Syntheses of (±)-Tetrahydropalmatine and Spirobenzylisoquinolines by Thermolysis of Benzocyclobutene Derivatives

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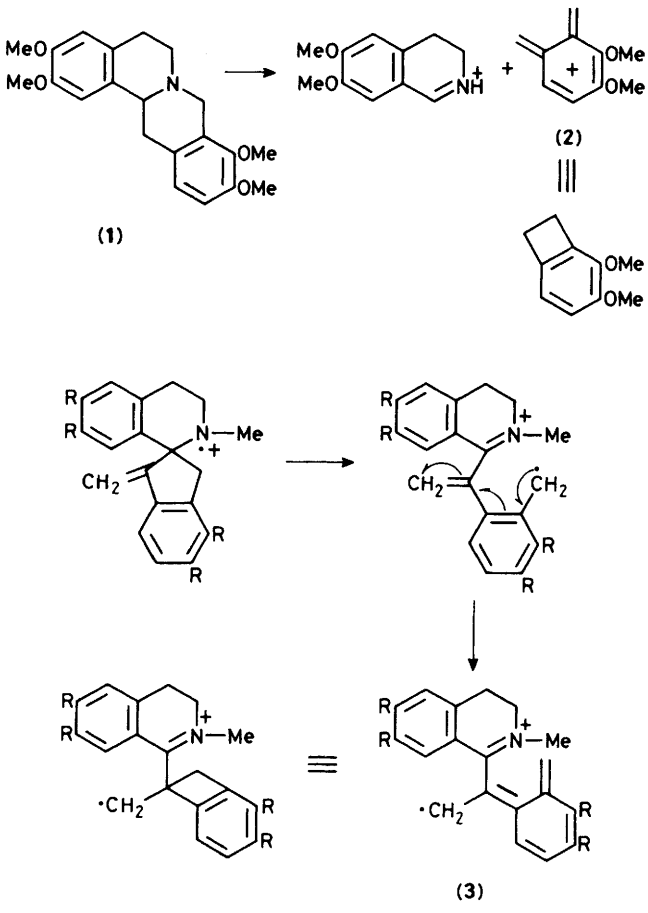
The tetrahydroprotoberberine alkaloid, (±)-tetrahydropalmatine (**1**) was synthesized by heating the 1-benzocyclobutenyl-3,4-dihydroisoquinoline (**16**), followed by reduction of the dehydro compound (**20**) with sodium borohydride. Ochotensine type spirobenzylisoquinolines (**18**) and (**19**) were prepared by the electrocyclic reaction of the corresponding benzocyclobutene derivatives (**14**) and (**15**).

Retro mass spectral analysis[1] has been found to provide a feasible synthetic pathway to various types of natural products. Although this synthetic strategy has already been applied to the preparation of several isoquinoline alkaloids,[2] the protoberberine alkaloids so far synthesized have had a 2,3,10,11-tetraoxygenated substitution pattern, and the spirobenzylisoquinolines an unnatural oxygenation pattern. It was, therefore, of interest in order to demonstrate the generality of the above synthetic strategy, to investigate its further application to the synthesis of 2,3,9,10-tetraoxygenated protoberberine alkaloids, which are also distributed widely in Nature, and the spirobenzylisoquinolines having a naturally occurring oxygenation system.

The mass spectrum[3] of tetrahydropalmatine (**1**) exhibits a characteristic ion (**2**) having an *o*-quinodimethane system which is known to be generated *in situ* by thermolysis[4] of the benzocyclobutene derivative, together with a 3,4-dihydroisoquinolinium ion as shown in the Scheme. Moreover, the *o*-quinodimethane derivative (**3**) would be equivalent to the rearranged molecular ion appearing in the mass spectrum[5] of spirobenzylisoquinoline.

Thus, the benzocyclobutene (**6**), chemically equivalent to the *o*-quinodimethane (**2**), was prepared as described below.



Scheme.

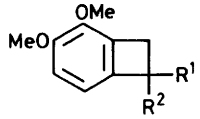
Results and Discussion

Bromination of 3-(2,3-dimethoxyphenyl)propanenitrile (**4**) in acetic acid afforded the 3-(2-bromo-5,6-dimethoxyphenyl)-propanenitrile (**5**), whose treatment with sodium amide in liquid ammonia furnished the desired benzocyclobutene[6] (**6**) *via* the benzyne intermediate.[7] First, an intermolecular cycloaddition reaction of the benzocyclobutene (**6**) with 3,4-dihydro-6,7-dimethoxyisoquinoline (**12**) was carried out in refluxing *o*-dichlorobenzene to give the 13-cyanoprotoberberine (**13**) regioselectively, in 52% yield. These results suggested that the reactivity of 3,4-dimethoxybenzocyclobutene-1-carbonotrile (**6**) was similar to that of 4,5-dimethoxybenzocyclobutene-1-carbonitrile, whose reaction with (**12**) afforded 13-cyano-2,3,10,11-tetramethoxyprotoberberine.[8] Since difficulties were encountered in the decyanation of the product (**13**), an alternative pathway which involves an electrocyclic reaction was then investigated to synthesize naturally occurring 2,3,9,10-tetramethoxyprotoberberine. The acid (**7**) prepared from the cyanide (**6**) by hydrolysis was converted into its acid chloride (**8**) on treatment with oxalyl chloride. Schotten–Baumann reaction of (**8**) with 3,4-dimethoxyphenethylamine gave rise to the amide (**14**), in 80% yield, whose Bischler–Napieralski reaction yielded the 3,4-dihydroisoquinoline hydrochloride (**16**). Thermolysis of (**16**) at 160 °C followed by sodium borohydride reduction furnished, *via* (**20**), tetrahydropalmatine (**1**), which was identical with an authentic specimen.[9]

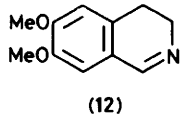
We next focused our attention on the synthesis of spirobenzylisoquinolines with a naturally occurring oxygenation pattern. When the free base of (**16**) in chloroform was allowed to stand at ambient temperature for 24 h, formation of a new base was observed,[10] the structure of which was determined on the basis of its spectral data to be a spirobenzylisoquinoline (**18**). This type of reaction was also applied to the synthesis of an ochotensine-type isoquinoline[11] as follows. Methylation of the benzocyclobutene (**6**) with methyl iodide in the presence of sodium hydride in dimethylformamide afforded the methyl substituted derivative (**9**), in 98% yield, which was then converted into the corresponding acid (**10**) by hydrolysis. Schotten–Baumann reaction of the acid chloride (**11**) [prepared from the acid (**10**) with oxalyl chloride] with *N*-methyl-3,4-dimethoxyphenethylamine furnished the amide (**15**) in quanti-

tative yield. Bischler–Napieralski reaction of the amide (**15**) with phosphoryl chloride in refluxing benzene for 22 h afforded, *via* (**17**), the desired spirobenzylisoquinoline (**19**), which is structurally related to ochotensine.

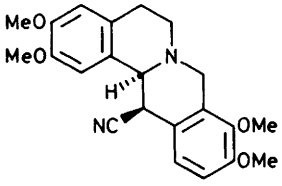
(4) R = H
(5) R = Br



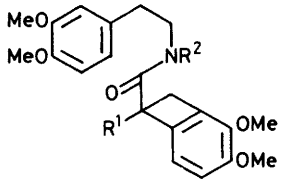
(6) R^1 = CN, R^2 = H
(7) R^1 = CO_2H, R^2 = H
(8) R^1 = COCl, R^2 = H
(9) R^1 = CN, R^2 = Me
(10) R^1 = CO_2H, R^2 = Me
(11) R^1 = COCl, R^2 = Me



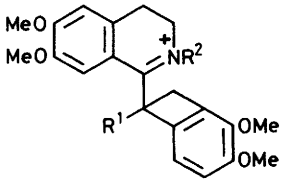
(12)



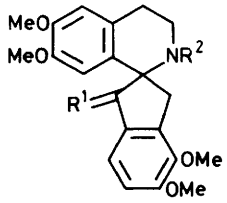
(13)



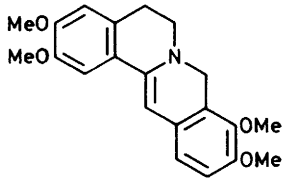
(14) R^1 = H, R^2 = H
(15) R^1 = Me, R^2 = Me



(16) R^1 = H, R^2 = H
(17) R^1 = Me, R^2 = Me



(18) R^1 = O, R^2 = H
(19) R^1 = CH_2, R^2 = Me



(20)

Thus, the syntheses of tetrahydropalmatine, 2,3,9,10-tetraoxygenated protoberberine and ochotensine type spirobenzylisoquinoline have successfully been achieved by adopting retro mass spectral analysis, and this strategy has been demonstrated to provide a general synthetic route.

Experimental

General Methods.—M.p.s are uncorrected. I.r. spectra were recorded on a Hitachi 260-10 spectrophotometer. N.m.r. spectra were measured on JEOL JNM-PMX-60 and JEOL PS 100 spectrometers. Chemical shifts are reported as δ_H values relative to internal $SiMe_4$. Mass spectra were taken on a JEOL-JMS-D 300 spectrometer. All new compounds described in the experimental section were homogeneous on t.l.c. Ether refers to diethyl ether.

3-(2-*Bromo*-5,6-*dimethoxyphenyl*)*propanenitrile* (**5**).—To a stirred mixture of 3-(2,3-dimethoxyphenyl)propanenitrile (**4**) (21 g), sodium acetate (10.3 g), and acetic acid (400 ml) was added bromine (20 g) in acetic acid (50 ml) dropwise at room temperature, and the stirring was continued overnight. The mixture was poured into water and extracted with benzene. The extract was washed with aqueous sodium thiosulphate and water, dried (Na_2SO_4), and evaporated to give the residue, which was chromatographed on silica gel. Elution with benzene gave a colourless solid, which was recrystallised from ethanol to afford the *cyanide* (**5**) (19.3 g, 65.0%) as colourless needles, m.p. 54—56 °C (Found: C, 49.1; H, 4.5; N, 5.15. $C_{11}H_{12}BrNO_2$ requires C, 48.9; H, 4.5; N, 5.2%); $\nu_{max.}$($CHCl_3$) 2 225 and 2 250 cm^{-1} (CN); δ_H (100 MHz; $CDCl_3$) 2.57 (2 H, t, *J* 8 Hz, CH_2), 3.14 (2 H, t, *J* 8 Hz, CH_2), 3.83 (3 H, s, OMe), 3.88 (3 H, s, OMe), 6.72 (1 H, d, *J* 8.5 Hz, ArH), and 7.21 (1 H, d, *J* 8.5 Hz, ArH); *m/z* 269 (M^+).

3,4-*Dimethoxybenzocyclobutene*-1-*carbonitrile* (**6**).—The nitrile (**5**) (5.0 g) in dry THF was added dropwise to a solution of sodium amide, prepared from liquid ammonia (200 ml) and sodium metal (1.7 g), and the mixture stirred at room temperature for 2 h. After addition of an excess of ammonium chloride, the mixture was allowed to stand at room temperature overnight. The mixture was poured into water and extracted with benzene. The organic layer was separated, washed with water, dried (Na_2SO_4), and evaporated to give the residue, which was chromatographed on silica gel. Elution with benzene gave a colourless solid, which was recrystallised from ethanol to afford the *benzocyclobutene* (**6**) (2.17 g, 62%) as colourless needles, m.p. 112.5—113 °C (Found: C, 69.9; H, 5.85; N, 7.4. $C_{11}H_{11}NO_2$ requires C, 69.8; H, 5.85; N, 7.4%); $\nu_{max.}$($CHCl_3$) 2 245 cm^{-1} (CN); δ_H (100 MHz; $CDCl_3$) 3.78 (2 H, d, *J* 4 Hz, CH_2), 3.84 (3 H, s, OMe), 3.97 (3 H, s, OMe), 4.18 (1 H, t, *J* 4 Hz, CH), 6.75 (1 H, d, *J* 8 Hz, ArH), and 6.82 (1 H, d, *J* 8 Hz, ArH); *m/z* 189 (M^+).

13-*Cyano*-2,3,9,10-*tetramethoxytetrahydroprotoberberine* (**13**).—A solution of 6,7-dimethoxy-3,4-dihydroisoquinoline (**12**) (320 mg) and benzocyclobutene (**6**) (320 mg) in *o*-dichlorobenzene (20 ml) was refluxed for 6 h. Evaporation of the solvent gave an oil, which was chromatographed on silica gel. Elution with benzene–ethyl acetate (9:1, v/v) afforded a solid, which was recrystallised from chloroform–ethanol to give the *protoberberine derivative* (**13**) (330 mg, 52%) as colourless needles, m.p. 191—193 °C (Found: C, 69.25; H, 6.25; N, 7.35. $C_{22}H_{24}N_2O_4$ requires C, 69.45; H, 6.35; N, 7.35%); $\nu_{max.}$($CHCl_3$) 2 245 cm^{-1} (CN); δ_H (60 MHz; $CDCl_3$) 2.28—3.48 (4 H, m, 5- and 6-CH_2), 3.65—3.80 (2 H, m, 8-H and 13-H), 3.87 (12 H, s, OMe × 4), 4.18 (1 H, d, *J* 3 Hz, 13a-H), 4.35 (1 H, d, *J* 10 Hz, 8-H), 6.60 (1 H, s, ArH), 6.65 (1 H, s, ArH), 6.82 (1 H, d, *J* 8 Hz, ArH), and 7.03 (1 H, d, *J* 8 Hz, ArH); *m/z* 380 (M^+).

3,4-*Dimethoxybenzocyclobutene*-1-*carboxylic Acid* (**7**).—A mixture of the benzocyclobutene (**6**) (500 mg) and saturated ethanolic potassium hydroxide (20 ml) was kept at room temperature overnight. After addition of water (20 ml) the mixture was refluxed for 3 h and then poured into water. The resulting alkaline layer was washed with ether and acidified with 10% hydrochloric acid. The aqueous layer was extracted with chloroform, and the extract was washed with water, dried (Na_2SO_4), and evaporated to give a colourless solid, which was recrystallised from benzene to afford (**7**) (543 mg, 98.5%) as *colourless plates*, m.p. 123—124 °C (Found: C, 63.3; H, 5.85. $C_{11}H_{12}O_4$ requires C, 63.45; H, 5.8%); $\nu_{max.}$($CHCl_3$) 1 720 cm^{-1} (CO); δ_H (60 MHz; $CDCl_3$) 3.63 (2 H, d, *J* 4 Hz, CH_2), 3.79 (3 H, s, OMe), 3.93 (3 H, s, OMe), 4.21 (1 H, t, *J* 4 Hz, CH), 6.70 (2 H, s, ArH × 2), and 10.62 (1 H, br s, CO_2H); *m/z* 208 (M^+).

N-(3,4-*Dimethoxyphenyl*)-3,4-*dimethoxybenzocyclobutene*-1-*carboxamide* (**14**).—A solution of the acid (**7**) (500 mg) and oxalyl chloride (0.73 ml) in methylene chloride (20 ml) was refluxed for 1 h. Evaporation of the solvent and the excess reagent afforded the corresponding chloride (**8**), which was dissolved in ether (5 ml). The above ethereal solution was added to a solution of 3,4-dimethoxyphenethylamine (440 mg) in ether (20 ml) in the presence of sodium hydrogen carbonate at 0 °C. The resulting mixture was stirred for 2 h at room temperature and extracted with chloroform. The organic layer was washed with 2% hydrochloric acid, aqueous sodium hydrogen carbonate, and water, dried (Na_2SO_4), and evaporated to give a colourless solid which was recrystallised from ethanol to afford the *amide* (**14**) (716 mg, 80.4%) as colourless needles, m.p. 138—140 °C (Found: C, 67.45; H, 6.75; N, 3.9. $C_{21}H_{25}NO_5$ requires C, 67.9; H, 6.8; N, 3.75%); $\nu_{max.}$($CHCl_3$) 3 430 (NH) and 1 660 cm^{-1} (CO); δ_H (60 MHz; $CDCl_3$) 2.74 (2 H, t, *J* 7 Hz, CH_2), 3.22—3.80 (4 H, m, CH_2 × 2), 3.80 (6 H, s, OMe × 2), 3.85 (3 H, s, OMe), 3.94 (3 H, s, OMe), 3.98—4.20 (1 H, m, CH), 5.77 (1 H, br s, NH), and 6.40—6.91 (5 H, m, ArH × 5); *m/z* 371 (M^+).

3,4-*Dihydro*-6,7-*dimethoxy*-1-(3,4-*dimethoxybenzocyclobutenyl*)*isoquinoline Hydrochloride* (**16**).—A solution of the amide (**14**) (300 mg) and phosphoryl chloride (0.2 ml) in dry benzene (2 ml) was refluxed for 2 h. After cooling, the mixture was poured into hexane, and the yellow powder precipitated was separated by decantation to give the *hydrochloride* (**16**), which was characterised as its free base; $\nu_{max.}$($CHCl_3$) 1 630 cm^{-1} (C=N); δ_H (60 MHz; $CDCl_3$) 2.51 (2 H, t, *J* 7.5 Hz, CH_2), 3.25—3.67 (4 H, m, CH_2 × 2), 3.69 (3 H, s, OMe), 3.78 (3 H, s, OMe), 3.82 (3 H, s, OMe), 3.88 (3 H, s, OMe), 4.67 (1 H, br s, CH), 6.48—6.70 (3 H, m, ArH × 3), and 6.98 (1 H, s, ArH) (Found: M^+ *m/z* 353.1594. $C_{21}H_{23}NO_4$ requires M^+ 353.1625).

(±)-*Tetrahydropalmatine* (**1**).—A suspension of (**16**) (30 mg) in *o*-dichlorobenzene (2 ml) was heated at 180 °C for 1 h. After an excess of hexane had been added to the mixture, pale yellow crystals of (**20**) (27 mg, 100%) separated and were dissolved in methanol. To the above stirred solution was added sodium borohydride (100 mg) at ambient temperature. After evaporation of the solvent, the residue was extracted with chloroform. The organic layer was washed with water, dried (Na_2SO_4), and evaporated to give a pale yellow oil, which was chromatographed on silica gel. Elution with chloroform–methanol (99:1, v/v) afforded (±)-tetrahydropalmatine (**1**) (17 mg, 62%), which was identical with an authentic sample.[3]

1′,2,2′,3,3′,4′-*Hexahydro*-4,5,6′,7′-*tetramethoxyspiro*[*indene*-2,1′-*isoquinoline*]-1-*one* (**18**).—A solution of the free base of 3,4-dihydro-6,7-dimethoxy-1-(3,4-dimethoxybenzocyclobutenyl)-isoquinoline hydrochloride (**16**) (150 mg) in chloroform (2 ml) was set aside at room temperature for 24 h. After removal of the solvent, the residue was dissolved in benzene (20 ml) and the resulting solution was washed with saturated aqueous sodium hydrogen carbonate and then extracted with 10% hydrochloric acid. The acidic layer was basified with 10% ammonium hydroxide and extracted with chloroform. The chloroform extract was washed with water, dried (Na_2SO_4), and evaporated to give the residue, which was chromatographed on silica gel. Elution with benzene–ethyl acetate (83:17, v/v) afforded (**18**) (63 mg, 39.7%) as a pale yellow *gum*; $\nu_{max.}$ 1 710 cm^{-1} (CO); δ_H (60 MHz, CCl_4) 3.20 (2 H, s, 3-CH_2), 3.49 (3 H, s, OMe), 3.63 (3 H, s, OMe), 3.72 (3 H, s, OMe), 3.80 (3 H, s, OMe), 5.88 (1 H, s, ArH), 6.34 (1 H, s, ArH), 6.78 (1 H, d, *J* 8.5 Hz, ArH), and 7.28 (1 H, d, *J* 8.5 Hz, ArH) (Found: M^+ *m/z*, 369.1571. $C_{21}H_{23}NO_5$ requires M^+ 369.1574).

3,4-*Dimethoxy*-1-*methylbenzocyclobutene*-1-*carbonitrile* (**9**).—60% Sodium hydride (0.2 g) was added to a stirred solution of the cyclobutene (**6**) (510 mg) in dimethylformamide (10 ml) at 0 °C and the mixture was stirred for 0.5 h; methyl iodide was then added, and the resulting mixture warmed at 40 °C for 2 h. The mixture was then poured into water, extracted with benzene and the extract dried (Na_2SO_4), and evaporated to give a crude solid; this was recrystallised from ethanol to afford (**9**) (540 mg, 98.5%) as colourless needles, m.p. 133.5—138 °C (Found: C, 70.85; H, 6.45; N, 6.9. $C_{12}H_{13}NO_2$ requires C, 70.9; H, 6.45; N, 6.9%); $\nu_{max.}$ ($CHCl_3$) 2 245 cm^{-1} (CN); δ_H (60 MHz; $CDCl_3$) 1.62 (3 H, s, C-Me), 3.30 (1 H, d, *J* 14 Hz, 2-H), 3.83 (1 H, d, *J* 14 Hz, 2-H), 3.71 (3 H, s, OMe), 3.81 (3 H, s, OMe), and 7.69 (2 H, s, ArH × 2); *m/z* 203 (M^+).

3,4-*Dimethoxy*-1-*methylbenzocyclobutene*-1-*carboxylic Acid* (**10**).—A mixture of the nitrile (**9**) (537 mg) and saturated ethanolic potassium hydroxide (3 ml) was set aside for 20 h at room temperature. After addition of water (5 ml), the mixture was refluxed for 3 h. The mixture was diluted with water and acidified with 10% hydrochloric acid and extracted with benzene. The benzene extract was washed with water, dried (Na_2SO_4), and evaporated to give a colourless oil, which was crystallised from benzene–hexane to give the *acid* (**10**) (410 mg, 70%) as colourless needles, m.p. 127—128 °C (Found: C, 64.35; H, 6.35. $C_{12}H_{14}O_4$ requires C, 64.85; H, 6.35%); $\nu_{max.}$($CHCl_3$) 1 705 cm^{-1} (CO), δ_H (60 MHz; $CDCl_3$) 1.70 (3 H, s, CMe), 3.24 (1 H, d, *J* 14 Hz, 2-H), 3.95 (1 H, d, *J* 14 Hz, 2-H), 3.84 (3 H, s, OMe), 3.97 (3 H, s, OMe), and 6.77 (2 H, s, ArH × 2); *m/z* 222 (M^+).

N-3,4-*Dimethoxyphenethyl*-N-*methyl*-1-(3,4-*dimethoxy*-1-*methylbenzocyclobutenyl*)*carboxamide* (**15**).—A solution of the acid (**10**) (100 mg) and oxalyl chloride (0.1 ml) in methylene chloride (5 ml) was refluxed for 1 h. Evaporation of the solvent and an excess of reagent afforded the corresponding chloride (**11**), which was dissolved in ether (2 ml) and added to a solution of *N*-methyl-3,4-dimethoxyphenethylamine (100 mg) in ether (5 ml) in the presence of saturated aqueous sodium hydrogen carbonate at 0 °C. The mixture was stirred for 2 h at room temperature and extracted with chloroform. The extract was washed with 2% hydrochloric acid, water, saturated aqueous sodium hydrogen carbonate, and water, and dried (Na_2SO_4). Evaporation of the solvent gave the residue, which was chromatographed on silica gel. Elution with chloroform afforded a colourless solid, which was recrystallised from benzene–ether to give the *amide* (**15**) (179 mg, 100%) as colourless needles, m.p. 125.5—126 °C (Found: C, 68.7; H, 7.4; N, 3.6. $C_{23}H_{29}NO_5$ requires C, 69.15; H, 7.3; N, 3.5%); $\nu_{max.}$($CHCl_3$) 1 620 cm^{-1} (CO); δ_H (60 MHz; $CDCl_3$) 1.53 (3 H, s, CMe), 2.84 (3 H, s, NMe), 2.55—3.65 (6 H, m, CH_2 × 3), 3.71 (6 H, s, OMe × 2), 3.73 (2 H, s, OMe), 3.81 (3 H, s, OMe), 6.55—6.90 (4 H, m, ArH × 4), and 7.16 (1 H, s, ArH); *m/z* 399 (M^+).

1′,2,2′,3,3′,4′-*Hexahydro*-4,5,6′,7′-*tetramethoxy*-2′-*methyl*-1-*methylenespiro*[*indene*-2,1′-*isoquinoline*] (**19**).—A mixture of the amide (**15**) (179 mg), phosphoryl chloride (0.1 ml), and dry benzene (5 ml) was refluxed for 22 h. After evaporation of the solvent and excess of reagent the residue was basified with 10% ammonium hydroxide. The resulting mixture was extracted with methylene chloride, and the extract was washed with water, and dried (Na_2SO_4). Removal of the solvent gave an oil, which was chromatographed on silica gel. Elution with chloroform–methylene chloride (1:1, v/v) afforded starting material (**15**) (83 mg) and further elution with chloroform yielded the desired spiro compound (**19**) (10 mg, 5.8%); $\nu_{max.}$($CHCl_3$) 860 cm^{-1} (C=C); δ_H (60 MHz; $CDCl_3$) 2.05 (3 H, s, NMe), 2.48—3.37 (6 H, m, CH_2 × 3), 3.48 (3 H, s, OMe), 3.70 (3 H, s, OMe). 3.73 (3 H, s,

OMe), 3.83 (3 H, s, OMe), 4.80 (1 H, s, vinylic H), 5.47 (1 H, s, vinylic H), 6.08 (1 H, s, ArH), 6.32 (1 H, s, ArH), 6.70 (1 H, d, J 8 Hz, ArH), and 7.07 (1 H, d, J 8 Hz, ArH) (Found: M^+ m/z, 381.1961. $C_{23}H_{27}NO_4$ requires M^+ 381.1940).

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