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Novel Synthetic Strategy Towards Taxol by Macrocyclization Reaction – Conformational Requirement of Ring A

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The synthesis of a completely substituted ring A of Taxol is reported and it is shown that the C^{13}-OP group must have a β configuration to succeed in the formation of 12-membered rings, a requisite for the construction of the B and C rings of Taxol by a macrocyclization step.

Introduction

Our laboratory is involved in the development of novel and powerful synthetic strategies based on transannular processes on macrocycles.[1] We are planning to use such a strategy for the construction of Taxol[2] starting from a fully substituted ring A to which a 12-membered ring would be incorporated, being confident that an appropriate transannular reaction would then lead to the Taxol skeleton (Figure 1). In this paper, we wish to report the synthesis of a fully substituted chiral ring A and a study which indicates that the OP group at C^{13} must have β configuration in order to successfully construct 12-membered macrocyclic rings.

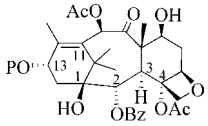
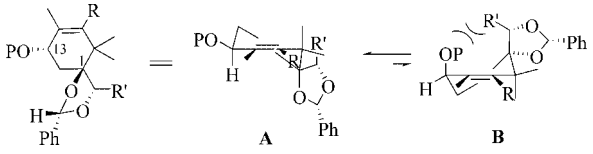


Figure 1. Taxol.

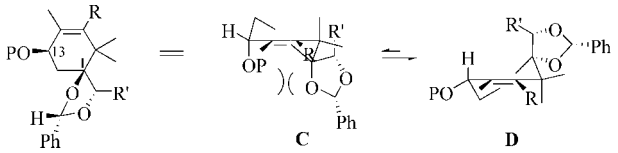
Results and Discussion

We have first theoretically examined the influence of an α-oriented OP group at C^{13} on the A ring conformation and its effect on a subsequent macrocyclization reaction. Molecular models indicate that such intermediate will preferentially exist in the half-chair conformer **A** rather than **B** (Scheme 1). In half chair **B**, there is a severe 1,3-diaxial steric interaction between the OP group at C^{13} and the side chain at C^1 and a steric effect of that magnitude is absent in **A**. On the other hand, the side chain at C^1 in the more stable conformer **A** is oriented equatorially and the R′ group takes a direction far away from the R group. It thus appears difficult to approach these two alkyl groups close enough for a successful macrocyclization and polymerization would likely occur.



Scheme 1. Stability of half chair of ring A with Taxol stereochemistry.

However, if a ring A intermediate epimeric at C^{13} is contemplated, the most stable conformation should now be reversed (Scheme 2). The half chair **D** is now more stable as **C** has a severe 1,3-diaxial steric interaction between the OP group at C^{13} and the tertiary oxygen atom at C^1. In addition, in the more stable conformation **D**, the side chain at C^1 is oriented axially and has the R′ group approaching the direction of the R group. Their relative proximity could thus ease macrocyclization in preference to oligomerization.



Scheme 2. Stability of half chair of ring A with Taxol epimeric stereochemistry.

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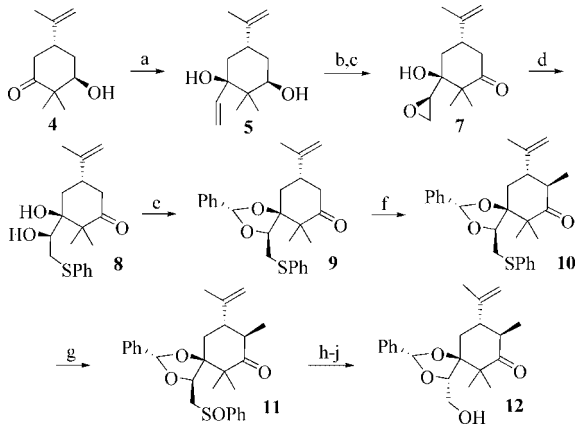
In any event, we decided to construct ring A intermediates **23** and **23′**, which are epimeric at C^{13} (Scheme 7) in order to verify their conformational preference and their ease of macrocyclization.

(–)-(*R*)-Carvone,[3] which is an abundant chiral natural product, was first transformed in two steps into the known compound **4**[4] (Scheme 3).



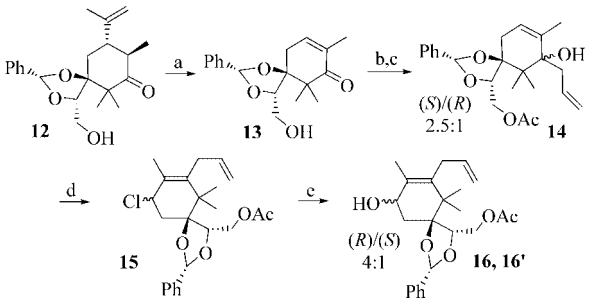
Scheme 3. (a) Tetravinyltin, BuLi, THF, –78 °C, 96%; (b) VO(acac)$_2$, *t*BuOOH, CH_2Cl_2; (c) Jones reagent, acetone, 60% over 2 steps; (d) K_2CO_3, PhSH, CH_3CN, 91%; (e) $PhCH(OMe)_2$, NSA, CH_2Cl_2, 92%; (f) *t*BuOK, MeI, THF, 97%; (g) $NaIO_4$, MeOH, 94%; (h) $(CF_3CO)_2O$, pyridine, THF, 0 °C; (i) K_2CO_3, H_2O; (j) $LiAlH(OCMe_3)_3$, THF, 0 °C, 81% overall.

Addition of vinyllithium to **4** at low temperature occurred with complete selectivity providing **5** in 96% yield. Epoxidation with VO(acac)$_2$ and *t*BuOOH followed by Jones oxidation of the resulting secondary alcohol gave **7** after recrystallization in 60% yield. Epoxide opening with thiophenolate led to diol **8** in 91% yield and this structure was confirmed by X-ray diffraction analysis.

Diol **8** was converted into benzylidene acetal **9** (92%) which was monomethylated using *t*BuOK and MeI in THF to produce **10** in 97%. The thioether was transformed into the corresponding sulfoxide **11** in 94% yield using $NaIO_4$. A Pummerer reaction was then achieved with trifluoroacetic anhydride, which was followed by treatment with a saturated solution of K_2CO_3. This sequence provides first the corresponding aldehyde, which is then isomerized into the more stable epimeric aldehyde. Being somewhat unstable, this aldehyde was selectively reduced with a hindered hydride to give the hydroxy ketone **12** in 81% overall yield.

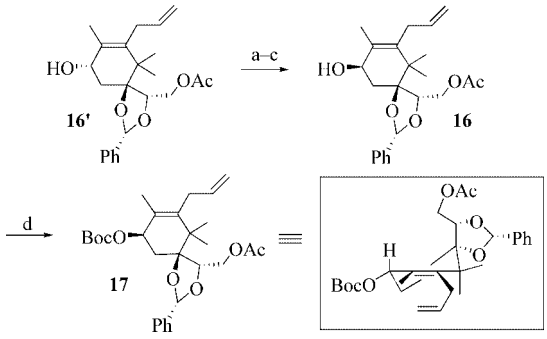
Compound **12** was treated with ozone in MeOH and the resulting peroxide was treated with Cu(OAc)$_2$ and $FeSO_4$[5] to give the enone **13** in 77% yield (Scheme 4).

Addition of allyl Grignard reagent at 0 °C followed by protection of the primary alcohol as an acetate produced in 90% yield a 2.5:1 mixture (*S*)/(*R*) of tertiary alcohol **14**. By treatment of this mixture with $SOCl_2$ at –20 °C, an S_N2' reaction with retention of configuration yielded **15** and S_N2 on Al_2O_5[6] provided a mixture of epimeric alcohols **16** and **16′** in a 4:1 ratio and with 71% overall yield. These two epimers can be easily separated by chromatography.



Scheme 4. (a) O_3, MeOH, –78 °C, Cu(OAc)$_2$, $FeSO_4$, 77%; (b) allyl Grignard reagent, THF, 0°C; (c) Ac_2O, NEt_3, CH_2Cl_2, 90% over 2 steps; (d) $SOCl_2$, CH_2Cl_2, –20 °C; (e) Al_2O_5, 71% over 2 steps.

It is also possible to convert epimer **16′** into **16** under Mitsunobu conditions in 52% overall yield as shown in Scheme 5. The O-Boc derivative **17** was prepared from **16** and NMR study[7] indicated that **17** exists preferentially in the desired half-chair conformation **D** (Schemes 3 and 5).

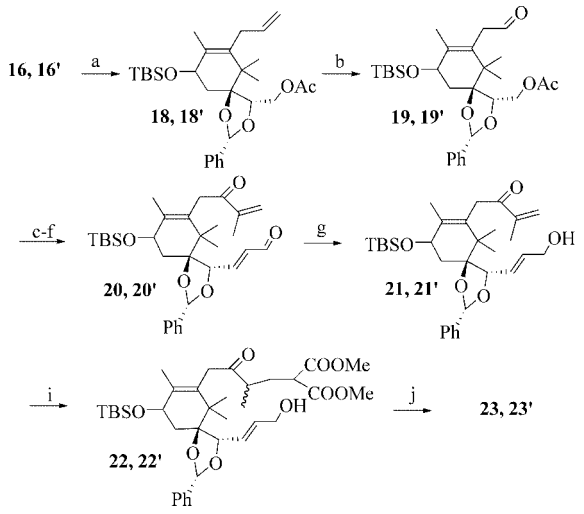


Scheme 5. Conversion of **16′** into **16** and formation of **17**. (a) PPh_3, DIAD, PhCOOH, THF; (b) K_2CO_3, MeOH; (c) Ac_2O, NEt_3, CH_2Cl_2, 52% overall; (d) DMAP, Boc_2O, CH_3CN, 61%.

For synthetic convenience, we have preferred to work with O-TBS-protected products (Scheme 6).

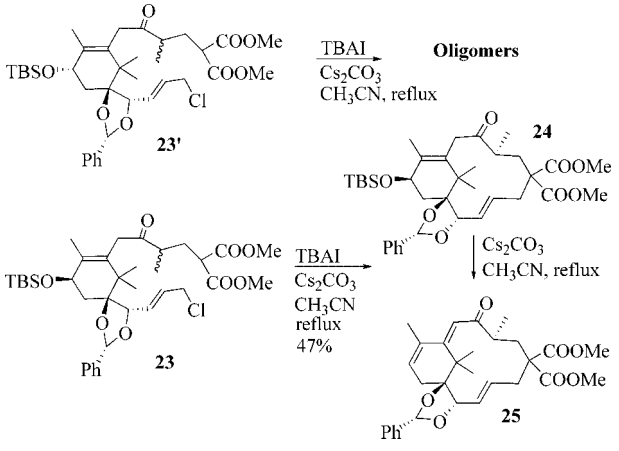
The following chemical transformations were carried out on the two epimers **16** and **16′**, respectively (Scheme 6). The secondary alcohol in **16** was protected as a TBS ether and reductive ozonolysis with Ph_3P gave aldehyde **19** in 88% yield. Addition of isopropenylmagnesium bromide to **19** followed by methanolysis (K_2CO_3, MeOH), oxidation (Dess–Martin periodinane) and Wittig reaction [(formylmethyl)triphenylphosphonium chloride and Et_3N] afforded the doubly conjugated compound **20** in 55% overall yield. Selective reduction of the aldehyde with $LiAlH(OCEt_3)_3$ gave allylic alcohol **21** (87%), and dimethyl malonate Michael addition gave an epimeric mixture of **22** in 86% yield. Finally, the corresponding mixture of epimeric chlorides **23** was obtained in 91% yield by a mild efficient method using 1-chloro-*N*,*N*,2-trimethyl-1-propenylamine.[8] A mixture of epimeric chlorides **23′** was also obtained from **16′** in similar yields for each step.

At this stage, we were ready to test the macrocyclization step (Scheme 7). Treatment of allylic chlorides **23′** with Cs_2CO_3 and TBAI in acetonitrile led only to oligomeric material which remained at the base line on TLC. On the other hand, we were pleased to see that treatment of β iso-



Scheme 6. Synthesis of **23** and **23′**. (a) TBDMSCl, imidazole, DMF, 92%; (b) O_3, MeOH, PPh_3, –78 °C, 88%; (c) $CH_2{=}C(CH_3)$-MgBr, THF, –78 °C; (d) K_2CO_3, MeOH; (e) Dess–Martin periodinane, CH_2Cl_2; (f) $PPh_3{=}CH(CHO)$, toluene, 55% overall; (g) $LiAlH(OCEt_3)_3$, THF, –78 °C, 87%; (i) dimethyl malonate, Cs_2CO_3, CH_3CN, 86%; (j) $(CH_3)_2NCCl{=}C(CH_3)_2$, CH_2Cl_2, 91%.

mer **23**, which corresponds to the unnatural epimer at C^{13}, provided a mixture (1:3) of two macrocycles **24** and **25** in 47% yield, which were separated by chromatography.[9]



Scheme 7. Attempts of macrocyclization on two different diastereoisomers.

Both macrocycles **24** and **25** correspond to one single diastereoisomer, i.e., they are not a mixture of epimers due to the presence of the secondary methyl group. A molecular modeling study suggests that the carbon atom bearing the secondary methyl group has the (*R*) configuration as shown. In addition, it was shown that macrocycle **24** is slowly converted into **25** upon reaction with Cs_2CO_3 in CH_3CN. This transformation must come from the enolization of **24** followed by elimination of the silyl ether group.

This work has established that the β configuration of the C^{13}-OP group is a prerequisite for a successful macrocyclization.[10,11] Starting from key intermediate **19**, we are now investigating the formation of various macrocycles which can lead to the basic tricyclo[6.8.6] framework of Taxol by a subsequent transannular reaction. Work is now in progress in these directions.

Experimental Section

General: Unless otherwise indicated, ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ solutions. Chemical shifts are reported in ppm on the δ scale. Multiplicities are described as s (singlet), d (doublet), dd, ddd, etc. (doublet of doublets, doublet of doublets of doublets, etc.), t (triplet), q (quartet) m (multiplet), and further qualified as app (apparent), b (broad), c (complex). Coupling constants, *J*, are reported in Hz. Specified IR spectra were recorded with a Perkin–Elmer 1600 FTIR spectrometer. Absorbance frequencies are given at maximum of intensity in cm^{-1}.Mass spectra (*m*/*z*) were measured in the chemical ionization (CI, ammonia as the reagent gas) or in the electronic impact (EI) mode.

[(2*S*,4*S*,5*S*)-7-Allyl-9-hydroxy-6,6,8-trimethyl-2-phenyl-1,3-dioxaspiro[4.5]dec-7-en-4-yl]methyl Acetate (16 and 16′): To a solution of **14** (1.16 g, 3 mmol) in dry CH_2Cl_2 (50 mL) at –20 °C, $SOCl_2$ (0.71 g, 6 mmol) and pyridine (0.56 g, 7 mmol) were added. After 30 min, the reaction mixture was treated with a saturated solution of $NaHCO_3$ (30 mL). The mixture was diluted with ethyl acetate (100 mL) and brine (50 mL), the aqueous solution was removed and washed one time with ethyl acetate (50 mL). The organic layers were collected and washed once with brine (50 mL); the organic layer was dried with sodium sulfate and concentrated to provide a mixture of chloro compounds percolated on Al_2O_3/6% H_2O (116 g). The product was eluted slowly for 4 h and the solvents were evaporated under vacuum, the mixture was purified on silica gel (25:75, ethyl acetate/hexane) to afford a pale yellow oil (0.82 g, 2.1 mmol, 71% over 2 steps), (*R*)/(*S*) = 4:1. The two diastereoisomers were easily separated, the minor (*S*) is the more polar one. **16:** $[\alpha]_D^{25}$ = +21 ($CHCl_3$, *c* = 2.4). IR (neat): $\tilde{\nu}$ = 3350, 2975, 1742, 1237, 1062 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 7.45 (m, 2 H, C_6H_5), 7.37 (m, 3 H, C_6H_5), 6.09 (s, 1 H, PhC*H*), 5.75 (m, 1 H, C*H*CH_2), 5.02 (dm, *J* = 17.0 Hz, 1 H, CH=CH_2), 4.97 (dm, *J* = 10.2 Hz, 1 H, CH=CH_2), 4.45 (t, *J* = 5.6 Hz, 1 H, C*H*O), 4.29 (d, *J* = 12.6 Hz, 1 H, CH_2OCOCH$_3$), 4.23 (d, *J* = 12.6 Hz, 1 H, CH_2OCOCH$_3$), 3.88 (dd, *J* = 11.6, 4.6 Hz, 1 H, C*H*OH), 2.96 (d, *J* = 11.6 Hz, 1 H, O*H*), 2.88 (dd, *J* = 17.0, 6.0 Hz, 1 H, CH_2), 2.81 (dd, *J* = 17.0, 5.2 Hz, 1 H, CH_2), 2.41 (dd, *J* = 14.4, 1.4 Hz, 1 H, CH_2), 2.09 (s, 3 H, CH_3), 2.02 (dd, *J* = 14.4, 5.0 Hz, 1 H, CH_2), 1.78 (s, 3 H, CH_3), 1.22 (s, 3 H, CH_3), 1.05 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 171.1, 136.5, 136.3, 135.1, 130.4, 129.7, 128.4, 127.1, 115.2, 101.5, 87.1, 77.9, 69.2, 63.9, 41.9, 32.7, 29.4, 24.7, 20.9, 20.0, 17.6 ppm. HRMS (IE): calcd. for $C_{23}H_{30}O_5$ 386.2093; found 386.2084. **16′:** $[\alpha]_D^{25}$ = –4 ($CHCl_3$, *c* = 1.2). ^1H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 7.45 (m, 2 H, C_6H_5), 7.37 (m, 3 H, C_6H_5), 6.01 (s, 1 H, PhC*H*), 5.75 (m, 1 H, C*H*=CH_2), 5.00 (m, 2 H, CH=CH_2), [4.41–4.18] (m, 4 H), 2.88 (dd, *J* = 16.6, 5.2 Hz, 1 H, CH_2), 2.80 (dd, *J* = 16.6, 5.2 Hz, 1 H, CH_2), 2.81 (dd, *J* = 16.6, 5.2 Hz, 1 H, CH_2), 2.41 (dd, *J* = 13.0, 6.4 Hz, 1 H, CH_2), 2.08 (s, 3 H, CH_3), 1.75 (dd, *J* = 13.0, 10.2 Hz, 1 H, CH_2), 1.66 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3), 1.09 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 171.0, 136.5, 135.4, 130.8, 129.5, 128.4, 127.1, 127.0, 115.2, 101.9, 86.7, 77.5, 68.7, 64.4, 41.9, 33.1, 31.5, 25.8, 21.0, 20.2, 14.7 ppm.

[(2*S*,4*S*,5*S*)-7-Allyl-9-{[*tert*-butyl(dimethyl)silyl]oxy}-6,6,8-trimethyl-2-phenyl-1,3-dioxaspiro[4.5]dec-7-en-4-yl]methyl Acetate (18

and 18′): To a solution of **16** (1.93 g, 5 mmol) in dry DMF (20 mL) was added imidazole (0.82 g, 12 mmol) and TBDMSCl (0.9 g, 6 mmol). The reaction mixture was stirred overnight and directly purified on silica gel (1:9, ethyl acetate/hexane) to afford a pale yellow oil (2.3 g, 4.6 mmol, 92%). Compound **18′** was prepared under the same conditions and with similar yield. **18:** $[\alpha]_D^{25}$ = +3 ($CHCl_3$, *c* = 0.7). IR (neat): $\tilde{\nu}$ = 2955, 1738, 1462, 1234, 1076, 1030 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 7.48 (m, 2 H, C_6H_5), 7.37 (m, 3 H, C_6H_5), 6.06 (s, 1 H, PhC*H*), 5.78 (m, 1 H, *CH*=CH_2), 5.06 (dm, *J* = 16.2 Hz, 1 H, CH=CH_2), 5.01 (dm, *J* = 10.2 Hz, 1 H, CH=CH_2), 4.28 (m, 2 H, CH_2OCOCH$_3$), 4.19 (t, *J* = 10.2 Hz, 1 H, C*H*O), 4.07 (dd, *J* = 6.3, 3.6 Hz, 1 H, C*H*OTBS), 2.88 (d, *J* = 5.8 Hz, 2 H, CH_2), 2.28 (dd, *J* = 14.6, 4.4 Hz, 1 H, CH_2), 2.17 (dd, *J* = 14.6, 6.8 Hz, 1 H, CH_2), 2.11 (s, 3 H, CH_3), 1.67 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3), 1.07 (s, 3 H, CH_3), 0.90 [s, 9 H, C(CH_3)$_3$], 0.12 (s, 3 H, CH_3), 0.10 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 171.0, 137.6, 136.5, 136.1, 130.3, 129.1, 128.2, 127.0, 115.2, 101.4, 85.7, 77.8, 68.8, 64.2, 41.8, 33.0, 32.5, 25.9, 23.1, 22.7, 21.0, 18.0, 17.3, –3.9, –4.8 ppm. HRMS (IE): calcd. for $C_{29}H_{43}O_5Si$ [M – H^+] 499.2880; found 499.2871. **18′:** $[\alpha]_D^{25}$ = –16 ($CHCl_3$, *c* = 1.3). ^1H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 7.48 (m, 2 H, C_6H_5), 7.37 (m, 3 H, C_6H_5), 5.99 (s, 1 H, PhC*H*), 5.78 (m, 1 H, C*H*=CH_2), 5.00 (m, 2 H, CH=CH_2), 4.35 (m, 3 H), 4.18 (dd, *J* = 12.2, 9.2 Hz, 1 H, CH_2OCOCH$_3$), 2.89 (dd, *J* = 16.2, 5.4 Hz, 1 H, CH_2), 2.79 (dd, *J* = 16.2, 5.4 Hz, 1 H, CH_2), 2.29 (dd, *J* = 13.0, 6.0 Hz, 1 H, CH_2), 2.11 (s, 3 H, CH_3), 1.79 (dd, *J* = 13.0, 9.6 Hz, 1 H, CH_2), 1.68 (s, 3 H, CH_3), 1.19 (s, 3 H, CH_3), 1.12 (s, 3 H, CH_3), 0.90 [s, 9 H, C(CH_3)$_3$], 0.12 (s, 3 H, CH_3), 0.11 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 171.0, 137.4, 136.8, 134.0, 132.0, 129.6, 128.4, 127.1, 115.1, 102.0, 86.8, 77.5, 68.9, 64.5, 41.7, 33.3, 31.7, 25.9, 25.6, 21.0, 20.2, 18.1, 15.2, –4.1, –4.7 ppm.

[(2*S*,4*S*,5*S*)-9-{[*tert*-Butyl(dimethyl)silyl]oxy}-6,6,8-trimethyl-7-(2-oxoethyl)-2-phenyl-1,3-dioxaspiro[4.5]dec-7-en-4-yl]methyl Acetate (19 and 19′): Ozone was passed through a solution of **18** (0.5 g, 1 mmol) in dry methanol (50 mL) at –78 °C until the reaction became lightly blue. The solution was then purged with argon for 10 min and warmed to room temperature. PPh_3 (0.26 g, 1 mmol) was added and the reaction mixture was stirred for 10 min. The solution was concentrated under vacuum and the residue was purified on silica gel (1:4, ethyl acetate/hexane) to provide a colorless oil (0.44 g, 0.88 mmol, 88%). Compound **19′** was prepared under the same conditions and with similar yield. **19:** $[\alpha]_D^{25}$ = +5 ($CHCl_3$, *c* = 0.7). IR (neat): $\tilde{\nu}$ = 2956, 2857, 1742, 1720, 1236, 1078, 1030 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 9.59 (s, 1 H, C*H*O), 7.46 (m, 2 H, C_6H_5), 7.37 (m, 3 H, C_6H_5), 6.02 (s, 1 H, PhC*H*), 4.41 (dd, *J* = 8.0, 3.8 Hz, 1 H, C*H*O), 4.23 (m, 2 H, CH_2OCOCH$_3$), 4.11 (dd, *J* = 6.6, 3.2 Hz, 1 H, C*H*OTBS), 3.21 (d, *J* = 18.6 Hz, 1 H, CH_2), 3.19 (d, *J* = 18.6 Hz, 1 H, CH_2), 2.29 (dd, *J* = 14.6, 3.2 Hz, 1 H, CH_2), 2.12 (dd, *J* = 14.6, 3.2 Hz, 1 H, CH_2), 2.08 (s, 3 H, CH_3), 1.69 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3), 1.08 (s, 3 H, CH_3), 0.91 [s, 9 H, C(CH_3)$_3$], 0.14 (s, 3 H, CH_3), 0.08 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 200.1, 171.0, 137.4, 133.5, 130.5, 129.2, 128.2, 127.0, 101.6, 85.3, 77.8, 68.4, 64.0, 44.3, 41.3, 32.1, 25.9, 25.8, 22.9, 22.8, 21.0, 18.0, 17.7, –3.9, –4.8 ppm. HRMS (IE): calcd. for $C_{28}H_{42}O_6Si$ 502.2750; found 502.2740. **19′:** $[\alpha]_D^{25}$ = –17 ($CHCl_3$, *c* = 0.9). ^1H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 9.53 (t, *J* = 2.4 Hz, 1 H, C*H*O), 7.46 (m, 2 H, C_6H_5), 7.37 (m, 3 H, C_6H_5), 5.97 (s, 1 H, PhC*H*), 4.43 (dd, *J* = 10.0, 6.0 Hz, 1 H, C*H*OTBS), 4.38 (m, 2 H, CH_2OCOCH$_3$), 4.12 (dd, *J* = 11.5, 8.5 Hz, 1 H, C*H*O), 3.11 (d, *J* = 17.3 Hz, 1 H, CH_2), 3.07 (dd, *J* = 17.3, 2.4 Hz, 1 H, CH_2), 2.35 (dd, *J* = 13.2, 6.0 Hz, 1 H, CH_2), 2.08 (s, 3 H, CH_3), 1.75 (dd, *J* = 13.2, 10.2 Hz, 1 H, CH_2), 1.60 (s, 3 H, CH_3), 1.11 (s, 6 H, 2 CH_3), 0.91 [s, 9 H, C(CH_3)$_3$], 0.10 (s, 3 H, CH_3), 0.09 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 200.7, 171.0, 137.1, 135.5, 129.7, 128.5, 128.4, 127.1, 102.1, 86.5, 77.6, 68.7, 64.3, 44.3, 41.3, 31.7, 25.9, 25.8, 25.2, 21.0, 20.5, 18.1, 15.7, –4.1, –4.7 ppm.

(2*E*)-3-[(2*S*,4*S*,5*S*)-9-{[*tert*-Butyl(dimethyl)silyl]oxy}-6,6,8-trimethyl-7-(3-methyl-2-oxobut-3-en-1-yl)-2-phenyl-1,3-dioxaspiro[4.5]-dec-7-en-4-yl]acrylaldehyde (20 and 20′): To a solution of **19** (0.42 g, 0.84 mmol), in dry THF (20 mL) at –78 °C under argon, was added a solution of isoprenyl bromide (2 mL, 1 mmol, 0.5 M/L). The reaction mixture was stirred for 1 h, treated with a saturated solution of NH_4Cl (10 mL), diluted with ethyl acetate (40 mL) and brine (20 mL). The aqueous solution was removed and washed one time with ethyl acetate (25 mL). The organic layers were collected and dried with sodium sulfate and the solvents were evaporated. The mixture was diluted with methanol (20 mL) and K_2CO_3 solid (70 mg, 0.5 mmol) was added. The solution was stirred for 1 h, filtered through silica gel and concentrated to give a mixture (1:1). To a solution of the residue in dry CH_2Cl_2 (10 mL), Dess–Martin reagent (1.28 g, 3 mmol) was added. The reaction mixture was stirred for 1 h, diluted with ethyl acetate (30 mL) and treated with a mixture (1:1) of Na_2CO_3/$Na_2S_2O_3$ (20 mL) and brine (30 mL). The organic layer was dried with sodium sulfate and the solvents were evaporated. The corresponding aldehyde is not very stable, and was used directly without further purification. The corresponding residue was diluted with toluene (15 mL) under argon, NEt_3 (0.2 g, 2 mmol) and (formylmethyl) triphenylphosphonium chloride (340 mg, 1 mmol) were added. The reaction mixture was stirred overnight, concentrated under vacuum and purified on silica gel (12:88, ethyl acetate/ hexane) to afford a pale yellow oil (0.29 g, 0.55 mmol, 55% over 4 steps). Compound **20′** was prepared under the same conditions and with similar yield. **20:** $[\alpha]_D^{25}$ = +5 ($CHCl_3$, *c* = 0.8). IR (neat): $\tilde{\nu}$ = 2930, 2857, 1692, 1066 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 9.67 (d, *J* = 7.8 Hz, 1 H, C*H*O), 7.47 (m, 2 H, C_6H_5), 7.37 (m, 3 H, C_6H_5), 7.11 (dd, *J* = 15.6, 4.8 Hz, 1 H, C*H*=CH), 6.66 (ddd, *J* = 15.6, 7.8, 1.6 Hz, 1 H, C*H*=CH), 6.12 (s, 1 H, PhC*H*), 6.05 (s, 1 H, C=CH_2), 5.83 (d, *J* = 1.4 Hz, 1 H, C=CH_2), 5.03 (dd, *J* = 5.0, 1.4 Hz, 1 H, C*H*O), 4.01 (t, *J* = 8.0 Hz, 1 H, C*H*OTBS), 3.61 (s, 2 H, COCH_2), 2.38 (dd, *J* = 13.8, 8.6 Hz, 1 H, CH_2), 2.17 (dd, *J* = 14.2, 7.2 Hz, 1 H, CH_2), 1.92 (s, 3 H, CH_3), 1.51 (s, 3 H, CH_3), 1.23 (s, 3 H, CH_3), 1.06 (s, 3 H, CH_3), 0.88 [s, 9 H, C(CH_3)$_3$], 0.05 (s, 3 H, CH_3), 0.02 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 199.5, 193.3, 152.8, 144.3, 137.8, 134.3, 132.8, 132.2, 129.2, 128.4, 126.4, 124.6, 101.4, 89.0, 78.8, 69.5, 40.7, 37.9, 35.2, 26.5, 25.8, 20.1, 18.0, 17.9, 17.1, –4.1, –4.8 ppm. HRMS (IE): calcd. for $C_{31}H_{44}O_5Si$ 524.2958; found 524.2961. **20′:** $[\alpha]_D^{25}$ = +33 ($CHCl_3$, *c* = 0.3). ^1H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 9.67 (d, *J* = 7.6 Hz, 1 H, C*H*O), 7.48 (m, 2 H, C_6H_5), 7.37 (m, 3 H, C_6H_5), 6.81 (dd, *J* = 15.6, 4.4 Hz, 1 H, C*H*=CH), 6.56 (dd, *J* = 7.6, 1.6 Hz, 1 H, C*H*=CH), 6.03 (s, 2 H, PhC*H* + C=CH_2), 5.78 (d, *J* = 1.4 Hz, 1 H, C=CH_2), 4.92 (dd, *J* = 4.4, 1.6 Hz, 1 H, C*H*O), 4.42 (dd, *J* = 9.2, 6.2 Hz, 1 H, C*H*OTBS), 3.52 (d, *J* = 18.0 Hz, 1 H, COCH_2), 3.48 (d, *J* = 18.0 Hz, 1 H, COCH_2), 2.23 (dd, *J* = 13.4, 6.0 Hz, 1 H, CH_2), 1.91 (s, 3 H, CH_3), 1.75 (dd, *J* = 13.4, 9.6 Hz, 1 H, CH_2), 1.51 (s, 3 H, CH_3), 1.13 (s, 6 H, CH_3), 0.92 [s, 9 H, C(CH_3)$_3$], 0.08 (s, 3 H, CH_3), 0.07 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 198.3, 192.9, 152.2, 144.6, 137.2, 134.4, 133.1, 130.6, 129.6, 128.4, 126.9, 123.8, 102.4, 88.0, 78.7, 68.7, 41.2, 37.6, 33.6, 25.9, 25.8, 25.3, 20.4, 17.9, 15.8, –4.1, –4.7 ppm.

1-{(2*S*,4*S*,5*S*)-9-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-[(1*E*)-3-hydroxy-prop-1-en-1-yl]-6,6,8-trimethyl-2-phenyl-1,3-dioxaspiro[4.5]dec-7-en-7-yl}-3-methylbut-3-en-2-one (21 and 21′): To a solution of **20**

(0.27 g, 0.52 mmol) in dry THF (10 mL) at –78 °C under argon a solution of lithium tris[(3-ethyl-3-pentyl)oxy]hydridoaluminate in THF (1.2 mL, 0.6 mmol, 0.5 mol/L) was added. After 30 min (conscientiously checked by TLC), the reaction mixture was treated with a saturated solution of NH_4Cl (5 mL) and the mixture was diluted with ethyl acetate (20 mL) and brine (10 mL). The aqueous solution was removed and washed once with ethyl acetate (15 mL). The organic layers were collected and washed once with brine (20 mL), the organic layer was dried with sodium sulfate and the solvents were evaporated. The residue was purified on silica gel (1:3, ethyl acetate/hexane) to afford a pale yellow oil (243 mg, 0.46 mmol, 89%). Compound **21′** was prepared under the same conditions and with similar yield. **21:** $[\alpha]_D^{25} = -28$ ($CHCl_3$, $c = 0.5$). IR (neat): $\tilde{\nu}$ = 3470, 2828, 1681, 1066 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 7.48 (m, 2 H, C_6H_5), 7.39 (m, 3 H, C_6H_5), [6.14–6.02] (m, 4 H), 5.79 (d, J = 1.4 Hz, 1 H, C=CH_2), 4.86 (d, J = 6.6 Hz, 1 H, C*H*O), 4.24 (d, J = 3.2 Hz, 1 H, CH_2OH), 4.14 (t, J = 7.8 Hz, 1 H, C*H*OTBS), 3.55 (d, J = 18,0 Hz, 1 H, COCH_2), 3.50 (d, J = 18.0 Hz, 1 H, COCH_2), 2.34 (dd, J = 13.8, 8.0 Hz, 1 H, CH_2), 2.18 (dd, J = 13.8, 8.0 Hz, 1 H, CH_2), 1.91 (s, 3 H, CH_3), 1.46 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3), 0.93 (s, 3 H, CH_3), 0.88 [s, 9 H, C(CH_3)$_3$], 0.07 (s, 3 H, CH_3), 0.04 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 199.3, 144.4, 137.8, 133.5, 133.3, 133.1, 128.9, 128.2, 126.7, 126.5, 124.2, 100.8, 87.6, 80.5, 69.8, 62.9, 41.5, 37.8, 35.3, 26.2, 25.9, 20.0, 18.1, 17.9, 16.9, –4.1, –4.7 ppm. HRMS (IE): calcd. for $C_{31}H_{46}O_5Si$ 526.3114; found 526.3118. **21′:** $[\alpha]_D^{25} = +29$ ($CHCl_3$, $c = 2.2$). ^1H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 7.50 (m, 2 H, C_6H_5), 7.36 (m, 3 H, C_6H_5), 6.08 (dt, J = 16.0, 5.4 Hz, 1 H, C*H*=CH), 6.07 (s, 2 H, PhC*H* + C=CH_2), 5.79 (dd, J = 16.0, 6.6 Hz, 1 H, C*H*=CH), 5.77 (s, 1 H, C=CH_2), 4.68 (d, J = 6.6 Hz, 1 H, C*H*O), 4.50 (dd, J = 10.2, 6.0 Hz, 1 H, C*H*OTBS), 4.22 (d, J = 5.0 Hz, 2 H, CH_2OH), 3.52 (d, J = 17,8 Hz, 1 H, CH_2), 3.50 (d, J = 17.8 Hz, 1 H, CH_2), 2.33 (dd, J = 13.2, 5.8 Hz, 1 H, CH_2), 1.92 (s, 3 H, CH_3), 1.76 (dd, J = 13.2, 10.4 Hz, 1 H, CH_3), 1.48 (s, 3 H, CH_3), 1.11 (s, 3 H, CH_3), 1.04 (s, 3 H, CH_3), 0.92 [s, 9 H, C(CH_3)$_3$], 0.09 (s, 3 H, CH_3), 0.07 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 198.5, 144.7, 138.3, 134.1, 133.9, 131.0, 129.2, 128.3, 126.9, 126.8, 123.6, 101.8, 87.3, 79.4, 69.2, 62.9, 41.0, 37.6, 32.9, 25.9, 25.4, 20.4, 18.2, 18.0, 15.8, –4.1, –4.7 ppm.

Dimethyl (4-{(2*S*,4*S*,5*S*)-9-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-[(1*E*)-3-chloroprop-1-en-1-yl]-6,6,8-trimethyl-2-phenyl-1,3-dioxaspiro[4.5]-dec-7-en-7-yl}-2-methyl-3-oxobutyl)malonate (23 and 23′): To a solution of **21** (105 mg, 0.2 mmol) in dry acetonitrile (5 mL) were added dimethyl malonate (105 mg, 0.8 mmol) and Cs_2CO_3 (197 mg, 0.6 mmol). The reaction mixture was stirred overnight, concentrated under vacuum and directly purified on silica gel (1:4, ethyl acetate/hexane) to afford a pale yellow oil (113 mg, 0.17 mmol, 86%) of an epimeric mixture (1:1). To the corresponding mixture (66 mg, 0.1 mmol) in dry CH_2Cl_2 (5 mL) was added 1-chloro-*N*,*N*,2-trimethyl-1-propenylamine (40 mg, 0.3 mmol). The reaction mixture was stirred for 45 min, treated with a saturated solution of $NaHCO_3$ (5 mL) and diluted with ethyl acetate (15 mL) and brine (10 mL). The aqueous solution was removed and washed once with ethyl acetate (15 mL). The organic layers were collected and dried with sodium sulfate and the solvents were evaporated. The residue was purified on silica gel (15:85, ethyl acetate/hexane) to afford a pale yellow oil (62 mg, 0.091 mmol, 91%). Compound **23′** was prepared under the same conditions and with similar yield. These compounds were used immediately in the next reaction.

Dimethyl (2*S*,3a*S*,5*R*,10*S*,14*E*,15a*S*)-5-{[*tert*-Butyl(dimethyl)-silyl]oxy}-6,10,16,16-tetramethyl-9-oxo-2-phenyl-4,5,8,9,10,11,13,15a-octahydro-12*H*-3a,7-methanocyclotetradeca[*d*][1,3]dioxole-12,12-dicarboxylate (24) and Dimethyl (2*S*,3a*S*,7*Z*,10*S*,14*E*,15a*S*)-6,10,16,16-Tetramethyl-9-oxo-2-phenyl-4,9,10,11,13,15a-hexahydro-12*H*-3a,7-methanocyclotetradeca[*d*][1,3]dioxole-12,12-dicarboxylate (25): To a refluxed suspension of Cs_2CO_3 (82 mg, 0.25 mmol) and TBAI (74 mg, 0.2 mmol) in dry acetonitrile (40 mL) was added **23** (34 mg, 0.05 mmol) in dry acetonitrile (5 mL) with a syringe pump over 6 h. After 15 h of stirring, the solution was filtered quickly through silica gel (1:3, ethyl acetate/hexane) and the solvents were evaporated under vacuum. The residue was purified on silica gel (1:4, ethyl acetate/hexane) to afford two colourless oils, **24** (3.8 mg, 0.0059 mmol, 12%) and **25** (8.9 mg, 0.0174 mmol, 35%). **24:** $[\alpha]_D^{25} = +15$ ($CHCl_3$, $c = 0.7$). IR (neat): $\tilde{\nu}$ = 2930, 2856, 1732, 1711, 1455, 1258, 1092, 1042 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 7.45 (m, 2 H, C_6H_5), 7.38 (m, 3 H, C_6H_5), 6.29 (tm, J = 11.5 Hz, 1 H, C*H*=CH), 6.08 (s, 1 H, PhC*H*), 5.39 (dd, J = 15.4, 10.2 Hz, 1 H, C*H*=CH), 4.42 (d, J = 10.2 Hz, 1 H, C*H*O), 4.16 (t, J = 8.2 Hz, 1 H, C*H*OTBS), 3.74 (s, 3 H, COOCH_3), 3.71 (s, 3 H, COOCH_3), 3.22 (d, J = 16.2 Hz, 1 H, COCH_2), 3.20 (m, 1 H, COC*H*CH_3), 3.18 (dm, J = 15.4 Hz, 1 H, CH_2), 2.99 (d, 1 H, COCH_2), 2.81 (dd, J = 14.2, 9.0 Hz, 1 H, CH_2), 2.41 (t, J = 13.7 Hz, 1 H, CH_2), 2.03 (m, 2 H, 2 CH_2), 1.72 (d, J = 14.5 Hz, 1 H, CH_2), 1.54 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 1.20 (s, 3 H, CH_3), 0.91 [s, 9 H, C(CH_3)$_3$], 0.82 (d, J = 6.8 Hz, 3 H, CH_3), 0.12 (s, 3 H, CH_3), 0.08 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 212.9, 171.9, 171.8, 139.9, 137.3, 134.8, 131.8, 128.7, 128.4, 125.9, 124.9, 100.2, 87.9, 79.7, 69.1, 54.8, 53.0, 52.2, 43.2, 39.7, 39.3, 38.4, 36.1, 34.8, 28.9, 25.8, 21.5, 18.0, 17.0, 15.8, –3.9, –4.8 ppm. HRMS (IE): calcd. for $C_{36}H_{52}O_8Si$ 640.3431; found 640.3444. **25:** $[\alpha]_D^{25} = +214$ ($CHCl_3$, $c = 0.5$). IR (neat): $\tilde{\nu}$ = 2962, 2922, 1731, 1694, 1436, 1260, 1090 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 21 °C): δ = 7.45 (m, 2 H, C_6H_5), 7.38 (m, 3 H, C_6H_5), 6.01 (s, 1 H, PhC*H*), 5.88 (s, 1 H, C=C*H*CO), 5.85 (br., 1 H, C*H*=CCH_3), 5.59 (m, 2 H, C*H*=CH), 4.29 (d, J = 8.8 Hz, 1 H, C*H*O), 3.72 (s, 6 H, 2 COOCH_3), 2.89 (dm, J = 19.0 Hz, 1 H, CH_2), 2.82 (d, J = 8.5 Hz, 1 H, CH_2), 2.68 (m, 1 H, COCHCH_3), 2.40 (dm, J = 19.0 Hz, 1 H, CH_2), 2.16 (d, J = 14.2 Hz, 1 H, CH_2), 1.76 (dd, J = 14.8, 11.2 Hz, 1 H, CH_2), 1.70 (s, 3 H, CH_3), 1.29 (s, 3 H, CH_3), 1.20 (s, 3 H, CH_3), 0.90 (d, J = 6.4 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 21 °C): δ = 210.2, 171.7, 171.4, 151.0, 139.5, 133.0, 131.4, 129.0, 128.5, 128.4, 127.4, 126.1, 123.4, 101.0, 85.0, 79.3, 54.9, 53.1, 52.6, 42.0, 40.6, 35.1, 33.7, 31.2, 24.4, 23.5, 19.6, 13.5 ppm. HRMS (IE): calcd. for $C_{30}H_{36}O_7$ 508.2461; found 508.2449.

Supporting Information (see footnote on the first page of this article): Experimental details and data for compounds **5**–**14** and **17**.

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[1] a) A. Toro, P. Nowak, P. Deslongchamps, *J. Am. Chem. Soc.* **2000**, *122*, 4526–4527; b) J. Germain, P. Deslongchamps, *J. Org. Chem.* **2002**, *67*, 5269–5278; c) A. Toro, P. Deslongchamps, *J. Org. Chem.* **2003**, *68*, 6847–6858; d) P. Soucy, A. L'Heureux, A. Toro, P. Deslongchamps, *J. Org. Chem.* **2003**, *68*, 9983–9987; e) review: E. Marsault, A. Toro, P. Nowak, P. Deslongchamps, *Tetrahedron* **2001**, *57*, 4243–4260.

[2] a) K. C. Nicolaou, Z. Yang, J. J. Liu, H. Ueno, P. G. Nantermet, R. K. Guy, C. F. Claiborne, J. Renaud, E. A. Couladouros, K. Paulvannan, E. J. Sorensen, *Nature* **1994**, *367*, 630–634; b) R. A. Holton, C. Somoza, H. B. Kim, F. Liang, R. J.

Biediger, P. D. Boatman, M. Shindo, C. C. Smith, S. Kim, H. Nadizadeh, Y. Suzuki, C. Tao, P. Vu, S. Tang, P. Hang, K. K. Murthi, L. N. Gentile, J. H. Liu, *J. Am. Chem. Soc.* **1994**, *116*, 1597–1598; c) J. J. Masters, J. T. Link, L. B. Snyder, W. B. Young, S. J. Danishefsky, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1723–1726; d) P. A. Wender, N. F. Badham, S. P. Conway, P. E. Floreansic, T. E. Glass, J. B. Houze, N. E. Krauss, D. Lee, D. J. Marquess, P. L. McGrane, W. Meng, M. G. Natchus, A. J. Shuker, J. C. Sutton, R. E. Taylor, *J. Am. Chem. Soc.* **1997**, *119*, 2757–2758; e) T. Mukaiyama, I. Shiina, H. Iwadare, H. Sakoh, Y. Tani, M. Hasegawa, K. Saitoh, *Proc. Jpn. Acad. Ser. B* **1997**, *73*, 95–100; f) K. Morihara, R. Hara, S. Kawahara, T. Nishimori, N. Nakamura, H. Kusama, I. Kuwajima, *J. Am. Chem. Soc.* **1998**, *120*, 12980–12981.

[3] a) A. Srikrishna, T. J. Reddy, K. P. Praveen, *Chem. Commun.* **1996**, 1369–1370; b) A. Srikrishna, T. J. Reddy, K. P. Praveen, *J. Chem. Soc., Perkin Trans. 1* **1998**, 3143–3144; c) G. Mehta, S. K. Chattopadhyay, J. D. Umarye, *Tetrahedron Lett.* **1999**, *40*, 4881–4884.

[4] Epoxidation of (–)-(*R*)-Carvone followed by Birch reduction and methylation of the resulting enolate gave **4** in 60% overall yield: J. D. McChesney, T. N. Thompson, *J. Org. Chem.* **1985**, *50*, 3473–3481.

[5] S. L. Schreiber, *J. Am. Chem. Soc.* **1980**, *102*, 6163–6165.

[6] B. Boulin, B. Arreguy-San Miguel, B. Delmond, *Tetrahedron* **2000**, *56*, 3927–3932.

[7] The proton at C^{13} in **17** is axial [δ = 5.32 (dd, *J* = 9.4, 6.8 Hz, 1 H) ppm] as in compound **18′** [δ = 4.18 (dd, *J* = 12.2, 9.2 Hz, 1 H) ppm].

[8] F. Munyemana, A. M. Frisque-Hesbain, A. Devos, L. Ghosez, *Tetrahedron Lett.* **1989**, *30*, 3077–3080.

[9] We tried with palladium to generate the π-allyl complex in order to form the macrocycle, but to our disapointment this methodology failed.

[10] Several studies have been undertaken to prepare Taxol from an intermolecular reaction starting from a polyfunctionalized ring A. Much work has failed, just few examples have given some useful results and only when a simpler ring A precursor was used: a) Y. Lu Fung, A. G. Fallis, *Tetrahedron Lett.* **1993**, *34*, 3367–3370; b) D. Crich, S. Natarajan, *J. Chem. Soc., Chem. Commun.* **1995**, *1*, 85–86; c) Y. F. Lu, C. W. Harwig, A. G. Fallis, *Can. J. Chem.* **1995**, *73*, 2253–2262; d) C. W. Harwig, S. Py, A. G. Fallis, *J. Org. Chem.* **2001**, *66*, 4170–4179; e) J. D. Winkler, S. K. Bhattacharya, R. A. Batey, *Tetrahedron Lett.* **1996**, *37*, 8069–8072; f) G. Chouraqui, M. Petit, P. Phansavath, C. Aubert, M. Malacria, *Eur. J. Org. Chem.* **2006**, *6*, 1413–1421.

[11] In some total syntheses,[2a,2c,2f] one of the key steps was the formation of an eight-membered ring on a substituted ring A having no OP at C^{13}. The yield for the medium ring formation was moderate (ca. 50%) in all cases. It is thus possible, that it could be substantially improved by starting with a ring A precursor containing a β-OP group at C^{13}.

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