Tandem Oxidative Cyclization with Rhenium Oxide. Total Synthesis of 17,18-*bisepi*-Goniocin

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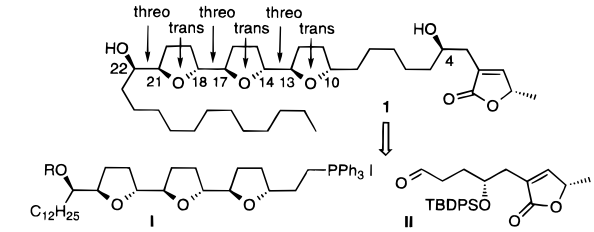
Many of the acetogenins isolated from the Annonaceae plants[1] have shown remarkable cytotoxic, antitumor, antimalarial, immunosuppressive, pesticidal, and antifeedant activities.[2] Classification of these fatty acid derivatives into three subgroups is based on the number and relative positioning of the tetrahydrofuran moieties within the molecule: the mono-THF, the adjacent bis-THF, and the nonadjacent bis-THF acetogenins.[1] We have recently shown that many acetogenins of the first and second subgroups, including solamin, reticulatacin, asimicin, bullatacin, trilobacin, and trilobin, can be efficiently synthesized[3] either by a convergent approach or via the "naked" carbon skeleton strategy,[4,5] combining the Sharpless asymmetric dihydroxylation (AD) reaction[6] with the Kennedy oxidative cyclization reaction.[7]

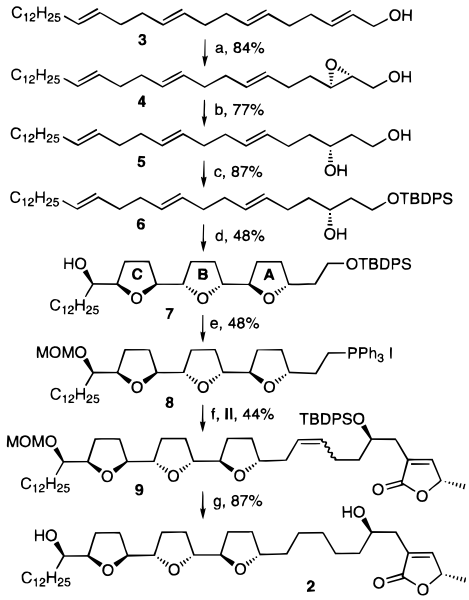
Goniocin, which has been recently isolated from *Goniothalamus giganteus*,[8] possesses three adjacent THF rings and, therefore, represents the first example of a new subclass of Annonaceous acetogenins. Structure **1** was proposed for goniocin on the basis of its MS and ^{1}H and ^{13}C NMR data.[8] Clearly, construction of the tris-*trans*-THF fragment **I** with the appropriate configuration of the seven stereogenic carbinol centers represents the main challenge in the synthesis of **1**. Our retrosynthetic analysis (Scheme 1) was based on previous findings that two consecutive oxidative cyclizations with 4,8-dienols can be carried out in a single step to produce bis-THF derivatives.[9] We reasoned that **I** could be synthesized from a 4,8,12-trienol substrate using the tandem oxidative cyclization methodology. Coupling of **I** with the butenolide fragment **II** could lead to an efficient total synthesis of **1**.

Here, we report that all *trans*-4,8,12-trienol substrates indeed undergo a highly stereospecific triple oxidative cyclization reaction in the presence of a rhenium(VII) reagent to produce a single stereoisomer of a tris-THF product. Surprisingly, however, the product's stereochemistry is not *trans-threo-trans-threo-trans-threo* as expected, but *trans-threo-cis-threo-cis-threo*. Consequently, we have synthesized 17,18-*bisepi*-goniocin (**2**) rather than **1**.

Scheme 1



Scheme 2. Total Synthesis of **2**, First Approach[a]



[a] (a) $Ti(OiPr)_4$, (−)-DIPT, TBHP, powdered Molecular Sieves 4A, −20 °C, 6 h. (b) Red-Al, THF, 0 °C, 4 h. (c) TBDPSCl, diisopropylethylamine, CH_2Cl_2, room temperature (rt) 16 h. (d) Re_2O_7, TFAA, THF, rt, 1 h, concentration under vacuum and washing with cold pentane, then alcohol **6**, TFAA, CH_2Cl_2, 0 °C to rt, 6 h. (e) i. MOMCl, diisopropylethylamine, CH_2Cl_2, 0 °C to rt, 16 h; ii. TBAF, THF, 0 °C to rt, 2 h; iii. I_2, PPh_3, 0 °C to rt, 2 h; iv. PPh_3, $NaHCO_3$, CH_3CN, 45 °C, 48 h. (f) BuLi, THF, 0 °C, then aldehyde **II**. (g) i. H_2, Wilkinson's catalyst (20%, w/w), C_6H_6−EtOH (4:1), rt, 4 h; ii. 4% AcCl in MeOH/CH_2Cl_2 (1:1, v/v), rt, 16 h.

The key intermediate in our synthesis (Scheme 2) is the "naked" carbon skeleton (**6**) which is easily prepared from (*E*,*E*)-ethyl heneicosa-4,8-dienoate[3a] (see the Supporting Information). Asymmetric epoxidation[10] of **3** using $Ti(OPr)_4$ and (−)-DIPT produces epoxy alcohol **4** in more than 95% ee. Reductive cleavage of the epoxide ring using Red-Al affords the 1,3-diol **5**,[11] which is then monoprotected at the primary position to give the silyl ether **6**.

We planned to use the single stereogenic center in **6** as the only source of chirality at the tris-THF fragment and achieve the other six stereogenic carbinol centers by a tandem oxidative cyclization reaction using a Re(VII) reagent. We found that both reagents originally used by Kennedy, i.e. Re_2O_7/lutidine and Re_2O_7/H_5IO_6 in dichloromethane, are useful for monocyclization with simple substrates possessing one double bond. However, for double cyclization with substrates containing two double bonds, the more reactive mixture, Re_2O_7/H_5IO_6, was

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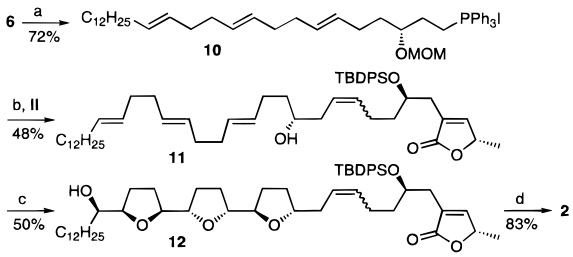
found to be more useful in terms of both reaction rate and yield.[9] Yet, for triple cyclization, although this reagent does produce a tris-THF product, the reaction conditions are too acidic to be compatible with the silyl protecting group. Therefore, we examined various alternative perrhenate reagents, including the Wilkinson's mononuclear perrhenate complex[12] (trifluoroacetyl)perrhenate ($CF_3CO_2ReO_3$), which has been recently used by McDonald.[13] We found that a mixture of $CF_3CO_2ReO_3$ and trifluoroacetic anhydride in dichloromethane is a better reagent for oxidative polycyclizations. Thus, when trienol **6** was treated with a mixture of $CF_3CO_2ReO_3$ and trifluoroacetic anhydride, a stereochemically pure tris-THF product was isolated in 48% yield.[14,15] Surprisingly, ^1H and ^{13}C NMR data of this product did not match the expected characteristics of the *trans-threo-trans-threo-trans-threo* stereoisomer **1**. We assigned the stereochemistry of **7** as *trans-threo-cis-threo-cis-threo* on the basis of 2D-NMR experiments ($^1H-^1H$ COSY, TOCSY, and ROESY)[16] as well as by independent synthesis.[17]

The tris-THF derivative **7** was converted to the phosphonium salt **8** in a four-step sequence: we protected the secondary alcohol in the form of a MOM ether, deprotected the primary alcohol by desilylation, converted it to the corresponding iodide, and then substituted with triphenylphosphine to produce **8**. Wittig reaction of the latter with aldehyde **II** (for the synthesis of **II**, see the Supporting Information) afforded alkene **9**. Finally, hydrogenation and removal of the protecting groups afforded **2**.

In the above-described synthesis of **2**, we placed the triple-cyclization step at an early stage of the synthetic scheme, before the attachment of the butenolide fragment. Alternatively, since the tandem oxidative cyclization reaction is compatible with many functional groups, it could be carried out in a much later stage, after the completion of the molecular carbon skeleton. To check this possibility, we converted trienol **6** to the phosphonium salt **10** and then coupled it with aldehyde **II** (Scheme 3). The resultant tetraenol (**11**) represents an interesting substrate for the tandem oxidative cyclization reaction because it is far more complex than substrate **6** in terms of both molecular size and number of functional groups that could potentially bind the rhenium metal. Moreover, substrate **11** provides an interesting opportunity to examine the relative reactivity of the rhenium reagent toward homoallylic and bis-homoallylic alcohols. In principle, as the secondary carbinol center in **11** is both homoallylic and bis-homoallylic, competition between the two oxidative cyclization alternatives might have occurred. Nevertheless, cyclization with trifluoroacetyl perrhenate and trifluoroacetic anhydride took place exclusively at the bis-homoallylic site, producing the tris-THF intermediate **12** in 50% yield. This is a remarkable observation, considering the fact that six new stereogenic centers are formed in a single transformation with very high diastereoselectivity, producing a compound that is only two steps away from the final target molecule. Indeed, hydrogenation and deprotection of **12** afforded **2**.

Scheme 3. Total Synthesis of **2**, Second Approach[a]



[a] (a) i. MOMCl, diisopropylethylamine, CH_2Cl_2, 0 °C to rt, 16 h; ii. TBAF, THF, 0 °C to rt, 2 h; iii. I_2, PPh_3, 0 °C to rt, 2 h; iv. PPh_3, $NaHCO_3$, CH_3CN, 45 °C, 48 h. (b) i. BuLi, THF, 0 °C, then aldehyde **II**, 0.5 h; ii. TMSBr, CH_2Cl_2, −30 °C, 1 h. (c) Re_2O_7, TFAA, THF, rt, 1 h, concentration under vacuum and washing with cold pentane, then alcohol **11**, CH_2Cl_2, TFAA, 0 °C to rt, 3 h. (d) i. H_2, Wilkinson's catalyst (20%, w/w), C_6H_6−EtOH (4:1), rt, 4 h; ii. 4% AcCl in MeOH, CH_2Cl_2 (1:1, v/v), rt, 16 h.

In conclusion, we have shown that the use of trifluoroacetyl perrhenate for oxidative polycyclization is a general reaction, compatible with complex molecular structures and a variety of functional groups, including a homoallylic alcohol, a silyl ether, and an α,β-unsaturated γ-lactone. The very high regio- and diastereoselectivity of this reaction make it a powerful tool for synthesis of polyoxygenated carbon skeletons and for the Annonaceous acetogenins in particular. Thus, the asymmetric total synthesis of **2** has been achieved via two alternative routes (in 11 steps with 4.97% yield or in 12 steps with 8.07% yield), starting from the achiral hydrocarbon **3**. All asymmetric centers in the main fragment have been introduced in two synthetic steps: asymmetric epoxidation and tandem oxidative cyclization reaction.

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Supporting Information Available: ^1H NMR spectra of compounds **2**−**4**, **6**, **8**, **9**, **11** and **12**, ^{13}C NMR spectra of compounds **2**−**4**, **8**, and **9**, NMR spectra of two samples of **7** obtained from oxidative cyclization and from the independent synthesis, $^1H-^1H$ COSY, TOCSY, and ROESY spectra of **7a**, and information about the independent synthesis of **7** and synthesis of aldehyde **II** (28 pages). See any current masthead page for ordering and Internet access instructions.

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(14) The general procedure used for the tricyclization reaction with $CF_3CO_2ReO_3$ was similar to the one reported in ref 13: Re_2O_7 (1.94 g, 4 mmol) was placed in a dry flask under argon. Dry THF (40 mL) was added followed by addition of TFAA (0.75 mL, 5.3 mmol), and the mixture was stirred at room temperature (rt) for 1 h. Solvents were removed under reduced pressure at 0 °C, and the residue was washed twice with cold, dry pentane. Dry CH_2Cl_2 (40 mL) was added followed by TFAA (0.75 mL, 5.3 mmol) at 0 °C. A solution of trienol **6** (644 mg, 1 mmol) in dry CH_2Cl_2 (5 mL) was added, and the mixture was stirred at 0 °C to rt for 6 h and then was worked up by slow addition of saturated aqueous $NaHCO_3$ (10 mL) and H_2O_2 (2 mL) and extraction with ether. Purification by column chromatography (neutral alumina above silica gel; ethyl acetate:hexane, 1:4) afforded pure **7** (335 mg, 48%) as the only isolatable product, $[\alpha]_D = -3.7$ ($c = 5.46$, $CHCl_3$).

(15) Triple-oxidative cyclization with this reagent has been recently reported independent of our work: Towne, B. T.; McDonald, F. E. *J. Am. Chem. Soc.* **1997**, *119*, 6022.

(16) Compound **7** (which was obtained from the reaction with the rhenium reagent) was desilylated and the resultant diol was converted to the corresponding bis(4-nitrobenzoate) derivative **7a**. The latter was analyzed by 2D $^1H-^1H$ COSY, TOCSY, and ROESY NMR (Bruker Avance DRX 600) to assign the hydrogens (for consistency, we use here the goniocin numbering) attached to the oxycarbons H-8 (δ 4.45, m), H-10 (4.16, m), H-13 (4.01, q), H-14 (3.81, q), H-17 (3.92, q), H-18 (3.85, q), H-21 (4.07, q) and H-22 (5.19, q). The ROESY spectrum shows strong NOE correlation between H-8 and H-10, between H-14 and H-17, and between H-18 and H-21. It is evident from the latter two correlations that the stereochemistry of rings B and C is *cis*. Two weak NOE correlations are observed between H-10 and H-14 and between H-13 and H-22. The absence of an NOE correlation between H-10 and H-13 confirms the *trans* stereochemistry of ring A.

(17) For the synthesis of compound **7** using the AD reaction, see Supporting Information and Sinha, S. C.; Sinha, S. C.; Keinan, E. Submitted.