Total Synthesis of Goniocin and Cyclogoniodenin T. Unique Biosynthetic Implications

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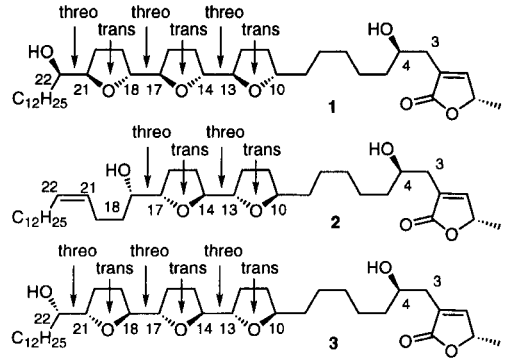
The growing interest in Annonaceous acetogenins[1,2] arises from their antimalarial, immunosuppressive, pesticidal, and antifeedant activities and particularly from their remarkable antitumor activity.[3]

Goniocin, which has been recently isolated from *Goniothalamus giganteus*,[4] represents the first, and so far the only, example of a new subgroup of the Annonaceous acetogenins which possesses three adjacent THF rings. Structure **1** was proposed for goniocin on the basis of its MS and ^{1}H and ^{13}C NMR data.[4]



The all-trans geometry of the THF rings as well as the (*R*,*R*) configuration of carbon atoms 21 and 22 was determined on the basis of the NMR spectra of the natural product and of its Mosher esters.[4] On the basis of these data, an (*S*) configuration was assigned for the carbon atom 10. From a biosynthetic standpoint, this assignment is remarkable, due to the fact that in almost all of the other structurally related acetogenins isolated from *G. giganteus* to date carbon atom 10 was assigned an (*R*) configuration.[1,5]

This biogenetic issue recently became even more intriguing when goniodenin, **2**, was isolated from the same plant.[6] The structure of **2** was found to be closely related to that of **1**. In fact, nonstereoselective epoxidation of **2** with *m*-chloroperoxybenzoic acid (*m*-CPBA) followed by acid-catalyzed ring closure afforded two new stereoisomers of **1**.[6] One of them, **3**, containing an all-trans tris-THF structure, was named cyclogoniodenin T. It has been reported that compounds **1** and **3** are different from one another on the basis of the ^{1}H and ^{19}F NMR spectra of their Mosher's esters. Yet, their biological activity was found to be similar. Hence, before drawing any further conclusions from a seemingly extraordinary biogenetic event, where two structurally similar but stereochemically very different natural products, **1** and **2**, coexist in the same plant, it became necessary to verify the absolute configuration of **1** and **3** by total synthesis.

Clearly, the main challenge in the synthesis of **1** and **3** is the construction of the *trans*-tris-THF fragment with the appropriate configuration of the seven stereogenic carbinol centers. In our earlier efforts to employ the tandem oxidative cyclization reactions with rhenium(VII) reagents using trienol substrates, we discovered that this highly stereospecific method produces the *trans-threo-cis-threo-cis-threo*-tris-THF system rather than the all-trans system required here.[7] Therefore, we employed alternative synthetic methods, including the Sharpless asymmetric dihydroxylation (AD)[8] and epoxidation (AE)[9] reactions as well as the Williamson etherification reaction (Schemes 1 and 2).

Our synthesis of **1** (Scheme 1) started with trienol **4** which is obtained from ethyl heptadec-4-enoate using AD-mix-β[10] followed by a sequence of reactions similar to that described in ref 7 (see the Supporting Information). Asymmetric epoxidation of **4** using (−)-DET produced epoxide **5** in more than 95% enantiomeric excess (ee). Reductive cleavage of **5** with Red-Al gave the corresponding 1,3-diol, whose primary hydroxyl group was protected in the form of a *tert*-butyldiphenylsilyl (BPS) ether **6**. Oxidative cyclization of the latter with $CF_3CO_2ReO_3$ and lutidine produced the *trans*-THF derivative, whose spectral characteristics (^{1}H and ^{13}C NMR) were found to be very similar to those of other *trans*-THF analogues.[11] Protection of the free hydroxyl group as a *tert*-butyldimethylsilyl (BMS) ether afforded **7**. Asymmetric dihydroxylation of **7** using AD-mix-α followed by double mesylation produced **8**. Acidic cleavage of the acetonide and the silyl ethers followed by heating of the resultant tetrol in pyridine produced the desired all-trans tris-THF diol **9**. The primary alcohol was protected in the form of a BPS ether and the secondary alcohol in the form of a MOM ether. The silyl ether was then hydrolyzed, and the resultant primary alcohol was converted to an iodide and then to the phosphonium salt **10**. The latter was converted to the corresponding Wittig reagent and then reacted with aldehyde **11**[7] to produce alkene **12**. Finally, catalytic hydrogenation and deprotection of both MOM and BPS groups afforded goniocin, **1**.

Cyclogoniodenin-T, **3**, was synthesized (Scheme 2) using a strategy that is very similar to the above-described synthetic

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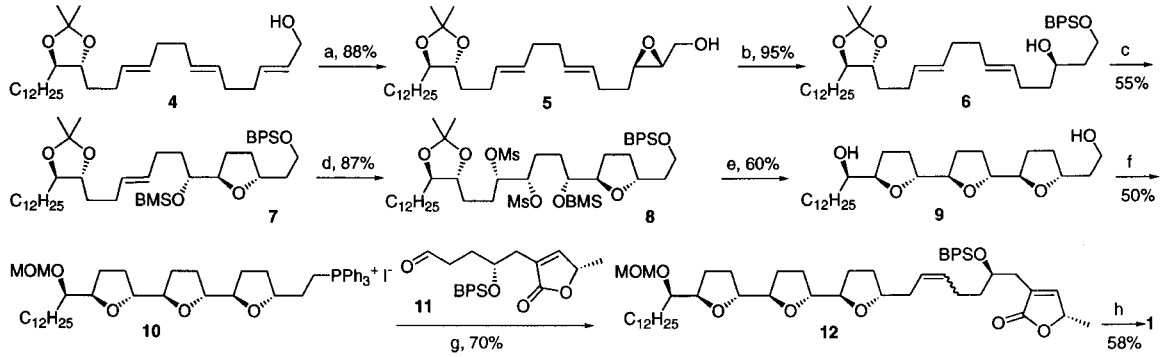
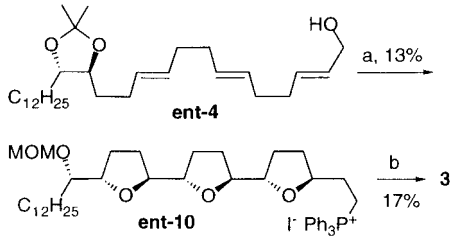
Scheme 1[a]



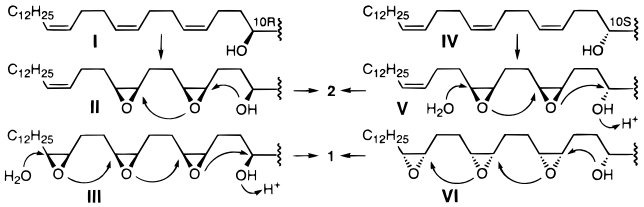
[a] Key: (a) Ti-*i*-(OPr)$_4$, (−)-DET, TBHP, molecular sieves, CH_2Cl_2; (b) i. Red-Al, THF, 0 °C, 4 h; ii. TBDPSCl, diisopropylethylamine, CH_2Cl_2, rt, 16 h; (c) i. $CF_3CO_2ReO_3$, lutidine, CH_2Cl_2, 16 h; ii. TBDMSCl, imidazole, DMF, rt, 16 h; (d) i. AD-mix-α, *t*-BuOH−H_2O, 0 °C, 16 h; ii. MsCl, Et_3N, CH_2Cl_2, 0 °C, 2 h; (e) i. TsOH, H_2O−MeOH, then pyridine, reflux, 2 h; (f) i. TBDPSCl, diisopropylethylamine, CH_2Cl_2, rt, 16 h, then 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, imidazole, 0 °C to rt, 2 h; iv. PPh_3, $NaHCO_3$, CH_3CN, 45 °C, 48 h; (g) BuLi, THF, 0 °C, then aldehyde **11**; (h) 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.

Scheme 2[a]



[a] Key: (a) The same set of reactions described in Scheme 1 (a−f) was used here except that (+)-DET and AD-mix-β were used instead of (−)-DET and AD-mix-α; (b) the same reactions described in Scheme 1 (g−h) were used here.

Scheme 3



approach. Ethyl heptadec-4-enoate was dihydroxylated with AD-mix-α[10] and converted to the allylic alcohol **ent-4** (see the Supporting Information). Asymmetric epoxidation using (+)-DET produced **ent-5** in more than 95% ee. The latter was reduced to **ent-6** which was oxidatively cyclized to **ent-7** as described above for the enantiomeric system. Dihydroxylation with AD-mix-β followed by double mesylation afforded **ent-8** which underwent Williamson-type ring closure to **ent-9**. The latter was converted to the phosphonium salt **ent-10.** The synthesis was completed as described in Scheme 1 to give **3**.

As both the ^{1}H and ^{13}C NMR spectra of **1** and **3** are virtually indistinguishable from one other, the absolute stereochemistry of our synthetic **1** and **3** was proved by comparison of the ^{1}H NMR spectra of their (*R*) and (*S*) bis Mosher esters with the original spectra of the esters of the naturally occurring **1** and the semisynthetic **3**.[12]

It is remarkable that the two nearly enantiomeric natural products, **1** and **2**, occur in the same plant. Although the co-existence of both enantiomers of simple natural products having one or two asymmetric centers have been reported, there are very few such cases with more complex structures. The co-occurrence of both enantiomers of nonactic acid, which has four asymmetric carbon atoms, is probably the closest case to our findings.[13] It has been postulated that the biosynthesis of the poly-THF structure in most Annonaceous acetogenins involves a polyepoxide precursor that undergoes sequential ring closure reactions.[1] Thus, one can envision a common intermediate in the biosynthesis of both **1** and **2**. Theoretically, either of the two pentaepimeric precursors (**II** and **V**, Scheme 3) may lead to **2**, depending on the direction of the tandem epoxide opening cascade. Similarly, either of the two heptaepimeric precursors, **III** and **VI**, may lead to **1**. If **III** is the precursor of **1**, then the original 10(*R*) hydroxyl group must be a good leaving group, e.g., by protonation (as shown in Scheme 3), acetylation, phosphorylation, etc.

In conclusion, the first asymmetric total syntheses of goniocin, **1**, and cyclogoniodenin T, **3**, have been achieved in 17 steps from **4** and **ent-4**, respectively. The synthetic materials, **1** and **3**, were found to be identical to the naturally occurring compounds, thereby confirming their proposed absolute configurations. We interpret the remarkable coexistence of nearly enantiomeric natural products, **1** and **2**, in the same organism to be a result of two alternative modes of tandem ring-closure routes, both starting with a common polyepoxide intermediate. Feeding experiments with isotopically labeled precursors could verify this biosynthetic hypothesis.

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Supporting Information Available: The synthetic schemes of **4** and **ent-4**; spectral data for **4**−**10** (or **ent-4**−**10**); ^{1}H and ^{13}C NMR spectra of **1** and **3**−**10**; ^{1}H NMR apectra of (*R*) and (*S*) Mosher bis-esters of **1** and **3** (27 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(12) We found that the most significant differences were observed in the signals of the methoxy hydrogens in the spectra of the Mosher's bis-esters of **1** and **3**. For the (*R*) bis-esters of both the synthetic and the naturally occurring **1**, the two methoxy signals appear at 3.63 and 3.49 ppm. For the (*S*) bis-esters, they appear at 3.55 and 3.50 ppm. With both synthetic and authentic samples of **3**, the methoxy signals of the (*R*) bis-esters appear at 3.55 and 3.49 ppm. For the (*S*) bis-esters of **3**, these signals appear at 3.63 and 3.50 ppm. Although this information is not given in ref 4, we compared our data directly with the original spectra provided by Prof. J. L. McLaughlin (see the Supporting Information). An intrinsic signature of the (*R*) and (*S*) configurations of the Mosher esters is evident from the following: The two protons at position 3 of the bis-Mosher esters of **1** and **3** exhibit very characteristic ^{1}H NMR signals: for the (*S*) ester, these protons appear as a narrow multiplet at 2.58 ppm, and for the (*R*) ester, they appear as an ABX system 2.66 (dd) and 2.58 (dd) ppm.

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