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The Bromination of β-Angelica Lactone Revisited: Synthesis of New 3-Bromo-5-methylene- and 3-Bromo-5-methyl-2(5*H*)-furanones.

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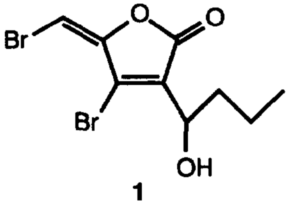
Abstract: *Several title compounds have been synthesized efficiently from β–angelica lactone by using simple and mild methods that combine bromination and dehydrobromination or debromination processes accomplished in a convenient order.*

INTRODUCTION

Furanones containing one of more bromine atoms are found as structural moieties in several known natural or designed products.[1] For instance, the fimbrolide **1** was isolated from *Delisea fimbriata*,[1] the butenolide **2** was later obtained and identified from *Delisea elegans*,[2] and the unnatural bromolactone **3** was easily synthesized from levulinic acid.[3] Whereas a bromine atom at the β-carbonyl position is a very common feature as can be realized by inspecting products **1-3**, α-bromobutenolides are very scarce.[4]



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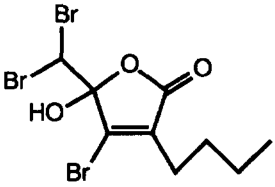

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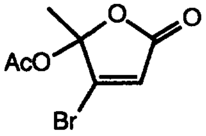

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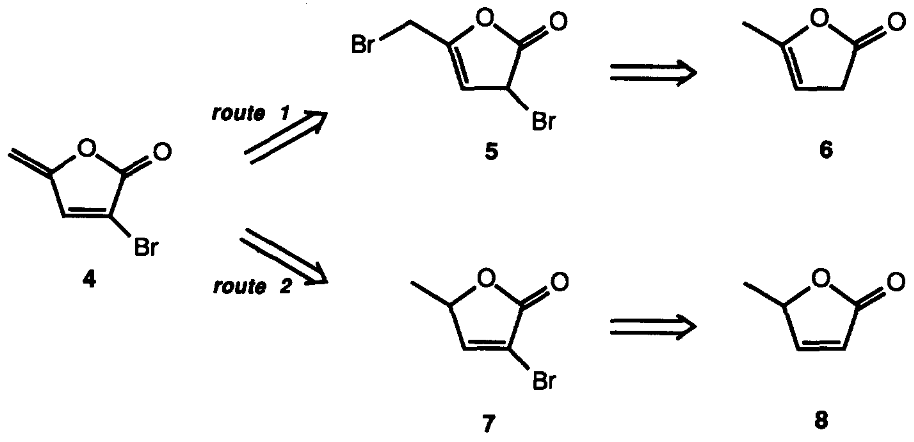
In connection with our studies on the synthesis and the reactivity of yilidene-furanones,[5] we decided to prepare the previously undescribed 3-bromo-5-methylene-2(5*H*)-furanone, **4**, and related products starting from available materials. One possibility was a monodehydrobromination from the intermediate **5** which could be obtained from α-angelica lactone, **6**[6] (Scheme 1, route 1). The synthetic pathway would involve a double allylic bromination of **6** to give compound **5**. This transformation was attempted by using *N*-

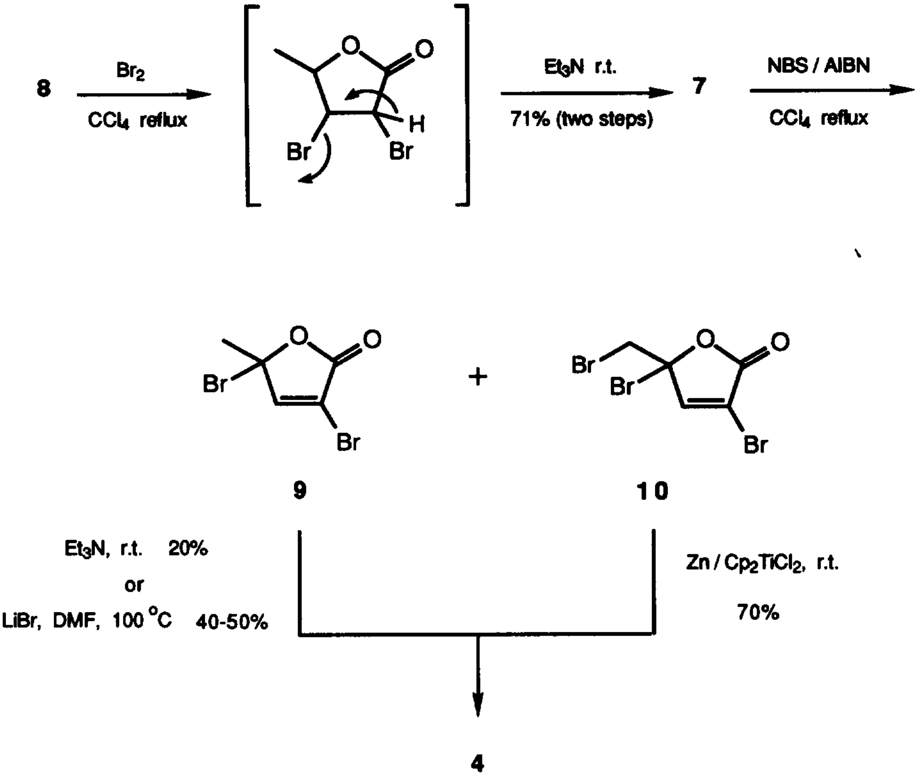
bromosuccinimide (NBS, 1 or 2 equivalents) in CCl_4 in the presence of benzoyl peroxide. In no case, however, were defined products identified.



Scheme 1

Therefore, we intended to prepare **4** from β-angelica lactone, **8**, which is easily obtained from **6**.[6] According to Scheme 1, route 2, the first step consisted in the synthesis of 3-bromo-5-methyl-2(5*H*)-furanone, **7** as a key intermediate. This compound had been previously synthesized in 54% yield by reaction of **8** with equimolecular amount of bromine in carbon tetrachloride at room temperature for 15 h, followed by treatment of the crude dibromide with 2 molar amount of triethylamine in benzene at 0 °C for 3 h.[4] Nevertheless, characterization of this product by its physical constants and spectral data had not been reported prior to our work. In our laboratory, lactone **7** has been fully characterized and prepared in higher yield (71%) by treatment of **8** with 1.5 mol of bromine in refluxing carbon tetrachloride for 1.5 h followed by reaction with 1.5 mol of triethylamine at room temperature for 2 hours, without isolation of the intermediate dibromolactone (Scheme 2).

Reaction of **7** with NBS[7,8] and azobisisobutyronitrile (AIBN) in refluxing carbon tetrachloride afforded a mixture of dibromide **9** and tribromide **10**, whose composition was verified to be dependent upon the number of equivalents of NBS and the reaction time, as shown in Table 1. Conditions to produce exclusively dibromide **9** were not found, but lactone **10** was obtained in 63% yield as the only reaction product by using 2.7 equivalents of NBS for 72 hours. Formation of the dibromolactone **10** can be rationalized by assuming an initial monobromination of **7** to give **9**, followed by dehydrobromination to produce **4** and subsequent addition of bromine to the exocyclic double bond. A similar explanation was reported to rationalize the production of some related bromolactones obtained by reaction between β-angelica lactone and NBS.[8] Although furanone **4** was never detected, the evolution of lactone **9** to **10** in the reaction conditions is in accordance with the fact that formation of **10** is favoured when increasing the number of equivalents of NBS and that the ratio of **9** to **10** decreases with time.



Scheme 2

Table 1. Reactions of bromolactone 7 with *N*-bromosuccinimide

Entry	eq NBS	reaction time (hr)	% yield	% relative ratio [a]		
				7	9	10
1	1.1	18	65	65	32	3
2	1.1	26	55	20	60	20
3	1.6	51	66	44	11	45
4	2.2	41	54	30	9	61
5	2.7	72	63	---[b]	---[b]	63

[a] Determined from isolated products. [b] Product not detected.

Conversion of both bromoderivatives **9** and **10** into the methylene-furanone **4** was independently studied. Base-promoted dehydrobromination of **9** was tried by using DBU or triethylamine.[7] Unaltered starting material was always recovered as the only defined product in the former case while in the later, compound **4** was obtained in 20% yield after 20 hours at room temperature. The use of more than one equivalent of base did not improve the yield of conversion. Better results were obtained when **9** was treated with 1 mol of LiBr in DMF[7] at 100 °C for 1 hour, giving **4** in 40-50% yield. Instability of compound **9** could account for these low yields because of its progressive decomposition in the reaction conditions.

In turn, lactone **4** resulted from **10** through a reductive debromination by using zinc dust in tetrahydrofuran in the presence of dicyclopentadienyltitanium(IV) dichloride (Cp_2TiCl_2) as a catalyst at room temperature for 30 minutes, affording **4** in 70% yield. Inexpensive and commercially available Cp_2TiCl_2 undergoes zinc reduction under the reaction conditions to generate Cp_2TiCl which is the reducing species.[10] The use of this reagent provides a mild method for rapid and clean debromination of *vic*-halides and allowed the synthesis of compound **4** satisfactorily.

In view of these results, the best synthetic route to convert **7** into **4** involves the reaction of **7** with NBS in the conditions of Table 1, entry 5, to give tribromide **10** in 63% yield, followed by debromination according to the procedure described above.

In this way, the new bromo-furanones **4, 9** and **10**, as well as **7**, could be easily and efficiently synthesized and characterized.

EXPERIMENTAL SECTION

Flash column chromatography was carried out on silica gel (240-400 mesh). Melting points were determined on a hot stage and are uncorrected. Distillation of small amounts of material was effected in a bulb-to-bulb distillation apparatus, with oven temperatures (o.t.) being reported. Electron-impact mass spectra were recorded at 70 eV. Chemical shifts in NMR spectra are given in ppm relative to internal TMS (δ scale).

Synthesis of 3-bromo-5-methyl-2(5*H*)-furanone, 7. Bromine (0.54 mL, 10.5 mmol) in CCl_4 (7 mL) was added dropwise during 30 min to a stirred solution of lactone **8** (670 mg, 6.84 mmol) in CCl_4 (20 mL). The mixture was heated to reflux for 1.5 hr, cooled at room temperature and then triethylamine (1.46 mL, 10.5 mmol) was added slowly and the resulting solution was stirred at room temperature for 2 hours. Then the precipitated tetrabutylammonium bromide was filtered and washed several times with CCl_4. The combined filtrate and washings were washed succesively with 5% HCl (25 mL) and with water (25 mL) and then dried. The solvent was removed to give an oil that was purified by column chromatography (3:1 hexane-ether as eluent) to afford bromo-furanone **7** (860 mg, 71%) as a colorless oil, o.t. 65 °C (0.08 Torr). IR (film) 1771 (s), 1609 (m) cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) 1.47 (d, $J_{6,5}$ = 6.8 Hz, 3H, CH_3), 5.07 (dq, $J_{5,6}$ = 6.8 Hz, $J_{5,4}$ = 1.6 Hz, H_5), 7.49 (d, $J_{4,5}$ = 1.6 Hz, H_4); 62.5-MHz ^{13}C NMR ($CDCl_3$) 18.7 (C_6), 79.0 (C_5), 113.2 (C_3), 153.5 (C_4), 168.2 (C_2); MS, m/e (%) 178 and 176 (M^+, 12), 163 and 161 (9), 43 (100). Anal. Calcd. for $C_5H_5BrO_2$: C, 33.93; H, 2.85; Br, 45.15. Found: C, 33.83; H, 2.81; Br, 45.30.

Reaction of furanone 7 with NBS / AIBN: **3,5-dibromo-5-methyl-2(5*H*)-furanone, 9, and 3,5-dibromo-5-bromomethyl-2(5*H*)-furanone, 10.** Experiment shown in Table 1, entry 5, is described. A mixture consisting of furanone **7** (1.53 g, 8.6 mmol), NBS (3.1 g, 17.3 mmol), AIBN (43 mg) and 20 mL of CCl_4 was heated to reflux. Additional 50-mg portions of AIBN were added after 8, 24 and 32 hr, and NBS (1.1 g) was further added after 32 hr and then reflux was continued for a total of 72 hr.[11] The mixture was cooled to room temperature, and the succinimide was filtered and washed with CCl_4. The solvent was evaporated to give an orange solid that was chromatographed (3:1 hexane-dichloromethane) to furnish 1.8 g (63%) of tribromide **10** as a white solid. Crystals (from ether-pentane), m.p. 84-85 °C; IR (KBr) 1785 (s), 1602 (m) cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) 4.00 (d, $J_{6,6'}$ = 11.6 Hz, H_6), 4.22 (d, $J_{6',6}$ = 11.6 Hz, $H_{6'}$), 7.52 (s, H_4); 62.5-MHz ^{13}C NMR ($CDCl_3$) 35.1 (C_6), 88.0 (C_5), 114.8 (C_3), 151.7 (C_4), 163.9 (C_2); MS, m/e (%) 335 (M^+, 2), 257 (46), 255 (100), 253 (50), 123 (15), 121 (15), 53 (43), 42 (33). Anal. Calcd. for $C_5H_3Br_3O_2$: C, 17.93; H, 0.90; Br, 71.56. Found: C, 18.05; H, 0.86; Br, 71.66.

Working in the conditions listed in Table 1, entries 1-4, dibromide **9** was formed and isolated as an oil. Its instability precluded a correct microanalysis. Spectral data follow. IR (film) 1792 (s), 1602 (m) cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) 2.17 (s, 3H, CH_3), 7.65 (s, H_4); 62.5-MHz ^{13}C NMR ($CDCl_3$) 31.0 (C_6), 89.4 (C_5), 112.8 (C_3), 154.9 (C_4), 164.5 (C_2); MS, m/e (%) 177 and 175 (M^+- 79, 33), 134 and 132 (3), 106 and 104 (4), 43 (100).

Synthesis of 3-bromo-5-methylene-2(5*H*)-furanone, 4.

1. Through dehydrobromination of 9.

Method a: Use of triethylamine as a base. Triethylamine 86 μL (0.6 mmol) was added dropwise to a stirred solution of dibromide 9 (158 mg, 0.6 mmol) in 4 mL of CCl_4. After stirring at room temperature for 10 hr the mixture was diluted with dichloromethane (25 mL) and washed twice with 10 mL-portions of 5% HCl and with water (10 mL), and then dried. The solvent was removed and the residue was chromatographed (7:2 hexane-dichloromethane) affording 15.3 mg of unreacted **9** (10% recovery) and 21.6 mg of monobromide **8** (20% yield).

Method b: Use of LiBr / DMF. A mixture consisiting of dibromide **9** (127 mg, 0.5 mmol), LiBr (87 mg, 1 mmol) and DMF (8 mL) was heated at 100 °C for 1 hr, then cooled a room temperature and diluted with water (15 mL). This mixture was extracted with ether (4x25 mL) and the combined organic extracts were washed with water and dried. The solvent was removed and the residue was chromatographed (2:1 hexane-dichloromethane) to afford furanone **4** (35.1 mg, 40% yield).

2. Through debromination of 10.

A mixture consisting of tribromide **10** (1.2 g, 3.6 mmol), Cp_2TiCl_2 (173 mg, 0.7 mmol), zinc (733 mg, 11.2 mol) and THF (20 mL) was stirred under nitrogen atmosphere at room temperature for 30 min. The colour of the mixture turned from orange to green during this time.[8] Then the mixture was diluted with dichloromethane (20 mL) and filtered through celite. The solvent was evaporated and the residue was chromatographed (3:1 hexane-ether) to afford methylene-furanone **4** as a white solid (441 mg, 71% yield). Description of physical constants and spectral data for **4** follows.

Crystals (from ether-pentane), m.p. 47-49 °C; IR (KBr) 1757 (s), 1645 (w) cm^{-1}; 250-MHz ^{1}H NMR (CDCl$_3$) 4.96 (d, $J_{6,6'}$ = 2.7 Hz, H$_6$), 5.26 (d, $J_{6',6}$ = 2.7 Hz, H$_{6'}$), 7.48 (s, H$_4$); 62.5-MHz ^{13}C NMR (CDCl$_3$) 98.7 (C$_6$), 115.1 (C$_3$), 141.0 (C$_5$), 153.1 (C$_4$), 165.1 (C$_2$); MS, m/e (%) 176 and 174 (M$^+$, 100), 148 and 146 (20), 134 and 132 (27), 120 and 118 (12), 106 and 104 (19), 67 (47), 53 (70), 51 (14), 50 (20), 42 (62). Anal. Calcd. for $C_5H_3BrO_2$: C, 34.32; H, 1.73; Br, 45.66. Found: C, 34.12; H, 1.63; Br, 45.56.

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11. The reaction was shown to be very slow as monitored by TLC. The above conditions were necessary to force the reaction to completion.

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