JOC*Note*

pubs.acs.org/joc

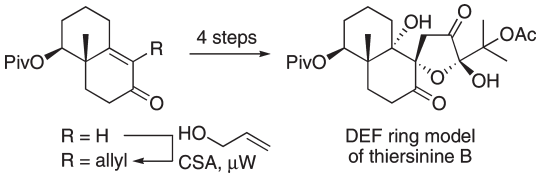
Expeditious Construction of the DEF Ring System of Thiersinine B

Masaru Enomoto and Shigefumi Kuwahara*

Laboratory of Applied Bioorganic Chemistry, Graduate School of Agricultural Science, Tohoku University, Tsutsumidori-Amamiyamachi, Aoba-ku, Sendai 981-8555, Japan

skuwahar@biochem.tohoku.ac.jp

Received June 28, 2010



Construction of a DEF ring model of thiersinine B has been achieved from a Wieland−Miescher ketone derivative by a five-step sequence featuring a one-pot regioselective α-allylation of the starting α,β-unsaturated ketone via the Claisen rearrangement and a double dihydroxylation of a dienone intermediate.

Thiersines A (**1**) and B (**2**) were isolated by Gloer and co-workers from fermentation cultures of *Penicillium thiersii*, a fungicolous fungus colonizing stromata of a wood decay fungus of the genus *Hypoxylon*, as antiinsectans exhibiting potent growth inhibitory activity against the fall armyworm *Spodoptera frugiperda* (Figure 1).[1] They belong to a large family of natural products known as indole diterpenes which is characterized by a hybrid molecular architecture consisting of an indole nucleus and a cyclic diterpenoid moiety with high structural diversity.[2] Many of indole diterpenoids are known to possess intriguing biological properties such as tremorgenic,[2] insecticidal,[3] and anti-MRSA[4] activities, which, coupled with interest in their unique indole/diterpene conjugate structures, prompted extensive studies from various viewpoints including their biosynthesis and genetic analysis[2,5] as well as the mode of action.[6] As for total synthesis, a series of studies by Smith and co-workers have been conducted and successfully led to the total syntheses of (−)-paspaline,[7] (+)-paspalicine,[8] (+)-paspalinine,[8] (+)-emindole,[9] (−)-21-isopentenylpaxilline,[10] (−)-penitrem D,[11] and (+)-nodulisporic acid F.[12] A distinctive structural feature of **1** and **2** is that they both incorporate a unique spirocyclic substructure (EF ring moiety) on the right side of the molecules, which is unprecedented in this class of natural products. As part of our efforts toward the total synthesis of thiersinines A and B, we describe herein the expeditious construction of **3** which we set as a DEF ring model of thiersinine B (**2**).

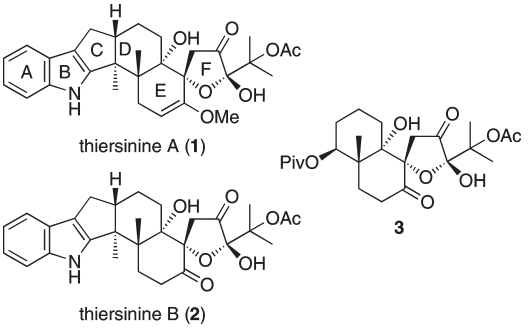


FIGURE 1. Thiersinines A (**1**) and B (**2**), and targeted DEF ring model **3**.

Scheme 1 outlines our synthetic plan for **3**. By opening its five-membered hemiacetal ring, compound **3** was traced retrosynthetically to tetrahyroxy ketone **4**; this tetraol would

(1) Li, C.; Gloer, J. B.; Wicklow, D. T.; Dowd, P. F. *Org. Lett.* **2002**, *4*, 3095–3098.

(2) Saikia, S.; Nicholson, M. J.; Young, C.; Parker, E. J.; Scott, B. *Mycol. Res.* **2008**, *112*, 184–199 and references cited therein.

(3) (a) Gloer, J. B. *Acc. Chem. Res.* **1995**, *28*, 343–350. (b) Belofsky, G. N.; Gloer, J. B. *Tetrahedron* **1995**, *51*, 3959–3968. (c) Ondeyka, J. G.; Helms, G. L.; Hensens, O. D.; Goetz, M. A.; Zink, D. L.; Tsipouras, A.; Shoop, W. L.; Slayton, L.; Dombrowski, A. W.; Polishook, J. D.; Ostlind, D. A.; Tsou, N. N.; Ball, R. G.; Singh, S. B. *J. Am. Chem. Soc.* **1997**, *119*, 8809–8816. (d) González, M. C.; Lull, C.; Moya, P.; Ayala, L.; Primo, J.; Yúfera, E. P. *J. Agric. Food Chem.* **2003**, *51*, 2156–2160. (e) Singh, S. B.; Ondeyka, J. G.; Jayasuriya, H.; Zink, D. L.; Ha, S. N.; Dahl-Roshak, A.; Greene, J.; Kim, J. A.; Smith, M. M.; Shoop, W.; Tkacz, J. S. *J. Nat. Prod.* **2004**, *67*, 1496–1506.

(4) Ogata, M.; Ueda, J.; Hoshi, M.; Hashimoto, J.; Nakashima, T.; Anzai, K.; Takagi, M.; Shin-ya, K. *J. Antibiot.* **2007**, *60*, 645–648.

(5) For examples, see: (a) Byme, K. M.; Smith, S. K.; Ondeyka, J. G. *J. Am. Chem. Soc.* **2002**, *124*, 7055–7060. (b) Xiong, Q.; Zhu, X.; Wilson, W. K.; Ganesan, A.; Matsuda, S. P. T. *J. Am. Chem. Soc.* **2003**, *125*, 9002–9003. (c) Fueki, S.; Tokiwano, T.; Toshima, H.; Oikawa, H. *Org. Lett.* **2004**, *6*, 2697–2700. (d) Ireland, C.; Peekhaus, N.; Lu, P.; Sangari, R.; Zhang, A.; Masurekar, P.; An, Z. *Appl. Microbiol. Biotechnol.* **2008**, *79*, 451–459. (e) Mantle, P. G. *Phytochemistry* **2009**, *70*, 7–10. (f) Nicholson, M. J.; Koulman, A.; Monahan, B. J.; Pritchard, B. L.; Payne, G. A.; Scott, B. *Appl. Environ. Microbiol.* **2009**, *75*, 7469–7481 and references cited therein.

(6) For examples, see: (a) Huang, X.-H.; Tomoda, H.; Nishida, H.; Masuma, R.; Omura, S. *J. Antibiot.* **1995**, *48*, 1–4. (b) Smith, M. M.; Warren, V. A.; Thomas, B. S.; Brochu, R. M.; Ertel, E. A.; Rohrer, S.; Schaeffer, J.; Schmatz, D.; Petuch, B. R.; Tang, Y. S.; Meinke, P. T.; Kaczorowski, G. J.; Cohen, C. J. *Biochemistry* **2000**, *39*, 5543–5554. (c) Imlach, W. L.; Finch, S. C.; Dunlop, J.; Dalziel, J. E. *Eur. J. Pharmacol.* **2009**, *605*, 36–45 and references cited therein.

(7) (a) Smith, A. B., III; Mewshaw, R. *J. Am. Chem. Soc.* **1985**, *107*, 1769–1771. (b) Smith, A. B., III; Leenay, T. L. *J. Am. Chem. Soc.* **1989**, *111*, 5761–5768.

(8) (a) Smith, A. B., III; Sunazuka, T.; Leenay, T. L.; Kingery-Wood, J. *J. Am. Chem. Soc.* **1990**, *112*, 8197–8198. (b) Smith, A. B., III; Kingery-Wood, J.; Leenay, T. L.; Nolen, E. G.; Sunazuka, T. *J. Am. Chem. Soc.* **1992**, *114*, 1438–1449.

(9) Rainier, J. D.; Smith, A. B., III. *Tetrahedron Lett.* **2000**, *41*, 9419–9423.

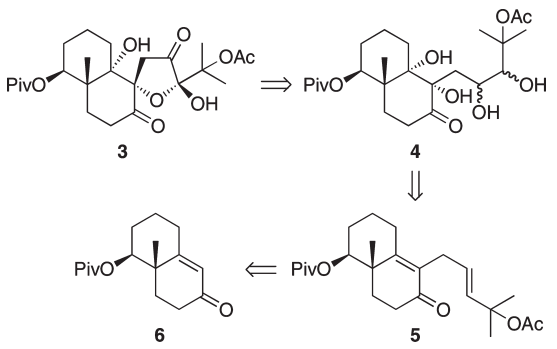
(10) (a) Smith, A. B., III; Cui, H. *Org. Lett.* **2003**, *5*, 587–590. (b) Smith, A. B., III; Cui, H. *Helv. Chim. Acta* **2003**, *86*, 3908–3938.

(11) (a) Smith, A. B., III; Kanoh, N.; Ishiyama, H.; Hartz, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 11254–11255. (b) Smith, A. B., III; Kanoh, N.; Ishiyama, H.; Minakawa, N.; Rainier, J. D.; Hartz, R. A.; Cho, Y. S.; Cui, H.; Moser, W. H. *J. Am. Chem. Soc.* **2003**, *125*, 8228–8237.

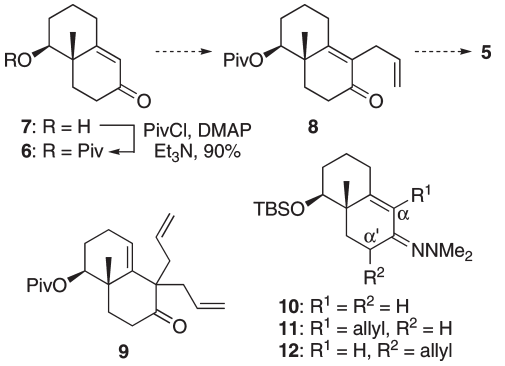
(12) (a) Smith, A. B., III; Davulcu, A. H.; Kürti, L. *Org. Lett.* **2006**, *8*, 1665–1668. (b) Smith, A. B., III; Davulcu, A. H.; Cho, Y. S.; Ohmoto, K.; Kürti, L.; Ishiyama, H. *J. Org. Chem.* **2007**, *72*, 4596–4610.

Published on Web 08/18/2010 DOI: 10.1021/jo101258f

SCHEME 1. Retrosynthetic Analysis of 3



SCHEME 2. Attempts for α-Allylation of 6

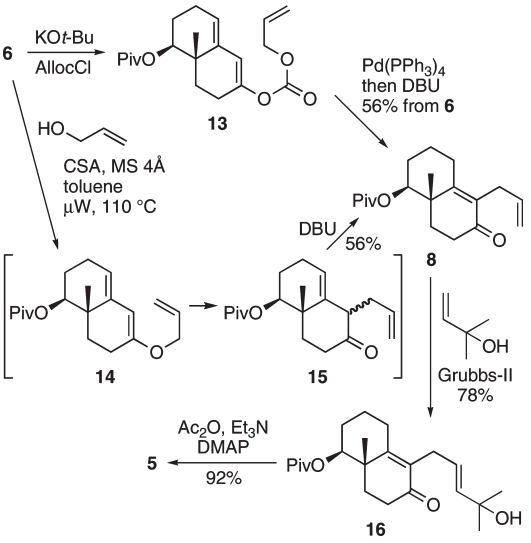


lead to **3** by oxidation of the two secondary hydroxyls and subsequent spontaneous hemiacetalization. The tetraol intermediate **4** would be obtainable by double dihydroxylation of the two olefinic bonds of **5**, and the dienyl ketone **5** in turn would be derived from Wieland−Miescher ketone derivative **6** by regioselective installation of the side chain at the α position of the α,β-unsaturated ketone system.

For the preparation of **5**, we envisaged a stepwise construction of its side chain moiety via α-allylation of **6** to **8** and subsequent chain elongation of **8** to **5** using a cross-metathesis reaction (Scheme 2). The allylation of **6** (obtained by treating **7**[13] with PivCl/DMAP/Et_3N/THF) was attempted, at first, by its conversion into the corresponding dienolate under thermodynamic conditions (NaH/DMSO/THF,[14] NaH/THF/HMPA, KO*t*-Bu/THF,[15] or KO*t*-Bu/THF/HMPA) followed by allylation of the dienolate intermediate with allyl bromide. These conditions, however, resulted in the formation of a mixture of the desired monoallylation product **8**, the starting material **6**, and a substantial amount of diallylation product **9**. Allylation of hydrazone **10** (prepared by treatment of the TBS ether[16] of **7** with Me_2NNH_2 and AcOH in toluene) by Stork's metalloenamine protocol (LDA, THF, reflux, 5 h, then allyl bromide, 0 °C)[8,10,11,17] was also unsuccessful, giving a mixture of α- and α′-allylation products (**11** and **12**, respectively) with the undesired α′-allylation product **12** predominating.

Fortunately, the transformation of **6** into **8** was found to be successfully achieved by applying Tsuji's palladium-catalyzed allylation protocol via an allyl enol carbonate intermediate (Scheme 3).[18] According to the reported procedure, the conjugated enone **6** was first converted into **13**, which was then treated with $Pd(PPh_3)_4$ in DME to give **8** in an acceptable yield of 56% for the two steps after in situ conjugation of the initially formed β,γ-double bond with DBU. More gratifyingly, **6** proved to be directly convertible to **8** in one pot (56% yield) by microwave irradiation of a mixture of **6** and allyl alcohol in toluene (110 °C) in the presence of camphorsulfonic acid and 4 Å molecular sieves

SCHEME 3. Three-Step Conversion of 6 into 5

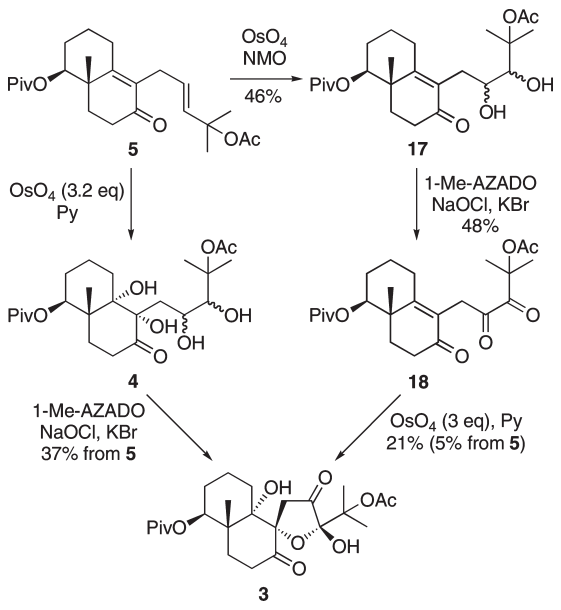


followed by treatment with DBU.[19] This transformation is considered to have taken place via the formation of thermodynamically more stable allyl dienyl ether **14**, its Claisen rearrangement to α-allyl β,γ-unsaturated ketone **15**, and finally the conjugation of the double bond by DBU.[20] Chain elongation of **8** by cross-metathesis with 2-methyl-3-buten-2-ol proceeded smoothly to give **16**, which, upon acetylation, afforded **5**.[21]

Having achieved the efficient one-pot allylation of **6** into **8** and subsequent chain elongation of **8** into **5**, we next set about the dihydroxylation of the double bonds of **5** (Scheme 4). In our first attempt, compound **5** was exposed to a catalytic amount of OsO_4 and *N*-methylmorpholine *N*-oxide (2 equiv) in CH_3CN/H_2O at room temperature for 3 h. Under these conditions, only the side chain double bond underwent dihydroxylation to give **17** in 46% yield. The oxidation of the diol **17** to **18** was troublesome, giving a complex mixture when **17** was treated with *o*-iodoxybenzoic acid in DMSO,[22] and C−C bond cleavage product **19** (Figure 2) as the only identifiable

(13) Peng, X.-S.; Wong, H. N. C. *Chem. Asian J.* **2006**, 111–120.
(14) Sucrow, W.; Brinkkoetter, G. *Chem. Ber.* **1985**, *118*, 4330–4340.
(15) Gutzwiller, J.; Meier, W.; Fürst, A. *Helv. Chim. Acta* **1977**, *60*, 2258–2269.
(16) Kaliappan, K. P.; Ravikumar, V. *Org. Lett.* **2007**, *9*, 2417–2419.
(17) Stork, G.; Benaim, J. *J. Am. Chem. Soc.* **1971**, *93*, 5938–5939.
(18) Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1983**, *24*, 1793–1796.
(19) The direct α-allylation of **6** into **8** could also be effected by conventional heating, albeit in somewhat lower yields.
(20) To the best of our knowledge, this type of α-allylation of α,β-unsaturated ketones is unprecedented. For the only analogous reaction with a β-alkoxy aldehyde diethyl acetal as the substrate, see: Baker, R.; Selwood, D. L. *Tetrahedron Lett.* **1982**, *23*, 3839–3840.
(21) Cross-metathesis of **8** with 1,1-dimethylallyl acetate to directly form **5** did not proceed, resulting in the recovery of **8**.
(22) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019–8022.

SCHEME 4. Completion of the Synthesis of 3



product upon exposure of **17** to the Dess−Martin periodinane/$NaHCO_3/CH_2Cl_2$[23] (58% yield) or to 1-Me-AZADO (1-methyl-2-azaadamantane *N*-oxyl) and $PhI(OAc)_2$ in CH_2Cl_2 (56% yield).[24] Oxidation with TPAP/NMO/MS4 Å/CH_2Cl_2 afforded the desired product **18**, albeit in only 22% yield.[25] After some additional unsuccessful attempts, we found that this conversion could be effected in a moderate yield of 48% by employing the 1-Me-AZADO oxidation protocol using NaOCl (instead of $PhI(OAc)_2$) as co-oxidant.[24] Finally, dihydroxylation of the sterically hindered electron-deficient double bond of **18** was conducted by using 3 equiv of OsO_4 in ether in the presence of pyridine to afford the targeted tricyclic product **3** in 28% yield. The overall yield for the conversion of **5** into **3** in three steps was, however, only 5%, which made us seek an alternative route to improve the efficiency of this transformation. Thus, we examined the double dihydroxylation of **5** into **4** and subsequent oxidation of the two secondary hydroxyl groups of the resulting tetraol **4** into **3**. As shown in Scheme 4, the double dihydroxylation was realized by subjecting **5** to 3.2 equiv of OsO_4/Py in ether,[26] and the product **4** was oxidized by the

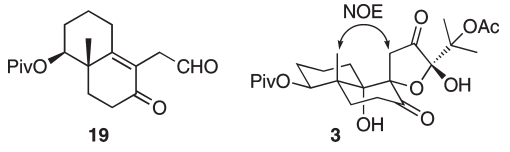


FIGURE 2. The structure of byproduct **19** and a NOE correlation observed for **3**.

1-Me-AZADO-mediated procedure to **3** in an acceptable overall yield of 37% for the two steps.[27] The stereochemistry of **3** was confirmed by the observation of a diagnostic NOE correlation shown in Figure 2.

In conclusion, the construction of the DEF ring model **3** from the Wieland−Miescher ketone derivative **6** has been achieved in a five-step sequence that features the efficient one-pot α-allylation of the enone **6** and the double dihydroxylation of the sterically hindered, electron deficient enone intermediate **5**. Our efforts directed toward the total synthesis of thiersinines A and B are now in progress and will be reported in due course.

Experimental Section

(1*S,8a*S**)-5-Allyl-8a-methyl-6-oxo-1,2,3,4,6,7,8,8a-octahydronaphthalen-1-yl 2,2-Dimethylpropanoate (8).** A mixture of **6** (250 mg, 0.946 mmol), allyl alcohol (1.0 mL), camphorsulfonic acid (66.0 mg, 0.284 mmol), and crushed 3 Å molecular sieves (250 mg) in toluene (3.0 mL) was put in a sealed tube and irradiated under microwave conditions at 110 °C for 1 h (300 W, CEM Discover System). The mixture was cooled to rt, and then DBU (250 μL) was added. After being stirred for 2.5 h at rt, the mixture was poured into 1 M HCl precooled with an ice−water bath, and extracted with Et_2O. The extract was successively washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over SiO_2 (hexane/EtOAc, 50:1−20:1) to give 162 mg (56%) of **8** as a colorless oil: IR ν_{max} 2960 (m), 1726 (s), 1670 (s); ^{1}H NMR δ 1.22 (9H, s), 1.30 (3H, s), 1.37−1.49 (1H, m), 1.64−1.95 (5H, m), 2.09 (1H, ddd, J = 14.0, 14.0, 4.8 Hz), 2.436 (1H, dd, J = 10.0, 4.8 Hz), 2.437 (1H, dd, J = 8.8, 4.8 Hz), 2.63−2.70 (1H, m), 3.06 (1H, dddd, J = 15.6, 5.8, 1.8, 1.8 Hz), 3.13 (1H, dd, J = 15.6, 5.8 Hz), 4.63 (1H, dd, J = 12.0, 3.0 Hz), 4.89 (1H, ddd, J = 17.0, 3.4, 1.6 Hz), 4.93 (1H, ddd, J = 10.0, 4.3, 1.6 Hz), 5.74 (1H, dddd, J = 17.0, 10.0, 5.8, 5.8 Hz); ^{13}C NMR δ 17.3, 22.5, 26.3, 26.9, 27.1 (3C), 29.1, 33.2 (2C), 38.9, 40.9, 78.8, 114.3, 132.1, 135.7, 161.1, 177.5, 197.4; HRMS (EI) m/z calcd for $C_{19}H_{28}O_3$ (M^+) 304.2038, found 304.2042.

(1*S,8a*S**)-5-(4-Hydroxy-4-methyl-2-pentenyl)-8a-methyl-6-oxo-1,2,3,4,6,7,8,8a-octahydronaphthalen-1-yl 2,2-Dimethylpropanoate (16).** To a stirred solution of **8** (264 mg, 0.866 mmol) in CH_2Cl_2 (20 mL) were added 2-methyl-3-buten-2-ol (373 mg, 4.33 mmol) and the second-generation Grubbs catalyst (50.0 mg, 0.061 mmol) at rt under Ar. The mixture was heated at reflux for 30 min, and then additional 2-methyl-3-buten-2-ol (186 mg, 2.16 mmol) and the catalyst (20.0 mg, 0.0024 mmol) were added. After being heated at reflux for an additional hour, the mixture was diluted with brine and extracted with EtOAc. The extract was successively washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over SiO_2 (hexane/EtOAc, 4:1−2:1) to give 245 mg (78%) of **16** as a slightly brown oil: IR ν_{max} 3480 (s), 2969 (s), 1725 (s), 1667 (s); ^{1}H NMR δ 1.22 (9H, s), 1.27 (6H, s), 1.29 (3H, s) 1.35−1.45 (1H, m), 1.64−1.95 (5H, m), 2.08 (1H, ddd, J = 14.0, 14.0, 5.2 Hz), 2.430 (1H, dd, J = 10.0, 4.8 Hz), 2.432 (1H, dd, J = 8.4, 4.8 Hz), 2.63−2.71 (1H, m), 3.06 (2H, d, J = 3.6 Hz), 4.63 (1H, dd, J = 11.6, 4.4 Hz), 5.50−5.52 (2H, m); ^{13}C NMR δ 17.3, 22.6, 26.3, 26.9, 27.1 (3C), 27.7, 29.6 29.7, 33.16, 33.23, 39.0, 40.9, 70.5, 78.8, 124.2,

(23) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287. (b) Banerjee, S.; Zeller, M.; Brückner, C. *J. Org. Chem.* **2010**, *75*, 1179–1187. (c) Nagasawa, T.; Shimada, N.; Torihata, M.; Kuwahara, S. *Tetrahedron* **2010**, *66*, 4965–4969.

(24) Shibuya, M.; Tomizawa, M.; Suzuki, I.; Iwabuchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 8412–8413.

(25) Liu, J. Semi-Synthetic Route for the Preparation of Paclitaxel, Docetaxel and 10-Deacetylbaccatin III from 9-Dihydro-13-acetylbaccatin III. Can. Pat. Appl. 2549951, Dec 12, 2007. *Chem. Abstr.* **2007**, *148*, 55223.

(26) For examples of OsO_4 oxidation of electron-deficient tetrasubstituted olefins, see: (a) Vedejs, E.; Ahmad, S.; Larsen, S. D.; Westwood, S. *J. Org. Chem.* **1987**, *52*, 3937–3948. (b) Siu, T.; Cox, C. D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5629–5634. (c) Tsubuki, M.; Okita, H.; Honda, T. *Heterocycles* **2006**, *67*, 731–748. (d) Henderson, D. A.; Collier, P. N.; Pavé, G.; Rzepa, P.; White, A. J. P.; Burrows, J. N.; Barrett, A. G. M. *J. Org. Chem.* **2006**, *71*, 2434–2444.

(27) Compound **3** (mp 185−186 °C) was synthesized from the alcohol **7** prepared by reduction of the Wieland−Miescher ketone with a specific rotation ($[\alpha]^{24}_D$ (*c* 1.50, toluene)) of +64.9. From the specific rotation value reported for the optically pure Wieland−Miescher ketone ($[\alpha]^{25}_D$ +97.3 (*c* 1.0, toluene)), we are estimating the optical purity of **3** to be around 67%. For the preparation and specific rotation of the Wieland−Miescher ketone, see: Buchschacher, P.; Fürst, A.; Gutzwiller, J. *Organic Syntheses*; Wiley & Sons: New York, 1990; Collect. Vol. No. VII, pp 368−372.

132.6, 138.1, 161.1, 177.6, 197.5; HRMS (EI) m/z calcd for $C_{22}H_{34}O_4$ (M^+) 362.2459, found 362.2457.

(1*S,8a*S**)-5-(4-Acetoxy-4-methyl-2-pentenyl)-8a-methyl-6-oxo-1,2,3,4,6,7,8,8a-octahydronaphthalen-1-yl 2,2-Dimethylpropanoate (5).** To a stirred solution of **16** (125 mg, 0.345 mmol) in triethylamine (4.8 mL, 34.5 mmol) were added acetic anhydride (1.63 mL, 17.3 mmol) and 4-(dimethylamino)pyridine (42.2 mg, 0.345 mmol) at rt under N_2. After being stirred for 3 h, the mixture was poured into saturated aq NH_4Cl at 0 °C, and extracted with Et_2O. The extract was successively washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over SiO_2 (spherical neutral; hexane/EtOAc, 7:1) to give 129 mg (92%) of **5** as a colorless oil: IR ν_{max} 2976 (s), 1726 (s), 1669 (s); ^{1}H NMR δ 1.22 (9H, s), 1.29 (3H, s), 1.35−1.42 (1H, m), 1.45 (6H, s), 1.63−1.95 (5H, m), 1.95 (3H, s), 2.07 (1H, ddd, J = 14.8, 14.8, 5.6 Hz), 2.432 (1H, dd, J = 10.0, 4.8 Hz), 2.433 (1H, dd, J = 8.8, 4.8 Hz), 2.62−2.70 (1H, m), 3.02−3.13 (2H, m), 4.63 (1H, dd, J = 11.6, 4.4 Hz), 5.48 (1H, dt, J = 16.0, 5.6 Hz), 5.66 (1H, dt, J = 16.0, 1.6 Hz); ^{13}C NMR δ 17.4, 22.4, 22.6, 26.4, 26.75, 26.82, 26.89, 27.2 (3C), 27.8, 33.2, 33.3, 39.0, 41.0, 78.8, 80.4, 126.4, 132.4, 134.4, 161.6, 169.9, 177.6, 197.5; HRMS (FAB) m/z calcd for $C_{24}H_{36}O_5Na$ ($[M + Na]^+$) 427.2460, found 427.2464.

DEF Ring Model (3). To a stirred solution of **5** (44.3 mg, 0.110 mmol) in Et_2O (4.5 mL) were added OsO_4 (66.8 mg, 0.263 mmol) and pyridine (120 μL, 1.48 mmol) at rt. After 18 h, additional OsO_4 (21.5 mg, 0.085 mmol) and pyridine (30 μL, 0.371 mmol) was added, and the mixture was stirred for an additional 10 h at rt. The reaction was quenched by successive addition of saturated aq $NaHSO_3$ and saturated aq $NaHCO_3$, and the resulting mixture was stirred for 20 h before being extracted with ethyl acetate. The extract was successively washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over SiO_2 (spherical neutral; hexane/EtOAc, 1:1−0:1) to give 38.3 mg of **4** (diastereomeric mixture) as a yellow oil, which was then dissolved in CH_2Cl_2−saturated aq $NaHCO_3$ (1:1, 7.2 mL). To the mixture were added KBr (1.0 mg, 0.008 mmol), 1-Me-AZADO (1.2 mg, 0.008 mmol), and 8% aq NaOCl (377 μL, 0.405 mmol) at 0 °C, and the mixture was vigorously stirred for 40 min at 0 °C. The mixture was diluted with CH_2Cl_2 and water, and extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over SiO_2 (spherical neutral; hexane/EtOAc, 5:1−1:1) to give 18.8 mg (37% from **5**) of **3** as a crystalline solid: mp 185−186 °C;[27] IR ν_{max} 3724 (s), 2940 (s), 1770 (s), 1716 (s); ^{1}H NMR δ 1.21 (9H, s), 1.22 (3H, s), 1.48−1.55 (1H, m), 1.63−1.78 (3H, m), 1.70 (3H, s), 1.71(3H, s), 1.82−1.95 (3H, m), 1.92 (3H, s), 2.22−2.27 (1H, m), 2.41 (1H, s, OH), 2.54 (1H, d, J = 17.1 Hz), 2.56−2.59 (2H, m), 2.81 (1H, d, J = 17.1 Hz), 5.20 (1H, dd, J = 12.0, 4.0 Hz), 5.57 (1H, s, OH); ^{13}C NMR δ 14.1, 18.5, 19.2, 19.9, 22.3, 25.4, 25.9, 27.2 (3C), 29.9, 34.3, 39.0, 42.0, 43.6, 75.3, 81.7, 85.4, 87.6, 98.7, 168.5, 177.5, 207.6, 213.8; HRMS (FAB) m/z calcd for $C_{24}H_{37}O_9$ ($[M + H]^+$) 469.2438, found 469.2441.

Acknowledgment. We are grateful to Prof. Yoshiharu Iwabuchi (Tohoku University) for a gift of 1-Me-AZADO. This work was financially supported, in part, by a Grant-in-Aid for Scientific Research (B) from the Ministry of Education, Culture, Sports, Science and Technology, Japan (No. 22380064).

Supporting Information Available: Experimental procedures, characterization data, and NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.