THF, 0 °C to room temperature, 3 h, then NaOH, H_2O_2, −20 °C to room temperature, 10 h, 83%; (f) PMBBr, NaH, THF/DMF, 0 °C to room temperature, 13 h, 94%; (g) TBAF, DMPU, 4 Å MS, 80 °C, 5 h, 76%; (h) 2-bromo-*N*,*N*-dimethylacetamide, NaH, THF, room temperature, 8 h, 99%; (i) DDQ, CH_2Cl_2, pH 7.4 buffer, 0 °C, 1 h, 85%; (j) CCl_4, Oct_3P, pyridine, 80 °C, 4 h, 87%; (k) PTSA, EtOH, room temperature, 1 h, 99%; (l) CBr_4, Ph_3P, pyridine, CH_2Cl_2, −20 °C, 30 min, 89%; (m) LiHMDS, THF, room temperature, 40 min, 86%; (n) EtMgBr, THF, 0 °C, 1 h, 92%; (o) L-Selectride, THF, −78 °C, 1 h, 100%; (p) DIAD, Ph_3P, *p*-NO_2PhCO_2H, THF, 0 °C, 3 h, 82%; (q) $LiAlH_4$, THF, 0 °C, 1 h, 96%; (r) CBr_4, Oct_3P, 1-methylcyclohexene, toluene, room temperature to 80 °C, 4 h, 86%; (s) DDQ, CH_2Cl_2, pH 7.4 buffer, 0 °C to room temperature, 1 h, 97%; (t) Dess−Martin periodinane, CH_2Cl_2, room temperature, 1 h; (u) CHI_3, $CrCl_2$, THF, 0 °C to room temperature, 4 h, 68% (for two steps); (v) TMS−acetylene, $(Ph_3P)_4Pd$, CuI, Et_2NH, room temperature, 1 h, >73%; (w) TBAF, THF, 0 °C, 1 h, 97%; (x) $[Ph_3P^+CHI]I^-$, KHMDS, THF, −30 to −78 °C, 1 h, 92% (for two steps); (y) TMS−acetylene, $(Ph_3P)_4Pd$, CuI, Et_2NH, room temperature, 4 h, 73%; (z) TBAF, THF, 0 °C, 1 h, 96%.

of the primary alcohol **20** and subsequent Takai olefination[18] of the resulting unstable aldehyde **21** with $CHI_3/CrCl_2$ produced (*E*)-vinyl iodide **22a** as the major isomer (*E*:*Z* = 8:1) in 68% total yield for the two steps. On the other hand, isomeric (*Z*)-vinyl iodide **22b** was selectively synthesized from the same aldehyde **21** using Stork's iodophosphorane ($[Ph_3PCH_2I]^+I^-$, KHMDS)[19] as a single stereoisomer in 92% yield from alcohol **20**.

Sonogashira[20] coupling reaction of each (*E*)- and (*Z*)-vinyl iodide (**22a** and **22b**) with (trimethylsilyl)acetylene in the presence of $(PPh_3)_4Pd$/CuI provided (*E*)-enyne **23a** (73%) and (*Z*)-enyne **23b** (73%), respectively. Finally, simple removal of the trimethylsilyl protecting groups of (*E*)-enyne **23a** and (*Z*)-enyne **23b** with TBAF afforded (+)-**4a** and (+)-**4b** in 97% and 96% yield, respectively, whose ^1H and ^{13}C NMR spectral data were in good agreement with those reported for the natural products.[21]

Conclusion

We have accomplished the first total syntheses of the eight-membered ring ether marine natural products (+)-3-(*E*)- and (+)-3-(*Z*)-pinnatifidenyne utilizing a novel and efficient "olefin geometry-dependent" internal alkylation with excellent stereoselectivity. The scope of the present methodology and its application to the synthesis of other natural products are under investigation in our laboratories.

Acknowledgment. This research was supported by the Ministry of Health and Welfare (01-PJ2-PG6-01NA01-0002), and 2002 BK21 Project for Medicine, Dentistry, and Pharmacy.

Supporting Information Available: General experimental procedures including spectroscopic and analytical data for all new compounds along with copies of the ^1H and ^{13}C NMR spectra for **4a**, **4b**, **5**, **6**, **8**−**20**, and **22a**−**23b** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA035538U

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(21) For copies of ^1H and ^{13}C NMR spectra, see the Supporting Information.