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Stereocontrolled Synthesis of the CD Subunit of the Marine Macrolide Altohyrtin A

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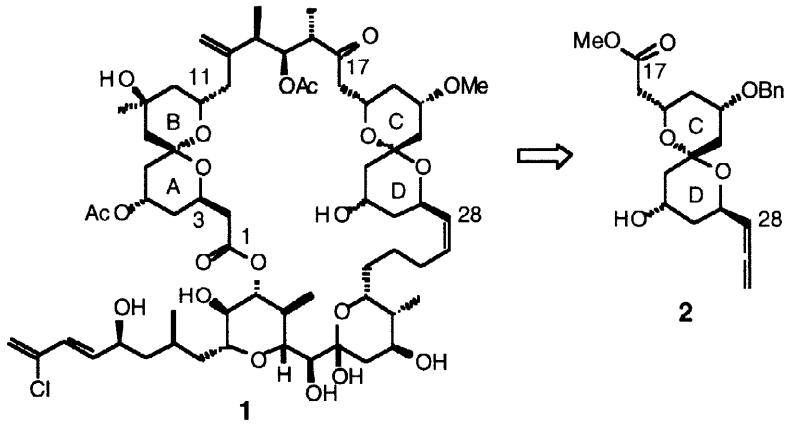
Abstract: *A* synthesis of the C17-C28 segment of altohyrtin A is reported. The synthesis uses a coupling step between two chiral subunits, both of which were synthesized from L-malic acid. The remaining stereocenters were obtained through a combination of stereoselective reactions and thermodynamic equilibration.

Macrocyclic natural products of marine origin represent a growing source of anticancer agents with clinical potential. Altohyrtin A (**1**) and its congeners[1] are among the newest members of this valuable class of compounds, displaying remarkable antineoplastic activity. Through total synthesis, the Evans group[2] has recently proven the long-held suspicion that the spongistatins[3] and cinachyrolides[4] are identical to the altohyrtins. Given their biological importance, we became interested in developing our own synthetic route to these compounds. Viewing the allene group as a masked aldehyde, spiroketal **2** was considered a viable substructure for the C17-C28 segment of altohyrtin A.[5] Herein we report the synthesis of compound **2** from a single chiral source provided by L-malic acid.



1 **2**

Scheme 1 outlines our synthetic plan from the chiral subunits **6** and **7**, the design of which was based on the results of model studies.[6] Our goal was to isolate structure **2** from a mixture of spiroketals **2** and **3**, prepared from the spirolactols **4** using a stereoselective C2-allenation reaction, followed by removal of the TIPS protective group. Even though literature reports made it almost impossible to predict the equilibrium position between compounds **2** and **3**, our own model studies were encouraging.[6] Spirolactols **4** would be prepared from ketoaldehyde **5**, making use of a novel tandem cyclization strategy recently developed by us.[6]

Epoxide **7** was synthesized first (Scheme 2). Acetonide **8**, prepared in two steps from L-malic acid,[7] was protected as its p-methoxybenzyl ether, and then hydrolyzed to give the diol **9**. Regioselective mesylation of the primary alcohol then allowed base-induced ring closure to provide epoxide **7**.

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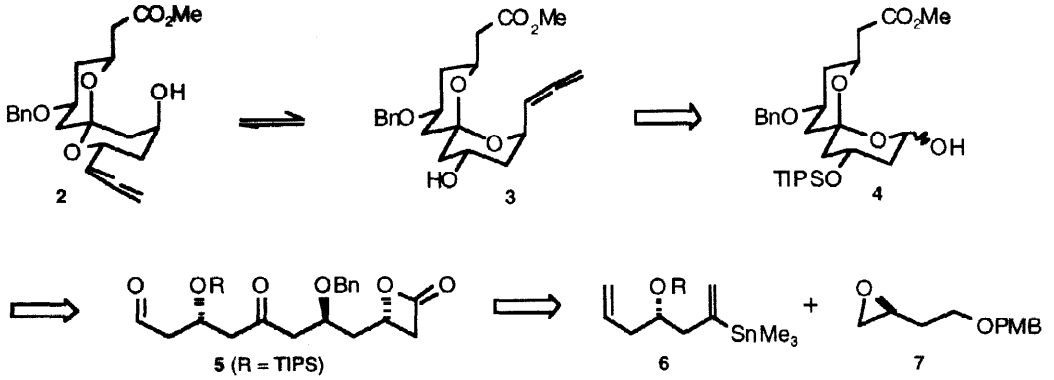
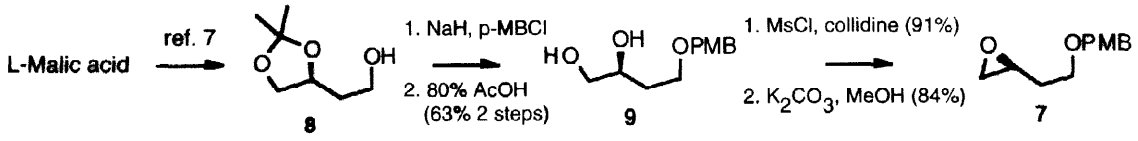
Scheme 1

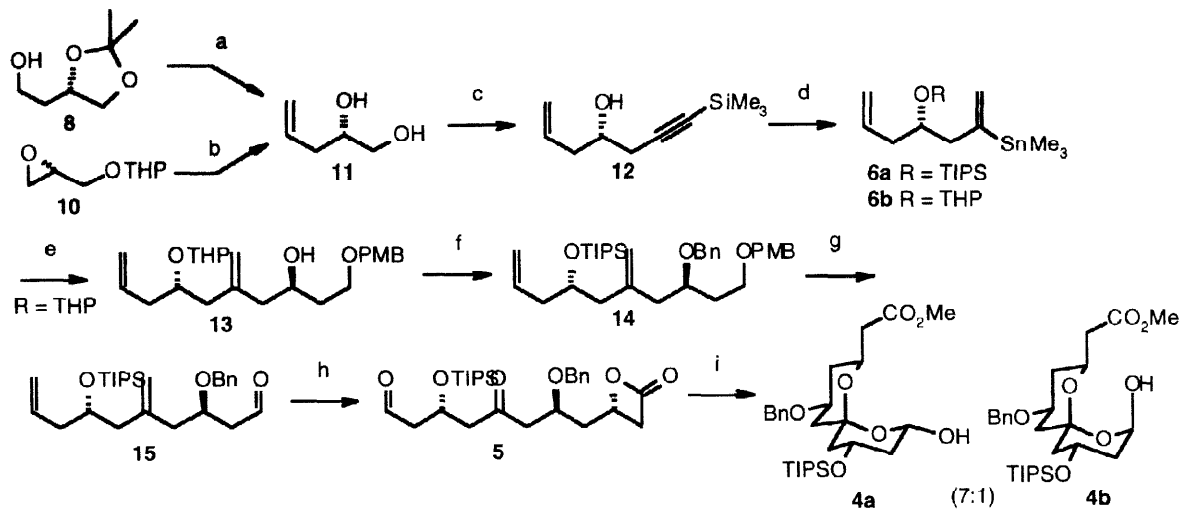


Vinyl stannanes **6a** and **6b** (Scheme 3) were both synthesized in four steps from diol **11**, which could be prepared in multigram quantities from either L-malic acid, *via* acetonide **8**, or from THP-protected (R)-glycidol **10**.[8] Making use of the Forsyth[9] protocol, diol **11** was converted to the alkynyl silane **12** in a one-pot procedure.

Scheme 2

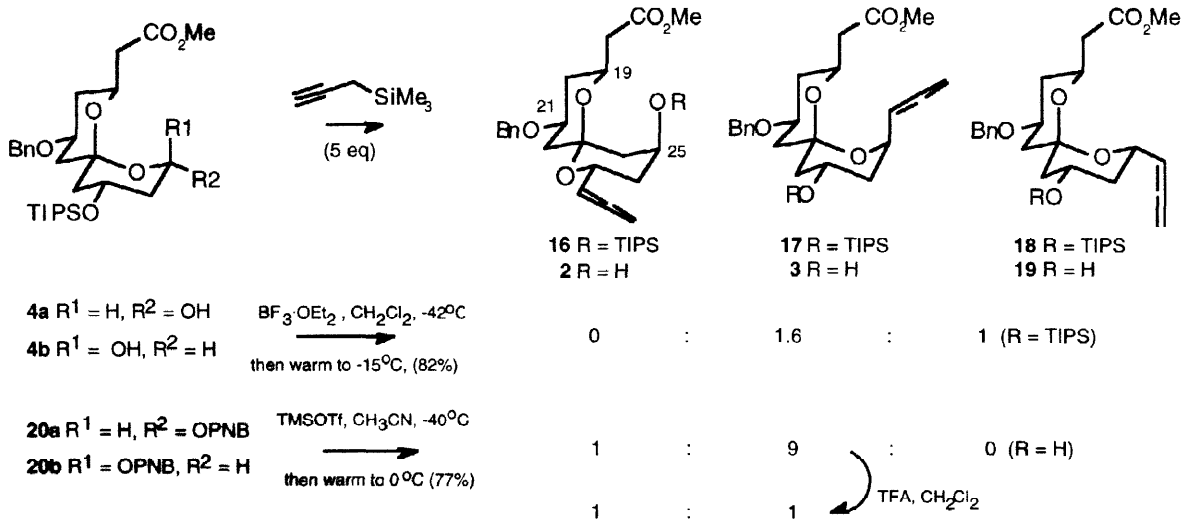


Scheme 3



Reagents: [a](i) CrO_3·2Pyr (90%); (ii) $Ph_3P{=}CH_2$, THF (47%); (iii) 80% AcOH (82%); [b](i) $CH_2{=}CHMgBr$, CuI; (ii) TsOH, MeOH (88%, for 2 steps); [c](i) 1-(2,4,6-Triisopropylbenzenesulfonyl)imidazole, NaH; (ii) lithium (trimethylsilyl)acetylide (91%); [d](i) DHP, TsOH, CH_2Cl_2 (89%) or TIPSCl, imidazole (94%); (ii) K_2CO_3, MeOH (93%); (iii) 3 equiv. $Me_3SnCu{\cdot}LiBr$ (77%); [e](i) MeLi, THF, -78°C; (ii) Lithium 2-thienylcyanocuprate; (iii) Epoxide **7** (56% from **6b**); [f](i) BnBr, KH, THF; (ii) TsOH, MeOH; (iii) TIPSCl, imidazole (69%, for 3 steps); [g](i) DDQ; (ii) Swern oxidation (88% for 2 steps); [h](i) TMS-ketene, $MgBr_2{\cdot}OEt_2$, CH_2Cl_2, -60°C, 12h; (ii) $KF{\cdot}2H_2O$, CH_3CN (77% for 2 steps); (iii) O_3, CH_2Cl_2, -78°C; Ph_3P (72%); [i]K_2CO_3, MeOH (94%).

Scheme 4

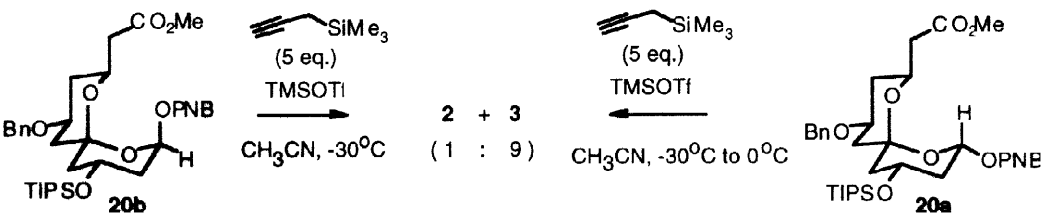


From compound **12**, stannanes **6a** and **6b** were obtained in a three-step sequence which entailed alcohol group protection, alkyne desilylation, and finally regioselective stannyl cuprate addition to the monosubstituted triple bond.[10] Unfortunately, the Brook rearrangement prevented the formation of a stable alkenyllithium reagent from the TIPS-protected stannane **6a**,[11] and thus a direct route to intermediate **14**. However, this problem could be circumvented using stannane **6b** instead, which, following metal exchange and addition to epoxide **7**, provided alcohol **13** in 56% overall yield. The conversion of compound **13** to aldehyde **15** proceeded without event, in acceptable yields. A chelation-controlled 2+2 cycloaddition reaction of aldehyde **15** with TMS-ketene proceeded with complete anti-selectivity;[12] low temperature ozonolysis then provided ketoaldehyde **5** as a single diastereomer. Base-induced ring opening of compound **5** (K_2CO_3, MeOH, 1 min) liberated the required β-hydroxy methyl ester, which immediately cyclized to a mixture (7:1) of spirolactols **4a** and **4b**.

With the spiroketal ring formed, we were ready to attempt the necessary substitution reaction at C2 (Scheme 4). Unlike our model studies, the stereoselectivity of the C2-allenation on this framework was found to be substrate-dependent. Treatment of the mixture of spirolactols **4a** and **4b** with propargylsilane (5 equiv.) and BF_3OEt_2 (2 equiv.) in CH_2Cl_2 at -42°C gave a mixture of spiroketals **17** and **18** in a 1.6:1 ratio (82%). Surprisingly, the monoanomeric spiroketal product **16** was completely absent from the product mixture. A different result was observed when the corresponding p-nitrobenzoates **20a** and **20b** were used. Allenation of this mixture with TMSOTf in CH_3CN solvent gave a 9:1 mixture of the desilylated spiroketals **3** and **2**[13] (77%), favoring the undesired bis-anomeric product. In this case, spiroketal **19**, was absent. Fortunately, the 9:1 ratio of spiroketals **2** and **3** could be equilibrated to a ca. 1:1 mixture using the conditions reported by Heathcock (TFA, CH_2Cl_2).[5b] Spiroketal **2** could be separated from **3** by column chromatography. The undesired spiroketal **3** could then be re-equilibrated to allow further isolation of the desired product. Rigorous NOE difference experiments confirmed the structure of spiroketal **2**. Irradiation of the axial C19-proton gave diagnostic signal enhancements of both the axial C21-proton and the C25-hydroxy proton.

Other observations are worthy of note. The p-nitrobenzoate anomers **20a** and **20b**, separated by column chromatography, reacted individually (Scheme 5) to give identical product mixtures, providing strong evidence for reaction via a C2-oxonium ion. Not unexpectedly, the axial isomer **20b** reacted at -30°C, while the equatorial isomer **20a** required warming to 0°C in order to take the reaction to completion, also consistent with oxonium ion formation.

Scheme 5



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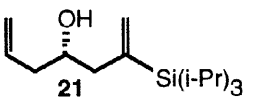
11. Compound **21** was the only product formed when vinyl stannane **6a** was treated with MeLi at -78°C. Analogous rearrangements were observed with both TBS and TBDMS protective groups.



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13. ^{1}H nmr (C_6D_6, 300 MHz) δ 1.04 (1H, dd, J = 11.7, 11.7 Hz), 1.09 (1H, dd, J = 14.4, 4.2 Hz), 1.50 (1H, dddd, J = 12.9, 4.2, 2.1, 2.1 Hz), 1.55-1.61 (1H, m), 1.71 (1H, dd, J = 12.6, 12.6 Hz), 1.94 (1H, ddd, J = 14.7, 2.1, 2.1 Hz), 1.97 (1H, dd, J = 16.5, 2.9 Hz), 2.01 (1H, dd, J = 4.8, 1.8 Hz), 2.05 (1H, dd, J = 4.2, 1.8 Hz), 2.32 (1H, dd, J = 16.5, 9.9 Hz), 3.28 (1H, m), 3.30 (3H, s), 3.71 (1H, m), 3.99 (1H, dddd, J = 10.2, 6.0, 3.3, 3.3 Hz), 4.09 (1H, d, J = 10.2 Hz), 4.22-4.31 (2H, AB m), 4.51-4.63 (2H, m), 5.17 (1H, m), 5.35 (1H, ddd, J = 6.6, 6.6, 6.6 Hz), 7.15-7.30 (5H);

    ^{13}C nmr (C_6D_6, 75 MHz) δ 35.00, 37.57, 38.50, 40.81, 43.69, 51.37, 63.72, 67.03, 67.58, 69.68, 71.39, 76.91, 93.40, 99.75, 127.56, 127.85, 128.53, 139.26, 171.47, 208.39