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Asymmetric synthesis of the F-pyran fragment of the altohyrtins

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Abstract

The asymmetric synthesis of a differentially protected F-pyran ring of the altohyrtins has been achieved through an intramolecular cyclisation of a C_{43} hydroxyl group onto a C_{38}–C_{39} epoxide. Absolute stereochemistry was derived from an Evans boron aldol to control C_{40} and C_{41}, the C_{42}–C_{43} hydroxyl stereocentres from a Sharpless (–)-diethyl tartrate controlled epoxidation and the remaining stereocentres from substrate controlled diastereoselection.

Keywords: asymmetric synthesis; cyclisation; epoxide; pyran.

The structurally complex spongipyran macrolides, isolated from marine sponges, are extremely cytotoxic against a number of human cancer cell lines.[1] This activity has prompted a number of synthetic studies of these molecules[2] culminating in the total synthesis of altohyrtin C by Evans[3] and altohyrtin A by Kishi,[4] the structures of which serve as representatives of this class. We have also been involved with synthetic studies towards this class of molecules and wish to report our synthesis of the differentially protected F-pyran.[5]

Our retrosynthetic analysis of the altohyrtins followed the proven late stage macrolactonisation and prior coupling of the northern and southern hemispheres by a Wittig reaction.[2] The synthesis of the southern hemisphere (**1**), the E,F-bis-pyran of the macrolide, can be simplified by *retro*-lactolisation and then aldol disconnection (Scheme 1).[6] The stereocontrolled synthesis of differentially protected **2** was achieved through a cyclisation of the C_{43} hydroxyl onto an epoxide derived from **3**, which represents an alternative to the published strategies for the synthesis of this ring system.[3b,4b,5] Introduction of the *Z*-alkene was from Still's modification of the Wadsworth–Horner–Emmons reaction and introduction of the C_{42} and C_{43} hydroxyl stereocentres from regioselective hydrolysis following a (–)-diethyl tartrate controlled epoxidation. The remaining 1,2-*syn* relationship of C_{40}–C_{41} was set up by an Evans boron aldol reaction.

Monoprotection of *Z*-2-butene-1,4-diol followed by Swern oxidation[7] proceeded with concomitant isomerisation and gave the thermodynamically more stable *E*-α,β-unsaturated aldehyde **4** in 55% yield over two steps (Scheme 2).[8] This was then added to the *Z*-boron enolate derived from **5**[9] to give the

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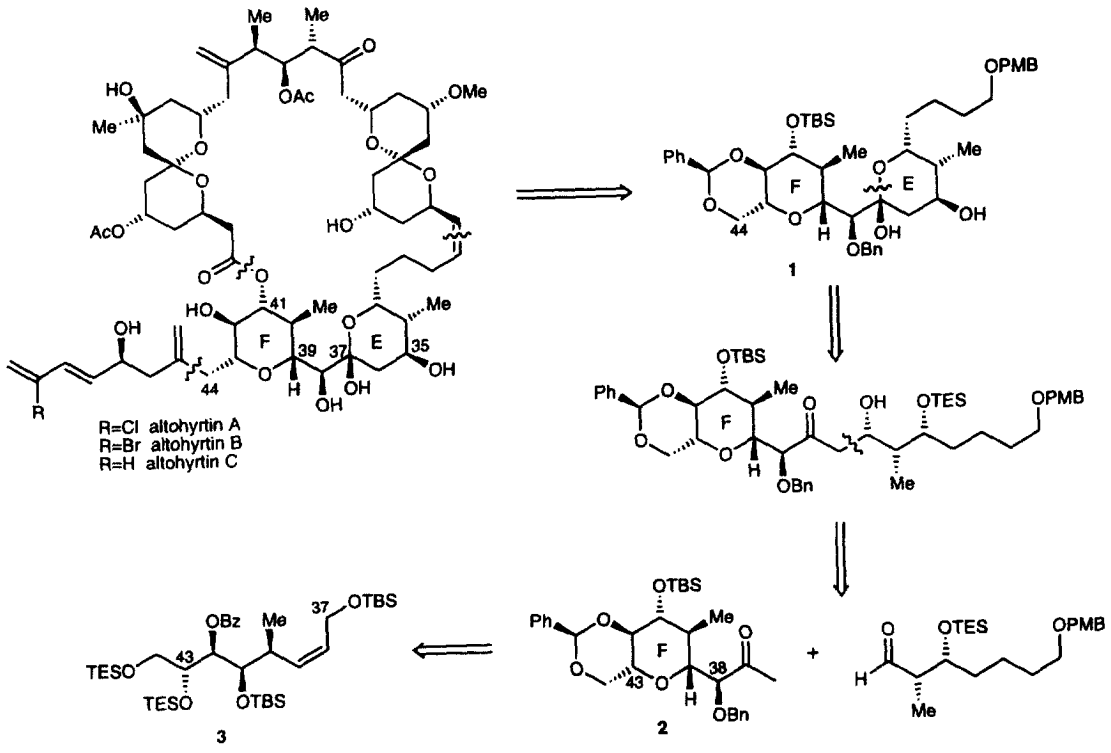
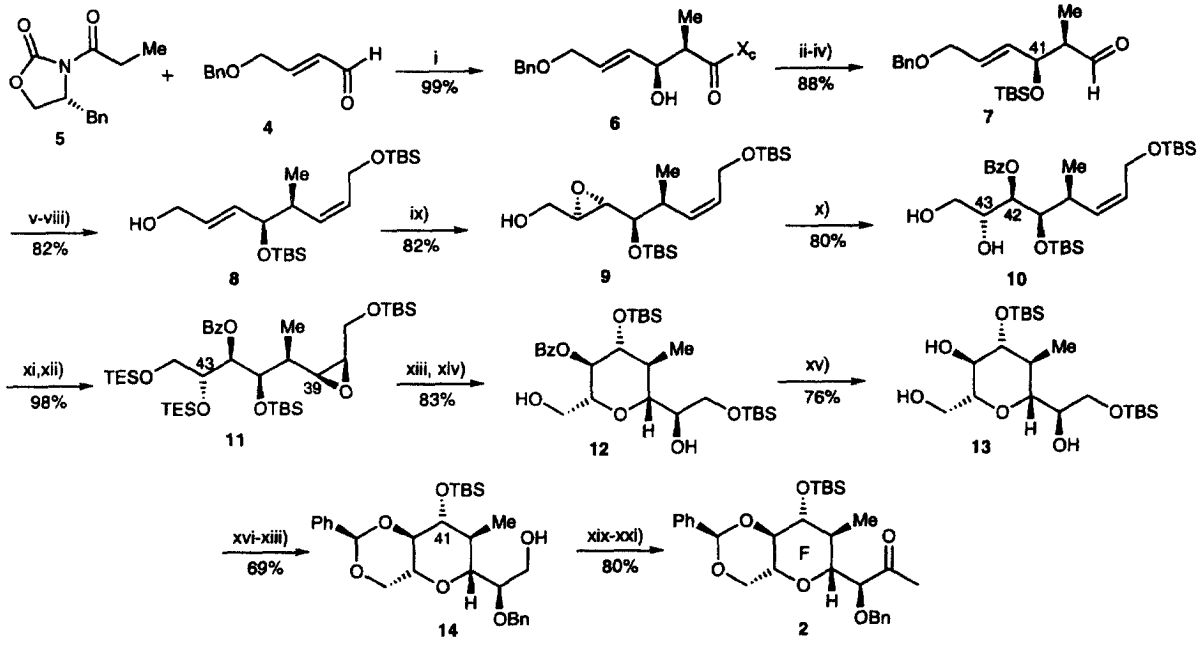


Scheme 1.

syn-aldol product **6** with a diastereoselection of greater than 95:5 judged by ^{1}H NMR, in excellent yield providing freshly prepared dibutylboron triflate[10] was used (Scheme 2[11]). Transamidation to the Weinreb amide,[12] protection of the C_{41} hydroxyl as its TBS ether and treatment with DIBALH provided the protected aldehyde **7**. A *Z*-selective alkenylation reaction proceeded in high yield with complete diastereoselection according to Still's protocol.[13] Reduction, TBS protection of the resultant primary alcohol and deprotection of the benzyl ether with LDBB[3a,11,14] gave diene **8**. Differential epoxidation of the allylic alcohol **8** relying upon substrate controlled diastereoselection to give epoxide **9** was unsuccessful. Resorting to reagent control with (−)-diethyl tartrate under Sharpless conditions[15] gave **9** as a single diastereoisomer in high yield after chromatography. Regioselective ring opening with benzoic acid under Lewis acidic conditions[16] set up the required *anti* relationship between the C_{42} and C_{43} hydroxyl stereocentres in **10**.[17] After considerable experimentation bis-TES protection of diol **10** was required before substrate controlled epoxidation with dimethyl dioxirane[18] furnished the desired epoxide **11** (98%, ds 7:1). An optimal two step procedure for the formation of the pyran **12** required the selective deprotection of the TES groups and then acid induced cyclisation of the C_{43} hydroxyl onto the C_{39} terminus of the epoxide. After purification by chromatography the diastereoselection was upgraded to 10:1 in 83% yield over two steps. Deprotection of the benzoyl group gave a crystalline solid **13** amenable to single-crystal X-ray analysis which unequivocally confirmed the structure of this advanced intermediate.[19] Standard protecting group manipulations involved protection of the 1,3-diol as its benzylidene acetal which will allow selective unmasking of the C_{41} hydroxyl in the planned late stage macrolactonisation. Benzyl protection and then selective deprotection of the primary TBS ether gave **14**. Manipulation to methyl ketone **2** was achieved by standard means. Swern oxidation was followed by addition of methyl lithium and Dess Martin periodinane[20] oxidation gave **2**.[21]

We have synthesised the F-pyran of the altohyrtins in differentially protected form in a high yielding



Scheme 2. (i) Bu_2BOTf, Et_3N, CH_2Cl_2, −78 to 0°C; H_2O_2, 0°C, 99%; (ii) MeONMe·HCl, $AlMe_3$, THF, −15°C then; (iii) TBSCl, imidazole, DMF, rt 99%; (iv) DIBALH, CH_2Cl_2, −78°C, 89%; (v) $(CF_3CH_2O)_2POCH_2CO_2Me$, KHMDS, 18-C-6, THF, −78°C, 85%; (vi) DIBALH, CH_2Cl_2, −78°C then; (vii) TBSCl, imidazole, DMF, rt, then; (viii) LDBB, THF, −78°C, 97%; (ix) (−)-DET, $Ti(^iPrO)_4$, ^{t}BuOOH, 4 Å mol. sieves, CH_2Cl_2, −20°C, 82%; (x) $PhCO_2H$, $Ti(^iPrO)_4$, THF, rt, 80%; (xi) TESCl, Et_3N, CH_2Cl_2, rt, 99%; (xii) DMO, CH_2Cl_2, −20°C, 99%; (xiii) CSA, CH_2Cl_2/MeOH (1:10), −20°C then; (xiv) CSA, CH_2Cl_2, rt, 83%; (xv) DIBALH, CH_2Cl_2, −78°C, 76%; (xvi) $PhCH(OMe)_2$, CSA, CH_2Cl_2, rt, 80%; (xvii) KH, BnBr, THF, 0°C, 98%; (xviii) HF·Py, Py, THF, rt, 88%; (xix) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C; DIPEA, −78 to −40°C then; (xx) MeLi, Et_2O, −78°C then; (xxi) Dess Martin periodinane, Py, CH_2Cl_2, rt, 80%

and stereoselective synthesis using a key intramolecular epoxide induced cyclisation. Aldol studies and final lactonisation to provide the E,F-bis-pyran **1** are presently under investigation and will be reported in due course.

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11. The structure assigned to each new compound is in accord with IR, ^{1}H and ^{13}C NMR, MS, HRMS and/or elemental analysis. Abbreviations: Bn=benzyl; Bz=benzoyl; CSA=camphorsulfonic acid; DET=diethyltartrate; DIBALH=diisobutylaluminium hydride; DIPEA=diisopropylethylamine; DMSO=dimethylsulfoxide; KHMDS=potassium hexamethyldisilazide; LDBB=di-*tert*-butylbiphenyllithium; Py=pyridine; TBS=*tert*-butyldimethylsilyl; TES=triethylsilyl; Tf=trifluoromethanesulfonyl.
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21. Characterisation data for **2**, amorphous white solid, mp 88–90°C, $[\alpha]_D$=–22.2 (c=0.9, CH_2Cl_2, rt), IR (thin film) 1716 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.00 (3H, s, SiMe), 0.07 (3H, s, SiMe), 0.76 (3H, d, *J*=6.7, CH*Me*), 0.91 (9H, s, Si^{t}Bu), 2.01–2.19 (1H, m, C*H*Me), 2.31 (3H, s, MeCO), 3.35 (1H, dt, *J*=10.1, 4.9, C_{43}-H), 3.45–3.59 (2H, m, C_{44}-H_2), 3.55 (1H, dd, *J*=10.4, 2.4, C_{39}-H), 3.81 (1H, t, *J*=10.2, C*H*OTBS), 3.90 (1H, d, *J*=2.1, C*H*OBn), 4.20 (1H, dd, *J*=10.4, 4.9, C_{42}-H), 4.45 (1H, d, *J*=11.9, PhCH_2O), 4.89 (1H, d, *J*=11.9, PhCH_2O), 5.53 (1H, s, PhC*H*), 7.37–7.56 (10H, m, Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 12.9, 18.4, 26.0, 27.6, 39.2, 68.6, 71.2, 73.7, 75.8, 82.7, 83.0, 83.1, 102.1, 126.4, 128.1, 128.4, 128.6, 128.7, 129.0, 136.6, 137.4, 211.5; MS (CI$^+$) 527 (MH$^+$); HRMS $C_{30}H_{43}O_6Si$ calcd 527.2829, found 527.2806.