Stereocontrolled total synthesis of (±)-tochuinyl acetate and facile total synthesis of (±)-α-cuparenone and (±)-cuparene

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Dedicated to Professor (Mrs.) A. Chatterjee on the occasion of her 85th birthday
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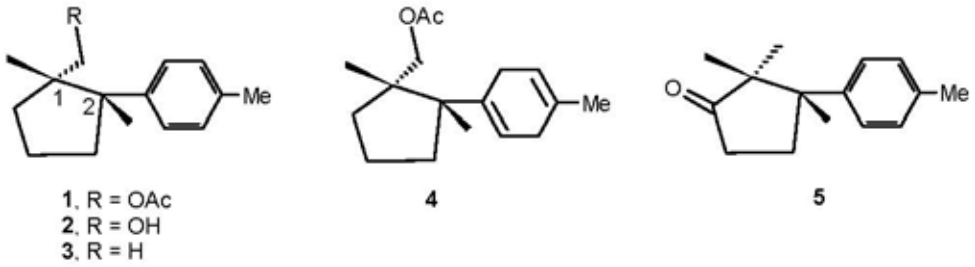
Abstract
A stereocontrolled total synthesis of (±)-tochuinyl acetate has been successfully accomplished involving intramolecular cyclisation of methyl 3-methyl-3-*p*-tolyl-6-bromohexanoate and in situ methylation of the resulting cyclopentanecarboxylate as the key reaction. A total synthesis of (±)-α-cuparenone has been achieved using α, α -dimethylation of methyl 3-methyl-3-*p*-tolyl-6,6-ethylenedioxyhexanoate as a key step.

Keywords: Conjugate addition, intramolecular cyclisation, alkylation of ester enolates, marine sesquiterpenes, α -cuparenone

Introduction

Cuparane and isocuparane sesquiterpenes possessing sterically crowded cyclopentane moieties belong to an expanding family of sesquiterpenes and have become popular synthetic targets in recent years, as some members exhibit interesting biological activities. Tochuinyl acetate 1, a cuparene-type sesquiterpene, was isolated[1] by Andersen and Williams, along with dihydrotochuinyl acetate **4**, from the skin extracts of the dendronotid nudibranch *Tochuina tetraquetra,* collected from Port Hardy, British Columbia. Subsequently, the acetates **1** and **4** were also isolated[1] from the extracts of the soft coral *Gersemia rubiformis,* which was found to be a feed for *T. tetraquetra*. The presence of a sterically congested cyclopentane ring with stereogenic quaternary centres at C-1 and C-2 makes the acetate **1** an interesting synthetic target. The related sesquiterpene ketone α -cuparenone **5** was first isolated[2] by Dev et al. from the essential oil of *Thuja orientalis.* Subsequently, **5** was also isolated[3] from the liverwort *Mannia fragrans* and its presence was detected in a number of essential oils. The total synthesis of naturally occurring sesquiterpenes containing 1,1,2-trisubstituted-2-arylcyclopentane ring system

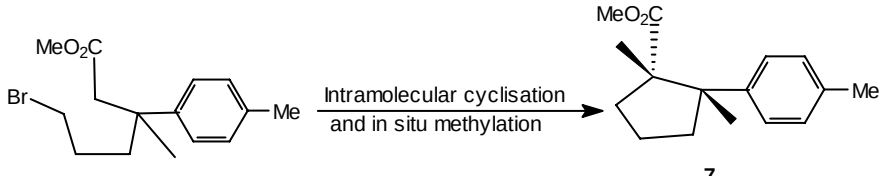


1, R = OAc
2, R = OH
3, R = H

4 **5**

Figure 1

has been an active area of research in recent times and current interest in sesquiterpenes **1**[4] and **5**[5] (Figure 1) is reflected in a number of diverse synthetic approaches to these compounds. The synthesis of these sesquiterpenes is associated with the difficulty in the generation of two adjacent quaternary carbon atoms at C-1 and C-2 on a cyclopentane ring and a substitued aromatic ring at C-2. The first synthesis of (±)-**1** was accomplished by Ishibashi *et al.*[6] using a thiochromane approach, and later Taber and coworkers[7] synthesised (±)-**1** involving rhodium catalysed intramolecular C-H insertion of a diazo ketone as a key step. Srikrishna *et al*.[8] reported the total syntheses of (±)-**1** and (±)-**4** involving cyclopentenone annulation of *p*-methoxyacetophenone via a Claisen rearrangement-Wacker oxidation sequence to generate 5-methyl-5-*p*-tolylcyclopent-2-en-1-one as a key intermediate to **1**. Very recently, Srikrishna and co-workers achieved[4] the synthesis of (±)-**1** employing a ring-closing metathesis reaction based methodology. In order to generate 1,1,2,2-tetrasubstitutedcyclopentane ring system related to the sesquiterpene **1**, we envisaged that an intramolecular cyclisation of methyl 3-methyl-3-*p*-tolyl-6-bromohexanoate **6** in the presence of base and in situ methylation of the resulting cyclopentanecarboxylate from the less hindered side would stereoselectively generate, in one step, *cis*-1,2-dimethyl-1-methoxycarbonyl-2-*p*-tolylcyclopentane **7** as a key intermediate to **1**, as shown in Scheme 1. Based on this approach, we have successfully accomplished a highly



6 **7**

Scheme 1

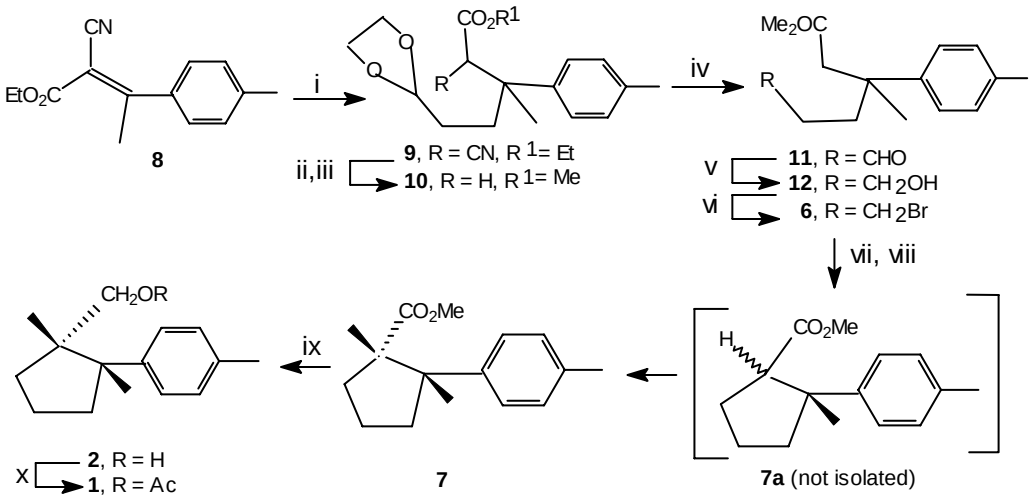
Scheme 1

stereoselective total synthesis of (±)-**1**. The present method may be easily adapted for the synthesis of several other bicyclic sesquiterpenes of the cuparane and isocuparane (herbertane) family. Since Birch reduction of the alcohol **2** and subsequent acetylation provides[8] (±)-

dihydrotochuinyl acetate **4** in high yield, the present work also constitues a formal total synthesis of (±)-**4**. We have also achieved facile total synthesis of (±)-α -cuparenone **5** and (±)-cuparene **3** involving one pot α, α -dimethylation of methyl 3-methyl-3-*p*-tolyl-6,6-ethylenedioxyhexanoate **10** as a key step (Scheme 3).

Results and Discussion

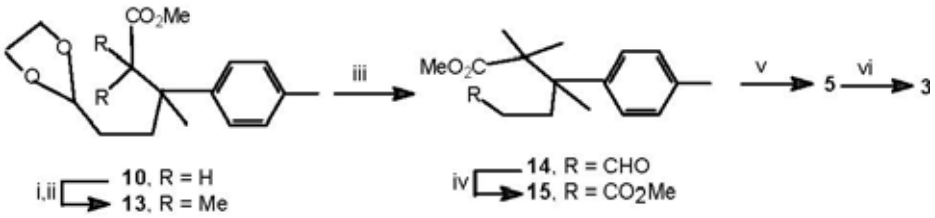
Our synthesis of (±)-tochuinyl acetate **1** is outlined in Scheme **2**. The first quaternary carbon atom was created through conjugate addition to the unsaturated cyanoester **8**.[9] Thus, conjugate addition of 3,3-ethylenedioxypropylmagnesium bromide[10] to the unsaturated cyanoester **8** in the presence of $CuBr.S(CH_3)_2$ provided **9** which was contaminated with **8** (ca. 33%). Separation of **9** from **8** was effected by a simple procedure. The mixture was treated with calculated quantity of the sodium salt of cyanoacetamide in EtOH at room tmperature for several hours. On dilution with water, **8** was removed completely as a water soluble salt[11] and the desired conjugate addition product **9** was recovered in a pure state in 58% overall yield. Hydrolysis of **9** with KOH in refluxing ethylene glycol : water (4:1) followed by decarboxylation and esterification afforded the ester **10** in 75% yield. Deacetalisation of **10** followed by reduction of the resulting aldehyde **11** with $NaBH_4$ afforded the primary alcohol **12** (83%) which was treated with PBr_3 to give the bromoester **6** in 74% yield. The bromoester **6** was converted into the cyclopentanecarboxylate **7** (85%) in a one pot process involving an intramolecular cyclisation of **6** by treatment with LDA (1.2 equiv.) in THF and HMPA at –70°C followed by alkylation with MeI at 0°C in the presence of LDA (1.6 equiv.) and HMPA (2 equiv.), without isolating the initial cyclised product **7a.** The second quaternary carbon atom was thus generated very efficiently and in a stereoselective manner, highlighting the potential of the present method. High stereoselectivity observed in the transformation of **6** into **7** is due to methylation taking place from the less hindered side of the intermediate enolate of the ester **7a**. In the ^{1}H NMR spectrum of **7**, the ester methyl signal appeared at δ 3.25 ppm indicating shielding of the methoxycarbonyl group by the vicinal *cis* aryl group.



Scheme 2. *Reagents and conditions*: (i), 3,3-ethylenedioxypropylmagnesium bromide,[10] CuBr.Me_2S, THF, Et_2O, 0 to 25^{0}C; (ii), KOH, $HOCH_2CH_2OH$, H_2O, reflux, AcOH, 0 °C; (iii), CH_2N_2, Et_2O, 0^{o}C; (iv), AcOH-H_2O (4:1), 25 to 60^{o}C; (v), $NaBH_4$, MeOH, 0 to 25^{o}C; (vi), PBr_3, C_6H_6, 0 to 70^{o}C; (vii), LDA (1.2 equiv.), THF, HMPA (1.5 equiv.), -70^{o}C; (viii), LDA (1.6 equiv.), HMPA (2 equiv.), THF, 0^{o}C, MeI, 0^{o}C; (ix), LAH, Et_2O, reflux; (x), Ac_2O, C_5H_5N, 25^{o}C.

The stereostructure **7** of the ester, as shown in Scheme 2, was further confirmed by conversion of **7**, which is suitably functionalised, into (±)-tochuinyl acetate **1**. Thus, reduction of **7** with $LiAlH_4$ followed by acetylation of the resulting alcohol **2** furnished (±)-**1** in 74% overall yield. The spectral data of synthetic **1** were identical with those of the natural product.

For the synthesis of α-cuparenone **5**, the acetal-ester **10** was used as an internediate. This was converted in high yield into the corresponding α,α -dimethylated ester **13** (Scheme 3) in a single step employing a sequential methylation of **10**. Thus, alkylation of **10** with MeI at –78 °C in the presence of LDA (1 equiv.) as the base yielded the corresponding monomethyl ester which without isolation was again alkylated with MeI at 0 °C in the presence of LDA (1.7 equiv.) and HMPA (2 equiv.) to give the α,α-dimethylated ester **13** in 88% yield. The second quaternary carbon atom of α-cuparenone **5** was thus generated in an extremely facile manner. Deacetalisation of **13** followed by oxidation of the resulting aldehyde **14** with Jones reagent and esterification with CH_2N_2 furnished the diester **15** in 74 % overall yield. The spectral characteristics of the compounds **13 -15** as revealed through their ^{1}H and ^{13} C NMR spectra were fully in accord with their structures.



Scheme 3. Reagents and conditions: (i), LDA (1 equiv.), THF, -20°C; MeI, HMPA, -78°C; (ii), LDA (1.7 equiv.), HMPA (2 equiv.), THF, 0°C; MeI, 0°C; (iii), AcOH-H_2O (4:1), 25-60°C; (iv), Jones reagent, Me_2CO, 0-25°C; CH_2N_2, Et_2O, 0°C; (v), *t*-BuOK, C_6H_6, reflux, then H_3O^+; DMSO, NaCl, 155°C; (vi), N_2H_4, N_2H_4.2HCl, $(HOCH_2CH_2)_2O$, 125°C; KOH, 210°C.

Dieckmann cyclisation of the diester **15** in the presence of *t*-BuOK followed by decarbomethoxylation of the resulting crude в-ketoester furnished (±)-α-cuparenone **5** in 75% yield. Huang-Minlon reduction of **5** yielded the parent hydrocarbon (±)-cuparene **3** (82%). The identities of our synthetic compounds **5** and **3** were secured through comparison of ^{1}H NMR and ^{13}C NMR data with those of authentic compounds.

In conclusion, we have achieved a stereoselective total synthesis of the marine sesquiterpene (±)-tochuinyl acetate involving intramolecular cyclisation of methyl 3-methyl-3-*p*-tolyl-6-bromohexanoate and in situ methylation of the resulting cyclopentanecarboxylate as the key reaction. A new total synthesis of (±)-α-cuparenone has been accomplished involving α,α-dimethylation of methyl 3-methyl-3-*p*-tolyl-6,6-ethylenedioxyhexanoate as a key step.

Experimental Section

General Procedures. The compounds described here are all racemates. IR spectra were recorded in thin film on Perkin-Elmer model PE 298 and Shimadzu FTIR- 8300 spectrophotometers. Unless otherwise stated, ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 300 MHz and 75 MHz respectively on a Bruker DPX-300 spectrometer with $SiMe_4$ as internal standard. Moisture sensitive reactions were carried out using standard syringe-septum technique. Anhydrous solvents were obtained by standard procedures. All solvent extracts were dried over anhydrous Na_2SO_4. Product purities were routinely checked by TLC. Ether refers to diethyl ether and light petroleum refers to the fraction of petroleum ether in the boiling point range 60 – 80^0 C.

Ethyl 2-cyano-3-methyl-3-(4-methylphenyl)-6,6-ethylenedioxyhexanoate (9). Copper bromide-dimethyl sulfide complex (0.8 g, 3.9 mmol) was added to a solution of the unsaturated cyanoester **8**[9] (3.5 g, 15 mmol) in anhydrous ether (15 mL) containing dry tetrahydrofuran (8 mL). The mixture was stirred at 0 °C for 10 min and then a solution of 3,3-ethylenedioxypropylmagnesium bromide[10] in tetrahydrofuran (15 mL) [prepared from

magnesium (0.51 g, 0.021 g-at.) and 3,3-ethylenedioxypropyl bromide (3.3 g, 18 mmol)] was added under nitrogen during 30 min with vigorous stirring. The mixture was further sitrred at 0 °C for 2 h and then allowed to stand at room temperature for 6 h. It was then cooled in an ice-bath, decomposed with saturated solution of ammonium chloride (50 mL) and extracted with ether (3x60 mL). The combined ethereal extract was washed with water (2x50 mL), dried and concentrated. The residue was evaporatively distilled at 174-176 °C (bath temperature)/0.2 mmHg to afford a colourless oil (4.5 g). From integration of the ^{1}H NMR signals, the oil was estimated to contain **9** and **8** in a ratio of 2:1. A solution of the oil (4.5 g) in EtOH (5 mL) was added under nitrogen to a stirred suspension of sodium salt of cyanoacetamide [prepared from EtONa (0.4 g, 5.88 mmol) and cyanoacetamide (0.5 g, 5.95 mmol)] in EtOH (8 mL). After 16 h at 25 °C, the reaction mixture was diluted with water (30 mL) and extracted with ether (3x50 mL). The combined ethereal extract was washed with water (2x30 mL), dried and concentrated. The residue was chromatographed over silica gel using ether: light petroleum (1:3) as eluent to afford the cyano-ester **9** (2.93 g, 58%) as a colourless oil (diastereomeric mixture), IR: 2240, 1736 cm^{-1}: ^{1}H NMR δ 0.95, 1.15(2t, J = 7 Hz each, total 3H), 1.60,1.62 (2s, total 3H, *Me*), 1.20-2.35(m, 4H), 2.30, 2.31 (2s, total 3H, Ar*Me*), 3.70, 3.72 (2s, total 1H), 3.77-4.15 (m, 6H), 4.79, 4.84 (2t, J = 4.5 Hz, 1H), 7.11-7.26 (m, 4H, Ar*H*). Anal. Calcd. for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found, C, 68.73, H, 7.71, N, 4.08%.

Methyl 3-methyl-3-(4-methylphenyl)-6,6-ethylenedioxyhexanoate (10). The cyano-ester **9** (2.7 g, 8.15 mmol) was hydrolysed by refluxing under nitrogen for 24 h with a solution of potassium hydroxide (10 g) in ethylene glycol (32 mL) and water (8 mL). The mixture was cooled to room temperature, diluted with water (35 mL) and the neutral material was extracted with ether. The alkaline solution was then acidified at 0 °C with cold dilute acetic acid (1:1) and extracted with ether (3x60 mL). The organic extract was washed with water (2x30 mL), dried and concentrated. The crude product was decarboxylated by heating it at 190 °C for 20 min. and the resulting acid (1.8 g) was esterified by treatment with an excess of ethereal solution of diazomethane at 0 °C. Usual work-up of the reaction mixture followed by chromatography of the crude product over neutral alumina and elution with benzene : light petroleum (1:4) afforded the methyl ester **10** (1.79 g, 75%) as a colourless oil; IR: 1735 cm^{-1}: ^{1}H NMR δ 1.46 (s, 3H, *Me*), 1.30-1.98(m, 4H), 2.29 (s, 3H, Ar*Me*), 2.58, 2.68 (AB_q, 2H, J = 14 Hz, C*H*$_2$CO$_2$Me), 3.51 (s, 3H, CO$_2$*Me*), 3.76-3.91 (m, 4H), 4.75 (t, J= 4.7 Hz, 1H), 7.09,7.18 (2xd, J = 8.2 Hz, 2x2H, Ar*H*); ^{13}C NMR δ 20.8, 24.4, 28.7, 36.2, 39.5, 47.1, 51.1, 64.7, 64.8, 104.6, 125.8 (2C), 128.9 (2C), 135.3, 142.7, 171.9. Anal. Calcd. for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found, C, 69.61, H, 8.41%.

4-Methyl-4-(4-methylphenyl)-5-methoxycarbonylpentan-1-al (11). A solution of the acetal-ester **10** (1.7 g, 5.81 mmol) in aqueous acetic acid (12 mL, 80%) was stirred at room temperature for 20 h and at 60 °C for 2 h. It was then cooled, diluted with water (15 mL) and extracted with chloroform (3x20 mL). The organic extract was washed with saturated aqueous $NaHCO_3$ (2x15 mL), dried and concentrated in vacuum. The residue was purified by chromatography on silica gel. Elution with ether : light petroleum (1 : 4) furnished the aldehyde-ester **11** (1.33 g, 92%) as a colourless oil; IR : 1732, 1716 cm^{-1}; ^{1}H NMR δ 1.45 (s, 3H, *Me*), 1.91-2.05 (m, 1H), 2.08-2.25

(m, 3H), 2.30 (s, 3H, Ar*Me*), 2.61, 2.69 (AB_q, 2H, J = 14.1 Hz, C*H*$_2$CO$_2$Me), 3.54 (s, 3H, CO$_2$*Me*), 7.13, 7.17 (2xd, J = 8.4 Hz, 2x2H, Ar*H*), 9.61 (s, 1H, C*H*O); ^{13}C NMR δ 20.7, 24.3, 33.8, 39.3, 39.4, 46.7, 51.2, 125.7 (2C), 129.0 (2C), 135.7, 141.9, 171.6, 201.8. Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.67; H, 8.30%.

Methyl 3-methyl-3-(4-methylphenyl)-6-hydroxyhexanoate (12). Sodium borohydride (0.18 g, 4.76 mmol) was added in small portions during 30 min to an ice-cold stirred solution of the aldehyde-ester **11** (1.2 g, 4.85 mmol) in methanol (10 mL). After the addition, the mixture was stirred at 0°C for 4h and left at room temperature for 4 h. After the removal of most of the methanol under reduced pressure, the reaction mixture was diluted with water (20 mL), cooled, acidified with dilute hydrochloric acid (2 mL, 3N) and extracted with ether (3x30 mL). The ethereal extract was washed with aqueous sodium bicarbonate and water, dried and concentrated. The crude product was purified by column chromatography on silica gel using ether: light petroleum (1:5) as eluent to furnish the alcohol-ester **12** (1.1 g, 91%) as a colourless oil; IR: 3439, 1734 cm^{-1}; ^{1}H NMR δ 1.45 (s, 3H, *Me*), 1.35-1.43 (m, 1H), 1.66-1.92 (m, 3H), 2.30 (s, 3H, Ar*Me*), 2.61, 2.68 (AB_q, 2H, J = 14 Hz, C*H*$_2$CO$_2$Me), 3.54 (s, 3H, CO$_2$*Me*), 3.54 (t, J = 6.4 Hz, 2H, *CH*$_2$OH), 7.11, 7.19 (2xd, J = 8.2 Hz, 2x2H, Ar*H*); ^{13}C NMR δ 20.8, 24.7, 27.7, 38.3, 39.7, 46.9, 51.2, 63.3, 125.8 (2C), 128.9 (2C), 135.4, 143.1, 172.1. Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.20; H, 8.77%.

Methyl 3-methyl-3-(4-methylphenyl)-6-bromohexanoate (6). Phosphorus tribromide (0.7 g, 2.58 mmol) was added dropwise at 0°C to a stirred solution of the alcohol **12** (1 g, 4 mmol) in benzene (10 mL). The mixture was stirred at 70 °C for 3 h and then poured into crushed ice. The product was extracted with benzene (3x25 mL). The organic extract was washed with aqueous sodium bicarbonate, dried and concentrated. The crude product was chromatographed over silica gel using ether: light petroleum (1:19) as eluent to furnish the bromo ester **6** (0.93 g, 74%) as a colourless oil; IR : 1738 cm^{-1}; ^{1}H NMR δ 1.46 (s, 3H, *Me*), 1.50-1.99 (m, 4H), 2.31 (s, 3H, Ar*Me*), 2.60, 2.67 (AB_q, 2H, J = 14.1 Hz, C*H*$_2$CO$_2$Me), 3.29 (t, J = 6.6 Hz, 2H, C*H*$_2$Br), 3.54 (s, 3H, CO$_2$*Me*), 7.12, 7.18 (2xd, J = 8.4 Hz, 2x2H, Ar*H*); ^{13}C NMR δ 20.8, 24.6, 27.8, 34.2, 39.6, 40.8, 46.9, 51.2, 125.7 (2C), 129.0 (2C), 135.6, 142.7, 171.8. Anal. Calcd. for $C_{15}H_{21}O_2Br$: C, 57.51; H, 6.76. Found: C, 57.32; H, 6.50%.

(1SR,2SR)-1-Methoxycarbonyl-1,2-dimethyl-2-(4-methylphenyl)cyclopentane (7). A solution of the bromo-ester **6** (0.9 g, 2.87 mmol) in tetrahydrofuran (2 mL) was added dropwise under nitrogen at -70°C to a stirred solution of lithium diisopropylamide [prepared by adding 1.4 M *n*-butyllithium (2.4 mL, 3.36 mmol) in hexane to a stirred solution of diisopropylamine (0.36 g, 3.56 mmol) in tetrahydrofuran (4 mL) at 0°C] containing hexamethylphosphoramide (0.77 g, 4.30 mmol). After the addition, the mixture was stirred at -70°C for 30 min and the temperature was gradually raised to 0°C. It was then slowly added at 0°C to a stirred solution of lithium diiisopropylamide [prepared by adding 1.4 M *n*-butyllithium (3.3 mL, 4.62 mmol) in hexane to a solution of diisopropylamine (0.5 g, 4.95 mmol) in tetrahydrofuran (4 mL) at 0°C] and hexamethylphosphoramide (1.02 g, 5.7 mmol) under nitrogen. After stirring the mixture at 0°C for 2h, methyl iodide (2 g, 14 mmol) was slowly added and the resulting mixture was further

stirred at 5°C for 2h. It was then diluted with cold water (20 mL) and extracted with ether (3x30 mL). The ethereal extract was washed with water (3x15 mL) , dried and concentrated. The residue was chromatographed over silica gel (30 g). Elution with ether: light petroleum (1:5) furnished the desired cyclopetanecarboxylate **7** (0.6 g, 85%) as a colourless oil; IR: 1722 cm^{-1}; ^1H NMR δ 1.31 (s, 3H, *Me*), 1.40 (s, 3H, *Me*), 1.56-2.00 (m, 4H), 2.27-2.37 (m, 1H), 2.28 (s, 3H, Ar*Me*), 2.52-2.60 (m, 1H), 3.25 (s, 3H, CO_2*Me*), 7.05, 7.17 (2xd, J = 8.4 Hz, 2x2H, Ar*H*); ^{13}C NMR δ 20.3, 20.7, 21.1, 24.2, 35.8, 37.9, 50.9, 51.4, 56.6, 126.2 (2C), 128.3 (2C), 135.3, 143.4, 176.9. Anal. Calcd. for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.23; H, 9.14%

(1SR,2RS)-1-Hydroxymethyl-1,2-dimethyl-2-(4-methylphenyl)cyclopentane (2). A solution of the ester **7** (0.55 g, 2.23 mmol) in anhydrous ether (6 mL) was added dropwise at room temperature to a stirred suspension of $LiAlH_4$ (0.16 g, 4.21 mmol) in ether (15 mL). After the addition, the mixture was refluxed for 4h and then cooled. Excess of hydride was carefully destroyed by addition of saturated aqueous sodium sulfate and the mixture was filtered through celite. The residue was thoroughly washed with ether (3x25 mL). The combined filtrate was washed with brine, dried and concentrated. The crude product was chromatographed on silica gel using ether: light petroleum (1:3) as eluent to furnish the alcohol **2** (0.43 g, 88%) as a colourless oil; IR: 3340 cm ; ^1H NMR δ 1.10 (s, 3H, *Me*), 1.29 (s, 3H, *Me*), 1.46-2.55 (m, 6H), 2.30 (s, 3H, Ar*Me*), 3.02, 3.05 (AB_q, J = 11.2 Hz, 2H, CH_2OH), 7.10, 7.27 (2xd, J = 8.2 Hz, 2x2H, Ar*H*); ^{13}C NMR δ 19.2, 20.1, 20.7, 25.0, 34.7, 37.3, 49.1, 49.4, 69.2, 126.5 (2C), 128.7 (2C), 135.3, 143.3. Anal. Calcd. for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82. 43; H, 9.98%.

(±)-Tochuinyl acetate (1). To a solution of the alcohol **2** (0.2 g, 0.92 mmol) in dry pyridine (2 mL) was added acetic anhydride (1 mL) and the resulting solution was allowed to stand at room temperature for 24 h. The reaction mixture was then poured into cold water (15 mL) and after 2h extracted with ether (3x20 mL). The combined etheral extract was washed successively with water, 2% hydrochloric acid, aqueous sodium bicarbonate, water again until neutral, and dried. The residue remaining upon evaporation of the solvent was purified by chromatography over silica gel using ether : light petroleum (1 : 9) as eluent to afford (±)-tochuinyl acetate **1** (0.2 g, 84%) as a colourless oil; IR 1740 cm^{-1} ; ^{1}H NMR δ 1.12 (s, 3H, *Me*), 1.33 (s, 3H, *Me*), 1.51-1.57 (m, 1H), 1.71-1.86 (m, 4H), 1.93 (s, 3H, OCO*Me*), 2.30 (s, 3H, Ar*Me*), 2.43-2.54 (m, 1H), 3.36, 3.59 (AB_q, 2H, J = 11.1 Hz, CH_2OAc), 7.08 , 7.22 (2xd, J = 8.1 Hz, 2x2H, Ar*H*) ; ^{13}C NMR δ 19.5, 20.1, 20.7, 20.8, 24.9, 34.7, 37.5, 47.4, 49.8, 70.5, 126.6 (2C), 128.5 (2C), 135.2, 142.9, 171.1. Anal. Calcd. for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78. 23; H, 9.38%.

Methyl 2,2,3-trimethyl-3-(4-methylphenyl)-6,6-ethylenedioxyhexanoate (13). To a stirred solution of diisopropylamine (0.61 g, 6.03 mmol) in dry tetrahydrofuran (8 mL) at 0 °C was added under nitrogen *n*-butyllithium (1.4 M in hexane, 4.2 mL, 5.88 mmol). After stirring at 0 °C for 20 min, the mixture was cooled to -78 °C and a solution of the ester **10** (1.7 g, 5.81 mmol) in tetrahydrofuran (4 mL) was slowly added. The resulting mixture was stirred at -20 °C for 2 h and then cooled to -78 °C. Methyl iodide (1 g, 7.04 mmol) in hexamethylphosphoramide (1.06 g, 5.91 mmol) was added dropwise at -78 °C and the mixture was allowed to warm to 0 °C. After stirring at 0 °C for 3 h, the mixture was slowly added under nitrogen to a stirred solution of

lithium diisopropylamide [prepared by adding 1.4 M n-butyllithium (7 mL, 9.8 mmol) in hexane to a solution of diisopropylamine (1.03 g, 10.2 mmol) in tetrahydrofuran (4.5 mL) at 0 °C] containing hexamethylphosphoramide (2.1 g, 11.7 mmol). After stirring the mixture at 0 °C for 2h, methyl iodide (4 g, 28.2 mmol) was slowly added and the resulting mixture was further stirred at 5 °C for 2h. It was then diluted with cold water (40 mL) and extracted with ether (3x50 mL). The combined ethereal extract was washed with water (3x25 mL), dried and concentrated. The residue was chromatographed over neutral alumina. Elution with benzene: light petroleum (1: 4) furnished the α,α-dimethyl ester **13** (1.64 g, 88%) as a colourless oil; IR: 1735 cm^{-1}; ^1H NMR δ 1.03 (s, 3H, *Me*), 1.13 (s, 3H, *Me*), 1.37 (s, 3H, *Me*), 1.24-1.75(m, 3H), 2.30 (s, 3H, Ar*Me*), 2.30-2.42 (m, 1H), 3.52 (s, 3H, CO_2*Me*), 3.79-3.94 (m, 4H), 4.84 (t, J= 4.7 Hz, 1H), 7.10,7.13 (2xd, J = 8 Hz, 2x2H, Ar*H*); ^{13}C NMR δ 20.8, 21.3, 21.8, 22.2, 28.8, 29.3, 45.2, 49.8, 51.2, 64.8, 64.9, 105.0, 128.1 (2C), 128.3 (2C), 135.4, 139.5, 177.2. Anal. Calcd. for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found, C, 70.98, H, 9.07%.

Dimethyl 2,2,3-trimethyl-3-(4-methylphenyl)adipate (15). Deacetalisation of the acetal-ester **13** (1.5 g, 4.68 mmol), as described for **11**, provided the aldehyde-ester **14**. Purification of the crude product on a silica gel column using ether: light petroleum (1 : 4) as eluent furnished **14** (1.14 g, 88%) as a colourless oil [IR : 1727, 1716, 1604 cm^{-1}; ^1H NMR δ 1.04 (s, 3H, *Me*), 1.15 (s, 3H, *Me*), 1.35 (s, 3H, *Me*), 1.85-2.70 (m, 4H), 2.31 (s, 3H, Ar*Me*), 3.54 (s, 3H, CO_2*Me*), 7.09-7.20 (m, 4H, Ar*H*), 9.72 (bs, 1H, C*H*O); ^{13}C NMR δ 20.8, 21.3, 21.8, 22.2, 26.8, 40.2, 45.1, 49.7, 51.3, 128.0 (2C), 128.3 (2C), 135.9, 138.9, 177.0, 202.3]. Without further characterization, this was coverted into the diester **15** according to the following procedure.

To a magnetically stirred solution of the aldehyde **14** (1.1 g, 3.98 mmol) in acetone (15 mL) at 5 °C was added dropwise under nitrogen Jones reagent (8 N) until the colour of the reagent persisted. After stirring at 20^0 C for 30 min, a few drops of MeOH were added to destroy the excess reagent and the reaction mixture was diluted with water (15 mL). The product was extracted with ether (3x20 mL) The combined ether layer was extracted with saturated aqueous $NaHCO_3$ (2x15 mL). The bicarbonate extract was acidified with cold 6N HCl and extracted with ether (3x20 mL). The ether extract was washed with brine, dried and concentrated. The residue was treated with an ethereal solution of CH_2N_2 [prepared from 3 g of nitrosomethyl urea] at 0 °C to provide the diester **15**. Purification of the diester on a silica gel column using ether: light petroleum (1 : 4) as eluent afforded **15** (1.03 g, 84%) as a colourless oil; IR 1733 cm^{-1} ; ^1H NMR δ 1.03 (s, 3H, *Me*), 1.15 (s, 3H, *Me*), 1.36 (s, 3H, *Me*), 1.93-2.17 (m, 5H), 2.31 (s, 3H, Ar*Me*), 2.59-2.68 (m, 1H), 3.53 (s, 3H, CO_2*Me*), 3.62 (s, 3H, CO_2*Me*), 7.08-7.17 (m, 4H, Ar*H*); ^{13}C NMR δ 20.7, 21.0, 21.6, 22.1, 29.9, 30.1, 45.1, 49.6, 51.2, 51.4,128.0 (2C), 128.2 (2C), 135.6, 138.8, 174.5, 176.9. Anal. Calcd. for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found, C, 70.38, H, 8.41%.

(±)-α- Cuparenone (5). To a stirred suspension of potassium *tert*-butoxide (7.3 g, 65.2 mmol) in dry benzene (60 mL) was added under nitrogen a solution of the dimethyl ester **15** (0.8 g, 2.61 mmol) in benzene (20 mL). The mixture was refluxed for 5 h and then cooled, acidified with 3N hydrochloric acid (24 mL) and extracted with benzene. The organic extract was washed with aqueous sodium bicarbonate, water and dried. The solvent was evaporated off. The residue was

dissolved in distilled dimethy sulfoxide (5 mL). After the addition of sodium chloride (0.4 g) and water (0.4 mL), the mixture was stirred under nitrogen at 155 °C for 4h. It was then cooled, diluted with water (15 mL) and extracted with ether (3x25 mL). The ethereal extract was washed with water (2x20 mL), dried and concentrated. Chromatography of the crude product over silica gel and elution with ether : light petroleum (1 : 19) furnished α- cuparenone **5** (0.42 g, 75%) as a colourless oil; IR 1739 cm^{-1} ; ^{1}H NMR δ 0.61 (s, 3H, *Me*), 1.17 (s, 3H, *Me*), 1.26 (s, 3H, *Me*), 1.87-1.95 (m, 1H), 2.34 (s, 3H, Ar*Me*), 2.37-2.72 (m, 3H), 7.16,7.28 (2xd, J = 8.1 Hz, 2x2H, Ar*H*) ; ^{13}C NMR δ 18.4, 20.8, 22.1, 25.3, 29.6, 33.7, 48.3, 53.2, 126.4 (2C), 128.9 (2C), 135.8, 141.9, 222.6. Anal. Calcd. for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found, C, 83.37, H, 9.17%.

(±)-Cuparene (3). A mixture of the ketone **5** (0.24 g, 1.11 mmol), hydrazine hydrate (3.6 mL, 99%), hydrazine dihydrochloride (0.96 g) and diethylene glycol (12 mL) was heated to 125 °C in an atmosphere of nitrogen and kept at that temperature for 2h. The reaction mixture was then cooled to 80 °C and solid pellets of potassium hydroxide (1.6 g) were added. The temperature was gradually raised to 210 °C by distilling off low boiling materials. The reaction mixture was maintained at 210-220 °C for 3h, then cooled, poured into water (20 mL), and extracted with ether (3x30 mL). The distillate containing the low boiling materials was also diluted with water (15 mL) and extracted with ether (3x20 mL). The combined ethereal extract was washed with cold dilute hydrochloric acid (20 mL, 3N), water (2x30 mL), and dried. After removal of ether, the residue was chromatographed on neutral alumina. Elution with light petroleum furnished (±)-cuparene (**2**) (0.18 g, 82%) as a colourless oil; ^{1}H NMR δ 0.56 (s, 3H, *Me*), 1.06 (s, 3H, *Me*), 1.25 (s, 3H, *Me*), 1.51-1.85 (m, 5H), 2.31 (s, 3H, Ar*Me*), 2.44-2.54 (m, 1H), 7.09, 7.24 (2xd, J = 8 Hz, 2x2H, Ar*H*); ^{13}C NMR δ 19.7, 20.8, 24.2, 24.4, 26.4, 36.8, 39.7, 44.2, 50.2, 126.9 (2C), 128.2 (2C), 134.7, 144.5. Anal. Calcd for $C_{15}H_{22}$: C, 89.04; H, 10.96. Found: C, 88.90; H, 10.79%.

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