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TOTAL SYNTHESIS OF (±)-PHASEIC ACID

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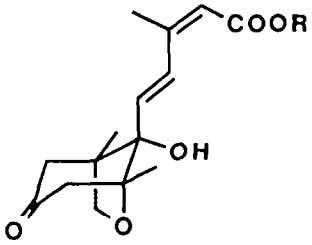
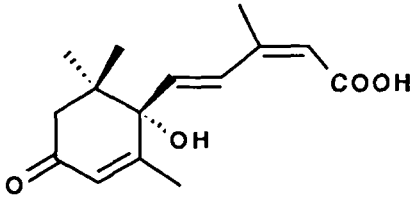
Abstract: A highly stereoselective synthesis of (±)-phaseic acid is described. Photochemical reaction of the nitrite derived from trans-4-hydroxy-2,2,6-trimethylcyclohexanone functionalizes the methyl group of the geminal pair cis to the hydroxyl group of the starting alcohol. The oxime formed is converted in four steps to a conjugated 6-oxabicyclo[3.2.1]octenone, to which the side chain synthon is added as an alkynyl lithium to give a single adduct in high yield. Further transformation yields (±)-phaseic acid free of its unwanted epimer.

(-)-Phaseic acid (**1a**)[1-3] is an important early metabolite along a major pathway by which the plant hormone abscisic acid (**2**) is metabolized by plants.[4] Evidence that phaseic acid has significant phytobiological activity[5] has provoked widespread interest in the rôle this metabolite may play in the complex processes that regulate plant growth, development, and response to environmental stress. We required a ready supply of the metabolite, and wished to secure intermediates suitable for the synthesis of modified derivatives of phaseic acid for our continuing study of the biological activity of substances related to abscisic acid in plants. This paper describes a highly stereoselective synthesis of (±)-phaseic acid that is proving capable of providing quantities sufficient for biological evaluation.



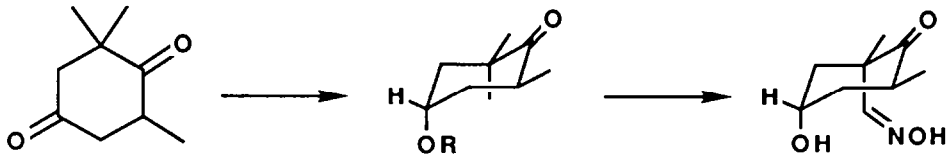
1 **a** **R = H**
b **R = Me**



2

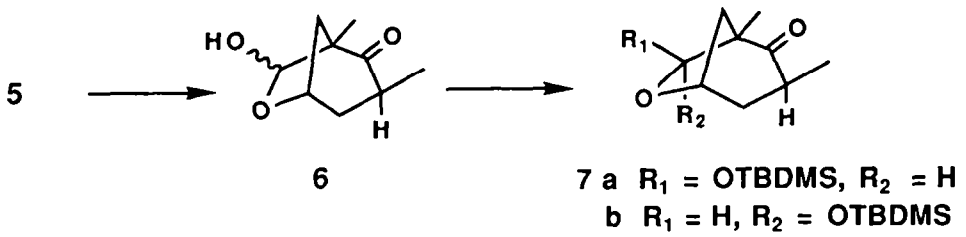
A synthesis of (±)-methyl phaseate (**1b**) had appeared[6] prior to the commencement of our work, and during the course of the investigation a short communication[7] was published outlining a chiral synthesis from (-)-β-pinene of (+)-methyl phaseate, the ester of the "unnatural" antipode of the metabolite. Neither of the synthetic routes enabled control of the stereochemistry at the point of attachment of the 3-methylpentadienoate side chain to the bicyclic ring system, and in both instances the unwanted epimer was generated preferentially. While the present manuscript was in preparation, a paper by Kitahara *et al* appeared[8] describing a stereocontrolled synthesis of both enantiomers of phaseic acid and their respective methyl esters.

The starting material for our synthesis is the trimethylcyclohexanedione **3**, readily obtained[9] by zinc - acetic acid reduction of commercially available oxoisophorone, which contains the network of carbons incorporated in the bicyclic ring system of phaseic acid.

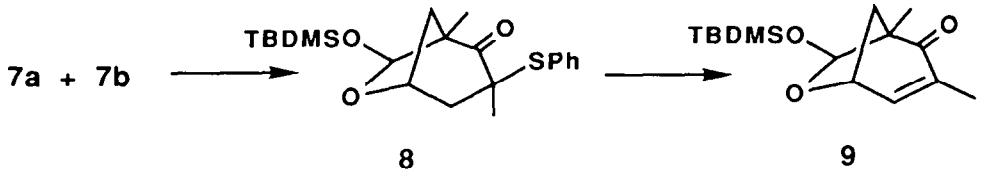


3 **4 a R = H** **b R = NO** **5**

Stereoselective reduction of **3** under appropriate conditions produces the known trans alcohol **4a**.[10,11] In a key step of our approach the hydroxyl group of **4a** is utilized in a Barton photochemical reaction[12] to functionalize the proximal but unactivated methyl group of the geminal pair on the six membered ring. Thus the crude nitrite **4b**, simply obtained by the exchange reaction[13] of alcohol **4a** with *tert*-butyl nitrite in chloroform, was irradiated in benzene through Pyrex with a high pressure mercury lamp. The nitroso dimer that precipitated was collected and heated at reflux with 2-propanol to afford the crystalline oxime **5** in 29% overall yield from **4a**.

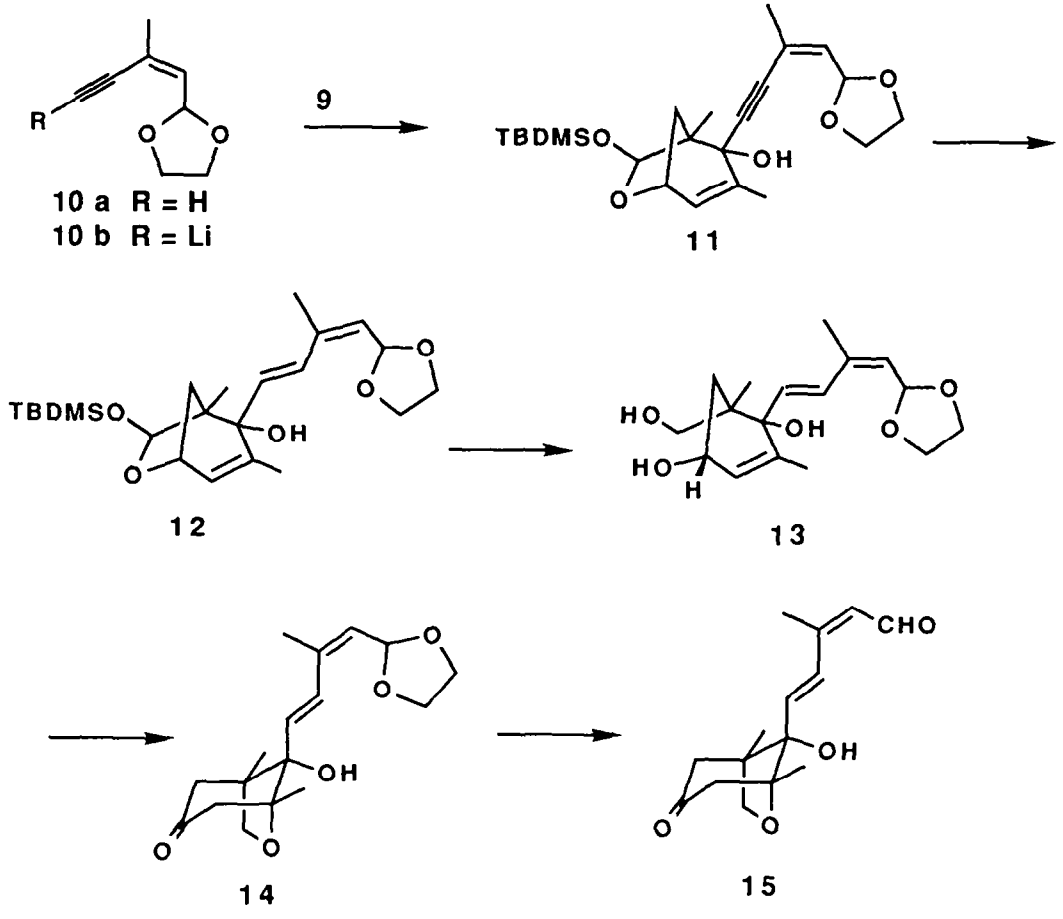


Acid - catalyzed hydrolysis of the oxime gave the lactols **6** in 95% yield. The crystalline solid had mp 101-103 °C; the proton nmr spectrum of **6** showed the two stereoisomers to be in the ratio 2:1 in deuterochloroform solution. A singlet at δ 9.49 ppm, integrating for 0.06 proton, was attributed to the presence of a few percent of the corresponding monocyclic aldehyde in the mixture. Treatment of **6** at 35°C in dimethylformamide with *tert*-butyldimethylsilyl chloride and imidazole gave, in 89% yield, the bicyclic silyl acetals **7a** and **7b** as a 5:1 mixture of isomers. The major isomer is assigned the structure **7a**, in which the bulky *tert*-butyyldimethylsilyloxy group is *exo* and thus does not interact sterically with the three-carbon bridge of the bicyclic ring system.



A single phenyl thioether, assigned structure **8**, was isolated in 78% yield after exposure of the mixture of **7a** and **7b** to lithium diisopropylamide followed by diphenyl disulfide. The electrophilic disulfide would reasonably be expected to attack the enolate anions derived from either **7a** or **7b** at the side of the bicyclic

system that is unencumbered by the two-atom bridge and its appended silyl ether protecting group. As the attack proceeds the developing sp^3 character of the C-3 carbon will force the methyl group at C-3 into increasing steric interaction with the nearer of the substituents at C-7. This compression will severely retard the rate of reaction of the anion of **7b**, and as a consequence **8** is formed preferentially. Treatment of thioether **8** with *m*-chloroperoxybenzoic acid, followed by heating of the crude oxidation product at 60 °C for one hour, effected smooth elimination of the elements of thiophenol and provided the key bicyclic intermediate **9** in 96% yield.



10 a R = H
10 b R = Li

11

12

13

14

15

The side chain synthon **10a**, prepared simply in 57% yield by acid - catalyzed ketalization of (Z)-3-methylpent-2-en-4-ynal[14] with ethylene glycol, was converted in tetrahydrofuran solution to the lithio derivative **10b** by the action of *n*-butyllithium. Reaction of **10b** with the bicyclic ketone **9** at -78 to -50 °C gave, after chromatography, a single alcohol **11** in 94% yield. The relative configuration assigned to the newly created stereocentre of **11** was confirmed by the successful conversion of **11** to (±)-phaseic acid as described below. The excellent stereoselectivity achieved in the attachment of the side chains in the recently disclosed syntheses of (+)- and (-)-phaseic acids by Kitahara *et al*[8] was attained by using enantiomeric conjugated 6-oxabicyclo[3.2.1]octenones similar to **9** as the electrophilic substrates for the alkylation reactions.

Reduction of the triple bond to the required E olefinic linkage with sodium *bis*(2-methoxyethoxy)aluminum hydride afforded triene **12** in 61% yield. Removal of the *tert*-butyldimethylsilyl protecting group of **12** by means of tetrabutylammonium fluoride in tetrahydrofuran[15] gave, in 90% yield, an equilibrium mixture of hemiacetals and the corresponding dihydroxy aldehyde. The triol **13** was produced in 49% yield by reduction of the mixture with methanolic sodium borohydride. Oxidation of the triol with activated manganese dioxide in dichloromethane resulted in concomitant intramolecular cyclization under the reaction conditions, and the masked aldehyde **14**, having the desired ring system of phaseic acid, was obtained directly in 64% yield. The aldehyde **15**, liberated in 91% yield by acid catalyzed hydrolysis of **14**, was oxidized and esterified in a single step[16] to methyl phaseate (**1b**) in 82% yield. Saponification of **1b** gave, in 76% yield, (±)-phaseic acid (**1a**).

Experimental

General

Melting points were determined with a microscope hot stage apparatus and are uncorrected. Gas chromatographic (GC) separations were performed with a Varian 3700 instrument equipped with a 30 m x 0.32 mm (i.d.) DB-1701 capillary column (J & W Scientific Durabond) and a flame ionization detector. Helium at a flow rate of ca. 2.5 ml min^{-1} was used as carrier gas. Silica gel for column chromatography was 70 - 230 mesh (Sigma); for medium - pressure flash chromatography 230 - 400 mesh Kieselgel 60 (EM Reagents) was employed. Infrared spectra (IR) were recorded with a Perkin-Elmer 257 Grating Infrared Spectrophotometer, and ultraviolet spectra (UV) with a Beckman DU-8 instrument. Proton nuclear magnetic resonance spectra (^{1}HNMR) were obtained at 360 MHz with a Bruker AM-360-WB spectrometer. Chemical shifts are reported in ppm downfield from tetramethylsilane, and coupling constants are given in Hz. Low resolution mass spectra were obtained with a Finnigan 4500 GC-MS instrument equipped with a 60-meter DB-5 capillary column and operated in either the electron impact (EIMS) or chemical ionization

(CIMS) mode. High resolution electron impact (HREIMS), fast ion bombardment (FIBMS), and high resolution fast ion bombardment (HRFIBMS) mass spectra were recorded with a VG 70-250SEQ double-focussing hybrid spectrometer. For the FIB experiments, a beam of 35-keV cesium atoms was focussed on the sample in a glycerol matrix.

Tetrahydrofuran was dried by distillation from sodium and benzophenone. Benzene was distilled from lithium aluminum hydride, and dimethylformamide was distilled from calcium hydride and stored over molecular sieves. Elemental analyses were performed by the Microanalytical Laboratory of the University of Alberta, Edmonton, Canada.

(4R*,6R*)-2,2,6-Trimethyl-4-hydroxycyclohexan-1-one (4a)

To a stirred solution of 2,2,6-trimethylcyclohexane-1,4-dione[9] (**3**) (16.2 g, 0.105 mol) in dry toluene (634 mL) under nitrogen at -65°C was added 147 mL of triisobutylaluminum (1.0 M in toluene; 1.4 mol-equiv) over 10 min. The reaction mixture was stirred at -40°C for 90 min, poured into an ice - cold mixture of 10% HCl (200 mL) and CH_2Cl_2 (200 mL) and stirred well for 10 min. The phases were separated, and the aqueous layer was extracted thoroughly with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography over silica gel with 50% ether-hexanes gave 8.1 g (49%) of the trans alcohol **4a** as an oil. IR (film) 3460, 1700 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 1.01 (d, J=6.9 Hz, 3H, $CHCH_{3eq}$), 1.02 (s, 3H, $C(CH_3)_2$), 1.33 (s, 3H, $C(CH_3)_2$), 1.66 (ddd, J=13.9, 13.9, 3.4 Hz, 1H, H-5_{ax}), 1.77 (dd, J=14.5, 3.8 Hz, 1H, H-3_{ax}), 1.96 (ddd, J=14.5, 3.8, 3.2 Hz, 1H, H-3_{eq}), 2.10 (dddd, J=13.9, 5.6, 4.4, 3.2 Hz, 1H, H-5_{eq}), 3.14 (m, 1H, H-6_{ax}) and 4.2 ppm (m, 1H, H-4_{eq}); EIMS (70 eV) m/z 156 (M^+,10), 138 (M^+-18, 8), 88 (41) and 83 (89%).

(2R*,4S*,6S*)-2-Oximinomethyl-2,6-dimethyl-4-hydroxycyclohexan-1-one (5)

Alcohol **4a** (11.1 g, 71.0 mmol) and *tert*-butyl nitrite (77 ml) in $CHCl_3$ (175 mL) were stirred at room temperature for 1.75 hr. Rapid evaporation of the solvent, excess *tert*-butyl nitrite, and the byproduct *tert*-butyl alcohol under vacuum left 12.5 g of oily crude nitrite **4b** as an 84:9 mixture of **4a** and **4b** (GC analysis). IR (film) 1715, 1650 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 1.05 (d, J=6.5 Hz, 3H, $CH(CH_3)_{eq}$), 1.07 (s, 3H, $C(CH_3)_2$), 1.20 (s, 3H, $C(CH_3)_2$), 1.91(ddd, J=14.2, 14.2, 3.6 Hz, 1H, H-5_{ax}), 2.04 (dd, J=14.9, 3.6 Hz, 1H, H-3_{eq}), 2.26 (dddd, J=14.2, 5.6, 3.6, 3.6 Hz, 1H, H-5_{eq}), 2.95 (m, 1H, H-6_{ax}) and 5.76 ppm (dddd, J=3.6, 3.6, 3.6, 3.6 Hz, 1H, H-4_{eq}); CIMS (CH_4, 100 eV) m/z 184 (M^+-1, 6.9), 156 (100%).

The crude nitrite was dissolved in dry benzene (200 mL) and irradiated at 0°C through Pyrex for 4.25 hr with a 450-Watt Hanovia high - pressure mercury lamp. Constant agitation was provided by passing nitrogen through the reaction vessel. The nitroso dimer that precipitated (4.17 g) was collected by filtration, washed with benzene , and heated at reflux in 2-propanol (100 mL) for 3.5 hr. The residue remaining on evaporation of the solvent under reduced pressure was recrystallized from 1:1 hexane - acetone to give oxime **5** (3.86 g, 29% from **4a**), mp 152-154°C. IR (KBr) 3628, 1668 cm^{-1}; ^{1}HNMR (CD_3OD) δ 1.09 (d, J=7.3 Hz, 3H, $CH(CH_3)_{eq}$), 1.24 (s, 3H, $(CH_3)_{eq}$ at C-2), 1.35 (dd, J=13.2, 9.8

Hz, 1H, H-3_{ax}), 1.61 (ddd, J=13.2, 8.0, 4.7 Hz, 1H, H-5_{ax}), 1.72 (dddd, J=13.2, 6.6, 4.5, 1.7 Hz, 1H, H-5_{eq}), 1.91 (ddd, J=13.2, 4.5, 1.7 Hz, 1H, H-3_{eq}), 2.34-2.43 (m, 1H, H-6_{ax}), 3.94 (m, 1H, H-4_{eq}) and 7.25 ppm (d, J=0.5 Hz, HC:NOH); HRFIBMS m/z 186.1130 (M^++1) (calcd. for $C_9H_{16}NO_3$: 186.1131).

Anal. Calcd. for $C_9H_{15}NO_3$: C, 58.34; H, 8.17; N, 7.57%. Found: C, 58.13; H, 8.07; N, 7.41%.

(1R*,3S*,5S*,7R*)-and(1R*,3S*,5S*,7S*)-1,3-Dimethyl-7-hydroxy-6-oxabicyclo-[3.2.1]octan-2-ones (6)

Oxime **5** (1.67 g, 9.02 mmol), acetone (40 mL), water (8 mL) and conc. HCl (0.96 mL) were stirred under an atmosphere of nitrogen at room temperature overnight. The mixture was concentrated to small volume under reduced pressure, neutralized with saturated aqueous $NaHCO_3$, and extracted (4 x 50 mL) with $CHCl_3$. The combined organic extracts were washed with water, dried over Na_2SO_4, filtered, and the solvent evaporated to give 1.77 g of residue. Column chromatography over silica gel with 50% ether - hexanes afforded 1.42 g (93%) of crystalline **6**, mp 101-103°C. IR ($CHCl_3$) 3600,1715 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 1.07, 1.10 (d, J=6.6 Hz, 2/3(3H) and d, J=6.8 Hz, 1/3(3H), exo $CHCH_3$), 1.14 (s, 3H, bridgehead methyl), 1.32 (m, 1H, H-4_{exo}), 1.69, 1.79 (d, J=11.7 Hz, 2/3(H) and d, J=12.3 Hz, 1/3(H), H-8_{syn}), 2.24-2.51 (m, 3H, H-3_{endo}, H-4_{endo} and H-8_{anti}), 4.45, 4.64 (t, J=4.5 Hz, 1/3(H) and t, J=5.0 Hz, 2/3(H), bridgehead H) and 5.15, 5.34 ppm (br s, 2/3(H) and br s, 1/3(H), H-7); EIMS (70 eV) m/z 170 (M^+, 0.8), 142 (M^+-28, 3.6) 124 (M^+-46, 53) and 82 (100%).

Anal. Calcd. for $C_9H_{14}O_3$: C, 63.49; H, 8.29%. Found: C, 63.54; H, 8.44%.

(1R*,3S*,5S*,7S*)-and(1R*,3S*,5S*,7R*)-1,3-Dimethyl-7-(*tert*-butyldimethyl-siloxy)-6-oxabicyclo[3.2.1]octan-2-ones (7a and 7b)

To a solution of the hemiacetals **6** (1.42 g, 8.34 mmol) in dimethylformamide (6 mL) was added *tert*-butyldimethylsilyl chloride (1.51 g, 10 mmol) and imidazole (1.42 g, 20 mmol). The mixture was stirred at 35°C for 2.5 hr, then diluted with 50 mL of water and extracted (4 x 50 mL) with hexanes. The combined organic extracts were washed with water, dried over Na_2SO_4, and filtered. Concentration of the filtrate under reduced pressure left 2.37 g of crude product from which was obtained 2.13 g (90%) of a 5:1 mixture of silyl acetals **7a** and **7b** as an oil after column chromatography over silica gel using 20% ether - hexane as eluent. IR (film) 1715 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 0.05, 0.06 (s, 1/6(3H), CH_3Si and s, 1/6(3H), CH_3Si), 0.07, 0.10 (s, 5/6(3H), CH_3Si and s, 5/6(3H), CH_3Si), 0.86, 0.87 (s, 1/6(9H), $(CH_3)_3CSi$ and s, 5/6(9H), $(CH_3)_3CSi$), 1.05 (d, J= 6.6 Hz, 3H, exo $CHCH_3$), 1.09, 1.12 (s, 5/6(3H), bridgehead methyl and s, 1/6(3H), bridgehead methyl), 1.26 (dd, J=12.9, 11.5 Hz, 1H, H-4), 1.61 (d, J=11.4 Hz, 1H, H-8), 2.25-2.47 (m, 3H, H-3, H-4, H-8), 4.50 (t, J=5.0 Hz, 1/6H, H-5), 4.55 (t, J-5.0 Hz, 5/6H, H-5), 4.79 (s, 1/6H, H-7) and 5.08 ppm (s, 1/6H, H-7); EIMS (70 eV) m/z 284 (M^+, 0.5), 269 (M^+-15, 2.1), 227 (80), 171 (55) and 75 (100%).

Anal. Calcd. for $C_{15}H_{28}SiO_3$: C, 63.34; H, 9.93. Found: C, 63.03; H,10.09%.

(1R*,3S*,5R*,7S*)-1,3-Dimethyl-3-phenylthio-7-(*tert*-butyldimethylsiloxy)-6-oxabicyclo[3.2.1]octan-2-one (8)

Lithium diisopropylamide was prepared at -78°C under an atmosphere of argon by adding 9.36 mL (15 mmol) of *n*-butyllithium (1.6 M in hexanes) to a solution of diisopropylamine (1.52 g, 15.0 mmol) in dry tetrahydrofuran (20 ml), and stirring for 15 min. Silyl acetals **7a** and **7b** (5:1 mixture; 2.13 g, 7.49 mmol) in tetrahydrofuran (15 ml) were added dropwise to the cold amide solution, the mixture was warmed to 0°C, and diphenyldisulfide (1.96 g, 8.98 mmol) in tetrahydrofuran (10 ml) was added. The reaction mixture was allowed to warm to room temperature, stirred for 2 hr, and poured into an ice-cold mixture of diethyl ether (100 mL) and 10% aqueous HCl (100 mL). The phases were separated, and the ether solution was washed with a second portion of 10% HCl, saturated aqueous $NaHCO_3$, and water. The residue remaining

after drying (Na_2SO_4), filtration, and concentration of the ether solution was chromatographed on a column of silica gel using 10% ether - hexane to afford 2.3 g (78%) of **8**, mp 62-64°C. IR ($CHCl_3$) 1695 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 0.05 (s, 3H, CH_3Si) 0.06 (s, 3H, CH_3Si), 0.87 (s, 9H, $(CH_3)_3CSi$), 1.24 (s, 3H, endo CH_3), 1.30 (s, 3H, bridgehead CH_3), 2.12 (br d, J=2.4 Hz, 2H, H-4_{endo} and H-4_{exo}), 2.25 (dd, J=11.9, 6.5 Hz, 1H, H-8_{anti}), 2.54 (d, J=11.8 Hz, 1H, H-8_{syn}), 4.49 (dt, J=6.5, 2.6 Hz, 1H, bridgehead H), 4.76 (s, 1H, H-7) and 7.29-7.41 ppm (m, 5H, Ar-H); EIMS (70 eV) m/z 377 (M^+-15, 0.9), 335 (M^+-57, 10), 307 (11) and 157 (100%).

Anal. Calcd. for $C_{21}H_{32}SSiO_3$: C, 64.25; H,8.22%. Found: C, 64.18; H, 8.23%.

(1R*,5R*,7S*)-1,3-Dimethyl-7-(*tert*-butyldimethylsiloxy)-6-oxabicyclo [3.2.1]oct-3-en-2-one (9)

To an ice-cold solution of the phenylthioether **8** (0.80 g, 2.0 mmol) in CH_2Cl_2 (10 mL) was added a solution of 3-chloroperoxybenzoic acid (0.62 g of tech. peracid, ca. 3.0 mmol) in CH_2Cl_2 (10 mL) that had been chilled to -78°C. The solution was stirred at 0°C under a nitrogen atmosphere for 30 min, then poured into a separatory funnel containing Et_2O (100 mL) and 10% aqueous Na_2SO_3 (100 mL) and shaken. The phases were separated, the aqueous layer was washed with Et_2O (100 mL), and the combined organic layers were washed twice with saturated aqueous $NaHCO_3$, once with water, and dried over Na_2SO_4. The yellow-white residue (0.78 g) that remained after filtration and removal of the solvent under reduced pressure was dissolved in CCl_4 (10 mL) and heated at 60°C for 1 hr. Flash column chromatography over silica (40% ether - hexanes) of the crude product obtained on evaporation of the CCl_4 afforded 0.54 g (94%) of **9** as an oil. IR (film) 1680 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 0.06 (s, 3H, CH_3Si), 0.07 (s, 3H, CH_3Si), 0.86 (s, 9H, $(CH_3)_3CSi$), 1.20 (s, 3H, bridgehead CH_3), 1.70 (d, J=1.4 Hz, 3H, vinyl CH_3), 2.04 (d, J=10.9 Hz, 1H, H-8_{syn}), 2.24 (ddd, J=10.9, 5.5, 1 Hz, H-8_{anti}), 4.64 (t, J=5.5 Hz, 1H, bridgehead H), 4.89 (s, 1H, H-7) and 7.09 ppm (ddq, J=5.5, 1.4, 1.0 Hz, vinyl H); EIMS (70 eV) m/z 267 (M^+-15, 0.23), 225 (41), 207 (7), 197 (8) and 122 (25%).

Anal. Calcd. for $C_{15}H_{26}SiO_3$: C, 63.79; H, 9.29%. Found: C, 63.41; H, 9.03%.

2-[(Z)-2-Methylbut-1-en-3-yn-1-yl]-1,3-dioxolane (10a)

(Z)- 3-Methyl-2-penten-4-ynal[14] (3.2 g, 34 mmol), ethylene glycol (2.5 mL, 1.3 mol-equiv), pyridinium p-toluenesulphonate (0.85 g, 0.11 mol-equiv) and benzene (100 mL) were stirred and heated at reflux with provision for azeotropic removal of water for 1.25 hr. Saturated aqueous NaCl was added, the phases were separated, and the aqueous layer was extracted twice with ether. The combined organic solutions were washed once with saturated NaCl solution and dried over Na_2SO_4. Filtration and concentration of the filtrate under reduced pressure left 3.6 g of amber liquid, from which was obtained 2.7 g (57%) of liquid ketal **10a** by bulb-to-bulb distillation at 110-117°C (13 Torr). IR (film) 3290, 2890, 2090 (w), 1642, 1145, 1060 and 950 cm^{-1}; UV (hexane) 239 nm (ε 640); ^{1}HNMR ($CDCl_3$) δ 1.91 (d, J=1.4 Hz, 3H, CH_3), 3.16 (d, J=0.5 Hz, 1H, alkynyl H), 3.84-4.02 (m, 4H, -CH_2CH_2-), 5.67 (d, J=7.7 Hz, 1H, -OCHO-) and 5.69-5.73 ppm (m, 1H, vinyl H); HREIMS (70 eV) m/z 138.0678 (M^+). Calcd. for $C_8H_{10}O_2$: m/z 138.0681.

(1R*,2R*,5S*,7R*)-1,3-Dimethyl-2-[(Z)-3-methyl-5,5-ethylenedioxypent-3-en-1-yn-1-yl]-2-hydroxy-7-(*tert*-butyldimethylsiloxy)-6-oxabicyclo[3.2.1]oct-3-ene (11)

To a stirred solution of ketal **10a** (190 mg, 1.38 mmol) in dry tetrahydrofuran (5 mL) at -78°C under an atmosphere of argon was added 1.4 mmol of *n*-butyllithium (1.6 M in hexanes). Stirring was continued at -78°C for 15 min, then a solution of ketone **9** (301 mg, 1.07 mmol) in tetrahydrofuran (5 ml) was added over two min, and the stirred solution was allowed to warm to -50°C over 45 min. The reaction was quenched by adding saturated aqueous NH_4Cl and stirring at room temp for 5 min. The phases

were separated, the aqueous layer was extracted (4 x 20 mL) with CH_2Cl_2, and the combined CH_2Cl_2 phases were washed with water followed by saturated aqueous NaCl. The tetrahydrofuran and washed CH_2Cl_2 solutions were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography over silica with 7:1 ether - hexane gave 426 mg (95%) of **11** as an oil. IR (film) 3460 and 1640 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 0.09 (s, 6H, CH_3Si), 0.88 (s, 9H, $(CH_3)_3CSi$), 1.30 (s, 3H, bridgehead CH_3), 1.79 (d, J=1.4 Hz, 3H, ring vinyl CH_3), 1.84 (dd, J=11.4, 5.3 Hz, 1H, H-8_{anti}), 1.90 (d, J=1.4 Hz, 3H, sidechain vinyl CH_3), 1.98 (d, J=11.4 Hz, 1H, H-8_{syn}), 3.85-4.00 (m, 4H, -OCH_2CH_2O-), 4.27 (dd, J=5.3, 5.3 Hz, 1H, bridgehead H), 5.38 (s, 1H, H-7), 5.58 (d, J=7.5 Hz, 1H, sidechain -OCHO-), 5.67, (dd, J=7.5, 1.4 Hz, 1H, sidechain vinyl H) and 5.81 ppm (br d, J=5.3 Hz, 1H, ring vinyl H); CIMS (isobutane, 100 eV) m/z 421 (M^++1).

Anal. Calcd. for $C_{23}H_{36}SiO_5$: C, 65.68; H, 8.63%. Found: C, 65.97; H, 8.57%.

(1R*,2S*,5S*,7R*)-1,3-Dimethyl-2-[(1E,3Z)-3-methyl-5,5-ethylenedioxypenta-1,3-dien-1-yl]-2-hydroxy-7-(*tert*-butyldimethylsiloxy)-6-oxabicyclo[3.2.1]oct-3-ene (12)

To a stirred solution prepared from 0.52 mL (1.8 mmol) of sodium *bis*(2-methoxyethoxy)aluminum hydride (3.4 M in toluene) and tetrahydrofuran (5 mL), cooled to an internal temperature of -10°C and under an atmosphere of nitrogen, was added dropwise a solution of the dienyne **11** (190 mg, 0.452 mmol) in tetrahydrofuran (5 mL) while maintaining the temperature at -5°C or lower. After 90 min the mixture was warmed to 0°C and treated with water (5 mL). The resulting mixture was extracted with ether (2 x 50 mL) followed by $CHCl_3$ (2 x 50 mL). The combined organic extracts were washed twice with water and once with saturated NaCl, dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by column chromatography over silica gel using 1:1 ether - hexane gave 116 mg (61%) of liquid triene **12**. IR ($CHCl_3$) 3440, 1650 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 0.09 (s, 6H, $(CH_3)_2Si$), 0.88 (s, 9H, $(CH_3)_3CSi$), 1.00 (s, 3H, bridgehead CH_3), 1.54 (d, J=1.4 Hz, 3H, ring vinyl CH_3), 1.77 (dd, J=11.0, 5.3 Hz, 1H, H-8_{anti}), 1.87 (d, J=11.0 Hz, 1H, H-8_{syn}), 1.89 (d, J=1.2 Hz, 3H, sidechain vinyl CH_3), 3.87-4.03 (m, 4H, -OCH_2CH_2O-), 4.29 (dd, J=5.3, 5.3 Hz, 1H, bridgehead H), 5.39 (d, J=6.9 Hz, 1H, sidechain -OCHO), 5.46 (s, 1H, H-7), 5.68 (br d, J=6.9 Hz, 1H, sidechain H-4), 5.84 (d, J=15.8 Hz, 1H, sidechain H-1), 5.89 (d, J=5.3 Hz, 1H, ring vinyl H) and 6.65 ppm (d, J=15.8 Hz, 1H, sidechain H-2); CIMS (isobutane, 100 eV) m/z 423 (M^++1).

Anal. Calcd. for $C_{23}H_{38}Si\,O_5$: C, 65.38; H, 9.07%. Found: C, 65.34; H, 9.03%.

(1R*,4R*,6R*)-1-[(1E,3Z)-3-Methyl-5,5-ethylenedioxypenta-1,3-dien-1-yl]-2,6-dimethyl-6-hydroxymethylcyclohex-2-en-1,4-diol (13)

To a stirred solution of the silylated lactol **12** (380 mg, 0.899 mmol) in tetrahydrofuran (5 mL) at 0°C was added dropwise 1.78 mL (1.8 mmol) of a 1.0 M solution of tetrabutylammonium fluoride in tetrahydrofuran. Stirring was continued at 0°C for 5 min, then at room temperature for 1 h. Water was added, and the resulting mixture was extracted thoroughly with $CHCl_3$. The combined organic extracts were washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by flash chromatography over silica using 9:1 ether - hexane afforded 250 mg (90%) of a 1:1.6 liquid mixture of hemiacetals with the corresponding open form. IR ($CHCl_3$) 3610, 1710 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 9.60 (s, 1H, -CHO of open form), 6.66 (d, J=15.6 Hz, 0.6 H, sidechain H-2 of hemiacetals) and 6.67 ppm (d, J=15.7 Hz, 1 H, sidechain H-2 of open form); CIMS (NH_3, 100 eV) m/z 309 (M^++1).

The hemiacetal - hydroxyaldehyde mixture (250 mg, 0.811 mmol) in methanol (5 mL) at 0°C was stirred with sodium borohydride (36.9 mg, 0.975 mmol) for 10 min, saturated aqueous NH_4Cl (5 mL) was added, and stirring was continued for a further 5 min. The resulting mixture was extracted with $CHCl_3$ (4 x 20 mL). The combined organic extracts were washed with saturated aqueous NaCl, dried over Na_2SO_4, and filtered. Evaporation of the solvent left a residue which yielded 123 mg (49%) of triol **13** as a viscous

syrup after column chromatography over silica using 2% MeOH in CH_2Cl_2 as eluent. IR ($CHCl_3$) 3630, 3540 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 0.79 (s, 3H, CH_3 at C-6 of ring), 1.65 (d, J=1.3 Hz, 3H, ring vinyl CH_3), 1.83 (d, J=4.8 Hz, 2H, cyclohexene ring -CH_2-), 1.86 (d, J=1.2 Hz, 3H, sidechain CH_3), 3.46 (d, J=11.7 Hz, 1H, -CH_AH_BOH), 3.75 (d, J=11.7 Hz, 1H, -CH_AH_BOH), 3.87-4.02 (m, 4H, -OCH_2CH_2O-), 4.23 (m, 1H, H-4), 5.37 (d, J=7.2 Hz, 1H, -OCHO-), 5.62-5.70 (m, 3H, H-3, and sidechain H-1 and H-4) and 6.70 ppm (d, J=15.6 Hz, 1H, sidechain H-2); FIBMS m/z 311 (M^++1). HREIMS (70 eV) m/z 310.1798. Calcd. for $C_{17}H_{26}O_5$: m/z 310.1780.

(1R*,5R*,8S*)-1,5-Dimethyl-8-hydroxy-8-[(1E,3Z)-3-methyl-5,5-ethylenedioxy penta-1,3-dien-1-yl]-6-oxabicyclo[3.2.1]octan-3-one (14)

A mixture of triol **13** (92 mg, 0.30 mmol), activated manganese dioxide (99.7 mg, 1.2 mmol) and dry CH_2Cl_2 (15 mL) was stirred at room temperature for 4 hr, then filtered through a short column of celite. The column was washed with 10% MeOH - CH_2Cl_2, and the combined filtrate and washings evaporated to dryness. Column chromatography over silica gel with 5% MeOH - CH_2Cl_2 as eluent afforded 57 mg (60%) of the masked aldehyde **14** as an oil. IR ($CHCl_3$) 3610, 1725 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 0.98 (s, 3H, CH_3 at C-1), 1.19 (s, 3H, CH_3 at C-5), 1.89 (d, J=1.2 Hz, 3H, vinyl CH_3), 2.43 (d, J=18.5 Hz, 1H, H-2_{endo}), 2.54 (dd, J=18.5, 2.6 Hz, 1H, H-2_{exo}), 2.60 (s, 2H, H-4_{endo} and H-4_{exo}), 3.76 (d, J=8.2 Hz, 1H, H-7_{endo}), 3.88-4.04 (m, 5H, -OCH_2CH_2O- and H-7_{exo}), 5.47 (br d, J=6.9 Hz, 1H, -OCHO-), 5.71 (d, J=6.9 Hz, 1H, sidechain H-4), 5.92 (d, J=15.4 Hz, 1H, sidechain H-1) and 7.08 ppm (d, J=15.4 Hz, 1H, sidechain H-2); FIBMS m/z 309 (M^++1).

Anal. Calcd. for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85%. Found: C, 65.97; H, 7.51%.

(1R*,5R*,8S*)-1,5-Dimethyl-8-hydroxy-8-[(1E,3Z)-3-methyl-5-oxopenta-1,3-dien-1-yl]-6-oxabicyclo[3.2.1]octan-3-one [(±)-Phaseyl aldehyde] (15)

To a stirred solution of the acetal **14** (42 mg, 0.14 mmol) in acetone (2 mL) at room temperature was added p-toluenesulfonic acid monohydrate (2.6 mg, 0.014 mmol) and a drop of water. Stirring was continued for 5 min, then the reaction was stopped by adding ice - cold saturated aqueous $NaHCO_3$. The resulting mixture was extracted with $CHCl_3$ (4 x 10 mL). The combined organic layers were washed with water and saturated aqueous NaCl, dried over Na_2SO_4, filtered, and evaporated to dryness. Column chromatography of the residue over silica gel with 2% MeOH - CH_2Cl_2 as eluent gave 32 mg (86%) of liquid aldehyde **15**. IR ($CHCl_3$) 3600, 1725, 1670 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 1.02 (s, 3H, CH_3 at C-1), 1.21 (s, 3H, CH_3 at C-5), 2.07 (d, J=1.2 Hz, 3H, vinyl CH_3), 2.48 (dd, J=18.4, 1.8 Hz, 1H, H-2_{endo}), 2.55 (dd, J=18.4, 2.3 Hz, 1H, H-2_{exo}), 2.60 (d, J=18.5 Hz, 1H, H-4_{exo}), 2.68 (dd, J=18.5, 1.8 Hz, 1H, H-4_{endo}), 3.81 (d, J=8.5 Hz, 1H, H-7_{endo}), 3.92 (dd, J=8.5, 2.3 Hz, 1H, H-7_{exo}), 5.95 (d, J=7.8 Hz, 1H, sidechain H-4), 6.22 (d, J=15.3 Hz, 1H, sidechain H-1), 7.73 (d, J=15.3 Hz, 1H, sidechain H-2) and 10.25 ppm (d, J=7.8 Hz, 1H, -CHO); CIMS (isobutane, 100 eV) m/z 265 (M^++1). HREIMS (70 eV) m/z 264.1343. Calcd. for $C_{15}H_{20}O_4$: m/z 264.1362.

(±)-Methyl phaseate (1b)

To a stirred solution of 28.5 mg of aldehyde **15** (0.108 mmol) in methanol (2 mL) was added sequentially activated manganese dioxide (131 mg, 1.51 mmol), sodium cyanide (10.3 mg, 0.210 mmol) and acetic acid (11.4 mg, 0.190 mmol). Stirring was continued for 1 hr, then the mixture was filtered through a short column of celite using 1:25:25 MeOH - EtOAc - $CHCl_3$ as washing solvent. The residue remaining after evaporation of the combined filtrate and washings was purified by column chromatography over silica gel using 2% MeOH in CH_2Cl_2 as eluent to give 26.2 mg (82%) of (±)-methyl phaseate, mp 154-155.5°C (lit.[6] 153.5-155°) after recrystallization from ether - hexanes. IR ($CHCl_3$) 3450, 1710, 1700 cm^{-1}; UV (MeOH) 263 nm (ε 17000); ^{1}HNMR ($CDCl_3$) δ 1.02 (s, 3H, CH_3 at C-1), 1.27 (s, 3H, CH_3 at C-5), 1.99 (d, J=1.2 Hz, 3H, vinyl CH_3), 2.45 (dd, J=18.4, 1.7 Hz, 1H, H-2_{endo}), 2.54 (dd,

J=18.4, 2.6 Hz, 1H, H-2_{exo}), 2.57 (d, J=18.3 Hz, 1H, H-4_{exo}), 2.65 (dd, J=18.3, 1.7 Hz, 1H, H-4_{endo}), 3.71 (s, 3H, -$COOCH_3$), 3.75 (d, J=8.1 Hz, 1H, H-7_{endo}), 3.96 (dd, J=8.1, 2.6 Hz, 1H, H-7_{exo}), 5.78 (s, 1H, sidechain H-4), 6.21 (d, J=15.8 Hz, 1H, sidechain H-1) and 8.14 ppm (d, J=15.8 Hz, 1H, sidechain H-2); EIMS (70 eV) m/z 294 (M^+, 27), 276 (26), 233 (23), 207 (23), 125 (80) and 83 (100%). HREIMS (70 eV) m/z 294.1474 (M^+). Calcd. for $C_{16}H_{22}O_5$: m/z 294.1467.

(±)-Phaseic acid (1a)

Ester **1b** (25.2 mg, 0.0856 mmol), methanol (2 mL), and 5% aq potassium hydroxide (1.2 mL) were stirred together at room temperature under an atmosphere of nitrogen for 3.5 h. The methanol was removed on the rotary evaporator, and the remaining mixture was diluted with water and washed with ether (2 x 10 mL). The aqueous layer was acidified with ice - cold aq HCl and extracted with ether (4 x 10 mL). The combined organic extracts were washed with water, dried over Na_2SO_4, filtered, and evaporated to leave a residue which was purified by preparative thin layer chromatography on a Merck 20 cm x 20 cm x 1 mm silica GF_{254} plate developed with 50:30:4 toluene - EtOAc - HOAc. The major band visible under short wavelength uv light was scraped from the plate and extracted with 25:25:2 EtOAc - $CHCl_3$ - MeOH to afford 18.3 mg (76%) of (±)-phaseic acid (**1a**), mp 192-195°C. Attempted recrystallization from Et_2O raised the mp to 206-208°C, but the solid was possibly amorphous. IR ($CHCl_3$) 3550-2500, 1720, 1625 cm^{-1}; UV (MeOH) 257 nm (ε 15600); ^{1}HNMR (CD_3OD) δ 1.00 (s, 3H, CH_3 at C-1), 1.21 (s, 3H, CH_3 at C-5), 2.05 (d, J=1.1 Hz, 3H, vinyl CH_3), 2.37 (dd, J=18.0, 2.5 Hz, 1H, H-2_{endo}), 2.46 (dd, J=17.8, 2.5 Hz, 1H, H-4_{endo}), 2.70 (dd, J=18.0, 2.9 Hz, 1H, H-2_{exo}), 2.80 (d, J=17.8 Hz, 1H, H-4_{exo}), 3.66 (d, J=7.6 Hz, 1H, H-7_{endo}), 3.94 (dd, J=7.6, 2.9 Hz, 1H, H-7_{exo}), 5.78 (br s, 1H, sidechain H-4), 6.44 (d, J=15.9 Hz, 1H, sidechain H-1) and 8.09 ppm (d, J=15.9 Hz, 1H, sidechain H-2); CIMS (isobutane, 100 eV) m/z 281 (M^++1). HREIMS (70 eV) m/z 280.1321. Calcd. for $C_{15}H_{20}O_5$: m/z 280.1311.

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Footnotes and References

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11. The stereoselective reduction of the R enantiomer of **3** in good yield to the corresponding enantiomer of **4a** with triisobutylaluminum in toluene has been reported.[10] In our hands, reduction of racemic **3** by this method gave only a moderate yield (49%) of **4a**; careful quenching and workup of the reaction mixture was required to prevent the formation of mixtures from which it was difficult to isolate the trans alcohol efficiently. Use of the readily available[10] R enantiomer of **3** as the starting material for our synthesis would result in the production of the "unnatural" (+)-phaseic acid.

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