

Asymmetric Synthesis of (+)-Polyanthellin A

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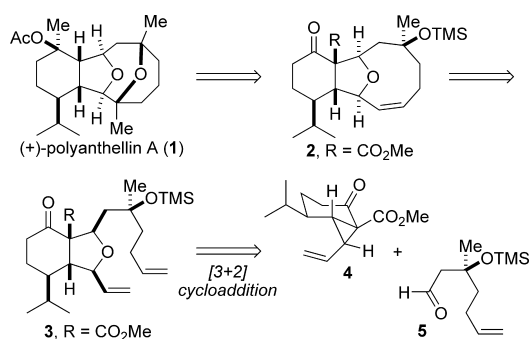
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Gorgonian octocorals produce novel metabolites in myriad natural product families, of which cladiellins and related C2/C11-cembranoids have attracted significant interest from the chemistry community. These compounds intrigue synthetic chemists in 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 agent⁷ and has the unusual feature of being isolated independently in each antipodal form, first in the waters off east Australia⁸ 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.

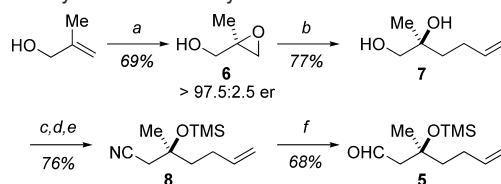
Scheme 1. Retrosynthesis of (+)-Polyanthellin A



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

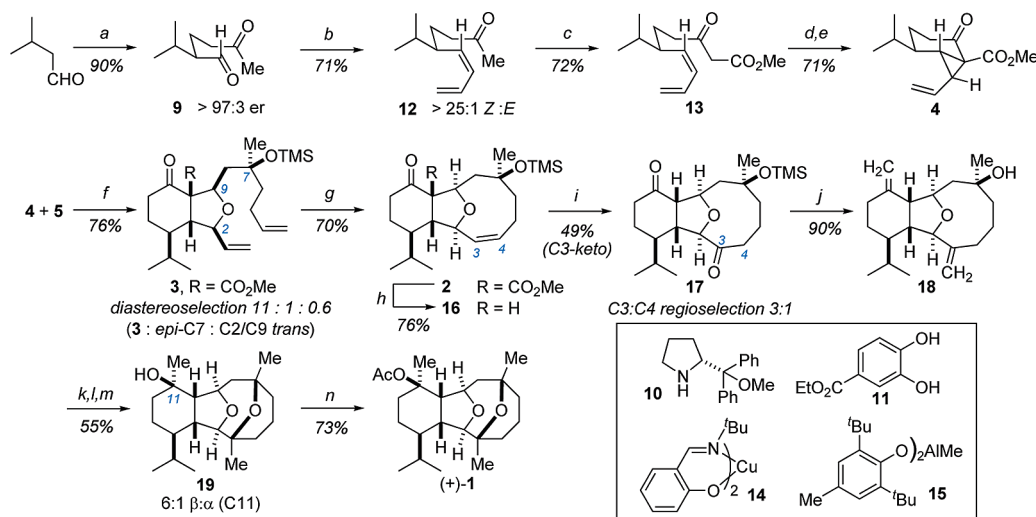
catalytic Sharpless conditions,^{12,13} the epoxide^{14,15} **6** was opened using allyl cuprate to furnish diol **7**. The primary alcohol was selectively converted to the nitrile by tosylation and cyanide substitution, and the tertiary alcohol was protected as the TMS-ether. DIBAL-H reduction of the nitrile in CH_2Cl_2 provided aldehyde **5**.

Scheme 2. Synthesis of Aldehyde **5**^a

^a Conditions: (a) $\text{Ti}(\text{O}^i\text{Pr})_4$ (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 reagent²⁰ provided ketoester **13**. Direct cyclopropanation of **13** failed using Yang's protocol ($\text{Mg}(\text{ClO}_4)_2/\text{I}_2/\text{Et}_3\text{N}$);²¹ therefore, a two-step protocol through the intermediate diazo compound was used. $\text{Cu}(\text{BuSal})_2$ (**14**)²² catalyzed intramolecular cyclopropanation in 78% yield when the diazo compound was added via syringe pump over 20 h. Various Rh-catalysts were evaluated, 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 , $\text{Sn}(\text{OTf})_2$). 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 oxidation²⁸ 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**.

Scheme 3^a

^a Conditions: (a) 1.5 equiv of MVK, **10** (5 mol %), **11** (20 mol %), neat, 4 °C; (b) Ph₂PCH₂CH=CH₂, ^tBuLi, THF, −78 to 0 °C; Ti(OⁱPr)₄, −78 to 0 °C; MeI, 0 °C to rt; (c) LiTMP, THF, −78 °C; HMPA; MeOC(O)CN; (d) *p*-AcHNHC₆H₄SO₂N₃, Et₃N, MeCN; (e) **14** (4 mol %), C₆H₆, reflux, slow addition of diazo over 20 h; (f) 3.0 equiv of **5**, MAD (**15**, 15 mol %), HNTf₂ (10 mol %), CH₂Cl₂, −30 °C; (g) Hoveyda–Grubbs II (10 mol %), 0.0011 M, (CH₂Cl)₂, 80 °C, N₂ sparge; (h) 10 equiv of NaBr, aq. DMF, 120 °C; (i) BH₃·THF, Et₃O; NMO, 4 Å MS, CH₂Cl₂; TPAP; (j) 6.0 equiv of MePPh₃Br, 5.0 equiv of NaHMDS, C₇H₈, 80 °C; THF, 1.0 M HCl; (k) I₂, NaHCO₃, 4 Å MS, MeCN; (l) Hg(OAc)₂, 1:1 acetone/H₂O; (m) Bu₃SnH, AIBN, C₆H₆, 60 °C; (n) Ac₂O, DMAP, Et₃N, CH₂Cl₂.

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 Bu₃SnH/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 MADNTf₂ 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.

Acknowledgment. We thank Prof. Deukjoon Kim for providing an authentic synthetic sample of polyanthellin A. This research was supported by the NSF (CHE-0749691) and Novartis (Early Career Award to J.S.J.).

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

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JA904136Q