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cis-Decalins from Quinic Acid: Toward a Synthesis of Branimycin

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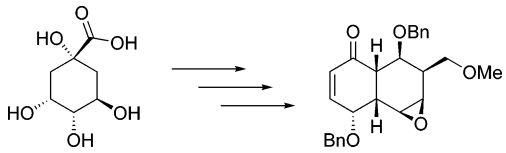
ABSTRACT



Starting from (−)-quinic acid an efficient synthesis of highly functionalized *cis*-α,β-unsaturated ketone 3, an advanced precursor of branimycin, has been accomplished via two key step reactions: a ring closing metathesis reaction to prepare the *cis*-decalin system, and a highly stereoselective epoxidation reaction.

The synthesis of highly functionalized *cis*-decalin systems has been a longstanding problem. In many cases Diels−Alder-based annulations to *p*-quinoids have been employed, but despite the conceptual simplicity of this approach the subsequent elaboration of stereogenic centers and appendages has proved problematic. Intrigued by the low price of quinic acid we looked for possibilities to annulate a second ring to this template. By using a non-Diels−Alder methodology, a richly elaborated *cis*-decalin system should be generated. As a target for this strategy we chose branimycin (**1**),[1,2] an unusual member of the nargenicin antibiotic family,[3] which has been isolated from *Streptomyces* by the Laatsch group in Göttingen.[4] Biological tests have shown that branimycin is active against *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus*, and in particular *Streptomyces viridochromogenes*. Apart form the biological activity, the complex *cis*-fused decalin core, the 1,4-oxygen bridge, and the 9-membered macrolide ring make **1** an attractive target for total synthesis.

The retrosynthetic concept is shown in Figure 1. As a key disconnection the 1,2-addition of vinyllithium subunit **2** to bicyclic 7,8-epoxy-12-ketone **3** was envisaged. This highly convergent approach necessitates efficient syntheses of both **2** and **3**. As outlined before, (−)-quinic acid[5] **7** was chosen as a starting material for **3**, to explore whether the existing chiral centers could be used to control the synthesis of an enantiomerically and diastereomerically pure *cis*-decalin system. Ring B should be constructed by a ring closing metathesis[6] (RCM) of **4**, in which the required monosubstituted double bonds were to be installed via two successive Claisen−Ireland rearrangements,[7] from protected diol precur-

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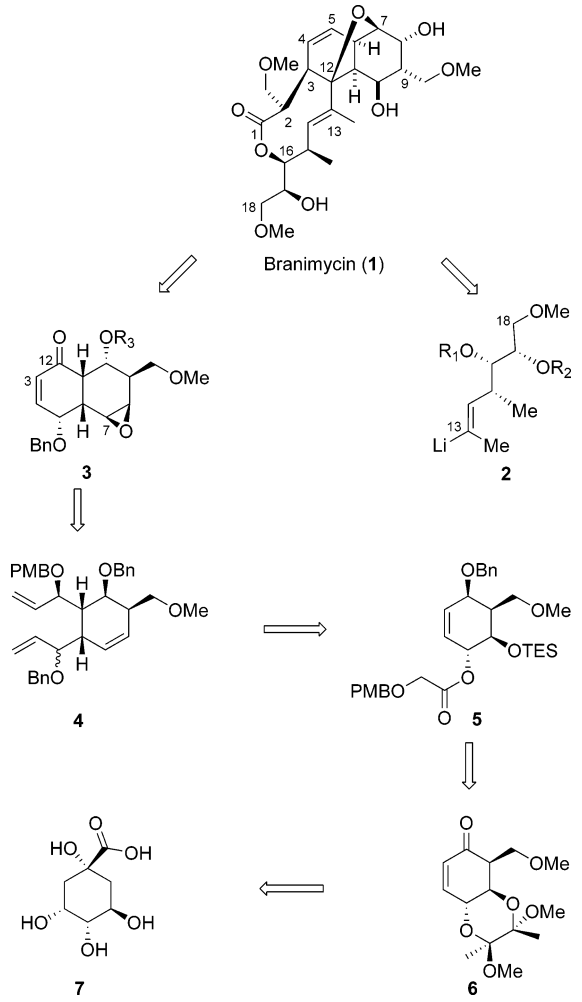


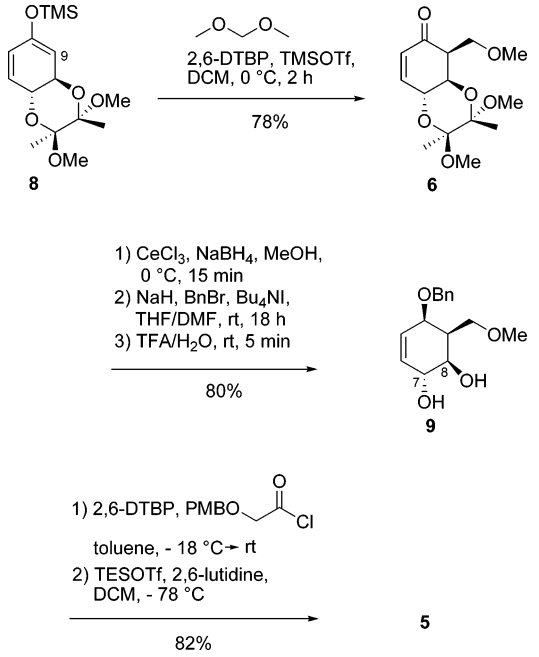
Figure 1. Retrosynthetic analysis.

sor **5**. In turn, **5** would be assembled in stereoselective fashion from enone **6**.

Our synthesis started from the known compound **8**,[8] which was subjected to a Mukaiyama-type condensation with dimethoxymethane[9] (Scheme 1) to afford **6** as a single diastereomer in moderate yield (55%, 78% after recycling). The same stereoselectivity has been observed with use of *m*-CPBA and NBS as electrophiles, which is a consequence of the conformational rigidity due to the trans-diequatorial-protected 1,2-diol. An axial attack on the electron-rich C9 avoids a twist boat conformation.[10]

Longer reaction times improved the yield remarkably, but with a sacrifice in diastereomeric ratio. Luche reduction of **6** occurred exclusively from the less hindered side. This

Scheme 1. Synthesis of Rearrangement Precursor **5**



newly formed stereocenter is planned to be inverted in a later stage of the synthesis. Benzylation and removal of the BDA[11] group furnished diol **9** in 80% yield over three steps. Conversion of **9** to **5** was achieved in a two-step sequence—regioselective acylation of the C7-hydroxy group of **9** (p-$MeOC_6H_4OCH_2COCl$,[12] 2,6-di-*tert*-butylpyridine,[13] 82% yield) followed by TES protection at the C8-hydroxy group—which set the scene for the first Claisen−Ireland rearrangement. Following Corey's procedure[14] ester **5** was converted to the silylketene acetal under internal quench conditions (TMSCl/LHMDS) and subsequently heated to give **10** (94% after one recycling step) as a mixture of isomers (Scheme 2). The low stereoselectivity for C12 was inconsequential as this stereogenic center becomes oxidized later in the synthesis. Nevertheless, the diastereomers were separated to avoid ambiguous spectra information for the proximate reaction steps. The synthesis was carried on with pure main isomer **10**, whose configuration was assigned by 2D NMR studies of the corresponding iodolactone **10a**.[15]

Acid **10** was transformed to olefin **11** in 3 steps via reduction to the corresponding aldehyde and subsequent

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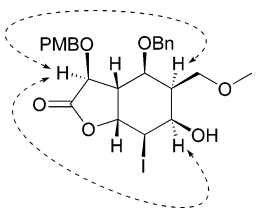
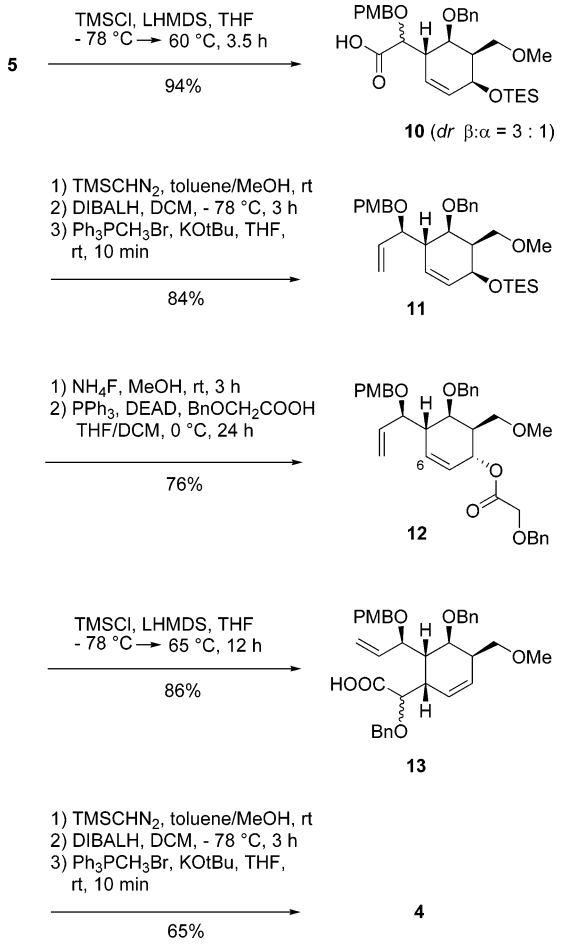
(15) Selected NOE data for **10a**.



Scheme 2. Preparation of RCM Precursor **4**



Wittig olefination[16] in 84% overall yield. To initiate the second Claisen−Ireland rearrangement **11** was desilylated and the resulting allylic alcohol was acylated to give ester **12** via Mitsunobu inversion.[17] In the course of this reaction the C6-appendage was introduced simultaneously. The conversion of **12** to di-olefin **4** followed the established four-step sequence: rearrangement to **13**, followed by esterification, reduction to the corresponding aldehyde, and Wittig olefination (dr 2:1, 56% overall yield). The RCM reaction was carried out with either the Grubbs' second generation catalyst[18] or Hoveyda−Grubbs' second generation catalyst.[19] Unfortunately it turned out that Grubbs' second generation catalyst underwent decomposition in the course of the reaction at the required temperature (ca 75 °C), whereas Grubbs−Hoveyda catalyst was stable enough to give 65% of *cis*-decalin **14** with only starting material left, which could be recycled (Scheme 3). After chromatographic separation the pure isomer **14** was deprotected (DDQ/DCM/buffer) and

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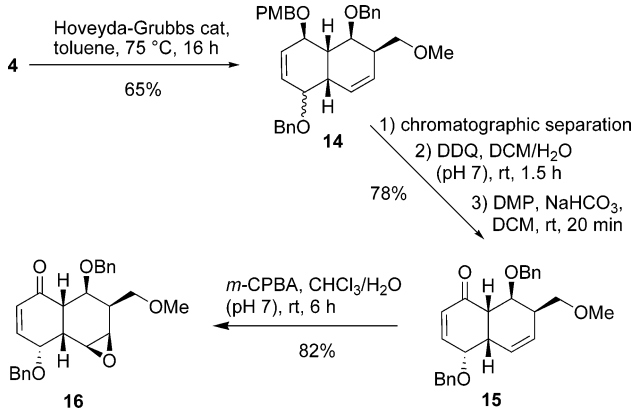
Scheme 3. Synthesis of Epoxyketone **16**



subsequently oxidized (DMP)[20] to give **15** in 78% yield (Scheme 3). 2D NMR spectra confirmed that none of the dreaded epimerization at C11 had occurred.

Stereo- and regioselective epoxidation of the C7−C8 double bond with *m*-CPBA furnished diastereomerically pure crystalline epoxyketone **16** whose relative configuration was established by single-crystal diffraction (Figure 2).

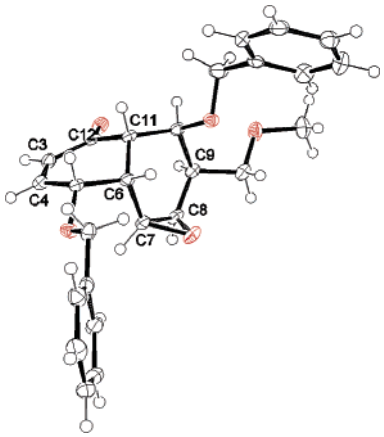


Figure 2. ORTEP-3[21] projection (ellipsoid: 50% probability) of epoxyketone **3**.

In conclusion, we have shown that quinic acid is a suitable substrate for stereocontrolled annulations via the Claisen−Ireland rearrangement; RCM protocol. Quite obviously the configurations at C6 and C11 can be manipulated at will by acylating diol **9** under retention or inversion of configuration so that *cis*- and *trans*-decalins with either absolute configuration should be available under perfect stereocontrol. Specifically, we have described an efficient route to the *cis*-decalin core of branimycin, whose further synthesis is actively pursued in our laboratory.

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Supporting Information Available: Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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