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# Preparation and reactions of some 2,2-difunctional 1,1-dibromocyclopropanes

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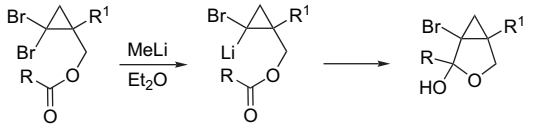
**Abstract**—The synthesis of 2,2-dibromocyclopropane-1,1-dicarboxylic acids is described. Reaction of substituted 1,1-dibromo-2-acyloxymethylcyclopropanes with methyl lithium at low temperature leads to a bromine–lithium exchange and then either formal protonation to give the corresponding monobromocyclopropanes or intramolecular cyclisation to give a substituted 3-oxabicyclo[3.1.0]hexane. Oxidative ring opening of these compounds leads stereoselectively to 1,1,2,2-tetrasubstituted cyclopropanes with four functionalities on the ring.


## 1. Introduction

The cyclopropane ring is a key structural element of many natural products[1] and the synthesis of specifically substituted cyclopropanes has therefore grown important. Dibromocyclopropanes, which are normally readily available by addition of dibromocarbene to alkenes, undergo a range of useful transformations many of which can be used to produce other cyclopropanes in a stereocontrolled manner.[2] One example is their reaction with methyl lithium, which is known to lead to a very rapid lithium–bromine exchange, followed in most cases by formal elimination of lithium bromide to produce a cyclopropylidene (or a related carbenoid), which often rearranges efficiently to form an allene.[3] At low temperature or, in some cases, if there is a coordinating group present in the molecule, the organolithium may be trapped in intermolecular processes by reaction with electrophiles.[3] There are also many examples of intramolecular trapping of the cyclopropylidene. Thus, insertion into CH bonds is of considerable synthetic potential.[4,5] For example, in ethers,[6] amines,[7] sulfides[8] and acetals[9] insertion occurs exclusively at the C–H bond adjacent to the heteroatom and 5,6-related to the carbenic carbon (1,5-insertion) to give bicyclic heterocycles. There are fewer cases of similar intramolecular reactions of the lithiobromides acting as nucleophiles; one such is the 1,3-elimination of HBr from 1,1-dibromo-2-(halogenomethyl)cyclopropanes on reaction with methyl lithium.[10,11] We recently reported that reaction of 2,2-dibromo-1-acyloxymethylcyclopropanes with methyl lithium leads to hemiacetals, apparently derived by cyclisation of an intermediate lithiobromide (Scheme 1).[12]




**Scheme 1**.

## 2. Results and discussion

The reaction of α,β-unsaturated esters with bromoform and base under phase transfer conditions (probably proceeding by addition of the tribromomethyl anion rather than the carbene) provides 1,1-dibromocyclopropane-2-carboxylates that can be resolved to provide useful chiral building blocks for synthesis.[13] This reaction has also been applied to alkylidenemalonates to produce esters of 3-alkyl-2,2-dibromocyclopropane-1,1-dicarboxylic acid.[14] In this work, the preparation and reactions of some 1,1-dibromocyclopropanes having two functional groups at the 2-position were studied. The synthesis of cyclopropanes **1a–c** was carried out according to Scheme 2. Treatment of di-*tert*-butyl methylenemalonate[15] with bromoform and aqueous sodium

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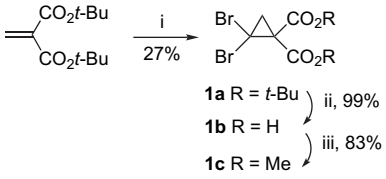
hydroxide in the presence of a phase transfer catalyst produced di-*tert*-butyl ester **1a** in 27% yield. The $^1$H NMR spectrum of ester **1a** contains signals of the methylene protons at 2.32 ppm and the methyl groups at 1.52 ppm. The $^{13}$C NMR spectrum consists of signals for the three-membered ring carbon atoms at 23.3 ppm ($CBr_2$), 32.6 ppm ($CH_2$) and 44.4 ppm (C) and carboxylate groups. The structure of compound **1a** was confirmed by X-ray diffraction studies (Fig. 1).




**Scheme 2**. Reagents and conditions: (i) $CHBr_3$, 40% aq NaOH, TEBA, $CH_2Cl_2$; (ii) TFA; (iii) $CH_2N_2$.

Hydrolysis of cyclopropane **1a** with trifluoroacetic acid led to diacid **1b** in 99% yield. Dimethyl 2,2-dibromocyclopropane-1,1-dicarboxylate **1c** was obtained by treatment of the acid **1b** with an ethereal solution of diazomethane in 83% yield. The $^1$H NMR spectrum of the ether **1c** showed the signals of the methylene group protons at 2.52 ppm and the methyl group protons at 3.87 ppm.

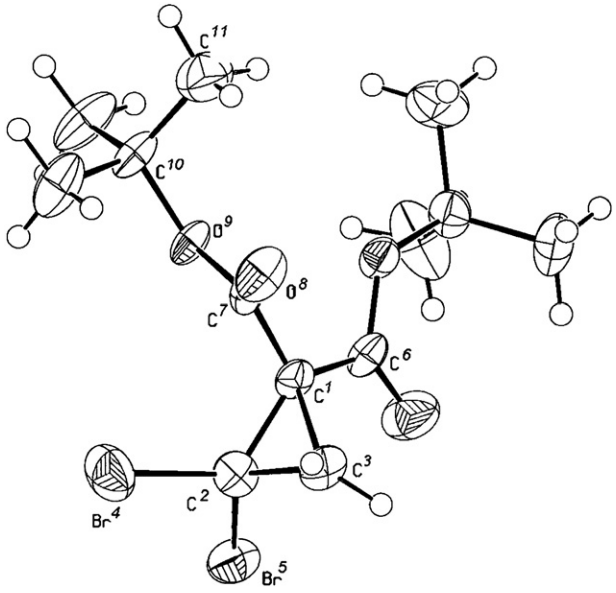
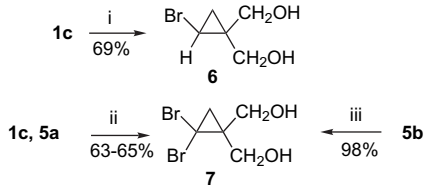



**Figure 1**. The X-ray crystal structure of compound **1a**.

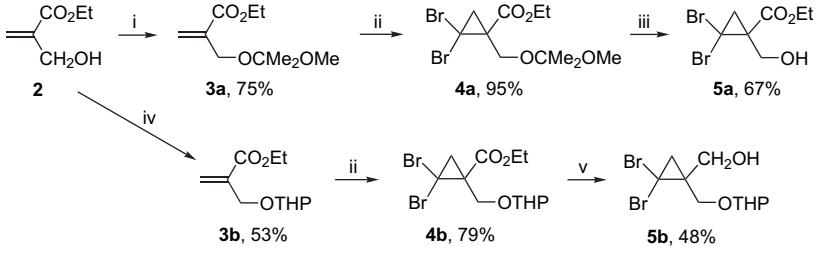
Cyclopropanes **5a**,**b** were synthesised as in Scheme 3. Treatment of ethyl acrylate with formaldehyde and DABCO as catalyst produced ethyl α-hydroxymethylacrylate **2**.[16] Protection of the hydroxyl group with 2-methoxy-1-propene or 3,4-dihydro-2*H*-pyran to give esters **3a**,**b** (yields 75% or 53% correspondingly) and subsequent cyclopropanation led to compounds **4a**,**b** in yields 95% or 79%. The $^1$H NMR spectrum of cyclopropane **4a** included the cyclopropane methylene group as two doublets at 1.84 and 2.45 ppm, the oxymethylene group as two doublets at 3.97 and 4.07 ppm, two singlets for methyl groups at 2.17 and 3.49 ppm, and the signals of the ethyl group. Cyclopropane **4b** was obtained as a mixture of diastereomers in 1:1 ratio. Reaction of cyclopropane **4a** with aqueous methanol in the presence of *p*-toluenesulfonic acid led to compound **5a** in 67% yields.

A selective reduction of ester **4b** with DIBAL-H at −78 °C gave THP protected alcohol **5b** in 48% yield. Reduction of ester **1c** with lithium aluminium hydride afforded 1-bromo-2,2-bis(hydroxymethyl)cyclopropane **6** with a yield of 69%. Thus, reduction of the ester group and also one of C–Br bond has occurred. The $^1$H NMR spectrum of compound **6** showed the signals for the cyclopropane ring protons as double doublets at 0.93 ($J$=6.6 and 4.4 Hz), 1.21 ($J$=7.5 and 6.6 Hz) and 3.10 ppm ($J$=7.5 and 4.4 Hz). Using a mixture of lithium aluminium hydride–aluminium chloride allowed selective reduction only of the ester groups of esters **1c** and **5a** to give 1,1-dibromo-2,2-bis(hydroxymethyl)cyclopropane **7**[17] with a yield of up to 65%. Deprotection of **5b** was carried out with PTSA in methanol at 50 °C to give diol **7** in 98% yield (Scheme 4). The $^1$H NMR spectrum of compound **7** showed singlets at 1.64 ppm ($CH_2$ of the cyclopropane ring) and at 2.44 ppm (OH), and two doublets at 3.94 and 4.13 ppm ($CH_2O$).




**Scheme 4**. Reagents and conditions: (i) $LiAlH_4$, $Et_2O$; (ii) $LiAlH_4$–$AlCl_3$, $Et_2O$; (iii) MeOH, PTSA.

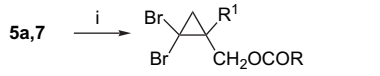
Despite the fact that the one-step synthesis of diol **7** is possible from ester **1c**, this way is not optimal as far as ester **1c** itself is the product of three-step synthesis (from methylenemalonate) with summarised yield around 23% (the summarised yield of diol **7** from methylenemalonate is around




**Scheme 3**. Reagents and conditions: (i) Me(MeO)C=$CH_2$, PPTS; (ii) $CHBr_3$, aq NaOH, TEBA, $CH_2Cl_2$; (iii) $H^+$/aq MeOH; (iv) 3,4-dihydro-2*H*-pyran, PPTS; (v) DIBAL, −78 °C, 12 h.

14%). Therefore, we attempted two additional ways to prepare the diol **7** from hydroxymethylacrylates. The summarised yield of diol **7** is around 31% and 20% (using 2-methoxy-1-propene and 3,4-dihydro-2*H*-pyran, respectively, as protecting group) (Schemes 3 and 4).

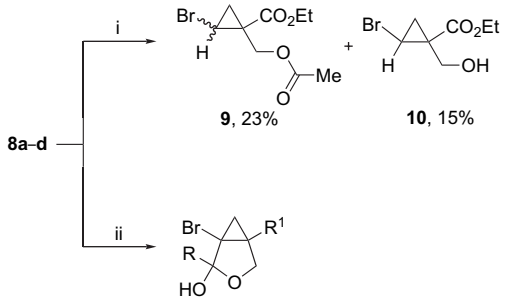
Treatment of compounds **5a** and **7** with a series of acid chlorides in pyridine led to the formation of esters **8a–f** (Scheme 5) with yields of 62–85%.




**8a** $R^1 = CO_2Et$, R = Me, 62%
**8b** $R^1 = CO_2Et$, R = Pr, 68%
**8c** $R^1 = CO_2Et$, R = *i*-Pr, 63%
**8d** $R^1 = CO_2Et$, R = Ph, 71%
**8e** $R^1 = CH_2OCOPr$, R = Pr, 85%
**8f** $R^1 = CH_2OCOMe$, R = Me, 73%

**Scheme 5**. Reagents and conditions: (i) RCOCl, Py.

The reaction of esters **8a–f** with methyl- or butyl lithium was investigated under various conditions. Reaction of ester **8a** with methyl lithium in tetrahydrofuran at −109 °C to −100 °C for 30 min followed by quenching with water at this temperature produced only a mixture of cis- and trans-monobromides **9** (23%, 3:1 ratio by $^1$H NMR spectroscopy) and **10**—as a single cis-isomer (15%) (Scheme 6). When the reaction mixture was warmed to −30 °C, −10 °C or 0 °C and kept at this temperature for a range of times, formation of hemiacetal **11a** was observed after quenching. Reaction of ester **8a** with a slight excess of *n*-butyl or methyl lithium at −100 °C, warming to 0 °C and maintaining at 0–1 °C for a further 20–30 min, then quenching with methanol led to formation of hemiacetal **11a** (up to 21%) and cyclopropane **9** in a 8:1 ratio. Additional reactions were carried out with compound **8a** under different conditions with butyl lithium in order to increase the yield of **11a**. In all cases, a decrease in the mass was noticed after reaction mixtures were worked-up (chromatography), but attempts to isolate other compounds from the mixtures were unsuccessful. The amount of monobromocyclopropanes (determined from the $^1$H NMR spectra of crude products) depended on how long

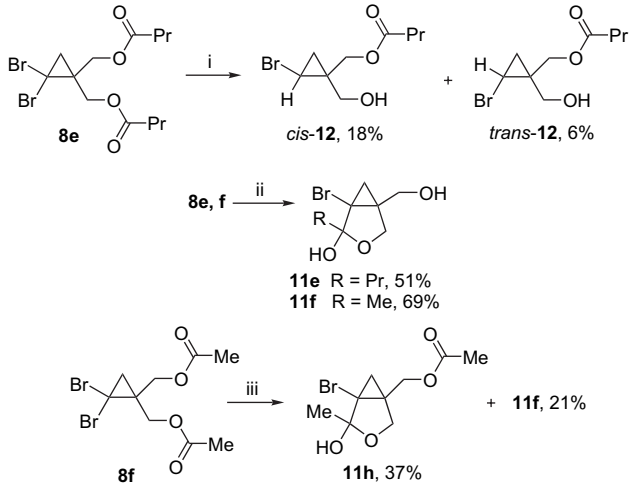



**11a** $R^1 = CO_2Et$, R = Me, 21%
**11b** $R^1 = CO_2Me$, R = Pr, 10%
**11c** $R^1 = CO_2Me$, R = *i*-Pr, 10%
**11d** $R^1 = CO_2Et$, R = Ph, 6%
**11g** $R^1 = CO_2Me$, R = Ph, 3%

**Scheme 6**. Reagents and conditions: (i) (a) MeLi, THF, −109 °C to −100 °C, 30 min, (b) $H_2O$; (ii) (a) MeLi or BuLi, $Et_2O$, −100 to 0 °C, 20 min, (b) MeOH.

the reaction was kept at low temperature. By an analogous process hemiacetals **11b–d,g** were prepared by reaction of esters **8b–d**, respectively, with a slight excess of methyl lithium (Scheme 6). Moreover, methyl esters **11b,c,g** were obtained as a result of transesterification of ethyl esters.

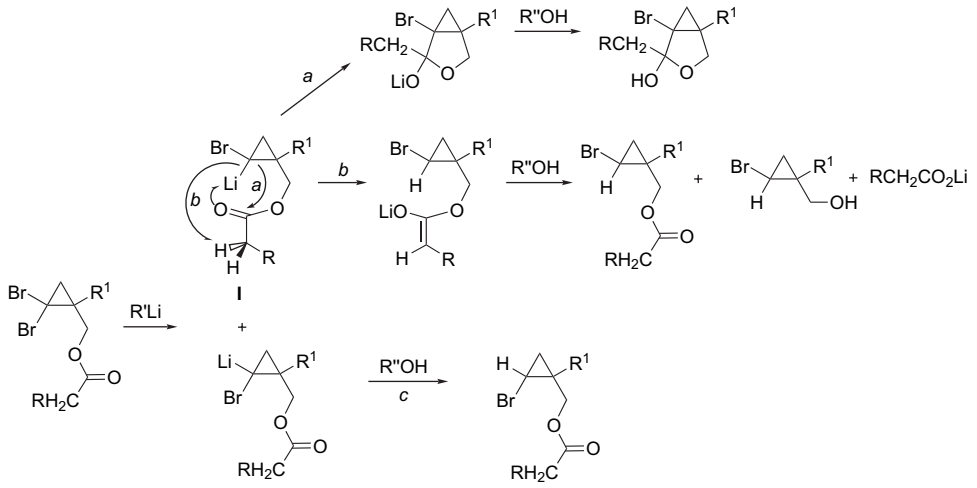
Reaction of cyclopropane **8e** with methyl lithium in tetrahydrofuran at −110 °C to −100 °C for 30 min followed by quenching at this temperature with water led to the formation of monobromocyclopropane **12** (24%) as a mixture of cis- and trans-isomers in a 7:1 ratio, respectively, whereas warming to 0 °C immediately after the addition of methyl lithium, and stirring at this temperature for 20 min afforded hemiacetal **11e** (Scheme 7). The reaction of cyclopropane **8f** with methyl lithium generally followed a similar pattern. It is interesting to note that quenching the reaction mixture in the last case with saturated aqueous ammonium chloride afforded a mixture of protected and unprotected compounds, whereas quenching with methanol afforded only compounds unprotected on the second hydroxymethyl group.




**Scheme 7**. Reagents and conditions: (i) (a) MeLi, THF, −100 °C to −95 °C, 30 min, (b) $H_2O$; (ii) (a) MeLi, $Et_2O$, −100 °C to 0 °C, 20 min, (b) MeOH; (iii) (a) MeLi, $Et_2O$, −100 °C to 0 °C, 20 min, (b) aq $NH_4Cl$.

The configurations of compounds **9** and **10** were determined on the basis of chemical shifts. A comparison of the signal protons $H^1$, $H^2$ and the protons of the $CH_2$-group of compounds **5a** and **7** showed $H^1$ to be 0.81 (2.45–1.64) ppm lower field in the ester and $H^2$ to be 0.2 (1.84–1.64) ppm lower field while the protons of the geminal $CH_2$-group were at −0.01±0.01 ppm. A comparison of the signals of the protons $H^1$, $H^2$ and the protons of $CH_2$-group of compounds **5** and its acylated analogue **8a** showed the effect of acetylation to be +0.03 ppm for $H^1$, +0.10 ppm for $H^2$ and +0.56±0.22 ppm for the protons of $CH_2$-group. In the same way the influence of the bromine atom was determined by comparison of the mono- and dibromodiols. The effect of the bromine atom is +0.71 ppm for $H^1$, +0.42 ppm for $H^2$, +0.35±0.01 ppm for the trans-related $CH_2$-group and +0.06±0.05 ppm for the cis-related $CH_2$-group.

A plausible mechanism for transformation of lithiation products of dibromocyclopropanes into monobromocyclopropanes and hemiacetals is shown below (Scheme 8). On alkyl lithium attack one of the bromine atoms (the one



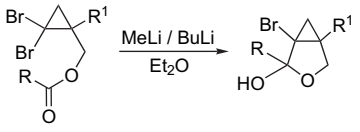
**Scheme 8**. A plausible mechanism of formation of products **9**–**12**.

cis- to the acyloxymethyl group) is replaced selectively by lithium with formation of the organolithium species, promoted by coordination of lithium to the oxygens of the ester group.[18] This can undergo two transformations: *a*—intramolecular attack by the anionic carbon atom of the ring at the carbon atom of the carboxylic group with the formation of bicyclic acetal; *b* and *c*—replacement of the lithium atom by a hydrogen with the formation of monobromide. If the quenching of the reaction mixture with methanol proceeds faster than transformation of the lithium carbenoid (the reaction proceeds at low temperature; $R^1$=$CO_2Et$, $CH_2OCOR$), a stereoisomeric mixture of monobromides is formed (reactions *b* and *c*). If the transformation of the lithium carbenoid proceeds faster than quenching of the reaction mixture with methanol (the reaction proceeds at higher temperature; $R^1$=H, Alk, $CH_2OCOR$), a corresponding cyclisation product is formed (reaction *a*). In case $R^1$=$CO_2Et$ the same carbenoid is formed at the first step but due to its unstability the yields of corresponding cyclisation product are low and polymer products are formed. This scheme explains also the predominated formation of carbenoid **13** and both the stereochemistry of cyclisation and reduction of one of the bromine atoms in the initial dibromide (preferentially cis-H substitution to acyloxymethyl group).

Table 1 summarises data on the influence of substituents on the cyclisation products' yields, both from the literature[12] and found in this work. The yield of cyclisation products strongly depends on the substituent and decreases in the order $R^1$=Me≥H≥$CH_2OCOR$>$CO_2Et$. This suggests that the carboxylate group and acyloxymethyl group more strongly promote substitution of the *cis*-bromine by lithium with formation of carbenoid, which cannot in the former case rearrange to bicycle.

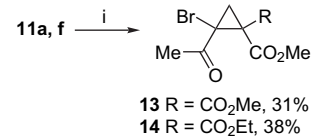
Some applications of the products of cyclisation were examined. Oxidative ring opening of **11f** using periodic acid and catalytic ruthenium trichloride gave the corresponding 2-acetyl-2-bromocyclopropane-1,1-dicarboxylic acid, which was isolated as methyl ester **13** (Scheme 9). The $^{13}C$ NMR spectrum of the product showed the expected signal for the ester carbonyl group in the region of 166 ppm and the ketone at 198 ppm. By an analogous process, cyclopropane **14** was prepared from hemiacetal **11a** (Scheme 9). Tandem transformation of 1-acyloxymethyl-2,2-dibromocyclopropanes to 2-keto-2-bromocyclopropane-1-carboxylates can therefore be successfully used in the synthesis of various 1,2,3,4-tetrasubstituted cyclopropanes.

**Table 1**. Yields of cyclisation products



| $R^1$ | R | Yield[a] (%) | $R^1$ | R | Yield (%) |
|---|---|---|---|---|---|
| H | Me | 55 | $CO_2Et$ | Me | 21 |
| H | *n*-Pr | 46 | $CO_2Et$ | *n*-Pr | 10 |
| H | $CF_3$ | 90 | $CO_2Et$ | *i*-Pr | 10 |
| H | Ph | 64 | $CO_2Et$ | Ph | 6[b] |
| H | –CH=$CH_2$ | 39 | $CO_2Me$ | Ph | 3[b] |
| Me | Me | 60 | $CH_2OH$ | Me | 69 |
| Me | *n*-Pr | 74 | $CH_2OH$ | Pr | 51 |
| Me | Ph | 82 | $CH_2OH$ | Me | 21[c] |
| Me | –CH=$CH_2$ | 68 | $CH_2OCOMe$ | Me | 37[c] |
| Me | *i*-Pr | 80 | | | |
| Me | *t*-Bu | 81 | | | |

[a] Data from Ref. 12.
[b] As a mixture from ethyl 2,2-dibromo-1-(phenylcarbonyloxymethyl)-cyclopropane-1-carboxylic acid (**8d**).
[c] As a mixture from 1,1-di(acetoxymethyl)-2,2-dibromocyclopropane (**8f**).



**13** R = $CO_2Me$, 31%
**14** R = $CO_2Et$, 38%

**Scheme 9**. Reagents and conditions: (i) (a) $H_5IO_6$, $RuCl_3$, (b) $CH_2N_2$.

## 3. Conclusion

Two new synthetic blocks, dialkyl 2,2-dibromocyclopropane-1,1-dicarboxylates and 2,2-dibromo-1-hydroxymethylcyclopropane-1-carboxylates, were used for synthesis of cyclopropanes containing three C substituents. Reaction

of 1-acyloxymethyl-2,2-dibromocyclopropanes with alkyl lithium is sensitive to the substituents on the ring.

## 4. Experimental

### 4.1. General methods

Infrared spectra were obtained as KBr discs or as liquid films on a Perkin–Elmer 1600 FTIR spectrometer or for 2% solutions in chloroform on a Carl Zeiss UR-20 spectrometer and data are given in $cm^{-1}$. Melting points were determined on a Boetius instrument or a Gallenkamp melting point apparatus and are uncorrected. $^1H$ and $^{13}C$ NMR spectra were recorded in $CDCl_3$ or DMSO-$d_6$ as solvent using a Bruker AC250 (250 and 62.9 MHz for $^1H$ and $^{13}C$, respectively), Bruker DPX-300 (300 and 75 MHz), or a Bruker Avance500 (500 and 125 MHz). Elemental analyses were performed on a Hewlett-Packard 185B apparatus or on a Carlo Erba Model 1106 CHN analyser. Low-resolution mass spectra were measured using electron impact (EI) at 70 eV on a Finnigan MAT 8340 spectrometer. The X-ray diffraction data were measured with a Hilger and Watts (Y290) diffractometer. Reactions were monitored by TLC analysis using silica gel 60 $F_{254}$ thin layer plates. Organic solutions were dried over anhydrous magnesium sulfate.

### 4.2. Experimental procedures

**4.2.1. Di-*tert*-butyl 2,2-dibromocyclopropane-1,1-dicarboxylate (1a).** Di-*tert*-butyl methylenemalonate[15] (0.5 g, 2.2 mmol), bromoform (0.3 mL, 3.4 mmol), TEBA (0.05 g) and dichloromethane (4 mL) were put in a flask equipped with a magnetic stirrer and thermometer. A 50% solution of sodium hydroxide (0.26 g) was added dropwise with cooling in an ice-salt bath ($T<5$ °C). The mixture was stirred for 12 h at ambient temperature and quenched with water. The organic layer was separated and washed with water. The aqueous layer was extracted with dichloromethane. The combined organic layers were dried. The solvent was removed and the residue was crystallised from hexane giving ester **1a** as a colourless solid (0.24 g, 27%), mp 94–96 °C; IR ($CHCl_3$) 1130, 1170, 1340, 1370, 1740 v.s, 2980, 3050 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.52 (18H, s, $CH_3$), 2.32 (2H, s, $CH_2$); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 23.3 (C), 28.3 ($CH_3$), 32.6 ($CH_2$), 44.4 (C), 83.9 (C), 163.9 (C=O). Anal. Calcd for $C_{13}H_{20}Br_2O_4$: C, 39.03; H, 5.04. Found: C, 38.9; H, 5.1.

**4.2.2. 2,2-Dibromocyclopropane-1,1-dicarboxylic acid (1b).** Ester **1a** (0.4 g, 1 mmol) and trifluoroacetic acid (0.5 mL) were allowed to stand for 1 h at ambient temperature. The product was filtered and washed with hexane to give acid **1b** as a colourless solid (0.29 g, 99%), mp 180–183 °C; IR ($CHCl_3$) 690 s, 770, 790, 900 s, 1040, 1160, 1250 s, 1300 s, 1410 s, 1680 v.s, 1720 v.s, 3000 br s $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO) $\delta$ 2.31 (2H, s, $CH_2$), 10.43 (2H, br s, OH); $^{13}C$ NMR (300 MHz, DMSO) $\delta$ 23.8 (C), 32.6 ($CH_2$), 43.8 (C), 166.5 (C=O). Anal. Calcd for $C_5H_4Br_2O_4$: C, 20.86; H, 1.40. Found: C, 20.8; H, 1.4.

**4.2.3. Ethyl 1-(1-methoxy-1-methyl-ethoxymethyl)acrylate (3a).** Pyridinium-*p*-toluene sulphonate (PPTS) (7 mg) was added to a stirred solution of ethyl α-(hydroxymethyl)-acrylate **2**[16] (3.13 g, 24 mmol) and 2-methoxy-1-propene (6.9 mL, 72 mmol) in dry ether at below 0 °C. After 1 h, sodium bicarbonate (1 g) was added and the mixture was stirred for 10 min, filtered and washed with ether. The solvent was removed and residue was distilled under vacuum giving ether **3a** (3.44 g, 70%), bp 74–84 °C (1 mmHg). IR ($CHCl_3$) 851, 950, 1054 s, 1084 s, 1153 s, 1214, 1273, 1303, 1381, 1460, 1640, 1718 v.s, 2829, 2992 s $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 1.31 (3H, t, $J$=7.0 Hz, $CH_3$), 1.39 (6H, s, $CH_3$), 3.20 (3H, s, $CH_3$), 4.16 (2H, m, $CH_2$), 4.22 (2H, q, $J$=7.0 Hz, $CH_2$), 5.89 (1H, d, $J$=1.6 Hz, $CH_2$), 6.26 (1H, d, $J$=1.6 Hz, $CH_2$); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) $\delta$ 14.3 ($CH_3$), 24.4 ($CH_3$), 48.6 ($CH_3$), 59.2 ($CH_2$), 60.6 ($CH_2$), 100.3 (C), 124.8 ($CH_2$), 138.0 (C), 166.0 (C=O); MS (ESI) *m/z*: 225 ($M^+$+Na). Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.2; H, 8.9.

**4.2.4. Ethyl 2-(tetrahydropyran-2-yloxymethyl)acrylate (3b).** 3,4-Dihydro-2*H*-pyran (3.2 g, 3.4 mL, 40.0 mmol) was added to a stirred solution of ethyl α-(hydroxymethyl) acrylate **2** (2.2 g, 15.0 mmol) in dry dichloromethane and PPTS (0.2 g, 0.8 mmol) at 0 °C. The mixture was stirred for 12 h, then quenched with satd aq sodium bicarbonate (10 mL) and extracted with dichloromethane (3×20 mL). The combined organic layers were dried, filtered and the solvent evaporated in vacuo to give the crude product as a pale yellow liquid. Chromatography on silica gel eluting with petrol–ether (5:3) gave a colourless liquid, ester (**3b**) (2.78 g, 13.1 mmol, 53%). IR ($CHCl_3$) 817, 870, 907, 979, 1037 s, 1068, 1122 s, 1180, 1202, 1271, 1325, 1387, 1455, 1638, 1724 s, 2872, 2943 s $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 1.31 (3H, t, $J$=7.2 Hz, $CH_3$), 1.85–1.51 (6H, m, $CH_2$), 3.54 (1H, br dt, $J$=11.4, 4.4 Hz, $OCH_2$), 3.89 (1H, ddd, $J$=11.4, 8.8, 2.9 Hz, $OCH_2$), 4.20 (1H, dt, $J$=14.2, 1.4 Hz, $OCH_2$), 4.23 (2H, q, $J$=7.2 Hz, $CH_2$), 4.46 (1H, dt, $J$=14.2, 1.6 Hz, $OCH_2$), 4.70 (1H, t, $J$=3.5 Hz, OCHO), 5.89 (1H, br d, $J$=1.6 Hz, =$CH_2$), 6.30 (1H, br d, $J$=1.6 Hz, =$CH_2$); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 14.2 ($CH_3$), 19.2 ($CH_2$), 25.4 ($CH_2$), 30.5 ($CH_2$), 60.6 ($CH_2$), 62.0 ($CH_2$), 65.3 ($CH_2$), 98.2 (CH), 125.4 ($CH_2$), 137.5 (C), 165.8 (C=O). ESI-MS: 237 ($M^+$+Na), 68 ($M^+$−OTHP, OEt). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 62.0; H, 8.4.

**4.2.5. Ethyl 2,2-dibromo-1-(1-methoxy-1-methylethoxymethyl)cyclopropane-1-carboxylate (4a).** Ester **3a** (30.0 g, 0.148 mol), bromoform (75.1 g, 26.6 mL, 0.30 mol), cetrimide (2.5 g), triethylamine (20 drops) and dichloromethane (50 mL) were stirred and sodium hydroxide (95.0 g) in water (95.0 mL) was added dropwise with cooling in an ice-salt bath. The mixture was stirred vigorously for 20 h at ambient temperature. The layers were separated and the aqueous layer was extracted with dichloromethane (3×50 mL). The combined organic layers were washed with brine (50 mL), dried and evaporated under reduced pressure. To the residue was added the same volume of hexane; after stirring for 15 min the mixture was filtered. Removing the solvent gave cyclopropane **4a** (52.9 g, 95%). IR ($CHCl_3$) 858, 1024 s, 1096, 1156 s, 1180 s, 1223 s, 1266 s, 1326, 1371, 1444, 1465, 1730 v.s, 2981, 3088, 3428 br $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 1.34 (3H, t, $J$=7.0 Hz, $CH_3$), 1.84 (1H, d, $J$=8.2 Hz, $CH_2$), 2.17 (6H, s, $CH_3$), 2.45 (1H, d, $J$=8.2 Hz, $CH_2$), 3.49 (3H, s, $CH_3$), 3.97 (1H, d,

$J$=12.2 Hz, $CH_2$), 4.07 (1H, d, $J$=12.2 Hz, $CH_2$), 4.29 (1H, q, $J$=7.0 Hz, $CH_2$), 4.30 (1H, q, $J$=7.0 Hz, $CH_2$); $^{13}$C NMR (62.9 MHz, $CDCl_3$) $\delta$ 15.7 ($CH_3$), 26.8 ($CBr_2$), 32.3 ($CH_2$), 32.4 ($CH_3$), 40.9 (C), 52.4 ($CH_3$), 63.9 ($CH_2$), 67.7 ($CH_2$), 142.5 (C), 170.0 (C=O); MS *m/z*: $M^+$ (not observed), 130, 113, 101, 85, 73, 53.

**4.2.6. Ethyl 2,2-dibromo-1-(tetrahydropyran-2-yloxymethyl)cyclopropane carboxylate (4b).** Sodium hydroxide solution (4.2 g in 4.2 mL water) was added slowly to a rapidly stirred solution of the ester **3b** (2.24 g, 10.5 mmol), triethylamine (0.25 mL), bromoform (3.96 g, 15.7 mmol) and TEBACl (0.2 g, 1.1 mmol) in dichloromethane (25 mL) at 0 °C. The mixture was allowed to reach room temperature, stirred for 6 h, monitored by GLC and TLC, then cooled to 0 °C, water (2 mL) and dichloromethane (20 mL) were added. The organic layer was separated and washed with brine (3×20 mL). The combined organic layers were dried, filtered and evaporated in vacuo to give a dark brown oil. Chromatography on silica eluting with petrol–ether (5:2) gave a colourless liquid, bromide (**4b**) (0.98 g, 2.52 mmol, 79%) as a mixture of diastereomers. IR ($CHCl_3$) 682, 816, 871, 904, 1029 s, 1067, 1183, 1260, 1351, 1442, 1454, 1466, 1740 s, 2873, 2943 s cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$, minor diastereomer was marked by asterisk *) $\delta$ 1.33 (3H, t, $J$=7.3 Hz, $CH_3$), 1.35* (3H, t, $J$=7.3 Hz, $CH_3$), 1.84–1.52 (6H, m, $CH_2$), 1.93 (1H, dd, $J$=9.9, 8.8 Hz, $CH_2$), 2.47 (1H, ddd, $J$=7.9, 4.6, 1.3 Hz, $CH_2$), 3.46 (1H, d, $J$=10.7 Hz, $CH_2$), 3.68 (1H, d, $J$=10.4 Hz, $CH_2$), 3.82 (1H, t, $J$=11.4 Hz, CH), 3.83* (1H, t, $J$=11.4 Hz, CH), 4.34–4.24 (2H, m, $CH_2$), 4.40 (1H, dd, $J$=10.7, 1.3 Hz, $CH_2$), 4.62 (1H, dd, $J$=10.7, 1.3 Hz, $CH_2$), 4.64* (1H, t, $J$=3.8 Hz, OCHO), 4.70 (1H, t, $J$=3.2 Hz, OCHO); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 14.1* ($CH_3$), 14.3 ($CH_3$), 18.7* ($CH_2$), 19.2 ($CH_2$), 24.9 (C), 25.3 ($CH_2$), 30.2* ($CH_2$), 30.4 ($CH_2$), 30.7 ($CH_2$), 31.0* ($CH_2$), 38.5 (C), 38.8* (C), 61.6* ($CH_2$), 62.0 ($CH_2$), 62.1 ($CH_2$), 62.2* ($CH_2$), 69.6 ($CH_2$), 71.3* ($CH_2$), 97.8 (CH), 99.5* (CH), 167.7 (C=O), 167.8* (C=O). ESI-MS: 409 ($M^+$+Na). Anal. Calcd for $C_{12}H_{18}Br_2O_4$: C, 37.33; H, 4.70. Found C, 37.6; H, 4.8.

**4.2.7. Ethyl 2,2-dibromo-1-hydroxymethylcyclopropane-1-carboxylate (5a).** *p*-Toluenesulfonic acid (0.4 g) was added to a solution of cyclopropane **4a** in aq methanol (12 mL of water and 60 mL of methanol) and stirred for 30 min. Sodium bicarbonate (1 g) was added and the mixture was stirred for another 10 min, filtered and the organic layer was dried and evaporated under reduced pressure. The residue was distilled under vacuum giving ester **5a** (30.2 g, 67%), bp 150 °C (0.3 mmHg). IR ($CHCl_3$) 688 s, 858, 1024 s, 1157, 1181 s, 1222, 1268 s, 1329, 1371, 1422, 1464, 1731 v.s, 2903, 2980 s, 3089, 3442 br s cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.27 (3H, t, $J$=7.2 Hz, $CH_3$), 1.77 (1H, d, $J$=7.9 Hz, $CH_2$), 2.18 (1H, s, OH), 2.38 (1H, d, $J$=7.9 Hz, $CH_2$), 3.90 (1H, d, $J$=12.2 Hz, $CH_2$), 4.01 (1H, d, $J$=12.2 Hz, $CH_2$), 4.22 (1H, dq, $J$=10.8, 7.2 Hz, $CH_2$), 4.24 (1H, dq, $J$=10.8, 7.2 Hz, $CH_2$); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 14.2 ($CH_3$), 25.4 (C), 30.8 ($CH_2$), 39.4 (C), 62.4 ($CH_2$), 66.2 ($CH_2$), 168.5 (C=O). Anal. Calcd for $C_7H_{10}Br_2O_3$: C, 27.84; H, 3.34. Found: C, 27.6; H 3.3.

**4.2.8. 2,2-Dibromo-1-(tetrahydropyran-2-yloxymethyl)-cyclopropylmethanol (5b).** DIBAL in hexane (1.42 g, 0.99 mL, 1.0 M, 0.99 mmol) was added slowly to a stirred solution of the dibromide **4b** (76.0 mg, 0.19 mmol) in dry dichloromethane at −78 °C under argon. The mixture was allowed to reach room temperature for 2 h. TLC and GLC showed starting material was still present. The mixture was stirred for a further 10 h and then quenched with satd aq sodium bicarbonate (1 mL) and extracted with dichloromethane (3×10 mL). The combined organic layers were dried and evaporated in vacuo to give a light brown solid. This was purified by chromatography on silica gel eluting with petrol–ethyl acetate (1: 1) to give a colourless liquid alcohol **5b** as a mixture of diastereomers (32.5 mg, 0.1 mmol, 48%). IR ($CHCl_3$) 688, 868, 904, 1032 s, 1062, 1122, 1201, 1353, 1385, 1440, 1455, 2871, 2943 s, 3406 br s cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.60 (1H, d, $J$=7.6 Hz, $CH_2$), 1.64–1.55 (2H, m, $CH_2$), 1.65 (1H, d, $J$=7.8 Hz, $CH_2$), 1.69* (1H, d, $J$=7.6 Hz, $CH_2$), 1.90–1.74 (2H, m, $CH_2$), 2.96 (2H, quintet, $J$=6.9 Hz, $CH_2$), 3.59–3.54 (2H, m, $CH_2$), 3.69 (1H, d, $J$=10.7 Hz, $OCH_2$), 3.78* (1H, dd, $J$=12.0, 7.2 Hz, $CH_2$), 3.83 (1H, d, $J$=10.7 Hz, $OCH_2$), 3.90 (1H, m, $CH_2$), 4.01 (1H, m, $CH_2$), 4.08* (1H, d, $J$=10.7 Hz, $OCH_2$), 4.14 (1H, dd, $J$=12.0, 6.3 Hz, $CH_2$), 4.23* (1H, d, $J$=10.7 Hz, $OCH_2$), 4.66* (1H, dd, $J$=5.3, 2.4 Hz, OCHO), 4.69 (1H, dd, $J$=4.6, 3.0 Hz, OCHO); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 19.6 ($CH_2$), 19.9* ($CH_2$), 25.1 ($CH_2$), 25.2 ($CH_2$), 30.5* ($CH_2$), 30.6* ($CH_2$), 30.6 ($CH_2$), 31.8* (C), 31.9 (C), 33.7 (C), 34.0* (C), 62.9* ($CH_2$), 63.2 ($CH_2$), 66.9 ($CH_2$), 67.0* ($CH_2$), 71.4 ($CH_2$), 71.5* ($CH_2$), 99.4 (CH), 99.8* (CH). ESI-MS: 364.9, 366.9, 368.8 ($M^+$+Na); HRMS calcd for $^{12}C_{10}{}^1H_{16}{}^{79}Br_2{}^{16}O_3$ ($M^+$) 341.9466, found: 341.9466.

**4.2.9. 1-Bromo-2,2-dihydroxymethylcyclopropane (6).** An ethereal solution of lithium aluminium hydride (4 mL, 2.9 mmol) was added dropwise with stirring and cooling in an ice bath to the ester **1c** (0.3 g, 1.0 mmol) in ether (15 mL). The mixture was stirred for 1 h, and then the excess of lithium aluminium hydride was quenched by addition of water (0.1 mL), 15% aq sodium hydroxide (0.3 mL) and water (0.3 mL). The mixture was stirred for 30 min, the precipitate was filtered off and the solution was dried. Removing the solvent gave diol **6** as a colourless solid (0.12 g, 69%), mp 52–54 °C. IR ($CHCl_3$) 1130 s, 1150 s, 1260, 1320, 1380, 1420, 2890, 2950, 3040, 3610 br s cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.93 (1H, dd, $J$=6.6, 4.4 Hz, $CH_2$), 1.22 (1H, dd, $J$=7.5, 6.6 Hz, $CH_2$), 2.40 (2H, s, OH), 3.10 (1H, dd, $J$=7.5, 4.4 Hz, CH), 3.60 (1H, d, $J$=9.5 Hz, $CH_2$), 3.77 (1H, d, $J$=9.5 Hz, $CH_2$), 3.83 (1H, d, $J$=11.9 Hz, $CH_2$), 4.12 (1H, d, $J$=11.9 Hz, $CH_2$); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 18.6 ($CH_2$), 25.0 (CH), 28.9 (C), 66.4 ($CH_2$), 66.6 ($CH_2$). Anal. Calcd for $C_5H_9BrO_2$: C, 33.17; H, 5.01. Found: C, 33.3; H, 5.2.

**4.2.10. 1,1-Dibromo-2,2-di(hydroxymethyl)cyclopropane (7).** *From ester **5a***. A solution of aluminium chloride (4.86 g, 36.4 mmol) in ether (15 mL) was added dropwise with stirring and cooling in an ice bath to lithium aluminium hydride (1.52 g, 40.1 mmol) and dry ether (15 mL), followed by the ester **5** (5.5 g, 18.2 mmol) in ether (10 mL). The mixture was stirred for 70 min, then the excess of lithium aluminium hydride was quenched by addition of water (1 mL), 15% aq sodium hydroxide (1 mL) and water (2 mL). The precipitate was filtered off, more water (5 mL) was added and the product was extracted with ether. The combined solution was

dried; the solvent removed to give diol **7**[17] as a colourless solid (3.0 g, 63%), mp 96–98 °C. IR ($CHCl_3$) 1040 s, 1060 s, 1240, 1380, 1420, 2890, 2960, 3040, 3610 br s $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.64 (2H, s, $CH_2$), 2.44 (2H, s, OH), 3.94 (2H, d, $J$=11.6 Hz, $CH_2$), 4.13 (2H, d, $J$=11.6 Hz, $CH_2$); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 30.8 ($CH_2$), 32.2 (C), 35.7 (C), 68.3 ($CH_2$). Anal. Calcd for $C_5H_8Br_2O_2$: C, 23.10; H, 3.10. Found: C, 23.4; H, 3.2.

*From alcohol **5b***. Methanol (10 mL), PTSA (10 mg) and the alcohol **5b** (20 mg, 0.06 mmol) were stirred at 50 °C for 6 h giving a crude product. Methanol was evaporated and the residue purified by column chromatography elution with petrol–ethyl acetate (1: 1) to give diol **7** (15 mg, 0.06 mmol, 98%). TLC, GLC and NMR of the crude product were identical to those above.

*From ester **1c***. Dry aluminium chloride (0.17 g, 1.3 mmol) in ether (8 mL) was added dropwise to a stirred suspension of lithium aluminium hydride (1.55 mL, 1.4 mmol) in ether (5 mL). The mixture was cooled in an ice bath and ester **1c** (0.2 g, 0.64 mmol) in ether (10 mL) was added dropwise and stirred for 1 h. The excess of lithium aluminium hydride was quenched by the addition of water (five drops), 15% aq sodium hydroxide (five drops), water (15 drops) and stirred for another 20 min. The precipitate was filtered off, and the resulting solution was dried and evaporated to give a residue (157 mg), containing 65% of diol **7**. It was difficult to separate the product from impurities; however, the crude material could be acylated and the resulting ester purified.

**4.2.11. Ethyl 2,2-dibromo-1-acetoxymethylcyclopropane-1-carboxylate (8a).** Acetyl chloride (1.65 mL, 23.2 mmol) was added dropwise to a solution of ester **5a** (3.5 g, 11.6 mmol) in pyridine (30 mL) and cooled in an ice bath ($T$<5 °C). The ice bath was removed and the mixture was stirred for 6 h. The excess of acetyl chloride was quenched with water. The mixture was dried, the solvent was removed under reduced pressure and the product was extracted with hexane (3×30 mL). The organic layer was then washed in turn with 10% hydrochloric acid (20 mL), water (20 mL), 10% aq sodium hydroxide (20 mL), then brine (20 mL) and dried. Removal of the solvent gave crude product (3.44 g), which was then columned using silica to give pure ester **8a** (2.45 g, 62%, $R_f$ 0.60, 4:1 hexane–ethyl acetate). IR ($CHCl_3$) 1040, 1260 s, 1380, 1740 v.s, 2980, 3030 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 1.34 (3H, t, $J$=7.3 Hz, $CH_3$), 1.94 (1H, d, $J$=8.2 Hz, $CH_2$), 2.08 (3H, s, $CH_3$), 2.48 (1H, d, $J$=8.2 Hz, $CH_2$), 4.30 (2H, q, $J$=7.3 Hz, $CH_2$), 4.31 (1H, d, $J$=11.6 Hz, $CH_2$), 4.84 (1H, d, $J$=11.6 Hz, $CH_2$); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 14.6 ($CH_3$), 21.1 ($CH_3$), 25.0 (C), 31.3 ($CH_2$), 38.1 (C), 62.8 ($CH_2$), 67.3 ($CH_2$), 167.5 (C=O), 170.8 (C=O); MS (EI) $m/z$ (%): 345 (0.5) [$M^+$], 211 (16), 205 (76), 203 (69), 177 (92), 175 (100), 158 (42), 149 (56), 147 (46), 121 (17), 119 (25), 116 (43), 113 (59), 85 (22). HRMS calcd for $^{12}C_9{}^1H_{12}{}^{79}Br_2{}^{16}O_4$ 341.9102, found 341.9127. Anal. Calcd for $C_9H_{12}Br_2O_4$: C, 31.42; H, 3.53. Found: C, 31.6; H, 3.5.

**4.2.12. 1,1-Dibromo-2,2-di(butyryloxymethyl)cyclopropane (8e).** Compound **8e** (0.69 g, 85%, $R_f$ 0.61, 4:1 hexane–ethyl acetate) was prepared in an analogous manner from diol **7** (0.53 g, 2.0 mmol) and butyryl chloride (0.63 mL, 6.0 mmol) in pyridine. IR ($CHCl_3$) 696, 995 s, 1044, 1090 s, 1172 v.s, 1253 s, 1303, 1382, 1461, 1740 v.s, 2875, 2965 s $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 0.96 (6H, t, $J$=7.3 Hz, $CH_3$), 1.68 (4H, sextet, $J$=7.3 Hz, $CH_2$), 1.75 (2H, s, $CH_2$), 2.35 (4H, t, $J$=7.3 Hz, $CH_2$), 4.25 (2H, d, $J$=11.9 Hz, $CH_2$), 4.42 (2H, d, $J$=11.9 Hz, $CH_2$); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) $\delta$ 13.6 ($CH_3$), 18.4 ($CH_2$), 29.5 (C), 30.8 ($CH_2$), 30.9 (C), 65.9 ($CH_2$), 173.2 (C=O); MS (EI) $m/z$ (%): 400 (1.5) [$M^+$], 146 (14), 145 (15), 144 (67), 143 (14), 71 (100), 66 (11), 65 (24). HRMS calcd for $^{12}C_{13}{}^1H_{21}{}^{79}Br_2{}^{16}O_4$ ($M^+$+H) 398.9807, found 398.9790; calcd for $^{12}C_{13}{}^1H_{21}{}^{79}Br^{81}Br^{16}O_4$ ($M^+$+H) 400.9786, found 400.9798; calcd for $^{12}C_{13}{}^1H_{21}{}^{81}Br_2{}^{16}O_4$ ($M^+$+H) 402.9766, found 402.9766.

**4.2.13. 1,1-Di(acetoxymethyl)-2,2-dibromocyclopropane (8f).** Acetyl chloride (1.54 g, 19.6 mmol) was added dropwise to a solution of diol **7** (1.70 g, 6.5 mmol) in pyridine (15 mL) ($T$<5 °C). The ice bath was removed and the mixture was stirred for 6 h. The excess of acetyl chloride was quenched with water (0.5 mL). The mixture was dried, evaporated under reduced pressure and the product was extracted with hexane (3×30 mL). The organic layer was washed in turn with 5% sulfuric acid (10 mL), water (10 mL), 5% aq sodium hydroxide (10 mL), then brine (10 mL) and dried. Removal of the solvent gave ester **8f** (1.66 g, 73%, $R_f$ 0.45, 4:1 hexane–ethyl acetate). IR ($CHCl_3$) 990, 1050, 1270, 1370, 1440, 1470, 1750 v.s, 2970, 3050 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 1.76 (2H, s, $CH_2$), 2.13 (6H, s, $CH_3$), 4.24 (2H, d, $J$=11.7 Hz, $CH_2$), 4.43 (2H, d, $J$=11.7 Hz, $CH_2$); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) $\delta$ 21.2 ($CH_3$), 29.9 (C), 31.2 ($CH_2$), 66.4 ($CH_2$), 171.0 (C=O); MS (EI) $m/z$ (%): 344 (1) [$M^+$], 244 (23), 242 (27), 240 (23), 212 (20), 205 (20), 203 (23), 162 (25), 161 (25), 160 (24), 133 (27), 131 (21), 117 (29), 116 (100), 115 (58), 99 (44), 98 (36), 81 (52), 74 (61). Anal. Calcd for $C_9H_{12}Br_2O_4$: C, 31.42; H, 3.53. Found: C, 31.6; H, 3.5.

**4.2.14. Ethyl 2-bromo-1-acetoxymethylcyclopropane-1-carboxylate (9) and ethyl 2-bromo-1-hydroxymethylcyclopropane-1-carboxylate (10).** An ethereal solution of methyl lithium (0.60 mL, 0.9 mmol) was added dropwise at −100 to −109 °C to ester **8a** (0.21 g, 0.6 mmol) in dry tetrahydrofuran (10 mL). The mixture was stirred for another 30 min at the same temperature and the excess of methyl lithium was quenched with water (1 mL). The layers were separated and the product was extracted twice from the aqueous layer with dichloromethane. The combined organic phase was washed with brine and dried. Removing the solvent gave crude material (0.127 g, 76%, mixture of **9** and **10** in ratio 61:39, respectively), which was then columned over silica eluting with petrol–ether (3:2) to afford compounds **9** (41.6 mg, 23%) as a mixture of cis- and trans-isomers (ratio 3:1, $R_f$ 0.63) and **10** (22.5 mg, 15%, $R_f$ 0.24) as a single isomer.

**4.2.14.1. Compound cis-9.** IR ($CHCl_3$) 860, 940, 983, 1033, 1095, 1159, 1181, 1233 s, 1314, 1339, 1370, 1446, 1738 s, 2934, 2982 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 1.31 (3H, t, $J$=7.0 Hz, $CH_3$), 1.51 (1H, dd, $J$=7.8, 6.9 Hz, $CH_2$), 1.89 (1H, dd, $J$=6.9, 5.7 Hz, $CH_2$), 2.06 (3H, s, $CH_3$), 3.16 (1H, dd, $J$=7.8, 5.7 Hz, CH), 3.99 (1H, d, $J$=12.0 Hz, $CH_2$), 4.26 (2H, q, $J$=7.0 Hz, $CH_2$), 4.61

(1H, d, $J$=12.0 Hz, $CH_2$); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 14.3 ($CH_3$), 19.9 ($CH_2$), 20.8 ($CH_3$), 22.3 (CH), 25.4 (C), 61.8 ($CH_2$), 65.1 ($CH_2$), 168.4 (C=O), 170.7 (C=O).

**4.2.14.2. Compound trans-9.** $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 1.27 (3H, t, $J$=7.0 Hz, $CH_3$), 1.89 (1H, dd, $J$=6.9, 5.7 Hz, $CH_2$), 2.08 (3H, s, $CH_3$), 3.60 (1H, dd, $J$=7.8, 5.7 Hz, CH), 4.17 (2H, q, $J$=7.0 Hz, $CH_2$), 4.42 (1H, d, $J$=12.0 Hz, $CH_2$), 4.59 (1H, d, $J$=12.0 Hz, $CH_2$).

**4.2.14.3. Compound 10.** $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 1.34 (3H, t, $J$=7.0 Hz, $CH_3$), 1.44 (1H, dd, $J$=7.6, 7.0 Hz, $CH_2$), 1.87 (1H, dd, $J$=7.0, 5.8 Hz, $CH_2$), 2.60 (1H, s, OH), 3.21 (1H, dd, $J$=7.6, 5.8 Hz, CH), 3.57 (1H, d, $J$=12.2 Hz, $CH_2$), 3.85 (1H, d, $J$=12.2 Hz, $CH_2$), 4.28 (1H, q, $J$=7.0 Hz, $CH_2$), 4.29 (1H, q, $J$=7.0 Hz, $CH_2$); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) $\delta$ 14.3 ($CH_3$), 20.3 ($CH_2$), 22.3 (CH), 32.8 (C), 61.7 ($CH_2$), 65.2 ($CH_2$), 170.4 (C=O). HRMS calcd for $^{12}C_7{}^1H_{10}{}^{79}Br^{16}O_2$ ($M^+$−OH) 204.9864, found 204.9878; calcd for $^{12}C_7{}^1H_{10}{}^{81}Br^{16}O_2$ ($M^+$−OH) 206.9844, found 206.9868.

**4.2.15. Ethyl 5-bromo-4-hydroxy-4-methyl-3-oxabicyclo[3.1.0]hexane-1-carboxylate (11a).** Butyl lithium in hexane (2.20 mL, 3.5 mmol) was added dropwise at −100 °C to −105 °C to ester **8a** (1.01 g, 2.9 mmol) in dry ether (10 mL). The cooling bath was removed immediately; the temperature was allowed to increase to 0 °C for 20 min. The excess of butyl lithium was quenched with methanol (2 mL) and hexane (10 mL) was added. The layers were separated and the product was extracted three times with dichloromethane. The combined organic layer was dried and evaporated to give crude material (0.440 g), which was columned on silica eluting with petrol–ethyl acetate (2:1) to afford compound **11a** (180 mg, 21%, $R_f$ 0.72). IR ($CHCl_3$) 882, 947, 1018, 1044, 1077, 1182, 1274, 1321, 1381, 1445, 1723 v.s, 2898, 2938, 2985, 3092, 3440 br s $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 1.31 (3H, t, $J$=6.6 Hz, $CH_3$), 1.43 (1H, d, $J$=6.0 Hz, $CH_2$), 1.53 (3H, s, $CH_3$), 1.94 (1H, d, $J$=6.0 Hz, $CH_2$), 3.04 (1H, s, OH), 3.84 (1H, d, $J$=9.1 Hz, $CH_2$), 4.26 (1H, m, $CH_2$), 4.51 (1H, d, $J$=8.8 Hz, $CH_2$); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 14.2 ($CH_3$), 21.7 ($CH_3$), 23.8 (C), 33.4 (C), 46.7 (C), 61.6 ($CH_2$), 66.2 ($CH_2$), 103.9 (C), 167.7 (C=O); MS (EI) $m/z$ (%): 265 (1) [$M^+$], 219 (13), 206 (14), 185 (14), 178 (77), 177 (16), 176 (81), 175 (25), 173 (18), 141 (15), 139 (44), 113 (21), 111 (27), 97 (100), 95 (14), 86 (16), 69 (48). HRMS calcd for $^{12}C_9{}^1H_{13}{}^{79}Br^{16}O_4$ ($M^+$+Na) 286.9895, found 286.9871.

An ethereal solution of methyl lithium (1.00 mL, 1.5 mmol) was added dropwise at −95 °C to −80 °C to **8a** (0.401 g, 1.2 mmol) in ether (10 mL). Work up as above gave crude material (0.130 g), which was columned over silica eluting with petrol–ethyl acetate (2:1) to afford compound **11a** (28 mg, 9%).

**4.2.16. Methyl 5-bromo-4-hydroxy-4-propyl-3-oxabicyclo[3.1.0]hexane-1-carboxylate (11b).** An ethereal solution of methyl lithium (6.50 mL, 9.7 mmol) was added dropwise at −100 °C to −95 °C to ester **8b** (2.78 g, 7.5 mmol) in dry ether (25 mL). The cooling bath was removed immediately, the temperature was allowed to increase to 0 °C and the mixture was stirred at this temperature for 20 min. The excess of methyl lithium was quenched with methanol (10 mL) and hexane (20 mL) was added. Work up as above gave crude material (0.63 g), which was columned over silica eluting with 2:1 petrol–ethyl acetate to give ester **11b** (0.20 g, 10%, $R_f$ 0.66), mp 79–80 °C. IR ($CHCl_3$) 858, 898, 914, 945, 1016, 1046, 1060, 1096, 1129, 1161, 1187, 1246, 1278, 1304, 1324, 1352, 1384, 1408, 1432, 1453, 1708 v.s, 2870, 2890, 2920, 2930, 2958, 3431 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 0.75 (3H, t, $J$=7.0 Hz, $CH_3$), 1.29 (1H, d, $J$=6.0 Hz, $CH_2$), 1.31–1.39 (2H, m, $CH_2$), 1.45−1.52 (2H, m, $CH_2$), 1.63–1.70 (2H, m, $CH_2$), 1.74 (1H, d, $J$=6.3 Hz, $CH_2$), 2.56 (1H, s, OH), 3.58 (3H, s, $CH_3$), 3.62 (1H, d, $J$=8.8 Hz, $CH_2$), 4.30 (1H, d, $J$=8.8 Hz, $CH_2$); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) $\delta$ 12.0 ($CH_3$), 14.3 ($CH_2$), 21.7 ($CH_2$), 32.6 (C), 35.4 ($CH_2$), 44.3 (C), 50.2 ($CH_3$), 63.9 ($CH_2$), 102.6 (C), 165.9 (C=O). Anal. Calcd for $C_{10}H_{15}BrO_4$: C, 43.03; H, 5.42. Found: C, 43.2; H, 5.5.

**4.2.17. 1-Bromo-5-hydroxymethyl-2-methyl-3-oxabicyclo[3.1.0]hexane-2-ol (11f) and 1-acetoxy-methyl-5-bromo-4-methyl-3-oxabicyclo[3.1.0]hexane-4-ol (11h).** An ethereal solution of methyl lithium (5.48 mL, 8.2 mmol) was added dropwise at −105 °C to −90 °C to ester **8f** (2.18 g, 6.3 mmol) in dry ether (20 mL). The cooling bath was removed immediately; the temperature was allowed to increase to 0 °C for another 20 min. The excess of methyl lithium was quenched with satd aq ammonium chloride (4 mL). The organic layer was separated; the product was extracted with ether (20 mL) and dried. Removing the solvent gave crude material (1.64 g), which was then columned over silica eluting with petrol–ethyl acetate (2:1) to afford compounds **11f** (0.29 g, 21%) and **11h** (0.61 g, 37%, $R_f$ 0.24).

**4.2.17.1. Compound 11f.** Mp 115–117 °C. IR ($CHCl_3$) 870, 897, 925, 996, 1044, 1056, 1071, 1159, 1214, 1326, 1366, 1421, 2863, 2942, 2974, 2994, 3361 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 1.07 (1H, d, $J$=6.0 Hz, $CH_2$), 1.19 (1H, d, $J$=6.0 Hz, $CH_2$), 1.51 (3H, s, $CH_3$), 2.89 (1H, s, OH), 3.74 (1H, d, $J$=12.2 Hz, $CH_2$), 3.78 (1H, d, $J$=8.5 Hz, $CH_2$), 3.98 (1H, s, OH), 4.07 (1H, d, $J$=12.2 Hz, $CH_2$), 4.28 (1H, d, $J$=8.5 Hz, $CH_2$); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) $\delta$ 23.0 ($CH_3$), 23.8 ($CH_2$), 35.9 (C), 46.3 (C), 63.9 ($CH_2$), 68.5 ($CH_2$), 105.0 (C). HRMS calcd for $^{12}C_7{}^1H_{10}{}^{79}Br^{16}O_2$ ($M^+$−OH) 204.9864, found 204.9850; calcd for $^{12}C_7{}^1H_{10}{}^{81}Br^{16}O_2$ ($M^+$−OH) 206.9844, found 206.9832. Anal. Calcd for $C_7H_{11}BrO_3$: C, 37.69; H, 4.97. Found: C, 37.9; H, 4.9.

**4.2.17.2. Compound 11h.** Mp 59–62 °C. IR ($CHCl_3$) 860, 914, 951, 984, 1011, 1049, 1076, 1118, 1172, 1270, 1328, 1368, 1414, 1709 v.s, 2859, 2938, 2962, 2994, 3079, 3406 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 1.27 (1H, d, $J$=6.3 Hz, $CH_2$), 1.32 (1H, d, $J$=6.3 Hz, $CH_2$), 1.59 (3H, s, $CH_3$), 2.16 (3H, s, $CH_3$), 2.97 (1H, s, OH), 3.88 (1H, d, $J$=8.8 Hz, $CH_2$), 4.16 (1H, d, $J$=8.8 Hz, $CH_2$), 4.40 (1H, d, $J$=12.3 Hz, $CH_2$), 4.44 (1H, d, $J$=12.3 Hz, $CH_2$); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 18.6 ($CH_3$), 19.4 ($CH_3$), 20.4 ($CH_2$), 28.9 (C), 42.8 (C), 62.8 ($CH_2$), 66.1 ($CH_2$), 101.8 (C), 168.9 (C=O). HRMS calcd for $^{12}C_9{}^1H_{14}{}^{81}Br^{16}O_4$ ($M^+$+H) 267.0055, found 267.0043. Anal. Calcd for $C_9H_{13}BrO_4$: C, 40.78; H, 4.94. Found: C, 40.7; H, 4.8.

An ethereal solution of methyl lithium (1.79 mL, 2.7 mmol) was added dropwise at −100 °C to −85 °C to ester **8f**

(0.71 g, 2.1 mmol) in dry ether (10 mL). The cooling bath was removed immediately; the temperature was allowed to reach 0 °C for 20 min. The excess of methyl lithium was quenched by methanol (1 mL) and hexane (10 mL) was added. Work up as before gave compound **11f** (0.32 g, 69%, $R_f$ 0.23, 4:1.5 hexane–ethyl acetate).

**4.2.18. 1-Bromo-2-hydroxymethyl-2-(butyryloxymethyl)cyclopropane (12).** An ethereal solution of methyl lithium (0.40 mL, 0.6 mmol) was added dropwise at −100 °C to −109 °C to ester **8e** (0.20 g, 0.5 mmol) in tetrahydrofuran (10 mL) and the mixture was stirred for 30 min at that temperature and the excess of methyl lithium was quenched with water (2 mL). The layers were separated and the product was extracted twice with dichloromethane. The combined organic phase was washed with brine, dried and evaporated to give crude material (0.12 g), which was then columned on silica eluting with petrol–ether (1:1) to afford compound **12** (30 mg, 24%) as the mixture of cis- and trans-isomers (ratio 7:1, respectively, $R_f$ 0.36). For cis-/trans-**12**: IR ($CHCl_3$) 988, 1045, 1091, 1179, 1257, 1381, 1460, 1732 s, 2876, 2963, 3424 br s $cm^{-1}$; Found: 250.0216 (98.61). $^{12}C_9{}^1H_{15}{}^{79}Br^{16}O_3$ requires 250.0205. For cis-**12**: $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.90 t (3H, $J$=7.3 Hz, $CH_3$), 1.20 (1H, t, $J$=7.6 Hz, $CH_2$), 1.60–1.75 (3H, m, $CH_2$), 2.10 (1H, s, OH), 2.30 (2H, t, $J$=7.3 Hz, $CH_2$), 2.96 (1H, dd, $J$=7.6, 4.6 Hz, CH), 3.36 (1H, d, $J$=11.6 Hz, $CH_2$), 3.49 (1H, d, $J$=11.6 Hz, $CH_2$), 4.18 (1H, d, $J$=12.1 Hz, $CH_2$), 4.45 (1H, d, $J$=12.1 Hz, $CH_2$); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 13.7 ($CH_3$), 18.4 ($CH_2$), 18.5 ($CH_2$), 23.6 (CH), 26.9 (C), 36.1 ($CH_2$), 64.9 ($CH_2$), 66.2 ($CH_2$), 174.3 (C═O). For trans-**12**: $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 2.25 (2H, d, $J$=7.3 Hz, $CH_2$), 2.99 (1H, dd, $J$=7.6, 4.6 Hz, $CH_2$), 3.61 (1H, d, $J$=11.6 Hz, $CH_2$), 3.87 (1H, d, $J$=11.6 Hz, $CH_2$), 3.91 (1H, d, $J$=12.1 Hz, $CH_2$), 4.21 (1H, d, $J$=12.1 Hz, $CH_2$).

**4.2.19. Dimethyl 2-acetyl-2-bromocyclopropane-1,1-dicarboxylate (13).** Water (4 mL), periodic acid (1.79 g, 7.8 mmol) and ruthenium trichloride hydrate (10 mg) were added to alcohol **11f** (0.25 g, 1.1 mmol) in carbon tetrachloride (4 mL) and acetonitrile (4 mL). The mixture was refluxed for 12 h. Water (10 mL) was added. The water layer was extracted with ether (4×25 mL) and the combined organic layer was washed with water (2×20 mL), dried, concentrated to ca. 5 mL and a solution of diazomethane in ether was added (8 mL). The mixture was stirred for 12 h and then evaporated. Chromatography on silica eluting with petrol–ethyl acetate (3:1) gave ester **13** (98 mg, 31%, $R_f$ 0.45). IR ($CHCl_3$) 889, 926, 980, 1059, 1125, 1202, 1256, 1308, 1355, 1439, 1458, 1744, 2956, 3015 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 2.10 (1H, d, $J$=7.0 Hz, $CH_2$), 2.42 (1H, d, $J$=7.0 Hz, $CH_2$), 2.52 (3H, s, $CH_3$), 3.72 (3H, s, $CH_3$), 3.86 (3H, s, $CH_3$); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) $\delta$ 25.1 ($CH_2$), 27.9 ($CH_3$), 40.9 (C), 43.2 (C), 53.3 ($CH_3$), 53.5 ($CH_3$), 164.9 (C═O), 166.0 (C═O), 197.7 (C═O); MS (EI) $m/z$ (%): 249 (13), 248 (16), 247 (14), 246 (15), 217 (21), 215 (23), 199 (100), 167 (40), 157 (46), 125 (69). HRMS calcd for $^{12}C_9{}^1H_{11}{}^{79}Br^{16}O_5$ ($M^+$+H) 277.9790, found 277.9790.

**4.2.20. Ethyl, methyl 2-acetyl-2-bromocyclopropane-1,1-dicarboxylate (14).** Water (3 mL), periodic acid (1.55 g, 6.8 mmol) and ruthenium trichloride hydrate (20 mg) were added to ester **11a** (0.12 g, 0.4 mmol) in carbon tetrachloride (3 mL) and acetonitrile (3 mL). The mixture was refluxed for 50 h and then water (10 mL) was added. The layers were separated and the water layer was extracted with ether (3×20 mL). The combined organic layer was washed with water (20 mL), dried, concentrated to ca. 5 mL and a solution of diazomethane in ether added (3 mL). The mixture was stirred for 12 h and then evaporated. Chromatography on silica eluting with petrol–ethyl acetate (4:1) gave ester **14** (50 mg, 38%, $R_f$ 0.55). IR ($CHCl_3$) 858, 905, 979, 1012, 1065, 1125, 1240, 1286, 1360, 1437, 1732 v.s, 2849, 2907, 2959, 2984, 3098 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 1.33 (3H, t, $J$=7.0 Hz, $CH_3$), 2.09 (1H, d, $J$=6.7 Hz, $CH_2$), 2.40 (1H, d, $J$=6.7 Hz, $CH_2$), 2.53 (3H, s, $CH_3$), 3.72 (3H, s, $CH_3$), 4.32 (2H, q, $J$=7.0 Hz, $CH_2$); $^{13}C$ NMR (62.9 MHz, $CDCl_3$) $\delta$ 14.1 ($CH_3$), 24.9 ($CH_2$), 27.9 ($CH_3$), 41.0 (C), 43.2 (C), 53.2 ($CH_2$), 62.8 ($CH_2$), 164.4 (C═O), 166.1 (C═O), 197.8 (C═O).

### 4.3. X-ray analysis of ester (1a)

Formula: $C_{13}H_{20}Br_2O_4$. Unit cell parameters: $a$ 9.194(8), $b$ 9.380(6), $c$ 10.360(7); $\alpha$ 86.30(5), $\beta$ 84.16(6), $\gamma$ 66.09(6); space group $P$-1. Selected bond lengths (Å) and bond angles (degree) were presented: $C^1$–$C^2$ 1.516(43), $C^1$–$C^3$ 1.525(38), $C^2$–$C^3$ 1.484(29), $C^1$–$C^7$ 1.511(23), $C^{10}$–$C^{11}$ 1.509(46), $Br^4$–$C^2$ 1.908(46), $O^8$–$C^7$ 1.200(37), $O^9$–$C^7$ 1.327(39), $O^9$–$C^{10}$ 1.485(18); $C^2C^3C^1$ 60.50(44), $C^2C^1C^3$ 58.42(47), $C^3C^2C^1$ 61.08(44), $C^6C^1C^7$ 117.01(51), $C^7C^1C^2$ 115.91(54), $C^7C^1C^3$ 117.34(57), $C^3C^2Br^4$ 116.56(47), $C^1C^2Br^4$ 116.88(48), $Br^4C^2Br^5$ 110.58(34), $O^8C^7O^9$ 126.12(52), $C^7O^9C^{10}$ 121.38(47), $O^8C^7C^1$ 123.00(52), $O^9C^7C^1$ 110.88(51), $O^9C^{10}C^{11}$ 109.42(48), $C^{12}C^{10}C^{11}$ 110.41(60). The complete set of crystallographic data was deposited at the Cambridge Crystallographic Data Centre (entry no. CCDC 283250).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## Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.04.104.

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