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Left and Right-half Taxoid Building Blocks from (S)-(+)-Hajos-Parrish Ketone

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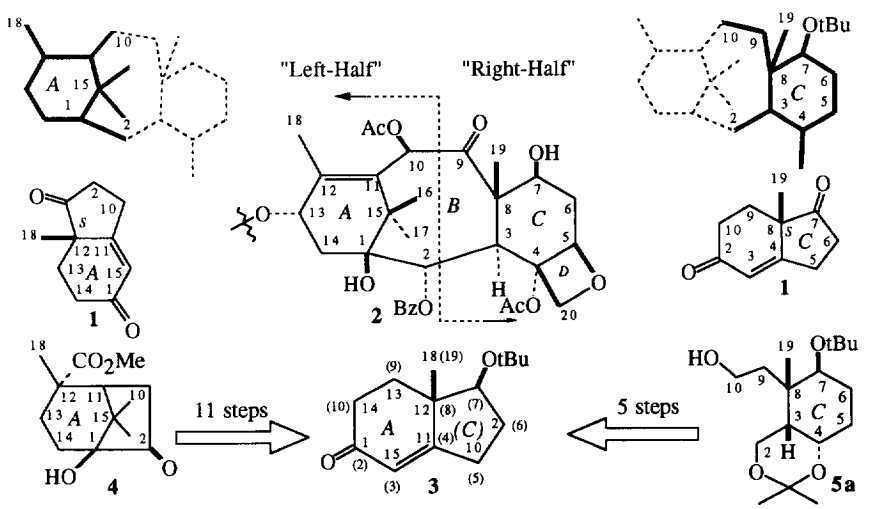
Abstract: *An efficient 11-step synthesis of the optically homogeneous bridged ring system* ***4****, and a 5-step synthesis of the cyclohexane derivative* ***5a*** *from Hajos-Parrish ketone is presented.*

Since the discovery of taxol's mode of action, extensive chemical and biological studies have been carried out resulting in the publication of three total syntheses so far over a period of two decades.[1] Even allowing for this progress, there still exists a need for the development of a higher yielding synthetic route and the challenges associated with assembling the complex ABC core of taxoids continue to stimulate a widespread interest. Our interest in the taxoid synthesis has focused on the use of the well-known (S)-(+)-Hajos-Parrish ketone as a precursor for the entire taxoid framework. We felt that the 20-carbons of the taxoid diterpene skeleton **2** could be obtained from the Hajos-Parrish ketone with the only extra carbons being derived from methyl iodide. Thus we needed an efficient route to elaborated left- and right-half taxoid building units starting from the same precursor (Scheme 1).

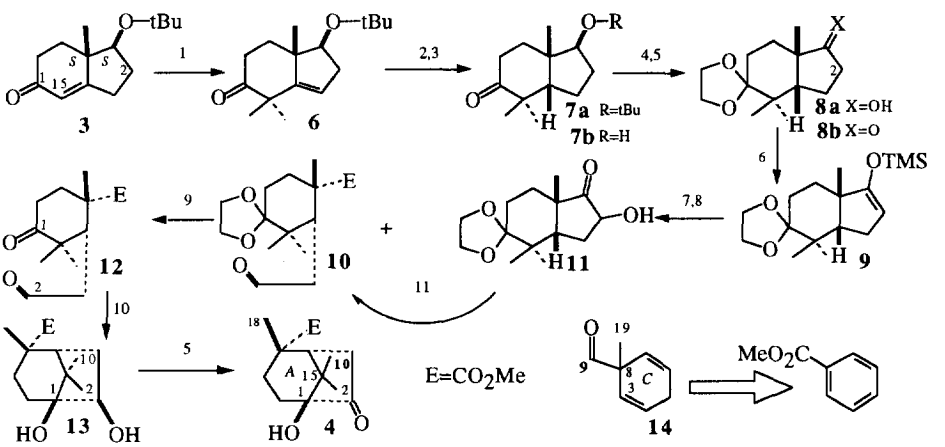


Scheme 1

Recognition of the pattern that connects the Hajos-Parrish ketone to the target involves an obvious disconnection for the left-half, while as far as the right half is concerned there is no direct link between the starting material and the taxoid C-ring. Efforts to link the Hajos-Parrish ketone to the taxoid right-half gave rise to a new process, the one-pot multi-stage transformations mediated by lead tetraacetate, which constitutes a direct route to the C-ring of taxoids. As an illustration of our efforts in this field we reported the synthesis of a bicyclo[3.2.1]octane[2] and the lead tetraacetate (LTA) mediated oxidative fragmentation of unsaturated bicyclic diols;[3] this work set the stage for the synthesis of both left and right-half taxoid building blocks starting from the (S)-(+)-Hajos-Parrish ketone **1** in a divergioconvergent manner and in this paper we present a full description of a short and efficient synthesis of both the A- and C-ring taxoid substructures in their optically pure form.

Left-half taxoid building unit from Hajos-Parrish ketone:

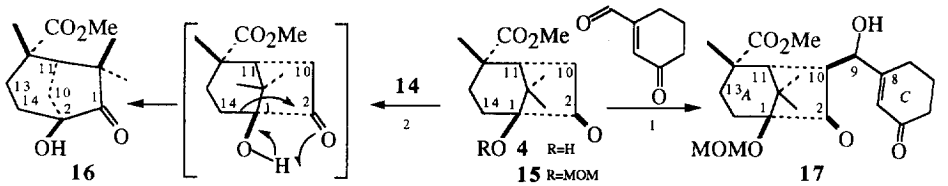
We have previously reported the retrosynthetic analysis of the bicyclo[3.2.1]octane derivative **4** (ref 2). Briefly, an oxidative cleavage sets the conditions for a pinacol coupling to effect C1-C2 bonding while stereospecific SmI_2 mediated reductive coupling[4] (as a consequence of the *cis*-ring junction in the hydrindenone **7a**) allows conversion of keto-aldehyde **12** into the bicyclo[3.2.1]octane **13** and fixes the absolute configuration at the C-1 center.



Scheme 2: 1) t-BuOK,t-BuOH, MeI. 2) H_2-Pd/C 10%, benzene-heptane, r.t. 3) $BF_3.Et_2O$, DCM, r.t. 4) $HO(CH_2)_2OH$, pTosOH, benzene, Δ. 5) DMSO, $(COCl)_2$, Et_3N, DCM, -60°C. 6) TMSOTf, collidine, DCM, r.t. 7) O_3, DCM, Py, -78°C, then PPh_3. 8) CH_2N_2, Et_2O, 0°C. 9) 1N HCl-THF, r.t. 10) SmI_2, THF-MeOH, -25°C. 11) $NaIO_4$, THF-H_2O, r.t.

Hydrindenone **6**, bearing the C-15 geminal methyl group was prepared from **3** by treatment with t-BuOK in t-BuOH at 0°C for 30 min, followed by addition of excess methyl iodide[5] (Scheme 2). Catalytic reduction in benzene-heptane (H_2-Pd/C, 50psi, 30 h) afforded a diastereomeric mixture of *cis* and *trans* fused hydrindanones **7** in 86% yield and in a 32:1 ratio respectively; these were easily separated by crystallization from pentane thus affording the optically pure *cis*-fused **7a**. Removal of the t-butyl protecting group ($BF_3.Et_2O$, DCM, r.t.)[6] gave **7b** in 99% yield. Ketalization of the C-1 carbonyl with ethylene glycol (benzene, pTosOH, Δ, Dean-Stark, **8a**, 96%), followed by Swern oxidation of the free hydroxyl group (oxalyl chloride, DMSO, Et_3N, DCM, -60°C) furnished ketone-ketal **8b** (90%). Formation of its corresponding silyl enol ether **9** (TMSOTf, collidine, DCM,

r.t., 93%) and subsequent ozonolysis (DCM, Py,-78°C), followed by work-up with triphenylphosphine and esterification with diazomethane afforded the ester-aldehyde **10** (61%) and the acyloin **11** (23%) as a side product. Acid catalyzed deketalization of **10** with 1N HCl in THF at r.t. gave the desired keto-aldehyde **12** (97%). The acyloin **11**, produced in significant amounts, was smoothly converted into the desired product **10** by treatment with $NaIO_4$ in THF-H_2O at r.t. for 10 min and esterification with diazomethane, increasing considerably the yield of the required keto-aldehyde **12**. Conversion of the latter into bicyclic α-ketol **4** by a SmI_2 mediated reductive coupling (2.8 equivalents of SmI_2, 2.2 equiv of MeOH in THF at -25°C, **13**, 91%) followed by Swern oxidation (as above, 91% isolated yield) occurred stereospecifically. The configurations at the newly formed asymmetric centers are assigned to be as depicted by considering the compulsory bottom-side attack of C-1 carbonyl thus insuring the facial selectivity at C-1. Our initial approach to the synthesis of the taxoid ABC framework involved establishing of the A-C ring linkage. Thus, the aim was to couple this A-ring segment **4** (the "left-half" aldol partner) to a C-ring equivalent ("right-half" partner) using enolate chemistry. The required achiral aldehyde **14** chosen as the model-precursor to ring C, in order to simplify the aldol reaction outcome (homotopic faces on the aldehyde), was prepared on large scale from methyl benzoate *via* a Birch reductive alkylation in a three step sequence using slightly modified literature conditions.[7] We next carried out studies on aldol condensation between **4**, or its hydroxy-protected derivative **15**, and the aldehyde **14**. Lithium, titanium, cerium or boron enolates of **4** proved to be inefficient. On the other hand, heating the α-ketol **4** (or its MOM-protected derivative **15**) and the aldehyde **14** in benzene in the presence of a catalytic amount of pTosOH for 4 h initiated an α-ketol rearrangement with C14-C1 bond migration leading to the α-ketol **16** in 72% yield.[8] We attributed the failure of this aldol condensation to steric factors and so we investigated less sterically congested C-ring models such as aldehydes lacking the angular methyl group.[9]

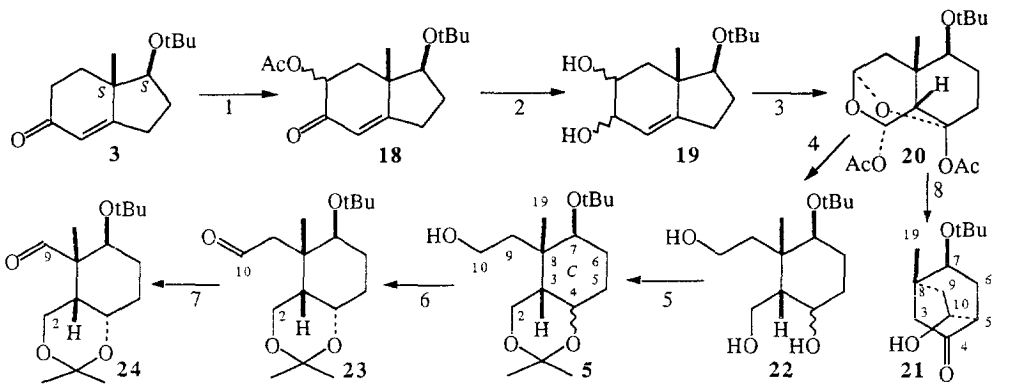


Scheme 3: 1) LDA-THF, -40°C, then -78°C and aldehyde. 2) PhH, pTosOH, reflux.

Thus, aldol condensation (LDA, THF, -40°C, 2h, then addition of 3-formyl cyclohexenone[10] at -78°C, 10 min) afforded the B-seco taxane framework **17** in 80 % isolated yield together with recovered starting material (Scheme 3). Following the C10-C9 bond formation the stage was set for the A-C-ring linking: this provided an opportunity for further elaboration using a conjugate addition of dimethyl cuprate (installation of the missing 19-methyl group) which could be followed by an intramolecular aldol reaction for a C2-C3 bonding.

Right-half taxoid building unit from Hajos-Parrish ketone:

To complete our synthetic project we required an enantioselective synthesis of a six-membered ring possessing four contiguous substituents and bearing a quaternary center, the "right-half", starting again from the (S)-(+)-Hajos-Parrish ketone **1**. This part of the synthesis is achieved utilising a previously unknown reaction sequence affording the highly oxygenated, ring-expanded product **20** (ref. 3). This procedure is outlined in Scheme 4.



Scheme 4: 1)$Pb(OAc)_4/C_6H_6$, r. 2)$LiAlH_4/Et_2O$. 3)$Pb(OAc)_4/CH_3CN$. 4)$LiAlH_4$/THF. 5) acetone-CSA 6)tBuOMgBr/THF/tBuOH then ADD/THF. 7) KH-AcCl-DMAP/DME then O_3 /DCM, Py,PPh_3. 8)K_2CO_3-MeOH-H_2O

Enantiomerically pure (S)-(+)-Hajos-Parrish ketone **1** was converted to **3** and then to the acetoxyenone derivative **18** as an epimeric mixture (ref.5) which was then reduced ($LiAlH_4$, Et_2O, 0°C to r.t.) to the unsaturated diols **19** (98%) prior to oxidation. Treatment of **19** with 3 equiv. of LTA in acetonitrile (r.t., 15 h) followed by filtration through Celite and silica gel afforded **20** in 82% isolated yield. The structure of **20**, was unambiguously established by extensive NMR studies and confirmed by X-ray analysis (Figure 1).

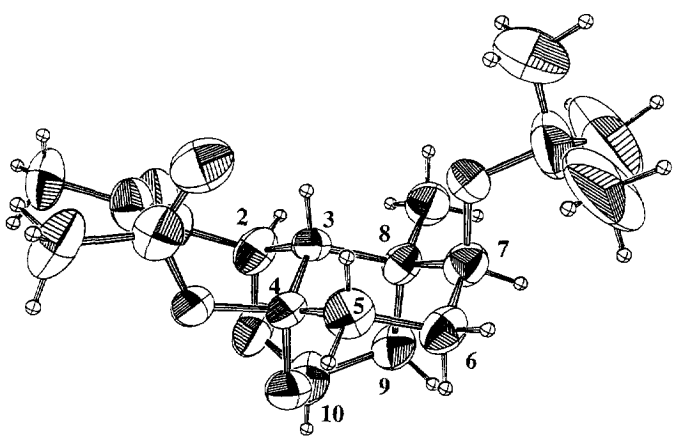
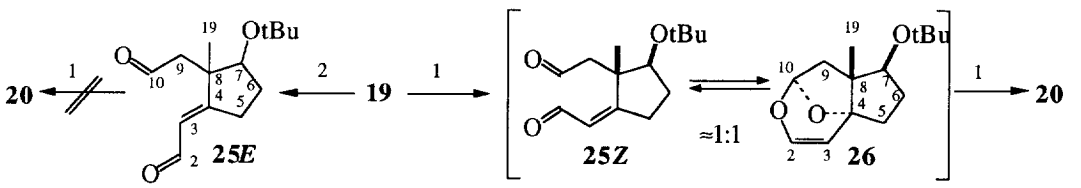


Figure 1: Perspective drawing of the X-ray structure of **20**.

Conversion of **20** to **5** was accomplished by reduction with excess $LiAlH_4$ to the triol **22** (9:1 epimeric mixture) and subsequent selective acetonide formation (acetone, CSA, r.t., 24 h) in 80% combined yield. The mixture of acetonides thus obtained was easily purified on silica gel (eluent: ethyl acetate-heptane, 1:3) to afford pure *syn* (major) acetonide **5a** and *anti* (minor) acetonide **5b**. Oxidation of the major (*syn*) acetonide **5a** with 1,1'-(azodicarbonyl)dipiperidine (tBuOMgBr, THF, 0°C, then ADD, THF, 0°C to r.t., 1h)[11] led in 89% yield to the corresponding aldehyde **23**, a useful taxoid C-ring building block, containing 10 out of the 20 carbon atoms, oxygen functionalities at C-2, C-4, C-7, C-10 and the required absolute configuration on C-8, C-7. Searching for a C-ring component suitable for a C-9/C-10 coupling, we further transformed **23** to **24** through its enol

acetate (KH, DME, -5°C, 15 min for the enolate formation, then AcCl, DME, DMAP, r.t., 15 min) followed by ozonolysis (O_3, DCM, Py, -70°C, then PPh_3) in 61% yield. Base treatment of **20** (K_2CO_3, MeOH-H_2O, r.t., 15h) led to the bicyclo[2.2.2.]octane framework **21** in 92% yield.

These experiments were designed to explore a stereocontrolled and flexible approach to the taxoid ABC-ring substructure with the intention of subsequently synthesizing taxoid analogues via an A+C---> AC ---> ABC strategy. Following a conventional A-C ring linking (using an A-ring model derived from 2,6,6-trimethyl-2-cyclohexene-1,4-dione), the fully functional ABC-taxoid framework could have conceivably been reached in less then ten linear steps. We anticipate that installation of the oxygen functionalities at C-10, and C-9 in such a structure would be reasonably easy by arranging the C9-C10 part and the mode of bonding at C10-C11 (or C1-C2). The overall LTA-mediated transformation, combined multiple bond-breaking and bond-forming sequences in a one pot reaction, starting from diol **19** gave rise to a ring expansion leading to a tetrasubstituted cyclohexane. Since this process represents a versatile new methodology for producing vicinally functionalized molecular systems we felt that additional studies were warranted. Control experiments have been carried out to ascertain whether the non-isolable tricyclic enol ether **26** might be an intermediate in the formation of the ring-enlarged product **20**. Treatment of **19** with only one equivalent of lead tetraacetate produced the aldehyde ***25Z*** when the reaction was stopped after only 5 min; this was rapidly characterized by ^1H and ^{13}C-NMR spectra. On standing in the NMR tube for approximately 2 h, equilibrium was established and a mixture of ***25Z*** and **26** in a nearly 1:1 ratio (characterized as a mixture) was obtained. This mixture can be stored for weeks without any detectable change. Resubmission to the cascade conditions, with two equiv. of LTA, leads to **20**, thus making it reasonable to conclude that **26** is formed as an intermediate. Changing the solvent to benzene had only marginal effects on the reaction rate and chemical yield (slightly slower reactions and comparable yield). The same equilibrium mixture was also obtained by treatment of **19** with sodium periodate (3.5 equiv.) in THF-H_2O for 5 min at room temperature, but prolonged reaction (2 h) afforded the *E*-dialdehyde ***25E*** (86%). This dialdehyde remained unchanged upon treatment with lead tetraacetate as above (Scheme 5).

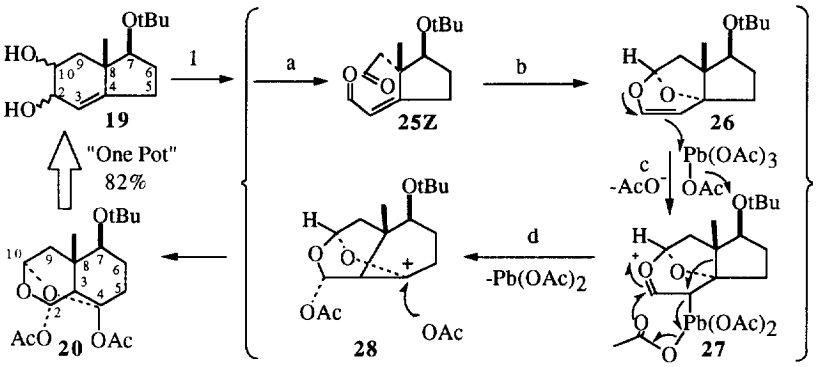


Scheme 5: 1) $Pb(OAc)_4/CH_3CN$. 2) $NaIO_4$, THF-H_2O

Rationalizing the mechanism of the cascade transformations

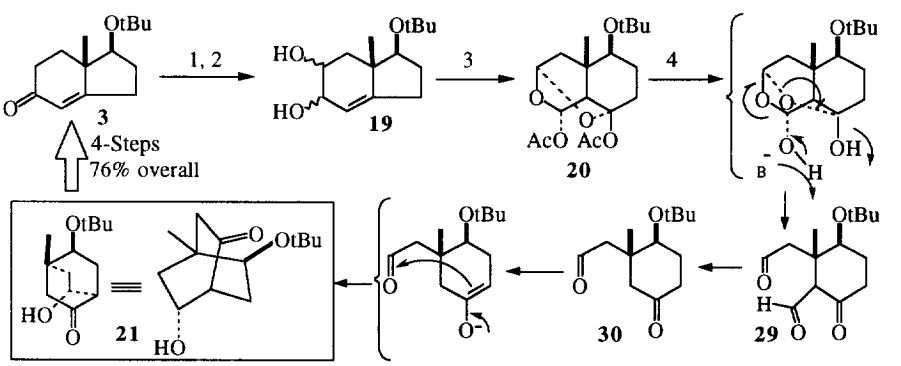
Lead has the largest covalent radius in group IVA. This leads to large interatomic distances and correspondingly small bonding energies. The key transformation is triggered by an electrophilic attack of the metal on the electron rich double bond which sets up the ring expansion process. Reactions of metals with double bonds are well known in the literature and metal salts of Tl^{3+}, Hg^{2+} and Pb^{4+} (which are isoelectronic: $5d^{10}$) are known Lewis acids and react as electrophiles with olefins.[12] The most interesting and useful aspect of lead chemistry is the ease with wich Pb^{4+} undergoes reduction to Pb^{2+}.[13] With these considerations in mind, most mechanistic details can reasonably be rationalized by Scheme 6. Thus, formation of the tricyclic product **26** involves the formation of the intermediate dialdehyde ***25Z*** (oxidative fragmentation, job-a); this collapses to give **26** via an intramolecular hetero-Diels-Alder (job-b), setting the conditions for the next step: an electrophilic

attack of the metal to the electron rich olefin (job-c) leading to **27**. The strain associated with this ring system then favors a ring expansion (job-d) leading to the bridgehead cation **28** with concomitant loss of a $Pb(OAc)_2$ unit and acylation at C-2 (taxoid numbering). The thermodynamically favourable valence change and the ability of Pb^{4+} to act as a multi-job reagent, such as an oxidizing agent (job-a), or a Lewis acid (job-c and probably job-b, catalyzing the IMDA) and the high polarizability of the Pb-C bond, associated with its low dissociation energy, account well for the proposed mechanism of the cascade transformations.



Scheme 6: 1) $Pb(OAc)_4$, CH_3CN; transformations: a) oxidative cleavage, b) intramolecular hetero-Diels-Alder, c) electrophilic attack of the double bond, d) ring expansion.

Formation of the bicyclo[2.2.2]octanone **21** upon basic hydrolysis can be rationalized by a saponification leading to **29**, followed by a decarbonylation to give **30** and subsequent aldol condensation (Scheme 7).



Scheme 7: 1) $Pb(OAc)_4$, PhH, r. 2) $LiAlH_4$, Et_2O. 3) $Pb(OAc)_4$, CH_3CN. 4) K_2CO_3-MeOH-H_2O

Not only was important mechanistic information obtained by use of the unsaturated diols **19** as cascade precursors but they also appear to be excellent synthetic intermediates in taxoid and other natural product syntheses. The exact scope of the skeletal rearrangement described above remains to be determined; the use of other metals as well as a catalytic cycle aimed at the "greening" of organic synthesis also merits investigation.

Conclusion:

We have developed an efficient route to elaborated left- and right-half taxoid building units which can

either be used in our main strategy (the aldol-annelation-fragmentation, C9-C10, C2-C3, C2-/-C10, sequence) or could be used in several other literature approaches leading to taxoid frameworks.[14] Samarium iodide mediated pinacol coupling provided an excellent method for the assembly of multigram quantities of the bicyclo[3.2.1.]octane unit. The interesting biological activities found among molecules containing the relatively rigid bicyclo[3.2.1]octane ring system makes such routes of considerable value.[15] In parallel, the LTA mediated cascade-transformation has been demonstrated to be an effective ring expansion route for medium rings.

In summary, a concise synthesis of **4** (left-half, A-ring moiety) and of **5**, **23**, **24** (right-half, C-ring moiety) was achieved. The utility of a new methodology for preparing the taxol A- and C-ring substructures starting from a common starting point establishes the viability of the divergioconvergent strategy. We now intend to apply the methodology developed to fully functionalized variants of the above cited taxoid segments.

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Experimental section:

Flash chromatographies were run on silica gel (Merck 60, 230-400 mesh) with the solvent mixture indicated. Thin layer chromatography was performed on commercial silica gel glass plates that were developped by immersion in 5% phosphomolybdic acid in 95% ethanol. Experiments which required an inert atmosphere were carried out under dry argon or nitrogen in a flame dried glass system. THF and benzene were freshly distilled from $LiAlH_4$ and sodium wire respectively, and were transferred via syringe. Methylene chloride was distilled from P_2O_5. Triethyl and diisopropyl amines were distilled from KOH pellets. Commercial reagents were purchased from Aldrich Chemicals and used as received. "Usual work up" means washing of the organic layer with brine, drying on anhydrous $MgSO_4$, and evaporating *in vacuo* with a rotary evaporator at aspirator pressure. **Optical rotations** were recorded in $CHCl_3$ solution in a 1 dm cell using a Perkin-Elmer 243 polarimeter. **IR** spectra were recorded on a Nicolet 205 FTIR instrument, neat or in chloroform. Melting points are uncorrected. **^{1}H-NMR** spectra were obtained on Bruker AM 400, AM300, AC250 (400, 300 and 250 MHz respectively) instruments in $CDCl_3$. Chemical shifts are expressed in ppm downfield from TMS (the ^{1}H-NMR data is presented in the order: δ value of the signal, integrated number of protons, peak multiplicity (abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet) and coupling constants in Hertz. Nuclear Overhauser enhancements by the NOEDIFF method[16] were obtained with the aid of the Aspect 3000 microprograms, which allow direct accumulations of difference FID's. N.O.e's were successfully obtained with extremely low irradiating power levels (40 dB); 320 transients were acquired in n.O.e. experiments, and an exponential line broadening of 0.3 Hz was used. ^{13}C spectra were measured at 62.5 and 75 MHz and the chemical shifts are reported relative to $CDCl_3$ triplet centered at 77.00 ppm. For all compounds investigated, multiplicities of ^{13}C resonances were assigned by the SEFT technique.[17] Two-dimensional homo and heteronuclear correlation experiments were performed with standard Bruker software. Mass spectra (**MS**), recorded on an AEI MS-50 (electron impact spectra, **EI**), an AEI MS-9 (chemical ionization spectra, **CI**), or a Kratos MS-50 (high resolution mass spectra, **HR**) instruments are reported in the form: "m/z (intensity relative to base peak=100%)". Molecular mechanics calculations were run using Still's Macromodel program version 3.1 operated on a Silicon Graphics work-station. Structures were constructed by means of the interactive graphics input and then subjected to the MM2 minimization using the Monte Carlo option of the program for the search of all conformers and the evaluation of their energy (indicated solvent: chloroform).

Synthesis of the *cis*-fused hydrindanone 7a: Starting from the O-tBu-protected hydrindenone derivative (S)-(+)-**3** and proceeding as described in ref. 5, 15,15-dimethyl hydrindenone **6** was obtained and was further hydrogenated in a Parr hydrogenator at 50 psi and room temperature, by first placing 10% palladium on activated carbon (3 g) in the flask, followed by **6** (3.27 g, 13.05 mmol) dissolved in anhydrous benzene (10 mL) and heptane (20 mL). The mixture was allowed to react for 30 h. After disappearance of **6** as indicated by TLC the catalyst was removed by filtration on Celite and rinsed with ethyl acetate. Removal of the solvent of the filtrate gave a solid which was purified by SiO_2 flash chromatography (eluent: heptane-ethyl acetate, 7:1) to give the *cis* and *trans* fused hydrindanones **7a** 2.83 g (11.3 mmol, 86% combined yield and 32:1 ratio). Crystallization from pentane afforded 83.4% of pure *cis*-fused **7a** (2.73 g, 10.8 mmol): **m.p.**: 72-73°C (pentane). $[\alpha]_D$: +64 (*c* 1.0). **IR** (nujol): 2970, 2871, 1702, 1456, 1383, 1370, 1191, 1104, 1025 cm^{-1}. **^{1}H-NMR**: 1.00 (3H, s); 1.14 (3H, s); 1.17 (9H, s); 1.22 (3H, s); 1.48 (2H, m); 1.73 (2H, m); 1.85 (3H, m); 2.24 (1H, m); 2.54 (1H, m); 3.51 (1H, t, J= 7.1). **^{13}C-NMR** (62.5MHz): 23.5, 24.6, 26.6, 26.7, 28.7, 32.0, 32.1, 34.7, 42.2, 47.1, 54.8, 72.6, 79.4, 217.1. **EIMS**: 252 ($M^{+\cdot}$, 16), 196 (100), 178 (10), 168 (22), 136 (16), 125 (18), 93 (14), 82 (16), 71 (24), 57 (63).

trans-fused **7a** (2.6%, 85.5 mg, 0.339 mmol): oil. $[\alpha]_D$: +12 (*c* 1.0). **IR** (film): 2970, 2930, 2871, 1702, 1456, 1383, 1370, 1191, 1104, 1025 cm^{-1}. **^{1}H-NMR** (400MHz): 1.01 (3H, s); 1.04 (3H, s); 1.09 (3H, s); 1.13 (9H, s); 1.40-2.05 (7H, m); 2.31 (1H, ddd, J=2.4; 5.6, 16.1); 2.66 (1H, ddd, J= 6.8; 13.0, 16.1); 3.37 (1H, dd, J= 7.8, 8.9). **^{13}C-NMR** (62.5MHz): 12.1, 20.2, 20.9, 25.7, 28.7, 31.3, 34.7, 35.9, 42.1, 47.5, 53.3, 72.4, 80.0, 217.1. **EIMS**: 252 ($M^{+\cdot}$, 14), 196 (34), 135 (26), 125 (39), 107 (20), 95 (17), 93 (19), 83 (20), 81 (20), 71 (24), 69 (17), 67 (15), 57 (100).

Removal of the tBu-protective group: According to ref 6; to a stirred solution of the *cis*-fused hydrindanone **7a** (2.7 g, 10.7 mmol) in 50 mL of methylene chloride were added 5 mL of $BF_3.Et_2O$ at room temperature. TLC monitoring indicated no starting material after stirring for 30 min. The reaction was then quenched with a saturated aq. solution of $NaHCO_3$ and extracted with methylene chloride. Usual work up gave 2.10g, 10.7 mmol of pure **7b** (quantitative yield): $[\alpha]_D$: +22 (*c* 1.0). **IR** (film): 3442, 2957, 2937, 2867, 1706, 1474, 1453, 1385, 1143, 1101, 1052, 984, 963, 869, 843 cm^{-1}. **^{1}H-NMR** (400MHz): 1.01 (3H, s); 1.25 (3H, s); 1.26 (3H, s); 1.50-1.70 (3H, m); 1.90 (2H, s); 1.98 (2H, m); 2.20 (1H, m); 2.62 (1H, m); 3.80 (1H, t, J= 5.8). **^{13}C-NMR** (62.5MHz): 23.2, 23.6, 26.9, 30.0, 31.2, 32.2, 34.4, 42.7, 47.0, 55.0, 81.1, 217.0. **EIMS**: 196 ($M^{+\cdot}$, 100), 153 (21), 127 (39), 97 (49), 93 (28), 81 (28), 69 (42).

Ketal protection of the C-1 carbonyl: In a two-necked flask, equipped with a Dean-Stark apparatus, a solution of **7b** (1.57 g, 7.92 mmol) in 80 mL of benzene and 5 mL of ethylene glycol was refluxed in the presence of a catalytic amount (50 mg) of pTosOH for 35 min (TLC monitoring, ethyl acetate-heptane, 1:1) then quenched with a saturated aq. solution of $NaHCO_3$, extracted with methylene chloride and worked up as usual to give 1.843 g (7.68 mmol, 96%) of **8a**: **m.p.**: 54-55 °C. $[\alpha]_D$: +11 (*c* 0.9). **IR**: 3250, 2967, 2925, 2850, 2400, 1782, 1762, 1445, 1382, 1353, 1250, 1230, 1182, 1100, 1050 cm^{-1}. **^{1}H-NMR** (250MHz): 0.89 (3H, s); 1.07 (3H, s); 1.14 (3H, s); 1.22 (1H, m); 1.50 (3H, m); 1.78 (4H, m); 2.08 (1H, m); 3.71 (1H, m); 3.90 (4H, m). **^{13}C-NMR** (62.5MHz): 22.2, 22.3, 24.8, 26.4, 27.2, 30.0, 30.9, 40.2, 44.8, 53.8, 64.1, 65.0, 82.2, 113.1. **EIMS**: 240 ($M^{+\cdot}$, 77), 222 (38), 197 (38), 171 (50), 153 (30), 100 (80), 99 (100), 97 (28), 87 (84), 86 (99), 81 (30), 55 (30). **HREIMS**: calc. for $C_{14}H_{24}O_3$ m/z 240.1725, found 240.1721.

Swern oxidation of 8a: Oxalyl chloride (30 mL 0.6 M in methylene chloride, 18 mmol) was added to a solution of dry DMSO (15 mL, 36 mmol) in dry methylene chloride (10 mL) at -60°C, under argon. The mixture was stirred for 30 min and a solution of **8a** (1.896 g, 7.9 mmol) in methylene chloride (10 mL) was added.

Upon 30 min additional stirring at -60°C, Et_3N (6 mL) was added , and the mixture was allowed to warm up to 0°C, poured into ice cold water, diluted with methylene chloride and worked up in the usual way to give after silica gel chromatography (ethyl acetate-heptane, 1:3) 1.692 g (7.1 mmol, 90%) of **8b** as an oil: $[\alpha]_D$: +15 (*c* 1.0). **IR**: 2957, 2938, 2871, 2366, 1736, 1453, 1385, 1209, 1141, 1102, 1069, 1029, 970, 907 cm^{-1}. **^{1}H-NMR**: 0.88 (3H, s); 1.11 (3H, s); 1.18 (3H, s); 1.20-2.40 (9H, m); 3.90 (4H, m). **^{13}C-NMR**: 20.9, 21.2, 23.7, 25.7, 26.6, 27.2, 35.7, 40.1, 47.6, 54.8, 64.4, 65.1, 112.4, 222.4. **EIMS**: 238 ($M^{+\cdot}$, 36), 100 (44), 99 (100), 87 (99), 86 (99), 81 (16), 69 (14), 67 (20), 55 (30).

Preparation of silyl enol ether 9, oxidative cleavage and esterification: To a stirred solution of **8b** (700 mg, 2.94 mmol) and collidine (1.5 mL, 11.35 mmol) in dry methylene chloride (30 mL) at 0°C, was added trimethylsilyl trifluoromethanesulfonate (1.5 mL, 7.76 mmol). The reaction mixture was stirred at r. t. for 10 min, diluted with heptane and quenched with a saturated solution of aq. $NaHCO_3$. The organic layer was washed with water and purified on silica gel (ethyl acetate-heptane, 1:9) to yield 847 mg (2.73 mmol, 93%) of **9**: $[\alpha]_D$: +1.0 (*c* 1.0). **IR** (film): 2956, 2930, 2864, 1646, 1463, 1387, 1341, 1305, 1260, 1234, 1128, 1102, 1077, 1026, 970, 925, 879, 838, 793, 757 cm^{-1}. **^{1}H-NMR** (250 MHz): 0.18 (9H, s); 0.88 (3H, s); 1.14 (3H, s); 1.15 (3H, s); 1.40-1.85 (5H, m); 2.00 (1H, m); 2.43 (1H, m); 3.80 (4H, m); 4.42 (1H, s). The silyl enol ether thus obtained was then dissolved in dry methylene chloride (80 mL) 1.5 mL of pyridine was added and the resulting solution was ozonized at -78°C (until blue colour disappeared). Triphenylphosphine (1.13 g, 4.31 mmol) was then added, the reaction mixture was allowed to reach r.t. and concentrated under reduced pressure. The residue was dissolved in ether and a solution of diazomethane (30 mL, 0.3 M in Et_2O) was added at 0°C. After 5 min the reaction mixture was concentrated and purified by column chromatography (ethyl acetate-heptane, 1:3) to afford **10** (472 mg, 1.66 mmol, 61% yield) together with 159 mg (0.63 mmol, 23%) of the acyloin **11** as by-product. **10**: **m.p.**: 55-56 °C. $[\alpha]_D$: +48 (*c* 1.1). **IR** ($CHCl_3$): 2956, 2875, 1722, 1468, 1385, 1300, 1223, 1198, 1165, 1139, 1110, 1079, 1050, 1003, 983, 950, 921 cm^{-1}. **^{1}H-NMR** (250 MHz): 0.70 (3H, s); 0.78 (3H, s); 1.16 (3H, s); 1.56 (2H, m); 1.93-2.21 (2H, m); 2.50 (1H, dd, J=2.7, 6.8); 2.64 (1H, ddd, J=2.3, 6.8, 19.0); 3.15 (1H, dd, J= 2.5, 18.9); 3.65 (3H, s); 3.91(4H, m); 9.78 (1H, d, J= 2.1). **^{13}C-NMR** (62.5 MHz): 18.2 , 21.6 , 28.0 ; 28.3 , 33.7 , 42.3 , 43.3 , 43.7, 45.4 , 51.5, 64.9, 65.1, 112.3, 171.3, 202.7. **EIMS**: 284 ($M^{+\cdot}$, 1), 186 (100), 114 (18), 99 (78), 86 (86), 87 (30), 70 (36), 57 (29).

11: **^{1}H-NMR** (300 MHz): 0.86 (3H, s); 1.14 (3H, s); 1.25 (3H, s); 1.29 (1H, m); 1.51 (1H, m); 1.70 (1H, dd, J=3.6, 10.2); 1.82 (1H, dd, J=3.7, 10.2); 1.90 (1H, ddd, J=3.3, 8.0, 14.4); 2.11 (1H, t, J=8.1); 2.49 (1H, dt, J=8.1, 14.4); 3.92 (4H, m); 4.14 (1H, dd, J=3.3, 8.1). **^{13}C-NMR** (75 MHz): 21.1, 23.8, 25.7, 26.7, 27.8, 30.4, 39.9, 47.2, 51.7, 64.5, 65.3, 71.3, 112.2, 221.4.

Acyloin **11** was then recycled as follows: to a solution of **11** (540 mg, 2.12 mmol) in 16 mL of THF and 4 mL of water was added 1 g (4.7 mmol) of $NaIO_4$. The mixture was stirred at r.t. for 10 min, diluted with water and extracted with ethyl acetate. Following usual work up the residue was dissolved in 30 mL of Et_2O, and 30 mL of a 0.3 M solution of diazomethane was added at 0°C. Upon 10 min stirring at r.t. the reaction mixture was concentrated and the residue chromatographed (ethyl acetate-heptane, 2:5) to afford 451.5 mg (1.59 mmol, 75%) of **10**.

Preparation of the keto-aldehyde 12: A solution of 0.73 g (2.567 mmol) of **10** in THF (30 mL) and 5% hydrochloric acid in water (30 mL) was stirred at r.t. for 2 h, while TLC monitored (TLC control: heptane-EtOAc 1:1; Rf: **10**-0.48, **12**-0.40). The reaction mixture was quenched with solid sodium bicarbonate, concentrated under reduced pressure, diluted with water, and extracted with methylene chloride. Following usual work up the residue was purified by silica gel flash chromatography. Elution with heptane-ethyl acetate (3:2)

afforded 598.5 mg (2.493 mmol, 97%) of **12** $[\alpha]_D$: +78 (*c* 1.0). **IR** ($CHCl_3$): 2984, 2947, 2844, 1722, 1456, 1397, 1357, 1231, 1151, 1124, 1071, 1045, 978 cm^{-1}. **^{1}H-NMR** (250 MHz): 0.92 (3H, s); 0.94 (3H, s); 1.21 (3H, s); 1.59 (1H, dt, J=4.8, 13.8); 2.32 (1H, ddd, J=2.4, 6.0, 13.8); 2.50 (2H, m); 2.74 (1H, dd, J=6.1, 19.8); 2.94 (1H, dt, J=6.0, 14.6); 3.31 (1H, dd, J=3.6, 19.8); 3.74 (3H, s); 9.80 (1H, s). **^{13}C-NMR** (62.5 MHz): 20.5, 23.9, 27.4, 35.7, 36.0, 42.5, 44.0, 47.0, 48.5, 52.0, 176.6, 201.0, 213.6. **EIMS**: 240 ($M^{+\cdot}$, 1), 186 (8), 142 (100), 114 (57), 99 (33), 86 (17).

Intramolecular pinacol coupling: To a stirred solution of keto-aldehyde **12** (480 mg, 2.00 mmol) and methanol (0.2 mL, 4.938 mmol, 2.47 eq.) in dry THF (15 mL) under argon at -25°C was added 50 mL (5 mmol, 2.5 eq.) of 0.1 M samarium(II) iodide in THF with a syringe pump for 6 h (TLC control: heptane-EtOAc 1:1; Rf: **12**-0.40, **13**-0.22). The mixture was allowed to warm to r.t. for 1 h, quenched with saturated solution of sodium bicarbonate, concentrated under reduced pressure, diluted with 1M HCl, and extracted with methylene chloride. The combined extracts were washed with water, brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel. Elution with heptane-ethyl acetate (1:2) afforded 24 mg (5%) of starting keto-aldehyde **12** and 440 mg (1.82 mmol, 91%, 96% based on recovered **12**) of diol **13 m.p.**: 107-108°C (pentane-ether). $[\alpha]_D$: -21 (*c* 0.9). **IR** (nujol): 3356, 2951, 1722, 1460, 1450, 1260, 1080, 1050 cm^{-1}. **^{1}H-NMR** (400MHz): 1.07 (3H, s, Me-15α); 1.16 (3H, s, Me-15β), 1.32 (3H, s, Me-12); 1.37 (1H, ddd, J=4.0, 6.6, 12.8, H-14ax); 1.53 (1H, dd, J=8.1, 14.9, H-10α); 1.58 (1H, m, H-13eq); 1.97 (1H, ddd, J=3.5, 7.4, 14.9, H-10β); 2.00 (1H, m, H-13ax); 2.07 (1H, dd, J=5.8, 13.6, H-14eq); 2.12 (1H, dd, J=1.4, 7.3, H-11); 2.63 (1H, br.s); 2.87 (1H, br.s); 3.65 (3H, s, CO_2Me); 3.83 (1H, dd, J=3.6, 8.1, H-2). **^{13}C-NMR** (62.5MHz): 21.6 (Me-15β) , 25.1 (Me-15α), 25.6 (Me-12), 27.5 (C-13), 30.4 (C-14), 37.1 (C-10), 43.9 (C-15), 46.8 (C-12), 49.6 (C-11), 51.9 (CO_2Me), 73.4 (C-2), 78.6 (C-1), 178.0 ($\underline{C}O_2$Me). **EIMS**: 242 ($M^{+\cdot}$, 65), 227 (4), 224 (8), 210 (100), 183 (23), 167 (31), 165 (39), 142 (64), 139 (63), 101 (58), 59 (8). **HREIMS**: calc. for $C_{13}H_{22}O_4$ m/z 242.1518, found 242.1513.

Preparation of the key intermediate 4: To a stirred solution of oxalyl chloride (0.45 mL, 5.158 mmol, 1.55 eq.) in dry methylene chloride (10 mL) under argon at -60°C was added a solution of 0.75 mL (10.569 mmol, 3.18 eq.) of dimethyl sulfoxide in dry methylene chloride (5 mL) during 5 min. The mixture was stirred at -60°C for 10 min, a solution of 400 mg (1.661 mmol) of alcohol **13** in dry methylene chloride (5 mL) was added, and stirring at -60°C was continued for 15 min. Triethylamine (1.5 mL, 10.762 mmol, 2.09 eq.) was added, cooling stopped, and the temperature of the reaction mixture was rapidly (2-3 min) increased to 0°C. After dilution with water, the aqueous layer was extracted with methylene chloride (TLC control: heptane-EtOAc 1:1 Rf: **13**=0.22, **4**=0.34). The combined extracts were washed with 1 M hydrochloric acid, water, saturated sodium bicarbonate, brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography. Elution with heptane-ethyl acetate 1:1 afforded 365 mg (1.52 mmol, 91%) of α-ketol **4: m.p.**: 71-72°C (pentane). $[\alpha]_D$: +43 (*c* 1.0). **IR** (nujol): 3436, 2977, 2937, 2904, 2851, 1742, 1722, 1456, 1377 cm^{-1}. **^{1}H-NMR** (400MHz): 0.92 (3H, s, Me-15α); 1.33 (3H, s, Me-15β); 1.46 (3H, s, Me-12); 1.48 (1H, m, H-14eq); 1.73 (1H, m, H-13eq); 1.79 (1H, d, J=19.5, H-10α); 2.06 (1H, dt, J=6.4, 14.6, H-13ax); 2.14 (1H, dt, J=6.1, 12.8, H-14ax); 2.45 (1H, d, J=7.6, H-11); 2.55 (1H, dd, J=7.6, 19.5, H-10β); 3.66 (3H, s, CO_2Me). **^{13}C-NMR** (62.5MHz): 20.9 (Me-15β), 25.4 (Me-15α), 25.6 (Me-12), 27.8 (C-13), 29.4 (C-14), 39.8 (C-10), 42.9 (C-15), 46.3 (C-11), 46.9 (C-12), 52.1 (CO_2Me), 82.6(C-1), 178.9 ($\underline{C}O_2$Me), 218.8 (C-2). **EIMS**: 240, ($M^{+\cdot}$, 3), 212 (100), 180 (67). **HREIMS**: calcd for $C_{13}H_{20}O_4$ m/z 240.1361, found 240.1368.

Protection of the C-1 hydroxy group: To an ice-cold solution of **4** (1.0 g, 4.16 mmol) in 50 mL of dry

methylene chloride, under argon, was added chloromethyl methylether (1.34 g, 16 mmol, 4 eq) and diisopropylethylamine (2.226 g, 17.5 mmol, 4.2 eq). The reaction mixture was allowed to warm and stirred at r.t. for 26 h (while TLC-monitored), then quenched with water. The aqueous phase was extracted with methylene chloride and the combined organic layers were washed with dilute HCl, a saturated aq. solution of $NaHCO_3$ and brine. The combined organic extracts were dried over $MgSO_4$, concentrated and purified by column chromatography (ethyl acetate-heptane, 1:3) to give 1.10 g (3.87 mmol, 93%) of **15**: **m.p.**: 73-74°C (pentane ether). $[\alpha]_D$ -60 (*c* 1.1). **IR** (nujol): 2957, 2930, 2854, 1739, 1465, 1378, 1269, 1219, 1155, 1105, 1045, 1029, 989, 919 cm^{-1}. **^{1}H-NMR** (400 MHz): 1.02 (3H, s); 1.32 (3H, s); 1.45 (3H, s); 1.66 (1H, d, J=19.1); 1.75-2.15 (4H, m); 2.36 (1H, dd, J=7.9, 0.8); 2.52 (1H, dd, J=7.7, 19.1); 3.38 (3H, s); 3.66 (3H, s); 4.76 (1H, d, J=7.2); 5.29 (1H, d, J=7.2). **^{13}C-NMR** (62.5 MHz): 21.2 (2 Me), 25.5, 26.2, 27.6, 40.9, 43.5, 46.4, 46.8, 52.0, 55.1, 86.0, 92.0, 177.7, 217.3. **EIMS**: 284 ($M^{+\cdot}$, 2), 256 (56), 253 (17), 239 (3), 224 (13), 211 (8), 200 (80), 197 (54), 179 (68), 169 (24), 165 (22), 151 (50), 141 (50), 140 (100), 133 (40), 121 (49), 109 (57), 96 (28), 81 (22), 45 (86). **HREIMS**: calcd for $C_{15}H_{24}O_5$ m/z 284.1623, found 284.1606.

Aldol condensation of 4+14: the α–ketol rearrangement: In a two-necked flask, equipped with a Dean-Stark apparatus, was placed a solution of **4** (300 mg, 1.25 mmol) in 30 mL of dry benzene to which was added **14** (300 mg, 2.5 mmol, 2 eq.) and pTosOH (220 mg, 1.25 mmol, 1 eq.). The reaction mixture was refluxed for 4 h, then cooled to room temperature, quenched with a saturated aq. solution of $NaHCO_3$, benzene was removed under reduced pressure and the residue was taken in methylene chloride, and worked up as usual. Purification on silica gel (ethyl acetate-heptane, 1:4) gave a 72% yield (216 mg, 0.9 mmol) of the rearranged ketol **16** together with 27 mg (0.112 mmol, 9%) unreacted starting material. Under identical conditions the C-1 MOM-protected derivative **15**, gave after deprotection during the reaction, the same compounds, with the same yields. Finally heating **4** or **15** in benzene, in the presence of pTosOH afforded cleanly the α-ketol rearrangement. **16**: **m.p.**: 86-88°C (pentane-ether). $[\alpha]_D$ +52 (*c* 1.0). **IR** (film): 3455, 2957, 1746, 1731, 1634, 1477, 1458, 1389, 1271, 1193, 1170, 1108, 1054, 1021, 982, 914, 775 cm^{-1}. **^{1}H-NMR** (400 MHz): 1.22 (3H, s); 1.29 (3H, s); 1.31 (3H, s); 1.39 (1H, ddd, J=6.2, 13.5, 14.5); 1.57 (1H, d, J=12.6); 1.62 (1H, dddd, J=1.4, 3.0, 6.2, 12.2); 1.98 (1H, ddd, J=6.4, 12.4, 13.2); 2.24 (1H, ddd, J=3.0, 5.4, 12.6); 2.31 (1H, ddt, J=1.6, 6.4, 14.6); 2.46 (1H, dd, J=5.0, 17.0); 2.79 (1H, s); 3.75 (3H, s). **^{13}C-NMR** (75 MHz): 21.2, 24.8, 28.1, 28.6, 35.3, 39.1, 47.3, 47.5, 48.2, 52.0, 78.8, 176.9, 223.4. **EIMS**: 240 ($M^{+\cdot}$, 12), 212 (100), 180 (27), 169 (6), 152 (15), 112 (35), 107 (16), 97 (9), 79 (10), 69 (13), 55 (6). **HREIMS**: calcd for $C_{13}H_{20}O_4$ m/z 240.1361, found 240.1356.

Preparation of aldol 17, the A-C ring linking: To a solution of diisopropylamine (0.28 mL, 2.025 mmol, 1.56 eq.) in dry THF (3 mL) under argon at -30°C was added 1.27 mL (2.025 mmol, 1.15 eq.) of 1.6 M n-BuLi in hexane. After stirring the mixture at -30°C for 15 min, a solution of **15** (500 mg, 1.76 mmol) in dry THF (5 mL) was added, the mixture was stirred at -40°C for 2.5 h, cooled to -78°C, and 3-formyl-cyclohex-2-en-1-one (655 mg, 5.28 mmol, 3 eq.) was added. The mixture was stirred at -78°C for 10 min, quenched with saturated aqueous solution of ammonium chloride (2 mL/mmol), and extracted with methylene chloride. The combined extracts were washed with 1M hydrochloric acid and following usual work up the residue was purified by flash chromatography on silica gel (ethyl acetate-heptane, 1:1) to afford 575 mg (1.408 mmol, 80%) of the *threo* aldol (C10/C9 bonding from the convex face of the molecule) together with unreacted starting material (85 mg, 17%). **17**: $[\alpha]_D$ -131 (*c* 1.0). **IR** (film): 3479, 3037, 2951, 2891, 2825, 1729, 1671, 1633, 1455, 1434, 1393, 1347, 1327, 1269, 1218, 1190, 1156, 1111, 1050, 987, 967, 920, 894, 863, 784, 735 cm^{-1}. **^{1}H-NMR** (400 MHz): 1.12 (3H, s); 1.33 (3H, s), 1.43 (3H, s); 1.70-2.60 (12H, m); 3.39 (3H, s); 3.58 (3H, s); 4.49

(1H, d, J=1.3); 4.57 (1H, d, J=8.7); 4.77 (1H, d, J=7.4); 5.25 (1H, d, J=7.4); 5.94 (1H, s). **^{13}C-NMR** (62.5 MHz): 21.4, 21.8, 24.5, 24.7, 25.8, 27.3, 27.5, 37.2, 43.7, 47.3, 49.5, 52.0, 53.6, 54.9, 77.6, 87.1, 91.8, 126.6, 162.2, 176.4, 199.3, 221.2 **EIMS**: 408 ($M^{+\cdot}$, 3), 380 (16), 318 (17), 256 (36), 151 (17), 142 (100), 124 (25). **HREIMS**: calcd for $C_{22}H_{32}O_7$ m/z 408.2148, found 408.2153.

Preparation of the unsaturated diol 19: To a suspension of $LiAlH_4$ (22.5 mmol) in 20 mL of anhydrous Et_2O, cooled at 0°C, was added dropwise a solution of acetoxyenone **18** (1.57 g, 5.62 mmol) in 10 mL anhydrous ether. After stirring at room temperature for 30-40 min (TLC monitoring) the mixture was diluted with wet Et_2O and treated with a small amount of 15% aq.NaOH solution. The organic layer was worked up as usual to give 1.32 g (5.51 mmol, 98%) of the desired diols after silica gel chromatography (ethyl acetate-heptane, 1:1).

Cascade transformations: A dry flask was charged with 4.108 g of diol **19** (15.8 mmol) and 21 g of $Pb(OAc)_4$ (47.4 mmol, 3 eq.) vacuumed, flushed with argon and cooled to nearly 0°C. Acetonitrile (60 mL) was added, the ice bath removed soon after and the mixture was stirred at room temperature for 15h, diluted with acetonitrile, filtered through Celite, the filtrate concentrated and purified by silica gel chromatography using ethyl acetate-heptane, 1:3 as an eluent to give **20** (4.612 g, 12.9 mmol, 82%): **m.p.**: 103-104°C (pentane-ether). $[\alpha]_D$ -33 (*c* 0.9). **IR** ($CHCl_3$): 2973, 2933, 1738, 1390, 1368, 1269, 1256, 1245, 1192, 1140, 1098, 1080, 976, 951, 937, 917 cm^{-1}. **^{1}H-NMR** (400 MHz): 1.21 (9 H, s, tBu), 1.29 (3 H, s, Me-8), 1.58 - 1.77 (2H, m, H-5αeq and H-6βeq), 1.64 (1H, dd, J=1.6, 14.1, H-9β), 1.77 (1H, dd, J=2.6, 14.1, H9α), 1.88 (1H, ddt, J = 2.4, 4.8, 13.2 , H-6αax), 2.10 and 2.11 (6 H, s, Ac), 2.71 (1H, dt, J = 4.8, 13.0, H-5βax), 3.14 (1H, d, J=0.8, H-3), 3.29 (1H, t, J = 2.4, H-7), 5.32 (1H, t, J = 1.6, H-10), 6.42 (1H, d, J = 1.1, H-2). **^{13}C-NMR** (75 MHz): 21.2 and 22.5 (Ac), 25.4 (C-6), 25.7 (Me-8), 28.4 (C-5), 28.9 (tBu), 36.1 (C-8), 36.7 (C-3), 39.6 (C-9), 72.7 (C-7), 73.5 (tBu), 90.8 (C-2), 92.6 (C-10), 104.2 (C-4), 169.2 and 169.6 (Ac). **CIMS**: 297 [(M+H)-AcOH, 99], 57 (100). **HRCIMS**: calc. for $C_{16}H_{25}O_5$ [(M+H)-AcOH] m/z 297.1701, found 297.1693

X-ray structure determination of 20: $C_{18}H_{28}O_7$: Mr=356.42, orthorhombic, $P2_12_12_1$, a=7.969(4), b=9.533(4), c=24.921(3) Å, V=1893(2) $Å^{-3}$, Z=4, D_x=1.250 Mg.m-3, λ(MoKα)=0.70926Å, μ=0.89 cm-1, F(000)=768, T=294 K. The sample (0.10*0.25*0.35 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 0,10 K 0,11 L -15,15, intensity controls without appreciable decay (0.3%) gave 1746 reflections from which 1013 independant with $I>2.0\sigma(I)$. After Lorenz and polarization corrections the structure was solved with Direct Methods which revealed the non hydrogen atoms of the molecule. After isotropic (R=0.13), then anisotropic refinement (R=0.086), the hydrogen atoms were found with a Fourier Difference (between 0.36 and 0.17 $eÅ^{-3}$). 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; 227 variables and 1013 observations; $w=1/\sigma(F_o)^2=[\sigma^2(I)+(0.04F_o^2)^2]^{-1/2}$) with the resulting R=0.068, R_w=0.066 and S_w=1.518 (residual $\Delta\rho \leq 0.24$ $eÅ^{-3}$). 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).

One pot preparation of the bicyclo[2.2.2]octanone 21: To a stirred solution of **20** (920 mg, 2.58 mmol) in a mixture of methanol (30 mL) and water (5 mL), was added potassium carbonate (2.0 g, 14.5 mmol, 5.62 eq.). The mixture was stirred at room temperature for 15 h, diluted with water, and extracted with methylene chloride. Following usual work up the residue was purified by flash chromatography on silica gel.

Elution with heptane-ethyl acetate (3:2) afforded 536 mg (2.37 mmol, 92%) of **21**: **m.p.**: 94-95°C (pentane). $[\alpha]_D$ +55 (*c* 1.3). **IR** ($CHCl_3$): 3418, 3018, 2977, 2929, 2872, 1710, 1391, 1365, 1216, 1196, 1088, 1043 cm^{-1}. **^{1}H-NMR** (400 MHz): 0.96 (3 H, s, Me-8), 1.18 (9 H, s, tBu), 1.44 (1H, ddd, J = 0.9, 2.4, 14.7, H-9), 1.69 (1H, ddd, J = 2.4, 3.4, 14.5, H-6), 1.91 (1H, dd, J = 1.5, 16.3, H-3), 1.91 (1H, ddd, J = 3.0, 8.9, 14.7, H-9'), 2.06 (1H, ddd, J = 2.6, 8.4, 14.6, H-6'), 2.41 (1H, m, H-5), 2.58 (1H, dd, J = 2.6, 16.2, H-3'), 3.32 (1H, ddd, J = 1.6, 2.3, 8.4, H-7), 4.16 (1H, ddd, J = 1.7, 3.6, 9.0, H-10). **^{13}C-NMR** (75 MHz): 23.5 (Me-8), 28.6 (tBu), 34.5 (C-6), 36.6 (C-8), 41.3 (C-9), 44.0 (C-3), 51.3 (C-5), 68.7 (C-10), 69.6 (C-7), 73.2 (Bu-t), 209.2 (C-4). **EIMS**: 226 ($M^{+\cdot}$, 15), 170 [(M-56), 44], 57 (100). **HREIMS**: calc. for $C_{13}H_{22}O_3$ m/z 226.1569, found 226.1570.

Reduction of 20 and selective acetonide formation: To a stirred suspension of lithium aluminum hydride (800 mg, 21.26 mmol, 3 eq.) in THF (40 mL) a solution of **20** (1.38 g, 4.05 mmol) in THF (20 mL) was added at -70°C. The mixture was stirred at -70°C for 3 h, then at room temperature for 6 h, quenched with 0.80 mL of water, 0.80 mL of 15% NaOH, 2.40 mL of water, and stirring was continued at room temperature for 1 h. Filtration and concentration under reduced pressure yielded a mixture of alcohols **22**. The latter was dissolved in dry acetone (100 mL) and 100 mg of camphorsulfonic acid (CSA) was added. The mixture was stirred under argon at room temperature for 24 h. To this mixture was added solid $NaHCO_3$ (2.0 g), the acetone evaporated off and the residue was extracted with ethyl acetate. The organic layer was washed successively with water, a saturated aq. solution of $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and the filtrate was concentrated under reduced pressure to give a mixture of **5a** and **5b** (972 mg, 3.24 mmol, 80% combined yield and 9:1 ratio. The residue was purified by flash chromatography on silica gel. Elution with heptane-ethyl acetate 3:1 afforded 875 mg (2.9 mmol, 72%) of the first eluting major-*syn* acetonide **5a**: **m.p.**: 72-73°C (pentane-ether). $[\alpha]_D$ +59 (*c* 1.0). **IR** ($CHCl_3$): 3444, 3019, 2976, 2939, 2875, 2360, 1384, 1364, 1251, 1216, 1192, 1161, 1102, 1067, 1045, 1001 cm^{-1}. **^{1}H-NMR** (250 MHz): 1.00 (3H, s, Me-8), 1.15 (9H, s, tBu), 1.38 (1H, m, H-3), 1.40 and 1.45 (6H, s, CMe_2), 1.40 - 1.56 (2H,m, H-5_{eq},6), 1.93 (1H, m, H-6'), 2.12 (1H, m, H-5_{ax}), 2.18 (2H, m, H-9,9'), 3.45 (1H, d, J = 3.8, H-7), 3.73 (2H, m, H-10,10'), 3.99 (2H, m, H-2,2'), 4.13 (1H, m, H-4). **^{13}C-NMR** (62.5 MHz): 19.0 ($C\underline{Me}_2$), 29.8 ($C\underline{Me}_2$), 23.0 (Me-8), 23.1, 25.3, 28.9 (tBu), 38.1 (C-3), 38.9 (C-8), 40.2 (C-9), 60.0 (C-10), 61.0 (C-2), 67.2 (C-4), 72.2 (C-7), 73.0 ($\underline{C_q}$-tBu), 98.1 (C_q of acetonide). **CIMS**: 301 [(M+H), 22], 243 [(M+H)-Me_2CO, 58], 169 (29), 151 (22), 57 (100). **HRCIMS**: for $C_{17}H_{33}O_4$ m/z 301.2379, found 301.2376; and 97.2 mg (0.32 mmol, 8%) of the second eluting minor-*anti* acetonide **5b**: $[\alpha]_D$ +49 (*c* 0.5). **IR** ($CHCl_3$): 3446, 3027, 2975, 2885, 1461, 1377, 1364, 1261, 1209, 1196, 1158, 1125, 1055, 1022 cm^{-1}. **^{1}H-NMR** (300 MHz): 0.94 (3H, s); 1.16 (9H, s); 1.39 (3H, s); 1.46 (3H, s); 1.39-2.00 (7H, m); 3.38 (1H, br.s, OH), 3.65-4.01 (6H, m). **^{13}C-NMR** (75 MHz): 19.4 (Me-19), 22.2 ($C\underline{Me}_2$), 26.0 (C-6), 26.4 (C-5), 28.8 (tBu), 29.7($C\underline{Me}_2$), 35.9 (C-9), 39.0 (C_q-8), 43.1 (C-3), 58.1 (C-10), 60.2 (C-2), 68.6 (C-4), 70.3 (C-7), 73.0 ($\underline{Cq}$-tBu), 98.0 (Cq of acetonide). **EIMS**: 300 ($M^{+\cdot}$, 0.5), 285 (3), 242 (8), 129 (100), 57 (73).

Preparation of the C-10 electrophile 23: To a stirred solution of t-BuOH (260 mg, 3.50 mmol) in THF (8.0 mL) was added a 2M in THF solution of EtMgBr (1.2 mL, 2.4 mmol, 4.6 eq.) at 0°C. The mixture was stirred at 0°C for 10 min and a solution of **5a** (157 mg, 0.522 mmol) in THF (2.0 mL) was added. The mixture was stirred at 0°C for 10 min and 340 mg (1.344 mmol, 2.6 eq.) of ADD (1,1'-(azodicarbonyl)dipiperidine) was added. The mixture was stirred at room temperature for 1 h, quenched with a saturated solution of NH_4Cl, extracted with methylene chloride. The combined extracts were worked up as usual. The residue was purified by flash chromatography on silica gel. Elution with heptane-ethyl acetate (4:1) afforded 137.5 mg (0.46 mmol,

89%) of **23**: **m.p.**: 52-53°C (pentane). $[\alpha]_D$ +68 (*c* 1.0). **IR** ($CHCl_3$): 2974, 2927, 2904, 2871, 1717, 1463, 1381, 1364, 1276, 1250, 1225, 1193, 1163, 1103, 1070, 1003 cm^{-1}. **^{1}H-NMR** (250 MHz): 1.17 (9H, s, t-Bu), 1.19 (3H, s, Me-8), 1.25 - 1.60 (3H, m, H-3,5_{eq},6_{ax}), 1.36 (3H, s, C$\underline{Me}_2$), 1.45 (3H, s, C$\underline{Me}_2$), 1.91 (1H, ddt, J = 1.5, 3.6, 14.0, H-6_{eq}), 2.12 (1H, m, H-5_{ax}), 2.88 (1H, dd, J = 3.4, 16.4, H-9), 3.12 (1H, dd, J = 1.9, 16.4, H-9'), 3.60 (1H, d, J = 2.6, H-7), 3.97 and 4.05 (AB of ABX, J_{AB}= 12.8, J_{AX}= 3.4, J_{BX}= 1.0, H-2, 2'), 4.14 (1H, m, H-4), 9.90 (1H, dd, J = 2.1, 3.4, H-10). **^{13}C-NMR** (62.5 MHz): 18.8 and 29.6 (C$\underline{Me}_2$), 23.2 (Me-8), 22.9, 25.0, 28.8 (tBu), 37.6 (C-3), 39.2 (C-8), 51.6 (C-9), 60.7 (C-2), 67.0 (C-4), 72.0 (C-7), 73.3 (C_q-tBu), 98.4 (C_q of acetonide), 203.7 (C-10). **EIMS**: 298 ($M^{+\cdot}$, 1), 242 (8), 185 (20), 127 (78), 57 (100).

Preparation of the C-9 electrophile 24: To a stirred suspension of KH (1.67 mmol, 3.55 eq. from a 35% suspension of KH in oil, washing with pentane) in DME (2.0 mL) was added a solution of **23** (140 mg, 0.469 mmol) in DME (2 mL) at -5°C. The mixture was stirred at -5°C for 15 min and added with a syringe to a suspension of AcCl (0.142 mL, 2.0 mmol, 4.26 eq.) and DMAP (1.0 mmol, 2.13 eq.) in DME (3 mL) at room temperature. The mixture was stirred at room temperature for 15 min, poured into an ice-water mixture, and extracted with heptane. The combined extracts were washed with water, saturated solution of $NaHCO_3$, brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was dissolved in methylene chloride (10 mL) and 50 µL of pyridine was added. Ozone was passed into this solution at -70°C until a blue color persisted, and triphenylphosphine (200 mg, 0.763 mmol, 1.63 eq.) was 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 - ether (5:1) afforded 81.2 mg (0.286 mmol, 61%) of **24**: **m.p.**: 63-64°C (pentane). $[\alpha]_D$ +75 (*c* 0.9). **IR** ($CHCl_3$): 2971, 2949, 2937, 2919, 2876, 1710, 1461, 1409, 1382, 1371, 1277, 1251, 1228, 1195, 1164, 1102, 1065, 1004, 964, 907 cm^{-1}. **^{1}H-NMR** (250 MHz): 1.10 (3H, s, Me-8), 1.17 (9H, s, tBu), 1.34 and 1.46 (6H, s, Me of acetonide), 1.48 - 1.61 (2H, m, H-5_{ax},6_{ax}), 1.69 (1H, m, H-3), 1.84 - 2.18 (2H, m, H-5_{eq},6_{eq}), 3.82 (1H, d, J = 3.1, H-7), 4.03 and 4.09 (AB of ABX, J_{AX}= 2.9, J_{AB}= 11.2, H-2, 2'), 4.12 (1H, m, H-4), 10.20 (1H, s, H-9). **^{13}C-NMR** (62.5 MHz): 19.1(C$\underline{Me}_2$), 19.2 (Me-8), 24.7, 25.3, 28.8 (tBu), 29.6 (C$\underline{Me}_2$), 40.1 (C-3), 52.4 (C-8), 61.0 (C-2), 66.9 (C-4), 69.2 (C-7), 73.6 (C_q-tBu), 98.9 (C_q of acetonide), 206.4 (C-10). **EIMS**: 269 [(M-15), 5], 198 (16), 153 (14), 142 (28), 124 (100).

25*Z*+26: To an ice cold solution of **19** (1.10g, 4.57 mmol) in acetonitrile (50 mL) was added $Pb(OAc)_4$ (4.0 g, 9.02 mmol, 1.97 eq.) under argon. The ice bath was removed and the mixture stirred at room temperature for 5 min, diluted with acetonitrile, filtered through Celite and concentrated to yield 1.044 g (4.38 mmol, 96%) of the dialdehyde **25*Z*** which can be rapidly characterized by its ^{1}H and ^{13}C-NMR spectra. **25*Z* : ^{1}H-NMR** (250 MHz) 1.17 (9H, s); 1.23 (3H, s); 1.69 (1H, m); 2.12 (1H, m); 2.66 (2H, m); 2.97 (1H, d, J=18.4, H-9); 3.126 (1H, d, J=18.4, H-9); 3.98 (1H, dd, J=6.0, 10.0, H-7); 5.92 (1H, d, J=7.8); 9.70 (1H, s, H-10); 10.01 (1H, d, J=7.8, H-2). **^{13}C-NMR** (62.5 MHz) 22.3, 28.4, 30.0, 32.4, 39.5, 52.4, 73.4 (C_q-tBu), 77.0 (C-7), 124.0, 173.3, 189.1, 200.2. On standing, an equilibrium was established in approximately 2 h, and the non-isolable tricyclic enol ether **26** was characterized as a mixture. **26**: **^{1}H-NMR** (250 MHz): 1.06 (3H, s); 1.13 (9H, s); 1.98 (1H, t, J=14.0); 1.50-2.20 (4H, m); 2.31 (1H, dd, J=5.1, 14.0); 3.93 (1H, dd, J=7.7, 10.8); 4.84 (1H, d, J=6.0); 5.63 (1H, d, J=5.1); 6.21 (1H, d, J=6.0). **^{13}C-NMR** (62.5 MHz): 13.6 (Me-19), 28.2, 28.6 (tBu), 32.7, 47.2 (C-9), 50.0, 72.2 (C_q-tBu), 78.8 (C-7), 91.8, 101.2, 106.4, 140.6. Upon treatment with 2 equiv. of $Pb(OAc)_4$ at r.t. in acetonitrile, this mixture (otherwise stable) afforded cleanly **20**.

$NaIO_4$ cleavage of diol 19: dialdehyde 25*E*: To a stirred solution of **19** (1.35g, 5.62 mmol) in a mixture of THF (40 mL) and water (10 mL) was added $NaIO_4$ (4.25 g, 19.87 mmol, 3.53 eq.). TLC control upon 5 min

stirring indicated the presence of **25*Z*** and **26**. Upon prolonged stirring the *Z*-dialdehyde (and thus the tricyclic enol ether **26**) disappeared. The mixture was stirred at room temperature for 2h, diluted with ether, and filtered through silica gel with heptane-ethyl acetate (1:1) to yield 1.149 g (4.83 mmol, 86%) of **25*E***: : $[\alpha]_D$ +16 (*c* 1.3). **IR** (film): 2976, 2935, 2907, 2878, 2835, 2748, 1721, 1675, 1639, 1611, 1460, 1391, 1365, 1256, 1234, 1196, 1144, 1102, 1075, 896 cm^{-1}. **^{1}H-NMR** (200 MHz): 1.10 (3H, s, Me-10); 1.17 (9H, s, tBu); 1.75, 2.10, 2.83, and 3.14 (4 H, m, H-5,5',6,6'), 2.62 (AB of ABX, $J_{AX,BX}$= 1.9, J_{AB}= 17, H-9,9'); 4.02 (1H, dd, J= 6.2, 8.8 H-7); 5.80 (1H, dt, J= 2.5, 7.7, H-3); 9.71 (1H, t, J = 1.9, H-10); 9.89 (1H, d, J= 7.7, H-2). **^{13}C-NMR** (50 MHz): 21.2 (Me-19), 26.5, 30.2, 28.5 (tBu), 48.7 (C_q-8), 50.7 (C-9), 73.5 (C_q-tBu), 75.4 (C-7), 122.0 (C-3), 175.0 (C-4), 190.9, 200.4. **EIMS**: 238 ($M^{+\cdot}$, 0.5), 198 (23), 182 (30), 57 (100).

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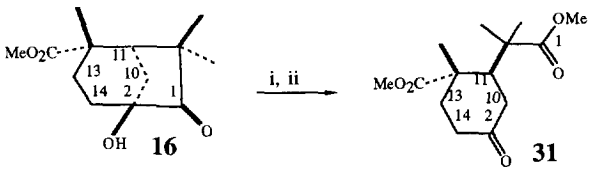
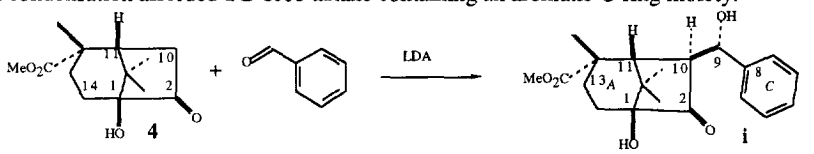
8. **16** (350 mg, 1.46 mmol) was subjected to an oxidative fragmentation (i: 680 mg $NaIO_4$, 20 mL THF-5 mL H_2O, 1 h, r.t.) and esterification (ii: excess CH_2N_2, Et_2O, 0°C) for further characterization, to give upon silica gel flash column chromatography (ethyl acetate-heptane, 1:3) **31** (315mg, 1.166 mmol, 80%). $[\alpha]_D$ +9 (*c* 1.0). **IR**: 2984, 2951, 1725, 1460, 1434, 1395, 1370, 1334, 1275, 1210, 1148, 1047, 987, 870, 815. **^{1}H-NMR**: 1.17 (3H, s); 1.19 (3H, s); 1.36 (3H, s); 1.77 (1H, m); 2.11 (1H, m); 2.28-2.53 (4H, m); 2.91 (1H, dd, J=4.5, 12.5, H-11); 3.66 (3H, s); 3.72 (3H, s). **^{13}C-NMR**: 17.1, 23.7, 24.6, 36.3 (CH_2), 37.6 (CH_2), 39.9 (CH_2), 45.0 (C_q), 45.4 (C_q), 47.5 (C-11), 51.9 ($CO_2\underline{Me}$), 52.1 ($CO_2\underline{Me}$), 177.1 ($\underline{C}O_2Me$), 177.8 ($\underline{C}O_2Me$), 210.2 (C=O). **EIMS**: 270 ($M^{+\cdot}$, 3), 256 (6), 239 (17), 211 (31), 210 (50), 185 (23), 169 (100), 155 (15), 151 (21), 149 (21), 141 (46), 109 (56), 102 (37), 91 (58), 81 (46), 57 (33), 55 (38).



9. Studying the reactivity of **4** in aldol type condensations we investigated the benzaldehyde as C-ring aldol partner. The aldol condensation afforded a B-seco taxane containing an aromatic C-ring moiety.



To a stirred solution of 3.3 mmol (3.3 eq.) of diisopropylamine in dry THF (18 mL) under argon at -30°C was added 3.2 mmol (3.2 eq.) of 1.6 M n-butyllithium in hexane. The mixture was stirred at -30°C for 15 min, a solution of 240 mg (1 mmol) of **(+)-4** in THF (10 mL) was added, the mixture was stirred at -30°C for 1 h, cooled to -70°C, and a solution of 5.0 mmol (5 eq.) of benzaldehyde in THF (5 mL) was added. The mixture was stirred at -70°C for 10 min, quenched with saturated solution of ammonium chloride at -70°C, and extracted with methylene chloride. The combined extracts were washed with 1M hydrochloric acid, water, brine, dried over sodium sulfate, and concentrated under reduced pressure The residue was purified by flash chromatography on silica gel (heptane - ethyl acetate, 2:1) to afford 240 mg (0.72 mmol, 72%) of **i** (TLC control: heptane-ethyl acetate, 1:1, Rf: **(+)-4** - 0.30, **i** - 0.19): $[\alpha]_D$ +8 (*c* 0.8). **IR** (film): 3420, 2931, 1656, 1600, 1488, 1125 cm^{-1}. **^{1}H-NMR** (200 MHz): 1.15 (3 H, s); 1.31 (3H, s); 1.36 (3H, s); 1.30-2.40 (5 H, m); 2.32 (1 H, br.d, J= 9.0, H-10); 2.65 (1H, br.s, OH); 2.92 (3 H, s, $CO_2\underline{Me}$); 4.57 (1H, br.s, OH); 4.95 (1 H, d, J= 9.0, H-9); 7.35 (5 H, m, Ph). **^{13}C-NMR** (50 MHz): 21.7, 26.1, 27.7, 28.0, 29.1, 45.0, 47.1, 49.6, 52.3, 56.5, 77.5, 127.2, 128.1, 128.6, 176.4, 221.1. **CIMS**: 347 [(M+H), 3], 329 [(M+H)-H_2O, 74], 241 [(M+H)-PhCHO, 46], 57 (100). **HRCIMS**: calc. for $C_{20}H_{25}O_4$ [(M+H)-H_2O] m/z 329.1752 found 329.1748.

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