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Synthetic studies on altohyrtins (spongistatins): synthesis of the C29–C44 (EF) portion

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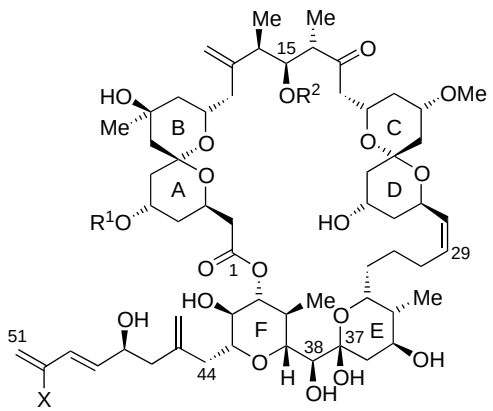
Abstract—The C29–C44 portion of altohyrtins (spongistatins) has been prepared from 1,5-pentanediol and D-glucose in a stereoselective manner. The convergent synthesis relied on a coupling reaction of the C29–C37 vinyl bromide and the C38–C44 Weinreb amide, diastereoselective reduction of the C38 ketone, and stereoselective formation of the C33–C37 (E ring) acetal.

In 1993, the Pettit,[1] Kitagawa,[2] and Fusetani[3] groups isolated and characterized potent antitumor macrolides, designated as the spongistatins, altohyrtins, and cinachyrolides, respectively (Fig. 1). These marine natural products comprise the most potent anticancer agents identified.[4] Their promising biological activity and novel architecture have led to wide interest in the synthetic community. To date, the Evans,[5] Kishi,[6] and Smith[7] groups have succeeded in the total syntheses of members of this class. As part of our program directed toward the total synthesis of altohyrtins,[8] we have developed the stereocontrolled synthesis of the C29–C44 portion of altohyrtins.

Our analysis for the synthesis of the C29–C44 portion **1** commenced with disconnection of the C37–C38 (altohyrtins numbering) bond to generate two major subunits, i.e. the C38–C44 (F) fragment **2** and the C29–C37 (E) fragment **3** (Scheme 1). The Weinreb coupling[9] of **2** and **3** would construct the C37–C38 bond. We envisioned that the C38–C44 fragment **2** could be prepared from the anhydrosugar derivative **4**, which is available from D-glucose in eight steps,[10,11] and the C29–C37 vinyl bromide **3** from 1,5-pentanediol (**5**) through Brown crotylboration.[12]

Synthesis of **2** commenced with benzylation of the known **4**[10c] followed by treatment with Ac_2O and trifluoroacetic acid to afford an anomeric mixture of diacetates **6a**[13] and **6b**[13] (Scheme 2). We then installed one carbon unit corresponding to the C38 position; a mixture of **6a** and **6b** was treated with trimethylsilyl cyanide in the presence of boron trifluoride etherate,[14] yielding a mixture of cyanides **7a** and **7b**. Basic hydrolysis of the mixture and methyl ester formation (HCl–MeOH) gave a separable mixture of the desired methyl ester (91%) and its C39 epimer (9%). After protection



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
Cinachyrolide A (Spongistatin 4): X=Cl, R^1=Ac, R^2=H

Figure 1.

Keywords: altohyrtins; spongistatins; stereoselective synthesis; Weinreb coupling.

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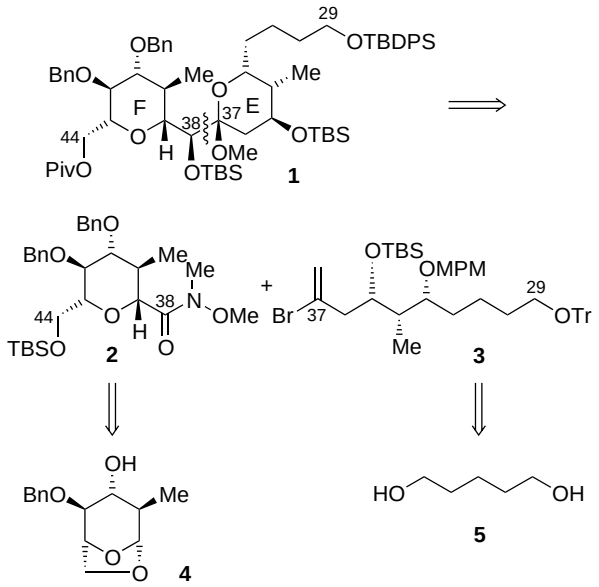
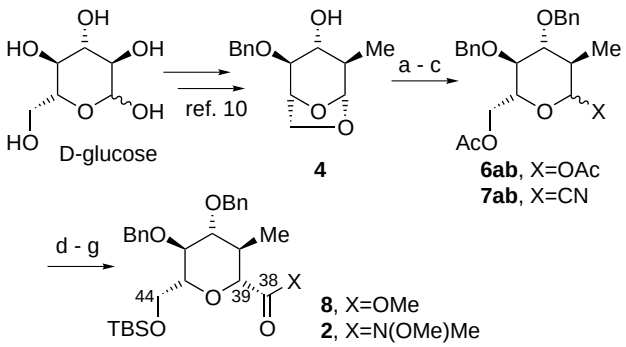


Scheme 1. Retrosynthetic analysis.



Scheme 2. (a) BnBr, NaH, DMF, rt, 1.5 h (93%); (b) TFA, Ac_2O, 0°C, 1 h (α:β = 3.5:1); (c) TMSCN, $BF_3{\cdot}OEt_2$, MeCN, 0°C, 2 h (100% for two steps: α:β = 4.5:1); (d) 5 M aq. NaOH, MeOH, reflux, 2 h; (e) HCl, MeOH, reflux, 5 h (91% for two steps); (f) TBSCl, imidazole, DMF, rt, 1 h (97%); (g) MeNH(OMe)·HCl, Me_3Al, CH_2Cl_2, rt, 12 h (98%).

of the primary alcohol as its *t*-butyldimethylsilyl (TBS) ether, the resulting **8** was subjected to transamidation using the Weinreb procedure[9] to provide the C38–C44 fragment **2**.

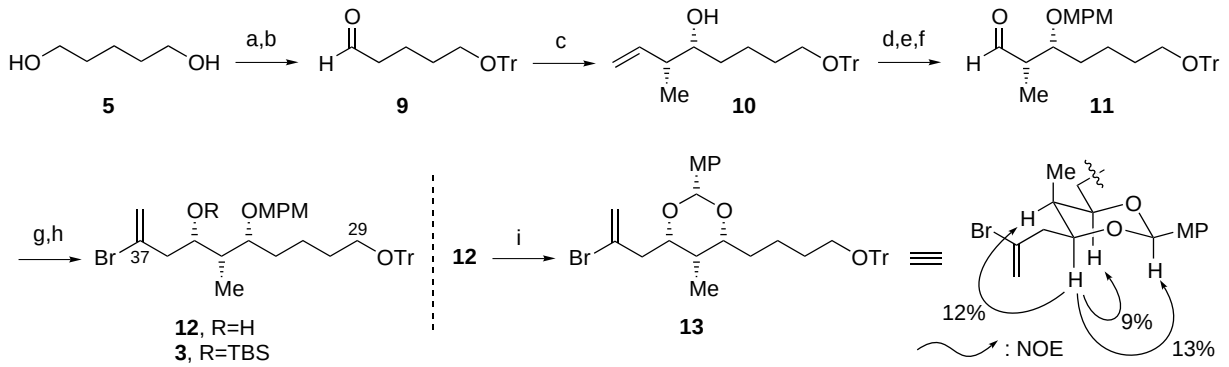
Synthesis of **3** began with monotritylation of 1,5-pentanediol (**5**) followed by PCC oxidation, yielding aldehyde **9** (Scheme 3). The Brown crotylboration[12] of **9** afforded alcohol **10** in 90% ee[15] and 68% yield from 1,5-pentanediol. Protection of the secondary hydroxy group in **10** as its *p*-methoxybenzyl (MPM) ether followed by successive oxidations of the terminal olefin afforded aldehyde **11**. Stereoselective introduction of the 2-bromo-2-propenyl group was achieved by using the Mandai–Otera protocol.[16,17] That is, when aldehyde **11** was added to the premixed, sonicated mixture of 2,3-dibromopropene and Sn powder in THF–EtOH–H_2O (8:1:1), the desired alcohol **12** was obtained as the major product (64%) along with the undesired diastereomer (13%). The stereochemical assignment of the newly generated stereocenter in **12** was established by observing NOEs after leading to its *p*-methoxybenzylidene acetal derivative **13**. Finally, silylation of **12** provided the C29–C37 vinyl bromide **3**.

With both fragments in hand, we next focused on the coupling of the two fragments and the stereoselective introduction of the C38 stereocenter (Scheme 4). Treatment of **3** with *t*-BuLi in Et_2O at −78°C generated the vinyl lithium reagent which was directly subjected to the coupling with **2**, leading to enone **14** in 77% yield. Stereoselective reduction of the C38 ketone in **14** was accomplished by using the Luche conditions;[18,19] reduction of **14** with $NaBH_4$ in the presence of $CeCl_3$ gave **15** with 18:1 stereoselectivity.[20] We also examined the coupling reaction of **3** with aldehyde **17**, which was prepared by DIBALH reduction of **8** in 86% yield, in order to obtain allyl alcohol **15** in one-step. However, in all cases attempted,[21] the Felkin adduct **16**, which has the undesired stereochemistry at the C38 stereocenter was obtained as the major product.

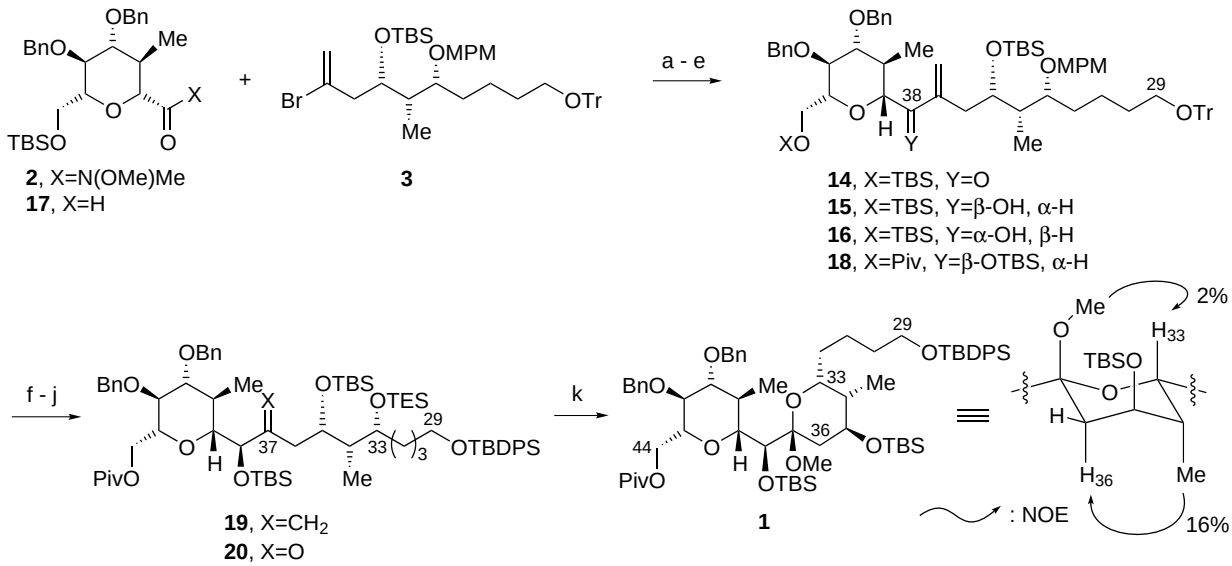
Conversion of **15** into **19** was then achieved in seven steps through **18**. It should be mentioned that the acid-stable protecting group on the C29 hydroxy group is critical to the cyclization of the E ring. When the intermediate having the free C29 hydroxy group or having trityl group on the C29 hydroxy group was used for the cyclization, only a small amount of the desired bis(tetrahydropyran) was obtained. Temporary protection of the C33 hydroxy group as its triethylsilyl (TES) ether is also effective for the cyclization (vide infra).

Two more steps were needed to complete the synthesis of the fully functionalized C29–C44 fragment **1**. The C37 *exo* olefin was unmasked at this stage to the carbonyl group by ozonolysis, producing ketone **20**. This ozonolysis could be carried out without the C33 TES group. But in that case, low yielding was observed in the E ring cyclization. Finally, treatment of **20** with PPTS in MeOH–THF afforded bis(tetrahydropyran) **1**. NOE data shown in Scheme 4 confirmed the configuration of the C37 stereocenter and the conformation of the E ring.

In summary, we have accomplished the convergent synthesis of the C29–C44 portion of altohyrtins. The Weinreb coupling and the following Luche reduction were used to set the C38 stereocenter with high stereoselectivity. Coupling of this fragment with the C45–C51 side chain and completion of the synthesis will be reported in due course.



Scheme 3. (a) TrCl, triethylamine, CH_2Cl_2, 0°C, 1 h (96% from TrCl); (b) PCC, MS4AP, CH_2Cl_2, rt, 1.5 h; (c) *cis*-2-butene, *n*-BuLi, *t*-BuOK, (−)-Ipc_2BOMe, $BF_3{\cdot}OEt_2$, THF, −78°C, then **9**, −78°C (71% for two steps); (d) MPMCl, NaH, DMF, rt, 3 h (93%); (e) OsO_4, *N*-methylmorpholine *N*-oxide, acetone–H_2O (6:1), rt, 2 days (94%); (f) $Pb(OAc)_4$, benzene, rt, 0.5 h (96%); (g) 2,3-dibromopropene, Sn powder, THF–EtOH–H_2O (8:1:1), rt, sonication, 4 h (64% for **12**, 13% for its C35 epimer); (h) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 0.5 h (96%); (i) DDQ, PhH, rt, 45 min (78%). MS4AP = molecular sieves 4 Å powder, Ipc = isopinocampheyl, MP = *p*-methoxyphenyl.



Scheme 4. (a) **3**, *t*-BuLi, Et_2O, −78°C, 5 min, then **2**, −78°C, 20 min (77%); (b) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, EtOH–THF (4:1), rt, 1 h (71% for **15**, 4% for **16**); (c) TBAF, THF, 60°C, 2 h (98%); (d) PivCl, DMAP, CH_2Cl_2, 0°C, 1 h (96%); (e) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 0.5 h (99%); (f) HCO_2H–Et_2O (3:2), 0°C, 10 min (89%); (g) TBDPSCl, imidazole, DMF, rt, 0.5 h (94%); (h) DDQ, CH_2Cl_2–pH 7 phosphate buffer (10:1), rt, 0.5 h (94%); (i) TESCl, imidazole, DMF, 60°C, 0.5 h (87%); (j) O_3, CH_2Cl_2–MeOH (2:1), −78°C, 10 min, then Me_2S (91%); (k) PPTS, MeOH–THF (2:1), rt, 1 h (72%). Piv = 2,2-dimethylpropionyl, TBDPS = *t*-butyldiphenylsilyl.

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