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An Expedient Access To Highly Functionalized B-seco Taxoid Frameworks

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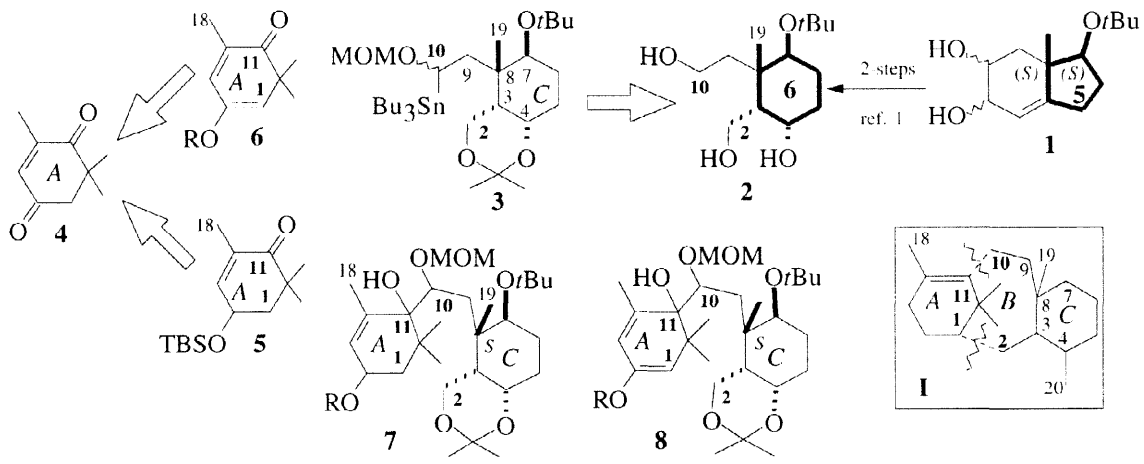
Abstract: *We report a convergent approach which proceeds in the A+C-->AC direction and leads in a straightforward manner to the conveniently functionalized B-seco-taxane frameworks 7 and 8, offering linkage possibilities at C1-C2.*

The central feature of the chemistry described in this paper involves application of a new ring expansion methodology. Discovered in this laboratory[1] as a result of our efforts towards the total synthesis of taxoids,[2] it allows the taxoid C-ring precursor **2** to be assembled in two steps starting from the known unsaturated diol **1**. The $Pb(OAc)_4$ mediated oxidative cleavage of the latter, obtained from the (S)-(+)-Hajos-Parrish ketone, provided a convenient route to the tetrasubstituted triol **2** possessing functionality and absolute configuration that are appropriate for C-ring elaboration. To illustrate the viability of this methodology, we have explored its utility in the context of an A+C approach towards the taxoid backbone. The proposed pathway starts from **2**, and the readily available 4-oxo-isophorone **4**, and places emphasis on step-efficiency. We hypothesized that, following an A+C ring linking, using **5** or **6** as A-ring electrophiles and **3** as C-ring nucleophile, the ABC-taxoid substructure **I** could be reached in a few steps. In this work we describe a concise route to "top" linked B-seco taxanes of type **7** and **8**, *via* the C10-C11 linking of left and right half partners as portrayed in Scheme 1.



Scheme 1: An efficient B-secotaxoid construction using an enantiopure C-ring precursor.

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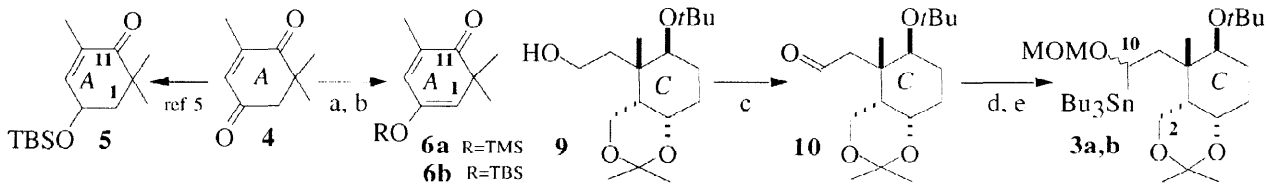
Conversion of triol **2** to acetonide **9** was accomplished according to our previous work.[1] Swern oxidation[3] of **9** afforded the required aldehyde **10** which was subsequently *umpoled* and used in the synthetic scheme as a C-10 nucleophile (Scheme 2). Thus, the requisite α-alkoxy organostannanes **3** were prepared, in a stereorandom manner but with good isolated yield, using Still's procedure[4] as follows. Aldehyde **10** (1 mmol) was treated with tri-*n*-butylstannyllithium (1 mmol, itself prepared from equimolar quantities of Bu_3SnH and LDA) in THF (5 mL per mmol) and protected immediately with chloromethylmethyl ether in the presence of iPr_2NEt at room temperature in CH_2Cl_2, to yield an approximately 1:1 diastereomeric mixture of α-alkoxy organostannanes **3** in 72% isolated yield [C-10 configuration undefined; faster eluting isomer **3a:** $[\alpha]_D$ +67 (*c* 1.0); slower eluting isomer **3b:** $[\alpha]_D$ +2 (*c* 1.0)].

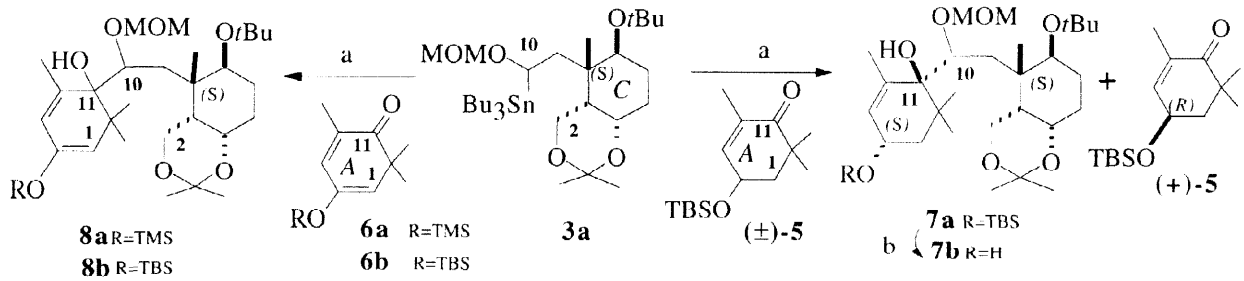
Enol ethers **6a**, **6b**, which were designed to serve as C-11 electrophiles (A-ring precursors), were cleanly prepared in a single-step procedure from 4-oxo-isophorone **4**. Stirring a sample of **4** with 1.2 equiv of trimethylsilyl triflate in dry toluene, in the presence of 1.5 equiv of collidine, under argon, at -40°C, (TLC monitoring) produced TMS enol-ether **6a** in 90% isolated yield (silica gel column chromatography, heptane-ethyl acetate, 4:1). Proceeding as for **6a**, treatment of **4** with 1.2 equiv of *tert*-butyldimethylsilyl triflate furnished TBS enol-ether **6b** in 87% yield. In addition, oxo-isophorone **4** also served as starting material for **5** (used as C-11 electrophile), which was prepared according to the literature.[5]



Scheme 2: a) TMSOTf, collidine, PhMe, -40°C. b) TBSOTf, collidine, PhMe, -40°C. c) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -60°C. d) Bu_3SnLi, THF, -70°C. e) MOMCl, iPr_2NEt, r.t.

With an effective preparation of left half (**5**, **6a**, **6b**) and right half (**3**) partners achieved, we turned our attention to formation of B-secotaxanes via C10-C11 coupling (Scheme 3). Although the C-10, C-11 stereocenters of **7** and **8** have no long-term significance in this synthetic scheme (as they are programmed to be destroyed in later steps), we anticipated that the facial selectivity during the C10-C11 bonding might be conformation controlled, while the C-10 stereocenter, derived from the conformationally rigid α-alkoxyorganolithium reagents[6] **3a** or **3b**, could exhibit some preference for one of the two enantiomers of the A-ring component (±)-**5**. Consequently we elected to use stereopure C-ring components to facilitate product characterization. To this end, the α-alkoxy organolithium reagents prepared by transmetallation of the chromatographically separated higher and lower eluting diastereomers of MOM-protected stannylcarbinols (**3a**, **3b** respectively) were individually reacted with their A-ring counterparts (±)-**5**, **6a** and **6b**, to afford the corresponding top linked A-seco taxanes. Thus, α-alkoxy organostannane **3a** (1 mmol) was treated with *n*BuLi (0.96 mmol) in THF (5 mL) at -70°C for 5 min to give the corresponding transmetallated intermediate which in turn was reacted with (±)-**5** (1.9 mmol) for 10 min at -70°C. The crude reaction profile showed a single product,[7] which was purified chromatographically (heptane-ethyl acetate, 20:1) to afford **7a** [single diastereomer; unknown configuration at C-10, $[\alpha]_D$ +66 (*c* 1.0)] in 72% isolated yield along with (*R*)-(+)-**5** [for optically pure (*R*)-**5**, ref. 5 gives $[\alpha]_D$ +57 (*c* 0.4)], indicating that a kinetic resolution had indeed occured. Fluoride promoted deprotection of the TBS-protected hydroxyl group (nBu_4NF, THF, 50°C, 1.5 h) furnished

after chromatography (heptane-ethyl acetate, 4:1), **7b** in 98% yield [m.p.: 140-142°C, ethanol, $[\alpha]_D$ +78 (*c* 1.0)].



Scheme 3: a) *n*BuLi-THF, -70°C. b) *n*Bu_4NF, THF, r.t. c) TPAP-NMO, 4Å MS, MeCN, r.t.

In parallel fashion, carrying out the same sequence as described above, **6a** and **6b** (C-11 electrophiles) were coupled with the right half precursor **3a** (C-10 nucleophile) to afford B-seco taxoids **8a** and **8b**, respectively, both as a diastereomeric mixture and in comparable yields (*ca.* 70%). At this stage, the absolute configuration at C-10, C-11 could not be assigned, nor could the products be separated. Proceeding as with **3a**, coupling of carbinyl carbanion equivalent **3b** (slower eluting organostannane, C-10 configuration unknown) with either (±)-**5** or **6a** or **6b** led to inseparable diastereomeric mixtures of B-secotaxoids (type **7** and **8**, respectively) in comparable yields. Finally, in a model study, double bond migration from C12-C13 to the required C11-C12 position was succesfully achieved.[8]

In conclusion, the sequence of reactions presented provides a rapid entry to B-seco taxoids, and is likely to lead to efficient syntheses of analogues in this area. The AC-linked intermediates **7a** and **8** thus obtained could then be transformed into the taxoid ABC-diterpene core since the C1-C2 linking for B-ring formation would only necessitate functional group manipulation designed to raise these key intermediates to the required substitution level. The large scale construction of the homochiral and conveniently functionalized taxoid C-ring segment **3** and the A-C-ring linking having been successfully achieved, we now intend to undertake a practical total synthesis of simpler taxoid analogues for biological evaluation.[9]

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References and notes

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2. Review articles: Boa, A. N.; Jenkins, P. R. and Lawrence, N. J. *Contemporary Organic Synthesis* **1994**, *1*, 47-75; Nicolaou, K. C.; Dai, W. M.; Guy, R. K. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 15-44.
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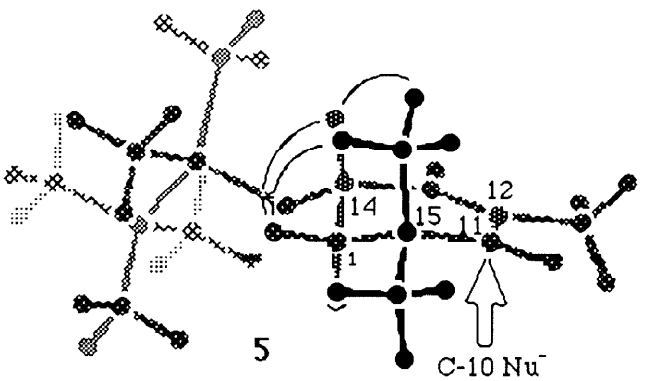
4. Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651-1660. Initially, this compound was accessed by oxidation with 1,1'-(azodicarbonyl)dipiperidine (ADD, ref. 1). Tetrapropylammonium perruthenate (TPAP, 0.05 equiv) catalyzed oxidation of the isopropylidene-alcohol **9** in the presence of NMO (1.6

equiv.) and 4Å molecular sieves, in CH_3CN, also afforded the desired aldehyde **10**, but we could not avoid partial further oxidation to the corresponding carboxylic acid during purification: Ley, S. V.; Norman, J. ; Griffith, W. P.; Marsden, S. P. *Synthesis*, **1994**, 639; Griffith, W. P.; Ley, S. V. *Aldrichimica Acta* **1990**, *23*, 13.

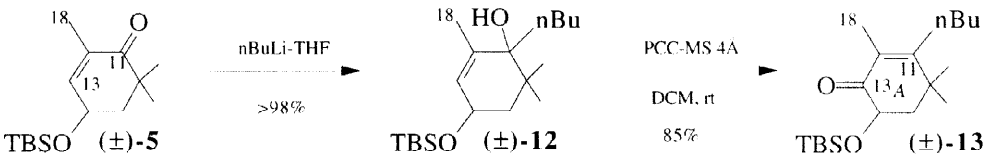
5. Tanaka, A.; Yamamoto, H.; Oritani, T. *Tetrahedron : Asymmetry*, **1995**, *6*, 1273-1278.
6. Organometallic carbon nucleophiles generally react with carbon electrophiles with retention of configuration: Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.*, **1980**, *102*, 1201-1202; Sawyer, J. S.; Macdonald, T. L.; McGarvey, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 3376-3377.
7. Molecular mechanics calculations (MM3/MonteCarlo) on A-ring electrophile **5** were used to predict the face selectivity upon C-ring Nu attack at C11. Portrayed in the Figure below is the lowest energy conformer of **5**. The favored sense of attack at C-11 is from the α-face, as indicated, leading to AC-linked **7a** (stereochemistry as depicted in Scheme 3).



Application of the Altona equation to the torsion angles found in the lowest energy conformer of **7a** gave J-values calculated from MM3 that correlate fairly well with the experimentally determined values derived from the J-analysis (400 MHz ^{1}H-NMR, $CDCl_3$). J_{calcd} H14-H1ax=10.9 Hz; found: 9.5 Hz. J_{calcd} H14-H1eq=5.1 Hz; found: 5.6 Hz. J_{calcd} H14-H13=2.7 Hz; found: 3.2 Hz. Arrows indicate diagnostic n.O.e.'s.

7a: **I.R.**: 3478, 2940, 2927, 2874, 1597, 1462, 1383, 1362, 1276, 1252, 1193, 1159, 1100, 1064, 1046, 1016, 910, 875, 844, 748 cm^{-1}. **^{1}H-NMR** (300 MHz, C_6D_6) 1.11 (3H, s), 1.16 (9H, s), 1.21 (3H, s), 1.23 (3H, s), 1.36 (3H, s), 1.45 (1H, m), 1.60 (3H, s), 1.68 (1H, m), 1.96 (1H, dd, *J*=13.9, 8.9), 2.04 (3H, t, *J*=1.5), 2.10-2.24 (2H, m), 2.27 (1H, d, *J*=16.6), 2.38 (1H, dd, *J*=13.9, 3.5), 2.44 (1H, dd, *J*=16.8, 9.0), 3.16 (3H, s), 3.55 (1H, d, *J*=11.5), 3.66 (1H, d, *J*=4.3), 3.69 (1H, dd, *J*=12.9, 4.1), 3.84 (1H, d, *J*=12.9), 4.11 (1H, d, *J*=9.1), 4.50 (1H, m), 4.74 (2H, m), 5.88 (1H, m). **^{13}C-NMR**: (75 MHz, $CDCl_3$) 18.8, 19.7, 22.4, 24.23, 24.8,25.1, 26.7, 29.1, 29.9, 38.2, 39.5, 40.5, 42.1, 45.9, 56.9, 60.7, 65.2, 66.7, 71.0, 73.1, 77.6, 86.6, 98.8, 100.1, 128.2, 137.7. **C.I.M.S.** (NH_3) m/z 516 (MNH_4^+, 3), 498 (MNH_4-H_2O, 100). The C-10 configuration remains unknown for all the compounds investigated.

8. Transformation of the model allylic tertiary alcohol **12** to the transposed α, β-unsaturated ketone **13** was carried out according to: Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682-685.



9. Complete **I.R.**, **Mass**, **^{1}H** and **^{13}C-NMR** data were obtained for each compound synthesized. Optical rotations were measured in $CHCl_3$.