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An Expedient Synthesis of a Conveniently Functionalized Optically Homogeneous Taxoid ABC Ring System

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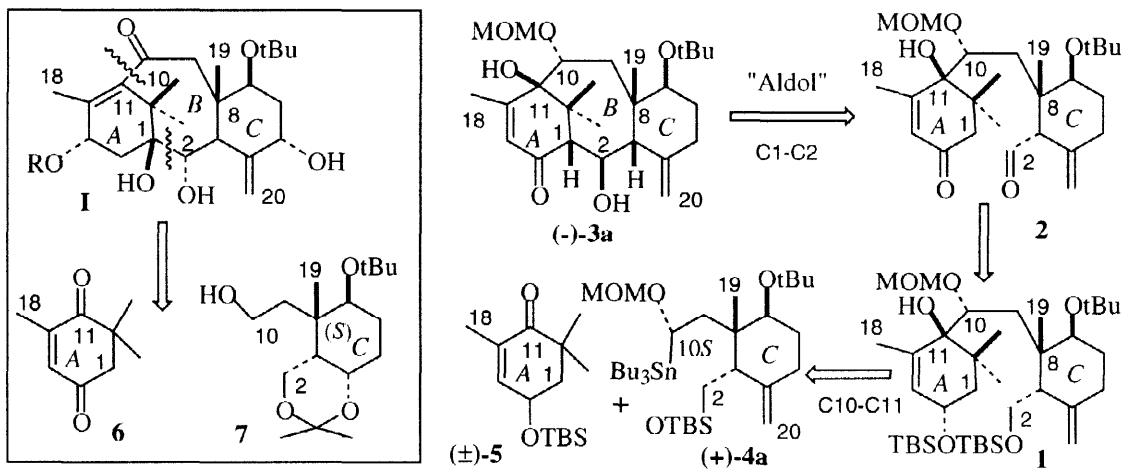
Abstract: *We present a four-step A+C route to an optically pure taxoid ABC framework* ***3a*** *containing suitable functionalities for further elaboration.*

Preoccupied with the task of synthesizing elaborated taxoid ABC ring systems of type **I**,[1] and having secured routes to B-seco taxoids,[2] we became interested in the development of a more functionalized variant of the process, specifically one which would give access to appropriately functionalized, optically pure, taxoid diterpene skeleton embodying the whole carbon framework. In this communication we report the ease with which the B-seco taxoid derivative **1**, obtained in one step from (±)-**5** and (+)-**4a**, may be unmasked, oxidized and undergo intramolecular aldol reaction to provide the taxoid ABC core **3a** (Scheme 1). We have recently



Scheme 1: A four-step preparation of the optically pure taxoid ABC framework **3a**.

reported the preparation of α-alkoxystannanes derived from **7** and described their use in the synthesis of B-secotaxane derivatives in preliminary form. A similar procedure used to prepare the new C-ring precursor **4** is outlined in Scheme 2. Starting from **7**,[3], benzyl protection at C-10 afforded **8** in quantitative yield. The latter, upon removal of the isopropylidene group afforded the corresponding diol (92%) which following a chemoselective transformation of C-2 and C-4 hydroxyls, was first selectively TBS-protected at C-2 (95%) and

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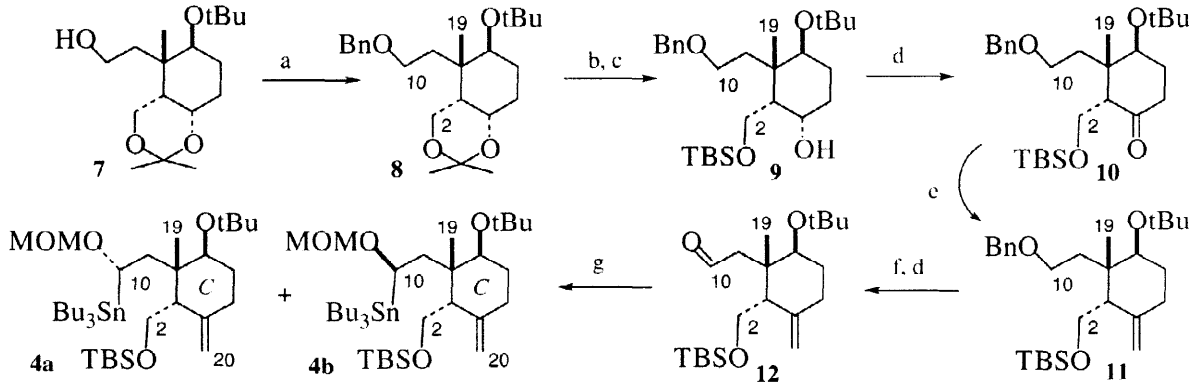
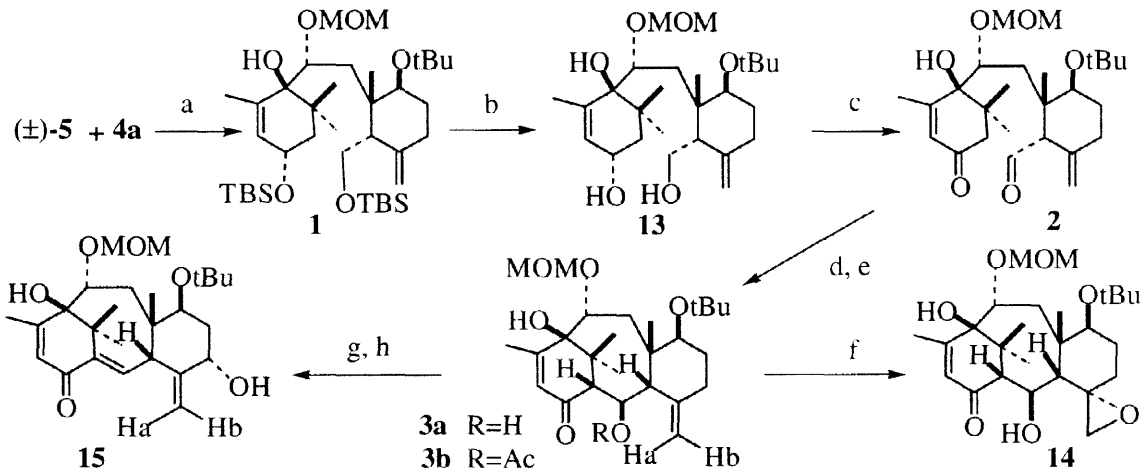
further oxidized to the C10-OBn, C2-OTBS protected ketone **10** using the Swern protocol (96%). Olefination of **10** was efficiently accomplished with the Tebbe[4] reagent in 50% isolated yield along with recovered starting



Scheme 2: a) BnBr, NaH, DMF, r.t., 15 h. b) 5%HCl-THF, 1:1, r.t., 4 h. c) TBDMSCl, DMAP, CH_2Cl_2, 0°C to r.t., d) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -60°C. e) Tebbe reagent, THF, 0°C, 40 min., f) Li-NH_3liq, *t*BuOH, THF, -78°C. g) *n*Bu_3SnLi, THF, -70°C then MOMCl, *i*Pr_2NEt, r.t.

material (48%), which was recycled thus securing the C-20 incorporation in high yield. The preparation of the requisite aldehyde **12** was then accomplished straightforwardly in two steps; cleavage of the benzyl protective group using Li-NH_3liq at -78°C and subsequent Swern oxidation of the derived C-10 hydroxyl furnished **12** in 90% yield. The latter was then elaborated into the required α-alkoxyorganostannanes **4** upon treatment with lithium tributylstannylate and subsequent protection of the secondary hydroxyl groups as their MOM ethers. This gave the C-10 epimers **4a** ($[\alpha]_D$ +22, *c* 2.0) and **4b** ($[\alpha]_D$ -57, *c* 2.0) in a 2.5:1 ratio respectively and 92% yield. The assignment of the absolute configuration to (10*S*)-**4a** is based on the absolute configuration for (10*S*)-**3a**, itself deduced from spatial proximity measurements and the assumption of retentive transmetallation.[5] Coupling of the subunits (±)-**5**[2], and **4a** was accomplished by deprotonation of the latter with *n*BuLi to generate a configurationally stable α-alkoxy lithium anion, (C-ring nucleophile) which was efficiently reacted with racemic **5** (A-ring electrophile) affording a diastereomeric mixture of four A+C adducts in 90% combined yield, with nucleophilic attack occuring exclusively at the C-11 electrophilic terminus. For convenience, only the major A+C adduct **1** (stereochemistry as depicted) is presented in Scheme 3, as the C-10, C-11, C-14 centers have no long term significance.[6] Deprotection of the *tert*-butyldimethylsilyl groups afforded the corresponding diol **13** (SiO_2 EtOAc-Heptane, 3:1, 90%, $[\alpha]_D$ +37, *c* 1.0) which was then subjected to TPAP oxidation.[7] The resulting enone-aldehyde **2** (SiO_2, EtOAc-Heptane, 1:1, 85%, $[\alpha]_D$ -30, *c* 2.9) was dissolved in dry THF (0.1 mmol of **2** in 10 mL) under argon, 2 equiv of LDA was added at -78°C, and after 5 min, the reaction mixture was diluted with heptane and quenched with saturated NH_4Cl solution to give the desired aldol **3a** (31%) along with unreacted starting material (45%). Following chromatographic separation (SiO_2, EtOAc-Heptane, 1:3), the recovered **2** was resubjected to aldol conditions as above, repeatedly, to give the taxoid ABC-framework **3a** and unreacted **2** in nearly the same ratio and yields. The C1-C2 linking, thus achieved, is not optimized and could be certainly improved. In further transformations, en route for taxol analogs, epoxidation of **3a** using $VO(acac)_2$ afforded the α-epoxide on the $\Delta^{4,20}$ double bond **14** (*t*BuOOH in decane, PhH, 10 min reflux, SiO_2, EtOAc-heptane, 1:2, 80%), whereas acetylation gave **3b**. The latter could then be transformed to **15** either in a two-step sequence (crotonization with DBU in pyridine then cat. SeO_2, tBuOOH) or in one-pot, by treating **3b** with cat. SeO_2, and *t*BuOOH 70% in H_2O at room temperature overnight, in nearly 50% yield (from **3b**).



Scheme 3: a) *n*BuLi-THF, -70°C. b) nBu$_4$NF, THF, 50°C, 2.5 h. c) TPAP-NMO, 4Å MS, MeCN, r.t., 0.5 h. d) LDA-THF, -78°C, 10 min e) Ac_2O, Py, DMAP, 0°C f) $VO(acac)_2$, *t*BuOOH in decane, PhH, reflux, 20 min g) Py, DBU, r.t.. h) cat. SeO_2, *t*BuOOH 70% in H_2O, rt.

In conclusion, we developed conditions for the 4-step preparation of an advanced taxoid ABC tricyclic intermediate **3a** from (±)-**5** and (+)-**4a**. These results pave the way for future investigations toward practical syntheses of taxoid analogs, which are currently under way in our laboratories. Comprehensive 1 and 2D NMR experiments (800 MHz, in $CDCl_3$) which included n.O.e.'s and HMBC correlations, allowed all carbons and their respective protons to be assigned with confidence. Optical rotations were measured in chloroform.[8]

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8. **3a: mp**: 168-170°C (heptane-ether). $[\alpha]_D$ -60 (*c* 0.9). **IR**: 3546, 3075, 2854, 1717, 1656, 1460, 1363, 1266, 1190, 1150, 1090, 1068, 1047, 1039, 911 cm^{-1}. **^{1}H-NMR** (800 MHz): 0.98 (3H, s, Me-19), 1.08 (9H, s, *t*Bu), 1.22 (3H, s, Me-17), 1.42 (3H, s, Me-16), 1.52 (1H, dd, *J*=6.3, 17.5, H-9ax), 1.53 (1H, dddd, *J*=5.1, 11.1, 12.5, 14.4, H-6ax), 1.70 (1H, d, *J*=17.5, H-9eq), 1.79 (1H, dddd, *J*=2.0, 4.7, 5.6, 12.5, H-6eq), 2.04 (3H, t, *J*=1.1, Me-18), 2.18 (1H, bdd, *J*=5.1, 14.4, H-5eq), 2.30 (1H, m *J*=2.0, 5.6, 14.4, H-5ax), 2.57 (1H, d, *J*=11.2, H-3), 2.80 (1H, s, H-1), 3.19 (1H, dd, *J*=4.7, 11.1, H-7), 3.47 (3H, s, OMe), 3.89 (1H, s, OH), 4.06 (1H, d, *J*=6.3, H-10), 4.38 (1H, d, *J*=11.2, H-2), 4.64 (1H, d, *J*=6.8, OCH_2O), 4.77 (1H, d, *J*=6.8, OCH_2O), 4.87 (1H, bs, H-20_a), 5.02 (1H, t, *J*=2.0, H-20_b), 6.13 (1H, dq, *J*=1.1, 1.1, H-13). **^{13}C-NMR** (75 MHz): 20.0 (Me-16), 20.5 (Me-19), 21.5 (Me-18), 28.9 (*t*Bu), 30.9 (C-5), 31.0 (C-6), 31.8 (Me-17), 39.1 (Cq-8), 40.2 (C-9), 40.9 (Cq-15), 56.1 (OMe), 56.8 (C-3), 61.4 (C-1), 69.4 (C-2), 71.7 (C-7), 73.5 (Cq-*t*Bu), 76.8 (C-10), 79.6 (C-11), 94.3 (-OCH_2O-), 115.3 (C-20), 127.9 (C-13), 147.4 (C-4), 163.3 (C-12), 198.3 (C-14). **CIMS:** 451 ($[M+H]^+$, 100), 433 (23), 419 (37), 389 (25), 377 (45). **HRCIMS:** calcd for $C_{26}H_{43}O_6$ m/z 451.3059, found 451.3052.
15: IR (film): 3450, 2973, 2926, 1733, 1671, 1665, 1656, 1625, 1459, 1390, 1376, 1364, 1247, 1192, 1148, 1091, 1067, 1048, 1021, 920 cm^{-1}. **^{1}H-NMR** (800 MHz): 1.03 (3H, s, Me-19), 1.12 (9H, s, *t*Bu), 1.32 (3H, s, Me-17), 1.52 (3H, s, Me-16), 1.55 (1H, dd, *J*=8.0, 15.9, H-9ax), 1.75 (1H, ddd, *J*=2.8, 11.5, 14.2, H-6ax), 1.88 (1H, d, *J*=15.9, H-9eq), 2.03 (3H, t, *J*=1.4, Me-18), 2.07 (1H, ddd, *J*=2.8, 4.1, 14.2, H-6eq), 3.48 (3H, s, OMe), 3.56 (1H, d, *J*=12.3, H-3), 3.70 (1H, dd, *J*=4.1, 11.5, H-7), 3.91 (1H, s, OH), 4.15 (1H, d, *J*=8.0, H-10), 4.43 (1H, t, *J*=2.8, H-5eq), 4.67 (1H, d, *J*=6.7, -OCH_2O-), 4.76 (1H, d, *J*=6.7, -OCH_2O-), 4.91 (1H, t, *J*=1.8, H-20_a), 5.06 (1H, t, *J*=1.8, H-20_b), 6.10 (1H, q, *J*=1.4, H-13), 6.45 (1H, d, *J*=12.3, H-2). **^{13}C-NMR** (75 MHz): 16.3 (Me-19), 20.5 (Me-18), 22.8 (Me-16), 26.0 (Me-17), 28.7 (*t*Bu), 36.1 (C-6), 40.2 (C-9), 44.0 (Cq-15), 46.0 (Cq-8), 49.0 (C-3), 56.5 (OMe), 67.1 (C-7), 73.1 (C-5), 73.2 (Cq-*t*Bu), 77.2 (C-10), 83.0 (C-11), 94.7 (-OCH_2O-), 116.9 (C-20), 129.8 (C-13), 135.9 (C-2), 146.0 (C-4), 147.0 (C-1), 160.8 (C-12), 194.9 (C-14). **CIMS:** 449 ($[M+H]^+$, 100), 431 (33), 417 (12), 391 (16).

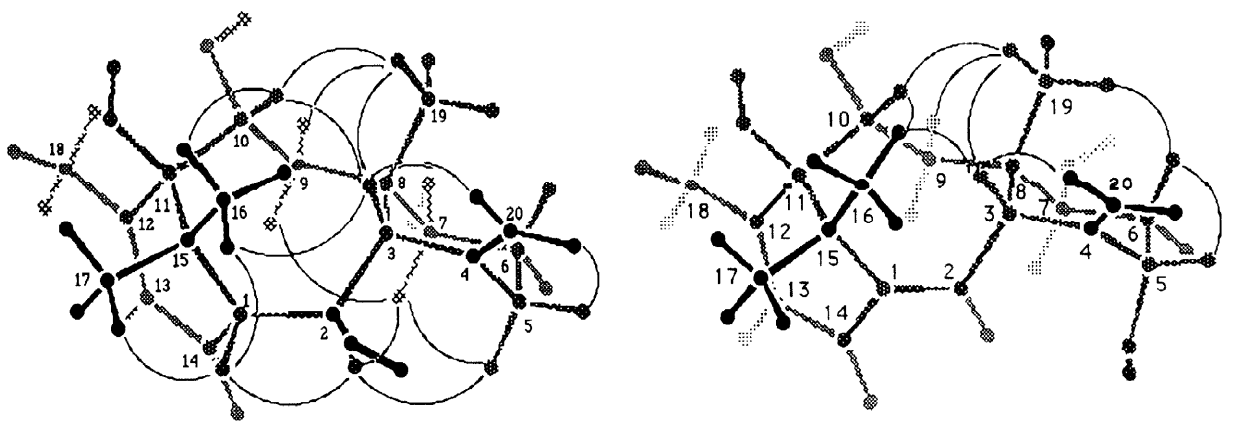

Figure 1: Computer drawing (lowest energy conformers, calculated by MM3 using n.O.e. constraints) of **3a** and **15** (MOM and *t*Bu parts omitted to simplify the presentation). Arcs indicate diagnostic n.O.e.'s.