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Synthetic studies on altohyrtins (spongistatins): synthesis of the C15–C28 (CD) spiroacetal portion

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Abstract

The C15–C28 portion of altohyrtins (spongistatins) was prepared in a convergent manner from methyl (*S*)-3-hydroxy-2-methylpropionate, D-arabitol, and diacetone-D-glucose via dithiane couplings with epoxides as the key segment coupling process.

Keywords: altohyrtins; dithianes; epoxides; spiro compounds.

We have recently reported the synthesis of the C1–C14 (AB) spiroacetal portion **1** of altohyrtins (spongistatins) from the commercially-available carbohydrate, 3,4,6-tri-*O*-acetyl-D-glucal, as a chiral building block (Fig. 1).[1] We now report in this letter the synthesis of the C15–C28 (CD) spiroacetal portion **2**. The altohyrtins, spongistatins, and cinachyrolide A have been isolated from marine sponges by the Kitagawa, Pettit, and Fusetani groups, respectively.[2] Their extremely potent antitumor activities and unique, exciting structures have promoted a number of synthetic studies.[3] Recently, the Evans and Kishi groups have independently succeeded in the total synthesis of altohyrtin C (spongistatin 2) and altohyrtin A (spongistatin 1), respectively.[3]

We envisioned that the three consecutive stereocenters of C14, 15, and 16 should be constructed by an aldol reaction. The C1–C14 ethyl ketone **1**[1] was prepared for a candidate of the ketone segment. We selected the C15–C28 aldehyde **2** as an aldehyde candidate (Fig. 1). Since stereoselectivity of the aldol reactions between the structurally complex ethyl ketones and α-methyl-β-alkoxyaldehydes is generally capricious,[4] it is difficult to correctly predict the influence of the C17-configuration in **2** on the selectivity of our aldol reaction. Therefore, it is essential for future success to obtain both compounds **2a** and **2b**. Aldehydes **2a** or **2b** would be obtained from the acyclic precursors **4a** or **4b** via spiroacetals **3a** or **3b** (Scheme 1). It was expected that **4a** or **4b** would be obtained from three segments, the C15–C17 dithiane derivative **5**, the C18–C22 diepoxide **6**, and the C23–C28 dithiane derivative **7**. The dithiane derivative **5**

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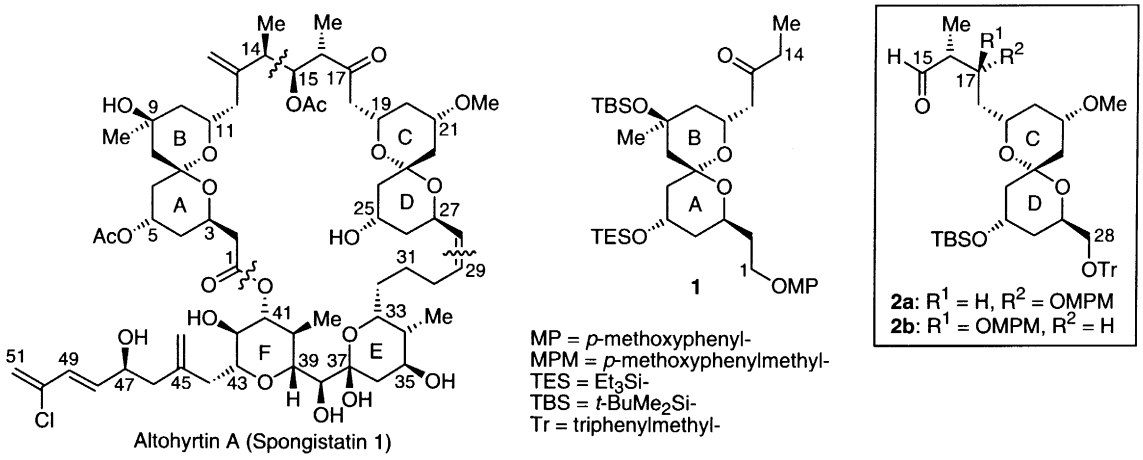
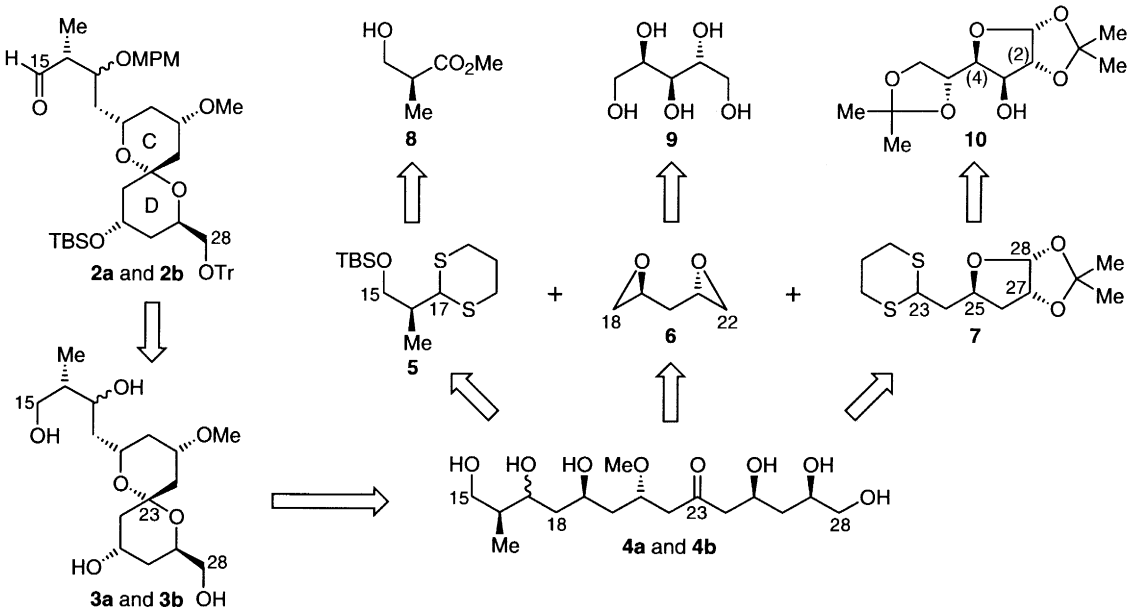


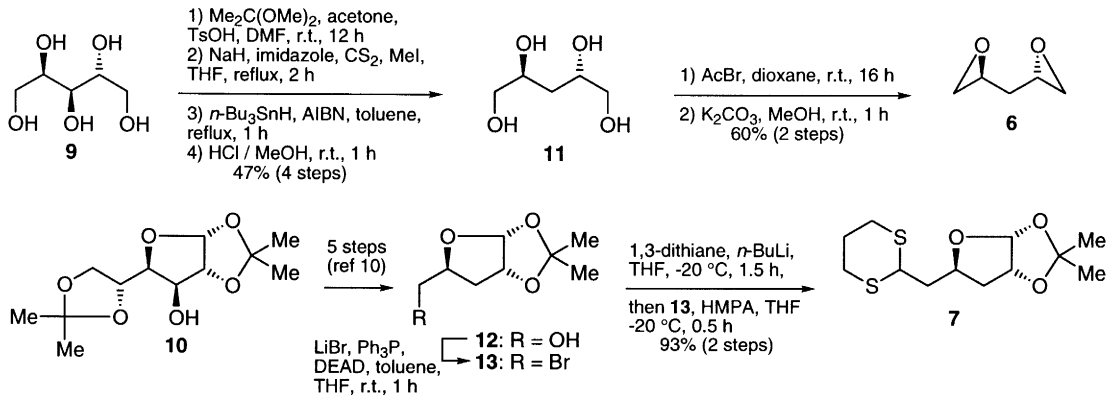
Fig. 1.

is known[5] and can be prepared from methyl (*S*)-3-hydroxy-2-methylpropionate (**8**). Diepoxide **6** is also known[6] but we prepared it from D-arabitol (**9**) via a new route. The dithiane derivative **7** was prepared from diacetone-D-glucose (**10**); the C2- and C4-hydroxy groups of the latter can be used as the C27- and C25-hydroxy groups of **4a** or **4b**.



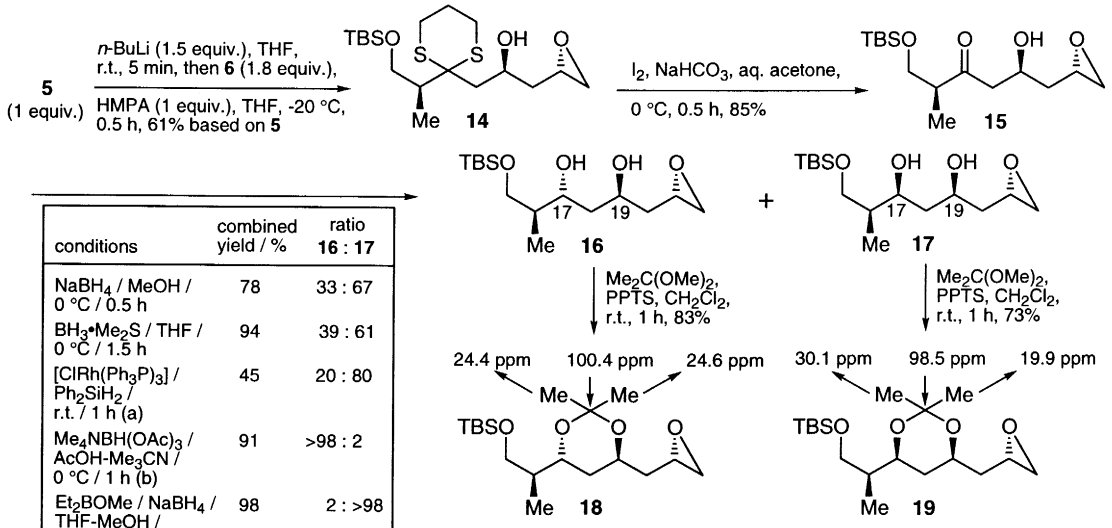
Scheme 1.

To obtain diepoxide **6**,[6] we first prepared tetraol **11** by Sakai's procedure[7] with modifications (Scheme 2). D-Arabitol (**9**) was subjected to selective acetonization followed by deoxygenation and deacetonization to afford tetraol **11** in 47% yield from **9**. Acetyl-bromination[8] of **11** followed by alkaline treatment gave the desired diepoxide **6** in 60% yield.[9] The dithiane derivative **7** was prepared from **10** as follows. Following the literature procedure,[10] **10** was transformed into the known **12**. Bromination of **12** gave bromide **13**,[11] which underwent smooth addition by 2-lithio-1,3-dithiane, giving **7**[11] in 93% yield from **12**.



Scheme 2.

The coupling of the anion derived from **5**[5] (1 equiv.) and *n*-BuLi (1.5 equiv.) with diepoxide **6** (1.8 equiv.) afforded **14**[11] in 61% yield based on **5** (Scheme 3).[12] De-dithioacetalization of **14** with I_2 in aq. acetone[13] gave ketone **15** in 85% yield. The stereo- and chemoselective reduction of the carbonyl group in epoxy-ketone **15** was next investigated. The relevant data are shown in Scheme 3. The C17,19-*anti* product **16** was obtained by using $Me_4NBH(OAc)_3$[14] in 91% yield as the only reduction product without any epoxide opening. In contrast, the C17,19-*syn* product **17** was obtained as the only reduction product by using $Et_2BOMe–NaBH_4$[15] in 98% yield. The stereochemistries of **16** and **17** were confirmed by ^{13}C NMR analysis[16] of their acetonides, **18**[11] and **19**.[11]



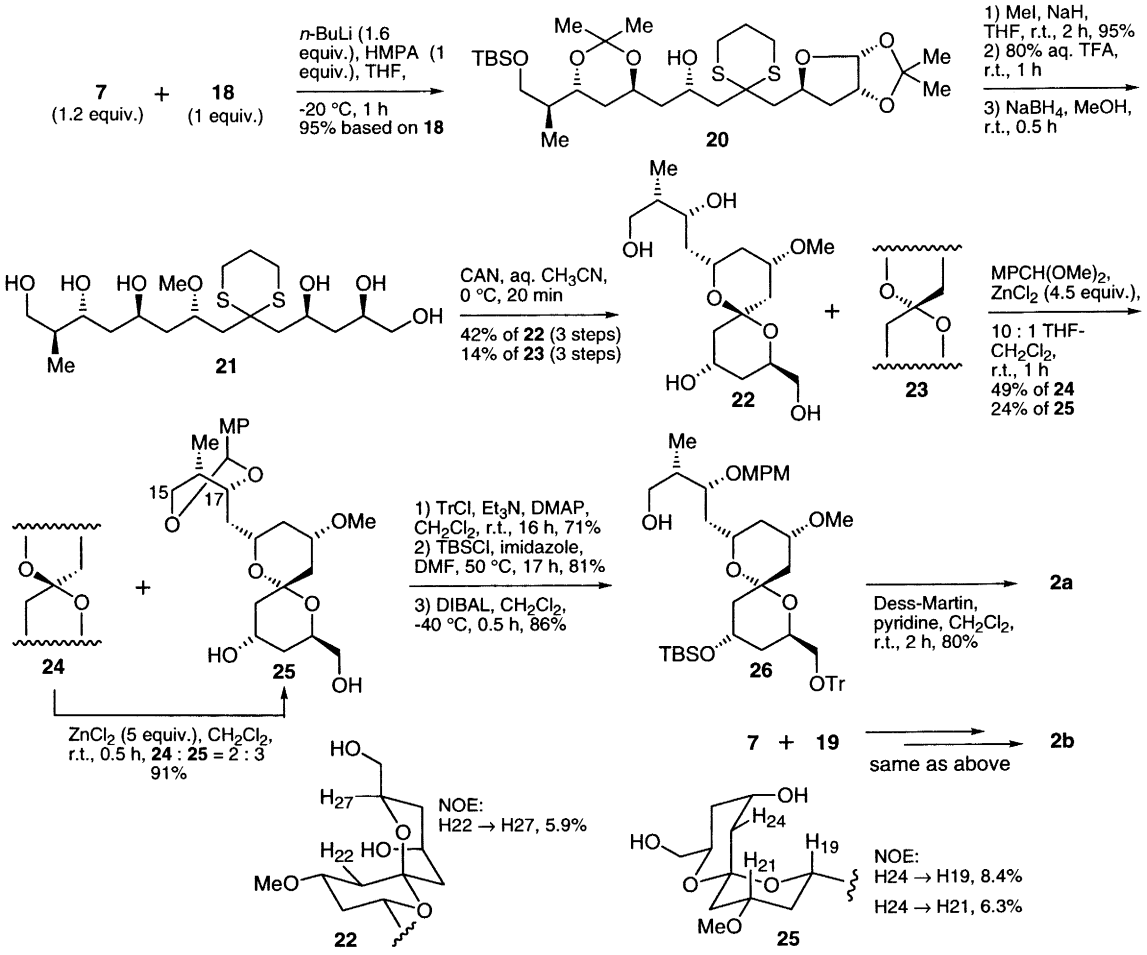
conditions	combined yield / %	ratio **16** : **17**
$NaBH_4$ / MeOH / 0 °C / 0.5 h	78	33 : 67
$BH_3•Me_2S$ / THF / 0 °C / 1.5 h	94	39 : 61
$[ClRh(Ph_3P)_3]$ / Ph_2SiH_2 / r.t. / 1 h (a)	45	20 : 80
$Me_4NBH(OAc)_3$ / AcOH-Me_3CN / 0 °C / 1 h (b)	91	>98 : 2
Et_2BOMe / $NaBH_4$ / THF-MeOH / -78 °C / 2 h (c)	98	2 : >98

(a) See ref. 19. (b) See ref. 14. (c) See ref. 15.

Scheme 3.

The second dithiane coupling was conducted by the addition of *n*-BuLi (1.6 equiv.) to the mixture of **7** (1.2 equiv.), epoxide **18** (1.0 equiv.), and HMPA (1.0 equiv.) in THF at −20°C, giving the adduct **20**[11] in 95% yield (Scheme 4). Methylation of **20** (95%) followed by deprotection and reduction gave **21**. De-dithioacetalization of **21** with ammonium cerium(IV) nitrate (CAN)[17] gave, with concomitant spiroacetalization, the unnatural spiroacetal **22**[11] and the desired spiroacetal **23**[11] in 42 and 14% yields,

respectively. The spiroacetal configuration of **22** was verified by ^{1}H NMR NOE measurements as shown in Scheme 4. All attempts to effect isomerization of **22** into **23** under protic and Lewis acid conditions resulted in a ca. 1–3:1 equilibrium mixture of **22** and **23**. Moreover, it was found that the next *p*-methoxybenzylidenation of the C15- and C17-hydroxy groups in each spiroacetal **22** and **23** was accompanied by partial isomerization at the spiroacetal center. Therefore, this equilibration was tried at the next stage. The 3:1 mixture of **22** and **23** was treated with *p*-methoxybenzaldehyde dimethyl acetal and $ZnCl_2$ in 10:1 THF–CH_2Cl_2 at rt for 1 h to afford a separable mixture of **24**[11] and **25**[11] in 49 and 24% yields, respectively. The spiroacetal configuration of **25** was verified by ^{1}H NMR NOE measurements as shown in Scheme 4. At this stage, the isomerization of **24** into **25** was best achieved by subjecting **24** to the conditions of $ZnCl_2$[3n] (5 equiv.) in CH_2Cl_2 (rt, 0.5 h), giving a 2:3 mixture of **24** and **25** in 91% combined yield. The obtained **25** was converted to aldehyde **2a** by standard transformations. On the other hand, the isomer **19** was also converted to **2b** by almost the same procedures as described above for the case of **18**.[18,19]



Scheme 4.

The convergent synthesis described herein makes available the C15–C28 (CD) spiroacetal portion of the altohyrtins (spongistatins) in significant quantities. The aldol reaction of the ethyl ketone **1** with this aldehyde **2** and the preparation of the complete C1–C28 portion are now in progress.

Acknowledgements

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