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A Desymmetrization Approach toward Highly Oxygenated *cis*-Decalins

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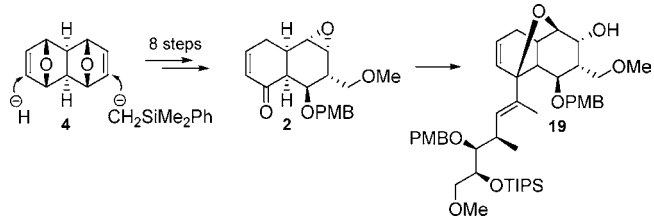
ABSTRACT



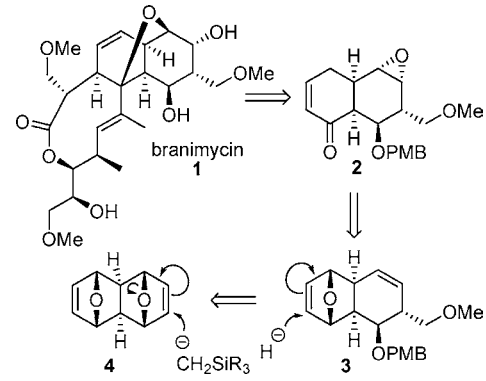
The *cis*-decalin core 2 of the antibiotic branimycin has been prepared by desymmetrization of diepoxynaphthalene 4. The key steps involve two successive S_N' opening of the oxa-bridges. An improved procedure for the synthesis of 4 is also described.

In recent years, our group became interested in the development of various novel approaches toward the synthesis of highly functionalized *cis*-decalins in the context of an ongoing study toward the total synthesis of the highly active antibiotic branimycin[1,2] (**1**).

In our new approach, we envisioned that the construction of the *cis*-decalin core **2** of branimycin (**1**) could be accomplished by desymmetrization of diepoxynaphthalene **4** (Scheme 1) via two successive S_N' reactions.[3]

First a copper-mediated S_N' opening of one of the oxa-bridges was performed with a Grignard reagent containing a silyl group as a latent hydroxy group, followed by an enantioselective S_N' opening of the second oxa-bridge with a formal hydride anion.

Scheme 1. Retrosynthetic Overview of Compound **2**



The synthesis of diepoxynaphthalene **4**[4] commenced with the 2-fold Diels−Alder reaction between methyl propiolate and furan (Scheme 2). When we performed this reaction at 0 °C for 4 h, both diastereomers **5a** (52%) and **5b** (14%) were formed. However, on longer reaction times, the

(1) (a) Enev, V. S.; Drescher, M.; Mulzer, J. *Org. Lett.* **2008**, *10*, 413–416. (b) Enev, V. S.; Drescher, M.; Mulzer, J. *Tetrahedron* **2007**, *63*, 5930–5939. (c) Marchart, S.; Mulzer, J.; Enev, V. S. *Org. Lett.* **2007**, *9*, 813–816. (d) Felzmann, W.; Arion, V. B.; Mieusset, J. L.; Mulzer, J. *Org. Lett.* **2006**, *8*, 3849–3851. (e) Review: Mulzer, J.; Castagnolo, D.; Felzmann, W.; Marchart, S.; Pilger, C.; Enev, V. S. *Chem. Eur. J.* **2006**, *12*, 5992–6001.

(2) (a) Isolation and biological activity of branimycin : Speitling, M. Ph.D. Thesis, Universität Göttingen, 1998. (b) Speitling, M.; Grün-Wollny, I.; Hannske, F. G.; Laatsch, H. IRSEER Naturstofftage der DECHEMA e.V. Irsee 2000, 2001, poster sessions 12 and 13.

(3) For similar desymmetrizations, see: (a) Lautens, M.; Fillion, E. *J. Org. Chem.* **1996**, *61*, 7994–7995. (b) Lautens, M.; Fillion, E. *J. Org. Chem.* **1998**, *63*, 647–656. (c) Webster, R.; Böing, C.; Lautens, M. *J. Am. Chem. Soc.* **2009**, *131*, 444–445.

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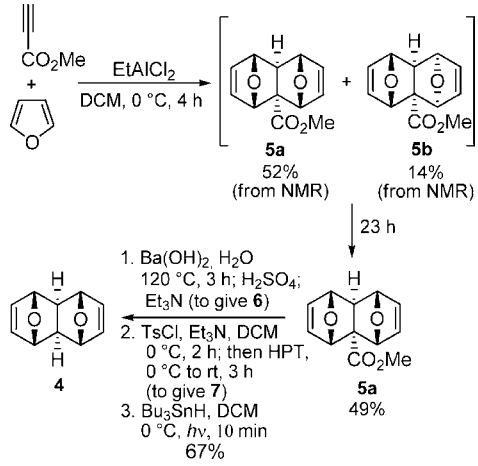
undesired diastereomer **5b** slowly disappeared, leaving **5a** as a single diasteromer along with some decomposition products.[5] This protocol avoids the tedious chromatographic separation of **5a** and **5b** and is suitable for the synthesis of **5a** on a multigram scale.

Scheme 2. Synthesis of Tetracycle **4**[a]



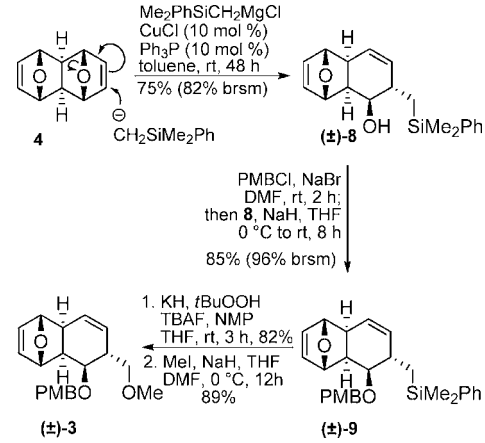
[a] HPT = 1-hydroxypyridine-2(1*H*)-thione.

The four-step elaboration of ester **5a** to diepoxynaphthalene **4** proved straightforward.[4] Saponification of **5a** provided the corresponding acid, which was isolated as the triethylammonium salt **6**. Activation of the carboxylate via the acyl tosylate and conversion to *N*-thionopyridyl ester **7** was followed by reductive Barton decarboxylation to furnish the desired tetracyclic compound **4** in 67% overall yield from **5a**.

With a reliable route to diepoxynaphthalene **4** in hand, the selective opening of the oxa-bridges could be tested. We were delighted to find that exposure of **4** to $Me_2PhSiCH_2MgCl/CuCl/Ph_3P$ under the conditions described by Carretero et al.[6] resulted in an *anti* S_N' opening of only one of the oxa-bridges to give compound **8** in 75% yield (82% brsm). Alcohol **8** was protected as a PMB-ether with PMBBr (prepared in situ from PMBCl[7] and NaBr in DMF). Next, the C−Si bond was cleaved oxidatively to deliver the corresponding primary alcohol which was converted to methyl ether **3** in 73% yield over two steps (Scheme 3).

The stage was now set for the conversion of the remaining oxa-bridge into the α,β-unsaturated ketone moiety of **2** (Scheme 4). Following a procedure by Lautens et al.,[8] racemic compound **3** was treated with DIBAL and

Scheme 3. Desymetrization of Compound **4**[a]



[a] brsm = based on recovered starting material.

$Ni(COD)_2/(R)$-BINAP. Indeed, a pseudoenantiotopos-selective hydrogen attack was achieved on both enantiomers of **3** to give the enantiomerically enriched regioisomers **11**[9] and **12** in 91% yield, easily separable by chromatography.[10]

The synthesis of **2** was continued with a Dess−Martin oxidation of **11**, followed by base-catalyzed double-bond isomerization to provide α,β-unsaturated ketone **14** in 88% yield. Regioselective epoxidation of diene **14** with *m*-CPBA gave a 3:1 mixture of diastereomeric epoxides, easily separable by chromatography. To avoid competitive Bayer−Villiger oxidation, the reaction was stopped at ca. 50% conversion. The relative configuration of the major diastereomer **2** was determined by single-crystal diffraction (see the Supporting Information).

To secure the absolute configuration of our products, racemic compound **3** was separated into the enantiomers by chiral HPLC. Under the same conditions used for the racemate, enantiomer (+)-**3** gave **11**. On the other hand, (−)-**3** was converted into alcohol **15** and then into crystalline urethane **16**, the X-ray analysis of which allowed the determination of the absolute configuration based on the anomalous dispersion of chlorine atoms.

(4) For preliminary studies on the synthesis of **4**, see: Gromov, A.; Enev, V.; Mulzer, J. *Synth. Commun.*, in press.

(5) For a discussion of this phenomenon, see comment 1 in the Supporting Information.

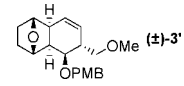
(6) Arrayás, R. G.; Cabrera, S.; Carretero, J. C. *Org. Lett.* **2003**, *5*, 1333–1336.

(7) For a reliable scalable procedure for preparation of PMBCl, see: Chaudhari, S. S.; Akamanchi, K. G. *Synlett* **1999**, *11*, 1763–1765.

(8) Lautens, M.; Rovis, T. *Tetrahedron* **1998**, *54*, 1107–1116.

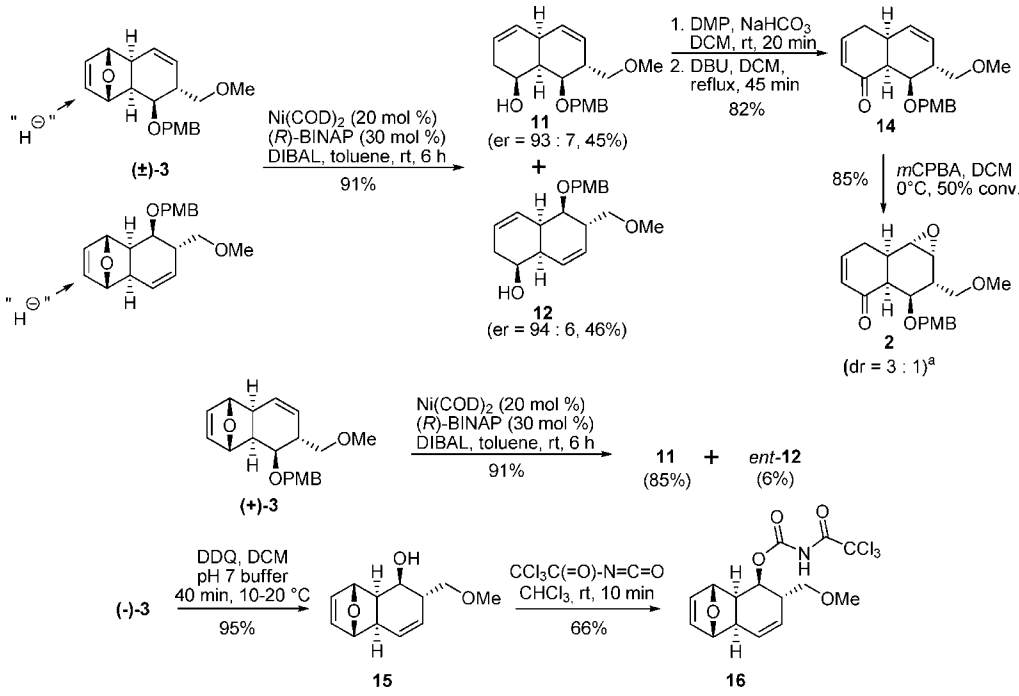
(9) It has to be pointed out that skipped dienes **11** and **13** (not shown, see the Supporting Information) proved to be air sensitive to give dienyl hydroperoxides (for a discussion, see comment 2 in the Supporting Information).

(10) Toluene as a solvent was essential for a high yield of the desired products. Performing the reaction in THF resulted in thformation of ca 50% of compound **3′**.



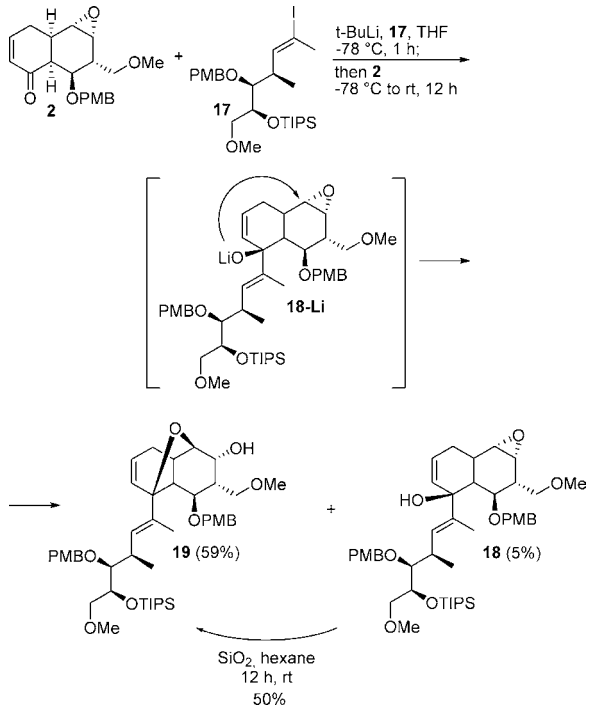
This solvent effect might be attributed to the higher Lewis acidity of aluminum species in the non-coordinating toluene. An increase in Lewis acidity presumably favors coordination of Al with the oxa-bridge and therefore facilitates the C−O bond cleavage. For other examples of the influence of Lewis acids on oxa-bridge opening, see: Lautens, M.; Chiu, P.; Ma, S.; Rovis, T. *J. Am. Chem. Soc.* **1995**, *117*, 532–533.

Scheme 4. Opening of the Second Oxa-Bridge and Synthesis of Compound **2**[a]



[a] The major diastereomer is shown.

Scheme 5. Coupling of **2** and **17** and Formation of the Oxa-Bridge



Finally, pursuing the strategy envisioned in our group,[1a,e,11] we coupled ketone **2** and the lithitiated side chain obtained from iodide **17** (Scheme 5).[12] Nucleophilic addition of the vinyllithium species to the carbonyl group led to lithium alcoholoate **18-Li**. On raising the temperature, cyclization of the lithium alkoxide onto the epoxide was achieved to give tricycle **19** with the desired oxa-bridge. Uncyclized **18** was isolated in trace amounts and was converted to the desired **19** by strring with silica gel, thus giving **19** in 61% combined yield.

In conclusion, we have demonstrated that organometallic catalysis can be used for a successive desymmetrization of diepoxynaphthalene **4**. This opens a direct access to highly functionalized *cis*-decalin systems as exemplified by the core of branimycin.

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Supporting Information Available: Experimental procedures and analytical data for all new compounds and crystal data of compounds **2** and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL900834C

(11) Cf. also: Plata, D. J.; Kallmerten, J. *J. Am. Chem. Soc.* **1998**, *110*, 4041–4042.

(12) Felzmann, W.; Castagnolo, D.; Rosenbeiger, D.; Mulzer, *J. Org. Chem.* **2007**, *72*, 2182–2186.