Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 783–797

TETRAHEDRON: *ASYMMETRY*

# Taxoid C-ring building blocks from Hajos–Parrish ketone. Practical synthesis of an enantiomerically pure taxoid ABC ring system

José Ignacio Martín Hernando, José Quílez del Moral, Maria del Rosario Rico Ferreira, José Ignacio Candela Lena and Siméon Arseniyadis *

*Institut de Chimie des Substances Naturelles,32+13 CNRS, F-91198 Gif-sur-Yvette, France*

Received 27 January 1999; accepted 19 February 1999

**Abstract**

A synthesis and characterization of conveniently functionalized taxoid C-ring building blocks to be used in an A+C approach is presented. Subsequently, a four-step entry to the tricyclic taxoid ABC skeleton, which allows for a high degree of convergency and is highlighted by a stannylene-mediated coupling to link the left- and right-half moieties, followed by an intramolecular aldol reaction to effect the B-ring closure, is described. 

## 1. Introduction

Ongoing efforts, directed towards enantioselective construction of the taxoid[1] ABC core **I**, required methodology for the construction of the enantiomerically-pure cyclohexane derivative **1** containing four adjacent substituents and a quaternary center. Prior studies from our laboratories[2] have realized significant progress towards this end, including the development of a new ring-expansion/rearrangement sequence that afforded **1**, in only three steps from the Hajos–Parrish[3] ketone-derived unsaturated diol **2**. The heavily substituted cyclohexane derivative **1**, constitutes an excellent right-half building block providing 10 out of 20 carbons of the taxoid diterpene skeleton with the correct absolute stereochemistry at C-8; this stereocenter then controls the relative (and consequently the absolute) configuration of the remaining stereocenters. Therefore, we sought to exploit the synthetic methodology developed in our laboratories and designed a convenient route to the taxoid C-ring moiety offering linking possibilities at C-2 and C-10. Our objective was to devise an efficient A+C route to taxoid diterpene skeleton **I** from **1** and commercially available 4-oxoisophorone **3**, that would allow the introduction of required substituents

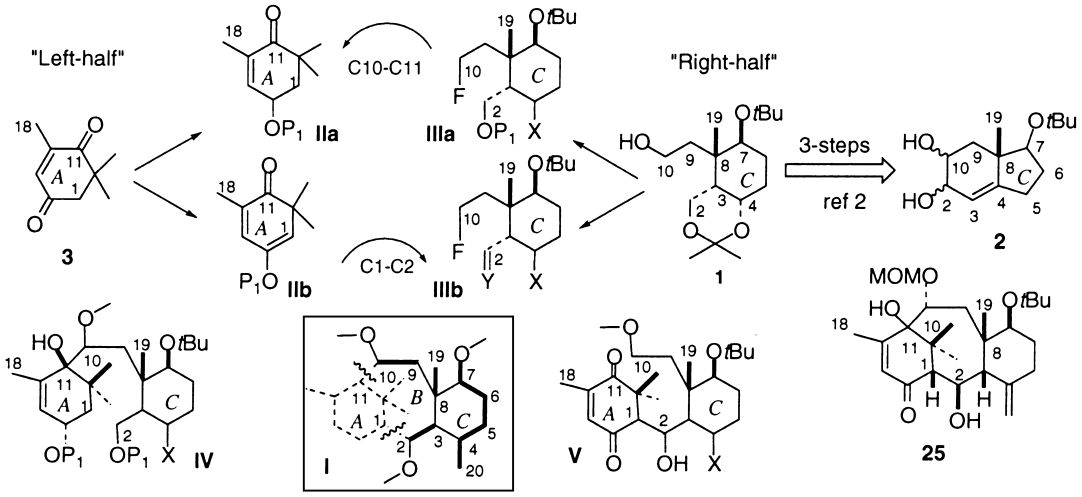
* Corresponding author. Fax: +33-1-69-07-72-47; e-mail: simeon.arseniyadis@icsn.cnrs-gif.fr

0957-4166/99/$ - see front matter 
*PII:* S0957-4166(99)00062-2

at the C-1, C-5, C-9 and C-13 positions. Model studies designed to test the feasibility of this strategy have been published recently.[4] From the foregoing results, it seemed desirable to generate a tricyclic intermediate that incorporates all carbon atoms of the final taxoid skeleton; therefore, modifications of the C-ring were addressed. The latter has to contain a functional moiety that could ultimately be used to introduce the C-20 carbon offering further elaboration, thereby ensuring access into oxirane-, oxetane- or olefin-containing taxoid families. Reported herein are the complete details of various C-ring building blocks, as well as a synthetic approach which culminated in a concise synthesis of the 20 carbon taxoid ABC subunit **25** in its enantiomerically pure form. In this paper, we also report that the organotin–acetal functionality can be used as a versatile protective group which is compatible with several protective-group manipulations commonly employed in synthesis.

## 2. Synthetic planning

Our synthetic plan involved the union of two fragments of unequal complexity, two six-membered ring subunits, **II** and **III** (the A- and C-ring precursors respectively) which, taken together, constitute the 20 carbon atoms of taxoid diterpene skeleton **I** (shown in the box, Scheme 1).




Scheme 1. A+C strategies based on 4-oxoisophorone **3** and the Hajos–Parrish ketone derived diol **2**

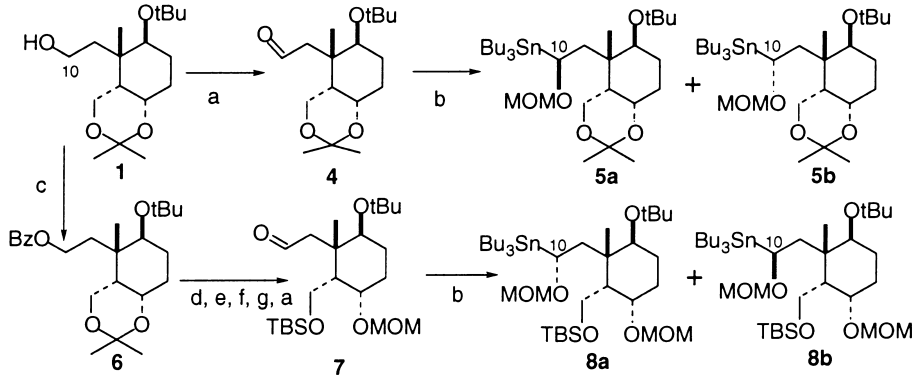
Investigations would start with the 'A+C' coupling reactions, carried out according to the protocol developed by Still[5] which involves a stannylation–destannylation process to afford the corresponding top-linked B-secotaxanes, thus setting the stage for the C1–C2 bottom linking. In the ensuing discussion we describe in sequence the construction and characterization of right-half fragments of type **IIIa** and **IIIb** (F stands for MOM-protected tributyltin acetal) placing emphasis on **5**, **8**, **14**, and **20**, protected α-hydroxy organostannanes to be used as C-10 nucleophiles via transmetallation. The left-half fragments of type **IIa** were described elsewhere; **IIb** is only one step away from commercially available 4-oxo-isophorone[4] and could be used as either C-11 electrophile or C-1 nucleophile in a top or bottom side (a Kende like approach)[6] linking strategy, respectively. We then show how the method of Still can be used to join these two fragments and finally we connect C1–C2 carbons using intramolecular aldol chemistry for the crucial B-ring closure. One of the fundamental assumptions of our synthetic plan is that all newly created stereogenic centers in the left-half moiety of the B-secotaxane unit have no long-term significance as they are programmed to be destroyed in later steps. The oxetane D-ring construction is deferred to the

end of the synthetic scheme, and so is the C-3 stereochemistry. A concise route to either 'top' (such as **IV**) or 'bottom' (such as **V**) linked B-secotaxoid frameworks, is retrosynthetically outlined in Scheme 1.

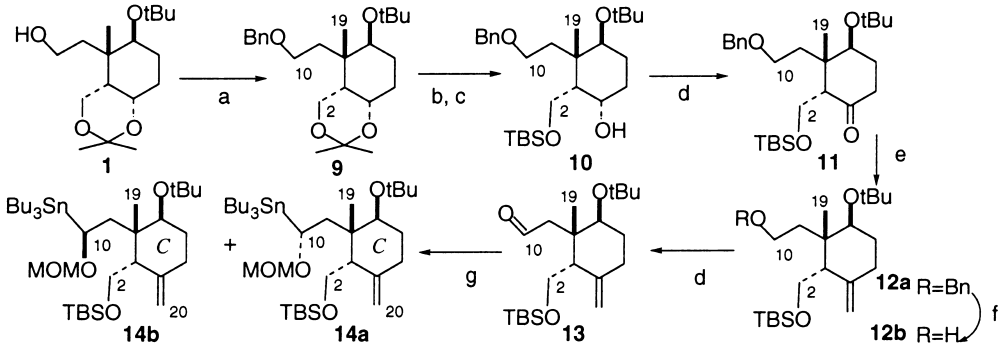
## 3. Results and discussion

### 3.1. Synthesis of the right-half segments

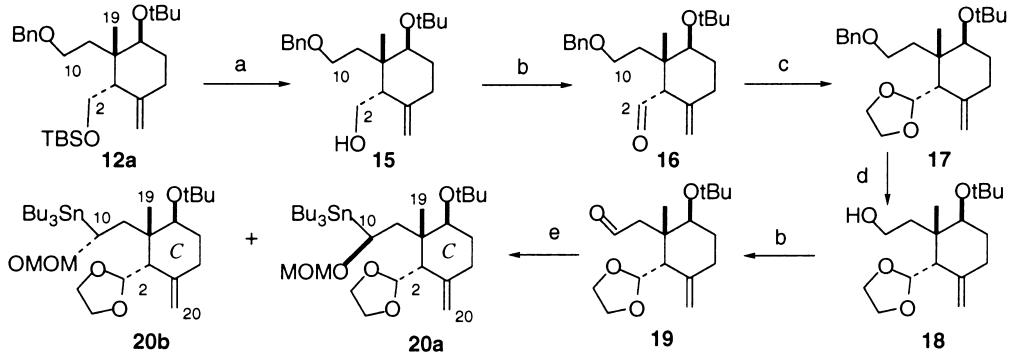
The key synthetic intermediate **1** has been synthesized in multigram quantities in three steps and 82% overall yield from diol **2** according to our previous work.[7] Enantiomeric purity was secured via our lipase-catalyzed hydrolysis[8] rather than using the proline-catalyzed asymmetric Robinson annelation.[3] A series of α-alkoxyorganostannanes of the general type **III** were prepared using Still's procedure from the corresponding aldehydes by treatment with lithium tributylstannylate, followed by protection of the resulting alcohol using chloromethyl methyl ether in the presence of Hünig's base ($i$Pr$_2$NEt). The assembly of C-ring fragments such as α-alkoxyorganostannanes **5**, **8**, **14**, and **20** to be used as C-10 nucleophiles for the synthesis of type **IV** B-secotaxane derivatives, and aldehyde **16** or its acetal **17** to be used as C-2 electrophiles for type **V** B-secotaxane synthesis is outlined in Schemes 2–4.




Scheme 2. (a) DMSO, $(COCl)_2$, $Et_3N$, $CH_2Cl_2$, −60°C. (b) $Bu_3SnLi$, THF, −70°C then MOMCl, $i$Pr$_2$NEt, $CH_2Cl_2$, rt. (c) BzCl, $Et_3N$, $CH_2Cl_2$, rt, 1 h. (d) $p$TosOH, EtOH–$H_2O$, rt, 0.5 h. (e) TBDMSCl, DMAP, $CH_2Cl_2$, 0°C to rt, 2 h. (f) MOMCl, $i$Pr$_2$NEt, $CH_2Cl_2$, rt. (g) $LiAlH_4$, THF, 0°C, 0.5 h




Scheme 3. (a) BnBr, NaH, DMF, rt, 15 h. (b) 5% HCl–THF, 1:1, rt, 4 h. (c) TBDMSCl, DMAP, $CH_2Cl_2$, 0°C to rt. (d) DMSO, $(COCl)_2$, $Et_3N$, $CH_2Cl_2$, −60°C. (e) Tebbe reagent, THF, 0°C, 40 min. (f) Li–$NH_3$ liq., $t$BuOH, THF, −78°C. (g) $Bu_3SnLi$, THF, −70°C then MOMCl, $i$Pr$_2$NEt, $CH_2Cl_2$, rt




Scheme 4. (a) $n$Bu$_4$NF, THF, rt, 5 h. (b) DMSO, $(COCl)_2$, $Et_3N$, $CH_2Cl_2$, −60°C. (c) $HOCH_2CH_2OH$, $p$TosOH. (d) Li–$NH_3$ liq., $t$BuOH, THF, −78°C. (e) $Bu_3SnLi$, THF, −70°C then MOMCl, $i$Pr$_2$NEt, $CH_2Cl_2$, rt

Thus, as shown in Scheme 2, type **5** organostannane was obtained as a diastereomeric mixture (C-10 epimers) starting from isopropylidene alcohol **1**, as follows. Swern oxidation of the latter afforded the required aldehyde **4** which was subsequently umpoled by treatment with tri-*n*-butylstannyllithium (1.1 equiv., prepared from equimolar quantities of $Bu_3SnH$ and LDA) in dry THF and protected immediately after with chloromethyl methyl ether (MOMCl) in the presence of $i$Pr$_2$NEt at room temperature in dry $CH_2Cl_2$ to afford **5a** (faster eluting isomer) and **5b** (slower eluting isomer), easily separable by $SiO_2$ flash column chromatography, in 88% isolated yield and an 1:1 ratio (C-10 configuration undefined). The second requisite building block, type **8** organostannane, was readily accessed carrying out the sequence described in Scheme 2. First, the free hydroxyl group at C-10 of **1** was protected as its benzoate ester by treatment with BzCl in methylene chloride, in the presence of triethylamine. C10–O–Benzyl derivative **6** thus obtained, was then converted to organostannane **8** in six straightforward steps as follows. Acetonide cleavage using $p$TosOH in ethanol–water furnished the free diol (98%) which was then stirred in dry methylene chloride with *tert*-butyldimethylsilyl chloride (TBDMSCl) in the presence of 4-DMAP at 0°C to rt for 2 h to effect the preferential protection of the primary hydroxyl group at C-2 as its *tert*-butyldimethylsilyl ether, in the presence of the free secondary alcohol at C-4. The resulting C10–OBz, C2–OTBS protected alcohol (98%) was subsequently subjected to MOM-protection of the secondary hydroxyl group at C-4, using MOMCl, in the presence of Hünig's base in dry $CH_2Cl_2$ to give a 98% yield of the desired MOM-ether. Treatment of the latter with excess of $LiAlH_4$ in dry THF at 0°C for 30 min yielded quantitatively the corresponding C-10 free hydroxy compound. Swern oxidation of the latter afforded aldehyde **7** in 95% yield. Finally, addition of $n$Bu$_3$SnLi followed by etherification with chloromethylmethyl ether furnished the C-ring subunit **8a** (faster eluting isomer) and **8b** (slower eluting isomer) in ca. 75% yield and a 1:1 ratio (epimeric at C-10 position). Attention was then turned to preparation of the target **14**, a more conveniently functionalized variant to be used as a C-ring nucleophile, containing C-20 carbon and offering better possibilities for further elaboration. Scheme 3 depicts the synthesis of type **14** organostannane.

Starting from **1**, exposure to benzyl bromide in the presence of sodium hydride in dry DMF afforded **9**, which upon treatment with dilute hydrochloric acid in THF, and subsequent selective protection of the resulting diol as above, furnished C-4 alcohol **10** in 88% combined yield (3 steps). The C-20 carbon atom was then introduced via a Swern oxidation (96%) which was followed by a Tebbe olefination[9] cleanly affording **12a**. This material was converted into organotin acetal **14** in a straightforward three-step sequence. Thus, cleavage of the benzyl protective group in **12a**, using Li–$NH_3$ liq. at −78°C, quantitatively afforded **12b**. Swern oxidation gave the required aldehyde **13** (91%) which, upon treatment as above with $n$Bu$_3$SnLi and protection of the secondary hydroxyl groups as their MOM ethers, gave α-

alkoxyorganostannanes **14a**:**14b** in a 1:2.5 ratio and 92% yield. It should be pointed out, that attempted Wittig olefination under various literature conditions failed to produce the desired olefin, leading mainly to TBS deprotection and retro-aldol fragments.

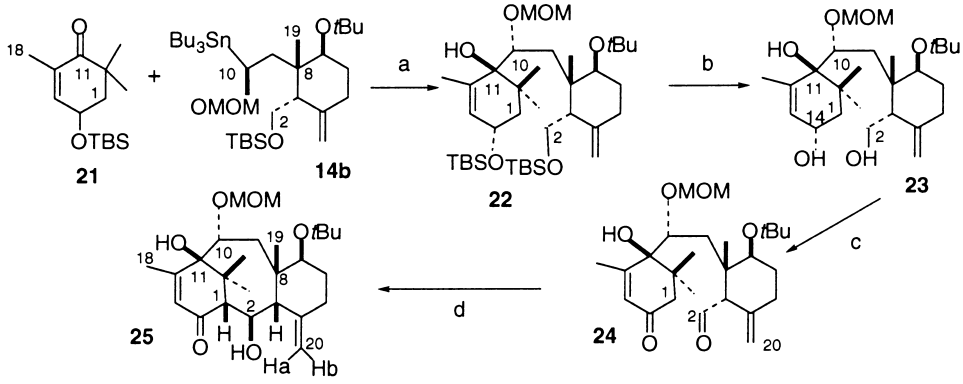
Our next goal was to design a substrate, the precursors of which could be easily incorporated into one of several distinct types of taxane construction, as shown retrosynthetically in Scheme 1. Scheme 4 provides an outline for the synthesis of such a target, compound **20**, along with its precursors **16**, **17**, **18** and **19** which could be used as either C-ring nucleophiles or C-ring electrophiles depending upon the nature of the substituents at C-10 and C-2 and the type of A+C coupling (top or bottom side linking). Starting from **12a**, fluoride promoted deprotection using $n$Bu$_4$NF in THF, and furnished **15** (99%), which was subjected to a Swern oxidation to afford **16** (which could be used as a C-2 electrophile) in 93% isolated yield. Following protection of C-2 carbonyl as its acetal (**17**) and removal of the benzyl group with lithium in ammonia at −70°C, the intermediate alcohol **18** thus obtained (98%, two steps) was oxidized to aldehyde **19** (could be used as a C-10 electrophile) in 93% yield using the Swern protocol.

The latter was then converted into **20** (C-10 nucleophile), obtained as a diastereomeric mixture in ca. 1:1.4 ratio for the faster **20a** and slower eluting isomer **20b**, respectively, using the same protocol as above, in 78% isolated yield. At this point, the C-10 configuration remained unknown for all the α-alkoxyorganostannanes synthesized.

### *3.2. The A+C coupling and B-ring closure*

In our previous work,[4] B-secotaxoids of type **IV** (Scheme 1) were synthesized to gain familiarity with the proposed chemistry and also to check its feasibility. Accordingly, the key fragment coupling was accomplished by transmetallation of the major organostannane **14b** followed by addition of the A-ring electrophile, racemic **21**, which was prepared according to the literature.[10] The addition product **22** was obtained in 90% yield as a 7:1:1 mixture of diastereoisomers favoring the one depicted in Scheme 5. In fact, this reaction, like that of **5a**, **5b**,[4a] **8a** and **8b**[4b] with **21** was regioselective, with nucleophilic attack of the α-alkoxy carbanion occurring exclusively at the C-11 electophilic terminus. It was satisfying to find that the A+C coupling of organostannane **14b** gave a higher yield than did organostannanes **5** and **8** in the model studies. At this stage (**22**) the absolute stereochemistry of diastereomers at C-10, C-11 could not be assigned, nor could the products be separated in a synthetically useful way. Although we were unable to synthesize **22** with the level of stereoselectivity previously obtained on B-secotaxanes originating from **5** and **8**, we progressed in anticipation that this stereochemical imperfection would not pose any problems at subsequent stages of the synthesis. Nevertheless, at least initially, we separated the major isomer by flash chromatography and used isomerically homogeneous **23** in the subsequent exploratory steps for characterization purposes. Finishing the synthesis of the tricyclic core of taxoid diterpene **25** from the intermediate **22** required an adjustment of the oxidation states of the A- and C-rings. This was attempted by a two-step approach that had been successful in model studies.[4] The first step involved fluoride-promoted deprotection of the bis-*tert*-butyldimethylsilyl ether **22** affording the corresponding diol **23** in quantitative yield. The intermediate possessing functionality for the final C1–C2 coupling was then accessed in an additional step via a tetrapropylammonium perruthenate (TPAP)-catalyzed oxidation[11] of the C-14 and C-2 alcohols. Treatment of diol **23** with NMO and catalytic TPAP (0.025 equiv.) in dry MeCN in the presence of 4Å MS, at room temperature led to the desired enone-aldehyde **24**, in 86% yield. This conversion not only set the conditions for the following transformation, the C1–C2 bond formation, but also helped to elucidate the location of the stereoisomers (Scheme 5). The resulting enone-aldehyde was then subjected to standard aldol conditions (LDA, THF, −78°C, 5 min) to give the desired aldol **25** in an unoptimized 31% isolated yield along with the unreacted starting

material (50%). In all cases quasi-quantitative recovery of the unreacted starting material was possible via column chromatography and the recovered compound, which appeared spectroscopically identical to the original material (no epimerization at C-3 was detected), could be reused. Our strategy, as illustrated in Scheme 5, is exemplified by a four-step construction of the enantiopure taxoid ABC tricyclic core **25**, thus demonstrating the potential of this methodology.




Scheme 5. (a) *n*BuLi–THF, −70°C. (b) *n*Bu$_4$NF, THF, 50°C, 2.5 h. (c) TPAP–NMO, 4Å MS, MeCN, rt, 0.5 h. (d) LDA–THF, −78°C, 10 min

The structure of ABC tricyclic intermediate **25** was assigned on the basis of coupling patterns and spatial proximity measurements in the proton NMR spectrum. The stereochemistry of the C-ring moiety was known prior to the NMR investigations. The remaining four unknown stereogenic centers of **25** (C-1, C-2, C-10, C-11) have been determined with a high degree of reliability as follows. After a complete assignment of the proton and carbon resonances, exhaustive NOEDIFF experiments were performed at 300 and 800 MHz to explore spatial relationships. This secured the relative configuration of all the chiral centers. The map of diagnostic NOEs is depicted in Fig. 1 (see Experimental) for the most significant effects. By far the most important were the observed enhancements at the C-10 proton on irradiation of the C-16 methyl group at δ 1.42, of the C-19 methyl group at δ 0.98 and of the bridgehead proton at C-3 at δ 2.57 which provided evidence that they are all on the same face of the molecule as shown in Fig. 1. Observation of an enhancement of the signal for the bridgehead proton at C-3 upon irradiation of the C-8 angular methyl group (Me-19) protons confirmed a *syn*-geometry, consistent with lack of epimerization at C-3 during the aldol process. Turning now to the concave face of the ABC tricycle **25**, upon irradiation of the C-2 hydrogen at δ 4.38 we see a strong NOE to the α-face hydrogens such as C-7 proton at δ 3.19, and C-5α axial proton at δ 2.30, confirming that the C-2 proton is on the α-face of the molecule. This assignment confirmed the *threo*-aldol formation as expected.[12] The absence of vicinal coupling for H-1 at δ 2.80 is consistent with an *endo*-orientation for H-2 at δ 4.38 based upon the near 90° dihedral angle relationship for H-1 and H-2. This justifies the two-way NOE, observed upon irradiation of either H-1 or H-2 even though the two dipoles do not possess a *syn*-geometry. Finally, NOEs upon irradiation of C-7 proton strong NOEs were observed for the C-9α proton at δ 1.52, the C-2 proton as well as for the C-5α axial proton, thus confirming the conformations adopted from the C and B-rings of the molecule.

### *3.3. Assignment of C-10 absolute configurations based on **14b**; correlation studies*

A series of protecting group manipulations and functional group interconversions were performed to correlate the known (vide supra) C-10 absolute stereochemistry of **14b** with the undefined C-10 centers of all the remaining organotin acetals and also demonstrate the versatility of organotin acetal functionality

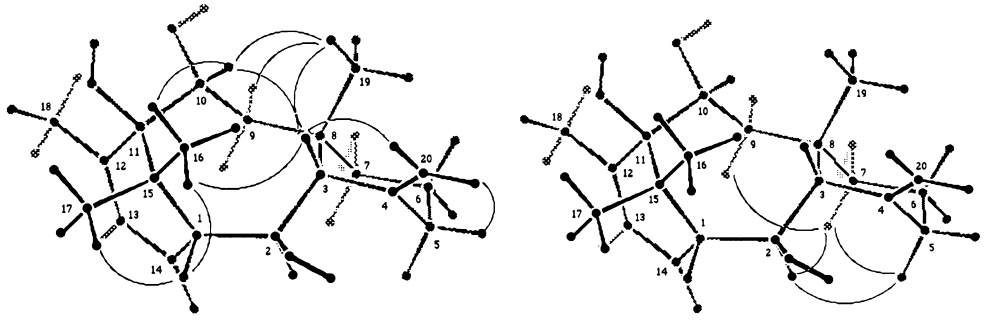
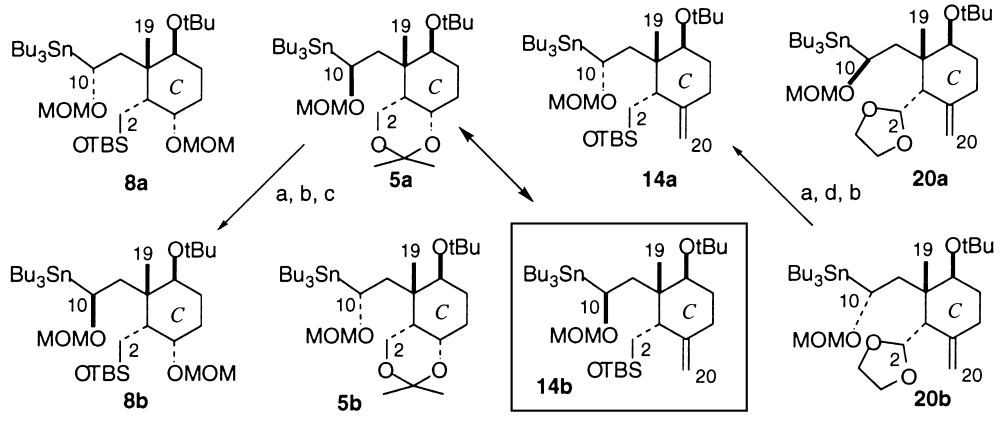


Figure 1. Diagnostic NOEs shown separately on the β (left) and α (right) faces of **25**. The observed NOEs were used as restraints (r) for the simulations in MM3 studies (lowest energy conformer shown)

as a protecting group. Assignment of the absolute configuration to (10*S*)-**14b** is based on relative stereochemistry of the C-10 stereocenter in **25** and assumption of the retentive transmetallation,[13] which by inference, proved the C-10 stereochemistry of organostannanes **5a**,**b**, **8a**,**b** and **20a**,**b** (Scheme 6).




Scheme 6. (a) *p*TosOH, EtOH–$H_2O$, rt, 0.5 h. (b) TBDMSCl, DMAP, $CH_2Cl_2$, 0°C to rt, 2 h. (c) MOMCl, *i*$Pr_2NEt$, $CH_2Cl_2$, rt. (d) $LiAlH_4$, THF, −30°C, 0.5 h

Organostannanes **5**, **8**, **14**, and **20**, that can be stored for long periods and are stable unless exposed to acid, could be incompatible with many protective group manipulations and functional group interconversion protocols. The compatibility map generated during functional group interconversions on organotin–acetal containing substrates is outlined in Scheme 6, which served for correlation studies, and was further extended to several common transformations. Thus, the tributyltin–MOM grouping was perfectly stable in fluoride-promoted TBS deprotection as well as in Swern conditions but not in the formation of acetal. For example, **14a** was desilylated with tetrabutylammonium fluoride to afford the corresponding alcohol which was further oxidized using the Swern protocol to the resulting aldehyde in nearly quantitative yield. Attempts to protect the aldehyde as its corresponding acetal under various conditions failed, thus revealing incompatibility of the organotin acetal with standard acetal formation conditions. The primary hydroxyl at C-2 of α-alkoxyorganostannane **14a** could thus be deprotected, reacetylated or oxidized, but the resulting aldehyde could not stand conditions for acetal formation. The C-10 absolute configurations of the organostannanes were assigned through the correlation sequence outlined in Scheme 6. Organostannane **5a** was taken to the final ABC tricyclic compound **25**, by coupling with **21** according to our previous work.[14] Removal of the acetonide protection in the B-secotaxoid derivative thus obtained Swern oxidation, followed by TBS-monoprotection, and Tebbe olefination furnished

**22** which was processed to **25** as above (Scheme 5). This unambiguously proved its C-10 stereochemistry as (*S*). Selective removal of the isopropylidene group in (10*S*)-**5a** resulted in the corresponding diol which was converted to **8b** in a two-step sequence. Selective deprotection in the presence of a tributyltin–MOM protecting group was carried out by room temperature treatment in EtOH with catalytic *p*TosOH while the two remaining steps, selective TBS protection at C-2 and MOM-protection at C-4 were performed as above. On the other hand, acetal deprotection proceeded smoothly on **20b** affording the corresponding aldehyde which was reduced with lithium aluminum hydride in THF at −30°C. The primary hydroxyl thus formed was protected by reaction with TBDMSCl and imidazol in DMF or by treatment with TBS–triflate in toluene in the presence of collidine to give organotin acetal **14a**. These transformations permitted correlation of organostannanes **5a**, **8b** and **20a** with **14b** which served as reference.

## 4. Conclusion

These studies further establish the synthetic utility of $Pb(OAc)_4$ mediated one-pot multi-stage transformations of bicyclic unsaturated 1,2-diols for the construction of taxoid C-ring building blocks, offering C-10 and C-2 linking possibilities. Stereochemistry of the originally unknown C-10 stereocenter in a series of C-ring building blocks thus synthesized, was confirmed by reaction of racemic **21** with enantiopure **14b**, which furnished **22**; the latter following a deprotection–oxidation–intramolecular aldol protocol provided **25** as a single diastereoisomer. The reactions portrayed in Scheme 6 are of special significance since not only the unknown C-10 absolute configurations of all new organostannanes were established, but compatibility of MOM–$Bu_3Sn$ grouping is also proved in various oxidation–reduction–protection–deprotection operations. In summary, synthetically useful taxoid C-ring segments were synthesized and fully characterized, and conditions have been found for the direct assembly of the eight-membered B-ring.[15] Improvements to the intramolecular aldol reaction (C1–C2 linking) and completion of the synthesis will be the subject for further focus in this area.

## 5. Experimental

### *5.1. General*

General experimental details were as previously described.[16] NMR spectra were run in $CDCl_3$ and specific rotations were measured in chloroform. ‘Usual work up’ means washing of the organic layer with brine, drying over anhydrous magnesium sulfate, and evaporating in vacuo with a rotary evaporator at aspirator pressure. Flash chromatographies were run on silica gel (230–400 mesh).

### *5.2. Preparation of right-half segments*

#### *5.2.1. Preparation of α-alkoxyorganostannanes **5***

Starting from the known aldehyde **4**,[7] and according to the procedure developed by Still,[5] α-alkoxyorganostannanes **5** were synthesized uneventfully as follows. To a magnetically stirred solution of diisopropylamine (0.72 mL, 5.11 mmol) in dry THF (9 mL) under argon at 0°C, *n*BuLi (1.9 mL of a 2.5 M hexane solution, 4.69 mmol) was added dropwise. The solution was stirred for 15 min, *n*$Bu_3SnH$ (1.3 mL, 4.69 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 **4** (1.27 g, 4.26 mmol) in dry THF (5 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 $CH_2Cl_2$ (15 mL). To this solution was added, under argon, *i*PrNEt$_2$ (13.3 mL, 77 mmol) and after 10 min at 0°C addition of MOMCl (3.9 mL, 51 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 1 N HCl, sat. $NaHCO_3$, and following usual work up, chromatography (heptane:ether, 99:1 as eluent) afforded 1.16 g of the faster eluting isomer **5a** (44%), and 1.16 g of the slower eluting isomer **5b** (44%), in 88% combined yield. **5a**: $[\alpha]_D$ +72.2 (*c* 2.00). IR (film): 2957, 2925, 2871, 2866, 1465, 1379, 1362, 1276, 1249, 1226, 1193, 1164, 1149, 1104, 1047, 1028, 1002, 967, 935, 920 cm$^{-1}$. $^1$H NMR (300 MHz): 0.85–0.93 (15H, m), 0.95 (3H, s), 1.16 (9H, s), 1.25–1.62 (16H, m), 1.38 (3H, s), 1.44 (3H, s), 2.06 (1H, dd, *J*=1.6, 16.2), 2.13 (1H, dd, *J*=1.8, 9.5), 2.73 (1H, dd, *J*=10.9, 16.2), 3.37 (3H, s), 3.86 (1H, d, *J*=12.5), 3.94 (1H, d, *J*=5.4), 3.97 (1H, dd, *J*=4.2, 12.5), 4.11 (1H, m), 4.27 (1H, dd, *J*=1.6, 10.9), 4.53 (1H, d, *J*=6.8), 4.55 (1H, d, *J*=6.8). $^{13}$C NMR (50.3 MHz): 9.5 (3C), 13.6 (3C), 18.8, 23.2 (2C), 25.3, 27.5 (3C), 29.0 (3C), 29.2 (3C), 30.0, 38.4, 41.2, 41.7, 55.9, 60.8, 67.2, 70.9, 71.7, 72.7, 96.4, 97.8. CIMS: 635 ([M+H]$^+$, 3), 577 (100), 545 (50), 515 (87), 503 (57). Anal. calcd for $C_{31}H_{62}O_5$ Sn C 58.77 H 9.86, found: C 59.02 H 9.57. **5b**: $[\alpha]_D$ −2.3 (*c* 1.45). IR (film): 2956, 2925, 2874, 2856, 1463, 1378, 1362, 1250, 1226, 1194, 1163, 1147, 1104, 1064, 1047, 1029, 1002 cm$^{-1}$. $^1$H NMR (300 MHz): 0.87–0.96 (15H, m), 1.07 (3H, s), 1.18 (9H, s), 1.26–1.58 (15H, m), 1.37 (3H, s), 1.44 (3H, s), 1.74 (1H, m), 2.12 (1H, m), 2.29 (1H, dd, *J*=11.0, 16.2), 2.49 (1H, bd, *J*=14.7), 3.36 (3H, s), 3.68 (1H, d, *J*=3.5), 3.96–4.06 (2H, m), 4.10 (1H, dd, *J*=3.4, 6.6), 4.27 (1H, dd, *J*=1.9, 11.0), 4.55 (1H, d, *J*=6.5), 4.58 (1H, d, *J*=6.5). $^{13}$C NMR (75 MHz): 9.4 (3C), 13.6 (3C), 19.3, 23.6, 24.0, 25.4, 27.5 (3C), 28.9 (3C), 29.2 (3C), 29.9, 39.1, 40.7, 41.1, 56.0, 60.6, 67.1, 70.5, 70.9, 72.9, 96.7, 97.8. CIMS: 635 ([M+H]$^+$, 35), 603 (9), 577 (56), 545 (65), 515 (13), 291 (15), 151 (43), 125 (56), 73 (100). Anal. calcd for $C_{31}H_{62}O_5$ Sn C 58.77, H 9.86, found: C 58.34, H 9.91.

### *5.2.2. Preparation of α-alkoxyorganostannanes **8***

Benzoyl protection of **1** (1.285 g, 4.28 mmol) was carried out under standard conditions using BzCl (1.09 g, 7.75 mmol), in the presence of $Et_3N$ (1.02 g, 10.04 mmol) in 30 mL of dry $CH_2Cl_2$. Following room temperature stirring for 1–5 h (TLC monitoring) usual work up and filtration on silica gel afforded quantitatively the desired benzoate ester **6**: $[\alpha]_D$ +52.8 (*c* 1.06). IR (film): 2974, 2927, 2907, 1719, 1382, 1276, 1251, 1193, 1159, 1069, 1002, 910 cm$^{-1}$. $^1$H NMR (200 MHz): 1.06 (3H, s), 1.14 (9H, s), 1.38 (3H, s), 1.46 (3H, s), 1.20–1.60 (3H, m), 1.96–2.34 (3H, m), 2.60 (1H, td, *J*=7.6, 15.2), 3.60 (1H, d, *J*=3.2), 3.93–4.06 (2H, m), 4.15 (1H, bs), 4.28 (2H, t, *J*=7.6), 7.38–7.58 (3H, m), 8.04 (2H, dd, *J*=7.0, 1.6). $^{13}$C NMR (50.3 MHz): 18.7, 23.0 (2C), 25.0, 28.7 (3C), 29.6, 35.4, 37.8, 38.8, 60.6, 62.2, 66.9, 71.3, 72.9, 97.8, 128.1 (2C), 129.3 (2C), 130.3, 132.5, 166.3. EIMS: 404 (M$^+$, 4), 389 (15), 333 (17), 328 (9), 291 (47), 273 (16), 233 (47), 193 (24), 111 (100). Anal. calcd for $C_{24}H_{36}O_5$ C, 71.26; H, 8.97; found: C, 71.19, H, 8.85.

Acetonide cleavage on **6** was catalyzed by *p*TosOH (0.1 equiv.), in 95% EtOH in $H_2O$ (5 mL per mmol), at room temperature. After stirring for 0.5 h, the reaction mixture was diluted with $CH_2Cl_2$ and worked up as usual which furnished the corresponding diol in 98% isolated yield after filtration on silica gel. Selective protection of the primary hydroxyl group at was then effected as follows. A solution of 1,3-diol thus obtained (1.285 g, 3.53 mmol), DMAP (1.39 g, 11.39 mmol), and *tert*-butyldimethylsilyl chloride (845 mg, 5.60 mmol), in $CH_2Cl_2$ (15 mL), was stirred at 0°C to room temperature for 1.5 h. The reaction mixture was then diluted with $CH_2Cl_2$, washed with 1 N HCl, then sat. aq. $NaHCO_3$ and worked up as usual to give the title compound as a white solid in 98% isolated yield after filtration on silica gel (heptane:EtOAc, 4:1 as eluent). The OBz–TBS protected alcohol thus obtained was then MOM-protected

on C-4 secondary hydroxyl group as follows. A solution of the latter (1.55 g, 3.24 mmol), was treated with methoxymethyl chloride (0.8 mL, 10.5 mmol) and diisopropylethylamine (2.0 mL, 11.48 mmol) in $CH_2Cl_2$ (15 mL) at room temperature for 12 h. The reaction was stopped by addition of water and extracted with $CH_2Cl_2$. Following the usual work up, the resulting oil was purified by chromatography (heptane:EtOAc, 2:1 as eluent) to give the corresponding MOM-ether (1.66 g, 98%). Target aldehyde **7** was then prepared in two straightforward steps. Lithium aluminium hydride (946 mg, 24.92 mmol) was suspended in dry THF (40 mL) and the mixture cooled to −70°C. To this, C-10 OBz (1.66 g, 3.18 mmol) in THF (10 mL) was slowly added, then the reaction mixture was allowed to reach 0°C within 30 min, after which water (0.9 mL) and aq. NaOH (15%, 0.9 mL) were added and the mixture stirred for 30 min. After dilution with technical ether, the white solid was filtered off and the filtrate concentrated under reduced pressure to quantitatively give the C-10 free hydroxy compound which was taken to aldehyde **7** using a Swern protocol. Thus, to dimethyl sulfoxide (1.4 mL, 19.7 mmol) in dichloromethane (15 mL) was added oxalyl chloride dropwise (4.0 mL, 8.0 mmol, 2 M in dichloromethane) at −60°C. The reaction mixture was stirred for 30 min at −60°C and then the C-10 alcohol (1.32 g, 3.15 mmol) in dichloromethane (15 mL) was slowly added. Following additional stirring for 30 min, triethylamine (5.0 mL, 35.8 mmol) was added then the reaction flask was placed in an ice bath and stirring continued for 1–2 h. The organic layer was washed with 1 N HCl, sat. aq. $NaHCO_3$ and worked up as usual to give (heptane:EtOAc, 9:1) after chromatography, a 95% isolated yield of **7**.

For the preparation of α-alkoxyorganostannanes **8**, Still's procedure was repeated as above using 2.26 mmol of **7** to afford, after chromatography using heptane:EtOAc (92:8 as eluent), a 75% combined yield of **8a**:**8b** as a 1:1 mixture. **8a** (faster eluting isomer): $[\alpha]_D$ +34.7 (*c* 1.05). IR (film): 2929, 1464, 1362, 1265, 1192, 1145, 1042, 837, 775, 742 $cm^{-1}$. $^1H$ NMR (300 MHz): 0.03 (3H, s), 0.04 (3H, s), 0.85–0.93 (24H, m), 0.99 (3H, s), 1.17 (9H, s), 1.25–2.06 (18H, m), 2.58 (1H, dd, *J*=11.5, 16.1), 3.37 (6H, s), 3.64–3.70 (2H, m), 3.81 (1H, d, *J*=3.2), 3.97 (1H, m), 4.21 (1H, bd, *J*=11.5), 4.51 (1H, d, *J*=6.4), 4.54 (1H, d, *J*=6.4), 4.63 (1H, d, *J*=7.3), 4.66 (1H, d, *J*=7.3). $^{13}C$ NMR (62.9 MHz): −5.4 (2C), 9.6 (3C), 13.6, 13.7 (3C), 18.2, 26.0 (3C), 26.8, 27.5 (3C), 27.8, 29.2 (6C), 39.9, 41.8, 47.4, 55.2, 56.0, 59.5, 71.9, 72.1, 72.6, 73.9, 96.5, 97.1. CIMS: 753 ($[M+H]^+$, 21), 721 (26), 707 (14), 695 (24), 691 (38), 665 (24), 647 (10), 573 (12), 515 (12), 477 (36), 133 (83), 113 (67), 73 (100). **8b** (slower eluting isomer): $[\alpha]_D$ −18.9 (*c* 1.05). IR (film): 2956, 2928, 1464, 1361, 1254, 1193, 1147, 1099, 1060, 1041, 836 $cm^{-1}$. $^1H$ NMR (300 MHz): 0.06 (6H, s), 0.87–0.93 (24H, m), 1.05 (3H, s), 1.18 (9H, s), 1.32 (6H, sext, *J*=7.2), 1.46–1.90 (12H, m), 2.31 (1H, m), 3.34 (3H, s), 3.35 (3H, s), 3.68–3.97 (4H, m), 4.30 (1H, d, *J*=11.6), 4.50 (1H, d, *J*=6.5), 4.53 (1H, d, *J*=6.5), 4.64 (2H, s). $^{13}C$ NMR (62.9 MHz): −5.4 (2C), 9.5 (3C), 13.7 (4C), 18.2, 26.0 (4C), 27.6 (3C), 29.2 (7C), 39.7 (2C), 48.1, 55.1, 56.2, 59.6, 71.1, 71.6, 72.9, 73.9, 96.5, 97.1. CIMS: 753 ($[M+H]^+$, 52), 721 (100), 695 (50), 665 (21), 253 (50), 133 (48), 73 (44).

### *5.2.3. Preparation of α-alkoxyorganostannanes **14***

Sodium hydride (60% w/w in mineral oil; 530 mg, 13.3 mmol) was washed twice with dry hexane under argon atmosphere and the remainder of the hexane removed via syringe and the flask vacuumed then filled with argon. *N*,*N*-Dimethylformamide (30 mL) and alcohol **1** (2.0 g, 6.6 mmol) were added. After stirring for 0.5 h the reaction mixture was cooled to 0°C and BnBr (1.25 g, 7.3 mmol) and *N*,*N*-dimethylformamide (10 mL) were added and the mixture stirred for 20 h. Water and ether were added, the two phases separated and the organic phase was worked up as usual. Chromatography of the residue (hexane:EtOAc, 1:1) gave **9** (2.57 g, 99%). Acetonide cleavage as above afforded the corresponding diol which was monoprotected on C-2 primary hydroxyl group using the standard method (vide supra) to give **10** in 88% combined yield. Swern oxidation as above on alcohol **10** (2.82 g, 6.1 mmol) afforded after chromatography (heptane:EtOAc, 10:1) 2.70 g (96%) of the required **11**: $[\alpha]_D$ +2.8 (*c* 2.48). IR (film):

2958, 2931, 2882, 2855, 1714, 1472, 1390, 1360, 1251, 1194, 1145, 1102, 1079, 834, 778, 740, 698 $cm^{-1}$. $^1H$ NMR (300 MHz): 0.04 (3H, s), 0.05 (3H, s), 0.88 (9H, s), 1.07 (3H, s), 1.21 (9H, s), 1.45–1.70 (2H, m), 1.85–2.07 (2H, m), 2.28 (1H, dt, *J*=5.6, 13.6), 2.64 (1H, ddd, *J*=6.5, 10.2, 13.6), 2.79 (1H, dd, *J*=4.1, 6.8), 3.43–3.54 (2H, m), 3.63 (1H, dd, *J*=4.1, 10.3), 3.73 (1H, dd, *J*=3.0, 5.2), 4.06 (1H, dd, *J*=6.8, 10.3), 4.46 (2H, s), 7.27–7.38 (5H, m). $^{13}C$ NMR (62.9 MHz): −5.7, −5.6, 18.0, 21.5, 25.7 (3C), 28.7 (3C), 29.0, 34.6, 37.1, 44.7, 58.5 (2C), 66.0, 70.9, 72.8, 73.2, 127.1 (2C), 127.2, 128.1 (2C), 138.1, 211.4. EIMS: 462 ($M^+$, 3), 405 (4), 388 (4), 373 (4), 349 (22), 331 (99), 257 (13), 242 (29), 239 (74), 225 (35), 223 (37), 215 (36), 197 (33), 165 (27), 153 (24), 92 (58), 91 (100), 75 (79), 73 (76). Anal. calcd for $C_{27}H_{46}O_4Si$ C, 70.08; H, 10.02; found: C, 69.73; H, 10.11.

Methylenation of C-4 ketone **11** (9.84 g, 21.3 mmol) was carried out using Tebbe's reagent (0.5 M solution, 25 mL, 12.5 mmol) in dry THF (90 mL), at 0°C, under argon. The reaction mixture was stirred at rt 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, 20:1–10:1) afforded 4.94 g (50%) of **12a** and 4.66 g (47%) of recovered starting ketone. **12a**: $[\alpha]_D$ −15.6 (*c* 3.89). IR (film): 3064, 3030, 2960, 2928, 2859, 1649, 1464, 1365, 1252, 1192, 1105, 1071, 1030, 1008, 887, 777, 732 $cm^{-1}$. $^1H$ NMR (200 MHz): 0.05 (6H, s), 0.91 (9H, s), 0.92 (3H, s), 1.19 (9H, s), 1.49–1.67 (2H, m), 1.77 (1H, m), 2.02 (1H, ddd, *J*=6.5, 9.1, 15.5), 2.15–2.28 (3H, m), 3.55–3.62 (3H, m), 3.72–3.85 (2H, m), 4.53 (2H, s), 4.62 (1H, d, *J*=2.2), 4.77 (1H, d, *J*=2.2), 7.28–7.40 (5H, m). $^{13}C$ NMR (62.9 MHz): −5.4 (2C), 18.2, 19.5, 25.9 (3C), 29.1 (3C), 30.6 (2C), 35.8, 40.4, 53.9, 62.1, 67.0, 72.7, 72.9, 73.0, 110.2, 127.4, 127.5 (2C), 128.2 (2C), 138.6, 147.3. CIMS: 461 ($[M+H]^+$, 64), 405 (62), 387 (100), 329 (29), 297 (25), 273 (21), 255 (18), 237 (14). Anal. calcd for $C_{28}H_{48}O_3Si$ C, 72.99; H, 10.50; found: C, 72.80; H, 10.54.

To a stirred solution of **12a** (1.86 g, 4.04 mmol) in liquid ammonia (150 mL) and THF (44 mL) in the presence of *t*BuOH (3.7 mL) 280 mg of lithium metal was added portionwise at −78°C. The mixture was stirred for 10 min (blue color). Ammonia was evaporated while technical heptane was added periodically. Evaporation to dryness dilution with ether and the usual work up afforded, after chromatography (heptane:EtOAc, 5:1), 1.49 g (100%) of the required debenzylated compound **12b**. $[\alpha]_D$ −20.1 (*c* 1.47). IR (film): 3319, 2957, 2930, 2885, 1648, 1472, 1389, 1362, 1255, 1193, 1102, 1070, 1020, 1006, 887, 836 $cm^{-1}$. $^1H$ NMR (300 MHz): 0.05 (6H, s), 0.89 (9H, s), 0.92 (3H, s), 1.19 (9H, s), 1.50–1.64 (2H, m), 1.78 (1H, m), 1.93 (1H, dt, *J*=7.1, 14.2), 2.16–2.25 (3H, m), 2.47 (1H, bs, OH), 3.55 (1H, dd, *J*=4.3, 10.1), 3.66–3.79 (3H, m), 3.84 (1H, dd, *J*=4.8, 10.2), 4.63 (1H, bs), 4.74 (1H, bs). $^{13}C$ NMR (75 MHz): −5.5 (2C), 18.2, 18.6, 25.9 (3C), 29.1 (3C), 30.6, 30.7, 39.1, 40.6, 55.5, 59.3, 62.9, 72.8, 73.4, 110.3, 147.3. CIMS: 371 ($[M+H]^+$, 43), 353 (12), 315 (13), 297 (100). Anal. calcd for $C_{21}H_{42}O_3Si$ C, 68.05; H, 11.42; found: C, 68.31; H, 11.44. The latter (1.58 g, 4.27 mmol) was then subjected to Swern conditions as above to give after chromatography (heptane:EtOAc, 6:1) 1.43 g (91%) of **13**: IR (film): 3072, 2953, 2861, 2725, 1712, 1647, 1484, 1387, 1360, 1257, 1197, 1094, 1067, 1002, 888, 829, 764, 682 $cm^{-1}$. $^1H$ NMR (300 MHz): 0.04 (6H, s), 0.89 (9H, s), 1.15 (3H, s), 1.17 (9H, s), 1.54 (1H, m), 1.81 (1H, m), 2.16–2.35 (2H, m), 2.27 (1H, d, *J*=4.9), 2.31 (1H, dd, *J*=2.1, 15.8), 2.64 (1H, dd, *J*=3.2, 15.8), 3.77 (1H, m), 3.79 (2H, d, *J*=4.9), 3.66–3.79 (3H, m), 4.68 (1H, bs), 4.79 (1H, bs), 9.90 (1H, dd, *J*=2.1, 3.2). $^{13}C$ NMR (62.9 MHz): −5.7, −5.6, 18.0, 19.4, 25.8 (3C), 28.9 (3C), 30.3, 31.0, 41.2, 51.4, 55.3, 63.7, 72.1, 73.4, 111.0, 147.1, 203.4.

For the preparation of α-alkoxyorganostannanes **14**, Still's procedure was repeated as above using 2.26 mmol of **13** to afford 75% combined yield of **14a** and **14b** as a 1:2.5 mixture. Purification on silica gel (heptane:ether, 99:1 as eluent) furnished **14a** (faster eluting isomer): $[\alpha]_D$ −62.1 (*c* 1.49). IR (film): 3068, 2956, 2927, 2855, 1652, 1471, 1464, 1398, 1376, 1361, 1254, 1194, 1145, 1097, 1055, 1039, 1006, 884, 859, 836, 774 $cm^{-1}$. $^1H$ NMR (300 MHz): 0.04 (6H, s), 0.84–0.94 (15H, m), 0.90 (9H, s), 0.93 (3H,

s), 1.19 (9H, s), 1.27–1.39 (6H, m), 1.44–1.58 (6H, m), 1.64 (1H, m), 1.77 (1H, m), 1.93–2.05 (2H, m), 2.20 (1H, dt, *J*=4.9, 13.6), 2.36 (1H, ddd, *J*=5.6, 12.6, 13.6), 2.46 (1H, dd, *J*=3.5, 7.6), 3.38 (3H, s), 3.68 (1H, dd, *J*=4.5, 9.7), 3.91 (1H, dd, *J*=3.5, 9.8), 4.01 (1H, dd, *J*=7.6, 9.8), 4.37 (1H, dd, *J*=6.3, 8.0), 4.53 (2H, s), 4.57 (1H, bs), 4.73 (1H, bs). $^{13}$C NMR (75 MHz): −5.4 (2C), 9.6 (3C, *J*=286.8), 13.6 (3C), 18.2, 18.7, 26.0 (3C), 27.5 (3C, *J*=53.5), 29.3, 30.8, 31.2, 39.5, 43.1, 54.2, 56.2, 62.9, 71.7 (*J*=390.9), 72.2, 72.9, 97.2, 109.6, 148.5. CIMS: 705 ([M+H]$^+$, 4), 673 (91), 647 (100), 573 (9), 541 (12), 291 (17). Anal. calcd for $C_{35}H_{72}O_4SiSn$ C, 59.73; H, 10.31; found: C, 59.61; H, 10.44. **14b** (slower eluting isomer): $[\alpha]_D$ +25.7 (*c* 2.08). IR (film): 3078, 2955, 2927, 2873, 2856, 1652, 1464, 1398, 1377, 1362, 1255, 1195, 1148, 1097, 1068, 1056, 1032, 1006, 993, 886, 837, 774 cm$^{-1}$. $^1$H NMR (300 MHz): 0.03 (6H, s), 0.86–0.92 (15H, m), 0.88 (9H, m), 1.03 (3H, s), 1.18 (9H, s), 1.26–1.38 (6H, m), 1.46–1.63 (8H, m), 1.80 (1H, m), 2.13–2.36 (3H, m), 2.45 (1H, dd, *J*=3.4, 8.2), 3.37 (3H, s), 3.57–3.63 (2H, m), 3.72 (1H, dd, *J*=8.2, 9.8), 4.28 (1H, d, *J*=11.8), 4.52 (1H, d, *J*=6.6), 4.55 (1H, d, *J*=6.6), 4.62 (1H, d, *J*=2.0), 4.78 (1H, bs). $^{13}$C NMR (75 MHz): −5.3 (2C), 9.6 (3C, *J*=286.8), 13.6 (3C), 18.2, 20.7, 25.9 (3C), 27.5 (3C, *J*=53.8), 29.0 (3C), 29.2 (3C), 30.4, 30.8, 40.3, 43.0, 52.0, 56.1, 61.4, 71.1 (*J*=386.4), 72.7, 73.1, 97.1, 109.4, 147.3. CIMS: 705 ([M+H]$^+$, 21), 673 (64), 647 (100), 631 (53), 559 (34), 291 (34). Anal. calcd for $C_{35}H_{72}O_4SiSn$ C, 59.73; H, 10.31; found: C, 59.61; H, 10.36.

### *5.2.4. Preparation of α-alkoxyorganostannanes **20***

Starting from **12a**, the target organostannanes were synthesized in five steps as follows. Tetrabutylammonium fluoride (1 M in THF, 11.7 mL, 11.7 mmol) was added to the TBS-protected alcohol **12a** (1.80 g, 3.91 mmol) in dry THF (15 mL) and the reaction mixture stirred at room temperature for 5 h. Dilution with ethyl acetate and the usual work up followed by chromatography (heptane:EtOAc, 4:1 to 2:1) afforded 1.34 g (99%) of **15**: $[\alpha]_D$ −13.8 (*c* 2.12). IR (film): 3451, 3069, 3029, 2978, 2878, 1646, 1458, 1390, 1366, 1258, 1191, 1097, 1076, 1030, 949, 890, 737, 696 cm$^{-1}$. $^1$H NMR (200 MHz): 0.90 (3H, s), 1.15 (9H, s), 1.42–1.68 (2H, m), 1.77 (1H, m), 1.97 (1H, dt, *J*=3.5, 7.0), 2.08–2.32 (4H, m), 3.41 (1H, dd, *J*=4.2, 9.5), 3.55 (2H, dd, *J*=7.2, 7.6), 3.62 (1H, dt, *J*=3.0, 10.4), 3.77 (1H, ddd, *J*=3.5, 4.7, 10.4), 4.49 (2H, s), 4.72 (1H, bs), 4.89 (1H, bs), 7.26–7.34 (5H, m). $^{13}$C NMR (50.3 MHz): 19.2, 28.9 (3C), 29.4, 30.3, 35.5, 40.1, 54.5, 59.1, 66.6, 72.2, 72.8, 73.0, 111.8, 127.4, 127.5 (2C), 128.2 (2C), 138.2, 146.0. CIMS: 347 ([M+H]$^+$, 54), 291 (100), 273 (89), 261 (23), 255 (13), 243 (21), 183 (60), 165 (43), 107 (33). Alcohol **15** (1.31 g, 3.79 mmol) was then oxidized to the corresponding aldehyde using the Swern protocol as above to give, after $SiO_2$ flash chromatography (heptane:EtOAc, 10:1), 1.28 g (98%) of **16**: $[\alpha]_D$ −194.0 (*c* 3.49). IR (film): 3070, 3031, 2973, 2935, 2874, 2724, 1720, 1643, 1455, 1389, 1363, 1254, 1192, 1100, 1071, 1046, 1027, 898, 736, 697 cm$^{-1}$. $^1$H NMR (250 MHz): 0.90 (3H, s), 1.17 (9H, s), 1.57 (1H, m), 1.79 (1H, m), 1.89–1.97 (2H, m), 2.07 (1H, m), 2.25 (1H, dt, *J*=4.8, 14.1), 3.22 (1H, d, *J*=2.5), 3.50–3.64 (2H, m), 3.91 (1H, dd, *J*=4.2, 9.8), 4.41 (1H, d, *J*=11.9), 4.47 (1H, d, *J*=11.9), 4.75 (1H, bs), 4.95 (1H, bs), 7.24–7.33 (5H, m), 9.56 (1H, d, *J*=2.5). $^{13}$C NMR (62.9 MHz): 18.2, 29.0 (3C), 30.2 (2C), 35.1, 40.5, 64.7, 66.8, 72.1, 72.9, 73.1, 113.9, 127.4 (2C), 127.5 (2C), 128.2, 138.2, 141.0, 200.4. CIMS: 345 ([M+H]$^+$, 23), 327 (4), 289 (100), 271 (15), 181 (58), 107 (13). Standard acetal formation (ethyleneglycol, *p*TosOH, molecular sieves, rt) afforded **17** (1.26 g, 3.25 mmol) which, upon debenzylation with lithium metal in liquid ammonia as above, furnished after chromatography (heptane:EtOAc, 1:1) 969 mg (100%) of **18**: $[\alpha]_D$ −36.2 (*c* 0.95). IR (film): 3405, 2973, 2886, 1648, 1473, 1459, 1439, 1389, 1363, 1254, 1228, 1192 1141, 1122, 1067, 1049, 1023, 969, 942, 889 cm$^{-1}$. $^1$H NMR (250 MHz): 0.92 (3H, s), 1.20 (9H, s), 1.58 (1H, ddt, *J*=5.5, 10.7, 13.0), 1.66–1.88 (3H, m), 2.03 (1H, dt, *J*=7.1, 14.2), 2.20 (1H, m), 2.31 (1H, dt, *J*=5.2, 13.2), 2.43 (1H, d, *J*=4.7), 3.72–4.03 (7H, m), 4.65 (1H, bs), 4.85 (1H, t, *J*=2.2), 5.14 (1H, d, *J*=4.7). $^{13}$C NMR (62.9 MHz): 18.0, 29.0, 30.6, 31.2, 38.6, 40.7, 56.0, 59.1, 64.3, 64.4, 72.1, 73.3, 103.5, 112.4, 144.8. CIMS: 299 ([M+H]$^+$, 46), 281 (3), 237

(39), 225 (34), 181 (100), 163 (11). Anal. calcd for $C_{17}H_{30}O_4$ C, 68.42; H, 10.13; found: C, 68.25; H, 10.19.

Swern oxidation of **18** (1.74 g, 5.83 mmol) produced, after chromatography (heptane:EtOAc, 5:1), 1.60 g (92.7%) of **19**: $[\alpha]_D$ −22.0 (*c* 1.16). IR (film): 3076, 2975, 2938, 2887, 1716, 1654, 1476, 1389, 1379, 1363, 1255, 1223, 1191 1146, 1115, 1069, 1049, 1026, 995, 972, 944, 891 $cm^{-1}$. $^1H$ NMR (250 MHz): 1.11 (3H, s), 1.14 (9H, s), 1.50 (1H, ddt, *J*=5.7, 10.9, 12.7), 1.81 (1H, m), 2.14–2.33 (2H, m), 2.41 (1H, bd, *J*=16.7), 2.51 (1H, d, *J*=4.9), 2.60 (1H, dd, *J*=3.0, 16.7), 3.70–3.95 (5H, m), 4.69 (1H, bs), 4.87 (1H, bs), 5.04 (1H, dd, *J*=1.2, 4.9), 9.84 (1H, m). $^{13}C$ NMR (62.9 MHz): 19.1, 29.0 (3C), 30.5, 31.2, 40.5, 51.2, 56.0, 64.1, 64.6, 71.8, 73.6, 103.7, 113.3, 144.2, 203.5. CIMS: 297 ($[M+H]^+$, 55), 297 (100), 223 (40), 198 (11), 179 (11), 113 (18), 73 (26), 71 (14).

The procedure developed by Still was repeated as above on **19** (1.6 g, 5.41 mmol) to afford after chromatography (heptane:EtOAc, 20:1) a 78% epimeric mixture of **20a**:**20b** in a 1:1.4 ratio. **20a** (faster eluting isomer): $[\alpha]_D$ +12.2 (*c* 0.93). IR (film): 2956, 2926, 2873, 2855, 1650, 1465, 1459, 1388, 1377, 1362, 1194, 1171, 1147, 1128, 1095, 1066, 1052, 1032, 990, 939, 887 $cm^{-1}$. $^1H$ NMR (200 MHz): 0.83–0.94 (15H, m), 1.02 (3H, s), 1.19 (9H, s), 1.21–1.68 (13H, m), 1.78 (1H, m), 1.82 (1H, d, *J*=15.5), 2.20–2.27 (2H, m), 2.41 (1H, dd, *J*=11.2, 15.5), 2.58 (1H, d, *J*=5.1), 3.38 (3H, s), 3.70 (1H, dd, *J*=4.3, 10.1), 3.73–3.84 (2H, m), 3.86–3.99 (2H, m), 4.36 (1H, d, *J*=11.2), 4.52 (1H, d, *J*=6.5), 4.57 (1H, d, *J*=6.5), 4.69 (1H, d, *J*=2.3), 4.87 (1H, d, *J*=2.3), 4.92 (1H, d, *J*=5.1). $^{13}C$ NMR (50.3 MHz): 9.6 (3C), 13.6 (3C), 19.4, 27.6 (3C), 29.0 (3C), 29.2 (3C), 30.7, 31.6, 41.0, 42.6, 53.7, 56.3, 64.3, 64.4, 71.7, 72.5, 73.0, 97.2, 103.4, 111.9, 145.2. CIMS: 633 ($[M+H]^+$, 100), 601 (21), 575 (70), 559 (24), 527 (82), 486 (17). Anal. calcd for $C_{31}H_{60}O_5Sn$ C, 58.96; H, 9.58; found: C, 58.82; H, 9.51. **20b** (slower eluting isomer): $[\alpha]_D$ −83.7 (*c* 1.19). IR (film): 3050, 2956, 2926, 2873, 2856, 1648, 1465, 1459, 1388, 1377, 1362, 1193, 1145, 1098, 1052, 1028, 1007, 935 $cm^{-1}$. $^1H$ NMR (250 MHz): 0.86–0.94 (6H, m), 0.90 (9H, t, *J*=7.5), 0.93 (3H, s), 1.19 (9H, s), 1.25–1.39 (6H, m), 1.45–1.66 (7H, m), 1.80 (1H, m), 2.05 (1H, dd, *J*=3.2, 15.2), 2.16 (1H, m), 2.17 (1H, dd, *J*=11.7, 15.2), 2.44 (1H, dt, *J*=6.0, 12.5), 2.75 (1H, bs), 3.38 (3H, s), 3.72–3.98 (5H, m), 4.39 (1H, dd, *J*=3.2, 11.7), 4.50 (1H, d, *J*=7.5), 4.53 (1H, d, *J*=7.5), 4.61 (1H, bs), 4.85 (1H, t, *J*=2.1), 5.48 (1H, d, *J*=2.6). $^{13}C$ NMR (62.9 MHz): 9.5 (3C), 13.6 (3C), 17.3, 27.4 (3C), 29.1 (6C), 31.1, 32.5, 39.2, 42.8, 54.5, 56.0, 63.9, 64.8, 71.5, 71.6, 72.8, 97.0, 104.6, 112.6, 145.1. Anal. calcd for $C_{31}H_{60}O_5Sn$ C, 58.96; H, 9.58; found: C, 58.84; H, 9.63.

### *5.3. The A+C linking*

#### *5.3.1. Preparation of B-secotaxoid **22** and setting the stage for the eight-membered B-ring formation*

To a magnetically stirred solution of **14b** (510 mg, 0.725 mmol) in 3.5 mL of anhydrous THF cooled at −78°C under argon, *n*BuLi (2.5 M in hex, 0.3 mL, 1.05 equiv.) was added and the mixture was stirred at this temperature for 10 min before (±)-**21** (388 mg, 1.45 mmol) was added. After stirring for 20 min at −78°C, the reaction mixture was diluted with ether, and quenched with a saturated solution of $NH_4Cl$. Following the usual work up, $SiO_2$ column chromatography (eluent heptane:ether, 96:4) gave an unseparable mixture of A+C adducts **22** (435 mg, 90%, only the major isomer is shown) along with an unreacted **21**. For the deprotection of *tert*-butyldimethylsilyl ethers at C-14 and C-2, this mixture was heated at 50°C in 4 ml of THF in the presence of $nBu_4NF$ (1 M solution in THF 3 mL, 3 mmol) for 2.5 h. Dilution with ethyl acetate, the usual work up and $SiO_2$ flash chromatography (heptane:EtOAc, 1:3) furnished 261 mg of a mixture of triols (90%). The major isomer (obtained pure after chromatography, shown in Scheme 5) **23**: $[\alpha]_D$ +41.1 (*c* 1.04). IR (film): 3416, 3075, 2975, 2881, 1640, 1460, 1391, 1367, 1250, 1196, 1165, 1144, 1062, 1016, 943, 906, 889, 741 $cm^{-1}$. $^1H$ NMR (300 MHz): 1.01 (3H, s), 1.03 (3H, s), 1.07 (3H, s), 1.19 (9H, s), 1.62 (1H, dd, *J*=5.4, 13.6), 1.60–1.94 (8H, m), 1.76 (3H, t, *J*=1.6), 2.11

(1H, dt, *J*=5.1, 13.3), 2.44 (1H, m), 2.54 (1H, m), 3.46 (3H, s), 3.53 (1H, dd, *J*=2.7, 5.1), 3.80 (1H, dd, *J*=7.5, 11.3), 3.86–3.92 (2H, m), 4.17 (1H, m), 4.67 (1H, d, *J*=5.7), 4.73 (1H, bs), 4.78 (1H, d, *J*=5.7), 4.90 (1H, s), 5.55 (1H, bs). $^{13}$C NMR (75 MHz): 19.4, 22.2, 25.3, 26.2, 29.2 (3C), 29.4, 30.8, 38.5, 39.5, 42.6, 44.6, 50.7, 56.9, 60.1, 65.3, 72.2, 73.1, 77.8, 83.0, 100.0, 107.9, 128.2, 138.3, 147.9. CIMS: 455 ($[M+H]^+$, 30), 437 (90), 419 (31), 405 (36), 387 (21), 301 (40), 237 (34), 181 (50), 163 (100). Anal. calcd for $C_{26}H_{46}O_6$ C, 68.69; H, 10.20; found: C, 68.49; H, 9.97.

To a stirred solution of **23** (159 mg, 0.35 mmol) in 3.5 mL of dry acetonitrile under argon at room temperature, was added 200 mg of powdered 4Å molecular sieves followed by NMO (123 mg, 1.05 mmol) and a catalytic amount of $n$Pr$_4$NRuO$_4$ (TPAP, 19.7 mg, 0.056 mmol). After 30 min the solvent was removed under reduced pressure and the reaction mixture was taken up in $CH_2Cl_2$ prior to filtration through a short silica gel column (eluted with heptane:EtOAc, 1:1) to furnish the desired enone-aldehyde (86%). **24**: $[\alpha]_D$ −33.7 (*c* 2.92). IR (film): 3463, 2971, 2937, 1720, 1663, 1470, 1388, 1364, 1310, 1252, 1192, 1069, 1026, 908, 734 cm$^{-1}$. $^1$H NMR (200 MHz): 1.03 (3H, s), 1.08 (3H, s), 1.13 (9H, s), 1.14 (3H, s), 1.57–2.43 (7H, m), 2.00 (3H, bs), 2.71 (1H, d, *J*=18.6), 3.24 (1H, s, OH), 3.34 (1H, bs), 3.46 (3H, s), 3.69 (1H, dd, *J*=3.2, 6.4), 3.94 (1H, dd, *J*=2.1, 10.1), 4.68 (1H, bs), 4.68 (1H, d, *J*=6.2), 4.78 (1H, d, *J*=6.2), 4.92 (1H, bs), 5.91 (1H, s), 9.65 (1H, d, *J*=1.9). $^{13}$C NMR (50.3 MHz): 20.3, 21.0, 24.0, 27.7, 29.1 (3C), 29.6, 30.6, 37.0, 42.0, 50.0 (2C), 56.9, 62.0, 72.1, 73.3, 78.7, 85.5, 100.2, 112.5, 128.2, 141.7, 163.0, 198.1, 201.8.

*5.3.2. The C1–C2 linking: synthesis of the ABC taxoid **25***

LDA (0.27 mmol, 2 equiv.) was prepared at −20°C in 9 ml of dry THF, cooled at −78°C and stirred at this temperature for 15 min. Then the enone-aldehyde **24** (60 mg, 0.13 mmol) was added in 10 ml of THF. After 5 min, the solution was diluted with heptane and the reaction was quenched at −78°C by careful addition of a sat. aq. $NH_4Cl$ solution. The organic layer was then separated and washed with brine until pH 7. Usual work up followed by chromatography (heptane:EtOAc, 3:1) furnished 18.6 mg of the aldol **25** (31%), and 30 mg of starting material (50%). **25**: mp: 168–170°C (heptane–ether). $[\alpha]_D$ −66.3 (*c* 0.9). IR (film): 3546, 3075, 2854, 1717, 1656, 1460, 1363, 1266, 1190, 1150, 1090, 1068, 1047, 1039, 911 cm$^{-1}$. $^1$H NMR (800 MHz): 0.98 (3H, s, Me-19), 1.08 (9H, s, *t*Bu), 1.22 (3H, s, Me-17), 1.42 (3H, s, Me-16), 1.52 (1H, dd, *J*=6.3, 17.5, H-9ax), 1.53 (1H, dddd, *J*=5.1, 11.1, 12.5, 14.4, H-6ax), 1.70 (1H, d, *J*=17.5, H-9eq), 1.79 (1H, dddd, *J*=2.0, 4.7, 5.6, 12.5, H-6eq), 2.04 (3H, t, *J*=1.1, Me-18), 2.18 (1H, bdd, *J*=5.1, 14.4, H-5eq), 2.30 (1H, tdt, *J*=2.0, 5.6, 14.4, H-5ax), 2.57 (1H, d, *J*=11.2, H-3), 2.80 (1H, s, H-1), 3.19 (1H, dd, *J*=4.7, 11.1, H-7), 3.47 (3H, s, OMe), 3.89 (1H, s, OH), 4.06 (1H, d, *J*=6.3, H-10), 4.38 (1H, d, *J*=11.2, H-2), 4.64 (1H, d, *J*=6.8, $OCH_2O$), 4.77 (1H, d, *J*=6.8, $OCH_2O$), 4.87 (1H, bs, H-20a), 5.02 (1H, t, *J*=2.0, H-20b), 6.13 (1H, dq, *J*=1.1, 1.1, H-13). $^{13}$C NMR (75 MHz): 20.0 (Me-16), 20.5 (Me-19), 21.5 (Me-18), 28.9 (*t*Bu), 30.9 (C-5), 31.0 (C-6), 31.8 (Me-17), 39.1 (Cq-8), 40.2 (C-9), 40.9 (Cq-15), 56.1 (OMe), 56.8 (C-3), 61.4 (C-1), 69.4 (C-2), 71.7 (C-7), 73.5 (Cq-*t*Bu), 76.8 (C-10), 79.6 (C-11), 94.3 (–$OCH_2O$–), 115.3 (C-20), 127.9 (C-13), 147.4 (C-4), 163.3 (C-12), 198.3 (C-14). CIMS: 451 ($[M+H]^+$, 100), 433 (23), 419 (37), 401 (5), 389 (25), 377 (45). HRCIMS: calcd for $C_{26}H_{43}O_6$ m/z 451.3059, found 451.3052.

## Acknowledgements

The authors thank the Ministerio de Educacion y Cultura (Spain) for fellowships to Dr. J. Quílez del Moral and Dr. J. I. Martín Hernando, the European Commission for a Research Training Grant to Dr. J. I. Candela Lena, and Professor Pierre Potier for his kind interest and constant encouragements.

## References


1. For review articles see: Nicolaou, K. C.; Dai, W. M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl*. **1994**, *33*, 15–44; Boa, A. N.; Jenkins, P. R. and Lawrence, N. J. *Contemporary Organic Synthesis* **1994**, *1*, 47–75.
2. Arseniyadis, S.; Brondi Alves, R.; Pereira de Freitas, R.; Muñoz-Dorado M.; Yashunsky, D. V.; Potier, P.; Toupet, L. *Heterocycles* **1997**, *46*, 727–764.
3. Hajos, Z. G.; Parrish, D. R. *J. Org. Chem*. **1974**, *39*, 1615–1621.
4. (a) Arseniyadis, S.; Martín Hernando, J. I.; Quílez del Moral, J.; Yashunsky, D. V.; Potier, P. *Tetrahedron Lett*. **1998**, 39, 3489–3492; (b) Arseniyadis, S.; Martín Hernando, J. I.; Quílez del Moral, J.; Yashunsky, D. V.; Potier, P. *Synlett* **1998**, 1010–1012.
5. Still, W. C. *J. Am. Chem. Soc*. **1978**, *100*, 1481–1486.
6. Kende, A. S.; Johnson, S.; Sanfilippo, P.; Hodges, J. C.; Jungheim, L. N. *J. Am. Chem. Soc*. **1986**, *108*, 3513–3515.
7. Arseniyadis, S.; Yashunsky, D. V.; Pereira de Freitas, R.; Muñoz-Dorado, M.; Potier, P.; Toupet, L. *Tetrahedron* **1996**, *52*, 12443–12458.
8. Arseniyadis, S.; Rodriguez, R.; Muñoz-Dorado, M.; Brondi Alves, R.; Ouazzani, J.; Ourisson, G. *Tetrahedron* **1994**, *50*, 8399–8426.
9. Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc*. **1978**, *100*, 3611–3613; for an improved, water and air tolerant titanium-mediated methylenation see: Petasis, N. A.; Lu, S. P.; Bzowej, E. I.; Fu, D. K.; Staszewski, J. P.; Akritopoulou Zanze, I.; Patane, M. A.; Hu, Y. H. *Pure & Appl. Chem*. **1996**, *68*, 667–670.
10. Tanaka, A.; Yamamoto, H.; Oritani, T. *Tetrahedron: Asymmetry* **1995**, *6*, 1273–1278.
11. Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639–666; Griffith, W. P.; Ley, S. V. *Aldrichimica Acta* **1990**, *23*, 13.
12. Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D. Ed. Academic Press: New York, 1984; vol. 3, pp. 111–212.
13. Organometallic carbon nucleophiles generally react with carbon electrophiles with retention of configuration: Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc*. **1980**, *102*, 1201–1202; Sawyer, J. S.; Macdonald, T. L.; McGarvey, G. J. *J. Am. Chem. Soc*. **1984**, *106*, 3376–3377.
14. Arseniyadis, S.; Martín Hernando, J. I.; Quílez del Moral, J.; Rico Ferreira, M.; Birlirakis, N.; Potier, P. *Tetrahedron Lett*. **1998**, 39, 9011–9014.
15. For an excellent review see: Petasis, N. A; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757–5821.
16. Arseniyadis, S.; Rico Ferreira, M.; Quílez del Moral, J.; Martín Hernando, J.; Potier, P.; Toupet, L. *Tetrahedron: Asymmetry* **1998**, *9*, 4055–4071; Arseniyadis, S.; Rico Ferreira, M.; Quílez del Moral, J.; Martín Hernando, J.; Birlirakis, N.; Potier, P. *Tetrahedron: Asymmetry* **1999**, *10*, 193–206.