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Total Synthesis of (±)-9-Deoxygoniopypyrone

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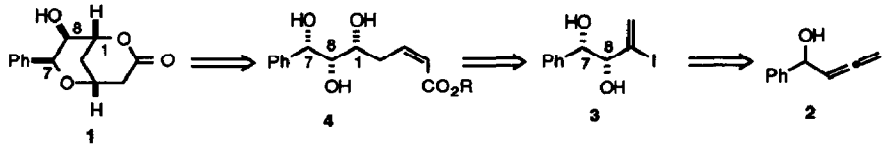
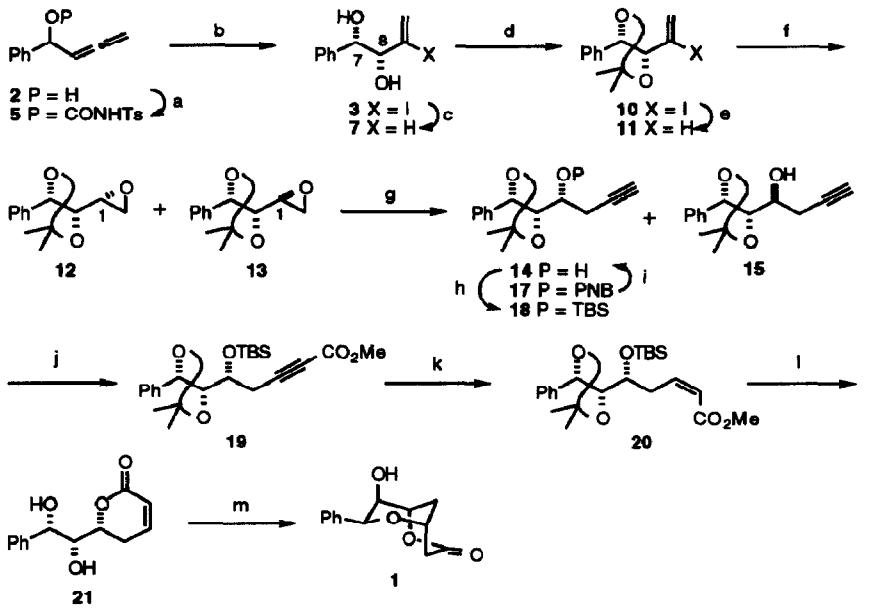
Abstract: The total synthesis of (±)-9-deoxygoniopypyrone (**1**) from the α-allenic alcohol **2** is described. The synthesis is accomplished in 10 steps with the relative configuration of the three contiguous asymmetric centers being established by the highly diastereoselective formation of the *syn*-vicinal diol **3** via the iodo-cyclofunctionalization reaction of the allenic carbamate **5** and the epoxidation of the olefinic acetonide **11**.

Several novel bicyclic styryl lactones possessing cytotoxic activity were recently isolated from the stem bark of *Goniothalamus giganteus* Hook. f. & Thomas (Annonaceae).[1] One of the active components was identified as 9-deoxygoniopypyrone (**1**).[1b] A subsequent report by Honda and co-workers described the synthesis of (+)-**1** from 2,3-*O*-isopropylidene-D-glyceraldehyde, securing the absolute configuration of the

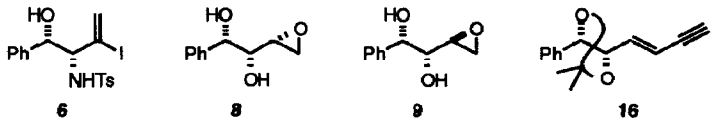


natural compound as depicted.[2] We have been interested in the synthesis of polyfunctionalized acyclic systems via the stereocontrolled cyclofunctionalization of secondary α-allenic alcohol derivatives[3] and viewed **1** as an ideal target for synthesis using our recently described method for the highly diastereoselective preparation of *syn*-vicinal diols.[3b] Applying our iodocyclofunctionalization protocol to the α-allenic alcohol **2** would establish the requisite relative cis stereochemistry between the C7 and C8 hydroxy moieties (9-deoxygoniopypyrone numbering) in putative intermediate **3**. The functionality present in **3** would also allow for subsequent transformation to **1** via the α,β-unsaturated ester triol **4** using a stereoselective epoxidation of the unsaturated diol and chain extension. Herein, we describe the synthesis of (±)-**1** according to this strategy (Scheme 1).[4]

The α-allenic alcohol **2**[3c] was converted via its N-toluensulfonyl carbamate derivative **5** into vinyl iodo *syn*-diol **3**, using our previously reported iodocyclofunctionalization procedure,[3b] in 66% overall yield. We could find no evidence for the formation of the corresponding *anti*-diol isomer (diastereoselectivity >50:1) while the related amino alcohol **6** was observed upon inspection of the crude reaction mixture by ^{1}H NMR (ratio **3**:**6** ~20:1) in accord with our earlier observations. Deiodination of **3** proceeded without incident to afford the unsaturated diol **7**.



Scheme 1[4] *Reagents and Conditions:* (a) TsNCO, Et_2O, 0°C, 15 min. (b) I_2, Et_2O, rt, 45 min; Ag_2CO_3, MeCN-Et_2O (1:10), rt, 3h; 6N NaOH, MeOH, rt, 15h (66% from 2). (c) *n*-Bu_3SnH, AIBN, PhMe, reflux, 2h (81%). (d) 2-methoxypropene, cat. CSA, THF, rt, 2h (92%). (e) Ph_3SnH, AIBN, PhMe, reflux, 90 min (87%). (f) 3 eq. mCPBA, CH_2Cl_2, rt, 3 days (96%). (g) lithium acetylide-EDA, THF-HMPA (4:1), rt, 15h (81%). (h) TBDMSOTf, Et_3N, CH_2Cl_2, 0°C→rt, 2h (96%). (i) K_2CO_3, MeOH, rt, 24h (95%). (j) MeLi, THF, -78°C→0°C, 30 min; $ClCO_2Me$, 0°C (91%). (k) H_2, Lindlar's catalyst, THF. (l) HOAc/1N HCl/THF (1:1:1), 65°C, 3h. (m) 1% DBU-THF (v/v), rt, 24h (60% from 19).



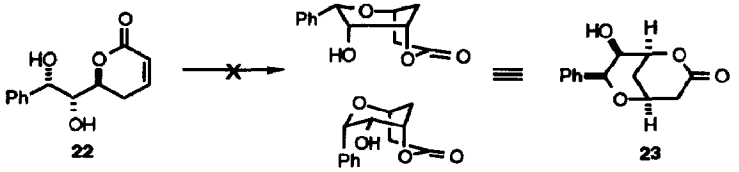
The installation of the C1 stereocenter required that the epoxidation of **7** occur in a cis-selective fashion relative to the hydroxy moieties at C7 and C8 to form **8**. While there are many procedures available for carrying out directed diastereoselective epoxidation reactions of allylic or homoallylic alcohols, few of these methods exhibit the desired cis-selectivity when dealing with terminal, unsubstituted olefins.[5] Transition metal (Ti, V) mediated epoxidations of allylic alcohols typically afford anti-isomers with good to excellent diastereoselectivity.[5,6] Conversely, the mCPBA mediated epoxidations of both allylic and homoallylic alcohols are marginally cis-diastereoselective (3:2 for 3-buten-2-ol and 1.2:1 for 4-penten-2-ol).[6] Since the diastereofacial preference using mCPBA is the same for each type of alcohol, we were intrigued by the possibility that the combination of both of these directing effects in the same substrate, **7**, might result in an enhancement of this diastereoselection by some synergistic effect. Unfortunately, mCPBA epoxidation of **7** yielded a 3:2 mixture of the epoxides **8** and **9**, suggesting that the allylic alcohol is acting alone in the diastereoselection. Although the crude reaction mixture appeared to be extremely clean by TLC and ^1H

NMR analysis, **8** and **9** were isolated in a combined yield of only 45%. Presumably the low yield is due to the water solubility and polarity of **8/9** with losses occurring during workup and/or chromatography. We have also studied the epoxidation reactions of monoprotected alcohol derivatives of **7** (TBDPS and MOM) using mCPBA as well as the $VO(acac)_2$/t-BuOOH[7] epoxidation system. All of these reactions were unsatisfying, resulting in either poor conversion, low stereoselectivity or undesired side reactions.

An alternative approach involved conversion of **3** into the acetonide **10**, followed by deiodination to afford the olefin **11**. Surprisingly, epoxidation of **11** with mCPBA was moderately diastereoselective, producing the epoxides **12** and **13** in a ratio of 2:1 and in a combined yield of 96%. Since it was anticipated that inversion of the stereocenter at C1 in the undesired trans-isomer **13** could be accomplished in a straightforward fashion at a later stage, we carried on with the synthesis using this epoxide mixture.

Alkylation with lithium acetylide•EDA complex in THF/HMPA afforded the readily separable alcohols **14** and **15** in isolated yields of 55% and 26%, respectively. Unfortunately, treatment of **15** according to the Mitsunobu conditions described by Martin and Dodge[8] (Ph_3P, *p*-nitrobenzoic acid and DEAD in PhMe at 25°C) resulted in the formation of *E*-enyne **16** in 76% and the desired benzoate **17** in only 7% yield. The alcohol **14** was protected as the TBDMS ether **18** and was then deprotonated with MeLi. Trapping of the resulting lithium acetylide with methyl chloroformate provided the α,β-acetylenic ester **19**. Semihydrogenation of the alkyne over Lindlar's catalyst (5% Pd on Ca_2CO_3 poisoned with Pb) very cleanly produced the *Z*-olefin **20**. There was no evidence for the formation of the corresponding *E*-olefin or overreduced product in the ^1H NMR spectrum of the crude reaction mixture and, therefore, the crude material was used in the subsequent reaction. Complete removal of both the silyl and acetal protecting groups in **20** as well as cyclization to the lactone diol **21** was effected in HOAc/1N HCl/THF (1:1:1) at 65°C. There was some indication that a small amount of cyclization of **21** to **1** (~10% by ^1H NMR analysis) had occurred under the acidic reaction conditions. Thus, the crude mixture was used once again and cyclization of **21** to **1** was completed under basic conditions using 1% DBU in THF (v/v) at room temperature.[2] The yield of **1** for the three steps from the α,β-acetylenic ester **19** is 60%. Synthetic (±)-9-deoxygoniopypyrone (**1**) (mp 185-186°C, EtOH) exhibited spectral data (^1H and ^{13}C NMR, IR) identical to that reported for the natural material.[1b]

We have also carried the trans-epoxide **13** through the sequence described above and have isolated the diol lactone **22**. It is very interesting to note that treatment of **22** with 1% DBU in THF at 25°C, conditions that bring about the cyclization of **21** to **1**, does not result in the formation of **23**. Starting material is recovered intact after 24h. Presumably, severe 1,3-diaxial interactions between either the phenyl substituent or the hydroxy group and the lactone moiety in the intramolecular Michael addition transition states that lead from **22** to **23** prevent the cyclization from occurring.



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4. Compounds were characterized by ^{1}H and ^{13}C NMR, IR and elemental analysis or high resolution mass spectral analysis. For selected data, see reference 9.
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9. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra at 100 MHz, both in $CDCl_3$.

   3: mp 68.5-69.5°C. ^{1}H δ 3.09 (br s, 1H), 3.23 (br s, 1H), 3.72 (br d, 1H, *J* = 6.0 Hz), 4.77 (d, 1H, *J* = 6.5 Hz), 5.80 (d, 1H, *J* = 1.8 Hz), 6.10 (dd, 1H, *J* = 1.0, 1.8 Hz), 7.26-7.39 (m, 5H). ^{13}C δ75.8, 81.5, 111.6, 126.7, 128.2, 128.3, 128.6, 139.5.

   10: ^{1}H δ 1.59 (s, 3H), 1.63 (s, 3H), 3.63 (dd, 1H, *J* = 0.8, 8.0 Hz), 4.83 (d, 1H, *J* = 8.0 Hz), 5.99 (d, 1H, *J* = 1.5 Hz), 6.28 (dd, 1H, *J* = 0.8, 1.5 Hz), 7.28-7.38 (m, 5H). ^{13}C δ 27.4, 27.5, 82.8, 88.0, 109.0, 110.3, 126.5, 128.36, 128.42, 130.0, 136.7.

   11: ^{1}H δ 1.53 (s, 3H), 1.57 (s, 3H), 4.17 (app t, 1H, *J* = 8.4 Hz), 4.64 (d, 1H, *J* = 8.4 Hz), 5.20-5.27 (m, 2H), 5.87 (m, 1H), 7.26-7.58 (m, 5H). ^{13}C δ 27.0, 27.1, 82.9, 84.7, 109.3, 119.3, 126.4, 128.2 128.4, 133.9, 137.2.

   12: ^{1}H δ 1.50 (s, 3H), 1.55 (s, 3H), 2.48 (dd, 1H, *J* = 2.6, 5.3 Hz), 2.75 (dd, 1H, *J* = 4.2, 5.3 Hz), 3.06 (ddd, 1H, *J* = 2.6, 4.2, 5.0 Hz), 3.62 (dd, 1H, *J* = 5.0, 8.7 Hz), 4.91 (d, 1H, *J* = 8.7 Hz), 7.35 (m, 5H).

   13: ^{1}H δ 1.52 (s, 3H), 1.54 (s, 3H), 2.67 (dd, 1H, *J* = 2.6, 5.0 Hz), 2.81 (dd, 1H, *J* = 4.0, 5.0 Hz), 3.14 (ddd, 1H, *J* = 2.6, 4.0, 5.1 Hz), 3.73 (dd, 1H, *J* = 5.1, 8.1 Hz), 4.94 (d, 1H, *J* = 8.1 Hz), 7.35 (m, 5H).

   14: ^{1}H δ 1.51 (s, 3H), 1.56 (s, 3H), 1.95 (t, 1H, *J* = 2.7 Hz), 2.36 (ddd, 1H, *J* = 2.7, 6.5, 16.7 Hz), 2.37 (br s, 1H), 2.47 (ddd, 1H, *J* = 2.7, 7.3, 16.7 Hz), 3.74 (br m, 1H), 3.91 (dd, 1H, *J* = 2.0, 8.6 Hz), 4.91 (d, 1H, *J* = 8.6 Hz), 7.30-7.41 (m, 5H). ^{13}C δ 25.3, 26.9, 27.2, 67.3, 70.5, 79.1, 80.2, 83.8, 109.5, 126.8, 128.4, 128.7, 137.3.

   15: ^{1}H δ 1.47 (s, 3H), 1.53 (s, 3H), 1.97 (t, 1H, *J* = 2.7 Hz), 2.15 (br s, 1H), 2.41-2.44 (m, 2H), 3.92-3.99 (m, 2H), 4.98 (AB q, 1H, *J* = 3.8, 11.2 Hz), 7.26-7.37 (m, 3H), 7.41-7.45 (m, 2H). ^{13}C δ 23.7, 27.0, 27.2, 70.4, 71.1, 79.9, 80.3, 84.0, 109.5, 127.4, 128.3, 128.5, 138.4.

   18: mp 60.5-61.5°C. ^{1}H δ 0.07 (s, 3H), 0.12 (s, 3H), 0.89 (s, 9H), 1.50 (s, 3H), 1.55 (s, 3H), 1.93 (t, 1H, *J* = 2.7 Hz), 2.39 (ddd, 1H, *J* = 2.7, 6.0, 16.6 Hz), 2.58 (ddd, 1H, *J* = 2.7, 7.1, 16.6 Hz), 3.90 (ddd, 1H, *J* = 3.0, 6.0, 7.1 Hz), 4.07 (dd, 1H, *J* = 3.0, 8.4 Hz), 4.97 (d, 1H, *J* = 8.4 Hz), 7.34 (m, 5H). ^{13}C δ -4.5, -4.2, 18.1, 24.2, 25.8, 27.0, 27.4, 69.6, 70.4, 78.6, 81.1, 84.2, 109.1, 127.2, 128.2, 128.5, 138.3.

   19: mp 50.5-51.5°C. ^{1}H δ 0.02 (s, 3H), 0.11 (s, 3H), 0.84 (s, 9H), 1.47 (s, 3H), 1.52 (s, 3H), 2.49 (dd, 1H, *J* = 6.2, 17.0 Hz), 2.69 (dd, 1H, *J* = 5.7, 17.0 Hz), 3.71 (s, 3H), 3.96-4.08 (m, 2H), 4.91 (d, 1H, *J* = 8.0 Hz), 7.25-7.40 (m, 5H). ^{13}C δ -4.6, 18.0, 24.3, 25.7, 26.9, 27.3, 52.4, 69.3, 74.4, 78.6, 84.3, 86.3, 109.2, 127.2, 128.3, 128.5, 138.0, 153.8.

   20: ^{1}H δ 0.01 (s, 3H), 0.05 (s, 3H), 0.82 (s, 9H), 1.48 (s, 3H), 1.51 (s, 3H), 2.89 (m, 2H), 3.66 (s, 3H), 3.85-3.96 (m, 2H), 4.90 (d, 1H, *J* = 8.2 Hz), 5.74 (td, 1H, *J* = 1.8, 11.5 Hz), 6.30 (td, 1H, *J* = 7.3, 11.5 Hz), 7.25-7.40 (m, 5H).

   21: mp 99-100°C. ^{1}H δ 2.11 (dddd, 1H, *J* = 0.7, 3.8, 6.3, 18.6 Hz), 2.81 (tdd, 1H, *J* = 2.4, 12.6, 18.6 Hz), 3.31 (br s, 1H), 3.44 (br s, 1H), 3.63 (br m, 1H), 4.18 (ddd, 1H, *J* = 2.2, 3.8, 12.6 Hz), 4.95 (d, 1H, *J* = 7.3 Hz), 5.92 (ddd, 1H, *J* = 0.7, 2.4, 9.8 Hz), 6.84 (ddd, 1H, *J* = 2.4, 6.3, 9.8 Hz), 7.33 (m, 5H).

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