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Studies Towards the Total Synthesis of Taxoids. A Straightforward Procedure for the Taxoid BC Substructure

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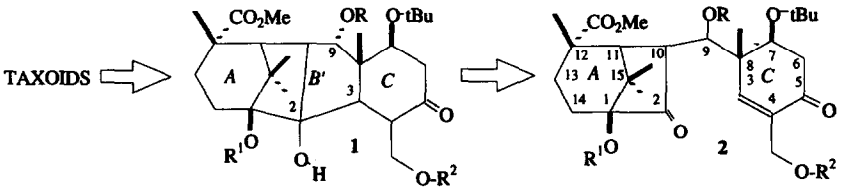
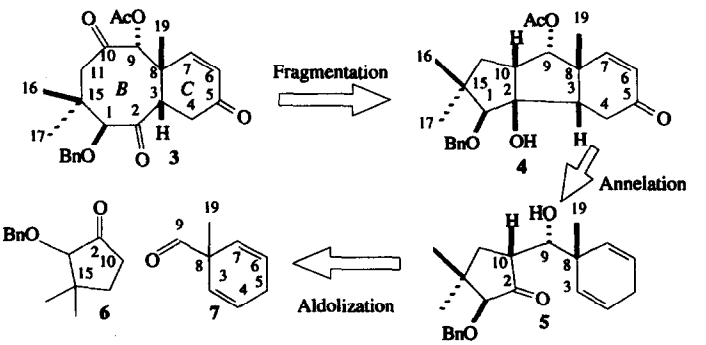
Abstract: *The aldol condensation of the ketone* **6** *and the aldehyde* **7** *followed by an annelation-fragmentation afforded the bicyclo[6.4.0]dodecane derivative* **3** *with the appropriate functionalities for further elaboration.*

Recently, we reported an efficient approach to the functionalized bicyclo[3.2.1]octane derivative in its optically pure form as an A-ring component of the taxoid skeleton[1]. Our strategy towards this objective is based on the use of a combined aldol-type C-10/C-9 bond formation- samarium iodide induced C-2/C-3 annelation, to generate the tetracyclic skeleton **1**, which upon fragmentation would lead to the desired taxoid eight-membered ring (Scheme 1).



Scheme 1

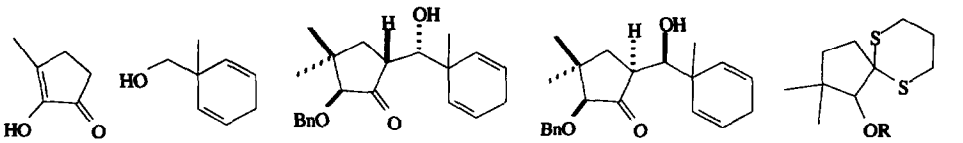
As an extension to this first approach directed towards the total synthesis of taxoids, we have also explored a conceptually similar approach involving an aldol condensation-annelation-fragmentation process. Herein we report the successful synthesis of the BC framework **3**, which sets the stage for the construction of taxol's "B"-ring (Scheme 2).



Scheme 2

The aldol precursors **6** and **7** were readily prepared according to literature. The aldehyde **7** was prepared

from methyl benzoate by a classical three step sequence. Thus Birch reductive alkylation of methyl benzoate (Na-NH_3liq, tBuOH-THF,-70°C, then MeI-THF, 47%) followed by reduction (DIBAH, 1M in Heptane, CH_2Cl_2, -78°C to r.t.) afforded the corresponding alcohol **9**[2] in an almost quantitative yield. This alcohol was then oxidized under Swern conditions[3] to the aldehyde **7** (82%). An attractive candidate for the ketone **6** (conveniently prepared according to the method described in reference[4]) was cyclotene (3-methyl 1,2-cyclopentanedione) **8**, a readily available substance of natural occurance. Transformation of **8** into **10a** was achieved in 50% overall yield as described in reference 4. The racemic dithiane-acetate (±)-**10b** was subjected to enzymatic hydrolysis by employing horse liver esterase (100mg of H.L.E. for 100mg of (±)-**10b**, 30ml of phosphate buffer pH=7, 1ml of toluene, 4°C)[5]. When reaction was allowed to proceed to 42% conversion, carbinol (-)-**10a** (96% e.e.) was obtained alongside (+)-**10b**. Following chromatographic separation, acetate (+)-**10b** can be obtained in high optical purity (96% e.e.) by simply repeating the enzymatic hydrolysis just once. (+)-**10b** was converted to (+)-**10a** (K_2CO_3, MeOH-H_2O, r.t.). The benzyl ethers (+)-**10c** and (-)-**10c** were prepared from each enantiomer. We thus assured homochiral segments in the very beginning of the synthesis. However, we further achieved our synthetic scheme on racemic material for obvious reasons. Benzylation of racemic **10a** (NaH-BnBr, DMF, r.t.) followed by mercury assisted hydrolysis ($HgCl_2$-$CaCO_3$, acetone-water, Δ) afforded the desired ketone **6** in 90% yield.

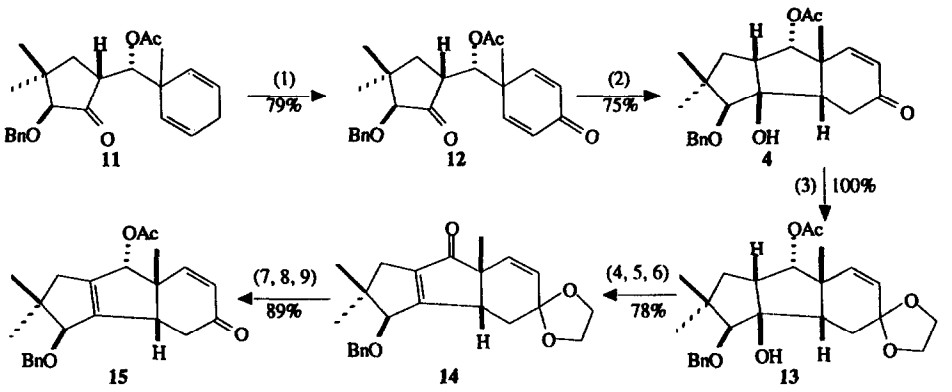


8 **9** **5a** **5b** **10** a: R= H b: R=Ac c: R= Bn

The ketone **6** and the aldehyde **7** were smoothly assembled via an aldol condensation (1h at -40°C for the enolate formation on **6** with LDA (1.5eq) in THF, then cooling to -78°C, followed by addition of the aldehyde (2.5eq.). After an additional reaction time of 10 min the reaction mixture was quenched with aqNH_4Cl. The residue was chromatographed on silica gel (heptane-ether 5:1) to afford two aldols **5a** and **5b** in a 13.3:1 ratio and 86% yield. The major aldol **5a** was acetylated (Ac_2O, Py, DMAP, r.t., 1h, 95%) prior to allylic oxidation (PDC, tBuOOH,CH_2Cl_2, -20°C, 48h) to afford **12** (79%), one step from the tricyclic intermediate **4**. To effect the C-2/C-3 bond formation (annelation) we decided to try a samarium iodide mediated reductive coupling, with some care to prevent overreduction and possible deoxygenation at C-1. After considerable investigation of various alternatives, it was found that conversion of **12** into **4** could be carried out in an efficient manner under carefully defined conditions by adding a mixture of **12** and methanol (20eq.) as a 0.15M solution in THF to a stirred solution of 0.1 M samarium(II) iodide (2.15eq.) in THF and HMPA (24.6eq.) at -80°C. Work-up after an additional reaction time of 3.5 h at this temperature gave a crude mixture which upon subjection to column chromatography (elution with heptane-ethyl acetate, 1:1), yielded 75% of the desired tricyclic enone **4**[6] the stucture of which was first assigned as depicted in Scheme 2 by extensive NMR experiments (especially difference n.O.e.'s). In order to confirm this structural assignement a single crystal X-ray analysis was performed on **4**; an ORTEP drawing of the molecular structure of the latter is shown in figure 1.

Elaboration of the latter to the target alkene **15**, required a few steps. Thus ketal protection of **4** (ethylene glycol, PhH, p-TsOH, 3h reflux, quant.), saponification of the acetyl group at C-9 (NaOH, MeOH-H_2O, overnight, r.t., 95%) followed by oxidation of the resulting hydroxy ketone with the Dess-Martin periodinane reagent[7] (1.88eq., in dry CH_2Cl_2 and pyridine, overnight, r.t.) and subsequent elimination without further purification of the crude oxidation product (t-BuOK, Et_2O, 10 min at r.t.), afforded enone **14** (78% combined yield for the two steps). To ensure selective C-2/C-10 fragmentation and C-7 functionalization we further transformed **14** into **15** in three additional steps and 89% overall

yield. Thus, reduction of the C-9 carbonyl (L-Selectride in dry THF at -70°C, 15 min r.t., then work up with 15% aq.NaOH, 30% H_2O_2), acetylation of the resulting alcohol (Ac_2O, pyridine, DMAP, 15 min at r.t.) and finally deketalization (1M HCl, THF-H_2O, r.t., 2h) gave **15** (Scheme 3).



Scheme 3:
1)PDC-tBuOOH/DCM, -20°C, 2)SmI_2-MeOH/THF/HMPA, -80°C, 3)$HOCH_2$-CH_2OH, TsOH/PhH, Δ. 4)NaOH/H_2O-MeOH r.t., 5)Dess-Martin, Py/DCM, r.t.,6)tBuOK/Et_2O, r.t., 7)L-Selectride-THF, r.t., 8)Ac_2O, Py, DMAP, r.t., 9)HCl/ H_2O/THF, r.t.

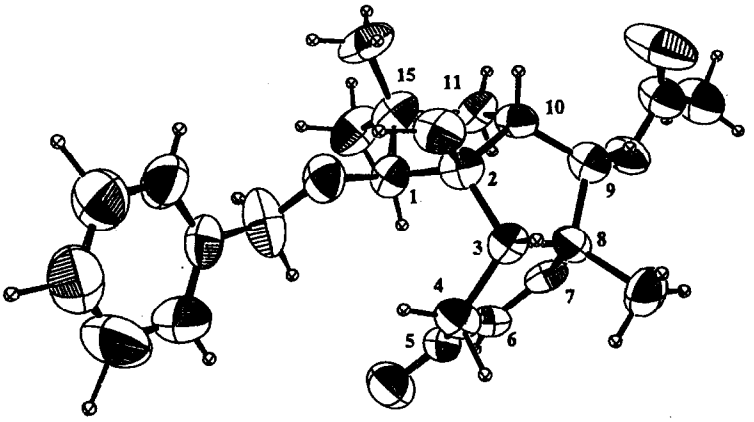


Figure 1: ORTEP drawing of **4**

The transformation of **15** into **3** could be achieved by a selective oxidative cleavage of the unconjugated double bond (O_3, CH_2Cl_2, -78°C, then Ph_3P, 30min) to afford **3**[8] in 73% yield.This overall strategy thus provides an efficient way of preparing conveniently functionalized bicyclo[6.4.0]dodecane derivatives, promising precursors for the synthesis of taxoids, and complements the existing methodologies for the construction of 6+8 fused ring systems[9].

Further application of this methodology to taxoid synthesis is now under investigation[10].

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References and Notes:

1 Arseniyadis,S.; Yashunsky,D.V.; Pereira de Freitas; R., Muñoz-Dorado M.; Toromanoff, E; Potier, P. *Tetrahedron Lett.* **1993,** *34*, 1137-1140 and references cited therein.

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5 The selection of this lipase (Liver Acetone Powder, Sigma) was based on our previous results, Arseniyadis, S.; Rodriguez, R.; Spanevello, R.; Ouazzani, J; Ourisson, G. *Microbial Reagents in Organic Synthesis* , Ed.; Stefano Servi, Kluwer Academic Publishers, Dordrecht, The Netherlands, **1992**; pp. 313-321.

6 The desired enone **4** initially obtained in 67% yield was accompanied with its corresponding allylic alcohol which was reoxidized with PDC in DCM to give an additional 7.5% recovery of **13: m.p.:** 122-123°C (heptane); **IR**($CHCl_3$)**:** 3515, 3024, 2964, 2938, 2871, 1742, 1676, 1457, 1370, 1244, 1105, 1072, 1038, 1005; **^{1}H-NMR** (400MHz, $CDCl_3$) δ 0.99(3H,s); 1.04(3H,s); 1.17(1H, t,J=12.0); 1.26(1H,dd,J=9.0, 12.0); 1.31(3H,s); 2.10(3H,s); 2.34(1H,ddd,J=1.5, 3.2, 6.7); 2.60(1H,dd, J=6.8, 18.4); 2.73(1H,dd,J=3.2, 18.4); 2.97(1H,ddd,J=8.6, 9.0, 10.0); 3.31(1H,s); 4.56 and 4.65(2H, AB quartet, J=10.7); 5.08(1H,d,J=8.6); 6.07(1H,d,J=10.3); 6.97(1H,dd,J=1.6, 10.3); 7.30-7.40(5H,m); **^{13}C-NMR** (75MHz, $CDCl_3$) d 20.6, 20.7, 25.9, 28.4, 34.0, 35.8, 43.1, 45.8, 49.6, 53.0, 73.2, 79.8, 87.2, 89.0,127.7, 127.8, 128.3, 128.6, 137.9, 151.8, 169.9, 198.1; **EIMS**: 398 ($M^{+\cdot}$, 2); 338(4), 307(25), 292(15), 247(59), 121(57), 109(75), 91(100); **HREIMS**: calcd. for $C_{24}H_{30}O_5$: 398.2093, fd.: 398.2077.

7 Dess,D.B; Martin, J.C. *J.Org.Chem.* **1983**,*48*, 4155-4156; Ireland,R.E.; Liu, L. *J.Org.Chem.* **1993**, *58*, 2899.

8 **3**: **IR**($CHCl_3$): 3020, 2985, 2965, 2929, 2873, 1739, 1717, 1704, 1682, 1470, 1455, 1393, 1346, 1307, 1274, 1239, 1217, 1116, 1088, 1072, 1031, 1019, 995 cm^{-1}; **^{1}H-NMR** (400MHz, $CDCl_3$) δ 1.01 (3H,s); 1.13 (3H,s); 1.39 (3H,s); 1.97 (1H,dd,J=1.5, 17.3); 1.98 (1H,d,J=11.11.7); 2.10 (3H,s); 2.50 (1H,dd,J=4.8, 17.3); 3.40 (1H,s); 3.52 (1H,d,J=11.7); 3.77 (1H,s); 4.69 and 4.54 (AB quartet, J=11.7); 5.26(1H, s); 5.95 (1H, d,J=10.7); 7.05 (1H, dd, J=1.1,10.7); 7.40-7.20 (m, 5H); **^{13}C-NMR** (75MHz, $CDCl_3$) δ 20.1, 23.6, 26.1, 29.9, 37.0, 40.9, 44.6, 48.0, 50.7, 75.7, 81.0, 91.3, 127.6, 128.1, 128.6, 128.9, 136.3, 146.1, 170.3, 195.6, 207.6, 214.1; **EIMS**: 413(M+H, 2), 321(5), 305(32), 276(43, 234(76), 91(100); **HREIMS**: calcd. for $C_{24}H_{28}O_6$: 412.1886, fd.: 412.1915.

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10 Structures for compounds **5**, **11**, **12**, **13**, **16** and **3** were established by high field 1 and 2DNMR techniques and supported by molecular mechanics calculations. Ratios are based on integration of 300 and 400MHz ^{1}H-NMR spectra. Enantiomeric purities of (+) and (-)-**10a** were measured on the corresponding lactate esters, obtained by treatment with (S)-O-acetyllactylchloride (DMAP, Py, DCM, r.t.) either by NMR or GC analyses on a ST1 capillary column (0.32mmx25m) operated at 170°C with Helium as carrier gas .

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