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A MODULAR APPROACH TO MARINE MACROLIDE CONSTRUCTION. 2. CONCISE STEREOCONTROLLED SYNTHESIS OF THE C17-C28 (CD) SPIROACETAL COMPONENT

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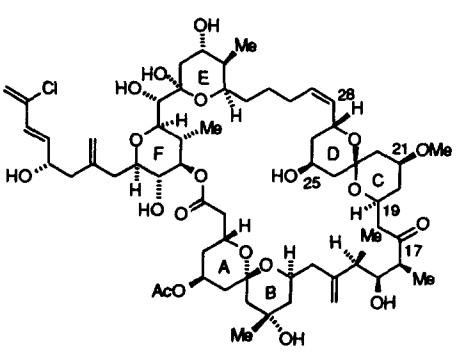
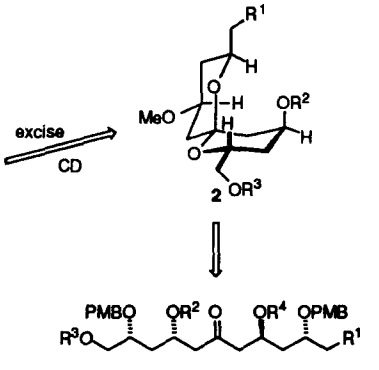
Abstract: The CD spiroacetal ring system of altohyrtin A, which houses one-fifth of the stereogenic centers resident in the macrolide, has been synthesized through a combination of aldol condensations having different stereocontrol elements. © 1997 Elsevier Science Ltd.

The spongistatins,[2] altohyrtins,[3] and cinachyrolide A[4] are structurally novel and exceedingly potent cytotoxins having a complex macrocyclic lactone polyether core. The further exploitation of these compounds for human health is plagued by their exceedingly limited supply. In pursuit of their total synthesis for the purpose of providing material for more extensive biological evaluation, we[5] and others[6,7] have previously addressed issues surrounding construction of their AB spiroacetal sector. The first successful elaboration of the distinctive CD segment of altohyrtin A (**1**) is reported herein. Significantly, the present route, which is concise, convergent, and highly stereocontrolled, should prove as readily applicable to preparation of the enantiomer as required.[5]



1



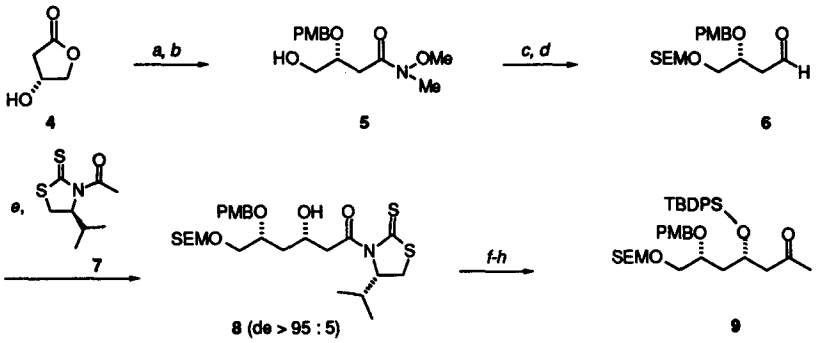
3

Retrosynthetically, **2** was expected to derive from building block **3** following simultaneous oxidative removal of the pair of PMB protecting groups. For this reason, we chose to pursue proper installation of the several oxygenated centers in this highly functionalized ketone. As will be seen,

practical asymmetric synthesis of **3** takes maximum advantage of the protocols developed at the fundamental level by Nagao[8] and Mukaiyama.[9]

Construction of the left half of **3** began with enantiomerically pure lactone **4**, which is easily generated from (*R*)-malic acid.[10] Once conversion to the PMB derivative had been accomplished, ring opening was brought about by the Weinreb reagent[11] to furnish **5** (Scheme 1). Capping of the primary hydroxyl group in **5** as the SEM derivative made possible smooth reduction to aldehyde **6** in 95% yield. Tin(II) triflate-promoted coupling of (*S*)-**7** with **6** in the presence of N-ethylpiperidine was deployed for the purpose of setting the requisite syn-1,3-diol relationship. The highly stereocontrolled course of this transformation, which led to **8** (78%) of greater than 95% de, had significant positive implications for the ensuing generation of methyl ketone **9**.

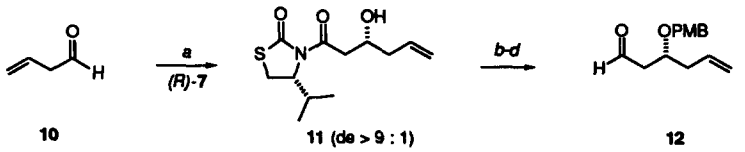
Scheme 1



[a] $PMBOC(=NH)CCl_3$, CSA, CH_2Cl_2, rt, 12 h, 76%. [b] $Me_2AlN(Me)OMe$, CH_2Cl_2, -20 °C to rt, 12 h, 95%. [c] SEMCl, Hünig's base, CH_2Cl_2, 12 h, 91%. [d] Dibal-H, CH_2Cl_2, -78 °C, 1 h, 95%. [e] $Sn(OTf)_2$, N-ethylpiperidine, -50 to -40 °C, 4 h; **6**, -78 °C, 2 h, 78%. [f] As in *b*, 91%. [g] TBDPSCl, imid, CH_2Cl_2, (DMF), reflux, 12 h, 98%. [h] MeMgBr, Et_2O, -20 to 0 °C, 1 h, 91%.

The complementary right half was assembled from the previously described 3-butenal (**10**).[12] We were not disappointed to observe that **10** could be condensed with (*R*)-**7** under conditions involving minimal migration of its double bond (Scheme 2). The singular production of **11** (92% isolated) was followed by conversion to the Weinreb amide in advance of PMB protection and reduction to the desired aldehyde **12**.

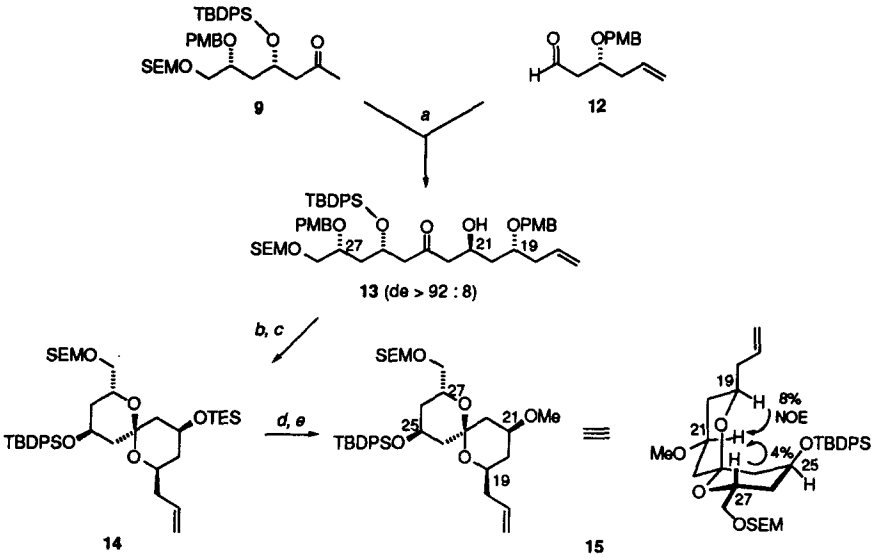
Scheme 2



[a] (*R*)-**7**, $Sn(OTf)_2$, N-ethylpiperidine, CH_2Cl_2, -40 to -50 °C, 2 h; **10**, -78 °C, 2 h, 92%. [b] $Me_2AlN(Me)OMe$, CH_2Cl_2, -20 °C to rt, 12 hr, 98%. [c] $PMBOC(=NH)CCl_3$, CSA, CH_2Cl_2, rt, 12 h, 78%. [d] Dibal-H, CH_2Cl_2, -78 °C, 1 h, 70%.

With the cross-coupling partners **9** and **12** in hand, their proper amalgamation was effected via the silyl enol ether of the ketone under catalysis by boron trifluoride etherate.[13] In this way, advantage was taken of the ability of the β-OPMB substituent in **12** to guide 1,3-induction heavily in the anti direction by means of its electrostatic involvement. Indeed, this effect proved to be significant, **13** being produced with a level of facial bias in excess of 92:8 (Scheme 3). A highly chemoselective two-step sequence was employed to install a triethylsilyl (TES) ether into **13** at C21 and to remove the *p*-methoxybenzyl groups at C19 and C27. Spontaneous cyclization to deliver **14** followed the unmasking of the pair of hydroxyl substituents. Hydrolysis of **14** with aqueous acetic acid resulted in conversion to the C21 alcohol from which **15** was obtained by conventional O-methylation.

Scheme 3



[a] (1) **9**, $LiN(SiMe_3)_2$, Me_3SiCl, THF, -78 to 0 °C, 7 h; (2) **12**, $BF_3{\cdot}OEt_2$, THF, -78 °C, 2 h, 77%. [b] TESCl, imid, CH_2Cl_2, (DMF), 1 h, 100%. [c] DDQ, CH_2Cl_2, H_2O, rt, 1 h, 89%. [d] HOAc/THF/H_2O (5:5:1), 5 h, 93%. [e] MeOTf, 4-methyl-2,6-di-*tert*-butylpyridine, $CHCl_3$, reflux, 12 h, 75%.

The stereochemical definition of **15** rests on the following points. The absolute configuration of C27 has its origins in **4** and is therefore incontrovertible. The tactic utilized to introduce C19 and C25, *viz.*, a diasterocontrolled aldol reaction between the tin(II) enolate of the *R*- or *S*-enantiomer of the N-acetyl isopropyl-1,3-thiazolidine-2-thione **7**, has proven itself to be widely reliable in a variety of contexts.[14] Less experience has been reported for the 1,3-asymmetric induction protocol deployed to secure **13**.[15] However, the diagnostic 300 MHz ^1H NMR spectrum of **15** (in C_6D_6 solution) nicely confirms each of the stereochemical expectations. Thus, H19 (δ 3.97) exhibits a significant NOE interaction with H21 (δ 3.75), and neither of these protons is in close proximity to

H25. These data require that H19 and H21 be axially disposed as shown. Further, the multiplets from H25 (δ 4.27) and H27 (δ 4.16) were completely resolved in $CDCl_3$ at 300 MHz; selective irradiation of H27 gave rise to an NOE interaction (2%) with phenyl protons of the TBDPS group. The features and the equatorial nature of H25 closely mimic the conformation of the CD sector present in **1**.[3d]

In summary, a unified, highly convergent synthesis of the CD spiroacetal subunit of **1** has been devised, confirming the latter part structure. The successful route exploited enantioselective and diastereoselective C-C bond-forming reactions so as to maximize convergency. We expect to report on the further elaboration of **1** and its congeners in due course.

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