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Synthesis of novel caged bis-hemiacetals and their facile conversion to symmetric bis-α-halo-γ-lactones†

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Abstract

A highly efficient method for the construction of novel bis-α-halo-γ-lactones (**4a**,**b**) via oxidative cleavage of caged bis-hemiacetals (**9a**,**b**) has been developed. Furthermore, a new base-catalyzed cleavage of diketo diacetate (**8b**) leading to the formation of α-monobromo-bis-γ-lactone (**10**) and the synthesis of bis-γ-lactone (**11**) are described.

Keywords: Bis-hemiacetals, γ-lactones, α-diketones, tetrahalonorbornenes.

1. Introduction

Tetrachloronorbornene derivatives (**1a**) serve as important building blocks by rendering themselves as a powerful, inextricable template in the synthesis of complex natural and unnatural products.[1] The flexibility of incorporating the desired substituents R^1 and R^2 directly via the atom economic[2] *endo*-selective Diels–Alder reaction between commercially available 1,2,3,4-tetrachloro-5,5-dimethoxycyclopenta-1,3-diene and a suitable dienophile possessing R^1 and R^2 groups makes these derivatives attractive starting materials in organic synthesis. The range of substituents R^1 and R^2 that are available can be further enhanced by a routine functional group manipulation exercise on a suitable and easily accessible Diels–Alder adduct, particularly in cases where a dienophile with the required substituents is either unavailable, unreactive or less selective. Since 1,2,3,4-tetrachloro-5,5-dimethoxycyclopenta-1,3-diene has been used as cyclopentadienone equivalent as the latter is unstable due to self-dimerization, the four chlorine atoms are therefore wasteful groups that are invariably knocked off subsequently in a reductive manner. Further, unlike tetrachloronorbornenes (**1a**), the tetrabromo analogs (**1b**), which could also be obtained easily via a Diels–Alder reaction,[3] did not receive any attention as useful building blocks. This, in our opinion, is due to lack of methods for selective utilization of the two sets (vinylic and bridgehead) of halogens. Any strategy that involves the complete reduction of halogens is quite uneconomical for the tetrabromo analogs (**1b**) due to molecular weight loss that accompanies the process. We have recently reported, for the first time, the selective exploitation of bridgehead halogens for C–C bond formation[4] and subsequently disclosed in a preliminary account[5] the utility of vinylic halogens to obtain synthetically useful α-diketones (**2a**,**b**) with the retention of bridgehead halogens employing both tetrachloro and tetrabromo analogs (**1a**,**b**) in high yield (Scheme 1).[5]

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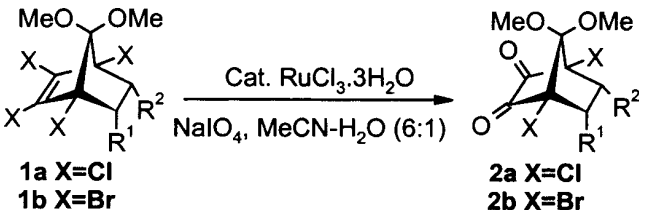
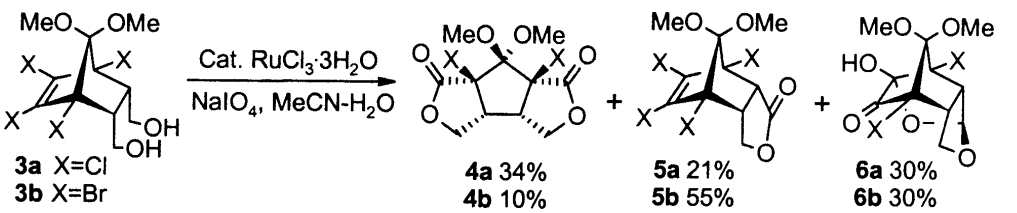


Scheme 1.

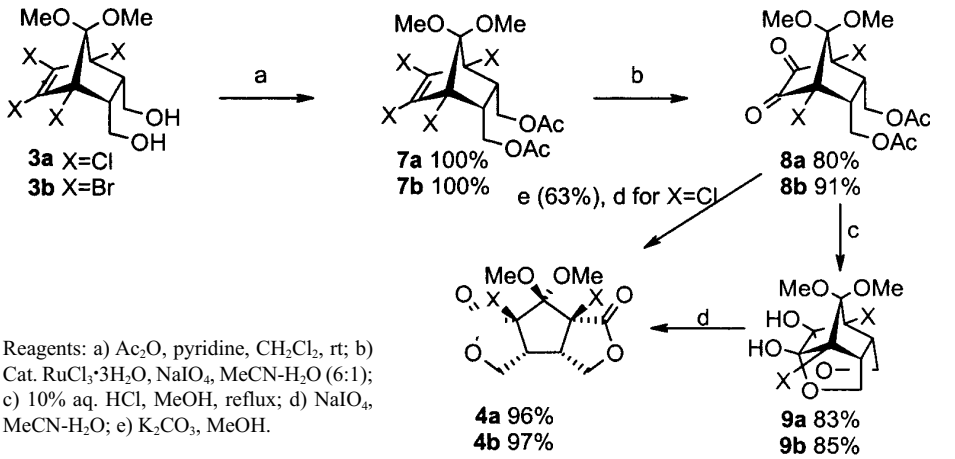
The bis-γ-lactone moiety is the key structural feature in a variety of biologically active natural products.[6] Depending upon the regio- and stereochemical requirements and whether the γ-lactone moieties are directly fused[7] or separated by a ring,[8] a few synthetic methods are available in the literature. Recently we observed[5] that when **3** (**a** or **b**) is subjected to $NaIO_4$/cat. $RuCl_3{\cdot}3H_2O$, conditions develop for the conversion of vicinal dihalo alkenes to α-diketones, forming a mixture of three products (**4**, **5** and **6**) (Scheme 2). The formation of **4**, although in low yield, could be rationalized based on the assumption that the initially formed α-diketone would give rise to the caged bis-hemiacetal, which in turn undergoes cleavage under the reaction conditions. On the other hand, **5** and **6** originate from the partial oxidation of one of the primary hydroxyl groups to the aldehyde which then forms lactol to undergo further oxidation to **5** or intramolecular hemiacetal formation in a molecule wherein α-diketone moiety is already released to give **6**. These observations provided us the stimulus to develop highly efficient methods to symmetric bis-α-halo-γ-lactones (**4a**,**b**) and herein report our results.



Scheme 2.

2. Results and discussion

Since the free hydroxyl groups in **3a**,**b** are responsible for the formation of **5** and **6** (Scheme 2), they were first converted into the corresponding diacetates (**7a**,**b**) in quantitative yields[9] in order to achieve the synthesis of **4a**,**b**. Treatment of **7a**,**b** with 10 mol% of $RuCl_3{\cdot}3H_2O$ and 1.75 equivalent of $NaIO_4$ in acetonitrile–water (6:1) furnished the corresponding diketones **8a**,**b** in high yield. The deprotection of the acetate groups in **8a**,**b** was first attempted employing the usual basic conditions with K_2CO_3 in MeOH. The dichloro derivative (**8a**) furnished the caged bis-hemiacetal (**9a**) in moderate yield (63%). Contrary to our expectations, the dibromo analog (**8b**) under identical conditions gave a new product **10**, which is depicted in Scheme 4. Changing the deprotection conditions to aqueous HCl in MeOH at reflux temperature furnished the desired caged bis-hemiacetal (**9a**,**b**) in good yields. The ^{13}C NMR spectrum of compound **9a**,**b** showed only 7 lines and the characteristic hemiacetal carbon peak at δ 106.6 and 106.7, respectively. The glycol cleavage of caged hemiacetals (**9a**,**b**) employing $NaIO_4$ in acetonitrile–water at room temperature generated the title lactones (**4a**,**b**) in nearly quantitative yield (Scheme 3). It was gratify-

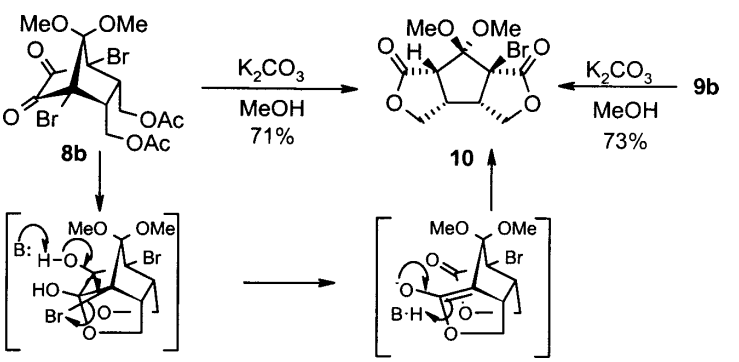


Reagents: a) Ac_2O, pyridine, CH_2Cl_2, rt; b) Cat. $RuCl_3{\cdot}3H_2O$, $NaIO_4$, MeCN-H_2O (6:1); c) 10% aq. HCl, MeOH, reflux; d) $NaIO_4$, MeCN-H_2O; e) K_2CO_3, MeOH.

Scheme 3.

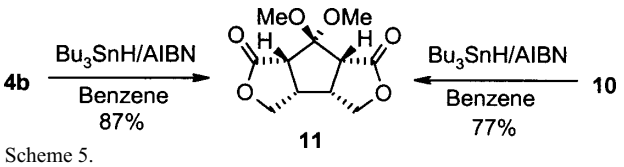
ing to note that the compounds **4a**,**b** were obtained from diols **3a**,**b** (4 steps) in 64% and 71% overall yield, respectively. The bis-α-halo-γ-lactones (**4a**,**b**) showed a 7-line ^{13}C NMR spectrum with the lactone carbonyls at δ 170.1 and 170.6, respectively.

The base-catalyzed deprotection of dibromo diketo diacetate (**8b**) afforded directly α-monobromo-bis-γ-lactone (**10**) in 71% of yield (Scheme 4). The unsymmetrical nature was evident from both ^1H and ^{13}C NMR spectral data. Since Br is a better leaving group than Cl, the base-catalyzed reaction proceeds as shown in Scheme 4 for the diacetate **8b**. This is further unambiguously confirmed by converting the preformed **9b** to **10** under similar conditions. The compound **10** in its ^{13}C NMR spectrum showed 11 lines having the lactone carbonyls at δ 172.6 and 170.6.



Scheme 4.

Further structural proof for the new compound **10** obtained via the base-catalyzed cleavage of **8b** was established by chemical conversion method. The symmetric bis-α-bromo-γ-lactone (**4b**) was treated with Bu_3SnH and AIBN in refluxing benzene to afford *cis, syn, cis*- bis-γ-lactone (**11**) in excellent yield (Scheme 5), which showed a 6-line ^{13}C NMR spectrum, with the lactone carbonyl at δ 172.7. The α-monobromo-bis-γ-lactone (**10**) upon treating with 1.5 equivalent of Bu_3SnH and AIBN in refluxing benzene also furnished a compound whose melting point and spectral data was superimposable with symmetrical bis-γ-lactone (**11**) (Scheme 5).



Scheme 5.

3. Conclusion

We have demonstrated a facile synthesis of new types of caged bis-hemiacetals and their conversion to bis-α-halo-γ-lactones fused with a central cyclopentane dimethyl acetal in *cis, syn, cis* manner, which are difficult to access via the existing routes. The 4-step process was accomplished in 64% overall yield in the case of **4a** and 71% in the case of **4b**. A direct and convenient access to the α-monobromo-bis-γ-lactone was achieved via the base-catalyzed deprotection of the dibromo diketo diacetate in good yield. Also, an expedient synthesis of the *cis, syn, cis*-bis-γ-lactone (**11**) in excellent yield was established.

4. Experimental

Melting points are uncorrected and were recorded on JSGW melting point apparatus. IR spectra were recorded on Perkin–Elmer 1320 and Shimadzu 420 spectrophotometers as KBr pellets (solids), or thin films (liquids). ^{1}H NMR spectra were recorded at 400 MHz on Jeol spectrophotometer. Data are reported in standard manner. Proton-decoupled ^{13}C NMR spectra were recorded at 100 MHz. DEPT were recorded at 135° angle. Samples for NMR were made in $CDCl_3$ and insoluble compounds were made to dissolve by adding additional 3–4 drops of DMSO-d_6 into the $CDCl_3$ solution. Tetramethylsilane was used as the internal standard. Column chromatography was performed using Acme's silica gel (100–200 mesh), and 15–25% ethyl acetate in hexane was used as eluant. Acetonitrile was distilled over P_2O_5. Distilled water was used for the reactions. $RuCl_3 \cdot 3H_2O$ was purchased from Arora Mathey and $NaIO_4$ from Spectrochem.

4. 1. *Preparation of diacetates (**7a,b**)*

To a solution of tetrahalo diol (**3a**,**b**) (1 mmol) in dichloromethane (4 ml), acetic anhydride (0.8 ml) and pyridine (1.6 ml) were added. The mixture was stirred at room temperature for 6 h and then diluted with 10% HCl. The separated aqueous layer was extracted with dichloromethane (3×5 ml) and combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel using 10% ethyl acetate–hexane to furnish quantitative yield of diacetate.

Tetrachloro diacetate (**7a**): m.p. 61–63°C (lit.[9] 72–74°C).

3-Acetoxymethyl-1,4,5,6-tetrabromo-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-ylmethyl acetate (**7b**). Yield: quantitative, colorless solid, m.p. 81–83°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.34 (dd, 2H, J=11.9 and 3.9 Hz), 4.16–4.11 (m, 2H), 3.65, 3.61 (2s, 6H, OMe), 3.11 (m_c, 2H), 2.04 (s, 6H, OCOMe); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9 (C=O), 124.4 (C=C), 111.5, 70.9 ($C_{1,4}$), 60.0, 53.0 (OMe), 51.5 (OMe), 48.9 ($C_{2,3}$), 20.5 (OCOMe); IR (KBr) 2850, 1720, 1560, 1180 cm^{-1}.

4. 2. *Preparation of diketo diacetates (**8a,b**)*

To a vigorously stirred solution of the tetrahalo diacetate (**7a**,**b**) (1 mmol) in acetonitrile (12 ml) at 0–5°C (ice-water bath) was added a solution of $RuCl_3 \cdot 3H_2O$ (0.1 mmol) and $NaIO_4$ (1.75 mmol)

in water (2 ml). The mixture was stirred for 6–8 h and continuously monitored by TLC. The resulting suspension was filtered through a thin pad of silica gel, which was then washed with ethyl acetate (15 ml). Concentration of the filtrate followed by a short silica gel column chromatography gave the product.

3-Acetoxymethyl-1,4-dichloro-7,7-dimethoxy-5,6-dioxobicyclo[2.2.1]hept-2-ylmethyl acetate (**8a**). Yield: 80%, yellow solid, m.p. 58–60° C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.30–4.24 (m, 4H), 3.75, 3.57 (2s, 6H, OMe), 3.21 (brs, 2H), 1.98 (s, 6H, OAc); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.1 (C=O), 169.6, 101.2 (C_7), 77.6 ($C_{1,4}$), 59.0, 52.8 (OMe), 52.1 (OMe), 43.9 ($C_{2,3}$), 20.2 (OCOMe); IR (KBr) 2900, 1720, 1190 cm^{-1}.

3-Acetoxymethyl-1,4-dibromo-7,7-dimethoxy-5,6-dioxobicyclo[2.2.1]hept-2-ylmethyl acetate (**8b**). Yield: 91%, yellow solid, m.p. 86–88°C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.34–4.24 (m, 4H), 3.79, 3.61 (2s, 6H, OMe), 3.21–3.20 (m, 2H), 1.97 (s, 6H, OAc); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.4 (C=O), 169.6, 101.3 (C_7), 70.7 ($C_{1,4}$), 59.6, 53.0 (OMe), 52.3 (OMe), 45.2 ($C_{2,3}$), 20.3 (OCOMe); IR (KBr) 2950, 1730, 1210 cm^{-1}.

4. 3. *Preparation of caged bis-hemiacetals (**9a,b**)*

To a stirred solution of substrate **8a**,**b** (1 mmol) in methanol (4 ml) was added 10% aqueous hydrochloric acid (2 ml) and the mixture was refluxed for 5 h. The reaction mixture was then allowed to cool, diluted with water and neutralized with aqueous $NaHCO_3$ solution. The reaction mixture was extracted with ethyl acetate (4 × 5 ml). The combined ethyl acetate layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel using 40% ethyl acetate–hexane to furnish the bis-hemiacetals (**9a**,**b**).

Dichloro bis-hemiacetal (**9a**). Yield: 83%, colorless crystals (dichloromethane/hexane), m. p. 150–152°C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.26 (td, 2H, *J*=9.5, 1.7 Hz), 4.13 (d, 2H, *J*=9.5 Hz), 3.66, 3.65 (2s, 6H, OMe), 2.87 (t, 2H, *J*=1.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 106.6, 99.6, 74.7, 65.3, 52.3 (OMe), 51.4 (OMe), 46.7; IR (KBr) 3050, 2900, 1200 cm^{-1}; Anal. calc. for $C_{11}H_{14}Cl_2O_6$: C, 42.19; H, 4.51. Found: C, 42.37; H, 4.70.

Dibromo bis-hemiacetal (**9b**). Yield: 85%, colorless crystals (dichloromethane/hexane), m. p. 122°C (dec), ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31 (td, 2H, *J*=9.5 and 1.9 Hz), 4.13 (d, 2H, *J*=9.5 Hz), 4.05 (s, OH, exchangeable with D_2O), 3.70, 3.69 (2s, 6H, OMe), 2.90 (t, 2H, *J*=1.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 106.7, 99.8, 68.8, 65.2, 52.5 (OMe), 51.5 (OMe), 47.8; IR (KBr) 3150, 2950, 1190 cm^{-1}; Anal. calc. for $C_{11}H_{14}Br_2O_6$: C, 32.86; H, 3.51. Found: C, 32.50; H, 3.62.

4.4. *Preparation of bis-α-halo-γ-lactones (**4a,b**)*

To a vigorously stirred solution of the substrates (**9a**,**b**) (1 mmol) in acetonitrile (6 ml) at room temperature was added a solution of $NaIO_4$ (3 mmol) in water (6 ml). The mixture was stirred for 3 h (15 h in the case of dibromo derivative). After the completion of the reaction, the mixture was diluted with water and extracted with ethyl acetate (3 × 10 ml). The combined ethyl acetate layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel using 20% ethyl acetate–hexane to furnish the product **4a**,**b**.

6a,7a-Dichloro-7,7-dimethoxyhexahydrocyclopenta[1,2-c:3,4-c']difuran-1,6-dione (**4a**). Yield: 96%, colorless crystals (dichloromethane/hexane), m.p. 184–185°C. ^{1}H NMR (400 MHz, $CDCl_3$)

δ 4.53–4.45 (m, 2H), 4.33–4.29 (m, 2H), 3.77 (s, 3H, OMe), 3.75–3.71 (m, 2H), 3.51 (s, 3H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1 (O–C=O), 110.4, 75.2, 65.8 (CH_2), 54.6 (CH_3), 52.6 (CH_3), 49.6 (CH); IR (KBr), 3000, 1780, 1220, 1020 cm^{-1}; Anal. calc. for $C_{11}H_{12}Cl_2O_6$: C, 42.47; H, 3.89. Found: C, 42.66; H, 3.99.

6a,7a-Dibromo-7,7-dimethoxyhexahydrocyclopenta[1,2-c:3,4-c']difuran-1,6-dione (**4b**). Yield: 97%, colorless crystals (dichloromethane/hexane), m.p. 140°C (dec). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50–4.46 (m, 2H), 4.31-4.28 (m, 2H), 3.80–3.78 (m, 2H), 3.78 (s, 3H, OMe), 3.55 (s, 3H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6 (O–C=O), 109.9, 66.1, 64.9, 54.9, 53.8, 51.1; IR (KBr) 2900, 1760, 1150, 1010 cm^{-1}; Anal. calc. for $C_{11}H_{12}Br_2O_6$: C, 33.03; H, 3.02. Found: C, 33.19; H, 2.90.

4.5. *Base-catalyzed deprotection of dichlorodiketodiacetate (**8a**)*

To a solution of dichlorodiketodiacetate **8a** (1 mmol) in 8 ml of MeOH, K_2CO_3 (1.5 mmol) was added and stirred at room temperature for 5 h. The reaction mixture was diluted with water and extracted thrice with ethyl acetate. The combined organic layer was washed once with brine, dried over Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel using 40% ethyl acetate–hexane to give 63% of the crystalline diol (**9a**).

4.6. *Preparation of α-monobromo-bis-γ-lactone (**10**) (6a-Bromo-7,7-dimethoxyhexahydrocyclopenta[1,2-c:3,4-c']difuran-1,6-dione) by base catalyzed deprotection of dibromodiketodiacetate (**8b**)*

Treatment of dibromodiketodiacetate (**8b**) with 1.5 equivalent of K_2CO_3 in methanol for 1 h, as described above gave selectively the monobromobislactone (**10**) as colorless crystals (dichloromethane/hexane), m.p. 156–157°C, in 71% of yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.52–4.48 (m, 1H), 4.45–4.40 (m, 2H), 4.30 (dd, 1H, J=9.5 and 5.9 Hz), 3.68–3.65 (m, 1H), 3.62–3.55 (m, 2H), 3.59 (s, 3H, OMe), 3.53 (s, 3H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6 (O-C=O), 170.6 (O–C=O), 110.2, 67.5, 67.1, 67.0, 53.4, 52.7, 52.2, 51.9, 36.7; IR (KBr) 2900, 1750, 1150, 1010 cm^{-1}; Anal. calc. for $C_{11}H_{13}BrO_6$: C, 41.14; H, 4.08. Found: C, 41.37; H, 3.93.

4. 7. *Base-catalyzed cleavage of dibromodiol (**9b**)*

Treatment of dibromodiol **9b** (1 mmol) with K_2CO_3 (1.5 mmol) in methanol for 2.5 h, as described above, also furnished the monobromobislactone (**10**) in 73% of yield.

4. 8. *Symmetrical bis-γ-lactone **11** (7,7-Dimethoxyhexahydrocyclopenta[1,2-c:3,4-c']difuran-1,6-dione) from reduction of dibromobislactone (**4b**)*

A solution of dibromolactone (**4b**) (70 mg, 0.175 mmol), Bu_3SnH (128 mg, 0.44 mmol) and azobisisobutyronitrile (3 mg, 0.018 mmol) in benzene (2 ml) was refluxed under argon for 11 h. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel (eluted first with hexane then with 50% ethyl acetate-hexane) to give 37 mg (87%) of the reduced bislactone **11** as colorless crystals (CH_2Cl_2–hexane), m.p. 143–145°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.36–4.30 (m, 4H), 3.55 (s, 3H, OMe), 3.42 (s, 3H, OMe), 3.32 (brs, 4H); ^{13}C NMR (100 MHz, $CDCl_3$:DMSO-d_6=15:1) δ 172.7 (O–C=O), 109.4, 66.9, 52.1, 50.8 (C_2), 49.4; IR (KBr) 2850, 1740, 1100, 1030 cm^{-1}; Anal. calc. for $C_{11}H_{14}O_6$: C, 54.54; H, 5.83. Found: C, 54.29; H, 5.79.

4. 9. *Reduction of monobromobislactone (**10**)*

Reduction of monobromolactone in the manner described above with 1.5 mmol of Bu_3SnH and catalytic amount of AIBN in refluxing benzene gave 77% of the reduced product **11**.

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