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In Pursuit of Pestalotiopsin A via Zirconocene-Mediated Ring Contraction

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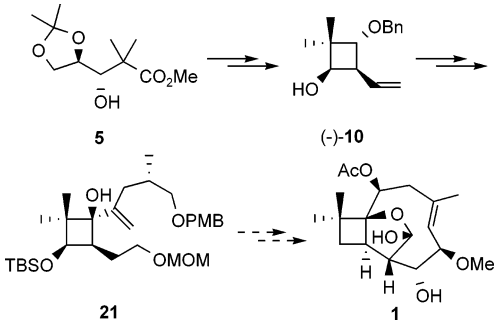
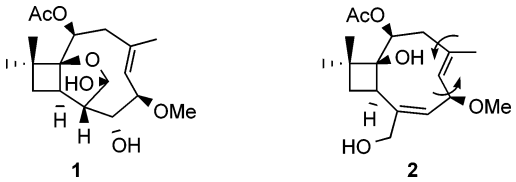
ABSTRACT



An asymmetric route from the epimeric *β*-hydroxy esters 4 and 5 to the densely functionalized (+)-10 and (–)-10, respectively, is described. Either cyclobutanol can be made available as the predominant product. The levorotatory antipode has been transformed into the advanced intermediate 21 bearing side chains destined to become incorporated into the cyclononene ring of the title compound (1).

The highly successful introduction of taxol[1] into cancer chemotherapy[2] has caused its natural habitat, the Pacific yew *Taxus brevifolia*, to be thoroughly examined for secondary metabolites. Associated microorganisms have likewise come under intense scrutiny. This surge of activity has been rewarded with the discovery and isolation of two endophytic fungi having novel properties. The first microorganism to be recognized was *Taxomyces andreanae*, a species capable of producing taxol in pure cultures.[3] The second was identified as a *Pestalotiopsis* species, the interest in which stems from its ability to generate the caryophyllene-type sesquiterpenes defined as pestalotiopsins A (**1**) and B (**2**).[4] Together these natural products constitute a unique pair of compounds, in that **1** shows very respectable immunosuppressive activity in the mixed lymphocyte reaction (IC_{50} = 3−4 μg/mL), whereas **2** exhibits little interesting biology. The oxatricyclic architecture resident in **1** has therefore been singled out as the sector likely responsible for its pharmacological profile,[5] which also includes cytotoxicity at roughly the same applicable level of effectiveness. Whereas the architectural features associated with **1** rigidify the structural framework, **2** exists as two slowly equilibrating atropisomers in chloroform solution at room temperature.



In light of these findings, **1** has become an attractive synthetic target. The Procter group has examined a stereocontrolled approach to a functionalized 2-oxabicyclic intermediate that takes advantage of the ability of samarium diiodide to effect a key 4-*exo*-*trig* cyclization.[5,6] More recently, Tadano has explored an asymmetric route that features a Lewis acid catalyzed [2 + 2] cycloaddition as the

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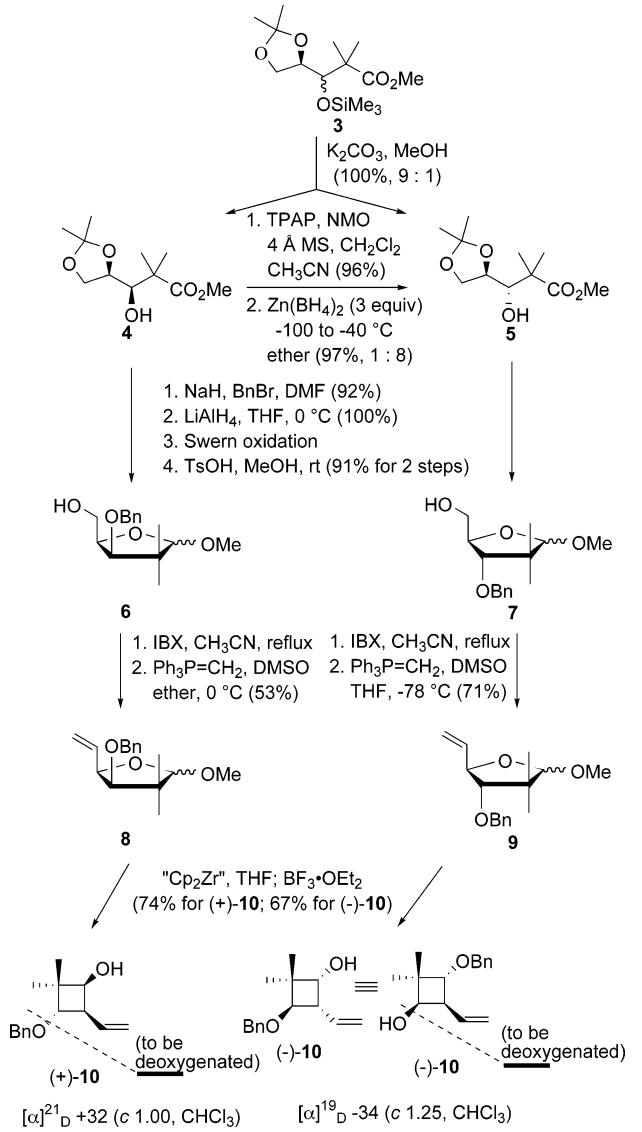
means to craft an enantioenriched cyclobutane precursor to a related lactone.[7]

We have recently demonstrated that the deoxygenative ring contraction of vinylated furanosides can be applied successfully to the elaboration of enantiopure polysubstituted cyclobutanes that feature several stereogenic centers of defined absolute configuration.[8] With this success as a backdrop, we have presently focused our attention on the enantioselective construction of the core of **1**. The pathway originated with D-glyceraldehyde acetonide, a building block readily available from D-mannitol.[9]

Kita and co-workers have demonstrated that Lewis acid catalyzed aldol reactions of such aldehydes with ketene silyl acetals proceed diastereoselectively to give the corresponding β-siloxy ester exemplified by **3** (Scheme 1).[10] In this instance, the hydroxyl group could be unmasked quantitatively with potassium carbonate in methanol, thereby allowing for the convenient, large-scale separation of **4** from **5** (9:1). Because the direct generation of **5** as the major product through an uncatalyzed aldol reaction is not practical,[11] inversion of the epimeric ratio to 1:8 was realized by perruthenate oxidation[12] of the original **4**/**5** mixture followed by low-temperature (−100 to −40 °C) reduction of the resulting ketone with zinc borohydride in ether.[13] In turn, both hydroxy esters were *O*-benzylated in a highly efficient manner provided that the addition of benzyl bromide was conducted at a very slow rate. The independent reduction of these products with $LiAlH_4$ generated the primary carbinols, making it possible to effect sequential oxidation to the aldehyde level under Swern conditions and cyclization to the methyl furanosides **6** and **7** with *p*-toluenesulfonic acid in methanol. Advantage was next taken of the ability of IBX in refluxing acetonitrile[14] to bring about conversion to the sensitive aldehydes, which were submitted directly to Wittig olefination without column chromatography. The extent of competing β-elimination was more extensive when producing **8** relative to **9**, presumably as the direct result of a more sterically crowded *trans* E_2 elimination option available to the former. Alternatively, this phenomenon may reflect the increased accessibility of the enolizable proton in the aldehyde leading to **8** with respect to that leading to **9**.

Significantly, all four vinylated furanosides proved to be responsive to the zirconocene ring contraction conditions,[15] thus providing experimental verification of this route as a tactic well suited to accessing the enantiomerically pure *gem*-dimethyl substituted cyclobutanols (+)-**10** and (−)-**10**. The desirability of crafting both antipodes of **10** originated from our recognition of the fact that reductive removal of the benzyloxy substituent in (+)-**10** or the hydroxyl group in (−)-**10** permits targeting of the *same enantiomer* of pestalotiopsin A. Furthermore, since the absolute configuration of **1** is presently unknown, deoxygenation of (+)-**10** or (−)-**10** in the reverse fashion would allow acquisition of the other enantiomer of the target. Different chemical challenges were anticipated. As matters have worked out, (−)-**10** lends itself well to efficient conversion to **17** (Scheme 2). Deoxygenation studies performed at the vinylcyclobutanol stage proved to be uniformly unsuccessful. To skirt this problem, the next steps involved protection as the TBS ether and anti-Markovnikov hydration. To ensure a high yield of **12**, the hydroboration reaction was performed with a low loading

Scheme 1. Synthesis of Cyclobutanols (+)-**10** and (−)-**10**



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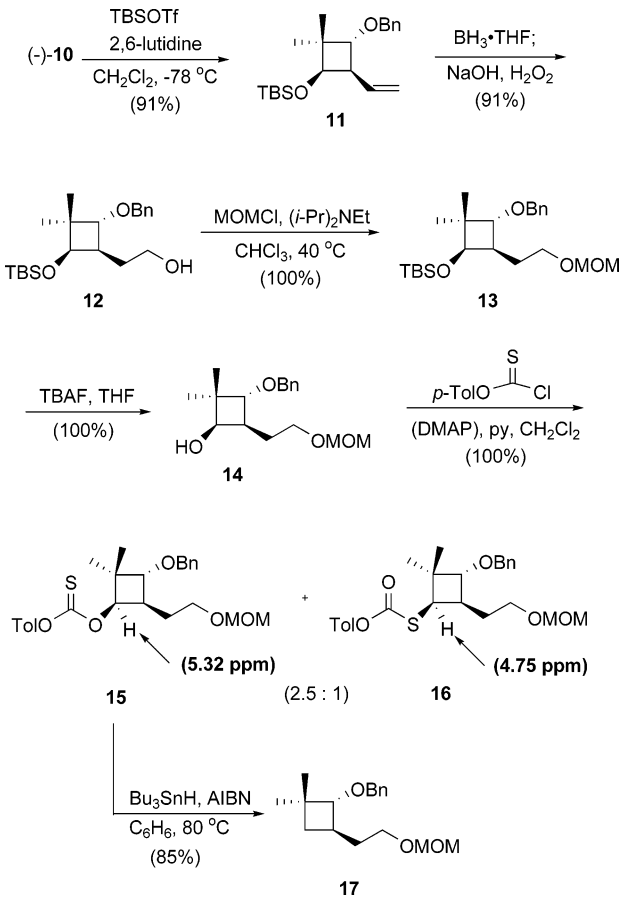
Scheme 2. Adjusting Functionality on the Four-Membered Ring



of borane as well as alkaline hydrogen peroxide, but not sodium perborate. The road to **17** was subsequently paved by coupling **12** to MOMCl in advance of desilylation and functionalization of the hydroxyl group with *O*-*p*-tolyl chlorothionoformate.[16] The latter step proceeded slowly but led in quantitative fashion to the isomeric products **15** and **16** (2.5:1).[17] The major constituent was deemed to be the *O*,*O*-thiocarbonate on the strength of the downfield shift of H-1 (5.32 ppm) relative to that exhibited by the *O*,*S*-thiocarbonate **16** (4.75 ppm). The intense IR band displayed by **16** at 1761 cm^{-1} provided added confirmation. Furthermore, the stereochemical assignments to **15** and **16** are based on the application of NOESY methods that reveal strong correlation of the 1,3-related cyclobutane protons with different components of the *gem*-dimethyl group. As anticipated, **15** underwent efficient reduction to **17** (85%) when heated with tributyltin hydride and AIBN in benzene.

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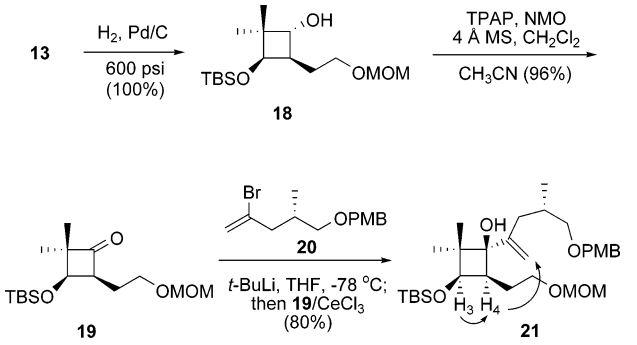
Although the pathway embodied in Scheme 2 demonstrates the feasibility of a key deoxygenative step, we viewed removal of the OTBS group in **13** to be somewhat premature. As part of an alternative strategy, reliance could be placed on its β-orientation to relegate installation of the upper chain to the opposite face of the cyclobutane ring. Computational studies involving cyclobutanone **19** revealed the preferred trajectory of an incoming nucleophile likely to involve an angle of 107° from below plane[18] in order to avoid the steric blockade brought on by the bulky silyl moiety. To take advantage of these options, **13** was hydrogenolized at 600 psi to give **18** as a prelude to perruthenate oxidation (Scheme 3). Cyclobutanone **19** prepared in this manner was treated

Scheme 3. Attachment of Functionalized Side Chain



with $CeCl_3$ followed by vinyl bromide (*S*)-**20**, which had previously been lithiated with *tert*-butyllithium in THF at −78 °C. The single carbinol that was thereby produced (80%) was identified as **21** on the basis of COSY and NOESY correlations between H_3 and H_4 in addition to a NOESY interaction involving H_4 and a vinyl proton.

In summary, an asymmetric synthesis of the multiply functionalized cyclobutane **21** has been devised. The strategy is based on the complementary deoxygenative ring contraction of **8** and **9** and features matching of the readily available **13** with a stereocontrolled 1,2-carbonyl addition to arrive at the advanced intermediate. We hope to report on associated transformations and on the successful acquisition of **1** soon.

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Supporting Information Available: Experimental details and ^1H NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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