NEW AND IMPROVED SYNTHESIS OF (±)-4-BROMO-7,8-DIMETHOXY-ISOCHROMAN-3-ONE, A KEY INTERMEDIATE FOR THE ELABORATION OF (±)-*cis*-ALPININE AND (±)-*cis*-ALPINIGENINE

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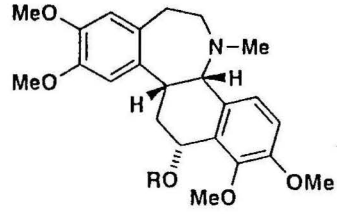
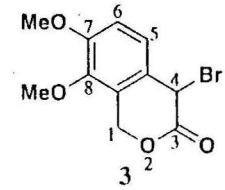
The Rhoeadine-Papaverrubine alkaloids constitutes a small family of natural products, elaborated almost exclusively by the *Papaver* genus; many of the members of this family have potentially useful biological activity.[1] In 1982, Ahmad and Snieckus[2] reported a convergent entry into the rhoeadan skeleton and a formal total synthesis of (±)-*cis*-alpinigenine (**1**) and the related (±)-*cis*-alpinine (**2**), using bromolactone **3** as key intermediate. The bromolactone was prepared by these authors employing different approaches; however, regioselectivity problems arising

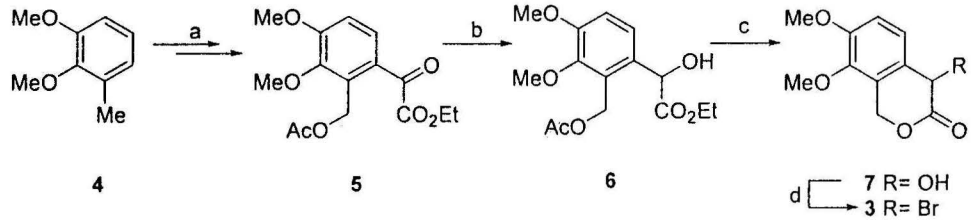


1 R = H; **2** R = Me



3

during isochromanone ring formation and in the final bromination step under free radical conditions, lead to mixtures of regioisomeric isochroman-3-one derivatives, as well as nuclear and benzylic brominated products; moreover, in spite that improved syntheses of precursors of **3** have been reported,[3,4] the efficiency of the overall sequence demonstrated to be rather poor. Here, we report a convenient, alternative and efficient synthesis of bromolactone **3**, starting from 2,3-dimethoxytoluene (**4**), which proceeds through the known glyoxylate **5**.[5]



4 **5** **6**

Reagents and conditions: a. See ref. 5 (75%); b) $NaCNBH_3$, $AcOH_{gl}$, EtOH, RT, overnight (91%); c) Camphorsulfonic acid (5 mol %), MeOH, RT, 6 h (89%); d) 1. SMe_2, NBS, CH_2Cl_2, RT→0°C; 2. α-hydroxylactone **7**, 0°C→RT, overnight (89%).

The sequence is based on the acid-catalyzed lactonization of **6**, which avoids production of regioisomeric isochroman-3-ones and a bromodehydroxylation reaction of the resulting hydroxylactone **7**, which does not generate nuclearly halogenated products. Selective reduction of **5** with sodium cyanoborohydride in ethanol, to which glacial acetic acid was added in order to accelerate the reaction, smoothly and cleanly afforded 91% of mandelate **6**. Next, lactonization was carried out by exposure of **6** to camphorsulfonic acid in dry methanol at room temperature,[6] furnishing 89% of α-hydroxyketone **7** as a solid. Finally, bromination of **7** was undertaken; however, the $PPh_3.Br_2$ adduct in DMF[7] gave disappointingly low yields (Table), while the PPh_3-NBS reagent[8] furnished only 41% of **3** (Entries 1 and 2) and the conditions shown in Entry 3 provided 32% of the related chloride.

Table. Elaboration of Bromolactone **3** by Bromodehydroxylation of **7**

Entry N°	Reagent	Conditions	Yield (%)
1	$PPh_3 \cdot Br_2$	DMF, RT	< 10
2	PPh_3, NBS	CH_2Cl_2, 0°C	41
3	$MeSO_2Cl$, EtN_3, LiBr, $Bu_4N^+Br^-$	CH_2Cl_2, 0°C→RT, overnight	-
4	SMe_2, NBS	$CHCl_3$, 0°C→60°C, 30 min	< 30
5	SMe_2, NBS	$CHCl_3$, 0°C	38
6	SMe_2, NBS	CH_2Cl_2, -10°C→reflux	56
7	SMe_2, NBS	CH_2Cl_2, -20°C→RT	59
8	SMe_2, NBS (RT)	CH_2Cl_2, 0°C	70
9	SMe_2, NBS (RT)	CH_2Cl_2, 0°C→RT, overnight	89

Yields improved when the SMe_2-NBS[9] couple was employed. Preparation of the reagent at 0°C in $CHCl_3$ followed by reflux in the presence of **7**, produced **3** (< 30%) and inseparable side products (Entry 4). However, when the reaction was heated at lower temperature, 56% of the product was recovered; yields did not improve significantly when the reagents were mixed at –20°C and allowed to attain room temperature (Entries 5 and 7). However, preparation of the SMe_2-NBS reagent at room temperature (Entries 8 and 9) produced considerable enhancements in generation of brominated product, furnishing the best yields (89%) when the reaction was left overnight at room temperature. Under these conditions, the overall yield of **3** from **4** was 54%, more than twice the reported yields for the elaboration of this key intermediate. Compound **3** is highly sensitive to moisture; its spectral data fully agreed with those reported in the literature.

In conclusion, we have developed a simple, practical and efficient synthesis of bromolactone **3**, which proceeds in six high-yield steps from commercially available 2,3-dimethoxytoluene; this procedure is devoid of the drawbacks affecting previous syntheses.

EXPERIMENTAL SECTION

The melting points were taken on an Ernst Leitz Wetzlar model 350 hot-stage microscope and are uncorrected. FT-IR spectra were determined with a Bruker IFS 25 infrared spectrophotometer. The ^{1}H and ^{13}C-NMR spectra were acquired with a Bruker AC200-E spectrometer (200.13 MHz for ^{1}H), employing $CDCl_3$ as solvent; the chemical shifts are expressed in δ ppm downfield from the internal standard (TMS). High resolution mass spectral data were obtained from the Kent Mass Spectrometry Unit 1 (Kent, UK). Reagents and solvents were used as received; dry MeOH was obtained by distillation from magnesium methoxide. Dry $CHCl_3$ and CH_2Cl_2 were accessed by reflux over P_2O_5, followed by distillation. Flash column chromatographies were carried out with silica gel 60 H and eluted with hexane-EtOAc employing gradient techniques. All new compounds gave single spots on TLC plates (Merck, art. 5554) run in different solvent systems. Chromatographic spots were detected by exposure to UV light (254 nm) followed by spraying with ethanolic *p*-anisaldehyde/sulfuric acid reagent and careful heating of the plates for better selectivity.

(±)-Ethyl {2-[(Acetoxy)methyl]-3,4-dimethoxyphenyl}hydroxyacetate (6).- Under a dry nitrogen atmosphere, a solution of keto ester **5**[5] (1001.4 mg, 3.23 mmol) in absolute ethanol (40 mL) was successively treated with glacial acetic acid (0.184 mL, 3.23 mmol) and sodium cyanoborohydride (223.7 mg, 3.55 mmol) and the mixture was strirred overnight at room temperature. The reaction was quenched with 1N NaOH (5 mL), diluted with brine (10 mL) and extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed once with brine (5 mL), dried (Na_2SO_4), concentrated under reduced pressure and chromatographed to provide mandelate **6** (918 mg, 91%), as a colorless oil; IR (film): 3460, 2980, 2850, 1740, 1730, 1600, 1500, 1460, 1280, 1090 and 810 cm^{-1}; ^{1}H NMR: δ 1.22 (s, 3H, J = 8.6, OCH_2Me), 1.60 (bs, 1H, OH), 2.07 (s, 3H, $MeCO_2$), 3.84 (s, 3H, OMe), 3.86 (s, 3H, OMe), 4.20 (dq, 2H, J = 1.0, 8.6, OCH_2Me), 5.35 (s, 2H, $ArCH_2O$), 5.40 (s, 1H, ArCHOH), 6.92 (d, 1H, J = 8.6, ArH) and 7.10 (d, 1H, J = 8.6, ArH); ^{13}C NMR: δ 13.88 ($MeCH_2$), 20.86 ($MeCO_2$), 55.56 (OMe-7), 57.60 ($ArCH_2O$), 61.20 (OMe-8), 61.97 ($MeCH_2O$), 69.77 (ArCHOH), 112.71 (C-5), 122.97 (C-6), 128.03 (C-2), 130.88 (C-1), 148.46 (C-4), 152.65 (C-3), 170.73 (C=O) and 173.60 (C=O). HRMS for $C_{15}H_{20}O_7$. Calcd.: 312.12087. Found: 312.12087.
Anal. Calcd for $C_{15}H_{20}O_7$: C, 57.69; H, 6.45. Found: C, 57.60; H, 6.52

(±)-4-Hydroxy-7,8-dimethoxy-isochroman-3-one (7).- A mixture of mandelate **6** (250 mg, 0.80 mmol) and camphorsulfonic acid (93 mg, 0.4 mmol) in anhydrous MeOH (8 mL) was warmed to 40°C and stirred for 6 h. After cooling, the reaction mixture was diluted with brine (10 mL), and extracted with EtOAc (3 x 10 mL); the organic extracts were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuum.* Chromatography of the residue give hydroxylactone **7** (160 mg, 89%), as a white solid mp. 126-128°C (hexane-EtOAc). IR (KBr): 3466, 2980, 2870, 1734, 1496, 1456, 1380, 1276, 1258, 1206, 1142, 1086, 1024, 818 and 806

cm^{-1}; ^1H NMR: δ 3.62 (bs, 1H, $w_{1/2}$ = 8 Hz, OH), 3.87 (s, 3H, OMe), 3.88 (s, 3H, OMe), 5.10 (bs, 1H, H-4), 5.16 (d, 1H, *J* = 14.5, ArCH_2O), 5.64 (d, 1H, *J* = 14.5, ArCH_2O), 6.98 (d, 1H, *J* = 8.4, H-6) and 7.30 (d, 1H, *J* = 8.4, H-5); ^{13}C NMR: δ 55.86 (OMe-7), 61.04 (OMe-8), 64.06 (C-1), 67.24 (C-4), 113.01 (C-6), 118.92 (C-7a), 122.90 (C-5), 126.59 (C-4a), 144.40 (C-7), 151.66 (C-8) and 173.76 (C-3). HRMS for $C_{11}H_{12}O_5$. Calcd.: 224.06847. Found: 224.06823.
Anal. Calcd. for $C_{11}H_{12}O_5$: C, 58.93; H, 5.39; Found: C, 58.98; H, 5.35

(±)-4-Bromo-7,8-dimethoxy-isochroman-3-one (3).- Under a dry nitrogen atmosphere, a stirred solution of NBS (159 mg, 0.89 mmol) in anhydrous CH_2Cl_2 (2 mL) was treated dropwise with methyl sulfide (0.082 mL, 1.37 mmol) at room temperature. The mixture was cooled to 0°C, a solution of hydroxylactone **7** (100 mg, 0.35 mmol) in CH_2Cl_2 (2 mL) was introduced dropwise and the system was left to attain room temperature. When the reaction was completed (TLC), brine (5 mL) was added and the products were extracted with EtOAc (3 x 15 mL); the combined organic extracts were washed once with brine (5 mL), dried (Na_2SO_4), concentrated and chromatographed, furnishing **3** (114 mg, 89%) as an oil which crystallized upon standing in the refrigerator, furnishing a solid mp. 121-123°C, *lit.*[2] 122-123°C; IR (film): 3000, 2950, 2840, 1750, 1600, 1490, 1380, 1280, 1160, 1090, 1049, 990, 970, 895, 820, 765 and 690 cm^{-1}; ^1H NMR: δ 3.87 (s, 3H, OMe), 3.89 (s, 3H, OMe), 5.40 (s, 1H, H-4), 5.44 (d, 1H, *J* = 15.3, ArCH_2O), 5.61 (d, 1H, *J* = 15.3, ArCH_2O), 6.92 (d, 1H, *J* = 8.4, H-6) and 7.12 (d, 1H, *J* = 8.4, H-5); ^{13}C NMR: δ 39.46 (C-4), 55.83 (C-7), 60.96 (C-7), 65.16 (C-1), 112.90 (C-6), 123.83 (C-8a), 123.91 (C-5), 126.76 (C-4a), 144.95 (C-7), 153.45 (C-8) and 165.66 (C-3); EI-MS, *m/z* (%): 288, 286 (M^+, 6), 208 (26), 207 (100), 179 (24) and 151 (41).

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