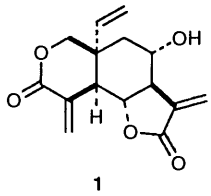
Preparation of Key Intermediates for the Asymmetric Synthesis of Oxygenated Elemanoids

Michiharu Kato,* Fusao Kido, Masataka Watanabe, Yoshiaki Masuda and Bahlul Z. Awen
Institute for Chemical Reaction Science, Tohoku University, Katahira, Aoba-ku, Sendai 980, Japan

In connection with search for chiral key intermediates useful for the synthesis of elemanoids, (3*R*,4*S*)-3-acetoxymethyl- and 3-*tert*-butyldimethylsiloxymethyl-4-isopropenyl-3-vinylcyclohexanone, (**12a**, R = Ac and TBDMS) and (1*S*,4*S*,5*R*)-4-isopropenyl-1-methoxy-5-vinyl-7-oxabicyclo[3.2.1]octane (**24**, R = Me) have been synthesised in good overall yields from (1*R*,5*S*)-nopinone **5** *via* (1*R*,5*S*)-4-hydroxymethyl-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one, **17a**, (1*R*,4*R*,5*S*)-4-acetoxymethyl-6,6-dimethyl-4-vinylbicyclo[3.1.1]heptan-2-one **20**, and its cyclobutane-ring opened product, (4*S*,5*R*)-1-acetoxy-5-acetoxymethyl-4-isopropenyl-5-vinylcyclohex-1-ene **21**. The enantiomer of **17a**, (1*S*,5*R*)-**17b**, was prepared from (1*R*,5*S*)-**5** as the common starting material. The above compounds, (3*R*,4*S*)-**12a** as well as 24, are useful for the asymmetric synthesis of (5*S*,10*R*)-elemanoid with oxygen functions at the C–8 and C-14 positions, while the compounds (3*S*,4*R*)-**12b**, enantiomers of **12a** which could be derived from **17b** according to a sequence of reactions for the preparation of **12a** from **17a** are useful for the synthesis of (5*R*,10*S*)-oxygenated elemanoid.

Elemanes constitute a large class of terpenoids the isolation, characterisation, and synthesis of which have been reported.† Since the 1950s, a number of synthetic routes to these compounds have been described.[2] Specifically, in the 1970s, isolation of the elemanolide vernolepin **1** [3] possessing cytotoxic and antitumour activity stimulated a variety of ingenious strategies in the synthetic study of these compounds.[2b,4] Recently, the trisubstituted cyclohexanone **2** was proposed as a promising synthetic intermediate for this class of compound and, in fact, racemic compound **2** was not only derived from the Hagemann ester in a short route,[5a-c] but also successfully transformed into racemic β-elemenone **3**[5] and a variety of elemanolides represented by eleman-8β, 12-olide **4**[5a] However, most of the syntheses hitherto reported have given racemic compounds, little being known about the synthetic work in an optically active form.



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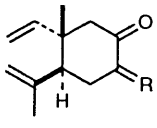
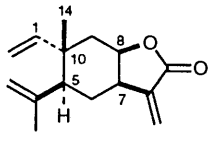
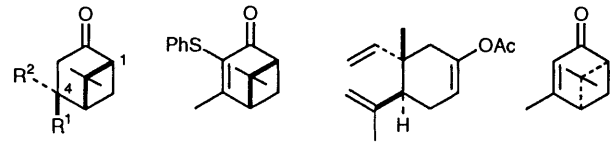


2a,b R = H_2
3a,b R = CMe_2

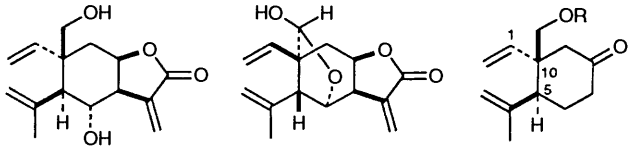


4a,b

We have been studying the utility of (1*R*,5*S*)-nopinone **5** as the chiral source for an asymmetric synthesis, and reported its effective chemical transformation *via* (1*R*,5*S*)-(+)-3-(-phenylthio)verbenone **6a** into (1*R*,4*S*,5*S*)-(+)-4,6,6-trimethyl-4-vinylnopinone **7**,[6b] followed by boron trifluoride–ether (BF_3·OEt_2)-promoted cyclobutane-ring opening[6a] to give (4*S*,5*S*)-(−)-1-acetoxy-4-isopropenyl-5-methyl-5-vinylcyclohex-1-ene **8**. Hydrolysis of the acetate **8** gave (3*S*,4*S*)-(−)-**2a**,[6b] from which (+)-**3a** and (+)-**4a** were synthesised in optically active forms.[6b] Furthermore, we have recently developed a general and



5 $R^1 = R^2 = H$ **6a,b** **8** **9**
7 R^1 = Me, $R^2 = CH{=}CH_2$
13a,b $R^1 = CH_2OH$, $R^2 = CH{=}CH_2$



10 **11** **12a,b**

convenient transformation of **5** into (1*S*,5*S*)-verbenone **9**[7] (*vide infra*). Starting with the ketone **9**, the other enantiomer, (3*R*,4*R*)-(+)-**2b** was synthesised according to the route for the preparation of **2a**,[7] thus completing a formal synthesis of (−)-**3b** and (−)-**4b** from a common starting material.

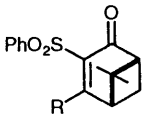
Of the elemanoids isolated from natural sources, a number have oxygen functions at the C-6, C-8 and C-14 positions, for example, (+)-**1**, (+)-schkuhridin **B** **10**,[8] and (+)-elemanschkuhridide **11**.[9] In the proposed asymmetric synthesis of such elemanes, the trisubstituted cyclohexanone **12a** possessing an oxygenated methyl group could serve as a key intermediate for the synthesis of (5*S*,10*R*)-elemanolides such as **10**, with possible introduction of an additional oxygen function at the C-6 position *via* a 6,7-epoxy derivative of **12a**; such a possibility has been discussed by Bohlmann.[5a] The cyclohexanone **12b**, the enantiomer of **12a**, is suitable for the synthesis of (5*R*,10*S*)-elemanolides such as **11** from the same reason. The 4,4-disubstituted nopinones **13a**, **b**, possessing a hydroxymethyl group which serves in a later stage as the C-14-oxygenated methyl function of natural elemanoids, are the proposed synthetic intermediates for the synthesis of **12a**, **b**. Herein we show, starting with (1*R*,5*S*)-nopinone **5** as the common starting material, an efficient synthesis of the two enantiomers

† With regard to the structural formulae in this report, the compounds denoted by compound number **a** have the absolute stereostructures as depicted, whereas the compounds denoted as **b** are their enantiomers and have the opposite absolute stereostructures.

of 10-hydroxyverbenone **17a**, **b** (Scheme 1), a stereocontrolled synthesis of **13a** from **17a**, and transformation of **13a** to 12a.[10]

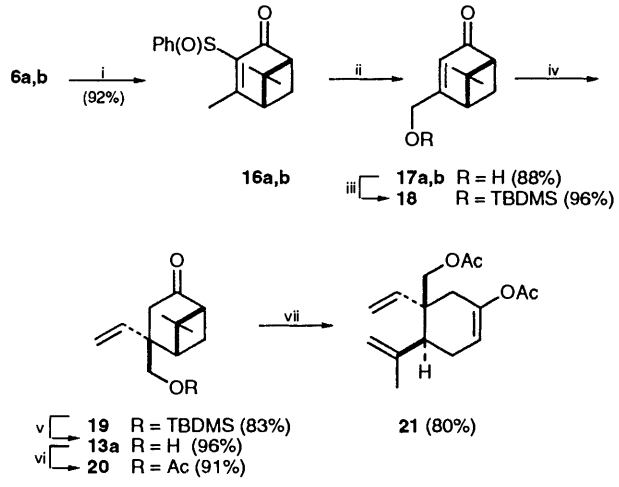
Result and Discussion

The present study began with an attempted, but unsuccessful, introduction of an oxygen function into the olefinic methyl group in verbenones. In this, the sulfone **14**,[6b] readily obtainable from the sulfide **6a**,[6b] was subjected to allylic oxidation using butyllithium and *N,N,N',N'*-tetramethylethylenediamine (TMEDA) followed by treatment with oxygen.[11] Unfortunately, the reaction gave only quantitative recovery of the sulfone **14**. In contrast, conventional allylic oxidation of the sulfone **14** with selenium dioxide in ethanol provided the diethyl acetal **15** in a moderate yield.



14 R = Me
15 R = $CH(OEt)_2$

The optimum result for oxygenation of the olefinic methyl group was obtained when the sulfoxide **16a**, accessible in 92% yield by oxidation of the sulfide **6a**[6b] with *m*-chloroperoxybenzoic acid (MCPBA) (1.0 equiv), was adopted as the starting material, and subjected to a [2.3]-sigmatropic rearrangement (Scheme 1). This synthesis is based on the observation that some verbenones are readily isomerised to the corresponding deconjugated enones (4-methylenebicyclo[3.1.1]heptan-2-ones) by base.[12] Thus, when compound **16a** was gently warmed in aqueous pyridine, deconjugated enone formation occurred and this was followed by a smooth sulfoxide–sulfenate rearrangement[13] to give (1*R*,5*S*)-10-hydroxyverbenone **17a**, in 88% yield $[\alpha]_D^{17}$ +270.7 ($CHCl_3$). Although alcohol **17**, a rare monoterpene alcohol found in Nature, has not had its optical rotation recorded,[14] its identity was confirmed by comparison of ^1H NMR spectral data.

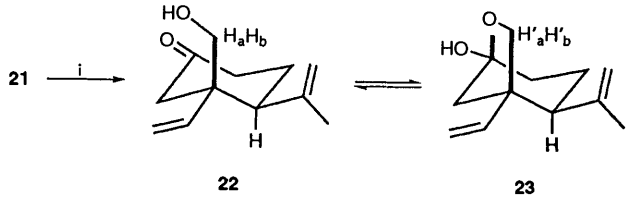


Scheme 1 *Reagents and conditions:* i, MCPBA (1 equiv.), CH_2Cl_2; ii, pyridine, H_2O, 60 °C; iii, TBDMSCl, imidazole, DMF; iv, CH_2=CHMgBr, CuBr·Me_2S, THF; v, TBAF, THF; vi, Ac_2O, Et_3N, DMAP, CH_2Cl_2; vii, BF_3·OEt_2, $Zn(OAc)_2$, Ac_2O, room temp., 4 days

With the desired alcohol **17a** in hand, we turned our attention to its conversion into the 4,4-disubstituted nopinone and subsequent cyclobutane-ring opening according to our methodology established earlier.[6a] The alcohol **17a** was first protected as the *tert*-butyldimethylsilyl (TBDMS) ether **18**, the conjugate addition of which to vinylmagnesium bromide in the presence of a catalytic amount of copper(I) bromide–dimethyl sulfide complex (CuBr·Me_2S) proceeded in a highly stereoselective fashion. In this, the nucleophile approaches the reaction site from the less hindered side, away from the gem-dimethyl bridge,[6b] giving the adduct **19** as the sole product. Subsequent deprotection with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF) provided the alcohol **13a** in 61% overall yield from **6a**.

Earlier,[6a,c] we have reported that reagent, BF_3·OEt_2–zinc acetate–acetic anhydride is effective for the regioselective cyclobutane-ring opening of nopinones with no loss of optical integrity. The alcohol **13a** was protected as the acetate **20** *prior to* the cyclobutane-opening reaction, since the TBDMS ether function is ineffective as protective group being labile under the reaction conditions employed here. BF_3·OEt_2-promoted cyclobutane-ring opening of the acetate **20** was performed at room temperature over 3 days to provide, in a synthetically satisfactory yield, the enol acetate **21**, as the sole product $[\alpha]_D^{20}$ +10.9 ($CHCl_3$).

Upon methanolysis of **21** with K_2CO_3 in methanol, the initially formed hydroxy ketone **22** was in equilibrium with 7-oxabicyclo[3.2.1]octan-1-ol **23** (Scheme 2). This is a result of attack by the neighbouring axial hydroxymethyl group on the ketone function, the cyclohexane ring being fixed with equatorially orientated vinyl and isopropenyl groups. In the ^1H NMR (400 MHz) spectra, the methylene protons bonded with the oxygen atom exhibited a strong temperature-dependent phenomenon. At room temperature, these protons appeared as two resonances in a 1:1 ratio from integration at δ 4.00 (br s) and 3.75 (d, J 9.5 Hz), which were deformed as the temperature was lowered. At −60 °C, the broad bands resolved into two pairs of AB quartets centred at δ 4.02 (J_{H_a,H_b} = 8.5 Hz, $\Delta\nu$ = 156 Hz) and 3.68 ($J_{H'_a,H'_b}$ = 10 Hz, $\Delta\nu$ = 54 Hz), indicating the presence of an equilibrium mixture of **22** and **23** in a ratio of 1:6 by integration. Structural assignment of the equilibrium isomers was performed by the IR(neat) analyses, *i.e.*, at room temperature, the carbonyl stretching band of the equilibrium mixture is obtained at 1707 cm^{-1} with medium intensity (approximately equal to intensity of the double bond stretching band at 1639 cm^{-1}), whereas at −60 °C, the carbonyl stretching band at 1704 cm^{-1} is weak (approximately one-half the intensity of the double bond band at 1641 cm^{-1}).*



Scheme 2 *Reagents and conditions:* i, K_2CO_3, MeOH, room temp.

Our attention was then focused on the isolation of the equilibrium isomer in the form of stable derivatives. Protection of hydroxy groups in the equilibrium mixture was dependent on the reaction conditions employed, giving cyclohexanones **12a** and/or 7-oxabicyclo[3.2.1]octanes **24**. Results are shown in Table 1. Acetylation under the usual reaction conditions provided the acetoxy ketone **12a** (R = Ac) as the sole product (run 1). This is accounted for by the preponderance of the primary hydroxy group over the tertiary one in acylation. Similarly, silylation with TBDMSCl gave the siloxy ketone **12a** (R = TBDMS) in 80% yield (run 5). On the other hand, acetylation using acetyl chloride to the sodium alkoxide, prepared from the equilibrium mixture with sodium hydride

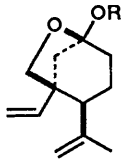
* Details of the temperature-dependent equilibrium will be reported elsewhere in due course.

Table 1 Protection of hydroxy groups in the equilibrium mixture

Run	Conditions	Product (%) 12a	24
1	Ac_2O, Py	R = Ac (74)	—
2	AcCl, Et_3N,[a] DMAP,[b] CH_2Cl_2	R = Ac (25)	R = Ac (9)
3	AcCl, NaH, THF	—	R = Ac (77)
4	BzCl, Et_3N, DMAP, CH_2Cl_2[c]	—	R = Bz (84)
5	TBDMSCl,[d] imidazole, DMF[e]	R = TBDMS (80)	—
6	MeI, NaH, THF	—	R = Me (84)
7	$CH(OMe)_3$, *p*-TsOH, PhH	—	R = Me (100)

[a] Triethylamine; [b] 4-dimethylaminopyridine; [c] on treatment with benzyl chloride in pyridine, the starting material was recovered unchanged; [d] *tert*-butyldimethylsilyl chloride; [e] *N,N*-dimethylformamide

(NaH), gave **24** (R = Ac) in a high yield (run 3), while methylation with methyl iodide (MeI) resulted in formation of the acetal **24** (R = Me) (run 6). The latter was obtained quantitatively by reaction with methyl orthoformate in acidic conditions (run 7). Interestingly, acetylation with acetyl chloride in the presence of triethylamine (Et_3N) and 4-dimethylaminopyridine (DMAP) gave a mixture of two isomeric acetates, **12a** (R = Ac) and **24** (R = Ac), albeit in a low combined yield (run 2). In addition, benzoylation with benzoyl chloride in pyridine resulted in recovery of the starting material, whereas the reaction in the presence of Et_3N and DMAP produced **24** (R = Bz) as the sole product (run 4). The cyclohexanones **12a** (R = Ac and TBDMS) obtained are our target compounds, and could serve as promising synthetic intermediates directed toward the asymmetric synthesis of elemanoids. Since the product **24** (R = Me) is regarded as the compound wherein both hydroxy and ketone groups in **12a** (R = OH) are protected intramolecularly as the acetal function, the use of **24** (R = Me) as the key intermediate would be advantageous when manipulation of the side chains (vinyl and isopropenyl groups) is desired in an earlier stage of the natural product synthesis.[10]



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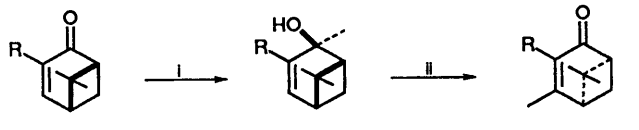
We planned the preparation of the diene **12b**, the enantiomer of **12a**, next. Since we have recently succeeded in an effective transformation of (1*R*,5*R*)-(−)-apoverbenone **25**, readily accessible from (1*R*,5*S*)-**5**, into (1*S*,5*S*)-(−)-verbenone **9** *via* the allylic alcohol **26**[7] (Scheme 3), conversion of the sulfide **27**[6b] into **6b** using this methodology may be possible. Procurement of **6b** is synthetically equivalent to the preparation of **12b**, because a synthetic route to **12a** from **6a** has now been accomplished.



25 R = H
27 R = SPh

26 R = H
28 R = SPh (100%)

9 R = H
6b R = SPh (56%)

Scheme 3 *Reagents and conditions:* i, MeLi, ether; ii, PCC, CH_2Cl_2

Methylation of the sulfide **27**[6b] with MeLi proceeded cleanly by 1,2-addition to give the allylic alcohol **28** in quantitative yield. Oxidative rearrangement of the latter was effected, upon exposure to pyridinium chlorochromate (PCC) in CH_2Cl_2 at 0 °C, to give **6b** in 56% yield. The compound **6b** was also obtained by phenylsulfenylation of the lithium enolate of **9**[7] with *S*-phenyl benzenethiosulfonate,[15] in 50% yield. The physical data for **6b**, $[\alpha]_D^{21}$ −142.8 ($CHCl_3$), are identical with those of its enantiomer **6a**, $[\alpha]_D^{23}$ +144.0($CHCl_3$),[6b] except for the sign of the optical rotation.

Finally, the enantiomeric synthesis of the natural product **17** was performed from **6b** according to the synthetic route in Scheme 1. The constituent reactions provided compounds **16b** and **17b** in the same yields and physical data as those of the corresponding compounds in the **a** series except for the sign of the optical rotation.

In conclusion, starting with (1*R*,5*S*)-nopinone **5** as the common chiral source, (1*R*,5*S*)- *and* (1*S*,5*R*)-10-hydroxyverbenone (**17a**, **b**) were synthesised in high overall yields. The synthetic route of the trisubstituted cyclohexanones **12a** (R = Ac, TBDMS) *via* regio- and stereo-selective cyclobutane-ring opening reaction of the 4,4-disubstituted nopinone **20** was developed using **17a**. Synthesis of the enantiomer **12b** was possible on application of the present methodology to **17b**. The above trisubstituted cyclohexanones could serve as promising intermediates for the asymmetric synthesis of C-6, C-8 and C-14-oxygenated elemanes. In the present synthesis, the following characteristic features are involved; (1) oxygenation of the olefin methyl group in **6a**, **b** is successfully achieved in a high yield using [2,3]-sigmatropic rearrangement of the sulfoxides derived from **6a**, **b**; (2) BF_3·OEt_2-promoted cyclobutane-ring opening of **20** proceeds in regio- and stereo-selective fashion to give the enol acetate **21** in a high yield; (3) while hydrolysis of **21** provides an equilibrium mixture (a 1:1 ratio) of the hydroxy ketone **22** and the hemiacetal **23**, selective protection of two kinds of hydroxy groups is dependent upon the reaction conditions employed, giving **12a** (R = Ac and TBDMS) by acetylation and silylation under the usual conditions, respectively, as well as **24** (R = Me) by methylation with methyl orthoformate. The asymmetric synthesis of polyoxygenated elemanoids possessing additional oxygen functions at the C-9 and C-15 positions, for example as seen in dicotomentolide[16] and zinaflavin,[17] may be possible by modification of the present methodology.

Experimental

Melting points are uncorrected. IR spectra were obtained with a JASCO IR/FT-8300 spectrophotometer. ^1H NMR spectra were recorded on a JEOL FX90 spectrometer, *J* values are given in Hz. [α] Values are given in units of 10^{-1} deg cm^2 g^{-1}. All organic solvents were purified and dried using standard procedures. All reactions were carried out under dry N_2 or Ar

atmosphere with use of standard procedures for the exclusion of moisture except those under aqueous reaction conditions. Extracts obtained on aqueous work-up of the reaction mixtures were washed successively with water and brine and dried ($MgSO_4$). Column and flash column chromatography were performed on 70–230 and 230–400 mesh silica gel (Merck), respectively, and Kieselgel GF_{254} was employed for preparative thin-layer chromatography (TLC). Solvents for elution are shown in parentheses. Ether refers to diethyl ether.

(1R,5S)-*and*(1S,5R)-4,6,6-*Trimethyl*-3-*phenylsulfoxybicyclo*-[3.1.1]*hept*-3-*en*-2-*one* **16a** *and* **b**.—To a stirred solution of the sulfide **6a** [6b] (107 mg, 0.41 mmol) in CH_2Cl_2 (5 cm^3) was added at 0 °C a solution of MCPBA (80% purity; 89 mg, 0.41 mmol) in CH_2Cl_2 (5 cm^3). After being stirred for an additional 1 h, the reaction mixture was washed successively with aqueous K_2CO_3, water and brine and dried. An oily residue obtained by evaporation of the solvent was chromatographed on silica gel (hexane–EtOAc, 1:2) to give the *title compound* **16a** (104 mg, 92%) as a mixture of diastereoisomers with regard to the sulfoxy function, [HRMS(EI)), Found M^+, 274.1043. $C_{16}H_{18}O_2S$ requires *M*, 274.1027]; ν_{max}(neat)/cm^{-1} 1674; δ_H($CDCl_3$) 0.76 (3 H, s, 8-Me), 1.44 (3 H, s, 9-Me), 2.15 (1 H, d, *J* 9, 7-H_{exo}),* 2.46 (3 H, s, =C-Me), 2.4–3.0 (3 H, m), 7.3–7.6 (3 H, m, Ph) and 7.6–7.8 (2 H, m, Ph).

In a similar manner, the sulfide **6b** (*vide post*) provided the *title compound* **16b** whose IR and ^1H NMR data are identical with those of **16a**.

4-{(1R,5S)-6,6-*Dimethyl*-3-*phenylsulfonylbicyclo*[3.1.1]*hept*-3-*en*-2-*one*} *carbaldehyde Diethyl Acetal* **15**.—A mixture of the sulfone **14** [6b] (29 mg, 0.1 mmol) and selenium dioxide (95% purity, 36 mg, 0.3 mmol) in ethanol (3 cm^3) was gently refluxed for 20 h, and concentrated under reduced pressure. Filtration of the residue through a short silica-gel column (ether) followed by evaporation of the filtrate left an oil, which was purified by preparative TLC (CH_2Cl_2) to give, together with unchanged **14** (8 mg), the *title compound* **15** (19 mg, 53%, $[\alpha]_D^{20}$ +119.5 (*c* 0.44 in $CHCl_3$) (Found: C, 63.30; H, 6.8. $C_{20}H_{26}O_5S$ requires C, 63.48; H, 6.93%); ν_{max}(neat)/cm^{-1} 1700; δ_H($CDCl_3$) 0.81 (3 H, s, 8-Me), 1.25 (3 H, t, *J* 7, OCH_2Me), 1.30 (3 H, t, *J* 7, OCH_2Me), 1.45 (3 H, s, 9-Me), 2.00 (1 H, d, *J* 9, 7-H_{exo}), 2.60–2.97 (2 H, m), 3.24 (1 H, t, *J* 6, 1-H), 3.60–4.0 (4 H, m, 2 × OCH_2Me), 6.78 (1 H, s, O-CH-O), 7.45–7.65 (3 H, m, Ph) and 7.95–8.17 (2 H, m, Ph).

(1R,5S)-*and* (1S,5R)-4-*Hydroxymethyl*-6,6-*dimethylbicyclo*-[3.1.1]*hept*-3-*en*-2-*one* (10-*Hydroxyverbenone*) **17a** *and* **b**.—A mixture of **16a** (2.26 g, 10.8 mmol), pyridine (144 cm^3) and water (46 cm^3) was warmed with stirring at 60 °C for 15 h, then concentrated under reduced pressure insofar as possible. The oily residue was dissolved in CH_2Cl_2, and the resulting solution was dried. Removal of the solvent followed by chromatography of the residue on silica gel (hexane–EtOAc; 2:3) gave the *title compound* **17a** (1.58 g, 88%) as an oil, $[\alpha]_D^{17}$ +270.7 (*c* 1.18 in $CHCl_3$); [HRMS(EI), Found: M^+, 166.0994. $C_{10}H_{14}O_2$ requires *M*, 166.0993]; ν_{max}($CHCl_3$)/cm^{-1} 3300 and 1671; δ_H($CDCl_3$) 1.00 (3 H, s, 8-Me), 1.50 (3 H, s, 9-Me), 2.10 (1 H, d, *J* 9, 7-H_{exo}), 2.40 (1 H, t, *J* 5.5, 5-H), 2.60–3.0 (2 H, m), 4.32 (2 H, br s, OCH_2) and 5.95 (1 H, s with fine splittings, 3-H). ^1H NMR (400 MHz) spectral data of the synthetic **17a** are identical with those of the natural **17**.[5]

In a similar manner **16b** gave the *title compound* **17b**, $[\alpha]_D^{20}$ −269.0 (*c* 0.70 in $CHCl_3$).

* The term *exo* refers to the proton pointing away from the gem-dimethyl bridge.

(1R,5S)-4-tert-*Butyldimethylsiloxymethyl*-6,6-*dimethylbicyclo*[3.1.1]*hept*-3-*en*-2-*one* **18**.—A solution of the alcohol **17a** (1.10 g, 6.3 mmol), imidazole (1.70 g, 25 mmol) and TBDMSCl (1.90 g, 13.0 mmol) in DMF (25 cm^3) was stirred at room temperature for 20 h. To this reaction mixture was added water, and the product was extracted with ether. Removal of the solvent left an oil which was purified by chromatography on silica gel (hexane–EtOAc, 15:1) to give the *title compound* **18** (1.70 g, 96%) as crystals, m.p. 137–138 °C (hexane–ether); $[\alpha]_D^{22}$ +163.5 (*c*. 1.25 in $CHCl_3$) (Found: C, 68.3; H, 10.2. $C_{16}H_{28}O_2Si$ requires C, 68.51; H, 10.06%); ν_{max}($CHCl_3$)/cm^{-1} 1669, 1624 and 1087; δ_H($CDCl_3$) 0.08 (6 H, s, $SiMe_2$), 0.93 (9 H, s, $SiCMe_3$), 1.00 (3 H, s, 8-Me), 1.48 (3 H, s, 9-Me), 2.08 (1 H, d, *J* 9, 7-H_{exo}), 2.35 (1 H, td, *J* 5.5, 1.8, 5-H), 2.58–2.97 (2 H, m), 4.15 and 4.38 (1 H, dd each, *J* 16.5, 1.5, OCH_2) and 5.97 (1 H, s with fine splittings, 3-H).

(1R,4R,5S)-4-tert-*Butyldimethylsiloxymethyl*-6,6-*dimethyl*-4-*vinylbicyclo*[3.1.1]*hept*-3-*en*-2-*one* **19**.—To a stirred solution of CuBr·Me_2S (31 mg, 0.23 mmol) in THF (6 cm^3) was added at −78 °C a solution of vinylmagnesium bromide in THF (0.88 mol dm^{-3}; 5.2 cm^3, 4.5 mmol). After being stirred briefly, a solution of the ketone **18** (638 mg, 2.3 mmol) in THF (9 cm^3) was added, and stirring was continued for an additional 30 min. The reaction mixture was quenched with aqueous NH_4Cl, filtered through a small bed of Celite 545 and the filtrate extracted with ether. Evaporation of the solvent left an oil which was purified by chromatography on silica gel (hexane–EtOAc, 15:1) to give the *title compound* **19** 577 mg, 83%) as an oil, $[\alpha]_D^{22}$ +75.9 (*c* 0.76 in $CHCl_3$) (Found: C, 70.3; H, 10.45. $C_{18}H_{32}O_2Si$ requires C, 70.07; H, 10.46%); ν_{max}($CHCl_3$)/cm^{-1} 1701 and 1636; δ_H($CDCl_3$) 0.01 (6 H, s, $SiMe_2$), 0.83 (9 H, s, $SiCMe_3$), 1.03 (3 H, s, 8-Me), 1.37 (3 H, s, 9-Me), 2.1–2.63 (6 H, m), 3.59 (2 H, s, OCH_2), 4.95 (1 H, d, *J* 17.3, =CH_aH_b) 5.09 (1 H, d, *J* 10.9, =CH_aH_b) and 5.82 (1 H, dd, *J* 17.3, 10.9, =CH-).

(1R,4R,5S)-4-*Hydroxymethyl*-6,6-*dimethyl*-4-*vinylbicyclo*-[3.1.1]*heptan*-2-*one* **13a**.—A solution of tetrabutylammonium fluoride (TBAF) in THF (1.0 mol dm^{-3}; 1.5 cm^3, 1.50 mmol) was added to a solution of the protected alcohol **19** (423 mg, 1.37 mmol) in THF (9 cm^3) at 0 °C, and the resulting solution was stirred for 10 h at room temperature. Water was added and the product was extracted with ether. Removal of the solvent followed by purification of the residue by chromatography on silica gel (hexane–EtOAc, 1:1) to give the *title compound* **13a** (255 mg, 96%) as an oil, $[\alpha]_D^{21}$ +107.4 (*c* 1.02 in $CHCl_3$) (Found: C, 74.4; H, 9.5. $C_{12}H_{18}O_2$ requires C, 74.18; H, 9.34%); ν_{max}(neat)/cm^{-1} 3440, 1709, 1038 and 917; δ_H($CDCl_3$) 1.04 (3 H, s, 8-Me), 1.37 (3 H, s, 9-Me), 1.4–1.70 (2 H, m), 2.17–2.65 (5 H, m), 3.43–3.90 (2 H, m, OCH_2), 5.11 (1 H, dd, *J* 17.2, 1.2, =CH_aH_b), 5.33 (1 H, dd, *J* 9.7, 1.2, =CH_aH_b) and 5.72 (1 H, dd, *J* 17.2, 9.7, =CH-).

(1R,4R,5S)-4-*Acetoxymethyl*-6,6-*dimethyl*-4-*vinylbicyclo*-[3.1.1]*heptan*-2-*one* **20**.—A solution of the alcohol **13a** (2.92 g, 15.2 mmol), acetic anhydride (7.0 cm^3, 75 mmol), Et_3N (10.5 cm^3, 75 mmol) and DMAP (919 mg, 7.5 mmol) in CH_2Cl_2 (60 cm^3) was stirred at room temperature for 20 h. To this solution was added methanol (7 cm^3) at 0 °C, and the reaction mixture was stirred for an additional 1 h. The reaction mixture was washed successively with aqueous HCl, water and brine and dried. Evaporation of the solvent left an oil which was chromatographed on silica gel (hexane–EtOAc, 6:1) to give the *title compound* **20** (3.24 g, 91%) as crystals, m.p. 67–68 °C (hexane–ether); $[\alpha]_D^{25}$ +98.8 (*c* 1.16 in $CHCl_3$) (Found: C, 71.1; H, 8.6. $C_{14}H_{20}O_3$ requires C, 71.16; H, 8.53%); ν_{max}($CHCl_3$)/cm^{-1} 3080, 1736, 1709, 1642, 1038 and 922; δ_H($CDCl_3$) 1.07 (3 H, s, 8-Me), 1.39 (3 H, s, 9-Me), 1.55–1.65 (2 H, m), 2.04 (3 H, s, COMe),

2.1–2.74 (4 H, m), 4.10 (1 H, d, *J* 13.0, OCH_aH_b), 4.25 (1 H, d, *J* 13.0, OCH_aH_b), 5.03 (1 H, d, *J* 18.0, =CH_aH_b), 5.18 (1 H, d, *J* 10.8, =CH_aH_b) and 5.75 (1 H, dd, *J* 18.0, 10.8, =CH-).

(4S,5R)-1-*Acetoxy*-5-*acetoxymethyl*-4-*isopropenyl*-5-*vinylcyclohex*-1-*ene* **21**.—A mixture of the acetate **20** (3.23 g, 13.7 mmol), freshly distilled BF_3·OEt_2 (0.1 cm^3, 1.2 mmol), zinc acetate (2.51 g, 13.7 mmol) and acetic anhydride (30 cm^3) was stirred at room temperature over 3 days. Water (40 cm^3) was added, and the reaction mixture was stirred for an additional 30 min. The product was extracted with ether, and the combined extracts were washed successively with aqueous $NaHCO_3$, water and brine and dried. Evaporation of the solvent left an oil, which was chromatographed on silica gel (hexane–EtOAc, 6:1) to give the *title compound* **21** (2.68 g, 71%; 80% based on the consumed acetate **20**) along with unchanged **20** (352 mg): **21**, an oil; $[\alpha]_D^{22}$ +10.9 (*c* 1.81 in $CHCl_3$) (Found: C, 68.85; H, 8.0. $C_{16}H_{22}O_4$ requires C, 69.04; H, 7.97%); ν_{max}($CHCl_3$)/cm^{-1} 3080, 1740, 1639, 1227, 1041, 920 and 905; δ_H($CDCl_3$) 1.79 (3 H, s with fine splittings, =CMe), 2.01 (3 H, s, COMe), 2.13 (3 H, s, COMe), 2.1–2.22 (5 H, m), 3.95 (1 H, d, *J* 11.2, OCH_aH_b), 4.16 (1 H, d, *J* 11.2, OCH_aH_b), 4.92 (2 H, br s, =CH_2), 5.14 (1 H, d, *J* 11.1, CH=CH_aH_b), 5.20 (1 H, d, *J* 16.6, CH=CH_aH_b), 5.38 (1 H, br s, OC=CH) and 5.78 (1 H, dd, *J* 16.6, 11.1, C*H*=CH_2).

Hydrolysis of the Diacetate **21**.—A mixture of the diacetate **21** (216 mg, 0.78 mmol) and K_2CO_3 (236 mg, 1.71 mmol) in methanol (4 cm^3) was stirred at 0 °C for 1 h, diluted with water and extracted with ether. Concentration of the extract left an oil which was chromatographed on silica gel (hexane–EtOAc, 3:1) to give an equilibrium mixture of (3R,4S)-3-*hydroxymethyl*-4-*isopropenyl*-3-*vinylcyclohexanone* **22** and (1S,4S,5R)-4-*isopropenyl*-5-*vinyl*-7-*oxabicyclo*[3.2.1]*octan*-1-*ol* **23** (134 mg, 89%) as an oil, [HRMS(EI) Found: M^+, 194.1315, $C_{12}H_{18}O_2$ requires *M*, 194.1306]; ν_{max}(neat)/cm^{-1} 3408, 3080, 1707(w), 1639, 1149, 1009, 914 and 819; δ_H(400 MHz, $CDCl_3$) 1.78 (3 H, s, Me), 1.7–2.4 (8 H, m), 3.75 (1 H, d, *J* 9.5, OCH_aH_b), 4.00 (1 H, br s, OCH_aH_b), 4.89 and 4.91 (1 H, s each, =CH_2), 4.99 (1 H, d, *J* 17.7, CH=CH_aH_b), 5.08 (1 H, d, *J* 11.0, CH=CH_aH_b) and 5.81 (1 H, dd, *J* 17.7, 11.0, C*H*=CH_2).

(3R,4S)-3-*Acetoxymethyl*-4-*isopropyl*-3-*vinylcyclohexanone* **12a** (R = Ac) *and* (1R,4S,5R)-4-*Isopropenyl*-5-*vinyl*-7-*oxabicyclo*[3.2.1.]*octane* **24** (R = Ac).—(*a*, Table 1, run 1) A solution of the equilibrium mixture of the ketone **22** and the hemiacetal **23** (16.9 mg, 0.087 mmol), pyridine (0.2 cm^3) and acetic anhydride (0.2 cm^3) was stirred at 0 °C for 1 h and then at room temperature for 15 h. After the usual extractive work-up (ether), the product was purified using MPLC with hexane–EtOAc (3:1) to give the *title compound* **12a** (R = Ac) (15.4 mg, 74%) as an oil, $[\alpha]_D^{20}$ +7.6 (*c* 0.18 in $CHCl_3$) (Found: C, 71.3; H, 8.5. $C_{14}H_{20}O_3$ requires C, 71.16; H, 8.53%), ν_{max}(neat)/cm^{-1} 3084, 1745, 1717, 1641, 1234, 1041 and 902; δ_H($CDCl_3$) 1.83 (3 H, br s, =C-Me), 2.00 (3 H, s, COMe), 1.7–2.6 (7 H, m), 4.05 and 4.22 (1 H, d each, *J* 10.6, OCH_2), 4.82 and 5.08 (1 H, br s each, C=CH_2), 4.98 (1 H, d, *J* 17.5, CH=CH_aH_b), 5.15 (1 H, d, *J* 10.9, CH=CH_aH_b) and 5.78 (1 H, dd, *J* 17.5, 10.9, C*H*=CH_2).

(*b*, run 3) To a stirred suspension of NaH (5.2 mg, 0.22 mmol) in THF (0.3 cm^3) was added dropwise at 0 °C a solution of the equilibrium mixture **22–23** (32.2 mg, 0.17 mmol) in THF (0.8 cm^3). After stirring for 30 min, acetyl chloride (15.3 mm^3, 0.22 mmol) was added and the reaction mixture was stirred at 0 °C for 2 h, and quenched with aqueous NH_4Cl. Extractive work-up (ether) followed by chromatography on silica gel (hexane–EtOAc, 3:1) gave the *title compound* **24** (R = Ac) (30.1 mg, 77%) as an oil, $[\alpha]_D^{22}$ −33.7 (*c* 0.20 in $CHCl_3$) (Found: C, 71.4; H, 8.4. $C_{14}H_{20}O_3$ requires C, 71.16; H, 8.53%); ν_{max}(neat)/cm^{-1} 3082, 1743, 1642, 1255, 1116, 1013 and 894; δ_H($CDCl_3$) 1.72 (3 H, s, =CMe), 2.07 (3 H, s, COMe), 1.7–2.5 (7 H, m), 3.84 and 4.24 (1 H, d each, *J* 8.1, OCH_2), 4.7–5.2 (4 H, m, =CH_2, CH=CH_2) and 5.84 (1 H, dd, *J* 16.0, 10.8, C*H*=CH_2).

(*c*, run 2) A solution of the equilibrium mixture **22–23** (31.4 mg, 0.16 mmol), Et_3N (0.11 cm^3, 0.81 mmol) and DMAP (9.9 mg, 0.08 mmol) in CH_2Cl_2 (1 cm^3) was stirred at 0 °C, as acetyl chloride (46.1 mm^3, 0.65 mmol) was added, and stirring was continued for an additional 2 h. Work-up followed by purification according to the procedures described in method *a* gave the *title compound* **12a** (R = Ac) (9.6 mg, 25%) and the *title compound* **24** (R = Ac) (3.1 mg, 9%).

(1R,4S,5R)-1-*Benzoyloxy*-4-*isopropenyl*-5-*vinyl*-7-*oxabicyclo*[3.2.1]*octane* **24** (R = Bz).—(run 5) A solution of the equilibrium mixture of **22** and **23** (134 mg, 0.6 mmol), Et_3N (0.48 cm^3. 3.50 mmol), and DMAP (42 mg, 0.35 mmol) in CH_2Cl_2 (3 cm^3) was stirred at 0 °C as benzoyl chloride (0.24 cm^3, 2.10 mmol) was added dropwise, and stirring was continued for 6 h at room temperature. Extractive work-up (CH_2Cl_2) followed by chromatography on silica gel (hexane–EtOAc, 20:1) gave the *title compound* **24** (R = Bz) (172 mg, 84%) as an oil, $[\alpha]_D^{22}$ − 52.4 (*c* 0.90 in $CHCl_3$) [HRMS(EI) Found: M^+ 298.1566, $C_{19}H_{22}O_3$ requires *M*, 298.1568]; ν_{max}(neat)/cm^{-1} 3080, 1717, 1642, 1602, 1122, 999 and 900; δ_H($CDCl_3$) 1.76 (3 H, s, =CMe), 1.96–2.48 (7 H, m), 3.93 and 4.31 (1 H, d each, *J* 8.2, OCH_2), 4.85 (2 H, br s, = CH_2), 5.00 (1 H, d, *J* 17.3, CH=CH_aH_b) 5.05 (1 H, d, *J* 10.8, CH=CH_aH_b) and 5.84 (1 H, dd, *J* 17.3, 10.8, C*H*=CH_2).

(3R,4S)-3-tert-*Butyldimethylsiloxymethyl*-4-*isopropenyl*-3-*vinylcyclohexan*-1-*one* **12a** (R = TBDMS).—(run 6) A solution of the equilibrium mixture of **22** and **23** (9.8 mg, 0.05 mmol), imidazole (20.4 mg, 0.3 mmol) and TBDMSCl (22.8 mg, 0.15 mmol) in DMF (0.5 cm^3) was stirred at room temperature for 15 h. Extractive work-up (ether) in the usual manner followed by purification with MPLC (hexane–EtOAc, 6:1) gave the *title compound* **12a** (R = TBDMS) (12.2 mg, 80%) as an oil, $[\alpha]_D^{22}$ +13.4 (*C* 0.50 in $CHCl_3$) (Found: C, 70.3; H, 10.15. $C_{18}H_{32}O_2Si$ requires C, 70.07; H, 10.45%); ν_{max}(neat)/cm^{-1} 3082, 1718, 1640, 1251, 1090, 917 and 899; δ_H($CDCl_3$) 0.03 (6 H, s, $SiMe_2$), 0.88 (9 H, s, $SiCMe_3$), 1.85 (3 H, s, =CMe), 1.7–2.6 (7 H, m), 3.40 and 3.85 (1 H, d each, *J* 10.1, OCH_2), 4.8–5.15 (4 H, m, =CH_2, CH=CH_2) and 5.76 (1 H, dd, *J* 16.5, 10.8, C*H*=CH_2).

(1S,4S,5R)-4-*Isopropenyl*-1-*methoxy*-5-*vinyl*-7-*oxabicyclo*[3.2.1]*octane* **24** (R = Me).—(*a*, run 7) To a stirred mixture of NaH (5.3 mg, 0.22 mmol) in THF (0.2 cm^3) was added dropwise at 0 °C a solution of the equilibrium mixture of **22** and **23** (33.1 mg, 0.17 mmol) in THF (0.8 cm^3). After the mixture had been stirred briefly, MeI (42 mm^3, 0.68 mmol) was added to it and stirring was continued for an additional 5 h at room temperature. Extractive work-up (ether) in the usual manner followed by chromatography of the residue on silica gel (hexane–EtOAc, 10:1) gave the *title compound* **24** (R = Me) (29.8 mg, 84%) as an oil, $[\alpha]_D^{20}$ −55.2 (*c* 1.61 in $CHCl_3$) (Found: C, 74.9; H, 9.9. $C_{13}H_{20}O_2$ requires C, 74.96; H, 9.68%); ν_{max}(neat)/cm^{-1} 3081, 1640, 1031, 1014 and 878; δ_H($CDCl_3$ 1.40–2.40 (7 H, m), 1.75 (3 H, s, =CMe), 3.38 (3 H, s, OMe), 3.75 and 4.23 (1 H, d each, *J* 9.0, OCH_2), 4.80–5.50 (4 H, m, =CH_2, CH=CH_2) and 5.86 (1 H, dd, *J* 18.0, 10.8, C*H*=CH_2).

(*b*, run 8) A solution of the equilibrium mixture **22–23** (42.7 mg, 0.22 mmol), ethyl orthoformate (72.1 mm_3, 0.66 mmol) and toluene-*p*-sulfonic acid (7.6 mg, 0.04 mmol) in benzene (2 cm^3) was stirred at room temperature for 12 h. Extractive work-up (ether) followed by chromatography on silica gel (hexane–EtOAc, 15:1) gave the *title compound* **24** (R = Me) (45.8 mg, quantitative).

(1R,2S,5R)-2,6,6-*Trimethyl*-3-*phenylthiobicyclo*[3.1.1]*hept*-3-*en*-2-*ol* **28**.—To a stirred solution of the sulfide **27**[6b] (1.05 g, 4.29 mmol) in ether (20 cm^3) was added dropwise at 0 °C a solution of MeLi in ether (1.02 mol dm^{-3}; 6.13 cm^3, 8.59 mmol), and stirring was continued for an additional 30 min. The reaction mixture was quenched with aqueous NH_4Cl and the product was extracted with ether. Removal of the solvent left an oil which was chromatographed on silica gel (hexane–EtOAc, 10:1) to give the *title compound* **28** (1.11 g, quantitative) as an oil (Found: C, 74.0; H, 7.7. $C_{16}H_{20}OS$ requires C, 73.79; H, 7.74); ν_{max}/cm^{-1} 3482 and 742; $\delta_H(CDCl_3)$ 1.12, 1.32, 1.36 (3 H, s each, 3 × Me), 1.42–2.68 (5 H, m), 6.38 (1 H, m, =CH) and 7.20–7.60 (5 H, m, Ar).

(1S,5R)-4,6,6-*Trimethyl*-3-*phenylthiobicyclo*[3.1.1]*hept*-3-*en*-2-*one* **6b**.—(*a*) A mixture of the sulfide **28** (108 mg, 0.41 mmol) and pyridinium chlorochromate (PCC) (183 mg, 0.82 mmol) in CH_2Cl_2 (4 cm^3) was stirred at room temperature for 1 week. The reaction mixture was washed with aqueous $NaHSO_3$, and filtered through a short column of Celite 545 (CH_2Cl_2). The filtrate was washed successively with aqueous $CuSO_4$, water and brine and dried. Concentration followed by chromatography of the residue on silica gel (hexane–EtOAc, 20:1) gave the *title compound* **6b** (60 mg, 56%) as an oil, $[\alpha]_D^{20}$ −142.8 (*c* 0.38 in $CHCl_3$), whose IR and ^1H NMR data are identical with those of compound **6a**.

(*b*) To a stirred solution of diisopropylamine (168 mm^3, 1.2 mmol) in THF (1 cm^3) was added dropwise a solution of BuLi in hexane (1.49 mol dm^{-3}; 0.8 cm^3, 1.2 mmol), and stirring was continued for an additional 30 min. To this reaction mixture, a solution of the ketone **9**[7] (150 mg, 1.0 mmol) in THF (1 cm^3) was added, and the reaction mixture was allowed to warm to 0 °C with stirring over 2 h and then recooled to −78 °C. A solution of *S*-phenyl benzenethiosulfonate[15] (250 mg, 1.0 mmol) in THF (1 cm^3) was added, and the mixture was stirred at −78 °C for 2 h, and then at 0 °C for 30 min. The reaction mixture was quenched with 10% aqueous HCl, and extracted with ether. The combined extracts were washed successively with aqueous $NaHCO_3$ and brine and dried. Evaporation followed by purification of the residue by chromatography on silica gel gave the *title compound* **6b** (124 mg, 47%).

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References

1 *Dictionary of Organic Compounds, Fifth Edition*, ed. J. Buckingham, Chapman & Hall, London, 1982–1991, vol. 1–9 and supplement 1–9.
2 (*a*) J. W. ApSimon, C. H. Heathcock, J. W. Hooper, D. Taub and A. F. Thomas, *The Total Synthesis of Natural Products*, ed. J. ApSimon, Wiley-Interscience, New York, 1973, vol. 2, pp. 265–274; (*b*) C. H. Heathcock, S. L. Graham, M. C. Pirrung, F. Plavac and C. T. White, *The Total Synthesis of Natural Products*, ed. J. ApSimon, Wiley-Interscience, New York, 1983, vol. 5, pp. 84–107.
3 S. M. Kupchan, R. Hemingway, D. Werner and A. Karim, *J. Am. Chem. Soc.*, 1968, **90**, 3596; S. M. Kupchan, R. Hemingway, D. Werner, A. Karim, A. McPhall and G. A. Sim, *J. Org. Chem.*, 1969, **34**, 3903.
4 T. Wakamatsu, H. Hara and Y. Ban, *J. Org. Chem.*, 1985, **50**, 103 and references cited therein; C. G. Francisco, R. Freire, M. S. Rodriguez and E. Suarez, *Tetrahedron Lett.*, 1987, 3397.
5 (*a*) D. Friedrich and F. Bohlmann, *Tetrahedron*, 1988, **44**, 1369; (*b*) T.-L. Ho and T. W. Hall, *Synth. Commun.*, 1982, 97; (*c*) O. Soria and L. A. Maldonado, *Synth. Commun.*, 1982, 1093; (*d*) (related synthesis) G. Majetich, P. A. Grieco and M. Nishizawa, *J. Org. Chem.*, 1977, **42**, 2327; (*e*) (Optically active form) T. Sato, Y. Gotoh, M. Watanabe and T. Fujisawa, *Chem. Lett.*, 1983, 1533.
6 (*a*) M. Kato, V. P. Kamat, Y. Tooyama and A. Yoshikoshi, *J. Org. Chem.*, 1989, **54**, 1536; (*b*) M. Kato, M. Watanabe, B. Vogler, B. Z. Awen, Y. Masuda, Y. Tooyama and A. Yoshikoshi, *J. Org. Chem.*, 1991, **56**, 7071; (*c*) M. Kato, M. Watanabe, Y. Tooyama, B. Vogler and A. Yoshikoshi, *Synthesis*, 1992, 1055.
7 M. Watanabe, B. Z. Awen and M. Kato, *J. Org. Chem.*, 1993, **58**, 3923.
8 G. Delgado, S. Guzman and A. Romo de Vivar, *Phytochemistry*, 1987, **26**, 755.
9 G. Delgado, H. Hernandez and A. Romo de Viar, *J. Org. Chem.*, 1984, **49**, 2994.
10 (Preliminary communication, in part): M. Kato, F. Kido, Y. Masuda and M. Watanabe, *J. Chem. Soc., Chem. Commun.*, 1992, 697.
11 R. J. Crawford, W. F. Erman and C. D. Broaddus, *J. Am. Chem. Soc.*, 1972, **94**, 4298.
12 G. Ohloff and W. Giersh, *Helv. Chim. Acta*, 1977, **60**, 1496; M. Kato, M. Watanabe and B. Z. Awen, *J. Org. Chem.*, 1993, **58**, 5145.
13 D. A. Evans and G. L. Andrews, *Acc. Chem. Res.*, 1974, **7**, 147; F. Kido, Y. Noda and A. Yoshikoshi, *J. Am. Chem. Soc.*, 1982, **104**, 5509.
14 F. Bohlmann, J. Jakupovic, A. Schuster, R. M. King and H. Robinson, *Planta Med.*, 1984, **50**, 202; J. Jakupovic, R. X. Tan, F. Bohlmann, P. E. Bolt and Z. J. Jia, *Phytochemistry*, 1991, **30**, 1573.
15 B. M. Trost and G. S. Massiot, *J. Am. Chem. Soc.*, 1977, **99**, 4405.
16 C. Zdero and F. Bohlmann, *Phytochemistry*, 1990, **29**, 183.
17 A. Ortega, A. Romo de Vivar, R. A. Toscano and E. Maldonado, *Chem. Lett.*, 1983, 1607; A. Ortega and E. Maldonado, *Phytochemistry*, 1985, **24**, 2635.

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