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A practical access into conveniently functionalized, homochiral C-ring system of taxuyunnanine C

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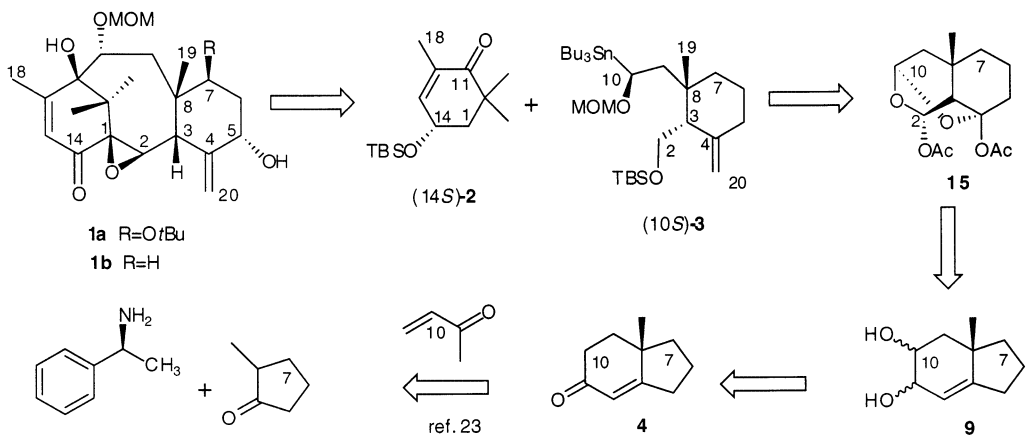
Abstract—The preparation of a homochiral 7-nor taxoid C-ring framework, to be used in an A+C approach for the synthesis of low oxygenation pattern taxoids with an exocyclic olefin at C(4)–(20) and oxygenation at C(14), is described. Retrosynthetic analysis associated with the preparation of **3** has been designed around the targets **11** and **15** which could be produced by functional group manipulation starting from the known hydrindenone **4**, obtained with a moderate e.e. (ca. 70%). A lipase was used to perform clean and high yield saponification on its corresponding acetoxy enone, while chemical resolution of the resulting acyloins allowed straightforward access to diastereomerically pure material.

1. Introduction

Taxoids have been the subject of immense interest and six total syntheses of taxol have been published to date.[1] We reported recently a concise synthesis of **1a**, corresponding to a taxoid ABC building block common to various taxoid representatives.[2] This 'A+C' strategy[3] is exemplified by the seven-step construction of **1a** and further by a modular approach which provides a convenient handle for the step-efficient preparation of various representatives of the taxane family (Scheme 1).

Our initial interest in this area was stimulated by the need for rapid entry to a variety of heavily substituted optically homogeneous six-membered ring systems as precursors of the taxoid left-half and right-half building blocks.[4] The key element of our retrosynthetic strategy was the use of a new ring expansion/rearrangement methodology developed in our laboratory.[5] The utility of these domino transformations[6] with regard to the synthesis of biologically active natural products was demonstrated by the practical syntheses of skeleton-modified steroids,[7] by the construction of a fully func-



Scheme 1.

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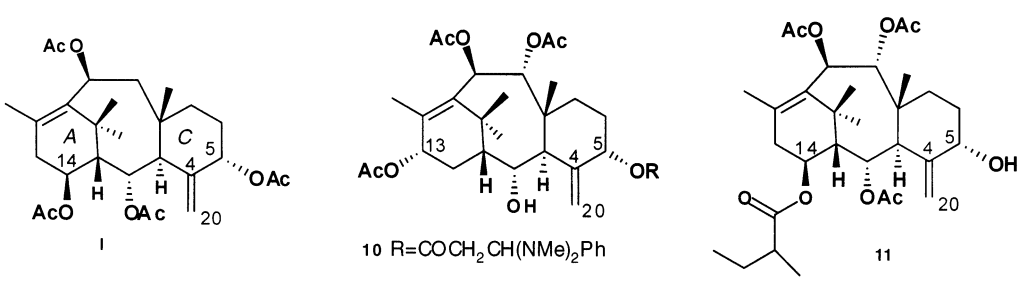
tional taxoid C-ring intermediate and its use in the synthesis of advanced taxoid ABC frameworks.[8] The C-ring has to contain a functional moiety that could ultimately be used to introduce the C(20) carbon offering further elaboration towards oxirane-, oxetane- or olefin-containing taxoid families. To extend this methodology to natural taiwanxan type 7-nor taxoids,[9] such as taxuyunnanine C **I**,[10] 2,7-deacetoxyaustrospicatine **10**[11] and taiwanxan **11**,[12] modification of the C-ring had to be addressed based on our earlier models (Scheme 2).

Taxoids related to taxuyunnanine C, differing only in their C(2), C(3), C(4) and C(14) ester parts (either H, acetyl, propionyl or 2-methylbutyryl) have NGF-like activity and have been claimed to be useful for the treatment of Alzheimer's disease.[13] On the other hand, 2,7-deacetoxyaustrospicatine **10** is reported to be a potent inhibitor of the P-glycoprotein efflux-function, acting as MDR-resistance reversing agents.[14] Closely related taxoids such as taxuspine C and 2-deacetoxy taxinine[15] are also highly effective for binding to the glycoprotein, thus inhibiting the influx of the antitumor drug from the cancer cells. These taxoid diterpenes differ from the representatives of the oxetane family, for the D-ring has not been formed. Our retrosynthetic analysis calls for taxoid **1b** to be assembled from the left- and right-half fragments **2** and **3**, respectively. Fragment **2**, (*S*)-phorenol is a versatile intermediate used in the synthesis of carotenoids, degraded carotenoids[16] and (+)-absicic acid.[17] We considered that α-alkoxyorganostannane **3** should be available from **4**[18] by treatment of its derivative, the unsaturated 1,2-diol **9**, with $Pb(OAc)_4$ and subsequent elaboration of the resulting ring-expanded intermediate **15** according to our published procedure (Scheme 1). The need to generate large quantities of diastereomerically pure **3** dictated the way advance was made towards its acquisition. To this end, we attempted enzymatic hydrolysis on scalemic **5** to circumvent problems encountered during acetate hydrolysis and classical techniques of resolution of the resulting acyloins **7**, with the aim to ensure enantiomeric purity as early as possible in the synthetic scheme. Herein, we report additional studies which further establish the synthetic utility of the $Pb(OAc)_4$-mediated oxidative cleavage of selected unsaturated 1,2-diols for the construction of the taxoid C-ring precursor **3**, offering C(10) and C(2) linking possibilities, for the top and bottom side linking, respectively.

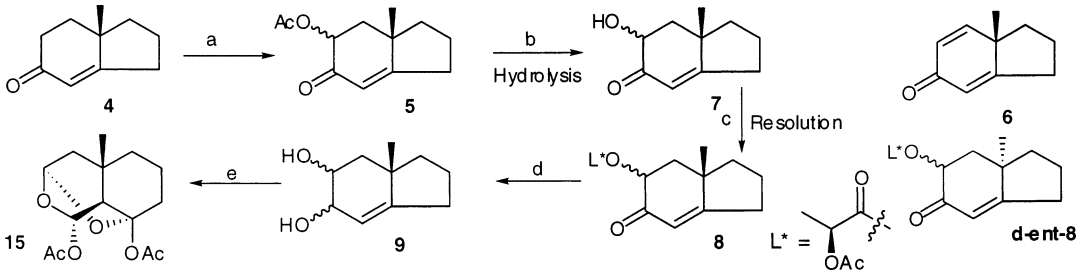
2. Results and discussion

The problem to be addressed was the construction of two appropriately functionalized cyclohexane derivatives such as (14*S*)-**2** and (10*S*)-**3**, the left- and right-half of the taxoid diterpene skeleton, respectively. To accomplish this task, we took advantage of the strategy developed previously, in which the C-ring precursor was derived from the 7-nor Hajos–Parrish ketone derivative **9** by means of a one-pot $Pb(OAc)_4$-mediated multistage transformation. Our right-half targets were analogues of the Hajos–Parrish ketone-derived[19] series, for which a successful synthetic route to taxanes was described.[2] α-Alkoxystannanes[20] were investigated as readily available and function-reach substrates. Analysis of structure **1b** in terms of the route summarized in Scheme 1 shows that the appropriate starting materials are the known (14*S*)-*O*-TBDMS-protected phorenol **2**[21] and the hydrindene diol **9**, which, to the best of our knowledge, is not described in the literature. As for the identical protecting groups on both segments, previous work had showed that a TBS protecting group at C(2) (right-half moiety) and C(14) (left-half moiety) was suitable, as they are removed simultaneously before the crucial intramolecular aldol step. The substrates were prepared according to the general route shown in Scheme 3. The first step involved acetoxylation of the enone with $Pb(OAc)_4$. Conversion of the resultant acetoxyenones **5** into the corresponding diols **9** under lithium aluminium hydride reduction conditions and treatment with $Pb(OAc)_4$ then provided the ring-expanded intermediate **15**, to be used as a taxoid C-ring precursor.

The synthesis of initial substrates **5** began with (*S*)-hydrindenone **4**, available in 72% e.e. through deracemizing alkylation catalyzed by (*R*)-(1)-phenylethylamine.[22] The low e.e. obtained and the tedious recrystallizations needed to increase the e.e. to acceptable levels led us to develop a practical alternative route where enzymatic hydrolysis is used as a simple basic reagent to promote clean high-yielding saponification, while enantiomeric purity is ensured on the derived acyloins by chemical resolution using lactate derivatives. Thus, rather than proceeding as described in the literature,[23] to increase the low e.e. of **4**, we went on subjecting the scalemic mixture to $Pb(OAc)_4$-mediated α-acetoxylation (3.5 equiv., 4 days at reflux in dry benzene, under argon). Scalemic 10α- and 10β-acetoxyenones **5** were obtained in 78% yield



Scheme 2.

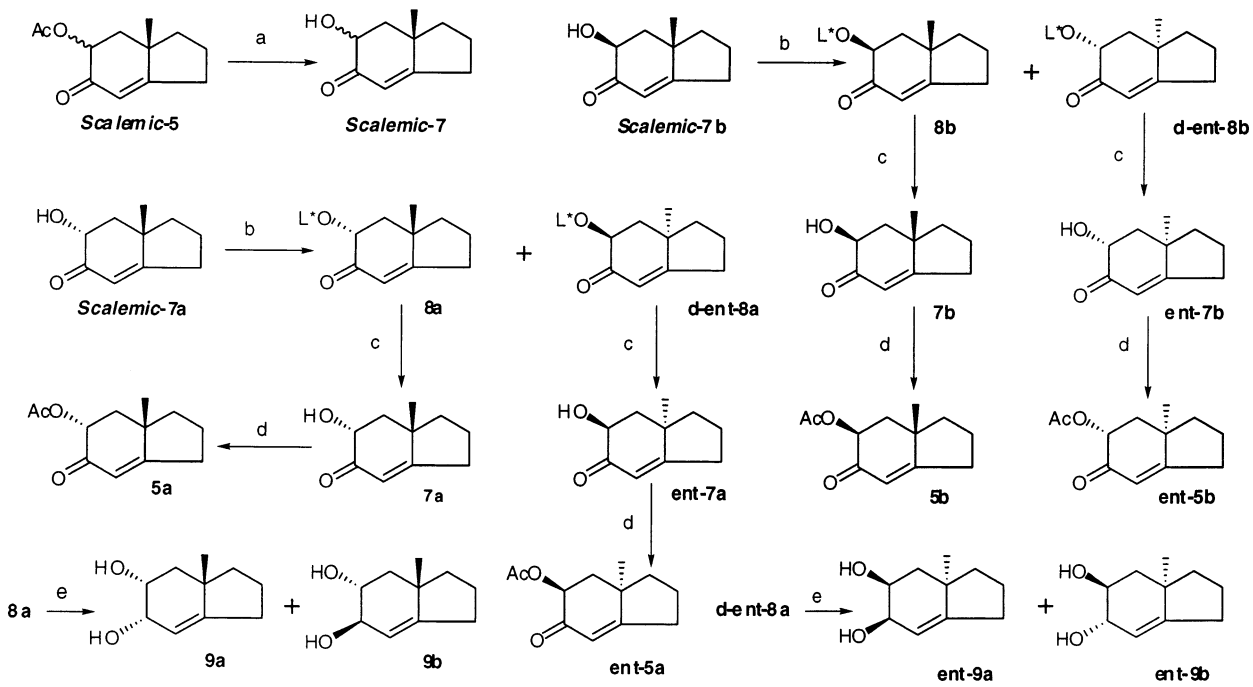


Scheme 3. (a) $Pb(OAc)_4$, PhH, reflux; (b) HLE, pH 7, rt; (c) (*S*)-2-acetoxypropionyl chloride, Et_3N, DMAP, CH_2Cl_2, 0°C; (d) $LiAlH_4$, Et_2O, 0°C; (e) $Pb(OAc)_4$, MeCN, rt.

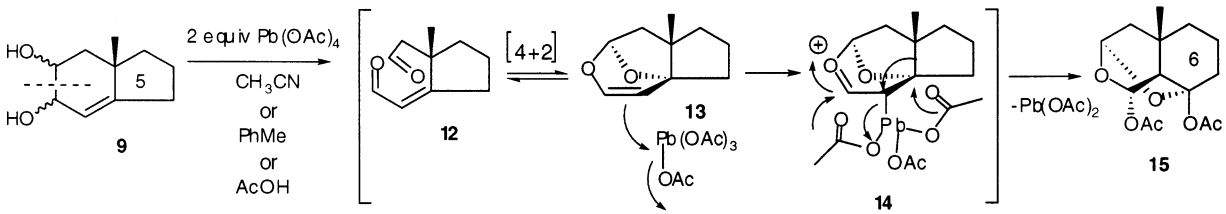
(epimeric mixture of α- and β-acetates, ca. 60:40 ratio) along with side product **6** arising from acetate elimination.[24] The acetoxyenones thus obtained formed an epimeric mixture which was difficult to separate in large scale preparations. However, the corresponding acyloins **7** were easily separated at larger scale by silica gel column chromatography as were the corresponding lactate derivatives **8**. This was suggestive of a resolution at the acyloin level, provided that acetate hydrolysis could be accomplished in high yields on a large scale. Both chemical and enzymatic hydrolysis protocols have been described to access α-ketols. Chemical hydrolysis (K_2CO_3–MeOH) performed on small scales led to some epimerization leading at room temperature mainly to the 10α-alcohol, while at 0°C to a 4:1 mixture of α- and β-alcohols was obtained. A further drawback of chemical hydrolysis is that upon scale-up a considerable amount of unidentified rearrangement products were obtained. Difficulties in saponifying acetyl esters having a carbonyl group in the α-position have been noted previously, but were circumvented by us using a lipase. We thus focused on a lipase-mediated hydrolysis and therefore started screening a number of relatively inexpensive lipases, searching simply for a high-yield hydrolysis.[25] *Horse liver esterase* (*HLE*, acetone powder) cleaved the acetates cleanly, affording the desired acyloins in quantitative yield. Even though enantioselective hydrolysis was possible by varying the experimental conditions, we preferred chemical resolution via the lactate derivatives **8**,[26] which are easily separable by chromatography, thus affording diastereomerically pure material straightforwardly. The scalemic α-acetoxyenones **5** were first purified by silica gel column chromatography to remove the side product **6** formed during the acetoxylation process. Lipase-catalyzed hydrolysis of scalemic acetoxy enone **5** was then carried out under various conditions. We found that a 10:1 ratio of substrate to lipase was enough to hydrolyze both (*R*)- and (*S*)-acetates at room temperature in phosphate buffer after overnight stirring (only 10% of the starting material was left unreacted). Using equal masses of the substrate and the enzyme preparation did not affect the result to an appreciable extent. In a typical experiment 10 g of substrate and 2 g of the lipase (20% *HLE* by weight) were stirred magnetically on the bench (no need for an incubator/shaker) in 1 L of phosphate buffer pH 7, in the presence of a small amount of toluene to solubilize the sample (but this is not even necessary) to afford quantitative yields of the acyloins **7**. A key feature of this combined enzymatic hydrolysis/chemical resolution, where the enzyme is used as a simple basic reagent to perform saponification, is that multigram quantities can be easily prepared and excellent chemical yields are obtained, without any detectable formation of side products. Enantiodifferentiation of scalemic secondary alcohols **7a** and **7b** was carried out following chromatographic separation by diastereoselective derivatization with (*S*)-*O*-acetyllactyl chloride as a chiral auxiliary.[27] Thus, starting from **7a**, diastereomeric derivatization with (*S*)-2-acetoxypropionyl chloride in the presence of triethylamine and DMAP in dry CH_2Cl_2 at 0°C under an inert atmosphere afforded the corresponding esters **8a** (steroid series) and **d-ent-8a** (anti-steroid series) as a mixture of diastereomers, which were then separated by flash chromatography using toluene–ether (8:1) as eluent. Starting from **7b** and proceeding as above, lactates **8b** (steroid series) and **d-ent-8b** (anti-steroid series) were obtained and portions used for small-scale characterization purposes, while the remaining amounts were taken through to the next steps. All of the possible acyloins and α-acetoxy enones were obtained in diastereomerically pure form using the combined enzymatic hydrolysis/chemical resolution sequence outlined in Scheme 4.

Small quantities of the lactate derivatives **8** were carefully saponified (K_2CO_3, MeOH–H_2O, 10:1, −20°C) affording the corresponding acyloins **7**, while the major lactates **8a** and **8b** (steroid series) were reduced directly to the required unsaturated diols **9** ($LiAlH_4$, Et_2O, 0°C) prior to oxidative cleavage. On the other hand, acetylation at C(10) of the homochiral acyloins **7** thus obtained (Ac_2O, Py, DMAP, 0°C, 1 h) afforded 90–95% yields of the corresponding C(10) acetates **5**, for characterization.

Treatment of diastereomerically pure **9** (steroid series) with 2 equivalents of $Pb(OAc)_4$ in acetonitrile (room temperature, 15 h) followed by filtration through Celite and silica gel cleanly afforded the conveniently substituted cyclohexane (C-ring precursor) **15** in 82% isolated yield. This is a reliable procedure, which we have carried out several times on a multigram scale. The mechanism of this one-pot multistage transformation, resulting in ring expansion and functionality redistribution, has not been unequivocally established, but one reasonable possibility is outlined in Scheme 5. The presence of 2 equivalents of $Pb(OAc)_4$ is required for



Scheme 4. (a) HLE, pH 7, rt; (b) (*S*)-2-acetoxypropanoyl chloride, Et_3N, DMAP, CH_2Cl_2, 0°C; (c) K_2CO_3, MeOH–H_2O, 10:1, –20°C; (d) Ac_2O, Py, DMAP, 0°C; (e) $LiAlH_4$, Et_2O, 0°C. L* = $CH_3CH(OAc)CO$.



Scheme 5.

the synthesis of the ring-expanded product **15**; the first equivalent is used for the cleavage while the second is used in the oxyplumbation, which promotes ring expansion. A mechanistic rationale involves initial formation of **12** which collapses to **13** setting the stage for the next transformation, electrophilic attack of the metal to the olefin, leading to the formation of a carbon–lead bond in the transient organolead intermediate **14**. The strain associated with the ring system and the geometry in the transient organolead intermediate then favor ring expansion, with concomitant loss of a $Pb(OAc)_2$ unit and acylation. All of this occurs in one-pot, which makes an average 96% yield per transformation. The ability of Pb^{4+} to perform different tasks, acting as an oxidizing agent and as a Lewis acid, the low dissociation energy of the C–Pb bond (31 Kcal/mol) and the thermodynamically favorable valence change (redox potential of Pb^{4+}/Pb^{2+} is 1.7 V) account well for the proposed mechanism of the cascade transformation, even though this has not been convincingly established.[28]

The assembly of the target α-alkoxyorganostannanes **3** to be used as C(10) nucleophiles for the A+C linking was realized straightforwardly starting from the ring enlarged key intermediate **15** as follows. Conversion of **15** to **16**+**17** was accomplished by reduction with excess $LiAlH_4$ to the corresponding triol (epimeric mixture) and subsequent selective acetonide formation (acetone, *p*TosOH, rt, 24 h) in 78% combined yield and 3.5:1 ratio. Part of the mixture of acetonides thus obtained was easily purified on silica gel (eluent: ethyl acetate–heptane, 1:1) to afford pure *syn*-acetonide **16** (major isomer) and *anti*-acetonide **17** (minor isomer) for characterization, while the remaining crude was used in the next step without separation. Exposure of isopropylidene acetals **16**+**17** to benzyl bromide in the presence of sodium hydride at room temperature in dry DMF afforded a diastereomeric mixture of the corresponding C(10)-*O*-benzyl ethers **18**+**19** in 88% combined yield. This mixture was then converted to the aldehyde **24**, precursor of organostannanes **3** in five steps as follows. Acetonide cleavage on **18** and **19**, by treatment with 2N aqueous HCl–THF, 1:1, at 0°C to room temperature furnished the C(2),C(4) free diol (93%) as an epimeric mixture, which was used directly in the next reaction in the sequence. Subsequent selective protection of the latter by stirring in dry methylene chloride with *tert*-

butyldimethylsilyl chloride (TBDMSCl) in the presence of 4-DMAP at 0°C to room temperature for 2 h converted the primary hydroxyl group at C(2) to its *tert*-butyldimethylsilyl ether, in the presence of the free secondary alcohol at C(4) (98%). The C(20) carbon atom was then introduced via Swern oxidation (92%) which was followed by Tebbe[29] olefination (0.6 equivalents of commercial Tebbe reagent, THF, 0°C to room temperature) affording cleanly **22** (50% along with unreacted starting material, 47%) bearing the exocyclic C(4)–(20) olefin. Cleavage of the benzyl protective group using Li-NH_3(liq.) at −78°C afforded the corresponding alcohol **23** quantitatively. Swern oxidation provided the required aldehyde **24** in 93% yield. This material was converted to the organotin acetal in a two-step sequence using the Still protocol. Addition of *n*-Bu_3SnLi (1.1 equiv. prepared from equimolar quantities of *n*-Bu_3SnH and LDA) in dry THF followed by etherification with chloromethyl methyl ether in the presence of *i*-Pr_2NEt at room temperature in dry CH_2Cl_2, furnished the requisite α-alkoxyorganostannanes (10*S*)-**3** and (10*R*)-**3** as a diastereomeric mixture (C(10) epimers) in ca. 1:1 ratio and 75% combined yield (Scheme 6).

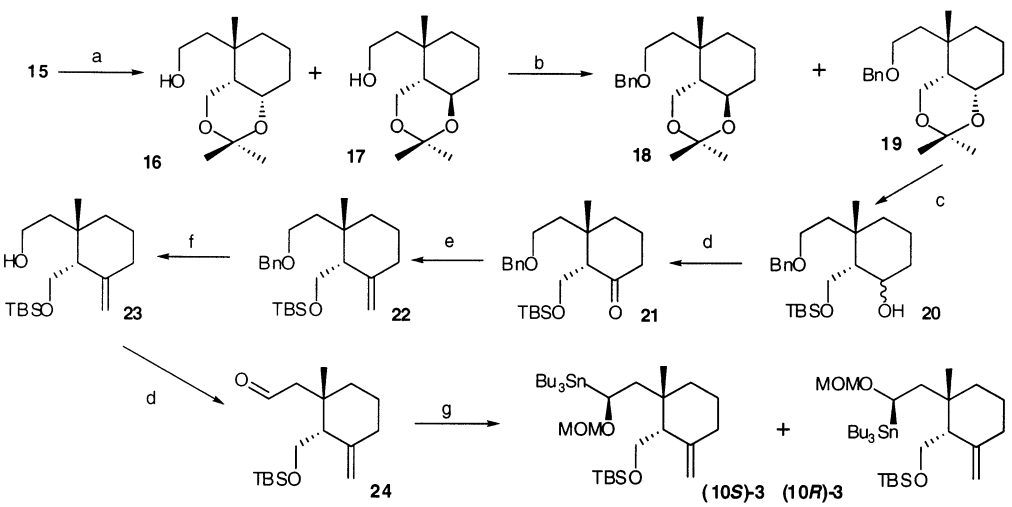
The specific rotations of all non-racemic substrates obtained in this process were in good agreement with those values measured on the Hajos–Parrish ketone derived analogues of known absolute stereochemistry. The configurations at C(10) were assigned by analogy to the Hajos–Parrish series on the basis of our previous work, where the C(10) absolute stereochemistry of the C(7)-*O*-*t*Bu analogues was established by their conversion to the taxoid ABC-ring system.

3. Conclusion

This paper reports the synthesis and characterization of new hydrindene derivatives and their use in taxoid C-ring construction. The original aim of our investigations in this area was to determine if implementation of the $Pb(OAc)_4$-mediated cascade methodology could lead to solutions of the length-problems in synthesizing stereodefined polysubstituted cyclic systems. The preparation of the desired C-ring precursor **3** in diastereomerically pure form demonstrates the applicability of this approach to various taxoid representatives. Furthermore, we provide complete characterization of all intermediates. The enantiomeric purity of (*S*)-hydrindenone **4** rests on that of (*R*)-hydrindenone; that compound was reported to have an e.e. of 90%.[18] Our route gives more reliable exact values as it is based on diastereomeric separation of lactate derivatives.

4. Experimental

Experiments which required an inert atmosphere were carried out under dry argon in a flame dried glass system. Solvents and reagents used in this work were purified according to standard literature techniques and stored under argon. THF and benzene were freshly distilled from $LiAlH_4$ and CaH_2, respectively, and were transferred via syringe. Methylene chloride was distilled from P_2O_5. Acetonitrile was distilled from CaH_2. Commercial reagents were purchased from Aldrich Chemicals and used as received. 'Usual work up' means washing of the organic layer with brine, drying over anhydrous $MgSO_4$, filtering and evaporating the filtrate in vacuo with a rotary evaporator at aspirator pressure. Optical rotations were recorded in $CHCl_3$ solution in a 1 dm cell using a JASCO P-1010 polarimeter. IR spectra were recorded on a Perkin Elmer BX FTIR instrument, neat or in chloroform. Melting points were taken on a Büchi B-540 melting point apparatus and are reported uncorrected. ^1H NMR spectra were obtained on Bruker AM300 instrument in $CDCl_3$. Chemical shifts are expressed in ppm downfield from TMS; the



Scheme 6. (a) $LiAlH_4$, THF, reflux, then acetone, *p*TosOH, rt; (b) BnBr, NaH–DMF; (c) 2N HCl–THF, 1:1, 0°C then DMAP, TBSCl, CH_2Cl_2, 0°C to rt; (d) DMSO, oxalyl chloride, Et_3N, CH_2Cl_2, −60°C; (e) Tebbe reagent, THF, 0°C to rt; (f) Li-NH_3(liq), THF, *t*BuOH, −78°C; (g) *n*-Bu_3SnLi, THF, −78°C then MOMCl, *i*-Pr_2NEt, 0°C to rt.

^{1}H NMR data, measured at 300 MHz, 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. ^{13}C NMR spectra were measured at 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.[30] Mass spectra (MS) are abbreviated as follows: electron impact spectra, EI, chemical ionization spectra, CI, fast atom bombardment FAB, spectra acquired in the positive ion mode under electron spray ionization (ES^+) using a mobile phase of methanol, ESIMS (MeOH), high resolution mass spectra, HR and are reported in the form: 'm/z (intensity relative to base peak = 100%)'. Microanalyses were performed by the microanalytical laboratory of this institute. 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 developed by immersion in 5% phosphomolybdic acid in 95% ethanol. Horse liver esterase was purchased from Sigma Chemical Co.

4.1. General procedure for the preparation of α-acetoxyenones

To enone **4** (68.5 mmol) in a three-neck flask, equipped with a Dean–Stark apparatus, was added $Pb(OAc)_4$ (225 mmol) and the reaction vessel was vacuum dried while flushed with argon. Freshly distilled benzene (240 mL) was then added and the reaction mixture was refluxed for 4 days under an inert atmosphere. After cooling to room temperature, a large volume of ether was added (five times the volume of the solvent) and the reaction mixture was stirred for an additional 1 h, filtered and the filtrate was washed with brine and water. The organic layer was then dried over anhydrous magnesium sulfate, concentrated under reduced pressure and chromatographed on silica gel. Yields for the acetoxylation were nearly quantitative, taking into account that byproduct **6** (22%; e.e. 72%) was formed from the acetoxy enones **5**. Dienone **6** was known in its racemic form, synthesized by treating the also known hydrindenone **4** with selenium dioxide according to the method of Bloom.[24] Later, Caine et al.[18] resynthesized racemic **6** and described its 60 MHz ^{1}H NMR spectrum in CCl_4. **6**: $[\alpha]_D$ −54 (c 1.42). IR (film): 2968, 1664, 1637, 1603, 1460, 1391, 1095, 981, 912, 866, 732 cm^{-1}. ^{1}H NMR: 1.20 (3H, s), 1.58 (1H, dd, J = 9.5, 11.2), 1.75–2.13 (3H, m), 2.48 (1H, ddd, J = 5.9, 9.5, 15.2), 2.80 (1H, dddd, J = 2.4, 5.4, 7.7, 11.0), 6.02 (1H, q, J = 1.8), 6.13 (1H, dd, J = 1.7, 9.8), 7.02 (1H, d, J = 9.8). ^{13}C NMR: 20.9, 25.6, 29.0, 34.8, 46.4, 121.9, 127.7, 153.5, 174.3, 186.8. EIMS: 148 ($[M]^+$, 92), 147 (46), 133 (54), 122 (38), 120 (79), 119 (47), 106 (32), 105 (99), 104 (56), 103 (46), 93 (29), 92 (95), 91 (100), 90 (52), 79 (76), 77 (84), 76 (36), 67 (21), 65 (71), 63 (61), 55 (59). HREIMS: calcd for $C_{10}H_{12}O$ 148.0888, found 148.0882.

4.2. General procedure for *horse liver esterase*-catalyzed hydrolysis of the acetates

The enone acetates **5**, obtained pure after silica gel column chromatography, were first recrystallized in ether, at 0°C. This precipitates only the α-acetate in quasi-racemic form ($[\alpha]_D$ +5), thus increasing the e.e. of the scalemic mixture. To a mixture of acetates (100 mg) in phosphate buffer (20 mM, pH 7, 30 mL) and toluene (1 mL) as co-solvent was added commercially available horse liver esterase (20 mg acetone powder) at room temperature. The mixture was stirred (magnetic stirrer) for 12 h monitoring the reaction by TLC. Typically the reaction was complete after 24 h. The mixture was diluted with ethyl acetate and filtered through Celite. The extract was washed with brine, dried over magnesium sulfate filtered and the filtrate concentrated in vacuo. The residue was chromatographed on silica gel.

This procedure can be scaled up without problem; the ratio of enzyme to substrate can in many cases be lowered to 0.1 without a marked effect on the rate of the reaction (nearly 90% hydrolysis along with unreacted starting material). We did not attempt enantioselective hydrolysis as chromatographic separation of the lactate derivatives was practical enough.

4.3. General procedure for preparation of the unsaturated diols by LAH reduction

To a suspension of $LiAlH_4$ (4 mmol) in anhydrous Et_2O (5 mL), cooled at 0°C, was added dropwise a solution of the acetoxyenone (1 mmol) in anhydrous ether (2 mL). After stirring at 0°C 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 the desired diols after silica gel chromatography (ethyl acetate–heptane, 1:1). The same procedure was used to directly reduce the lactates **8** into the diols **9**.

4.4. General procedure for the acetylation of the stereopure α-ketols 7

Acetic anhydride (0.3 mL) was added to a stirred mixture of the acyloins **7** (95 mg, 0.57 mmol) and DMAP (catalytic) in pyridine (2.0 mL) at 0°C under argon. After 50 min, the mixture was diluted with CH_2Cl_2 quenched with satd aq. $NaHCO_3$, washed with aqueous hydrochloric acid (1N), saturated sodium bicarbonate, water, brine and dried over magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was chromatographed (SiO_2, eluent heptane–EtOAc, 3:1) to give 113 mg (95%) of **5**. **5a**: mp: 53–55°C (heptane–ether). $[\alpha]_D$ +114 (c 2.28). IR (Nujol): 2970, 2867, 1753, 1696, 1635, 1463, 1380, 1227, 1145, 1110, 1070, 1046, 895, 875, 840, 704 cm^{-1}. ^{1}H NMR: 1.30 (3H, s), 1.55 (1H, dt, J = 8.1, 11.6), 1.78–2.03 (3H, m), 1.99 (1H, dd, J = 12.1, 13.4), 2.18 (3H, s), 2.30 (1H, dd, J = 5.3, 12.1), 2.50 (1H, m), 2.74 (1H, m), 5.59 (1H,

dd, $J=5.3$, 13.4), 5.84 (1H, t, $J=1.9$). ^{13}C NMR: 20.6, 20.8, 22.9, 30.3, 40.8, 42.0, 44.0, 70.7, 119.9, 170.2, 177.6, 193.3. EIMS: 208 ([M]$^+$, 1), 166 (2), 123 (14), 122 (100), 121 (28), 107 (16), 79 (34), 77 (23). Anal. calcd for $C_{12}H_{16}O_3$ C, 69.21; H, 7.74%; found: C, 69.04; H, 7.81%. **Ent-5a**: $[\alpha]_D$ −112 (*c* 2.24). **5b**: $[\alpha]_D$ +32 (*c* 1.55). IR (film): 2963, 1744, 1675, 1639, 1462, 1372, 1296, 1229, 1155, 1099, 1028, 972, 887, 863, 736, 702 cm^{-1}. ^1H NMR: 1.24 (3H, s), 1.46 (1H, dt, $J=8.2$, 11.8), 1.75–2.04 (3H, m), 1.98 (1H, dd, $J=5.7$, 14.9), 2.08 (3H, s), 2.31 (1H, dd, $J=1.9$, 14.9), 2.54 (1H, m), 2.77 (1H, m), 5.21 (1H, dd, $J=1.9$, 5.7), 5.90 (1H, t, $J=1.9$). ^{13}C NMR: 20.7, 21.0, 26.0, 30.8, 40.1, 40.4, 41.8, 69.7, 119.9, 169.6, 180.3, 192.5. EIMS: 208 ([M]$^+$, 16), 166 (47), 123 (69), 122 (100), 121 (87), 120 (34), 108 (19), 107 (79), 106 (30), 95 (42), 94 (69), 91 (72), 80 (57), 79 (92), 77 (82), 67 (52), 65 (63), 55 (70). **Ent-5b**: $[\alpha]_D$ −31 (*c* 1.18).

4.5. General procedure for mild hydrolysis of C(10) lactyl functionality: preparation of stereopure α-ketols

Diastereopure lactate derivative **8a** (377 mg, 1.34 mmol) was dissolved in MeOH (7 mL), K_2CO_3 (742 mg, 5.38 mmol, 4 equiv.) and then water (0.7 mL) were added at −25°C. After stirring for 55 min at this temperature (TLC monitoring) MeOH was evaporated under reduced pressure without heating and the residue was taken into ethyl acetate. Following washing with brine, the organic layer was dried over $MgSO_4$ and flash chromatographed (eluent heptane–EtOAc, 3:1) to yield **7a** (204 mg, 92%): $[\alpha]_D$ +122 (*c* 2.15). IR (film): 3475, 2964, 2936, 2864, 1674, 1637, 1463, 1422, 1379, 1275, 1218, 1169, 1110, 1074, 963, 922, 877, 840 cm^{-1}. ^1H NMR: 1.23 (3H, s), 1.50 (1H, dt, $J=7.9$, 11.6), 1.67–2.10 (4H, m), 2.41 (1H, dd, $J=5.4$, 12.2), 2.51 (1H, m), 2.71 (1H, m), 3.65 (1H, d, $J=1.6$), 4.34 (1H, ddd, $J=1.6$, 5.4, 13.1), 5.83 (1H, t, $J=1.9$). ^{13}C NMR: 20.2, 22.7, 30.5, 40.9, 44.0, 44.7, 69.2, 118.4, 179.7, 199.7. EIMS: 166 ([M]$^+$, 3), 123 (24), 122 (100), 121 (77), 120 (25), 107 (38), 94 (28), 93 (29), 91 (23), 80 (24), 79 (85), 78 (50), 77 (49), 76 (26), 66 (30), 65 (41), 55 (41). **Ent-7a**: $[\alpha]_D$ −121 (*c* 1.98). **7b**: mp: 71–73°C (heptane–ether). $[\alpha]_D$ +25 (*c* 1.35). IR (film): 3434, 3055, 2964, 1660, 1422, 1378, 1266, 1236, 1209, 1169, 1103, 1050, 963, 893, 846, 739, 704 cm^{-1}. ^1H NMR: 1.25 (3H, s), 1.51 (1H, dt, $J=8.3$, 11.6), 1.75–2.03 (3H, m), 2.01 (1H, dd, $J=6.6$, 14.4), 2.19 (1H, dd, $J=3.2$, 14.4), 2.52 (1H, m), 2.75 (1H, m), 3.04 (1H, m), 4.08 (1H, m), 5.89 (1H, t, $J=1.8$). ^{13}C NMR: 20.8, 27.0, 30.7, 40.1, 40.6, 42.3, 69.1, 118.6, 180.1, 198.6. EIMS: 166 ([M]$^+$, 4), 123 (25), 122 (100), 121 (60), 107 (50), 94 (33), 91 (29), 80 (27), 79 (85), 77 (60), 66 (31), 65 (39), 55 (28). Anal. calcd for $C_{10}H_{14}O_2$ C, 72.26; H, 8.49; found: C, 71.99; H, 8.47%. **Ent-7b**: $[\alpha]_D$ −24 (*c* 1.33).

4.6. Resolution of scalemic acyloins: preparation of lactate derivatives 8

Scalemic **7a** (6.64 g, 40 mmol) was dissolved in dry CH_2Cl_2 (400 mL) at 0°C; Et_3N (33 mL, 240 mmol, 6 equiv.), DMAP (9.77 g, 80 mmol, 2 equiv.) and 10 min later (*S*)-*O*-acetyllactyl chloride (18 mL, 160 mmol, 4 equiv.) were added at 0°C. After 25 min at this temperature (TLC monitoring) the reaction mixture was quenched with a saturated solution of aqueous $NaHCO_3$. Extraction with CH_2Cl_2, washing with 1N aq HCl, $NaHCO_3$, water and brine and finally drying over $MgSO_4$ afforded a crude residue from which the lactates were separated on silica gel (eluent toluene–ether, 8:1 to 6:1) to give 1.67 g (96% combined yield) of a mixture of lactates **8a** (steroid series, 952 mg, 89%) and **d-ent-8a** (anti-steroid series, 115 mg, 11%). **8a**: $[\alpha]_D$ +46 (*c* 4.16). IR (film): 2940, 1744, 1686, 1638, 1454, 1372, 1307, 1236, 1132, 1101, 1067, 1051, 1018, 949, 877 cm^{-1}. ^1H NMR: 1.22 (3H, s), 1.49 (1H, m), 1.49 (3H, d, $J=7.1$), 1.72–1.98 (4H, m), 2.04 (3H, s), 2.23 (1H, dd, $J=5.4$, 12.1), 2.45 (1H, m), 2.67 (1H, m), 5.12 (1H, q, $J=7.1$), 5.47 (1H, dd, $J=5.4$, 13.4), 5.75 (1H, t, $J=1.8$). ^{13}C NMR: 16.9, 20.5 (2C), 22.8, 30.2, 40.7, 41.6, 43.9, 68.6, 71.4, 119.7, 169.9 (2C), 177.7, 192.1. EIMS: 280 ([M]$^+$, 1), 187 (2), 166 (2), 123 (28), 122 (100), 121 (56), 115 (26), 107 (26), 94 (18), 93 (21), 91 (25), 87 (60), 79 (49), 77 (35), 67 (14), 65 (17), 56 (14), 55 (48), 44 (26), 43 (96), 41 (25). **d-Ent-8a**: mp: 68–69°C (heptane–ether). $[\alpha]_D$ −93 (*c* 1.98). IR (film): 2966, 2940, 2871, 1743, 1687, 1639, 1455, 1425, 1373, 1307, 1241, 1197, 1134, 1102, 1067, 1052, 1017, 878, 735 cm^{-1}. ^1H NMR: 1.38 (3H, s), 1.68 (1H, m), 1.71 (3H, d, $J=7.1$), 1.90–2.15 (3H, m), 2.24 (3H, s), 2.36–2.49 (2H, m), 2.60 (1H, m), 2.83 (1H, m), 5.20 (1H, q, $J=7.1$), 5.72 (1H, dd, $J=5.4$, 13.6), 5.91 (1H, bs). ^{13}C NMR: 16.9, 20.6 (2C), 22.9, 30.3, 40.8, 41.8, 44.0, 68.6, 71.2, 119.7, 170.3 (2C), 177.9, 192.5. EIMS: 280 ([M]$^+$, 2), 166 (3), 123 (35), 122 (100), 121 (53), 115 (15), 107 (34), 94 (20), 93 (25), 91 (31), 87 (45), 79 (54), 77 (41), 65 (19), 55 (40). Anal. calcd for $C_{15}H_{20}O_5$ C, 64.27; H, 7.19; found: C, 64.22; H, 7.27%. **8b**: $[\alpha]_D$ +39 (*c* 4.16). IR (film): 2964, 1749, 1675, 1637, 1456, 1373, 1296, 1239, 1194, 1133, 1099, 1052, 1018, 958, 918, 868, 733 cm^{-1}. ^1H NMR: 1.28 (3H, s), 1.49 (1H, m), 1.50 (3H, d, $J=7.1$), 1.77–2.01 (3H, m), 2.02 (1H, dd, $J=5.9$, 14.9), 2.13 (3H, s), 2.37 (1H, dd, $J=1.9$, 14.9), 2.56 (1H, m), 2.81 (1H, m), 4.99 (1H, q, $J=7.1$), 5.25 (1H, dd, $J=1.9$, 5.9), 5.92 (1H, t, $J=1.9$). ^{13}C NMR: 16.6, 20.5, 20.9, 26.3, 31.0, 40.0, 40.4, 41.9, 68.7, 70.5, 119.9, 169.9, 170.3, 180.8, 191.8. EIMS: 280 ([M]$^+$, 1), 166 (2), 123 (25), 122 (100), 121 (49), 115 (16), 107 (22), 94 (16), 93 (21), 91 (25), 87 (38), 79 (46), 77 (36), 67 (14), 65 (17), 55 (38). **d-Ent-8b**: $[\alpha]_D$ −42 (*c* 2.11). IR (film): 2965, 1747, 1675, 1639, 1456, 1373, 1267, 1240, 1168, 1132, 1098, 1051, 1018, 958, 884, 738, 704 cm^{-1}. ^1H NMR: 1.19 (3H, s), 1.47 (3H, d, $J=7.1$), 1.50 (1H, m), 1.74–2.17 (4H, m), 2.06 (3H, s), 2.24 (1H, dd, $J=1.9$, 15.1), 2.53 (1H, m), 2.74 (1H, m), 5.12 (1H, q, $J=7.1$), 5.28 (1H, dd, $J=1.9$, 5.8), 5.89 (1H, t, $J=1.9$). ^{13}C NMR: 16.8, 20.6, 20.9, 26.4, 31.0, 40.2, 40.4, 41.8, 68.6, 70.1, 120.1, 169.6, 170.0, 180.4, 191.6. EIMS: 280 ([M]$^+$, 1), 166 (2), 123 (16), 122 (100), 121 (29), 107 (16), 94 (10), 93 (14), 91 (19), 87 (33), 79 (34), 77 (26), 65 (10), 55 (19).

4.7. General procedure for the preparation of the unsaturated diols 9

To a suspension of $LiAlH_4$ (855 mg, 22.5 mmol) in anhydrous ether (20 mL), cooled at 0°C, was added

dropwise a solution of diastereomerically pure lactate **8a** (1.57 g, 5.62 mmol) in anhydrous ether (10 mL). The reaction mixture was stirred at 0°C for 1 h at which point no starting material remained (TLC monitoring), and then diluted with wet ether and treated with a small amount of 15% aq. NaOH solution. The organic layer was worked up as usual to give diols **9a** and **9b** as an epimeric mixture (915 mg, 97% combined yield) after filtration on silica gel (ethyl acetate–heptane, 1:1). **9a**: $[\alpha]_D$ +159 (*c* 0.60). IR (film): 3368, 2957, 2929, 1676, 1459, 1434, 1262, 1164, 1119, 1059, 1025, 1000, 980, 908, 894, 855 cm^{-1}. ^1H NMR: 1.02 (3H, s), 1.17–1.43 (2H, m), 1.39 (1H, t, $J=12.1$), 1.65–1.88 (4H, m), 1.81 (1H, dd, $J=3.7$, 12.1), 2.26 (1H, m), 2.45 (1H, m), 3.94 (1H, td, $J=4.0$, 12.5), 4.08 (1H, bs), 5.50 (1H, bs). ^{13}C NMR: 20.3, 23.9, 28.5, 39.8, 40.9, 43.5, 66.3, 67.6, 116.6, 154.5. **9b**: mp: 80–82°C (heptane–ether). $[\alpha]_D$ +3 (*c* 1.14). IR (film): 3350, 2957, 2930, 2858, 1680, 1460, 1375, 1113, 1058, 1022, 944, 877, 841 cm^{-1}. ^1H NMR (300 MHz): 1.04 (3H, s), 1.29 (1H, q, $J=10.7$), 1.47 (1H, t, $J=12.4$), 1.57–1.85 (3H, m), 1.91 (1H, dd, $J=3.6$, 12.4), 2.14 (1H, m), 2.38 (1H, m), 3.88 (1H, m), 4.08 (1H, bs), 4.37 (2H, bs), 5.18 (1H, bs). ^{13}C NMR: 20.6, 24.5, 28.0, 40.9, 43.1, 43.5, 72.2, 75.2, 117.9, 151.3. CIMS: 169 ($[MH]^+$, 29), 152 (10), 151 (100), 147 (7), 133 (92), 130 (10), 124 (25), 119 (10). Anal. calcd for $C_{10}H_{16}O_2$ C, 71.39; H, 9.59; found: C, 71.31; H, 9.52%. **Ent-9a**: $[\alpha]_D$ −152 (*c* 0.85). **Ent-9b**: $[\alpha]_D$ −3 (*c* 1.08).

4.8. Cascade transformations in acetonitrile

A dry flask was charged with the mixture of diols **9a**+**9b** (16.6 g, 99 mmol) and $Pb(OAc)_4$ (131.5 g, 297 mmol, 3 equiv.) the flask was placed under vacuum, flushed with argon and cooled to nearly 0°C. Acetonitrile (400 mL) was added, the ice bath was removed soon after and the mixture was stirred at room temperature for 24 h, diluted with acetonitrile, filtered through Celite, the filtrate was concentrated and purified by silica gel chromatography using ethyl acetate–heptane (1:2) as eluent to give **15** (24.5 g, 87%). Proceeding similarly but in different solvents, such as acetic acid, toluene or dichloromethane, the ring expanded compound was obtained in 75–85% isolated yields. **15**: mp: 77–79°C (heptane–ether). $[\alpha]_D$ −83 (*c* 1.08). IR (film): 2941, 1733, 1445, 1368, 1256, 1224, 1191, 1071, 1035, 981, 913, 840, 733, 648 cm^{-1}. ^1H NMR: 1.28 (3H, s), 1.31–1.87 (5H, m), 1.69 (1H, dd, $J=1.5$, 14.0), 1.84 (1H, dd, $J=2.8$, 14.0), 2.11 (3H, s), 2.12 (3H, s), 2.28 (1H, m), 2.75 (1H, s), 5.31 (1H, dd, $J=1.5$, 2.8), 6.47 (1H, d, $J=1.0$). ^{13}C NMR: 18.8, 21.2, 22.5, 27.8, 31.7, 33.4, 38.0, 39.6, 41.3, 90.6, 92.2, 104.1, 169.6 (2C). ESIMS (MeOH): 323 ($[MK]^+$, 5), 307 ($[MNa]^+$, 68). Anal. calcd for $C_{14}H_{20}O_6$ C, 59.14; H, 7.09; found: C, 58.97; H, 7.11%. **Ent-15**: $[\alpha]_D$ +82 (*c* 1.08).

4.9. Reduction of 15 and selective acetonide formation

To a stirred suspension of lithium aluminum hydride (11.9 g, 313 mmol) in THF (500 mL) a solution of **15** (17.8 g, 63 mmol) in THF (20 mL) was added at room temperature. The mixture was heated under reflux for 4 h and then stirred at room temperature for 6 h, the reaction was quenched with water, and after addition of 15% NaOH and water, stirred at room temperature for 1 h. Filtration and concentration under reduced pressure yielded a mixture of alcohols. A portion of the thus obtained alcohols (7.14 g, 38.0 mmol) was dissolved in dry acetone (310 mL) and *p*TosOH (723 mg, 3.8 mmol) was added. The mixture was stirred under argon at 0°C for 1 h. The reaction mixture was filtered through a pad of alumina using EtOAc–MeOH (9:1) as solvent, the filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel. Elution with heptane–ethyl acetate (1:1) afforded a 78% combined yield (in a 3.5:1 ratio). First eluting major-*syn* acetonide **16**: $[\alpha]_D$ +21 (*c* 1.74). IR (film): 3414, 2991, 2936, 2874, 1642, 1459, 1384, 1362, 1281, 1259, 1229, 1173, 1145, 1103, 1074, 1048, 1026, 1000, 984, 933, 869, 859, 756 cm^{-1}. ^1H NMR: 0.92 (3H, s), 0.93 (1H, m), 1.28–2.20 (6H, m), 1.34 (3H, s), 1.40 (3H, s), 1.50 (1H, td, $J=4.2$, 13.1), 1.84 (1H, quintet, $J=7.5$), 2.34 (1H, quintet, $J=7.5$), 3.61 (2H, t, $J=7.7$), 3.88–4.02 (2H, m), 4.09 (1H, dd, $J=3.5$, 6.5). ^{13}C NMR: 17.0, 19.0, 27.5, 29.5, 31.9, 34.3, 36.9, 38.2, 44.1, 59.6, 60.6, 67.0, 98.0. CIMS: 229 ($[MH]^+$, 39), 225 (14), 213 (79), 199 (4), 183 (10), 171 (60), 153 (100), 151 (44), 135 (28). Second eluting minor *anti*-acetonide **17**: $[\alpha]_D$ +17 (*c* 1.08). IR (film): 3402, 2992, 2938, 2881, 1652, 1461, 1382, 1265, 1199, 1165, 1123, 1100, 1073, 1050, 1021, 944, 894, 853, 755 cm^{-1}. ^1H NMR: 0.94 (3H, s), 1.08 (1H, dt, $J=3.4$, 13.2), 1.24–1.66 (7H, m), 1.37 (3H, s), 1.45 (3H, s), 1.80–1.95 (2H, m), 3.64 (2H, t, $J=6.9$), 3.77–3.86 (2H, m), 3.92 (1H, ddd, $J=4.4$, 10.6, 15.0). ^{13}C NMR: 19.4, 20.0, 26.5, 29.8, 32.5, 34.3, 34.9, 36.9, 50.7, 58.9, 60.2, 68.8, 98.1. CIMS: 229 ($[MH]^+$, 39), 225 (14), 213 (79), 199 (4), 183 (10), 171 (60), 153 (100), 151 (44), 135 (28). HRCIMS calcd for $C_{13}H_{25}O_3$ 229.1803, found 229.1802.

4.10. C(10) *O*-Bn protection

Sodium hydride (60% w/w in mineral oil; 0.71 g, 29.6 mmol) was washed twice with dry hexane under an argon atmosphere and the remainder of the hexane removed via syringe and the flask vacuumed, then filled with argon. DMF (2 mL) at 0°C and then isopropylidene alcohols **16**+**17** (1.02 g, 4.47 mmol) in DMF (6 mL) were added dropwise. After stirring for 0.5 h at room temperature, the reaction mixture was cooled to 0°C and BnBr (1.59 mL, 13.4 mmol) was added dropwise and the mixture was stirred for 4 h. Water and ether were added, the two phases separated and the organic phase was worked up as usual. Chromatography of the residue (eluent: heptane–EtOAc, 8:1 to 3:1) gave **18** and **19** in 88% combined yield. C(10)-*O*-Bn minor *trans*-acetonide **18**: $[\alpha]_D$ +8 (*c* 2.27). IR (film): 2936, 1455, 1381, 1265, 1199, 1165, 1102, 1074, 855, 736 cm^{-1}. ^1H NMR: 0.95 (3H, s), 1.07 (1H, ddd, $J=4.4$, 14.3, 18.5), 1.20–1.66 (5H, m), 1.38 (3H, s), 1.45 (3H, s), 1.77–2.02 (3H, m), 3.46 (2H, m), 3.76–3.91 (2H, m), 3.93 (1H, ddd, $J=4.4$, 10.3, 15.0), 4.50 (2H, s), 7.26–7.40 (5H, m). ^{13}C NMR: 19.4, 20.0, 26.4, 29.8, 31.8, 32.5, 34.3, 36.9, 50.7, 60.2, 66.7, 68.7, 73.2, 98.0, 127.5 (3C), 128.3 (2C), 138.2. CIMS: 319 ($[MH]^+$, 52), 303

(22), 261 (100), 243 (30), 231 (18), 211 (7), 153 (98), 135 (18), 123 (8), 109 (7), 91 (34). HRCIMS calcd for $C_{20}H_{31}O_3$ 319.2273, found 319.2281. C10-*O*-Bn major *cis*-acetonide **19**: $[\alpha]_D$ +13 (*c* 2.35). IR (film): 2935, 1455, 1380, 1362, 1259, 1229, 1198, 1145, 1104, 1027, 969, 861, 828, 735, 698 cm^{-1}. ^1H NMR: 0.99 (3H, s), 0.99 (1H, m), 1.42 (1H, m), 1.43 (3H, s), 1.48 (3H, s), 1.57 (1H, td, $J=3.7$, 13.2), 1.67–1.90 (4H, m), 1.99 (1H, quintet, $J=7.4$), 2.51 (1H, quintet, $J=7.4$), 3.57 (2H, dd, $J=6.6$, 8.1), 4.00–4.05 (2H, m), 4.16 (1H, dd, $J=3.5$, 6.5), 4.54 (2H, s), 7.28–7.38 (5H, m). ^{13}C NMR: 17.2, 19.2, 27.6, 29.6, 32.0, 34.4, 34.5, 36.7, 44.2, 60.6, 67.1, 67.6, 72.5, 97.9, 127.2, 127.3 (2C), 128.2 (2C), 138.9. HRCIMS calcd for $C_{20}H_{31}O_3$ 319.2273, found 319.2277.

4.11. Installation of the C(4)–(20) exocyclic olefin

Acetonide cleavage (2N HCl–THF, 1:1, 0°C to room temperature, 4 h) of **18**+**19** (2.62 g, 8.23 mmol) afforded the corresponding diol (2.13 g, 93%) which was monoprotected at the C(2) primary hydroxyl group as follows. A crude solution of 1,3-diol thus obtained (2.27 g, 8.16 mmol), DMAP (3.21 g, 26.3 mmol), and *tert*-butyldimethylsilyl chloride (1.95 g, 12.9 mmol), in CH_2Cl_2 (35 mL), was stirred at 0°C to room temperature for 4 h. The reaction mixture was then diluted with CH_2Cl_2, washed with 1N HCl, then saturated aq. $NaHCO_3$ and worked up as usual. Filtration of the crude product on silica gel (heptane–EtOAc, 6:1 as eluent) afforded **20** as a white solid (3.14 g, 98%) (C(4) epimeric mixture), which was used without diastereomeric separation for the Swern oxidation. To a stirred solution of dimethyl sulfoxide (1.41 mL, 19.9 mmol) in CH_2Cl_2 (10 mL) cooled at −60°C, was added dropwise a solution of oxalyl chloride (2 M in CH_2Cl_2, 4.97 mL, 9.93 mmol) in CH_2Cl_2 (45 mL) under argon. The reaction mixture was stirred for 30 min and then a solution of alcohol **20** (1.95 g, 4.97 mmol) in CH_2Cl_2 (40 mL) was added slowly. The reaction mixture was stirred for 30 min, triethylamine (3.46 mL, 24.8 mmol) was added and the reaction mixture was allowed to warm quickly to 0°C and stirred for 1.5 h before water was added. The organic layer was diluted with CH_2Cl_2, washed with 1N HCl, satd $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated under reduced pressure. Silica gel flash column chromatography (heptane–EtOAc, 20:1 to 6:1) afforded 92% of **21**: $[\alpha]_D$ −22 (*c* 2.43). IR (film): 3065, 3031, 2931, 2856, 1716, 1496, 1472, 1463, 1382, 1363, 1310, 1256, 1214, 1090, 1028, 1006, 940, 886, 838, 814, 777, 736, 698 cm^{-1}. ^1H NMR: 0.04 (6H, s), 0.87 (9H, s), 1.05 (3H, s), 1.45–1.62 (3H, m), 1.79–1.89 (3H, m), 2.24–2.27 (3H, m), 3.48 (2H, t, $J=7.1$), 3.73 (1H, dd, $J=4.8$, 10.2), 4.02 (1H, dd, $J=7.9$, 10.2), 4.47 (2H, s), 7.25–7.38 (5H, m). ^{13}C NMR: −5.6 (2C), 18.1, 22.2, 25.5, 25.8 (3C), 34.8, 35.8, 39.8, 40.3, 59.5, 63.2, 66.2, 73.0, 127.4 (3C), 128.3 (2C), 138.2, 211.9. CIMS: 391 ($[MH]^+$, 10), 335 (10), 283 (19), 259 (10), 241 (16), 225 (8), 199 (8), 167 (19), 151 (8), 125 (12), 91 (100). HRCIMS: calcd for $C_{23}H_{39}O_3Si$ 391.2668, found 391.2671.

Methylenation of the C(4) ketone **21** (831 mg, 2.13 mmol) was carried out using Tebbe's reagent (0.5 M solution, 2.5 mL, 1.25 mmol) in dry THF (9 mL), at 0°C, under argon. We found it more economically favourable to proceed using half of the required amount, as using even large excesses of such an expensive reagent gave reproducibly yields not exceeding 50%. The reaction mixture was stirred at room temperature for 40 min, then cooled at 0°C, diluted with ether and 0.1 M NaOH was added dropwise until gas evolution ceased. Filtration through a pad of Celite and $MgSO_4$ followed by chromatography (heptane–EtOAc, 6:1) afforded **22** (413 mg, 50%) and recovered starting ketone **21** (391 mg, 47%). **22**: $[\alpha]_D$ −18 (*c* 2.25). IR (film): 3018, 2930, 2885, 2857, 1648, 1472, 1463, 1378, 1364, 1257, 1216, 1100, 1028, 1006, 939, 891, 838, 814, 758, 698, 668 cm^{-1}. ^1H NMR: 0.04 (6H, s), 0.90 (9H, s), 0.98 (3H, s), 1.29 (1H, m), 1.50–1.73 (5H, m), 2.01 (1H, dd, $J=4.8$, 7.7), 2.06–2.20 (2H, m), 3.56 (2H, t, $J=6.8$), 3.73 (1H, dd, $J=8.2$, 10.0), 3.83 (1H, dd, $J=4.7$, 10.1), 4.52 (2H, s), 4.46 (1H, bs), 4.80 (1H, bs), 7.28–7.38 (5H, m). ^{13}C NMR: −5.4 (2C), 18.2, 23.0, 25.2, 25.9 (3C), 33.1, 35.1, 35.9, 37.8, 55.6, 61.4, 66.9, 73.0, 110.0, 127.4, 127.5 (2C), 128.3 (2C), 138.6, 147.6. ESIMS (MeOH): 427 ($[MK]^+$, 15), 411 ($[MNa]^+$, 75), 389 ($[MH]^+$, 42).

4.12. Preparation of the C(10) aldehyde

To a stirred solution of **22** (783 mg, 2.02 mmol) in liquid ammonia (150 mL) and THF (22 mL), in the presence of *t*BuOH (1.85 mL), lithium metal (140 mg) was added portionwise at −78°C. The mixture was stirred for 10 min (blue color). Ammonia was evaporated while heptane (technical grade) was added periodically. Evaporation to dryness, dilution with ether and usual work up, afforded after chromatography (heptane–EtOAc, 6:1) 601 mg (100%) of the C(10) *O*-debenzylated compound **23**: $[\alpha]_D$ −36 (*c* 1.36). IR (film): 3350, 2929, 2856, 1648, 1471, 1462, 1388, 1377, 1360, 1255, 1102, 1041, 1005, 887, 836, 773 cm^{-1}. ^1H NMR: 0.06 (6H, s), 0.89 (9H, s), 0.98 (3H, s), 1.16–1.30 (1H, m), 1.40–1.60 (4H, m), 1.68 (1H, t, $J=7.9$), 1.72 (1H, t, $J=7.9$), 1.95–2.13 (2H, m), 2.18 (1H, t, $J=5.9$), 3.65 (1H, dd, $J=6.0$, 10.2), 3.68–3.80 (2H, m), 3.89 (1H, dd, $J=6.0$, 10.2), 4.65 (1H, bs), 4.75 (1H, bs). ^{13}C NMR: −5.4 (2C), 18.3, 22.8, 24.3, 25.9 (3C), 32.7, 35.0, 35.9, 41.3, 55.4, 59.2, 62.8, 109.8, 148.1. ESIMS (MeOH): 337 ($[MK]^+$, 32), 321 ($[MNa]^+$, 100). This was converted to the aldehyde **24** using a Swern protocol as above. To a stirred solution of dimethyl sulfoxide (1.18 mL, 16.6 mmol, 6 equiv.) in CH_2Cl_2 (7 mL) cooled at −60°C, was added dropwise a solution of oxalyl chloride (2 M in CH_2Cl_2, 4.15 mL, 8.31 mmol, 3 equiv.) under argon. The reaction mixture was stirred for 30 min and a solution of the alcohol **23** (825 mg, 2.77 mmol) in CH_2Cl_2 (20 mL) was added slowly. The reaction mixture was stirred for 30 min, triethylamine (3.86 mL, 27.7 mmol) was added and the reaction mixture was allowed to warm quickly to 0°C and stirred for 1.5 h before water was added. The organic layer was diluted with CH_2Cl_2, washed with 1N HCl, satd $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated under reduced pressure. Silica gel flash column chromatography (heptane–EtOAc, 15:1 to 5:1) afforded 763 mg (93%) of **24**: $[\alpha]_D$ −16 (*c* 1.36). IR (film): 2929, 2856, 1732, 1721, 1716, 1651, 1471, 1463, 1389, 1361, 1256, 1099, 1005, 890, 837, 775 cm^{-1}. ^1H NMR: 0.02 (6H, s),

0.85 (9H, s), 1.12 (3H, s), 1.33 (1H, td, $J=4.6$, 13.1), 1.50–1.77 (3H, m), 2.09 (2H, t, $J=5.9$), 2.18 (1H, t, $J=5.7$), 2.28 (1H, dd, $J=3.1$, 15.2), 2.45 (1H, dd, $J=2.4$, 15.2), 3.68 (1H, dd, $J=5.6$, 10.4), 3.86 (1H, dd, $J=5.9$, 10.4), 4.67 (1H, bs), 4.78 (1H, bs), 9.85 (1H, t, $J=2.8$). ^{13}C NMR: −5.5 (2C), 18.2, 22.6, 25.4, 25.9 (3C), 33.0, 35.2, 36.8, 52.2, 55.2, 63.0, 110.4, 147.5, 203.6.

4.13. Preparation of the taxoid C-ring precursor

According to the procedure developed by Still, α-alkoxyorganostannanes **3** were synthesized as follows: To a magnetically stirred solution of diisopropylamine (0.9 mL, 6.28 mmol) in dry THF (6 mL) under argon at 0°C, *n*-BuLi (3.6 mL of a 1.6 M hexane solution, 5.76 mmol) was added dropwise. The solution was stirred for 15 min, *n*-Bu_3SnH (1.6 mL, 5.76 mmol) was added and stirring continued for 15 min at 0°C. The reaction mixture was chilled to −78°C before a solution of aldehyde **24** (1.55 g, 5.24 mmol) in dry THF (16 mL) was added dropwise. After 20 min the cold reaction mixture was quenched with saturated NH_4Cl, diluted with Et_2O and extracted. The combined organic layers were worked up as usual and the residue dissolved in dry CH_2Cl_2 (40 mL). To this solution was added, under argon, *i*-Pr_2NEt (13.7 mL, 78.6 mmol) and after 10 min at 0°C addition of MOMCl (4.0 mL, 52.4 mmol) followed. The reaction mixture was stirred overnight at room temperature then quenched with H_2O (at 0°C) and extracted with CH_2Cl_2. The combined organic layers were washed with 1N HCl, satd $NaHCO_3$ and, following usual work up, chromatography (heptane:ether, 150:1 as eluent) afforded 1.25 g of the faster eluting isomer (10*R*)-**3** (35%) and 1.32 g of the slower eluting isomer (10*S*)-**3** (40%), in 75% combined yield. The absolute stereochemistry of the C(10) stereocenter was confirmed by analogy with the α-alkoxyorganostannanes derived from the Hajos–Parrish ketone. (10*R*)-**3**: $[\alpha]_D$ −64 (*c* 2.30). IR (film): 3067, 2954, 2926, 2871, 2854, 1648, 1463, 1375, 1360, 1340, 1254, 1145, 1096, 1034, 1005, 883, 836, 773 cm^{-1}. ^{1}H NMR: 0.03 (6H, s), 0.83–2.28 (36H, m), 0.87 (9H, s), 1.05 (3H, s), 3.37 (3H, d, $J=1.3$), 3.77 (1H, t, $J=9.3$), 3.92 (1H, dd, $J=3.8$, 9.3), 4.30 (1H, d, $J=11.6$), 4.52 (2H, s), 4.62 (1H, bs), 4.79 (1H, bs). ^{13}C NMR: −5.3 (2C), 9.5 (3C, $J=142.5$), 13.7 (3C), 18.3, 23.4, 25.7, 26.0 (3C), 27.5 (3C, $J=29.3$), 29.2 (3C), 33.7, 35.2, 38.4, 41.8, 56.1, 56.3, 61.3, 71.0, 97.0, 109.5, 148.2. ESIMS (MeOH): 669 ([MK]$^+$, 11), 653 ([MNa]$^+$, 60). (10*S*)-**3**: $[\alpha]_D$ +19 (*c* 1.82). IR (film): 3066, 2954, 2927, 2872, 2854, 1645, 1463, 1375, 1255, 1145, 1096, 1034, 918, 884, 836, 773 cm^{-1}. ^{1}H NMR: 0.03 (6H, s), 0.84–1.01 (17H, m), 0.88 (9H, s), 0.98 (3H, s), 1.21–1.39 (5H, m), 1.40–1.66 (10H, m), 1.97–2.18 (4H, m), 3.36 (3H, s), 3.70 (1H, t, $J=10.1$), 3.75 (1H, dd, $J=5.1$, 10.1), 4.29 (1H, dd, $J=1.8$, 10.7), 4.51 (1H, d, $J=7.5$), 4.53 (1H, d, $J=7.5$), 4.61 (1H, bd, $J=2.0$), 4.78 (1H, bs). ^{13}C NMR: −5.3 (2C), 9.6 (3C, $J=147.8$), 13.7 (3C), 18.3, 23.1, 24.8, 26.0 (3C), 27.6 (3C, $J=26.3$), 29.2 (3C), 33.0, 34.9, 38.2, 43.4, 56.2, 56.4, 61.3, 71.0, 96.8, 109.8, 148.0.

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