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Studies Towards the Total Synthesis of Taxoids: An Efficient Formal Total Synthesis of an A-seco Taxane Framework[1]

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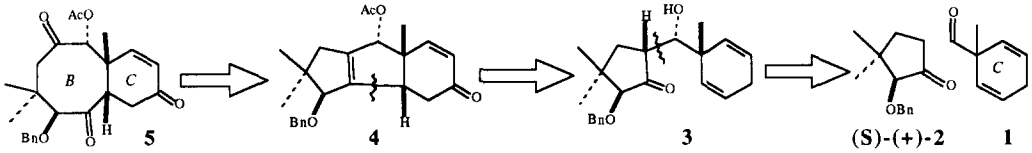
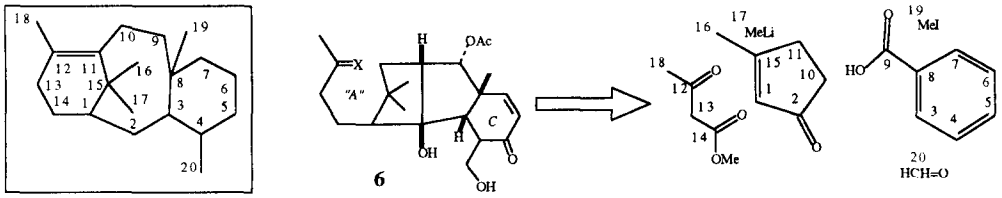
Abstract: *Compounds 6 and 19 embodying the whole carbon framework and suitable functionalities of the taxane skeleton have been assembled starting from readily available chemicals.*

An efficient method for the construction of the tricyclic carbon skeleton remains a major task in taxane synthesis.[2] Developing a synthetic methodology in this field we have published recently a straightforward approach from **1** and optically homogeneous **2** towards the BC-subunit of taxoids in which the olefin **4** was fragmented to **5** in 75% yield when treated with ozone in CH_2Cl_2.[3] This model study was designed to set the stage for the construction of the 6+8 fused substructure of taxoids with an appropriately substituted B-ring moeity.

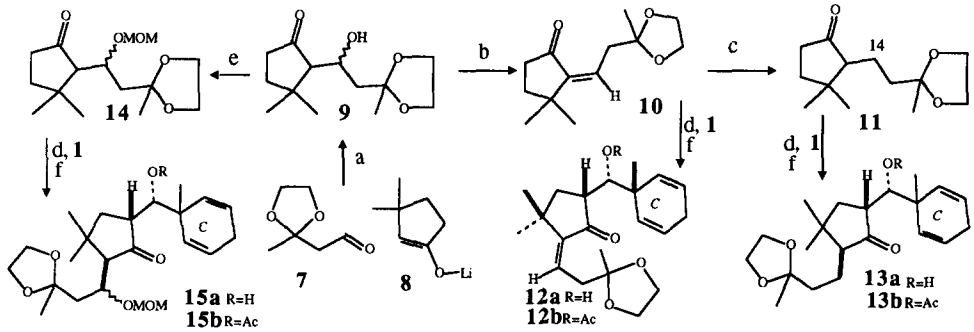


In an effort to extend this methodology to synthetically more interesting examples we describe in this paper an alternative protocol that provides the twenty carbons of the taxane framework together with oxygen functionalities for further elaboration using methylacetoacetate, methylcyclopentenone, methyllithium, benzoic acid , methyl iodide and formalin as carbon and oxygen source. Starting from **9** and the previously prepared aldehyde **1** an eight step procedure yielded the A-seco taxane precursor **6**, ready for the construction of the tricyclo[9.3.1.0.^{3,8}]pentadecane skeleton, equiped with the appropriate functionalization for further elaboration.



Ketones **10**, **11** and **14** containing eleven out of twenty carbons of the taxane framework were selected as the initial targets due to their ready availability. The synthesis began with methylacetoacetate which upon trivial transformations afforded ketal aldehyde **7**. Thus, protection of the ketone carbonyl (ethylene glycol, pTos-OH, PhMe, reflux, 1 h, 75%) followed by $LiAlH_4$ reduction in THF (rt, 10 min, 100%) and finally PCC oxidation of the resulting alcohol (CH_2Cl_2, rt, 4 h) gave **7**. The latter was used without purification in the

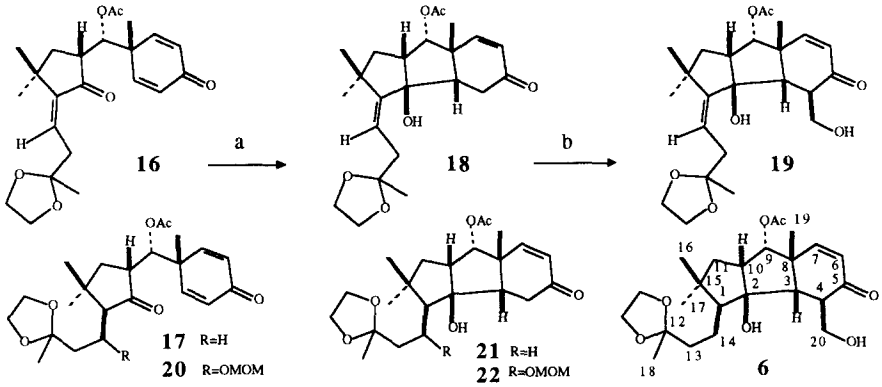
coupling with the methyl cuprate generated enolate[4] **8**, (Me_2S-CuBr, MeLi, Et_2O, -10°C, 15 min, then methylcyclopentenone, 0°C, 20 min). **7** and **8** were cooled to -20°C and reacted in the presence of 1.6 eq. of $ZnCl_2$ (0.1 M in ether), to give **9**, as a mixture of two threo aldols[5] in 7:1 ratio and 50% overall yield (from methyl acetoacetate). Separation of the two isomers was not necessary for the next step. The diastereomeric mixture **9** was first crotonized (Ac_2O, Py, DMAP, rt, 2h then DBU, rt, 3 h) to yield **10** (97%). Lithium-ethylamine reduction of the latter (Li, $EtNH_2$, tBuOH-THF, -78°C, 15 min) afforded **11** in 82% isolated yield. Both **10** and **11** were then subjected to a second highly threo selective[6] aldol reaction (LDA, THF, -40°C, 2 h, for enolate formation) with the benzoic acid derived achiral aldehyde **1** (THF, -78°C, 10 min) to afford **12a** (70%) and **13a** (93%). Although the diastereomeric aldols were chromatographically separable, neither **12a** nor **13a** need to be further purified. Indeed when the minor aldols (which account for well below 10% of the diastereomeric mixture) were subjected to the annelation conditions separately, they both decomposed, giving no trace of annelated diastereomeric compounds. This fact constitutes a reaction-mediated separation of the undesired minor diastereoisomers so the mixture of aldols was carried forward as such. Next we have focussed our attention on the appropriately substituted tricyclic compounds **19**, and **6**, which upon fragmentation would lead to the desired BC-subunit, creating the conditions for the A-ring formation through aldol chemistry.[7]



a). $ZnCl_2$, Et_2O, -20°C b). Ac_2O, Py, DMAP, rt, 2h, then DBU, rt, 12 h c) Li-$EtNH_2$, tBuOH-THF, -78°C, 15 min. d) LDA, THF, -40°C, 2h, then cool to -78°C, add **1**, 5 min e) MOMCl, iPr_2EtNH_2, CH_2Cl_2, rt f) Ac_2O, Py, DMAP, rt, 1h.

Acetylation of the aldols thus obtained (Ac_2O, Py-DMAP, 0°C, 1 h) afforded 92% of **12b** and 95% of **13b**. Subsequent allylic oxidation (CrO_3, 3,5-dimethylpyrazole, tBuOOH-CH_2Cl_2, rt, 5h for **12b**, 1 h for **13b**) led to **16** and **17** in 60 and 75% yields respectively. Annelation was achieved by samarium diiodide[8] promoted intramolecular reductive coupling via a *5-exo-trig* process[9] according to previous work.[3] Thus treatment of **16** and **17** with 2 equiv of SmI_2 in THF-HMPA-MeOH (6.6, 4.0, 0.8 ml/mmol respectively) at -90°C for 30 min, followed by quenching with aqueous $NaHCO_3$ (2 ml/mmol) gave after flash chromatography (ethyl acetate-heptane, 1:1) the *cis-syn-cis* tricyclic intermediates **18** (60%) and **21** (70%). An analysis of the crude reaction mixture by ^{1}H-NMR indicated no trace of cyclization of the corresponding minor aldols but predominantly consisted of the desired tricyclic derivatives along with small amounts of the C-5 carbonyl reduction after cyclization. The latter could be converted back to **18** and **21** in high yield via a Swern oxidation. When the whole sequence was applied to the MOM-protected derivative **14** (MOMCl, iPr_2EtN, CH_2Cl_2, rt, 20 h, 88%) till the annelated tricyclic intermediate **22** the yields for the aldol condensation-acetylation (**15b**, 50%) oxydation (**20**, 30%) and annelation (**22**, 50%) were considerably lower. Morover, dealing with additional diastereoisomers in conjuction with extra care needed in the presence of the MOM-protective group renders this route less attractive.

With the desired tricyclic derivatives in hand, the C-20 unit was then introduced by a water tolerant Lewis acid ($Yb(OTf)_3$)[10] catalyzed aldol reaction in H_2O-THF. Towards this end enones **18** and **21** were treated with LDA (2.9 equiv of iPr_2NH, 2.4 equiv nBuLi) in THF at -40°C, 2h, for the enolate formation followed by addition of TMSCl (3.2 equiv) and Et_3N (2.9 equiv in pentane), at -70°C. The reaction mixture was stirred at this temperature for 1.5 h, quenched with a saturated solution of NH_4Cl and extracted with CH_2Cl_2. The resulting stable dienolsilylethers were then reacted with commercial aqueous formaldehyde (30% solution in H_2O, 6 ml/mmol) in THF (12 ml/mmol) in the presence of 0.9 equiv of $Yb(OTf)_3$ for 90 h to yield **19**[11] and **6**[12] in ca 70% yield, along with recovered starting enones **18** and **21**.



a) SmI_2-HMPA, THF-MeOH, -90°C, 30 min b) 1. LDA-THF, -40°C, 1.5 h, TMSCl, Et_3N, -70°C, 1.5 h 2. $Yb(OTf)_3$, HCHO, THF-H_2O, 70h, 3.TBAF, THF, rt, 10 min.

The stereochemistry of the *cis-syn-cis* tricyclic intermediates **18** and **21**, ensures the desired relative configurations during further transformations, with only the β-face of the molecule being accessible. Furthermore, we observed an easy chemodifferentiation of the two double bonds ($\Delta^{1,14}$, versus $\Delta^{6,7}$) in **18** and **19**. For instance, epoxidation of **18** using $VO(acac)_2$, tBuOOH, PhH, rt, 48 h, afforded the β-epoxide on the $\Delta^{1,14}$ double bond (setting the stage for the C1-β-oxygen functionality), whereas Ra-Ni reduction of **18** and **19** (H_2, Ra-Ni, MeOH, rt, 10 min, quantitative) reduced only the $\Delta^{6,7}$ double bond on the C-ring of each compound. Moreover the C10 carbonyl group which will be introduced during the fragmentation step is well situated for an aldol type A-ring formation. The overall sequence can be readily modified to produce the required carbon/oxygen skeleton offering several distinct ways for further elaboration on the way for bioactive taxoid analogues.[13]

References and notes

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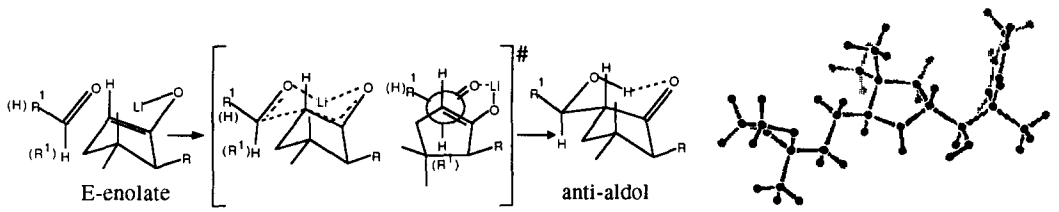
4. For a review see: Lipshutz, B.H.; Sengupta, S. Organic Reactions vol.41, **1992**, published by John Wiley & Sons, Edited by Paquette L. et al.

5. The stereochemistry of this aldol condensation is pointless as the stereogenic center at C-14 is destroyed on each of the following two steps leading to **10** and **11**.
6. Aldols **12, 13** and **15** must be converted with some care to the corresponding acetates to avoid rapid epimerization (and/or crotonization) leading to the erythro-aldols in some extent. The *threo* (*erythro*) Zimmerman-Traxler transition states account well for the observed simple diastereoselection and π-facial selectivity. A transition state rationale as well as the hydrogen bonded conformation of major threo (anti) aldol's lowest energy conformer (MM2 molecular mechanics calculations) is shown below.



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10. Kobayashi, S. *Synlett* **1994**, 689-701; Kobayashi, S. *Chem. Lett.* **1991**, 2187-2190.
11. **19**: **IR** (film) 3449, 2959, 2934, 2884, 1741, 1664, 1376, 1240, 1053 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.92 (3H, s, Me-17), 1.06 (3H,s, Me-16), 1.29 (1H, dd, J=8.4, 13.2, H-11b), 1.35 (3H,s, Me-18), 1.39 (3H,s, Me-19), 1.57 (1H, t, J=13.2, H-11a), 2.12 (3H,s, OCOMe), 2.49 (1H, dd, J = 5.8, 13.7, H-13), 2.56 (1H, br.s, H-3), 2.61 (1 H, OH-20), 2.74 (1 H, ddd, J = 1.5, 6.1, 8.3, H-4), 2.85 (1H, dd, J = 11.2, 13.7, H-13), 2.94 (1H, ddd, J = 7.0, 8.4, 12.8, H-10), 3.80 (2H, m, H-20), 3.94 (4H, m), 5.25 (1H, d, *J* = 7.0 Hz, H-9), 5.54 (1H, dd, J = 5.8, 11.2, H-14), 5.98 (1H, d, J = 10.4, H-6), 7.00 (1H, dd, J = 0.6, 10.4, H-7); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 20.8 ($OCO\underline{CH_3}$), 24.8 (Me-18), 28.1 (Me-17), 29.0 (Me-19), 33.5 (Me-16), 37.6 (C-11) 38.7 (C-13), 41.8 (C-15), 44.5 (C-8), 49.3 (C-4), 54.2 (C-10), 56.0 (C-3), 64.9, 65.0 (ketal $\underline{CH_2}$), 65.9 (C-20), 81.8 (C-9), 91.5 (C-2), 109.5 (C-12), 121.3 (C-14), 126.6 (C-6), 155.0 (C-7), 157.3 (C-1), 170.1 ($O\underline{C=O}$), 200.0 (C-5); **EIMS**: m/z 434 ($M^{+\cdot}$, 4), 419 (9), 401 (7), 313 (29), 295 (40), 191 (43), 151 (47), 87 (100). **HRCIMS**: calc. for $C_{24}H_{35}O_7$ M 435.2382 found: 435.2359.
12. **6**: **IR** (film) 3448, 3018, 2960, 2935, 2894, 1736, 1663, 1376, 1241, 1217, 1049 cm^{-1}; **^{1}H NMR** (400 MHz, C_6D_6) δ 0.94 (3H, s, Me-16), 1.01 (3H, s, Me-17), 1.14 (3H, s, Me-19), 1.25 (1H,m, H-11b), 1.39 (1H, m, H-11a), 1.26-1.80 (5H, m), 1.44 (3H, s, Me-18), 2.49 (1H, br s, H-3), 3.02 (1H, ddd, J= 8.6, 9.2, 11.6, H-10), 3.21 (1H, t, J=7.8, H-4), 3.60-3.80 (4H, m), 3.72 (1H, dd, J= 8.4, 10.5, H-20), 4.04 (1H, dd, J= 7.1, 10.5, H-20), 5.18 (1H, d, J=8.6, H-9), 5.92 (1H, d, J=10.3, H-6), 6.65 (1H, dd, J=1.5, 10.3, H-7) ; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 20.5, 20.6, 22.1, 23.5, 28.5, 29.8, 37.8, 40.9, 42.8, 45.5, 47.4, 52.4, 55.9, 57.7, 64.2, 64.5, 79.9, 91.3, 110.0, 127.7, 152.2, 170.2, 199.5; **EIMS**: m/z 436 ($M^{+\cdot}$, 0.4). **CIMS:** m/z 437 ($M^{+\cdot}$, 1); 375 (100), 345 (87). **HRCIMS**: calc. for $C_{24}H_{37}O_7$ M 437.2539 found: 437.2548.
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