Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of 1-p-Methoxyphenyl and 1-p-Methoxyphenyl-4-methylbicyclo-[2.2.1]heptan-7-one. The Oxidation of 7-Hydroxy-1-p-methoxyphenyl-4-methylbicyclo[2.2.1]heptan-7-carboxylic Acid with Lead Tetraacetate

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Published online: 23 Sep 2006.

SYNTHETIC COMMUNICATIONS, 23(7), 913-924 (1993)

SYNTHESIS OF 1-p-METHOXYPHENYL AND 1-p-METHOXYPHENYL-4-METHYLBICYCLO-[2.2.1]HEPTAN-7-ONE. THE OXIDATION OF 7-HYDROXY-1-p-METHOXYPHENYL-4-METHYLBICYCLO[2.2.1]HEPTAN-7-CARBOXYLIC ACID WITH LEAD TETRAACETATE

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Abstract : A simple synthetic route to 1-p-methoxyphenyl and 1-p-methoxyphenyl-4-methylbicyclo[2.2.1]heptan-7-one **6b,a** has been developed through benzilic acid rearrangement of the bicyclo[2.2.1]octandiones **2b,a.** The oxidation of 7-hydroxy-1-p-methoxyphenyl-4-methylbicyclo[2.2.1]heptan-7-carboxylic acid **3a** with lead tetraacetate gives the carbolactone **7a** which is also formed by the reaction of the ketone **6a** with m-chloroperbenzoic acid.

Although a number of synthetic methods for 7-oxygenated norbornanes are known[1-3] these are not applicable to the respective bridgehead substituted derivatives. The only recorded synthesis of 1-methyl- and 1,4-dimethyl-7-oxonorbornanes was achieved through a bicyclo[3.2.0]heptane to bicyclo[2.2.1]heptane rearrangement[4]. We report here a synthesis of the novel-1-p-methoxyphenyl- and 1-p-

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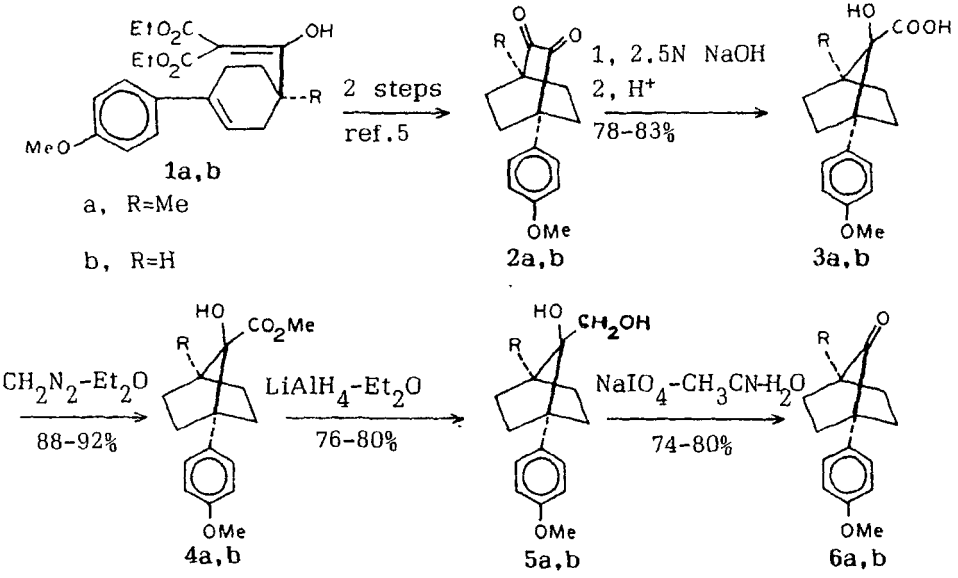
methoxyphenyl-4-methyl-7-oxonorbornanes **6b,a** involving benzilic acid rearrangement of the bicyclo[2.2.2]octandiones **2b,a** to the bicyclo[2.2.1]heptane acids **3b,a** followed by oxidative cleavage of the respective diols **5b,a** (Scheme-1).

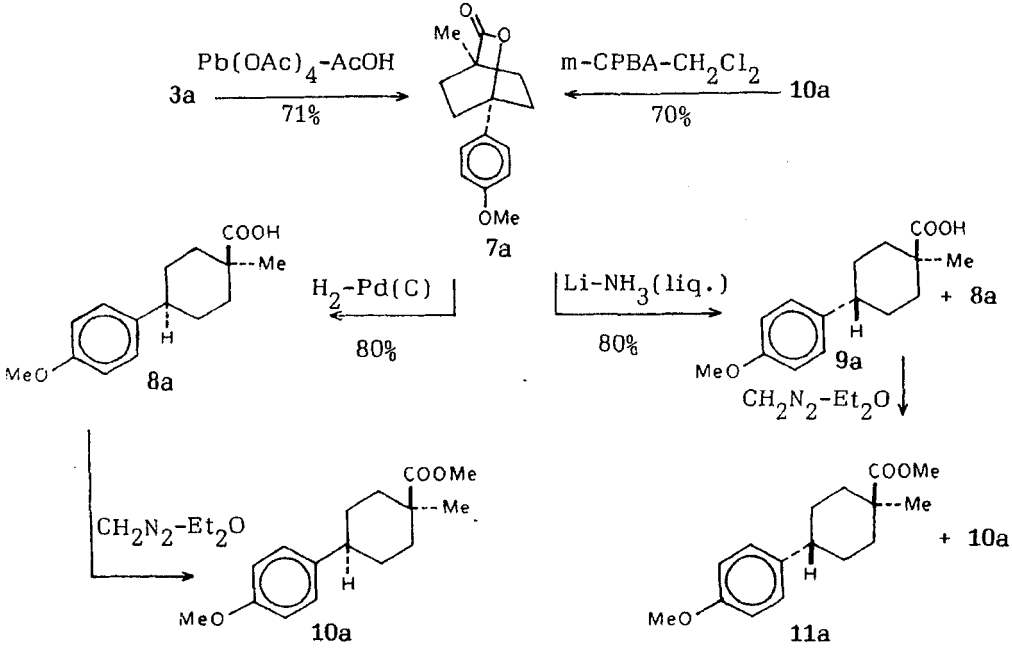
The readily accessible diones **2a,b** were prepared by an intramolecular acid-catalyzed cyclization and decarboxylation of the enolized β-ketodiesters **1a,b** followed by oxidation as described earlier[5]. Benzilic acid rearrangement[6] **2a,b** with aquous sodium hydroxide afforded the respective α-hydroxy acids **3a,b**. The methyl esters **4a,b**, obtained by esterification of the acids **3a,b** with diazomethane, were reduced with lithium aluminium hydride and the resulting diols **5a,b** were smoothly transformed to the ketones **6a,b** by oxidation with sodium metaperiodate[7].

Scheme - 1



The oxidative decarboxylation of the α-hydroxy acid 3a with lead tetraacetate[8] in acetic acid produced the lactone 7a (Scheme-2), which was also obtained by Bayer-Villiger oxidation of the ketone 6a with m-chloroperbenzoic acid[9]. To our knowledge the formation of Bayer-Villiger product in the oxidation of α-hydroxy acid with lead tetraacetate has not been observed earlier[10]. The structure of the benzylic lactone 7a was established by its reductive cleavage on catalytic hydrogenolysis in the presence of palladium-charcoal in ethanol to a single epimeric acid, assigned as 8a, involving inversion at the benzylic chiral centre by analogy with earlier observations[11] in similar systems.

Scheme - 2



The ^{1}H NMR and GLC analyses of the methyl ester **10a**, of the acid **8a**, established its homogeneity. In contrast the reductive cleavage of the benzylic bond in 7a with lithium-liquid ammonia[11] produced a mixture of the diastereoisomeric acids 8a and 9a, characterized through the respective methyl esters 10a and 11a, evidently involving inversion and retention of configuration at the benzylic centre[11].

EXPERIMENTAL

The compounds described are all racemates. Melting points taken in open capillary, are uncorrected. IR spectra were recorded on a Perkin-Elmer model 298 spectrometer. ^{1}H NMR spectra (unless otherwise stated) were taken in $CDCl_3$ on a Varian Associates XL-200 spectrometer with TMS acting as internal standard. Elemental analysis were performed by Mr. P.P. Bhattacharya and Mr. S.K. Sarkar of this laboratory. Column chromatography was performed on 'Brockman' neutral alumina (BDH, India), petroleuum and light petroleum refer to the fraction with b.p. 60-80°C and 40-60°C respectively. GLC were performed on a Shimadzu GC-9A model with flame ionization detector emplying a 1.5% OV-17 column. Mass spectra were recorded on a Finnegan 4000 spectrometer.

7-Hydroxy-1-p-methoxyphenyl-4-methylbicyclo[2.2.1]heptane-7-carboxylic Acid (3a) : The diketone **2a**[5] (450 mg, 1.74 mmol) in aqueous sodium hydroxide solution (2.5 N; 90 ml) was

heated under reflux for 3 h. The cooled solution was acidified with hydrochloric acid (6N) and extracted with ether (3 x 50 ml). The ether extract was repeatedly washed with 5% sodium hydroxide solution (3 x 25 ml) and washed with brine. The alkaline extract was acidified in cold with hydrochloric acid (6N) and extracted with ether (3 x 50 ml), washed with brine and dried (Na_2SO_4). Removal of solvent afforded the solid acid **3a** (390 mg, 83%); m.p. 130°C (ether/petroleum). IR(KBr) : 3600, 3540(OH); 1670(C=O); 1610(Ar) cm^{-1}. Anal calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found C, 69.78; H, 7.36.

The acid **3a** (340 mg) was esterified with an excess of ethereal diazomethane. Excess diazomethane was decomposed with dilute acetic acid and extracted with ether (3 x 30 ml). The ether extract was washed with 5% sodium bicarbonate solution, brine and dried (Na_2SO_4). Evaporation of the solvent gave a liquid, which was purified by filtration through a wide short column of alumina. Elution with ether-petroleum (1:3) afforded the hydroxyester **4a**, as an oil (330 mg, 92%). IR (film) : 3600, 3540(OH), 1700(C=O), 1610(Ar) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (s, 3H, CH_3), 1.37-2.04 (m, 6H, CH_2), 2.31-2.54 (m, 2H, CH_2), 3.34 (s, 1H, OH), 3.70 (s, 3H, CO_2CH_3), 3.80 (s, 3H, OCH_3), 6.86 (d, 2H arom, J = 8 Hz), 7.32 (d, 2H arom, J = 8 Hz).

Methyl-7-Hydroxy-1-p-methoxyphenyl bicyclo[2.2.1]heptane-7-carboxylate (4b) : The diketone 2b[5] (360 mg, 1.47 mmol) in aqueous sodium hydroxide (2.5 N, 72 ml was heated under reflux or 3 h. The cooled reaction mixture on usual work-up afforded the acid 3b (300 mg, 78%), m.p. 152-154°C. IR (KBr) : 3410(OH) 1675(C=O), 1610(Ar) cm^{-1}.

The acid 3b (270 mg) was esterified with excess ethereal diazomethane and worked up in the usual way. Evaporation of the solvent afforded the solid ester 4b (250 mg, 88%), m.p. 74°C (ether/petroleum). IR (KBr) : 3400(OH), 1700(CO_2CH_3), 1610(Ar) cm^{-1}, ^1H NMR ($CDCl_3$) : δ 1.36-1.84 (m, 4H, CH_2), 2.00-2.58 (m, 5H, CH_2+CH), 3.12 (br s, 1H, OH), 3.68 (s, 3H, CO_2CH_3), 3.80 (s, 3H, OCH_3), 6.86 (d, 2H arom, J = 8 Hz), 7.32 (d, 2H arom, J = 8 Hz). Anal cacld for $C_{10}H_{20}O_4$: C, 69.54; H, 7.30. Found : C, 69.31; H, 7.40.

7-Hydroxymethyl-1-p-methoxyphenyl-4-methylbicyclo[2.2.1] heptan-7-ol (5a) : A solution of the hydroxy ester 4a (250 mg, 0.90 mmol) in dry ether (5 ml) was added dropwise to a suspention of lithium aluminium hydride (60 mg, 1.58 mmol) in ether (15 ml). The mixture was then refluxed for 4 h, coolded, decomposed with saturated aqueous sodium sulphate solution, and filtered through anhydrous sodium sulphate. Removal of the solvent afforded a solid. Recrystallisation from ether-petroleum gave pure 5a (180 mg, 80%), m.p. 96-97°C. IR

(KBr) : 3500, 3470(OH), 1615(Ar) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.98 (s, 3H, CH_3), 1.16-2.52 (m, 8H, CH_2), 2.90 (br s, 1H, OH), 3.60 (m, 2H, OCH_2), 3.76 (s, 3H, OCH_3), 6.88 (d, 2H arom, J = 8 Hz), 7.49 (d, 2H arom, J = 8 Hz). Anal. calcd. for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found : C, 73.41; H, 8.39.

7-Hydroxymethyl-1-p-methoxyphenyl bicyclo[2.2.1]heptan-7-ol (5d). The hydroxyester **5a** (220 mg, 0.79 mmol) in dry ether (5 ml) was reduced with lithium aluminium hydride (60 mg, 1.5 mmol) in ether (15 ml) to afford the diol **5b** (150 mg, 76%), m.p. 88°C (ether petroleum). IR (KBr) : 3350(OH), 1615(Ar) cm^{-1}; ^1H NMR ($CDCl_3$) : δ 1.08-2.48 (m, 9H, CH_2+CH), 1.58 (br s, 1H, OH), 3.64 (m, 2H, OCH_2), 3.76 (s, 3H, OCH_3), 6.91 (d, 2H arom, J = 8 Hz), 7.45 (d, 2H arom, J = 8 Hz). Anal. calcd. for $C_{15}H_{20}O_3$; C, 72.55; H, 8.12. Found : C, 72.56; H, 8.15.

1-p-Methoxyphenyl-4-methylbicyclo[2.2.1]heptan-7-one (6a) : The diol **5a** (100 mg, 0.38 mmol) in acetonitrile (3 ml) and water (3 ml) was stirred at room temperature with sodium metaperiodate (244 mg, 11.5 mmol) for 4 h. The reaction mixture was diluted with water and extracted with ether (3 x 25 ml). The combined ether extract was washed with brine and dried (sodium sulphate). Removal of the solvent afforded **6a** (70 mg, 80%), m.p. 58°C (ether-light petroleum). IR (KBr) 1760(C=O), 1605(Ar) cm^{-1}; ^1H NMR ($CDCL_3$); δ 1.10 (s, 3H,

CH_3), 1.70-2.30 (m, 8H, CH_2), 3.80 (s, 3H, OCH_3), 6.94 (d, 2H arom, J = 8 Hz), 7.26 (d, 2H arom, J = 8 Hz); MS : m/z 230 (M^+); Anal. calcd. for $C_{15}H_{18}O_2$: C, 78.06; H, 8.17. Found : C, 78.23; H, 7.88.

1-p-Methoxyphenyl bicyclo[2.2.1]heptan-7-one (6b) : A solution of the diol **5b** (125 mg, 0.5 mmol) in acetonitrile (3 ml) and water (3 ml) was oxidized with sodium metaperiodate (320 mg, 1.5 mmol) to afford the ketone **6b** (80 mg, 74%), m.p. 80-81°C (ether-light petroleum). IR (KBr) : 1760(C=O), 1605(Ar) cm^{-1}; ^1H NMR ($CDCl_3$) : δ 1.36-2.40 (m, 9H, CH_2+CH), 3.78 (s, 3H, OCH_3), 3.91 (d, 2H arom, J = 8 Hz), 7.23 (d, 2H arom, J = 8 Hz); MS : 217 (M+1). Anal. calcd. for $C_{14}H_{16}O_2$: C, 77.75; H. 7.76. Found : C , 77.93; H, 7.76.

c-4-Hydroxy-1-methyl-t-4-p-methoxyphenyl-r-1,4-carbolactone (7a) - (A) : A mixture of the hydroxy acid **4a** (75 mg, 0.27 mmol) and lead tetraacetate (123 mg, 1.1 eq.) in acetic acid (8 ml) was heated at 65-70°C for 1 h. The cooled solution was diluted with water (25 ml) and extracted with ether (3 x 25 ml). The ether extract was washed with water and dried (Na_2SO_4). Removal of the solvent gave an oil which on chromatography on neutral alumina and elution with ether-petroleum (1:3) afforded the lactone **11a** as a crystalline solid (45 mg, 71%), m.p. 112°C (ether-petroleum). IR (KBr) : 1740 (lactone C=O), 1610 (Ar) cm^{-1}; ^1H NMR ($CDCl_3$) : δ 1.28 (s, 3H, CH_3), 1.86 (t, 4H, J = 8 Hz, CH_2), 1.96-2.26 (m, 4H,CH_2)

3.84 (s, 3H, OCH_3), 6.94 (d, 2H arom, J = 8 Hz), 7.42 (d, 2H arom, J = 8 Hz); MS : 247 (M+1). Anal. calcd. for $C_{15}H_{18}O_3$: C, 72.93; H, 7.57; Found : C, 73.14; H, 7.37.

(B) : The ketone **6a** (50 mg, 0.28 mmol) in methylene chloride (10 ml) was stirred with m-chloroperbenzoic acid (50 mg, 0.28 mmol) and sodium bicarbonate (110 mg) at room temperature for 48 h. Usual work-up afforded a mixture of lactone **7a** and the unreacted ketone **6a** (by IR). Chromatography on silica gel with 5 to 15% of ether-petroleum afforded the recovered pure ketone **6a** (10 mg). Further elution with 20 to 30% ether-petroleum gave the pure lactone **7a** (30 mg, 70%), m.p. and m.m.p. 112°C, identical in all respect (IR, NMR, GLC) with the sample obtained by Method A.

Catalytic Reduction of lactone (7a). 1-Methyl-4-t-p-methoxyphenylcyclohexane-r-1-carboxylic Acid (8a) : The lactone 7a (25 mg, 0.1 mmol) was hydrogenated in ethanol (5 ml) in the presence of 10% palladium-charcoal (10 mg) at room temperature and pressure. After complete uptake of hydrogen, the catalyst was filtered and removal of the solvent afforded a solid (25 mg) which on recrystallisation from ether-petroleum gave the pure acid **8a** (20 mg, 80%), m.p. 110°C. IR (KBr) : 1690(C=O), 1605(Ar) cm^{-1}. Anal. calcd. for $C_{15}H_{20}O_3$: C, 72.59; H, 8.15. Found : C, 72.55; H, 8.12.

The acid 8a was esterified with excess of ethereal diazomethane to afford the ester **10a**. IR (KBr) : 1730(C=O) cm^{-1}; ^1H NMR ($CDCl_3$) : δ 1.21 (s, 3H, CH_3), 1.26-1.88 (m, 6H, CH_2), 2.24-2.52 (m, 3H, CH_2+CH), 3.76 (s, 3H, CO_2CH_3), 3.82 (s, 3H, OCH_3), 6.88 (d, 2H arom, J = 8 Hz), 7.16 (d, 2H arom, J = 8 Hz). GLC : R_t = 2.73 min at column temperature 210°C by coinjection with the authentic sample.

Lithium-Ammonia Reduction of (7a) to the Acids (8a) and (9a) : To a well-stirred solution of 7a (25 mg, 0.1 mmol) in dry tetrahydrofuran (5 ml) and dry liquid ammonia (ca. 30 ml) distilled from sodium, was added freshly scrapped lithium metal (20 mg, 3 mg atom) in small portions during 5 min. After another 5 min, the blue colour was discharged by cautious addition of solid ammonium chloride. After evaporation of ammonia, the residue was diluted with water (15 ml) and extracted with ether (3 x 20 ml). The combined ether extract was washed with 2% potassium hydroxide solution. The aqueous extract was acidified with (6N) hydrochloric acid solution. Usual work-up afforded a mixture of the acids **8a** and **9a** (20 mg, 80%). IR (KBr) : 1690(C=O) cm^{-1}.

The above acid mixture on esterification with an excess of ethereal diazomethane gave the corresponding ester mixture **10a** and **11a** GLC and ^1H NMR showed the ester to be a mixture of diastereomers, **10a** and **11a** in a ratio of 35:65. IR:

1730(CO_2CH_3) cm^{-1}; ^1H NMR ($CDCL_3$) : δ 1.21, 1.29 (s, CH_3, minor and major respectively), 1.32-1.90 (m, CH_2), 3.70,3.72 (s, each CO_2CH_3, major and minor respectively), 3.78, 3.80 (s, each OCH_3, minor and major respectively), 6.82 - 7.00 (m, 2H arom), 7.08-7.26 (m, 2H arom). GLC : R_t = 2.74 min (35%), 3.34 min (65%) at column temperature 210°C, by coinjection with the authentic sample.

Acknowledgement : We thank CSIR, New Delhi for the award of a RA to RC.

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(Received in UK 30 September 1992)