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An efficient and stereoselective construction of the C(9)–C(17) dihydropyran segment of swinholides A–C via a novel reductive cleavage of an epoxy aldehyde

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Abstract

An efficient and highly stereoselective construction of the C(9)–C(17) dihydropyran segment of swinholides A–C, which involves a novel reductive cleavage of an epoxy aldehyde by an organoselenium reagent and the intramolecular conjugate addition of an acetal alkoxide anion of δ-hydroxy-α,β-unsaturated ester as the key steps, is described.

Keywords: swinholides; pyrans; stereocontrol; reduction; epoxides; aldehydes.

The marine natural products swinholides A (**1**), B (**2**) and C (**3**), 44-membered dimeric macrolides isolated from the Okinawan marine sponge *Theonella swinhoei*,[1] have been revealed to exhibit potent cytotoxicity against a variety of human carcinoma cell lines, as well as a broad spectrum of antifungal activity.[1–3]

Their structures are characterized by the C_2-symmetrical dimeric macrolides in which two polypropionate-derived chains, including a gigantic lactone ring, take axial orientation on a tetrahydropyran ring. Their unique structures and potent anticancer activities have elicited much attention from synthetic organic chemists.[4,5]

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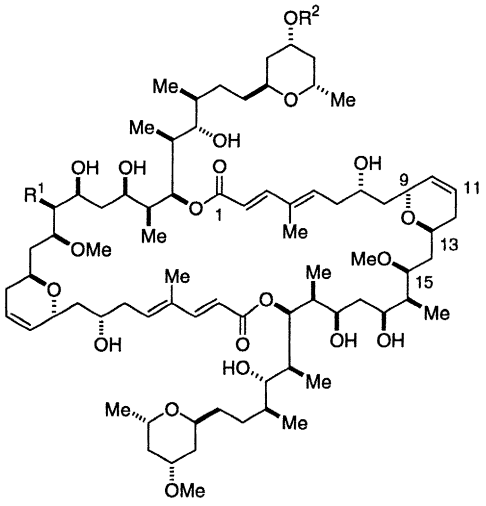
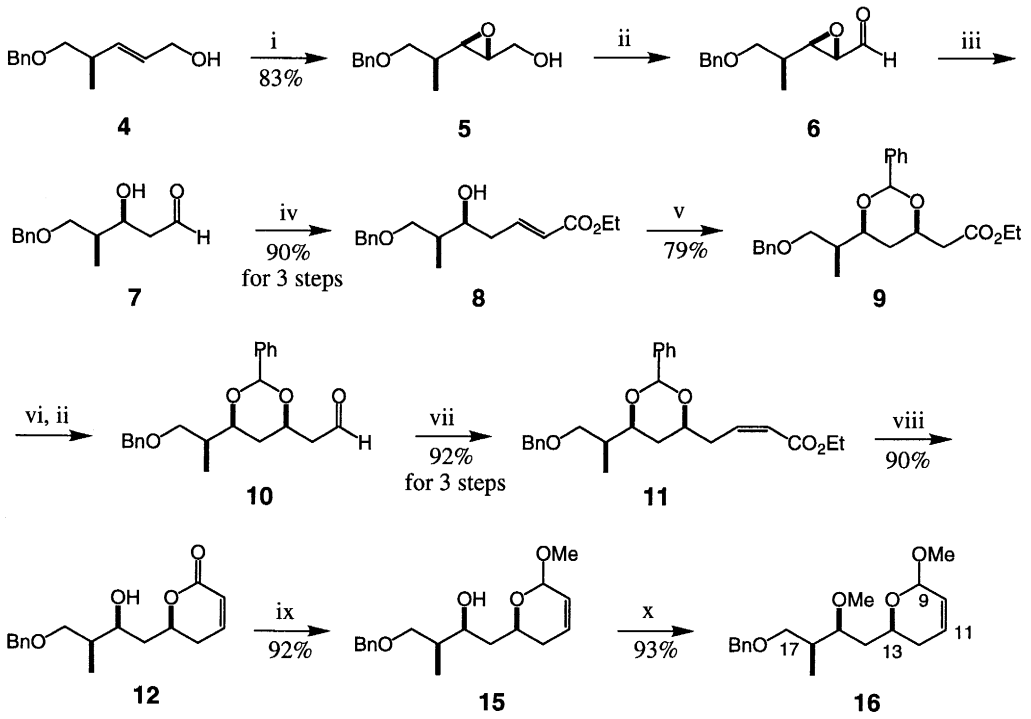


Swinholide A (**1**): n=1, R^1=R^2=Me
Swinholide B (**2**): n=1, R^1=H, R^2=Me
Swinholide C (**3**): n=1, R^1=Me, R^2=H

As part of our synthetic program toward the polypropionate-derived bioactive compounds possessing characteristic sequences of alternating methyl- and hydroxyl-substituted carbons,[6] we undertook asymmetric total synthesis of the swinholide family. We report here an efficient and highly stereoselective synthetic route to the C(9)–C(17) dihydropyran segment of swinholides A–C (**1**–**3**) which involves the chemo- and regio-selective reductive cleavage of an epoxy aldehyde by an organoselenium reagent and the intramolecular conjugate addition of an acetal alkoxide anion of δ-hydroxy-α,β-unsaturated ester as the key steps.

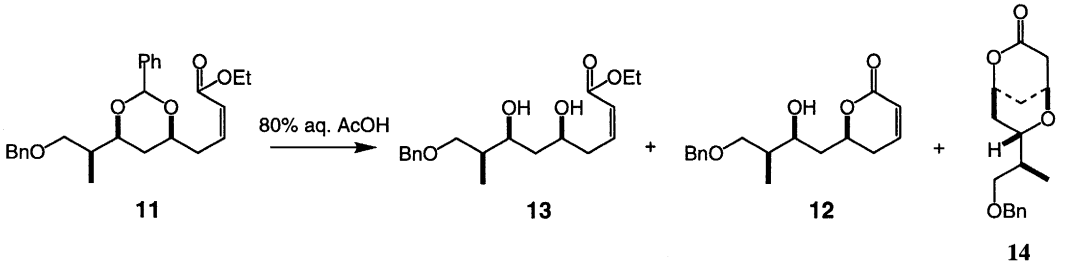
The starting material **4**, a chiral allylic alcohol easily available from (*S*)-3-benzyloxy-2-methylpropanol,[7] was subjected to the Katsuki–Sharpless asymmetric epoxidation[8] with D-(−)-ethyl tartrate to give the β-epoxy alcohol **5** in 83% yield (Scheme 1). The resulting alcohol **5** was converted to the epoxy aldehyde **6** by Swern oxidation, which was directly submitted to the regioselective reductive cleavage of an epoxide, a key step in the present synthesis, in order to lead to the β-hydroxy aldehyde **7**. Although the reductive cleavage of an epoxide in the presence of an aldehyde function seems very difficult, this key step was carried out by the organoselenium-mediated reduction methodology recently developed by us.[9] Thus, on treatment of the epoxy aldehyde **6** with sodium (phenylseleno)triethylborate[9] (5 equiv.), a selenium reagent easily prepared by reduction of diphenyldiselenide with sodium borohydride in ethanol, and acetic acid (7 equiv.) in ethanol at 0°C for 1 h, chemoselective reductive cleavage of the epoxide occurred cleanly and regioselectively, giving rise to the desired β-hydroxy aldehyde **7**, which was directly subjected to Horner–Emmons reaction with triethyl phosphonoacetate to afford the δ-hydroxy-α,β-unsaturated ester **8** in 90% isolated yield for the three steps. Subsequent conversion of **8** into the benzylidene acetal **9** was successfully performed according to the Evans protocol,[10] namely, by treatment with benzaldehyde and *t*-BuOK in THF at 0°C, in 79% yield. The acetal ester **9** thus obtained was transformed into the *cis*-unsaturated ester **11** by a three-step reaction sequence: (i) reduction with lithium aluminum hydride in Et_2O; (ii) Swern oxidation; (iii) *Z*-selective Horner–Emmons reaction of the resulting aldehyde **10** with ethyl (di-*o*-tolylphosphono)acetate, the Ando reagent[11] in 92% overall yield. In this Horner–Emmons reaction, the desired *cis*-unsaturated ester **11** was exclusively formed.

With the key intermediate **11** in hand, we presumed that subsequent lactonization to **12** would readily



Scheme 1. *Reagents*: (i) $Ti(O^iPr)_4$, D-(−)-DET, TBHP, CH_2Cl_2, −20°C; (ii) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C, then Et_3N; (iii) $Na[PhSeB(OEt)_3]$ (5 equiv.), AcOH (7 equiv.), EtOH, 0°C; (iv) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0°C, then aldehyde, 0°C; (v) C_6H_5CHO, *t*-BuOK, THF, 0°C; (vi) $LiAlH_4$, Et_2O, 0°C; (vii) $(o\text{-}CH_3C_6H_4O)_2P(O)CH_2CO_2Et$, NaH, THF, −78~0°C; (viii) 80% aq. AcOH, 60°C, 12 h; (ix) DIBAL-H, CH_2Cl_2, −78°C, then CSA in MeOH; (x) KH, CH_3I, THF, 0°C~rt

occur under normal hydrolytic conditions. However, this conversion was found to be susceptible to the hydrolytic conditions since the lactone **12** formed in situ was readily transformed into the bicyclic compound **14** under the conditions by way of the intramolecular conjugate addition of the hydroxyl group. Therefore, we investigated minutely the conditions for lactonization. The results are listed in Table 1. As shown, the conversion of **11** to **12** was found to be highly dependent on the reaction temperature as well as the reaction time. Eventually, we found that the reaction conditions in entry 4 were optimal for the present lactonization, resulting in the formation of 90% isolated yield of the hydroxy lactone **12**.



Conversion of **12** to the target molecule **16** was successfully performed by the following two-step reaction sequence: (i) reduction with diisobutylaluminum hydride (DIBAL-H) in CH_2Cl_2 followed by treatment with methanolic 10-camphorsulfonic acid; (ii) methylation with potassium hydride and MeI in THF, in 85% overall yield. The product was a 4:1 anomeric mixture. Thus, an efficient and highly stereoselective synthetic route to the C(9)–C(17) dihydropyran segment of swinholides A–C (**1**–**3**) has been established.[12] Stereoselective alkylation at the C(9) position has been reported by several groups.[4,5]

Table 1
Reaction of **11** with 80% aq. AcOH

entry	concentration (ml/ mmol)	temp. (°C)	time (h)	yield (%) **13**	**12**	**14**
1	40	50 - 60	3	> 90		
2	40	60	4	55	45	
3	40	60	11		86	
4	40	60	12		90	
5	40	60 - 70	35		56	44
6	20	73	18		33	67
7	40	75	22		68	32
8	40	100	12			> 90

The present method should also provide a facile entry to a variety of δ-hydroxy-α,β-unsaturated esters and 1,3-*syn*-polyols as well as *syn*-7-hydroxy-α,β-unsaturated-δ-lactones.

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12. Compound **12**: ^{1}H NMR (270 MHz, $CDCl_3$): 0.95 (3H, d, *J*=7.2 Hz), 1.73 (1H, ddd, *J*=13.9, 7.3, 3.1 Hz), 1.95 (1H, m), 2.05 (1H, ddd, *J*=13.9, 10.1, 5.6 Hz), 2.44 (2H, m), 2.94 (1H, d, *J*=4.6 Hz), 3.51 (1H, dd, *J*=8.9, 6.6 Hz), 3.60 (1H, dd, *J*=8.9, 4.3 Hz), 3.99 (1H, dddd, *J*=7.4, 5.6, 4.6, 3.1 Hz), 4.51 (2H, s), 4.69 (1H, dddd, *J*=10.1, 7.3, 6.9, 5.9 Hz), 6.02 (1H, dt, *J*=9.7, 1.8 Hz) and 6.88 (1H, ddd, *J*=9.7, 5.2, 3.2 Hz).