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Formal total synthesis of altohyrtin C (spongistatin 2). Part 1: Aldol approach to unite AB and CD spiroacetals

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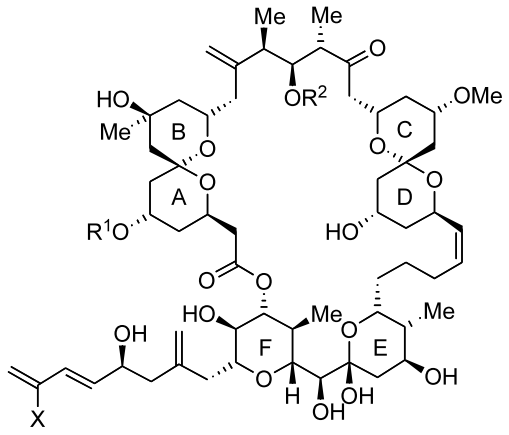
Abstract—The Mukaiyama aldol coupling of the second-generation C1–C14 (AB) fragment of altohyrtins (spongistatins) with the model α-methyl-β-alkoxyaldehydes revealed that the stereochemistry at the newly formed carbon centers was controlled by the β-alkoxy chiral center of the model aldehydes. The union of the AB fragment with the C15–C28 (CD) fragment under the same conditions gave the fully elaborated C1–C28 (ABCD) subunit in good yield.

The altohyrtins, spongistatins, and cinachyrolide A (**1**–**4**) were isolated from marine sponges by the Kitagawa, Pettit, and Fusetani groups, respectively (Fig. 1).[1] The structural complex family of macrolides displays extremely potent antitumor activities against several tumor cell lines. Since their isolation in 1993, many synthetic groups have focused on the total synthesis in this area.[2–18] The relative and absolute stereochemistries of the family, which were established on the basis of extensive spectroscopic analyses of natural samples, were confirmed via the total syntheses of altohyrtin C (spongistatin 2) (**3**) by Evans[2] and altohyrtin A (spongistatin 1) (**1**) by Kishi.[3] After their elegant total syntheses, Smith,[4] Paterson,[5] and Crimmins[6] have also achieved the total synthesis of the altohyrtin family.

As part of our program directed toward the total synthesis of the altohyrtins,[19] we previously reported the synthesis of the C1–C14 (AB)[19a] and the C15–C28 (CD) spiroacetals[19b] as well as the C29–C44 (EF) bis-tetrahydropyran.[19c] We envisioned that the three consecutive stereochemistries on C14-C16 in the ABCD fragment **5**, having the unnatural C23 configuration,[20] should be constructed by an aldol coupling of the AB silyl enol ether **6** and the CD aldehyde **7** (Fig. 2). As it is difficult to predict the influence of the C17 configuration in **7** on the stereoselectivity of the aldol reaction, we first examined the coupling of **6** with the model aldehydes **8** and **9**.



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

Figure 1.

Keywords: altohyrtins; spongistatins; stereoselective synthesis; aldol reaction.

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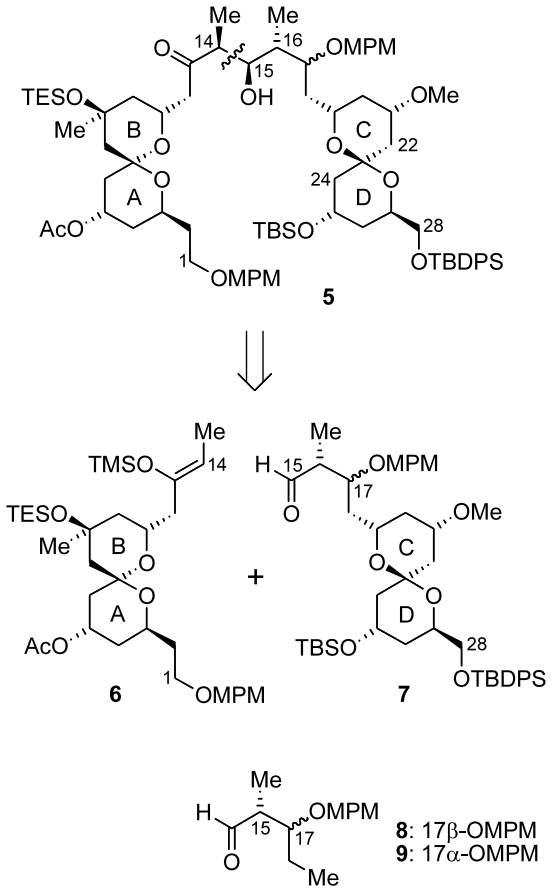


Figure 2.

Our second-generation AB fragment **6** was prepared as shown in Scheme 1. The synthesis commenced with the coupling of dithiane **10**[19a] with epoxide **11**[19a] to afford alcohol **12** in 85% yield. A series of deprotections and protections was efficiently accomplished to give β-hydroxyketone **13** in 71% yield. Removal of TBS and Bn groups followed by an acidic treatment (PPTS, CH_2Cl_2) afforded spiroacetal **14** in 57% yield. Selective *p*-methoxybenzyl (MPM) ether formation followed by protection of the resultant diol as triethylsilyl (TES) ethers, DIBALH reduction, and Dess–Martin oxidation[21] afforded aldehyde **15** in 40% overall yield. Ethylation at C13 and subsequent oxidation gave ethyl ketone **16** in 87% yield. Finally, after conversion of the C5–TES ether in **16** to the C5–acetate (73% yield), enol silylation of the C13 ketone (TMSOTf, 2,6-lutidine) furnished the silyl enol ether **6** in good regio- (>99:1) and stereoselectivities (>96%).

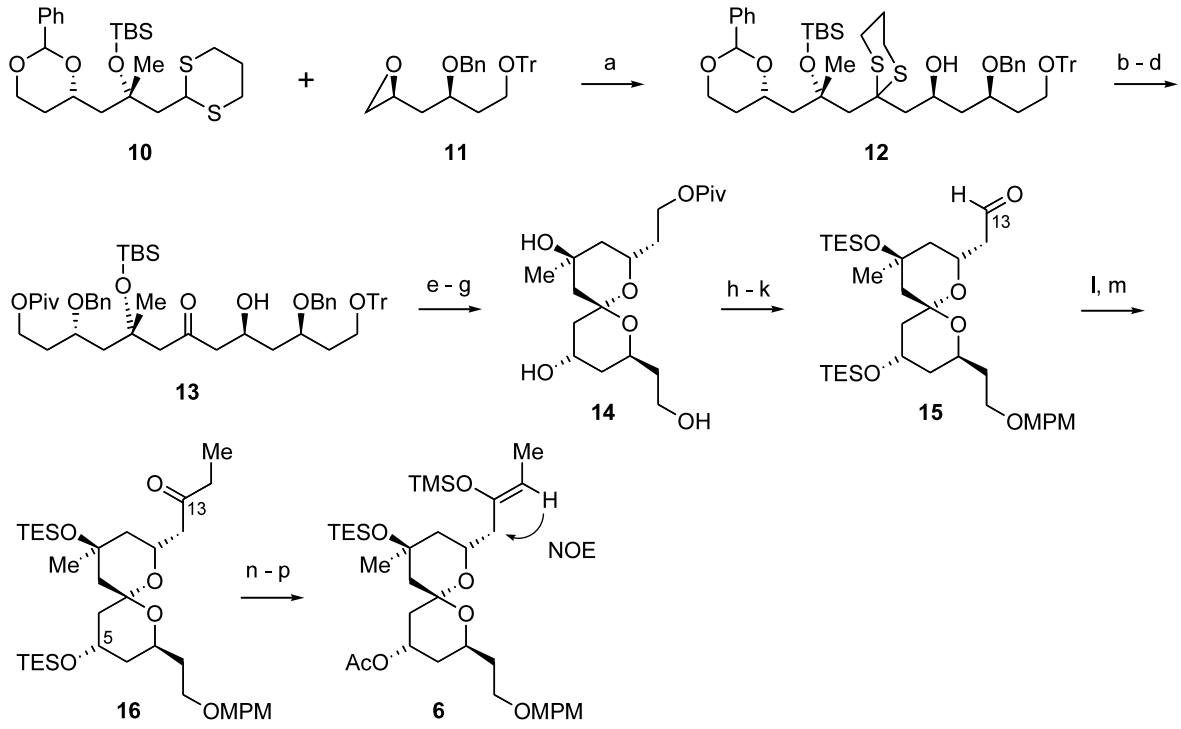
With the required compound **6** in hand, we then focused on the Mukaiyama aldol reaction[22] by using the model aldehydes **8**[23] and **9**.[23] Treatment of **6** and **8** with $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at −78°C generated the coupling product **17** in 60% yield as a single product (Scheme 2). To elucidate the C14 and C15 stereochemistries of **17**, the C13 ketone was first reduced by DIBALH[24] in a stereoselective manner to afford triol, which was then treated with 2,2-dimethoxypropane and PPTS in CH_2Cl_2 to give acetonide **18**. Rychnovsky analysis[25] of the acetonide portion revealed that the 1,3-dioxane existed in a well-defined chair conformation, suggesting that the relative stereochemistry of the C13, C15-diol is 1,3-*syn*. Furthermore, NOE studies revealed that the methyl group at C14 is *syn* to the C13 and C15 hydroxy groups.

To determine the C15 absolute configuration of **17**, the C15 hydroxy group was converted to its MTPA ester **19** (Scheme 3). As the result of the Kakisawa–Kusumi test[26] was unclear, the C17 MPM group was cleaved by oxidative removal using DDQ to prepare hemiacetal **20**. Extensive ^1H NMR analysis showed that the coupling constant between H_{15} and H_{16} was 4.8 Hz, determining the absolute stereochemistry at C15 to be shown in Schemes 2 and 3. Therefore, the stereochemistry of **17** was confirmed as C14,C15-*syn* and C15,C16-*anti*, which is in accord with that of the natural products.

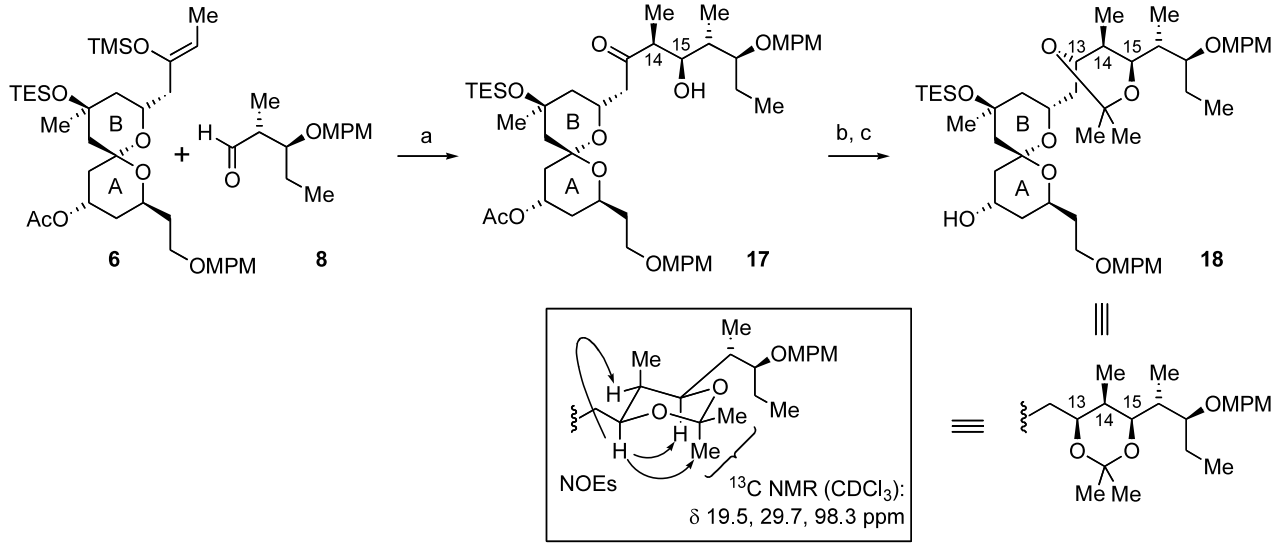
The Mukaiyama aldol reaction using aldehyde **9** was also examined (Scheme 4). The reaction proceeded under the same conditions but in lower yield (31%) to give β-hydroxyketone **21**. By using the same analysis described above, the stereochemistry of **21** was determined to be C14,C15-*syn* and C15,C16-*syn*. These results suggested that the stereoselectivity of the aldol reaction was controlled by the C17 chiral center as anticipated.[7b,22b]

Based on these results, we next focused on the coupling of the intact fragments (Scheme 5). Our previously synthesized diol **22**[19b] was transformed to the C15–C28 (CD) aldehyde **23** in 44% overall yield. The coupling reaction between **6** and **23** proceeded smoothly without any epimerization at C23 to produce the C1–C28 (ABCD) fragment **24**[27] in 69% yield as a single adduct. When the C23-epimer of **23**, having the correct stereochemistry at C23, was used for the aldol coupling reaction, partial epimerization at C23 was observed.[28] The next objective is to introduce the C13 exomethylene. Unfortunately, all attempts to provide **25** (e.g. Tebbe methylenation, Wittig reaction, Julia olefination, Peterson olefination, Takai olefination using **24** (R = H, Ac, TMS, MEM)) failed.[29]

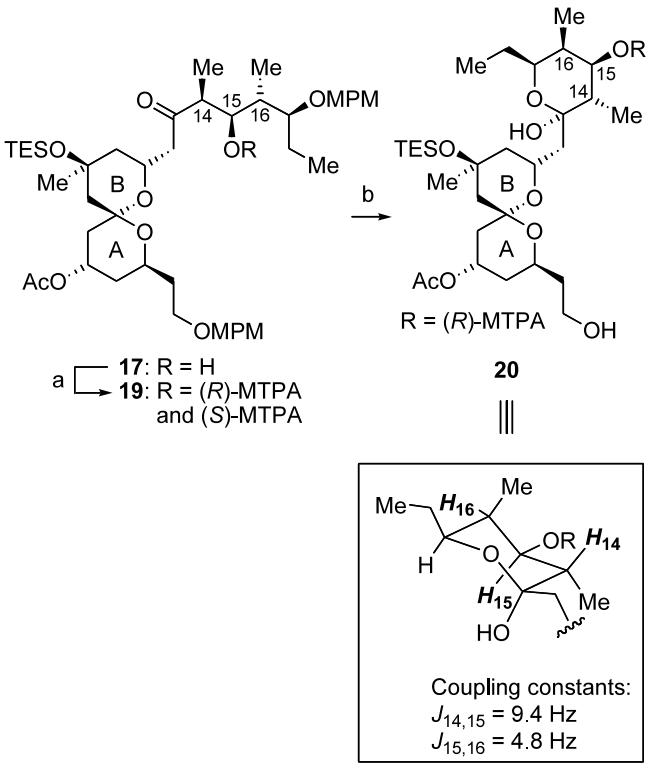
In summary, we have demonstrated that the stereochemical outcome on C14 and C15 was completely controlled by the β-alkoxy chiral center of the aldehydes. Although the planned exomethylenation to form the crucial C13 olefin did not proceed, we describe in the following communication[30] our next generation strategy to construct the C14–C15 linkage and a formal total synthesis of altohyrtin C.



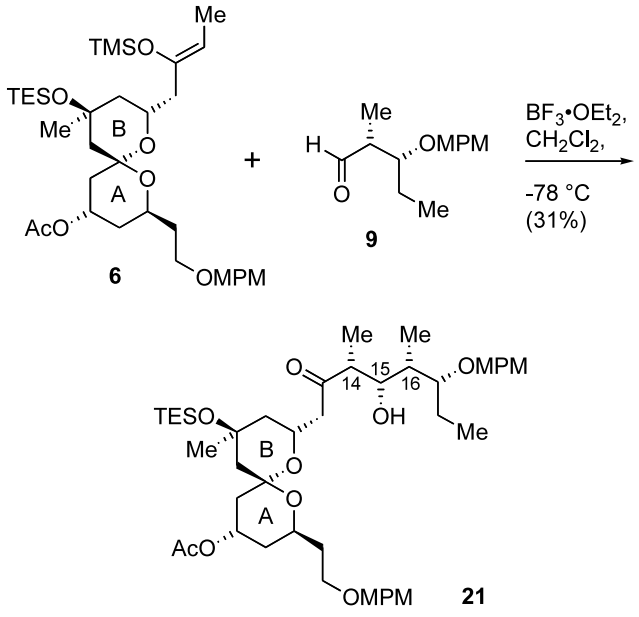
Scheme 1. Synthesis of the AB fragment **6**. *Reagents and conditions*: (a) **10**, *n*-BuLi, HMPA, THF, −20°C, then **11** (85%); (b) DIBALH, CH_2Cl_2–hexane, rt; (c) PivCl, Et_3N, CH_2Cl_2, rt; (d) $Hg(ClO_4)_2$, $CaCO_3$, THF–H_2O, 0°C (71% for three steps); (e) aq. HF, MeCN, 40°C (89%); (f) H_2, Pd–C, EtOAc, rt; (g) PPTS, CH_2Cl_2, rt (64% for two steps); (h) $MPMOC(=NH)CCl_3$, PPTS, CH_2Cl_2, rt (54%); (i) TESOTf, 2,6-lutidine, CH_2Cl_2, 0°C (93%); (j) DIBALH, CH_2Cl_2–hexane, −78°C (86%); (k) Dess–Martin periodinane, pyridine, CH_2Cl_2, rt (92%); (l) EtMgBr, ether, 0°C; (m) Dess–Martin periodinane, pyridine, CH_2Cl_2 (87% for two steps); (n) PPTS, CH_2Cl_2–MeOH, 0°C; (o) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt (73% for two steps); (p) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0°C (89%). Piv = 2,2-dimethylpropionyl.



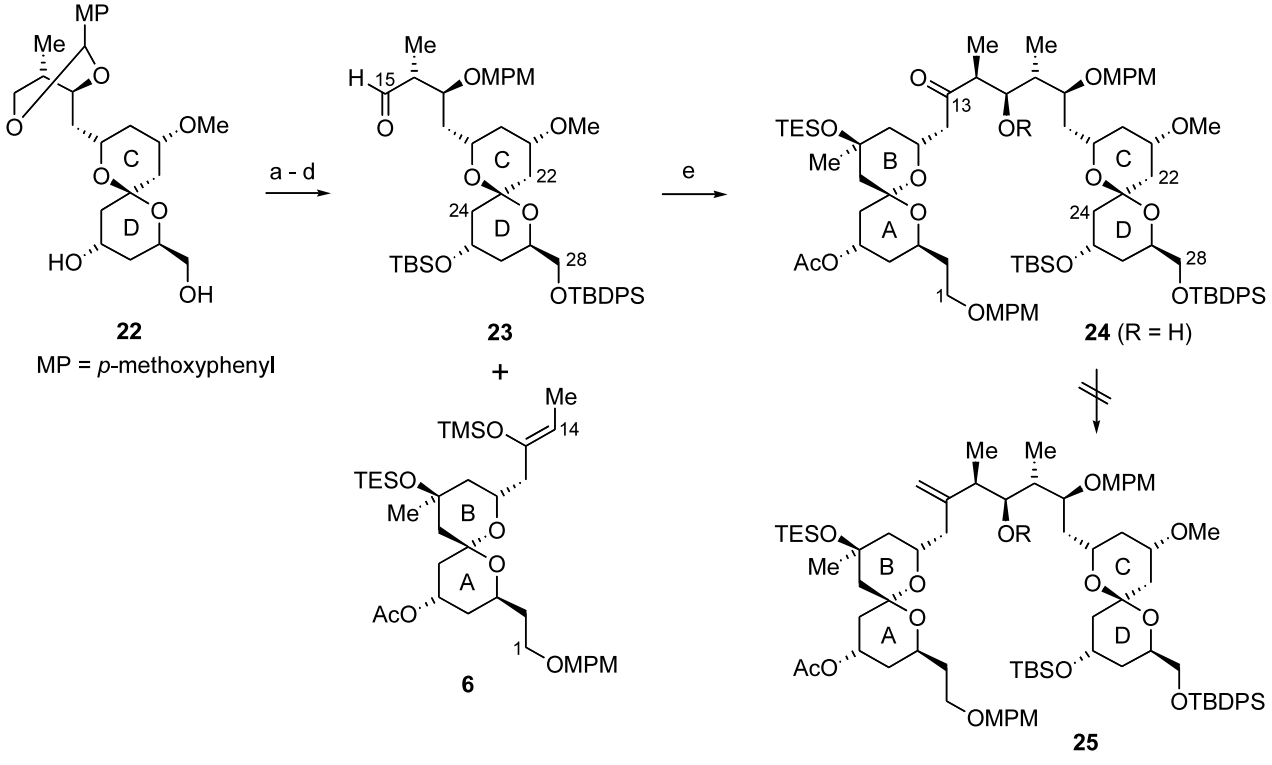
Scheme 2. Mukaiyama aldol reaction of **6** with **8**. *Reagents and conditions*: (a) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78°C (60%); (b) DIBALH, THF, −78°C (86%); (c) $Me_2C(OMe)_2$, PPTS, CH_2Cl_2, rt (82%).



Scheme 3. Determination of the C14-16 stereochemistry of **17**. *Reagents and conditions*: (a) (*S*)-(+)-MTPACl or (*R*)-(−)-MTPACl, Et_3N, DMAP, CH_2Cl_2, rt (80%); (b) DDQ, CH_2Cl_2–H_2O, rt (75%). MTPA = 2-methoxy-2-phenyl-2-(trifluoromethyl)acetyl.



Scheme 4. Mukaiyama aldol reaction of **6** with **9**.



Scheme 5. Preparation of the C1-C28 (ABCD) fragment **24**. *Reagents and conditions*: (a) TBDPSCl, imidazole, DMF, rt (75%); (b) TBSCl, imidazole, DMF, 50°C (85%); (c) DIBALH, CH_2Cl_2–hexane, 0°C (72%); (d) IBX, DMSO–THF, rt (96%); (e) BF_3·OEt_2, CH_2Cl_2, −78°C (69%). IBX = *o*-iodoxybenzoic acid.

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23. The model aldehydes **8** and **9** were prepared from methyl (*S*)-3-hydroxy-2-methylpropionate as follows: (a) TrCl, Et_3N, DMAP, CH_2Cl_2, rt; (b) DIBALH, CH_2Cl_2–hexane, −78°C; (c) EtMgBr, ether, rt; (d) CSA, MeOH, rt, separation of two diastereomers, which were identical with authentic samples by comparison of their optical rotations and ^1H NMR spectra, see: Fujisawa, T.; Tajima, K.; Sato, T. *Chem. Lett*. **1984**, 1669–1672; Kayano, A.; Akazome, M.; Fujita, M.; Ogura, K. *Tetrahedron* **1997**, *53*, 12101–12114; (e) *p*-$MeOPhCH(OMe)_2$, CSA, CH_2Cl_2, rt; (f) DIBALH, CH_2Cl_2–hexane, −40°C; (g) Dess–Martin oxidation.
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27. Since it was difficult to determine the stereochemistry at the newly formed carbon centers (C14, C15), it was tentatively assigned as depicted, depending on the model studies as described above. Moreover, the fact that the coupling constants ($J = 8.8$, 2.4 Hz) around the C15 stereocenter of acetate **24** (R = Ac) were close to those ($J = 9.2$, 2.8 Hz) of the Paquette's compound supports the assignment. See Ref. 7b.
28. Other groups also experienced a similar epimerization in their synthetic studies. See Refs. 3a and 4a.
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