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Some Diastereoselective Radical Reactions of Substituted 1,3-Dioxolan-4-ones

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Dedicated with affection and respect to Professor Sir Derek Barton on the occasion of his 75th birthday

Abstract: The radical **3**, generated (i) from reactions of 5-substituted 2-*tert*-butyl-1,3-dioxolan-4-ones with *N*-bromosuccinimide, (ii) from related bromo compounds by reaction with tributylstannane or with allyltributyltin, and (iii) by radical addition to 5-methylene-1,3-dioxolan-4-one, undergoes carbon-bromine, carbon-hydrogen, and carbon-carbon bond formation trans to the *tert*-butyl group with moderate to high diastereoselectivity

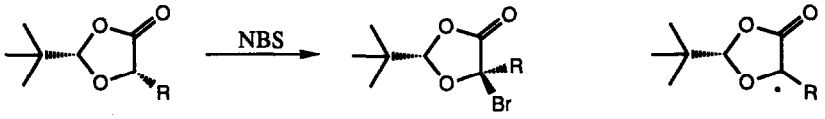
The rational exploitation of the synthetic potential of organic free radical reactions requires the identification and precise definition of those factors affecting their chemo-, regio-, and diastereo-selectivity. The behaviour of highly functionalised radicals is of especial interest, not only because of the information provided about substituent effects on radical stability and reactivity, but also because of the opportunity for further synthetic elaboration that the functionality bestows upon the products. In this paper we describe some reactions involving the intermediacy of radicals of the general type **3** derived from 5-substituted-1,3-dioxolan-4-ones. Such species are significant because of their potential for use in the development of enantioselective routes to α-hydroxy acids.[2] Furthermore, their behaviour may afford insights into the unresolved question of whether captodative substitution of a carbon-centred radical affects its reactivity.[3] Previous ESR studies of substituted dioxolanyl radicals such as **3** showed that there is extensive delocalisation of the unpaired electron, but that this appeared not to affect the ease of their formation.[4] Similarly, in the present work we find no behaviour explicitly attributable to the captodative effect, although the moderate to good diastereoselectivity of many of the reactions may reflect, in part, the enhanced stability of the intermediate radicals by comparison with unsubstituted alkyl radicals.[5]

Results

Radical bromination of substituted 1,3-dioxolan-4-ones

The bromo-compounds required for various aspects of this work were prepared by interaction of the appropriate dioxolanones with *N*-bromosuccinimide (NBS). Such reactions are highly regio- and stereo-selective.[6] Thus, the racemates of **1a** and **1b**[7] reacted cleanly and in excellent yield to give only **2a** and **2b** respectively. The reaction of the dioxolanone **1c** with NBS has been reported to give a mixture containing both bromination and dehydrobromination products,[8] but in our hands the usual treatment with NBS of the

diastereomeric mixture of dioxolanes derived from racemic malic acid gave only (±)-**2c** the assignment of stereochemistry to which is based on comparison of its ^{1}H NMR spectrum with those of other bromodioxolanones.[9]



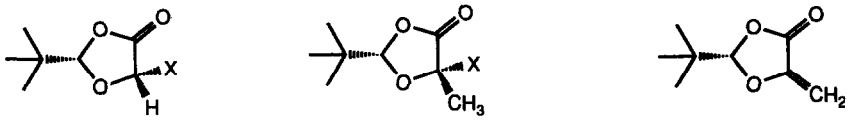
1a, R = H
1b, R = CH_3
1c, R = CH_2CO_2H

2a, R = H
2b, R = CH_3
2c, R = CH_2CO_2H

3

The high selectivity of the bromination reactions was confirmed by careful ^{1}H NMR examination of the reaction mixtures which failed to detect other possible isomers. Clearly, the reaction mechanism involves hydrogen-atom abstraction exclusively from the 5-position of the substrates to afford the corresponding radicals of type **3**. Although essentially the same outcome was observed whether the reaction was conducted in solvents (CH_2Cl_2, CH_3CN) or under conditions (5-10 molar equivalents of 1,2-dichloroethylene) thought to favour the intermediacy of succinimidyl radicals, or in carbon tetrachloride solvent, which favours the intermediacy of bromine atoms,[10] we consider that the brominations conducted under our standard conditions all involved bromine atom chains

The relative stereochemistry of **2b** has been previously established.[6] In further confirmation, S_N2 substitution of the racemate of **2b** with *p*-chlorothiophenolate anion gave the sulfide (±)-**5a**, the stereochemistry of which was tentatively assigned by 1-D nOe experiments and confirmed by X-ray crystallography.[11] Similar treatment of (±)-**2a** gave mainly (±)-**4** but some of its *trans*-isomer was also detected. The reaction of (±)-**2b** with sodium phenylselenate gave (±)-**5b** as the sole detectable product.



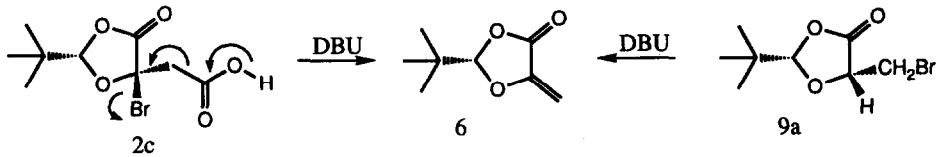
4, X = *p*-ClC_6H_4S

5a, X = *p*-ClC_6H_4S
5b, X = C_6H_5Se

6

Preparation of 2-tert-*butyl-5-methylene-1,3-dioxolan-4-one*

Three different methods were employed for the preparation of the methylene compound **6**. The first involved dehydrobromination of (±)-**2b** with DBU as described by Seebach[6] to give (±)-**6** in good yield. In a second approach to **6** treatment of the bromo compound (±)-**2c** with a slight excess of DBU in benzene in the usual way gave both the unsaturated acid (±)-**7**[8] and the methylene compound (±)-**6** With slightly less base only the latter was formed, arising presumably from decarboxylative dehydrobromination (Scheme 1).

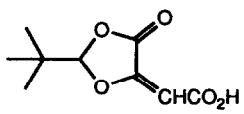


2c 6 9a

Scheme 1

The methylene compound **6** was also formed when **2c** was treated with potassium carbonate in the presence of 18-crown-6 as catalyst. The optically active *cis*-(2*S*,5*S*)-diastereomer **1c** was thus converted *via* its bromo derivative into the pure (2*S*)-enantiomer of **6** with $[\alpha]_D^{22}$ = -15.1° in $CHCl_3$ (lit.$[\alpha]_D^{20}$ = -14.9°).[12] Similarly, the *trans*-(2*R*,5*S*)-diastereomer of **1c** gave the pure (2*R*)-enantiomer of **6**[13] with $[\alpha]_D^{22}$ = +15.3°.

The third method of preparation of **6** involved the prior conversion of (±)-**1c** into its Barton ester (±)-**8**. Decomposition of (±)-**8** in bromotrichloromethane then afforded the bromo compound, (±)-**9a**, treatment of which with DBU afforded the methylene compound (±)-**6**. The configuration at C-2 is maintained throughout the reaction sequence. Thus, the optically active (2*S*) enantiomer of **6** ($[\alpha]_D^{23}$ = -14.8° in $CHCl_3$) was obtained when the *cis*-(2*S*,5*S*)-dioxolanane **1c** was used as starting material. Similar treatment of the Barton ester of the (±)-*trans* isomer of **1c** also gave (±)-**6** in moderate overall yield. Since the *trans*-(2*R*,5*S*) enantiomer of **1c** is readily available,[14] this reaction should provide a convenient route to the (2*R*)-enantiomer of **6.**



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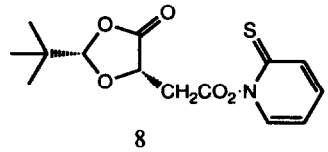

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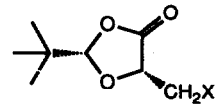


9a, X = Br
9b, X = S-2-pyridyl

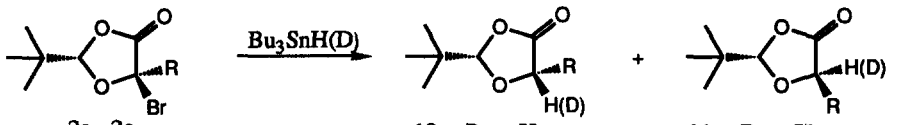
The availability of the Barton ester **8** allowed some of the other typical reactions of this type of compound[15] to be studied. Thus, UV irradiation of (±)-**8** in benzene in the absence of other reactants proceeded in the usual way to afford the *cis*-sulfide (±)-**9b**. As expected, treatment of (±)-*trans*-isomer of the Barton ester **8** with tributylstannane gave solely the *trans*-isomer of (±)-**1b**. Repetition of the reaction with the Barton ester of the *cis*-(2*S*,5*S*)-dioxolanone **1c** derived from (*S*)-malic acid, afforded the *cis*-(2*S*,5*S*)-dioxolanone **1b** in high optical purity: $[\alpha]_D^{23}$ + 44.6° in $CHCl_3$ (*cf.*$[\alpha]_D^{20}$ + 44.8° in $CHCl_3$).[14]

The methods described above for preparation from malic acid of the methylene compound **6** and the diastereomers of the methyl-dioxolanone **1b**, either as racemates or as pure enantiomers, offer simple practical alternatives to the usual methods. The literature procedures[14] involve the initial conversion of lactic acid into a mixture of diastereomeric dioxolanones, the separation of which requires a technically difficult crystallisation of the lower melting isomer at -70°C. Fortunately, the diastereomeric dioxolanes formed from malic acid are solids at ordinary temperatures, and can be readily separated and purified by crystallisation.[14] Since reactions of the Barton ester proceed without any loss of configurational integrity at C-2 or C-5, the use of pure diastereomers derived from (*S*)-malic acid ensures the formation of enantiomerically pure products.

Reactions of bromodioxolanones with tributylstannane

The bromination reactions described above demonstrate that radicals of type **3** undertake bromine-atom transfer with very high diastereoselectivity. The reduction of **2a**, **2b** and **2c** with tributylstannane allows the diastereoselectivity of hydrogen-atom transfer to radicals of the same type (**3**) to be assessed. The reactions were conducted under standard conditions with a slight molar excess of the stannane (or deuteride in the case of **2a**) in benzene, and were initiated thermally with AIBN at 80°C or photochemically at 10°C. The diastereoselectivities of the reactions, which proceeded in good yield, were estimated by ^1H or ^2H NMR spectroscopy using authentic compounds for reference. The results (see Table) show that hydrogen-atom transfer from Bu_3SnH, like bromine-atom transfer from NBS, occurs preferentially on the face of the

intermediate radical, **3**, trans to the bulky *tert*-butyl group. However, the diastereoselectivity of the stannane reduction is a good deal less than that for bromination.



2a - 2c

10a, R = H
10b, R = CH_3
10c, R = CH_2CO_2H

11a, R = H
11b, R = CH_3
11c, R = CH_2CO_2H

Table *Products and ratios of yields from reactions involving the intermediacy of the radical* **3**

Entry	Substrate	Reagent	Temp./°C	Products	Ratio of yields
1	**1a**	NBS	*ca* 80	**2a** (96%)	–[a]
2	**1b**	NBS	*ca* 80	**2b** (95%)	–[a]
3	**1c**	NBS	*ca* 80	**2c** (92%)	–[a]
4	**2a**	Bu_3SnD	80	**10a** : **11a**	3 : 1
5	**2a**	Bu_3SnD	10	**10a** : **11a**	6 : 1
6	**2b**	Bu_3SnH	80	**10b** : **11b**	7 : 1
7	**2b**	Bu_3SnH	10	**10b** : **11b**	11 : 1
8	**2c**	Bu_3SnH	80	**10c** : **11c**	8 : 1
9	**6**	$PhCH_2I/Bu_3SnH$	*ca* 23	**12a** : **13a**	6 : 1
10	**6**	$PhCH_2CH_2I/Bu_3SnH$	*ca* 23	**12b** : **13b**	7 : 1
11	**6**	$c\text{-}C_6H_{11}HgCl/NaBH_4$	*ca* 23	**12c** : **13c**	>7 : 1
12	**2a**	$Bu_3SnCH_2CH{=}CH_2$	*ca* 23	**14a** : **15a**	2 : 1
13	**2b**	$Bu_3SnCH_2CH{=}CH_2$	*ca* 23	**14b** : **15b**	7 : 1
14	**2a**	$CH_2{=}CHCO_2Me/Bu_3SnH$	*ca* 23	**16a** : **17a**[b]	4 : 1
15	**2b**	$CH_2{=}CHCO_2Me/Bu_3SnH$	*ca* 23	**16b**[b]	–[a]

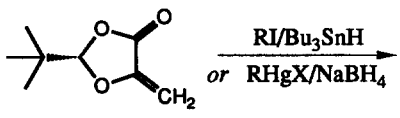
[a] Only one isomer was detected in the product mixture.

[b] The products of direct reduction (*i.e.* **1a**, **1b**) were also formed.

Radical addition to the methylenedioxolanone, 6

Although it has been claimed that captodatively substituted olefins react particularly readily with carbon-centred radicals,[16] the rates of intramolecular addition in appropriately constituted radicals do not exhibit, to any marked degree, the putative synergistic effect.[17] Nevertheless, when methyl or *tert*-butyl radicals were generated in the ESR cavity in the presence of **6**, strong spectra were recorded for the appropriate adduct radicals: **3** (R = CH_3CH_2) *a*-H_β = 12.45, 13.52; *a*-H_γ = 9.25 G; **3** (R = Bu^tCH_2) *a*-H_β = 11.23, 9.02; *a*-H_γ = 9.40 G. Encouraged by this observation, we examined the addition to **6** of radicals generated from alkylmercury halides[18] or by interaction of alkyl iodides with tributylstannane. Both methods gave disappointing yields; major experimental problems arose from the propensity of **6** to undergo polymerisation, and, in the case of reactions involving the stannane, from the difficulty of separating products from tin compounds. Nevertheless, the results (Table) show the reaction to be moderately selective. The

relative yields of products were determined by integration of the signals in the δ 4 - 5 region of the ^{1}H NMR spectra. For most 2,5-disubstituted dioxolanones the C-2 proton in the *cis*-isomer resonates at lower field than does that in the *trans*.[19] For example, (±)-**12c** has a resonance at δ 4.31; the corresponding proton in the *trans*-isomer resonates at δ 4.42. The results (Table) show the reaction to be moderately selective.

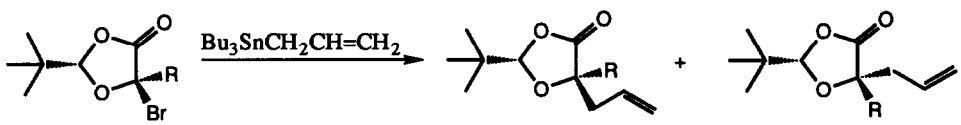


6

12a, R = $PhCH_2$ **13a**, R = $PhCH_2$
12b, R = $PHCH_2CH_2$ **13b**, R = $PHCH_2CH_2$
12c, R = *c*-C_6H_{13} **13c**, R = *c*-C_6H_{13}

Reactions of bromodioxolanones with allyltributyltin

The aim of these experiments was to compare the diastereoselectivity of carbon-carbon bond formation by radicals of type **3** with that of atom-transfer processes. In a trial experiment 5-bromo-1,3-dioxolan-4-one underwent smooth allylation in good yield (75%). The reactions of the bromo compounds (±)-**2a** and (±)-**2b** were conducted with a slight excess of allyltributyltin in benzene at 20-25°C under UV irradiation. The relative yields of the products **14a** : **15a**, and **14b** : **15b** (Table) were determined by gas chromatography and ^{1}H NMR spectroscopy. Stereochemical assignments were made by application of 1-D nOe and 2-D noesy techniques. The results indicate that the allylation reaction is diastereoselective with the new bond being formed to trans to the bulky *tert*-butyl group in the intermediate radicals of type **3**.

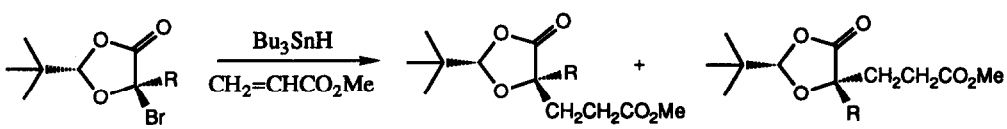


2a, 2b

14a, R = H **15a**, R = H
14b, R = CH_3 **15b**, R = CH_3

Reactions of bromodioxolanones with methyl acrylate

The mechanism of the reactions of the bromo compounds (±)-**2a** and (±)-**2b** with methyl acrylate and tributylstannane involves the intermediacy of the corresponding radicals of type **3** which then undertake addition to the double bond of the ester. Hydrogen atom transfer from the stannane to the adduct radicals completes the process to form the products. The yields were low (20-40%) because hydrogen-atom transfer from the stannane to the intermediate radicals **3** competes directly with the addition step. Nevertheless, the results (Table) are clear cut. They show that carbon-carbon bond formation occurs preferentially trans to the *tert*-butyl group in the radicals **3**.[20]

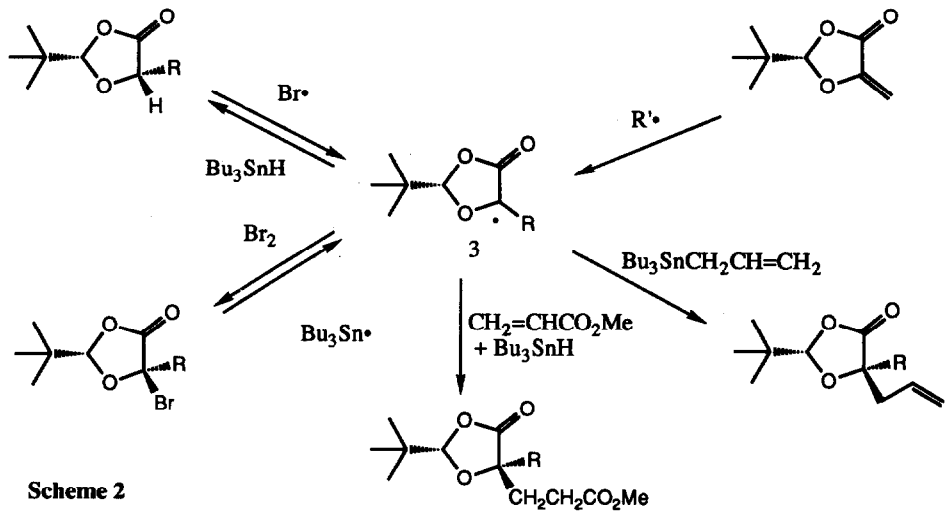


6

16a, R = H **17a**, R = H
16b, R = CH_3 **17b**, R = CH_3

Discussion

Except for the dehydrobrominations leading to **6** and for the preparation of **8** and its transformations, all of the reactions described above involve the intermediacy of substituted dioxolanonyl radicals **3**. The reaction mechanisms are summarised in Scheme 2 in which only the major diastereomer of each product is shown. The reactions of **3** fall into two general categories: (i) those involving atom transfer, *i.e.* bromination (Table entries 1-3), stannane reductions (entries 4-8), and additions to **6** (entries 9-11), and (ii) those involving addition of **3** to double bonds, *i.e.* reactions with allyltributyltin (entries 12 and 13), and Giese addition to methyl acrylate (entries 14 and 15). All of these processes are diastereoselective in the same sense; in each case the new bond to **3** is formed trans to the *tert*-butyl group.



Scheme 2

The degree of selectivity depends on the nature both of the reagent and of the substituent on **3**. In those cases where both possible diastereomers are formed the selectivity seems to increase with increase in the size of R (*cf* entries 4, 6, and 8, and entries 12 and 13). The relationship between the nature of the reagent and stereoselectivity is less obvious. It is very high for bromination but less so for C-H or C-C bond formation. Since both the reduction of bromodioxolanones and the additions to **6** have hydrogen atom transfer from stannane in common as the second step, their diastereoselectivities should be the same. This was found to be essentially so (*cf* entries 9-11 with entries 6-8).

The full identification of the factors influencing the diastereoselectivity of the reactions of **3** awaits the outcome of theoretical calculations now in progress. However, it appears that product stability cannot be important since the *cis* forms of 2,5-disubstituted dioxolanones are more stable than the *trans*. Semi-empirical calculations (AM1-UHF)[22] indicate that the radical **3** (R = H) has both the ring and the radical centre planar. Approach of a reagent towards the face bearing the bulky *tert*-butyl group would clearly be severely sterically hindered. If, as we believe, bromination proceeds by the bromine atom mechanism, and if increasing bulk of the substituent R enhances the stability of **3**, then all of the reactions appear to conform to the principle that selectivity increases with decreasing exothermicity. However, this conflicts with the view that the transition structures for weakly exothermic reactions should reflect in part the stabilities of the products. On this ground bromination would be expected to afford significant yields of the *cis* products.

The specificity of the brominations gives rise to another question. Why is this reaction confined solely to the 5-position of **1a** and **1b**, when attack by *tert*-butoxyl radicals on the same substrates occurs at both positions? The difference between the behaviour of the two reagents probably reflects both the greater electrophilicity of *tert*-butoxyl radicals by comparison with bromine atoms and the greater exothermicity of its hydrogen abstraction reactions. The influence of polar factors on reactions of *tert*-butoxyl radicals with dioxolanes has been previously discussed.[4]

Although the interplay of polar, steric, stereoelectronic and thermochemical factors has yet to be fully unravelled, it is clear that some of the reactions of substituted dioxolanones are sufficiently diastereoselective to be synthetically useful. In particular the ready availability of the enantiomers of the methylene compound **6** from (*S*)-malic acid make it an attractive intermediate for the enantioselective synthesis of α-hydroxy acids.

Experimental

Melting points were determined on a Reichert hot-stage microscope and are uncorrected. Electron impact mass spectra (MS) were measured on a VG Micromass 7070F mass spectrometer operating at 70 eV. High resolution mass spectra (exact mass) were determined on an AEI MS 902 mass spectrometer. Infrared (IR) spectra were measured on a Perkin-Elmer 683 infrared spectrophotometer. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter (Na lamp at 589 nm) in $CHCl_3$ at 23°C. Gas liquid chromatography (GC) was carried out on Varian 3400 and Varian 6000 gas chromatographs equipped with flame ionization detectors. ^1H and ^{13}C NMR spectra were recorded on either one of the following spectrometers: JEOL FX-200 (^{13}C NMR at 50.1 MHz); Varian XL-200 (^{13}C NMR at 50.3 MHz); Gemini-300 (^{13}C NMR at 75 MHz): Varian VXR-300 (^{13}C NMR at 75 MHz). ^2H NMR spectra were recorded on a Varian VXR-300 spectrometer at 42.4 MHz.on solutions in benzene or $CHCl_3$ with a trace of deuterated solvent as reference. Electron spin resonance spectra were recorded on a Bruker 200D-SRC EPR spectrometer. Elemental analyses were carried out by the ANU Analytical Service Unit.

Nuclear Overhauser enhancement (nOe) experiments (1D and 2D) were conducted on a Varian VXR-500. 1D nOe data were obtained in the interleave mode by taking difference spectra with data sets using an on resonance and an off resonance selective pre-irradiation pulse. Two dimensional noesy spectra were acquired in the pure absorption mode with 2048 data points in the t_2 dimension stored in alternate blocks and 128 FID's in the t_1 dimension. FID's were apodized by either a 45° sine bell or a 45° squared sine bell in the first dimension and by gaussian multiplication in the second dimension. Samples were made up in $CDCl_3$ in special Wilmad Taperlok NMR tubes and were degassed by freeze-thaw methods.

The dioxolanones **1a**, **1b** and its racemate, and **1c** and its racemate and *trans*-isomer,were prepared as previously described.[6,12,14,23]

(2*R*5*R*,2*S*5*S*)-5-Bromo-2-(1,1-dimethylethyl)-1,3-dioxolane-4-one [(±)-2a]. The dioxolanone (±)-**1a** (3.0 g, 20.8 mmol), NBS (4.1 g, 23.0 mmol) and AIBN were heated in dry carbon tetrachloride under reflux (N_2) for 3 h. The mixture was then cooled to 0°C, the succinimide was removed by filtration, and the solvent was evaporated under reduced pressure. Purification of the crude product by Kugelrohr distillation at 90°C/80 mm Hg gave (±)-**2a** (4.46 g, 96%) as a white solid, mp 47-49°C; ^1H NMR ($CDCl_3$) δ 1.00 (s, 9H), 5.38 (s, 1H), 6.48 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 23.25, 33.81, 73.86, 109.76, 165.94; IR (CCl_4) 2980, 1830, 1300, 1220, 1205, 1170, 1090, 960, 890 cm^{-1}; MS (%) 167 (4.3), 165 (4.3), 143 (12.9), 87 (100.0); exact mass calcd. for $C_7H_{11}O_3$ (M^+-Br) 143.0708, found 143.0708.

(*2R5R,2S5S*)-5-Bromo-2-(1,1-dimethylethyl)-5-methyl-1,3-dioxolan-4-one [(±)-2b]. Treatment of (±)-**1b** with NBS as described above gave (±)-**2b** (95%) with spectral characteristics identical to those previously recorded.[6]

(*2R5R,2S5S*)-5-Bromo-2-(1,1-dimethylethyl)-4-oxo-1,3-dioxolane-5-acetic acid [(±)-2c]. The reaction of (±)-**1c** (0.99 g, 4.90 mmol) with NBS (0.97 g, 5.5 mmol), as described above gave (±)-**2c** as an unstable white solid (1.27 g, 92%) which decomposed on heating or long standing; ^{1}H NMR ($CDCl_3$) δ 1.01 (s, 9H), 3.67 (d, 2H, J = 2 Hz), 5.23 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 23.60, 33.64, 43.35, 87.08, 108.57, 166.27, 172.07; IR ($CHCl_3$) 2980, 1815, 1725, 1480, 1410, 1298, 1170, 1055 cm^{-1}; MS (%) 156 (2.7), 99 (7.5), 86 (7.8), 71 (7.8), 57 (100.0); exact mass calcd. for $C_8H_{12}O_3$ (M^+-Br-COOH) 156.0786. found 156.0785.

(*2R5S,2S5R*)-2-(1,1-Dimethylethyl)-5-(*p*-chlorophenylthio)-1,3-dioxolan-4-one [(±)-4]. DBU (0.76 g, 5.25 mmol) was added to a solution of *p*-chlorothiophenol (0.76 g, 5.3 mmol) in dry benzene and stirred for 10 min. On addition of the bromodioxolanone (±)-**2a** (1.17 g, 5.24 mmol) the reaction mixture became warm and a white precipitate formed. After being stirred for a further 3 h the reaction mixture was filtered, washed with ice-cold water, dried over sodium sulfate, and evaporated to give a mixture (7:1) of (±)-**4** and its *trans*-isomer (1.22g, 81%), crystallisation of which from hexane gave pure (±)-**4**, mp 56-57°C; ^{1}H NMR ($CDCl_3$) δ 0.83 (s, 9H), 5.10 (s, 1H), 5.50 (s, 1H), 7.23-7.50 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 23.24, 34.49, 81.47, 109.82, 128.51, 129.29, 135.72, 135.80, 168.57; IR (CCl_4) 2990, 2970, 1810, 1480, 1410, 1340, 1225, 1175, 1098, 1080, 1017, 980 cm^{-1}; Anal. calcd. for $C_{13}H_{15}ClO_3S$: C, 54.45; H, 5.27; S, 11.18; Cl, 12.36. Found: C, 54.59; H, 5.62; S, 10.81; Cl, 12.00.

(*2R5S,2S5R*)-2-(1,1-Dimethylethyl)-5-(*p*-chlorophenylthio)-5-methyl-1,3-dioxolan-4-one [(±)-5a]. Treatment of (±)-**2b** (1.33 g, 5.6 mmol) with DBU (0.85 g, 5.58 mmol) and *p*-chlorothiophenol (0.81 g, 5.60 mmol) as in the preceding experiment gave only one detectable diastereomer (de > 95%) of (±)-**5a** (1.48 g, 88%), which crystallised from ether/hexane, mp 114-115°C; ^{1}H NMR ($CDCl_3$,) δ 0.76 (s, 9H), 1.70 (s, 3H), 5.08 (s, 1H), 7.3-7.63 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 21.79, 23.24, 34.17, 87.98, 107.45, 127.07, 129.18, 136.62, 138.32, 171.66; IR (CCl_4) 2980, 2960, 1800, 1480, 1225, 1135, 1100, 1090 cm^{-1}; Anal. calcd. for $C_{14}H_{17}ClO_3S$: C, 55.90; H, 5.70; S, 10.66; Cl, 11.79. Found: C, 55.52; H; 5.61; S, 10.93; Cl, 11.50. The stereochemistry of the product was confirmed by X-ray crystallography.[11]

(*2R5S,2S5R*)-2-(1,1-Dimethylethyl)-5-methyl-5-(phenylselenyl)-1,3-dioxolan-4-one [(±)-5b]. A solution of diphenyl diselenide (208 mg, 0.67 mmol) in ethanol (5 mL) was stirred at room temperature while sodium borohydride (55 mg, 1.46 mmol) was added in small portions. After complete formation of sodium phenylselenide as indicated by the disappearance of the yellow colour, the solution was added to the bromo dioxolanone (±)-**2b** (315 mg, 1.33 mmol) in benzene (10 mL) and the mixture was stirred for 4 h. Subsequent workup and evaporation of the solvent gave as a single diastereomer (±)-**5b** (335 mg, 80%), which crystallised from ether/hexane. ^{1}H NMR ($CDCl_3$) δ 0.78 (s, 9H), 1.68 (s, 3H), 5.15 (s, 1H), 7.3-7.7 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 23.28, 23.63, 34.31, 81.41, 108.88, 126.10, 129.10, 129.64, 137.74, 173.35; Anal. calcd. for $C_{14}H_{18}O_3Se$: C, 53.68; H, 5.79; Se 25.21. Found: C, 54.09; H, 5.74; Se 25.21.

(*2R5R,2S5S*)-2-(1,1-Dimethylethyl)-5-[*N*-(2-thionopyridyloxycarbonyl)methyl]-1,3-dioxolan-4-one [(±)-8]. *N*-hydroxypyridine-2-thione (306 mg, 1.2 mol equivalent) and 4-dimethylaminopyridine (25 mg, 0.1 mol equivalent) were added to the dioxolanone (±)-**1c** (406 mg, 2 mmol) in CH_2Cl_2 (20 mL) in a flask

wrapped with aluminium foil to prevent the access of light. A solution of DCC (622 mg, 1.5 mol equivalent) in CH_2Cl_2 (10 mL) was then added slowly and the mixture was stirred overnight at room temperature. After being filtered through a short column of silica the reaction mixture was evaporated under reduced pressure to afford the light-sensitive ester (±)-**8** which was sufficiently pure (>90%) to be used in subsequent reactions without further purification; ^{1}H NMR ($CDCl_3$) δ 0.95 (s, 9H), 3.52 (dd, 1H, J = 6.7, 14.5 Hz), 3.95 (dd, 1H, J = 6.7, 14.5 Hz), 4.62 (ddd, 1H, J = 1.4, 4.6, 5.4 Hz), 5.16 (d, 1H), 7.0-8.5 (m, 4H).

***(2R5R,2S5S)*-(1,1-Dimethylethyl)-5-(2-pyridylthiomethyl)-1,3-dioxolan-4-one [(±)-9b].** A solution of the Barton ester formed from (±)-**1c** (202 mg, 1.0 mmol) in benzene was irradiated with a sunlamp until the yellow colour disappeared. The reaction mixture was then evaporated and purified by preparative TLC (ether/hexane 4:1) to give (±)-**9b** (107 mg, 40% from **1c**); ^{1}H NMR ($CDCl_3$) δ 0.92 (s, 9H), 3.50 (dd, 1H, J = 6.6, 14.5 Hz), 3.90 (dd, 1H, J = 6.6, 14.5 Hz), 4.65 (ddd, 1H, J = 1.2, 4, 6.7 Hz), 5.14 (d, 1H, J = 1.2 Hz), 7.0-8.5 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 23.33, 29.85, 34.10, 74.43, 109.38, 119.72, 122.25, 135.92, 149.18, 157.06, 171.66; IR (CCl_4) 2966, 1795, 1580, 1450, 1300, 1215, 1190, 1120, 1045, 960, 760 cm^{-1}; MS (%) 266.9 (0.6), 209.9 (5.9), 181.9 (3.1), 165.9 (2.11), 153.9 (8.0), 135.9 (21.4), 124.0 (34.8), 110.9 (100.0); exact mass calcd. for $C_{13}H_{17}NO_3S$ (M^+) 267.0929. found 267.0928; Anal. calcd. for $C_{13}H_{17}NO_3S$: C, 58.42; H, 6.41; N, 5.24; S, 11.99. Found: C, 58.67; H, 6.76; N, 5.26; S, 11.98.

(2*S*,5*R*)-2-(1,1-Dimethylethyl)-5-methyl-1,3-dioxolan-4-one (11b). The (2*S*,5*R*)-isomer of **1c** (405 mg, 2.0 mmol) was converted into its Barton ester. After the usual workup procedure, the ester was dissolved in benzene (10 mL) and refluxed overnight with Bu_3SnH (1.1 mol equivalent) and AIBN (*ca* 5 mg). Chromatography (ethyl acetate/hexane=1:9) of the crude product gave the *trans*-(2*S*,5*R*)-dioxolanone **11b** (190 mg, 60% overall) with properties identical to those previously reported.[14]

(2*S*,5*S*)-2-(1,1-Dimethylethyl)-5-methyl-1,3-dioxolan-4-one (1b). Reduction of the Barton ester derived from the (2*S*,5*S*)-dioxolanone **1c** with Bu_3SnH as in the preceding experiment gave the *cis*-(2*S*,5*S*)-dioxolanone **1b**; $[\alpha]_D^{23}$ = 44.6° ($CHCl_3$, c = 0.6); (lit.[12] $[\alpha]_D^{23}$ = 44.8° ($CHCl_3$, c = 1.8).

2-(1,1-Dimethylethyl)-5-methylene-1,3-dioxolan-4-one (6); method 1. Treatment of (±)-**2b** with DBU as previously described gave (±)-**6** with spectral data in agreement with literature values.[12]

2-(1,1-dimethylethyl)-5-methylene-1,3-dioxolan-4-one (6); method 2 The (2*S*,5*S*)-dioxolanone **1c**, $[\alpha]_D^{23}$= -2.1°,[6] (560 mg, 2.78 mmol) was converted into the (2*R*,5*R*) bromo compound as described above. DBU (~0.98 mol equivalent) was then added to the bromo compound in benzene (20 mL) and the mixture was stirred for 45 min. After being filtered through a short column of silica the solution was evaporated to give the methylene compound (2*S*)-**6** (240 mg, 55% yield); $[\alpha]_D^{23}$ = -15.1° ($CHCl_3$, c = 1.3); lit. value[12] $[\alpha]_D^{24}$= -14.9° ($CHCl_3$, c = 1.6), with spectral characteristics identical to those previously recorded.[12]

Consecutive bromination of the (2*R*,5*S*)-isomer of **1c**, $[\alpha]_D^{23}$ = +24.8°, (lit.[6] $[\alpha]_D^{23}$ = +23.1°) and treatment of the product with DBU as described in the preceding experiment gave (2*R*)-**6** $[\alpha]_D^{23}$ = +15.3° ($CHCl_3$, c = 1.5).

2-(1,1-Dimethylethyl)-5-methylene-1,3-dioxolan-4-one (6); method 3. A solution of the Barton ester formed from the (±)-*trans*-isomer of **1c** (404 mg, 2.0 mmol) and AIBN (ca 5 mg) in bromotrichloromethane (25 mL), was refluxed for 3 h after which time the ^{1}H NMR spectrum of the crude reaction

mixture showed that the reaction had proceeded cleanly (>85% purity) to give the corresponding *trans*-isomer of the bromo compound **9a**; ^{1}H NMR ($CDCl_3$) δ 0.99 (s, 9H), 3.69 (d, 2H, J = 3 Hz), 4.78 (dt, 1H), 5.51 (d, 1H, J = 1.7 Hz). Upon addition of DBU the reaction mixture became warm and a precipitate was formed. The reaction mixture was then stirred for 1 h, filtered through a short plug of silica, and concentrated under reduced pressure. Chromatography of the residue with ether/hexane (1:4) gave the pure dioxolanone (±)-**6** (170 mg, 54% from **1c**). Repetition of this procedure with the Barton ester of (2*S*,5*S*)-**1c** gave (2*S*)-**9a**; ^{1}H NMR ($CDCl_3$) δ 1.04 (s, 9H), 3.66 (dd, 1H, J = 5, 12 Hz), 3.74 (dd, 1H, J = 5, 12 Hz), 4.60 (dt, 1H, J = 1, 4 Hz), 5.22 (d, 1H, small J), from which (2*S*)-**6** was obtained; $[\alpha]_D^{23}$= -14.8° ($CHCl_3$, c = 1.3).

Reduction of bromo dioxolanones with tributylstannane or tributyltin deuteride. A solution of the bromo dioxolanone, (±)-**2a**, (±)-**2b**, or (±)-**2c** (0.44 mmol), tributyltin hydride or deuteride (1 mol equiv.) and AIBN (*ca* 2 mg)in dry benzene (2 mL) was degassed by the freeze-thaw method, and sealed in an ampoule. For reactions at 80°C, the ampoule was placed in a constant temperature bath (80°C) for 12-16 h, whereas reactions at 10°C was conducted in a constant cooling bath and the reaction mixture was irradiated with UV light for 16-24 h. On completion, the reaction mixture was immediately analysed by ^{1}H NMR spectroscopy using authentic compounds[6,9,12,14] as standards. Yields were essentially quantitative. The ratio of the isomers was determined by the integration of ^{1}H NMR and/or ^{2}H NMR spectrum. The results are given in the table.

Radical addition to (±)-6: formation of (±)-12a. A solution of benzyl iodide (925 mg, 4.25 mmol) and (±)-**6** (440 mg, 2.82 mmol) in benzene (015 mL) was degassed then irradiated with UV light at room temperature while a solution of Bu_3SnH (1.23 g, 4.25 mmol) and AIBN (40 mg) in benzene (25 ml) was added slowly with a syringe pump at the rate of 0.15 mL/min. After 8 h, the reaction mixture was evaporated and the diastereoselectivity was determined by ^{1}H NMR spectroscopy (see table). Flash chromatography (ether/hexane 1:9) of the crude product afforded a mixture of (±)-**12a** and (±)-**13a** (6:1; 105 mg, 15%) from which was isolated a sample of (±)-*cis*-2-(1,1-dimethylethyl)-5-(2-phenylethyl)-1,3-dioxolan-4-one [(±)-**12a**]; ^{1}H NMR ($CDCl_3$) δ 1.02 (s, 9H), 2.1-2.3 (m, 2H), 2.83 (t, 2H, J = 5 Hz), 4.25 (dd, 1H, J = 1, 4 Hz), 5.17 (d, 1H, J = 1 Hz), 7.3-7.4 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 23.51, 31.84, 32.44, 34.34, 74.11, 109.47, 126.26, 128.51, 140.45, 173.30; IR (neat) 2960, 2920, 2870, 1800, 1195, 1115, 1072, 970 cm^{-1}; MS (%) 191 (3.6), 157 (3.2), 117 (29.9), 91 (56.3), 77 (3.7), 57 (100.0); exact mass calcd. for $C_{11}H_{11}O_3$ (M^+-57) 191.0708. found 191.0708.

Radical addition to (±)-6: formation of (±)-12b. Repetition of the preceding experiment with 2-phenylethyl iodide gave a mixture of **12b** and **13b** (7:1; 34%) from which was obtained a sample of (±)-*cis*-2-(1,1-dimethylethyl)-5-(3-phenylpropyl)-1,3-dioxolan-4-one [(±)-**12b**]; ^{1}H NMR ($CDCl_3$) δ 0.97 (s, 9H), 1.2-1.9 (m, 4H), 2.15 (m, 2H), 4.25 (m, 1H), 5.12 (s, 1H), 7.1-7.4 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 23.41, 29.08, 30.06, 34.18, 35.29, 74.91, 109.23, 125.86, 128.30, 141.47, 173.38 ; IR (neat) 2970, 2920, 2880, 1800, 1482, 1460, 1410, 1365, 1195, 1115, 1075, 972, 698 cm^{-1}; MS (%) 262 (1.0), 205 (7.7), 157 (1.5), 117 (8.1), 77 (4.7), 57 (100.0); exact mass calcd. for $C_{12}H_{13}O_3$ (M^+-57) 205.0865, found 205.0863.

Radical addition to (±) 6: formation of (±)-12c. (a) Treatment of cyclohexyl iodide (95 mg, 0.45 mmol) and (±)-**6** (209 mg, 1.34 mmol) with Bu_3SnH (131 mg, 0.45 mmol) following the above procedure gave a mixture of (±)-**12c** and (±)-**13c** (> 7:1; 83 mg, 26%) Flash chromatography afforded the major isomer (±)-*cis*-5-cyclohexylmethyl-2-(1,1-dimethylethyl)-1,3-dioxolan-4-one [(±)-**12c**]; ^{1}H NMR ($CDCl_3$) δ 0.97 (s,

9H), 1.2-1.8 (m, 13H), 4.31 (ddd, 1H, J = 1, 4, 9 Hz), 5.13 (d, 1H, J = 1 Hz); ^{13}C NMR ($CDCl_3$) δ 23.39, 25.98, 26.05, 26.28, 32.52, 33.46, 34.19, 34.27, 38.29, 73.35, 109.33, 174.22; IR (neat) 2910, 1800, 1485, 1450, 1410, 1300, 1215, 1190, 1110, 1040, 970 cm^{-1}; Anal. calcd. for $C_{14}H_{24}O_3$: C, 69.96; H, 10.06. Found: C, 70.09; H, 10.00.

(b) A mixture of cyclohexylmercury chloride (900 mg, 2.82 mmol) and (±)-**6** (186 mg, 1.19 mmol) was stirred vigorously at room temperature while a solution of sodium borohydride (400 mg) in water (7 mL) was added dropwise over 45 min. After being stirred for a further 2 h the reaction mixture was filtered through celite, and the organic layer was separated, dried and evaporated. The diastereoselectivity was determined by ^{1}H and ^{13}C NMR spectroscopy. Chromatography (ether/hexane 1:9) of the crude product gave a mixture of (±)-**12c** and (±)-**13c** (>7:1; 94 mg, 33%)

5-(2-Propenyl)-1,3-dioxolan-4-one. A solution of the (±)-5-bromo-1,3-dioxolan-4-one (431 mg, 2.58 mmol), allyltributyltin (870 mg, 2.62 mmol) and AIBN (5 mg) in dry benzene (8 mL) was degassed, then irradiated with UV light at room temperature under argon until all the starting material was consumed. The reaction mixture was then evaporated and the residue subjected to flash chromatography to afford (±)-5-(2-propenyl)-1,3-dioxolan-4-one as an oil (248 mg, 75%); ^{1}H NMR ($CDCl_3$) δ 2.5-2.7 (m, 2H), 4.33 (t, 1H), 5.13-5.28 (m, 2H), 5.45 (s, 1H), 5.53 (br s, 1H), 5.83 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 34.63, 72.59, 94.34, 119.37, 131.34, 172.22; IR (neat) 3080, 2905, 1805, 1200, 1030, 985 cm^{-1}; Anal. calcd. for $C_6H_8O_3$: C, 56.25; H, 6.29. Found: C, 56.12; H, 5.97.

Allylation of (±)-2a. Treatment of the bromodioxolanone (±)-**2a** (940 mg, 4.2 mmol) with allyltributyltin (1.3 mL, 4.21 mmol) as described above gave a mixture of **14a** and **15a** (530 mg, 68%, see Table), flash chromatography (ether/hexane 1:9) of which gave (±)-*trans*-2-(1,1-dimethylethyl)-5-(2-propenyl)-1,3-dioxolan-4-one [(±)-**14a**] as an oil ; ^{1}H NMR ($CDCl_3$) δ 0.93 (s, 9H), 2.53 (m, 2H), 4.45 (t, 1H, J = 5 Hz)), 5.28 (s, 1H), 5.15-5.28 (m, 2H), 5.83 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 23.24, 35.57, 35.77, 74.58, 110.75, 119.57, 131.51, 172.86; IR (CCl_4) 3080, 2960, 2905, 1800, 1485, 1402, 1320, 1200, 1100, 1035, 985 cm^{-1}; Anal. calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75.. Found: C, 65.08; H, 8.89; and (±)-**15a**; ^{1}H NMR ($CDCl_3$) δ 0.95 (s, 9H), 2.49 (m, 1H), 2.65 (m, 1H), 4.31 (t, 1H), 5.11 (s, 1H), 5.15-5.23 (m, 2H), 5.80 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 23.51, 34.34, 34.87, 74.60, 109.47, 118.87, 131.86, 172.51; IR (CCl_4) 3080, 2980, 2905, 2880, 1800, 1485, 1410, 1365, 1315, 1198, 1105, 990 cm^{-1}.

Allylation of (±)-2b. Treatment of the bromo dioxolanone (±)-**2b** (1.00 g, 4.22 mmol) with allyltributyltin (1.35 mL, 4.21 mmol) as described above gave a mixture of isomers (.60 g, 72%) found by GC to contain (±)-**14b** and (±)-**15b** in the ratio 7:1. The physical data for (±)-**14b** agreed with those previously reported.[14]

Reaction of (±)-2a with methyl acrylate. A degassed solution of the bromo compound (±)-**2a** (1.00 g, 4.48 mmol) and methyl acrylate (3.86 g, 4.5 mmol) in benzene (10 mL) was irradiated with UV light at room temperature while a solution of Bu_3SnH (1.98 g, 6.8 mmol) and AIBN (40 mg) in benzene (50mL) was added with a syringe pump at the rate of 0.15 mL/min. Flash chromatography (ethyl acetate/hexane=1:9) of the crude product afforded a mixture (4:1) of (±)-**16a** and (±)-**17a** (260 mg, 25%), further purification of which gave (±)-**16a**; ^{1}H NMR ($CDCl_3$) δ 0.95 (s, 9H), 2.13 (m, 2H), 2.50 (m, 2H), 3.70 (s, 3H), 4.44 (t, 1H, J = 6 Hz), 5.29 (d, 1H, J = 1.3 Hz); ^{13}C NMR ($CDCl_3$) δ 23.08, 25.99, 29.26, 35.50, 51.69, 73.58, 110.25, 172.63, 172.78; IR (neat) 2960, 1805, 1745, 1490, 1470, 1440, 1200, 1125, 1115, 1105, 1035, 982 cm^{-1}; Anal. calcd. for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.15; H, 7.91.

Reaction of (±)-2b with methyl acrylate. Treatment of (±)-**2b** (1.83 g, 7.72 mmol) with methyl acrylate (6.6 g, 76.7 mmol) and Bu_3SnH as described in the preceding experiment gave only (±)-**16b** (.57 g, 30%) after flash chromatography (ethyl acetate/hexane 1:19); ^1H NMR ($CDCl_3$) δ 0.90 (s, 9H), 1.43 (s, 3H), 2.00 (m, 1H), 2.17 (m, 1H), 2.45 (m, 2H), 3.68 (s, 3H), 5.19 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.82, 23.09, 28.17, 30.14, 34.29, 51.70, 78.66, 108.07, 172.89, 175.04; IR (neat) 2960, 2880, 1800, 1740, 1485, 1440, 1380, 1250, 1220, 1180, 1140, 1080, 980, 915 cm^{-1}; Anal. calcd. for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 59.25; H, 8.47.

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