ORGANIC LETTERS

2008
Vol. 10, No. 3
413−416

A Non-Diels–Alder Approach to the *cis*-Decalin Core of Branimycin

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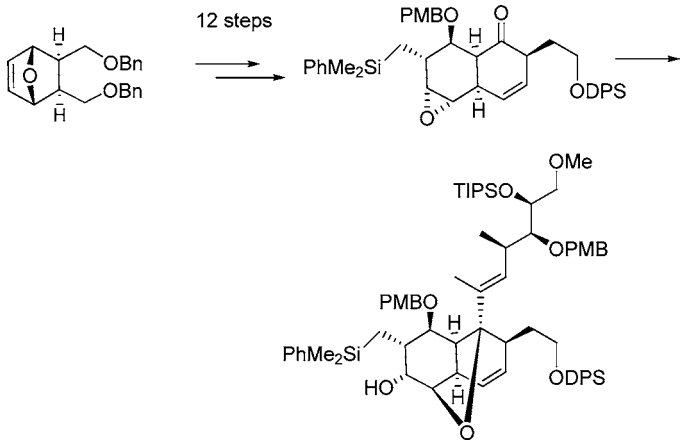
Received November 12, 2007

ABSTRACT



The synthesis of the highly substituted *cis*-decalin core of branimycin has been accomplished. A catalytic copper mediated S_N2' opening of oxabicycle 7 with Grignard reagent and ring-closing metathesis served as key transformations.

In our ongoing project toward the synthesis of the novel antibiotic branimycin **1**,[1,2] we were interested in developing a new non-Diels−Alder methodology for the synthesis of highly substituted *cis*-decalin system which turned out to be the main challenge in the synthesis of **1**.

Recently,[3] we have reported an efficient synthesis of advanced precursor of branimycin, from quinic acid via a multistep pathway including Claisen−Ireland rearrangements and ring-closing metathesis reactions. Although the synthesis was successful, some difficulties associated with it—lengthy, low diastereoselectivity and moderate yields in some steps—prompted us to develop a new approach to *cis*-decalin intermediate **3** which will be coupled at a late stage with **2** under concomitant epoxide opening and formation of the C2−C7−oxygen bridge in **1**.

In our retrosynthetic route to **3** (Scheme 1), we envisioned that the construction of the decalin core could be accomplished by a ring closing metathesis[4] (RCM) of **4**, which in turn was to be synthesized from aldehyde **5** via Hiyama−Nozaki−Kishi[5,6] reaction, followed by regio- and stereoselective epoxidation of the endocyclic double bond. Finally,

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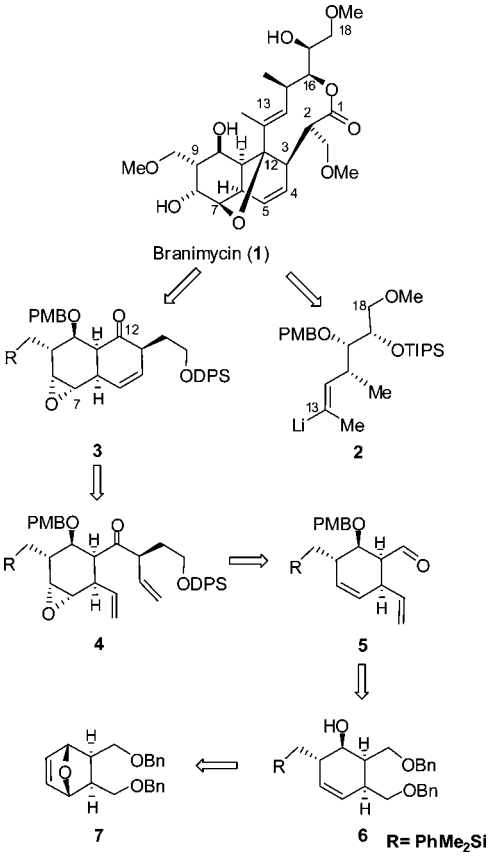
10.1021/ol7027338 CCC: $40.75
Published on Web 12/28/2007

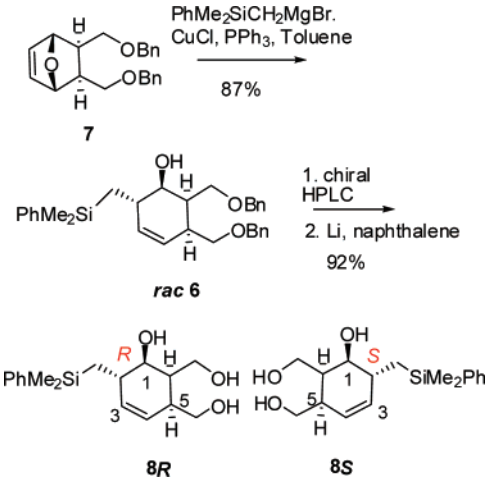
Scheme 1. Retrosynthetic Analysis of Branimycin



we anticipated that aldehyde **5** would arise from a copper-mediated S_N2' opening of oxabicycle[7,8] **7** with the Grignard reagent containing a dimethyl(phenyl)silyl group as a masked hydroxy group.[9]

The synthesis (Scheme 2) starts from the readily available dibenzyl ether **7**.[10] Following the slightly modified Arrayas' procedure, reaction of **7** with 1.6 equiv of $PhMe_2SiMgCl$ in the presence of 10 mol % CuCl and Ph_3P afforded after 24 h the desired compound **6** in a 87% yield as a single diastereomer. Separation of racemic **6** via chiral HPLC gave both enantiomers whose absolute stereochemistry was assigned using the Mosher method.[11]

Scheme 2. Synthesis of Compound **8**



The desired ***R***-enantiomer (***R*** refers to the absolute configuration at C-1) was deprotected, and the resulting diol **8*R*** was treated with *p*-methoxybenzaldehyde to give acetal **9** in 66% yield (Scheme 3).[12] Dess−Martin oxidation of **9** furnished aldehyde **10** (89%) which was used without further purification.

The direct conversion of aldehyde **10** to olefin **12**[13] proved more problematic than expected. Attempts to use Wittig-[14] or Tebbe olefination[15] or a Takai[16] reaction to install the vinyl group led to inseparable mixtures of unidentified products. Initial efforts to perform a Peterson olefination[17] using $LiCH_2TMS$ or $TMSCH_2MgCl$ also failed. It turned out that these reagents are too basic as they give a mixture of recovered aldehyde **10** and its conjugated isomer. Finally, the cerium reagent prepared from $LiCH_2TMS$ and $CeCl_3$[18] converted **10** into diastereomerically pure **11** as white needles in 92% yield. The configuration of the new stereogenic center was assigned by X-ray diffraction studies on single crystals of **11** (Figure 1)

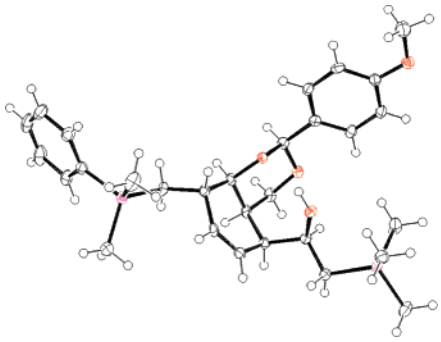


Figure 1. ORTEP-3[19] projection (ellipsoid: 50% probability) of compound **11**.

obtained by slow diffusion of hexane into a corresponding ethyl acetate solution.

The exclusive formation of only one diastereomer can be rationalized in terms of the transition state shown in Scheme 3.

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(8) For other examples of transition metal-catalyzed opening of oxabicyclic alkenes see: (a) Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48−58. (b) Lautens, M.; Hiebert, S. *J. Am. Chem. Soc.* **2004**, *126*, 1437−1447 and references therein. (c) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **2000**, *122*, 978−979. (d) Nakamura, M.; Matsuo, K.; Inoue, T.; Nakamura, E. *Org. Lett.* **2003**, *5*, 1373−1375.

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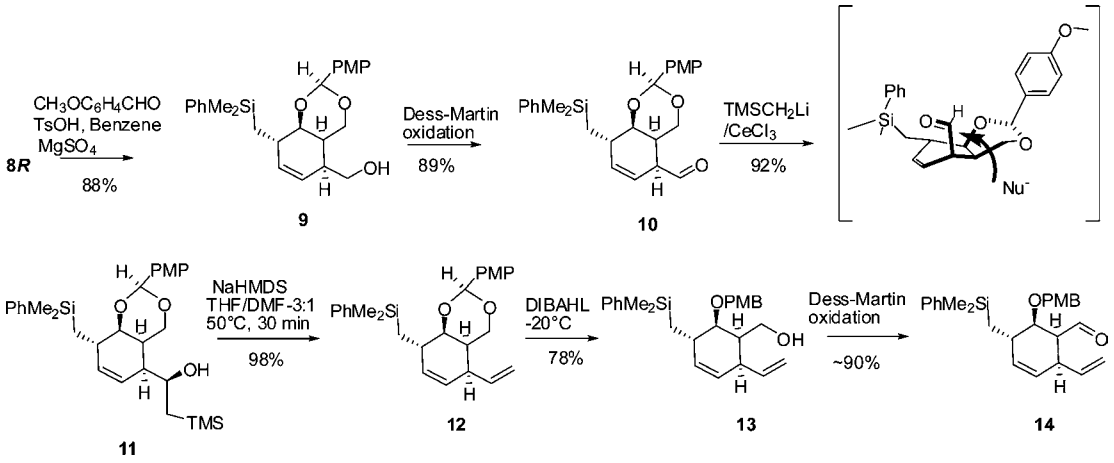
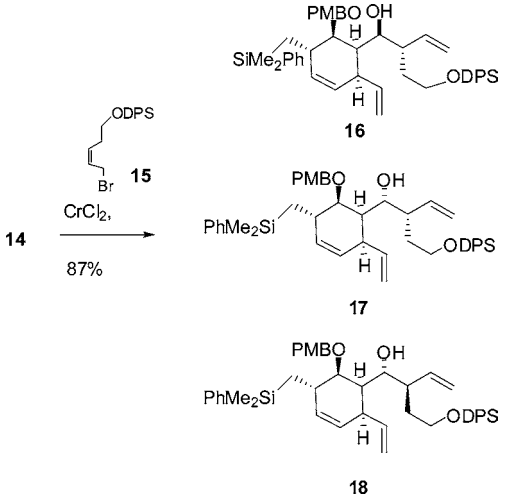
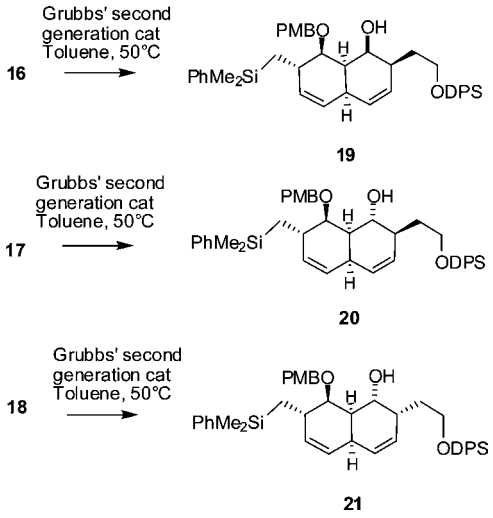
Scheme 3. Synthesis of Compound **14**



Scheme 4. Hiyama−Nozaki−Kishi Reaction Aldehyde **14**

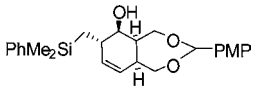


Scheme 5. Ring-Closing Metathesis of Compounds **16**−**18**



Conversion of β-hydroxysilane **11** into olefin **12** again proved tricky. Under standard conditions, KH/THF, elimination provided the undesired conjugated diene. We speculated that the initially formed potassium alkoxide was responsible for this isomerization. In fact, performing the reaction in high dilution improved the yield of **12** to 70% together with 20% of the conjugated diene. Additionally, replacement of KH with NaHMDS in THF/DMF fully suppressed the side reaction and gave the desired olefin **12** in almost quantitave yield. DIBAL-H reduction of **12**, followed by oxidation, gave aldehyde **14** in 72% yield over two steps.

(12) The side product of the reaction (25%) is compound **9a**.



9a

Conversion of **9a** under acidic conditions improved the yield of the desired acetal to 88%.

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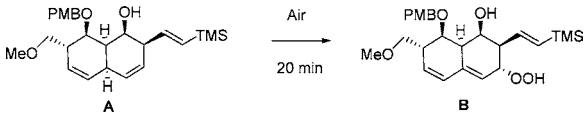
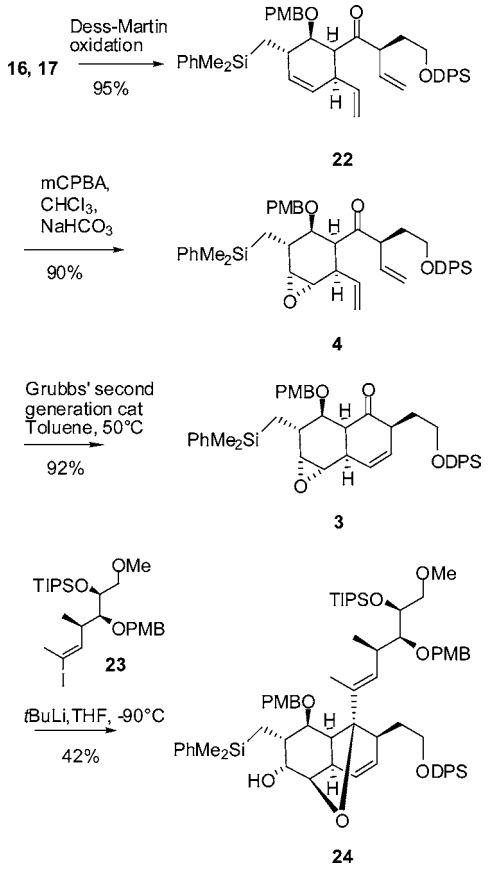
(21) It has to be pointed out that, although the RCM reaction was quantitative, attempts to subject compounds **19** and **20** to chromatography in the presence of air resulted in a substantial loss of the material, most probably via oxidation of the diene system. For example, exposure of structurally similar compound **A** to air gave after 20 min hydroperoxide **B** in 90% yield. Gromov, A. Ph.D. Thesis in preparation.



Scheme 6. Synthesis of Compound **24**



The stage was now set for the simultaneous introduction of the second double bond required for a RCM reaction and the C2-appendage (branimycin numbering). Thus, aldehyde **14** was treated with allylbromide **15**[20] (Scheme 4) according to Hiyama−Nozaki−Kishi protocol ($CrCl_2$, THF),[6] to give in 89% yield a mixture of compounds **16** (49%), **17** (21%), and **18** (19%). The relative *syn* and *anti* configurations of the products were established through conversion to their corresponding bicyclic derivatives (Scheme 5). RCM of alcohols **16**−**18** in the presence of 5 mol % of Grubb's second-generation catalyst provided in quantitative yields compounds **19**, **20**, and **21**, respectively, whose relative configurations were unambiguously elucidated by NOE experiments.[21]

Having proved that compounds **16** and **17** are C-12 epimers (branimycin numbering), both were oxidized (Scheme 6) to provide ketone **22** (63% yield from **14**). Epoxidation of **22** (mCPBA, 1.1 equiv) afforded epoxide **4** as a single regio- and stereoisomer in 85% yield.

Unfortunately, at this stage we were not able to assign the configuration of oxirane, but we hoped that the existing stereocenters in **22** will direct epoxidation to the desired α-epoxide. Finally, RCM of **4** in the presence of 5% Grubbs second-generation catalyst provided epoxyketone **3** in 90% yield. To confirm the configuration of the oxirane as well the feasibility to use **3** in our synthetic strategy toward branimycin, ketone **3** was reacted with **23**.[2b] As expected, the addition to the carbonyl group was followed by transannular epoxide opening under formation of the oxygen bridge in **24**. The structure and stereochemistry of **24** were confirmed by two-dimensional (2D) NMR studies.

In summary, we have demonstrated the utility of S_N2' opening of oxabicyclic alkenes in combination with RCM for a construction of highly substituted *cis*-decalin system which we regard as a promising intermediate in a synthesis of branimycin.

Acknowledgment. We thank Dr. Hans-Peter Kaehlig, Dr. Lothar Brecker, and Susanne Felsinger for NMR analysis, M. Zinke for performing the HPLC separations, and Prof. Vladimir Arion (all University of Vienna) for crystallography.

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.

OL7027338