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Synthetic Studies on Altohyrtins (Spongistatins): Synthesis of the C1-C14 (AB) Spiroacetal Portion

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Abstract

The C1-C14 portion of altohyrtins (spongistatins) was prepared in a convergent manner from 3,4,6-tri-*O*-acetyl-D-glucal via a chelation-controlled methylation of ketone, dithiane couplings with epoxides, and a thermodynamically-controlled spiroacetalization.

Keywords: Carbohydrates; Dithianes; Epoxides; Spiro compounds

The altohyrtins [1~4], the spongistatins [5~10], and cinachyrolide A [11] have been isolated from marine sponges by the Kitagawa, Pettit, and Fusetani groups, respectively. These macrolides exhibit extremely potent antitumor activities against a number of human cancer cell lines. Their exciting structures (the spongipyran framework, Fig. 1) and prominent biological activities have promoted a number of synthetic studies [12~22]. Very recently, the Evans [23~25] and Kishi [26, 27] groups have independently succeeded in the total synthesis of altohyrtin C (spongistatin 2) and altohyrtin A (spongistatin 1), respectively, so that the Kitagawa altohyrtin structural assignment and the identities of altohyrtin A with spongistatin 1 and altohyrtin C with spongistatin 2 were unambiguously verified. We now report in this letter the synthesis of the C1-C14 (AB) spiroacetal portion of altohyrtins (spongistatins) from the commercially-available carbohydrate, 3,4,6-tri-*O*-acetyl-D-glucal, as a chiral building block.

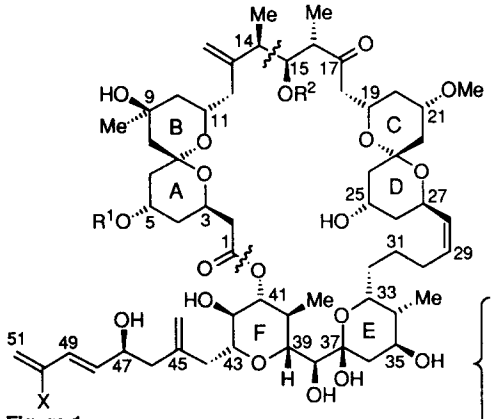
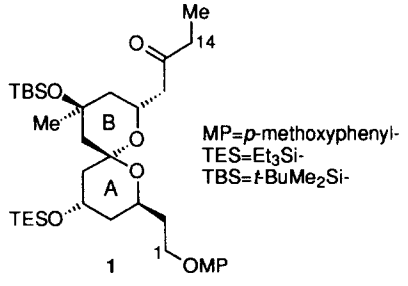


Figure 1



Altohyrtin A (Spongistatin 1): X=Cl, R^1=R^2=Ac
Altohyrtin B: X=Br, R^1=R^2=Ac
Altohyrtin C (Spongistatin 2): X=H, R^1=R^2=Ac
5-Desacetylaltohyrtin A (Spongistatin 3): X=Cl, R^1=H, R^2=Ac
Cinachyrolide A (Spongistatin 4): X=Cl, R^1=Ac, R^2=H

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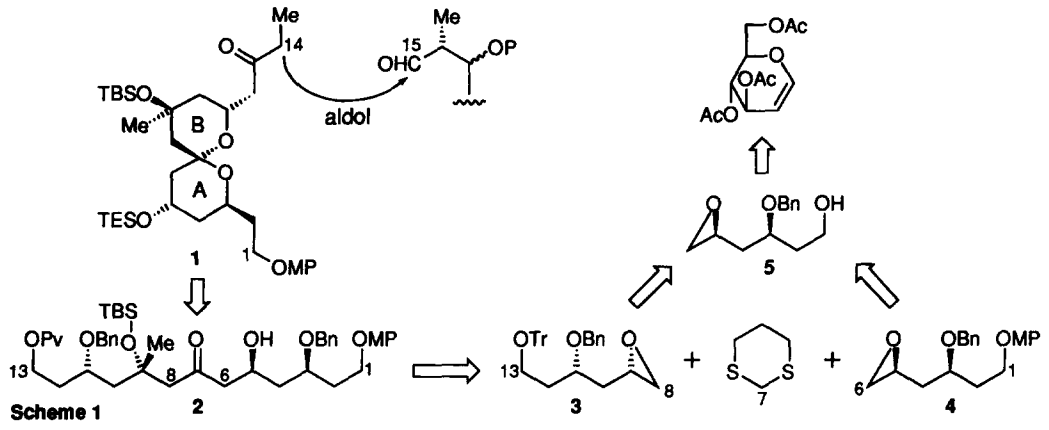
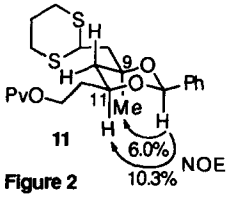


Scheme 1

We envisioned that the three consecutive stereocenters of C14, 15, and 16 should be constructed by the aldol reaction between the *Z*-enolate derived from the C1-C14 ethyl ketone and α-methyl substituted aldehyde (Scheme 1). After the aldol coupling, the methylenation at the C13-position should provide the actual form. Ethyl ketone **1** would be obtained from the acyclic precursor **2** by the thermodynamically controlled-spiroacetalization followed by the C14-elongation. It was expected that **2** would be obtained from the C7-dithiane unit and two epoxides, **3** and **4**. Both **3** and **4** are derived from the common intermediate **5**, which in turn is available from 3,4,6-tri-*O*-acetyl-D-glucal.

Epoxy ester **6** [28], prepared in large quantities from 3,4,6-tri-*O*-acetyl-D-glucal in the six known steps, was chemoselectively reduced with DIBALH and $NaBH_4$ to afford the common intermediate epoxy alcohol **5**[1] in 88% yield (Scheme 2). Protection of **5** as its *p*-methoxyphenyl (MP) ether by the Fukuyama procedure [29] furnished the C1-C6 epoxide **4**[1] in 72% yield. On the other hand, **5** was protected as its trityl ether (96% yield) and the resulting C8-C13 epoxide **3**[1] was treated with 2-lithio-1,3-dithiane followed by oxidation with o-iodoxybenzoic acid (IBX) [30] to afford **7**[1] in 96% yield. In order to introduce the C9-methyl group, stereoselective methylation of **7** under the chelation-controlled conditions was thoroughly investigated and it was found that MeMgCl in 1:1 THF-ether was the best so far, giving a 6.7:1 mixture of **8**[1] and its C9-epimer in 96% combined yield. The desired **8** was deprotected with BCl_3 and the resulting triol (64% yield) was subjected to benzylidenation to afford **9**[1] (11,13-benzylidene) and its positional isomer (9,11-benzylidene) in 63% and 9% yields, respectively, together with the recovered triol (9% yield). Silylation of **9** furnished the C7-C13 dithiane derivative **10**[1] in 98% yield. The C9-configuration was verified by ^1H NMR NOE measurements of **11** (Fig. 2), which was obtained from the positional isomer (9,11-benzylidene) of **9** by pivaloylation.



11 **Figure 2**

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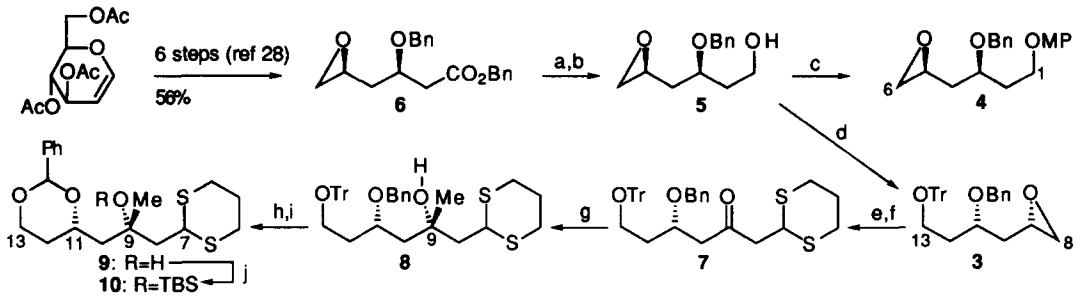
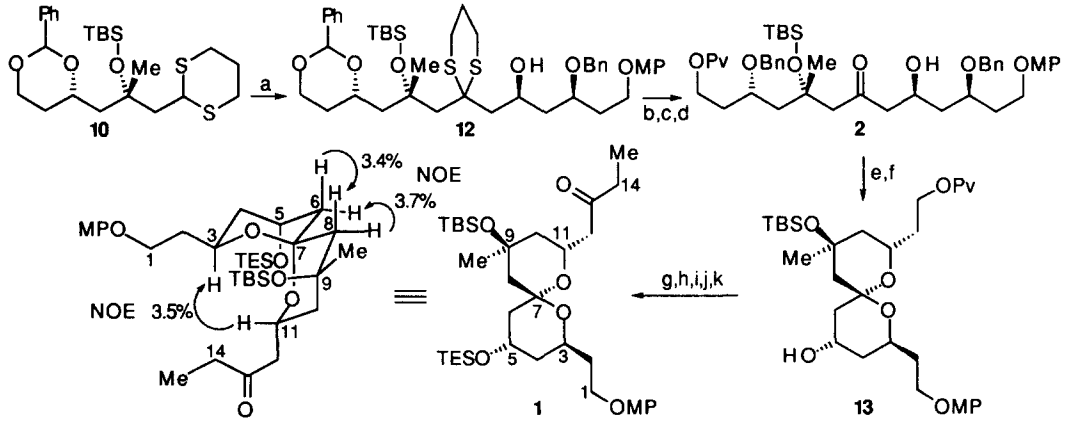
1) Satisfactory analytical data (NMR and IR spectra, elemental analyses, optical rotations) were obtained for all new compounds.



Scheme 2. (a) DIBALH, toluene, -78 °C, 0.5 h; (b) $NaBH_4$, MeOH, 0 °C, 0.5 h, 88%; (c) (*p*-MeO)PhOH, Bu_3P, DIAD, THF, 80 °C, 2 h, 72%; (d) TrCl, Et_3N, CH_2Cl_2, rt, 2 h, 96%; (e) 1,3-dithiane, *n*-BuLi, HMPA, THF, -20 °C, 2 h, then **3** in THF, -20 °C, 2 h; (f) IBX, 1:1 DMSO-THF, rt, 5 h, 96%; (g) MeMgCl, 1:1 THF-ether, rt, 1h, 83%; (h) BCl_3, 1,3-propanedithiol, CH_2Cl_2, rt, 1 h, 64%; (i) $PhCH(OMe)_2$, PPTS, CH_2Cl_2, rt, 2 d, 63%; (j) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 1 h, 98%.

We first planned the segment coupling between epoxide **4** and the C9-TBS ether of **8**. Anion formation of the latter was investigated by D_2O quenching under a variety of conditions. However, no indicative D-incorporation was observed. In contrast, the dithiane derivative **10** was smoothly lithiated with *n*-BuLi and the resulting anion was treated with epoxide **4** to afford the coupling product **12**[1] in 85% yield (Scheme 3). This was transformed to the acyclic precursor **2**[1] by reductive cleavage of the benzylidene group with DIBALH, pivaloylation of the primary hydroxy group, and de-dithioacetalization with $Hg(ClO_4)_2$ [31, 32] in 65% overall yield. Debenzylation of **2** followed by spiroacetalization with CSA in 1:1 CH_2Cl_2-MeOH afforded spiroacetal **13**[1] in 71% yield as the only cyclized product. Finally, the 5-step sequence of reactions of **13** gave the desired ethyl ketone **1**[1] in 63% overall yield. The stereochemical assignment of the spiroacetal part in **1** was determined by ^1H NMR NOE measurements.



Scheme 3. (a) *n*-BuLi, HMPA, THF, -20 °C, 1 h, then **4** in THF, -20 °C, 0.5 h, 85%; (b) DIBALH, CH_2Cl_2, rt, 1 h; (c) PvCl, Et_3N, CH_2Cl_2, rt, 10 h; (d) $Hg(ClO_4)_2$, $CaCO_3$, 9:1 THF-H_2O, 0 °C, 10 min, 65%; (e) H_2, Pd/C, EtOAc, rt, 14 h; (f) CSA, 1:1 CH_2Cl_2-MeOH, rt, 1 h, 71%; (g) TESCl, imidazole, DMF, rt, 1 h; (h) DIBALH, CH_2Cl_2, -78 °C, 10 min; (i) Dess-Martin periodinane, pyridine, CH_2Cl_2, rt, 2 h; (j) EtMgBr, ether, 0 °C, 0.5 h; (k) Dess-Martin periodinane, pyridine, CH_2Cl_2, rt, 1 h, 63%.

The convergent synthesis described herein makes available the C1-C14 (AB) spiroacetal portion of altohyrtins (spongistatins) in significant quantities. The aldol reaction of this ethyl ketone **1** with an appropriate aldehyde is now in progress.

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