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Convenient route to enantiopure aryl cyclopentanes via Diels–Alder reaction of asymmetric dienes. Total synthesis of (+)-herbertene and (+)-cuparene

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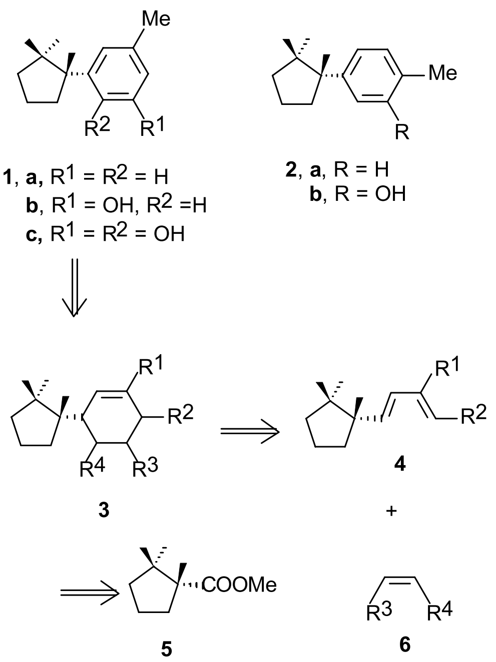
Abstract—A general route for the synthesis of highly substituted aryl cyclopentanes has been developed involving Diels–Alder reaction of asymmetric dienes prepared from (+)-camphoric acid followed by aromatization of the resulting cyclohexene derivatives. Employing this protocol enantiospecific synthesis of (+)-herbertene and (+)-cuparene has been accomplished.

1. Introduction

Aryl cyclopentanes with two adjacent quaternary centers on the cyclopentane ring constitute two expanding families[1] of sesquiterpenes, herbertanes and cuparanes. Representative examples include herbertene **1a**, herbertenol **1b**, herbertene diol **1c**, cuparene **2a**, δ-cuparenol **2b** etc. Several members of these families possess important biological properties such as antifungal, antibiotic, neurotrophic and anti-lipid peroxidation. Because of these biological properties along with the difficulty associated with the generation of two adjacent quaternary centers on a cyclopentane ring, herbertanes and cuparanes have recently become popular synthetic targets. The basic approaches that have been widely employed for their synthesis are construction of the cyclopentane ring at the benzylic carbon of an appropriately substituted aromatic ring[2] and addition of an aryl nucleophile to a cyclopentenone derivative.[3] However, only a few of these approaches deals with synthesis of enantiopure compounds. In continuation to our interest in cyclopentanoids,[4] we undertook a program to develop a general synthetic protocol for entry into both these families of sesquiterpenes in enantiomerically pure form. The key concept of the present strategy[5] involves construction of the aromatic ring onto an appropriate substituent on a preconstructed cyclopentane ring. We envisaged that the structures **1**, **2** may be obtained by aromatization of the cyclohexenes **3** (Scheme 1). The substitutents R^3 and R^4 in **3** may be removed to lead to the parent hydrocarbons **1a** and **2a** or may be modified after aromatization to provide the more functionalized members such as **1b**,**c**. The cyclohexene derivatives **3** may be obtained through Diels–Alder reaction of the asymmetric dienes **4** with the dienophiles **6**. The dienes **4** may, in principle, be easily available from the cyclopentane derivative **5**. The results of the investigation employing this protocol are described here[6] leading to the total synthesis of (+)-herbertene and (+)-cuparene.



Scheme 1.

Keywords: aromatization; asymmetric synthesis; decarboxylation; Diels–Alder reactions; terpenes and terpenoids.

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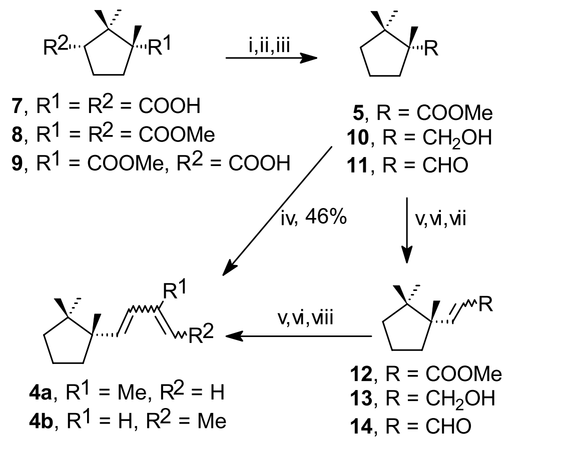
2. Results and discussion

The structural similarity of the cyclopentane derivative **5** to camphoric acid **7** dictates that the latter can be used to make the ester **5**. To this end dimethyl camphorate **8**, prepared from (+)-camphoric acid **7**, was partially hydrolyzed to afford the monocarboxylic acid **9**[5e] (Scheme 2). The free carboxylic acid group in the compound **9** could be easily decarboxylated by using the photodecarboxylation procedure developed by Okada et al.[7] to provide the desired ester **5**.

The ester **5** was then reduced with $LiAlH_4$ to provide the alcohol **10**. Swern oxidation of the resulting alcohol followed by Wittig olefination of the resulting aldehyde **11** with the ylide generated from methallyl triphenyl phosphonium chloride gave the diene **4a** as a single component in 46% yield. The appearance of two doublets in its ^{1}H NMR at δ 5.74 (1H, J=16 Hz) and 6.07 (1H, J=16 Hz) indicated it to be the *E*-isomer. The diene **4b** was prepared in the following way; Wittig–Horner reaction of the aldehyde **11** with trimethyl phosphonoacetate produced the unsaturated ester **12** in 70% yield as a mixture of *E*- and *Z*-isomers with the former predominating. A three-step sequence involving $LiAlH_4$ reduction, Swern oxidation and Wittig reaction with the ylide generated from ethyl(triphenyl phosphonium) bromide converted the unsaturated ester mixture **12** to the diene **4b** as a mixture of probably all the possible geometrical isomers in overall excellent yield.

The Diels–Alder reaction of the diene **4a** was initially investigated keeping in mind that the methyl ketone **16** obtained after aromatization of the adduct **15** would provide herbertenol **1b** (Scheme 3). Heating a solution of the diene **4a** with methyl vinyl ketone in a sealed tube at 140°C for 24 h afforded a liquid in 59% yield. The product was found mainly to be a mixture of two components in ca. 1:2 ratio from integration of the olefinic proton singlets at δ 5.32 and 5.45. That these two components are not the regioisomers was established by its transformation to the single aromatic ketone **16** through dehydrogenation by heating with 10% Pd/C. The presence of two doublets in ^{1}H NMR of the ketone **16** at δ 6.85 (J=7.8 Hz) and 6.93 (J=7.8 Hz) indicated the presence of two *ortho* protons establishing the structure of the aromatic ketone **16**. A portion of the major diastereoisomer of the mixture of adducts slowly crystallized out of a solution of petroleum ether 60–80°C after a few days at rt. Determination of structure by single crystal X-ray diffraction[8] showed that the major diastereoisomer has the structure **15**. When the reaction of the diene **4a** was carried out with a dienophile with more steric requirement such as maleic anhydride, diastereoselectivity was significantly improved to lead to an inseparable mixture of two adducts in ca. 1:4 ratio (from integration of the Me singlets in ^{1}H NMR). The major isomer was assigned the structure **17** based on analogy to the formation of the major adduct **15** from reaction of the diene **4a** with methyl vinyl ketone. On the other hand reaction of the diene **4a** with less sterically crowded dienophile such as dimethyl acetylene dicarboxylate gave a mixture of two products in ca. 1:1 ratio. The formation of the adducts **15** and **17** as the major products from Diels–Alder reaction of the diene **4a** may be rationalized by preferential approach of the dienophile from the *endo Si*-face of the diene (Fig. 1(a)) as approach from the *Re*-face (Fig. 1(b)) of the diene is blocked by the *gem*-dimethyl group on the cyclopentane ring. This is supported by the X-ray crystal structure (Fig. 2) of the compound **15** which clearly shows that the COMe group is located away from the gem-dimethyl group. As expected reaction of the diene **4b** with maleic anhydride was less selective producing a mixture of the adduct **19** along with its other diastereoisomer (ca. 2:1 ratio).

With the cyclohexene derivatives **17–19** in hand we



Scheme 2. *Reagents*: (i) MeOH, H_2SO_4, 92%; (ii) MeOH, KOH, 89%; (iii) hν, *t*-BuSH, quinoline, C_6H_6, 59%; (iv) $H_2C{=}C(Me)CH_2PPh_3^+Cl^-$, *n*-BuLi, Et_2O, 46%; (v) $LiAlH_4$, Et_2O; (vi) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 84%; (vii) NaH, $(MeO)_2POCH_2CO_2Me$, THF, 70%; (viii) *n*-BuLi, $EtPPh_3^+$ Br^-, THF, 83%.

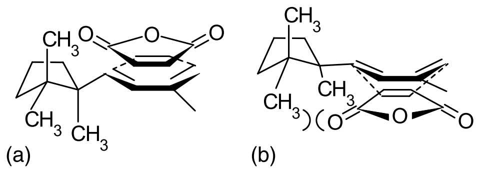


Figure 1.

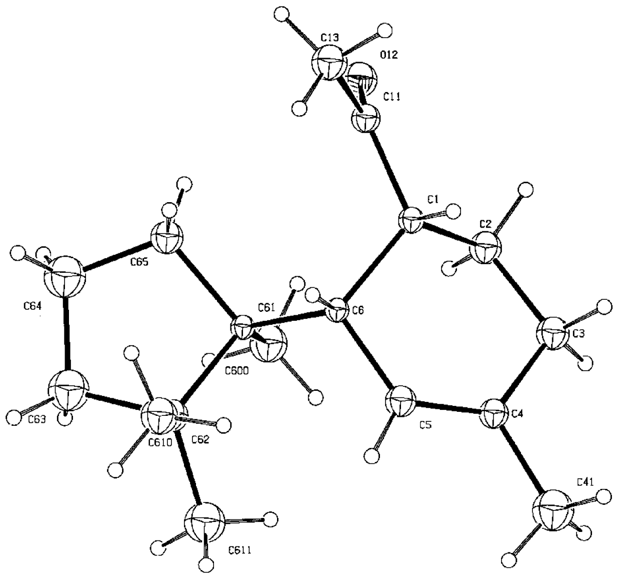
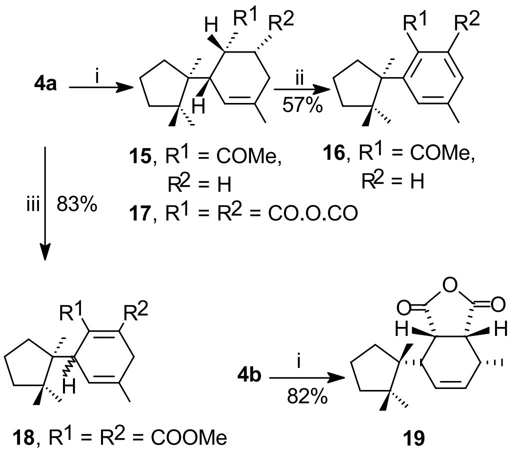
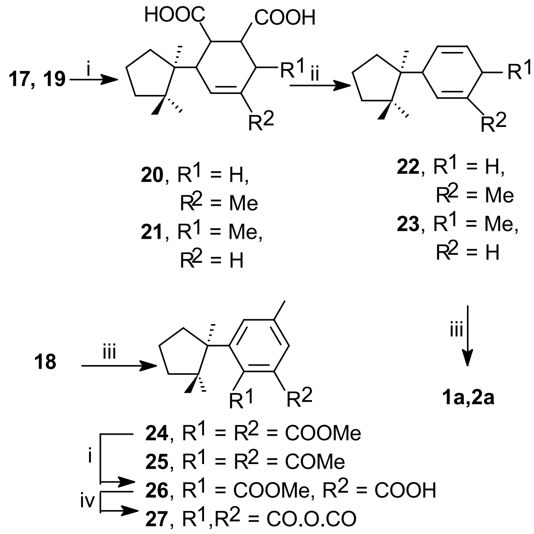


Figure 2. ORTEP plot of the ketone **15**.



Scheme 3. *Reagents*: (i) CH_2=CHCOMe, $C_6H_5CH_3$, 140°C, 82% (for **15**), maleic anhydride, $C_6H_5CH_3$, 80°C (for **17**), 140°C (for **19**), (63–82%); (ii) Pd–C (10%), Xylene, 150°C, 57%; (iii) dimethyl acetylene dicarboxylate, $C_6H_5CH_3$, 140°C, 83%.



Scheme 4. *Reagents*: (i) NaOH, H_2O, EtOH, 94%; (ii) hν, acridine, C_6H_6, (20–40%); (iii) DDQ, C_6H_6, 60°C, 70–73%; (iv) H_2SO_4 (98%), 86%.

focussed our attention on the synthesis of the natural products. For the synthesis of herbertene **1a**, the mixture of the anhydride **17** and its diastereoisomer was hydrolyzed to afford the dicarboxylic acids **20** (Scheme 4), these were subjected to decarboxylation. A conventional procedure involving $Pb(OAc)_4$ gave the diene **22** along with a trace of herbertene **1a** in only 25% yield. We reasoned that decarboxylation procedure (hν, quinoline or acridine, ^{t}BuSH, benzene) developed by Okada et al.[7] to make alkanes may be useful for bisdecarboxylation of vicinal dicarboxylic acids to provide olefin in improved yield if the reaction is carried out in the absence of proton source (^{t}BuSH).

Indeed, this protocol worked nicely to afford the diene **22** in 40% yield. Similarly decarboxylation of the crude dicarboxylic acids **21** obtained from hydrolysis of the anhydride mixture **19**, provided the diene **23** in moderate yield. Aromatization of the cyclohexadiene derivatives **22** and **23** was then effected by heating their benzene solution at 60°C with DDQ to afford (+)-herbertene **1a** and (+)-cuparene **2a** in 70 and 67% yields respectively. This accomplishes the first synthesis of non-natural enantiomer (+)-herbertene.

We next focused our attention on the synthesis of the more functionalized derivatives such as herbertene diol **1c**. The cyclohexadiene derivative **18** was aromatized with DDQ to provide the aromatic diester **24** in 72% yield (Scheme 4). It was envisaged that the ester functionalities in the aryl cyclopentane **24** could be easily transformed by reaction of the corresponding dicarboxylic acid with MeLi to the corresponding methyl ketone **25**. Baeyer–Villiger oxidation of the methyl ketone and hydrolysis of the resulting diacetate would accomplish the synthesis of herbertene diol **1c**. However alkaline hydrolysis of the diester **24** gave the monocarboxylic acid **26**. Attempted hydrolysis of the diester **24** under acidic conditions gave the anhydride **27**. In an attempt to make herbertenol **1b** Baeyer–Villiger reaction of the methyl ketone **15** using a variety of reagents also failed. These failures led us to conclude that nucleophilic addition to the carbonyl group at C-4 position on the aromatic ring is strongly inhibited due to steric crowding imposed by the *gem*-dimethyl group on the adjacent cyclopentane ring.

3. Conclusion

We have developed an asymmetric synthetic route to highly substituted cyclopentanes, which contain *gem*-dimethyl substituents and this has been used to access the natural products, (+)-herbertene and (+)-cuparene, enantioselectively. It involves Diels–Alder reaction of asymmetric dienes followed by aromatization of the resulting cyclohexenes. Since both enantiomer of camphoric acid are commercially available it provides opportunity for access to both enantiomers of aryl cyclopentanes.

4. Experimental

4.1. General

Melting points were measured in open capillary tubes in sulphuric acid bath and are uncorrected. All reactions were carried out under an atmosphere of Ar. A usual work up involved extraction with an organic solvent, washing of the organic extract with brine, drying over anhydrous Na_2SO_4 and removal of the solvent under vacuum. Column chromatography was performed on silica gel (60–120 mesh). IR spectra were recorded as neat for liquids and as KBr pellet for solids on a FTIR-8300, SHIMADZU spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions with TMS as internal standard at 300 and 75 MHz respectively on Bruker DPX-300 spectrometer. In case of inseparable mixture of isomers, NMR spectral data for the major and minor isomers have been reported from the spectra of the mixture. Elemental analyses were performed in the microanalytical laboratory of this department.

4.1.1. Methyl-1,2,2-trimethylcyclopentane carboxylate (5). The acid **9** was prepared from (1*R*, 3*S*)-(+)-camphoric acid according to the procedure described by Fuganti et al.[5e]

A solution of this carboxylic acid **9** (1.7 g, 7.94 mmol) in benzene (110 mL) containing quinoline (1.22 g, 9.53 mmol) and ^{t}BuSH (7.14 g, 79.43 mmol) was irradiated with a medium 450 W pressure Hanovia lamp through a water cooled pyrex immersion well for 6 h. The reaction mixture was then washed successively with HCl (2×15 mL, 6N), aqueous saturated $NaHCO_3$ solution (3×20 mL) and brine (3×20 mL). Evaporation of the solvent followed by column chromatography of the residual mass (4% diethyl ether–petroleum ether 60–80°C) afforded the ester **5** (800 mg, 59%) as a colorless liquid; [Found: C, 70.78; H, 10.25. $C_{10}H_{18}O_2$ requires C, 70.55; H, 10.66%]; $[\alpha]_D^{30}$=+5.29 (*c* 0.34, $CHCl_3$); ν_{max} (Neat) 2962, 2873, 1732 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.86 (3H, s, $-CH_3$), 1.03 (3H, s, $-CH_3$), 1.14 (3H, s, $-CH_3$), 1.50–1.73 (5H, m), 2.36–2.45 (1H, m), 3.65 (3H, s, $-COOCH_3$); δ_C (75 MHz, $CDCl_3$) 20.3 (CH_2), 21.2 (CH_3), 24.4 (CH_3), 26.0 (CH_3), 35.3 (CH_2), 40.0 (CH_2), 44.6 (C), 51.6 (CH_3), 55.2 (C), 176.8 (CO).

4.1.2. 1-Hydroxymethyl-1,2,2-trimethylcyclopentane (10). To a cooled (0°C) magnetically stirred suspension of $LiAlH_4$ (470 mg, 12.42 mmol) in diethyl ether (14 mL) was added dropwise a solution of the ester **5** (2.0 g, 11.76 mmol) in diethyl ether (25 mL). The reaction mixture was allowed to warm to rt and stirred for additional 2 h. It was again cooled to 0°C and quenched by sequential addition of water (0.5 mL), 15% aqueous NaOH (0.5 mL) and water (1.5 mL) and stirred for 15 min. The organic phase was separated and dried. The solvent was evaporated to give the corresponding alcohol **10** as a white solid (1.4 g, 84%), mp 138–140°C; [Found: C, 75.96; H, 12.83. $C_9H_{18}O$ requires: C, 75.99; H, 12.75%]; $[\alpha]_D^{30}$=+8.02 (*c* 0.57, $CHCl_3$); ν_{max} (KBr) 3323 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.89 (3H, s, $-CH_3$), 0.92 (3H, s, $-CH_3$), 0.93 (3H, s, $-CH_3$), 1.21–1.80 (6H, m), 3.47 (2H, q, *J*=9 Hz, $-CH_2OH$); δ_C (75 MHz, $CDCl_3$) 19.2 (CH_3), 19.7 (CH_2), 23.8 (CH_3), 25.3 (CH_3), 34.5 (CH_2), 40.4 (CH_2), 42.8 (C), 47.4 (C), 68.9 (OCH_2).

4.1.3. 1,2,2-Trimethylcyclopentane-1-carboxaldehyde (11). To a magnetically stirred cooled (−78°C) solution of oxalyl chloride (0.72 mL, 8.11 mmol) in dichloromethane (4 mL), a solution of DMSO (1.2 mL, 16.9 mmol) in dichloromethane (3 mL) was added dropwise. After stirring the reaction mixture at −78°C for 15 min, a solution of the alcohol **10** obtained as above (960 mg, 6.76 mmol) in dichloromethane (4 mL) was added and stirred for 45 min. Triethylamine (3.8 mL, 27.04 mmol) was added and the reaction mixture was allowed to attain rt and stirred for 1 h. The reaction mixture was quenched by addition of water (4 mL). The organic layer was separated and washed with water (3×3 mL), dried and concentrated to provide the extremely volatile aldehyde **11** (850 mg, 89%) as a colorless liquid; $[\alpha]_D^{35}$=+11.73 (*c* 0.52, $CHCl_3$); ν_{max} (Neat) 1718 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.96 (3H, s, $-CH_3$), 0.98 (3H, s, $-CH_3$), 1.02 (3H, s, $-CH_3$), 1.42–1.78 (5H, m), 2.15–2.19 (1H, m), 9.67 (1H, s, −CHO); δ_C (75 MHz, $CDCl_3$) 16.8 (CH_3), 20.5 (CH_2), 24.3 (CH_3), 25.0 (CH_3), 32.8 (CH_2), 40.7 (CH_2), 45.1 (C), 58.1 (C), 207.8 (CO).

4.1.4. 2-Methyl-4-(1′,2′,2′-trimethylcyclopentyl)-1,3-butadiene (4a). *n*-BuLi (0.8 mL, 1.1 mmol, 1.4 M) in hexane was added dropwise at rt to a stirred suspension of methallyltriphenylphosphonium chloride (0.50 g, 1.43 mmol) in diethyl ether (6 mL). The resulting deep red solution was cooled to 0°C and a solution of the aldehyde **11** (100 mg, 0.72 mmol) in diethyl ether (2 mL) was added dropwise. The reaction mixture was allowed to warm to rt and stirring was continued for 14 h. After quenching with water (1 mL) the reaction mixture was worked up with diethyl ether to afford a liquid which was chromatographed (4% diethyl ether–petroleum ether 60–80°C) to afford the diene **4a** (40 mg, 45%) as a colorless liquid; [Found: C, 87.37; H, 11.77. $C_{13}H_{22}$ requires C, 87.56; H, 12.44%]; $[\alpha]_D^{30}$=+20.16 (*c* 0.63, $CHCl_3$); ν_{max} (Neat) 1681, 1606 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.55 (3H, s, $-CH_3$), 0.89 (3H, s, $-CH_3$), 0.97 (3H, s, $-CH_3$), 1.26–1.92 (6H, m), 1.85 (3H, s, $-CH_3$), 4.88 (2H, br s, $=CH_2$), 5.74 (1H, d, *J*=16 Hz, =CH), 6.07 (1H, d, *J*=16 Hz, =CH); δ_C (75 MHz, $CDCl_3$) 19.2 (CH_3), 20.2 (CH_2), 22.1 (CH_3), 24.2 (CH_3), 25.8 (CH_3), 37.3 (CH_2), 39.7 (CH_2), 44.7 (C), 48.9 (C), 114.5 (CH_2), 129.8 (CH), 138.3 (CH), 142.9 (C).

4.1.5. Methyl-3-(1′,2′,2′-trimethylcyclopentyl)prop-2-ene carboxylate (12). Trimethyl phosphonoacetate (0.69 g, 3.79 mmol) was added dropwise at rt to a magnetically stirred suspension of sodium hydride (160 mg, 3.26 mmol, 50% suspension in mineral oil) in THF (7 mL). The resulting solution was stirred for 45 min. A solution of the aldehyde **11** (380 mg, 2.71 mmol) in THF (4 mL) was added to it. After stirring for 12 h, the reaction mixture was quenched by adding saturated aqueous NH_4Cl (4 mL) and worked up with diethyl ether in the usual way. The liquid obtained was chromatographed (5% diethyl ether–petroleum ether 60–80°C) to afford a mixture of the *E*- and *Z*-isomer of the ester **12** (440 mg, 83%); [Found: C, 73.86; H, 9.67. $C_{12}H_{20}O_2$ requires C, 73.44; H, 10.27%]; The pure *E*-isomer could be isolated in small amount during chromatography which has the following physical characteristics; $[\alpha]_D^{35}$=+12.43 (*c* 1.36, $CHCl_3$); ν_{max} (Neat) 1726 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.84 (3H, s, $-CH_3$), 0.92 (3H, s, $-CH_3$), 0.99 (3H, s, $-CH_3$), 1.43–1.90 (6H, m), 3.73 (3H, s, $-COOCH_3$), 5.75 (1H, d, *J*=15.9 Hz, =CH), 7.08 (1H, d, *J*=15.9 Hz, =CH); δ_C (75 MHz, $CDCl_3$) 20.2 (CH_2), 21.2 (CH_3), 24.2 (CH_3), 25.6 (CH_3), 36.8 (CH_2), 39.6 (CH_2), 45.0 (C), 49.8 (C), 51.7 (OCH_3), 118.3 (CH), 156.9 (CH), 167.9 (CO).

4.1.6. 3-(1′,2′,2′-Trimethylcyclopentyl)prop-2-ene-1-ol (13). A suspension of $LiAlH_4$ (0.31 g, 8.16 mmol) in diethyl ether (8 mL) was stirred for 0.5 h and allowed to settle. The clear solution (7 mL) was removed via syringe, leaving the remaining suspension in the reaction flask and was added dropwise to a cooled (−30°C) solution of the ester mixture **12** (800 mg, 4.08 mmol) in diethyl ether (8 mL). After stirring for 4 h at this temperature, the reaction mixture was quenched by sequential addition of water (0.3 mL), 15% NaOH (0.3 mL) and water (0.9 mL). The organic phase was separated and dried over Na_2SO_4. The residual oil after removal of solvent was chromatographed (12% diethyl ether–petroleum ether 60–80°C) to provide the alcohol **13** (0.48 g, 70%) as a mixture of *E*- and *Z*-isomers; [Found: C, 78.24; H, 11.89. $C_{11}H_{20}O$ requires C, 78.51; H, 11.98%]; ν_{max} (Neat) 3313 cm^{-1}; NMR: for the major isomer, δ_H (300 MHz, $CDCl_3$) 0.78 (3H, s, $-CH_3$), 0.84 (3H, s, $-CH_3$), 0.91 (3H, s, $-CH_3$), 1.21–2.06 (6H, m), 4.08 (2H, d, *J*=6 Hz, $-CH_2OH$), 5.53 (1H, dt, *J*=6 Hz, *J*=12 Hz,

=CH), 5.73 (1H, d, J=15.9 Hz, =CH); δ_C (75 MHz, $CDCl_3$) 20.1 (CH_2), 22.0 (CH_3), 24.1 (CH_3), 25.6 (CH_3), 37.1 (CH_2), 39.6 (CH_2), 44.2 (C), 48.7 (C), 64.5 (CH_2), 126.2 (CH), 140.3 (CH); for the minor isomer, δ_C (75 MHz, $CDCl_3$) 19.9 (CH_2), 21.4 (CH_3), 24.3 (CH_3), 25.0 (CH_3), 29.2 (CH_2), 32.7 (CH_2), 45.4 (C), 54.4 (C), 64.4 (CH_2), 130.0 (CH), 134.8 (CH).

4.1.7. 3-(1′,2′,2′-Trimethylcyclopentyl)prop-2-en-1-al (14). The alcohol **13** (380 mg, 2.26 mmol) was oxidised following the procedure described above for preparation of the aldehyde **11** to provide the aldehyde **14** (300 mg, 80%) as a mixture of the *E*- and *Z*-isomer; [Found: C, 79.38; H, 10.68. $C_{11}H_{18}O$ requires C, 79.46; H, 10.91%]; ν_{max} (Neat) 1685, 1689 cm^{-1}; NMR: for the major isomer, δ_H (300 MHz, $CDCl_3$) 0.87 (3H, s, $-CH_3$), 0.95 (3H, s, $-CH_3$), 1.05 (3H, s, $-CH_3$), 1.60–1.99 (6H, m), 6.07 (1H, dd, J=7.7, 15.9 Hz, =CH), 6.95 (1H, d, J=15.9 Hz, =CH), 9.52 (1H, d, J=7.7 Hz, –CHO); δ_C (75 MHz, $CDCl_3$) 19.8 (CH_2), 20.7 (CH_3), 23.8 (CH_3), 25.2 (CH_3), 36.5 (CH_2), 39.3 (CH_2), 44.9 (C), 45.4 (C), 130.4 (CH), 156.9 (CH), 194.2 (CO); for the minor isomer, δ_C (75 MHz, $CDCl_3$) 13.7 (CH_3), 15.1 (CH_3), 25.5 (CH_3), 27.1 (CH_2), 30.3 (CH_2), 36.4 (CH_2), 45.2 (C), 50.2 (C), 133.3 (CH), 160.2 (CH), 193.7 (CO).

4.1.8. 5-(1′,2′,2′-Trimethylcyclopentyl)-2,4-pentadiene (4b). A solution of the aldehyde **14** (0.38 g, 2.29 mmol) in THF (4 mL) on reaction with the ylide generated from ethyltriphenylphosphonium bromide (1.19 g, 3.20 mmol) according to the procedure described for preparation of diene **4a** afforded the diene **4b** (0.34 g, 83%) as a mixture of all the possible geometrical isomers with the *E*-isomer predominating; [Found: C, 87.83; H, 12.09. $C_{13}H_{22}$ requires C, 87.56; H, 12.44%]; $[\alpha]_D^{28}$=+25.8 (*c* 1.88, $CHCl_3$); NMR: for the major isomer, δ_H (300 MHz, $CDCl_3$) 0.80 (3H, s, $-CH_3$), 0.88 (3H, s, $-CH_3$), 0.97 (3H, s, $-CH_3$), 1.40–1.92 (6H, m), 5.78 (d, J=15.6 Hz), and 6.24 (dd, J=10.8, 15.6 Hz) merged under 5.30–6.28 (4H, m); δ_C (75 MHz, $CDCl_3$) 13.5 (CH_3), 19.9 (CH_2), 21.8 (CH_3), 23.9 (CH_3), 25.5 (CH_3), 36.8 (CH_2), 39.4 (CH_2), 44.6 (C), 49.3 (C), 122.2 (CH), 123.6 (CH), 130.4 (CH), 141.6 (CH).

Diels–Alder reaction of the dienes **4a** *and* **4b**

Unless otherwise stated Diels–Alder reactions were carried out by heating a mixture of the diene and the dienophile in toluene solution at 140°C for 24 h. The product was isolated after solvent removal and filtration of the residual mass through a short column of silica gel.

Reaction of the diene **4a** *with methyl vinyl ketone*

The crude adduct was obtained as a liquid in 82% yield as a mixture (2:1) of two diastereomers from which the major diastereomer **15** (40 mg, 14%) crystallized (petroleum ether 60–80°C); mp 114–116°C; [Found: C, 82.13; H, 11.11. $C_{17}H_{28}O$ requires C, 82.20; H, 11.36%]; $[\alpha]_D^{22}$=+111.29 (*c* 0.21, $CHCl_3$); ν_{max} (KBr) 1712 cm^{-1}; NMR: for the major adduct, δ_H (300 MHz, $CDCl_3$) 0.83 (3H, s, $-CH_3$), 0.97 (3H, s, $-CH_3$), 1.01 (3H, s, $-CH_3$), 1.69 (3H, s, $-CH_3$), 1.33–2.04 (10H, m), 2.21 (3H, s, $-COCH_3$), 2.70 (1H, br s), 2.81 (1H, m), 5.58 (1H, br s, =CH); δ_C (75 MHz, $CDCl_3$) 19.1 (CH_3), 19.4 (CH_2), 23.9 (CH_3), 24.0 (CH_3), 25.4 (CH_3), 25.4 (CH_2), 28.0 (CH_2), 30.8 (CH_3), 38.3 (CH_2), 41.1 (CH_2), 44.4 (CH_3), 45.4 (C), 49.2 (C), 50.7 (CH_3), 122.8 (CH), 133.8 (C), 213.0 (CO); for the minor adduct, δ_C (75 MHz, $CDCl_3$) 19.0 (CH_2), 19.8 (CH_3), 23.8 (CH_2), 24.5 (CH_3), 24.7 (CH_3), 25.8 (CH_3), 26.0 (CH_3), 26.4 (CH_2), 39.6 (CH_2), 40.4 (CH), 42.7 (CH_2), 43.2 (C), 47.7 (CH), 49.1 (C), 123.5 (CH), 134.2 (CH), 211.7 (CO).

Reaction of the diene **4a** *with maleic anhydride*

A mixture of the diene **4a** (400 mg, 2.24 mmol), maleic anhydride (240 mg, 2.47 mmol) and toluene (5 mL) was heated at 80°C for 2 h. The residue, after removal of toluene, was chromatographed (5% diethyl ether–petroleum ether 60–80°C) to afford a mixture of the adduct **17** and its diastereomer (380 mg, 61%) in 4:1 ratio; [Found: C, 73.46; H, 8.88. $C_{17}H_{24}O_3$ requires C, 73.88; H, 8.75%]; $[\alpha]_D^{30}$=+38.0 (*c* 0.60, $CHCl_3$); ν_{max} (Neat) 1841, 1778 cm^{-1}; NMR: for the major adduct, δ_H (300 MHz, $CDCl_3$) 0.81 (3H, s, $-CH_3$), 0.98 (3H, s, $-CH_3$), 1.07 (3H, s, $-CH_3$), 1.30–2.18 (10H, m), 2.29 (1H, br s), 2.63 (1H, d, J=13.5 Hz), 3.42 (2H, m) and 5.74 (1H, br s, =CH); δ_C (75 MHz, $CDCl_3$) 17.5 (CH_3), 19.5 (CH_2), 23.8 (CH_3), 25.2 (CH_3), 26.0 (CH_3), 29.7 (CH_2), 37.1 (CH_2), 40.4 (CH_2), 42.8 (CH), 43.1 (CH), 44.6 (CH), 45.5 (C), 46.2 (C), 125.0 (CH), 137.2 (C), 173.4 (CO), 174.4 (CO); for the minor adduct, δ_C (75 MHz, $CDCl_3$) 20.3 (CH_3), 21.8 (CH_3), 23.7 (CH_3), 24.6 (CH_3), 26.7 (CH_3), 30.2 (CH_2), 36.0 (CH_2), 40.6 (CH_2), 42.4 (CH), 42.5 (CH), 43.8 (CH), 46.0 (C), 46.9 (C), 127.1 (CH), 135.2 (C), 171.8 (CO), 174.5 (CO).

Reaction of the diene **4a** *with dimethylacetylene dicarboxylate*

The adduct **18** was obtained as a colorless liquid in 83% yield in ca. 1:1 mixture; ν_{max} (Neat) 1728 cm^{-1}; NMR: for one adduct, δ_H (300 MHz, $CDCl_3$) 0.73 (3H, s, $-CH_3$), 0.97 (3H, s, $-CH_3$), 1.05 (3H, s, $-CH_3$), 1.34–1.71 (6H, m), 1.78 (3H, s, $-CH_3$), 2.99 (1H, br d), 3.72 (3H, s, $-COOCH_3$), 3.74 (3H, s, $-COOCH_3$), 5.61 (1H, m, =CH); δ_C (75 MHz, $CDCl_3$) 17.3 (CH_3), 19.1 (CH_3), 19.9 (CH_2), 22.8 (CH_3), 25.5 (CH_3), 33.3 (CH_2), 37.4 (CH_2), 41.7 (CH_2), 45.0 (C), 47.2 (CH), 52.3 (OCH_3), 52.4 (OCH_3), 53.5 (C), 122.8 (CH), 131.4 (C), 135.2 (C), 138.9 (C), 168.9 (CO), 170.7 (CO); for the other adduct, δ_H 0.79 (s, $-CH_3$), 0.82 (s, $-CH_3$), 1.05 (s, $-CH_3$), 1.76 (s, $-CH_3$), 3.71 (s, $-COOCH_3$), 3.75 (s, $-COOCH_3$); δ_C (75 MHz, $CDCl_3$) 19.1 (CH_3), 19.2 (CH_2), 22.7 (CH_3), 24.4 (CH_3), 25.4 (CH_3), 34.3 (CH_2), 37.6 (CH_2), 41.9 (CH_2), 43.5 (OCH_3), 45.1 (C), 47.1 (CH), 52.4 (OCH_3), 53.8 (C), 125.1 (CH), 130.8 (C), 135.7 (C), 138.6 (C), 169.4 (CO), 169.9 (CO). An analytically pure sample could not be obtained due to its strong tendency to undergo aromatization.

Reaction of the Diene **4b** *with maleic anhydride*

The adduct **19** along with its other diastereoisomer was obtained as a colorless liquid in 82% yield in ca. 2:1 ratio; [Found: C, 73.48; H, 8.45. $C_{17}H_{24}O_3$ requires C, 73.88; H, 8.75%]; ν_{max} (Neat) 1847, 1776 cm^{-1}; NMR: for the major isomer, δ_H (300 MHz, $CDCl_3$) 0.82 (3H, s, $-CH_3$), 0.97 (3H, s, $-CH_3$), 1.12 (3H, s, $-CH_3$), 1.49 (d, J=7.3 Hz) merged with 1.41–2.43 (11H, m), 3.23–3.30 (1H, m), 3.44–3.71 (1H, m), 5.66–5.83 (1H, m, =CH), 6.09–6.18 (1H, m, =CH); δ_C (75 MHz, $CDCl_3$) 16.8 (CH_3), 18.0 (CH_3), 19.6 (CH_2), 24.4 (CH_3), 25.2 (CH_3), 31.0 (C), 31.1 (CH), 37.1 (CH_2), 40.4 (CH_2), 42.2 (CH), 46.6 (C), 46.9 (CH), 47.8 (CH), 132.1 (CH), 134.5 (CH), 171.9 (CO), 173.0 (CO); for the minor isomer, δ_H 0.81 (s, CH_3), 0.95 (s, CH_3), 1.15 (s, CH_3), 1.42 (d, J=7.3 Hz); δ_C (75 MHz, $CDCl_3$) 16.6 (CH_3), 20.5 (CH_2), 22.7 (CH_3), 24.4 (CH_3), 26.9 (CH_3), 31.0 (CH), 35.2 (CH_2), 40.2 (CH_2), 41.3 (CH), 45.5 (CH), 46.2 (C), 46.4 (C), 46.9 (CH), 132.3 (CH), 134.5 (CH), 166.7 (CO), 170.1 (CO).

4.1.9. 6-(1′,2′,2′-Trimethyl cyclopentyl)-p-tolyl acetophenone (16). A mixture of the methyl ketone **15** (50 mg, 0.2 mmol) and 10% Pd–C (50 mg) in xylene (1 mL) was heated at 150°C for 3 h. The mass obtained after removal of the solvent was chromatographed (8% diethyl ether–petroleum ether 60–80°C) to afford the aromatic ketone **16** (30 mg, 57%); [Found: C, 83.32; H, 9.87. $C_{17}H_{24}O$ requires C, 83.55; H, 9.90%]; ν_{max} (Neat) 1691, 1604 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.56 (3H, s, $-CH_3$), 1.14 (3H, s, $-CH_3$), 1.27 (3H, s, $-CH_3$), 2.27 (3H, s, $-CH_3$), 2.48 (3H, s, $-CH_3$), 6.86 (1H, d, J=7.8 Hz, C-3), 6.93 (1H, d, J=7.7 Hz, C-2), 7.19 (1H, s, C-5); δ_C (75 MHz, $CDCl_3$) 20.0 (CH_2), 21.9 (CH_3), 25.2 (CH_3), 26.2 (CH_3), 26.9 (CH_3), 33.2 (CH_3), 39.0 (CH_2), 40.5 (CH_2), 46.1 (C), 52.2 (C), 125.8 (CH), 126.2 (CH), 130.2 (CH), 138.0 (C), 140.9 (C), 144.8 (C), 208.8 (CO).

4.1.10. 6-(1′,2′,2′-Trimethyl cyclopentyl-4-methyl-cyclohex-4-ene-1,2-dicarboxylic acid (20). A solution of the anhydride **17** (300 mg, 1.09 mmol) in ethanol (5 mL), was refluxed with a solution of sodium hydroxide (110 mg, 2.72 mmol) in water (1.5 mL) for 1 h. The reaction mixture was concentrated under reduced pressure and worked-up with diethyl ether to remove unhydrolysed material. The basic aqueous part left after ether work-up was acidified by aqueous HCl (5 mL, 6N). Usual work-up with diethyl ether afforded the dicarboxylic acid **20** as a white solid (300 mg, 94%); mp 117–119°C; $[\alpha]_D^{30}$=+28.53 (c 0.34, $CHCl_3$); [Found: C, 69.76; H, 8.80. $C_{17}H_{26}O_4$ requires C, 69.36; H, 8.90%]; ν_{max} (KBr) 1710 cm^{-1}; NMR: for the major isomer, δ_H (300 MHz, $CDCl_3$) (dimethyl ester) δ 0.72 (3H, s, $-CH_3$), 0.91 (3H, s, $-CH_3$), 1.08 (3H, s, $-CH_3$), 1.26–2.26 (5H, m), 1.74 (3H, br s), 2.14–2.21 (2H, m), 2.60–2.64 (2H, m), 2.90–2.97 (1H, m), 3.08 (1H, t, J=3.8 Hz), 3.62 (3H, s, $-COOCH_3$), 3.68 (3H, s, $-COOCH_3$), 5.45 (1H, br s, =CH); δ_C (75 MHz, $CDCl_3$) 17.1 (CH_3), 19.0 (CH_2), 23.5 (CH_3), 25.8 (CH_3), 25.9 (CH_3), 30.2 (CH_2), 37.3 (CH_2), 41.3 (CH_2), 41.7 (CH), 44.4 (CH), 45.3 (C), 46.1 (CH), 47.2 (C), 51.2 (CH_3), 51.9 (CH_3), 120.2 (CH), 134.0 (C), 173.7 (CO), 174.4 (CO); for the minor isomer, δ_C (75 MHz, $CDCl_3$) 18.2 (CH_3), 18.9 (CH_2), 23.7 (CH_3), 24.6 (CH_3), 24.8 (CH_3), 29.7 (CH_2), 37.1 (CH_2), 42.2 (CH_2), 42.3 (CH), 44.4 (C), 44.5 (CH), 46.0 (C), 47.2 (CH), 51.1 (CH_3), 51.8 (CH_3), 121.7 (CH), 133.4 (C), 173.8 (CO), 174.2 (CO).

4.1.11. 6-(1′,2′,2′-Trimethylcyclopentyl)-3-methylcyclohex-4-ene-1,2-dicarboxylic acid (21). Following the above procedure the mixture of the anhydride **19** and its diastereoisomer (200 mg, 0.725 mmol) was hydrolysed to afford the dicarboxylic acid mixture **21** as a white solid (200 mg, 94%); mp 68–70°C; [Found: C, 69.16; H, 9.11. $C_{17}H_{26}O_4$ requires C, 69.36; H, 8.90%]; ν_{max} (KBr) 2960, 2873, 1710, 1469, 1425, 1375, 1284, 1226, 1180, 1109, 1095, 1041, 933 cm^{-1}.

4.1.12. Herbertene (1a). A solution of the diacid **20** (100 mg, 0.34 mmol) in benzene (12 mL) containing acridine (0.15 g, 0.82 mmol) was irradiated with a medium pressure 450W Hanovia Hg vapor lamp through a water cooled pyrex immersion well for 2 h. The reaction mixture was then washed successively with HCl (3×3 mL, 6N), saturated $NaHCO_3$ solution (3×2 mL) and brine (3 mL). Evaporation of the solvent followed by column chromatography of the residual mass (3% diethyl ether–petroleum ether 60–80°C) afforded an oil (28 mg, 40%) containing the diene **22** as the major component, δ_H (300 MHz, $CDCl_3$) 0.72 (3H, s, $-CH_3$), 1.02 (3H, s, $-CH_3$), 1.25 (3H, s, $-CH_3$), 1.57 (3H, s, $-CH_3$), 2.34–2.84 (3H, m), 2.84 (1H, br s), 5.31–5.81 (3H, m, =CH); δ_C (75 MHz, $CDCl_3$) 18.4 (CH_3), 19.8 (CH_2), 23.9 (CH_3), 25.4 (CH_3), 25.9 (CH_3), 30.1 (CH_2), 31.5 (CH_2), 39.0 (CH_2), 39.6 (C), 44.4 (CH), 50.4 (C), 122.3 (CH), 125.7 (CH), 129.2 (CH), 132.7 (C); and possibly a trace of the corresponding conjugated diene as indicated by the presence of two olefinic CH units and two olefinic quaternary carbons in ^{13}C NMR; δ_C (75 MHz, $CDCl_3$) 18.5 (CH_3), 19.7 (CH_2), 24.0 (CH_3), 25.4 (CH_3), 26.0 (CH_3), 30.1 (CH_2), 31.5 (CH_2), 39.0 (CH_2), 39.5 (C), 44.3 (CH), 50.5 (C), 123.5 (CH), 124.5 (C), 127.7 (CH), 130.8 (C). Without further purification a solution of this diene mixture **22** (40 mg, 0.196 mmol) in benzene (3 mL) was heated with DDQ (80 mg, 0.36 mmol) at 60°C for 24 h. Diethyl ether (5 mL) was added to the reaction mixture. The organic layer was washed with aqueous NaOH (3×1 mL, 1 M), brine (2×1 mL) and dried over Na_2SO_4. Evaporation of the solvent followed by column chromatography (4% diethyl ehter–petroleum ether 60–80°C) afforded herbertene **1a** (28 mg, 70%); $[\alpha]_D^{30}$=+56.85 (c 0.54, $CHCl_3$); [the natural enantiomer (−)-herbertene exhibits $[\alpha]_D^{30}$=−56 (c 1.4, $CHCl_3$)];[5c] δ_H (300 MHz, $CDCl_3$) 0.56 (3H, s, $-CH_3$), 1.07 (3H, s, $-CH_3$), 1.26 (3H, s, $-CH_3$), 1.64–1.81 (6H, m), 2.35 (3H, s, $-CH_3$), 6.99 (1H, m), 7.16 (2H, m), 7.26 (1H, m); δ_C (75 MHz, $CDCl_3$) 20.1 (CH_2), 22.2 (CH_3), 24.7 (CH_3), 24.8 (CH_3), 26.9 (CH_3), 37.2 (CH_2), 40.2 (CH_2), 44.6 (C), 50.9 (C), 124.5 (CH), 126.5 (CH), 127.7 (CH), 128.2 (CH), 137.1 (C), 148.0 (C). ^1H and ^{13}C NMR spectra data were found identical with those reported in the literature.[5b]

4.1.13. Cuparene (2a). Following the above procedure the diacid **21** (0.16 mg, 0.54 mmol) was bisdecarboxylated to afford the diene **23** (22 mg, 20%). Without further purification the crude product (40 mg, 0.2 mmol) was immediately aromatised with DDQ (80 mg, 0.36 mmol) according to the procedure used for the synthesis of herbertene to afford cuparene **2a** (18 mg, 67%); $[\alpha]_D^{32}$=+54.05 (c 0.42, $CHCl_3$) [lit.[9] $[\alpha]_D^{20}$=+65, c 5.9, $CHCl_3$]; δ_H (300 MHz, $CDCl_3$) 0.56 (3H, s, $-CH_3$), 1.06 (3H, s, $-CH_3$), 1.26 (3H, s, $-CH_3$), 1.54–1.81 (5H, m), 2.50 (1H, m), 2.31 (3H, s, $-CH_3$), 7.08 (2H, d, J=8.07 Hz), 7.24 (2H, d, J=8.25 Hz); δ_C (75 MHz, $CDCl_3$) 20.2 (CH_2), 21.2 (CH_3), 24.7 (CH_3), 24.8 (CH_3), 26.9 (CH_2), 44.6 (C), 50.7 (C), 127.3 (CH), 128.6 (CH), 135.1 (C), 144.9 (C).

4.1.14. 6-(1′,2′,2′-Trimethyl)-4-methylphenyl-1,2-dimethylcarboxylate (24). The diene **18** (300 mg, 0.94 mmol) on aromatization with DDQ (0.43 g, 1.88 mmol) afforded the diester **24** (210 mg, 72%). [Found: C, 71.28; H, 8.22. $C_{19}H_{26}O_4$ requires C, 71.67; H, 8.23]; ν_{max} (Neat) 1739, 1732, 1606 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.69 (3H, s, $-CH_3$), 1.23 (3H, s, $-CH_3$), 1.31 (3H, s, $-CH_3$), 1.50–1.84 (6H, m), 2.38 (3H, s, $-CH_3$), 3.85 (3H, s, $-COOCH_3$), 3.88 (3H, s. $-COOCH_3$), 7.58 (1H, s, C-5), 7.65 (1H, s, C-3); δ_C (75 MHz, $CDCl_3$) 19.9 (CH_2), 21.7 (CH_3), 25.5 (CH_3), 26.0 (CH_3), 27.1 (CH_3), 35.8 (CH_2), 40.4 (CH_2), 46.2 (C), 52.7 (C), 128.9 (CH), 129.0 (C), 131.9 (C), 134.6 (CH), 137.9 (C), 146.1 (C), 167.4 (CO), 172.0 (CO).

4.1.15. Hydrolysis of the diester 24. Synthesis of the monocarboxylic acid 26. A solution of the aromatic diester **24** (50 mg, 0.157 mmol) in aqueous (0.3 mL) ethanolic (2 mL) sodium hydroxide (30 mg, 0.8 mmol) was heated under reflux for 4 h. The reaction mixture was concentrated under reduced pressure and worked up with diethyl ether. The basic aqueous part left after work up was acidified by aqueous HCl (2 mL, 6N). Usual work up with diethyl ether afforded the monocarboxylic acid **26** as a white solid (45 mg, 94%); mp 154°C; [Found: C, 70.70; H, 7.59. $C_{18}H_{24}O_4$ requires: C, 71.04; H, 7.95.]; ν_{max} (KBr) 1704, 1699, 1606 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.69 (3H, s, $-CH_3$), 1.21 (3H, s, $-CH_3$), 1.32 (3H, s, $-CH_3$), 1.49–1.82 (6H, m), 2.39 (3H, s, $-CH_3$), 3.85 (3H, s, $-COOCH_3$), 7.62 (1H, s, C-5), 7.75 (1H, s, C-3); δ_C (75 MHz, $CDCl_3$) 19.9 (CH_2), 21.7 (CH_3), 25.5 (CH_3), 26.0 (CH_3), 27.0 (CH_3), 30.1 (C), 35.8 (CH_2), 40.4 (CH_2), 46.2 (C), 52.9 (OCH_3), 127.9 (C), 129.7 (CH), 132.3 (C), 133.7 (C), 135.4 (CH), 138.1 (C), 171.4 (CO), 171.9 (CO).

4.1.16. Attempted hydrolysis of the methylester 26. Synthesis of the anhydride 27. A solution of the methyl ester **26** (40 mg, 0.13 mmol) was added dropwise to a magnetically stirred ice-cold H_2SO_4 (0.8 mL, 96%) and stirring continued for 1 h at that temperature. The reaction mixture was poured into ice-cold water (0.5 mL) and worked up in the usual way with diethyl ether to afford the anhydride **27** as a white solid (30 mg, 86%); mp 113–115°C; [Found: C, 74.69; H, 7.27. $C_{17}H_{20}O_3$ requires C, 74.97; H, 7.40]; ν_{max} (KBr) 1838, 1778, 1616 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.78 (3H, s, $-CH_3$), 1.19 (3H, s, $-CH_3$) 1.60 (3H, s, $-CH_3$), 1.51–2.19 (6H, m), 2.54 (3H, s, $-CH_3$), 7.68 (1H, s, C-5), 7.70 (1H, s, C-3); δ_C (75 MHz, $CDCl_3$) 20.6 (CH_2), 22.6 (CH_3), 23.7 (CH_3), 25.5 (CH_3), 26.1 (CH_3), 39.8 (CH_2), 41.2 (CH_2), 46.5 (C), 52.7 (C), 124.1 (CH), 128.7 (C), 134.1 (C), 137.6 (CH), 146.8 (C), 152.3 (CO), 152.3 (C), 163.0 (CO).

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8. Crystallographic data for compound **15** has been deposited with the cambridge crystallographic data centre as supplementary publication number CCDC 204294. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: +44-1233-336033, e-mail: deposit@ccdc.cam.ac.uk.
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