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A Novel Approach toward the Synthesis of Kendomycin: Selective Synthesis of a *C*-Aryl Glycoside as a Single Atropisomer

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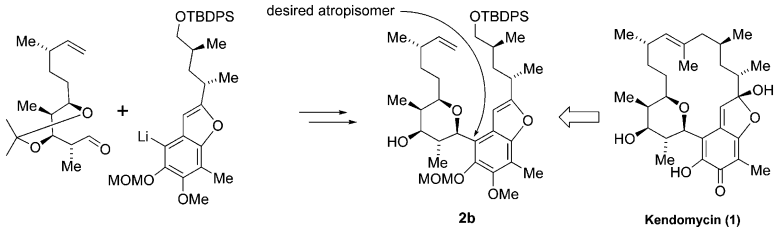
ABSTRACT



A convergent and concise route to an advanced precursor 2b of kendomycin (1) has been developed by applying a S_N1 ring cyclization as a key step. The resulting *C*-aryl glycoside was initially isolated as a rotameric mixture, but after MOM protection of the *o*-hydroxyl of the phenol, the conformation was frozen to the desired kendomycin-like atropisomer.

Kendomycin [(−)-TAN 2162] (**1**), a novel ansamycin compound isolated from *Streptomyces violaceoruber* (strain 3844-33C), was recently described as a potent endothelin receptor antagonist and antiosteoperotic compound with remarkable antibacterial and cytostatic activity.[1] The structure of kendomycin (**1**) features an aliphatic ansa chain with a highly substituted tetrahydropyran ring connected to a unique quinone methide chromophore. Its diverse pharmacological activity and challenging structure have motivated us to embark on a laboratory synthesis of **1**.

A central issue lies in the construction of the pseudo *C*-aryl glycosidic part of the molecule, which is highly sterically congested and shows atropisomeric behavior.[2] To reduce steric hindrance, a benzofuran intermediate such as **2** was envisaged that could then be macrocyclized in the C-9/C-11 region and oxidized to the final *p*-quinomethide.

With these considerations in mind, we reasoned that **2** might be obtained from the addition of aldehyde **4** to a carbanion, which could be generated by ortho-directed metalation from **5** (Scheme 1).

The synthesis of aldehyde **4** started with a *syn*-aldol addition of aldehyde **3**, readily available from citronellene, to β-keto imide **6** to give ketone **7**.[3]

After stereoselective reduction of **7** to the β-hydroxy alcohol,[4] the auxiliary was cleaved by treatment with base, and subsequent acidification with HCl gave the lactone **8** directly. In the presence of 2,2-dimethoxypropane and a catalytic amount of acid, methyl ester **9** was obtained, which

(1) (a) Funahashi, Y.; Kawamura, N.; Ishimaru, T. Japanese patent 08231551 [A2960910], 1996; *Chem. Abstr.* **1997**, *126*, 6553. (b) Funahashi, N.; Kawamura, N. Japanese patent 08231552, 1996; *Chem. Abstr.* **1996**, *125*, 326518. (c) Su, M. H.; Hosken, M. I.; Hotovec, B. J.; Johnston, T. L. US patent 5728727, 1998; *Chem. Abstr.* **1998**, *128*, 239489. (d) Bode, H. B.; Zeeck, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 323. (e) Bode, H. B.; Zeeck, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2665.

(2) (a) Martin, H. J.; Drescher, M.; Kählig, H.; Schneider, S.; Mulzer, J. *Angew. Chem.* **2001**, *113*, 3287. (b) Marques, M. B. M.; Pichlmair, S.; Martin, J. H.; Mulzer, J. *Synthesis* **2002**, *18*, 2766.

(3) (a) Evans D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866. (b) Evans, D. A.; Ng. H. P.; Clark, J. S.; Rieger, D. L. *Tetrahedron* **1992**, 2127.

(4) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

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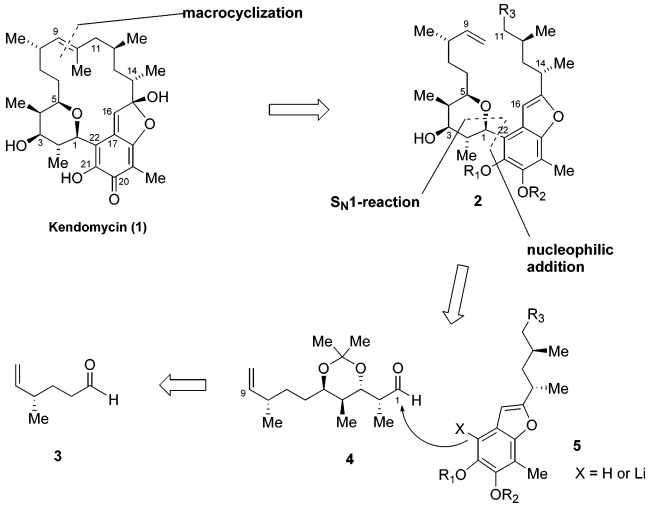
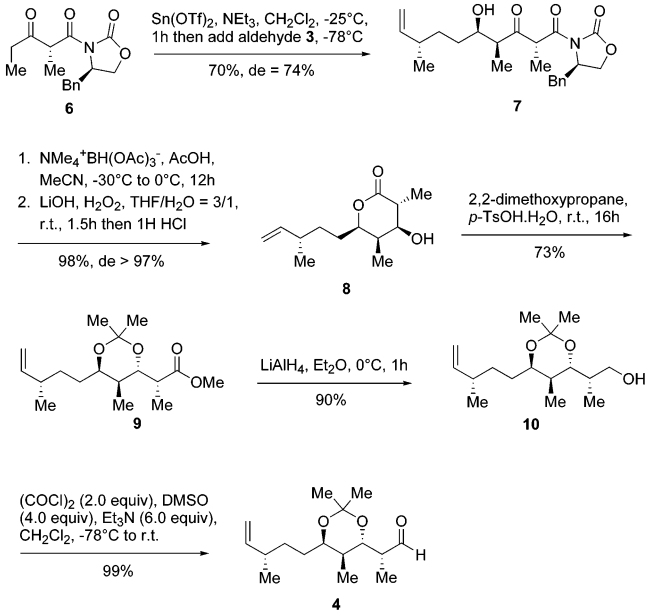
Scheme 1. Retrosynthetic Analysis of **1**



Scheme 2



was first reduced to primary alcohol **10** and then oxidized to aldehyde **4** by Swern oxidation (Scheme 2).

We then tackled the syntheses of two alternative "eastern fragments" from an identical precursor. TBDPS-protected Roche aldehyde **11** was subjected to a Horner−Wadsworth−Emmons olefination to afford the corresponding *N*-enoyl sultam ,which was α-methylated by using Oppolzer's 1,4-addition/enolate-trapping protocol.[5,6] We obtained **12** in 83% yield with good stereoselectivity (97:3).

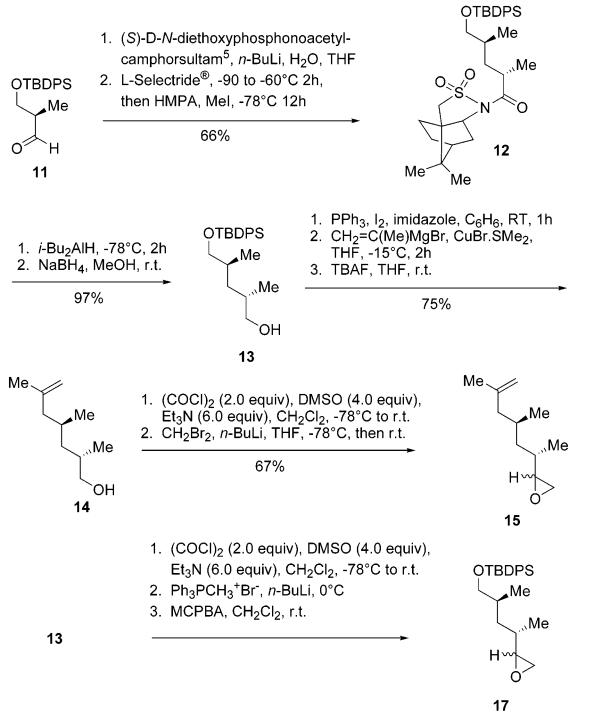
The sultam was removed by DIBAL-H reduction and the crude aldehyde was reduced with $NaBH_4$ to give alcohol **13**.

(5) For a reference to the preparation of (*S*)-*N*-diethoxyphosphonoacetylcamphorsultam see: Oppolzer, W.; Dupuis, D.; Poli, G.; Raynham, T. M.; Bernardinelli, G. *Tetrahedron Lett.* **1988**, *29* (46), 5885.

(6) Oppolzer, W.; Poli, G. *Tetrahedron Lett.* **1986**, *27* (39), 4717.

Epoxide **15** was obtained from primary alcohol **13** first by conversion to the iodide which was then coupled with isopropenylmagnesium bromide under Schlosser−Fouquet conditions.[7] TBDPS deprotection delivered alcohol **14** and Swern oxidation furnished the corresponding aldehyde, which was then transformed directly to **15** by addition of lithiated dibromomethane at low temperature and subsequent warming to room temperature.[8] Epoxide **17** was obtained by employing a high-yielding three-step procedure from alcohol **13** (Scheme 3).

Scheme 3[a]



[a] L-Selectride = lithium tri-*sec*-butylborohydride, HMPA = hexamethyl phosphoric triamide, MCPBA = *m*-chlorperbenzoic acid, TBAF = tetrabutylammonium fluoride.

At this stage, epoxide **15** was added to Grignard **19** and epoxide **17** to Grignard **22** to give alcohols **20** and **23**, respectively.[9,10] The alcohols were subjected to a Swern oxidation followed by an acidic catalyzed ring closure. Benzofurans **5a** and **24** were obtained in good yield. Phenol **24** was then reprotected to give the MOM phenol ether **5b** in nearly quantitative yield (Scheme 4).

After careful experimentation, directed ortho-lithiation of the 2-position of benzofurans **5a** and **5b** was performed with

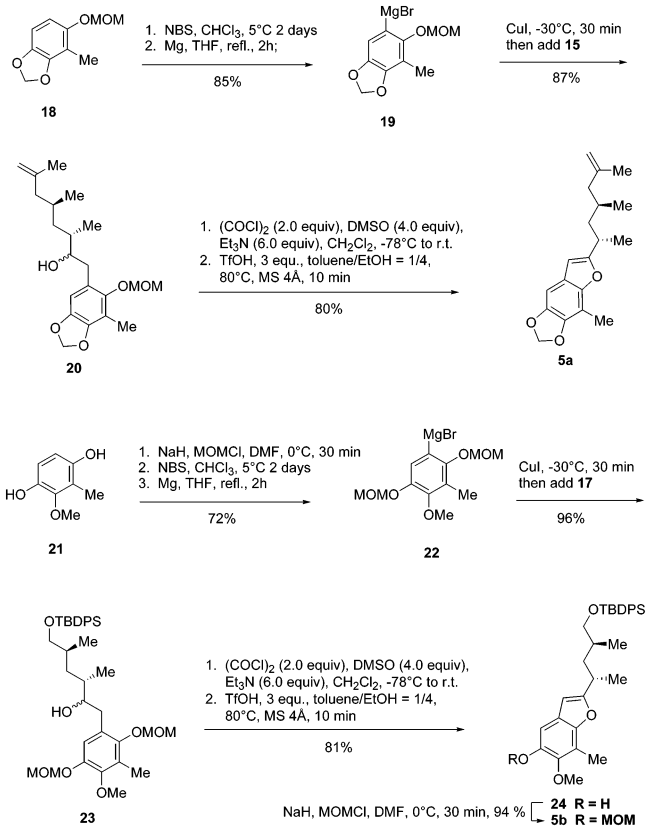
(7) (a) Hegedus, L.; Lipshutz, B.; Nozaki, M.; Reets, M.; Rittmeyer, P.; Smith, K.; Trotter, F.; Yamamoto, H. *Organometallics in Synthesis: A Manual*; Schlosser, M., Ed.; John Wiley & Sons Ltd: Chichester, UK, 1994; p 344. (b) Tamura, M.; Kochi, J. K. *J. Organomet. Chem.* **1972**, *42*, 205.

(8) Michnick, T. J.; Matteson, D. S. *Synlett* **1991**, *9*, 631.

(9) Suzuki, S.; Shiono, M.; Fujita, Y. *Synthesis* **1983**, 804.

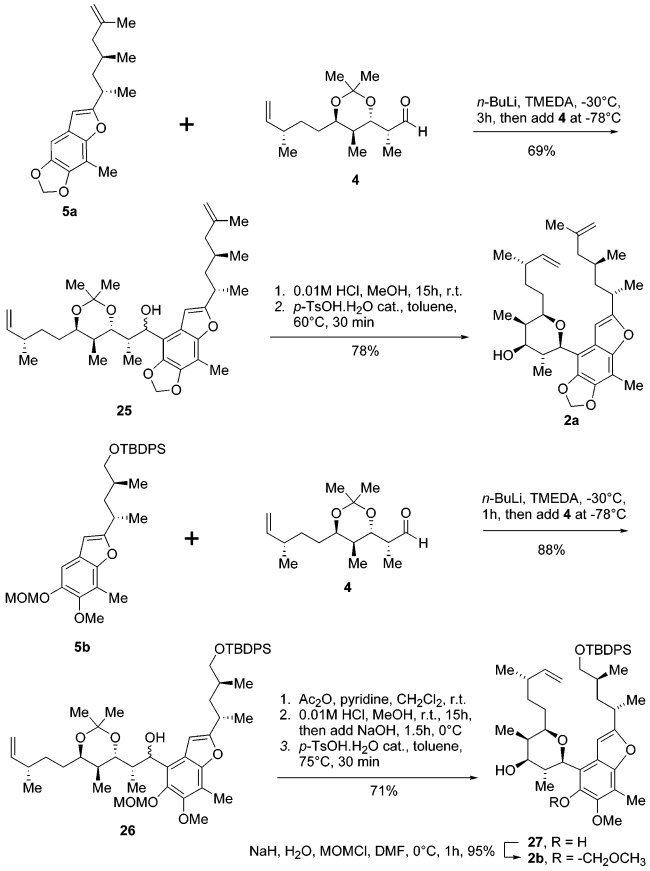
(10) For references to the preparation of **18** see: Corey, E. J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 9202. For references to the preparation of **21** see: Heckrodt, T. J.; Mulzer, J. *J. Am. Chem. Soc.* **2003**, *125*, 4680.

Scheme 4[a]



[a] NBS = *N*-bromosuccinimide, MOMCl = methoxymethyl chloride.

Scheme 5[a]



[a] TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylendiamine, MOMCl = methoxymethyl chloride.

n-BuLi in the presence of TMEDA with *n*-BuLi at −30 °C.[11] Addition of aldehyde **4** to these organolithium species at −78 °C gave the desired benzylic alcohols **25** and **26** in 69% and 88% yield as mixtures of diastereomers. Removal of the acetal protection group from **25** and subsequent heating in warm toluene with a catalytic amount of *p*-TsOH resulted in the desired S_N1-type ring closure as a key step in our synthesis (Scheme 5). In the case of **25**, we were disappointed to find that the resulting tetrahydropyran product **2a** exists as a 3:1 mixture of atropisomers favored to the undesired isomer at room temperature.

Unfortunately, the cyclization of **26** under analogous conditions was thwarted by the formation of a stable acetonide between the oxygens at C1 and C3. Hence, we applied a three-step procedure of acetylation, formation of the triol, and treatment with acid, which furnished **27** in reasonable overall yield. As before, we observed broad peaks in the ^{1}H NMR spectra, implying the formation of a rotameric mixture and that the coalescence temperature is around room temperature. To our delight MOM protection of the phenol **27** resulted in freezing of the conformation to the desired kendomycin-like atropisomer **2b**.

In conclusion, we have developed a convergent and stereoselective route to an advanced intermediate in the synthesis of kendomycin. A novel feature in our sequence is the stereocontrol over the formation of *C*-aryl glycoside atropsiomers, which has been exerted by a proper choice (i.e. MOM and OMe) of the phenolic *o*-hydroxyl groups. The atropisomer thus obtained has the proper geometry for the formation of the macrocyclic ring, which will be the next issue to face.

Acknowledgment. This paper is dedicated to Professor W. Steglich on the occasion of his 70th birthday. Financial support by the Austrian Science Foundation (FWF, projects M674 and P14729-CHE) and the Fundação para a Ciência e Tecnologia (SFRH/PBD/3561/2000) (Lisbon, Portugal) is gratefully acknowledged. We also thank Hanspeter Kählig for NMR and Sabine Schneider for HPLC support.

Supporting Information Available: Experimental procedures and NMR data for compounds **25**, **26**, **2a**, and **2b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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