Natural Products Synthesis

DOI: 10.1002/anie.200700430

Synthesis of the Carbocyclic Core of Zoanthenol: Implementation of an Unusual Acid-Catalyzed Cyclization**

*Douglas C. Behenna, Jennifer L. Stockdill, and Brian M. Stoltz**

The complex and elegant architecture of the zoanthamine alkaloids has captivated synthetic chemists for well over a decade.[1,2] Although numerous research groups have published efforts toward the zoanthamines,[1] the only completed synthesis of any member of this class was that of norzoanthamine by Miyashita et al. which appeared in 2004[3] (Figure 1).

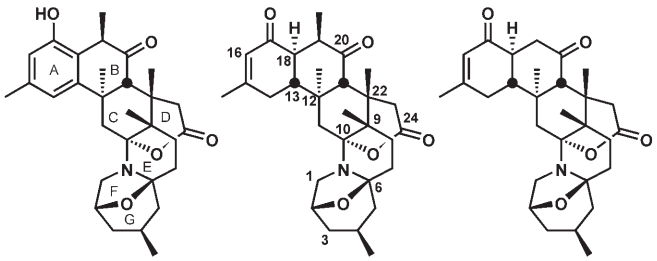


Figure 1. Selected members of the zoanthus family of alkaloids.

The zoanthamines exhibit a host of biological activities highlighted by the anti-osteoporotic activity of norzoanthamine hydrochloride.[4] Our interest in the zoanthamines was piqued by zoanthenol (**1**),[5] the sole family member possessing an aromatic A ring. Zoanthenol retains the major stereochemical challenges of the zoanthamines, while offering the opportunity to explore unique retrosynthetic possibilities. Herein, we describe an unusual S_N' cyclization to form the carbocyclic core of zoanthenol. An asymmetric stereoselective route to this core structure is enabled by asymmetric alkylation methodology recently developed in our laboratories.[6]

With seven rings and nine stereocenters confined to a 30-carbon framework, zoanthenol is a densely functionalized, topographically complex target molecule. The C ring poses the greatest stereochemical challenge with five contiguous stereocenters, three of which are all-carbon quaternary centers. Our overarching strategy was to generate one quaternary center in an enantioselective fashion and then derive the remaining stereocenters diastereoselectively. Another design feature was to convergently unite the A and C rings by a two-carbon tether and subsequently forge the B ring. We planned to introduce all the functionality of the heterocyclic C1 to C8 fragment in a single operation (i.e., **2** → **3** + **4**; Scheme 1). Previous work by the Kobayashi and Williams groups demonstrated that the complicated hemiaminals forming the DEFG rings are thermodynamically favored.[7] Thus, the DEFG heterocycles could be retrosynthetically unraveled to give triketone **2** (Scheme 1). Disconnection of the C8–C9 bond and removal of the methyl groups at C9 and C19 affords ketone **3** and enone **4**. We envisioned the cleavage of the tricyclic core structure **3** by scission of the C12–C13 bond employing an intramolecular conjugate addition of the A ring into a C ring enone (i.e., **5**).[8] We reasoned that this type of intramolecular Friedel–Crafts reaction would require a highly electron-rich arene for effective cyclization; therefore, oxygenation was incorporated at C16 of enone **5** to increase the nucleophilicity of the A ring. Enone **5** could arise from 1,2-addition of Grignard reagent **6** to enal **7**, which in turn could be derived from ketoester **8**, ultimately available by enantioselective decarboxylative allylation of β-ketoester **9**.

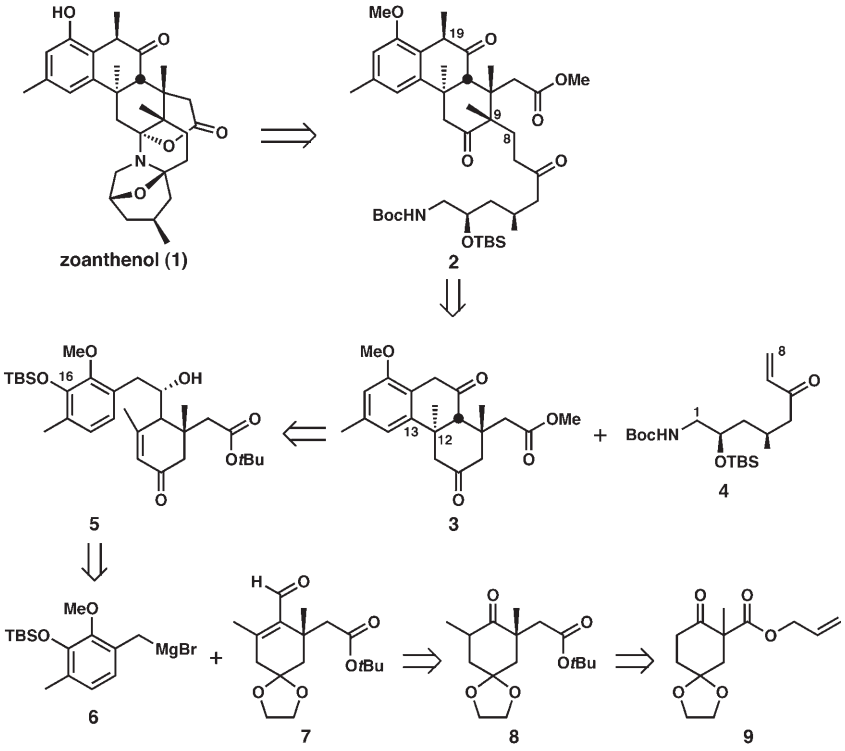
In order to determine the feasibility of the 6-*exo* conjugate addition, the target enal was synthesized as a racemate (Scheme 2). Known dimethyl ketone **10**[9] was deprotonated and alkylated to give ketoester **8** in excellent yield as a mixture of diastereomers. Deprotonation of methyl ketone **8** and quenching with $PhNTf_2$ afforded enol triflate **11**. After significant optimization to accommodate the steric challenges of the substrate, an efficient one-step reductive carbonylation of triflate **11** was developed. Treatment of triflate **11** under an atmosphere of CO with $Pd(OAc)_2$, 1,4-bis(dicyclohexylphosphino)butane as a ligand, and TES-H as a reducing agent afforded the desired enal **7** in good yield. To our knowledge, this is the first time that such a hindered vinyl triflate was carbonylated directly to the enal oxidation state. Addition of Grignard reagent **6**[10] to enal **7** produced allylic alcohol **12** in high yield and diastereoselectivity. Use of methylene chloride as a cosolvent for the addition reaction was critical, resulting in the formation of the *anti* diastereomer as the sole product, as confirmed by X-ray crystallography of the corresponding lactone (i.e., **16**, Figure 2).[10]

With the A and C rings joined, we could begin to investigate the 6-*exo* cyclization by exposing allylic alcohol **12** to TFA at reflux (Scheme 3). We anticipated that loss of

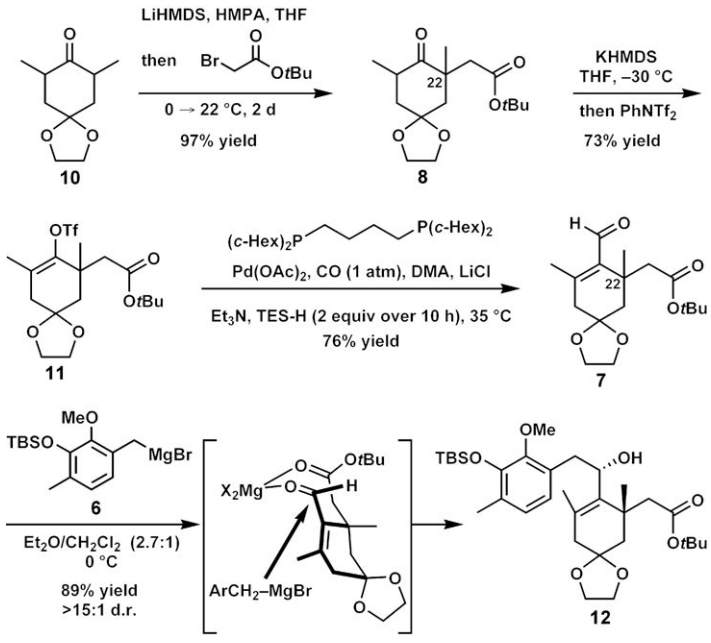
[*] D. C. Behenna, J. L. Stockdill, Prof. B. M. Stoltz
The Arnold and Mabel Beckman Laboratories of Chemical Synthesis
Division of Chemistry and Chemical Engineering
California Institute of Technology
1200 East California Boulevard, MC 164-30
Pasadena, CA 91125 (USA)
Fax: (+1) 626-564-9297
E-mail: stoltz@caltech.edu

[**] The authors wish to thank the Fannie and John Hertz Foundation (predoctoral fellowship to D.C.B), Novartis (predoctoral fellowship to J.L.S.), Merck, Pfizer, and Lilly for financial support.

Supporting information for this article (including information on the X-ray structures) is available on the WWW under http://www.angewandte.org or from the author.



Scheme 1. Retrosynthetic analysis of zoanthenol (**1**). Boc = *tert*-butyloxycarbonyl, TBS = *tert*-butyldimethylsilyl.



Scheme 2. Preparation of the cyclization substrate. *c*-Hex = cyclohexyl, DMA = -*N*,*N*-dimethylacetamide, HMDS = hexamethyldisilazane, HMPA = hexamethyl phosphoramide, Tf = trifluromethanesulfonyl, TES = triethylsilyl.

protecting groups and olefin migration would afford enone **13**, which would undergo 6-*exo* conjugate addition to form keto-alcohol **14**. To our delight, the ^{1}H NMR spectrum of the major product contains a single aromatic C–H as well as two isolated aliphatic CH_3 signals, indicating that the reaction generated a product containing the two desired quaternary centers. However, the spectrum also contains an olefinic resonance. Upon standing in $CDCl_3$, the major product (**15**) formed crystals suitable for X-ray diffraction. Interestingly, cyclization of allylic alcohol **12** had occurred, but by 6-*endo* S_N' cyclization to give acid **15**.[11,12] Additionally, the solid-state structure confirmed the *anti* disposition of the methyl groups at C12 and C22 in **15**.

The S_N' Friedel–Crafts reaction to produce carboxylic acid **15** achieved the important goal of generating the quaternary stereocenter at C12 with the desired relative configuration. To better understand the reaction pathway, we evaluated a number of parameters. The choice of acid in the reaction is crucial, as trifluoroacetic acid was unique in promoting S_N' cyclization. Both stronger acids (e.g., triflic acid) and weaker acids (e.g., acetic acid) failed to produce tricycle **15**. Even the dilution of neat TFA with methylene chloride, benzene, or acetic acid caused the cyclization to fail.

Interestingly, both lactone **16** and allylic acetate **17** underwent cyclization in TFA to give acid **15** with similar yields and diastereoselectivities (Figure 2).[13] Furthermore, C16 desoxy arene **18** failed to generate any cyclized products, confirming the importance of the nucleophilicity imparted by oxygenation at C16. Finally, the C20 epimers of the substrates do not readily undergo cyclization. The unique ability of TFA to mediate the reaction suggests that its properties as a strong acid and a dehydrating agent are important to the reaction mechanism. The selectivity of the system indicates that all three substrates (**12**, **16**, and **17**) may proceed through an intermediate lactone (i.e., allylic

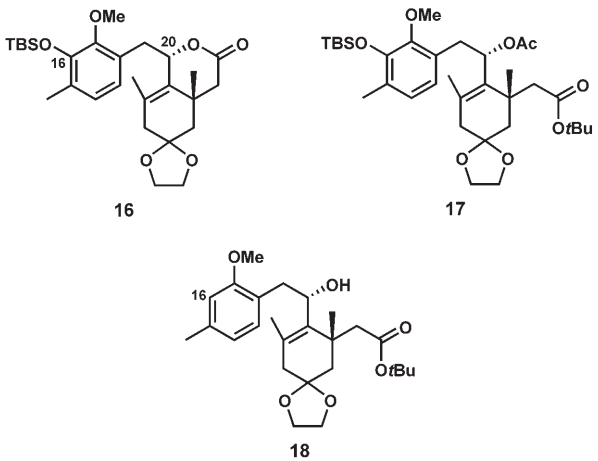
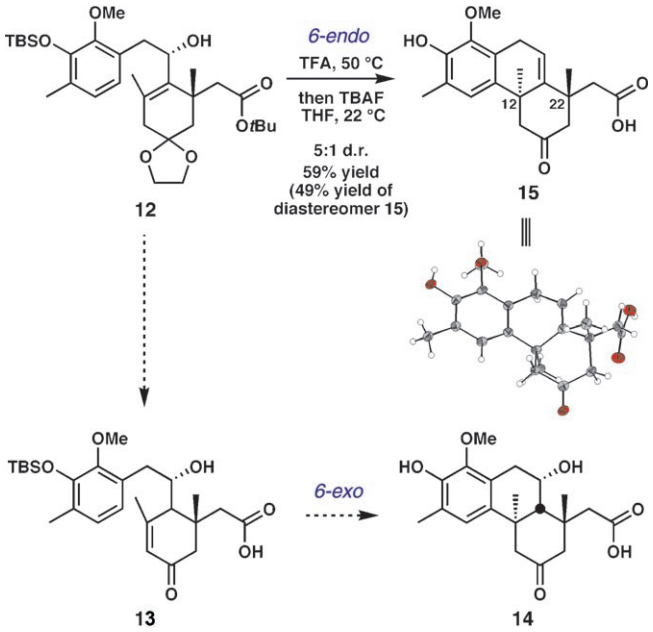


Figure 2. Other cyclization substrates.



Scheme 3. 6-*endo* S_N' cyclization of the B ring. TBAF = tetrabutylammonium fluoride.

alcohol **12** and acetate **17** may be converted to the lactone in situ), and that the reactions proceed by a partially concerted displacement relying on the directing ability of a carboxylate leaving group and not via a full allylic cation.

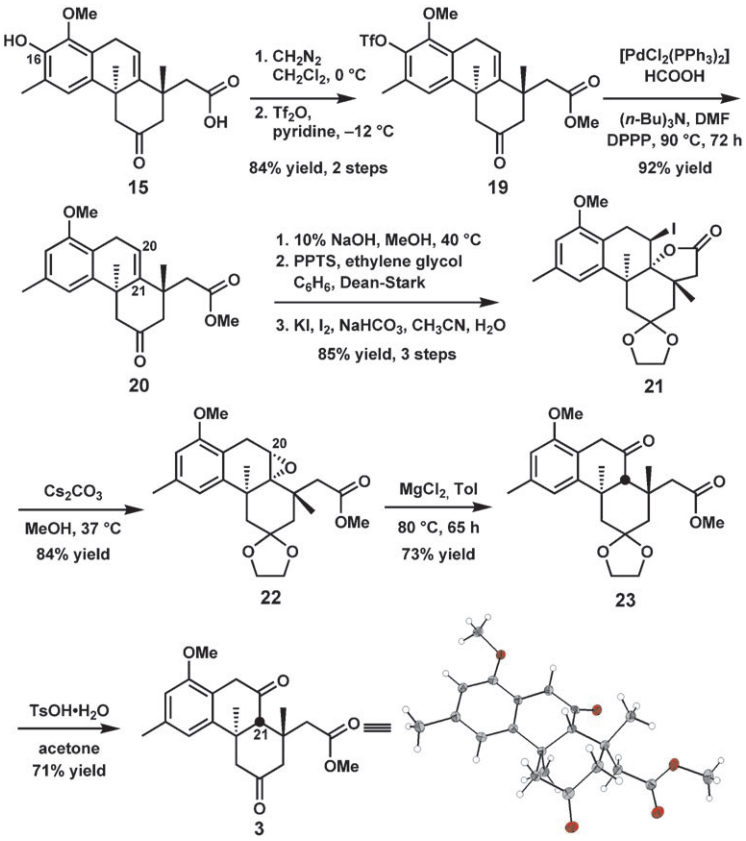
With an efficient route in hand to construct a zoanthenol carbocyclic ring system containing two of the three quaternary stereocenters, we turned our attention to the completion of our proposed intermediate **3**. Following diazomethane-mediated esterification, deoxygenation of the C16 phenol was accomplished by formation of aryl triflate **19** and subsequent treatment with $[PdCl_2(PPh_3)_2]$ and formic acid (Scheme 4).[14]

Owing to our serendipitous discovery of the S_N' reaction, we had not anticipated the reoxygenation of the olefin in our retrosynthetic planning. As such, significant experimentation was required to find a synthetic strategy to convert the $\Delta_{20,21}$ double bond of ketoester **20** into the desired C20 ketone.[15] The X-ray structure in Scheme 3 illustrates the pseudo-axial orientation of the methyl groups surrounding the olefin, which partially block the π bond and hinder the approach of typical oxidants.

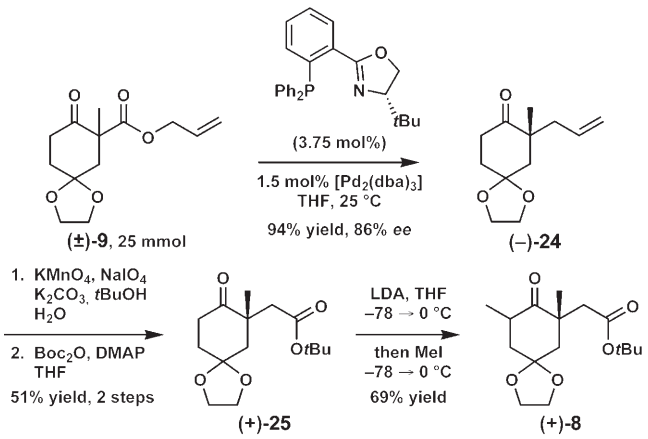
Thus, we chose to pursue an alternative, intramolecular method of olefin oxygenation. Our approach began with saponification of ketoester **20** followed by ketalization (Scheme 4). Treatment of the crude product with KI, I_2, and base gave iodolactone **21** in 85% yield over three steps after recrystallization. Lactone methanolysis under basic conditions afforded smooth conversion to epoxide **22**. Hydride migration from C20 was accomplished by heating epoxide **22** in toluene with $MgCl_2$,[16] providing clean conversion to rearranged ketoester **23** in 73% yield. Treatment of ketoester **23** with *p*-toluenesulfonic acid produced diketone **3**, which was characterized by X-ray crystallography. The solid-state structure confirmed the desired stereochemistry at C21 from the hydride shift.

Although racemic material was useful for exploratory studies, our goal from the outset was an asymmetric synthesis of zoanthenol. Toward this end, we were delighted to find that our recently developed asymmetric decarboxylative allylation methodology[6] was a reliable and efficient method to produce α-quaternary ketone (−)-**24** in excellent yield and high enantioselectivity on 25-mmol scale (Scheme 5). Oxidative olefin cleavage and esterification gave *tert*-butyl ester (+)-**25** in 51% yield over two steps. Subsequent methylation provided a good yield of methyl ketoester **8**, an intermediate in our C-ring synthesis (vide supra), allowing entry into a catalytic enantioselective synthesis of zoanthenol.

In conclusion, a concise method for the construction of the zoanthenol carbocyclic skeleton was developed. The synthesis is highlighted by an unusual diastereoselective S_N' cyclization of allylic alcohol **12** producing tricycle **15** bearing all-carbon-substituted quaternary centers at C12 and C22 in the desired *anti* configuration. This key step is flanked in our route by a number of interesting observations and discoveries. Most notably, we demonstrate an unusual palladium-catalyzed formylation of a hindered vinyl triflate, a highly diastereoselective Grignard addition to a congested enal, and the incorporation of the C20 ketone by use of the pendant C24 carboxylate by means of iodolactonization and subsequent



Scheme 4. Functionalization of the zoanthenol tricyclic core. DPPP = propane-1,3-diylbis(diphenylphosphine), Tol = toluene, Ts = toluenesulfonyl.



Scheme 5. Catalytic asymmetric alkylation for the enantioselective synthesis of ketoester (+)-**8**. dba = dibenzylideneacetone, DMAP = 4-dimethylaminopyridine.

epoxide rearrangement. Finally, application of our catalytic asymmetric decarboxylative alkylation methodology allows ready access to an enantioselective synthesis of zoanthenol. Our ongoing efforts to advance an enantioenriched tricyclic core to zoanthenol will be reported in due course.

Received: January 31, 2007
Published online: April 19, 2007

Keywords: alkaloids · asymmetric catalysis · cyclization · natural products

[1] For the most recent publication from each group, see: a) M. Juhl, T. E. Nelson, S. Le Quement, D. Tanner, *J. Org. Chem.* **2006**, *71*, 265–280; b) T. Irifune, T. Ohashi, T. Ichino, E. Sakia, K. Suenaga, D. Uemura, *Chem. Lett.* **2005**, *34*, 1058–1059; c) D. R. Williams, T. A. Brugel, *Org. Lett.* **2000**, *2*, 1023–1026; d) F. Rivas, S. Ghosh, E. A. Theodorakis, *Tetrahedron Lett.* **2005**, *46*, 5281–5284; e) N. Hikage, H. Furukawa, K. Takao, S. Kobayashi, *Chem. Pharm. Bull.* **2000**, *48*, 1370–1372; f) S. M. Moharram, H. Oguri, M. Hirama, *Egypt. J. Pharm. Sci.* **2003**, *44*, 177–193.

[2] D. Tanner, P. G. Anderson, L. Tedenborg, P. Somfai, *Tetrahedron* **1994**, *50*, 9135–9144.

[3] M. Miyashita, M. Sasaki, I. Hattori, M. Sakai, K. Tanino, *Science* **2004**, *305*, 495–499.

[4] a) M. Kuramoto, H. Arimoto, K. Hayashi, I. Hayakawa, D. Uemura, T. Chou, K. Yamada, T. Tsuji, K. Yamaguchi, K. Yazawa, *Symposium Papers, 38th Symposium on the Chemistry of Natural Products*, **1996**, 79–84; b) K. Yamaguchi, M. Yada, T. Tsuji, M. Kuramoto, D. Uemura, *Biol. Pharm. Bull.* **1999**, *22*, 920–924.

[5] A. H. Daranas, J. J. Fernández, J. A. Gavín, M. Norte, *Tetrahedron* **1999**, *55*, 5539–5546.

[6] a) D. C. Behenna, B. M. Stoltz, *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045; b) J. T. Mohr, D. C. Behenna, A. M. Harned, B. M. Stoltz, *Angew. Chem.* **2005**, *117*, 7084–7087; *Angew. Chem. Int. Ed.* **2005**, *44*, 6924–6927; c) R. M. McFadden, B. M. Stoltz, *J. Am. Chem. Soc.* **2006**, *128*, 7738–7739.

[7] a) N. Hikage, H. Furukawa, K. Takao, S. Kobayashi, *Tetrahedron Lett.* **1998**, *39*, 6237–6240; b) N. Hikage, H. Furukawa, K. Takao, S. Kobayashi, *Tetrahedron Lett.* **1998**, *39*, 6241–6244; c) D. R. Williams, G. A. Cortez, *Tetrahedron Lett.* **1998**, *39*, 2675–2678.

[8] a) T. Matsumoto, T. Ohmura, *Chem. Lett.* **1977**, 335–338; b) L. S. Liebeskind, R. Chidambaram, S. Nimkar, D. Liotta, *Tetrahedron Lett.* **1990**, *31*, 3723–3726; c) C. Schmidt, J. Thazhuthaveetil, *Can. J. Chem.* **1973**, *51*, 3620–3624; d) T. Matsumoto, S. Usui, T. Morimoto, *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1575–1579; e) T. Matsumoto, S. Usui, *Chem. Lett.* **1978**, 897–900; f) R. V. Stevens, G. S. Bisacchi, *J. Org. Chem.* **1982**, *47*, 2396–2399.

[9] a) M. Franck-Neumann, M. Miesch, F. Barth, *Tetrahedron* **1993**, *49*, 1409–1420; b) In our experience, dimethyl ketone **10** was best prepared by oxidation of 2,6-dimethylphenol with iodobenzene diacetate in ethylene glycol to give a quinone monoketal product, which was readily reduced to the ketone with Pd/C under hydrogen (60 psi).

[10] See the Supporting Information for details.

[11] For an excellent review of S_N' reactions, see: L. A. Paquette, C. J. M. Stirling, *Tetrahedron* **1992**, *48*, 7383–7423.

[12] For related cyclizations, see: S. Ma, J. Zhang, *Tetrahedron Lett.* **2002**, *43*, 3435–3438.

[13] The analogous trifluoroacetate underwent cyclization in TFA to give yields and diastereoselectivities comparable to those of the reaction of allylic alcohol **12**.

[14] These conditions were specifically designed for highly congested aryl triflates, see: J. M. Saá, M. Dopico, G. Martorell, A. G. García-Raso, *J. Org. Chem.* **1990**, *55*, 991–995.

[15] Typical epoxidation conditions such as *m*-CPBA, dimethyl dioxirane, urea hydroperoxide, iron(III) acetylacetate and hydrogen peroxide, hexafluoroacetone and hydrogen peroxide, potassium permanganate and copper(II) sulfate, and methyltrioxorhenium and hydrogen peroxide gave no reaction or oxidation at the benzylic C19 position. Hydroboration was also unsuccessful.

[16] a) Treatment with $BF_3{\cdot}Et_2O$ gave the desired hydride shift with concomitant deketalization; however, the yields were lower than the two-step protocol; b) S. M. Naqvi, J. P. Horwitz, R. Filler, *J. Am. Chem. Soc.* **1957**, *79*, 6283–6286.

