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Asymmetric Synthesis of (+)-Polyanthellin A

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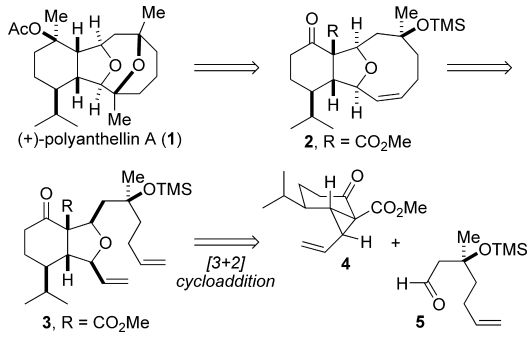
Gorgonian octocorals produce novel metabolites in myriad natural product families, of which cladiellins and related C2/C11-cembranoids have attracted significant interest from the chemistry community. These compounds intrigue synthetic chemists in part because of their unusual structural topology, which includes a tricyclic ring system composed of a hydroisobenzofuran core and an oxonane moiety. Certain members exhibit therapeutic biological activity that provides medical relevance. In this context, total syntheses of the antitumor agents schlerophytin A,[1,2] 11-acetoxy-4-deoxyasbestinin D,[3] and vigulariol[4,5] have been completed.[6]

Polyanthellin A (**1**) is a reported antimalarial agent[7] and has the unusual feature of being isolated independently in each antipodal form, first in the waters off east Australia[8] and more recently near the southwest coast of Puerto Rico.[7] Kim has reported the only asymmetric total synthesis of this novel structure containing two ether bridges,[9] while Molander has reported a synthesis of the 3,7-diastereomer.[10] This communication details a concise asymmetric synthesis of (+)-polyanthellin A that relies on a stereospecific and stereoselective cyclopropane/aldehyde cycloaddition to construct the core tetrahydrofuran.

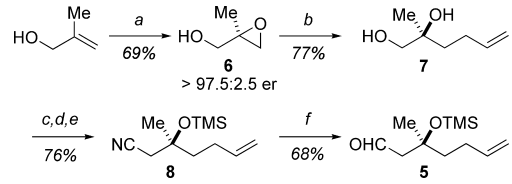
Scheme 1. Retrosynthesis of (+)-Polyanthellin A



We anticipated that the tertiary acetate and the tetrahydropyran in **1** could arise from inter- and intramolecular addition of oxygen nucleophiles to alkenes derived from **2**. The medium ring ether would be produced by a ring-closing metathesis of diene **3**. The functional groups presented in tetrahydrofuran **3** collectively constitute a retron for a Lewis acid catalyzed formal [3+2] cycloaddition of donor−acceptor cyclopropane **4** and β-silyloxy aldehyde **5**. These cycloadditions are known to provide *cis*-2,5-disubstituted tetrahydrofurans with high levels of diastereocontrol and proceed with inversion of the cyclopropane stereocenter bearing the donor group;[11] therefore, the preparation of the illustrated diastereomer of **4** with the vinyl group on the concave (α) face of the bicyclo[4.1.0]heptanone was projected to be essential for obtaining the characteristic cladiellin stereochemistry in the hydroisobenzofuran core.

Aldehyde **5** was synthesized from methallyl alcohol in six steps (Scheme 2). Following epoxidation of methallyl alcohol using catalytic Sharpless conditions,[12,13] the epoxide[14,15] **6** was opened using allyl cuprate to furnish diol **7**. The primary alcohol was selectively converted to the nitrile by tosylation and cyanide substitution, and the tertiary alcohol was protected as the TMS-ether. DIBAL-H reduction of the nitrile in CH_2Cl_2 provided aldehyde **5**.

Scheme 2. Synthesis of Aldehyde **5**[a]



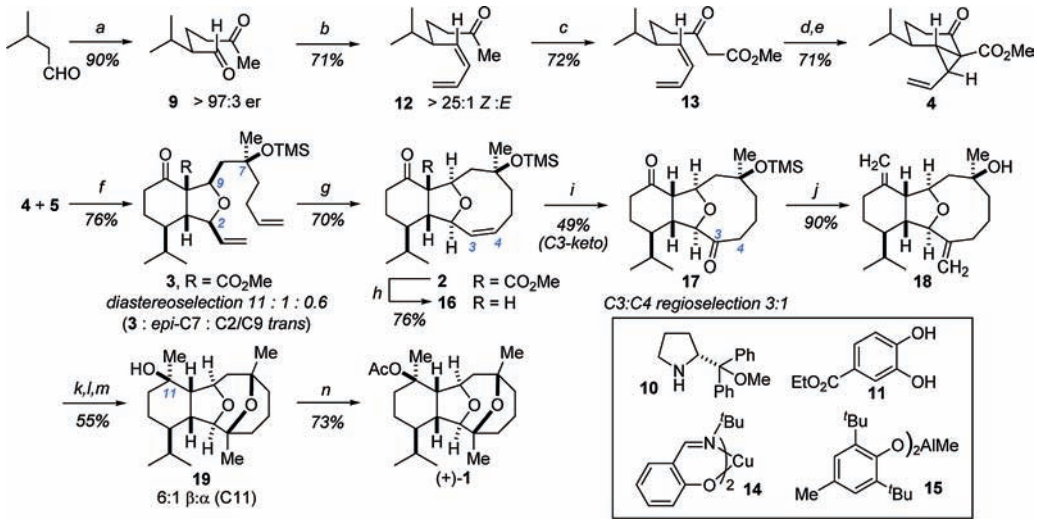
[a] Conditions: (a) $Ti(O^iPr)_4$ (7.5 mol %), (−)-DET (10 mol %), TBHP, 4 Å MS, CH_2Cl_2, −20 °C; (b) Li_2CuCl_4 (10 mol %), AllylMgCl, THF, −60 to −20 °C; (c) *p*-TsCl, Et_3N, DMAP, CH_2Cl_2; (d) KCN, 60% aq. EtOH; (e) TMSCl, imidazole, DMF; (f) DIBAL-H, CH_2Cl_2, −78 to −45 °C.

The synthesis of bicyclo[4.1.0]heptanone **4** began with an enantioselective organocatalytic conjugate addition of isovaleraldehyde to methyl vinyl ketone using diphenylprolinol methyl ether **10**.[16] In our hands the use of catechol **11** as a cocatalyst, although not specifically prescribed for **9**, was necessary for a reasonable reaction rate and product yield.[17,18] The aldehyde **9** was selectively converted to the (*Z*)-terminal diene **12** using titanated allyldiphenylphosphine.[19] Carboalkoxylation with LiTMP/Mander's reagent[20] provided ketoester **13**. Direct cyclopropanation of **13** failed using Yang's protocol ($Mg(ClO_4)_2/I_2/Et_3N$);[21] therefore, a two-step protocol through the intermediate diazo compound was used. $Cu(^tBuSal)_2$ (**14**)[22] catalyzed intramolecular cyclopropanation in 78% yield when the diazo compound was added via syringe pump over 20 h. Various Rh-catalysts were evalulated, but C−H insertion to provide cyclopentanone products was a competitive process.

Initial attempts to conduct the cycloaddition with **4** and **5** were met with failure due to the instability of aldehyde **5** toward both β-elimination and aldol reaction using standard Lewis acids ($SnCl_4$, $Sn(OTf)_2$). Extensive screening revealed the potent but sterically hindered $MADNTf_2$ catalyst,[23] formed *in situ* from the protonolysis of MAD[24] (**15**) with $HNTf_2$, provided **3** in 76% yield with good diastereoselection.[25] We propose the cycloaddition occurs through a cationic aluminum complex, which activates **4** via chelation.[26] Ring-closing metathesis (RCM) was conducted under high dilution conditions with H-G2 to provide nine-membered ether **2**. The use of chlorinated solvents was essential to inhibit formation of the corresponding eight-membered ring, presumably via an olefin isomerization event that occurs prior to the RCM.[27] Removal of the ester under Krapcho conditions gave the *cis*-ring juncture exclusively in 76% yield. Direct hydroboration/TPAP oxidation[28] of alkene **16** produced C3 ketone **17** selectively over the C4 regioisomer, although in moderate yield. The ketones were separated, after which a double Wittig methylenation of **16** and TMS-removal provided dienol **18**.

10.1021/ja904136q CCC: $40.75

Scheme 3[a]



[a] Conditions: (a) 1.5 equiv of MVK, **10** (5 mol %), **11** (20 mol %), neat, 4 °C; (b) $Ph_2PCH_2CH{=}CH_2$, ^{t}BuLi, THF, −78 to 0 °C; $Ti(O^iPr)_4$, −78 °C; **9**, −78 to 0 °C; MeI, 0 °C to rt; (c) LiTMP, THF, −78 °C; HMPA; MeOC(O)CN; (d) *p*-$AcHNC_6H_4SO_2N_3$, Et_3N, MeCN; (e) **14** (4 mol %), C_6H_6, reflux, slow addition of diazo over 20 h; (f) 3.0 equiv of **5**, MAD (**15**, 15 mol %), $HNTf_2$ (10 mol %), CH_2Cl_2, −30 °C; (g) Hoveyda−Grubbs II (10 mol %), 0.0011 M, $(CH_2Cl)_2$, 80 °C, N_2 sparge; (h) 10 equiv of NaBr, aq. DMF, 120 °C; (i) BH_3·THF, Et_2O; NMO, 4 Å MS, CH_2Cl_2; TPAP; (j) 6.0 equiv of $MePPh_3Br$, 5.0 equiv of NaHMDS, C_7H_8, 80 °C; THF, 1.0 M HCl; (k) I_2, $NaHCO_3$, 4 Å MS, MeCN; (l) $Hg(OAc)_2$, 1:1 acetone/H_2O; (m) Bu_3SnH, AIBN, C_6H_6, 60 °C; (n) Ac_2O, DMAP, Et_3N, CH_2Cl_2.

A double sequential oxymercuration with $Hg(OAc)_2$ was planned, in analogy with Kim's synthesis,[9] but only 10% of deacetylpolyanthellin A (**19**) was obtained using these conditions. Instead, a three-step protocol involving iodoetherification, oxymercuration, and global reduction with Bu_3SnH/AIBN was used to afford **19** as a 6:1 mixture of diastereomers. Both were acetylated and then separated to provide (+)-**1**, which matched the reported spectral and optical rotation data,[7−9] in 15 linear steps from methallyl alcohol.

In summary, an expeditious route to the cladiellin hydroisobenzofuran core and (+)-**1** is reported. Central to the completion of this synthesis was the discovery that $MADNTf_2$ enables the [3+2] cycloaddition of aldehydes and cyclopropanes containing labile functionality. This should permit this methodology to be applied to yet more complex systems.

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Supporting Information Available: Experimental procedures and compound chacterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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