Stereoselective Synthesis of the Functionalized Spirocyclic Core of Aranorosin

Peter Wipf* and Yuntae Kim

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

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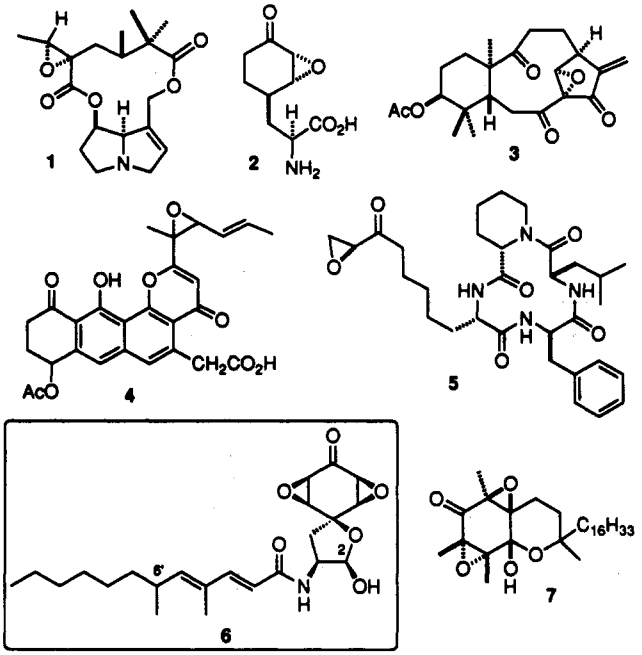
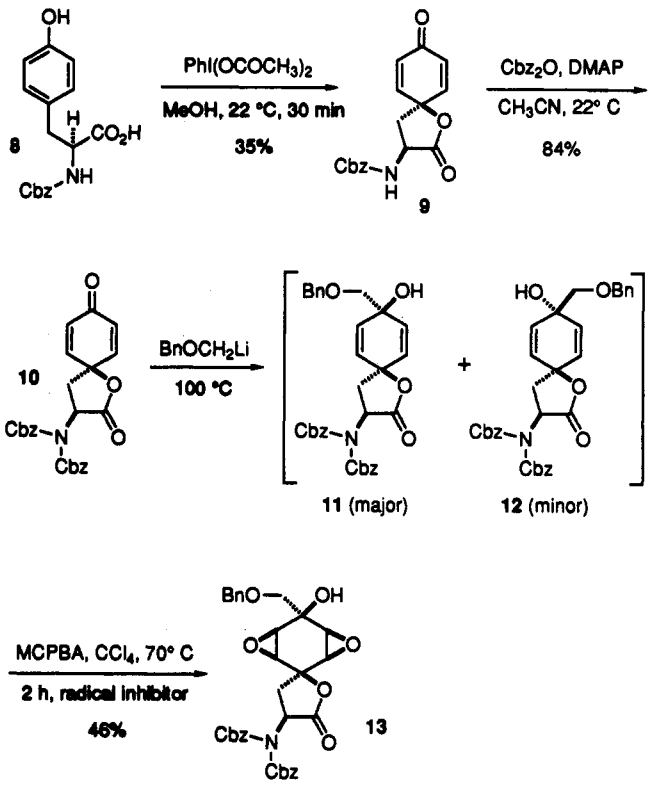
Summary: Oxidative cyclization of L-tyrosine, stereoselective addition of an α-alkoxy organolithium reagent, and hydroxyl-directed diepoxidation are key steps in the first synthesis of the fully functionalized core of aranorosin.

Due to their powerful, yet selective, alkylating capabilities, oxiranes are among the functional groups with the highest intrinsic potential for bioactivity. Natural products such as jacobine (**1**),[1] anticapsin (**2**),[2] epoxyshikoccin (**3**),[3] kapurimycin A3 (**4**),[4] and WF-3161 (**5**),[5] for example, share activated oxirane functionalities and potent antitumor and antibiotic properties.



The novel antibiotic aranorosin (**6**), recently isolated from the fungal strain *Pseudoarachniotus roseus*,[6] shows activities against a variety of bacteria and fungi on a micromolar scale. It also has cytostatic properties and is potentially useful for the treatment of malign tumors and leukemia.[7] Structurally, aranorosin is related to the vitamin E oxidation product **7**, but its 1-oxaspiro[4.5]-decane ring system is highly unusual and has already attracted considerable synthetic interest.[8] In this paper, we report the preparation of a fully functionalized analog of aranorosin.

Scheme I



As an extension of our studies of biologically important amino acid derivatives,[9] we decided to apply an oxidative cyclization[10] of tyrosine **8** with iodobenzene diacetate[11] for the preparation of key intermediate **9** (Scheme I). Attempted addition of organometallic reagents to dienone **9** led predominantly to lactone addition products. After introduction of a second *N*-Cbz protective group with dibenzyl pyrocarbonate,[12] 1,2-addition with 1.5 equiv of [(benzyloxy)methyl]lithium[13] proceeded smoothly at −78 °C to give a mixture of diastereomeric alcohols **11** (major) and **12** (minor).[14] Due to the lability of bisallylic alcohols **11** and **12**, the crude reaction mixture was directly subjected to a hydroxyl group-directed[15] bisepoxidation with *m*-chloroperbenzoic acid in the presence of Kishi's radical inhibitor[16] at 70 °C. Epoxy alcohol **13** was isolated as a single isomer in 46% overall yield from **10**.[17]

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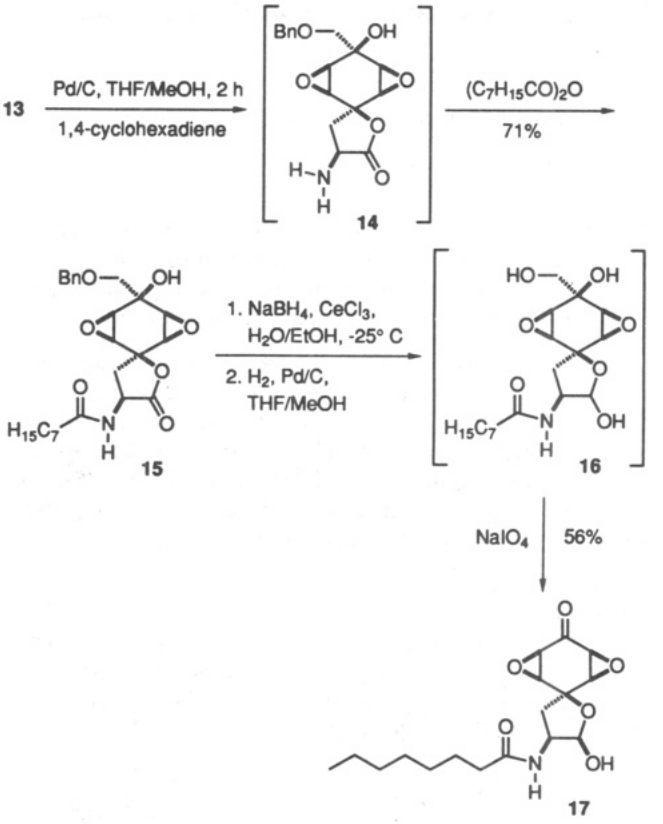
Catalytic hydrogen transfer with palladium on carbon in the presence of 1,4-cyclohexadiene was used for the selective removal of the N-protective groups (Scheme II). In situ acylation of amine **14** with octanoic anhydride as a model for the fatty acid side-chain of aranorosin gave amide **15** in 71% yield from **13**. Reduction of the lactone moiety to the desired lactol was controlled by treatment of bisepoxide **15** with $NaBH_4$ in the presence of $CeCl_3$[18] at −25 °C in aqueous ethanol. Subsequently, catalytic hydrogenation provided triol **16**. Due to its high polarity and dense functionalization, this intermediate was difficult to purify and was directly cleaved with sodium periodate to give ketone **17** as a >4:1 mixture of lactol anomers in 56% yield after silica gel chromatographic purification. The relative stereochemistry of **17** was determined by 1D NOE experiments[19] which clearly correlated all hydrogens of the 1-oxaspiro[4.5]decane. The excellent match between ^1H and ^{13}C NMR and NOE data for **17**[20] and the core structure of aranorosin confirms the structural assignment by Fehlhaber et al.[6a] for this novel ring system.

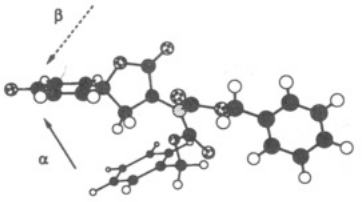
Scheme II



The preparation of aranorosin analog **17** represents the first synthesis of the highly functionalized spirocyclic core of the natural product. Key steps that are of broader interest include the diastereoselective addition of an α-alkoxy lithium reagent to dienone **10**, the kinetic resolution in the high-temperature epoxidation of **11** and **12**, and the various functional group manipulations that converge in the assembly of diepoxy ketone, lactol, and amide functionalities on the oxaspiro[4.5]decane. As expected, this ring system is highly reactive toward nucleophiles. Exposure of **17** to a solution of thiophenol, for example, led to the rapid incorporation of 2 equiv of thiol at 22 °C. Details of these studies will be reported elsewhere.

Supplementary Material Available: Experimental data for compounds **9**, **10**, **13**, **15**, and **17** and 1D NOE studies for **17** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(14) According to TLC and ^1H NMR analysis of the crude reaction mixture, the desired isomer **11** predominated over **12** in >5:1 selectivity. Addition of (methoxymethyl)lithium and methylmagnesium bromide to dienone **10** resulted in more stable addition products in 3:1 and 2:1 ratios (α:β-face additions). Separation and structural analysis of these derivatives allowed the tentative assignment of the stereochemistry of **11** and **12** as major and minor isomers, respectively. Molecular mechanics minimization (MM2* with MacroModel V3.5X: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440) of the geometry of dienone **10** revealed little steric bias for a face-selective addition of organometallics:



The remarkable α-selectivity of this addition could be explained by a stereoelectronic effect: The electron-withdrawing spiroether oxygen increases the acceptor reactivity of the dienone most strongly in an antiperiplanar position to the incoming nucleophile by electron transfer from the nucleophile into the low-lying σ^*_{C-O} orbital ("antiperiplanar effect" ((a) Caramella, P.; Rondan, N. G.; Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 2438)). This model is in agreement with Heathcock and Lodge's analysis of the diastereoface differentiation in additions to chiral aldehydes ((b) Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353), but contradicts Cieplak's theory ((c) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540). (d) For a dicussion of complexation effects in nucleophilic additions to enones, see: Swiss, K. A.; Hinkley, W.; Maryanoff, C. A.; Liotta, D. C. *Synthesis* **1992**, 127.

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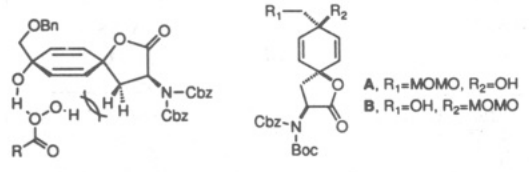
(17) The formation of **13** as a single isomer in this reaction is most likely due to a kinetic resolution effect. Hydroxyl group-directed epoxidation of the minor isomer **12** from the α-face is sterically hindered and therefore significantly slower than the β-face epoxidation of major isomer **11**. This hypothesis was confirmed by epoxidations of models **A** and **B**.



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(19) See supplementary material.

(20) Spectral data for **17**: $[\alpha]_D$ = +8.0° (*c* = 0.37, CH_2Cl_2, 21 °C); IR (CH_2Cl_2) 3335, 2926, 2855, 1727, 1620, 1547, 1244, 985 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.08 (d, 1 H, *J* = 8.1 Hz), 5.61 (bs, 1 H), 4.67–4.65 (m, 2 H), 3.69 (dd, 1 H, *J* = 3.2, 2.5 Hz), 3.55 (dd, 1 H, *J* = 3.9, 2.5 Hz), 3.47–3.41 (m, 2 H), 2.61 (dd, 1 H, *J* = 13.0, 8.4 Hz), 2.21 (t, 2 H, *J* = 7.7 Hz), 2.00 (dd, 1 H, *J* = 13.0, 10.1 Hz), 1.62 (m, 2 H), 1.28 (m, 8 H), 0.87 (bs, 3 H); ^{13}C NMR ($CDCl_3$) δ 198.4, 173.6, 96.6, 79.0, 64.3, 62.9, 55.9, 55.7, 51.9, 36.7, 36.0, 31.7, 29.3, 29.0, 25.7, 22.7, 14.2.