A Novel Synthesis of Cyclobutane Sesquiterpenes, (±)-Italicene and (±)-Isoitalicene

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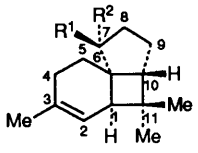
Cyclobutane sesquiterpenes (±)-italicene **1** and (±)-isoitalicene **2** have been synthesised from the benzocyclobutene derivative **20** employing an intramolecular γ-alkylation of the β,γ-unsaturated ketone **25** as a key reaction.

Italicene **1** and isoitalicene **2**,[1] isolated from Helichrysum oil (*Helichrysum italicum*) as the minor components of non-polar sesquiterpene hydrocarbons, have been used as perfumes in the Mediterranean region. Their unique structures, bearing a cyclobutane ring, were initially elucidated by chemical degradations and spectral analyses,[1] and were unambiguously determined by total synthesis[1] which involved an intramolecular [2 + 2]photocycloaddition reaction as a key step to construct a cyclobutane ring system. Although different routes to the cyclobutane terpenes have been investigated, so far [2 + 2]photocycloaddition reactions serve as the major synthetic tool for constructing the cyclobutane skeleton in many of these syntheses.



1 R^1 = Me, R^2 = H
2 R^1 = H, R^2 = Me

Recently, we have developed[2] a novel synthetic route to cyclobutane monoterpenes grandisol and lineatine, using benzocyclobutene derivatives as starting materials, in which a manipulation of a benzene ring of a benzocyclobutene was required to complete the synthesis. As an extension of this work, we have investigated a synthesis of (±)-italicene and (±)-isoitalicene, and herein report successful results involving an intramolecular γ-alkylation[3] of β,γ-unsaturated ketones as a key reaction to construct a relatively strained carbon framework.

Results and Discussion

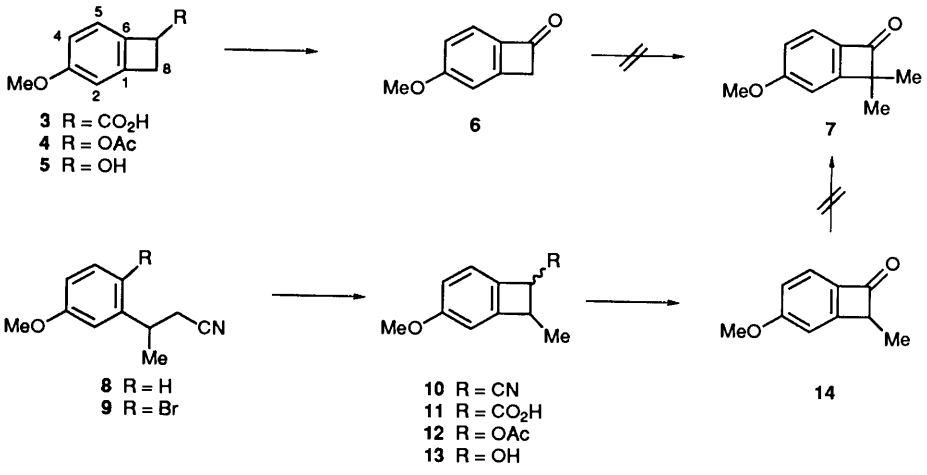
We first attempted a synthesis of a potential starting material, 4-methoxy-2,2-dimethylbenzocyclobuten-1-one **7**, as follows. Treatment of 4-methoxy-1,2-dihydrobenzocyclobutene-1-carboxylic acid **3**[4] with lead tetraacetate afforded 1-acetoxy-4-methoxy-1,2-dihydrobenzocyclobutene **4**, whose alkaline hydrolysis followed by oxidation of the resulting alcohol **5** by Swern oxidation[5] gave the ketone **6**[6] in 93.7% yield from **3** Scheme 1. Introduction of a geminal dimethyl group for **6**, however, gave none of the desired product under the various reaction conditions, presumably because of an instability of the cyclobutadienolate formed as an intermediate in this reaction. The alkylation of 4-methoxy-2-methylbenzocyclobuten-1(2*H*)-one **14**, prepared from the cyanide **8**[7] *via* the bromide **9**, cyanide **10**, acid **11**, acetate **12** and alcohol **13** in the usual manner, was next attempted, however again none of the desired product was isolated.

The requisite benzocyclobutene **20** bearing the geminal dimethyl group was synthesised as follows.

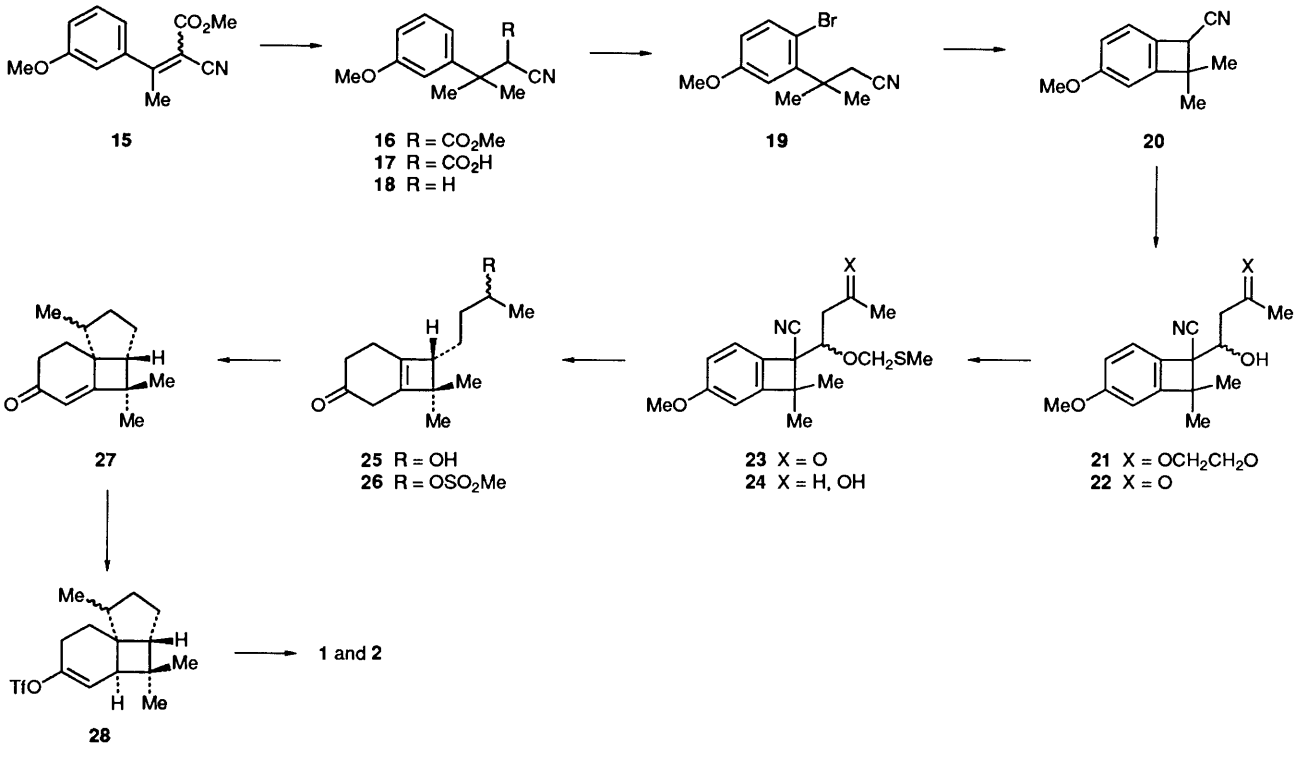
Condensation of 3-methoxyacetophenone with methyl cyanoacetate in refluxing benzene in the presence of benzylamine and acetic acid afforded the α,β-unsaturated cyanide **15**, which on treatment with lithium dimethylcuprate in ether provided the 1,4-addition product **16** in 95.3% yield from **15**. Hydrolysis of the ester **16**, followed by decarboxylation of the resulting acid **17** furnished the cyanide **18**, which was further converted into the bromide **19** on exposure to bromine in chloroform in the presence of sodium acetate in 67.6% yield from **16**. The desired benzocyclobutene **20** was obtained by treatment of the bromide **19** with sodium amide in liquid ammonia *via* the benzyne intermediate in 63.1% yield.

Having the key starting material in hand, we focused our attention on constructing a unique tricyclic carbon framework for which purpose we decided to employ an intramolecular γ-alkylation reaction of the β,γ-unsaturated enone **25** as shown in Scheme 2, since the direction of formation of the enolate as an intermediate can easily be restricted to the desired position by conjugation, suggesting that a highly site-selective alkylation would occur.

The introduction of a functionalised carbon unit corresponding to the five-membered ring of the target molecule was then investigated. Although a direct alkylation with alkyl halide did not take place under various reaction conditions, treatment of the benzocyclobutene **20** with 3,3-ethylenedioxybutyraldehyde in dry tetrahydrofuran in the presence of lithium diisopropylamide at −78 °C afforded the alcohol **21** successfully, which on exposure to toluene-*p*-sulphonic acid in acetone gave the ketone **22** in 83.4% yield from **20**. After protection of the hydroxy function of **22** as a methylthiomethyl group by reaction with dimethyl sulphoxide (DMSO) and acetic anhydride,[8] the ketone **23** was converted into the alcohol **24** by reduction with sodium borohydride in methanol in 80.3% yield from **22**. In order to synthesize the desired β,γ-unsaturated enone system, we decided to adopt Birch reduction conditions, since the removal of the cyano and the adjacent oxygen functions together with the reduction of aromatic ring under Birch reduction conditions was well documented in this field of chemistry.[9] Thus, Birch reduction of the alcohol **24** using sodium metal in liquid ammonia and tetrahydrofuran (THF) in the presence of ethanol, followed by acid treatment afforded the expected enone **25** in 74.3% yield. The enone **25** was first converted with methanesulphonyl chloride and triethylamine into the methanesulphonate **26**, which without purification was subjected to an intramolecular γ-alkylation reaction by treatment with potassium *tert*-butoxide in dry HMPA (hexa-



Scheme 1



Scheme 2

methylphosphoramide) to give the tricyclic compound **27** as an inseparable diastereoisomeric mixture in a ratio of 4:1 in 22.1% yield. Although the stereochemistry of the two isomers could not be determined at this stage, this mixture was further converted into natural products by reduction of the enone function and introduction of a methyl group at the 3-position. In order to control the stereochemistry at the 1-position, the Birch reduction was adopted since hydride reduction of the enone **27** would be considered to occur from the less hindered side of the molecule to give the opposite stereochemistry at the 1-position. Thus, reduction of the enone **27** with lithium metal in liquid ammonia and dry THF in the presence of *tert*-butyl-alcohol at −78 °C formed the enolate, which was trapped with *N*-phenyltrifluoromethanesulphonimide[10] to furnish the triflate **28**. Finally, reaction of the triflate **28** with lithium dimethyl-cuprate brought about a coupling reaction[11] to give (±)-italicene **1** and (±)-isoitalicene **2** in a ratio of 1:4 in 30.0% yield from **27** as an inseparable mixture. This ratio and poor yield obtained in a γ-alkylation reaction of the enone **26** was rationalised by assuming that this ring closure reaction would smoothly proceed through the sterically more favourable transition state **A** leading to (±)-isoitalicene. However in the transition state **B** leading to (±)-italicene, the colinear trajectory required for the cyclisation seemed to be unattainable because of steric hindrance between a methyl group on the side chain and a butene ring (see Fig. 1). Since the spectral data of those compounds were identical with those reported[1] and the separation of this mixture was also achieved,[1] our route constitutes a total synthesis of those natural products, although difficulties were encountered in our attempted separation.

Thus, the novel synthetic route to cyclobutane sesquiterpenes starting from a benzocyclobutene derivative is a strategy which is applicable to the synthesis of other types of polycyclic natural products having a cyclobutane ring system.

Experimental

General Methods.—M.p.s were measured with a Yanagimoto

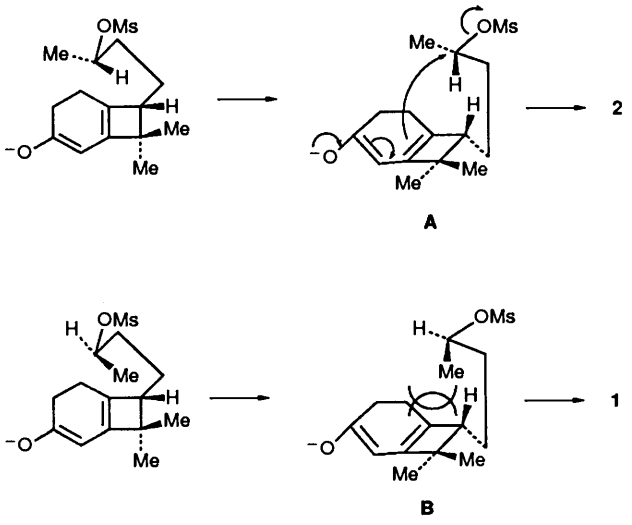


Fig. 1

MP apparatus and are uncorrected. IR spectra were recorded on a Hitachi 260-10 spectrophotometer. ^{1}H NMR spectra were obtained for solutions in $CDCl_3$ on a JEOL PMX GSX 270 instrument, and chemical shifts are reported in ppm on the δ scale from internal Me_4Si. J Values are given in Hz. Mass spectra were measured with a JEOL JMS D-300 spectrometer.

7-*Acetoxy*-3-*methoxybicyclo*[4.2.0]*octa*-1(6),2,4-*triene* **4**.—A mixture of the carboxylic acid **3**[4] (30 g, 168.5 mmol), lead tetraacetate (124.5 g, 252.8 mmol) and AcOH (120 cm^3, 2.1 mol) in tetrahydrofuran (THF) (600 cm^3) was stirred for 30 min at room temperature, and then ethylene glycol (6.28 g, 101.1 mmol) was added. After being stirred for 30 min, the reaction mixture was filtered and the filtrate concentrated to give a residue, which was taken up with AcOEt. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated to give a residue, which was purified by column chromatography on silica gel using benzene as eluent to afford the *acetate* **4** (31.2 g, 96.4%) as white crystals, m.p. 58.5 °C (Found: C, 68.8; H, 6.3. $C_{11}H_{12}O_3$ requires C, 68.5; H, 6.3%); $\nu_{max}(CHCl_3)$/cm^{-1} 1710; δ_H 2.01 (3 H, s, Me), 3.15 (1 H, d, J 2, CH*H*), 3.39 (1 H, d, J 4, C*H*H), 3.71 (3 H, s, OMe), 5.68 (1 H, dd, J 2 and 4, C*H*OAc), 6.65 (1 H, br, s, 2-H), 6.68 (1 H, d, J 2, 4-H) and 6.95 (1 H, d, J 2, 5-H); m/z 192 (M^+).

3-*Methoxybicyclo*[4.2.0]*octa*-1(6),2,4-*trien*-7-*ol* **5**.—A mixture of the acetate **4** (43.27 g, 224 mmol) and potassium carbonate (37.15 g, 269 mmol) in MeOH (1.4 dm^3) and water (140 cm^3) was stirred for 3 h at room temperature. Evaporation of the solvent gave a residue, which was extracted with AcOEt. The organic layer was washed with brine, dried (Na_2SO_4) and evaporated to give a residue, which was purified by column chromatography on silica gel using hexane–AcOEt (80:20, v/v) as eluent to afford the *alcohol* **5** (32.65 g, 97.2%) as white needles, m.p. 39–42 °C; $\nu_{max}(CHCl_3)$/cm^{-1} 3350; δ_H 2.96 (1 H, d, J 14, C*H*H), 3.54 (1 H, dd, J 4.3 and 14, CH*H*), 3.78 (3 H, s, OMe), 5.15–5.25 (1 H, m, C*H*OH), 6.71 (1 H, d, J 2.4, 2-H), 6.78 (1 H, dd, J 2.4 and 8.5, 4-H) and 7.13 (1 H, d, J 8.5, 5-H); m/z 149 ($M^+ - 1$) (Found: $M^+ - 1$, 149.0597. $C_9H_9O_2$ requires $M - 1$, 149.0602).

3-*Methoxybicyclo*[4.2.0]*octa*-1(6),2,4-*trien*-7-*one* **6**.—To a stirred solution of oxalyl chloride (0.64 cm^3, 7.33 mmol) in CH_2Cl_2 (20 cm^3) was added dropwise a solution of DMSO (dimethyl sulphoxide) (1.04 cm^3, 14.65 mmol) in CH_2Cl_2 (10 cm^3) at −50 °C and the mixture was stirred for 2 min. A solution of the alcohol **5** (1 g, 6.66 mmol) in CH_2Cl_2 (10 cm^3) was added and stirring was continued for 15 min at −50 °C. Et_3N (4.64 cm^3, 33.3 mmol) was added and the reaction mixture was allowed to warm to room temperature. Water was added and the product was extracted with AcOEt. The organic layer was washed with brine, dried (Na_2SO_4) and evaporated to give a residue, which was purified by column chromatography on silica gel using hexane–AcOEt (90:10, v/v) as eluent to afford the ketone **6** (987 mg, 100%) as colourless prisms, m.p. 47.5–48 °C (lit.,[6] m.p. 44–45 °C); $\nu_{max}(CHCl_3)$/cm^{-1} 1750; δ_H 3.88 (2 H, s, CH_2), 3.89 (3 H, s, OMe), 6.93 (1 H, dd, J 1.8 and 8.5, 4-H), 7.00 (1 H, d, J 1.8, 2-H) and 7.27 (1 H, d, J 8.5, 5-H); m/z 148 (M^+) (Found: M^+, 148.0521. $C_9H_8O_2$ requires M, 148.0523).

3-(2-*Bromo*-5-*methoxyphenyl*)*butyronitrile* **9**.—To a stirred suspension of the nitrile **8**[7] (23.32 g, 133.1 mmol) and NaOAc (16.37 g, 199.6 mmol) in $CHCl_3$ (300 cm^3) was added dropwise a solution of bromine (7.5 cm^3, 146.4 mmol) in $CHCl_3$ (100 cm^3) at 0 °C. Stirring was continued for 8 h at ambient temperature and then the mixture was poured into water. The product was extracted with $CHCl_3$ and the organic layer was washed with saturated aqueous $Na_2S_3O_3$ and brine, and then dried (Na_2SO_4). Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using hexane–AcOEt (95:5, v/v) as eluent to afford the *bromide* **9** (29.31 g, 86.7%) as a yellow oil; $\nu_{max}(CHCl_3)$/cm^{-1} 2200; δ_H 1.4 (3 H, d, J 7, Me), 2.5 (2 H, d, J 5, CH_2), 3.2–3.8 (1 H, m, CH), 3.7 (3 H, s, OMe), 6.5 (1 H, dd, J 3 and 9, 4-H), 6.7 (1 H, d, J 3, 6-H) and 7.3 (1 H, d, J 9, 3-H); m/z 255 ($M^+ + 2$) and 253 (M^+) (Found: M^+, 253.0108. $C_{11}H_{12}BrNO$ requires M, 253.0103).

3-*Methoxy*-8-*methylbicyclo*[4.2.0]*octa*-1(6),2,4-*triene*-7-*carbonitrile* **10**.—To a stirred solution of sodium amide [prepared from Na (3.62 g, 157.3 mmol) in liquid NH_3 (500 cm^3)] was added a solution of the nitrile **9** (5 g, 19.7 mmol) in THF (30 cm^3) at −78 °C and the reaction mixture was stirred for 25 min at the same temperature. After addition of NH_4Cl (15 g, 280.4 mmol), liquid NH_3 was evaporated off to give a residue. The product was extracted with benzene, and the organic layer was washed with brine and then dried (Na_2SO_4). Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using benzene as eluent to afford the *title compound* **10** (3.08 g, 90.3%) as an inseparable diastereoisomeric mixture (1.7:1), a colourless oil; $\nu_{max}(CHCl_3)$/cm^{-1} 2250; major product: δ_H 1.56 (3 H, d, J 7.3, Me), 3.79 (3 H, s, OMe), 3.81–3.94 (1 H, m, C*H*Me), 4.31 (1 H, d, J 6.1, CHCN), 6.69 (1 H, s, 2-H), 6.84 (1 H, d, J 8.5, 4-H) and 7.13 (1 H, d, J 8.5, 5-H); minor product: δ_H 1.50 (3 H, d, J 7.3, Me) and 3.64 (1 H, d, J 1.8, CHCN); m/z 173 (M^+) (Found: M^+, 173.0836. $C_{11}H_{11}NO$ requires M, 173.0839).

3-*Methoxy*-8-*methylbicyclo*[4.2.0]*octa*-1(6),2,4-*triene*-7-*carboxylic Acid* **11**.—A mixture of the nitrile **10** (1.5 g, 8.67 mmol) and potassium hydroxide (1.9 g, 34.68 mmol) in EtOH (15 cm^3) and water (15 cm^3) was refluxed for 3 h. Evaporation of the solvent gave a residue, which was poured into water. The aqueous layer was washed with benzene and then acidified with 10% HCl. The product was extracted with AcOEt. The organic layer was washed with brine, dried (Na_2SO_4) and evaporated to give a residue, which was purified by column chromatography on silica gel using hexane–AcOEt (60:40, v/v) as eluent to afford the *title compound* **11** (1.54 g, 92.8%) as an inseparable diastereoisomeric mixture (5:1), colourless prisms, m.p. 97.5–98.5 °C; $\nu_{max}(CHCl_3)$/cm^{-1} 3150 and 1700; major product: δ_H 1.48 (3 H, d, J 6.7, Me), 3.78 (3 H, s, OMe), 6.70 (1 H, d, J 2.4, 2-H), 6.79 (1 H, dd, J 2.4 and 7.9, 4-H) and 7.09 (1 H, d, J 7.9, 5-H); minor product: δ_H 1.39 (3 H, d, J 7.3, Me) and 3.75 (3 H, s, OMe); m/z 192 (M^+) (Found: M^+, 192.0784. $C_{11}H_{12}O_3$ requires M, 192.0785).

7-Acetoxy-3-methoxy-8-methylbicyclo[4.2.0]*octa*-1(6),2,4-*triene* **12**.—A mixture of the carboxylic acid **11** (2.59 g, 13.5 mmol), lead tetraacetate (10.6, 21.6 mmol), and AcOH (8 cm^3, 140 mmol) in THF (40 cm^3) was stirred for 30 min at room temperature, and then ethylene glycol (586 mg, 9.45 mmol) was added. After being stirred for 30 min, the reaction mixture was filtered and the filtrate concentrated to give a residue, which was taken up with AcOEt. The organic layer was washed with brine, dried (Na_2SO_4) and evaporated to give a residue, which was purified by column chromatography on silica gel using benzene as eluent to afford the *title compound* **12** (2.59 g, 92.9%) as an inseparable diastereoisomeric mixture (4:1), a colourless oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 1730; major product: δ_H 1.45 (3 H, d, *J* 6.7, Me), 2.10 (3 H, s, MeCO), 3.40–3.53 (1 H, m, C*H*Me), 3.79 (3 H, s, OMe), 5.33 (1 H, d, *J* 1.2, C*H*OAc), 6.70 (1 H, d, *J* 1.8, 2-H), 6.80 (1 H, dd, *J* 1.8 and 7.9, 4-H) and 7.16 (1 H, d, *J* 7.9, 5-H); minor product: δ_H 1.29 (3 H, d, *J* 6.7, Me), 2.12 (3 H, s, MeCO), 3.83–3.9 (1 H, m, C*H*Me) and 5.91 (1 H, d, *J* 4.3, C*H*OAc); *m/z* 206 (M^+) (Found: M^+, 206.0938. $C_{12}H_{14}O_3$ requires *M*, 206.0941).

3-Methoxy-8-methylbicyclo[4.2.0]*octa*-1(6),2,4-*trien*-7-*ol* **13**.—A mixture of the acetate **12** (2.58 g, 12.5 mmol) and potassium carbonate (2.07 g, 15 mmol) in MeOH (70 cm^3) and water (7 cm^3) was stirred for 3 h at room temperature. Evaporation of the solvent gave the residue, which was extracted with AcOEt. The organic layer was washed with brine, dried (Na_2SO_4) and evaporated to give a residue, which was purified by column chromatography on silica gel using hexane–AcOEt (80:20, v/v) as eluent to afford the *alcohol* **13** (1.92 g, 93.4%) as an inseparable diastereoisomeric mixture (4:1), a colourless oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 3300; major product: δ_H 1.39 (3 H, d, *J* 6.7, Me), 3.27 (1 H, q, *J* 6.7, C*H*Me), 3.79 (3 H, s, OMe), 4.66 (1 H, d, *J* 6.7, C*H*OH), 6.70 (1 H, d, *J* 2.4, 2-H), 6.78 (1 H, dd, *J* 1.8 and 7.9, 4-H) and 7.14 (1 H, d, *J* 7.9, 5-H); minor product: δ_H 1.29 (3 H, d, *J* 7.3, Me); *m/z* 164 (M^+) (Found: M^+, 164.0838. $C_{10}H_{12}O_2$ requires *M*, 164.0838).

3-Methoxy-8-methylbicyclo[4.2.0]*octa*-1(6),2,4-*trien*-7-*one* **14**.—To a stirred solution of oxalyl chloride (1.11 cm^3, 12.78 mmol) in CH_2Cl_2 (40 cm^3) was added dropwise a solution of DMSO (1.82 cm^3, 25.6 mmol) in CH_2Cl_2 (40 cm^3) at −50 °C and the mixture was stirred for 2 min. A solution of the alcohol **13** (1.91 g, 11.63 mmol) in CH_2Cl_2 (10 cm^3) was added and stirring was continued for 15 min at −50 °C. Et_3N (8.1 cm^3, 58.15 mmol) was added and the reaction mixture was allowed to warm to room temperature. Water was added and the product was extracted with AcOEt. The organic layer was washed with brine, dried (Na_2SO_4) and evaporated to give a residue, which was purified by column chromatography on silica gel using hexane–AcOEt (90:10, v/v) as eluent to afford the *ketone* **14** (1.73 g, 91.8%) as a pale yellow oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 1740; δ_H 1.4 (3 H, d, *J* 7, Me), 3.8 (3 H, s, OMe), 4.1 (1 H, q, *J* 7, CHMe) and 6.7–7.4 (3 H, m, ArH); *m/z* 162 (M^+) (Found: M^+, 162.0680. $C_{10}H_{10}O_2$ requires *M*, 162.0680).

Methyl 2-Cyano-3-(m-methoxyphenyl)crotonate **15**.—A solution of *m*-methoxyacetophenone (1 g, 6.66 mmol), methyl cyanoacetate (729 mg, 7.36 mmol), benzylamine (71 mg, 0.66 mmol), and acetic acid (0.33 cm^3, 5.76 mmol) in benzene (60 cm^3) was refluxed for 10 h using a Dean–Stark apparatus. The benzene solution was washed with 10% HCl, saturated aqueous $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4) and evaporated to give a residue, which was purified by column chromatography on silica gel using hexane–AcOEt (94:6, v/v) as eluent to afford the *crotonate* **15** (1.38 g, 90.2%) as colourless needles, m.p. 92.5–94 °C (Found: C, 67.5; H, 5.7; N, 6.0. $C_{13}H_{13}NO_3$ requires C, 67.5; H, 5.65; N, 6.05%); $\nu_{max}(CHCl_3)/cm^{-1}$ 2230 and 1740; δ_H 2.55 and 2.70 (3 H, each s, Me), 3.70, 3.83, 3.87 and 3.92 (3 H, × 2, each s, OMe and CO_2Me) and 6.70–7.60 (4 H, m, ArH); *m/z* 231 (M^+) (Found: M^+, 231.0886. $C_{13}H_{13}NO_3$ requires *M*, 231.0894).

Methyl 2-Cyano-3-(m-methoxyphenyl)-3-methylbutyrate **16**.—To a stirred solution lithium dimethylcuprate [prepared from CuI (8.1 g, 42.53 mmol) and MeLi (1.4 mol dm^{-3}; 56.6 cm^3, 79.24 mmol) in ether] was added dropwise a solution of the crotonate **15** (7 g, 30.3 mmol) in ether (50 cm^3) at −25 °C. The reaction mixture was stirred for 2 h at the same temperature and allowed to warm gradually to 0 °C. After addition of brine, the product was extracted with AcOEt. The organic layer was washed with brine, dried (Na_2SO_4) and evaporated to give a residue, which was purified by column chromatography on silica gel using hexane–AcOEt (95:5, v/v) as eluent to afford the *butyrate* **16** (7.63 g, 95.3%) as a colourless oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 2250 and 1740; δ_H 1.56 (6 H, s, Me × 2), 3.53 (3 H, s, CO_2Me), 3.67 (1 H, s, CHCN), 3.77 (3 H, s, OMe) and 6.63–7.37 (4 H, m, ArH); *m/z* 247 (M^+) (Found: M^+, 247.1205. $C_{14}H_{17}NO_3$ requires *M*, 247.1206).

3-(m-Methoxyphenyl)-3-methylbutyronitrile **18**.—A solution of the ester **16** (26.49 g, 107.1 mmol) and KOH (6 g, 107.1 mmol) in EtOH (107 cm^3) and 1,4-dioxane (107 cm^3) was refluxed for 10 h. The solvent was evaporated to give an oil, which was dissolved in water. The water layer was washed with benzene and acidified with 10% HCl. The product was extracted with AcOEt and the organic layer washed with brine, dried (Na_2SO_4) and evaporated to give the carboxylic acid **17**. A solution of the crude product **17** in *N,N*-dimethylacetamide (200 cm^3) was heated at 150 °C for 2 h. Evaporation of the solvent gave an oil, which was dissolved in benzene. The organic layer was washed with brine, dried (Na_2SO_4) and evaporated to give a residue, which was purified by column chromatography on silica gel using hexane–AcOEt (95:5, v/v) as eluent to afford the *nitrile* **18** (17.05 g, 84.1%) as a colourless oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 2250; δ_H 1.50 (6 H, s, 2 × Me), 2.57 (2 H, s, CH_2), 3.77 (3 H, s, OMe) and 6.60–7.33 (4 H, m, ArH); *m/z* 189 (M^+) (Found: M^+, 189.1152. $C_{12}H_{15}NO$ requires *M*, 189.1152).

3-(2-Bromo-5-methoxyphenyl)-3-methylbutyronitrile **19**.—To a stirred suspension of the nitrile **18** (5.85 g, 30.93 mmol) and NaOAc (5.07 g, 61.8 mmol) in $CHCl_3$ (100 cm^3) was added dropwise a solution of bromine (1.75 cm^3, 33.97 mmol) in $CHCl_3$ (50 cm^3) at 0 °C over 5 h. Stirring was continued for 8 h at ambient temperature and then the mixture was poured into water. The product was extracted with $CHCl_3$, and the organic layer was washed with saturated aqueous $Na_2S_2O_3$ and brine and then dried (Na_2SO_4). Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using hexane–AcOEt (95:5, v/v) as eluent to afford the *bromide* **19** (6.66 g, 80.4%) as a yellow oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 2250; δ_H 1.65 (6 H, s, 2 × Me), 3.10 (2 H, s, CH_2), 3.79 (3 H, s, OMe), 6.57 (1 H, dd, *J* 3 and 8, 4-H), 6.93 (1 H, d, *J* 3, 6-H) and 7.34 (1 H, d, *J* 8, 3-H); *m/z* 269 ($M^+ + 2$), 267 (M^+) (Found: M^+, 267.0254. $C_{12}H_{15}BrNO$ requires *M*, 267.0259).

3-Methoxy-8,8-dimethylbicyclo[4.2.0]*octa*-1(6),2,4-*triene*-7-*carbonitrile* **20**.—To a stirred solution of sodium amide [prepared from Na (13.7 g, 595 mmol) in liquid NH_3 (2 dm^3)] was added a solution of the nitrile **19** (20 g, 74.6 mmol) in THF (100 cm^3) at −78 °C and the reaction mixture was stirred for 40 min at the same temperature. After addition of NH_4Cl (70 g, 1.3 mol), liquid NH_3 was evaporated to give a residue. This was extracted with benzene, and the extract washed with brine, dried (Na_2SO_4), and evaporated to give a residue. This was purified

by column chromatography on silica gel using hexane–AcOEt (95:5, v/v) as eluent to afford the *title compound* **20** (8.82 g, 63.1%) as a colourless oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 2220; δ_H 1.48 (3 H, s, Me), 1.53 (3 H, s, Me), 3.75 (3 H, s, OMe), 6.62 (1 H, d, *J* 2.4, 2-H), 6.78 (1 H, dd, *J* 2.4 and 7.9, 4-H) and 7.11 (1 H, d, *J* 7.9, 5-H); *m/z* 187 (M^+) (Found: M^+, 187.0998. $C_{12}H_{13}NO$ requires *M*, 187.0998).

7-(3,3-*Ethylenedioxy*-1-*hydroxybutyl*)-3-*methoxy*-8,8-*dimethylbicyclo*[4.2.0]*octa*-1(6),2,4-*triene*-7-*carbonitrile* **21**.—To a stirred solution of lithium diisopropylamide [prepared from diisopropylamine (6.5 cm^3, 46.1 mmol) and BuLi (1.6 mol dm^{-3}; 28.8 cm^3, 46.1 mmol) in hexane] in THF (80 cm^3) was added a solution of the nitrile **20** (6.6 g, 35.5 mmol) in THF (20 cm^3) at −78 °C and stirring was continued for 1 h at the same temperature. A solution of 3,3-ethylenedioxybutyraldehyde (6 g, 46.1 mmol) in THF (20 cm^3) was added dropwise to the mixture at the same temperature and the reaction mixture was stirred for 1 h at −78 °C. After quenching with saturated aqueous NH_4Cl the solvent was removed to give a residue, which was taken up with AcOEt. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated to give a residue. This was purified by column chromatography on silica gel using hexane–AcOEt (85:15, v/v) as eluent to afford the *title compound* **21** (9.38 g, 83.4%) as an inseparable diastereoisomeric mixture (9:1), colourless needles, m.p. 155–156 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3400 and 2220; major product: δ_H 1.39 (3 H, s, Me), 1.59 (3 H, s, Me), 1.65 (3 H, s, Me), 2.17 (1 H, dd, *J* 1.8 and 10.4, CH*H*), 2.33 (1 H, dd, *J* 10.4 and 14.0, C*H*H), 3.79 (3 H, s, OMe), 3.97–4.06 [4 H, m, $O(CH_2)_2O$], 4.10 (1 H, ddd, *J* 1.2, 1.8 and 10.4, C*H*OH), 6.67 (1 H, d, *J* 2.4 2-H), 6.79 (1 H, dd, *J* 2.4 and 8.6, 4-H) and 7.09 (1 H, d, *J* 8.6, 5-H); minor product: δ_H 1.43 (3 H, s, Me), 1.61 (3 H, s, Me), 2.01 (1 H, d, *J* 14.7, CH*H*) and 2.26 (1 H, dd, *J* 10.8 and 14.7, C*H*H); *m/z* 317 (M^+) (Found: M^+, 317.1626. $C_{18}H_{23}NO_4$ requires *M*, 317.1626).

7-(1-*Hydroxy*-3-*oxobutyl*)-3-*methoxy*-8,8-*dimethylbicyclo*-[4.2.0]*octa*-1(6),2,4-*triene*-7-*carbonitrile* **22**.—A solution of the ketal **21** (200 mg, 0.63 mmol) in 5% aqueous acetone (10 cm^3) containing a catalytic amount of toluene-*p*-sulphonic acid was refluxed for 2 h. Removal of the solvent gave the residue which was extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated to give a residue. This was purified by column chromatography on silica gel using hexane–AcOEt (80:20, v/v) as eluent to afford the *ketone* **22** (172 mg, 100%) as an inseparable diastereoisomeric mixture (9:1), colourless crystals, m.p. 108–109 °C (Found: C, 70.3; H, 7.05; N, 5.1. $C_{16}H_{19}NO_3$ requires C, 70.3; H, 7.0; N, 5.15%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3500 and 2240; major product: δ_H 1.58 (3 H, s, Me), 1.65 (3 H, s, Me), 2.26 (3 H, s, Me), 2.94 (1 H, dd, *J* 1.8 and 17.7, CH*H*), 3.12 (1 H, dd, *J* 10.4 and 17.7, C*H*H), 3.39 (1 H, d, *J* 3.1, OH), 3.78 (3 H, s, OMe), 4.33 (1 H, ddd, *J* 1.8, 3.1 and 10.4, C*H*OH), 6.67 (1 H, d, *J* 2.4, 2-H), 6.79 (1 H, dd, *J* 2.4 and 7.5, 4-H) and 7.09 (1 H, d, *J* 7.5, 5-H); minor product: δ_H 1.62 (3 H, s, Me), 2.74 (1 H, dd, *J* 1.9 and 18.9, CH*H*), 3.41 (1 H, d, *J* 5.4, OH), 6.65 (1 H, d, *J* 2.4, 2-H), 6.82 (1 H, dd, *J* 2.4 and 7.4, 4-H) and 7.29 (1 H, d, *J* 7.4, 5-H); *m/z* 273 (M^+) (Found: M^+, 273.1372. $C_{16}H_{19}NO_3$ requires *M*, 273.1366).

3-*Methoxy*-8,8-*dimethyl*-7-(1-*methylthiomethoxy*-3-*oxobutyl*)*bicyclo*[4.2.0]*octa*-1,3,5-*triene*-7-*carbonitrile* **23**.—A solution of the alcohol **22** (172 mg, 0.63 mmol), Ac_2O (1.65 cm^3, 17.5 mmol), and AcOH (0.5 cm^3, 8.7 mmol) in DMSO (25 cm^3) was stirred for 48 h at room temperature. The reaction mixture was poured into a mixed solvent of AcOEt and saturated aqueous $NaHCO_3$ solution, and the resulting mixture was stirred for 1 h. The product was extracted with AcOEt and the organic layer was washed with brine and dried (Na_2SO_4). Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using hexane–AcOEt (85:15, v/v) as eluent to afford the *ether* **23** (198 mg, 94.3%) as an inseparable diastereoisomeric mixture (9:1), colourless crystals, m.p. 122.5–123 °C (Found: C, 64.9; H, 7.0; N, 4.2. $C_{18}H_{23}NO_3S$ requires C, 64.85; H, 6.95; N, 4.2%); $\nu_{max}(CHCl_3)/cm^{-1}$ 2200 and 1710; major product: δ_H 1.56 (3 H, s, Me), 1.63 (3 H, s, Me), 2.19 (3 H, s, COMe), 2.29 (3 H, s, SMe), 2.94 (1 H, dd, *J* 2.4 and 17.7, CH*H*), 3.30 (1 H, dd, *J* 7.3 and 17.7, C*H*H), 3.78 (3 H, s, OMe), 4.51 (1 H, dd, *J* 2.4 and 7.3, CHO), 4.66 (2 H, dd, *J* 9.9 and 11.6, OCH_2S), 6.67 (1 H, d, *J* 1.8, 2-H), 6.77 (1 H, dd, *J* 1.8 and 8.6, 4-H) and 7.03 (1 H, d, *J* 8.6, 5-H); minor product: δ_H 2.14 (3 H, s, COMe), 2.27 (3 H, s, SMe) and 3.79 (3 H, s, OMe); *m/z* 333 (M^+) (Found: M^+, 333.1397. $C_{18}H_{23}NO_3S$ requires *M*, 333.1397).

7-(3-*Hydroxy*-1-*methylthiomethoxy*-3-*oxobutyl*)-3-*methoxy*-8,8-*dimethylbicyclo*[4.2.0]*octa*-1(6),2,4-*triene*-7-*carbonitrile* **24**.—To a stirred solution of the ketone **23** (1.4 g, 4.2 mmol) in MeOH (20 cm^3) was added sodium borohydride (160 mg, 4.2 mmol) at 0 °C, and the reaction mixture was stirred for 1 h. After addition of 10% HCl, the product was isolated by AcOEt extraction. The organic layer was washed with brine, dried (Na_2SO_4) and evaporated to give a residue. This was purified by column chromatography on silica gel using hexane–AcOEt (80:20, v/v) as eluent to afford the *alcohol* **24** (1.2 g, 85.1%) as an inseparable diastereoisomeric mixture, colourless crystals, m.p. 92.5–94 °C (Found: C, 64.5; H, 7.6; N, 4.15. $C_{18}H_{25}NO_3S$ requires C, 64.45; H, 7.5; N, 4.2%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3550 and 2250; major product: δ_H 1.27 and 1.29 (3 H, each d, *J* 6.1, Me), 1.57 (3 H, s, Me), 1.64 and 1.65 (3 H, each s, Me), 1.85–2.2 (2 H, m, CH_2), 2.2 and 2.23 (3 H, each s, SMe), 3.78 (3 H, s, OMe), 4.05–4.29 (2 H, m, C*H*OH and C*H*OMOM), 4.65–4.83 (2 H, m, OCH_2S) and 6.65–7.13 (3 H, m, ArH); minor product: δ_H 1.59 (3 H, s, Me), 3.81 (3 H, s, OMe) and 6.69 and 6.7 (1 H, each s, ArH); *m/z* 335 (M^+).

7-(3-*Hydroxybutyl*)-8,8-*dimethylbicyclo*[4.2.0]*oct*-1(6)-*en*-3-*one* **25**.—To a stirred solution of the nitrile **24** (1 g, 3 mmol) in liquid NH_3 (100 cm^3), THF (20 cm^3) and EtOH (1.75 cm^3) was added sodium metal (688 mg, 30 mmol) at −78 °C. The mixture was stirred at the same temperature for a further 30 min and MeOH was added to the mixture to decompose the excess of sodium metal. Evaporation of the solvent gave a residue, which was extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4), and evaoporated to give a residue, which was used for the next reaction. A solution of the crude product in THF (18 cm^3) and water (2 cm^3) containing a catalytic amount of toluene-*p*-sulphonic acid was stirred at room temperature for overnight. The mixture was basified with saturated aqueous $NaHCO_3$ and evaporated to give a residue, which was extracted with CH_2Cl_2. The organic layer was washed with brine, dried (Na_2SO_4) and evaporated to give a residue. This was purified by column chromatography on silica gel using hexane–AcOEt (80:20, v/v) as eluent to afford the *enone* **25** (493 mg, 74.3%) as an inseparable diastereoisomeric mixture (1:1), colourless oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 3400 and 1680; δ_H 1.06 (3 H, s, Me), 1.16 (3 H, s, Me), 1.21 and 1.22 (3 H, each d, *J* 6.2, Me), 2.76 (2 H, m, $COCH_2$) and 3.81 (1 H, m, C*H*OH); *m/z* 222 (M^+) (Found: M^+, 222.1619. $C_{14}H_{22}O_2$ requires *M*, 222.1619).

2,6,6-*Trimethyltricyclo*[5.4.0.$0^{1,5}$]*undec*-7-*en*-9-*one* **27**.—To a stirred solution of the alcohol **25** (817 mg, 3.7 mmol) and Et_3N (0.77 cm^3, 5.5 mmol) in CH_2Cl_2 (50 cm^3) was added methanesulphonyl chloride (0.43 cm^3, 5.5 mmol) at −78 °C and then the mixture was stirred for 10 min. It was then poured into water and the product extracted with CH_2Cl_2. The extract was

washed with brine, dried (Na_2SO_4) and evaporated to give a residue. This was used for the next reaction without purification. A solution of the crude mesylate **26** in HMPA (30 cm^3) was added to a stirred suspension of Bu^{t}OK (1 g, 8.9 mmol) in HMPA (30 cm^3) at room temperature and the mixture was stirred for an additional 30 min. The reaction mixture was poured into ice-cold water and extracted with benzene. The extract was washed with brine, dried (Na_2SO_4) and evaporated to give a residue. This was purified by column chromatography on silica gel using hexane–AcOEt (95:5, v/v) as eluent to afford the *enone* **27** (164 mg, 22.1%) as an inseparable diastereoisomeric mixture (4:1), colourless oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 1640; major product: δ_H 1.09 (3 H, d, *J* 6.8, Me), 1.19 (3 H, s, Me), 1.25 (3 H, s, Me), 2.62–2.68 (2 H, m, CH_2) and 5.85 (1 H, s, C*H*CO); minor product: δ_H 1.06 (3 H, d, *J* 7.1, Me), 1.21 (3 H, s, Me), 1.27 (3 H, s, Me), 2.62–2.68 (2 H, m, CH_2) and 5.73 (1 H, s, C*H*CO); *m/z* 204 (M^+) (Found: M^+, 204.1515. $C_{14}H_{20}O$ requires *M*, 204.1514).

Italicene **1** *and Isoitalicene* **2**.—To a blue solution of lithium metal (204 mg, 2.9 mmol) in liquid NH_3 (20 cm^3) was added dropwise a solution of the enone **27** (100 mg, 0.5 mmol) and Bu^{t}OH (0.09 cm^3, 0.98 mmol) in THF (2 cm^3). After being kept at the same temperature for 20 min, the mixture was treated with isoprene (0.196 cm^3, 1.96 mmol) until the blue colour disappeared. Ammonia was evaporated and the residue was dissolved in THF. To the mixture was added *N*-phenyltrifluoromethanesulphonimide (350 mg, 0.98 mmol) at 0 °C and stirring was continued for 24 h at room temperature. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4) and evaporated to give a residue. This was used for the next reaction without purification. To a stirred solution of lithium dimethylcuprate [prepared from CuI (327 mg, 1.72 mmol) and MeLi (1.4 mol dm^{-3}; 1.75 cm^3, 2.45 mmol) in ether] in THF (4 cm^3) was added dropwise a solution of the enol triflate in THF (2 cm^3) at −15 °C. The reaction mixture was stirred for 8 h at the room temperature and poured into saturated aqueous NH_4Cl. The product was extracted with ether and the extract was washed with brine, dried (Na_2SO_4) and evaporated to give a residue, which was purified by HPLC using hexane as eluent to afford a mixture of italicene **1** and isoitalicene **2** (30 mg, 30.0%) as an inseparable diastereoisomeric mixture (1:4), colourless oil; for italicene: δ_H 0.77 (3 H, d, *J* 6.7, Me), 0.96 (3 H, s, Me), 1.71 (3 H, s, Me) and 5.32 (1 H, m, 3-H); for isoitalicene: δ_H 0.82 (3 H, d, *J* 6.1, Me), 0.89 (3 H, s, Me), 0.90 (3 H, s, Me), 1.72 (3 H, s, Me) and 5.38 (1 H, m, 3-H); *m/z* 204 (M^+) (Found: M^+, 204.1881. $C_{15}H_{24}$ requires *M*, 204.1879).

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References

1 J. Leimmer, H. Marshall, N. Meier and P. Weyerstahl, *Chem. Lett.*, 1984, 1769.
2 T. Kametani, T. Toya, K. Ueda, M. Tsubuki and T. Honda, *J. Chem. Soc., Perkin Trans. 1*, 1988, 2433.
3 E. Piers and M. Zbozny, *Can. J. Chem.*, 1979, **57**, 2249; T. Kametani, T. Toya, M. Tsubuki and T. Honda, *Chem. Pharm. Bull.*, 1986, **34**, 3169.
4 T. Kametani, H. Nemoto, H. Ishikawa, H. Matsumoto and K. Fukumoto, *J. Am. Chem. Soc.*, 1977, **99**, 3461.
5 A. J. Mancuso, S.-L. Huang and D. Swern, *J. Org. Chem.*, 1978, **43**, 2480.
6 M. Tomita, S. Minami and S. Ueo, *J. Chem. Soc., Chem. Commun.*, 1969, 183; R. V. Stevens and G. S. Bisacci, *J. Org. Chem.*, 1982, **47**, 2393.
7 J. T. Gupton, D. Zembower and J. Miller, *Synth. Commun.*, 1988, **18**, 1891.
8 J. A. Marshall and L. J. Karas, *J. Am. Chem. Soc.*, 1978, **100**, 3615.
9 T. Kametani, H. Nemoto, M. Tsubuki, G.-E. Purvaneckas, M. Aizawa and M. Nishiuchi, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2830; T. Kametani, M. Chihiro, T. Honda and K. Fukumoto, *Chem. Pharm. Bull.*, 1980, **28**, 2468.
10 P. A. Brown and P. R. Jenkins, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1303; N. Harada, T. Sugioka, Y. Ando, H. Uda and T. Kuriki, *J. Am. Chem. Soc.*, 1988, **110**, 8483; J. W. Huffman, X. Zhang, M. J. Wu and H. H. Joyner, *J. Org. Chem.*, 1989, **54**, 4741.
11 J. E. McMurry and W. J. Scott, *Tetrahedron Lett.*, 1983, **24**, 979.

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