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Aust. J. Chem. **2003**, *56*, 861–869

Competitive Intramolecular Diels–Alder Reactions of bis-α,β-Unsaturated Ester Derivatives of Enzymatically Derived and Enantiopure *cis*-1,2-Dihydrocatechols. Enantiodivergent Synthesis of Monochiral Bicyclo[2.2.2]oct-2-enes

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bis-Crotonate and related α,β-unsaturated ester derivatives of readily available and enantiomerically pure *cis*-1,2-dihydrocatechols engage, upon heating in refluxing toluene, in two competitive intramolecular Diels–Alder reactions to give varying mixtures of chromatographically separable and pseudo-enantiomeric bicyclo[2.2.2]oct-2-enes. Such adducts, many of which have been characterized by single-crystal X-ray analysis, are likely to serve as useful building blocks in natural products synthesis.

Manuscript received: 30 April 2003.
Final version: 22 May 2003.

Introduction

Bicyclo[2.2.2]-octanes and -octenes serve as useful building blocks in the chemical synthesis of both natural and non-natural products.[1] However, developing flexible and enantioselective routes to highly functionalized derivatives of these ring systems remains a challenge.[2] In connection with several on-going projects in this laboratory, we,[3] like others,[4] have been generating such derivatives through the intermolecular Diels–Alder reaction of acetal derivatives of the enzymatically derived and enantiomerically pure *cis*-1,2-dihydrocatechols[5] with various dienophiles. Related intramolecular processes have also been investigated, although to a lesser extent, with the most notable studies having been carried out by Hudlicky's group.[6] In particular, these workers have connected, through either ether or ester linkages, a single dienophilic residue to the *cis*-1,2-dihydrocatechol core and shown that the resulting conjugate engages, under thermal conditions, in the expected cycloaddition process to generate ring-fused bicyclo[2.2.2]octenes. An interesting extension of such work would be to explore the behaviour of systems in which two potentially dienophilic moieties are attached, one through each oxygen of the *cis*-1,2-dihydrocatechol framework, since two competing Diels–Alder processes could now occur and, thereby, lead to pseudo-enantiomeric bicyclo[2.2.2]octenes. Despite the potential of such processes to provide enantiodivergent routes to the title frameworks, relevant studies have not been reported to date, perhaps because of concerns that the requisite bis-ester derivatives of the *cis*-1,2-dihydrocatechols would be prone to elimination and subsequent re-aromatization. On the basis of the foregoing, we now report on the preparation of a series of bis-α,β-unsaturated derivatives of the *cis*-1,2-dihydrocatechols (1a)–(1e), and an examination of their capacities to engage in intramolecular Diels–Alder reactions so as to produce monochiral bicyclo[2.2.2]oct-2-enes.

Results and Discussion

Preliminary studies were carried out using, as starting material, the meso-*cis*-1,2-dihydrocatechol (1a) (Diagram 1), which is obtained on a large scale by enzymatic dihydroxylation of benzene.[5] The readily derived (see Experimental section) and surprisingly stable bis-crotonate derivative (2a) (91%) did indeed engage in the anticipated intramolecular Diels–Alder reaction upon heating in refluxing benzene, and the structure of the crystalline adduct (±)-(3a) (96%) was confirmed by single-crystal X-ray analysis (Fig. 1 and Table 1).

Encouraged by the results just described, an examination of the Diels–Alder reactions of the bis-crotonate derivative (−)-(2b) of the enantiomerically pure and chloro-substituted dihydrocatechol (+)-(1b)[5] was undertaken. Substrate (−)-(2b), which is clearly electronically less activated toward Diels–Alder cycloaddition than the parent system (2a), failed to react in refluxing benzene but in boiling toluene smooth conversion into a chromatographically separable 1.3 : 1 mixture of adducts (+)-(3b) and (−)-(4b) (87% combined yield) was observed (Table 2). The structure of the chromatographically less mobile and dextrorotatory adduct (+)-(3b) was established by single-crystal X-ray analysis (see Table 1 and Experimental section).

 10.1071/CH03112 0004-9425/03/090861

The thermochemical aspects of this conversion could be evaluated using differential scanning calorimetry (DSC) techniques.[7] Thus, heating a small sample of the neat bis-crotonate (−)-(2b) in the relevant apparatus at a rate of 5°C min^{-1} from 20°C results in the detection of a melting point endotherm of 4.21 kcal mol^{-1} at 48°C (Fig. 2) and a 23.72 kcal mol^{-1} exotherm from ca. 121°C. ^{1}H NMR analysis of the reaction mixture so formed reveals that it is composed entirely of the expected Diels–Alder adducts, that is, there was no contamination of these products by aromatic compounds arising from elimination of the elements of crotonic acid from the starting material (−)-(2b). Interestingly, AM1 calculations carried out using the MacSpartan Pro software package predict that the observed Diels–Alder reactions should be exothermic to the extent of 29 kcal mol^{-1}, which is in line with the experimentally determined value.

Under the same conditions as used for congener (−)-(2b), the bis-crotonate derivative (−)-(2c), derived from the enantiopure 'bromodiol' (+)-(1c), afforded a 1.4 : 1 mixture of adducts (+)-(3c) and (−)-(4c), with the structure of both products being confirmed by X-ray analysis (see Table 1 and Experimental section). In a similar manner, the bis-ester (+)-(2d) of iodobenzene-derived 'diol' (+)-(1d) afforded a 1 : 1.5 mixture of the expected adducts (+)-(3d) and (−)-(4b), with the structure of the former product once again being confirmed by single-crystal X-ray analysis (see

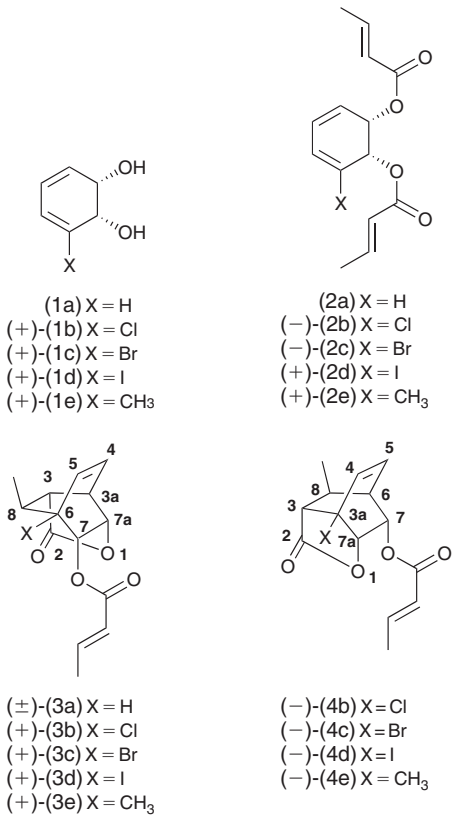

Diagram 1.

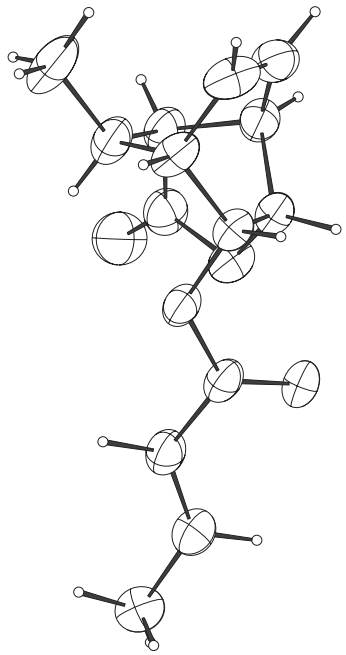

Fig. 1. ADEP derived from single-crystal X-ray analysis of compound (±)-(3a).

Table 1. X-Ray crystal data for selected compounds

	(±)-(3a)	(+)-(3b)	(+)-(3c)	(+)-(3d)	(−)-(4c)	(−)-(4f)	(−)-(4g)
Formula	$C_{14}H_{16}O_4$	$C_{14}H_{15}ClO_4$	$C_{14}H_{15}BrO_4$	$C_{14}H_{15}IO_4$	$C_{14}H_{15}BrO_4$	$C_{14}H_{15}ClO_4$	$C_{15}H_{18}O_4$
FW	248.278	282.723	327.179	374.174	327.179	282.723	262.305
Crystal system	monoclinic	monoclinic	monoclinic	monoclinic	monoclinic	orthorhombic	monoclinic
Space group	$P2_1/a$	$P2_1$	$P2_1$	$P2_1$	$P2_1$	$P22_12_1$	$P2_1$
a [Å]	11.5121(2)	8.7451(2)	11.5138(3)	8.04640(10)	8.31880(10)	6.69030(10)	6.79020(10)
b [Å]	9.6644(2)	7.72190(10)	7.8470(2)	8.33230(10)	15.5371(2)	16.5627(2)	11.9873(2)
c [Å]	11.8275(3)	10.5382(2)	16.5849(5)	10.6972(2)	21.7500(4)	24.7344(3)	8.2956(2)
β [°]	106.9630(11)	107.0087(9)	110.4440(13)	99.4297(8)	90.1467(6)	–	90.2959(7)
V [Å^3]	1258.65(5)	680.51(2)	1404.05(7)	707.50(2)	2811.18(7)	2740.80(6)	675.22(2)
Z/Z'	4/1	2/1	4/2	2/1	8/4	8/2	2/1
T [K]	200	200	200	200	200	200	200
μ [mm^{-1}]	0.096	0.29	2.93	2.27	2.93	0.286	0.09
No. of reflections	2863	3098	5994	4135	12705	6300	3069
Unique reflections	1318	2477	3391	3016	7535	3557	2065
R	0.048	0.028	0.034	0.022	0.041	0.029	0.028
R_w	0.056	0.031	0.035	0.024	0.047	0.033	0.032

Table 2. Products, product ratios, and yields observed in the intramolecular Diels–Alder reactions of bis-esters (2)

Substrate (2)	Diene substituent X	Dienophilic residues	(+)-Product (3)	(−)-Product (4)	Ratio (3) : (4)	Combined yield [%][A]
(−)-(2b)	Cl	bis-crotonate	(3b)	(4b)	1.3 : 1	87
(−)-(2c)	Br	bis-crotonate	(3c)	(4c)	1.4 : 1	93
(+)-(2d)	I	bis-crotonate	(3d)	(4d)	1.5 : 1	83
(+)-(2e)	Me	bis-crotonate	(3e)	(4e)	1 : 1.5	86
(+)-(2f)	Cl	bis-α-methylacrylate	NO[B]	(4f)	–	62
(+)-(2g)	Me	bis-α-methylacrylate	(3g)	(4g)	1 : 2.1	83
(−)-(2h)	Cl	bis-senecioate	(3h)	NO	–	11
(2i)	Cl	C1–crotonate C2–α-methylacrylate	NO	(4i)	–	88
(2j)	Cl	C1–acrylate C2–senecioate	(3j)	NO	–	84
(2k)	Cl	C1–senecioate C2–acrylate	NO	(4k)	–	84

[A] Total yield of isolated material(s). [B] NO = not observed.

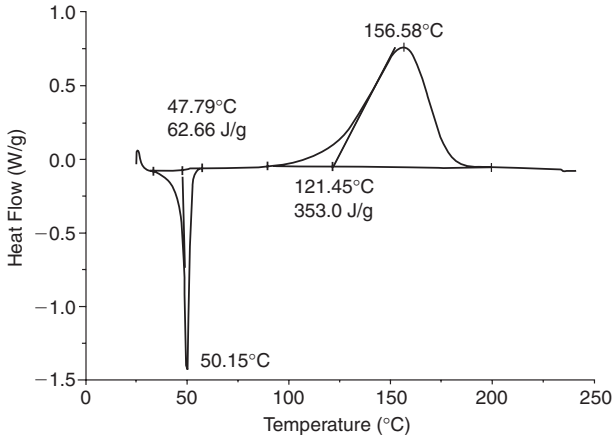

Fig. 2. DSC curve associated with the intramolecular Diels–Alder reactions of compound (−)-(2b).

Table 1 and Experimental section). Reaction of the bis-crotonate derivative (+)-(2e) in refluxing toluene gave a 1 : 1.5 mixture of Diels–Alder adducts (+)-(3e) and (−)-(4e), which could be separated chromatographically and fully characterized. Unfortunately, the derived data did not allow for unequivocal differentiation between these pseudo-enantiomeric compounds. Furthermore, and despite various attempts, it was not possible to grow crystals of either product (+)-(3e) or (−)-(4e) that were amenable to single-crystal X-ray analysis. At this stage, therefore, the structure assigned to these compounds is based upon using the sign of the optical rotation to indicate which pseudo-enantiomeric series, that is (3) or (4), each belongs to (see Table 3).

The selectivity of the competing Diels–Alder reactions just described, which must necessarily proceed through *exo*-type transition states, appears be sensitive to steric effects in that the crotonate residue furthest from the C3 substitutent (X) on the diene preferentially engages in the cycloaddition process (see Table 2) and, at least for the halogenated systems, all the more so as the size of X increases. In order to assess the steric effect of substituents on the dienophilic residue in these kinds of processes, the bis-α-methylacrylate (+)-(2f) (see Diagram 2) was prepared by standard methods from (+)-(1b). Heating a toluene solution of this bis-ester afforded, as the only characterizable reaction product, the

Table 3. Specific rotations of Diels–Alder adducts (3) and (4)

Compound	Specific rotation[A]	Compound	Specific rotation[A]
(+)-(3b)[B]	+209° (*c* 0.7)	(−)-(4b)	−97° (*c* 0.2)
(+)-(3c)[B]	+180° (*c* 0.4)	(−)-(4c)[B]	−65° (*c* 0.4)
(+)-(3d)[B]	+100° (*c* 0.85)	(−)-(4d)	−35° (*c* 0.9)
(+)-(3e)	+219° (*c* 0.6)	(−)-(4e)	−88° (*c* 1.5)
(+)-(3f)	+162° (*c* 0.45)	(−)-(4f)[B]	−86° (*c* 1.6)
(+)-(3g)	+210° (*c* 0.6)	(−)-(4g)[B]	−133° (*c* 0.6)
(+)-(3h)	+31° (*c* 0.2)	(−)-(4i)	−90° (*c* 1.8)
(3j)	ND[C]	(−)-(4k)	−135° (*c* 3.3)
(+)-(5)	+112° (*c* 0.3)	(−)-(5)	−111° (*c* 0.6)

[A] All optical rotations were carried out in $CHCl_3$.
[B] Structure proven by X-ray analysis.
[C] ND = not determined.

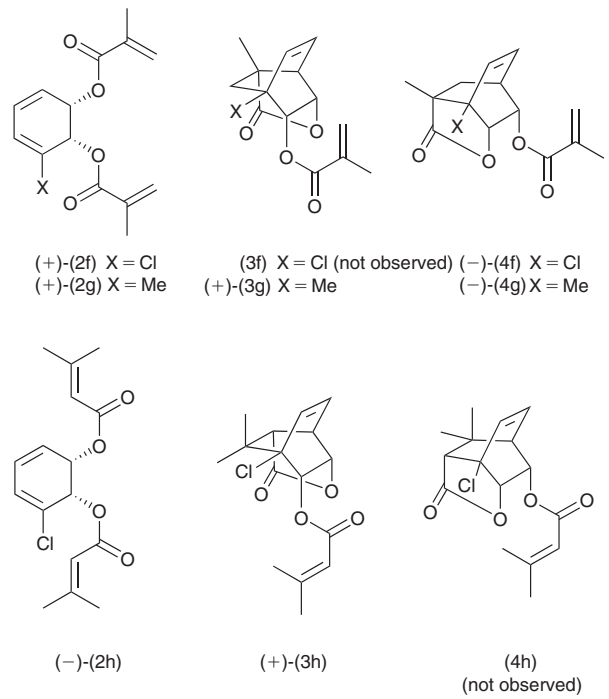

Diagram 2.

crystalline '*ortho*'-adduct (−)-(4f) (62%), the structure of which was confirmed by single-crystal X-ray analysis (see Table 1 and Experimental section). The anticipated isomer (3f) was not observed, although small amounts of an

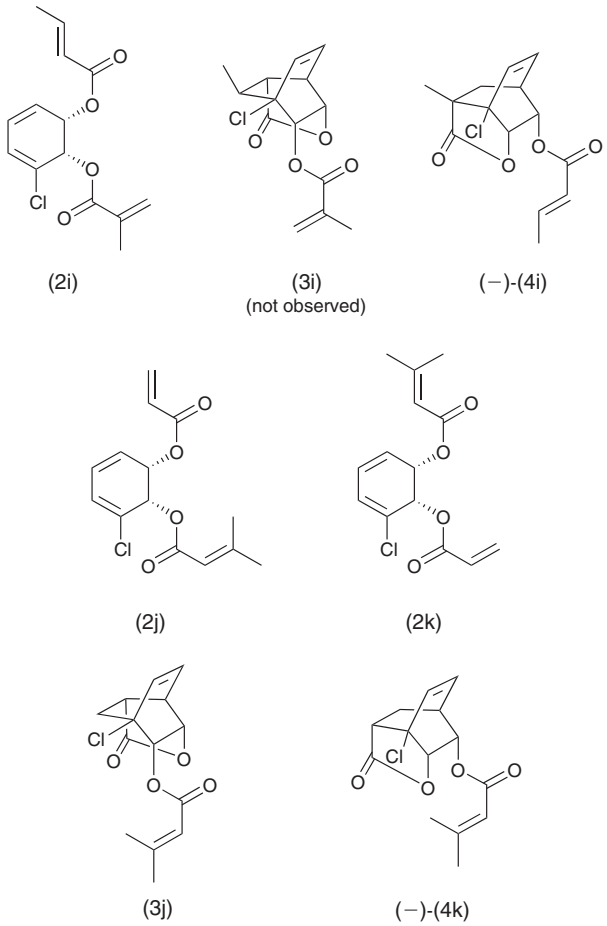

Diagram 3.

unidentified waxy by-product were obtained. The same preference was observed with the methyl-substituted system (+)-(2g) (X = Me), which yielded 27% of adduct (+)-(3g) and 56% of isomer (−)-(4g), the structures of which were confirmed by X-ray analysis (see Table 1 and Experimental section). Heating a toluene solution of the bis-senecioic ester (−)-(2h) at reflux for 48 h failed to induce any reaction, and is presumably an indication of the steric demands of the anticipated Diels–Alder cycloaddition process. However, using xylene as the reaction solvent and heating the resulting solution at reflux afforded the *gem*-dimethylated bicyclo[2.2.2]octene (+)-(3h) (11%) as the only isolable product of reaction. None of the anticipated regio-isomeric product (4h) was observed, but given the poor mass balance associated with the process no real significance can be attributed to this result.

In an effort to gain further insight into these competing intramolecular Diels–Alder reactions, mixed diesters such (−)-(2i) (see Diagram 3) were sought. Indeed, through sequential reaction of the diol (+)-(1b), in the presence of butyllithium, with one equivalent of crotonyl chloride then a second equivalent of butyllithium and one equivalent of α-methylacryloyl chloride, compound (2i) could be formed preferentially. Heating a benzene solution of this mixed bis-ester at reflux for 12 h afforded, in 88% yield, the crystalline '*ortho*'-adduct (−)-(4i) with none of the corresponding

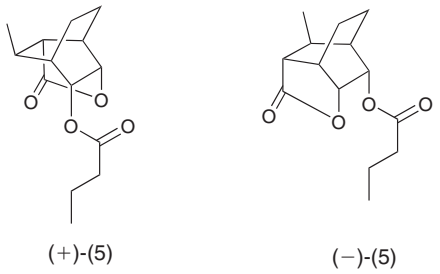

Diagram 4.

'*meta*'-adduct (3i) being detected. However, the presumably electronically-derived preference for formation of '*ortho*'-Diels–Alder adducts can be overridden by steric effects as evidenced by the behaviour of bis-ester (2j) (produced by the usual methods as a mixture with regioisomer (2k); 67% combined yield) under the same conditions. Thus, heating a toluene solution of bis-esters (2j) and (2k) at reflux for 16 h afforded a chromatographically separable mixture of adducts (+)-(3j) (84% from (2j)) and (−)-(4j) (84% from (2k)), which were each characterized in the usual fashion.

The pseudo-enantiomeric relationship between the Diels–Alder adducts of type (3) and (4) was confirmed by independent subjection of the iodinated compounds (+)-(3d) and (−)-(4d) to reaction with hydrogen in the presence of 10% Pd on C and *N*,*N*-diisopropylethylamine. In each instance, the two double bonds within these substrates were hydrogenated and the iodine reductively cleaved such that (+)-(5) and (−)-(5) (see Diagram 4), respectively, were formed, each in essentially quantitative yield. These products were identical, as judged by NMR, IR, and mass spectral analysis, whilst optical rotations were of essentially the same magnitude but opposite sign (see Table 3). Hydrogenation of lactone (±)-(3a) under essentially the same conditions (no added base) afforded the racemic modification of compound (5), also in near quantitative yield.

Conclusion

The work detailed here indicates that α,β-unsaturated bis-esters of the enantiomerically pure *cis*-1,2-dihydrocatechols (+)-(1b), (+)-(1c), (+)-(1d), and (+)-(1e) engage in competing intramolecular Diels–Alder reactions to give pseudo-enantiomeric Diels–Alder adducts of the general type (+)-(3) and (−)-(4). These products are, generally speaking, readily separated from one another by flash chromatographic and/or fractional crystallization techniques. The ratio of products (3) and (4) is influenced by the nature of the substituent (X) in substrate (2) but even more so by the nature of the groups associated with the ester residues. The capacity to generate either enantiomeric form of lactone-annulated bicyclo[2.2.2]octanes, e.g. (+)-and (−)-(5), from a common precursor, such as (+)-(2d), by the methods described here provides a further illustration of the synthetic potential arising from the 'hidden symmetry elements'[5] associated with *cis*-1,2-dihydrocatechols. Diels–Alder adducts of the type reported should be of value in developing enantioselective syntheses of important natural product targets such

as the phomoidrides,[3f] morellin, scortechinones A and B, forbesione, gaudichaudione H, and lateriflorone.[8]

Experimental

Melting points were recorded with a Kofler hot-stage apparatus and are uncorrected. Proton and carbon NMR spectra (δ_H and δ_C) were recorded with a Varian Unity 300 or Varian Gemini 300 spectrometer operating at 300 MHz for proton and 75 MHz for carbon. All such spectra were recorded in $CDCl_3$ solution at 22°C. The 'protonicities' of the carbon atoms observed in ^{13}C NMR spectra were determined by attached proton test (APT) experiments. Infrared spectra (ν_{max}) were recorded with either a Perkin–Elmer 983G IR spectrophotometer or a Perkin–Elmer 1800 FTIR instrument. Samples were analyzed either as thin films on sodium chloride plates (for liquids) or as potassium bromide disks (for solids). Low-resolution electron-impact mass spectra (m/z) were recorded at 70 eV on either a VG Micromass 7070F mass spectrometer or a JEOL AX-505H mass spectrometer. High-resolution mass spectra were recorded with a VG Micromass 7070F instrument. Optical rotations were measured at 20°C with a Perkin-Elmer 241 polarimeter at the sodium D-line (589 nm) using spectroscopic grade chloroform (Merck) and at the concentration (c) (g per100 mL) indicated. The measurements were carried out in a cell with a path length of 1 dm. Specific rotations ($[\alpha]_D^{20}$) were calculated using $[\alpha]_D = (100\,\alpha)/(c)$, and are given in units of 10^{-1} deg cm^2 g^{-1}. Tetrahydrofuran (THF) was distilled under nitrogen from sodium benzophenone ketyl, dichloromethane from calcium hydride, and methanol from magnesium methoxide. DSC studies were carried out using a TA Instruments DSC 2920 apparatus.

Synthetic Studies

General Procedure for Formation of bis-Esters (2a), (−)-(2b), (−)-(2c), (+)-(2d), (+)-(2e), (+)-(2f), (+)-(2g), and (−)-(2h)

A magnetically stirred solution of the relevant *cis*-1,2-dihydrocatechol (1) (1–15 mmol) in dry THF (ca. 15 mL mmol^{-1}) was cooled to −78°C (dry-ice/acetone bath) and was then treated, dropwise, with Bu^{n}Li (1.05 mole equiv. of a 2.5 M solution in hexane) over 5 min. The resulting solution was stirred at −78°C for 10 min, at which time the appropriate acid chloride (1 mole equiv.) was added over 5 min. The resulting solution was stirred for 1 h at −78°C then the dry-ice/acetone bath was removed and replaced with an ice/water bath. The reaction mixture was stirred for a further 1 h at ca. 0°C then cooled again to −78°C and treated, dropwise, with Bu^{n}Li (1.05 mole equiv. of a 2.5 M solution in hexanes). After 10 min the relevant acid chloride (1 mole equiv.) was added over 5 min and stirring was continued at −78°C for 1 h. The dry-ice/acetone bath was then replaced by an ice/water bath and stirring was continued for a further 1 h. The reaction mixture was then quenched with $NaHCO_3$ (5 mL of a sat. aqueous solution per mmol of (1)) and diluted with diethyl ether (ca. 20 mL mmol^{-1} of (1)). The separated organic phase was washed with NH_4Cl (ca. 1 × 5 mL of a sat. aqueous solution per mmol of (1)), then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography on silica gel to afford the relevant bis-ester (2). The instability of some of these compounds has precluded the acquisition of the usual range of spectroscopic and analytical data.

cis-*Cyclohexa-3,5-diene-1,2-diol bis-Crotonate (2a)*

Reaction of diol (1a) with crotonyl chloride under the conditions specified in the general procedure afforded a light-yellow oil upon workup. Subjection of this material to flash chromatography (5 : 95 v/v ethyl acetate/hexane elution) afforded, after concentration of the relevant fractions (R_f 0.3 in 1 : 9 v/v ethyl acetate/hexane), the title *bis-ester* (2a) (91%) as a clear, colourless oil (Found: M$^{+\bullet}$, 248.1046. $C_{14}H_{16}O_4$ requires M$^{+\bullet}$, 248.1049). ν_{max} (KBr)/cm^{-1} 1721, 1659, 1444, 1311, 1293, 1258, 1174, 1102, 968. δ_H 6.95 (2 H, m), 6.14 (2 H, m), 5.97 (2 H, m), 5.82 (2 H, d, J 15.0), 5.60 (2 H, br s), 1.90 (6 H, d, J 10.0). δ_C 165.8, 145.7, 126.4, 125.8, 122.5, 67.2, 18.5. m/z (EI, 70 eV) 248 (5%, M$^{+\bullet}$), 180 (16), 163 (41), 162 (48), 95 (45), 94 (60), 78 (100), 77 (45).

(1S,2S)-3-Chlorocyclohexa-3,5-diene-1,2-diol bis-Crotonate (−)-(2b)

Reaction of diol (+)-(1b) with crotonyl chloride under the conditions specified in the general procedure afforded a light-yellow oil upon workup. Subjection of this material to flash chromatography (5 : 95 v/v ethyl acetate/hexane elution) afforded, after concentration of the relevant fractions (R_f 0.25 in 1 : 4 v/v ethyl acetate/hexane), the title *bis-ester* (−)-(2b) (93%) as a clear, colourless oil, which solidified on standing in the fridge to give a solid, mp 49°C, $[\alpha]_D$ −20° (c 0.6 in $CHCl_3$) (Found: M$^{+\bullet}$, 282.0653. $C_{14}H_{15}{}^{35}ClO_4$ requires M$^{+\bullet}$, 282.0659). ν_{max} (KBr)/cm^{-1} 1728, 1658, 1443, 1293, 1251, 1170, 1102, 968. δ_H 7.08–6.90 (2 H, complex m), 6.30 (1 H, d, J 6.0), 6.04 (1 H, m), 5.92–5.72 (5 H, complex m), 1.85 (6 H, m). δ_C 165.4, 146.4, 146.2, 130.9, 125.4, 125.3, 124.4, 122.0(4), 121.9(6), 69.1, 68.9, 18.5 (two signals obscured or overlapping). m/z (EI, 70 eV) 284 and 282 (3 and 9%, M$^{+\bullet}$), 247 (5), 178 (100), 149 (58), 128 (46), 121 (84), 93 (95), 91 (91).

(1S,2S)-3-Bromocyclohexa-3,5-diene-1,2-diol bis-Crotonate (−)-(2c)

Reaction of diol (+)-(1c) with crotonyl chloride under the conditions specified in the general procedure afforded a light-yellow oil upon workup. Subjection of this material to flash chromatography (1 : 9 v/v ethyl acetate/hexane elution) afforded, after concentration of the relevant fractions (R_f 0.5 in 1 : 4 v/v ethyl acetate/hexane), the title *bis-ester* (−)-(2c) (89%) as a clear, colourless oil, $[\alpha]_D$ −10° (c 0.8 in $CHCl_3$) (Found: M$^{+\bullet}$, 326.0157. $C_{14}H_{15}{}^{79}BrO_4$ requires M$^{+\bullet}$, 326.0154). ν_{max} (KBr)/cm^{-1} 1729, 1658, 1293, 1250, 1177, 1102, 968. δ_H 7.10–6.90 (2 H, complex m), 6.76 (1 H, d, J 6.0), 6.04–5.74 (6 H, complex m), 1.87 (6 H, m). δ_C 165.3, 146.4, 146.2, 129.4, 125.9, 125.0, 122.1, 122.0, 120.8, 69.9, 69.0, 18.5 (two signals obscured or overlapping). m/z (EI, 70 eV) 328 and 326 (4 and 4%, M$^{+\bullet}$), 247 (36), 178 (100), 121 (41), 93 (64), 91 (83), 77 (79).

(1S,2S)-3-Iodocyclohexa-3,5-diene-1,2-diol bis-Crotonate (+)-(2d)

Reaction of diol (+)-(1d) with crotonyl chloride under the conditions specified in the general procedure afforded a light-yellow oil upon workup. Subjection of this material to flash chromatography (5 : 95 v/v ethyl acetate/hexane elution) afforded, after concentration of the relevant fractions (R_f 0.35 in 1 : 4 v/v ethyl acetate/hexane), the title *bis-ester* (+)-(2d) (89%) as a clear, colourless oil, $[\alpha]_D$ +3° (c 3.1 in $CHCl_3$). ν_{max} (KBr)/cm^{-1} 1728, 1658, 1560, 1443, 1293, 1250, 1177, 1101, 968, 835. δ_H 7.12–6.89 (2 H, m), 6.83 (1 H, d, J 6.0), 6.00–5.69 (6 H, complex m), 1.90 (6 H, m). δ_C 146.5, 146.1, 137.1, 126.4(4), 126.3(6), 126.1, 125.8, 122.2, 122.1, 95.0, 71.7, 68.0, 18.6, 18.5. m/z (EI, 70 eV) 374 (9%, M$^{+\bullet}$), 247 (3), 105 (2), 93 (3), 91 (5), 69 (100).

(1S,2R)-3-Methylcyclohexa-3,5-diene-1,2-diol bis-Crotonate (+)-(2e)

Reaction of diol (+)-(1e) with crotonyl chloride under the conditions specified in the general procedure afforded a light-yellow oil upon workup. Subjection of this material to flash chromatography (1 : 9 v/v ethyl acetate/hexane elution) afforded, after concentration of the relevant fractions (R_f 0.5 in 1 : 4 v/v ethyl acetate/hexane), the title *bis-ester* (+)-(2e) (96%) as a clear, colourless oil, $[\alpha]_D$ +96° (c 1.5 in $CHCl_3$). ν_{max} (KBr)/cm^{-1} 1722, 1657, 1444, 1308, 1293, 1256, 1175, 1102, 968. δ_H 7.04–6.86 (2 H, complex m), 6.05 (1 H, dd, J 9.5 and 5.6), 5.91–5.72 (4 H, complex m), 5.60 (2 H, br s), 1.85 (9 H, m). δ_C 166.1, 165.9, 145.7, 145.5, 134.8, 126.8, 123.0, 122.6, 122.4, 122.0, 69.8, 68.2, 20.0, 18.5, 18.4. m/z (EI, 70 eV) 262 (<1%, M$^{+\bullet}$), 177 (4), 176 (5), 109 (9), 108 (21), 92 (4), 91 (9), 69 (100).

(1S,2S)-3-Chlorocyclohexa-3,5-diene-1,2-diol bis-α-Methylacrylate (+)-(2f)

Reaction of diol (+)-(1b) with α-methylacryloyl chloride under the conditions specified in the general procedure afforded a light-yellow oil upon workup. Subjection of this material to flash chromatography (5 : 95 v/v ethyl acetate/hexane elution) afforded, after concentration of the relevant fractions (R_f 0.2), the title *bis-ester* (+)-(2f) (69%) as a clear, colourless oil, $[\alpha]_D$ +11° (c 0.8 in $CHCl_3$) (Found: M$^{+\bullet}$, 282.0659. $C_{14}H_{15}{}^{35}ClO_4$ requires M$^{+\bullet}$, 282.0659). ν_{max} (KBr)/cm^{-1} 1728, 1638,

1451, 1328, 1291, 1161, 944, 810, 683. δ_H 6.31 (1 H, d, *J* 6.0), 6.13 (1 H, m), 6.09–6.01 (2 H, complex m), 5.89–5.72 (3 H, complex m), 5.58 (2 H, m), 1.93 (3 H, m), 1.91 (3 H, m). δ_C 166.3(2), 166.2(8), 135.9, 135.8, 130.8, 126.7, 126.6, 125.3, 125.1, 124.6, 69.5, 69.4, 18.6(4), 18.5(7). *m/z* (EI, 70 eV) 284 and 282 (1 and 3%, $M^{+\bullet}$), 247 (1), 196 (15), 128 (17), 112 (14), 69 (100).

*(1*S*,2*R*)-3-Methylcyclohexa-3,5-diene-1,2-diol bis-α-Methylacrylate (+)-(2g)*

Reaction of diol (+)-(1e) with α-methylacryloyl chloride under the conditions specified in the general procedure afforded a light-yellow oil upon workup. Subjection of this material to flash chromatography (5 : 95 v/v ethyl acetate/hexane elution) afforded, after concentration of the relevant fractions (R_f 0.6 in 1 : 5 v/v ethyl acetate/hexane), the title *bis-ester* (+)-(2g) (70%) as a clear, colourless oil, $[\alpha]_D$ +113° (*c* 0.7 in $CHCl_3$) (Found: $M^{+\bullet}$, 262.1207. $C_{15}H_{18}O_4$ requires $M^{+\bullet}$, 262.1205). ν_{max} (KBr)/cm^{-1} 1723, 1638, 1451, 1317, 1169, 943. δ_H 6.08 (3 H, m), 5.85 (1 H, m), 5.78 (1 H, m), 5.65–5.48 (4 H, complex m), 1.92 (3 H, br s), 1.90 (3 H, br s), 1.82 (3 H, s). δ_C 166.8, 166.7, 136.3, 136.1, 134.6, 126.9, 126.0, 125.8, 122.6, 121.8, 70.3, 68.3, 19.6, 18.3(3), 18.2(8). *m/z* (EI, 70 eV) 280 (5%, $M^{+\bullet}$), 262 (15), 235 (10), 176 (14), 148 (100), 128 (40), 119 (38), 107 (67), 91 (57).

*(1*S*,2*S*)-3-Chlorocyclohexa-3,5-diene-1,2-diol bis-Senecioate (−)-(2h)*

Reaction of diol (+)-(1b) with senecioyl chloride under the conditions specified in the general procedure afforded a light-yellow oil upon workup. Subjection of this material to flash chromatography (1 : 9 v/v ethyl acetate/hexane elution) afforded, after concentration of the relevant fractions (R_f 0.3), the title *bis-ester* (−)-(2h) (94%) as a clear, colourless oil, $[\alpha]_D$ −43° (*c* 1.4 in $CHCl_3$) (Found: $M^{+\bullet}$, 310.0970. $C_{16}H_{19}{}^{35}ClO_4$ requires $M^{+\bullet}$, 310.0972). ν_{max} (KBr)/cm^{-1} 1728, 1651, 1575, 1446, 1379, 1352, 1262, 1226, 1146, 1112, 1088, 1042, 990, 847, 675. δ_H 6.28 (1 H, d, *J* 6.0), 6.03 (1 H, m), 5.83 (1 H, m), 5.77–5.68 (3 H, complex m), 5.63 (1 H, m), 2.15 (6 H, dm, *J* 4.0), 1.89 (6 H, dm, *J* 3.5). δ_C 165.4, 165.3, 158.4, 158.2, 131.3, 125.8, 125.1, 124.3, 115.6, 115.5, 68.5, 68.2, 27.8, 20.7 (two signals obscured or overlapping). *m/z* (EI, 70 eV) 312 and 310 (7 and 17%, $M^{+\bullet}$), 275 (2), 211 (15), 128 (17), 114 (21), 112 (44), 100 (26), 84 (100), 83 (68), 82 (34).

*(1*S*,2*S*)-3-Chlorocyclohexa-3,5-diene-1,2-diol 1-Crotonate 2-α-Methylacrylate (2i)*

A magnetically stirred solution of *cis*-1,2-dihydrocatechol (+)-(1b) (730 mg, 5 mmol) in dry THF (75 mL) was cooled to −78°C (dry-ice/acetone bath) then treated, dropwise, with Bu^nLi (2.1 mL of a 2.5 M solution in hexane, 5.25 mmol) over 5 min. The resulting solution was stirred at −78°C for 10 min then crotonyl chloride (479 μL, 5 mmol) was added over 5 min. The ensuing mixture was stirred for 1 h at −78°C then the dry-ice/acetone bath was removed and replaced with an ice/water bath. The reaction was stirred for a further 1 h at ca. 0°C then cooled again to −78°C and treated, dropwise, with Bu^nLi (2.1 mL of a 2.5 M solution in hexane, 5.25 mmol). After 10 min α-methylacryloyl chloride (483μL, 5 mmol) was added over 5 min and stirring was continued at −78°C for 1 h. The dry-ice/acetone bath was then replaced by an ice/water bath and stirring was continued for a further 1 h. The reaction mixture was then quenched with $NaHCO_3$ (25 mL of a sat. aqueous solution) and diluted with diethyl ether (100 mL). The separated organic phase was washed with NH_4Cl (1 × 25 mL of a sat. aqueous solution), then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (silica gel, 2.5 : 97.5 v/v ethyl acetate/hexane) and concentration of the relevant fractions (R_f 0.3) afforded the title *bis-ester* (2i) (440 mg, 31%) as a clear, colourless oil. δ_H (C_6D_6) 6.82 (1 H, m), 6.16 (1 H, br s), 5.93 (1 H, d, *J* 6.5), 5.74 (2 H, m), 5.64 (1 H, dm, *J* 15.5), 5.50 (1 H, dd, *J* 9.5 and 3.3), 5.37 (1 H, m), 5.14 (1 H, br s), 1.77 (3 H, d, *J* 1.1), 1.20 (3 H, dm, *J* 7.0). δ_C 166.2, 165.3, 146.1, 135.7, 130.9, 126.7, 125.1, 125.0, 124.8, 122.0, 69.4, 68.6, 18.6, 18.5.

*(1*S*,2*S*)-3-Chlorocyclohexa-3,5-diene-1,2-diol 1-Acrylate 2-Senecioate (2j) and (1*S*, 2*S*)-3-Chlorocyclohexa-3,5-diene-1,2-diol 2-Acrylate 1-Senecioate (2k)*

Reaction of diol (+)-(1b) (1.465 g, 10 mmol) with senecioyl chloride and then acryloyl chloride under the conditions specified immediately above afforded a ca. 1 : 1 mixture of the compounds (2j) and (2k) in 67% yield. Since these bis-esters could not be separated from one another the mixture was subjected to the competitive intramolecular Diels–Alder reaction (see below).

*(3*SR*,3a*RS*,6*SR*,7*RS*,7a*SR*,8*RS*)-2,3,3a,6,7,7a-Hexahydro-8-methyl-2-oxo-3,6-methanobenzofuran-7-yl Crotonate (±)-(3a)*

A solution of bis-crotonate (2a) (497 mg, 2 mmol) in benzene (10 mL) maintained under a nitrogen atmosphere was heated at reflux for 4 h then cooled to 18°C and concentrated under reduced pressure. The resulting light-yellow oil was purified by flash chromatography (silica, 1 : 4 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f 0.5) then afforded the *title compound* (±)-(3a) (479 mg, 96%) as white crystalline masses, mp 90°C (Found: $M^{+\bullet}$, 248.1049. $C_{14}H_{16}O_4$ requires $M^{+\bullet}$, 248.1049). ν_{max} (KBr)/cm^{-1} 1791, 1713, 1652, 1316, 1290, 1190, 1167, 1040, 1013, 709. δ_H 6.98 (1 H, m), 6.39 (1 H, tm, *J* 7.0), 6.11 (1 H, tm, *J* 7.0), 5.86 (1 H, dq, *J* 15.5 and 1.8), 4.53 (1 H, t, *J* 6.0), 4.36 (1 H, dd, *J* 6.0 and 2.5), 3.50 (1 H, m), 2.82 (1 H, m), 2.51 (1 H, m), 2.10 (1 H, dm, *J* 3.2), 1.88 (3 H, dd, *J* 6.9 and 1.8), 0.94 (3 H, d, *J* 7.0). δ_C 179.2, 165.8, 146.1, 134.5, 126.1, 122.1, 71.8, 69.8, 45.1, 41.8, 41.2, 31.9, 20.1, 18.5. *m/z* (EI, 70 eV) 248 (47%, $M^{+\bullet}$), 179 (11), 134 (14), 128 (9), 107 (30), 105 (52), 93 (100), 91 (96), 77 (74).

*(3*R*,3a*R*,6*R*,7*S*,7a*S*,8*S*)-6-Chloro-2,3,3a,6,7,7a-hexahydro-8-methyl-2-oxo-3,6-methanobenzofuran-7-yl Crotonate (+)-(3b) and (3*S*,3a*R*,6*S*,7*S*,7a*S*,8*S*)-3a-Chloro-2,3,3a,6,7,7a-hexahydro-8-methyl-2-oxo-3,6-methanobenzofuran-7-yl Crotonate (−)-(4b)*

A solution of bis-crotonate (−)-(2b) (420 mg, 1.5 mmol) in toluene (15 mL) maintained under a nitrogen atmosphere was heated at reflux for 5 h then cooled to 18°C and concentrated under reduced pressure. The resulting light-yellow oil was purified by flash chromatography (silica, 1 : 4 v/v ethyl acetate/hexane elution) to afford two fractions, A and B.

Concentration of fraction A (R_f 0.1) gave the *title compound* (+)-(3b) (208 mg, 49%) as white crystalline masses, mp 104°C (Found: C 59.1, H 5.5, Cl 12.3%; $M^{+\bullet}$, 282.0653. $C_{14}H_{15}{}^{35}ClO_4$ requires C 59.5, H 5.4, Cl 12.5%; $M^{+\bullet}$, 282.0659). ν_{max} (KBr)/cm^{-1} 1786, 1730, 1659, 1443, 1341, 1296, 1166, 1103, 1018, 972, 883, 715. δ_H 7.04 (1 H, m), 6.36 (1 H, dd, *J* 8.6 and 1.2), 6.14 (1 H, m), 5.93 (1 H, dm, *J* 15.5), 4.64 (1 H, m), 4.57 (1 H, d, *J* 6.9), 3.48 (1 H, m), 2.66 (1 H, q, *J* 7.0), 2.23 (1 H, m), 1.91 (3 H, dm, *J* 6.9), 1.10 (3 H, d, *J* 7.0). δ_C 177.4, 165.4, 146.8, 138.2, 125.5, 121.6(8), 72.9, 72.5, 70.0(7), 70.0(5), 46.4, 40.4, 39.9, 18.6, 17.4. *m/z* (EI, 70 eV) 284 and 282 (3 and 8%, $M^{+\bullet}$), 247 (10), 127 (27), 105 (39), 91 (100), 77 (70).

Concentration of fraction B (R_f 0.2) gave the *title compound* (−)-(4b) (161 mg, 38%) as white crystalline masses, mp 88°C (Found: $M^{+\bullet}$, 282.0654. $C_{14}H_{15}ClO_4$ requires $M^{+\bullet}$, 282.0659). ν_{max} (KBr)/cm^{-1} 1795, 1718, 1657, 1444, 1263, 1181, 1155, 1026, 972, 860, 727, 705. δ_H 7.01 (1 H, m), 6.40 (1 H, t, *J* 8.4), 6.24 (1 H, dd, *J* 8.6 and 1.3), 5.86 (1 H, dq, *J* 15.5 and 1.6), 4.60 (1 H, dd, *J* 6.7 and 1.5), 4.45 (1 H, dd, *J* 6.7 and 2.3), 2.82 (1 H, m), 2.64 (1 H, m), 2.25 (1 H, t, *J* 1.5), 1.90 (3 H, dd, *J* 6.9 and 1.5), 1.01 (3 H, d, *J* 7.2). δ_C 176.4, 165.5, 146.8, 133.4, 131.1, 121.7, 78.2, 70.9, 69.9, 55.1, 41.5, 35.0, 20.0, 18.6. *m/z* (EI, 70 eV) 284 and 282 (0.5 and 1.5%, $M^{+\bullet}$), 178 (11), 149 (6), 121 (11), 93 (16), 91 (13), 77 (10), 69 (100).

*(3*R*,3a*R*,6*R*,7*S*,7a*S*,8*S*)-6-Bromo-2,3,3a,6,7,7a-hexahydro-8-methyl-2-oxo-3,6-methanobenzofuran-7-yl Crotonate (+)-(3c) and (3*S*,3a*R*,6*R*,7*R*,7a*S*, 8*S*)-3a-Bromo-2,3,3a,6,7,7a-hexahydro-8-methyl-2-oxo-3,6-methanobenzofuran-7-yl Crotonate (−)-(4c)*

A solution of bis-crotonate (−)-(2c) (1.00 g, 3.07 mmol) in toluene (15 mL) maintained under a nitrogen atmosphere was heated at reflux

for 12 h then cooled to 18°C and concentrated under reduced pressure. The resulting light-yellow oil was purified by flash chromatography (silica, 5 : 95 v/v ethyl acetate/hexane elution) to afford two fractions, A and B.

Concentration of fraction A (R_f 0.3 in 3 : 7 v/v ethyl acetate/hexane) gave the *title compound* (+)-(3c) (541 mg, 54%) as white crystalline masses, mp 75°C (Found: C 51.4, H 4.7, Br 24.3%; $[M + H]^+$, 327.0239. $C_{14}H_{15}{}^{79}BrO_4$ requires C 51.4, H 4.6, Br 24.4%; $[M + H]^+$, 327.0232). ν_{max} (KBr)/cm^{-1} 2983, 1788, 1731, 1658, 1443, 1341, 1297, 1261, 1165, 1085, 1064, 1016, 973, 953, 880, 715. δ_H 6.99 (1 H, m), 6.45 (1 H, d, *J* 8.6), 6.04 (1 H, dd, *J* 8.6 and 6.4), 5.86 (1 H, dm, *J* 15.5), 4.56 (2 H, br s), 3.46 (1 H, m), 2.67 (1 H, q, *J* 7.0), 2.22 (1 H, d, *J* 4.3), 1.86 (3 H, dd, *J* 6.9 and 1.8), 1.09 (3 H, d, *J* 7.0). δ_C 177.4, 165.3, 146.8, 138.8, 126.0, 121.7, 73.5, 72.6, 64.5, 46.2, 40.5, 40.2, 18.8, 18.6. *m/z* (EI, 70 eV) 328 and 326 (5 and 5%, $M^{+\bullet}$), 247 (10), 133 (20), 105 (52), 93 (55), 91 (100).

Concentration of fraction B (R_f 0.35 in 3 : 7 v/v ethyl acetate/hexane) gave the *title compound* (−)-(4c) (388 mg, 39%) as white crystalline masses, mp 88°C (Found: C 51.6, H 4.7, Br 24.5%; $[M + H]^+$, 327.0242. $C_{14}H_{15}{}^{79}BrO_4$ requires C 51.4, H 4.6, Br 24.4%; $[M + H]^+$, 327.0232). ν_{max} (KBr)/cm^{-1} 2971, 1794, 1717, 1657, 1262, 1181, 1155, 1026, 972, 714, 704. δ_H 6.97 (1 H, m), 6.34 (2 H, m), 5.84 (1 H, dm, *J* 15.5), 4.65 (1 H, dm, *J* 6.7), 4.41 (1 H, dd, *J* 6.7 and 2.2), 2.81 (1 H, m), 2.64 (1 H, m), 2.34 (1 H, br s), 1.88 (3 H, dd, *J* 6.9 and 1.8), 0.99 (3 H, d, *J* 7.2). δ_C 176.5, 165.5, 146.8, 133.7, 132.0, 121.7, 78.6, 70.0, 62.3, 56.1, 41.0, 35.4, 20.1, 18.6. *m/z* (EI, 70 eV) 328 and 326 (each <1%, $M^{+\bullet}$), 247 (6), 178 (24), 149 (6), 121 (9), 93 (10), 91 (10), 69 (100).

*(3*R*,3a*R*,6*R*,7*S*,7a*S*,8*S*)-6-Iodo-2,3,3a,6,7,7a-hexahydro-8-methyl-2-oxo-3,6-methanobenzofuran-7-yl Crotonate (+)-(3d) and (3*S*,3a*R*,6*S*,7*S*,7a*S*,8*S*)-3a-Iodo-2,3,3a,6,7,7a-hexahydro-8-methyl-2-oxo-3,6-methanobenzofuran-7-yl Crotonate (−)-(4d)*

A solution of bis-crotonate (+)-(2d) (255 mg, 0.68 mmol) in toluene (5 mL) maintained under a nitrogen atmosphere was heated at reflux for 24 h then cooled to 18°C and concentrated under reduced pressure. The resulting light-yellow oil was purified by flash chromatography (silica, 1 : 9 v/v ethyl acetate/hexane elution) to afford two fractions, A and B.

Concentration of fraction A (R_f 0.1) gave the *title compound* (+)-(3d) (128 mg, 50%) as white crystalline masses, mp 96°C (Found: C 45.2, H 4.3, I 33.7%. $C_{14}H_{15}IO_4$ requires C 44.9, H 4.0, I 33.9%). ν_{max} (KBr)/cm^{-1} 2971, 1784, 1723, 1654, 1442, 1304, 1170, 1105, 1063, 1012, 968, 836, 715. δ_H 7.05 (1 H, m), 6.68 (1 H, dm, *J* 8.6), 5.98–5.86 (2 H, complex m), 4.58 (1 H, d, *J* 6.7), 4.51 (1 H, m), 3.50 (1 H, m), 2.71 (1 H, q, *J* 7.0), 2.29 (1 H, dt, *J* 4.7 and 1.5), 1.90 (3 H, dd, *J* 7.0 and 1.8), 1.16 (3 H, d, *J* 7.0). δ_C 177.5, 165.2, 147.0, 141.4, 126.4, 121.7, 74.9, 72.3, 46.4, 45.2, 41.8, 39.9, 21.5, 18.7. *m/z* (EI, 70 eV) 374 (10%, $M^{+\bullet}$), 91 (6), 69 (100).

Concentration of fraction B (R_f 0.2) gave the *title compound* (−)-(4d) (85 mg, 33%) as a clear, colourless oil. ν_{max} (KBr)/cm^{-1} 1791, 1723, 1656, 1443, 1259, 1176, 1101, 1025, 967, 790, 702. δ_H 6.99 (1 H, m), 6.57 (1 H, d, *J* 8.0), 6.22 (1 H, t, *J* 8.0), 5.85 (1 H, dm, *J* 15.5), 4.70 (1 H, d, *J* 6.7), 4.40 (1 H, dd, *J* 6.7 and 2.2), 2.83 (1 H, m), 2.70 (1 H, m), 2.42 (1 H, s), 1.89 (3 H, dm, *J* 7.2), 1.00 (3 H, d, *J* 7.0). δ_C 177.0, 165.5, 146.8, 134.7, 134.1, 121.7, 80.1, 69.7, 58.5, 40.4, 38.6, 35.4, 20.2, 18.6. *m/z* (EI, 70 eV) 374 (≪1%, $M^{+\bullet}$), 247 (8), 93 (10), 91 (10), 77 (10), 69 (100).

*(3*S*,3a*R*,6*S*,7*R*,7a*S*,8*R*)-6,8-Dimethyl-2,3,3a,6,7,7a-hexahydro-2-oxo-3,6-methanobenzofuran-7-yl Crotonate (+)-(3e) and (3*R*,3a*S*,6*R*,7*S*,7a*R*,8*S*)-3a,8-Dimethyl-2,3,3a,6,7,7a-hexahydro-8-methyl-2-oxo-3,6-methanobenzofuran-7-yl Crotonate (−)-(4e)*

A solution of bis-crotonate (+)-(2e) (400 mg, 1.5 mmol) in toluene (10 mL) maintained under a nitrogen atmosphere was heated at reflux for 30 h then cooled to 18°C and concentrated under reduced pressure. The resulting light-yellow oil was purified by flash chromatography (silica, 1 : 9 v/v ethyl acetate/hexane elution) to afford two fractions, A and B.

Concentration of fraction A (R_f 0.25) gave the *title compound* (+)-(3e) (135 mg, 35%) as a clear, colourless oil (Found: $M^{+\bullet}$, 262.1206. $C_{15}H_{18}O_4$ requires $M^{+\bullet}$, 262.1205). ν_{max} (KBr)/cm^{-1} 2970, 1790, 1723, 1657, 1446, 1260, 1171, 1024, 972, 895, 711. δ_H 6.97 (1 H, m), 6.07 (2 H, m), 5.86 (1 H, dm, *J* 15.5), 4.58 (1 H, m), 4.15 (1 H, d, *J* 6.7), 3.43 (1 H, m), 2.23 (1 H, m), 2.03 (1 H, dm, *J* 4.7), 1.87 (3 H, dm, *J* 6.9), 1.21 (3 H, s), 0.89 (3 H, d, *J* 7.0). δ_C 179.3, 166.0, 145.9, 139.6, 125.6, 122.1, 73.6, 73.1, 47.1, 42.4, 41.0, 37.2, 19.3, 18.5, 17.4. *m/z* (EI, 70 eV) 262 (44%, $M^{+\bullet}$), 176 (26), 119 (33), 107 (78), 91 (100).

Concentration of fraction B (R_f 0.3) gave the *title compound* (−)-(4e) (200 mg, 51%) as a clear, colourless oil (Found: $M^{+\bullet}$, 262.1207. $C_{15}H_{18}O_4$ requires $M^{+\bullet}$, 262.1205). ν_{max} (KBr)/cm^{-1} 2966, 1789, 1723, 1657, 1445, 1262, 1180, 1041, 1019, 969, 945, 849, 713. δ_H 6.94 (1 H, m), 6.33 (1 H, t, *J* 7.8), 5.90–5.76 (2 H, complex m), 4.33 (1 H, dd, *J* 6.6 and 2.2), 4.17 (1 H, dm, *J* 6.6), 2.73 (1 H, m), 2.48 (1 H, m), 1.84 (3 H, dd, *J* 6.9 and 1.5), 1.66 (1 H, s), 1.36 (3 H, s), 0.90 (3 H, d, *J* 7.0). δ_C 179.2, 165.8, 145.9, 133.7, 131.9, 122.1, 77.1, 70.7, 52.3, 45.5, 42.0, 33.7, 21.1, 20.1, 18.5. *m/z* (EI, 70 eV) 262 (9%, $M^{+\bullet}$), 148 (37), 128 (100), 119 (53), 107 (58), 105 (27), 91 (56).

*(3*S*,3a*R*,6*S*,7*S*,7a*S*)-3a-Chloro-2,3,3a,6,7,7a-hexahydro-8-methyl-2-oxo-3,6-methanobenzofuran-7-ylα-Methylacrylate (−)-(4f)*

A solution of bis-ester (−)-(2f) (320 mg, 1.13 mmol) in toluene (10 mL) maintained under a nitrogen atmosphere was heated at reflux for 16 h then cooled to 18°C and concentrated under reduced pressure. The resulting light-yellow oil was purified by flash chromatography (silica, 1 : 9 v/v ethyl acetate/hexane elution) to afford two fractions, A and B.

Concentration of fraction A (R_f 0.04) gave a wax (30 mg) of undetermined composition and structure.

Concentration of fraction B (R_f 0.08) gave the *title compound* (−)-(4f) (200 mg, 62%) as white crystalline masses, mp 75°C (Found: C 59.3, H 5.5, Cl 12.7%; $M^{+\bullet}$, 282.0662. $C_{14}H_{15}{}^{35}ClO_4$ requires C 59.5, H 5.4, Cl 12.5%; $M^{+\bullet}$, 282.0659). ν_{max} (KBr)/cm^{-1} 1797, 1715, 1453, 1163, 1076, 1019, 951, 816, 716. δ_H 6.52 (1 H, dd, *J* 8.5 and 7.2), 6.16 (1 H, dm, *J* 8.5), 6.13 (1 H, br s), 5.63 (1 H, m), 4.66 (1 H, d, *J* 6.7), 4.48 (1 H, m), 2.86 (1 H, m), 2.45 (1 H, dd, *J* 13.8 and 3.2), 1.93 (3 H, s), 1.30 (1 H, dt, *J* 13.8 and 1.9), 1.20 (3 H, s). δ_C 178.7, 166.5, 135.5, 134.7, 131.0, 127.1, 77.6, 75.4, 69.6, 48.1, 35.8, 35.0, 18.6, 18.1. *m/z* (EI, 70 eV) 284 and 282 (<1 and <1%, $M^{+\bullet}$), 247 (<1), 170 (8) and 168 (25), 128 (19), 121 (9), 93 (15), 91 (12), 77 (8), 69 (100).

*(3*S*,3a*S*,6*S*,7*R*,7a*S*)-2,3,3a,6,7,7a-Hexahydro-6-methyl-2-oxo-3,6-methanobenzofuran-7-yl α-Methylacrylate (+)-(3g) and (3*R*,3a*S*,6*R*,7*S*,7a*R*)-3a,8-Dimethyl-2,3,3a,6,7,7a-hexahydro-2-oxo-3,6-methanobenzofuran-7-yl α-Methylacrylate (−)-(4g)*

A solution of compound (+)-(2g) (1.31 g, 5 mmol) in toluene (50 mL) was heated at reflux for 24 h then cooled to 18°C and concentrated under reduced pressure. The residue thus obtained was subject to flash chromatography (silica, hexane to 6 : 94 v/v ethyl acetate/hexane gradient elution) thereby affording two fractions, A and B.

Concentration of fraction A (R_f 0.45 in 1 : 3 : 7 v/v/v ethyl acetate/dichloromethane/hexane) gave the *title compound* (+)-(3g) (353 mg, 27%) as a clear, colourless oil (Found: $M^{+\bullet}$, 262.1207. $C_{15}H_{18}O_4$ requires $M^{+\bullet}$, 262.1205). ν_{max} (KBr)/cm^{-1} 1786, 1722, 1453, 1291, 1161, 998, 717. δ_H 6.20 (1 H, d, *J* 8.2), 6.08 (1 H, s), 6.03 (1 H, dd, *J* 8.2 and 6.4), 5.56 (1 H, s), 4.57 (1 H, m), 4.10 (1 H, m), 3.09 (1 H, m), 1.99 (1 H, d, *J* 13.8), 1.91 (3 H, s), 1.15 (3 H, s), 1.06 (3 H, s), 0.94 (1 H, m). δ_C 181.3, 166.8, 141.5, 135.7, 126.4, 125.2, 71.9, 71.0, 46.3, 42.8, 40.2, 38.3, 20.6, 20.4, 18.3. *m/z* (EI, 70 eV) 262 (23%, $M^{+\bullet}$), 234 (4), 176 (18), 148 (21), 128 (25), 119 (17), 107 (28), 91 (22), 69 (100).

Concentration of fraction B (R_f 0.5 in 1 : 3 : 7 v/v/v ethyl acetate/dichloromethane/hexane) gave the *title compound* (−)-(4g) (733 mg, 56%) as white crystalline masses, mp 63.5–64°C (Found: C 69.0, H 7.2%; $M^{+\bullet}$, 262.1207. $C_{15}H_{18}O_4$ requires C 68.7, H 6.9%; $M^{+\bullet}$, 262.1205). ν_{max} (KBr)/cm^{-1} 1783, 1716, 1448, 1346, 1320, 1287, 1163,

1078, 1028, 949, 821, 720. δ_H 6.48 (1 H, t, *J* 8.2), 6.08 (1 H, s), 5.76 (1 H, br d, *J* 8.2), 5.55 (1 H, s), 4.34 (1 H, m), 4.20 (1 H, m), 2.74 (1 H, m), 2.27 (1 H, dm, *J* 13.9), 1.89 (3 H, br s), 1.25 (3 H, s), 1.07 (1 H, d, *J* 13.9), 0.93 (3 H, s). δ_C 181.4, 166.7, 135.7, 135.3, 131.4, 126.4, 76.2, 69.9, 47.4, 44.7, 34.9(3), 34.9(0), 18.2(3), 18.2(1), 16.9. *m/z* (EI, 70 eV) 262 (13%, $M^{+\bullet}$), 234 (5), 177 (4), 148 (55), 128 (25), 119 (26), 107 (32), 91 (22), 69 (100).

*(3*R*,3a*R*,6*R*,7*S*,7a*S*)-6-Chloro-8,8-dimethyl-2,3,3a,6,7,7a-hexahydro-2-oxo-3,6-methanobenzofuran-7-yl Senecioate (+)-(3h)*

A solution of diester (−)-(2h) (650 mg, 2.1 mmol) in xylene (10 mL) maintained under a nitrogen atmosphere was heated at reflux for 48 h then cooled to 18°C and concentrated under reduced pressure. The resulting light-yellow oil was purified by flash chromatography (silica, 1 : 9 v/v ethyl acetate/hexane elution) and preparative TLC (silica, 5 : 95 v/v ethyl acetate/hexane elution) to afford, after concentration of the relevant fractions (R_f 0.2 in 1 : 4 ethyl acetate/hexane), the *title compound* (+)-(3h) (71 mg, 11%) as white crystalline masses, mp 80–85°C (Found: $M^{+\bullet}$, 310.0971. $C_{16}H_{19}{}^{35}ClO_4$ requires $M^{+\bullet}$, 310.0972). ν_{max} (KBr)/cm^{-1} 1787, 1722, 1650, 1446, 1226, 1141, 849, 711. δ_H 6.46 (1 H, dd, *J* 8.5 and 1.1), 6.04 (1 H, dd, *J* 8.5 and 6.5), 5.76 (1 H, br s), 4.69 (1 H, m), 4.62 (1 H, d, *J* 6.5), 3.50 (1 H, m), 2.30 (1 H, d, *J* 5.0), 2.18 (3 H, s), 1.93 (3 H, s), 1.41 (3 H, s), 1.05 (3 H, s). δ_C 176.6, 165.4, 159.4, 142.4, 123.7, 115.2, 73.8, 73.4, 72.2, 49.7, 43.3, 41.0, 28.0, 27.9, 22.7, 20.9. *m/z* (EI, 70 eV) 312 and 310 (3 and 9%, $M^{+\bullet}$), 275 (8), 141 (24), 131 (49), 125 (35), 105 (44), 91 (100).

*(3*S*,3a*R*,6*S*,7*S*,7a*S*)-3a-Chloro-2,3,3a,6,7,7a-hexahydro-3-methyl-2-oxo-3,6-methanobenzofuran-7-yl Crotonate (−)-(4i)*

A solution of bis-ester (2i) (50 mg, 0.18 mmol) in benzene (15 mL) maintained under a nitrogen atmosphere was heated at reflux for 12 h then cooled to 18°C and concentrated under reduced pressure. The resulting light-yellow oil was purified by flash chromatography (silica, 1 : 4 v/v ethyl acetate/hexane elution). Concentration of the relevant fractions (R_f 0.1) then afforded the *title compound* (−)-(4i) (44 mg, 88%) as white crystalline masses, mp 55°C (Found: $M^{+\bullet}$, 282.0662. $C_{14}H_{15}{}^{35}ClO_4$ requires $M^{+\bullet}$, 282.0659). ν_{max} (KBr)/cm^{-1} 1792, 1719, 1651, 1297, 1180, 1108, 1079, 1026, 792, 715. δ_H 7.01 (1 H, m), 6.51 (1 H, t, *J* 8.5), 6.15 (1 H, d, *J* 8.5), 5.75 (1 H, dm, *J* 14.7), 4.66 (1 H, d, *J* 6.7), 4.45 (1 H, dt, *J* 6.7 and 1.9), 2.83 (1 H, m), 2.46 (1 H, dd, *J* 13.8 and 3.4), 1.90 (3 H, dm, *J* 6.9), 1.28 (1 H, dm, *J* 13.8), 1.19 (3 H, s). δ_C 178.8, 165.5, 146.7, 134.8, 130.9, 121.7, 77.5, 75.4, 69.3, 48.1, 35.6, 35.0, 18.6, 18.1. *m/z* (EI, 70 eV) 284 and 282 (<1 and 1%, $M^{+\bullet}$), 178 (6), 170 (6), 168 (18), 150 (6), 149 (4), 139 (6), 128 (15), 121 (14), 93 (18), 91 (14), 77 (8), 69 (100).

*(3*R*,3a*R*,6*R*,7*S*,7a*S*)-6-Chloro-2,3,3a,6,7,7a-hexahydro-2-oxo-3,6-methanobenzofuran-7-yl Senecioate (3j) and (3*S*,3a*R*,6*S*,7*S*,7a*S*)-3a-Chloro-2,3,3a,6,7,7a-hexahydro-2-oxo-3,6-methanobenzofuran-7-yl Senecioate (−)-(4k)*

The mixture of bis-esters (2j) and (2k) (1.05 g, 3.7 mmol), prepared as described above, was dissolved in toluene (10 mL) and the resulting solution was heated at reflux under a nitrogen atmosphere for 16 h then cooled to 18°C and concentrated under reduced pressure. The resulting light-yellow oil was purified by flash chromatography (silica, 1 : 4 v/v ethyl acetate/hexane) to afford two fractions, A and B.

Concentration of fraction A (R_f 0.1) gave the *title compound* (+)-(3j) [436 mg, 84% from (2j)] as a clear, colourless oil (Found: $M^{+\bullet}$, 282.0647. $C_{14}H_{15}{}^{35}ClO_4$ requires $M^{+\bullet}$, 282.0659). ν_{max} (KBr)/cm^{-1} 1794, 1718, 1648, 1450, 1226, 1139, 849, 705. δ_H 6.53 (1 H, m), 6.10 (1 H, m), 5.78 (1 H, m), 4.65 (1 H, m), 4.48 (1 H, m), 3.50 (1 H, m), 2.56 (1 H, m), 2.46 (1 H, d, *J* 13.3), 2.16 (3 H, s), 1.99 (1 H, tm, *J* 11.1), 1.93 (3 H, s). δ_C 177.9, 165.5, 159.4, 140.9, 125.3, 115.1, 72.6, 71.8, 64.2, 40.2, 38.7, 35.5, 28.0, 20.9. *m/z* (EI, 70 eV) 284 and 282 (7 and 20%, $M^{+\bullet}$), 247 (16), 183 (4), 91 (6), 83 (100), 82 (25).

Concentration of fraction B (R_f 0.2) gave the *title compound* (−)-(4k) [435 mg, 84% from (2e)] as white crystalline masses, mp 88°C (Found: C 59.3, H 5.6, Cl 12.5%; $M^{+\bullet}$, 282.0658. $C_{14}H_{15}{}^{35}ClO_4$ requires C 59.5, H 5.35, Cl 12.5%; $M^{+\bullet}$, 282.0659). ν_{max} (KBr)/cm^{-1} 1797, 1712, 1647, 1443, 1232, 1192, 1133, 1088, 1044, 1011, 951, 850, 717, 706. δ_H 6.52 (1 H, t, *J* 7.3), 6.19 (1 H, m), 5.70 (1 H, s), 4.63 (1 H, m), 4.38 (1 H, m), 2.87 (1 H, br s), 2.59 (1 H, dm, *J* 11.1), 2.29 (1 H, broadened d, *J* 13.3), 2.14 (3 H, s), 1.90 (3 H, s), 1.72 (1 H, t, *J* 13.3). δ_C 177.2, 165.5, 159.3, 135.4, 131.2, 115.0, 78.8, 70.9, 69.0, 47.0, 34.5, 28.1, 28.0, 20.8. *m/z* (EI, 70 eV) 284 and 282 (1 and 5%, $M^{+\bullet}$), 164 (100), 154 (27), 107 (61), 103 (23), 91 (41).

*(3*SR*,3a*RS*,6*SR*,7*RS*,7a*SR*,8*RS*)-8-Methyl-2,3,3a,4,5,6,7,7a-octahydro-2-oxo-3,6-methanobenzofuran-7-yl Butyrate (±)-(5), (3*S*,3a*R*,6*S*,7*R*,7a*S*,8*R*)-8-Methyl-2,3,3a,4,5,6,7,7a-octahydro-2-oxo-3,6-methanobenzofuran-7-yl Butyrate (+)-(5), and (3*R*,3a*S*,6*R*,7*S*,7a*R*,8*S*)-8-Methyl-2,3,3a,4,5,6,7,7a-octahydro-2-oxo-3,6-methanobenzofuran-7-yl Butyrate (−)-(5)*

A magnetically stirred solution of compound (±)-(3a) (74 mg, 0.3 mmol) in ethanol (15 mL) was treated with 10% Pd on C (30 mg) and a hydrogen atmosphere was then established above the reaction mixture. Stirring was continued at ca. 18°C for 16 h then the reaction mixture was filtered through a short pad of Celite which was washed with ethanol (15 mL). The combined filtrates were concentrated under reduced pressure and the resulting pale-yellow oil was purified by flash chromatography (silica, 3 : 7 v/v ethyl acetate/hexane elution). Concentration of the appropriate fractions (R_f 0.35) then afforded the *title compound* (±)-(5) (74 mg, 97%) as a clear, colourless oil (Found: $M^{+\bullet}$, 252.1360. $C_{14}H_{20}O_4$ requires $M^{+\bullet}$, 252.1362). ν_{max} (KBr)/cm^{-1} 2963, 1789, 1736, 1255, 1174, 1068, 1015, 972, 884. δ_H 4.83 (1 H, br t, *J* 6.6), 4.71 (1 H, dd, *J* 6.6 and 1.9), 2.59 (1 H, m), 2.43–2.23 (2 H, complex m), 2.08 (1 H, br d, *J* 4.5), 1.95 (1 H, m), 1.87–1.58 (6 H, complex m), 1.44 (1 H, m), 1.17 (3 H, d, *J* 7.2), 0.96 (3 H, t, *J* 7.3). δ_C 179.5, 173.3, 76.5, 72.2, 44.5, 37.0, 36.2, 34.9, 26.6, 20.2, 18.8, 18.2, 15.0, 14.1. *m/z* (EI, 70 eV) 252 (<1%, $M^{+\bullet}$), 224 (26), 181 (34), 164 (24), 136 (25), 109 (22), 107 (14), 71 (100).

Subjection of compound (+)-(3d) to the same reaction conditions as defined immediately above [except for the addition of *N*,*N*-diisopropylethylamine (180 mole equiv. with respect to the substrate) to the reaction mixture] afforded lactone (+)-(5) (98%) as a clear, colourless oil, which was identical, in all respects, with the racemic material (±)-(5) save for being optically active (see Table 3).

Subjection of compound (−)-(4d) to the same reaction conditions as defined immediately above [except for the addition of *N*,*N*-diisopropylethylamine (180 mole equiv. with respect to the substrate) to the reaction mixture] afforded lactone (−)-(5) (99%) as a clear, colourless oil, which was identical, in all respects, with the racemic material (±)-(5) save for being optically active (see Table 3).

Crystallography

Crystal Data

The crystal data for compounds (±)-(3a), (+)-(3b), (+)-(3c), (+)-(3d), (−)-(4c), (−)-(4f), and (−)-(4g) are presented in Table 1.

Structure Determinations

Intensity data were collected by a Nonius Kappa CCD diffractometer and extracted from diffraction images by the DENZO[9] package. Analytical absorption corrections were applied.[10] All structures were solved by direct methods[11] and expanded using Fourier techniques.[12] Full-matrix least-squares refinement was on *F*, non-hydrogen atoms were refined anisotropically, while hydrogen atoms were included at geometrically determined positions and ride on the carbon of attachment. The ADEP of (±)-(3a) was generated using CAMERON software.[13] The structure of (−)-(4c) comprises of four crystallographically independent molecules per asymmetric unit with one molecule being conformationally disordered. Compound (−)-(4f) crystallizes with two molecules per asymmetric unit with one of the two molecules being disordered at the side chain terminus. The disordered portions were restrained to reasonable bonding geometry and occupancy refined.

Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited with the Cambridge Crystallographic

Data Centre (CCDC nos: (±)-(3a) 208 292, (+)-(3b) 208 293, (+)-(3c) 208 294, (+)-(3d) 208 296, (−)-(4c) 208 295, (−)-(4f) 208 297, and (−)-(4g) 208 291).

Acknowledgments

We are grateful to the Institute of Advanced Studies (IAS) and the Australian Research Council for financial support. The Deutsche Forschungsgemeinschaft (DFG) is thanked for provision of a post-doctoral stipend to M.M.V. C.C. acknowledges Nanjing University of Science and Technology for financial support and for providing a period of study leave that enabled him to spend time in the Research School of Chemistry.

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