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Stereoselective Synthesis of an A-Seco-Taxoid Subunit Using the Aldol-Annelation-Fragmentation Strategy

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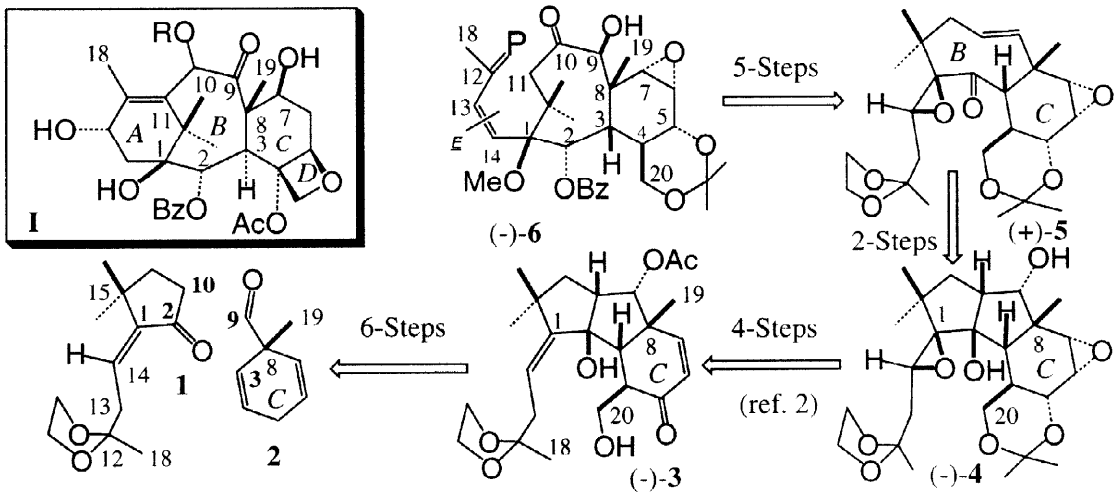
Abstract: *We present a concise route to an optically pure A-seco taxoid framework containing suitable oxygen functionalities for further elaboration.*

In our previous studies towards the taxoid diterpene skeleton **I**,[1] we described the development of a synthetic strategy, establishing the feasibility of incorporating all of the 20 carbons and of essential oxygen functionalities of the taxoid diterpene core in only 6 steps starting from **1** and **2**. The viability of this strategy was assesed by the synthesis of key intermediates, precursors of BC-subunits, with a high substitution pattern on the periphery.[2] In order to demonstrate the potential of this methodology, the synthesis of the advanced



Scheme 1

A-seco taxoid (-)-**6** (P= O-CH_2CH_2-O), illustrated in retrosynthetic form in Scheme 1, was investigated.[3] The present study deals with the structures of lactyl derivatives **7** and **8** and the conversion of the enantiomerically

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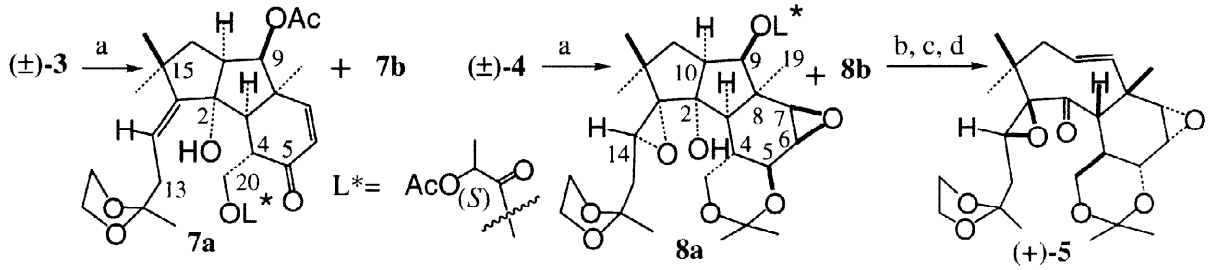
pure tricyclic BC precursor **8b** to the A-seco taxoid subunit (-)-**6**. The absolute configuration of the products was assigned through the resolution sequence outlined in Scheme 2, as follows:[4] acylation of (±)-**3** with (*S*)-O-acetyllactylchloride (O-acetyl lactyl chloride, NEt_3, DMAP, CH_2Cl_2, 0°C) gave **7a** (m.p. 54-57°C, Et_2O-C_7H_{16}, $[\alpha]_D$ +36, *c* 1.2, $CHCl_3$) and **7b** ($[\alpha]_D$ -73, *c* 0.9, $CHCl_3$), obtained optically pure (HPLC, C_7H_{16}-EtOAc, 2:1 with 0.1% AcOH). Proceeding as above racemic **4** afforded the chromatographically (SiO_2 chromatography, PhMe-Et_2O, 4:1 to 1:1) separable diastereomers **8a** (m.p. 194-196°C, Et_2O-C_7H_{16}, $[\alpha]_D$ +11, *c* 1.1, $CHCl_3$) and **8b** ($[\alpha]_D$ -43, *c* 0.8, absolute configuration of two quaternary centers at C-1 and C-8 as required) which can be further saponified to the corresponding alcohols. The structures of (*S*)-O-acetyllactyl derivatives **7** and **8** initially assigned on the basis of extensive NMR studies were confirmed by single crystal X-ray diffraction analyses of **7a** and **8a** (both *ent*-taxoid series) thus removing any ambiguity on all 11



Scheme 2: a) $CH_3CH(OAc)COCl$, NEt_3, DMAP, CH_2Cl_2, 0°C b) 2N NaOH, MeOH-H_2O, 0°C to rt. c) MsCl, DMAP, Py, 0°C, 1 h d) *t*BuOK/*t*BuOH-THF, 50°C

stereogenic centers of the fragmentation precursor **8b** (taxoid series) on which the synthetic scheme was pursued. The latter was successfully processed to the enantiomerically pure (+)-**5** in three steps. Saponification (2N NaOH, MeOH-H_2O, 0°C to rt.) gave the secondary alcohol, which without purification underwent

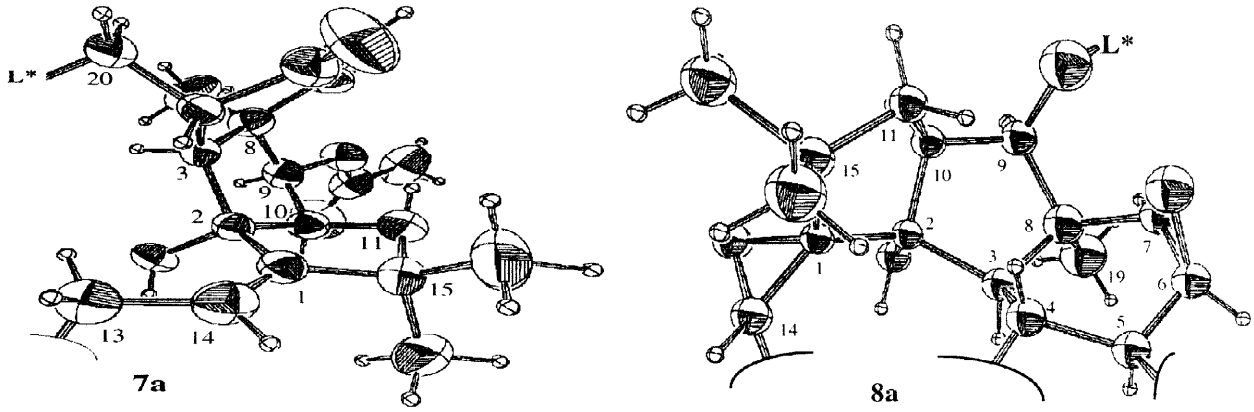
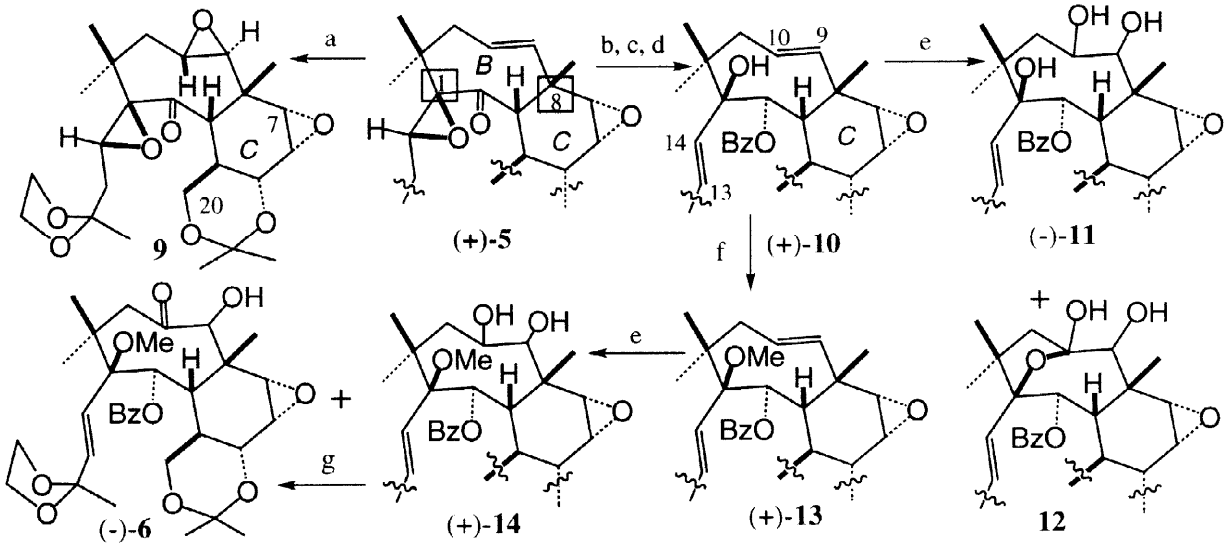


Figure 1: ORTEP drawings of **7a**, **8a** (ketal, acetonide and lactate parts omitted to simplify the presentation).

mesylation (1 mmol in 8 mL of Py, 5.7 equiv of MsCl, cat DMAP at 0°C, 40 min) to afford the corresponding mesylate (85% two steps) ready for a Grob type fragmentation.[5] When the mesylate was simply heated in THF at 50°C, for 1 h 20 min under argon, in the presence of 1M *t*BuOK in *t*BuOH (3 equiv) the [6+8] bicyclic system **5** which corresponds to the taxoid BC subunit was obtained in 86% yield following chromatographic

purification on SiO_2 using C_7H_{16}-EtOAc, 2:1 as eluent ($[\alpha]_D$ +21, *c* 1.3, $CHCl_3$, m.p. 168-169°C, Et_2O-C_7H_{16}).

At this point, the synthetic plan called for selective opening of the C14-C1 epoxide, which was accomplished efficiently using freshly prepared $LiEt_2N$ in THF, in the presence of 10 equiv of HMPA (0°C to room temperature, 10 min) affording 88% of the corresponding α-ketol ($[\alpha]_D$ +2, *c* 2.3, THF) along with 8% of recovered starting material (SiO_2, EtOAc-C_7H_{16}, 1:3). Reduction of the C-2 carbonyl group (excess of $LiAlH_4$ in THF, at 0°C TLC monitoring, CH_2Cl_2-MeOH, 98:2) and subsequent benzyl protection of the secondary hydroxy group of the resulting diol (BzCl, Et_3N, CH_2Cl_2, 0°C to rt) afforded (+)-**10** (SiO_2 flash chromatography, C_7H_{16}-EtOAc 2:1, m.p. 217-219°C, $[\alpha]_D$ +50, *c* 1.8, THF) in 85% yield (two steps). The following step involves chemoselective functionalization of the C9-C10 double bond in the presence of the C13-C14 double bond. Up until this point the synthetic scheme proceeded affording a single isomer for all transformations and not any detectable side product. The first undesired byproduct was obtained in this crucial step upon attempted osmylation (cat OsO_4, NMO, Py, *t*BuOH, H_2O, 75°C, 4.5 h) in the presence of a free hydroxy group at C-1, affording 57% of the desired diol (-)-**11** (m.p. 256-258°C, THF-C_7H_{16}, $[\alpha]_D$ -9, *c* 2.2, THF) along with 34% of the unwanted transannular hemi-acetal **12**. In an attempt to overcome this undesired reaction mode, the C-1 tertiary alcohol of (+)-**10** was converted to its corresponding methyl ether (+)-**13** (m.p. 204-206°C, THF-C_7H_{16}, $[\alpha]_D$ +86, *c* 0.5) by treatment with 12 equiv of powdered KOH, in DMSO (10 mL per mmol) and, immediately after, addition of excess, freshly distilled, MeI (30 min rt stirring) in 40% isolated yield along with 40% of unreacted starting material. Subsequent osmylation as above furnished not only the expected diol (+)-**14** in 52% ($[\alpha]_D$ +7, *c* 0.5, THF) but also directly the desired acyloin (-)-**6** [6] in 31.5% yield (SiO_2 C_7H_{16}-EtOAc, 2:1, $[\alpha]_D$ -24, *c* 0.7, THF). Furthermore, (+)-**14** was easily recycled by an additional oxidation (Dess-Martin periodinane, CH_2Cl_2, rt) step affording (-)-**6** quantitatively as the sole product (Scheme 3; dioxolane and acetonide parts of the molecules remain unchanged and have been omitted to simplify matters).



Scheme 3 a) $MeReO_3$, Py, H_2O_2, CH_2Cl_2, rt. b) $LiEt_2N$, THF, HMPA. c) $LiAlH_4$-THF. d) BzCl, Et_3N, CH_2Cl_2. e) OsO_4-NMO, Py, *t*BuOH-H_2O. f) KOH-DMSO, MeI. g) Dess-Martin periodinane, CH_2Cl_2, rt.

Compound (+)-**5** was further functionalized towards highly oxygenated, stereopure, [6+8] bicyclic framework containing targets. Upon treatment with methyltrioxorhenium (MTO, 0.5 mol %)[7] in the presence of

1.5 equiv of H_2O_2 in CH_2Cl_2 (2M) under argon at room temperature for 24 h, the corresponding epoxide **9** was obtained as a single isomer (eventhough optically pure, its α-value is near zero), assigned as depicted in Scheme 3 (88% yield, SiO_2, C_7H_{16}-EtOAc, 1:1).

These experiments provided two potential precursors, **9** and **6**, for the construction of the taxane framework, illustrating the synthetic utility of our approach. We thus have reached an advanced stage in the synthesis and are now in a position to address the C11-C12 bonding in order to achieve a step-efficient stereopure elaboration of the ABC-taxoid diterpene skeleton.

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3. This retrosynthesis did not account for the stereogenic center at C-3; however, we anticipated that this center could be controlled by equilibration after closure to the taxoid ABC system.
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6. (-)-**6:** I.R. (film): 3437, 2987, 2937, 1726, 1687, 1450, 1371, 1264, 1197, 1176, 1102, 1087, 1073, 1041, 929, 863 cm^{-1}. ^{1}H-NMR (300 MHz): 0.86 (3H, s), 1.08 (3H,s), 1.16 (3H, s), 1.37 (3H, s), 1.46 (3H, s), 1.49 (3H, s), 2.20 (1H, d, *J*=8.3), 2.53 (1H, d, *J*=16.4), 2.53-2.68 (1H, m), 3.04 (1H, d, *J*=5.2), 3.31 (3H, s), 3.34 (1H, d, *J*=16.4), 3.58-3.90 (5H, m), 3.74 (1H, d, *J*=5.2), 3.96 (1H, dd, *J*=4.3, 11.1), 4.23 (1H, d, *J*=4.0), 4.28 (1H, d, *J*=10.8), 5.69 (1H, d, *J*=4.0), 5.76 (1H, s), 5.78 and 5.94 (2H, AB system, *J*=16.6), 7.37-7.59 (3H, m), 7.95-8.00 (2H, m). ^{13}C-NMR (75 MHz): 19.2, 21.1, 22.2, 27.3, 29.6, 30.6, 39.7, 40.4, 40.6, 40.8, 49.9, 52.0, 54.5, 55.9, 64.3, 64.5, 65.4, 69.5, 77.4, 80.9, 81.9, 99.6, 107.2, 124.1, 128.6, 129.4, 130.3, 133.0, 137.6, 166.0, 211.3. CIMS: 601 ($[M+H]^+$, 61), 583 (41), 509 (47), 543 (41), 525 (19), 511 (34), 479 (100), 447 (61), 421 (40), 389 (31), 178 (81), 123 (100), 87 (100). HRCIMS: calcd for $C_{33}H_{44}O_{10}$ m/z 600.2935 found: 600.2938.
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