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Synthesis of the Taxol AB-System by Olefination of an A-Ring C1 Ketone and Direct B-Ring Closure

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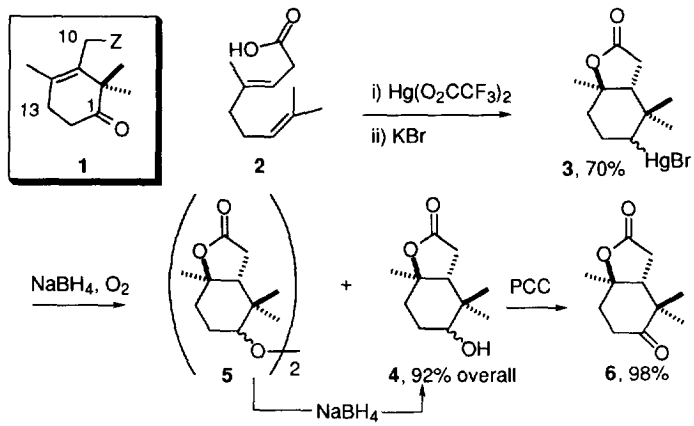
Abstract. Two syntheses of 13-deoxy-taxol C1 ketones are presented. Olefination of these C1 ketones is achieved, indirectly, via either the Meyer-Schuster reaction or by introduction of a vinyl group with vinylcerium dichloride followed by allylic rearrangement. Both methods provide the *E*-olefin exclusively. Dihydroxylation of these olefins is achieved with catalytic OsO_4 and NMNO in moderate yield, providing the taxol-1,2-diol unit with the correct relative stereochemistry. Closure of the B-ring is brought about in excellent yield by displacement of an allylic bromide at C9 by an α-sulfonyl anion at C10.

In the preceding paper,[1] in the context of a convergent approach to taxol, we described the asymmetric synthesis of a C-ring synthon by means of an aldol condensation/radical cyclization route. In accordance with our general strategy, we describe here two syntheses of 13-deoxy-taxol-A-rings, the appendage of the B-ring via nucleophilic attack at C1, subsequent nucleophilic formation of the C9,10 bond, and an interesting transannular reaction encountered in the course of fusion of a C-ring.[2]

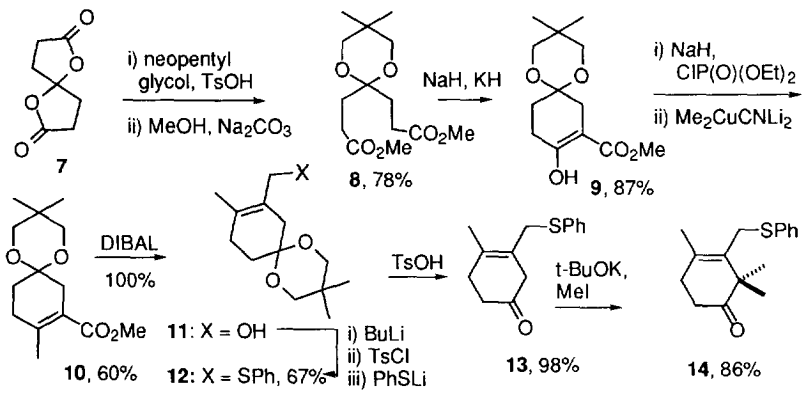
The general strategy we adopted called for the rapid, economic synthesis of an achiral A-ring **1** such that efforts could be concentrated on methods for afixing the B ring. In analysing **1**, we were struck by its terpene-like skeleton and were consequently drawn to oxidative cyclizations of readily available acyclic terpenoids such as geraniol and nerol. Initially, we explored Lewis acid induced cyclizations of geraniol 6,7-epoxide[3-6] and its esters but met with little success. Frejd has shown that related cyclizations may be achieved in high yield provided that a suitable terminus is built into the system.[7] Oxidative radical cyclizations of geranyl acetate, as described by Breslow,[8,9] were successful but unsuitable for use on a large scale due to tedious separation problems. Halogenative cyclizations of acyclic terpenoids with NBS and related species are reported to occur only in low yield,[10-14] and so we turned to the mercuric trifluoroacetate induced cyclization of homogeranic acid (**2**)[15-18] developed by Hoye,[18] and were delighted to obtain excellent yields of the cyclization product, which could be converted to the crystalline bromide salt **3** for storage (Scheme 1). This oxidative cyclization approach to the taxol A-ring differs from that employed originally by Kato in his biomimetic studies[12] in so far as the C1 position is suitably functionalised for eventual introduction of the requisite hydroxyl group. Subsequent to our preliminary communication[19] outlining this work, similar strategies were described by Stork,[20] Koskinen,[21] and Nishizawa.[22] Treatment of salt **3** with sodium borohydride under oxygen according to the Whitesides oxidative demercuration protocol[23] then gave the alcohol **4** in 92% overall yield as an approximately 1.7:1, unassigned mixture of diastereomers. We note that when this reaction was conducted on a relatively small scale (≤ 100 mg) it was a clean, spot to spot transformation from which the alcohol **4** could be isolated immediately in essentially quantitative yield. On a multigram scale, and despite considerable juggling with conditions, a byproduct was consistently formed which, fortuitously, was converted to **4** when the reaction mixture was allowed to stir overnight with excess

borohydride. We suspect therefore that this byproduct is likely to be the dialkyl peroxide **5** formed by coupling of two peroxyl radicals followed by loss of oxygen.[24] Finally, PCC oxidation provided the nicely crystalline, camphoraceous **6** in 98% yield (Scheme 1) which, it will be recognized, is effectively **1** with the 11,12-alkene protected as the lactone.



Scheme 1

Although this synthesis of **6** was concise, high-yielding, and proceeded from readily available materials, it suffered the one major defect of being stoichiometric in an expensive, toxic reagent with all its associated disposal problems. An alternative, perhaps less elegant but more practical, approach was therefore developed (Scheme 2).

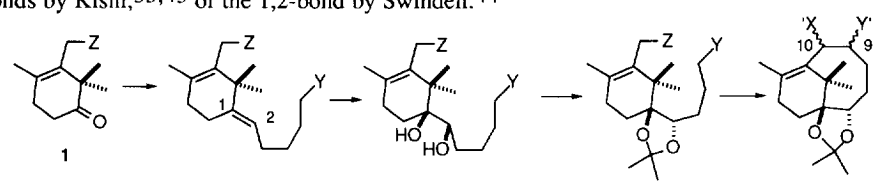


Scheme 2

The spirobislactone **7**, available in multi-hundred gram lots by simple fusion of succinic anhydride with catalytic KOH as described by Fuchs,[25] was treated with neopentyl glycol and catalytic TsOH and then with methanolic KOH to give the diester **8** in 78% overall yield. Dieckman cyclization then provided the highly enolized β-ketoester **9** in 87% yield, whose enol phosphate[26] reacted smoothly with a higher order cuprate to give **10**. DIBAL reduction of this α,β-unsaturated ester provided the somewhat unstable allylic alcohol **11**, which was converted to the corresponding thioether **12** by displacement of the derived tosylate

with lithium thiophenate in 67% yield, overall. This two step functional group exchange was preferred on a large scale over the more direct reaction of **11** with diphenyl disulfide and tributylphosphine[27] (71%) owing to greater ease of purification. Removal of the acetal protecting group with TsOH in aqueous acetone then gave **13** in 98% yield which, on exposure to excess methyl iodide and two equivalents of potassium t-butoxide, led to the target (**14**) in 86% overall yield from **12** (Scheme 2).[28] Careful TLC monitoring of the deprotection (**12** → **13**) was essential as prolonged exposure to the reaction conditions resulted in migration of the double bond into conjugation which, in turn, gave rise to competing alkylation adjacent to the phenylthio group.

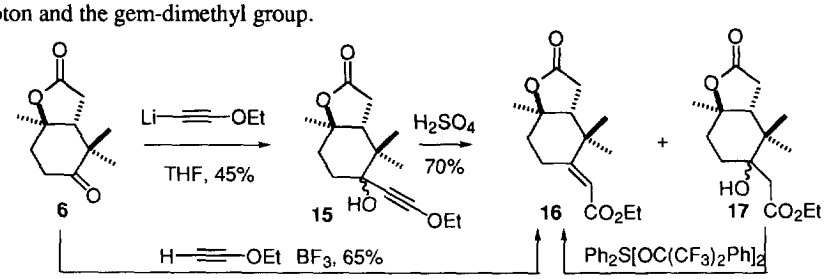
With two rapid entries into the A-ring established, we next turned our attention to model studies for the fusion of a simple B-ring. Our overall strategy called for *E*-selective olefination of the C1-ketone in **1**, *cis*-dihydroxylation of the exocyclic alkene to give the correct relative stereochemistry at C1 and C2, acetalization, and nucleophilic ring closure across C9 and C10 (Scheme 3). The reasons underlying this strategy were twofold. Firstly, we hypothesized, with the aid of molecular models, that the acetonide would orient the hydrocarbon chain favorably and so help overcome some of the entropic and transannular strain barriers normally associated with direct formation of medium sized rings.[29] A similar role can probably be attributed to the 1,2-cyclic carbonate ester in the Nicolaou and Danishefsky syntheses.[30-34] However, it should also be noted that Kishi, in his approach to taxoids, detected no benefit from the incorporation of a 1,2-acetonide on B-ring closure by formation of the 10,11-bond but attributed this to the slow step being activation of a vinyl iodide by a Ni(II)/Cr(II) couple rather than cyclization.[35] Secondly, there was good precedent for cyclization of B-rings by formation of the 9,10-bond. McMurray type couplings had been demonstrated as early as 1986 by the Kende group, [36] and were subsequently used in the Nicolaou synthesis, but the yields were low.[30-33] However, the beautiful work of Kuwajima, in which excellent yields for B-ring closure were achieved by formation of the 9,10 bond by means of the intramolecular Sakurai reaction,[37-39] prompted us to think in terms of coupling of suitable nucleophile/electrophile pairs at C9 and 10. While this project was in progress a very high yield B-ring synthesis by means of closure of a C9 nucleophile on a C10 electrophile was also described, so demonstrating the soundness of this approach.[40] Efficient strategies for direct B-ring formation by formation of the 10,11 bond have been devised by Danishefsky[34,41,42], by formation of the 1,2- or 10,11-bonds by Kishi,[35,43] or the 1,2-bond by Swindell.[44]



Scheme 3

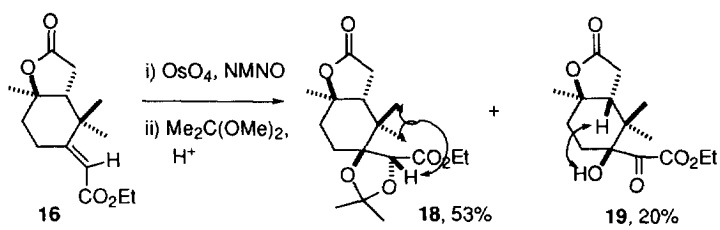
In attempting to carry out this strategy, the first problem to be encountered was that of olefination of the hindered ketone in either **6** or **14**. Not too surprisingly, standard olefination methods failed. Indeed, the poor reactivity of closely related ketones was noted by Nicolaou[31] and required both his group and Danishefsky's[34] to use the Shapiro reaction with C1 as a vinyl anion in the course of their taxol syntheses. It should, however, be noted that Wittig olefination of related, hindered ketones has been achieved, albeit under somewhat unusual conditions.[45] The essential clue to the solution of the present problem was provided by the work of Watt[46,47] wherein it was demonstrated that cyanohydrins of C1 ketones of the taxol A-ring could be prepared in high yield. We therefore turned to the use of acetylene based nucleophiles and the Meyer-Schuster reaction.[48] Treatment of **6** with the lithium salt of ethoxyacetylene provided the propargyl alcohol **15** in 45% yield together with considerable recovered substrate. Exposure to dilute sulfuric acid then

provided the desired α,β-unsaturated ester **16** in 70% yield together with 21% of the β-hydroxy ester **17**, which could be smoothly converted to **16** with the Martin sulfurane reagent.[49] A more direct procedure[50] for this Meyer-Schuster reaction involved simple stirring of **6** with ethoxyacetylene and BF_3.etherate, whereupon **16** was isolated directly in 65% yield, together with recovered substrate (18%) and **17** (8%). The relatively modest yields in the conversion of **6** to **15** and **16**, and the considerable recovered substrate in each case, can be ascribed to the murky brown, commercial solutions of unstable, ethoxyacetylene in hexanes which make quantitative dispensation difficult. Probably, higher yields could be obtained with freshly prepared ethoxyacetylene.[51] Likewise, recent modifications[52] of the rearrangement of proparyl alcohols might improve the yield of **16** from **15**. It is noteworthy, however, that either modification of this Meyer-Schuster reaction gave **16** as a single isomer, assigned the *E*-geometry on the basis of a n.O.e. correlation between the olefinic proton and the gem-dimethyl group.



Scheme 4

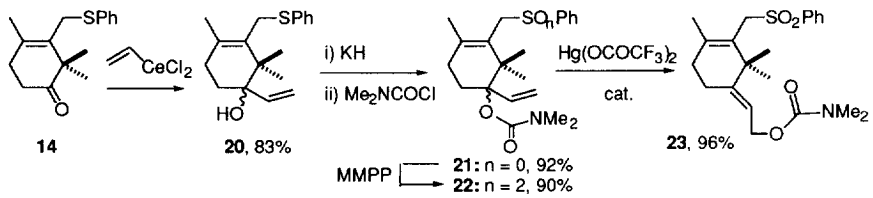
With the stereocontrolled olefination in hand, we turned our attention to dihydroxylation. Reaction of **16** with catalytic OsO_4 and *N*-methylmorpholine *N*-oxide (NMNO) as overall oxidant under the Van Rheenan conditions[53] was sluggish and led to a complex reaction mixture, containing unreacted substrate, from which the required diol could not be isolated pure. However, treatment of this mixture with 2,2-dimethoxypropane and catalytic TsOH enabled isolation of the desired acetonide **18** and the α-keto ester **19** in 53 and 20% overall yields, respectively, for the two steps (Scheme 5). Attempts to drive the dihydroxylation reaction to completion were self-defeating and resulted in the formation of ever greater quantities of **19**. The formation of such α-keto esters as byproducts in the Sharpless asymmetric dihydroxylation reaction has been discussed recently in the literature.[54] The stereochemistry of **18** and **19**, determined with the aid of the indicated n.O.e. measurements, leads to the conclusion that dihydroxylation occured, atypically,[55] from the axial direction.



Scheme 5

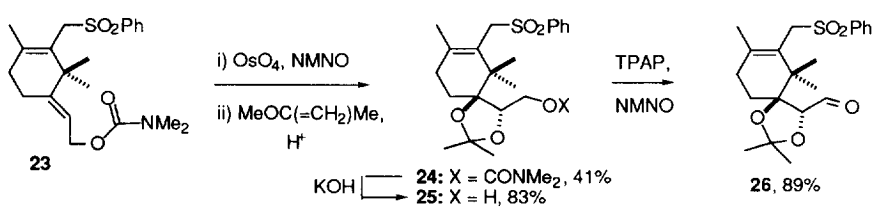
The problems of modest yield encountered in the Meyer-Schuster olefination of **6** and the poor reactivity of the electron deficient alkene **16** with respect to dihydroxylation prompted us to explore alternative strategies for the introduction of more reactive electron rich exocyclic alkenes with the A-ring synthon **14**. Attention was focused on the possibility of employing allylic type rearrangements as a means of access to the requisite functionality. To this end, **14** was treated with vinylmagnesium bromide resulting in the isolation of

the adduct **20** in 37% yield. The mass balance consisted of recovered substrate, whence the assumption that enolization of the hindered ketone was a competing process and that a shift to the less basic organocerium derivative would be beneficial. Indeed, transmetallation of vinylmagnesium bromide with rigorously dried cerium trichloride[56-58] followed by reaction with **14** enabled the isolation of **20** in 83% yield. This tertiary allylic alcohol was next converted to the carbamate derivative **21**, by sequential reaction with potassium hydride and *N,N*-dimethylcarbamoyl chloride, in good yield and the thioether then oxidized to the corresponding sulfone (**22**) with magnesium monoperoxyphthalate (MMPP).[59] Exposure of **22** to a catalytic quantity of mercuric trifluoroacetate smoothly provided the product (**23**) of allylic rearrangement as the pure *E*-isomer as verified by a strong n.O.e correlation between the olefinic proton and the gem-dimethyl group (Scheme 6). The mercury catalysed[60] rearrangement of the carbamate **22** was preferable to palladium (II) catalysed[61] transposition of the corresponding acetate as this latter gave an inferior yield of a 1:1 *E*:*Z*-mixture.



Scheme 6

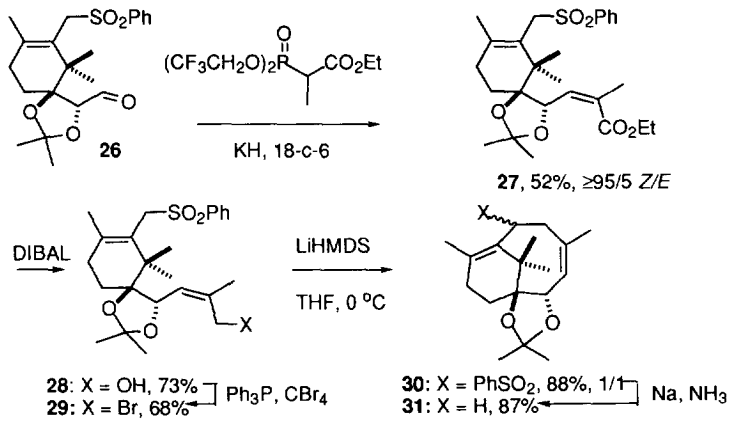
Dihydroxylation of **23** was again conducted according to the Van Rheenan protocol which, after protection with 2-methoxypropene, enabled the isolation of crystalline **24** in 41% overall yield for the two steps. Although the yield of this dihydroxylation reaction remains less than optimum, it at least established that the trisubstituted, exocyclic olefin could be functionalized in preference to the tetrasubstituted, endocyclic one. Moreover, sufficient material was readily available by this route to enable us to explore our strategy for appendage of the B-ring. With this in mind, saponification of **24** gave the alcohol **25**, which was oxidized with catalytic tetrapropylammonium perruthenate (TPAP) and NMNO according to the method of Ley and Griffith,[62] to give **26** (Scheme 7). This aldehyde was moderately unstable and the material was therefore best stocked as **25** and only converted to **26** for immediate use in the next step.



Scheme 7

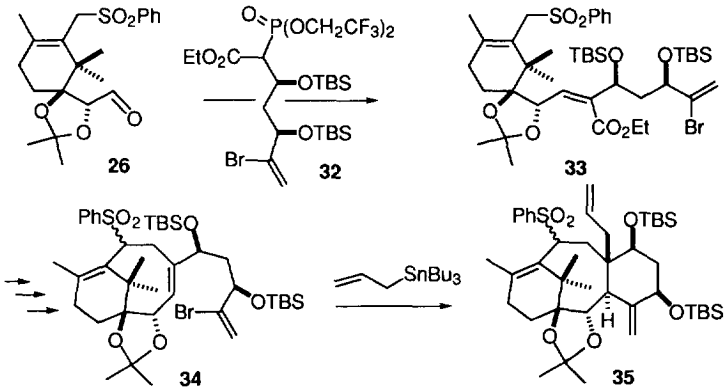
Z-Selective olefination of **26** with ethyl 2-[bis(2,2,2-trifluoroethyl)phosphono]propionate under Still conditions[63] provided **27** in 52% yield as ≥95:5 *Z*:*E*-mixture, with the geometry of the major isomer being confirmed by subsequent reactions (Scheme 8). In the ideal situation deprotonation of **27** followed by cyclization would have provided a seco-CD taxoid with the 9-keto functionality correctly installed and a phenylsulfonyl moiety poised for transformation to the required 10-acetoxy function of taxol itself. Unfortunately, we were unable to realize such a cyclization either on **27** itself, on a mixed anhydride derived by saponification of **27** and activation with isobutyl chloroformate, or on the corresponding aldehyde. While this work was in progress, the facile formation of cyclooctanones by condensation of α-sulfonyl anions onto

esters[64,65] and, later, π-allyl palladium complexes[66] and enones[67] appeared in the literature, indicating that such reactions are indeed possible. We reasoned that the failure of **27**, or the related mixed anhydride, to undergo cyclization might be due to the fragmentation of any tetrahedral intermediate, or adduct in the case of the aldehyde, in the reverse, rather than the forward direction, owing to the considerable strain in the tricyclic skeleton. This line of reasoning prompted us to explore intramolecular alkylations rather than acylations. Hence, **27** was reduced with DIBAL to the alcohol **28** which was then converted to the corresponding bromide **29** with triphenylphosphine and tetrabromomethane. Much to our delight, brief exposure of **29** to LiHMDS at 0 °C resulted in the formation of **30** in 88% yield as an approximately 1:1 mixture of diastereomers. That the mixture was indeed one of diastereomers, rather than one of regioisomers resulting from cyclization at either end of the sulfonyl allyl anion, was readily demonstrated by exposure to sodium in liquid ammonia whereupon an 87% yield of a single desulfonylated product (**31**) was obtained (Scheme 8).



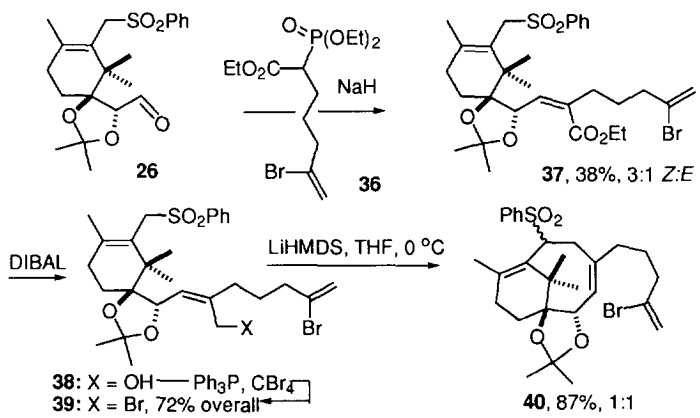
Scheme 8

The ease with which **29** was cyclized in high yield to **30** is doubtless a function of the allylic nature of the displaced bromide. Not only is this a very reactive electrophile, but also the double bond serves to further reduce the number of degrees of freedom available and to minimize transannular strain at the transition state. However, in a truly convergent synthesis of taxol bringing together preformed A and CD-ring moieties the corresponding cyclization would involve a saturated neopentyl bromide and consequently would be many orders of magnitude more difficult. This, and the realization that condensation of a C-ring synthon such as that prepared in the preceding paper with either **6** or **14** would be extremely difficult, led us to consider a more linear modification of our overall strategy. In this approach, aldehyde **26** would be condensed with a Horner Emmons reagent **32** leading to **33**. The ester could then be converted to the corresponding allylic bromide and cyclization conducted as in Scheme 8 to give **34** (Scheme 9). Radical cyclization of **34** with allyltributylstannane[68] (Scheme 9), or perhaps with hexaphenyl distannane and *t*-butylisonitrile,[69] would then lead to the required tricyclic skeleton (**35**) with concomitant formation of the quaternary center at C8. Under the correct conditions, good yields of 6-endo products from vinyl radical cyclizations can be obtained by rearrangement of the initial, kinetic 5-exo radical[70-73] as required by this reaction scheme. Also, from the study of molecular models, there was good reason to believe that both radical C-C bond forming reactions would occur selectively from the β-face of the AB-system resulting in the preferential formation of the correct relative stereochemistry at both C3 and C8 of the taxol system.



Scheme 9

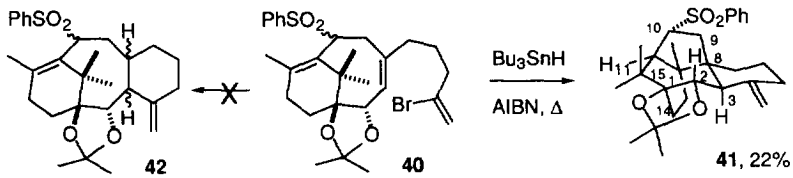
Toward this end, we undertook a model study with a simplified version (**36**) of **32** lacking the two asymmetric centers. Alkylation of triethyl phosphonoacetate with 2-bromo-5-iodo-1-pentene[74] gave **36** in 68% yield. Condensation of the sodium salt of **36** with aldehyde **26** in THF at 0 °C gave 40% of the desired olefin as a 3:1 *Z:E* mixture. No attempt was made in this model study to improve the *Z:E*-ratio or to prepare the bis(trifluoroethyl) analog of **36**. As in the simple system, **36** was converted to **39** via alcohol **38** in good overall yield. Treatment of **39** with LiHMDS in ether at 0 °C brought about cyclization to **40**, again in excellent yield, and as 1:1 mixture of diastereomers (Scheme 10).



Scheme 10

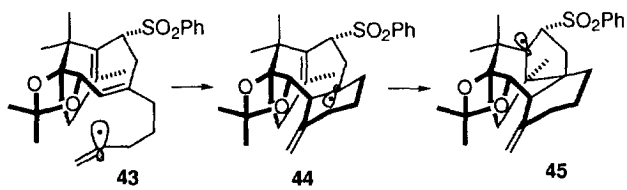
Dropwise addition of Bu_3SnH and catalytic AIBN to **40** in benzene at reflux resulted in a relatively clean reaction mixture from which a single major product was isolated, albeit only in 22% yield. Inspection of the ^{1}H-NMR spectrum of this product revealed the proton α-to the sulfone (H-10) to be a doublet of doublet of doublets (ddd) which ruled out the anticipated structure (**42**). Comparison of the chemical shift of the same proton (δ 3.6) with the corresponding signal in **40** (δ 4.1) suggested that it was no longer allylic and that the additional coupling arose from a new proton at C11. This new proton (H-11) is a simple doublet (δ 2.51) by virtue of its coupling to H-11 (J = 7.0 Hz) and its location between two quaternary carbons. The suspicion that the 11-12 double bond had been saturated was confirmed by the ^{13}C-NMR spectrum which revealed the

presence of only 6 sp^2 hybridized carbons, namely those of the phenylsulfonyl and exocyclic methylene moieties. The H-2 proton was a simple doublet of coupling constant J = 10.1 Hz, consistent with the vinyl radical cyclization having occured, as anticipated, from the β-face to give the overall, 6-endo-mode product. The H-3 signal at δ 2.19 was also a simple doublet, broadened by an unresolved allylic coupling, coupled only to H-2, and suggesting C8 to be a quaternary carbon. All of this information, together with confirmation of the molecular weight by mass spectrometry, leads us to tentatively suggest **41** as the structure of this product (Scheme 11).



Scheme 11

The formation of **41** may be readily rationalized (Scheme 12) by cyclization of the initial vinyl radical (**43**) onto the β- (or exo-) face of the bicyclic system, so installing the correct stereochemistry at C3, and giving rise to the cyclized radical **44**. This species then undergoes a transannular cyclization onto C12 of the 11-12 alkene leading to **45**, whose quenching by Bu_3SnH provides the final product. The cyclization of **44**, which may be formally viewed as either a 5-endo-trig or 7-exo-trig cyclization occuring within a *trans*-4-cyclodecen-1-yl system, is undoubtedly accelerated by its transannular nature, by the enforced proximity of the radical to the olefin, and by the relief of strain which accompanies it. We assign the stereochemistry at C10 on steric grounds, as models show that the opposite configuration would give rise to a severe steric interaction between the sulfone and the gem-dimethyl group. Unfortunately, the coupling constant $^3J_{H10,H11}$ (7.0 Hz) is compatible with either stereochemistry, and so does not allow unambiguous assignment. Transannular cyclizations of radicals in the taxane framework have previously been observed by a Bristol-Myers-Squibb group.[75-77] A related cyclization has also been described recently by Kende and co-workers.[78]



Scheme 12

Although the radical cyclization described in Scheme 11 did not result in isolation of the desired product, it did serve to demonstrate that the initial vinyl radical cyclization proceeded, at least in part, according to plan and with the requisite stereochemistry. If the ensuing transannular cyclization could be prevented, a rapid and versatile entry into taxoids would result. It seems reasonable to suggest that modification of the strategy to incorporate a C9 ketone before the radical cyclization might be all that is required, as the extra stabilization of the cyclized radical and the additional sp^2 center should significantly retard the transannular reaction step. This postulate remains to be tested.

Experimental Section

General. For general experimental see preceding paper in this issue.

(±)-*trans*-2,2,6(*S*)-Trimethyl-3(*R,S*)-hydroxy-7-oxabicyclo[4.3.0]nonan-8-one (4). Bromide **3**[18] (7.0 g, 15 mmol) was dissolved in dichloromethane (700 mL) in a three-necked flask equipped with a condensor and two oxygen inlets. Oxygen was bubbled through the stirred solution for 50 min before a solution of $NaBH_4$ (1.74 g, 45 mmol) in water (45 mL) was added dropwise throught the condenser over 3 h, with continuous bubbling of O_2, after which TLC showed consumption of **3**, and formation of **4** and an unidentified byproduct. A further portion of $NaBH_4$ (1.74 g, 45 mmol) in water (45 mL) was added and stirring maintained, without the passage of O_2, for 12 h. The reaction mixture was then filtered on a pad of Celite, which was subsequently rinsed with dichloromethane. The filtrate and washings were combined, washed with water (3 x 300 mL), dried ($MgSO_4$), and evaporated to give **4** (2.75 g, 92%, approx 1.7:1 mixture of diastereomers) as an oil which solidified on standing. M.p. 88-90 °C; ^{1}H-NMR, δ major isomer: 0.95 (s, 3 H), 1.00 (s, 3 H), 1.35 (s, 3 H), 1.55 (s, 1 H), 1.75-2.10 (m, 4 H), 2.20-2.65 (m, 3 H), 3.55 (m, $w_{1/2}$ = ~ 9 Hz, 1 H); δ minor isomer: 0.92 (s, 3 H), 1.05 (s, 3 H), 1.38 (s, 3 H), 3.45 (m, $w_{1/2}$ = ~ 25 Hz, 1 H); ^{13}C-NMR, δ: 14.4, 20.0, 20.2, 20.3, 26.3, 27.8, 28.1, 28.7, 29.1, 31.5, 35.8, 37.0, 37.1, 48.0, 53.6, 73.2, 77.5, 85.5, 86.5, 176.7. Anal. Calcd. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.56; H, 9.18.

(±)-trans-2,2,6(*S*)-Trimethyl-7-oxabicyclo[4.3.0]nonan-3,8-dione (6). Alcohol **4** (5.79 g, 29.3 mmol) was dissolved in dichloromethane (50 mL) at room temperature and powdered 4Å molecular sieves (~ 1 g), followed by PCC (9.65 g, 43.9 mmol), were added. The reaction mixture was stirred at room temperature for 17 h, then filtered on Celite and the solvent stripped off under reduced pressure. The residue was taken up in ether and passed through a short Florisil column then evaporated to give the crystalline ketone **6** (5.63 g, 98%). M.p. 114-116 °C; ^{1}H-NMR, δ: 1.12 (s, 3 H), 1.15 (s, 3 H), 1.35 (s, 3 H), 2.15 - 2.25 (m, 2 H), 2.40-2.65 (m, 3 H), 2.70 - 2.90 (m, 2 H); ^{13}C-NMR, δ: 19.8, 20.3, 27.8, 29.5, 34.6, 35.0, 45.6, 52.2, 83.4, 175.1, 213.1; IR, υ (cm^{-1}): 1765, 1700. Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.32; H, 7.98.

2,2-Di(2-methoxycarbonylethyl)-5,5-dimethyl-1,3-dioxane (8). A dry 2L flask was charged with spirobislactone **7**[25] (139.5 g, 0.89 mol), neopentyl glycol (372.5 g, 3.6 mol) and *p*-toluenesulphonic acid (6 g, 32 mmol), followed by the addition of toluene (800 mL). The reaction mixture was refluxed for 12 h under a Dean Stark separator at the end of which 41 mL of water had been collected. The reaction mixture was cooled and the solvent evaporated under reduced presure to give 510 g of an oil. This was dissolved in anhydrous methanol (1.8 L) followed by addition of Na_2CO_3 (151 g) and the reaction mixture allowed to stir at room temperature for 16 h before it was filtered and concentrated under reduced pressure. The residue was taken up in ether (1 L) and washed with water (3 x 200 mL), brine (2 x 200 mL), dried ($MgSO_4$) and evaporated to give the title compound as an oil (201.6 g, 78%). ^{1}H-NMR, δ: 0.85 (s, 6 H), 1.93 (t, J = 8.3 Hz, 4 H), 2.35 (t, J = 8.6 Hz, 4 H), 3.38 (t, J = 5.5 Hz, 4 H), 3.57 (s, 6 H); ^{13}C-NMR, δ: 22.5, 28.0, 28.9, 29.3, 51.5, 69.9, 173.9; IR, υ (cm^{-1}): 1730 cm^{-1}. Anal. Calcd for $C_{14}H_{24}O_6$: C, 58.31; H, 8.39. Found: C, 57.89; H, 8.41.

Methyl 9-Hydroxy-3,3-dimethyl-1,5-dioxaspiro[5.5]undec-8-en-8-carboxylate (9). A dry three neck 5 L flask fitted with a reflux condenser, a dropping funnel, and a stir bar was purged with nitrogen and charged with NaH (15.3 g, 60% solution in mineral oil, 381 mmol), washed free from mineral oil, and then KH (22.2 g, 35% in mineral oil, 139 mmol, 0.4 eq), also washed free from mineral oil. THF (500 mL)

was added and the suspension brought to a gentle reflux before lactone **8** (100 g, 347 mmol) in THF (200 mL) was added dropwise over a period of 1.5 h. During this addition a constant reflux was maintained and the evolved hydrogen gas efficiently vented out. The reaction mixture was refluxed for a 1 h after which TLC analysis indicated completion. After cooling to 0 °C, the reaction mixture was diluted with ether (1.5 L), quenched by careful addition of glacial acetic acid (30 mL), and washed with sat. sodium bicarbonate solution (3 x 500 mL), and brine (2 x 500 mL). The ether phase was then dried ($MgSO_4$) and concentrated under reduced presure to give 73.1 g (87%) of the title compound as a colorless oil. This crude product was sufficiently pure to use in the next step directly. B. p. = 192 °/0.2 mm Hg (Kugelrohr); ^{1}H-NMR, δ: 0.95 (s, 3 H), 1.02 (s, 3 H), 2.02 (t, J = 10.2 Hz, 2 H), 2.50 (t, J = 8.1 Hz, 2 H), 2.65 (s, 2 H), 3.60 (s, 4 H), 3.75 (s, 3 H), 12.20 (s, 1 H); ^{13}C-NMR, δ: 22.3, 22.3, 22.4, 26.7, 26.8, 30.0, 30.0, 30.8, 32.2, 33.3, 36.7, 51.2, 51.9, 52.5, 70.2, 70.3, 70.54, 94.1, 95.5, 96.2, 169.7, 171.3, 172.4. Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.86. Found: C, 60.60; H, 7.83.

Methyl 3,3,9-Trimethyl-1,5-dioxaspiro[5,5]undec-8-en-8-carboxylate (10). NaH, washed free from mineral oil (13.28 g, 60% solution in mineral oil, 332 mmol) was added in small portions over 1 h to an ice-cold solution of **9** (73.1 g, 302 mmol) in ether (1 L) resulting in vigorous evolution of hydrogen gas. When the addition was complete the reaction mixture was stirred for a further 0.5 h before diethyl chlorophosphate (46.0 mL, 317 mmol) was added slowly while the reaction temperature was maintained at 0 °C. After the addition the ice bath was removed and the reaction mixture was allowed to stir at room temperature for 12 h. The contents of the reaction mixture were then allowed to settle and the precipitate removed by careful filtration without exposure to moisture. Concentration of the filtrate provided 113 g of the enol phosphate as a clear, pale yellow oil which was used in the next step without further purification. CuCN (13.28 g, 149 mmol) was suspended in ether (100 mL) at 0 °C, treated dropwise with MeLi (198 mL, 1.5 M solution in ether, 300 mmol), then allowed to stir for 1 h when a clear colorless solution was formed. This solution was cooled to -78 °C and a solution of the above enol phosphate (46.71 g, 124 mmol) in ether (175 mL) was slowly added via a cannula. The reaction mixture was allowed to stir at -78 °C for 2 h, then warmed to -25 °C and stirred there for a further 0.5 h before it was transfered to a solution of 1 M HCl (500 mL). *[Caution : evolution of HCN].* The resultant mixture was basified by slow addition of ammonium hydroxide (6M, ca. 150 mL), the ether layer separated, and the aqueous layer extracted with ether (3 x 200 mL). The combined ethereal extracts were washed successively with ammonium hydroxide (2M, 200 mL), brine (2 x 200 mL), dried ($MgSO_4$), and concentrated under reduced presure. The residual oil was subjected to silica gel chromatography (eluent: ether/petroleum ether 1/4) yielding **10** (17.8 g, 60%) as an oil. ^{1}H-NMR, δ: 0.92 (s, 3 H), 1.02 (s, 3 H), 1.90 (t, J = 8.6 Hz, 2 H), 2.05 (s, 3 H), 2.25 (t, J = 6.0 Hz, 2 H), 2.62 (s, 2 H), 3.50 (s, 4 H), 3.70 (s, 3 H); ^{13}C-NMR, δ: 21.3, 22.0, 22.5, 27.5, 30.0, 32.1, 34.5, 51.0, 70.1, 96.5, 120.4, 147.0, 168.0; IR υ (cm^{-1}): 1706 cm^{-1}. Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.20; H, 8.79.

8-Hydroxymethyl-3,3,9-trimethyl-1,5-dioxaspiro[5.5]undec-8-ene (11). Compound **10** (18.7 g, 73.6 mmol) was dissolved in ether (300 mL) and cooled to -78 °C. A solution of DIBAL (108 mL, 1.5M solution in toluene, 162 mmol) was then added slowly via a syringe, and the reaction mixture allowed to stir at -78 °C for 3 h. Methanol (75 mL) was then added cautiously at -78 °C followed by stirring for 1 h leading to the formation of a white gelatinous precipitate. The reaction mixture was allowed to warm to room temperature and filtered under reduced pressure. The residue was taken up in ether (200 mL) and warmed in a water bath (50 °C) before a second filtration. The combined ether phases were dried ($MgSO_4$), and concentrated under reduced pressure to yield **11** (15.8 g, 100%) as an oil. ^{1}H-NMR, δ: 0.9 (s, 3 H), 1.02 (s, 3 H), 1.65 (s, 3 H), 1.88 (t, J = 6.4 Hz, 2 H), 2.02 (br. t, J = 6.8 Hz, 2 H), 2.42 (s, 2 H), 3.45 (d, J = 11.1

Hz, 2 H), 3.53 (d, J = 11.2 Hz, 2 H), 4.01 (s, 2 H); ^{13}C-NMR, δ: 16.0, 22.5, 22.6, 27.6, 30.1, 36.1, 62.5, 70.1, 97.5, 126.4, 129.6; IR υ (cm^{-1}): 3606. The crude product was clean and not purified or characterized further owing to its instability on silica gel.

3,3,9-Trimethyl-8-phenylthiomethyl-1,5-dioxaspiro[5.5]undec-8-ene (12). The allylic alcohol (**11**) (15.8 g, 73.8 mmol) was dissolved in THF (200 mL) along with a few crystals of 2,2'-bipyridine and the solution cooled to -78 °C. n-BuLi (36.8 mL, 2M solution in pentanes, 74 mmol) was then added slowly via syringe after which a slight pink coloration persisted. Freshly recrystallized TsCl (15.44 g, 81.0 mmol) was then added as a solution in THF (20 mL). After the addition the reaction mixture was allowed to warm to room temperature and stirred for 3 h. In the meantime, a solution of thiophenol (11.4 mL, 110 mmol) and a few crystals of 2,2'-bipyridine, in THF (75 mL) was cooled to -55 °C and treated dropwise with n-BuLi (55.2 mL, 2M solution in pentanes, 110 mmol). This pink thiophenate solution was then transferred via cannula to the flask containing the tosylate at room temperature. The resulting reaction mixture was stirred for 4 h at room temperature before it was diluted with ether (200 mL) and washed successively with a 2M solution of NaOH (2 x 100 mL) and brine (200 mL). The organic layer was dried ($MgSO_4$), concentrated under reduced presure, and the residue purified by chromatography on silica gel (eluent: ether/petroleum ether 1/9) to yield **11** (15 g, 67%) as a colorless oil. ^{1}H-NMR, δ: 0.95 (s, 3 H), 1.02 (s, 3 H), 1.40 (s, 3 H), 1.87 (t, J = 8.0 Hz, 2 H), 2.05 (t, J = 6.9 Hz, 2 H), 2.54 (s, 2 H), 3.53 (d, J = 14.1 Hz, 4 H), 3.6 (d, J = 14.1 Hz, 2 H), 7.1-7.4 (m, 5 H); ^{13}C-NMR, δ: 18.2, 22.6, 22.7, 29.13, 30.1, 30.2, 36.2, 38.1, 70.2, 97.4, 121.9, 126.5, 128.5, 130.9, 131.3, 136.4. Anal. Calcd for $C_{19}H_{26}O_2S$: C, 71.66; H, 8.23. Found: C, 71.46; H, 8.16.

4-Methyl-3-phenylthiomethyl-cyclohex-3-en-1-one (13). Compound **12** (8.6 g, 28.1 mmol) was dissolved in reagent grade acetone (300 mL) and water (25 mL) followed by addition of TsOH (0.53 g, 2.81 mmol). The reaction mixture was heated to gentle reflux until TLC analysis indicated disappearance of starting material (ca. 3 h). It was then cooled to room temperature and concentrated under reduced pressure. The residue obtained was extracted with ether (3 x 50 mL) and the combined extracts washed with brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give **13** (6.39 g, 98%) as a pale yellow oil. ^{1}H-NMR, δ: 1.47 (s, 3 H), 2.31 (m, 4 H), 2.93 (s, 2 H), 3.45 (s, 2 H), 7.14-7.31 (m, 5 H); ^{13}C-NMR, δ: 18.5, 31.5, 37.6, 38.5, 42.5, 123.2, 126.9, 128.7, 131.6, 131.6, 135.5, 210.4. This β,γ-unsaturated ketone is rather prone to isomerization to the α,β-unsaturated isomer but can be stored in the freezer for short periods of time. In general it was subjected to the next reaction immediately.

2,2,4-Trimethyl-3-phenylthiomethyl-cyclohex-3-en-1-one (14). The β,γ-unsaturated ketone **13** (5.8 g, 25 mmol) was dissolved in ether (100 mL) and the solution cooled to -25 °C. Iodomethane (7.78 mL, 125 mmol) was then added, followed, at the same temperature, by dropwise addition of t-BuOK (53.75 mL, 1M solution in t-butanol, 54 mmol) over 1 h, after which the solution was allowed to warm up to -15 °C and then stirred for another 0.5 h. The reaction mixture was then transferred via a cannula into a cold sat. ammonium chloride solution (500 mL). The layers were separated and the aqueous phase extracted with ether (3 x 50 mL). The combined ether extracts were washed successively with sodium thiosulphate solution (50 mL), brine (50 mL), and dried ($MgSO_4$), before being concentrated under reduced pressure. The residue obtained was subjected to chromatography on silica gel (eluent: ether/petroleum ether 1/4) to provide **14** (5.62 g, 86%) as an oil. ^{1}H-NMR, δ: 1.26 (s, 6 H), 1.63 (s, 3 H), 2.38 (t, J = 7.0 Hz, 2 H), 2.54 (t, J = 6.6 Hz, 2 H), 3.63 (s, 2 H), 7.15 - 7.35 (m, 5 H); ^{13}C-NMR, δ: 20.1, 24.7, 31.5, 33.1, 35.7, 47.7, 125.9, 128.8, 128.9, 131.4, 133.5, 137.9, 214.2; IR υ (cm^{-1}): 1780. Anal. Calcd for $C_{16}H_{20}OS$: C, 73.80; H, 7.74. Found: C, 73.85; H, 7.72.

(±)-*trans*-2,2,6(*S*)-Trimethyl-3(*E*)-(ethoxycarbonylmethylidene)-7-oxabicyclo[4.3.0]nonan-8-one (16): One Pot Procedure. Ketone (**6**) (4.50 g, 23.0 mmol) was dissolved in dichloromethane (90 mL), and cooled to -15 °C before $BF_3.OEt_2$ (2.82 mL, 23.0 mmol) was added. After stirring for 10 min, ethoxyacetylene (6.0 mL of 47% by weight in hexanes, 30 mmol) was added dropwise over 20 min. The reaction mixture was stirred at -15 °C for 12 h then treated with further $BF_3.OEt_2$ (2.82 mL, 23.0 mmol) and, after 10 min, ethoyxacetylene (4.3 mL of 47%, 16.5 mmol). Stirring was then continued for 4 h at -10 °C before the reaction was quenched by cautious addition of 20% K_2CO_3 (40 mL). The organic layer was separated and washed with K_2CO_3, and water, dried ($MgSO_4$), concentrated under vacuum, and purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 5/1) to give recovered **6** (0.81 g, 18%), β-hydroxyester **17** (0.52 g, 8%), and the title compound (**16**) (3.97 g, 65%) as a crystalline solid. β-Hydroxyester **17**: ^{1}H-NMR, δ: 0.92 (s, 3 H), 1.02 (s, 3 H), 1.30 (t, J = 7.0 Hz, 3 H), 1.40 (s, 3 H), 1.72-1.98 (m, 4 H), 2.10 (dd, J = 7.1 and 14.0 Hz, 1 H), 2.25 (dd, J = 7.1 and 16.6 Hz, 1 H), 2.48 (dd, J = 14.0 and 16.6 Hz, 1 H), 2.63 (d, J = 16.0 Hz, 1 H), 2.80 (d, J = 16.0 Hz, 1 H), 4.15 (s, 1 H), 4.20 (q, J = 7.0 Hz, 2 H). ^{13}C-NMR, δ: 14.1, 18.0, 20.6, 24.2, 29.6, 32.9, 35.0, 38.6, 39.9, 51.6, 61.3, 74.8, 85.4, 175.9, 176.1. α,β-Unsaturated ester **16**: M.p. 131 °C; ^{1}H-NMR, δ: 1.15 (s, 3 H), 1.19 (s, 3 H), 1.30 (t, J = 7.0 Hz, 3 H), 1.33 (s, 3 H), 1.95-2.10 (m, 2 H), 2.30-2.60 (m, 3 H), 3.25 (m, 1 H), 4.15 (q, J = 7.0 Hz, 2 H), 5.95 (s, 1 H); ^{13}C-NMR, δ: 14.3, 21.5, 22.2, 22.3, 29.6, 30.2, 36.3, 39.4, 52.7, 60.1, 85.1, 115.0, 165.4, 166.8, 175.7. Anal. Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.73; H, 8.39.

(±)-*trans*-2,2,6(*S*)-Trimethyl-3(*E*)-(ethoxycarbonylmethylidene)-7-oxabicyclo[4.3.0]nonan-8-one (16) via 15 and 17. Ethoxyacetylene (47% by weight in hexanes, 0.6 mL, 3.0 mmol) was dissolved in THF (18 mL) and treated at -78 °C with butyllithium (1.38 mL of 1.6 M, 2.2 mmol) and stirred for 40 min. This solution was then added with a cannula into a solution of ketone **6** (0.430 g, 2.2 mmol) in THF (26 mL) at -78 °C. Stirring was continued at that temperature for 2 h before MeOH (2 mL) was added and the reaction mixture allowed to warm to room temperature. The reaction mixture was diluted with ether, washed with water, dried ($MgSO_4$), filtered and concentrated under vacuum to give a residue which on purification by column chromatography on silica gel (eluent: hexane/ethyl acetate 3.5/1) gave recovered **6** (0.124 g, 29%) and propargyl alcohol **15** (0.251 g, 43%) in the form of a single, unassigned isomer. ^{1}H-NMR, δ: 0.95 (s, 3 H), 1.05 (s, 3 H), 1.35 (s, 3 H), 1.39 (t, J = 7.0 Hz, 3 H), 1.90-2.10 (m, 5 H), 2.25 (dd, J = 10.0, 2.0 Hz, 1 H), 2.35-2.50 (m, 2 H), 4.10 (q, J = 7.0 Hz, 2 H); ^{13}C-NMR, δ: 14.5, 16.7, 20.7, 25.7, 29.6, 31.0, 35.4, 36.1, 40.2, 40.4, 51.7, 74.9, 85.5, 95.2, 176.6. This alcohol (91.6 mg, 0.34 mmol) was dissolved in THF (15 mL) and treated with 10% aqueous H_2SO_4 (3.7 mL) dropwise over 5 min. The reaction mixture was then stirred at room temperature for 1.5 h before it was diluted with ether and water and, after decantation, the aqueous phase extracted twice with ether. The combined organic layers were washed with water, and brine, dried ($MgSO_4$) and purified by column chromatography on silica gel (eluent: hexane/ether 5/1) to give **16** (64.0 mg, 70%), identical with the sample described above, and the β-hydroxyester **17** (21.4 mg, 21%) also identical with the sample obtained from the one pot procedure. Brief treatment of this β-hydroxyester (**17**) (19 mg, 0.07 mmol) with the Martin sulfurane reagent[49] (44.7 mg, 0.07 mmol) in $CDCl_3$ at room temperature resulted in complete conversion to **16** as judged by ^{1}H-NMR spectroscopy.

(±)-Acetonide 18 and α-Keto ester 19. Exocyclic alkene (**16**) (200 mg, 0.75 mmol) was dissolved in THF (1.5 mL) and *t*-BuOH (1.5 mL) and treated with NMNO (190 mg, 1.6 mmol), pyridine (3 drops) and, then, OsO_4 (~10 mg), and the reaction mixture heated to reflux for 5 h. After cooling to room temperature saturated aqueous sodium metabisulfite (5 mL) was added and the reaction mixture stirred for 5 min, before it

was diluted with brine (50 mL) and extracted with ethyl acetate (5 x 30 mL). The extracts were dried ($MgSO_4$) and concentrated under vacuum and applied to a short plug of silica gel. Elution with dichloromethane gave the recovered substrate (27 mg, 14%). Subsequent elution with ethyl acetate gave a mixture of diol and α-ketoester which, after concentration, was taken up in dichloromethane (2 mL) and stirred at room temperature in the presence of 2,2-dimethoxypropane (0.5 mL) and TsOH (2 mg) for 24 h. After concentration, column chromatography on silica gel (eluent: hexane/ethyl acetate 4/1) gave acetonide **18** (136 mg, 53%) and the α-keto ester **19** (44 mg, 20%) both as crystalline solids. **Acetonide 18:** M.p. 164-165 °C (ether/petroleum ether); ^{1}H-NMR, δ: 1.01 (s, 3 H), 1.03 (s, 3 H), 1.28 - 1.40 (m, 6 H), 1.45 (s, 3 H), 1.55 (s, 3 H), 1.70 (m, 1 H), 1.85 - 2.00 (m, 2 H), 2.10 (m, 1 H), 2.28 (dd, J = 7.5 and 15.0 Hz, 1 H), 2.45 (t, J = 15.0 Hz, 1 H), 2.60 (dd, J = 7.5 and 15.0 Hz, 1 H), 4.15 - 4.30 (m, 2 H), 4.53 (s, 1 H); ^{13}C-NMR, δ: 14.2, 19.0, 20.3, 24.3, 27.3, 28.7, 28.8, 29.2, 33.4, 39.9, 50.9, 61.5, 78.3, 85.2, 87.6, 111.3, 170.0, 176.1; MS, m/z: 340 (M^+), 325 ($M-15^+$). Anal. Calcd. for $C_{18}H_{28}O_6$: C, 62.56; H, 8.03. Found: C, 62.78; H, 7.97. α-Keto ester **19**: M.p. 135-136 °C (EtOH); ^{1}H-NMR, δ: 1.00 (s, 3 H), 1.02 (s, 3 H), 1.38 (t, J = 7.0 Hz, 3 H), 1.40 (s, 3 H), 1.90 (m, 2 H), 2.10 (dt, J = 5.5 and 11.0 Hz, 1 H), 2.25 (dd, J = 6.5 and 14.2 Hz, 1 H), 2.38 (m, 1 H), 2.45 (t, J = 14.2 Hz, 1 H), 2.76 (dd, J = 14.0 and 6.5 Hz, 1 H), 3.60 (s, 1 H), 4.35 (q, J = 7.0 Hz, 2 H); ^{13}C-NMR, δ: 13.9, 19.0, 20.2, 24.5, 28.5, 30.8, 32.3, 40.6, 49.1, 62.7, 82.3, 85.2, 163.0, 175.8, 198.5; MS, m/z: 298 (M^+), 283 ($M-15^+$), 197 ($M-COCO_2Et^+$). Anal. Calcd. for $C_{15}H_{22}O_6$: C, 60.38; H, 7.43. Found: C, 60.30; H, 7.61.

(±)-2,2,4-Trimethyl-3-phenylthiomethyl-1-vinyl-3-cyclohexen-1-ol (20). Anhydrous cerium trichloride (8 g, 32.4 mmol) was taken up in a 250 mL base-washed flask charged with a stir bar. The flask was evacuated to 0.1 mm Hg and heated to 140 °C for 10 h. After cooling to room temperature under vacuum, Ar, followed by THF (50 mL), was introduced and the mixture stirred for 10 h at room temperature then cooled to -78 °C. Vinylmagnesium bromide (32.4 mL, 1M solution in THF, 32 mmol) was added and the cream colored suspension stirred at -78 °C for 2 h before a solution of **14** (3.0 g, 11.5 mmol) in THF (25 mL) was added. The reaction mixture was stirred for a further 3 h before it was diluted with ether (100 mL) and washed with 1M HCl (2 x 20 mL) and brine (20 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure then subjected to chromatography on silica gel (eluent: ether:petroleum ether, 1:4) to give **20** (2.76 g, 83%) as an oil. ^{1}H-NMR, δ: 1.06 (s, 3 H), 1.14 (s, 3 H), 1.78 (s, 3 H), 2.00 - 2.30 (m, 4 H), 3.63 (s, 2 H), 5.16 (dd, J = 1.6 and 10.9 Hz, 1 H), 5.36 (dd, J = 1.6 and 17.3 Hz, 1 H), 6.08 (dd, J = 10.9 and 17.3 Hz, 1 H), 7.14 - 7.34 (m, 5 H); ^{13}C-NMR, δ: 20.0, 22.1, 24.3, 29.4, 30.9, 33.1, 42.1, 75.6, 103.3, 113.3, 125.5, 128.5, 128.8, 130.7, 132.7, 138.4, 141.9; IR υ (cm^{-1}): 3601 and 3480. Anal. Calcd for $C_{18}H_{24}OS$: C, 74.95; H, 8.38. Found: C, 74.55; H, 8.46.

(±)-1-(Dimethylcarbamoyloxy)-2,2,4-trimethyl-3-phenylthiomethyl-1-vinyl-3-cyclohexene (21). The allylic alcohol **20** (2.76 g, 9.58 mmol) was dissolved in THF (20 mL) and cooled to 0 °C. KH (6.89 g, 35% solution in mineral oil, 43 mmol) was washed free of mineral oil and added to the reaction mixture portionwise. After the initial vigorous evolution of hydrogen had subsided the reaction mixture was allowed to warm to room temperature and stirred for 16 h, before it was again cooled to 0 °C and treated dropwise with freshly distilled dimethylcarbamoyl chloride (3.55 mL, 38.3 mmol). After stirring for 3 h, the reaction mixture was diluted with ether (50 mL) and quenched by addition of 1M NaOH (25 mL). The organic phase was washed successively with 1M NaOH (2 x 25 mL) and brine (25 mL) before drying ($MgSO_4$) and concentration under reduced pressure. The residue was subjected to chromatography on silica gel (eluent: ether:petroleum ether, 2:1) to yield **21** (3.16 g, 92%) as a viscous oil which crystallized on standing. Mp 46 °C; ^{1}H-NMR, δ: 1.01 (s, 3 H), 1.24 (s, 3 H), 1.79 (s, 3 H), 2.05 (m, 3 H), 2.65 (m, 1 H), 2.69 (br.s, 6 H), 3.52 (d, J = 10.9 Hz, 1 H), 3.73 (d, J = 10.9 Hz, 1 H), 5.06 (dd, J = 0.7 and 17.6 Hz, 1 H), 5.27 (dd, J =

0.6 and 10.5 Hz, 1 H), 6.05 (dd, *J* = 11.2 and 17.7 Hz, 1 H), 7.13 - 7.34 (m, 5 H); ^{13}C-NMR, δ: 19.9, 20.9, 24.3, 25.7, 29.0, 33.4, 42.9, 84.8, 114.9, 125.4, 128.3, 128.7, 129.5, 132.6, 138.6, 139.2. Anal. Calcd for $C_{21}H_{29}O_2NS$: C, 70.15; H, 8.13. Found: C, 70.16; H, 8.19.

(±)-1-(Dimethylcarbamoyloxy)-3-phenylsulfonylmethyl-2,2,4-trimethyl-1-vinyl-3-cyclohexene (22). Carbamate **21** (3.16 g, 8.80 mmol) in THF (50 mL) was treated portionwise with MMPP (5.71 g, 80% purity, 9.2 mmol) at room temperature for 2 h. The reaction mixture was then diluted with ether (100 mL) and washed successively with sat. $NaHCO_3$ (3 x 25 mL) and brine (25 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give **22** (2.82 g, 82%) as a crystalline solid. Mp 112-114 °C; ^{1}H-NMR, δ: 1.01 (s, 3 H), 1.23 (s, 3 H), 1.73 (s, 3 H), 2.12 (m, 3 H), 2.67 (m, 1 H), 2.86 (s, 3 H), 2.89 (s, 3 H), 3.97 (d, *J* = 14.5 Hz, 1 H), 4.02 (d, *J* = 15.0 Hz, 1 H) 5.06 (dd, *J* = 0.7 and 17.7 Hz, 1 H), 5.27 (dd, *J* = 0.6 and 11.3 Hz, 1 H), 6.03 (dd, *J* = 11.3 and 17.7 Hz, 1 H), 7.63-7.94 (m, 5 H); ^{13}C-NMR, δ: 21.6, 21.9, 24.2, 25.7, 29.6, 36.1, 42.6, 57.7, 84.9, 115.2, 124.1, 127.8, 129.2, 133.3, 138.3, 139.1, 141.7; IR υ (cm^{-1}): 1693. Anal. Calcd for $C_{21}H_{29}O_4NS$: C, 64.42; H, 7.46. Found: C, 64.32; H, 7.46.

1*E*-[2-(Dimethylcarbamoyloxy)ethylidene]-3-phenylsulfonylmethyl-2,2,4-trimethylcyclohex-3-ene (23). Compound **22** (2.82 g, 7.21 mmol) was dissolved in THF (10 mL) with stirring at room temperature and mercury trifluoroacetate (0.9 g, 2.16 mmol) added. After stirring for 3 h, Ph_3P (1.13 g, 4.3 mmol) was added to quench the reaction and the resulting black precipitate removed by filtration. The precipitate was washed with ether (2 x 10 mL) and the combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was subjected to silica gel chromatography (eluent: ether:petroleum ether, 1:2) to give **23** (2.7 g, 96%) as an oil. ^{1}H-NMR, δ: 1.20 (s, 6 H), 1.68 (s, 3 H), 2.18 (t, *J* = 8.6 Hz, 2 H), 2.45 (t, *J* = 8.6 Hz, 2 H), 2.90 (s, 6 H), 4.00 (s, 2 H), 4.67 (d, *J* = 8.6 Hz, 2 H), 5.45 (t, *J* = 8.7 Hz, 1 H), 7.5-8.0 (m, 5 H); ^{13}C-NMR, δ: 21.6, 23.2, 27.7, 34.0, 41.0, 57.6, 62.0, 114.6, 125.9, 127.6, 129.1, 133.3, 139.5, 140.5, 141.5, 150.0; IR υ (cm^{-1}): 1697. Anal. Calcd for $C_{21}H_{29}O_4NS$: C, 64.42; H, 7.46. Found: C, 64.12; H, 7.52.

(±)-(4*R*,5*S*)-2,2,6,6,8-Pentamethyl-4-(*N*,*N*-dimethylcarbamoyloxymethyl)-7-phenylsulfonylmethyl-1,3-dioxaspiro[4.5]dec-7-ene (24). Compound **23** (1.07 g, 2.7 mmol) was dissolved in 1.5 mL of a 10/1 (v/v) acetone/water mixture and cooled to 0 °C before pyridine (0.05 mL), methanesulfonamide (0.25 g, 2.7 mmol), NMNO (0.47 g, 4.05 mmol) and OsO_4 (0.075 g, 0.27 mmol) were added. The dark brown reaction mixture was allowed to warm to room temperature and stirred for 36 h before it was diluted with CH_2Cl_2 (15 mL) and sodium bisulfite (0.5 g) added. After stirring for 5 min, the reaction mixture was filtered, dried ($MgSO_4$), and evaporated. The residue was subjected to silica gel chromatography (eluent: ethyl acetate:petroleum ether, 1:1) to provide 0.806 g of a white foam. ^{1}H-NMR, δ: 1.20 (s, 3 H), 1.22 (s, 3 H), 1.67 (s, 3 H), 1.78 (m, 1 H), 1.92 (m, 1 H), 2.05 - 2.35 (m, 2 H), 2.91 (s, 6 H), 3.90 - 4.03 (m, 2 H), 4.05 - 4.18 (m, 2 H), 4.38 (dd, *J* = 3.5 and 12.3 Hz, 1 H), 7.5-8.0 (m, 5 H). Without further characterization this foam (0.806 g, 1.9 mmol) and TsOH (150 mg) were dissolved in CH_2Cl_2 (10 mL), cooled to 0 °C, and treated dropwise with 2-methoxypropene (0.9 mL, 9.5 mmol). The reaction mixture was stirred for 0.5 h at 0 °C and then 2 h at room temperature. It was then concentrated and redissolved in ethyl acetate (15 mL) and washed successively with water (2 x 15 mL), and brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography on silica gel (eluent: ethyl acetate:petroleum ether: triethyl amine, 1:1:0.01) and recrystallization from ether gave **24** as a solid (480 mg, 41% for the two steps). M.p. 86 °C; ^{1}H-NMR, δ: 1.16 (s, 3 H), 1.19 (s, 3 H), 1.35 (s, 3 H), 1.45 (s, 3 H), 1.70 (s, 3 H), 1.70 - 1.80 (m, 2 H), 2.04 (m, 1 H), 2.37 (m, 1 H), 2.92 (s, 6 H), 3.95 (d, *J* = 14.6 Hz, 1 H), 4.03 (d, *J* = 15.1 Hz, 1 H), 4.06 (dd, *J* = 8.25 and 11.5 Hz, 1 H), 4.27 (d, *J* = 8.31 Hz, 1 H), 4.40 (dd, *J* = 1.7 and 11.5 Hz,

1 H), 7.5 - 8.0 (m, 5 H); ^{13}C-NMR, δ: 21.8, 22.1, 24.0, 25.3, 26.8, 28.9, 29.0, 40.1, 57.8, 66.0, 77.6, 84.9, 107.7, 124.7, 127.8, 129.1, 133.2, 139.2, 141.2, 157.0; IR υ (cm^{-1}): 1690. Anal. Calcd for $C_{24}H_{35}O_6NS$: C, 61.91; H, 7.57. Found: C, 61.93; H, 7.60.

(±)-(4*S*,5*S*)-4-Hydroxymethyl-2,2,6,6,8-pentamethyl-7-phenylsulfonylmethyl-1,3-dioxaspiro[4.5]dec-7-ene (25). A solution of **24** (673 mg, 1.44 mmol) in MeOH (40 mL) was treated with 20% aqueous KOH (20 mL) followed by additional MeOH (25 mL) to homogenize the solution, and heated to reflux for 2.5 h. After cooling to room temperature and concentration under vacuum, the residue was taken up in ethyl acetate (100 mL) and washed successively with water (2 x 50 mL) and brine (50 mL), dried ($MgSO_4$), concentrated under reduced pressure, and subjected to silica gel chromatography (eluent: ether:petroleum ether, 1:2) to yield **25** (545 mg, 96%) as an oil. ^{1}H-NMR, δ: 1.15 (s, 3 H), 1.16 (s, 3 H), 1.36 (s, 3 H), 1.44 (s, 3 H), 1.63 (s, 3 H), 1.70 - 1.85 (m, 2 H), 2.01 (m, 1 H), 2.33 (m, 1 H), 3.76 (br.d, *J* = 6.0 Hz, 2 H), 3.92 (d , *J* = 14.3 Hz, 1 H), 4.03 (d, *J* = 14.6 Hz, 1 H) 4.21 (dd, *J* = 5.8, 5.8 Hz, 1 H), 7.5-8.0 (m, 5 H); ^{13}C-NMR, δ: 21.7, 22.5, 24.4, 25.1, 26.9, 29.1, 40.1, 57.8, 63.2, 80.0, 84.8, 107.6, 124.6, 127.8, 129.2, 133.4, 139.5, 141.3. Anal. Calcd for $C_{21}H_{30}O_5S$: C, 63.93; H, 7.66. Found: C, 64.05; H, 7.55.

(±)-(4*R*,5*S*)-4-Formyl-2,2,6,6,8-pentamethyl-7-phenylsulfonylmethyl-1,3-dioxaspiro[4.5]dec-7-ene (26). Alcohol **25** (545 mg, 1.38 mmol) in CH_2Cl_2 (6 mL) was treated with freshly activated, powdered molecular sieves (4 Å, 3 g), NMNO (0.24 g, 2 mmol) and, lastly, TPAP (24 mg, 5 mol%) and the resulting dark reaction mixture stirred at room temperature for 3 h. The reaction mixture was passed through a short plug of Florisil (5 g) and then concentrated, giving a residue which, after silica gel chromatography (eluent: ether:petroleum ether, 1:2 containing ~5% Et_3N), yielded **25** (455.mg, 83%) as a viscous oil. ^{1}H-NMR, δ: 1.20 (s, 3 H), 1.26 (s, 3 H), 1.39 (s, 3 H), 1.54 (s, 3 H), 1.68 (s, 3 H), 1.80 - 1.90 (m, 2 H), 2.04 (m, 1 H), 2.35 (m, 1 H), 3.95 (d, *J* = 14.5 Hz, 1 H), 4.10 (d, *J* = 14.5 Hz, 1 H), 4.42 (d, *J* = 4.0 Hz, 1 H), 7.5-8.0 (m, 5 H), 9.7 (d, *J* = 4.1 Hz, 1 H); ^{13}C-NMR, δ: 21.5, 22.8, 24.9, 25.9, 27.2, 28.8, 29.2, 40.4, 57.7, 83.4, 110.3, 124.7, 129.2, 133.5, 139.3, 199.7; IR υ (cm^{-1}): 1710. It was found that this aldehyde underwent decomposition on storage at room temperature. It was therefore used immediately after purification. For further characterization purposes it was converted to the tosyl hydrazone derivative by standard means. ^{1}H-NMR, δ: 0.82 (s, 3 H), 1.10 (s, 3 H), 1.32 (s, 3 H), 1.42 (s, 3 H), 1.59 (s, 3 H), 1.65 - 1.80 (m, 2 H), 1.9 (m, 1 H), 2.3 (m, 1 H), 2.43 (s, 3 H), 3.85 (d, *J* = 14.6 Hz, 1 H), 4.04 (d, *J* = 14.2 Hz, 1 H), 4.5 (d, *J* = 7.0 Hz, 1 H), 7.05 (d, J = 7.1 Hz, 1 H), 7.30-8.0 (m, 9 H); ^{13}C-NMR, δ: C 21.5, 21.6, 22.0, 24.4, 25.3, 25.6, 26.9, 28.7, 29.0, 29.3, 40.1, 57.6, 78.2, 86.3, 109.6, 127.7, 127.8, 129.0, 129.2, 129.3, 129.6, 129.8, 133.4, 133.5, 139.6, 141.2, 146.6. Anal. Calcd for $C_{28}H_{40}O_8S_2N_2$: C, 59.97; H, 6.47. Found : C, 59.84; H, 6.42.

(±)-(4*S*,5*S*)-2,2,6,6,8-Pentamethyl-7-phenylsulfonylmethyl-4-[2-(ethoxycarbonyl)-1*Z*-propenyl]-1,3-dioxaspiro[4.5]dec-7-ene (27). Ethyl 2-[bis(2,2,2-trifluoroethyl)phosphono]propionate[63] (0.16 g, 0.41 mmol) and 18-crown-6 (0.5 g, 2 mmol) were dissolved in THF (8 mL) and the solution cooled to -78 °C before KHMDS (0.82 mL of a 0.5 M solution in toluene, 0.4 mmol) was added slowly. The resulting yellow solution was stirred for 0.5 h at -78 °C, before a solution of aldehyde **26** (64.6 mg, 0.16 mmol) in THF (2 mL) was added via a syringe. The reaction mixture was then stirred for 2 h at -78 °C, quenched carefully with sat. aqueous NH_4Cl (2 mL), allowed to come to room temperature, and diluted with ether (10 mL). The organic phase was washed successively with water (2 x 10 mL) and brine (10 mL), dried (MgSO4), and concentrated. The residue was subjected to silica gel chromatography (eluent: petroleum ether:ether, 1:1) to yield **27** (41 mg, 52%) as a clear oil, with a *Z*/*E* ratio of ≥95/5. ^{1}H-NMR, d: 1.12 (s, 3 H), 1.22 (s, 3 H), 1.29 (t, *J* = 7.1 Hz, 3 H), 1.37 (s, 3 H), 1.45 (s, 3 H), 1.61 (s, 3 H), 1.80 - 1.95 (m, 2

H), 1.96 (s, 3 H), 2.04 (m, 1 H), 2.34 (m, 1 H), 3.89 (d, J = 14.8 Hz, 1 H), 4.02 (d, J = 14.6 Hz, 1 H), 4.20 (q, J = 5.4 Hz, 2 H), 5.52 (d, J = 9.7 Hz, 1 H), 5.90 (d, J = 9.7 Hz, 1 H), 7.5 - 8.0 (m, 5 H); ^{13}C-NMR, d: 14.2, 21.3, 21.6, 22.3, 24.4, 24.7, 26.9, 28.8, 29.5, 29.6, 40.0, 57.8, 60.6, 73.3, 86.7, 107.4, 125.0, 127.8, 129.1, 133.3, 134.9, 139.1, 167.0; IR υ (cm^{-1}): 1713. Anal. Calcd for $C_{26}H_{36}O_6S$: C, 65.52; H, 7.61. Found: C, 65.35; H, 7.65. The distinctive olefinic signals of the minor isomer were at δ 4.80 and 6.74 in the ^{1}H-NMR spectrum.

(±)-(4*S*,5*S*)-4-[2-(Hydroxymethyl)-1*Z*-propenyl]-2,2,6,6,8-pentamethyl-7-phenylsulfonylmethyl-1,3-dioxaspiro[4.5]dec-7-ene (28). A solution of **27** (20.1 mg, 0.04 mmol) in ether (6 mL) was treated at -78 °C with DIBAL (0.13 mL, 1.5 M solution in toluene, 0.2 mmol) and stirred at -78 °C for 2 h before MeOH (3 mL) was added and the reaction mixture allowed to warm up to room temperature, resulting in the formation of a white, gelatinous precipitate. The reaction mixture was filtered and the precipitate washed with ether (2 x 10 mL). The combined organic extracts were concentrated and the residue subjected to silica gel chromatography (eluent: petroleum ether:ether, 1:1) yielding **28** (13.5 mg, 75%) as a viscous oil. ^{1}H-NMR, δ: 1.10 (s, 3 H), 1.16 (s, 3 H), 1.38 (s, 3 H), 1.43 (s, 3 H), 1.66 (s, 3 H), 1.67 - 2.00 (m, 2 H), 1.85 (s, 3 H), 2.04 (m, 1 H), 2.36 (m, 1 H), 3.92 (d, J = 10.6 Hz, 1 H), 4.01 (d, J = 10.8 Hz, 1 H), 4.16 (d, J = 9.2 Hz, 1 H), 4.21 (d, J = 9 Hz, 1 H), 4.91 (d, J = 8.5 Hz, 1 H), 5.44 (d, J = 8.5 Hz, 1 H), 7.5 - 8.0 (m, 5 H); ^{13}C-NMR, δ: 21.6, 22.1, 22.9, 24.7, 24.9, 26.7, 28.9, 29.5, 40.1, 57.7, 62.1, 73.8, 85.7, 106.6, 122.3, 124.6, 127.8, 129.2, 133.3, 139.7, 141.2, 142.3. HRMS. Calcd for $C_{24}H_{34}O_5S$: 434.2126. Found: 434.2130 ($M^{+\cdot}$).

(±)-(4*S*,5*S*)-4-[2-(Bromomethyl)-1*Z*-propenyl]-2,2,6,6,8-pentamethyl-7-phenylsulfonylmethyl-1,3-dioxaspiro[4.5]dec-7-ene (29). Tetrabromomethane (102 mg, 0.31 mmol) and triphenylphosphine (81 mg, 0.31 mmol) were dissolved with stirring in THF (8 mL) resulting, after a few minutes, in a white precipitate at which stage the alcohol **28** (13.5 mg, 0.03 mmol) in THF (2 mL) was added. The reaction mixture was stirred for a further 6 h, then filtered and the precipitate washed with ether (2 x 5 mL). The combined organic extracts were concentrated and the residue subjected to chromatography on silica gel (eluent: petroleum:ether, 3:1) to yield bromide **29** (10.5 mg, 68%) as an oil. ^{1}H-NMR, δ: 1.10 (s, 3 H), 1.21 (s, 3 H), 1.40 (s, 3 H), 1.45 (s, 3 H), 1.69 (s, 3 H), 1.91 (s, 3 H), 1.85 - 2.00 (m, 2 H), 2.01 (m, 1 H), 2.40 (m, 1 H), 3.9-4.3 (m, 4 H), 4.77 (d, J = 9.0 Hz, 1 H), 5.5 (d, J = 8.9 Hz, 1 H), 7.5-8.0 (m, 5 H). No further characterization was attempted on this unstable substance which was used immediately in the next step.

(±)-(1*S*,5*S*,9*RS*)-3,3,7,11,14,14-Hexamethyl-(9-phenylsulfonylmethyl)-2,4-dioxa-tricyclo[8.3.1.0^{1,5}]tetradeca-6,10-diene (30). Bromide **29** (9 mg, 0.18 mmol) was dissolved in THF (3.6 mL) and the solution cooled to 0 °C in an ice bath. LiHMDS (0.4 mL of a 0.1M solution in THF, 0.04 mmol) was then added slowly. Immediately after addition of the base, monitoring by TLC indicated complete consumption of the starting material and the appearance of two new, closely migrating spots. The reaction was quenched with sat. aqueous NH_4Cl (2 mL) and allowed to warm up to room temperature before ether (5 mL) was added. The organic phase was washed with brine (3 mL), dried ($MgSO_4$), and concentrated. The residue was subjected to silica gel chromatography (eluent: petroleum ether:ether, 3:1) to yield 30 (6.6 mg, 88%, 1:1 mixture of diastereomers) as a foam. ^{1}H-NMR, δ (isomer 1): 0.95 (s, 3 H), 0.98 (s, 3 H), 1.22 (s, 3 H), 1.38 (s, 3 H), 1.83 (s, 3 H), 1.86 (s, 1 H), 2.5 (dd, J = 9.8 and 18.2 Hz, 1 H), 2.55 - 2.75 (m, 2 H), 2.96 (1H, dd, J = 9 and 17.6 Hz, 1 H), 4.13 (d, J = 6.0 Hz, 1 H), 4.36 (dd, J = 9.2 and 9.1 Hz, 1 H), 5.43 (d, J = 6.0 Hz, 1 H), 7.5-8.0 (m, 5 H); ^{1}H-NMR, δ (isomer 2): 1.16 (s, 3 H), 1.18 (s, 3 H), 1.36 (s, 3 H), 1.43 (s, 3 H), 1.47 (s, 3 H), 1.65 (s, 3 H), 1.85-2.0 (m, 8 H), 2.32 (dd, J = 4.9 and 13.2 Hz, 1 H), 3.05

(dd, J = 13.0 and 12.0 Hz, 1 H), 4.5 (d, J = 6.9 Hz, 1 H), 4.54 (dd, J = 5.0 and 12.8 Hz, 1 H), 5.52 (d, J = 7.0 Hz, 1 H), 7.5-8.0 (m, 5 H); ^{13}C-NMR, δ (both isomers): 20.6, 21.2, 22.4, 23.3, 23.7, 24.7, 25.3, 26.1, 26.2, 26.5, 27.1, 27.9, 28.0, 28.2, 30.3, 30.9, 32.4, 34.1, 40.6, 41.5, 66.6, 70.3, 87.4, 87.5, 106.3, 106.7, 124.8, 125.9, 126.9, 133.3, 133.5, 136.4, 136.7, 140.1, 141.2, 142.5, 146.1. HRMS. Calcd for $C_{24}H_{32}SO_4$: 416.20213. Found 416.20223 ($M^{+\cdot}$).

(±)-(1*S*,5*S*)-3,3,7,11,14,14-Hexamethyl-2,4-dioxa-tricyclo[8.3.1.0^{1,5}]tetradeca-6,10-diene (31). Ammonia (3 mL) was condensed into a 20 mL three-necked flask at -78 °C and sodium (3.1 mg, 0.13 g-atom) added, immediately imparting a blue coloration. Compound **30** (19.1 mg, 0.046 mmol) in THF (0.5 mL) was then added. After 5 min the blue coloration still persisted and the reaction was quenched by addition of solid NH_4Cl (1 g) before the whole was allowed to warm up to room temperature. After complete evaporation of the ammonia, the residue was dissolved in ether (10 mL) and washed successively with 1M HCl (3 mL), water (5 mL) and brine (3 mL), dried ($MgSO_4$), and concentrated. The residue obtained was subjected to chromatography on silica gel (eluent: petroleum ether:ether, 19:1) to give **31** (10.9 mg, 87%) as a colorless oil. ^{1}H-NMR, δ: 1.08 (s, 3 H), 1.25 (s, 3 H), 1.33 (s, 3 H), 1.42 (s, 3 H), 1.47 (s, 3 H), 1.75 (s, 3 H), 1.8-2.8 (m, 8 H), 4.32 (d, J = 6.7 Hz, 1 H), 5.5 (d, J = 6.8 Hz, 1 H); ^{13}C-NMR, δ: 15.2, 19.4, 21.5, 25.0, 25.6, 26.3, 27.4, 28.0, 29.3, 29.7, 30.2, 34.1, 40.0, 65.7, 87.3, 103.1, 106.1, 124.7, 139.1. HRMS. Calcd for $C_{18}H_{28}O_2$: 276.20893. Found: 276.20930 ($M^{+\cdot}$).

Ethyl 6-Bromo-2-(diethylphosphonyl)-6-heptenoate (36). NaH (0.23 g, 60% in mineral oil, 5.71 mmol) was added portionwise at 0 °C with stirring to triethyl phosphonoacetate (1.22 g, 5.71 mmol) in THF (5 mL) resulting in a vigorous evolution of hydrogen gas. The reaction mixture was stirred for a further 0.5 h after gas evolution was complete before 5-iodo-2-bromo-pent-1-ene[74] (1.0 g, 3.81 mmol) in THF (2 mL) was added to the clear solution. The reaction mixture was allowed to warm up to room temperature, stirred for 16 h, then diluted with ether (20 mL), and washed successively with 1M HCl (2 x 15 mL), and brine (20 mL), dried ($MgSO_4$), concentrated under reduced pressure, and the residue subjected to chromatography on silica gel (eluent: ethyl acetate:petroleum ether, 1:2) resulting in the isolation of **36** (0.96 g, 68%) as a colorless oil. This oil could be used without further purification in the next step; however, bulb to bulb distillation (125 °C at 0.25 mm Hg) was used to obtain an analytically pure sample. ^{1}H-NMR, δ: 1.18 - 1.30 (m, 9 H), 1.48 - 1.63 (m, 2 H), 1.70 - 2.00 (m, 2 H), 2.37 (t, J = 7.2 and 7.5 Hz, 2 H), 2.87 (ddd, J = 22.7, 10.7 and 4.0 Hz, 1 H), 4.00 - 4.20 (m, 6 H), 5.33 (s, 1 H), 5.51 (s, 1 H); ^{31}P-NMR, δ: 22.95; IR υ (cm^{-1}): 1728, 2962. Anal. Calcd for $C_{13}H_{24}O_5PBr$: C, 42.02; H, 6.51; Found : C, 41.96; H, 6.62.

(±)-(4*S*,5*S*)-2,2,6,6,8-Pentamethyl-7-phenylsulfonylmethyl-4-[2-(ethoxycarbonyl)-6-bromohepta-1*Z*,6-dienyl]-1,3-dioxaspiro[4.5]dec-7-ene (37). The phosphonoacetate **36** (0.26 g, 0.7 mmol) was dissolved in THF (2.5 mL) and treated portionwise with stirring at 0 °C with NaH (28 mg, 60% solution in mineral oil, 0.7 mmol) leading to a vigorous evolution of hydrogen. After stirring for 0.5 h, aldehyde **26** (73 mg, 0.19 mmol) in THF (1 mL) was added to the clear solution. The reaction mixture was then stirred for 16 h at room temperature before ether (15 mL) was added and the solution washed with 1M HCl (3 x 5 mL), and brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (eluent: ether:petroleum ether, 1:3) to give **37** (44 mg, 39%) as a 1:3 *E*:*Z* mixture of isomers in the form of a viscous oil. *Z*-isomer: ^{1}H-NMR, δ: 1.11 (s, 3 H), 1.21 (s, 3 H), 1.31 (t, J = 7.0 Hz, 3 H), 1.36 (s, 3 H), 1.44 (s, 3 H), 1.63 (s, 3 H), 1.55 - 1.65 (m, 2 H), 1.70 - 1.95 (m, 2 H), 2.1 (m, 1 H), 2.25 - 2.40 (m, 3 H), 2.41 (t, J = 7.5 Hz, 2 H), 3.92 (d, J = 14.8 Hz, 1 H), 4.02 (d, J = 14.7 Hz, 1 H), 4.22 (q, J = 6.3 Hz, 2 H), 5.39 (d, J = 9 Hz, 1 H), 5.40 (s, 1 H), 5.55 (s, 1 H), 5.85 (d, J = 9.6 Hz, 1 H), 7.5-8.0 (m, 5 H); ^{13}C-NMR, δ: 7.4, 15.2, 15.6, 16.2, 20.4, 20.6, 22.5, 23.2, 27.6,

34.2, 34.8, 52.6, 55.7, 68.9, 82.5, 104.1, 114.0, 122.3, 125.2, 126.5, 130.9, 131.4, 137.0, 165.9. The *E*-isomer is identified by its olefinic proton at δ 6.7 in the ^{1}H-NMR spectrum. Anal. Calcd for $C_{30}H_{41}O_6SBr$: C, 59.10; H, 6.78; Found: C, 58.93; H, 6.89.

(±)-(4*S*,5*S*)-2,2,6,6,8-Pentamethyl-7-phenylsulfonylmethyl-4-[2-(hydroxymethyl)-6-bromohepta-1*Z*,6-dienyl]-1,3-dioxaspiro[4.5]dec-7-ene (38). The α,β-unsaturated ester **37** (44 mg, 0.074 mmol) was dissolved in ether (10 mL) and treated at -78 °C, with DIBAL (0.13 mL, 1.5M solution in toluene, 0.19 mmol). After stirring for 2 h at -78 °C MeOH (2.5 mL) was added and the reaction mixture allowed to warm up to room temperature. A white gelatinous precipitate was removed by filtration amd washed with ether (3 x 10 mL) and the combined organic phases dried ($MgSO_4$), and concentrated under reduced pressure to give 43 mg of **38** which required no further purification for use in the next step. ^{1}H-NMR, δ: 1.11 (s, 3 H), 1.16 (s, 3 H), 1.39 (s, 3 H), 1.44 (s, 3 H), 1.66 (s, 3 H), 1.7-2.4 (m, 8 H), 2.43 (t, *J* = 7.3 Hz, 2 H), 3.9 (d, *J* = 14.6 Hz, 1 H), 4.01 (d, *J* = 14.7 Hz, 1 H), 4.15 (d, *J* = 10.5 Hz, 1 H), 4.30 (d, *J* = 11.1 Hz, 1 H) 4.92 (d, *J* = 8.22 Hz, 1 H), 5.40 (s, 1 H), 5.46 (d, *J* = 8.1 Hz, 1 H), 5.57 (s, 1 H), 7.5-8.0 (m, 5 H); ^{13}C-NMR, δ: 22.0, 23.0, 24.8, 25.1, 26.0, 27.0, 28.8, 29.7, 34.5, 40.1, 41.0, 57.5, 61.0, 74.5, 86.5, 107.1, 117.0, 122.8, 124.8, 127.8, 129.2, 133.5, 134.3, 139.7, 141.5, 145.6. HRMS. Calcd for $C_{28}H_{38}O_5BrS$: 566.17016. Found: 566.17048 (M^+).

(±)-(1*S*,2*S*,10*RS*)-4-Bromo-1,2-*O*-isopropylidene-19-nor-10-phenylsulfonyl-3,4-seco-3(8),4(20),11-taxatrien-1,2-diol (40). THF (10 mL) was added with stirring at 0 °C to a mixture of triphenylphosphine (0.2 g, 0.74 mmol) and tetrabromomethane (0.25 g, 0.74 mmol) leading to the formation of a white precipitate. After stirring for 1 h alcohol **38** (43 mg, 0.073 mmol) in THF (2 mL) was added and stirring continued for 10 h at room temperature. The reaction mixture was then concentrated to a syrup which was redissolved in ether (1 mL) and applied to a silica gel column (10 g). Elution with ether:petroleum ether (1:3) gave 32.1 mg (72%) of the bromide **39** as a colorless oil which was immediately used in the cyclization reaction. LiHMDS (0.07 mmoL, 0.7 mL of a 0.1 mM solution in THF) was added dropwise to a stirred solution of the above bromide (**39**) (20.2 mg, 0.032 mmoL) in THF (6 mL) at to 0 °C. After 5 min. saturated aqueous NH_4Cl (1 mL) followed by ether (5 mL) was added and the resulting organic phase washed succesively with water (2 x 2 mL), and brine (2 mL) before it was dried ($MgSO_4$), and concentrated under reduced pressure. The residue was subjected to chromatography on silica gel (eluent: petroleum ether:ether, 4:1) to give **40** (15.2 mg, 87%) as a 1:1 mixture of diastereomers in the form of a colorless oil. ^{1}H-NMR, δ: 0.93 (s, 3 H), 1.15 (s, 3 H), 1.23 (s, 3 H), 1.25 (s, 3 H), 1.37 (s, 3 H), 1.39 (s, 3 H), 1.43 (s, 3 H), 1.44 (s, 3 H), 1.65 (s, 3 H), 1.80 (s, 3 H), 1.7-3.2 (m, 24 H), 4.13 (d, *J* = 6.3 Hz, 1 H), 4.39 (dd, *J* = 8.7 and 10.2 Hz, 1 H), 4.47 (dd, *J* = 4.9 and 12.8 Hz, 1 H), 4.53 (d, *J* = 6.9 Hz, 1 H), 5.33 (s, 1 H), 5.40 (s, 1 H), 5.45 (d, *J* = 6.9 Hz, 1 H), 5.47 (s, 1 H), 5.50 (d, *J* = 6.9 Hz, 1 H), 5.56 (s, 1 H), 7.5-8.0 (m, 5 H); ^{13}C-NMR, δ: 21.6, 22.3, 23.7, 24.5, 25.4, 25.9, 26.8, 26.9, 28.7, 28.8, 29.1, 29.4, 40.2, 57.7, 124.9, 127.7, 127.8, 127.9, 129.1, 129.2, 129.5, 129.7, 133.3, 133.4, 140.8, 146.7. HRMS. Calcd for $C_{28}H_{37}O_4SBr$: 548.15904. Found: 548.15960 (M^+).

(±)-(1*S*,2*S*,10*R*)-8,12-Cyclo-1,2-*O*-isopropylidene-19-nor-10-phenylsulfonyl-4(20)-taxen-1,2-diol (41). A solution of Bu_3SnH (12.8 mg, 0.044 mmoL) and AIBN (1 mg) in dry, degassed benzene (4.4 mL) was added over 2 h with a syringe pump to a solution of vinyl bromide **40** (8.1 mg, 0.015 mmoL) in benzene (1.5 mL) at reflux. After the addition, reflux was continued for an additional 0.5 h, the reaction mixture allowed to cool to room temperature, and the volatiles removed under vacuum. Silica gel chromatography of the residue (eluent: petroleum ether:ether, 4:1) gave **41** (1.4 mg, 22%) as a colorless oil. ^{1}H-NMR, δ: 0.85 (s, 3 H), 1.15-1.35 (m, 8 H), 1.25 (s, 3 H), 1.37 (s, 3 H), 1.40 (s, 3 H), 1.60 (s, 3 H),

1.71 (dd, J = 9.0 and 4.1 Hz), 1.95 (m, 1 H), 2.14 (dd, J = 14.2, and 12.3 Hz, 1 x H-9), 2.19 (br. d, J = 10.3 Hz, H-3), 2.25 (m, 1 H), 2.51 (d, J = 7.0 Hz, 1 H, H-11), 3.71 (ddd, J = 7.0, 8.9 and 11.8 Hz, 1 H, H-10), 4.28 (d, J = 10.1 Hz, 1 H, H-2), 4.99 (s, 1 H), 5.09 (s, 1 H), 7.5-8.0 (m, 5 H); ^{13}C-NMR, δ: 23.3 (CH_3), 25.9 (CH_2), 26.3 (2C, CH_2 + CH_3), 27.3 (CH_2), 29.0 (CH_3), 30.0 (CH_3), 31.0 (CH_3), 32.2 (CH_2), 33.2 (CH_2), 36.0 (C), 36.7 (CH_2), 48.6 (C), 49.7 (CH), 50.9 (C), 62.1 CH), 67.3 (CH), 75.6 (CH), 83.7 (C), 106.5 (C), 110.3 (CH_2), 127.6 (CH), 129.1 (CH), 133.1 (C), 142.1 (C), 145.9 (C). HRMS. Calcd for $C_{28}H_{38}O_4S$: 470.24908. Found 470.24950 (M^+).

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References

1. Crich, D.; Jiao, X.-Y.; Bruncko, M. *Tetrahedron* **1997,** *53,* preceding paper in this issue.
2. Taxol numbering is used throughout the discussion.
3. Klein, E.; Rojahn, W.; Henneberg, D. *Tetrahedron* **1964,** *20,* 2025-2035.
4. Dodd, D. S.; Oehschlager, A. C.; Georgopapadakou, N. H.; Polk, A. M.; Hartman, P. G. *J. Org. Chem.* **1992,** *57,* 7226-7234.
5. Mousseron-Canet, M.; Mousseron, M.; Levallois, C. *Bull. Soc. Chim. Fr.* **1964,** 297-300.
6. Ohloff, G.; Schutte-Elte, K.-H.; Willhalm, B. *Helv. Chim. Acta* **1964,** *47,* 602-626.
7. Polla, M.; Frejd, T. *Tetrahedron* **1993,** *49,* 2701-2710.
8. Coates, R. M.; Melvin, L. S. *J. Org. Chem.* **1970,** *35,* 865-867.
9. Breslow, R.; Groves, J. T.; Olin, S. S. *Tetrahedron Lett.* **1966,** 4717-4720.
10. Hoye, T. R.; Kurth, M. J. *J. Org. Chem.* **1978,** *43,* 3693-3693.
11. van Tamelen, E. E.; Hessler, E. J. *J. Chem. Soc., Chem. Commun.* **1966,** 411-413.
12. Kato, T.; Ichinose, I.; Kamoshida, A.; Kitahara, Y. *J. Chem. Soc., Chem. Commun.* **1976,** 518-519.
13. Gonzalez, A. G.; Martin, J. D.; Pérez, C.; Ramirez, M. A. *Tetrahedron Lett.* **1976,** 137-140.
14. Wolinsky, L. E.; Faulkner, D. J. *J. Org. Chem.* **1976,** *41,* 597-600.
15. Tsuji, Y.; Yamada, N.; Tanaka, S. *J. Org. Chem.* **1993,** *58,* 16-17.
16. Murahashi, S. I.; Imada, Y.; Taniguchi, Y.; Higashima, S. *J. Org. Chem.* **1993,** *58,* 1538-1545.
17. Okano, T.; Okabe, N.; Kiji, J. *Bull. Chem. Soc. Jpn.* **1992,** *65,* 2589-2593.
18. Hoye, T. R.; Kurth, M. J. *J. Org. Chem.* **1979,** *44,* 3461-3467.
19. Crich, D.; Crich, J. Z. *Tetrahedron Lett.* **1994,** *35,* 2469-2472.
20. Doi, T.; Robertson, J.; Stork, G.; Yamashita, A. *Tetrahedron Lett.* **1994,** *35,* 1481-1484.
21. Karvinen, E. K.; Koskinen, A. M. P. *Tetrahedron Lett.* **1995,** *36,* 7555-7558.
22. Nishizawa, N.; Morikuni, E.; Takeji, M.; Asoh, K.; Hydod, I.; Imagawa, H.; Yamada, H. *Synlett.* **1996,** 927-928.
23. Hill, C. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974,** *96,* 870-876.
24. Plesnicar, B. Organic Polyoxides. In *The Chemistry of Peroxides;* Patai, S. Ed.; Wiley: Chichester, 1983; pp. 483-520.
25. Pariza, R. J.; Kuo, F.; Fuchs, P. L. *Synth. Commun.* **1983,** *13,* 243-254.
26. Adderice, M.; Sum, F. W.; Weiler, L. *Org. Synth. Coll. Vol.* **1990,** *7,* 351-356.
27. Cohen, T.; Guo, B. S. *Tetrahedron* **1986,** *42,* 2803-2808.
28. Crich, D.; Natarajan, S. *J. Chem. Soc., Chem. Commun.* **1995,** 85-86.
29. Petasis, N.; Patane, M. A. *Tetrahedron* **1992,** *48,* 5757-5821.
30. Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994,** *367,* 630-634.
31. Nicolaou, K. C.; Liu, J.-J.; Yang, Z.; Ueno, H.; Sorensen, E. J.; Claiborne, C. F.; Guy, R. K.; Hwang, C.-K.; Nakada, M.; Nantermet, P. G. *J. Am. Chem. Soc.* **1995,** *117,* 634-644.
32. Nicolaou, K. C.; Nantermet, P. G.; Ueno, H.; Guy, R. K.; Couladouros, E. A.; Sorensen, E. J. *J. Am. Chem. Soc.* **1995,** *117,* 624-633.
33. Nicolaou, K. C.; Yang, Z.; Liu, J.-J.; Nantermet, P. G.; Claiborne, C. F.; Renaud, J.; Guy, R. K.; Shibayama, K. *J. Am. Chem. Soc.* **1995,** *117,* 645-652.
34. Masters, J. J.; Link, J. T.; Snyder, L. B.; Young, W. B.; Danishefsky, S. J. *Angew. Chem. Int. Ed. Engl.* **1995,** *34,* 1723-1726.

35. Kress, M. H.; Ruel, R.; Miller, W. H.; Kishi, Y. *Tetrahedron Lett.* **1993,** *34*, 6003-6006.
36. Kende, A. S.; Johnson, S.; Sanfilippo, P.; Hodges, J. C.; Jungheim, L. N. *J. Am. Chem. Soc.* **1986,** *108*, 3513-3516.
37. Hara, R.; Furukawa, T.; Horiguchi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **1996,** *118*, 9186-9187.
38. Furukawa, T.; Morihara, K.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron* **1992,** *48*, 6975-6984.
39. Horiguchi, Y.; Furukawa, T.; Kuwajima, I. *J. Am. Chem. Soc.* **1989,** *111*, 8277-8279.
40. Wang, Z.; Warder, S. E.; Perier, H.; Grimm, E. L.; Berstein, M. A.; Ball, R. G. *J. Org. Chem.* **1993,** *58*, 2931-2932.
41. Masters, J. J.; Jung, D. K.; Danishefsky, S. J.; Snyder, L. B.; Park, T. K.; Isaacs, R. C. A.; Alaimo, C. A.; Young, W. B. *Angew. Chem. Int. Ed. Engl.* **1995,** *34*, 452-455.
42. Masters, J. J.; Jung, D. K.; Bormann, W. G.; Danishefsky, S. J. *Tetrahedron Lett.* **1993,** *34*, 7256-7259.
43. Kress, M. H.; Ruel, R.; Miller, W. H.; Kishi, Y. *Tetrahedron Lett.* **1993,** *34*, 5999-6002.
44. Swindell, C. S.; Chander, M. C.; Heerding, J. M.; Klimko, J. M.; Rahman, L. T.; Raman, V. J.; Venkataraman, H. *Tetrahedron Lett.* **1993,** *34*, 7005-7008.
45. White, J. D.; Somers, T. C. *J. Am. Chem. Soc.* **1994,** *116*, 9912-9920.
46. Golinski, M.; Vasudevan, S.; Floresca, R.; Brock, C. P.; Watt, D. S. *Tetrahedron Lett.* **1993,** *34*, 55-58.
47. Golinski, M.; Brock, C. P.; Watt, D. S. *J. Org. Chem.* **1993,** *58*, 159-164.
48. Swaminathan, S.; Narayanan, K. V. *Chem. Rev.* **1971,** *71*, 429-438.
49. Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1996,** *93*, 4327-4329.
50. Viereggе, H.; Schmidt, H. M.; Renema, J.; Bos, H. J. T.; Arens, J. F. *Rec. Trav. Chim. Pays Bas* **1966,** *85*, 929-951.
51. Brandsma, L.; Verkruijsse, H. D. *Synthesis of Acetylenes, Allenes, and Cumulenes: A Laboratory Manual*; Elsevier: Amsterdam, 1981.
52. Lorber, C. Y.; Osborn, J. A. *Tetrahedron Lett.* **1996,** *37*, 853-856.
53. Van Rheenan, V.; Cha, D. Y.; Hartley, W. M. *Org. Syn. Coll. Vol.* **1988,** *6*, 342-348.
54. Lohray, B. B.; Bhushan, V.; Kumar, R. K. *J. Org. Chem.* **1994,** *59*, 1375-1380.
55. Vedejs, E.; Dent, W. H. *J. Am. Chem. Soc.* **1989,** *111*, 6861-6862.
56. Dimitrov, V.; Kostova, K.; Genov, M. *Tetrahedron Lett.* **1996,** *37*, 6787-6790.
57. Evans, W. J.; Feldman, J. D.; Ziller, J. W. *J. Am. Chem. Soc.* **1996,** *118*, 4581-4584.
58. Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989,** *111*, 4392-4398.
59. Heaney, H. *Aldrichimica Acta* **1993,** *26*, 35-45.
60. Overman, L. E.; Campbell, C. B.; Knoll, F. M. *J. Am. Chem. Soc.* **1978,** *100*, 4822-4834.
61. Overman, L. E. *Angew. Chem. Int. Ed. Engl.* **1984,** *23*, 579-586.
62. Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639-666.
63. Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983,** *24*, 4405-4408.
64. Grimm, E. L.; Levac, S.; Coutu, M. L. *Tetrahedron Lett.* **1994,** *35*, 5369-5372.
65. Grimm, E. L.; Levac, S.; Trimble, L. A. *Tetrahedron Lett.* **1994,** *35*, 6847-6850.
66. Suh, Y.-G.; Koo, B.-A.; Kim, E.-N. *Tetrahedron Lett.* **1995,** *36*, 2089-2092.
67. Ihara, M.; Suzuki, S.; Tokunaga, Y.; Takeshita, H.; Fukumoto, K. *J. Chem. Soc., Chem. Commun.* **1996**, 1801-1802.
68. Keck, G. E.; Enholm, E. J.; Yates, J. B.; Wiley, M. R. *Tetrahedron* **1985,** *41*, 4079-4094.
69. Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1983,** *105*, 6765-6766.
70. Stork, G.; Mook, R. *Tetrahedron Lett.* **1986,** *27*, 4529-4532.
71. Beckwith, A. L. J.; O'Shea, D. M. *Tetrahedron Lett.* **1986,** *27*, 4525-4528.
72. Dowd, P.; Zhang, W. *Chem. Rev.* **1993,** *93*, 2091-2115.
73. Crich, D.; Hwang, J.-T.; Liu, H. *Tetrahedron Lett.* **1996,** *37*, 3105-3108.
74. Baldwin, J. E.; Adlington, R. M.; Singh, R. *Tetrahedron* **1992,** *48*, 3385-3412.
75. Chen, S. H.; Huang, S.; Kant, J.; Fairchild, C.; Wei, J.; Farina, V. *J. Org. Chem.* **1993,** *58*, 5028-5029.
76. Chen, S.-H.; Huang, S.; Gao, Q.; Golik, J.; Farina, V. *J. Org. Chem.* **1994,** *59*, 1475-1484.
77. Chen, S.-H.; Combs, C. M.; Hill, S. E.; Farina, V.; Doyle, T. W. *J. Org. Chem.* **1992,** *33*, 7679-7682.
78. Kende, A. S.; Journet, M.; Ball, R. G.; Tsou, N. N. *Tetrahedron Lett.* **1996,** *37*, 6295-6298.

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