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Total synthesis of marine diterpenoid stolonidiol

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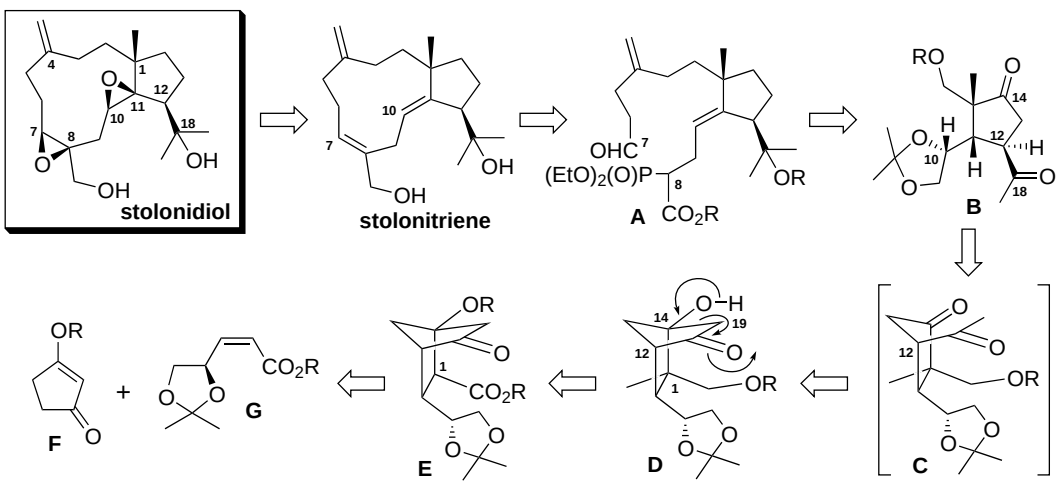
Abstract—Marine dolabellane diterpenoid stolonidiol was synthesized from L-ascorbic acid. The method for this total synthesis involves formation of the bicyclo[2.2.1]heptane derivative using a diastereoselective sequential Michael reaction, formation of cyclopentane derivative by the retro-aldol reaction and construction of an 11-membered carbocyclic ring through the intramolecular Horner–Wadsworth–Emmons reaction.

Stolonidiol and stolonitriene, isolated from the Okinawan marine soft coral *Clavularia* sp. by this laboratory, are dolabellane-type diterpenoids.[1,2] Most dolabellane-type diterpenoids possess *trans*-bicyclo[9.3.0]tetradecane and exhibit antimicrobial, antitumor and antiviral activity.[3,4] Stolonidiol is unique for multi biological activity and has been found to express potent cytotoxic activity toward P388 leukemia cells (IC_{50} 0.015 μg/mL) and ichthyotoxic activity toward killifish *Oryzias latipes* (minimum lethal concentration: 10 μg/mL).[1] Stolonidiol was recently noted to exhibit potent choline acetyltransferase (ChAT) inducible activity in primary cultured basal forebrain cells and clonal septal SN49 cells, suggesting a potent neurotrophic factor-like agent to be possibly present in the cholinergic nervous system.[2] These features prompted the present study for devising a method for the total synthesis of stolonidiol. The total synthesis[5,6] of, and synthetic studies[7] on, dolabellane-type diterpenoid have been reported, but no method is presently available for obtaining stolonidiol. The total synthesis of stolonidiol through application of the sequential Michael reaction, retro-aldol reaction and intramolecular Horner–Wadsworth–Emmons reaction as key steps is presented here.

The authors have been engaged in the synthesis of natural products using a bicyclic compound, prepared by sequential Michael reaction, as a chiral building



Scheme 1.

Keywords: antitumor compounds; marine metabolites; terpenes and terpenoids.

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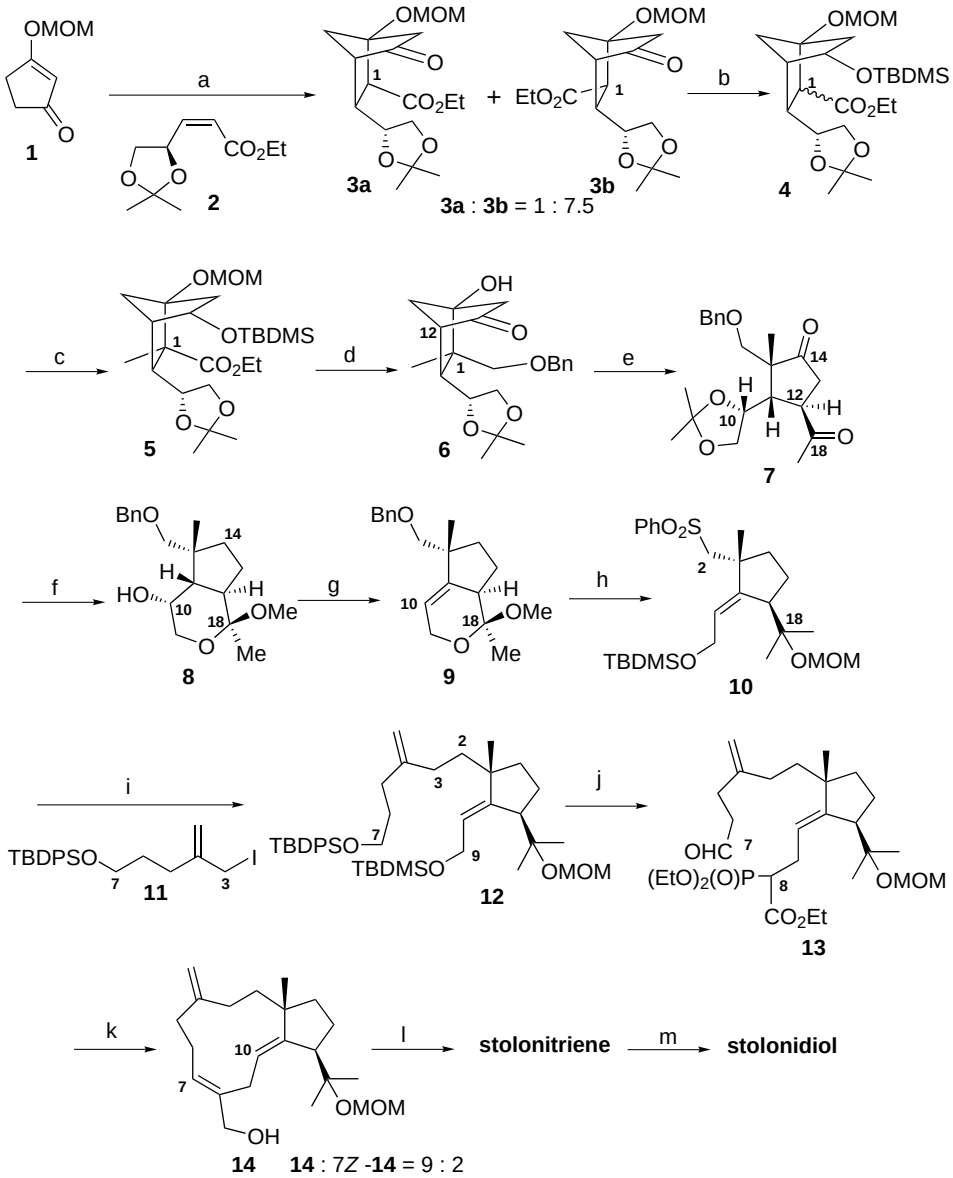
block.[5,8] This method was applied in this study for the total synthesis of stolonidiol. It was considered that the diastereoselective sequential Michael reaction of lithium enolate of cyclopentenone derivative **F** and chiral (*Z*)-α,β-unsaturated ester **G** would provide bicyclo[2.2.1]heptane derivative **E**. Bicyclic compound **E** would be converted to β-hydroxyketone **D**. Cleavage of the C(14)–C(19)[9] bond in β-hydroxyketone **D** by a retro-aldol reaction followed by epimerization at the C-12 position of diketone **C** would produce tetrasubstituted cyclopentane derivative **B**. Compound **B** would be converted to phosphono aldehyde **A** and intramolecular Horner–Wadsworth–Emmons reaction of phosphono aldehyde **A** would give dolabellane-type diterpenoid stolonitriene, a potential biogenetic precursor of stolonidiol. Finally, stereoselective epoxidation



Scheme 2. *Reagents and conditions*: (a) LDA, THF, −78°C, then **2**, −78°C to rt, 85%; (b) (1) $NaBH_4$, MeOH, 0°C; (2) TBDMSCl, imidazole, DMF, 97% (two steps); (c) LDA, THF, MeI, −78°C to rt, 86%; (d) (1) $LiAlH_4$, THF, 0°C; (2) BnBr, NaH, THF/DMF, 86% (two steps); (3) TBAF, DMF, 50°C; (4) BzCl, pyridine, rt; (5) TsOH, acetone, rt, 92% (three steps); (6) $LiAlH_4$, Et_2O, 0°C; (7) PDC, 4 Å MS, $CHCl_3$, rt, 85% (two steps); (e) K_2CO_3, MeOH, 40°C, 92%; (f) (1) TsOH, MeOH, rt, 98%; (2) H_2NNH_2, $O(CH_2CH_2OH)_2$, 130°C, then KOH, 205°C, 92%; (g) (1) TsCl, DMAP, $ClCH_2CH_2Cl$, rt; (2) DBU, toluene, reflux, 91% (two steps); (h) (1) Na, liq. NH_3/THF, −78°C, 88%; (2) PhSSPh, *n*-Bu_3P, pyridine, 40°C, 94%; (3) PPTS, THF/H_2O, rt; (4) MeLi, THF, −78°C, 80% (two steps); (5) TBDMSCl, imidazole, DMF, rt; (6) MOMCl, *i*-Pr_2NEt, $ClCH_2CH_2Cl$, rt; (7) TPAP, NMO, CH_3CN, rt, 85% (three steps); (i) (1) KHMDS, THF, 0°C, then **11**, 82%; (2) Na–Hg, MeOH, NaH_2PO_4, rt, 82%; (j) (1) PPTS, MeOH, rt, 81%; (2) NaH, Ph_3P, CBr_4, THF, then $(EtO)_2P(O)CH_2CO_2Et$, 75%; (3) TBAF, THF, rt; (4) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt, 68% (two steps); (k) (1) DBU, LiCl, 18-crown-6, CH_3CN, rt; (2) DIBAL-H, toluene, −78°C, 69% (two steps); (l) AcOH/H_2O (4:1), 40°C, 99%; (m) (1) Ac_2O, pyridine, rt; (2) TBHP, $VO(acac)_2$, CH_2Cl_2, rt; (3) K_2CO_3, MeOH, rt, 87% (three steps); (4) TBHP, L-(+)-DIPT, Ti(O-*i*-Pr)$_4$, CH_2Cl_2, −20°C, 95%.

of two olefins in stolonitriene would afford stolonidiol (Scheme 1).

Sequential Michael reaction of the enolate of cyclopentenone **1** with chiral (*Z*)-α,β-unsaturated ester **2**,[10] prepared from L-ascorbic acid, in THF at −78°C, gave bicyclo[2.2.1]heptane **3a** and **3b**[11] (**3a**:**3b** = 3: 1) in 73% yield (Scheme 2). A rise in reaction temperature from −78°C to rt produced bicyclo[2.2.1]heptane **3a** and **3b** (**3a**:**3b** = 1:7.5) in 85% yield. In this reaction, bicyclo[2.2.1]heptane **3a** was initially obtained at low temperature and bicyclo[2.2.1]heptane **3a** was isomerized to **3b** by thermodynamic control with a rise in reaction temperature, as confirmed by chemical conversion. Bicyclo[2.2.1]heptane **3a** was treated with LDA at −78°C and, with assumption of rt, bicyclo[2.2.1]heptane **3b** was obtained. Stereoselectivity in the sequential Michael reaction of **1** with the α,β-unsaturated ester **2** can be explained based on the transition state leading to **3a**: the dienolate of **1** approaches **2**, having a stable conformation, from the less hindered side with coordination between the lithium cation of dienolate of **1** and the carbonyl oxygen of **2** (Fig. 1).

With **3a** and **3b** still together, the ketone of **3ab** was reduced with $NaBH_4$ and the hydroxy group was protected as TBDMS ether to give silyl ether **4**. Lithium enolate of **4**, prepared from ester **4** and LDA, was reacted with MeI at −78°C to rt to give ester **5** as the sole product. Ester **5** was converted to β-hydroxyketone **6** in the following seven steps: (1) $LiAlH_4$ reduction to primary alcohol; (2) protection of the hydroxy group as Bn ether; (3) removal of TBDMS ether with TBAF to give a secondary alcohol; (4) protection of the hydroxy group as Bz ester; (5) removal of MOM ether with TsOH in MeOH; (6) reductive deprotection of Bz ester to a secondary alcohol; and (7) oxidation of this alcohol with PDC. Cleavage of the C(14)–C(19) bond in β-hydroxyketone **6** by retro-aldol reaction and then isomerization at the C-12 position proceeded smoothly by treatment with K_2CO_3 in MeOH at 40°C to give diketone **7** as the sole product. Selective protection of ketone at the C-18 position in **7** was then conducted by treatment with TsOH in MeOH to give methyl acetal, and ketone at the C-14 position was reduced by the Wolff–Kishner procedure[12] to afford alcohol **8**. The secondary hydroxy group of **8** was tosylated and subsequent treatment with DBU in toluene under reflux afforded dihydropyrane **9** equipped with requisite *E*-olefin. Dihydropyrane **9** was converted to sulfone **10**, which corresponds to the cyclopentane moiety of stolonidiol, as follows: (1) removal of the Bn group with Na in liq. NH_3 to alcohol; (2) conversion of the hydroxy group to phenyl sulfide with PhSSPh and n-Bu_3P in pyridine; (3) hydrolysis of methyl acetal to hemiacetal; (4) methylation with MeLi; (5) protection of the primary hydroxy group as TBDMS ether; (6) protection of the tertiary hydroxy group as MOM ether and (7) oxidation of sulfide to sulfone with TPAP and NMO.[13]

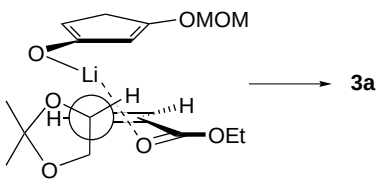


Figure 1.

Reaction of the anion of sulfone **10**, prepared from sulfone **10** and KHMDS, with allylic iodide **11**,[14] corresponding to the C(3)–C(7) segment, at 0°C in THF gave a coupling product and the phenylsulfonyl group was removed by treatment with Na–Hg in MeOH in the presence of NaH_2PO_4 to afford **12**. Silyl ether **12** was converted to aldehyde **13** via a coupling reaction with $(EtO)_2P(O)CH_2CO_2Et$ in four steps: (1) selective deprotection of the TBDMS group with PPTS to give allylic alcohol; (2) treatment with CBr_4 and Ph_3P in the presence of NaH and then $(EtO)_2P(O)CH_2CO_2Et$ to give a coupling product through in situ bromination; (3) deprotection of TBDPS group with TBAF; and (4) oxidation of the primary hydroxy group with Dess–Martin periodinane.[15] Intramolecular Horner–Wadsworth–Emmons reaction of aldehyde **13** was carried out by treatment with DBU in the presence of LiCl and 18-crown-6 in CH_3CN at rt to afford a mixture of geometric isomers of α,β-unsaturated esters.[16] The mixture was treated with DIBAL-H to give allylic alcohol **14** and the 7*Z* isomer of **14** (**14**: 7*Z* isomer of **14** = 9:2) in 69% yield (two steps). Following the separation of these compounds from each other, removal of the MOM group in **14** was carried out by treatment with $AcOH/H_2O$ (4:1) at 40°C to give stolonitriene. Spectral data and the sign of optical rotation of synthetic stolonitriene were identical with those of natural stolonitriene.[2] Finally, total synthesis of stolonidiol was accomplished by following stepwise stereoselective epoxidation of stolonitriene:[17] (1) selective acetylation of the primary hydroxy group; (2) diastereoselective epoxidation of the olefin at C-10 with TBHP and $VO(acac)_2$;[18] (3) deacetylation with K_2CO_3 in MeOH; and (4) asymmetric epoxidation of the olefin at C-7 with TBHP, L-(+)-DIPT and $Ti(O\text{-}i\text{-}Pr)_4$[19] to give stolonidiol, $[\alpha]_D^{26}$ −32.0° (*c* 0.2, $CHCl_3$). Spectral data and the sign of optical rotation of synthetic stolonidiol were identical with those for natural stolonidiol, $[\alpha]_D$ −31.6° (*c* 1.4, $CHCl_3$).[1]

Acknowledgements

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