Pergamon

Tetrahedron Letters 40 (1999) 1731–1734

TETRAHEDRON LETTERS

First Synthesis of (-)-Spongianolide A and Determination of Its Absolute Structure

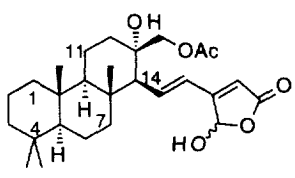
Toshiyuki Hata, Katsunori Tanaka and Shigeo Katsumura*

School of Science, Kwansei Gakuin University, Uegahara Nishinomiya 662-8501, Japan

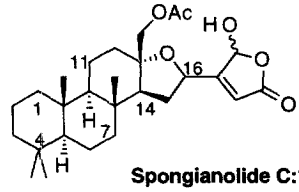
Received 2 December 1998; revised 21 December 1998; accepted 25 December 1998

Abstract; The first synthesis of (-)-spongianolide A (**1**), a cytotoxic sesterterpenoid, and determination of its absolute structure are described. In this synthesis, a simple and practical method for preparation of enantiomerically pure bicyclic and tricyclic β-ketoesters, and a new Wittig reagent, furanmethylide, were developed.

Various kinds of terpenoids bearing a γ-hydroxybutenolide moiety have been isolated from marine sources, and some of them represented by manoalide[1] and dysidiolide[2] have been paid much attention because of the quite attractive biological activities of their anti-inflammatory and antitumor properties.[2,3] (-)-Spongianolide A (**1**), which was isolated from a marine sponge, *Spongia* sp. along with spongianolide C and D, is a tricyclic sesterterpenoid possessing a γ-hydroxybutenolide moiety, and was reported to inhibit proliferation of the mammary tumor cell line MCF-7.[4] The structure of this terpenoid was determined by NMR, while its absolute



Spongianolide A (1)



Spongianolide C:16α-hydrogen
D:16β-hydrogen

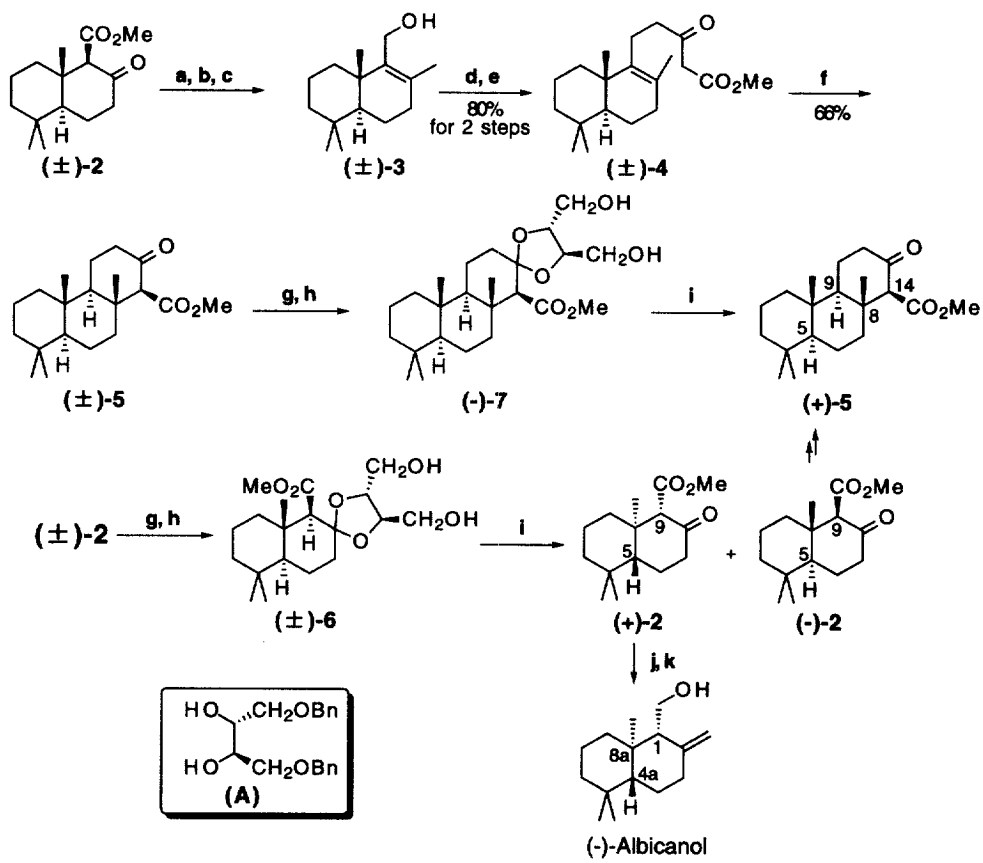
structure had not been confirmed yet. Herein, we report the first synthesis of (-)-spongianolide A and the determination of its absolute structure. In this synthesis, we developed a simple and practical method for preparation of enantiomerically pure bicyclic and tricyclic β-ketoesters **2** and **5**, and a new Wittig reagent, furanmethylide **14**.

Our strategy to synthesize the tricyclic skeleton of **1** is to repeat a sequence of the reactions for ring construction starting from an allyl alcohol *via* linear β-ketoester formation and then olefin cyclization with acid. This method would be very useful for preparation of enantiomerically pure bicyclic and tricyclic β-ketoesters if the enantiomers of both β-ketoesters were simply resolved by the same procedure, respectively. As shown in Scheme 1, bicyclic β-ketoester **2**, which was prepared from β-cyclogeraniol by a sequence of bromination, condensation with methyl acetoacetate and then tin tetrachloride treatment,[5] was transformed into allyl alcohol **3** by enol phosphonate formation with sodium hydride and diethyl chlorophosphate, introduction of a methyl group with lithium dimethylcuprate, and reduction of the ester group with LAH in 80% yield for three steps. Repeating the same sequence as that from cyclocitrol into **2**, we obtained tricyclic β-ketoester **5** from allyl alcohol **3** through **4** in

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00039-8

52% overall yield. Resolution of the enantiomers of both **2** and **5** was achieved by utilization of a chiral auxiliary for acetal formation. Acetal formation of **2** with 2,3-dihydroxybutandiol dibenzyl ether (**A**)[6] and then removal of the benzyl group gave diol **6**. The diasteromers of **6** were nicely separated by column chromatography on silica gel (eluted with $CHCl_3$ containing from 1% to 6% MeOH). Enantiomerically pure (+)-**2** obtained was transformed into a sesquiterpene, albicanol, whose physical and spectral data were in good agreement with those of (1*R*, 4a*R*, 8a*R*)-(-)-albicanol.[7] Thus, the absolute structure of (+)-**2** was determined as (5*R*, 9*S*, 10*R*). The enantiomer, (-)-**2** was transformed into tricyclic compound **5**, which showed plus sign of the optical rotation. Therefore, the absolute structure of (+)-**5** was determined as (5*S*, 8*R*, 9*R*, 10*S*, 14*S*). We next tried to resolve (±)-**5** by the same method. Fortunately, the diasteromers of diol **7**, which were obtained by the same procedure as that of **6**, were also separable by column chromatography.[8] Thus, enantiomerically pure **5**(m.p. 170-172 °C; $[\alpha]_D^{24}$ 29.1 (c 1.02, $CHCl_3$)) was readily obtained by a simple resolution procedure.[9]

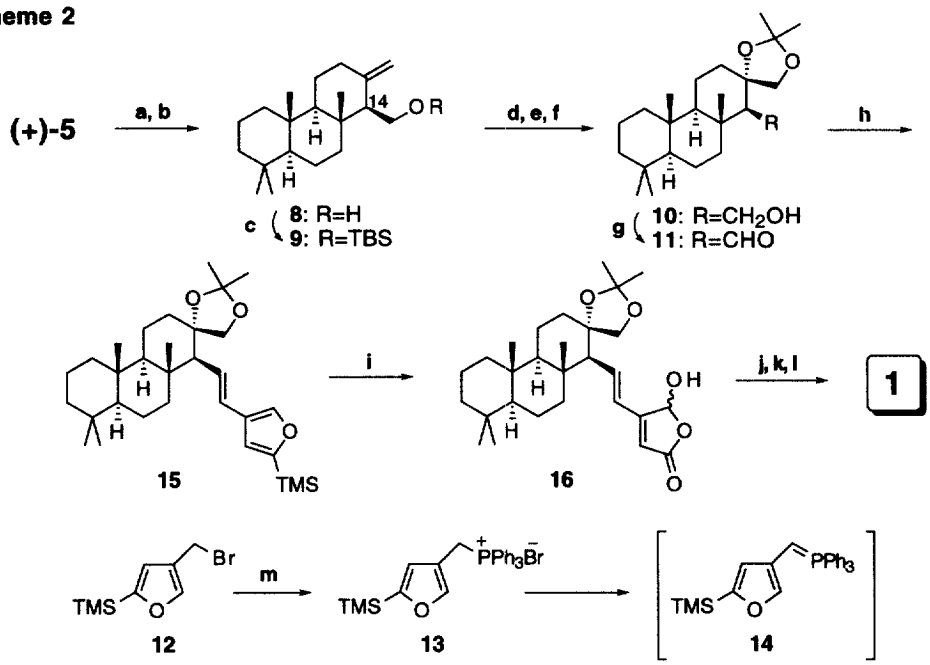
Scheme 1



a) NaH, $ClP(O)(OEt)_2$, THF, rt; b) MeLi, CuI, ether, -40 ℃→0 ℃; c) $LiAlH_4$, ether, rt, 80% for three steps; d) PBr_3, pyr., ether, 0 ℃, 1h; e) NaH, methyl acetoacetate, *n*-BuLi, THF, 0 ℃, 1h, 80% for two steps; f) $SnCl_4$, abs.CH_2Cl_2, rt, 20h, 66%; g) TsOH, (**A**), C_6H_6, 90 ℃, 1h, quant.; h) Pd-C, H_2, AcOEt, rt, 1d, quant.; i) 2N H_2SO_4aq., MeOH, 90 ℃, 2d, 70-80%; j) $MeP^+Ph_3Br^-$, $NaNH_2$, THF, rt, 30min., then (+)-**2**, rt, 30min; k) $LiAlH_4$, ether, rt, 86% for two steps

The synthesis of (-)-spongianolide A from (+)-**5** is shown in Scheme 2. The successful Wittig reaction of β-ketoester (+)-**5** with triphenylphosphonium methylide, followed by reduction of the ester group stereoselectively produced alcohol **8** (14α:14β=1:11) in excellent yield. Use of excess base in the Wittig reaction caused severe epimerization at the C-14 position. The Wittig reaction of the β-hydroxy ketone, which was derived from **5** by acetal formation, reduction and acid treatment, gave **8** in only poor yield. After protection of the hydroxy group in **8** with the *t*-butyldimethylsilyl group, oxidation of the exomethylene moiety with osmium tetroxide stereoselectively produced the corresponding diol as a single isomer, which was followed by acetonide formation with 2,2-dimethoxypropane. Treatment of the acetonide obtained with tetrabutylammonium fluoride and then Swern oxidation of the resulting hydroxy group yielded aldehyde **11**. Elongation of the five carbon unit containing the γ-hydroxybutenolide moiety was efficiently achieved by utilization of a new Wittig reagent, 3-(5-trimethylsilylfuryl)triphenylphosphonium methylide (**14**), followed by photosensitized oxygenation. Thus, unstable bromide **12** prepared from the corresponding alcohol[10] was heated with triphenylphosphine in benzene to produce the Wittig salt **13** as colorless crystals in 67% yield for two steps.[11] Reaction of aldehyde **11** with furanmethylide **14**, which was prepared from the Wittig salt **13** by treatment with *n*-BuLi in THF, nicely produced conjugated furan **15** in 86% yield.[12] To the best of our knowledge, furanmethylide **14** and hence the Wittig salt **13**, has not been reported so far, although it is quite useful for introduction of the 5-trimethylsilyl

Scheme 2



a) $MeP^+Ph_3Br^-$, $NaNH_2$, THF, rt, 30min, then (+)-**5**, 30min; b) $LiAlH_4$, ether, rt, 89% for two steps; c) Et_3N, DMAP, TBDMSCl, DMF, 0 ℃, quant.; d) OsO_4, pyr., 4h, then 2M $NaHSO_3$aq., 18h, rt, 89%; e) PPTS, $Me_2C(OMe)_2$, acetone, rt, 98%; f) TBAF, THF, 60 ℃, 3h, quant.; g) Swern Ox., 84%; h) *n*-BuLi, **13**, THF, then **11**, 0 ℃, 1h, 86%; i) O_2, TPP, hv, CH_2Cl_2, -78 ℃, 30min, 74%; j) 2N HClaq., THF, 60 ℃, 2d, 63%; k) Ac_2O, pyr., 50 ℃, 3h; l) $NaHCO_3$aq., MeOH, rt, 30min, 52% for two steps; m) PPh_3, C_6H_6, 2h, 70 ℃, 67% for 2 steps

furan moiety conjugated at the 3-position. Photosensitized oxygenation of silylfuran **15** chemoselectively proceeded and γ-hydroxybutenolide was regiospecifically produced to give **16** as a 1:1 mixture of stereoisomers at the hydroxy group in the butenolide ring.[13] Synthesis of (-)-spongianolide A was established by treatment of **16** with acid followed by acetylation and then chemoselective hydroysis of the acetyl group in the butenolide moiety by treatment with aqueous sodium hydrogen carbonate in methanol. The spectral and physical data of the synthesized compound were in good agreement with those reported.[4] Thus, the absolute structure (-)-spongianolide A was confirmed as (5*S*, 8*R*, 9*R*, 10*S*, 13*S*, 14*S*) by the present synthesis.

Acknowledgement: This work was supported by a Grant-in-Aid for Scientific Research 09480415 from the Ministry of Education, Science and Culture of Japan.

Reference and Notes

1. Silva, D. E.; Scheuer, P. J. *Tetrahedron Lett.* **1980**, *21*, 1611.
2. Gunasekera, S. P.; McCarthy, P. J.; Kelly-Borges, M. *J. Am. Chem. Soc.* **1996**, *118*, 8759.
3. de Freitas, J. C.; Blankemeier, L. A.; Jacobs, R. S. *Experrientia*, **1984**, *40*, 864.
4. He, H.; Kulanthaivel, P.; Baker, J. B. *Tetrahedron. Lett.* **1994**, *35*, 7189.
5. a) Skeean, R. D.; Trammell, G. L.; White, J. D. *Tetrahedron. Lett.* **1976**, *17*, 525. b) Nelson, D. J.; Cooper, P. J.; Coerver, J. M. *Tetrahedron Lett.* **1987**, *28*, 943.
6. Mash, E. A.; Nelson, K. A.; Deusen, S. V.; Hemperly, S. B. *Org. Syn. Vol.68*, p.92, White, J. D. ed., **1989**.
7. Ragoussis, V.; Liapis, M. *J. Chem. Soc. Perkin Trans 1* **1987**, 987.
8. Diastereomers of **7** were separated by flash chromatography on silica gel eluted with $CHCl_3$ containing MeOH (from 1% to 6%). Data for (-)-**7**; m.p. 223-225 °C; $[\alpha]^{25}_D$-45.1 (c 1.16, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12-4.10 (m, 3 H), 3.90 (d, *J*= 10.8 Hz, 1 H), 3.77 (ddd, *J* = 12.4, 4.8, 3.6 Hz, 1 H), 3.65 (s, 3 H), 3.55 (m, 1 H), 2.53 (s, 1 H), 1.97 (*J*= 8.0, 4.8 Hz, 1 H), 1.88 (ddd, *J* = 8.4, 3.6, 3.6 Hz, 1 H), 1.71-1.32 (m, 10 H), 1.18 (m, 1 H), 1.17 (s, 3 H), 0.85 (s, 6 H), 0.84 (s, 3 H), 0.8 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.21, 109.02, 77.60, 75.53, 63.11, 61.61, 59.80, 59.01, 56.68, 51.41, 41.99, 41.34, 40.01, 39.70, 38.02, 37.57, 33.27, 21.34, 18.97, 18.50, 18.08, 16.21, 15.98; IR (KBr, cm^{-1}) 3483, 1730, 1148, 1132, 1046.
9. The optically active compounds having a skeleton like **2** and **5** were prepared by (a) derivation from natural products; for example, Zoretic, P. A.; Fang, H. *J. Org. Chem.* **1998**, *63*, 1156, (b) bioresolution; for example, Nair, M. S.; Anilkumar, A. T. *Tetrahedron Asym.* **1996**, *7*, 511; Tanimoto, H.; Oritani, T. *Tetrahedron Asym.* **1996**, *7*, 1695 and (c) asymmetric olefin cyclization; for example, Corey, E. J.; Luo, G.; Lin, L. S. *J. Am. Chem. Soc.* **1997**, *119*, 9927 and references within.
10. Lee, G. C. M.; Holmes, J. M.; Harcourt, D. A.; Garst, M. E. *J. Org. Chem.* **1992**, *57*, 3126.
11. Data for **13**; m.p.166-167 °C(recrystallization from MeOH-hexane); ^{1}H NMR (400 MHz, CD_3OD) δ 7.92-7.88 (m, 3 H), 7.76-7.70 (m, 15 H), 7.47 (d, *J* = 4.4 Hz, 1 H), 6.05 (s, 1 H), 4,77 (d, *J* = 14.0 Hz, 2 H), 0.15 (s, 9 H); ^{13}C NMR (100 MHz, CD_3OD) δ 148.52 (d, *J* = 9.0 Hz), 136.46, 135.23 (d, *J* = 9.0 Hz), 131.40 (d, *J* = 12.0 Hz), 122.58, 119.48, (d, *J* = 85.0 Hz), 112.56, 21.16 (d, *J* = 51.0 Hz), -1.89; IR (KBr, cm^{-1}) 3070, 2880, 1595, 1442, 1242, 1114, 848, 688, 524.
12. Data for (-)-**15**; m.p.112-113 °C; $[\alpha]^{24}_D$-16.4 (c 0.97, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1 H), 6.70 (s, 1 H), 6.31 (d, *J* = 15.2 Hz, 1 H), 5.84 (dd, *J* = 15.2, 10.0 Hz, 1 H), 3.90 (dd, *J* = 8.4, 2.0 Hz, 1 H), 3.82 (d, *J* = 8.4 Hz, 1 H), 2.14 (d, *J*= 10.0 Hz, 1 H), 2.09 (ddd, *J* = 12.4, 3.2, 3.2 Hz, 1 H), 1.38 (s, 3 H), 1.69-1.00 (m, 12 H), 1.13 (s, 3 H), 0.95-0.77 (m, 3 H), 0.85 (s, 3 H), 0.83 (s, 3 H), 0.82 (s, 3 H), 0.79 (s, 3 H), 0.27 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.21, 143.85, 124.86, 124.78, 124.45, 117.20, 107.10, 83.86, 68.39, 62.17, 59.72, 56.51, 42.03, 39.99, 39.74, 38.60, 37.54, 33.27, 33.25, 28.37, 26.49, 21.40, 19.44, 18.57, 18.14, 16.41, 16.31, -1.68; IR (KBr, cm^{-1}) 1685, 1636, 1252, 844.
13. Katsumura, S.; Hori, K.; Fujiwara, S.; Isoe, S. *Tetrahedron Lett.* **1985**, *26*, 4625.