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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 CI-C2. © 1998 Published by Elsevier Science Ltd. All rights reserved.

The central feature of the chemistry described in this paper involves application of a new ring expansion methodology. Discovered in this laboratory¹ 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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0040-4039/98/\$19.00 © 1998 Published by Elsevier Science Ltd. All rights reserved. *PII:* S0040-4039(98)00600-5 Conversion of triol 2 to acetonide 9 was accomplished according to our previous work.¹ Swern oxidation³ 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 procedure⁴ as follows. Aldehyde 10 (1 mmol) was treated with tri-*n*-butylstannyllithium (1 mmol, itself prepared from equimolar quantities of Bu₃SnH and LDA) in THF (5 mL per mmol) and protected immediately with chloromethylmethyl ether in the presence of *i*Pr₂NEt at room temperature in CH₂Cl₂, 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: [α]_D +67 (*c* 1.0); slower eluting isomer 3b: [α]_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 tcluene, in the presence of 1.5 equiv of collidine, under argon, at -40°C, (TLC monitoring) produced TMS enclether **6a** in 90% isolated yield (silica gel column chromatography, heptaneethyl acetate, 4:1). Proceeding as for **6a**, treatment of **4** with 1.2 equiv of *tert*-butyldimethylsilyl triflate furnished TBS enclether **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, Et₃N, CH₂Cl₂, -60°C. d) Bu₃SnLi, THF, -70°C. e) MOMCl, *i*Pr₂NEt, 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 reagents⁶ 3a or 3b, could exhibit some preference for one of the two enantiomers of the A-ring component (\pm) -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 (\pm) -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 (nBu₄NF, 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) nBuLi-THF, -70°C. b) nBu4NF, 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 diastereorneric 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 (\pm)-**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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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 ¹H-NMR, CDCl₃). 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. ¹H-NMR (300 MHz, C₆D₆) 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). ¹³C-NMR: (75 MHz, CDCl₃) 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. (NH₃) m/z 516 (MNH₄+, 3), 498 (MNH₄-H₂O, 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, ¹H and ¹³C-NMR data were obtained for each compound synthesized. Optical rotations were measured in CHCl₃.