Dimethyl Sulfoxide–Trimethylsilyl Bromide–Amine System as a Bromonium Ion Source Containing a Potential Internal Nucleophile; Unusual Bromolactonisation of Cyclohex-3-enecarboxylic Acid Derivatives[1]

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Bromo lactones have been successfully obtained from unsaturated carboxylic acids by employing a dimethyl sulfoxide–trimethylsilyl bromide–amine system. The characteristic feature of this system is that unusual *cis*-addition and cyclisation of the sterically unfavourable carboxy group take place in the reaction of 6-unsubstituted and *trans*-6-phenylcyclohex-3-enecarboxylic acids **4** and **21b**, which can be clearly explained by taking account of formation of the sulfonium intermediate **3** from the bromonium intermediate **2** and dimethyl sulfide generated *in situ*.

Bromolactonisation is widely used as one of the methods for regio- and stereo-selective functionalisation of double bonds.[2] Available procedures include the reaction of an unsaturated carboxylic acid or metal carboxylate [sodium[3a,b] or thallium(I)[3c,d]] with an electrophilic bromonium ion source such as bromine,[3a–f] sodium hypobromite,[3g] *N*-bromo imides, *N*-bromo amides,[3b,e,h–l] *N*-bromohydantoins[3m–o] or acyl hypobromites[3p,q] and predominantly afford a *trans*-adduct. These bromonium ion sources contain a Br–Br, O–Br, or N–Br bond in their structures, but no examples of the bromonium ion source having an S–Br bond for bromolactonisation have been reported. Combination of dimethyl sulfoxide (DMSO) and trimethylsilyl halide (TMSX, X = Br or Cl) was first reported by Pagnoni and co-workers as an α-halogenating agent containing an S–X bond for ketones and aldehydes.[4] Recently, a silyl chloride–sulfoxide system was utilized as an oxidant for selective formation of the disulfide bond from cysteine residues in peptide synthesis.[5]

We expected that when this reagent **1** prepared from sulfoxide and TMSBr was utilised for electrophilic addition to the double bond, highly nucleophilic dimethyl sulfide generated by the bromonium ion leaving should interact with the cationic intermediate **2** and, as a result, stabilise the intermediate by formation of the sulfonium ion **3** (see Experimental section). By stabilisation of the reaction intermediate, it was expected that there would be different selectivity or reactivity from that of previously reported methods. Here, we describe a characteristic feature of the bromolactonisation employing a DMSO–TMSBr–amine system.

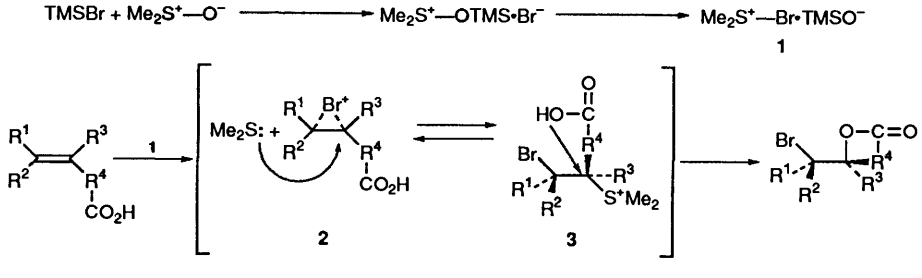
In the presence of the amine, bromolactonisation of the unsaturated carboxylic acids **4–9** took place smoothly to afford the bromo lactones **10–15** (Table 1), the structures of which were assigned from their spectral data (see Experimental section). The stereochemistry of the bromo lactones **10–12** was further confirmed by the fact that treatment of these compounds with methoxide afforded the bromohydrin **16** and the epoxy esters **17** and **18**, respectively. The two bromo lactones **10** and **15** are anomalous products, since both have a 5-or 6-membered lactone ring which is a *cis*-adduct.

Table 1 Bromolactonisation of the unsaturated carboxylic acids **4–9**

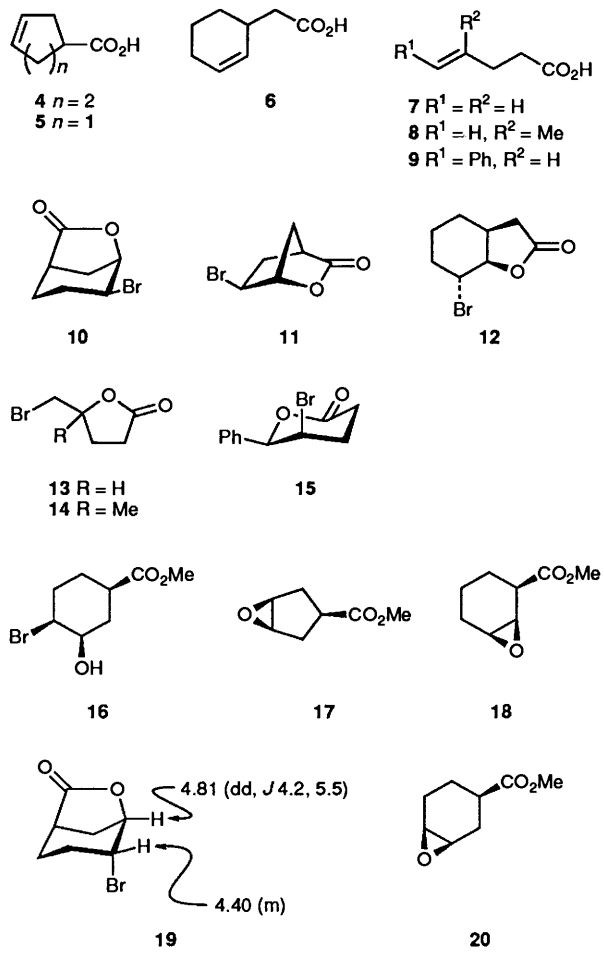
Unsaturated carboxylic acid	Amine	Reaction time (*t*/*h*)	Product	Yield (%)
4	Et_3N	12	**10**	54
4	Pr^i_2EtN	12	**10**	55
5	Et_3N	12	**11**	29
5	Pr^i_2EtN	12	**11**	40
6	Et_3N	12	**12**	41
6	Pr^i_2EtN	12	**12**	45
7	Et_3N	12	**13**	29
7	Pr^i_2EtN	12	**13**	23
8	Et_3N	12	**14**	52
8	Pr^i_2EtN	12	**14**	60
9	Et_3N	5	**15**	41
9	Pr^i_2EtN	5	**15**	40

Encouraged by these results, we compared our method with those previously reported, and two reported methods [method A: bromine–aq. sodium hydrogen carbonate;[3a] method B: lead tetraacetate–zinc bromide in 1,2-dimethoxyethane (DME)[3q]] were applied to the unsaturated carboxylic acids **4** and **9**. The same bromo lactone **15** was obtained as the sole product from compound **9** in 38% yield by method B. This may be because both reactions (our method and method B) proceed *via* formation of a stable cationic intermediate at the benzyl position. On the other hand, reactions of compound **4** by methods A and B stereoselectively afforded the *trans*-bromo lactone **19** in 26 and 70% yield, respectively. The stereochemistry of compound **19** was apparent from its ^1H NMR spectrum[6] and the result of methoxide treatment which afforded the epoxy ester **20**.

The obvious differences in stereoselectivity between our



Scheme 1



method and those previously reported were observed in the reaction of compound **4**. Therefore, effects of the stereochemistry of the carboxy group were also examined, as follows. As is obvious from a molecular model, *cis*-6-phenylcyclohex-3-enecarboxylic acid **21a** has an axially oriented carboxy group which is expected to participate easily in the halogenolactonisation reaction. Bromolactonisation of compound **21a** by method B stereoselectively afforded the 5-membered lactone **22*** in 90% yield as expected, while, under our conditions, two lactones **22** and **23**† were obtained in 16 and 19% yield accompanied by the methylthiomethyl ester **24** in 10% yield (Scheme 2). On the other hand, the *trans*-6-phenyl derivative **21b**, has an equatorially fixed carboxy group which is, of course, a situation unfavourable for lactonisation. Therefore, to our knowledge, there has been no report on intramolecular lactonisation using *trans*-6-substituted cyclohex-3-enecarboxylic acids. Reactions of the *trans*-6-phenyl derivative **21b** by methods A and B afforded only the dibromo carboxylic acid **25** and the lactone could not be obtained as expected. Surprisingly, under our conditions, the 5-membered lactone **26*** was stereoselectively obtained in good yield. Furthermore, it should be noted that the reaction of the *trans*-6-phenyl derivative **21b** proceeded in better yield than that of the 6-unsubstituted derivative **4** did.

Results and Discussion

Generally, halogenolactonisation is recognised to proceed *via* formation of the halogenium ion intermediate by addition of the electrophilic X^+ species to the unsaturated carboxylic acid and subsequent reaction with the intramolecular carboxy group as an S_N2 reaction and to give a halogenolactone which is a *trans*-adduct as a result. Therefore, the fact that *cis*-adducts were obtained in the reactions of *trans*-6-phenyl and 6-unsubstituted cyclohex-3-enecarboxylic acids, **21b** and **4**, under our conditions indicates that, in these cases, dimethyl sulfide generated *in situ* certainly interacts with the bromonium intermediate to form the sulfonium intermediate as expected. In other cases, nucleophilic attack of the neighbouring carboxy group seems to occur more rapidly than that of the dimethyl sulfide, and gives a *trans*-adduct.

Another characteristic of this system is that, in the reaction of *trans*-acid **21b**, the equatorially fixed carboxy group, which is unfavourable for lactonisation, cyclised to give the 5-membered lactone *via* a conformational change of the cyclohexane ring. A plausible mechanism for this reaction is shown in Scheme 3. When Br^+ is transferred from the same side as the carboxy group (Path A), the bromonium intermediate **27a** and dimethyl sulfide are formed. Subsequent nucleophilic attack of dimethyl sulfide at C-3 is more favourable than at C-4 because of the stereoelectronic circumstances, and provides the sulfonium intermediate **28a**. Two axial groups (Br and Me_2S^+) make the conformational change of the cyclohexane ring of **28a** to that of the diequatorial isomer **28b** easier and, following intramolecular displacement of the Me_2S^+ group by the neighbouring carboxy group, give the *cis*-adduct **26**. On the other hand, there are two possibilities of nucleophilic attack on the bromonium intermediate **27b** formed by Path B. Attack of dimethyl sulfide at C-4 gives the sulfonium intermediate **29**, but cannot give a bromo lactone due to the stereochemical relationship between the carboxy group and the Me_2S^+ group. In order to form the *trans*-bromo lactone **30** by direct participation of the carboxy group, the conformation of intermediate **27b** must be changed to that of **27c**. However, this is very difficult because two substituents (Ph and CO_2H) of intermediate **27b** should stand axially. As mentioned above, it is impossible to produce the *trans*-bromo lactone **30** and the stereoselective formation of the *cis*-bromo lactone **26** can be clearly explained by taking account of formation of the sulfonium intermediates **28**.

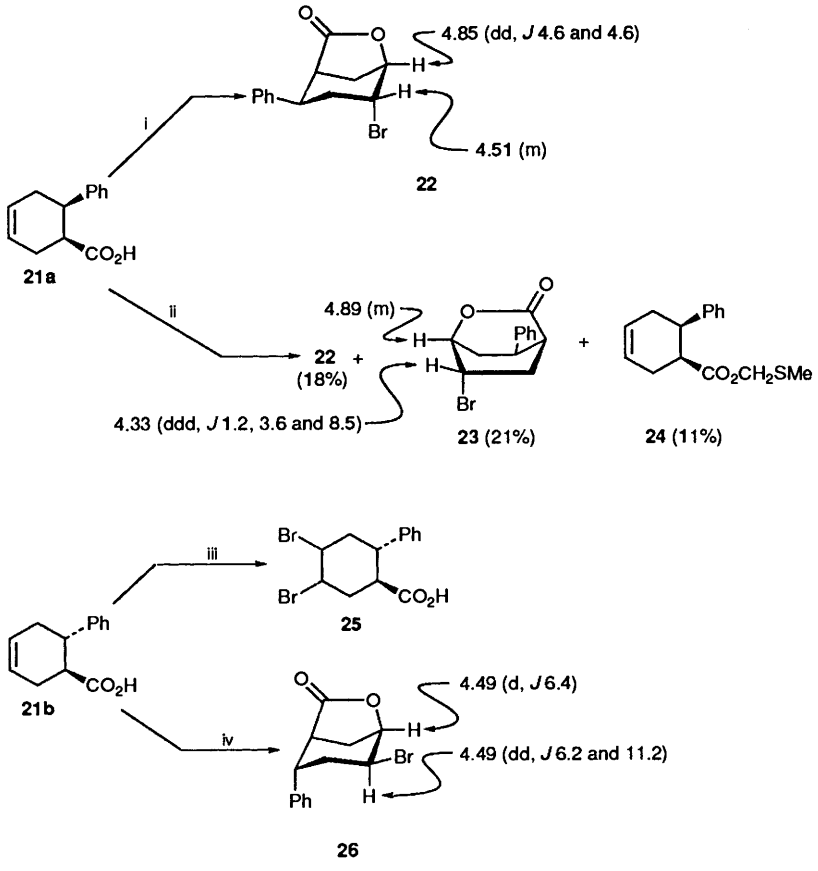
This is the first example of halogenolactonisation affording a *cis*-adduct and can be a potentially useful method for the synthesis and functionalisation of natural and unnatural products, especially those having a cyclohexane ring moiety.

Experimental

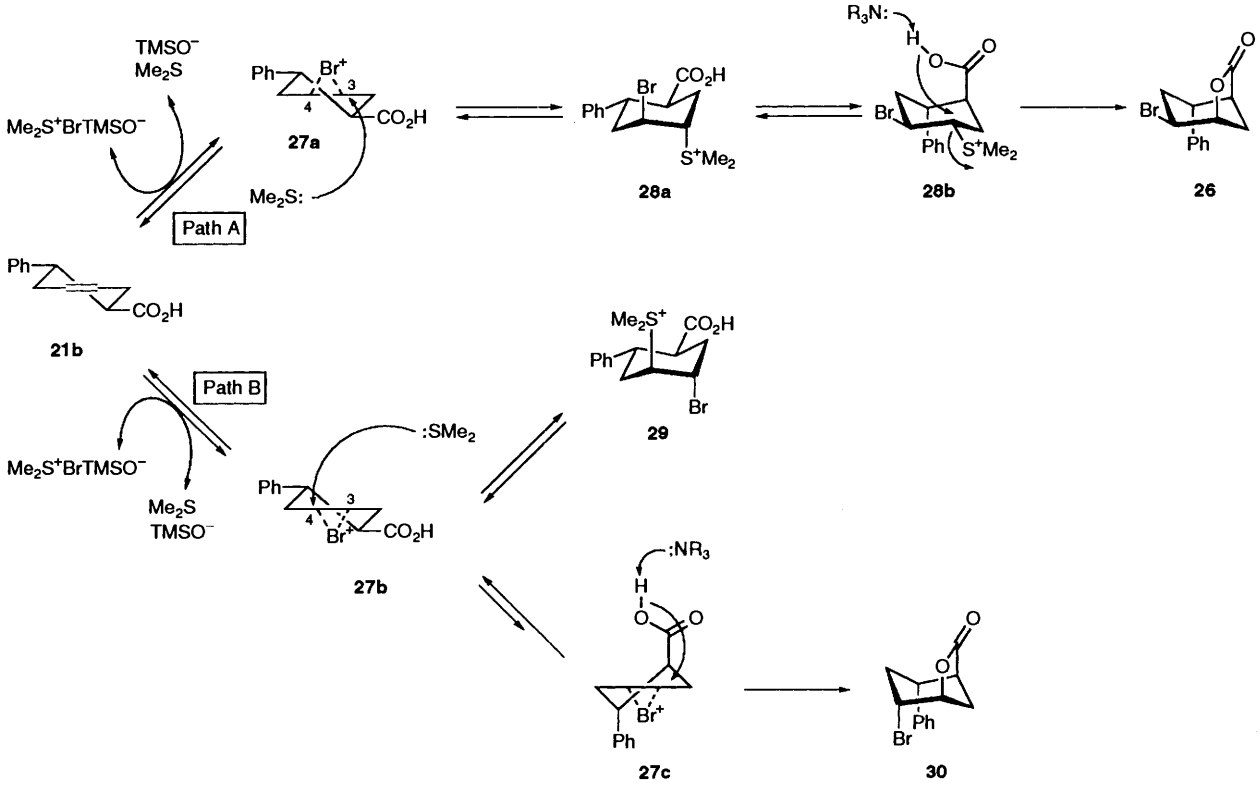
All m.p.s (measured on a Yanagimoto micro melting point apparatus) and b.p.s are uncorrected. IR spectra were recorded on a Hitachi 260-10 spectrometer, and ^1H NMR spectra on a Hitachi R-22 (90 MHz), a JEOL JNM-FX90Q (90 MHz) or a JEOL JNM-GX500 (500 MHz) spectrometer with tetramethylsilane as internal standard. *J*-Values are given in Hz. Low-resolution MS were obtained with a Shimadzu GCMS-QP1000 or a JEOL JMS-D300 instrument, and high-resolution MS with a JEOL JMS-D300 instrument. For column chromatography, Merck Kieselgel 60 (0.063–0.200 μm) was used. Cyclohex-3-enecarboxylic acid **4** and pent-4-enoic acid **7** were purchased

* The stereochemistries of the bromo lactones **22** and **26** were determined by comparison of their ^1H NMR data with those of the bromo lactones **10** and **19**.

† The structure of the bromo lactone **23** was assigned as shown in Scheme 2 from the following spectral data. The IR spectrum showed an absorption maximum at 1770 cm^{-1} attributable to the stretching band of the C=O bond of the 2-oxabicyclo[2.2.2]octan-3-one skeleton.[7] The *J*-values of the hydrogen (CHBr), obtained from the 500 MHz ^1H NMR spectrum, were 1.2, 3.6 and 8.5 Hz, indicating that the bromine occupies the axial position.



Scheme 2 *Reagents and conditions:* i, Method B (90%); ii, DMSO, TMSBr, Pr^i_2EtN, $CHCl_3$; iii, Method A (59%) or Method B (30%); iv, DMSO, TMSBr, Pr^i_2EtN, $CHCl_3$ (87%)



Scheme 3

from Tokyo Kasei Kogyo Co., Ltd. Cyclopent-3-enecarboxylic acid **5**,[8a] cyclohex-2-enylacetic acid **6**,[8b] 4-methylpent-4-enoic acid **8**,[8c] 5-phenylpent-4-enoic acid **9**,[8d] and *cis*- and *trans*-6-phenylcyclohex-3-enecarboxylic acids, **21a** and **21b**,[8e] were prepared according to the respective literature method.

Typical Procedure for Bromolactonisation.—TMSBr (0.21 cm^3, 1.6 mmol) was added dropwise to a stirred solution of DMSO (0.11 cm^3, 1.6 mmol) in dry $CHCl_3$ (1 cm^3) at 0 °C under argon and the mixture was stirred for 30 min at the same temperature. Then a solution of the unsaturated carboxylic acid (1.3 mmol) in dry $CHCl_3$ (1 cm^3) was added to the reaction mixture at 0 °C. After 10 min, diisopropylethylamine (0.27 cm^3, 1.6 mmol) or triethylamine (0.22 cm^3, 1.6 mmol) was added and the whole was stirred and refluxed for 12 h. The reaction mixture was cooled, diluted with diethyl ether, washed successively with water, 5% aq. HCl, water, and saturated aq. NaCl, dried (Na_2SO_4), and concentrated under reduced pressure to afford the bromo lactone in almost pure form. Further purification by recrystallisation or distillation gave the pure bromo lactone. Yields of the bromo lactones **10**–**15** are summarised in Table 1.

(1*RS*,4*SR*,5*RS*)-4-Bromo-6-oxabicyclo[3.2.1]octan-7-one **10**, needles, m.p. 101.5–102.0 °C (from hexane) (lit.,[9a] 101–102 °C) (Found: C, 40.8; H, 4.3; Br, 38.9. Calc. for $C_7H_9BrO_2$: C, 41.00; H, 4.42; Br, 38.97%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1780 (γ-lactone); $\delta(CDCl_3)$ 4.16 (1 H, dd, *J* 10.6 and 6.4, 4-H) and 4.92 (1 H, d, *J* 6.0, 5-H); *m/z* (EI) 204 and 206 (M^+, 6.6 and 6.5%) and 83 (100).

(1RS,4SR,6RS)-6-*Bromo*-2-*oxabicyclo*[2.2.1]*heptan*-3-*one* **11**, an oil, b.p. 160 °C/4 mmHg (bath temp.) (Found: C, 38.0; H, 3.7; Br, 41.8. $C_6H_7BrO_2$ requires C, 37.73; H, 3.69; Br, 41.83%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1800 (γ-lactone); $\delta(CDCl_3)$ 4.35 (1 H, m, 6-H) and 4.87 (1 H, m, 1-H); *m/z* (EI) 190 and 192 (M^+, 1.2 and 1.4%) and 67 (100).

(1*RS*,5*SR*,6*SR*)-5-Bromo-7-oxabicyclo[4.3.0]nonan-8-one **12**, needles, m.p. 37.5–40.0 °C (from hexane) (lit.,[9b] 58–59 °C) (Found: C, 43.7; H, 5.0; Br, 36.1. Calc. for $C_8H_{11}BrO_2$: C, 43.86; H, 5.06; Br, 36.47%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1780 (γ-lactone); $\delta(CDCl_3)$ 4.39–4.65 (2 H, m, 5- and 6-H); *m/z* (EI) 218 and 220 (M^+, 38 and 36%) and 95 (100).

5-(Bromomethyl)-4,5-dihydrofuran-2(3*H*)-one **13**, an oil, b.p. 120 °C/1 mmHg (bath temp.) (lit.,[9c] 135–140 °C/11mmHg) (Found: C, 33.6; H, 4.0; Br, 44.1. Calc. for $C_5H_7BrO_2$: C, 33.55; H, 3.94; Br, 44.64%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1780 (γ-lactone); $\delta(CDCl_3)$ 3.56 (2 H, m, CH_2Br) and 4.75 (1 H, m, 5-H); *m/z* (EI) 178 and 180 (M^+, 0.7 and 0.7%) and 85 (100).

5-(*Bromomethyl*)-5-*methyl*-4,5-*dihydrofuran*-2(3H)-*one* **14**, an oil, b.p. 140 °C/4 mmHg (bath temp.) (Found: C, 37.6; H, 4.6; Br, 40.7. $C_6H_9BrO_2$ requires C, 37.33; H, 4.70; Br, 41.39%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1775 (γ-lactone); $\delta(CDCl_3)$ 3.38–3.63 (2 H, AB type, CH_2Br); *M/Z* (EI) 177 and 179 (M^+ − Me, 1.9 and 2.0%) and 99 (100).

(5RS,6RS)-5-*Bromo*-6-*phenyl*-3,4,5,6-*tetrahydropyran*-2-*one* **15**, crystals, m.p. 109.5–111.0 °C (from hexane) (Found: C, 51.4; H, 4.35; Br, 30.85. $C_{11}H_{11}BrO_2$ requires C, 51.79; H, 4.35; Br, 31.32%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1740 (δ-lactone); $\delta(CDCl_3)$ 4.37 (1 H, ddd, *J* 4.8, 6.2 and 6.2, 5-H) and 5.52 (1 H, d, *J* 6.2, 6-H); *m/z* (EI) 254 and 256 (M^+, 19 and 18%) and 147 (100).

Typical Procedure for Methoxide Treatment of Bromo Lactones **10**, **11** *and* **12**.—A solution of sodium methoxide, prepared by dissolution of sodium (2.5 mg, 0.11 mg-atom) in absolute MeOH (1 cm^3), was added to a stirred solution of the bromo lactone (0.1 mmol) in absolute MeOH (1 cm^3) at room temperature. After being stirred for 1 h, the reaction mixture was diluted with ethyl acetate, washed successively with water and saturated aq. NaCl, and dried (Na_2SO_4). Evaporation, and purification by silica gel chromatography (C_6H_6–AcOEt 3:1), afforded the bromohydrin ester or the epoxy ester.

Methyl (1*RS*,3*RS*,4*SR*)-4-bromo-3-hydroxycyclohexanecarboxylate **16** (95%), needles, m.p. 65–67 °C (lit.,[9a] 65–66 °C); $\nu_{max}(CHCl_3)/cm^{-1}$ 3500–3600 (OH) and 1730 (ester); $\delta(CDCl_3)$ 2.42 (1 H, m, 1-H), 3.51 (1 H, m, 3-H), 3.70 (3 H, s, CO_2Me) and 4.61 (1 H, m, 4-H); *m/z* (EI) 236 and 238 (M^+, 8.1 and 8.2%) and 97 (100).

Methyl endo-3,4-*epoxycyclopentanecarboxylate* **17** (70%), an oil [Found: M^+ (EI), 142.0631. $C_7H_{10}O_3$ requires M, 142.0630]; $\nu_{max}(CHCl_3)/cm^{-1}$ 1740 (ester); $\delta(CDCl_3)$ 2.90–3.30 (2 H, m, 3- and 4-H) and 3.73 (3 H, s, CO_2Me); *m/z* (EI) 142 (M^+, 9.9%) and 56 (100).

Methyl [(1*RS*,2*RS*,3*SR*)-2,3-Epoxycyclohexyl]acetate **18**[3e] (89%), an oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 1730 (ester); $\delta(CDCl_3)$ 3.08–3.25 (2 H, m, 1- and 2-H) and 3.69 (3 H, s, CO_2Me); *m/z* (EI) 170 (M^+, < 0.1%) and 99 (100).

Bromolactonisation of Compound **4** *by Methods A and B.*—Reaction of compound **4** according to the reported procedures (methods A[3a] and B[3q]) and purification by silica gel column chromatography (C_6H_6–AcOEt 20:1) afforded the bromo lactone **19** in 26 and 70% yield, respectively.

(1*RS*,4*RS*,5*RS*)-4-Bromo-6-oxabicyclo[3.2.1]octan-7-one **19**, needles, m.p. 101.0–102.0 °C (from hexane) (lit.,[9a] 104–105 °C); $\nu_{max}(CHCl_3)/cm^{-1}$ 1780 (γ-lactone); $\delta(CDCl_3)$ 4.40 (1 H, m, 4-H) and 4.81 (1 H, br dd, *J* 4.2 and 5.5, 5-H); *m/z* (EI) 204 and 206 (M^+, < 0.1 and < 0.1%) and 81 (100).

Methoxide Treatment of Compound **19**.—Bromo lactone **19** (23 mg, 0.1 mmol) was treated with MeONa in MeOH according to the same procedure as described above to afford epoxide **20** (10.8 mg, 69%) as an oil.

Methyl (1*RS*,3*RS*,4*SR*)-3,4-epoxycyclohexanecarboxylate **20**,[10] $\nu_{max}(CHCl_3)/cm^{-1}$ 1730 (ester); $\delta(CDCl_3)$ 3.08–3.25 (2 H, m, 3- and 4-H) and 3.67 (3 H, s, CO_2Me); *m/z* (EI) 156 (M^+, < 0.1%) and 97 (100).

Bromolactonisation of Compound **21a** *by Method B.*—Reaction of acid **21a** according to the reported procedure,[3q] and purification by silica gel column chromatography (C_6H_6–AcOEt 20:1), afforded the bromo lactone **22** as crystals in 90% yield.

(1RS,2SR,4SR,5SR)-4-*Bromo*-2-*phenyl*-6-*oxabicyclo*[3.2.1]-*octan*-7-*one* **22**, m.p. 131.0–133.0 °C (from hexane) (Found: C, 55.5; H, 4.5; Br, 28.4. $C_{13}H_{13}BrO_2$ requires C, 55.54; H, 4.66; Br, 28.42%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1790 (γ-lactone); $\delta(CDCl_3)$ 4.51 (1 H, m, 4-H), 4.85 (1 H, dd, *J* 4.6 and 4.6, 5-H) and 7.24–7.39 (5 H, m, Ph); *m/z* (EI) 280 and 282 (M^+, 73 and 69%) and 91 (100).

Bromolactonisation of Compound **21a** *by the DMSO–TMSBr–*Pr^i_2EtN *System.*—Unsaturated carboxylic acid **21a** (263 mg, 1.3 mmol) reacted with DMSO (0.11 cm^3, 1.6 mmol), TMSBr (0.21 cm^3, 1.6 mmol), and Pr^i_2EtN (0.27 cm^3, 1.6 mmol) according to the procedure described above for 12 h and the reaction product was purified by silica gel column chromatography (C_6H_6–AcOEt 20:1) to afford compound **23** (69.4 mg, 19%) as an unstable powder, the isomer **22** (58.4 mg, 16%), and thiomethyl ester **24** (34.1 mg, 10%) as an oil.

(1RS,4RS,5SR,7RS)-7-*Bromo*-5-*phenyl*-2-*oxabicyclo*-[2.2.2]*octan*-3-*one* **23**, $\nu_{max}(CHCl_3)/cm^{-1}$ 1770 (δ-lactone); δ-(500 MHz; $CDCl_3$) 4.33 (1 H, ddd, *J* 1.2, 3.6 and 8.5, 7-H), 4.89 (1 H, m, 1-H) and 7.13–7.36 (5 H, m, Ph); *m/z* (EI) 280 and 282 (M^+, 39 and 40%) and 104 (100).

Methylthiomethyl cis-6-*phenylcyclohex*-3-*enecarboxylate* **24** [Found: M^+ (EI), 262.1024. $C_{15}H_{18}O_2S$ requires M, 262.1025]; $\nu_{max}(CHCl_3)/cm^{-1}$ 1740 (ester); $\delta(CDCl_3)$ 2.08 (3 H, s, SMe), 4.89 (1 H, m, 1-H), 5.05 (2 H, s, OCH_2S), 5.85 (2 H, m, 3- and 4-H) and 7.22–7.32 (5 H, m, Ph); *m/z* (EI) 262 (M^+, 9.2%) and 62 (100).

Bromolactonisation of Acid **21b** *by Methods A and B.*—Reaction of acid **21b** according to the reported procedures (methods A[3a] and B[3q]) and purification by silica gel column

chromatography (C_6H_6–AcOEt 20:1) afforded the dibromo carboxylic acid **25** as a powder in 59 and 30% yield, respectively.

4,5-*Dibromo*-trans-2-*phenylcyclohexanecarboxylic acid* **25**, $\nu_{max}(CHCl_3)/cm^{-1}$ 3600–2800 (OH) and 1710 (CO_2H); δ-($CDCl_3$) 4.35–4.75 (2 H, m, 4- and 5-H); *m/z* (EI) 360, 362 and 364 (M^+, 1.1, 2.2 and 0.9%).

Bromolactonisation of Acid **21b** *by the DMSO–TMSBr–Pr^i_2EtN System.*—Unsaturated carboxylic acid **21b** (263 mg, 1.3 mmol) reacted with DMSO (0.11 cm^3, 1.6 mmol), TMSBr (0.21 cm^3, 1.6 mmol), and Pr^i_2EtN (0.27 cm^3, 1.6 mmol) according to the procedure described above for 12 h, and the reaction product was purified by silica gel column chromatography (C_6H_6–AcOEt 20:1) to afford compound **26** (318 mg, 87%).

(1RS,2RS,4RS,5SR)-4-*Bromo*-2-*phenyl*-6-*oxabicyclo*[3.2.1]-*octan*-7-*one* **26**, needles, m.p. 115.0–116.0 °C (from $CHCl_3$–hexane) (Found: C, 55.5; H, 4.6; Br, 28.7. $C_{13}H_{13}BrO_2$ requires C, 55.54; H, 4.66; Br, 28.42%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1780 (γ-lactone); $\delta(CDCl_3)$ 4.49 (1 H, dd, *J* 6.2 and 11.2, 4-H), 4.94 (1 H, d, *J* 6.4, 5-H) and 7.11–7.48 (5 H, m, Ph); *m/z* (EI) 280 and 282 (M^+, 100 and 97%).

References

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