Methyl [4'α,5'α,6'β(2S*,3R*)]-2-[5',6',-dihydro-4',5'-*O,O*-isopropylidene-4'*H* 1',2'-oxazine-6'-yl]-3-methyl-4-oxoazetidine-1-carbamate 9 and methyl [1α,2β,3β,7α,10α,11α]-10,11-*O,O*-isopropylidene-3-methyl-9-oxa-4-oxo-5,6,8-triazatricyclo[5.2.2.0^{2,5}]-undecane-6-carboxylate 8c. - A stirred soln. of **8b** (238 mg ; 0.53 mmol) in AcOEt (10 ml) containing some 5 % Pd/C (50 mg) was put under H_2 (1 atm) at r.t. overnight. After filtration over Celite and evaporation of the solvent the residue was separated by FC(AcOEt/cyclohexane 7:3) leading to **9** (168 mg ; quantitative). In dilute $CDCl_3$ soln. **9** is in equilibrium with **8c** according to ^{1}H-NMR.

Oxazine 9 : Colourless resin. IR(KBr) : 3300, 2980, 1782, 1732, 1500(br), 1450, 1380, 1252(br) , 1211, 1157, 1065(br). ^{1}H-NMR (C_6D_6, 80 MHz, 318 K) : 7.34 (d, J=2.2, H-C(3')) ; 6.45 (s(br), H-N) ; 3.85 (dd, J=4.3, 2.8, H-C(2)) ; 3.83 (dd, J=9.5, 6.9, H-C(5')) ; 3.60 (dd, J=6.9, 2.2, H-C(4')) ; 3.29 (s, C*H*$_3$-O) ; 3.16 (dd, J=9.5, 4.3, H-C(6')) ; 3.08 (qdm, J=7.3, 2.8, H-C(3)) ; 1.26 (d, J=7.3, C*H*$_3$-C(3)) ; 1.19 and 1.04 (2q, J=0.4, C(C*H*$_3$)$_2$). ^{1}H-NMR of $CDCl_3$ ($CDCl_3$, 250 MHz, 328 K) : 7.72 (d, J=2.2, H-C(3')) ; 6.73 (s(br), H-N) ; 4.38-4.33 (m, H-C(4') and H-C(5')) ; 3.86 (dd, J=5.2, 2.6, H-C(2)) ; 3.78 (s, CH_3-O) ; 3.25 (ddd, J=9.6, 5.2, 0.8, H-C(6')) ; 3.18 (qdd, J=7.2, 2.6, 1.2, H-C(3)) ; 1.43 (d, J=7.2, CH_3-C(3)) ; 1.40 and 1.37 (2q, J=0.6, C(CH_3)$_2$). ^{1}H-NMR of **8c** ($CDCl_3$, 250 MHz, 328 K) : 6.32 (s(br), H-N) ; 5.17 (d, J=2.0, H-C(7)) ; 4.46 (dd, J=2.0, 1.6, H-C(2)) ; 4.38 (dd, J=8.6, 2.0, H-C(11)) ; 4.31 (dd, J=8.6, 1.6, H-C(10)) ; 3.94 (t, J=1.6, H-C(1)) ; 3.83 (s, CH_3-O) ; 2.85 (qd, J=7.2, 1.8, H-C(3)) ; 1.53 and 1.47 (2q, J=0.5, C(CH_3)$_2$) ; 1.45 (d, J=7.2, C*H*$_3$-C(3)). ^{13}C-NMR of **9** ($CDCl_3$, 62.9 MHz, 323 K) : 170.6 (s, C(4)) ; 155.2 (sq, O=*C*-O-Me) ; 150.7 (d, ^{1}J=186, C(3')) ; 109.1 (sm, *C*(CH_3)$_2$) ; 75.2 (d(br), ^{1}J=148, C(6')) ; 70.1 (dm, ^{1}J=155, C(4')) ; 64.9 (dd, ^{1}J=153, C(5')) ; 63.1 (dm, ^{1}J=153, C(2)) ; 52.4 (q, ^{1}J=147, O-*C*H$_3$) ; 43.6 (dm, ^{1}J=142, C(3)) ; 26.6 and 24.4 (2qq, J=127, C(*C*H$_3$)$_2$) ; 12.1 (qt, ^{1}J=129, *C*H$_3$-C(3)). Anal. calc. for $C_{13}H_{19}N_3O_6$ (313.27) : 49.84, H 6.11, N 13,41 ; found : C 50.0, H 6.1, N 13.7.

Methyl [2'α,3'β,4'β,5'α(2S*,3R*)]-2-[2-hydroxy-3',4'-*O,O*-isopropylidene tetrahydrofurane-6'-yl]-3-methyl-4-oxo-azetidine-1-carbamate 10b (β-anomer) and methyl [2'α,3'α,4'α,5'β(2S*,3R*)]-2-[2'-hydroxy-3',4'-*O,O*-isopropylidene tetrahydrofurane-6'-yl]-3-methyl-4-oxoazetidine-1-carbamate 10a (α-anomer).- A stirred soln. of **9** (107 mg ; 0.34 mmol) in 95 % EtOH (5 ml) containing some Raney nickel (100 mg) and 20 % NH_4OH (110 ml ; 1.02 mmol) was put under H_2 at r.t. for 2 h. 1N HCl (6 ml) was added and the soln. stirred until a green colour appeared. The soln. was extracted twice with AcOEt (10 ml), the organic soln. was washed with H_2O and dried over $MgSO_4$. After filtration and evaporation the residue was purified by FC to give **10b** and **10a** as a 67:33 mixture (NMR) (colourless resin). M.p. 147 °C. IR(KBr) : 3400, 3200, 2983, 2963, 2942, 1770 (O=C β-lactam), 1745 and 1726 (O=C carbamate), 1516, 1451, 1371, 1363, 1248(br), 1200, 1154, 1093, 1060(br), 1022.

10b : ^{1}H-NMR ($CDCl_3$, 250 MHz, 297 K) : 6.95 (s(br), H-N) ; 5.46 (s(br), H-C(2')) ; 4.73 (dd, J=6.0, 2.8, H-C(4')) ; 4.62 (d, J=6.0, H-C(3')) ; 4.25 (dd, J=6.8, 2.8, H-C(5')) ; 3.77 (s, CH_3-O) ; 3.73 (dd, J=6.8, 2.5, H-C(2)) ; 2.97 (qdd, J=7.4, 2.5, 1.0, H-C(3)) ; 1.66 (s(br), H-O) ; 1.37 (d, J=7.4, Me-C(3)) ; 1.49 and 1.33 (2s, CMe_2). ^{13}C-NMR ($CDCl_3$, 62.9 MHz, 323 K) : 171.8 (sm, C(4)) ; 155.8 (sq, O=*C*-O CH_3) ; 113.2 (sm, *C*(CH_3)$_2$) ; 102.5 (dm, ^{1}J=173, C(2')) ; 86.6 (dm, ^{1}J=148, C(5')) ; 86.3 (ds, ^{1}J=159, C(3')) ; 81.0 (dm, ^{1}J=156, C(4')) ; 65.5 (dm, ^{1}J=153, C(2)) ; 53.2 (qs, ^{1}J=148, O-*C*H3) ; 45.3 (dm, ^{1}J=141, C(3)) ; 26.7 and 25.2 (2qq, ^{1}J=127, C(*C*H$_3$)$_2$) ; 12.5 (qt, ^{1}J=129, *C*H$_3$-C(3)).

10a : ^{1}H-NMR ($CDCl_3$, 250 MHz, 297 K) : 6.72 (s(br), H-N) ; 5.31 (d, J=4.0, H-C(2')) ; 4.73 (dd, J=7.1,

4.0, H-C(3')) ; 4.67 (dd, J=7.1, 4.8, H-C(4')) ; 4.17 (dd, J=5.4, 4.8, H-C(5')) ; 3.76 (s, O-CH_3) ; 3.66 (dd, J=5.4, 2.5, H-C(2)) ; 2.91 (qdd, J=7.4, 2.5, 1.0 (H-C(3)) ; 1.66 (s(br), H-O) ; 1.38 (d, J=7.4, C*H3*-C(3)) ; 1.49 and 1.33 (2s(br), C($CH3)_2$). ^{13}C-NMR ($CDCl_3$, 62.9 MHz, 323 K) : 171.3 (sm, C(4)) ; 155.6 (sq, O=*C*-OCH_3) ; 116.11 (sm, *C* ($CH_3)_2$) ; 96.0 (dm, ^{1}J=176, C(2')) ; 80.6 (dm, ^{1}J=149, C(5')) ; 80.4 (dm, ^{1}J=156, C(3')) ; 80.1 (dd, ^{1}J=160, C(4')) ; 64.5 (dm, ^{1}J=154, C(2)) ; 53.1 (qs, ^{1}J=148, C-*C*H_3) ; 44.7 (dm, ^{1}J=140, C(3)) ; 26.4 and 25.2 (2qq, ^{1}J=127, C($CH_3)_2$) ; 12.4 (qt, J=129, *C*H_3-C(3)).

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A Chemoenzymatic Approach to the Taxoid BC-Substructure

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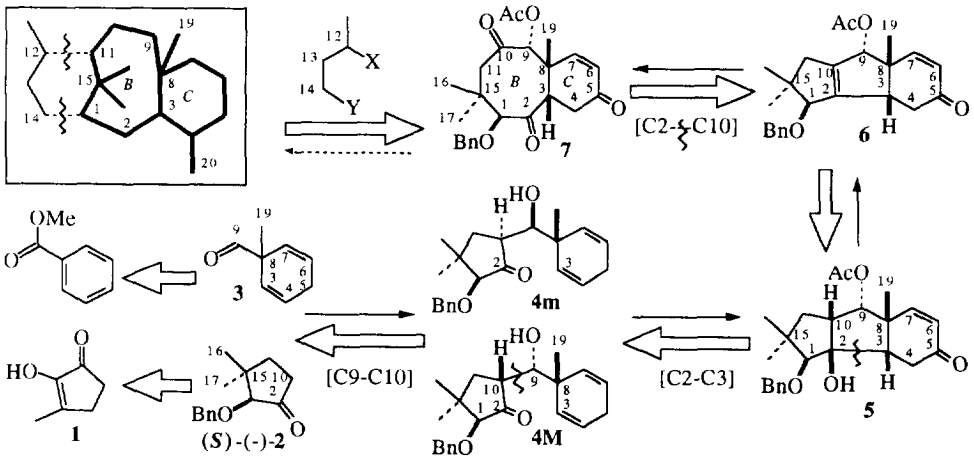
Abstract: *The synthesis of a homochiral taxoid BC-unit containing the required functionalities on the B-ring periphery and a conveniently functionalized C-ring moiety by combination of enzymatic hydrolysis and the aldol-annelation-fragmentation sequence is described.*

During the course of synthetic approaches directed towards the synthesis of the taxane framework we developed a strategy based upon the use of a three-reaction sequence, the aldol-annelation-fragmentation, for C10-C9 and C2-C3 bond formation and for C2-C10 cleavage, respectively.[1] A key feature of our strategy was the indirect formation of the B-ring, supposedly the most critical to achieve, especially when it contains the appropriate substitution pattern on the periphery. In considering a short and efficient route, which would also allow for the preparation of novel analogues, it occurred to us that the synthon (*S*)-(-)-**2**, obtained in high enantiomeric purity *via* an enzymatic hydrolysis[2] possessed a number of functional and stereochemical features amenable to an expeditious resolution of the B-ring problem.[3]



Scheme 1

Herein we report the details of an expanded study for the synthesis of a taxoid BC-substructure, with the correct absolute stereochemistry of the C-8 quaternary center established at an early stage of the synthetic scheme, which confirms our structural assignments and defines the scope of this approach.

Synthetic planning

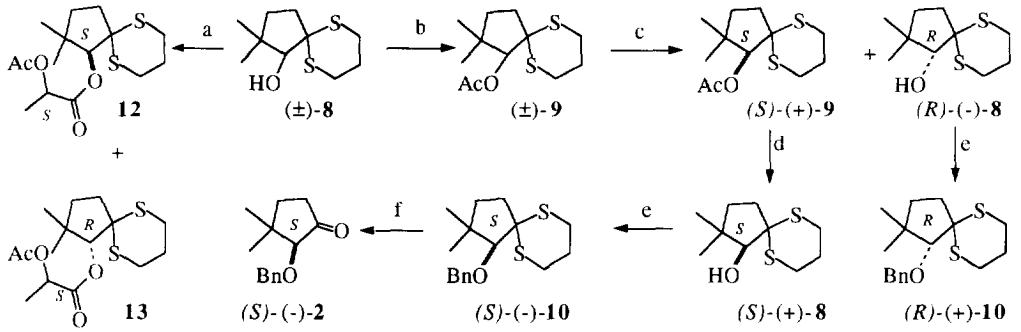
This study was designed to set the stage for the construction of the 6+8 fused BC-subunit of taxoids.[4] The pivotal step in this approach was the construction of the tricyclic intermediate **5** *via* a stereocontroled *5-exo-trig* cyclization.[5] Taking into account the factors that govern the aldol stereochemistry[6] and inspection of molecular models revealed that C10-C9 bond formation would occur preferentially from the α-face of the enolate leading to a *threo*-aldol (*anti*-selective homochiral enolate) and further, that annelation of **17**, derived from **4**, would clearly result in formation of the *cis-syn-cis* tricyclic framework **5**. The stereochemistry of the fragmentation precursor **5** should insure that the chiral centers at C-8 and C-1 have the desired configuration. Elaboration of the key intermediate **5** into the compound **6** from which the 6+8-fused ring system could in principle be obtained by oxidative ring cleavage[7] and would simply require temporary protection of the C-5 carbonyl group. Conversion to the target could then be achieved using known methodology. Moreover, the C-10 carbonyl group introduced during the fragmentation step would be well situated for an aldol type A-ring formation (Scheme 1). As a development of this approach, the introduction of the chiral centers at C-1 and C-8 stereoselectively into the fragmentation precursor was envisaged. Given the potential for further uses in natural product synthesis unambiguous structural assignements of the course of these three-reaction process was felt to be essential. We thus initiated a project to elucidate the structures of the annelated enone **5**, of its (*S*)-O-acetyllactyl derivative **14** and of the BC subunit **7** by extended NMR studies and single-crystal X-ray diffraction analyses. This confirmed the *threo-trans* stereochemistry of the major aldol adduct **4M**, the outcome of the annelation step, and the absolute stereochemistry introduced by an enzyme-catalyzed kinetic resolution on the stereochemically encumbered neopentyl acetate **9**. We describe below how these distinctions can be utilized to synthetic advantage.

Introduction of optical purity: The lipase mediated enzymatic hydrolysis.

For the introduction of the desired absolute stereochemistry at the beginning of the synthesis we needed large quantities of the appropriately functionalized cyclopentanone **2** in its optically pure (*S*)-form. An attractive candidate for ketone **2** was cyclotene (3-methyl-1,2-cyclopentanedione) **1**,[8] a readily available substance of natural occurence. Transformation of the latter into **8** was achieved in 50% yield as described in literature.[9]

With the requisite racemic substrates in hand,[10] the possibility of using bioconversions (either reduction or hydrolysis) at various stages, prior to coupling with the C-ring carbon framework was investigated, despite the existence of chemical approaches in preparing a homochiral cyclopentane framework.[11] Attempts for microbial reduction of the cyclotene derived dithiane-ketone, precursor of the alcohol **8**, failed.[12] We then turned to the lipase-mediated enantioselective hydrolysis searching for the conversion of **8** to its optically homogeneous form.[13] Racemic acetate **9**, prepared from **8** in the usual manner (Ac_2O-Py-DMAP) appeared to be the best candidate for an enantioselective enzyme-catalyzed kinetic resolution.[14] Several commercially available low-cost lipases were examined. After a screening with PLE (*Pig liver esterase*, acetone powder), PPL (*Porcine pancreatic lipase*, acetone powder), candida cylindraceae and HLE (Horse liver esterase, acetone powder)[15] we found that the latter gave the best results in terms of chemical yield and enantioselectivity, showing "*R*" specificity at an early stage of the synthesis. In a typical procedure, dithiane-acetate **9** and the powdered preparation of the lipase (HLE, acetone powder, Sigma) were combined in phosphate buffer pH=7 and a small amount of toluene (2-3‰ of the volume of the phosphate buffer) as cosolvent and vigorously stirred at 4°C with a magnetic stirrer. We can briefly summarize the main conclusions of the HLE mediated hydrolytic resolutions as follows: equal masses of the enzyme and the substrate were used but further experiments showed that a lipase to substrate ratio of 0.6 was

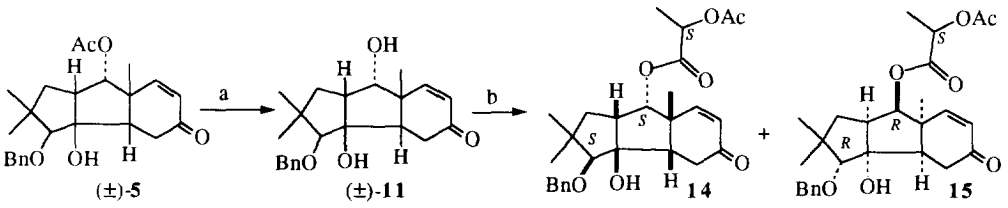
enough for the hydrolysis to run at comparable rates and that the use of toluene was unnecessary (although harmless). In order to optimize the optical purity of the alcohol **8**, the enzymatic hydrolysis (which could be monitored by GC) was stopped at an early stage of conversion and conversely, to optimize the optical homogeneity of the remaining acetate, either the reaction was terminated at a relatively late stage of conversion or the remaining acetate was resubjected to a second incubation under identical conditions. The procedure can be scaled up without problem; a 5.74 g (22 mmol) conversion in a 2 L Erlenmeyer flask was performed routinely. Typically, incubation of (±)-**9** at 4°C for 31 h gave 58% of acetate (+)-**9** (87% ee) and 42% of alcohol (-)-**8** (96% ee). Resubjection of the remaining acetate gave 88% of (+)-**9** (98% ee) and 12% of alcohol. In all cases investigated the experiments were simple and clean and the alcohols were separated from the unreacted acetates by silica gel flash column chromatography.



Scheme 2: a) (*S*)-O-acetyllactylchoride, Py or Et_3N, DMAP, CH_2Cl_2. b) Ac_2O, Py, DMAP. c) HLE, 4°C, 31 h. d) K_2CO_3, MeOH-H_2O. e) BnBr, NaH, DMF. f) $HgCl_2$, $CaCO_3$, acetone-H_2O.

The enantiomeric purities of (+) and (-)-**8** were measured on the corresponding lactate esters, obtained by treatment with (*S*)-O-acetyllactylchloride[16] (DMAP, Py or Et_3N, CH_2Cl_2, 0°C to r.t.) either by ^{1}H-NMR or GC analyses on a ST1 capillary column (0.32 mm x 25m) operated at 170°C with Helium as carrier gas. Acetates **9** were hydrolysed to the corresponding alcohols by standard procedures (K_2CO_3-MeOH-H_2O, r.t.) prior to derivatization.

The absolute configuration of the products was assigned through the resolution sequence outlined in Scheme 3, as follows: alkaline hydrolysis of (±)-**5** followed by acylation with (*S*)-O-acetyllactylchloride gave the easily separable diastereoisomers **14** and **15**, obtained optically pure (silica gel flash chromatography, CH_2Cl_2-EtOAc, 12:1), which can be further saponified to the corresponding alcohols.



Scheme 3: a)K_2CO_3, MeOH-H_2O. b) (*S*)-O-acetyllactylchoride, Py or Et_3N, DMAP, CH_2Cl_2.

The configuration of the (*S*)-O-acetyllactyl derivative **14** was established by a single crystal X-ray crystallographic study (Figure 1). In order to determine the absolute stereochemistry of (+) and (-)-**8**, correlation

with material from (+)-**11** was achieved by conversion of the former into **11** *via* **8**, **10**, **2** and the aldol-annelation sequence (the same series of reactions were carried out on both enantiomers from **8** leading to the tricyclic intermediate **5**, *vide infra*). Thus, relative to the known *S* configuration of the lactyl chloride used in the synthesis, the *S* absolute configuration of (+)-**8** was confirmed by comparing the signs of the optical rotations of (+)-**11** derived from **14** (X-ray sample) by alkaline hydrolysis to the same compound obtained through the sequence cited above.

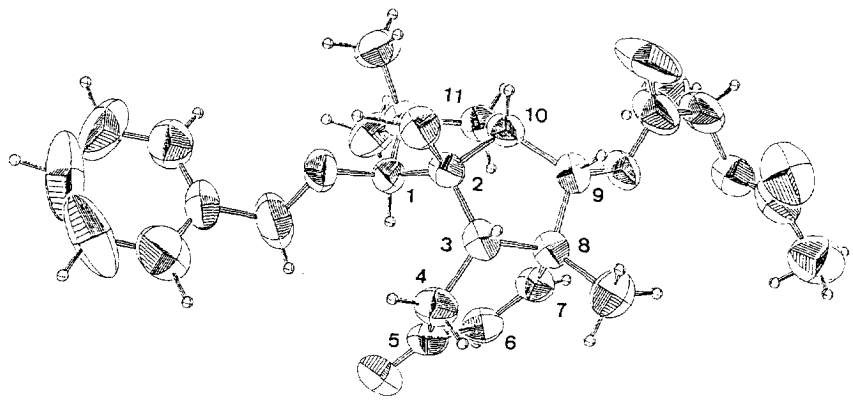


Figure 1: Perspective drawing of the X-ray structure of **14**

In the manner described above, the resolution of the hindered secondary alcohol **8** was readily accomplished by enantioselective enzymatic hydrolysis of the corresponding acetate ester **9** to yield multigram amounts of building blocks (both *S* and *R* enantiomers) in high enantiomeric excess. Moreover, the possibility of recycling the *R*-alcohol should ensure a total recovery. The benzyl ethers (-)-**10** and (+)-**10** were subsequently prepared from each enantiomer (NaH, BnBr, DMF, r.t.) in 98% isolated yield (flash SiO_2, heptane-ether, 19:1). Following benzyl protection, a mercury assisted hydrolysis ($HgCl_2$-$CaCO_3$, acetone-water, Δ) afforded the desired ketone **2** in 90% yield (both antipodes). We thus assured homochiral segments at the very beginning of the synthesis. A large scale transformation of the enantiomerically enriched (ee>96%) alcohol (*S*)-(+)-**8** thus obtained into the target tricyclic compound (1*S*, 9*S*)-(+)-**5** was then undertaken.

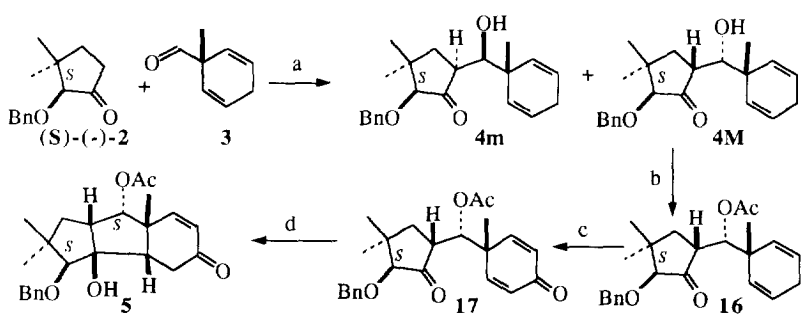
The C10-C9 bond construction: ALDOLIZATION

Control elements on which to base predictions were purposely concentrated on the enolate (*E*-geometry, *anti* selective-enolate)[17] to simplify the aldol reaction outcome (homotopic faces on the aldehyde). The required achiral aldehyde **3** chosen as the precursor to ring C, was prepared on large scale from methyl benzoate in a three-step sequence. Birch reductive alkylation[18] of methyl benzoate (Li, liqNH_3, *t*-BuOH-THF, -78°C, then MeI-THF, 90%) followed by reduction ($LiAlH_4$, Et_2O) afforded the corresponding alcohol in quantitative yield. This alcohol was then oxidized under the Swern conditions[19] to the required aldehyde (94%). Having synthesized the two carbonyl components from cyclotene and methyl benzoate, we proceeded to the C10-C9 carbon-carbon bond formation. The ketone (*S*)-(-)-**2** and the aldehyde **3** were assembled *via* an aldol condensation which was carried out at - 78°C by addition of the aldehyde **3** (2.5 equiv) to a solution of the enolate generated using lithium diisopropylamide at -40°C (1.5 equiv of LDA in THF, 1h at -40°C for the enolate formation on **2** then cooling to -78°C, followed by addition of the aldehyde **3**). After an additional reaction time of 5 min the reaction mixture was quenched at low temperature with a saturated aqueous ammonium chloride

solution (2 ml per mmol) affording a two component mixture which was separated by silica gel flash chromatography (heptane-ether, 5:1) to afford the two *threo (anti)* aldols **4M** and **4m** in a 13.3:1 ratio and 86% isolated yield. As anticipated,[20] due to the π-facial selectivity exerted by the chiral enolate, a high *threo-trans* (C1/C10) **4M**, to *threo-cis* (C1/C10) **4m** ratio was observed upon the aldol reaction while no *erythro* aldols were observed (the only other diastereomer isolated in sufficient quantity to be characterized was assigned on the basis of its ^{1}H-NMR analysis as the *threo-cis* aldol adduct **4m**). The configurations for the two diastereomeric aldols were characterized by ^{1}H-NMR, on the basis of nuclear Overhauser enhancement (1D-NOEDIFF) spectra and were further proven by subsequent conversion to the corresponding acetonides.[21] The separation, although easy to achieve by silica gel flash column chromatography, proved unnecessary because subsequent reductive pinacol coupling led to a single diastereoisomer with decomposition of the minor aldol derivative.

The C2-C3 bond construction: ANNELATION

The major aldol **4M** was acetylated prior to allylic oxidation to give **16** (Ac_2O, Py, DMAP, 0°C to r.t., 1h, 95%). Several methods were then tried for the allylic oxidation, such as CrO_3, *t*-BuOOH, 3,5-dimethyl pyrazol in dichloromethane at -20°C for 6 h (57%), or at 0°C for 6 h (72%),[22] PDC, *t*-BuOOH, PhH-Celite, room temperature, 3 h (68%).[23] Finally oxidation with PDC, *t*-BuOOH, in CH_2Cl_2, at -20°C, for 48 h afforded **17** in 79% yield. The latter method, being the most satisfactory, was used in the large scale transformation. The pathway leading from **2** + **3** to **5** which we chose is shown in Scheme 4. To effect the C2-C3 bond formation, a *5-exo-trig* cyclization, we elected to use the SmI_2 mediated reductive coupling,[24] with some care to prevent over-reduction and possible deoxygenation at C-1. After considerable investigation of various alternatives, it was found that conversion of **17** to **5** could be carried out in an efficient manner under carefully defined conditions by adding a mixture of 0.1M samarium (II) iodide (2.15 equiv) in THF, in the presence of MeOH as proton source, and HMPA at -85°C. Work-up after an additional reaction time of 3.5 h at this temperature gave a crude mixture which upon subjection to SiO_2 column chromatography (heptane-ethyl acetate, 1:1), yielded 75% of the desired tricyclic enone **5**[25] the structure of which was first assigned by extensive NMR experiments and subsequently confirmed by X-ray analysis.



Scheme 4: a) LDA-THF, -40°C, 1h then -78°C, 10 min b) Ac_2O-Py, DMAP c) PDC/*t*-BuOOH/CH_2Cl_2, -20°C. d) SmI_2-MeOH/THF/HMPA, -85°C.

Two diastereomeric annelated adducts could have been formed furnishing either the *cis-syn-cis* tricyclic enone **5** or the diastereomeric *cis-anti-cis* , with the wrong stereochemistry at the C-8 quaternary center. ^{1}H and ^{13}C-NMR spectra showed no evidence of the latter, with the angular methyl group at C-8 pointing downward.

The fact that only a single product was obtained was deemed rather significant. Based upon consideration of molecular models, it is reasonable to assume that stereoelectronic alignment of the Michael acceptor and the ketone carbonyl π networks can be better realized in a transition state leading to the *cis-syn-cis* arrangement, a situation which meets the main criteria for a facile *5-exo-trig* type cyclization. Indeed, the transition state leading to the *cis-anti-cis* isomer contains unfavorable steric interactions (for example eclipsing interactions between the angular methyl group 19 and the C9-acetate substituent); conversely, transition state leading to the *cis-syn-cis* isomer lacks such a destabilizing steric interaction, thus resulting in the desired stereochemistry at the C-8 quaternary center.

After a complete assignment of the proton and carbon spectra, n.O.e. experiments were performed to explore spatial relationships. The *cis-syn-cis* stereochemistry was verified as irradiation of the angular methyl group 19 (at C-8) provided n.O.e. of H-3, H-4β, H-9, H-10. Additional support for these assignments arises from the single-crystal X-ray structure of **5**, an ORTEP drawing of which is shown in Figure 3.

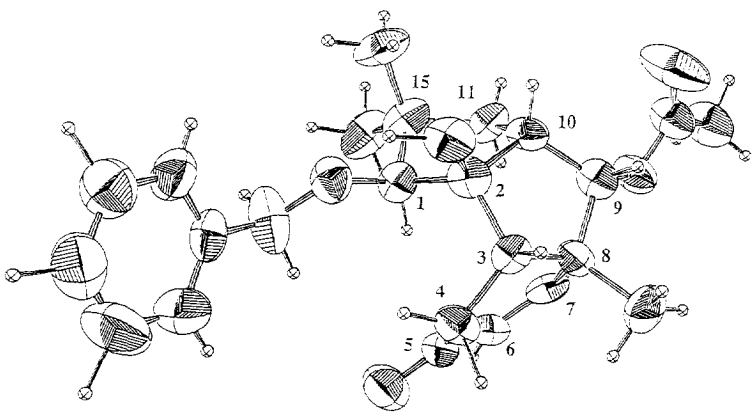
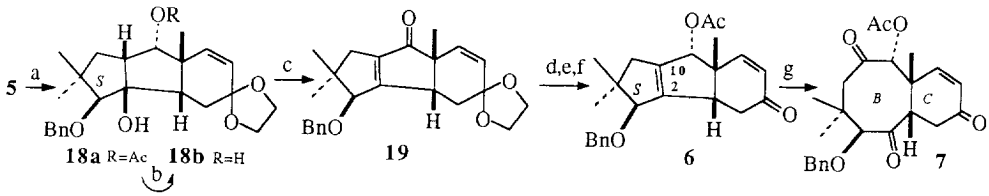


Figure 3: Perspective drawing of the X-ray structure of **5**.

The C2-C10 oxidative cleavage: Setting the stage for the B-ring formation.

With the foregoing stereochemical issues resolved, construction of ring B was then explored. Several methods were considered for the fragmentation of close derivatives of **5** into the desired BC-taxoid substructure and while a number of methods could eventually be successfully applied (such as Wharton[26] or retro-aldol type fragmentations), we chose the oxidative ring cleavage as the most practical way for achieving our goal. The former two processes would result in a net loss of functionality and chemoselectivity in proceeding from the starting material to the products, while an oxidative cleavage, such as ozonolysis, on **6** would yield the highest number of functional groups and an easy further elaboration next to C-10 carbonyl group. The requisite *cis-syn-cis* enone **5** was taken through to **6** as depicted in Scheme 5. Thus ketal protection of **5** (ethylene glycol, PhH, p-TsOH, reflux, 3 h) afforded **18a** (quant.). Saponification of the C-9 acetyl group (NaOH, MeOH-H_2O, r.t.) gave the diol **18b** (95%). Oxidation of the secondary alcohol at C-9 followed by *in situ* dehydration of the resulting hydroxyketone was then accomplished using the Dess-Martin periodinane[27] (2.17 equiv. in dry dichloromethane and Pyridine, r.t., 12 h) affording enone **19** in 84% yield (no other oxidant proved as effective as the Dess-Martin reagent). To ensure selective C2-C10 cleavage we further transformed **19** into **6** in three additional steps and 89% overall yield. Thus reduction of the C-9 carbonyl (L-Selectride in dry THF at -78°C to r.t., then work up with 15% aq. NaOH, 30% H_2O_2), reacetylation of the resulting alcohol (Ac_2O, Py, DMAP,

15 min, r.t.) and finally deketalization (1M HCl, THF-H_2O, r.t., 2 h) gave **6**.



Scheme 5: a) $HOCH_2$-CH_2OH, TsOH/PhH, Δ. b) NaOH/H_2O/MeOH. c) Dess-Martin periodinane, Py/CH_2Cl_2. d) L-Selectride-THF. e) Ac_2O, Py, DMAP. f) H_2O/HCl/THF. g) O_3, CH_2Cl_2,-78°C; PPh_3.

Transformation of **6** to **7** was achieved by a chemoselective oxidative cleavage of the unconjugated double bond (O_3, CH_2Cl_2, -78°C, then Ph_3P, 30 min, 73%) to afford after SiO_2 flash chromatography (heptane-ethyl acetate, 1:1) **7** as a crystalline material which was analyzed by X-ray diffraction studies (Figure 4).

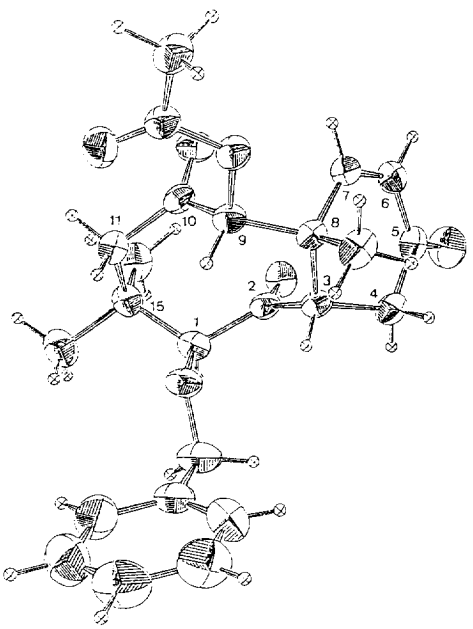


Figure 4: Perspective drawing of the X-ray structure of **7**.

Examination of this X-ray structure, which provides support for previous stereochemical assignments at the earlier stages of the synthesis, clearly reveals the chair-chair conformation for the eight-membered B-ring, as calculated also from MM2 studies. Obviously the C-10 carbonyl group in **7** is ideally positioned to facilitate the introduction of the remaining four carbon unit (C12-C13-C14-C18) for the construction of the A-ring.

Conclusion

The aldol-annelation-fragmentation strategy 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. With the efficient

synthesis of the taxoid BC-ring system **7** realized, the stage was now set for the completion of the synthesis. The shortness of the synthetic sequence, combined with good to excellent chemical and optical yields allows us to continue the synthesis on reasonable scale and cost. The overall sequence can be readily modified to produce the required carbon/oxygen skeleton offering several distinct ways for further elaboration. Moreover, the stereochemistry of the *cis-syn-cis* tricyclic intermediate **5**, ensures the desired relative configurations during further transformation, with only the β-face of the molecule being accessible. Our efforts along this line will be reported in due course.

Finally, since the reactions described herein are simple to carry out and proceed with high stereoselectivity, it seems reasonable to assume that this type of manipulative process could be applied to other synthetic intermediates intended to lead to simpler taxoid analogues for biological evaluation.

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Experimental section :

General experimental details were as previously described (ref 15). Complete ^{1}H and ^{13}C NMR data (1D and 2D experiments) were obtained for each compound synthesized in $CDCl_3$ at 400MHz and 75 MHz, and optical rotations were measured in $CHCl_3$ solution in a 1 dm cell using a Perkin-Elmer 243 polarimeter.

General procedure for determination of the enantiomeric purity : In all cases investigated the enantiomeric excess was measured after diastereomeric derivatization with (*S*)-O-acetyllactyl chloride.

The acetates were first converted to the corresponding alcohols by either one of the two following methods. 1) The acetate (1 mmol) was treated with solid potassium carbonate (2 mmol) in methanol (3 mL) and water (0.3 mL) at 0°C. The mixture was vigorously stirred for 2 h (TLC monitoring). The methanol was removed *in vacuo* and the resulting mixture diluted with water, then extracted with dichloromethane, dried and concentrated to give the corresponding alcohol. 2) The acetate (1 mmol) was treated with a solution of 15% aqueous NaOH (5 mL) in methanol (15 mL) at room temperature and worked up as above. Both (-)- and (+)-alcohols were converted to the corresponding lactates by treatment with (*S*)-O-acetyllactyl chloride, pyridine (or Et_3N), DCM, DMAP at room temperature for several minutes. Their GC analyses were carried out on a ST1 capillary column (0.32mm x 25m) operated at 170°C with helium as carrier gas (60Kpa), and compared to the racemic mixture.

Preparation of the aldehyde 3:

To liquid ammonia (500 mL) was added a solution of 20 g (147 mmol) of methylbenzoate and 11 g (147 mmol, 1.01 eq.) of *t*-BuOH in THF (50 mL) at -78°C, followed by portionwise addition of 2.57g (0.37 g.a., 2.5 eq.) of lithium. The mixture was stirred at -78°C for 5 min (blue color) and a solution of 40 mL (838 mmol, 5.47 eq.) of methyl iodide in THF (20 mL) was added at -78°C. The mixture was stirred at -78°C for 5 min, then allowed to warm to room temperature and heptane was added periodically while ammonia evaporated. After two hours, solid ammonium chloride was added and upon complete evaporation of ammonia the reaction mixture was rapidly washed with brine, worked up as usual and distilled (84-86°C, water pump pressure) to yield 20.25 g (90%) of the desired ester: **^{1}H-NMR**: 1.32 (3H, s, Me); 2.65 (2H, m); 3.68 (3H, s); 5.78 (4H, m). **^{13}C-NMR:** 25.7, 27.2, 43.7, 52.0, 124.3, 128.5, 175.4. The ester thus obtained was reduced to its corresponding alcohol as follows: To a stirred suspension of 22.0 g (578 mmol, 2.9 eq.) of $LiAlH_4$ in dry THF (500 mL) under argon at room temperature was added a solution of 61 g (402 mmol) of ester in dry THF (100 mL). The mixture was stirred at room temperature for 15 min, quenched with 22 mL of 15% NaOH, 66 mL of water, and

stirring was continued at room temperature for 1 h. Filtration, concentration under reduced pressure and subsequent distillation (bp 105-110°C, 100 mmHg) yielded the corresponding alcohol quantitatively: **^{1}H-NMR:** 1.01 (3H, s, Me), 2.66 (2H, m, allyl H), 3.32 (2H, s, CH_2OH), 5.46 and 5.90 (4H, m, vinyl H). **^{13}C-NMR:** 24.5, 26.2, 38.7, 70.6, 125.5, 131. This alcohol was then oxidized to the aldehyde **3** as follows: To a stirred solution of 4.9 mL (56.2 mmol, 1.22 eq.) of oxalyl chloride in dry dichloromethane (100 mL) under argon at -60°C was added 8 ml (112.7 mmol, 2.45 eq.) of dimethyl sulfoxide in dry dichloromethane (50 ml) during 5 min. The mixture was stirred at -60°C for 10 min, a solution of alcohol (5.7 g, 46 mmol) in dry dichloromethane (50 mL) was added, and stirring at -60°C was continued for 15 min. Triethylamine (15.0 mL, 107.6 mmol, 1.9 eq.) was added, cooling stopped, and the temperature of the reaction mixture was rapidly (2-3 min) elevated to 0°C, diluted with water, and the aqueous layer was extracted with dichloromethane. The combined extracts were washed with 1 M hydrochloric acid, saturated sodium bicarbonate, and worked up as usual. Distillation (bp 85-90°C, 75 mmHg) of the crude afforded 5.24 g (94%) of aldehyde **3 : IR:** 3031, 2977, 2938, 2878, 2818, 1729, 1672, 1457, 1105, 912, 753. **^{1}H-NMR**: 1.23 (3H, s, Me), 2.75 (2 H, m, allyl H), 5.95 and 5.45 (4 H, m, vinyl H), 9.33 (1H, s, CHO). **^{13}C-NMR:** 21.6, 26.5, 49.9, 126.3, 127.3, 199.1. **EIMS:** *m/z* 123 (M+H, 32), 93(100), 91 (73).

Preparation of the ketone (*S*)-(-)-2 :

HLE-catalyzed hydrolysis of the acetate **9**. Starting from the known racemic alcohol **8** (ref 9) acetylation (1 mmol of the alcohol, 2 mL of pyridine, 0.05 mmol of DMAP, 2.5 mmol of Ac_2O, 0°C, TLC monitoring and usual work up) afforded quantitatively racemic acetate **9** which was subjected to enzymatic hydrolysis by employing horse liver esterase. The following procedure is representative for large scale preparations: A mixture of 5.74 g of the racemic dithiane-acetate (±)-**9**, 5.0 g of HLE in 1.7 L of 20 mM potassium phosphate buffer pH=7 and 3mL of toluene were stirred (magnetic stirrer) at 4°C, while TLC and G.C.(capillary column) monitored. After 31h incubation the mixture was diluted with ethyl acetate and filtered through Celite. Following usual work up, the residue was chromatographed on silica gel. Thus, when reaction was allowed to proceed to 42% conversion (31 h), carbinol (-)-**8** (96% ee) was obtained alongside (+)-**9** (87% ee) . Following chromatographic separation, acetate (+)-**9** was obtained in high chemical yield (88%) and enantiomeric purity (96% ee) by simply repeating the enzymatic hydrolysis just once. For large scale preparations (50 g and more) the ideal eluent for silica gel chromatographic separation is toluene-ether (40:1). **(*S*)-(+)-9**: $[\alpha]_D$ +7 (*c* 4.2). **IR**: 2957, 2864, 1740, 1461, 1423, 1372, 1232, 1077, 1024, 915; 872. **^{1}H-NMR**: 1.01 (3H, s); 1.19 (3H, s); 1.72 (2H, dd, J= 6.3, 7.8); 1.99 (2H, m); 2.17 (3H, s); 2.26 (2H, m); 2.86 (4H, m); 5.10 (1H, s). **^{13}C-NMR**: 20.8, 23.9, 25.0, 27.7, 28.1, 29.1, 37.7, 39.6, 42.3, 58.0, 87.1, 170.0. **EIMS**: 260 ($M^{+\cdot}$, 15), 218 (10), 185 (15), 147 (25), 146 (27), 145 (100), 144 (25), 107 (17). **HREIMS**: calcd for $C_{12}H_{20}O_2S_2$ *m/z* 260.0905; found 260.0884.

Chemical hydrolysis of **(*S*)-(+)-9:** According to the general procedure, hydrolysis of 19.8 g (76.2 mmol) of **(*S*)-(+)-9** in 170 mL of MeOH (r.t., 1 h) proceeded smoothly to give 98% of **(*S*)-(+)-8** $[\alpha]_D$: +8.5 (*c* 4.0).

Derivatization of **(*S*)-(+)-8** as its (*S*)-O-acetyl lactylester **12:** Using the general procedure, followed by silica gel flash chromatography (CH_2Cl_2-EtOAc, 20:1) afforded the acetyllactylester derivative **12:** $[\alpha]_D$ -35 (*c* 1.1). **IR**: 2950, 1748, 1456, 1369, 1237, 1194, 1131, 1098, 1052, 1014, 950, 907, 867. **^{1}H-NMR**: 1.04 (3H, s); 1.24 (3H, s); 1.60 (3H, d, J= 7.1); 1.75 (2H, m); 1.97 (2H, m); 2.14 (3H, s); 2.24 (2H, m); 2.75 (2H, dd, J= 4.6, 6.9); 2.88 (2H, t, J= 5.6); 5.10 (1H, s); 5.15 (1H, q, J= 7.1). **^{13}C-NMR**: 16.7, 20.5, 24.2, 25.0, 27.7, 28.0, 29.5, 37.9, 39.5, 42.7, 58.4, 68.6, 86.9, 170.0 (2). **EIMS**: 332 ($M^{+\cdot}$, 35), 217 (1), 201 (4), 145 (100), 132 (6), 115 (22), 107 (18), 87 (32), 81 (9), 43 (24). **HREIMS**: calcd for $C_{15}H_{24}O_4S_2$ 332.1116, found 332.1113.

Derivatization of (*R*)-(-)-**8** as its (*S*)-O-acetyl lactylester **13**: Proceeding as above the lactate derivative **13** was obtained. $[\alpha]_D$ -30 (*c* 1.1). **IR**: 2957, 2871, 2360, 1748, 1458, 1369, 1235, 1199, 1133, 1100, 1052, 1011, 950, 907, 867. **^{1}H-NMR**: 0.99 (3H, s); 1.18 (3H, s); 1.58 (3H, d, J= 7.0); 1.70-2.20 (6H, m); 2.15 (3H, s); 2.70 (1H, ddd, J= 3.3, 6.3, 14.2); 2.80 (1H, ddd, J= 3.3, 6.5, 14.4); 2.93 (1H, ddd, J= 3.0, 10.0, 14.5); 3.03 (1H, ddd, J= 3.2, 10.5, 14.0); 5.21 (1H, q, J= 7.1); 5.25 (1H, s). **^{13}C-NMR**: 17.0, 20.6, 23.8, 24.8, 27.8, 28.0, 29.2, 37.6, 39.7, 42.9, 57.1, 68.6, 88.9, 170.0, 170.2. **EIMS**: 332 ($M^{+\cdot}$, 28), 217 (13), 201 (11), 200 (13), 185 (16), 145 (100), 115 (15), 107 (9), 87 (23), 81 (6), 43 (44).

Benzyl protection of the alcohol (*S*)-(+)-**8**: 860 mg of (*S*)-(+)-**8** in dry DMF (6 mL) were added to a suspension of 200 mg (8.33 mmol, 2.12 eq.) of NaH in dry DMF (5 mL). The mixture was stirred at room temperature for 15 min and 0.5 mL (4.21 mmol, 1.07 eq.) of benzyl bromide was added. After an additional 15 min stirring, the reaction was quenched with water, and extracted with ether. Following usual work up the residue was purified by flash chromatography on silica gel. Elution with heptane-ether (19:1) afforded 1.19 g (98%) of (*S*)-(-)-**10**: $[\alpha]_D$: -59 (*c* 2.8). **IR** (film): 2952, 1463, 1331, 1095, 745, 702. **^{1}H-NMR**: 0.97 (3H, s); 1.08 (3 H, s); 3.20-1.50 (10 H, m); 3.31 (1H, s); 4.65 and 5.10 (2H, ABq, J= 12.0, $PhCH_2O$); 7.15-7.45 (5 H, m). **^{13}C-NMR:** 22.5, 26.3, 27.0, 28.5, 29.8, 37.3, 41.1, 42.7, 72.2 (CS_2), 73.8 ($PhCH_2O$), 95.8 (CHOR), 127.7, 127.8, 128.2. **EIMS**: *m/z* 308 ($M^{+\cdot}$, 100), 217 (76), 202 (28), 189 (25), 187 (23), 147 (72), 113 (33), 107 (76), 91 (70). **HREIMS**: calcd for $C_{17}H_{24}OS_2$ 308.1268, found 308.1278.

Removal of the dithioketal protective group of (*S*)-(-)-**10**: To a solution of 1.19 g (3.86 mmol) of (*S*)-(-)-**10** in acetone (80 mL) and water (8 mL) was added 7.4 g (74 mmol) of $CaCO_3$ and 8.1 g (30 mmol, 7.8 eq.) of $HgCl_2$. The mixture was stirred under reflux for 2 h, filtered through Celite, the acetone was then removed under reduced pressure, diluted with water, extracted with dichloromethane and worked up as usual. The residue purified by flash chromatography on silica gel (heptane-ether 4:1) afforded 761 mg (90%) of (*S*)-(-)-**2**: $[\alpha]_D$: -47 (*c* 6.2). **IR:** 2966, 1750, 1455, 1103, 1061, 913, 738. **^{1}H-NMR:** 0.96 (3H, s); 1.11 (3H, s); 1.72 (2H, m); 2.24 (2H, m); 3.48 (1H, s); 4.69 and 5.00 (2H, ABq, J= 12.0, $PhCH_2O$); 7.20-7.45 (5H, m). **^{13}C-NMR**: 20.5, 27.1, 32.1 (2), 33.0 (2), 39.2, 72.7 ($PhCH_2O$), 88.6 (CHOR), 127.7, 127.9, 128.4 138, 213.1. **EIMS:** 218 ($M^{+\cdot}$, 0.5), 127 (29), 99 (51), 97 (88), 91 (100).

Establishing the absolute stereochemistry: correlation studies

Racemic acetate (±)-**5** was saponified using the general procedure to yield the corresponding alcohols, which in turn, were derivatized as the lactyl esters. SiO_2 flash chromatography (CH_2Cl_2-EtOAc, 12:1) afforded cleanly the two diastereomeric lactate esters.

(9*S*)-(*S*)-O-acetyllactyl ester **14** : $[\alpha]_D$: +31 (*c* 1.34). **IR:** 3509, 2944, 1745, 1674, 1453, 1369, 1235, 1202, 1138, 1103, 915, 737, 699. **^{1}H-NMR**: 0.99 (3H, s); 1.04 (3H, s); 1.08-1.25 (1H, m); 1.30 (3H, s); 1.38 (1H, dd, J= 9.0, 13.3); 1.52 (3H, d, J= 7.1); 2.14 (3H, s); 2.34 (1H, ddd, J= 1.5, 3.7, 6.4); 2.60 (1H, dd, J= 6.6, 18.4); 2.74 (1H, dd, J= 3.7, 18.4); 2.99 (1H, dt, J= 8.8, 11.9); 3.31 (1H, s); 3.90 (1H, s); 4.64 and 4.56 (2H, ABq, $PhCH_2O$, J= 10.7); 5.08 (1H, d, J= 8.7); 5.09 (1H, q, J= 7.5); 6.08 (1H, d, J= 10.4); 6.91 (1H, dd, J= 1.4, 10.4); 7.30-7.40 (m, 5H). **^{13}C-NMR**: 14.1, 17.0, 20.5, 20.7, 26.0, 34.3, 35.8, 43.3, 46.3, 50.1, 53.2, 60.2, 68.5, 73.4, 80.9, 87.5, 89.0, 127.8, 127.9 (2 C), 128.4, 129.0, 137.8, 151.2, 169.8, 170.1, 197.9. **EIMS:** 470 ($M^{+\cdot}$, 8), 379 (100), 364 (53), 339 (27), 338 (22), 248 (53), 247 (98), 91 (78). **HREIMS**: calc.for $C_{27}H_{34}O_7$ *m/z* 470.2304; found 470.2279.

X-Ray structure determination of 14: $C_{27}H_{34}O_7$: Mr=470.57, monoclinic, $P2_1$, a=10.600(2), b=12.415(2), c=9.918(9) Å, β=97.35(3), V=1295(1) $Å^{-3}$, Z=2, D_x=1.207 $Mg.m^{-3}$, λ(MoKα)= 0.70926Å, μ=0.81 cm^{-1}, F(000)=504, T=294 K. The sample (0.35*0.35*0.55 mm) was studied on an automatic

diffractometer CAD4 ENRAF-NONIUS with graphite monochromatized MoKα radiation. The cell parameters were obtained by fitting a set of 25 high-theta reflections. The data collection ($2\theta_{max}$ = 50°, scan $\omega/2\theta$ =1, t_{max}= 60 s, range HKL : H 0,13 K 0,15 L -12,12, intensity controls without appreciable decay (0.2%) gives 2884 reflections from which 1945 independant (R_{int}=0.007) with I>3σ(I). After Lorenz and polarization corrections the structure was solved with Direct Methods which revealed the non-hydrogen atoms of the molecule. After isotropic (R=0.117), then anisotropic refinement (R=0.074), the hydrogen atoms were found with a Fourier Difference (between 0.33 and 0.14 eÄ$^{-3}$). The whole structure was refined by the full-matrix least-square techniques (use of F magnitude; x , y, z, b_{ij} for C and O atoms and x, y, z for H atoms; 385 variables and 1945 observations; $w=1/\sigma(F_o)^2=[\sigma^2(I) + (0.04F_o^2)^2]^{-1/2}$) with the resulting R=0.047, R_w=0.042 and S_w=0.7 (residual $\Delta\rho \leq 0.18$ eÄ$^{-3}$).

(9*R*)-(*S*)-O-acetyllactyl ester **15:** $[\alpha]_D$: -71 (*c* 1.05) **IR :** 3508, 2959, 2868, 1748, 1674, 1455, 1370, 1235, 1197, 1100, 881, 752. **^{1}H-NMR**: 0.99 (3H, s); 1.04 (3H, s); 1.07-1.32 (2H, m); 1.33 (3H, s); 1.51 (3H, d, J= 7.1); 2.14 (3H, s); 2.35 (1H, m); 2.61 (1H, dd, J= 6.8, 18.3); 2.72 (1H, dd, J= 3.3, 18.4); 2.94 (1H, dt, J= 8.9, 11.9); 3.30 (1H, s); 3.91 (1H, s); 4.64 and 4.57 (ABq, $PhCH_2O$, J= 10.7); 5.12 (1H, q, J= 7.1); 5.18 (1H, d, J= 8.7); 6.09 (1H, d, J= 10.3); 6.93 (1H, d, J= 10.3); 7.30-7.40 (m, 5H). **^{13}C-NMR**: 17.1, 20.6, 20.8, 26.0, 28.5, 34.3, 36.1, 43.3, 46.4, 49.9, 53.3, 68.5, 73.5, 80.5, 84.7, 89.1, 127.8, 128.0 (2 CH), 128.5 (2 CH), 129.1, 137.8, 151.3, 170.0, 170.2, 198.0. **EIMS**: 471 ($[M+H]^+$, 100), 411(9), 381 (10), 363 (4), 321 (4), 287 (9).

Saponification of **14** using standard conditions gave (9*S*)-(+)-**11**: **m.p.**: 140-144°C (heptane-ether). $[\alpha]_D$: + 47 (c 1.01). IR: 3515, 3429, 3031, 2951, 2891, 2871, 1659, 1613, 1498, 1458, 1413, 1402, 1388, 1369, 1315, 1245, 1216, 1153, 1130, 1106, 1083, 1029, 1008, 968, 942, 877, 809, 750, 696. **^{1}H-NMR**: 1.00 (3H, s); 1.05 (3H, s); 1.30 (3H, s); 1.32-1.45 (2H, m); 2.27 (1H, m); 2.52-2.80 (4H, m); 3.29 (1H, s); 3.93 (1H, s, OH); 4.22 (1H, d, J= 8.6); 4.66 and 4.57 (ABq, $PhCH_2O$, J= 10.7); 6.07 (1H, d, J= 10.3); 7.09 (1H, d, J= 10.3); 7.31-7.40 (m, 5H). **^{13}C-NMR**: 20.8, 26.0, 28.5, 34.1, 35.9, 43.0, 46.5, 51.5, 53.2, 68.1, 73.4, 78.3, 87.1, 89.4, 127.8 (2 CH),128.4 (3 CH), 137.9, 153.2, 199.1. **EIMS**: 357 (M + 1, 19), 338 (17), 266 (13), 265 (78), 250 (30), 248 (28), 247 (100), 219 (17), 109 (24), 91 (70). **HREIMS:** calc.for $C_{22}H_{28}O_4$: *m/z* 356.1988; found 356.1989.

Aldol condensation:

To a solution of 1.4 mL (10.0 mmol, 1.56 eq.) of diisopropylamine in dry THF (30 mL) under argon at -30°C was added 6 mL (9.62 mmol, 1.50 eq.) of 1.6 M n-BuLi in hexane. The mixture was stirred at -30°C for 15 min, a solution of 1.40 g (6.41 mmol) of **2** in dry THF (20 mL) was added, the mixture was stirred at -40°C for 1 h, cooled to -78°C, and 2.05 g (16.8 mmol, 2.62 eq.) of **3** was added. The mixture was stirred at -78°C for 5 min, quenched with saturated aqueous solution of ammonium chloride (2 ml/mmol), and extracted with dichloromethane. The combined extracts were washed with 1M hydrochloric acid and following usual work up the residue was purified by flash chromatography on silica gel (heptane-ether 5:1) to afford 130 mg (6%) of the first eluting minor *threo* aldol **4m** and 1.75 g (80%) of the major *threo* aldol **4M**.

4m: **IR**: 3479, 3030, 2958, 2928, 2871, 2820, 1726, 1455, 1416, 1395, 1368, 1120, 1071, 1029. **^{1}H-NMR:** 0.97 (3H, s, Me-15α); 1.02 (3H, s, Me-15β); 1.15 (3H, s, Me-8); 1.75 (2H, d, J= 8.7, H-11); 2.42 (1H, m, H-10); 2.62 (2H, m, H-5); 3.34 (1H, d, J= 1.5, H-1); 3.55 (1H, dd, J= 2.4, 8.5, H-9); 4.54 (1H, d, J= 2.4, OH); 4.54 and 4.84 (2H, ABq, J= 12.2, $PhCH_2O$); 5.44 (1H, m, H-7); 5.66 (1H, m, H-6); 5.73 (1H, m, H-4); 5.82 (1H, m, H-3), 7.20-7.50 (m, 5 H). **^{13}C-NMR** : 22.2 (Me-15β), 26.3 (Me-15α), 26.6 (Me-8), 26.8 (C-5), 37.8 (C-15), 39.8 (C-11), 41.8 (C-8), 46.4 (C-10), 72.0 ($O\underline{CH_2}Ph$), 80.9 (C-9), 86.6 (C-1), 123.6, 124.9, 129.8,

132.7, 127.9, 128.4, 137.9, 213.0 (C-2). **EIMS** : 340 ($M^{+\cdot}$, 0.2) 322 (M-H_2O, 4), 248 (73), 220 (25), 202 (34), 128 (64), 95 (100).

4M: $[\alpha]_D$: +35 (*c* 1.0). **IR**: 3489, 3031, 2964, 2918, 2871, 2818, 1736, 1457, 1423, 1390, 1370, 1091, 739. **^{1}H-NMR**: 0.88 (3H, s), 1.10 (3H, s), 1.14 (3H, s), 1.41 (1H, dd, J= 12.0, 13.0, H-11); 1.81 (1H, dd, J= 9.1, 13.0, H-11); 2.33 (1H, m, H-10); 2.64 (2H, m, 2 H-5); 3.41 (1H, dd, J= 2.2, 8.1, H-9); 3.54 (1H, s, H-1); 3.88 (1H, d, J= 2.7, OH); 4.69 and 5.01 (2H, ABq, J= 12.2, $PhCH_2O$); 5.40-5.90 (4H, m, H-3,4,6,7); 7.20-7.50 (5H, m, Ph). **^{13}C-NMR**: 20.8, 26.6, 27.6, 26.8, 37.9, 39.2, 41.6, 47.6, 73.1, 79.6, 89.2, 124.2, 125.0, 129.8, 132.3, 127.8, 127.9, 128.4, 138.2, 213.0. **CIMS**: *m /z* 341 ($[M+H]^+$, 80), 323 ($[M+H-H_2O]^+$, 19), 235 (24), 217 (9), 119 (42), 107 (23), 105 (100), 91 (9).

Acetylation of the major aldol:

To a solution of 1.38 g (4.05 mmol) of **4M** and 50 mg (0.41 mmol, 0.1 eq.) of DMAP in pyridine (20 mL) was added 5 mL of acetic anhydride. The mixture was stirred at room temperature for 1 h, quenched with methanol, diluted with water, and extracted with dichloromethane. The combined extracts were washed with 1 M hydrochloric acid, worked up in the usual manner and the residue was purified by flash chromatography on silica gel. Elution with heptane-ether (5:1) afforded 1.48 g (95%) of **16**: **m.p.**: 96-97°C (pentane). $[\alpha]_D$: -8 (*c* 1.0). **IR** ($CHCl_3$): 3031, 2964, 2931, 2864, 1749, 1463, 1377, 1244, 1098, 1032, 746. **^{1}H-NMR**(C_6D_6): 0.99 (3H, s, Me-15-β); 1.16 (3H, s, Me-15-α); 1.24 (3H, s, Me-8); 1.60 (1H, dd, J= 10.0, 13.2, H-11-α); 1.85 (1H, dd, J= 9.2, 13.2, H-11-β); 2.08 (3H, s, Ac); 2.45 (2H, m, H-5); 2.61 (1H, m, H-10); 4.02 (1H, s, H-1); 4.84 (1H, d, J= 8.1, H-9); 4.85 and 5.33 (2H, ABq, J= 12.0, $PhCH_2O$); 5.40 (1H, ddd, J= 2.0, 4.2, 10.2, H-7); 5.62 (1H, m, H-6); 5.79 (1H, m, H-4); 5.94 (1H, ddd, J= 2.0, 4.0, 10.3, H-3); 7.20-7.60 (5H, m). **^{13}C-NMR** (C_6D_6) : 20.9 ($\underline{C}H_3C$=O), 21.0 (Me-15α), 26.6 (C-5), 26.8 (Me-8), 27.3 (Me-15β), 37.4 (C-15), 40.6 (C-11), 40.8 (C-8), 45.4 (C-10), 72.7 (O$\underline{C}H_2$Ph), 81.4 (C-9), 88.8 (C-1), 124.8 (C-6), 125.7 (C-4), 129.7 (C-3), 131.4 (C-7), 127.8, 128.4, 128.5, 139.0, 171.0 ($CH_3\underline{C}$=O), 213.0 (C-2) **CIMS**: *m /z* 323 ($[M+H-AcOH]^+$, 100), 205 (32), 107 (23), 105 (26), 91 (5). **HREIMS**: calcd for $C_{24}H_{30}O_4$ 382.2144, found 382.2129.

Allylic oxidation of 16:

To a solution of 700 mg (1.83 mmol) of **16** in dichloromethane (30 mL) at -20°C was added 2.10 g (5.6 mmol, 3.06 equiv.) of PDC followed by addition of 0.75 mL (8.0 mmol, 4.37 equiv.) of t-BuOOH (70% in water). The mixture was stirred at -20°C for 48 h, diluted with ether, passed through a pad of Celite and sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel. Elution with heptane-ethyl acetate (1:1) afforded 570 mg (79%) of **17**: **m.p.**: 106-7°C (pentane). $[\alpha]_D$: -21 (*c* 1.0). **IR** ($CHCl_3$): 3017, 2964, 2360, 2340, 1749, 1669, 1629, 1370, 1238, 1218, 1098, 1078, 1038, 872. **^{1}H-NMR**: 0.77 (3H, s, Me-15); 1.05 (3H, s, Me-15); 1.25 (3H, s, Me-8); 1.42 (1H, dd, J= 10.2, 13.0, H-11); 1.69 (1H, dd, J= 9.1, 13.0, H-11); 2.10 (1H, m, H-10); 2.13 (3H, s, Ac); 3.62 (1H, s, H-1); 4.89 (1H, d, J= 8.7, H-9); 4.54 and 4.94 (2H, ABq, J= 12.0, $PhCH_2O$); 6.31 (1H, dd, J= 1.7, 10.1, H-4); 6.42 (1H, dd, J= 1.7, 10.1, H-6); 6.81 (1H, dd, J= 3.0, 10.1, H-3); 7.07 (1H, dd, J= 3.0, 10.1, H-7); 7.20 - 7.40 (5H, m, Ph). **^{13}C-NMR**: 20.4 (Me-15), 20.6 (Ac), 23.1 (Me-8), 27.0 (Me-15), 37.0 (C-15), 39.4 (C-11), 44.4 (C-10), 45.1 (C-8), 72.4 (O$\underline{C}H_2$Ph), 78.3 (C-9), 88.4 (C-1), 128.5, 130.0, 127.5, 128.0, 129.6, 130.3, 150.4, 150.7, 170.5, 185.1 (C-5), 213.1 (C-2). **CIMS**: *m/z* 337 ($[M+H-AcOH]^+$, 100), 247 (28), 201 (17), 157 (11), 107 (10).

Annelation of 17 :

To a solution of 200 mL (20 mmol, 2.15 equiv.) of a 0.1M samarium (II) iodide in THF at - 85°C was

added HMPA (20 mL) followed by addition of 2.0 g (5 mmol) of **17** and methanol (4 mL) in dry THF (30 mL) under argon, over a period of 10 minutes. The mixture was stirred at -85°C for 3.5 h, quenched with a saturated solution of sodium bicarbonate, and extracted with ether. After usual work up the residue was purified by flash chromatography on silica gel. Elution with heptane-ethyl acetate (1:1) afforded 1.33 g (67%) of **5** along with a more polar fraction. The latter was dissolved in 10 mL dichloromethane, 520 mg (1.38 mmol) of PDC were added and the resulting mixture was stirred at room temperature for 1 h. Dilution with ether, filtration through silica, evaporation of the solvent and subsequent chromatography (heptane-ether, 1:1) afforded an additional 8% (159 mg) of the desired tricyclic enone **5 : m.p.:** 122-123°C (heptane). $[\alpha]_D$: +68 (*c* 1.0). **IR** ($CHCl_3$)**:** 3515, 3024, 2964, 2938, 2871, 1742, 1676, 1457, 1370, 1244, 1105, 1072, 1038, 1005. **^{1}H-NMR**: 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, ABq, 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:** 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, found: 398.2077.

X-Ray structure determination of 5: $C_{24}H_{30}O_5$: Mr=398.5, orthorhombic, $P2_12_12_1$, a=9.121(4), b=12.389(2), c=38.953(9) Å, V=4402(2) Å^{-3}, Z=8, D_x=1.203 Mg.m^{-3}, λ(MoKα)=0.70926Å, μ=0.77 cm^{-1}, F(000)=1712, T=294 K. The sample (0.25*0.45*0.45 mm) was studied on an automatic diffractometer CAD4 ENRAF-NONIUS with graphite monochromatized MoKα radiation. The cell parameters were obtained by fitting a set of 25 high-theta reflections. The data collection ($2\theta_{max}$=50°, scan $\omega/2\theta$ =1, t_{max}=60 s, range HKL: H 0,11 K 0,15 L 0,48, intensity controls without appreciable decay (0.2%) gave 2724 reflections from which 1945 independant with I>2σ(I). After Lorenz and polarization corrections the structure was solved with Direct Methods which reveal the non hydrogen atoms of the molecule. After isotropic (R= 0.11), then anisotropic refinement (R=0.077), the hydrogen atoms are found with a Fourier Difference (between 0.34 and 0.15 eÅ^{-3}). The whole structure was refined by the full-matrix least-square techniques (use of F magnitude; x , y, z, β_{ij} for C and O atoms and x, y, z for H atoms; 524 variables and 2724 observations; $w = 1/\sigma(F_o)^2 = [\sigma^2(I) + (0.04F_o^2)^2]^{-1/2}$) with the resulting R=0.050, R_w=0.049 and S_w=1.47 (residual $\Delta\rho \leq 0.18$ eÅ^{-3}).

Conversion of 5 to the fragmentation target 6:

Protection of C-5 carbonyl: To a solution of 3.0 g (7.53 mmol) of **5** and 2.1 mL (37.6 mmol, 5 equiv.) of ethylene glycol in 100 mL of benzene were added 200 mg (1.16 mmol, 0.15 equiv.) of p-TosOH. The mixture was refluxed for 3 h, cooled to room temperature, filtered through a pad of silica gel and sodium sulphate and worked up in the usual manner to afford quantitatively the desired ketal **18a**: **IR**: 3520, 3055, 3033, 2959, 2934, 2877, 1740, 1455, 1375, 1245, 1266, 1143, 1074, 1019, 938. **^{1}H-NMR**: 1.11 (3H, s); 1.13 (3H, s); 1.38 (3H, s); 2.00 (3H, s); 1.30-2.20 (5H, m); 3.07 (1H, m); 3.53 and 3.54 (2H, s, H-1 and OH); 3.80-4.05 (4H, m); 4.66 (2H, s, $PhCH_2O$); 4.97 (1H, dd, J= 1.0, 7.0, H-9); 5.59 (2H, m, H-6,7); 7.20-7.40 (5H, m,). **^{13}C-NMR:** 21.3, 21.8, 26.6, 29.0, 35.1, 35.7, 44.6, 51.3, 53.3, 53.6, 64.7, 64.8, 72.7, 80.2, 85.9, 89.9, 106.3, 128.6, 136.0, 127.2, 127.5, 128.0, 138.2, 170.1. **EIMS**: 442 ($M^{+\cdot}$, 2), 382 ([M-AcOH]$^+$, 6), 351 ([M-91]$^+$, 100), 91 (98). **HREIMS**: calcd. for $C_{26}H_{34}O_6$: *m/z* 442.2355, found: 442.2363.

Deprotection of the C-9 hydroxy group: To a solution of 580 mg (1.31 mmol) of **18a** in 15 mL of MeOH was added a 15% aq. solution of NaOH (5 mL). The resulting mixture was stirred at 4°C and monitored by TLC . Due to the tendancy of the resulting vinylogous aldol to epimerize *via* a retro-aldol process the saponification has

to be carried out carefully. Upon complete saponification (30 min to 2h at ice bath temperature) dilution with water, extraction with dichloromethane and usual work up gave 500 mg (95%) of **18b**: $[\alpha]_D$ +38 (*c* 3.6). **IR :** 3511, 3055, 2959, 2934, 2880, 1455, 1376, 1298, 1266, 1243, 1143, 1106, 1081, 1019, 998. **^{1}H-NMR**: 1.13 (3H, s); 1.16 (3H, s); 1.30 (3H, s); 1.30-2.20 (6H, m); 2.94 (1H, dt, J= 6.4, 10.1); 3.50 and 3.54 (2H, s, H-1 and OH); 3.70 (1H, d, J= 6.2); 3.80-4.05 (4H, m); 4.66 (2H, s, $PhCH_2O$); 5.67 (1H, d, J= 10.1); 5.83 (1H, d, J= 10.1); 7.20-7.40 (5H, m). **^{13}C-NMR:** 22.2, 26.5, 29.2, 34.8, 35.6, 44.6, 51.9, 53.4, 54.1, 64.6, 64.7, 72.8, 78.4, 86.7, 90.7, 106.4, 130.3, 135.7, 127.4, 127.8, 128.5, 138.6. **EIMS**: 400 ($M^{+\cdot}$, 3), 309 ($[M-91]^+$, 9), 291 (49), 247 (19), 91 (100). **HREIMS**: calcd. for $C_{24}H_{32}O_5$: *m/z* 400.2249, found 400.2244.

<u>One-pot Oxidation-dehydration with Dess-Martin periodinane:</u> To a solution of 1.84 g (4.6 mmol) of the above alcohol in dry dichloromethane (80 mL) and pyridine (10 mL) were added 10 g (2.17 equiv.) of periodinane and stirring continued at room temperature for 12 h. The mixture was diluted with dichloromethane and washed with a saturated aqueous solution of sodium bicarbonate then sodium thiosulphate solution and finally with 1 M HCl. Usual work up and silica gel column chromatography (ethyl acetate-heptane, 1:4) afforded 1.43 g (82%) of pure **19**: **IR:** 3019, 2964, 2929, 2872, 1701, 1216. **^{1}H-NMR**: 1.22 (3H, s); 1.26 (3H, s); 1.27 (3H, s); 1.78 (1H, dd, J= 3.9, 13.8, H-4); 1.90 (1H, dd, J= 6.2, 13.8, H-4); 2.12 and 2.30 (2H, ABq, J=15.9, H-11); 2.95 (1H, m, H-3); 3.55-3.95 (4H, m); 4.27 (1H, s); 4.56 and 4.77 (2H, ABq, J= 11.8, $PhCH_2O$); 5.58 (1H, d, J= 10.2); 5.67 (1H, d, J= 10.2, H-6,7); 7.20-7.40 (5H, m). **^{13}C-NMR:** 22.1, 23.6, 29.5 , 33.0 (C-4), 39.6 (C-11), 42.0 (C-3), 48.2 (Cq-15), 55.1 (Cq-8), 64.5 ($O\underline{C}H_2\underline{C}H_2O$), 73.8 ($Ph\underline{C}H_2O$), 86.9 (C-1), 103.9 (C-5), 135.3, 127.9, 128.1, 128.2, 128.6, 138.4, 144.6, 181.8 (C-2), 178.2 (C-9). **EIMS**: 380 ($M^{+\cdot}$, 100), 365 ($[M-CH_3]^+$, 63), 309 (20), 294 (30), 289 ($[M-91]^+$, 47), 274 (80), 203 (30), 91 (24). **HREIMS**: calcd. for $C_{24}H_{28}O_4$: *m/z* 380.1987, found: 380.2003.

<u>Reduction of the C-9 carbonyl, formation of the C-9 acetate and deketalization of C-5:</u> A solution of 1.8 g (4.7 mmol) of the enone **19** in THF (100 mL) was cooled to -78°C. A 1M solution of L-selectride in THF (10 mL, 10.0 mmol, 2.13 eq.) was added and the resulting solution was stirred at room temperature for 15 min, and the organoborane was oxidized with 15% NaOH in water and 30% H_2O_2. The mixture was stirred at room temperature for 40 min, diluted with water, extracted with dichloromethane and worked up as usual to yield the corresponding allylic alcohol. The latter was dissolved in pyridine (100 mL) and 10 mL of acetic anhydride (106 mmol, 22.5 eq.) was added, followed by addition of 100 mg of DMAP. The mixture was stirred at room temperature for 15 min, quenched with methanol, diluted with water, and extracted with dichloromethane. The combined extracts were worked up as usual to yield the corresponding acetate, which was hydrolyzed in THF (20 mL) with 1M hydrochloric acid (10 mL). After 2 h the mixture was quenched with a saturated aqueous solution of $NaHCO_3$, and extracted with dichloromethane. After usual work up the residue was purified by flash chromatography on silica gel. Elution with heptane-ethyl acetate (4:1) afforded 1.6 g (89%) of **6**: $[\alpha]_D$: +124 (*c* 2.0). **IR:** 3023, 2960, 2932, 2882, 1735, 1637, 1384, 1341, 1313, 1256, 1234, 1216, 1173, 1141, 1109, 1083, 993, 950, 922. **^{1}H-NMR**: 1.13 (3H, s, Me-15α); 1.18 (3H, s, Me-15β); 1.35 (3H, s, Me-8); 1.96 (1H, m, H-11α); 2.01 (3H, s, Ac); 2.20 (1H, m, H-11β); 2.25 (1H, dd, J= 9.4, 16.0, H-4β); 2.48 (1H, dd, J= 6.2, 16.0, H-4α); 2.77 (1H, m, H-3); 3.96 (1H, m, H-1); 4.50 and 4.63 (2H, ABq, J= 11.9, $PhCH_2O$); 5.38 (1H, m, H-9); 5.99 (1H, d, 1 H, J= 10.4, H-6), 6.60 (1H, d, J= 10.4, H-7); 7.20-7.40 (5H, m). **^{13}C-NMR:** 21.1 ($\underline{C}H_3C=O$), 23.6 (Me-15β), 26.2 (Me-8), 29.5 (Me-15α), 39.5 (C-4), 42.5 (C-11), 45.0 (C-3), 48.0 (Cq-15), 51.6 (Cq-8), 73.2 ($Ph\underline{C}H_2O$), 81.9 (C-9), 86.7 (C-1), 127.7, 127.9, 128.5 (C-6), 138.7, 144.6, 151.2 (C-7), 153.4, 170.8 ($CH_3\underline{C}=O$), 198.2 (C-5). **EIMS**: 380 ($M^{+\cdot}$, 17), 320 ($[M-AcOH]^+$, 40), 305 ($[M-AcOH-Me]^+$, 20), 289 ($[M-91]^+$, 13), 230 (99), 215 (100), 105 (77), 91 (80). **HREIMS**: calcd. for $C_{24}H_{28}O_4$: *m/z*

380.1987, found: 380.1976.

Oxidative cleavage of 6:

Ozone was passed into a stirred solution of 1.4 g (3.68 mmol) of **6** in dichloromethane (300 mL) at -78°C until a blue color persisted, and 5.2 g (19.8 mmol, 5.39 eq.) of triphenylphosphine were added. The mixture was stirred at room temperature for 30 min, concentrated under reduced pressure, and purified by flash chromatography on silica gel. Elution with heptane-ethyl acetate (1:1) afforded 1.1 g (72.5%) of **7: m.p.**: 63-64°C (pentane). $[\alpha]_D$: +145 (*c* 2.0). **IR** ($CHCl_3$): 3020, 2985, 2965, 2929, 2873, 1739, 1717, 1704, 1682, 1470, 1455, 1393, 1373, 1346, 1307, 1274, 1239, 1217, 1177, 1116, 1088, 1072, 1031, 1019, 995. **^{1}H-NMR:** 1.01 (3H, s, Me-15β); 1.13 (3H, s, Me-15α); 1.39 (3H, s, Me-8); 1.97 (1H, dd, J=1.5, 17.3, H-4α); 1.98 (1H, d, J gem= 11.8, H-11β); 2.10 (3H, s, Ac); 2.50 (1H, dd, J= 4.9, 17.3, H-4β); 3.40 (1H, s, H-1); 3.53 (1H, d, J gem = 11.8, H-11α); 3.78 (1H, m, H-3); 4.54 and 4.69 (2H, ABq, J= 11.7, $PhCH_2O$); 5.26 (1H, s, H-9); 5.95 (1H, d, J= 10.6, H-6); 7.06 (1H, dd, J= 1.1, 10.7, H-7); 7.20-7.40 (5H, m). **^{13}C-NMR:** 20.3 ($\underline{C}H_3C$=O), 23.8 (Me-15β), 26.2 (Me-8), 30.1 (Me-15α), 37.2 (C-4), 41.1 (C-15), 44.7 (C-8), 48.1 (C-3), 50.9 (C-11), 75.8 (Ph$\underline{C}H_2$O), 81.2 (C-9), 91.4 (C-1), 127.8 (C-6), 128.3, 128.8, 129.1, 136.5, 146.3 (C-7), 170.4 ($CH_3\underline{C}$=O), 195.8 (C-5), 207.8 (C-10), 210.8 (C-2). **EIMS**: 413 (M+H, 2), 412 ($M^{+\cdot}$, 0.5), 321 (5), 305 (32), 276 (43, 234 (76), 91 (100). **HREIMS**: calcd. for $C_{24}H_{28}O_6$: 412.1886, found: 412.1915.

X-Ray structure determination of 7: $C_{24}H_{28}O_6$: Mr=412.5, triclinic, P-1, a=7.690(6), b=11.894(3), c= 12.804(9) Ä, α=72.81(4), β=73.18(5), γ=88.83(4)°, V=1069(1) Å^{-3}, Z=2, D_x=1.282 Mg.m^{-3}, λ (MoKα)= 0.70926Å, μ=0.85 cm-1, F(000)=440, T=294 K. The sample (0.10*0.35*0.50 mm) was studied on an automatic diffractometer CAD4 ENRAF-NONIUS with graphite monochromatized MoKα radiation. The cell parameters were obtained by fitting a set of 25 high-theta reflections. The data collection ($2\theta_{max}$=50°, scan $\omega/2\theta$=1, t_{max}=60 s, range HKL: H -9,9 K -14,14 L 0,15, intensity controls without appreciable decay (0.3%) gave 4053 reflections from which 2453 independant (R_{int}=0.010) with I>3σ(I). After Lorenz and polarization corrections the structure was solved with Direct Methods which reveal the non-hydrogen atoms of the molecule. After isotropic (R = 0.10), then anisotropic refinement (R=0.083), the hydrogen atoms are found with a Fourier Difference (between 0.76 and 0.34 eÅ^{-3}). The whole structure was refined by the full-matrix least-square techniques (use of F magnitude; x, y, z, β_{ij} for C and O atoms and x, y, z for H atoms; 356 variables and 2453 observations; $w = 1/\sigma(F_o)^2 = [\sigma^2(I) + (0.04F_o^2)^2]^{-1/2}$) with the resulting R=0.033, R_w=0.031 and S_w=1.22 (residual $\Delta\rho \leq 0.19$ eÅ^{-3}). For all three X-ray analyses: Atomic scattering factors from International Tables for X-ray Crystallography (1974). All the calculations were performed on a Digital MicroVAX 3100 computer with the MOLEN package (Enraf-Nonius, 1990).

References and Notes:

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