Further investigations into the preparation and [4+2] cycloaddition reactions of vinyl norcaradiene derivatives

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Dedicated to Professor Keiichiro Fukumoto on the occasion of his 70th birthday

(received 30 May 03; accepted 22 July 03; published on the web 04 Aug 03)

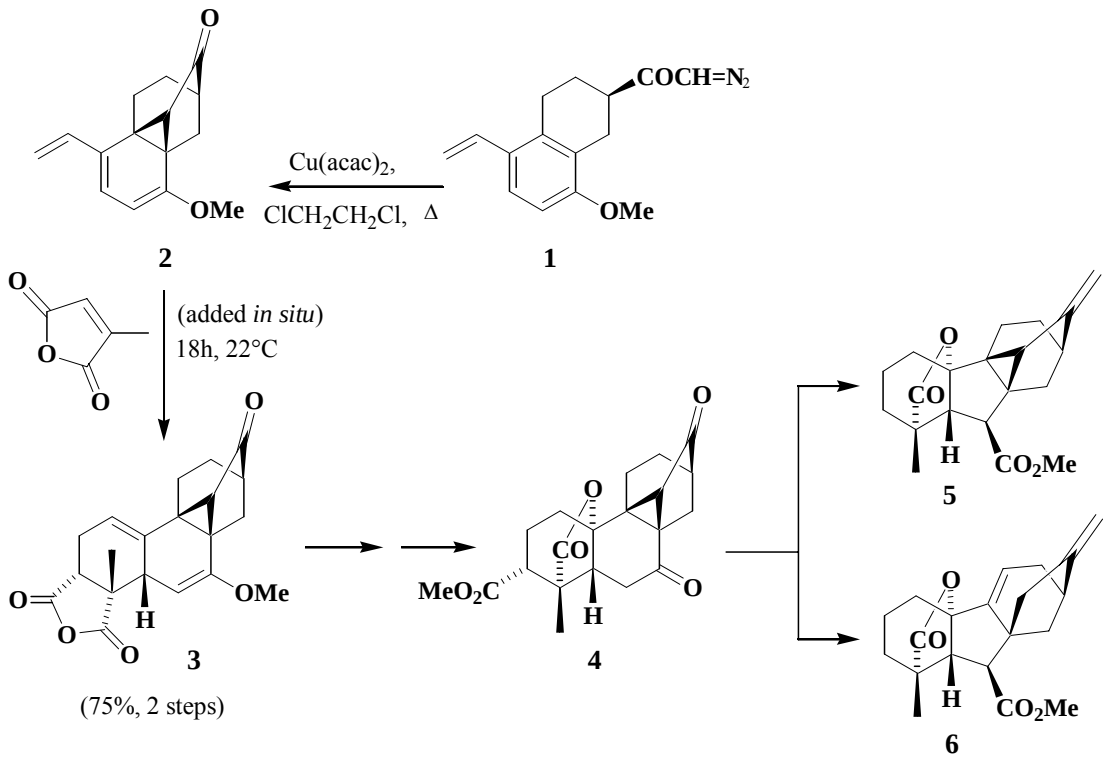
Abstract

Norcaradiene derivatives derived from the copper-catalyzed intramolecular cyclopropanation reactions of 2-(5-vinyl-1,2,3,4-tetrahydronaphthalene) diazomethyl ketones have been prepared and submitted to Diels–Alder reactions with a range of dienophiles, including methyl acrylate, methyl 2-chloroacrylate, maleic anhydride and citraconic anhydride. The cycloaddition reactions gave better yields and were more selective when the vinyl norcaradienes were based on 8-methoxynaphthyl diazoketones.

Keywords: Diazoketone, norcaradiene, Diels–Alder, cycloaddition

Introduction

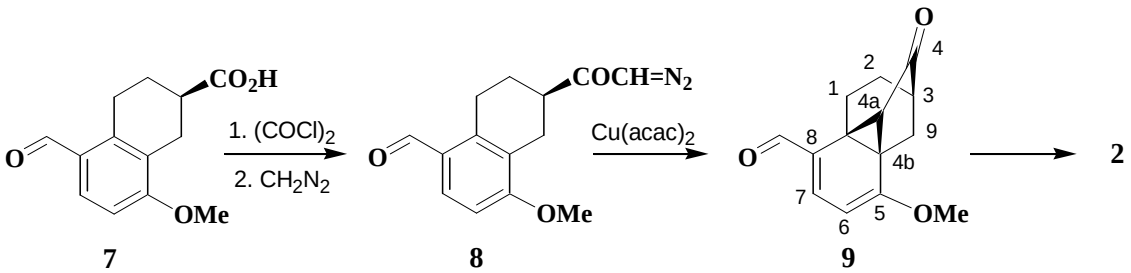
We recently described a new and efficient strategy for the synthesis of the gibberellin-derived antheridiogens **5** and **6** as outlined in Scheme 1.[1] Of special note is the cyclopropanation step followed by the pivotal *in situ* cycloaddition[2] to allow the stereocontrolled elaboration of the key intermediate **3**, an exceptionally versatile intermediate for the preparation of a wide range of tetracyclic diterpenoids.[3] This sequence, however, was the culmination of extensive explorations with several analogues of both the diene and dienophile participants. In this paper, we disclose the details of those investigations.



Scheme 1

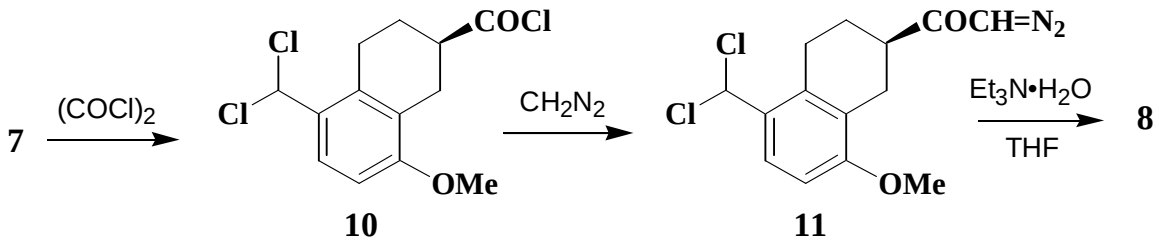
Results and Discussion

Our early attempts to prepare the styrene diazoketone **1** using standard procedures (diazomethane treatment of the acid chloride)[4] were thwarted by the polymerization of the styrene moiety on exposure to adventitious acid generated during formation of the acid chloride. We therefore decided to approach the preparation of the cyclopropyl ketone **2** *via* the analogous aldehyde, as outlined in Scheme 2.



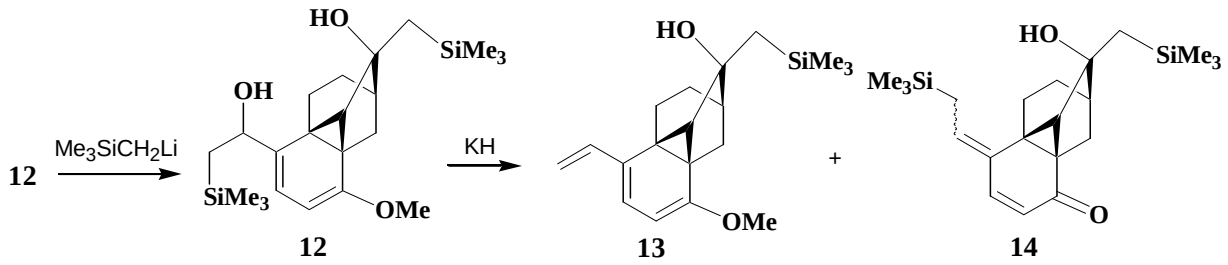
Scheme 2

Treatment of the acid **7**[5] with oxalyl chloride and a catalytic amount of DMF in dichloromethane (Scheme 3) resulted in a single compound, but ^{1}H- and ^{13}C NMR spectroscopy revealed the disappearance of the aldehyde functionality. The presence of an acid chloride moiety was confirmed by an absorption at 1790 cm^{-1} in the infrared spectrum, while the ^{1}H NMR spectrum was essentially the same as that of the acid, with the exception of a singlet resonating at 6.91 ppm in lieu of the aldehyde proton; the ^{13}C APT spectrum showed a methine resonance at 69.6 ppm. We concluded, therefore, that the carboxaldehye function had been replaced by a dichloromethyl group, and pressed on with the elaboration of the diazoketone **11** which, when dissolved in a mixture of triethylamine and aqueous acetone, afforded the desired diazoketone **8** in 63% overall yield. The presence of the diazoketone function was confirmed by the infrared absorption at 2105 cm^{-1} and a broad signal at 5.45 ppm in the ^{1}H NMR spectrum. The broadness of the peak from the proton attached to the diazoketone moiety has been ascribed to free rotation about the C–C bond being hindered as a result of the interaction of the π-electrons on the α-carbon with the π-system of the carbonyl group, resulting in an equilibrium mixture of *cis*- and *trans*- rotamers.[6] Finally, the diazoketone **8** was treated with catalytic $Cu(acac)_2$ in dry 1,2-dichloroethane at reflux, to give the formylnorcaradiene **9** in 65% yield.



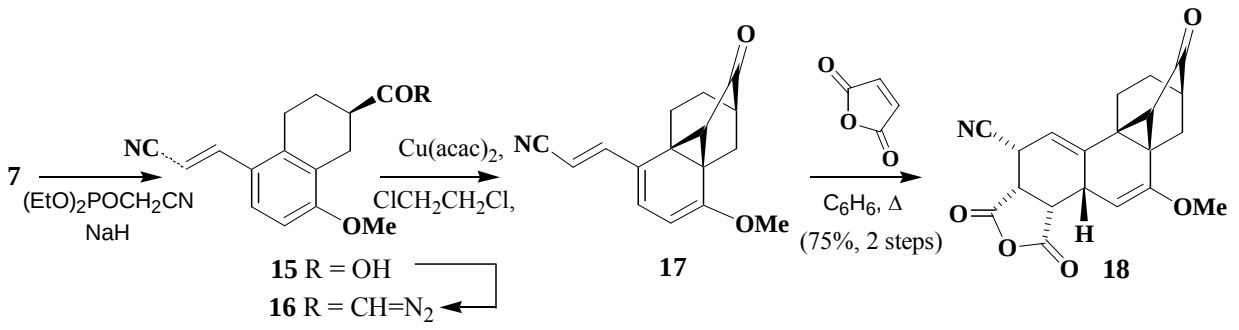
Scheme 3

Attempts to methylenate the aldehyde function in the norcaradiene **9** were initially fruitless, with the Wittig reaction, Lombardo–Oshima reaction,[7] and treatment with zirconium cyclopentadiene dichloride/diiodomethane[8] all resulting in rapid decomposition of the substrate. Limited success was achieved with the Peterson reagent, TMS-CH_2Li,[9] however (Scheme 4). Addition of three molar equivalents at 0 °C, followed by KH, resulted in the formation of two unstable compounds in low yield. One was identified as the desired triene **13** (from the ^{1}H NMR resonances typical of the vinyl group), while the other product appeared to be the enone **14**. ^{1}H NMR signals for two distinct TMS groups and a triplet at 6.05 ppm were considered diagnostic for the allyl-silane while a pair of doublets (J = 9.7 Hz) at 6.05 and 7.00 ppm was consistent with the α,β-enone moiety. The overall yield of these products was only 21% and this approach was accordingly abandoned.



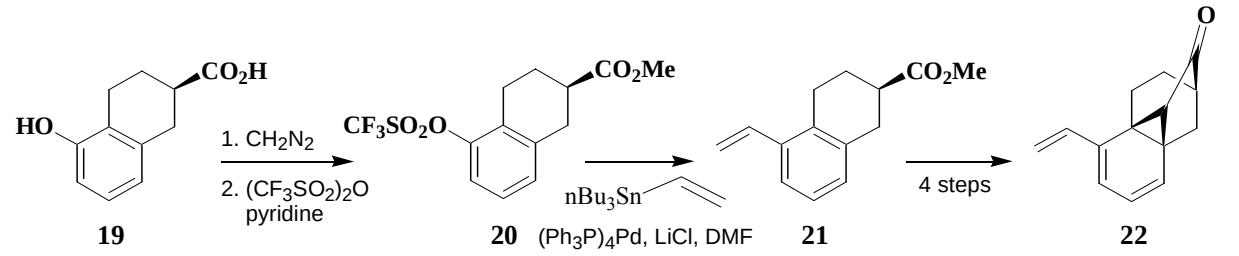
Scheme 4

Our next attempt to deal with the problem of the acid-promoted polymerization of the styrene functionality is outlined in Scheme 5. This approach involved the attachment of an electron-withdrawing group to the vinyl substituent. A nitrile group appeared particularly attractive, since nitriles, *inter alia*, can be converted into ketones *via* hydroperoxy derivatives[10] and would allow for straightforward functionalization of the A-ring subsequently. The cyanovinyl acid **15** was obtained as a 3:1 mixture of *E*- and *Z*- isomers from the formyl acid **7** in 90% yield using a Horner–Wadsworth–Emmons reaction.[11] Even though the *Z*-isomer was not expected to react under the Diels–Alder conditions,[12] the desired *E* isomer was easily separated by recrystallization from methanol. The large *trans* coupling (J = 16.4 Hz) of the alkene protons was compelling evidence for the stereochemistry of the double bond, while IR absorption at 2225 cm^{-1} and a ^{13}C NMR resonance at 118.8 ppm, confirmed that the nitrile group was present. When the *E*-cyanovinyl acid **15** was added to oxalyl chloride and a catalytic quantity of DMF in dichloromethane, a smooth reaction took place. Treatment of the crude product with an ethereal solution of diazomethane gave the diazoketone **16** as a yellow crystalline solid in 71% yield. Then cyclopropanation, under the same conditions as those used for the formyl diazoketone **8**, gave the *E*-cyanovinyl norcaradiene **17** in 60% yield. To test the use of the Diels–Alder reaction for the addition of the A-ring, norcaradiene **17** and maleic anhydride (carefully sublimed to remove any traces of maleic acid) were dissolved in benzene and the solution heated to 80 °C. After 48 hours the starting material had been totally consumed. Isolation and recrystallization of the residue from acetone afforded an especially insoluble white solid in 88% yield, with ^{1}H NMR spectroscopy indicating the presence of a single diastereomer presumed to be the *endo* adduct **18** resulting from addition to the lower face of triene **17** (cf., ref. 1). The small vicinal coupling constant between H-8 and H-9 indicated that these hydrogens were on the same side of the molecule (*i.e.*, *cis*), which confirmed that the *endo* adduct had been formed. In view of subsequent developments,[1] we have not yet pursued this chemistry further, but clearly, it has considerable potential.

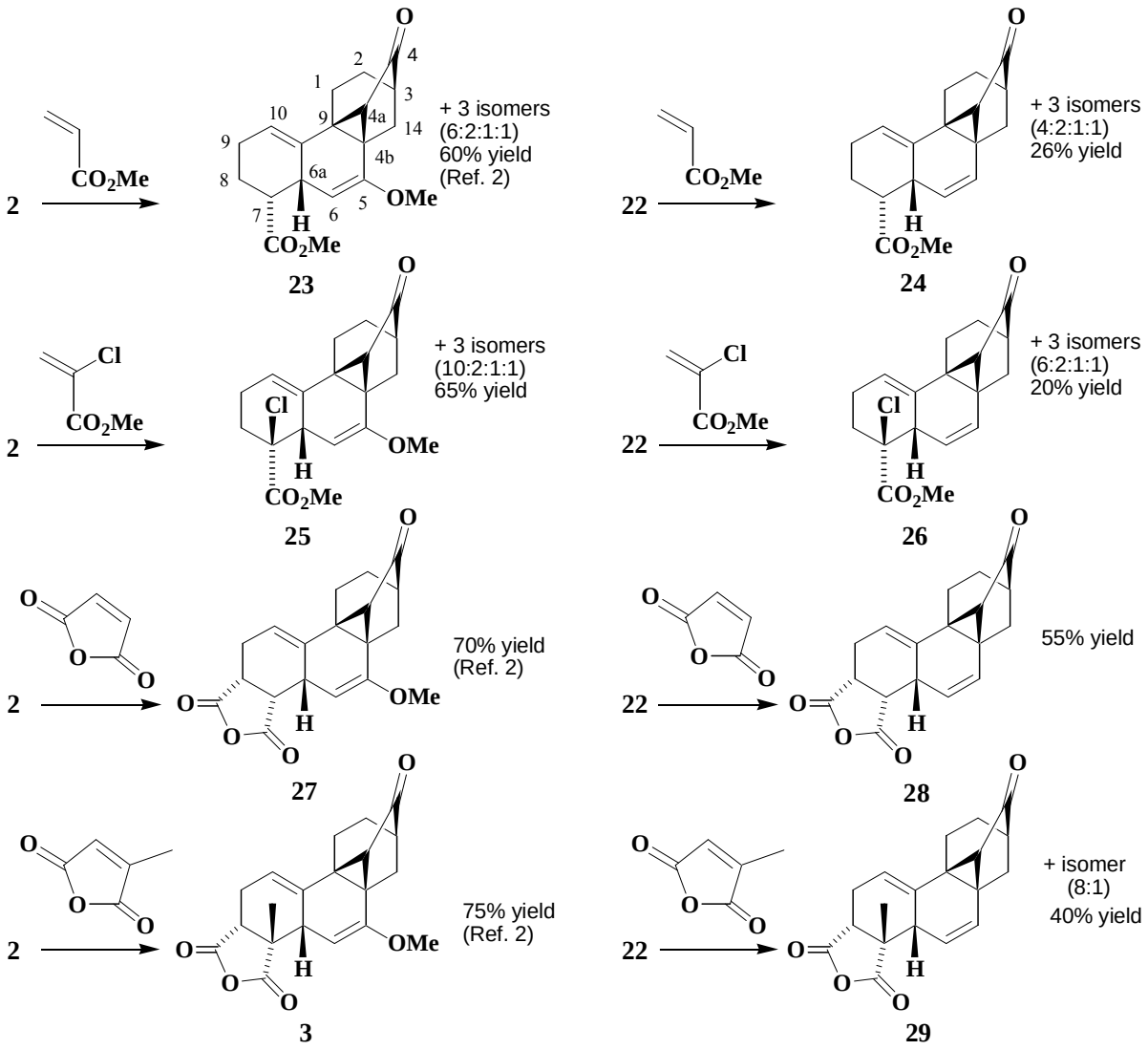


Scheme 5

As an alternative to deactivating the styrene functionality in the diazoketone precursors by the addition of an electron-withdrawing substituent, we decided to explore the prospects of utilizing the des-methoxy analogue of **1**, in the expectation that the reduction in electron density would afford more stable intermediates. The required starting material was prepared by means of a Stille coupling[13] (Scheme 6) and, indeed, the derived intermediates proved to be considerably more stable, allowing smooth elaboration of the vinyl norcaradiene **22** in good overall yield. In the meantime, we had solved the problem of preparing diazoketone **1** (as recorded elsewhere)[1,2] and so had in hand a good supply of both norcaradienes **2** and **22**, which allowed us to evaluate the suitability of various dienophiles for the addition of the A-ring. The results are summarized in Scheme 7, and include results from other studies for completeness. It is apparent from these outcomes that the more electron rich triene **2** affords superior yields and stereo-control, and so our efforts to date have been focused on its use. Nevertheless, the present disclosures allow us to define the scope and limitations of this strategy for the rapid assembly of kaurenoid- and related natural products. Minor variations in the substitution pattern of the initial substrates could allow access to atisane, stemarane and thyrsiflorane skeletons as well,[3] and although the present study has been conducted with racemates, good methodology for the enantioselective synthesis of tetralin carboxylic acids is available.[14]



Scheme 6



Scheme 7

Experimental Section

General Procedures. Infrared spectra (ν_{max}, cm^{-1}) were recorded on a Perkin–Elmer 1800 Fourier Transform Infrared spectrometer or a Perkin–Elmer 683 Infrared Spectrometer using NaCl or KI plates. NMR spectra were recorded on Varian Gemini 300 MHz or Varian VXR 500 MHz instruments. Chemical shifts are reported in parts per million (δ ppm). For proton spectra recorded in chloroform, the residual peak of $CHCl_3$ was used as the internal reference (7.26 ppm) while the central peak of $CDCl_3$ (77.0 ppm) was used as the reference for ^{13}C spectra. Multiplicities are abbreviated: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Coupling constants are recorded in Hertz (Hz). Distortionless enhancement by

polarization transfer (DEPT) and attached proton test (APT) experiments were used in the assignment of carbon spectra. Mass spectra (EIMS, 70 eV) were recorded on a VG Micromass 7070F double focusing mass spectrometer. Analytical thin layer chromatography (TLC) used Merck aluminum backed TLC sheets with silica gel 60 F254, or Merck glass-backed TLC plates coated with 0.2 mm thick silica gel GF254. The developed plates were visualized under short-wave UV light and exposed to an ammonium molybdate dip with heat. All flash chromatography used the flash technique as reported by Still[15] using Merck Kieselgel 60 and analytical reagent (AR) grade solvents as indicated. MPLC was conducted using a CfG Prominent Duramat® pump, a Waters Associates Differential Refractometer and Merck Lobar® Fertigsäule Größe LiChroprep® Si60 (40–63 μm) columns.

(2-*RS*)-Diazomethyl 5-formyl-8-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl ketone, (8). A solution of the acid **7**[5] (2 g, 8.55 mmol) in dichloromethane (150 mL) was added dropwise to a solution of oxalyl chloride (5 mL) and dichloromethane (15 mL) at room temperature under a nitrogen atmosphere. One drop of dry DMF was added (evolution of gas) and the resultant solution stirred for 14 h. The volatile components were removed *in vacuo* and the procedure repeated twice more to afford the *dichloromethyl acid chloride* **10** as a yellow oil (100%). IR ($CHCl_3$) 2950, 1790, 1590, 1480 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.00 (1H, m, H-3), 2.42 (1H, m, H-3), 2.79–3.00 (2H, m, H-2 and H-1), 3.05–3.30 (3H, m, H-1, H-4 × 2), 3.88 (3H, s, OMe), 6.81 (1H, d, *J* = 8.7 Hz, H-7), 6.91 (1H, s, C***H***Cl_2), 7.69 (1H, d, *J* = 8.7 Hz, H-6). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.4 (CH_2), 24.9 (CH_2), 25.9 (CH_2), 30.5 (C-2), 55.4 (OMe), 69.6 (***C***HCl_2), 107.5 (C-7), 122.8 (C-8a), 126.3 (C-6), 129.6 (C-4a), 132.7 (C-5), 158.0 (C-8), 176.4 (***C***OCl).

After 1 h under high vacuum, to remove any traces of HCl, the oil was dissolved in dichloromethane (100 mL) and added dropwise to fresh ethereal diazomethane (0.4 *M*, 5 equiv.) at –20 °C under nitrogen. After stirring for 15 h, the yellow solution was filtered through Celite in a well-ventilated fume-hood. The solvent was removed *in vacuo* to afford the *dichloromethyl diazoketone* **11** as an orange oil (100%). IR ($CHCl_3$) 2970, 2105, 1640 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.80 (1H, m, H3), 2.15 (1H, m, H-3), 2.60 (1H, m, H-2), 2.55–3.15 (4H, m, H-1 and H-4), 3.82 (3H, s, OMe), 5.42 (1H, br s, COC***H***N_2), 6.76 (1H, d, *J* = 8.7 Hz, H-7), 6.90 (1H, s, C***H***Cl_2), 7.66 (1H, d, *J* = 8.7 Hz, H-6). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9 (2 × CH_2), 25.9 (CH_2), 44.2 (C2), 53.8 CO***C***HN_2), 55.2 (OMe), 69.6 (***C***HCl_2), 107.3 (C-7), 124.2 (C-8a), 125.9 (C6), 129.7 (C-4a), 133.3 (C5), 158.1 (C8), 197.0 (***C***$OCHN_2$).

The oil was dissolved in THF (65 mL), triethylamine (6 mL) and water (1.5 mL), and the resultant solution was stirred for 16 h. Most of the THF was removed *in vacuo* and the residue dissolved in dichloromethane. The solution was washed with water and brine. Evaporation of the solvent gave an orange oil, which was chromatographed on silica gel, using 50% ethyl acetate/hexane as eluent, to give in the following order of elution:

(1) (2-*RS*)-2-Chloromethyl 5-formyl-8-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl ketone as a white solid (265 mg, 12%); a small sample was recrystallized from ether as white needles, mp

145–147 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.75 (1H, m, H-3), 2.20 (1H, m, H-3), 2.70 (1H, dd, *J* = 12.0, 18.2 Hz, H-1), 2.95–3.20 (3H, m, H-1, H-2 and H-4), 3.54 (1H, dt, *J* = 4.6, 13.7 Hz, H-4), 3.92 (3H, s, OMe), 4.29 (2H, d, *J* = 1.3 Hz, COC***H*****$_2$**Cl), 6.85 (1H, d, *J* = 8.7 Hz, H-7), 7.68 (1H, d, *J* = 8.7 Hz, H-6), 10.04 (1H, s, CHO). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.6 (CH_2), 25.2 (CH_2), 26.3 (CH_2), 42.9 (***C***H_2Cl), 47.2 (C-2), 55.6 (OMe), 106.9 (C-7), 124.8 (C-8a), 127.1 (C-4a), 134.9 (C-6), 139.6 (C-5), 161.5 (C-8), 191.9 (CHO), 204.4 (***C***OCH_2Cl). MS (EI) *m/z* 266 (M^+, 25%), 230 (15), 217 (27), 189 (98), 187 (100), 161 (41), 144 (31), 128 (36), 115 (72), 91 (70), 77 (50), 63 (30), 51 (46). HRMS: found 266.0710; $C_{14}H_{15}{}^{35}ClO_3$ requires 266.0709.

(2) Diazoketone **8** as yellow crystals (1.39 g, 63%). A small sample was recrystallized from ether as yellow prisms, mp 126–128 °C. IR ($CHCl_3$) 2950, 2105, 1690, 1640, 1580, 1370 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70 (1H, m, H-3), 2.10 (1H, m, H-3), 2.53 (1H, m, H-2), 2.62 (1H, dd, *J* = 10.4, 17.5 Hz, H-1), 2.91 (1H, dd, *J* = 4.8, 17.5 Hz, H-1), 2.95 (1H, dd, *J* = 5.5, 10.8 Hz, H-4), 3.43 (1H, dt, *J* = 4.8, 18.4 Hz, H-4), 3.84 (3H, s, OMe), 5.45 (1H, br s, COC***H***N_2), 6.76 (1H, d, *J* = 8.7 Hz, H-7), 7.59 (1H, d, *J* = 8.7 Hz, H-6), 9.96 (1H, s, CHO). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0 (CH_2), 25.6 (CH_2), 26.1 (CH_2), 43.9 (C2), 53.7 (CO***C***HN_2), 55.4 (OMe), 106.7 (C7), 125.0 (C-8a), 126.8 (C-4a), 134.3 (C6), 139.6 (C5), 161.3 (C8), 191.6 (CHO), 197.1 (***C***OCHN_2). MS (EI) *m/z* 230 ($M^+ - N_2$, 51%), 202 (45), 187 (55), 175 (36), 159 (35), 144 (39), 128 (52), 115 (100), 91 (87), 77 (67), 63 (56), 51 (83). Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.83. Found: C, 64.88; H, 5.24; N, 10.60.

(3-*RS*,4a-*SR*,4b-*RS*,10b-*RS*)-8-Formyl-5-methoxy-2,3-dihydro-1-*H*-3,4b-methanocyclopropa-[1,2:1,3]-dibenzene-4-(4a-*H*)-one (9). Diazoketone **8** (45 mg, 0.174 mmol) in dry 1,2-dichloroethane (4 mL) was added to a solution of $Cu(acac)_2$ (0.9 mg, 2 mol %) in 1,2-dichloroethane (2 mL), heated at reflux, at a rate of 0.35 mL/min, using a syringe pump. The solution was then heated at reflux for 5 min. To remove the copper residues, the solution was filtered through a small plug of silica gel using 25% ethyl acetate/1,2-dichloroethane as the eluent to afford the impure norcaradiene as a yellow oil. The oil was purified using MPLC with 15% ethyl acetate/1,2-dichloroethane as eluent to give the *formyl norcaradiene* **9** as a yellow solid (27 mg, 65%). A small sample was sublimed at 100 °C at 0.01 mm Hg to give yellow needles, mp 151–153 °C. IR ($CHCl_3$) 2950, 1725, 1665, 1535 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (1H, s, H-4a), 1.80 (2H, m, H2×2), 1.82 (1H, d, *J* = 12.3 Hz, H-9α), 1.98 (1H, m, H-1α), 2.29 (1H, m, H-3), 2.77 (1H, m, H-9β), 3.49 (1H, m, H-1β), 3.66 (3H, s, OMe), 3.81 (3H, s, OMe), 5.36 (1H, d, *J* = 7.4 Hz, H-6), 6.82 (1H, d, *J* = 7.4 Hz, H-7), 9.38 (1H, br s, CHO). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2 (C1), 27.2 (C2), 27.7 (C9), 31.0 (C-4a), 41.2 (C3), 42.4 (C-4b), 44.7 (C-8a), 56.6 (OMe), 92.6 (C6), 130.9 (C8), 145.0 (C7), 167.3 (C5), 191.0 (CHO), 214.9 (C4). MS (EI) *m/z* 230 (M^+, 99%), 202 (71), 187(52), 174 (65), 161 (100), 146 (41), 131 (54), 115 (86), 103 (59), 91 (42), 77 (69), 63 (57), 51 (75). HRMS: found 230.0942; $C_{14}H_{14}O_3$ requires 230.0943. Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 73.35; H, 6.18.

Peterson reaction of formyl norcaradiene, 9

Trimethylsilylmethyllithium in pentane (1*M*, 1 mL) was added by syringe to an ice-cold solution of the cyclopropyl ketone **9** (63 mg, 0.274 mmol) in dry THF (10 mL) under a nitrogen

atmosphere. The solution was warmed to room temperature after 2 h. TLC analysis indicated that the starting material had been consumed and two new spots had appeared (in 10% ethyl acetate/hexane the two spots were at R_f 0.5 and 0.8). Potassium hydride (42 mg) was added and the suspension was stirred at room temperature for 18 h. The compound at R_f 0.5 had been replaced by a spot at R_f 0.3. Filtration through a very small plug of silica (to remove the potassium hydride) gave the mixture of compounds as an orange oil (60 mg). Chromatography on silica, using 10% ethyl acetate/hexane, gave the following, in order of elution:

(1) (3-*RS*,4-*RS*,4a-*SR*,4b-*RS*,10b-*RS*)-4-Hydroxy-5-methoxy-4-trimethylsilylmethyl-8-vinyl-2,3,4,4a-tetrahydro-1-*H*-3,4b-methanocyclopropa-[1,2:1,3]-dibenzene (13) (10 mg, 12%). The compound was unstable and only the ^{1}H NMR spectrum was recorded. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08 (9H, s, TMS), 0.52 (1H, s, H-4a), 1.00–1.45 (4H, m, CH_2TMS and H-2×2), 1.12 (1H, d, *J* = 9.8 Hz, H-9α), 1.70–2.00 (2H, m, H-1α and H-3), 2.40–2.55 (2H, m, H-1β and H-9β), 3.62 (3H, s, OMe), 4.90 (1H, d, *J* = 6.1 Hz, H-6), 4.95 (1H, dd, *J* = 1.0, 9.1 Hz, CH=C***H***$_2$), 5.35 (1H, dd, *J* = 1.0, 15.2 Hz, CH=C***H***$_2$), 5.92 (1H, d, *J* = 6.1 Hz, H-7), 6.41 (1H, dd, *J* = 9.1, 15.2 Hz, C***H***=CH_2).

(2) (3-*RS*,4-*RS*,4a-*SR*,4b-*RS*,10b-*RS*)-8-(Trimethylsilylethylidene)-4-hydroxy-5-methoxy-4-trimethylsilylmethyl-2,3,4,4a-tetrahydro-1-*H*-3,4b-methanocyclopropa-[1,2:1,3]-dibenzen-5-one (14) (9 mg, 9%). The compound was unstable and only the ^{1}H NMR spectrum was recorded. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (6H, s, TMS), 0.08 (12H, s, TMS), 1.05 (2H, AB system, δ_A = 1.02, δ_B = 1.08, J_{AB} = 12.0 Hz, CH_2TMS), 1.25 (2H, s, CH_2TMS), 1.40–2.10 (6H, m, H1×2, H-2×2, H-3 and H-4a), 2.50 (2H, m, H-9β and H-1β), 5.78 (1H, d, *J* = 1.0, 9.7 Hz, H-7), 6.05 (1H, dt, *J* = 1.0, 7.6 Hz, H-10), 7.00 (1H, d, *J* = 9.7 Hz, H-6).

(2-*RS*)-*E*- and *Z*-5-Cyanovinyl-8-methoxy-1,2,3,4-tetrahydro-2-naphthoic acid (15). Diethyl cyanomethyl phosphonate (3.2 mL, 4 equiv.) in dry THF (15 mL) was added dropwise to sodium hydride (765 mg) under a nitrogen atmosphere at 0 °C. The suspension was stirred for 5 min and the aldehyde **7** (1.5 g, 6.4 mmol) in THF (40 mL) was added rapidly from a dropping funnel. After stirring at 0 °C for 1 h the solution was warmed to room temperature and stirred for 2 h. The reaction was quenched with water and acidified to pH 1 with concentrated hydrochloric acid. The aqueous solution was extracted with ethyl acetate and the combined organic extracts washed with water and brine. The solvent was removed *in vacuo* to give a brown solid, which was purified by column chromatography using 1% CH_2Cl_2/50% ethyl acetate/49% hexane as eluent to give the mixture of *acids* **15** as a cream solid (1.48 g, 90%). ^{1}H NMR spectroscopy revealed that there was a 3:1 mixture of *E*- to *Z*- isomers. Two recrystallizations of the mixture with methanol gave the *E*- *acid* as pale yellow prisms (1.02 g, 62%), mp 189–191 °C. IR ($CHCl_3$) 3000, 2225, 1750, 1710, 1590 cm^{-1}. ^{1}H NMR (300 MHz, d_6-acetone) δ 1.85 (1H, m, H-3), 2.28 (1H, m, H-3), 2.63–2.85 (3H, m, H-2, H-1 and H-4), 2.96 (1H, dt, *J* = 5.0, 17.6 Hz, H-4), 3.08 (1H, m, H-1), 3.84 (3H, s, OMe), 5.66 (1H, d, *J* = 16.4 Hz, CH=CHCN), 6.71 (1H, d, *J* = 8.6 Hz, H-7), 7.36 (1H, d, *J* = 8.6 Hz, H-6), 7.62 (1H, d, *J* = 16.4 Hz, CH=CHCN). ^{13}C NMR (75 MHz, d_6-acetone) δ 24.8 (CH_2), 25.6 (CH_2), 25.8 (CH_2), 38.3 (C2), 55.4 (OMe), 94.5 (CH=***C***HCN), 107.5 (C7), 118.8 (CN), 124.6 (C-8a or C-4a), 124.7 (C6), 124.8 (C-4a or C-8a),

136.0 (C5), 147.8 (***C***H=CHCN), 159.5 (C8), 179.1 (CO_2H). MS (EI) *m/z* 257 (M^+, 32%), 210 (59), 195 (59), 180 (100), 167 (22), 153 (23), 140 (42), 128 (40), 115 (91), 102 (18), 84 (71), 77 (44), 63 (60), 51 (65). Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.17; H, 6.16; N, 5.12.

Concentration of the mother liquor gave the *Z*-acid as white prisms (0.43 g, 26%), mp 196–198 C. IR ($CHCl_3$) 3000, 2225, 1750, 1710, 1590 cm^{-1}. ^1H NMR (300 MHz, d_6-acetone) δ 1.82 (1H, m, H-3), 2.28 (1H, m, H-3), 2.66–2.85 (3H, m, H-2, H-1 and H-4), 2.86 (1H, dt, *J* = 5.0, 17.6 Hz, H-4), 3.04 (1H, m, H-1), 3.85 (3H, s, OMe), 5.48 (1H, d, *J* = 12.0 Hz, CH=CHCN), 6.91 (1H, d, *J* = 8.7 Hz, H-7), 7.40 (1H, d, *J* = 8.7 Hz, H-6), 7.76 (1H, d, *J* = 12.0 Hz, CH=CHCN). ^{13}C NMR (75 MHz, d_6-acetone) δ 26.3 (CH_2), 27.1 (CH_2), 27.3 (CH_2), 39.6 (C-2), 56.5 (OMe), 95.9 (CH=***C***HCN), 108.4 (C7), 118.9 (CN), 125.9 (C-8a or C-4a), 126.5 (C-4a or C-8a), 127.9 (C6), 137.7 (C5), 148.2 (***C***H=CHCN), 160.3 (C8), 177.4 (CO_2H). MS (EI) *m/z* 257 (M^+, 80%), 226 (17), 210 (94), 195 (69), 180 (100), 153 (28), 140 (30), 127 (27), 115 (63), 77 (37), 63 (41), 51 (43). HRMS: found 257.1053; $C_{15}H_{15}NO_3$ requires 257.1052.

(2-*RS*)-*E*-Diazomethyl-5-cyanovinyl-8-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl ketone (16). A solution of the *E*-acid **15** (1.02 g, 3.97 mmol) in dichloromethane (20 mL) was added dropwise to a solution of oxalyl chloride (5 mL) and dichloromethane (5 mL) at room temperature under a nitrogen atmosphere. One drop of dry DMF was added (evolution of gas) and the resultant solution stirred for 14 h. The volatile components were removed *in vacuo* and the procedure repeated twice more to afford the *acid chloride* as an orange solid. After 1 h under high vacuum, to remove any traces of HCl, the oil was dissolved in dichloromethane (30 mL) and added to fresh ethereal diazomethane at –20 C (methanol/ice bath) under nitrogen. After stirring for 15 h the yellow solution was filtered through Celite in a well-ventilated fume-hood. Evaporation of the solvent *in vacuo* gave an orange oil, which was chromatographed on silica gel using 50% ethyl acetate/5% 1,2-dichloroethane/45% hexane as eluent to give the *diazoketone* **16** as yellow crystals (796 mg, 71%). A small sample was recrystallized from ether to give yellow needles, mp 139–141 C. IR ($CHCl_3$) 2950, 2225, 2120, 1645, 1590 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.82 (1H, m, H-3), 2.15 (1H, m, H-3), 2.55 (1H, m, H-2), 2.60–2.80 (2H, m, H-4×2), 2.93 (2H, m, H-1×2), 3.84 (3H, s, OMe), 5.42 (1H, br s, $COCHN_2$), 5.66 (1H, d, *J* = 16.4 Hz, CH=CHCN), 6.71 (1H, d, *J* = 8.8 Hz, H-7), 7.35 (1H, d, *J* = 8.8 Hz, H-6), 7.60 (1H, d, *J* = 16.4 Hz, CH=CHCN). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.1 (CH_2), 25.9 (CH_2), 26.0 (CH_2), 44.2 (C2), 53.9 (CO***C***HN_2), 55.4 (OMe), 94.5 (CH=***C***HCN), 107.5 (C-7), 118.8 (CN), 124.7 (C-6), 124.7 (C-8a and C-4a), 136.0 (C-5), 147.7 (***C***H=CHCN), 159.4 (C-8), 196.9 ($COCHN_2$). MS (EI) *m/z* 281 (M^+, 2%), 253 (45), 210 (85), 195 (42), 155 (75), 140 (67), 128 (51), 115 (100), 77 (48), 63 (66), 51 (73). HRMS: found 281.1165; $C_{16}H_{15}N_3O_2$ requires 281.1164. Anal. Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 67.97; H, 5.42; N, 14.71.

(3-*RS*,4a-*SR*,4b-*RS*,10b-*RS*)-*E*-8-Cyanovinyl-5-methoxy-2,3,4,4a-tetrahydro-1*H*-3,4b-methanocyclopropa-[1,2:1,3]-dibenzene-4-one (17). The diazoketone **16** (796 mg, 2.83 mmol) in dry 1,2-dichloroethane (20 mL) was added to a solution of $Cu(acac)_2$ (7 mg, 2 mol %) in 1,2-dichloroethane (20 mL), at reflux, at a rate of 0.15 mL/min using a syringe pump. Upon addition

the solution was refluxed for 5 min. To remove the copper residues the solution was filtered through a small plug of silica gel using 50% ethyl acetate/1,2-dichloroethane as eluent to afford the impure norcaradiene as a yellow oil. The oil was purified using MPLC with 30% ethyl acetate/65% hexane/5% 1,2-dichloroethane as eluent to give the *cyano-norcaradiene* **17** as a yellow solid (430 mg, 60%). A small sample was recrystallized from ether as pale yellow needles, mp 130–132 °C. IR ($CHCl_3$) 2950, 2220, 1720, 1540 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (1H, d, *J* = 1.6 Hz, H-4a), 1.81 (1H, d, *J* = 12.4 Hz, H-9α), 1.80–2.05 (3H, m, H-2 × 2, H-1α), 2.30 (1H, m, H-3), 2.53 (1H, m, H-1β), 2.79 (1H, m, H-9β), 3.73 (3H, s, OMe), 5.19 (1H, d, *J* = 7.2 Hz, H-6), 5.44 (1H, d, *J* = 16.4 Hz, CH=CHCN), 6.35 (1H, d, *J* = 7.2 Hz, H-7), 7.09 (1H, d, *J* = 16.4 Hz, CH=CHCN). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3 (C1), 27.2 (C-2), 27.5 (C-9), 29.6 (C-4a), 40.7 (C-3), 42.0 (C-4b or -8a), 44.2 (C-8a or -4b), 56.1 (OMe), 92.6 (C-6), 93.2 (CH=***C***HCN), 118.8 (CN), 127.0 (C-8), 128.4 (C-7), 148.2 (CH=CHCN), 162.6 (C-5), 214.9 (C-4). MS (EI) *m/z* 253 (M^+, 100%), 202 (71), 187(52), 174 (65), 161 (100), 146 (41), 131 (54), 115 (86), 103 (59), 91 (42), 77 (69), 63 (57), 51 (75). Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.61; H, 5.96; N, 5.72.

(3-*RS*,4a-*SR*,4b-*RS*,6a-*SR*,7-*RS*,8-*SR*,9-*SR*,10b-*RS*)-9-Cyano-5-methoxy-2,3,6a,7,8,9-hexahydro-1-*H*-3,4b-methanobenzo-[1,3]-cyclopropa-[1,2-*a*]-naphthalen-4(4a-H)-one-7,8-dicarboxylic anhydride (18). The norcaradiene **17** (300 mg, 1.19 mmol) and freshly sublimed maleic anhydride (250 mg, 2.6 equiv.) were dissolved in dry benzene (30 mL). The solution was heated at 80 °C for 48 h, in which time a white solid precipitated from the reaction mixture. TLC analysis indicated that all of the starting material had been consumed. The solvent was removed on the rotary evaporator to afford a yellow solid (450 mg, >100%). ^1H NMR spectroscopy revealed that only one diastereoisomer had been formed. The solid was recrystallized from acetone to afford the *adduct* **18** as fine white needles (365 mg, 88%), m.p. 168–170 °C. ^1H NMR (300 MHz, d_6-acetone) δ 1.81 (1H, s, H-4a), 1.90 (1H, d, *J* = 12.3 Hz, H-11α), 1.90–2.10 (3H, m, H-2 ×2 and H-1α), 2.25 (1H, m, H-3), 2.69 (1H, m, H-1β), 2.78 (1H, m, H-11β), 3.35 (1H, m, H-6a), 3.78 (3H, s, OMe), 3.94 (1H, dd, *J* = 6.8, 9.3 Hz, H-7), 4.05 (1H, m, H-9), 4.20 (1H, dd, *J* = 5.3, 9.3 Hz, H-8), 4.89 (1H, d, *J* = 3.3 Hz, H-6), 6.39 (1H, m, H-10). ^{13}C NMR (75 MHz, d_6-acetone) δ 18.0 (C1), 25.1 (C-4a), 25.8 (C2), 26.1 (C-9), 33.1 (C-6a), 35.0 (C-4b or C-10b), 37.9 (C-10b or C-4b), 39.6 (C-7), 42.1 (C-8), 42.8 (C-3), 44.7 (C-9), 53.3 (OMe), 88.2 (C-6), 117.0 (CN), 119.7 (C-10), 139.4 (C-10a), 151.3 (C-5), 168.3 (C-12 or C-13), 169.6 (C-13 or C-12) 208.5 (C-4). MS (EI) *m/z* 351 (M^+, 28%), 323 (10), 278 (17), 253 (88), 236 (34), 222 (25), 210 (28), 197 (30), 166 (43), 153 (30), 140 (40), 127 (30), 115 (34), 89 (31), 77 (49), 63 (47), 55 (100), 51 (56). HRMS: found 351.11111; $C_{20}H_{17}NO_5$ requires 351.1108.

Methyl 5-hydroxy-1,2,3,4-tetrahydro-2-naphthoate. To a solution of 1,2,3,4-tetrahydro-5-hydroxy-2-naphthoic acid **19**[16] (4.0 g, 21 mmol) in ether (50 mL) was added an ethereal solution of diazomethane, until a persistent yellow coloration was observed. A drop of acetic acid was added and the excess diazomethane removed by bubbling nitrogen gas through the solution. The reaction mixture was filtered through a pad of Celite followed by removal of the solvent *in vacuo*. Purification by column chromatography (20% ethyl acetate/petrol) afforded *methyl 5-*

hydroxy-1,2,3,4-tetrahydro-2-naphthoate (3.95 g, 92%) as an off-white solid. IR (soln.) 3400–3200 (O–H), 3160 (ArC–H), 2960 (C–H), 1725 (C=O), 1590 (ArC=C) cm^{-1}. ^1H NMR δ 7.00 (1H, t, *J* = 7.9 Hz, H-7), 6.71 (1H, d, *J* = 7.9 Hz, H-8), 6.61 (1H, d, *J* = 7.9 Hz, H-6), 5.01 (1H, br s, OH), 3.73 (1H, s, OCH_3), 3.00–2.97 (2H, m, H-1), 2.88–2.86 (1H, m, H-4), 2.72–2.60 (2H, m, H-4 and H-2), 2.32–2.23 (1H, m, H-3), 1.91–1.77 (1H, m, H-3). ^{13}C NMR δ 176.2 (C=O), 153.3 (C5), 136.6 (C-8a), 126.4 (C7), 122.4 (C-4a), 121.3 (C8), 121.1 (C6), 51.9 (OCH_3), 39.6 (C2), 31.7 and 25.4 (C1 and C4), 22.3 (C3). LRMS 206 (M^+, 46%), 191 (M–CH_3, 2), 175 (M–OCH_3, 7), 146 (M–MeOH, CO, 100), 131 (32), 115 (22), 107 (18), 91 (26). HRMS: found (M^+) 206.0943; $C_{12}H_{14}O_3$ requires 206.0943.

Methyl 5-(trifluoromethanesulfonyloxy)-1,2,3,4-tetrahydro-2-naphthoate (20). To a solution of the phenol (3.65 g, 18 mmol) in pyridine (25 mL) at 0 C was added dropwise trifluoromethanesulfonic anhydride (freshly made from the acid: 4.5 mL, 1.5 equiv.) with fuming! The resulting red solution was allowed to warm overnight to room temperature, with stirring. The reaction mixture was poured into water and the aqueous layer extracted with ether (×3). The combined ethereal extracts were washed successively with water (×2), HCl (1 *M*, aq.), water, NaCl (satd. aq.) and finally dried over $MgSO_4$. Removal of the solvent under reduced pressure, followed by purification using column chromatography (5% ethyl acetate/petrol) afforded *methyl 5-(trifluoromethanesulfonyloxy)-1,2,3,4-tetrahydro-2-naphthoate* (**20**) (5.0 g, 83%) as a colorless oil, which formed white crystals when stored at 4 C. IR (soln.) 3030 (C=C–H), 2960 (C–H), 1760 (C=O), 1610 and 1550 (ArC=C), 1410 and 1210 (S=O), 1280 (C–F) cm^{-1}. ^1H NMR δ 7.15 (3H, m, Ar–H), 3.74 (3H, s, OCH_3), 3.11–3.04 (2H, m, H-1), 3.06–2.97 (1H, m, H-4), 2.82–2.70 (2H, m, H-4 and H-2), 2.33–2.23 (1H, m, H-3), 1.91–1.79 (1H, m, H-3). ^{13}C NMR δ 175.0 (C=O), 148.0 (C5), 138.4 (C-8a), 129.0 (C8), 128.9 (C-4a), 126.9 (C7), 118.6 (C6), 118.5 (q, $J_{C–F}$ = 320 Hz, CF_3), 51.9 (OCH_3), 38.9 (C2), 31.3 and 24.8 (C1 and C4), 22.8 (C3). LRMS 338 (M^+, 24%), 306 (M–MeOH, 20), 278 (M–MeOH, CO, 45), 145 (M–MeOH, CO, SO_2CF_3, 100), 69 (CF_3, 15). HRMS: found (M^+) 338.0437; $C_{13}H_{13}F_3O_5S$ requires 338.0436.

Methyl 5-vinyl-1,2,3,4-tetrahydro-2-naphthoate (21). To a solution of the triflate (5.0 g, 15 mmol), lithium chloride (1.9 g, 45 mmol, 3 equiv.) and palladium tetrakis-(triphenylphosphine) (870 mg, 0.75 mmol, 5 mol %) in dimethylformamide (50 mL) was added vinyl tri-*n*-butylstannane (5.3 mL, 18 mmol, 1.2 equiv.). The resulting pale yellow solution was heated to 100 C for 24 hours, during which the consumed catalyst was observed to form a black precipitate. After cooling to room temperature the reaction mixture was poured into NH_4OH solution (25%, aq) and the aqueous layer extracted with ether (× 3). The combined ethereal extracts were washed successively with additional NH_4OH (25%, aq), water (× 2), HCl (1 *M*, aq.), water, NaCl (satd aq.) and finally dried over $MgSO_4$. Removal of the solvent under reduced pressure, followed by purification using column chromatography (5% ethyl acetate/petrol) afforded the *vinyl ester* **21** (2.7g, 84%) as a colorless oil, IR (soln) 3090 and 3060 (C=C–H), 2930 (C–H), 1730 (C=O), 1630 (C=C), 1580 (ArC=C) cm^{-1}. ^1H NMR δ 7.32 (1H, d, *J* = 7.6 Hz, H-6), 7.13 (1H, t, *J* = 7.6 Hz, H-7), 7.05 (1H, d, *J* = 7.6 Hz, H-8), 6.91 (1H, dd, *J* = 17.3, 10.9 Hz, H-5a), 5.61 (1H, d, *J* = 17.3 Hz, H-5b-*trans*), 5.30 (1H, d, *J* = 10.9 Hz, H-5b-*cis*), 3.74 (3H,

s, OCH_3), 3.03 (2H, d, *J* = 8.1 Hz, H-1), 3.01–2.91 (1H, m, H-4), 2.80–2.66 (2H, m, H-4 and H-2), 2.31–2.25 (1H, m, H-3), 1.92–1.80 (1H, m, H-3). ^{13}C NMR δ 175.8 (C=O), 137.0 (C5), 135.0 (C-8a), 134.6 (C-5a), 132.9 (C-4a), 128.7 (C6), 125.8 (C8), 123.6 (C7), 115.8 (C-5b), 51.8 (OCH_3), 39.4 (C2), 32.2, 25.9 and 25.8 (3 × CH_2). LRMS 216 (M^+, 70%), 185 (M–OCH_3, 10), 156 (M–MeOH, CO, 100), 141 (73), 129 (54), 115 (50). HRMS: found (M^+) 216.1150; $C_{14}H_{16}O_2$ requires 216.1150.

5-Vinyl-1,2,3,4-tetrahydro-2-naphthoic acid. To a solution of the methyl ester (2.6 g, 12 mmol) in methanol (50 mL) was added sodium hydroxide solution (4 *M*, aq, from 14g NaOH in 100 mL, 30 equiv.). After 5 hours' stirring at room temperature the reaction mixture was acidified to pH 1. The aqueous solution was extracted with ethyl acetate (×3) and the combined organic layers washed with NaCl (satd aq.) and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded *5-vinyl-1,2,3,4-tetrahydro-2-naphthoic acid* (2.25 g, 94%) as a white solid. A small sample was recrystallized from ethyl acetate to afford white crystals, mp 118–120 C. IR (soln) 3400–3100 (O–H), 3090 and 3060 (C=C–H), 2940 (C–H), 1710 (C=O), 1625 (C=C), 1580 (ArC=C) cm^{-1}. ^{1}H NMR δ 7.35 (1H, d, *J* = 7.4 Hz, H-6), 7.15 (1H, t, *J* = 7.4 Hz, H-7), 7.07 (1H, d, *J* = 7.4 Hz, H-8), 6.93 (1H, dd, *J* = 17.4, 11.0 Hz, H-5a), 5.63 (1H, dd, *J* = 17.4, 1.5 Hz, H-5b-*trans*), 5.32 (1H, dd, *J* = 11.0, 1.5 Hz, H-5b-*cis*), 3.07 (2H, d, *J* = 8.2 Hz, H-1), 3.05–2.98 (1H, m, H-4), 2.82–2.72 (2H, m, H-4 and H-2), 2.38–2.28 (1H, m, H-3), 1.99–1.84 (1H, m, H-3). ^{13}C NMR δ 181.9 (C=O), 137.1 (C5), 134.7 (C-8a), 134.5 (C-5a), 132.8 (C-4a), 128.8 (C8), 125.9 (C6), 123.7 (C7), 115.9 (C-5b), 39.3 (C2), 31.9, 25.8 and 25.7 (3 × CH_2). LRMS 202 (M^+, 100%), 187 (M–CH_3, 8), 176 (4), 156 (M–H_2O, CO, 77), 141 (M–H_2O, CH_3, CO, 73), 129 (93), 115 (63). HRMS: found (M^+) 202.0994; $C_{13}H_{14}O_2$ requires 202.0994.

5-Vinyl-1,2,3,4-tetrahydro-2-naphthoyl chloride. To a solution of the acid (2.1 g, 11 mmol) in dichloromethane (50 mL) was added oxalyl chloride (10 mL, 120 mmol, 10 equiv.) and a single drop of dimethylformamide. After stirring at room temperature for 18 hours, the solvent was removed under reduced pressure, and the residue azeotroped with benzene (×3) [to remove residual oxalyl chloride and HCl]. The residue was dried under high vacuum for 1 hour, and the resulting orange oil was used directly in the next step. ^{1}H NMR δ 7.35 (1H, d, *J* = 7.4 Hz, H-6), 7.15 (1H, t, *J* = 7.4 Hz, H-7), 7.07 (1H, d, *J* = 7.4 Hz, H-8), 6.93 (1H, dd, *J* = 17.4, 11.0 Hz, H-5a), 5.63 (1H, dd, *J* = 17.4, 1.5 Hz, H-5b-*trans*), 5.32 (1H, dd, *J* = 11.0, 1.5 Hz, H-5b-*cis*), 3.20–3.08 (2H, m, H-1), 3.04–2.95 (1H, m, H-4), 2.83–2.73 (2H, m, H-4 and H-2), 2.48–2.39 (1H, m, H-3), 2.07–1.96 (1H, m, H-3). ^{13}C NMR δ 176.4 (C=O), 137.1 (C5), 134.2 (C-5a), 133.4 and 132.2 (C-8a and C-4a), 128.8 (C-8), 126.1 (C-6), 123.9 (C-7), 116.1 (C-5b), 51.3 (C-2), 32.2, 25.9 and 25.3 (3 × CH_2).

Diazomethyl 5-vinyl-1,2,3,4-tetrahydronaphthalen-2-yl ketone. To an ethereal solution of diazomethane at –20 C was added dropwise a solution of the crude acid chloride in dichloromethane (50 mL). The solution was allowed to warm gradually to room temperature with further stirring over 5 hours. Excess diazomethane was removed by bubbling nitrogen gas through the solution, after which the solution was filtered through a pad of Celite and the solvent removed in vacuo. Purification by column chromatography (20% ethyl acetate/petrol) afforded

diazomethyl 5-vinyl-1,2,3,4-tetrahydronaphthalen-2-yl ketone (2.0g, 80% from the acid) as a yellow crystalline solid. A small sample was recrystallized from dichloromethane to give pale yellow crystals, mp 59–61 C. IR (soln) 3050 and 3020 (C=C–H), 2940 (C–H), 2100 (C–HN_2), 1635 (C=O), 1580 (ArC=C), 1580 (C=N), 1455 and 1440 (N=N) cm^{-1}. ^{1}H NMR δ 7.35 (1H, d, *J* = 7.4 Hz, H-6), 7.15 (1H, t, *J* = 7.4 Hz, H-7), 7.07 (1H, d, *J* = 7.4 Hz, H-8), 6.93 (1H, dd, *J* = 17.4, 11.0 Hz, H-5a), 5.63 (1H, dd, *J* = 17.4, 1.5 Hz, H-5b-*trans*), 5.40 (1H, br s, CHN_2), 5.32 (1H, dd, *J* = 11.0, 1.5 Hz, H-5b-*cis*), 3.08–2.89 (3H, m, H-1 and H-4), 2.80–2.64 (2H, m, H-2 and H-4), 2.21–2.15 (1H, m, H-3), 1.92–1.82 (1H, m, H-3). ^{13}C NMR δ 197.2 (C=O), 136.9 (C5), 135.1 (C-8a), 134.5 (C-5a), 132.9 (C-4a), 128.7 (C8), 125.8 (C-6), 123.5 (C-7), 115.8 (C-5b), 53.8 (CHN_2), 45.1 (C-2), 32.3, 26.2 and 26.0 (3 × CH_2). LRMS 226 (M^+, 3%), 198 (M–N_2, 26%), 183 (23%), 170 (39), 155 (85), 141 (90), 128 (95), 115 (100). HRMS: found (M^+): 226.1105; $C_{14}H_{14}N_2O$ requires 226.1106. Anal. Calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.71; H, 6.40; N, 11.98.

8-Vinyl-2,3-dihydro-1*H*-3,4b-methanocyclopropa-[1,2:1,3]-dibenzene-4-(4a-*H*)-one (22). To a suspension of $Cu(acac)_2$ (2 mg, 2 mol%) in 1,2-dichloroethane (1 mL) at reflux was added dropwise via syringe pump a solution of diazoketone (46 mg, 0.2 mmol) in 1,2-dichloroethane (3 mL) over 1.5 hours. Complete consumption of the starting material was observed and the reaction allowed to cool to room temperature. Removal of the solvent under reduced pressure, followed by purification using column chromatography (10% ethyl acetate/petrol) afforded the major product **22** (12 mg, 32%) as a yellow oil. ^{1}H NMR δ 6.52 (1H, dd, *J* = 17.4, 11.0 Hz, H-10), 6.18 (1H, d, *J* = 13.7 Hz, H-5 or H-7), 6.15 (1H, d, *J* = 10.7 Hz, H-5 or H-7), 6.02 (1H, m, H-6), 5.48 (1H, d, *J* = 17.4 Hz, H-10a-*trans*), 5.14 (1H, d, *J* = 11.0 Hz, H-10a-*cis*), 2.56–2.48 (2H, m, H-9β, H-1), 2.27–2.25 (1H, m, H-3), 2.59–2.48 (1H, m, H-1), 2.52 (1H, d, *J* = 12.0 Hz, H-9α), 2.47–1.81 (2H, m, H-2), 1.78 (1H, s, H-4a). ^{13}C NMR δ 216.6 (C=O), 140.0 (CH_2=***C***H), 134.9 (C-8), 129.8, 122.7 and 119.7 (C-7, C-6 and C-5), 115.7 (CH_2=CH), 46.9 (C-8a), 44.6 (C-4b), 41.7 (C-3), 32.6 (C-4a), 30.7, 27.8 and 20.3 (3 × CH_2).

Methyl (3-*RS*,4a-*SR*,4b-*RS*,6a-*SR*,7-*RS*,10b-*RS*)-2,3,6a,7,8,9-hexahydro-1*H*-3,4b-methanobenzo-[1,3]-cyclopropa-[1,2-a]naphthalene-4-(4a*H*)-one-7-carboxylate (24). To a suspension of $Cu(acac)_2$ (5 mg, 2 mol%), in dichloroethane (5 mL) at reflux, was added dropwise *via* syringe pump a solution of the diazoketone (200 mg, 0.89 mmol) in dichloroethane (15 mL) over 1.5 hours. Complete consumption of the starting material was observed within 2 hours. Methyl acrylate (1.6 mL, 20 equiv.) was added and the solution heated to reflux for a further 20 hours, after which time the reaction was cooled to room temperature. Removal of the solvent *in vacuo*, followed by purification using column chromatography (20% ethyl acetate/petrol), afforded a mixture of three of the diastereomeric adducts (65 mg, 26%) in the ratio 4:2:1. The major isomer **24** was separated using MPLC. IR (soln) 2950 and 2870 (C–H), 1730 (C=O), cm^{-1}. ^{1}H NMR δ 5.85 (1H, dd, *J* = 9.6, 1.7 Hz, H-6), 5.61 (1H, m, H-1), 5.41 (1H, dd, *J* = 9.6, 1.7 Hz, H-7), 3.65 (3H, s, OCH_3), 2.89–2.84 (2H, m, H-4 and H-5), 2.39 (1H, s, H-15), 2.31–1.82 (10H, m), 1.99 (1H, d, *J* = 11.7 Hz, H-14α). ^{13}C NMR δ 213.4 (C16), 173.8 (C=O), 133.1 (C10), 127.5, 127.3 and 121.3 (C1, C6 and C7), 51.4 (OCH_3), 43.9, 43.2 and 41.9 (C4, C5 and C13), 40.8 and 38.9

(C8 and C9), 35.2 (C15), 32.4, 28.0, 24.1, 23.1 and 19.0 (5×CH_2). LRMS (M^+, 10%), 239 (32), 225 (M–CO_2CH_3, 12), 197 (retro-DA, 8), 180 (14), 169 (8), 152 (8), 141 (18), 132 (25), 84 (100). HRMS: found (M^+) 284.1413; $C_{18}H_{20}O_3$ requires 284.1412.

Methyl (3-*RS*,4a-*SR*,4b-*RS*,6a-*SR*,7-*SR*,10b-*RS*)-2,3,6a,7,8,9-7-chlorohexahydro-1*H*-3,4b-methano benzo-[1,3]-cyclopropa[1,2-a]naphthalene-4-(4a*H*),5(6*H*)-dione-7-carboxylate. To a suspension of $Cu(acac)_2$ (1 mg, 2 mol%), in dichloroethane (1 mL) at reflux, was added dropwise *via* syringe pump a solution of (±)-diazomethyl 8-methoxy-5-vinyl-1,2,3,4-tetrahydronaphthalen-2-yl ketone (40 mg, 0.16 mmol) in dichloroethane (4 mL) over the course of 1 hour. Complete consumption of the starting material was observed within 1.5 hours. Methyl 2-chloropropenoate (0.1 mL, 1.1 mmol, 7 equiv.) and 1,2-epoxybutane (0.2 mL) were added and the solution heated at reflux for a further 20 hours, after which the reaction was cooled to room temperature. Removal of the solvent *in vacuo* followed by purification using column chromatography (20% ethyl acetate/petrol) afforded a crude mixture of the four isomeric adducts, in the ratio 10:2:2:1. Further column chromatography isolated the major isomer as a pale yellow solid, which was determined to be the 5-one derived from hydrolysis of the enol ether **25** (35mg, 65%); IR (soln) 3030 (C=C–H), 2960 (C–H), 1740 (OC=O), 1690 (RC=O) cm^{-1}; ^{1}H NMR δ 5.79 (1H, m, H-1), 3.81 (3H, s, OCH_3), 3.02 (1H, s, H-15), 2.92 (1H, dd, *J* = 12.7, 6.0 Hz, H-14β), 2.70–2.40 (4H, m), 2.35–2.10 (5H, m), 2.05–1.85 (3H, m), 1.81 (1H, d, *J* = 12.7 Hz, H-14α). ^{13}C NMR δ 210.1 (C16), 209.7 (C7), 169.6 (C=O), 131.0 (C10), 121.7 (C1), 68.4 (C4), 53.0 (OCH_3), 47.8 and 44.9 (C8 and C9), 40.6, 40.5 and 38.6 (C5, C13 and C15), 29.5, 27.3, 26.9, 26.5, 22.2 and 18.4 (6 × CH_2). LRMS 334 (M^+, 92%), 298 (M–Cl, 62), 267 (M–Cl, OCH_3, 98), 239 (M–Cl, CO_2CH_3, 89), 214 (66), 128 (64), 91 (100). HRMS: found (M^+) 334.0971; $C_{18}H_{19}ClO_4$ requires 334.0972.

Methyl (3-*RS*,4a-*SR*,4b-*RS*,6a-*SR*,7-*SR*,10b-*RS*)-7-chloro-2,3,6a,7,8,9-hexahydro-1*H*-3,4b-methanobenzo-[1,3]-cyclopropa-[1,2-a]-naphthalene-4(4a-*H*)one-7-carboxylate (26). To a suspension of $Cu(acac)_2$ (2.5 mg, 2 mol%), in dichloroethane (2 mL) at reflux, was added dropwise *via* syringe pump a solution of the diazoketone (100 mg, 0.45 mmol) in dichloroethane (8 mL) over the course of 1 hour. Complete consumption of the starting material was observed within 1.5 hours. Methyl 2-chloropropenoate (0.2 mL, 2.2 mmol, 5 equiv.) was added and the solution heated to reflux for a further 20 hours, after which time the reaction was cooled to room temperature. Removal of the solvent *in vacuo* followed by purification using column chromatography (2% methanol/dichloromethane) afforded a crude mixture of three of the isomeric adducts. The major isomer **26** was separated by further column chromatography (20 mg, 15%). ^{1}H NMR δ 5.93 (1H, dd, *J* = 9.8, 3.2 Hz, H-6), 5.81 (1H, dd, *J* = 9.8, 2.2 Hz, H-7), 5.64–5.59 (1H, m, H-10), 3.76 (3H, s, OCH_3), 3.13–3.08 (1H, m, H-5), 2.45–2.18 (7H, m), 2.11–1.90 (3H, m) 2.05 (1H, s, H-15), 2.04 (1H, d, *J* = 11.7 Hz, H-14α). ^{13}C NMR δ 213.4 (C16), 169.3 (C=O), 132.4 (C10), 126.0, 125.1 and 120.3 (C1, C6 and C7), 69.7 (C4), 52.8 (OCH_3), 45.5 and 41.9 (C13 and C5), 43.4 and 38.4 (C8 and C9), 34.4 (C15), 31.5, 28.0, 24.3, 22.6, and 19.3 (5 × CH_2).

3-*RS*,4a-*SR*,4b-*RS*,6a-*SR*,7-*RS*,8-*RS*,10b-*RS*-2,3,6a,7,8,9-Hexahydro-1*H*-3,4b-methanobenzo -[1,3]-cyclopropa-[1,2-a]-naphthalene-4-(4a*H*)-one-7,8-dicarboxylic anhydride (28). To a suspension of $Cu(acac)_2$ (5 mg, 2 mol%), in dichloroethane (5 mL) at reflux, was added dropwise *via* syringe pump a solution of the diazoketone (200 mg, 0.89 mmol) in dichloroethane (15 mL) over the course of 1.5 hours. Complete consumption of the starting material was observed within 2 hours. Maleic anhydride (400 mg, 4 mmol, 4.5 equiv.) was added and the solution heated to reflux for a further 6 hours, after which time the reaction was cooled to room temperature. Removal of the solvent *in vacuo* followed by purification using column chromatography (50% ethyl acetate/petrol) afforded the major product **28** (140 mg, 53%) as a white solid. A small sample was recrystallized from hot acetone to give white needles, mp 240–242 C. ^{1}H NMR (DMSO-d_6) δ 6.19–6.16 (1H, m, H-1), 6.05 (1H, dd, *J* = 10.1, 2.3 Hz, H-6 or H-7), 5.73 (1H, dd, *J* = 10.1, 2.3 Hz, H-6 or H-7), 3.66–3.55 (2H, m, H-3 and H-4), 2.90–2.88 (1H, m, H-5), 2.64–2.36 (2H, m,), 2.29–2.13 (2H, m), 2.09 (1H, s, H-15), 1.87 (1H, d, *J* = 12.0 Hz, H-14α), 1.85–1.62 (4H, m). ^{13}C NMR (DMSO-d_6) δ 211.3 (C16), 175.8 and 172.0 (2 × C=O), 138.1 (C10), 126.4, 124.9, 123.2 (C1, C6 and C7), 45.8 (C4), 45.7 (C3), 41.2 (C15), 40.8 (C13), 38.8 and 36.1 (C8 and C9), 33.9 (C5), 32.0, 27.5, 24.7 and 19.2 (4 × CH_2). LRMS (M^+, 27%), 268 (M–CO, 100), 223 (M–CO_2H, CO, 87), 198 (retro-Diels–Alder, 30), 195 (M–CO_2H, 2 × CO, 93). HRMS: found (M^+) 296.1048; $C_{18}H_{16}O_4$ requires 296.1049.

3-*RS*,4a-*SR*,4b-*RS*,6a-*SR*,7-*RS*,8-*RS*,10b-*RS*-7-Methyl-2,3,6a,7,8,9-hexahydro-1*H*-3,4b-methano-benzo-[1,3]-cyclopropa-[1,2-a]-naphthalene-4-(4a-*H*)-one-7,8-dicarboxylic anhydride (29). To a suspension of $Cu(acac)_2$ (12 mg, 2 mol %), in dichloroethane (10 mL) at reflux, was added dropwise *via* syringe pump a solution of diazoketone (552 mg, 2.45 mmol) in dichloroethane (40 mL) over the course of 2.5 hours. Complete consumption of the starting material was observed within 3 hours, after which time citraconic anhydride (0.5 mL, 3 equiv.) was added and the solution heated at reflux for a further 18 hours. Removal of the solvent *in vacuo* followed by purification using column chromatography (40% ethyl acetate/petrol) afforded **29** plus a minor isomer in the ratio 8:1, (300 mg, 40%), as a cream solid. A small sample was recrystallized from chloroform to give white needles of the major isomer, mp 182–184 C. IR (soln) 3020 (C=C–H), 2900 and 2750 (C–H), 1780 (OC=O), 1720 (RC=O) cm^{-1}. ^{1}H NMR (COSY) δ 6.22 (1H, m, H-1), 6.82 (1H, dd, *J* = 10.3, 2.7 Hz, H-6), 5.82 (1H, ddd, *J* = 10.3, 3.1, 1.1 Hz, H-7), 3.04 (1H, dd, *J* = 6.0, 2.1 Hz, H-3), 2.82 (1H, ddd, *J* = 15.3, 7.7, 2.3 Hz, H-2), 2.49–2.47 (1H, m, H-5), 2.43–2.35 (1H, m, H-11), 2.29 (1H, ddd, *J* = 11.7, 5.8, 1.8 Hz, H-14β), 2.24–2.16 (2H, m, H-2 and H-13), 1.97 (1-H, d, *J* = 11.7 Hz, H-14α), 1.94–1.82 (3H, m, H-11 and 2xH-12), 1.58 (3H, s, CH_3), 1.49 (1H, s, H-15). ^{13}C NMR (HETCOR) δ 212.4 (C16), 173.6 and 172.8 (2 × C=O), 137.8 (C10), 128.9 (C6), 125.6 (C1), 121.0 (C7), 50.5 (C4), 49.3 (C3), 46.6 (C5), 41.6 (C15), 40.9 (C13), 39.9 and 34.5 (C8 and C9), 32.6 (C14), 27.8 (C12), 24.1 (C2), 22.1 (CH_3), 20.1 (C11). LRMS 310 (M^+, 10%), 282 (M–CO, 68), 237 (M–CO, CO_2H, 63), 209 (M–CO_2H, 2 × CO, 60), 198 (retro Diels–Alder, 93), 155 (100). HRMS: found (M^+) 310.1205; $C_{19}H_{18}O_4$ requires 310.1205.

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