ORGANIC LETTERS

2003
Vol. 5, No. 16
2967−2970

First Asymmetric Total Synthesis of Us-7 and -8, Novel *D-seco* Corynanthe-Type Oxindole Alkaloids from *Uncaria attenuata*: Structure Revision of Us-7 and Determination of Absolute Stereochemistry

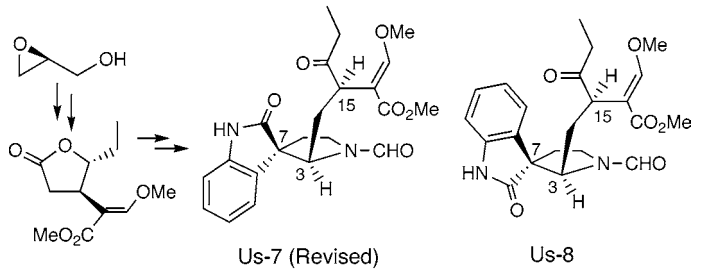
Hiromitsu Takayama,* Rika Fujiwara, Yasuko Kasai, Mariko Kitajima, and Norio Aimi

Graduate School of Pharmaceutical Sciences, Chiba University, 1-33 Yayoi-cho, Inage-ku, Chiba 263-8522, Japan

htakayam@p.chiba-u.ac.jp

Received June 19, 2003

ABSTRACT



Starting from (*S*)-glycidol, the asymmetric total synthesis of novel *D-seco* Corynanthe-type oxindoles Us-7 and Us-8 was accomplished. The structure of Us-7 was revised from the reported structure 1 with the (3*R*,7*S*) form to structure 22 with (3*S*,7*R*), and the absolute stereochemistry at C15 of both alkaloids was established.

In 1997, we communicated the isolation and structure elucidation of a new type of oxindole alkaloids, Us-7 (**1**) and Us-8 (**2**),[1] from a Rubiaceous plant, *Uncaria attenuata* Korth.[2] Their novel structures, which are the first examples of *D-seco* Corynanthe-type indole alkaloids, were elucidated by spectroscopic analyses and biogenetic consideration. In particular, the stereochemistry of the three chiral centers at C3, C7, and C15 was proposed by the following analyses. The absolute configuration at the C7 spiro center was inferred from the established circular dichroism (CD) criteria for natural oxindole alkaloids.[3] Thus, the CD spectra of the two compounds exhibited a negative Cotton effect at the longest wavelength absorption band, as shown in Figure 1. Comparison of those spectra with those of known alkaloids, rhynchophylline (**3**) with C7(*R*)[4] and isorhynchophylline (**4**) with C7(*S*), indicated that the spiro center of Us-7 and -8 had the *S* configuration. The C3 stereochemistry was elucidated by NOE experiments; NOE cross-peaks between H3 and H9 in Us-7 and between H9 and H14 in Us-8 revealed that the stereochemistry at C3 is *R* for Us-7 and *S*

(1) Aimi, N.; Shimizu, T.; Sada, H.; Takayama, H.; Sakai, S.; Wongseripipatana, S.; Ponglux, D. *J. Chem. Soc., Perkin Trans. 1* **1997**, 187.

(2) (a) Ponglux, D.; Supavita, T.; Verpoorte, R.; Phillipson, J. D. *Phytochemistry* **1980**, *19*, 2013. (b) Ponglux, D.; Wongseripipatana, S.; Aimi, N.; Nishimura, M.: Ishikawa, M.; Sada, H.; Haginiwa, J.; Sakai, S. *Chem. Pharm. Bull.* **1990**, *38*, 573. (c) Takayama, H.; Shimizu, T.; Sada, H.; Harada, Y.; Kitajima, M.; Aimi, N. *Tetrahedron* **1999**, *55*, 6841.

(3) (a) Pousset, J.-L.; Poisson, J.; Shine, R. J.; Shamma, M. *Bull. Soc. Chim. Fr.* **1967**, 2766. (b) Trager, W. F.; Lee, C. M.; Phillipson, J. D.; Haddock, R. E.; Dwumabadu, D.; Beckett, A. H. *Tetrahedron* **1968**, *24*, 523.

(4) Laus, G.; Wurst, K. *Helv. Chim. Acta* **2003**, *86*, 181 and references therein.

10.1021/ol035128a CCC: $25.00
Published on Web 07/17/2003

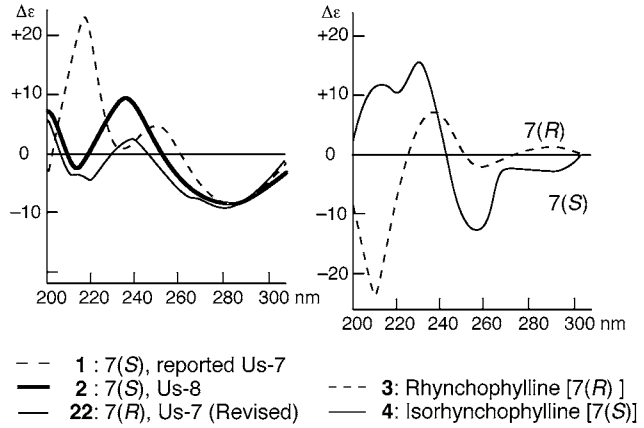
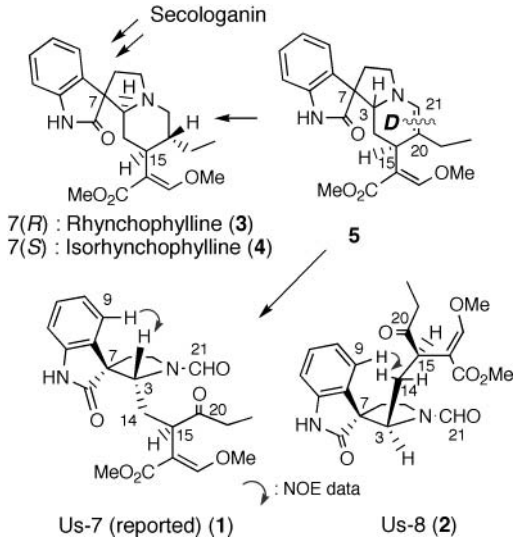


Figure 1. CD spectra of oxindole alkaloids.

for Us-8. The stereochemistry at the third position, C15, was deduced to be *R* by biogenetic consideration (Scheme 1).

Scheme 1. Possible Biogenetic Route of Us-7 and -8

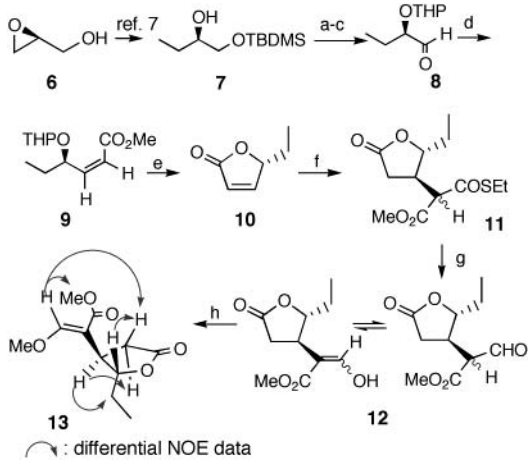


Thus, it was speculated that these alkaloids were formed by an oxidative cleavage at the enamine double bond (C20−C21) of the D-ring in the possible biogenetic intermediate **5**, in which the stereochemistry at C15 was inherited from the chiral center at C5 in secologanin, a biogenetic precursor of monoterpenoid indole alkaloids.[5] To clarify the structures including the absolute configurations of these molecules, we planned the asymmetric total synthesis of Us-7 and -8, in which (*S*)-glycidol (**6**) was used as the starting material and the formation of the carbonyl function at C20 was accomplished at the final stage of the total synthesis to prevent the epimerization at C15. In this paper, we report for the first time the successful asymmetric total synthesis of Us-7 and -8, including the structure revision of Us-7 and the determination of the absolute stereochemistries of these novel oxindole alkaloids.

Initially, a known chiral γ-butenolide (**10**)[6] was prepared from commercially available (*S*)-glycidol in good yield by a newly developed practical method. The literature-known alcohol **7**[7] prepared from **6** was transformed via a three-step operation into aldehyde **8**, which was then subjected to the modified Horner−Emmons olefination[8] to give *Z*-α,β-unsaturated ester **9** in quantitative yield. Lactonization of **9** by treatment with *p*-TsOH in MeOH gave the desired (−)-γ-butenolide (**10**) in 79% yield, the enantiomeric excess of which was determined to be 95% by chiral HPLC analysis. Next, to construct the monoterpenoid unit **13** possessing a β-methoxyacrylate residue, a malonate equivalent, methyl 3-ethylthio-3-oxopropanoate, was connected to α,β-unsaturated lactone **10** in 98% yield.

The stereochemistry of the newly constructed chiral center in **11** was determined afterward by NOE experiments of **13**. The thiol ester group in **11** was reduced to aldehyde using Fukuyama's procedure (Et_3SiH, 10% Pd−C)[9] in quantitative yield. The ^1H NMR spectrum of **12** revealed the presence of a tautomeric mixture of keto/enol forms, which were converged to a single product having the desired methyl β-methoxyacrylate residue by treatment with diazomethane. The stereochemistries of the *trans* relationship between the ethyl and β-methoxyacrylate groups on the γ-lactone ring as well as the *E*-configuration of the β-methoxyacrylate moiety in **13** were elucidated by NOE observations, as shown in Scheme 2.

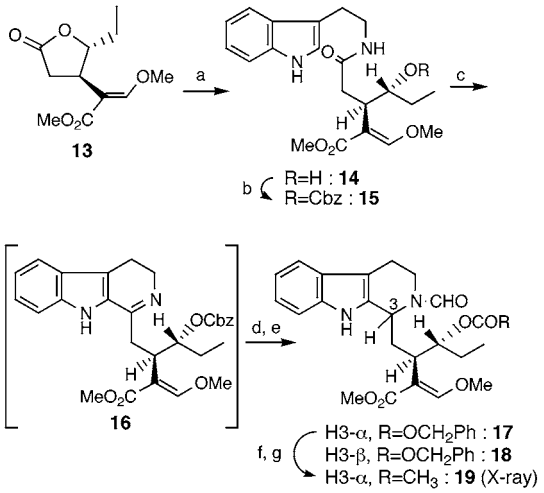
Scheme 2[a]



[a] Reagents and conditions: (a) DHP, cat. *p*-TsOH·H_2O, CH_2Cl_2, rt, 88%. (b) TBAF, THF, rt, quant. (c) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, −78 → 0 °C, 76%. (d) $(CF_3CH_2O)_2POCH_2CO_2Me$, $KN(TMS)_2$, 18-crown-6, THF, −78 °C, quant. (e) *p*-TsOH·H_2O, MeOH, rt, 79% (95% ee). (f) $EtSCOCH_2CO_2Me$, *t*-BuOK, dry *t*-BuOH, rt, 98%. (g) Et_3SiH, cat 10% Pd−C, acetone, quant. (h) CH_2N_2, EtOH, 0 °C, quant.

(5) For reviews, see: (a) Herbert, R. B. In *The Monoterpenoid Indole Alkaloids*; supplement to Vol. 25, Part 4 of The Chemistry of Heterocyclic Compounds; Saxton, J. E., Ed.; Wiley: Chichester, 1994; Chapter 1. (b) Kutchan, T. M. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol. 50, Chapter 7. (c) Takayama, H.; Sakai, S. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol. 50, Chapter 11.

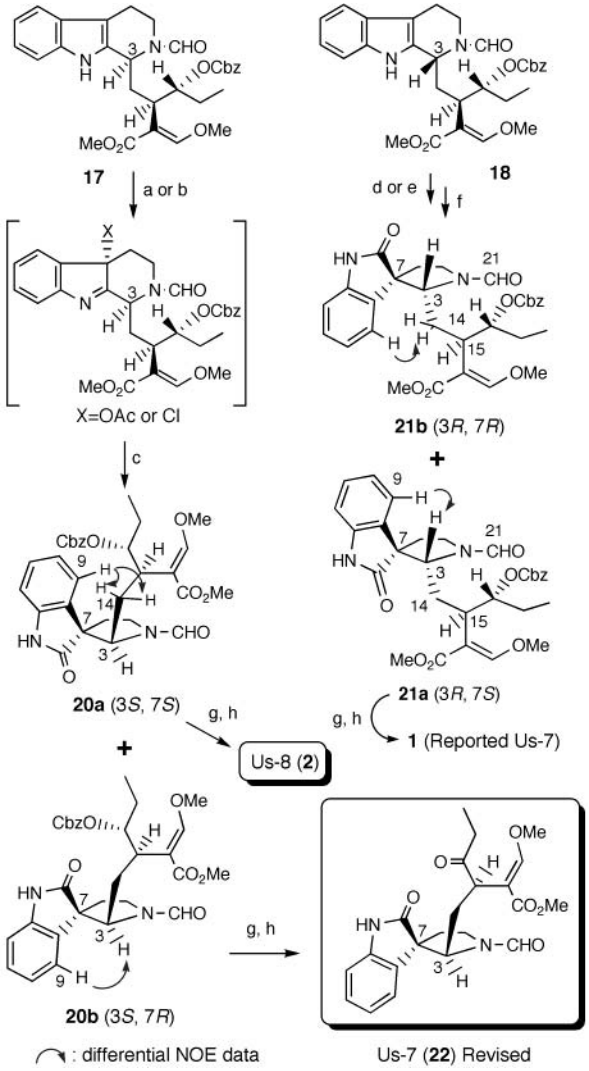
Scheme 3[a]



[a] Reagents and conditions: (a) tryptamine, $AlMe_3$ in hexane, CH_2Cl_2, rt, 85%. (b) $(PhCH_2OCO)_2O$, $CeCl_3$, THF, 60 °C, 85%. (c) $POCl_3$, benzene, reflux. (d) $NaBH_4$, MeOH, 0 °C. (e) C_6F_5OCHO, CH_2Cl_2, rt; **17**, 21% from **15**; **18**, 43% from **15**. (f) H_2, 10% Pd−C, EtOH, rt. (g) Ac_2O, DMAP, CH_2Cl_2, rt, 95% from **17**.

Trimethylaluminum-mediated regioselective aminolysis[10] of lactone **13** with tryptamine gave amide **14** in 85% yield (Scheme 3). The secondary hydroxyl group generated by the ring opening of the lactone was protected as the benzyl carbonate in 85% yield by treatment with dibenzyl dicarbonate in the presence of $CeCl_3$[11] in order to prevent the ring closure of the free hydroxyl group with the β-methoxyacrylate function. The thus obtained amide **15** was subjected to the Bischler−Napieralski reaction, and the resultant labile imine **16** was reduced with $NaBH_4$ in MeOH to produce two diastereomers at the C3 position in a ratio of ca. 1:2. After separation of the diastereomers by SiO_2 column chromatography, the secondary amine groups in the tetrahydro-β-carbolines were transformed into N_b-formyl derivatives by using pentafluorophenyl formate[12] to give amides **17** and **18** in 21% and 43% overall yields, respectively, from **15**. The stereochemistry at the C3 position in **17** was determined by X-ray crystallographic analysis to be *S* by using its *O*-acetyl derivative **19** (mp 231−233 °C), which was prepared from **17** by a conventional procedure. This X-ray analysis also confirmed the stereochemistries [15(*R*), 20(*R*), and *E*-configuration of the β-methoxyacrylate], which were inferred from NOE experiments of **13** as described above.

Scheme 4[a]



[a] Reagents and conditions: (a then c) $Pb(OAc)_4$, CH_2Cl_2, rt, then 1 drop AcOH, aq MeOH, reflux, **20a**, 49%. (b then c) *t*-BuOCl, Et_3N, CH_2Cl_2, −30 °C, then 1 drop AcOH, aq MeOH, reflux; **20a**, 68%; **20b**, 20%. (d then f) $Pb(OAc)_4$, CH_2Cl_2, rt, then 1 drop AcOH, aq MeOH, reflux; **21a**, 5%; **21b**, 69%. (e then f) *t*-BuOCl, Et_3N, CH_2Cl_2, −30 °C, then 1 drop AcOH, aq MeOH, reflux; **21a**, 41%; **21b**, 47%. (g then h) H_2, 10% Pd−C, EtOH, rt, then Dess−Martin periodinane, rt; **2**, 82% from **20a**; **1**, 56% from **21a**; **22**, 84% from **20b**.

The next requirement for the total synthesis is the transformation of the tetrahydro-β-carbolines into the oxindole derivatives (Scheme 4). To date, several procedures for the oxidative rearrangement employing $Pb(OAc)_4$,[13] *t*-BuOCl,[14] NBS,[15] or OsO_4[16] have been reported. After several attempts, it was found that oxidation of the indole nucleus with $Pb(OAc)_4$ and successive treatment of the resultant 7-acetoxyindolenine derivative with aqueous acid (one drop of acetic acid in aqueous methanol, reflux for 15 min) were

(6) (a) Vigneron, J. P.; Blanchard, J. M. *Tetrahedron Lett*. **1980**, *21*, 1739. (b) Tsuboi, S.; Sakamoto, J.; Yamashita, H.; Sakai, T.; Utaka, M. *J. Org. Chem*. **1998**, *63*, 1102. (c) Bertus, P.; Phansavath, P.; Ratovelomanana-Vidal, V.; Genet, J.-P.; Touati, A. R.; Homri, T.; Ben Hassine, B. *Tetrahedron: Asymmetry* **1999**, *10*, 1369. (d) Tiecco, M.; Testaferri, L.; Marini, F.; Sternativo, S.; Bagnoli, L.; Santi, C.; Temperini, A. *Tetrahedron: Asymmetry* **2001**, *12*, 1493.
(7) Cywin, C. L.; Webster, F. X.; Kallmerten, J. *J. Org. Chem*. **1991**, *56*, 2953.
(8) Still, W. C.; Gennari, C. *Tetrahedron Lett*. **1983**, *24*, 4405.
(9) Fukuyama, T.; Lin, S.-C.; Li, L. *J. Am. Chem. Soc*. **1990**, *112*, 7050.
(10) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett*. **1977**, 4171.
(11) Holton, R. A.; Zhang, Z.; Clarke, P. A.; Nadizadeh, H.; Procter, D. J. *Tetrahedron Lett*. **1998**, *39*, 2883.
(12) Kisfaludy, L.; Otvos, L. Jr. *Synthesis* **1987**, 510.
(13) (a) Finch, N.; Gemenden, C. W.; Hsu, I. H.-C.; Taylor, W. I. *J. Am. Chem. Soc*. **1963**, *85*, 1520. (b) Finch, N.; Gemenden, C. W.; Hsu, I. H.-C.; Kerr, A.; Sim, G. A.; Taylor, W. I. *J. Am. Chem. Soc*. **1965**, *87*, 2229.

efficient for the present system. Actually, starting from 3H-α derivative **17**, spiro-oxindole **20a** was obtained in 49% yield as a sole separable product. By contrast, from 3H-*β* derivative **18**, the two diastereomeric oxindoles **21b** and **21a** were produced in 69% and 5% yields, respectively. The stereochemistry at the C7 position in compounds **20a**, **21a**, and **21b** was unambiguously elucidated by extensive NMR analyses. By irradiating H9 on the benzene ring, a clear NOE was observed between the protons on C14 in **20a** and **21b**, demonstrating that **20a** and **21b** have 7(*S*) and 7(*R*) configurations, respectively. On the other hand, a clear NOE between H9 and H3 was observed in the differential NOE experiment of **21a**, revealing its 7(*S*) configuration. The predominant formation of diastereomeric oxindole derivatives through the lead tetraacetate oxidation/solvolytic rearrangement may be interpreted from the plausible mechanism discussed in previous papers.[13a,15b,c,16e] In contrast, the facile interconversion of rhynchophylline (**3**) and isorhynchophylline (**4**) under acidic conditions is well-known.[3b,14g,17] On the basis of the mechanism in the literature, the concomitant epimerization at C3 during the solvolytic rearrangement above may be considered. To examine this possibility, the oxindoles **20a**, **21a**, and **21b** obtained by the above reactions were treated under the conditions used for rearrangement (one drop of acetic acid, aqueous methanol, reflux for 30 min). As a result, the oxindoles were recovered in their completely intact forms, demonstrating that in the case of the N_b-formyl derivatives, no isomerization at C3 or C7 occurs and the stereochemistry at C3 of the products is the same as that of the starting materials.

The final stage of the total synthesis is the conversion of the functional group on the side chain in the oxindole derivatives. First, oxindole **20a** having the 3(*S*),7(*S*) configuration was used to complete the synthesis of Us-8. The protecting group of the secondary hydroxyl group was removed by hydrogenolysis, and the resulting alcohol was oxidized with Dess−Martin periodinane[18] to give ketone derivative **2** in 82% overall yield from **20a**. Synthetic **2** was completely identical in all respects (chromatographic behavior, mass, IR, UV, CD, ^{1}H and ^{13}C NMR, $[\alpha]_D$) with natural Us-8. Therefore, the structure including the absolute configuration of the chiral centers in **2** was established.

Next, for the completion of the total synthesis of Us-7, 3(*R*),7(*S*) isomer **21a** was employed for the transformation as above. However, surprisingly, product **1** was not identical with natural Us-7 by comparison of their ^{1}H and ^{13}C NMR spectra, although all spectral data including NOE data indicated that the product possessed the molecular structure of the reported Us-7 (**1**). As described in the introductory section, the stereochemistry at the spiro position (C7) was deduced by employing the empirical rule of the CD spectra for common Corynanthe-type oxindole alkaloids. At this stage, if we were to eliminate the information of the CD spectral data, an alternative structure **22** could be considered as a candidate structure for Us-7, which accounted for the observed NOE correlation between H3 and H9 in the natural product. Then, we shifted our synthetic target to oxindole **22** having the 3(*S*),7(*R*) configuration. To improve the diastereoselectivity of the reduction of imine **16** with $NaBH_4$, the use of several reaction conditions and reagents was attempted. When sodium tris[(*S*)-*N*-benzyloxycarbonylprolyoxy]hydroborate[19] was used for reducing imine **16**, the diastereomeric ratio of the amines was changed to ca. 1:1. As described above, the oxidative transformation of 3(*S*) isomer **17** using $Pb(OAc)_4$ gave oxindole **20a** with the 7(*S*) configuration as the sole product. However, by employing *t*-BuOCl instead of $Pb(OAc)_4$, 7(*R*) isomer **20b** was obtained in 20% overall yield, together with **20a** in 68% yield. The structure including the stereochemistry at C7 in **20b** was elucidated by extensive 2D-NMR analysis and differential NOE experiments (from H9 to H3) as above. The functional group on the side chain in **20b** was then converted into the ketone to furnish target molecule **22** in 84% overall yield. Synthetic **22** was completely identical in all respects (chromatographic behavior, mass, IR, UV, CD, ^{1}H and ^{13}C NMR, $[\alpha]_D$) with natural Us-7. Therefore, the structure of Us-7 was revised as formula **22**, and the absolute configuration of the chiral centers in Us-7 was established.

The present study revealed that the empirical rule of the Cotton effect used for the structure determination of common Corynanthe-type oxindole alkaloids is not applicable to the elucidation of the absolute stereochemistry at the C7 spiro center of *D-seco*-type compounds.

Acknowledgment. The authors thank Professor Dr. Kentaro Yamaguchi, Analysis Center of Chiba University, for X-ray crystallographic analysis.

Supporting Information Available: Experimental procedures and copies of ^{1}H and ^{13}C NMR spectral data for compounds **13**, **14**, **17**, **18**, synthetic and natural Us-8 (**2**), **1**, and synthetic and natural Us-7 (**22**), as well as X-ray data (ORTEP) for compound **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035128A

(14) (a) Finch, N.; Taylor, W. I. *J. Am. Chem. Soc*. **1962**, *84*, 3871. (b) Shavel, J., Jr.; Zinnes, H. *J. Am. Chem. Soc*. **1962**, *84*, 1320. (c) Hollinshead, S. P.; Grubisha, D. S.; Bennett, D. W.; Cook, J. M. *Heterocycles* **1989**, *29*, 529. (d) Martin, S. F.; Mortimore, M. *Tetrahedron Lett.* **1990**, *31*, 4557. (e) Stahl, R.; Borschberg, H.-J.; Acklin, P. *Helv. Chim. Acta* **1996**, *79*, 1361. (f) Martin, S. F.; Clark, C. W.; Ito, M.; Mortimore, M. *J. Am. Chem. Soc*. **1996**, *118*, 9840. (g) Ito, M.; Clark, C. W.; Mortimore, M.; Goh, J. B.; Martin, S. F. *J. Am. Chem. Soc*. **2001**, *123*, 8003.

(15) (a) Van Tamelen, E. E.; Yardley, J. P.; Miyano, M.; Hinshaw, W. B., Jr. *J. Am. Chem. Soc*. **1969**, *91*, 7333. (b) Pellegrini, C.; Strassler, C.; Weber, M.; Borschberg, H. J. *Tetrahedron: Asymmetry* **1994**, *5*, 1979. (c) Edmondson, S.; Danishefsky, S. J.; Sepp-Lorenzino, L.; Rosen, N. *J. Am. Chem. Soc*. **1999**, *121*, 2147.

(16) (a) Esmond, R. W.; Le Quesne, P. W. *J. Am. Chem. Soc*. **1980**, *102*, 7117. (b) Takayama, H.; Masubuchi, K.; Kitajima, M.; Aimi, N.; Sakai, S. *Tetrahedron* **1989**, *45*, 1327. (c) Takayama, H.; Kitajima, M.; Ogata, K.; Sakai, S. *J. Org. Chem*. **1992**, *57*, 4583. (d) Peterson, A. C.; Cook, J. M. *Tetrahedron Lett.* **1994**, *35*, 2651. (e) Peterson, A. C.; Cook, J. M. *J. Org. Chem*. **1995**, *60*, 120. (f) Wearing, X. Z.; Cook, J. M. *Org. Lett*. **2002**, *4*, 4237 and references therein.

(17) (a) Wenkert, E.; Udelhofen, J. H.; Bhattacharyya, N. K. *J. Am. Chem. Soc*. **1959**, *81*, 3763. (b) Seaton, J. C.; Nair, M. D.; Edwards, O. E.; Marion, L. *Can. J. Chem*. **1960**, *38*, 1035. (c) Phillipson, J. D.; Hemingway, S. R. *Phytochemistry* **1973**, *12*, 2795. (d) Awang, D. V. C.; Vincent, A.; Kindack, D. *Can. J. Chem*. **1984**, *62*, 2667. (e) Laus, G. *J. Chem. Soc., Perkin Trans. 2* **1998**, 315.

(18) Dess, D. B.; Martin, J. C. *J. Org. Chem*. **1983**, *48*, 4155.

(19) Yamada, K.; Takeda, M.; Iwakuma, T. *J. Chem. Soc., Perkin Trans. 1* **1983**, 265.