

Copper(II)-catalysed addition of O-H bonds to norbornene

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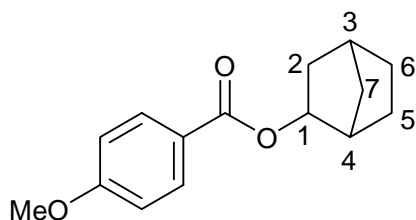
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Experimental

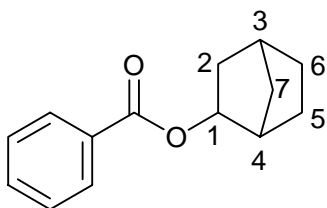
General Remarks. Column chromatography was performed on silica gel (Kieselgel 60, 63-200 μm). ^1H and ^{13}C NMR spectra were acquired using a Bruker DRX 400MHz instrument (^1H at 400 MHz and ^{13}C at 100 MHz). The chemical shifts are reported in δ (ppm) reference to residual protons and ^{13}C signals to deuterated chloroform. The coupling constants (J) are expressed in Hertz (Hz). Infrared spectra were recorded on a Mattson Instrument Satellite FTIR spectrometer; the samples were prepared as either a liquid film between NaCl plates, or pressed into KBr discs. Melting points (uncorrected) were determined using an Electrothermal Gallenham apparatus and a calibrated thermometer ($\pm 2^\circ\text{C}$). Boiling points were determined by distillation, heating in a Buchi B-580 glass oven under vacuum and measured with a thermometer ($\pm 2^\circ\text{C}$). Elemental analysis Service was provided by London Metropolitan University. Mass spectra (MS) were recorded on a Micromass Autospec-Q Mass Spectrometer. All dried solvents were purchased from Sigma-Aldrich and stored under nitrogen atmosphere. All other commercial reagents were used as received.

General Procedure for the preparation of norbornyl esters and ethers.

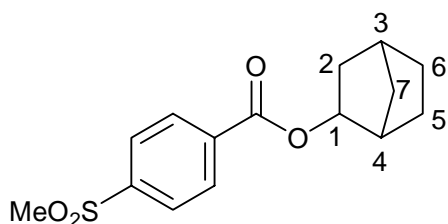
Catalytic reactions were conducted in parallel using Radley's 12-placed reaction carousel. For a typical catalytic experiment, reaction tubes are loaded with the catalyst and a Teflon coated stirrer bar, and fitted with a screw cap. The reaction tubes are placed on the reaction carousel and its atmosphere purged under vacuum for 20 minutes and subsequently flushed with nitrogen. Norbornene (144 mg, 1.5 mmol) and the requisite carboxylic acid/alcohol (1.0 mmol) was dissolved in of anhydrous 1,4-dioxane (1 mL) and introduced into the reaction tube through the rubber septum *via* a syringe needle. The reaction is refluxed at 80°C by controlled heating using a thermostat for 18 hours. Upon completion the reaction mixture was diluted with Et_2O (35 mL) and washed with 1M aq. NaHCO_3 (20mL). The layers were separated and the organic layer was dried over Na_2SO_4 , concentrated under vacuum, and purified by column chromatography (3:1 hexanes/ethylacetate). With the exception of **1c**, all oily products were subsequently distilled to furnish analytically pure samples.



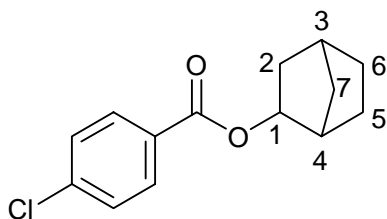
exo-Bicyclo[2.2.1]heptan-2-yl-4-methoxybenzoate, 1a. White crystalline solid. bp. 130°C, 1 mmHg; mp. 54-56°C; $R_f = 0.7$ (Hexanes/EtOAc, 3:1); ν_{\max} (KBr disc, cm^{-1}): 3054 (Ar-H), 2961 (Ar-O), 2874 (O-CH₃), 2305, 1704 (C=O), 1606, 1511, 1311, 1304 (O-CH), 1168, 1104, 761; δ_{H} (400 MHz, CDCl₃): 7.94 (2H, d, J 8.8, H_{meta}), 6.86 (2H, d, J 8.8 Hz, H_{ortho}), 4.78 (1H, d, J 6.6, H-1), 3.78 (3H, s, OCH₃), 2.39 (1H, br d, J 4.0, H-4), 2.27 (1H, br s, H-7), 1.77 (1H, ddd, J 2.0, 7.0, 13, H-2), 1.09-1.64 (7H, m, H-2, H-3, H-5, H-6 and H-7); δ_{C} (100 MHz, CDCl₃): 165.8 (C=O), 163.1 (C_{para}), 131.4 (C_{meta}), 123.2 (C_{ipso}), 113.4 (C_{ortho}), 79.9 (C-1), 55.3 (OMe), 41.5 (C-4), 39.6 (C-2), 35.3 (C-3), 35.1 (C-7), 28.2 (C-5), 24.3 (C-6); m/z (EI) 246 (M⁺, 8%), 152 (16%), 136 (11%), 135 (100%), 95 (6%), 77 (6%).



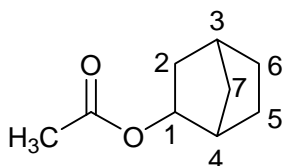
exo-Bicyclo[2.2.1]heptan-2-yl-benzoate (exo-2-benzoyloxynorbornane), 1b.¹ Pale yellow oil. bp. 125°C, 1 mmHg (lit. 131°C, 2 mmHg); $R_f = 0.6$ (Hexanes/EtOAc, 3:1). ν_{\max} (thin film, cm^{-1}): 3054 (Ar-H), 2963 (CH), 2875 (CH₂), 2305, 1711 (C=O), 1603, 1451, 1266, 1176 (O-CH), 1070, 977, 895; δ_{H} (400 MHz, CDCl₃): 8.01 (2H, dd, J 1.0, 7.0, H_{ortho}), 7.49 (1H, m, H_{para}), 7.38 (2H, m, H_{meta}), 4.84 (1H, d, J 6.5, H-1), 2.42 (1H, br s, H-4), 2.30 (1H, br s, H-7), 1.77-1.83 (1H, m, H-2), 1.09-1.64 (7H, m, H-2, H-3, H-5, H-6 and H-7); δ_{C} (100 MHz, CDCl₃): 166.0 (C=O), 132.6 (C_{para}), 129.4 (C_{ortho}), 130.8 (C_{ipso}), 128.2 (C_{meta}), 78.0 (C-1), 41.5 (C-4), 39.6 (C-2), 35.3 (C-3), 35.1 (C-7), 28.2 (C-5), 24.3 (C-6); m/z (EI): 216 (M⁺, 2%), 188 (2%), 173 (2%), 139 (4%), 119 (4%), 133 (3%), 120 (3%), 105 (100%), 94 (25%), 77 (25%).



exo-Bicyclo[2.2.1]heptan-2-yl-4-(methanesulfonyl)benzoate, 1c. Off-white solid after column chromatography. mp 102-104°C; $R_f = 0.5$ (Hexanes/EtOAc, 3:1). ν_{\max} (KBr disc, cm^{-1}): 3054 (Ar-H), 2971 (CH), 2871 (CH_2), 1713 (C=O), 1577, 1400, 1375 (SO_2), 1154 (O-CH), 1110, 976, 752; δ_{H} (400 MHz, CDCl_3): 8.21 (2H, d, J 8.4, H_{meta}), 8.02 (2H, d, J 8.4, H_{ortho}), 4.89 (1H, d, J 6.9, H-1), 3.02 (3H, s, SO_2Me), 2.39 (1H, br d, J 6.7, H-4), 2.35 (1H, br s, H-7), 1.78 (1H, ddd, J 2.0, 6.0, 13, H-2), 1.09-1.64 (7H, m, H-2, H-3, H-5, H-6 and H-7); δ_{C} (100 MHz, CDCl_3): 164.2 (C=O), 143.8 (C_{para}), 135.3 (C_{ipso}), 130.2 (C_{meta}), 127.2 (C_{ortho}), 78.9 (C-1), 44.0 (SO_2Me), 39.8 (C-4), 34.6 (C-3), 35.2 (C-2), 35.1 (C-7), 28.2 (C-5), 24.3 (C-6); m/z (EI): 294 (M^+ , 1%), 279 (2%), 215 (7%), 184 (2%), 183 (100%), 121(28%), 104 (13%), 94 (35%), 66 (56%); Anal. Calcd for $\text{C}_{15}\text{H}_{18}\text{O}_4\text{S}$: C, 61.20%; H, 6.16%. Found: C, 61.29%; H, 6.07%.

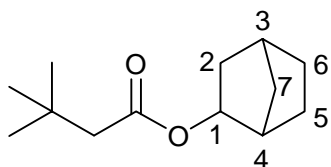


exo-Bicyclo[2.2.1]heptan-2-yl-4-chlorobenzoate, 1d. Pale yellow oil. bp. 140°C, 25 mmHg; $R_f = 0.8$ (Hexanes/EtOAc, 3:1); ν_{\max} (thin film, cm^{-1}): 3054 (Ar-H), 2965 (CH), 2875 (CH_2), 2306, 1712 (C=O), 1594, 1488, 1401, 1270 (O-CH), 1118, 1015, 675 (C-Cl); δ_{H} (400 MHz, CDCl_3): 7.92 (2H, d, J 8.3, H_{ortho}), 7.36 (2H, d, J 8.3, H_{meta}), 4.82 (1H, d, J 6.6, H-1), 2.41 (1H, br d, J 4.0, H-4), 2.31 (1H, br s, H-7), 1.81 (1H, ddd, J 2.0, 8.0, 15, H-2), 1.09-1.61 (7H, m, H-2, H-3, H-5, H-6 and H-7); δ_{C} (100 MHz, CDCl_3): 165.1 (C=O), 138.9 (C_{ipso}), 130.7 (C_{ortho}), 129.2 (C_{para}), 128.5. (C_{meta}), 78.3 (C-1), 41.5 (C-4), 40.1 (C-2), 35.3 (C-3), 35.1 (C-7), 28.5 (C-5), 24.3 (C-6); m/z (EI): 250 (M^+ , 2%), 215 (1%), 167 (4%), 154 (3%), 139 (100%), 94 (4%), 66 (20%); Anal. Calcd for $\text{C}_{14}\text{H}_{15}\text{O}_2\text{Cl}$: C, 67.07%; H, 6.03%. Found: C, 67.17%; H, 5.98%.

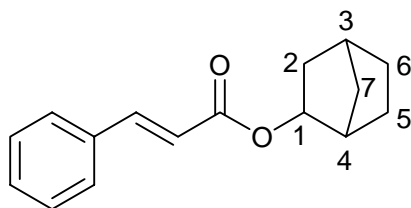


exo-Bicyclo[2.2.1]heptan-2-yl-acetate (2-exo-norbornyl acetate), 2a.² Transparent oil. bp. 95°C, 25 mmHg (lit. 91°C, 24 mmHg); $R_f = 0.8$ (Hexanes/EtOAc, 3:1); ν_{\max} (thin film, cm^{-1}): 2960 (CH), 2873 (CH_2), 2306, 1723 (C=O), 1451, 1584, 1451, 1265 (O-CH), 1175, 1089, 1024, 896; δ_{H} (400 MHz, CDCl_3): 4.58 (1H, d, J 7.0, H-1), 2.27 (1H, br s, H-4), 2.18 (1H, br s, H-7), 1.99 (3H, br s, CH_3), 1.77 (1H, ddd, J 2.0, 6.0, 13, H-2), 1.09-1.61 (7H, m, H-2, H-3, H-5, H-6 and H-7); δ_{C} (100

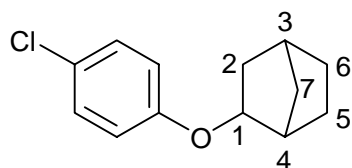
MHz, CDCl₃): 170.7 (C=O), 77.7 (C-1), 41.3 (C-4), 35.3 (C-3), 35.1 (C-2), 35.0 (C-7), 28.4 (C-5), 24.8 (C-6), 21.4 (CH₃); *m/z* (EI): 154 (M⁺, 1%), 111 (22%), 95 (89%), 66 (55%), 43 (100%).



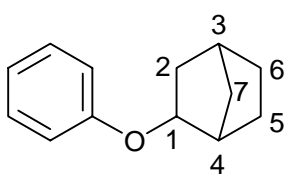
exo-3,3-Dimethyl-butyric acid-bicyclo[2.2.1]heptan-2-yl-ester, 2b. Transparent oil. bp. 110°C, 25 mmHg; *R_f* = 0.8 (Hexanes/EtOAc, 3:1); ν_{\max} (thin film, cm⁻¹): 2958 (CH), 2873 (CH₂), 2308, 1720 (C=O), 1475, 1367, 1324, 1251 (O-CH), 1132, 1070, 995; δ_{H} (400 MHz, CDCl₃): 4.57 (1H, br d, *J* 7.0, H-1), 2.25 (1H, br s, H-4), 2.16 (1H, br s, H-7), 2.11 (2H, br s, CH₂), 1.77 (1H, ddd, *J* 2.0, 6.0, 14, H-2), 1.02-1.59 (7H, m, H-2, H-3, H-5, H-6 and H-7), 0.98 (9H, s, CH₃); δ_{C} (100 MHz, CDCl₃): 171.9 (C=O), 77.1 (C-1), 48.2 (CH₂), 40.1 (C-4), 39.4 (C-2), 35.2 (C-3), 35.1 (C-7), 29.7 (CH₃), 29.1 (C-5), 24.7 (C-6); *m/z* (EI): 210 (M⁺, 1%), 196 (1%), 182 (6%), 99 (4%), 95 (100%), 94 (11%), 57 (42%).



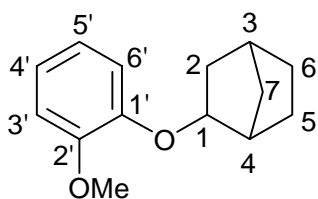
exo-Bicyclo[2.2.1]heptan-2-yl-cinnamate 2c. Yellow oil. bp. 155°C, 25 mmHg; *R_f* = 0.7 (Hexanes/EtOAc, 3:1); ν_{\max} (thin film, cm⁻¹): 3054 (Ar-H), 2986 (CH), 2685 (CH₂), 2305, 2254, 1704 (C=O), 1422 (Ar-C=C), 1265 (O-CH), 908, 734; δ_{H} (400 MHz, CDCl₃): 7.65 (1H, d, *J* 16, CH=CHCO), 7.49 (2H, m, H_{ortho, meta}), 7.36 (3H, dd, *J* 1.0, 4.0, H_{ortho, meta, para}), 6.42 (1H, d, *J* 16, PhCH=CH), 4.73 (1H, br d, *J* 6.8, H-1), 2.38 (1H, br s, H-4), 2.18 (1H, br s, H-7), 1.77 (1H, ddd, *J* 2.0, 7.0, 14, H-2), 1.0-1.6 (7H, m, H-2, H-3, H-5, H-6 and H-7); δ_{C} (100 MHz, CDCl₃): 166.6 (C=O), 144.2 (CH=CHCO), 134.5 (C_{ipso}), 130.1 (C_{ortho}), 128.8 (C_{meta}), 128.0 (C_{para}), 118.8 (PhCH=CH), 76.8 (C-1), 41.5 (C-4), 39.7 (C-2), 34.9 (C-3), 35.1 (C-7), 28.6 (C-5), 24.8 (C-6); *m/z* (EI): 242 (M⁺, 8%), 214 (5%), 148 (6%), 131 (100%), 95 (15%), 77(11%); Anal. Calcd for C₁₆H₁₈O₂: C, 79.31%; H, 7.49%. Found: C, 79.25%; H, 7.43%.



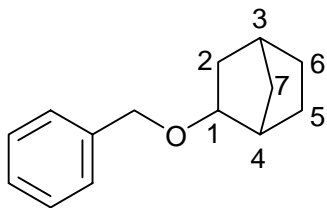
exo-2-(4-Chlorophenoxy)bicyclo[2.2.1]heptane, 3a. Pale yellow oil. bp. 145°C, 25 mmHg; $R_f = 0.6$ (Hexanes/EtOAc, 3:1); ν_{\max} (thin film, cm^{-1}): 3053 (Ar-H), 2962 (CH), 2874 (Ar-O), 2305, 1595, 1490 (C-Cl), 1265 (O-CH), 1075, 909, 826, 787 (C-Cl); δ_{H} (400 MHz, CDCl_3): 7.23 (2H, d, J 8.9, H_{meta}), 6.78 (2H, d, J 8.9, H_{ortho}), 4.12 (1H, d, J 6.7, H-1), 2.44 (1H, br s, H-4), 2.32 (1H, br s, H-7), 1.77 (1H, ddd, J 2.0, 7.0, 15, H-2), 1.0-1.6 (7H, m, H-2, H-3, H-5, H-6 and H-7); δ_{C} (100 MHz, CDCl_3): 156.3 (C_{ipso}), 129.3 (C_{meta}), 124.9 (C_{para}), 116.6 (C_{ortho}), 79.6 (C-1), 40.1 (C-4), 39.6 (C-2), 35.2 (C-3), 35.1 (C-7), 28.2 (C-6), 24.1 (C-5); m/z (EI): 222 (M^+ , 7%), 215 (1%), 167 (4%), 154 (4%), 139 (100%), 94 (4%), 66 (20%); Anal. Calcd for $\text{C}_{13}\text{H}_{15}\text{OCl}$: C, 70.11%; H, 6.79%. Found: C, 70.12%; H, 6.73%.



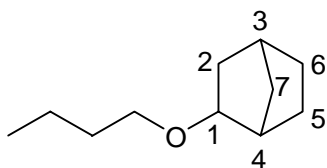
exo-2-phenoxybicyclo[2.2.1]heptane (2-exo-phoxynorbonane), 3b.³ Pale yellow oil. bp. 140°C, 25 mmHg (lit. 78-80°C, 0.3 mmHg); $R_f = 0.8$ (Hexanes/EtOAc, 3:1); ν_{\max} (thin film, cm^{-1}): 3052 (Ar-H), 2956 (Ar-O), 2872 (CH), 2305, 1710, 1597, 1265 (O-CH), 1176, 1082, 737; δ_{H} (400 MHz, CDCl_3): 7.31 (2H, m, $H_{\text{ortho,meta}}$), 6.97 (3H, m, $H_{\text{ortho,meta,para}}$), 4.22 (1H, d, J 6.5, H-1), 2.52 (1H, br s, H-4), 2.37 (1H, s H-7), 1.81 (1H, ddd, J 2.0, 7.0, 15, H-2), 1.0-1.6 (7H, m, H-2, H-3, H-5, H-6 and H-7); δ_{C} (100 MHz, CDCl_3): 157.8 (C_{ipso}), 129.4 (C_{ortho}), 120.2 (C_{para}), 115.4 (C_{meta}), 79.7 (C-1), 40.1 (C-4), 41.2 (C-2), 40.2 (C-3), 34.9 (C-7), 28.7 (C-6), 24.4 (C-5); m/z (EI): 188 (M^+ , 17%), 124 (6%), 95 (100%), 94 (77%), 67 (26%).



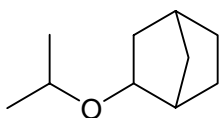
exo-2-(2-methoxyphenoxy)bicyclo[2.2.1]heptane, 3c. Pale yellow oil. bp. 125°C, 1 mmHg; $R_f = 0.8$ (Hexanes/EtOAc, 3:1); ν_{\max} (thin film, cm^{-1}): 3539 (Ar-O), 3445 (O- CH_3), 3054 (Ar-H), 2950 (CH), 2871 (CH_2), 1714, 1596, 1502, 1445, 1362, 1259 (O-CH), 1110, 1025, 901, 738; δ_{H} (400 MHz, CDCl_3): 7.31 (4H, m, H-3', H-4', H-5', H-6'), 4.21 (1H, d, J 6.3, H-1), 3.85 (3H, s, OCH_3), 2.52 (1H, br s, H-4), 2.33 (1H, s H-7), 1.81 (1H, m, H-2), 1.0-1.6 (7H, m, H-2, H-3, H-5, H-6 and H-7); δ_{C} (100 MHz, CDCl_3): 149.9 (C-2'), 147.4 (C-1'), 120.8 (C-5'), 120.7 (C-4'), 114.9 (C-6'), 112.2 (C-3'), 81.1 (C-1), 56.0 (OMe), 41.0 (C-4), 40.2 (C-2), 40.0 (C-3), 34.9 (C-7), 28.6 (C-6), 24.8 (C-5); m/z (EI): 218 (M^+ , 10%), 124 (100%), 109 (52%), 95 (97%), 67 (22%).



exo-2-benzyloxybicyclo[2.2.1]heptane (2-*exo*-benzyloxynorbornane), **4a**. Pale yellow oil. Bp. 80°C, 1 mmHg; $R_f = 0.8$ (Hexanes/EtOAc, 3:1); ν_{\max} (thin film, cm^{-1}): 3032 (Ar-H), 2959 (CH), 2873 (CH), 2253, 1732, 1453, 1265 (O-CH), 1091, 1049, 909, 734, 649; δ_{H} (400 MHz, CDCl_3): 7.34 (5H, m, $H_{\text{ortho, meta, para}}$), 4.55 (1H, d, J 12, CH_2Ph), 4.50 (1H, d, J 12.0, CH_2Ph), 3.50 (1H, d, J 6.4, H-1), 2.42 (1H, br s, H-4), 2.29 (1H, br s H-7), 1.73 (1H, m, H-2), 1.0-1.6 (7H, m, H-2, H-3, H-5, H-6 and H-7); δ_{C} (100 MHz, CDCl_3): 139.1 (C_{ipso}), 128.3 (C_{ortho}), 127.5 (C_{meta}), 127.3 (C_{para}), 82.1 (C-1), 70.2 (CH_2Ph), 40.9 (C-4), 40.2 (C-2), 35.2 (C-3), 34.9 (C-7), 28.6 (C-6), 24.9 (C-5); m/z (EI): 202 (M^+ , 1%), 111 (1%), 91 (100%), 67 (57%); Anal. Calcd for $\text{C}_{14}\text{H}_{18}\text{O}$: C, 83.12%; H, 8.97%. Found: C, 83.06%; H, 8.87%.



exo-2-butoxybicyclo[2.2.1]heptane (2-*exo-n*-butoxynorbornane), **4b**. Transparent oil. bp. 120°C, 25 mmHg; $R_f = 0.8$ Hexanes/EtOAc, 3:1; ν_{\max} (thin film, cm^{-1}): 2959 (CH_2), 2872 (CH), 2306, 1503, 1439, 1265 (O-CH), 1090, 737; δ_{H} (400 MHz, CDCl_3): 3.36 (3H, m, H-1, OCH_2), 2.28 (1H, br s, H-4), 2.19 (1H, br s, H-7), 1.1-1.9 (12H, m, 2 x CH_2 , H-2, H-5, H-6 and H-7), 0.88 (3H, t, J 7.3, CH_3); δ_{C} (100 MHz, CDCl_3): 82.4 (C-1), 67.9 (OCH_2), 40.2 (C-4), 39.5 (CH_2), 35.1 (C-2), 34.7 (C-3), 32.1 (C-7), 28.5 (C-6), 24.6 (C-5), 19.5 (CH_2), 13.9 (CH_3); m/z (EI): 168 (M^+ , 3%), 125 (3%), 111 (36%), 95 (83%), 91 (100%), 67 (78%), 66 (37%).



exo-2-isopropoxybicyclo[2.2.1]heptane (2-*exo*-isopropoxynorbornane), **4c**.⁴ Transparent oil. bp. 55°C, 25 mmHg (lit. 78-80 °C, 40 mmHg); $R_f = 0.8$ (Hexanes/EtOAc, 3:1); ν_{\max} (thin film, cm^{-1}): 2960 (CH_2), 2873 (CH), 2305, 1408, 1265 (O-CH), 1089, 909, 706; δ_{H} (400 MHz, CDCl_3): 3.59 (1H, sept, J 6.1, CHMe_2), 3.42 (1H, d, J 6.7, H-1), 2.21 (1H, br s, H-4), 2.15 (1H, br s, H-7), 1.81 (1H, m, H-2), 1.1-1.6 (7H, m, H-2, H-3, H-5, H-6 and H-7) 1.11 (3H, d, J 6.1, CH_3) 1.10 (3H, d, J

6.1, CH₃); δ_C (100 MHz, CDCl₃): 79.9 (C-1), 68.5 (CHMe₂), 40.9 (C-4), 40.0 (C-2), 34.9 (C-3), 32.1 (C-7), 28.5 (C-6), 24.7 (C-5), 22.6 (CH₃); m/z (EI): 154 (M⁺, <1%), 139 (5%), 111 (8%), 95 (100%), 67 (27%).

References

1. D. Despeyroux, R. B. Cole and J. C. Tabet, *Org. Mass Spec.* 1992, **27**, 300; (b) H. S. Dang, B. P. Roberts, D. A. Tocher, *Org. Biomol. Chem.*, 2003, **1**, 4073.
2. (a) M. N. Akhtar and W. R. Jackson, *J. Chem. Soc., Chem. Commun.*, **1972**, 813; (b) M. N. Akhtar, J. J. Rooney and W. R. Jackson, *J. Chem. Soc., Perkin Trans. 2*, **1976**, 595.
3. J. K. Stille and R. D. Hughes, *J. Org. Chem.* **1971**, *36*, 340.
4. Brown, H. C.; Kurek, J. T.; Rei, M. H.; Thompson, K. L. *J. Org. Chem.* **1984**, *49*, 2551.