A Concise Biomimetic Total Synthesis of (±)-Taxodione *via* a BF_3·$MeNO_2$ Promoted Cationic Cascade Annulation

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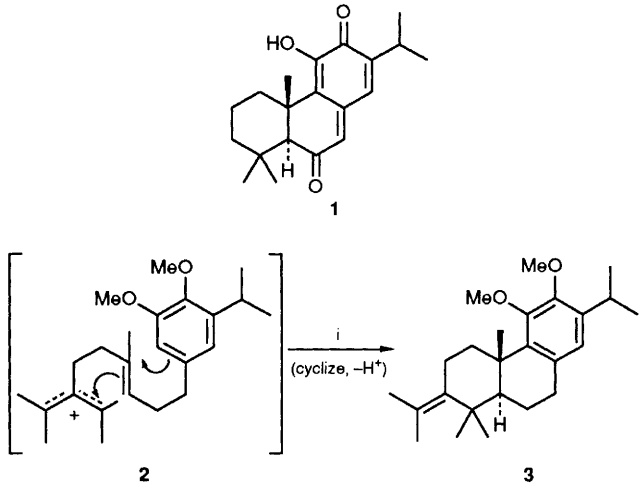
A highly convergent seven-step total synthesis of the antineoplastic agent (±)-taxodione **1** is described which utilizes a cationic cascade cyclization mediated by BF_3·$MeNO_2$ complex.

The interesting quinone methide diterpene taxodione **1**, isolated in 1968[1] from extracts of *Taxodium distichum* Rich (*Taxodiaceae*), has been shown to exhibit significant activity *in vivo* against Walker intramuscular carcinosarcoma 256 in rats and *in vitro* against cells derived from human carcinoma of the nasopharynx (KB). To date seven total syntheses[2a,g] and a relay synthesis[3] for this deceptively simple molecule have been reported. All of these, although interesting from an academic perspective, suffer from undue length and modest overall yield. The heuristically most appealing approach to this substance is a biomimetic formal synthesis reported by Johnson *et al.* in 1982.[3] In the central step of this synthesis, a rather specialized set of reaction conditions was found necessary to induce a bis tertiary allyl cation to engage a trisubstituted alkene in a cascade cyclization terminated by a hindered isopropylveratrole moiety.

Recently we disclosed that the complex formed between gaseous BF_3 and $MeNO_2$ is an unusually effective catalyst for promoting proton initiated cascade cyclizations of various 9-arylnona-2,6-dienes and related systems.[4] As would be expected, the principle caveat associated with the use of this catalyst involves its application to the cyclization of substrates which are sensitive to strong Lewis acids. In this communication we document the successful application of a BF_3·$MeNO_2$ cascade cyclization in a practical, highly convergent total synthesis of (±)-taxodione **1**.

Reduction of 3,4-dimethoxy-5-isopropylbenzoic acid **4**[5] with BMS (BH_3·SMe_2) followed by treatment of the resultant alcohol with $SOCl_2$ provided benzylic chloride **5** in 90% overall yield. Sequential lithiation of geranyl cyanide **6**‡ [LDA (lithium diisopropylamide)–THF (tetrahydrofuran), −78 °C] followed by alkylation with **5** (−78–20 °C) furnished the precyclization substrate **7** in 88% isolated yield. Exposure of this material to gaseous BF_3 (4.2 equiv.) dissolved in $MeNO_2$§ (12 h, 25 °C) afforded the essential tricyclic intermediate **8** as the *exclusive stereoisomer* in 83% yield after recrystallization.¶ The oxidative decyanation of **8** was effected by a variation of the procedure described by Watt.[6] Accordingly, lithiation of **8** followed by oxygenation of the resultant anion with O_2 at −78 °C and final hydroperoxide cleavage *in situ* [$SnCl_2$–HCl(aq)] gave ketone **9** (58% yield by GC) containing several impurities which were difficult to separate. As a consequence, the crude material obtained in this way was reduced ($LiAlH_4$) to provide the readily purifiable axial alcohol **10** directly in 54% chromatographed yield from **8**. Reoxidation of **8** to **9** [PDC (pyridinium dichromate) (2.2 equiv.), CH_2Cl_2 25 °C] proceeded without incident in 88% yield. Direct demethylation of **9** prepared in this manner (BBr_3)[2b] followed by resultant crude O_2 oxidation of the catechol on a column of silica gel as described by Matsumoto[2b] delivered (±)-taxodione **1** in 68% yield from the intermediate **8** (Scheme 2). The synthetic (±)-taxodione **1** prepared in this manner was identical to an authentic sample in all respects (mass spectrum, 300 MHz ^1H and 75 MHz ^{13}C NMR spectra).

This eminently practical synthesis of (±)-taxodione, which proceeds in seven steps and 21% overall yield, serves to



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Scheme 1 *Reagents and conditions*: i, 0.5% CF_3CO_2H–CH_2Cl_2, −45 °C

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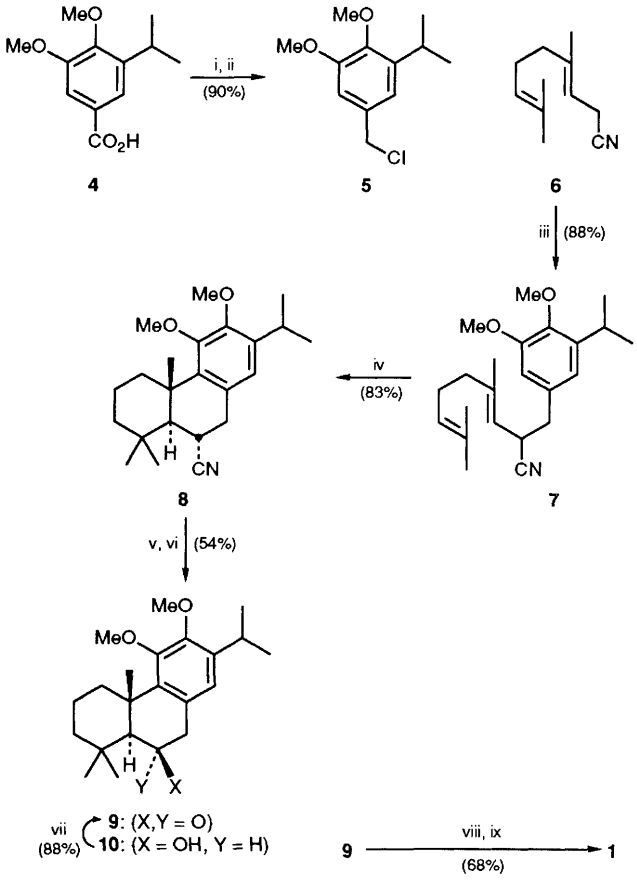
‡ Geranyl cyanide is most efficiently prepared by treating geranyl chloride with KCN in DMSO (dimethyl sulfoxide) at 20 °C (isolated yield: 85%).[4]

§ 9-Cyano-3,4-dimethoxy-2-(1-methylethyl)-4bβ,5,6,7,8,8aα,9,10-octahydro-5a,8,8-trimethylphenanthrene **8**. A flame dried 100 ml round bottomed flask equipped with a magnetic stirring bar, rubber septum and N_2 inlet was flushed with N_2 then charged with $MeNO_2$ (23.5 ml), and cooled to −20 °C. BF_3·$MeNO_2$ [(0.977 mol dm^{-3} in $MeNO_2$) 6.70 ml, 6.57 mmol] was added in one portion *via* syringe and the resulting solution was stirred for 5 min at −20 °C. A solution of the nitrile **7** (0.554 g, 1.56 mmol) in $MeNO_2$ (5 ml) was then added in one portion *via* syringe and the resulting mixture was stirred for 5 min at −20 °C, then overnight at room temperature. The reaction was quenched with saturated $NaHCO_3$ (5 ml), the layers were separated, and the organic phase was washed with H_2O (2 × 5 ml). The combined aqueous layers were back extracted with CH_2Cl_2 (3 × 5 ml) and the combined organic phase was dried with $MgSO_4$. The solvents were evaporated to furnish the crude product which was purified by MPLC (1 : 39 ethyl acetate : hexane for elution) to afford 0.460 g (83%) of **8** as a single diastereoisomer. For **8** as a white solid: m.p. 118–120 °C (recrystallized from 1 : 99 ethyl acetate : hexane) ^1H NMR ($CDCl_3$) δ 6.63 (s, 1H, ArH), 3.79 (s, 3H, OMe), 3.74 (s, 3H, OMe), 3.16 (m, 3H, CH, CH_2Ar), 2.94 [m, 2H, C(4)-H_e, CHCN], 1.69 (d, *J* 9.8 Hz, 1H, CH ring junction), 1.52 [m, 4H, C(4)-H_a, C(3)-H_e, C(2)H_2], 1.34 (s, 3H, Me), 1.29 (s, 3H, Me), 1.25 [buried m, 1H, C(3)-H_a], 1.20 (s, 3H, Me), 1.16 (d, *J* 6.9 Hz, 6H, 2Me); ^{13}C NMR ($CDCl_3$) δ 151.56 (C), 150.04 (C), 140.65 (C), 138.60 (C), 128.09 (C), 124.18 (C), 120.83 (CH), 59.95 (OMe), 59.78 (OMe), 53.60 (CH), 41.77 (CH_2), 40.88 (C), 37.70 (CH_2), 36.53 (CH_2), 34.32 (C), 33.92 (Me), 26.54 (CH), 24.97 (CH), 23.37 (Me), 23.11 (Me), 22.49 (Me), 22.43 (Me), 18.29 (CH_2); IR (ν/cm^{-1}) (KBr) 3075–2825 (CH envelope), 2230 (CN), 1472, 1400, 1330, 1316, 1302, 1252, 1064, 1048 and 1020; high resolution mass spectrum calc. for $C_{23}H_{33}NO_2$: 355.2511. Found: 355.2496.

¶ All new compounds have been fully characterized by IR, ^1H and ^{13}C NMR spectroscopy and possess satisfactory elemental (C,H) analysis by high resolution mass spectrometry.



Scheme 2 *Reagents and conditions*: i, BMS, THF; ii, $SOCl_2$, CH_2Cl_2; iii, (a) LDA, THF, (b) **5**; iv, BF_3, $MeNO_2$; v, (a) LDA, THF, (b) O_2, (c) $SnCl_2$, HCl (aq.); vi, $LiAlH_4$, THF; vii, PDC, CH_2Cl_2; viii, BBr_3, CH_2Cl_2; ix, O_2, silica gel

illustrate the utility that $BF_3{\cdot}MeNO_2$ promoted cationic cascade annulations possess for the elaboration of moderately complex polycyclic ring systems.

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