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Synthesis of (+)-testudinariol A, a triterpene metabolite of the marine mollusc *Pleurobrancus testudinarius*

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Abstract—Testudinariol A (**1**) is an ichthyotoxic and structurally unusual triterpene alcohol isolated from the skin and the mucus of the marine mollusc *Pleurobrancus testudinarius*. A stereoselective synthesis of (+)-**1** was achieved by starting from (*R*)-glycidol.

In 1997, Spinella et al. isolated testudinariol A (**1**) and its C-10′ epimer (testudinariol B, **2**) as metabolites of the marine mollusc *Pleurobrancus testudinarius*.[1] These compounds are structurally unique triterpene alcohols and thought to be defensive allomones of *P. testudinarius*, because **1** was ichthyotoxic against *Gambusia affinis*. The partially cyclized squalene skeleton present in **1** and **2** is biosynthetically unusual and has only been reported in the cases of limatulones [**3** and **3′**, defensive metabolites of the limpet *Achmeia* (*Collisella*) *limatula*][2] and naurols (**4** and **4′**, metabolites of the marine sponges).[3] In continuation of our synthesis of marine triterpenoid such as limatulones (**3** and **3′**)[4] and naurol A (**4**),[5] we initiated the synthesis of testudinariol A (**1**). Herein we report the first synthesis of (+)-**1** (Fig. 1).[6]

Scheme 1 shows our synthetic plan for **1**. The target compound **1** can be obtained by dimerization or its equivalent operation of **A**. The intermediate **A** may be prepared from **B**, which is derived from **C** by means of

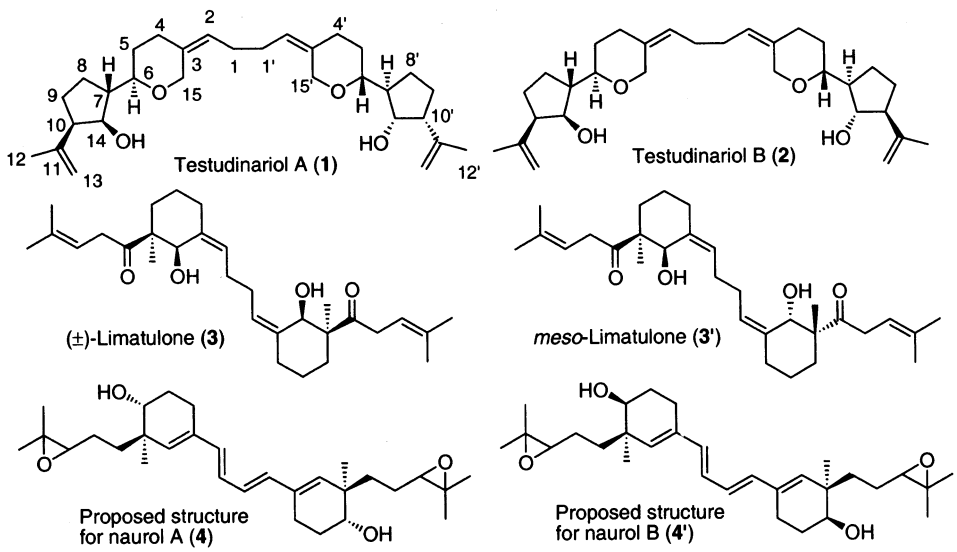

Figure 1. Structures of testudinariol A (**1**), B (**2**) and related metabolites.

Keywords: marine natural products; stereoselective synthesis; triterpenoids.
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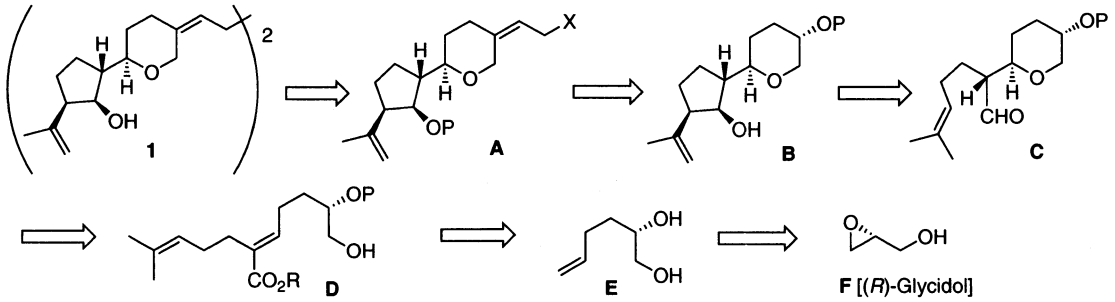
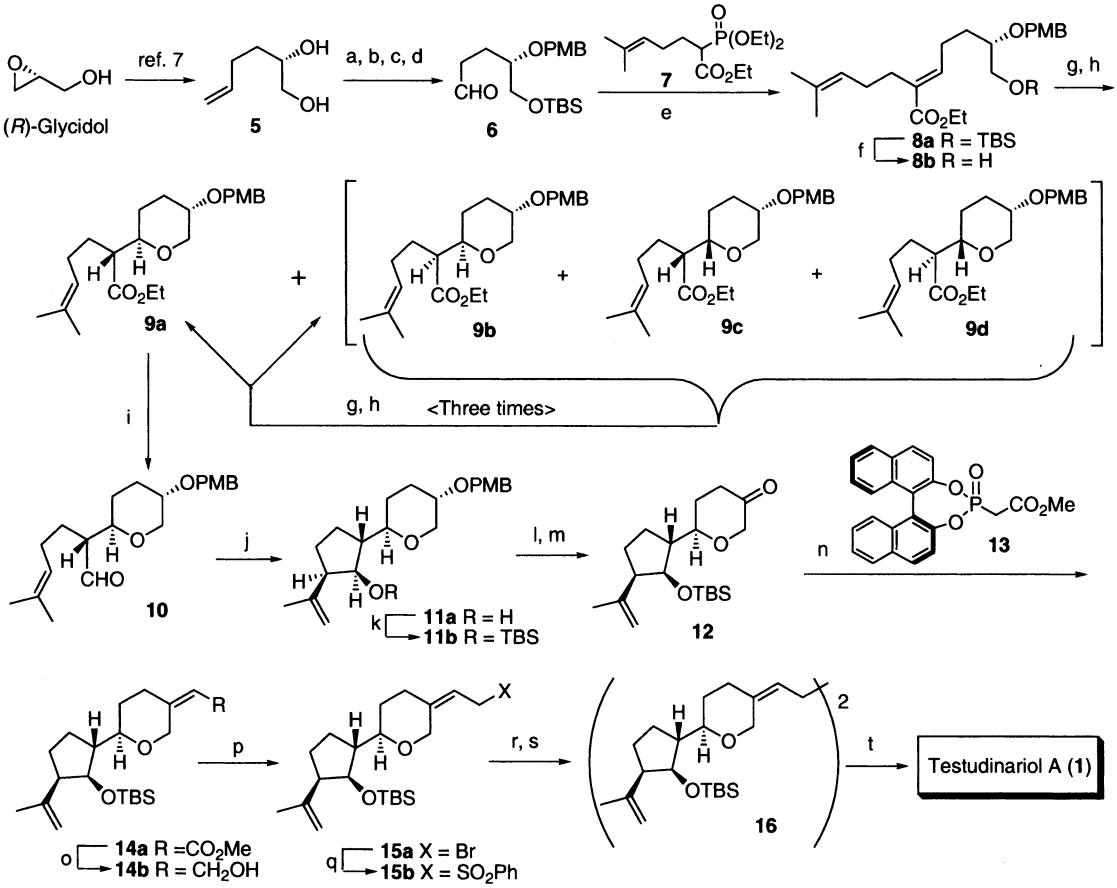


Scheme 1. Synthetic plan for **1**.

ene reaction. The Michael-type cyclization of **D** followed by several steps may afford **C**. The intermediate **D** can be synthesized from **F** [(*R*)-glycidol] via the known diol **E**.

The starting (*R*)-glycidol was converted to the known diol **5**.[7] Selective and stepwise protections of hydroxy groups of **5** were followed by oxidative cleavage of the terminal double bond to give **6** (70%, four steps). The aldehyde **6** was subjected to the Horner–Wadsworth–Emmons reaction with **7**[8] to afford **8a** (93%, *E*:*Z*=5:1).[9] After removal of the TBS protective group (99%), the resulting **8b** was exposed to intramolecular Michael-type cyclization. In spite of all our efforts, unfortunately, any appropriate conditions to furnish **9a** as the predominant isomer under kinetic control could



Scheme 2. Synthesis of testudinariol A (**1**). Reagents: (a) TBSCl, Et_3N, DMAP, CH_2Cl_2 (85%); (b) 4-methoxybenzyl trichloroacetimidate, TfOH, Et_2O (90%); (c) OsO_4, NMO, *t*-BuOH, acetone, H_2O (93%); (d) aq. $NaIO_4$, SiO_2, CH_2Cl_2 (98%); (e) **7**, *t*-BuOK, toluene, −20°C (93%, *E*:*Z*=5:1); (f) PPTS, MeOH (99%); (g) *t*-BuOK (0.1 equiv.), THF, −10 to −4°C (93% for a mixture of **9a**–**d**); (h) SiO_2 chromatog. (overall 68% for **9a**); (i) DIBAL, toluene, −78°C (98%); (j) 1.0 equiv. Me_2AlCl, CH_2Cl_2, 0°C (59%); (k) TBSOTf, 2,6-lutidine, CH_2Cl_2 (99%); (l) DDQ, aq. CH_2Cl_2 (97%); (m) Dess–Martin periodinane, pyridine, CH_2Cl_2 (94%); (n) **13**, NaHMDS, THF, −78 to −20°C (91%, *E*:*Z*=1:4); (o) DIBAL, CH_2Cl_2 (75%); (p) Ms_2O, LiBr, DMAP, collidine, DMF (80%); (q) $PhSO_2Na$, DMF (ca. 90%); (r) KHMDS, 18-crown-6, THF then **15a** (84%); (s) Na-Hg, Na_2HPO_4, MeOH; (t) TBAF, THF (48%, two steps).

not be found.[10] We therefore tried to obtain a mixture of all of the possible diastereomers under thermodynamic control. Thus, **8b** was treated with *t*-BuOK (0.1 equiv.) in THF at −10 to 4°C to give in 93% yield a mixture of **9a**–**d** (**9a**:**9b**:**9c**:**9d** = 5:5:2:2, as determined by ^{1}H NMR analysis[11]). Under these conditions, the geometry did not play any role in determining diastereoselectivity, and the ratio was due to the thermodynamic equilibrium. Although the desired **9a** was not predominant, chromatographic separation of diastereomers was possible, and the undesired three isomers (**9b**–**d**) could be recycled to the initial mixture by treatment with *t*-BuOK. By repeating this process three times, **9a** could be obtained in 68% yield.

After reduction of **9a** with DIBAL (98%), the aldehyde **10** was submitted to ene reaction by treatment with Me_2AlCl in CH_2Cl_2[12] to afford the cyclized product **11a**[13] (59%, **11a**:other isomers = 59:38). The hydroxy group of **11a** was protected as TBS ether (99%), and the resulting **11b** was converted to **12** in two steps (91%). The ketone **12** was treated with a chiral phosphonoacetate **13** developed by Fuji and his co-workers[14] in the presence of NaHMDS to give a mixture of **14a** and its *E*-isomer (91%; *E*:*Z* = ca. 1:4).[15] Reduction of **14a** with DIBAL was followed by SiO_2 chromatography to yield geometrically pure **14b** in 75% yield. The alcohol **14b** was then converted to the corresponding bromide **15a** (80%) and sulfone **15b** (ca. 90%) in the conventional manner. Initial attempts to dimerize **15a** by metal mediated homo-coupling of allylic halide[16,17] met with failure under several different conditions. However, the methodology employed for the synthesis of limatulones,[4] 'sulfone coupling', could be applied successfully to overcome the difficulty. Accordingly, **15b** was coupled with **15a** by treatment with KHMDS and 18-crown-6 in THF at −78°C to give the coupling product (84%),[18] which was subsequently employed for reductive desulfonylization to afford the dimerized product **16**. Final deprotection and careful chromatographic purification gave (+)-testudinariol A (**1**) (47% yield, two steps), $[\alpha]_D^{26} = +13.0$ ($c = 0.17$, $CHCl_3$) {Ref.[1] $[\alpha]_D^{25} = +15.2$ ($c = 0.3$, $CHCl_3$)}. Other physical and spectral data of synthetic **1**[19] were in good accord with those reported for the naturally occurring **1**. The overall yield was 4.4% based on **5** in 19 steps (Scheme 2).

In conclusion, the first synthesis of (+)-testudinariol A (**1**) was accomplished by starting from (*R*)-glycidol. The optimizations of each step and synthesis of testudinariol B (**2**) are in progress.

Acknowledgements

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5. Nozawa, D.; Takikawa, H.; Mori, K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2043.
6. Professor M. Kodama and his co-workers (Tokushima Bunri University, Japan) recently announced their synthesis of testudinariol A as an *E*/*Z* mixture: Kodama, M.; Hioki, H.; Yoshio, S.; Matsushita, M.; Hamano, M.; Kanehata, C.; Ohnishi, Y.; Umemori, Y.; Kubo, M.; Sakai, H. *Abstracts of Papers*, 42nd Symposium on the Chemistry of Natural Products, Okinawa, Nov. 6–8, 2000; pp. 235–240.
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8. Kodama, M.; Shiobara, Y.; Sumitomo, H.; Fukuzumi, K.; Minami, H.; Miyamoto, Y. *J. Org. Chem.* **1988**, *53*, 1437.
9. The described conditions achieved the best (*E*)-selectivity. However, it turned out that this geometry was not important for the diastereoselectivity in the later Michael-type cyclization.
10. A wide range of bases, NaH, LiH, K_2CO_3, Cs_2CO_3, TBAF, etc, and Lewis acids, $ZnCl_2$, $Sc(OTf)_3$, $TiCl_4$, etc. were examined under various conditions.
11. Structures of **9a** and **9b** were elucidated by ^{1}H NMR analyses of the corresponding alcohols after reduction of the ester portions. Those of **9c** and **9d** were also confirmed by a similar procedure (Fig. 2).

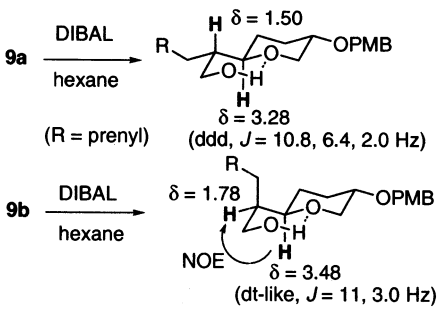

Figure 2.

12. (a) Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1989**, *111*, 6257; (b) Snider, B. B.; Rodini, D. J.; Karras, M.; Kirk, T. C.; Deutsch, E. A.; Cordova, R.; Price, R. T. *Tetrahedron* **1981**, *37*, 3927.
13. The ^{1}H NMR data and the results of NOE experiments of **11a** were in good accord with those of natural **1** concerning the cyclopentane portion.
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15. The NOE experiments strongly suggested that the major isomer possessed (*Z*)-geometry.
16. The following are the tested examples: K-naphthalenide in THF at −95°C; BaI_2, Li-biphenylide in THF at −78°C, etc. See: Yanagisawa, A.; Hibino, H.; Habaue, S.; Hisada, Y.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1263 and references cited therein.
17. Professor Kodama's group dimerized **15a** by treatment with $Ni(cod)_2$ and obtained a mixture of **16** and its isomer.[6]
18. It was noteworthy that the conventional conditions, *n*-BuLi in THF–HMPA, did not work at all, and the corresponding chloride did not react with **15b** completely even under our successful conditions.
19. Properties of synthetic (+)-**1**: colorless oil; $[\alpha]_D^{26}=+13$ ($c=0.17$, $CHCl_3$); IR ν_{max} ($CHCl_3$) 3680 (w, O–H), 1640 (w, C=C), 1075 (s, C–O) cm^{-1}; EIMS (*m*/*z*) 470, 452, 442, 434, 424, 370, 343, 327, 300, 234, 219; HREIMS obsd 470.3400 calcd for $C_{30}H_{46}O_4$ 470.3396; ^1H NMR (500 MHz, $CDCl_3$) $\delta=1.15$–1.28 (2H, m, 8/8′-H_a), 1.41 (2H, m, 5/5′-H_{ax}), 1.65–1.92 (8H, m, 5/5′-H_{eq}, 8/8′-H_b, 9/9′-H_2), 1.83 (6H, s, 12/12′-H_3), 1.91–2.03 (4H, m, 1/1′-H_a, 7/7′-H), 2.03–2.13 (2H, m, 1/1′-H_b), 2.17–2.27 (2H, m, 4/4′-H_a), 2.27–2.33 (2H, m, 4/4′-H_b), 2.40 (2H, ddd, $J=11.5$, 5.8, 5.5, 10/10′-H), 3.18 (2H, ddd, $J=10.4$, 8.5, 1.9, 6/6′-H), 3.73 (2H, d, $J=12.5$, 15/15′-H_{ax}), 4.15–4.20 (2H, m, 14/14′-H), 4.59 (2H, br d, $J=12.5$, 15/15′-H_{eq}), 4.81 (2H, s, 13/13′-H_a), 4.97 (2H, s, 13/13′-H_b), 5.16 (2H, br t, $J=5.8$, 2/2′-H); ^{13}C NMR (126 MHz, $CDCl_3$) $\delta=23.3$, 26.7, 27.1, 27.3, 32.0, 33.0, 52.0, 53.1, 66.7, 74.8, 80.7, 112.2, 123.4, 134.2, 144.4.