

Enantiospecific formal total synthesis of homogynolide-A

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Dedicated to Professor T. R. Govindachari

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Abstract

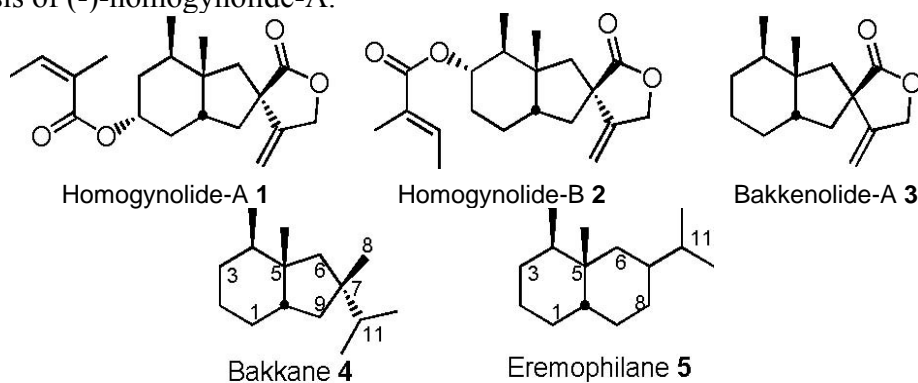
Formal total synthesis of both enantiomers of homogynolide-A, a sesquiterpene containing an α -spiro- β -methylene- γ -butyrolactone moiety fused to a bicyclo[4.3.0]nonane framework, is described. Thus, (*R*)-carvone was converted into both enantiomers of 3-methylcarvone **14**. A reductive allylation, Wacker oxidation and intramolecular aldol condensation sequence transformed 3-methylcarvone into the hydrindanone **18**. Regiospecific reduction of the enone followed by a three step degradation of the isopropenyl group converted the hydrindanone **18** into the dione **21**, which on regioselective ketalisation furnished the key intermediate ketoketal **13**. Methoxymethylene Wittig reaction followed by bromoacetalisation reaction transformed the ketoketal **13** into the bromoacetal **23**. The 5-*exo*-dig radical cyclisation of the bromoacetal **23** followed by the hydrolysis and oxidation of the resultant spiroacetal **24** furnished a 1:4 mixture of the Greene's precursor ketospirolactone **12** and its spiroepimer **26**.

Keywords: Homogynolide-A, reductive allylation, Wacker oxidation, intramolecular aldol condensation, Wittig reaction

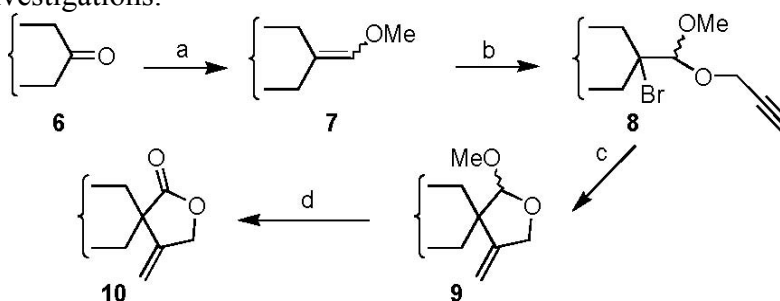
Introduction

The creativity of Nature in devising varied molecular architecture is revealed through the isolation of a wide range of natural products with remarkable skeletal build-up and multifarious functionalities. Sesquiterpenes, biogenetically derived from farnesyl pyrophosphate, are assembled in acyclic, monocyclic, bicyclic, tricyclic and even tetracyclic structures containing small, medium and large rings with a wide range of functionalities.¹ The great diversity in their molecular architecture has made synthesis of sesquiterpenoids a challenging and exciting area of research.² In 1976, Sorm and co-workers³ reported isolation of homogynolides-A **1** and B **2** along with bakkenolide-A **3** from *Homogyne alpina*. (L.) CASS. Homogynolides, belong to a small group of sesquiterpenes, bakkanes **4**, which are biogenetically derived from eremophilanes **5**, containing a novel α -spiro- β -methylene- γ -butyrolactone moiety spirofused to hydrindane framework.⁴ The homogynolides-A and B were found to possess antifeedant activity against certain types of beetle adults (*Sitophilus granarius*, *Tribolium confusum*) and larvae

(*Trogoderma granarium*, *Tribolium confusum*).⁵ The structures of homogynolides-A **1** and B **2** were established as the angelyl ester of 2-hydroxybakkenolide-A and tiglyl ester of 3-hydroxybakkenolide-A, respectively, *via* chemical degradation and spectral comparison with other bakkenolides. The unusual structural features of homogynolides coupled with their associated biological activities made them attractive and challenging synthetic targets. Despite their biological properties, homogynolides and bakkenolides have received only a limited attention from synthetic chemists.⁶⁻⁹ Only one approach by Greene and co-workers was reported in the literature for the total synthesis of homogynolides-A and B prior to the initiation of work in our laboratory, and after the completion of our synthesis,⁹ Mori and Matsushima^{7c} have reported the total synthesis of (-)-homogynolide-A.



In our laboratory, a general, radical cyclisation based methodology¹⁰ was developed for the construction of α -spiro- β -methylene- γ -butyrolactones starting from cyclic ketones, Scheme 1. Methoxymethylene Wittig reaction of a cyclic ketone **6** followed by bromoacetalisation of the resultant enol ether **7** with NBS and propargyl alcohol generates the bromoacetal **8**. The 5-*exo-dig*-radical cyclisation of the bromoacetal **8** followed by hydrolysis and oxidation of the resultant spiroacetal **9** furnishes the spiro lactone **10**. Based on this methodology, in continuation of our work on the synthesis of (\pm)-homogynolide-B,^{8b} we have achieved a formal total synthesis of both enantiomers of homogynolide-A,⁹ starting from (*R*)-carvone **11**, and herein we describe the details of these investigations.

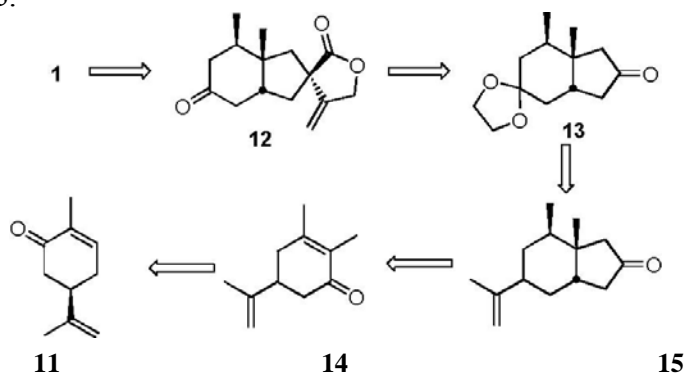


(a) $\text{Ph}_3\text{P}=\text{CHOMe}$; (b) NBS, $\text{HC}\equiv\text{CCH}_2\text{OH}$; (c) ${}^n\text{Bu}_3\text{SnH}$, AIBN; (d) Jones reagent.

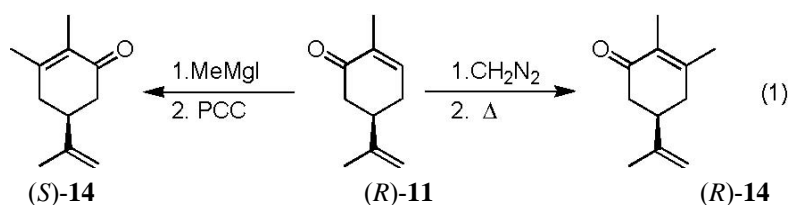
Scheme 1

The ketospirolactone **12**, the penultimate precursor in Greene's^{7a} synthesis of (-)-homogynolide-A was identified as the target molecule, whose retrosynthetic analysis is depicted in Scheme 2. Based on the radical cyclisation based methodology (*ca* Scheme 1), the ketoketal **13** was readily recognized as the key intermediate, and (*R*)-carvone **11** was chosen as the chiral

source. The isopropenyl group in carvone was readily recognised as a masked hydroxy group required for homogynolide-A. Since (*R*)-carvone **11** can be converted into either enantiomer of 3-methylcarvone **14** with equal efficiency (eqn. 1),¹¹ it was contemplated to use 3-methylcarvone as the starting material for the synthesis of both enantiomers of homogynolide-A. A reductive alkylation methodology for the generation of the secondary and tertiary methyl groups, and a Wacker reaction mediated cyclopentannulation methodology were envisaged for the generation of the hydrindanone **15**.

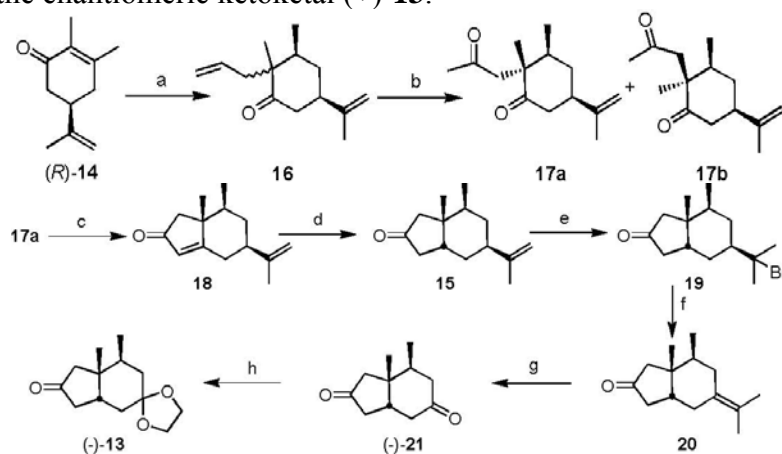


Scheme 2

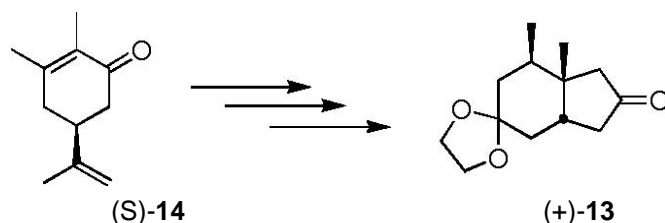


To begin with, (*R*)-carvone **11** was converted into both (*R*)- and (*S*)-enantiomers of 3-methylcarvone **14**, employing 1,3-dipolar cycloaddition of diazomethane followed by thermolysis of the resulting pyrazoline derivative, and regioselective 1,2-addition of methylmagnesium iodide followed by oxidation of the resultant tertiary alcohol, respectively.¹¹ The synthesis was carried out starting from both enantiomers, but for brevity the sequence employing (*R*)-enantiomer of 3-methylcarvone (*-*)-**14** is described here, Schemes 3 and 4. For the simultaneous generation of the secondary and tertiary methyl groups, reductive allylation of 3-methylcarvone **14** was explored. Thus, reduction of (*R*)-3-methylcarvone **14** using lithium, liquid ammonia and tertiary butyl alcohol followed by quenching the intermediate enolate with allyl bromide generated a mixture of epimers **16**, whose separation was found to be difficult and hence proceeded further. The regioselectivity of Wacker reaction¹² for the oxidation of mono substituted olefins was exploited for the conversion of the allyl into an acetyl group for the generation of a 1,4-diketone. Thus, reaction of an epimeric mixture of the allyl compound **16** with a catalytic amount of palladium chloride and cuprous chloride in dimethylformamide and water in an oxygen atmosphere (using a balloon) furnished a \approx 2:1 mixture of the diketones **17a** and **17b**, which were separated by column chromatography on silica gel. The structures of the diones **17a** and **17b** were established from their interrelated spectral data (IR, ¹H and ¹³C NMR). The stereochemistry of the secondary methyl group in the products was assigned as *cis* with respect to the isopropenyl group based on the thermodynamic considerations in the first step of the reductive allylation reaction. The stereochemistry at the α -carbon in the major product **17a** was assigned based on the preferential approach of the electrophile *trans* to the secondary methyl

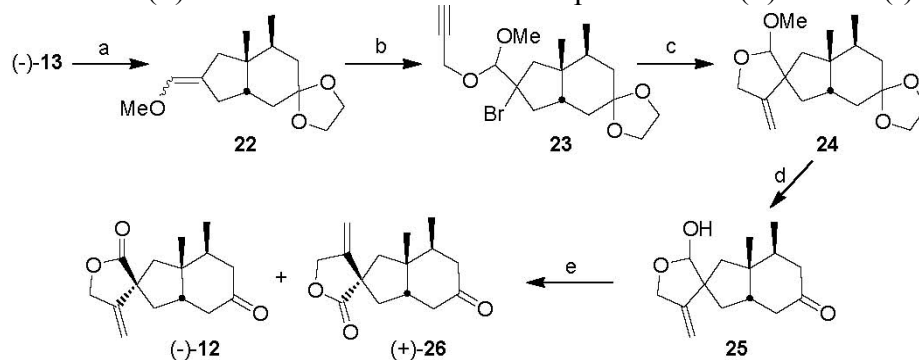
group in the alkylation step. The structures were confirmed by comparison of the spectral data with the other two diastereomers of the dione.¹³ Intramolecular aldol condensation of the dione **17a** using 10% aqueous potassium hydroxide in methanol cleanly furnished the enone **18**. For the conversion of the isopropenyl moiety into an acetoxy group, regioselective ozonation followed by Craigg rearrangement of the enone **18** was briefly explored. As it was found to be inefficient, regiospecific reduction of the *endo* cyclic olefin was addressed first, employing electron transfer methodology. Consequently, regiospecific 1,4-reduction of the enone moiety using lithium in liquid ammonia transformed the enone **18** into the hydrindanone **15** containing traces of the corresponding *trans* isomer. For the conversion of the isopropenyl moiety into a ketone functionality, three step sequence *viz.* addition of hydrogen halide, dehydrohalogenation and ozonolytic cleavage, was employed. Accordingly, addition of hydrogen bromide in ether at 0-5 °C followed by dehydrobromination of the resultant tertiary bromide **19** with DBU in benzene at 130 °C in a sealed tube transformed the hydrindanone **15** into the isomerised compound **20** in 89% yield. Ozonolysis of the isopropylidene group in **20** in methanol-methylene chloride followed by reductive work up with triphenylphosphine furnished the dione (-)-**21** in 88% yield, whose structure was established from its spectral data. The molecular ion at *m/z* 180 in the mass spectrum, presence of two carbonyl absorption bands at 1740 and 1710 cm^{-1} due to the 5- and 6-membered cyclic ketones, respectively, in the IR spectrum and absence of resonances due to the olefinic carbons in the ^{13}C NMR spectrum revealed the formation of the dione **21**. In the ^1H NMR spectrum, presence of a singlet at δ 1.21 and a doublet at 0.9 due to *tertiary* and *secondary* methyl groups, respectively, and the 11 lines ^{13}C NMR spectrum with diagnostic resonances at δ 215.9 and 210.4 due to carbonyl carbons of five and six membered cyclic ketones, respectively, at 40.7 due to the quaternary carbon, at 18.7 and 16.6 ppm due to two methyl groups confirmed the structure of the dione **21**. Regioselective protection of the 6membered ring ketone with ethylene glycol and a catalytic amount of *p*-toluenesulfonic acid (pTSA) in refluxing benzene using a Dean-Stark water separator transformed the dione **21** into the (-)-ketoketal **13** in 65% yield, the key intermediate in the sequence, whose structure was established from its spectral data. In a similar manner, (*S*)-methylcarvone (+)-**14** was transformed into the enantiomeric ketoketal (+)-**13**.



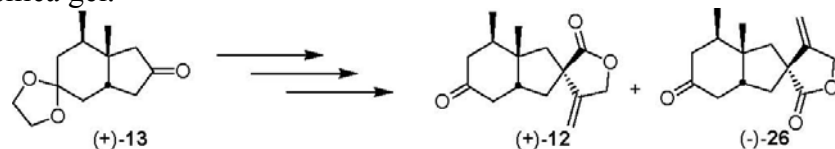
Scheme 3. (a) Li, liq. NH_3 ; $\text{CH}_2=\text{CHCH}_2\text{Br}$; (b) PdCl_2 , CuCl , $\text{DMF-H}_2\text{O}$, O_2 ; (c) KOH ; (d) Li, liq. NH_3 ; (e) HBr(g) ; (f) DBU; (g) O_3/O_2 ; PPh_3 ; (h) $(\text{CH}_2\text{OH})_2$, *p*-TSA.



After successful synthesis of both enantiomers of the keto ketal **13**, attention was then turned to the target molecule, the ketospirolactone **12**, Greene's precursor of homogynolide-A, Scheme 3. Methoxymethylene Wittig reaction of the keto ketal (-)-**13** with methoxymethyltriphenylphosphonium chloride and potassium tertiary amyloxyde in THF furnished a ~1:1 mixture of *E,Z* isomers of the enol ether **22**. A bromoacetalisation reaction¹⁴ with NBS and propargyl alcohol in methylene chloride at low temp. (-50 °C) transformed the enol ether **22** into a diastereomeric mixture of the bromoacetal **23**. The 5-*exo-dig* radical cyclisation reaction of the bromoacetal **23** using an *in situ* generated catalytic tri-*n*-butyltin hydride (ⁿBu₃SnCl-NaCNBH₃)¹⁵ in the presence of a catalytic amount of AIBN in refluxing tertiary butyl alcohol furnished a diastereomeric mixture of the spiro compound **24**. Simultaneous hydrolysis of the ketal and acetal moiety in **24** using 3 N HCl and oxidation of the resultant keto lactol **25** using PCC and silica gel furnished a *ca* 1:4 mixture of the spiro lactone (-)-**12** and its spiro epimer (+)-**26**, which were separated by careful column chromatography on silica gel. The ¹H NMR (270 MHz) spectrum of the minor ketospirolactone **12** exhibited signals, identical to that of an authentic sample prepared earlier by Greene *et al.* The structure of the epiketospirolactone **26** was established from its spectral data. In a similar manner, the enantiomeric ketoketal (+)-**13** was transformed into the spiro lactones (+)-**12** and (-)-**26**.

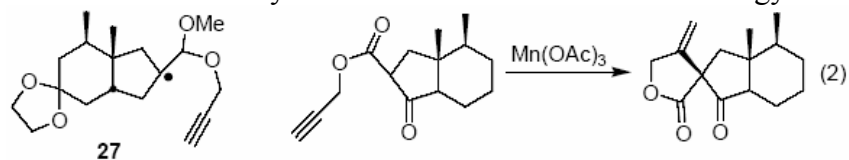


Scheme 4. (a) Ph₃P=CHOMe; (b) NBS, HC≡CCH₂OH; (c) ⁿBu₃SnCl, NaCNBH₃, AIBN; (d) 3N HCl; (e) PCC, silica gel.



The formation of the two epimers **12** and **26** was, obviously, a consequence of the cyclisation of the radical **27** *via endo* or *exo* face of the molecule. Even though the formation of the epispinolactone **26** was not anticipated based on the homogynolide-B synthesis,^{8c} recently, Greene *et al.* have also reported^{6j} a similar observation in the synthesis of one of the oxygenated bakkenolides employing a radical cyclisation strategy (Eq. 2). Since the spiro lactone (-)-**12** has already been transformed into (-)-homogynolide-A by Greene and coworkers,^{7b} the present

sequence constitutes a formal total synthesis of both enantiomers of homogynolide-A.



In conclusion, formal total synthesis of both enantiomers of homogynolide-A has been accomplished employing (*R*)-carvone as the source of chirality, *via* (*R*)- and (*S*)-enantiomers of 3-methylcarvone **14** and the hydrindane based ketoketal **13** as the key intermediates. A radical cyclisation based methodology was exploited for the spiroannulation of a β -methylene- γ -butyrolactone for the generation of Greene's precursor for homogynolide-A.

Experimental Section

General Procedures. Melting points are recorded using a Tempo melting point apparatus in capillary tubes and are uncorrected. IR spectra were recorded on Perkin-Elmer 781 spectrophotometer. ^1H (90, 200 and 270 MHz) and ^{13}C NMR (22.5, 50 and 100 MHz) spectra were recorded on Jeol FX90Q, Bruker ACF-200, WH-270 and AMX-400 spectrometers. The chemical shifts (δ ppm) and the coupling constants (Hz) are reported in the standard fashion with reference to either internal tetramethylsilane (for ^1H) or the central line (77.1 ppm) of CDCl_3 (for ^{13}C). In the ^{13}C NMR spectra off-resonance multiplicities, when recorded are given in parentheses. Low and High resolution mass measurements were carried out using a Jeol JMS-DX 303 GC-MS instrument using a direct inlet mode. Relative intensities of the ions are given in parentheses. Elemental analyses were carried out using a Carlo Erba 1106 CHN analyzer. Optical rotations were measured using a Jasco DIP-370 digital polarimeter and $[\alpha]_{\text{D}}$ values are given in the units of $10^{-1} \cdot \text{deg} \cdot \text{cm}^2 \cdot \text{g}^{-1}$. Ozonolysis was carried out using a Penwalt Wallace and Tierman ozonator. Acme's silica gel (100-200 mesh), approximately 15-20 g per 1 g of the crude product, was used for column chromatography. All small-scale dry reactions were carried out using standard syringe-septum technique. Dry THF was obtained by distillation over sodium-benzophenone ketyl. AIBN was recrystallised from methanol and stored in dark. HBr in ether was prepared by bromination of tetralin with bromine according to Vogel's procedure. (*R*)- and (*S*)-3-methylcarvones were prepared from (*R*)-carvone as described earlier.¹¹

(2*R*,3*S*,5*R*) and (2*S*,3*S*,5*R*)-2-Allyl-5-isopropenyl-2,3-dimethylcyclohexanones (16). To magnetically stirred ammonia (freshly distilled over sodium and FeCl_3 , 600 mL) was added lithium pieces (500 mg, 72.0 mmol) over a period of 5 min. To the resultant dark blue solution was added a solution of (*R*)-3-methylcarvone **14** (3.0 g, 18.3 mmol) and *tert*-BuOH (1.36 ml, 14.5 mmol) in 60 ml of THF, drop wise, over a period of 25 min. The reaction mixture was stirred for 50 min at the same temperature and allyl bromide (21.45 g, 15 mL, 177 mmol) was added. The reaction mixture was slowly warmed up to RT, stirred for 6 h, diluted with water (30 mL) and extracted with ether (3 x 20 mL). The combined organic extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (0:100 to 1:50) as eluent furnished a 2:1 epimeric mixture

of the allyl compound **16** (2.37 g, 63%) as an oil. IR (neat): ν_{\max} 3070, 1700, 1640, 900, 890 cm^{-1} . ^1H NMR (90 MHz, CDCl_3 , 2:1 mixture of diastereomers): δ 5.50-6.00 (1 H, m, H-2'), 4.85-5.20 (2 H, m, H-3'), 4.74 (2 H, br s, $\text{C}=\text{CH}_2$), 1.70 (3 H, s, olefinic CH_3), 0.96 and 1.04 (3 H, s, *tert* CH_3), 0.93 (3 H, d, $J=5.8$ Hz, *sec*- CH_3).

(2R,3S,5R) and **(2S,3S,5R)-5-Isopropenyl-2,3-dimethyl-2-(2-oxopropyl)cyclohexanones (17a) and (17b)**. A suspension of palladium chloride (95 mg, 0.54 mmol) and cuprous chloride (781 mg, 7.89 mmol) in DMF (10.5 ml) and water (3.2 ml) was magnetically stirred in an oxygen atmosphere, created via evacuative displacement of air using an oxygen balloon, for 1 h at RT. A solution of the 2:1 epimeric mixture of allyl compound **16** (2.2 g, 10.67 mmol) in 3 ml of DMF was then added, and the reaction mixture was stirred for 24 h at RT in the oxygen atmosphere. 3 N HCl (5 ml) was added to the reaction mixture and extracted with ether (3 x 10 ml). The ether layer was washed with saturated aq. NaHCO_3 solution followed by brine and dried (Na_2SO_4). Evaporation of the solvent and careful chromatography of the residue over a silica gel column using ethyl acetate-hexane (1:20 to 1:5) as eluent furnished the diketones **17a** (925 mg, 39%) and **17b** (475 mg, 20%). *For the major diketone (17a)*. $[\alpha]_{\text{D}}^{27}$: +81.6 (c 2.44, CHCl_3). IR (neat): ν_{\max} 3055, 1700, 1640, 890 cm^{-1} . ^1H NMR (90 MHz, CDCl_3): δ 4.75 (2 H, br s, $\text{C}=\text{CH}_2$), 2.89 and 2.47 (2 H, 2 x d, $J=19.0$ Hz, H-1'), 2.42 (2 H, m), 2.30-2.50 (1 H, m), 2.12 (3 H, s, COCH_3), 1.50-1.70 (3 H, m), 1.71 (3 H, s, olefinic CH_3), 1.00 (3 H, s, *tert*- CH_3), 0.89 (3 H, d, $J=6.4$ Hz, *sec*- CH_3). ^{13}C NMR (50 MHz, $\text{CHCl}_3+\text{CDCl}_3$): δ 214.2 (C-1), 207.1 ($\text{CH}_3\text{C}=\text{O}$), 147.4 ($\text{C}=\text{CH}_2$), 109.3 ($\text{C}=\text{CH}_2$), 50.6 (C-2), 48.0 (CH_2COCH_3), 42.9, 42.7, 36.4, 35.0, 30.8 (COCH_3), 20.3, 18.5, 15.7. Mass: m/z 222 (M^+ , 2%), 165 (100), 149 (10). HRMS: m/z for $\text{C}_{13}\text{H}_{19}\text{O}_2$ (M -Me), Calcd.: 207.1385. Found: 207.1390. *For the minor diketone 17b*: IR (neat): ν_{\max} 3060, 1700, 1660, 890 cm^{-1} . ^1H NMR (90 MHz, CDCl_3): δ 4.75 (2 H, br s, $\text{C}=\text{CH}_2$), 2.90 and 2.60 (2 H, 2 x d, $J=18$ Hz, CH_2COCH_3), 2.30-2.50 (3 H, m), 2.10 (3 H, s, COCH_3), 1.70 (3 H, s, olefinic CH_3), 1.40-1.70 (3 H, m), 1.06 (3 H, s, *tert*- CH_3), 0.97 (3 H, d, $J=6.0$ Hz, *sec*- CH_3). ^{13}C NMR (22.5 MHz, CDCl_3): δ 210.9 (C-1), 205.6 ($\text{CH}_3\text{C}=\text{O}$), 146.4 ($\text{C}=\text{CH}_2$), 108.4 ($\text{C}=\text{CH}_2$), 48.7 (C-2), 45.4, 44.7, 42.5, 41.9, 33.9, 30.0 (COCH_3), 19.4, 18.8, 14.8. Mass: m/z 222 (M^+ , 16%), 204 (10), 179 (12), 165 (100), 149 (16), 137 (20), 121 (23), 109 (42), 95 (58). Anal. for $\text{C}_{14}\text{H}_{22}\text{O}_2$, Calcd.: C, 75.63, H, 9.97. Found: C, 75.30, H, 9.96%.

(-)-(1R,2S,4R)-4-Isopropenyl-1,2-dimethylbicyclo[4.3.0]non-6-en-8-one (18). To a solution of the diketone **17a** (473 mg, 2.13 mmol) in 1 ml of methanol was added 10% aq. KOH (1.43 mL, 2.56 mmol), and the reaction mixture was heated in a sealed tube at 110 $^\circ\text{C}$ for 3.5 h. It was cooled and extracted with ether (3 x 10 ml). The ether extract was washed with water followed by brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:10) as eluent, furnished the enone **18** (364 mg, 84%) as yellow oil. $[\alpha]_{\text{D}}^{28}$: -103 (c 1.3, CHCl_3). IR (neat): ν_{\max} 1705, 1620, 890 cm^{-1} . ^1H NMR (270 MHz, CDCl_3): δ 5.79 (1 H, s, H-7), 4.78 (2 H, s, $\text{C}=\text{CH}_2$), 2.68 (1 H, d, $J=11.2$ Hz, H-9a), 2.10-2.40 (4 H, m), 1.77 (3 H, s, olefinic CH_3), 1.20-1.70 (3 H, m), 1.10 (3 H, s, *tert*- CH_3), 0.97 (3 H, d, $J=6.5$ Hz, *sec*- CH_3). ^{13}C NMR (22.5 MHz, CDCl_3): δ 205.3 (s, $\text{C}=\text{O}$), 186.2 (s, C-6), 146.8 (s, $\text{C}=\text{CH}_2$), 125.2 (d, C-7), 108.5 (t, $\text{C}=\text{CH}_2$), 49.1 (t, C-9), 45.3 (d, C-4), 44.9 (s, C-1), 41.2 (d, C-2), 34.0 (t), 31.1 (t), 19.5 (q), 17.2 (q), 15.9 (q). 2,4-DNP derivative, m.p. 158-159 $^\circ\text{C}$. Anal. for $\text{C}_{20}\text{H}_{24}\text{N}_4\text{O}_4$, Calcd.: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.47; H, 6.42; N, 14.24%. **(-)-(1R,2S,4R,6R)-4-Isopropenyl-1,2-dimethylbicyclo[4.3.0]nonan-8-one (15)**. To a dark blue

colored solution of lithium (80 mg, 11.5 mmol) in 180 ml of freshly distilled ammonia was added, drop wise, a solution of the enone **18** (540 mg, 2.64 mmol) and *t*-BuOH (0.5 mL, 5.33 mmol) in 20 ml of dry THF over a period of 15 min. The reaction mixture was stirred for 2 h and then quenched with ammonium chloride. Ammonia was evaporated; reaction mixture was diluted with water and extracted with ether (3 x 25 mL). The ether extract was washed with brine and dried (Na₂SO₄). Evaporation of the solvent furnished a mixture of hydrindanone **15** and the corresponding alcohol. To the crude mixture of ketone and alcohol in CH₂Cl₂ (5 ml) was added PCC (1 g, 4.65 mmol) and silica gel (1 g), stirred for 2 h and filtered through a small silica gel column. Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:40 to 1:20) as eluent furnished the ketone **15** (456 mg, 84%) as an oil. $[\alpha]_D^{28}$: -66 (c 1.3, CHCl₃). IR (neat): ν_{\max} 3075, 1745, 1645, 885 cm⁻¹. ¹H NMR (270 MHz, CDCl₃): δ 4.72 (2 H, br s, C=CH₂), 2.42 and 1.98 (2 H, 2 x d, J=18 Hz, H-9), 2.10-2.40 (3 H, m), 1.73 (3 H, s, olefinic CH₃), 1.10-1.70 (3 H, m), 1.05 (3 H, s, *tert*-CH₃), 0.84 (3 H, d, J=6.3 Hz, *sec*-CH₃). ¹³C NMR (100 MHz, CDCl₃): δ 218.6 (C=O), 149.6 (C=CH₂), 108.8 (C=CH₂), 53.1, 43.9, 40.9, 40.7, 39.1, 35.4, 35.8, 28.6, 21.0, 19.0, 16.4. Mass: *m/z* 206 (M⁺, 30%), 191 (10), 163 (30), 149 (25), 135 (15), 121 (40), 109 (100). HRMS: *m/z* for C₁₄H₂₂O, Calcd.: 206.1671. Found: 206.1679.

(-)-(1R,2S,6R)-4-Isopropylidene-1,2-dimethylbicyclo[4.3.0]nonan-8-one (20). To an ice cold magnetically stirred saturated solution of HBr in dry ether (50 ml) was added hydrindanone **15** (368 mg, 1.79 mmol) in 2 ml of dry ether. The reaction mixture was stirred at the same temp for 6 h, diluted with ether (30 ml), washed sequentially with water, aq. NaHCO₃ and brine, and dried (Na₂SO₄). Evaporation of the solvent furnished the tertiary bromide **19**, which was taken in 5 ml of benzene and DBU (0.323 mL, 2.12 mmol) was added and heated in a sealed tube at 130 °C for 30 min. The reaction mixture was then cooled, diluted with water and extracted with ether (3 x 10 ml). The ether extract was washed with 3 N HCl, saturated NaHCO₃ solution and brine, and dried (Na₂SO₄). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:20) as eluent furnished the isopropylidene compound **20** containing a trace amount of the starting material **15** (328 mg, 89% in two steps). $[\alpha]_D^{26}$: -79 (c 2.7, CHCl₃). IR (neat): ν_{\max} 1740 cm⁻¹. ¹H NMR (90 MHz, CDCl₃): δ 2.35 (1 H, d, J=18 Hz), 2.16 (2 H, s), 1.93 (1 H, d, J=18 Hz), 1.60-2.60 (6 H, m), 1.68 (3 H, s), 1.63 (3 H, s), 1.10 (3 H, s, *tert*-CH₃), 0.85 (3 H, d, J=6.3 Hz, *sec*-CH₃). ¹³C NMR (22.5 MHz, CDCl₃): δ 218.7 (s, C=O), 127.1 (s), 123.9 (s), 52.4 (t), 45.0 (d), 40.8 (s), 40.4 (t), 35.3 (d), 33.8 (t), 28.3 (t), 19.7 (2 C, q), 18.7 (q), 16.1 (q). Mass: *m/z* 206 (M⁺, 80%), 163 (40), 149 (45), 121 (75), 110 (40), 109 (100), 107 (50). HRMS: *m/z* for C₁₄H₂₂O, Calcd.: 206.1671. Found: 206.1668.

(-)-(1R,5S,6R)-5,6-Dimethylbicyclo[4.3.0]nonan-3,8-dione (21). Through a cold (-90 °C) solution of the compound **20** (390 mg, 1.89 mmol), methanol (0.4 ml) and NaHCO₃ (catalytic) in 10 ml of CH₂Cl₂ was passed a stream of pre-cooled ozone in oxygen gas until the reaction mixture turned to blue in color. Excess ozone was flushed off by passing oxygen gas. Triphenylphosphine (500 mg, 1.9 mmol) was added to the reaction mixture, allowed it to warm up to RT and stirred for 8 h. Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:5 to 2:5) as eluent furnished the dione **21** (300 mg, 88%). $[\alpha]_D^{24}$: -114 (c 2.1, CHCl₃). IR (neat): ν_{\max} 1740, 1710 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ 1.70-2.80 (10 H, m), 1.21 (3 H, s, *tert*-CH₃), 0.90 (3 H, d, J=6.6 Hz, *sec*-CH₃).

^{13}C NMR (100 MHz, CDCl_3): δ 215.9 (C, C-8), 210.4 (C, C-3), 51.9 (CH_2), 45.5 (CH), 45.0 (CH_2), 42.0 (CH_2), 40.7 (2 C, C & CH_2), 35.7 (CH), 18.7 (CH_3 , *tert*- CH_3), 16.6 (CH_3 , *sec*- CH_3). Mass: m/z 180 (M^+ , 25 %), 111 (10), 95 (10), 69 (100). HRMS: m/z for $\text{C}_{11}\text{H}_{16}\text{O}_2$, Calcd.: 180.1150. Found: 180.1143.

(-)-(1*R*,2*S*,6*S*)-4,4-Ethylenedioxy-1,2-dimethylbicyclo[4.3.0]nonan-8-one (13). A magnetically stirred solution of the dione **21** (320 mg, 1.77 mmol), ethylene glycol (0.1 ml, 1.8 mmol) and a catalytic amount of *p*-TSA in 50 ml of dry benzene was refluxed using a Dean-Stark water separator for 3 h. It was cooled, washed with saturated aqueous NaHCO_3 solution and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure and purification of the product over a silica gel column using ethyl acetate-hexane (1:5) as eluent furnished the ketoketal **13** (260 mg, 65%) as oil. $[\alpha]_{\text{D}}^{25}$: -64 (c 2.1, CHCl_3) {For the (1*S*,2*R*,6*R*)-enantiomer $[\alpha]_{\text{D}}^{25}$: +69 (c 1.64, CHCl_3)}. IR (neat): ν_{max} 1730 cm^{-1} . ^1H NMR (270 MHz, CDCl_3): δ 3.85-4.00 (4 H, m, $\text{OCH}_2\text{CH}_2\text{O}$), 2.93 (1 H, d of t, $J=16.0$ and 7.0 Hz), 1.40-2.50 (9 H, m), 1.06 (3 H, s, *tert*- CH_3), 0.85 (3 H, d, $J=6.7$ Hz, *sec*- CH_3). ^{13}C NMR (50 MHz, $\text{CHCl}_3+\text{CDCl}_3$): δ 219 (C=O), 109 (O-C-O), 64.4 and 63.5 ($\text{OCH}_2\text{CH}_2\text{O}$), 58.3, 52.2, 43.5, 41.5, 38.5, 31.8, 31.4, 18.4, 16.0. Mass: m/z 224 (M^+ , 5%), 154 (35), 139 (10), 113 (100). HRMS: m/z for $\text{C}_{13}\text{H}_{20}\text{O}_3$, Calcd.: 224.1412. Found: 224.1416.

(1*S*,5*S*,6*R*,8*R*) and (1*S*,5*S*,6*R*,8*S*)-5,6-Dimethylbicyclo[4.3.0]nonan-3-one-8,3'-spiro[4'-methylenedihydrofuran-2'(3'H)-one] (12) and (26). To a magnetically stirred solution of potassium tertiary amyloxyde (292 mg, 2.32 mmol) in dry THF (3 mL) at RT was added methoxymethyltriphenylphosphonium chloride (944 mg, 2.76 mmol) and the resulting red colored solution was stirred at RT for 15 min. To the methoxymethylenetriphenylphosphorane thus formed, was added the ketoketal **13** (165 mg, 0.736 mmol) and stirred at RT for 6 h. The reaction mixture was then diluted with ether (10 ml), washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a neutral alumina column using ethyl acetate-hexane (1:40 to 1:20) as eluent furnished a *E,Z* mixture of the enol ether **22** as a colourless oil, which was contaminated with small amount of triphenylphosphine. IR (neat): ν_{max} 1685 cm^{-1} . ^1H NMR (90 MHz, CDCl_3): δ 5.83 (1 H, br s, olefinic H), 3.90 (4 H, br s, $\text{OCH}_2\text{CH}_2\text{O}$), 3.52 (3 H, s, OCH_3), 1.20-2.80 (10 H, m), 0.93 and 0.90 (3 H, s, *tert*- CH_3), 0.84 and 0.81 (3 H, d, $J=6.3$ Hz, *sec*- CH_3). To a cold (-40 °C), magnetically stirred solution of NBS (200 mg, 1.12 mmol) and propargyl alcohol (385 mg, 0.4 ml, 6.87 mmol) in CH_2Cl_2 (4 ml) was added a solution of the enol ether **22** in CH_2Cl_2 (2 ml) over a period of 10 min. The reaction mixture was stirred for 45 min at the same temperature, diluted with CH_2Cl_2 (5 ml), washed with 1% aq. NaOH solution (5 ml) followed by brine, and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue on a neutral alumina column using ethyl acetate-hexane (1:20 to 1:10) as eluent furnished a diastereomeric mixture of the bromoacetal **23** (160 mg, 56% overall yield from ketoketal **13**) as a colourless oil. IR (neat): ν_{max} 3280, 2120 cm^{-1} . ^1H NMR (90 MHz, CDCl_3 , mixture of diastereomers): δ 4.60 & 4.54 (1 H, s, O-CH-O), 4.45 (2 H, d, $J=2.5$ Hz, $\text{OCH}_2\text{C}\equiv\text{CH}$), 3.90 (4 H, br s, $\text{OCH}_2\text{CH}_2\text{O}$), 3.65 & 3.64 (3 H, s, OCH_3), 2.50 (1 H, t, $J=2.5$ Hz, $\text{C}\equiv\text{CH}$), 1.20-2.70 (10 H, m), 1.04 (3 H, s, *tert*- CH_3), 0.88 (d, $J=5.8$ Hz) & 0.78 (d, $J=6.8$ Hz) [3 H, *sec*- CH_3]. A magnetically stirred solution of the bromoacetal **23** (159 mg, 0.4 mmol), tri-*n*-butyltin chloride (0.02 mL, 0.075 mmol), NaCNBH_3 (70 mg, 1.12 mmol) and a catalytic amount of AIBN in *t*-BuOH (2.5 ml) was refluxed for 2 h. The solvent was then evaporated under reduced pressure. The residue was taken in water (3 mL) and extracted with ether (3 x 5 mL).

The ether extract was washed with 1% aq. ammonia solution followed by brine, and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:40) as eluent furnished an epimeric mixture of the spiroacetal 24 (102 mg, 82%) as a colourless oil. IR (neat): ν_{max} 3080, 1660, 875 cm^{-1} . ^1H NMR (90 MHz, CDCl_3): δ 4.80-5.00 (2 H, m, $\text{C}=\text{CH}_2$), 4.66 & 4.58 (1 H, s, CHOMe), 4.30-4.50 (2 H, m, $\text{OCH}_2\text{C}=\text{}$), 3.85-4.00 (4 H, m, $\text{OCH}_2\text{CH}_2\text{O}$), 3.34 (3 H, s, OCH_3), 1.20-2.70 (10 H, m), 1.13 & 0.91 (3 H, s, *tert*- CH_3), 0.74-0.90 (3 H, m, *sec*- CH_3). A solution of the spiroacetal 24 (50 mg, 0.162 mmol) in THF (1 ml) and 3 N HCl (2 ml) was stirred for 4 h at RT. The reaction mixture was diluted with ether (5 ml), washed with water, saturated aq. NaHCO_3 solution and brine, and dried (Na_2SO_4). The solvent was evaporated and the residue was filtered through a silica gel column using ethyl acetate-hexane (1:5 to 2:5) as eluent to furnish an epimeric mixture of the ketospirolactol 25 (22.5 mg, 56%). IR (neat): ν_{max} 3400, 1710, 880 cm^{-1} . To a magnetically stirred solution of the spiroacetal 24 (22.5 mg, 0.09 mmol) in CH_2Cl_2 (0.3 ml) was added a homogeneous mixture of PCC (25 mg, 0.12 mmol) and silica gel (25 mg). The reaction mixture was stirred at RT for 4 h and then filtered through a silica gel column using CH_2Cl_2 as eluent. Evaporation of the solvent and careful purification of the residue on a silica gel column using ethyl acetate-hexane (1:5 to 2:5) as eluent furnished the ketospirolactones 12 (4 mg, 18%) and 26 (14 mg, 63%). For the ketospirolactone 12: $[\alpha]_{\text{D}}^{26}$: -45 (c 1.0, CHCl_3). ^1H NMR (270 MHz, CDCl_3): δ 5.06 (2 H, br s, $\text{C}=\text{CH}_2$), 4.76 (2 H, br s, OCH_2), 2.55-2.75 (2 H, m), 2.00-2.35 (5 H, m), 2.02 and 2.12 (2 H, AB q, $J=14.4$ Hz), 1.73 (1 H, t, $J=13.3$ Hz), 1.22 (3 H, s, *tert*- CH_3), 1.00 (3 H, d, $J=6.5$ Hz, *sec*- CH_3). For the epi ketospirolactone (26): $[\alpha]_{\text{D}}^{24}$: +35.0 (c 1.0, CHCl_3). {For the (*1R,5R,6S,8R*)-enantiomer $[\alpha]_{\text{D}}^{26}$: -33 (c 1.5, CHCl_3)}. IR (neat): ν_{max} 3080, 1760, 1700, 1665, 890 cm^{-1} . ^1H NMR (270 MHz, CDCl_3): δ 5.11 (1 H, s) and 5.05 (1 H, s) [$\text{C}=\text{CH}_2$], 4.79 (2 H, br s, OCH_2), 2.00-2.60 (8 H, m), 1.89 (1 H, dd, $J=12.8$ and 6.6 Hz), 1.68 (1 H, d, $J=14$ Hz), 1.19 (3 H, s, *tert*- CH_3), 0.96 (3 H, d, $J=6.6$ Hz, *sec*- CH_3). ^{13}C NMR (50 MHz, CDCl_3): δ 210.6 ($\text{C}=\text{O}$), 181.1 ($\text{OC}=\text{O}$), 151.1 ($\text{C}=\text{CH}_2$), 106.0 ($\text{C}=\text{CH}_2$), 70.1 (OCH_2), 49.8 (spiro C), 49.3, 49.1, 45.1, 44.0, 43.4, 40.4, 34.4, 19.2, 16.4. Mass: m/z 248 (M^+ , 18%), 164 (76), 138 (18), 119 (28), 105 (20), 84 (100), 69 (75). HRMS: m/z for $\text{C}_{15}\text{H}_{20}\text{O}_3$, Calcd.: 248.1412. Found: 248.1424.

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