Origins of stereoselectivity in the chelation-controlled addition of alkyl radicals to α-methylene-γ-oxycarboxylic acid esters †

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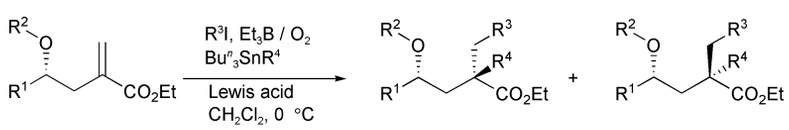
The diastereoselectivity in the chelation-controlled alkyl radical ($R^{3\bullet}$) additions to α-methylene-γ-oxycarboxylic acid esters **1**–**12** was rationalised by analysing the low-energy conformers of radical intermediate models **46**–**59** and **66**–**69**, which resemble the structures of early transition states of the exothermic transfer of a H-atom or allyl group. The sense of diastereoselectivity depends principally on the conformations of the sharply folded seven-membered chelate ring and the dihedral angle O=C–O–C of the ester moiety. The transfer reaction to the radical intermediate bearing an ethoxy group with *Z*-geometry (dihedral angle *ca.* 0°) occurs predominantly on the exposed outside face of the radical centre, whereas the ethoxy group with *E*-geometry (dihedral angle *ca.* 180°) shields the outside face of the radical centre and lowers the diastereoselectivity. The diastereoselectivity depends also on the conformation of the CH_2R^3 group attached to the radical centre. When the CH_2–R^3 bond is perpendicular to the radical face, R^3 shields the outside face of the radical centre. The intermediate bearing the ethoxy group with *Z*-geometry and the CH_2–R^3 bond parallel to the radical face affords the highest *syn*-selectivity in the reactions of γ-methoxymethoxy and γ-benzyloxy esters.

Introduction

During the past decade the stereochemical control of acyclic radical reactions has received considerable attention and significant levels of diastereoselectivity in reactions involving stereogenic centres adjacent to the radical centre (1,2-asymmetric induction) or chiral auxiliaries have been achieved when they adopt preferred conformations.[1] The use of Lewis acids offers the possibility of regulating conformations and improves the stereoselectivity in acyclic radical reactions.[2] However, to our knowledge, little is known about radical-mediated 1,3-asymmetric induction.[3] We have recently reported chelation-controlled 1,3-asymmetric induction in radical-mediated additions to α-methylene-γ-oxycarboxylic acid esters **1**–**12** (Schemes 1 and 2).[4] Salient results from these studies are shown in Table 1. The diastereoselectivity depended on the substituents R^1 and R^2 and the alkyl iodides R^3I. The radical reactions of γ-hydroxy, γ-methoxy and γ-methoxymethoxy (MOMO) esters **1**–**5** and **7**–**10** (R^2 = H, Me, MOM) with methyl, ethyl or isopropyl iodide (R^3 = Me, Et or Pr^i) performed in the presence of Lewis acid gave *syn*-adducts predominantly (Table 1, entries 1–4, 6–11, 13–15, 17–19, 21, 22 and 24–26). In the addition of the bulky *tert*-butyl radical, however, the selectivity was reversed and the major products were *anti*-adducts (entries 5, 16, 20, 23 and 27). In contrast to the substrates mentioned above, γ-benzyloxy esters **6**, **11** and **12** (R^2 = Bn) showed *syn*-selectivity irrespective of the bulk of the alkyl iodides (entries 10–12 and 29–33) except for entry 28.

† Electronic suppementary information (ESI) available: heats of formation and low energy conformers. See http://www.rsc.org/suppdata/p1/b2/b205613p/

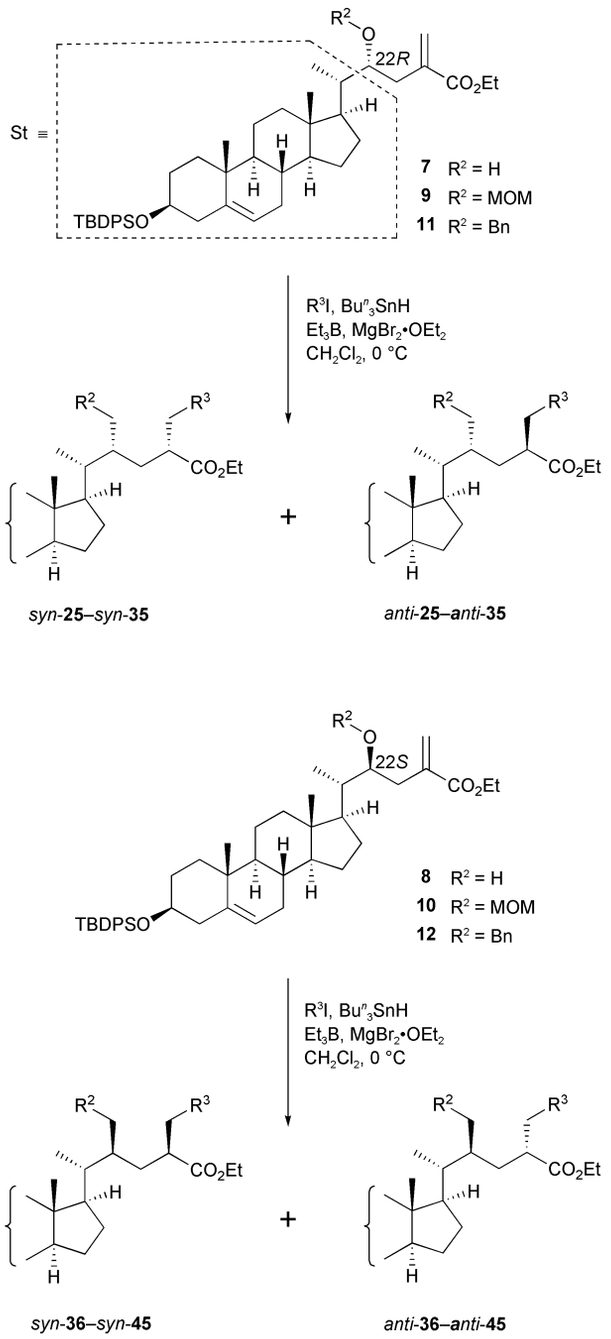


1–6 *syn*-**13**–*syn*-**24** *anti*-**13**–*anti*-**24**

1 R^1 = Ph, R^2 = H
2 R^1 = Bu^t, R^2 = H
3 R^1 = Ph, R^2 = Me
4 R^1 = Ph, R^2 = MOM
5 R^1 = Bu^t, R^2 = MOM
6 R^1 = Ph, R^2 = Bn

13 R^3 = Pr^i, R^4 = H
14 R^3 = Et, R^4 = allyl
15 R^3 = Pr^i, R^4 = H
16 R^3 = Et, R^4 = allyl
17 R^3 = Bu^t, R^4 = H
18 R^3 = Pr^i, R^4 = H
19 R^3 = Et, R^4 = allyl
20 R^3 = Pr^i, R^4 = H
21 R^3 = Et, R^4 = allyl
22 R^3 = Pr^i, R^4 = H
23 R^3 = Et, R^4 = allyl
24 R^3 = Bu^t, R^4 = H

Scheme 1 Radical reactions of α-methylene-γ-oxycarboxylic acid esters **1**–**6** with alkyl iodides R^3I in the presence of Lewis acids.



25,	**36**	R^2 = H, R^3 = Me		**42**	R^2 = MOM, R^3 = Pr^i
26,	**37**	R^2 = H, R^3 = Et	**31**,	**43**	R^2 = MOM, R^3 = Bu^t
27,	**38**	R^2 = H, R^3 = Pr^i	**32**		R^2 = Bn, R^3 = Me
28,	**39**	R^2 = H, R^3 = Bu^t	**33**,	**44**	R^2 = Bn, R^3 = Et
29,	**40**	R^2 = MOM, R^3 = Me	**34**		R^2 = Bn, R^3 = Pr^i
30,	**41**	R^2 = MOM, R^3 = Et	**35**,	**45**	R^2 = Bn, R^3 = Bu^t

Scheme 2 Radical reactions of α-methylene-γ-oxycarboxylic acid esters **7**–**12** with alkyl iodides R^3I in the presence of Lewis acids.

In this paper, we report the rationales for the observed diastereoselectivities in the alkyl radical addition to the electron deficient alkenes **1**–**12** by analysing the low-energy conformers of seven-membered chelate radical intermediate models **46**–**59** and **66**–**69**.[5] The transfer of a hydrogen atom or allyl group to the radical intermediates from Bu^n_3SnH or $Bu^n_3SnCH_2CH{=}CH_2$ would occur predominantly on the more exposed radical face of the low energy conformers resembling the structures of early transition states of the exothermic transfer reactions.[6]

Results and discussion

(1) Confirmation of the chelate ring formation by ^{1}H NMR spectroscopy

Lewis acids play two important roles, stereochemical control and rate enhancement, in radical-mediated C–C bond forming reactions. Complexation with Lewis acids lowers the LUMO energy of substrates and enhances the rate of nucleophilic radical addition reaction.[7] The stereochemical control can be achieved when the rotamer populations are restricted by complex formation and the complexed substrates react faster than the non-complexed substrates.

Before the conformational analysis of the radical intermediates, we confirmed the seven-membered chelate ring formation of the starting materials **4**–**6** by the use of complexation experiments with $MgBr_2{\cdot}OEt_2$.[8] The complexation of the substrates with 3 equiv. of $MgBr_2{\cdot}OEt_2$ in $CDCl_3$ was achieved by sonication at room temperature for 1 h. The $\Delta\delta$ values [δ_H(substrate + $MgBr_2{\cdot}OEt_2$) − δ_H(substrate)] of **4**–**6** are shown in Fig. 1. The large difference in chemical shift increments

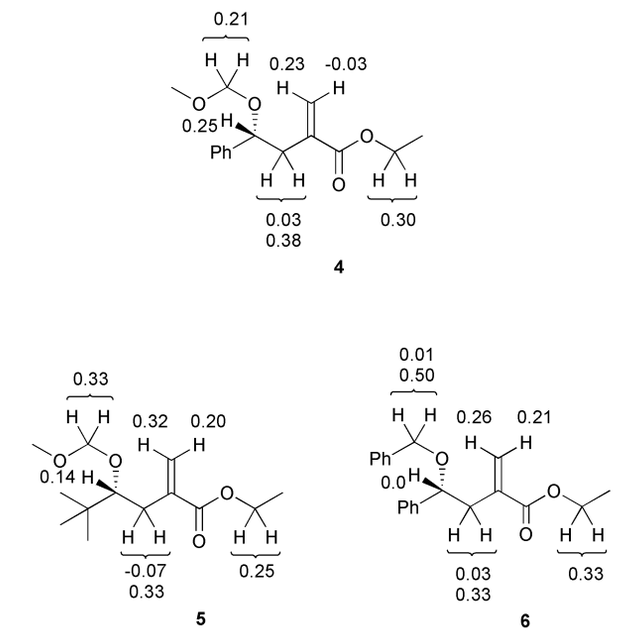


Fig. 1 Δδ values (ppm) for the substrates **4**–**6**. $\Delta\delta_H = \delta_H$(substrate + $MgBr_2{\cdot}OEt_2$) − δ_H(substrate) The δ_H(substrate + $MgBr_2{\cdot}OEt_2$) values were obtained after sonication of **4**–**6** with 3 equiv. of $MgBr_2{\cdot}OEt_2$ in $CDCl_3$.

between the diastereotopic β-methylene protons as well as the chemical shift increments Δδ on adding the Lewis acid suggest the formation of bidentate complexation.

(2) Conformational analysis of the radical intermediates

Exhaustive searches of low-energy conformers of the flexible seven-membered radical intermediates were performed with the program CONFLEX[9] using the MM2 force field for energy minimisation,[10,11] followed by semi-empirical molecular orbital calculations (PM3)[12] of the resulting conformers using the Hamiltonian implemented in MOPAC 6.0.[13] The calculations were performed for models with tetrahedral arrangements around the magnesium ion and the radical centre. Diethyl ether, as coordinated ligand, is omitted for the calculations. The reactions of **3** and **6** performed with $MgBr_2{\cdot}OEt_2$ instead of $MgBr_2$ also gave the *syn* products **16** and **23**, respectively, as the major products.[4b]

Metzger and co-workers have chosen $[Li(OH_2)_2]^+$ as Lewis acid instead of $MgBr_2$ because the lithium parameters for PM3 are more reliable compared to the magnesium parameters.[3b] However, in our case the replacement of the Lewis acid is not

Table 1 Diastereoselectivity in the radical reactions of α-methylene-γ-oxycarboxylic acid esters **1**–**12** with alkyl iodides R^3I in the presence of Lewis acids[a–c]

Entry	Substrate	R^1	R^2	R^3	R^4	Yield(%)	*syn* : *anti*
1	**1**	Ph	H	Pr^i	H	80	2.5 : 1
2	**2**	Bu^t	H	Et	Allyl	44	*syn* only
3	**3**	Ph	Me	Pr^i	H	96	4.3 : 1
4	**3**			Et	Allyl	53	12.2 : 1
5	**3**			Bu^t	H	91	1 : 3.8
6	**4**	Ph	MOM	Pr^i	H	63	2.8 : 1
7	**4**			Et	Allyl	48	5.5 : 1
8	**5**	Bu^t	MOM	Pr^i	H	78	10 : 1
9	**5**			Et	Allyl	63	*syn* only
10	**6**	Ph	Bn	Pr^i	H	86	15 : 1
11	**6**			Et	Allyl	66	16.7 : 1
12	**6**			Bu^t	H	82	3.8 : 1
13	**6** (22*R*)	St[d]	H	Me	H	87	5.1 : 1
14	**7**			Et	H	95	3.4 : 1
15	**7**			Pr^i	H	88	3.3 : 1
16	**7**			Bu^t	H	99	1 : 3.2
17	**8** (22*S*)	St	H	Me	H	78	6.5 : 1
18	**8**			Et	H	83	2.0 : 1
19	**8**			Pr^i	H	95	3.2 : 1
20	**8**			Bu^t	H	94	1 : 3.0
21	**9** (22*R*)	St	MOM	Me	H	49	3.1 : 1
22	**9**			Et	H	76	3.5 : 1
23	**9**			Bu^t	H	60	1 : 4.1
24	**10** (22*S*)	St	MOM	Me	H	71	3.8 : 1
25	**10**			Et	H	84	6.1 : 1
26	**10**			Pr^i	H	74	1.8 : 1
27	**10**			Bu^t	H	83	1 : 3.2
28	**11** (22*R*)	St	Bn	Me	H	51	1 : 1.3
29	**11**			Et	H	73	*syn* only
30	**11**			Pr^i	H	39	8.8 : 1
31	**11**			Bu^t	H	68	3.7 : 1
32	**12** (22*S*)	St	Bn	Et	H	84	1.4 : 1
33	**12**			Bu^t	H	84	2.0 : 1

[a] For entries 1, 3, 5, 6, 8, 10 and 12, see: ref. 4*a*; for entries 2, 4, 7, 9 and 11, see: ref. 4*b*; for entries 13–20, 22, 25 and 27–33, see: ref. 4*c*; for entries 21, 23, 24 and 26 see: Experimental section of this work. [b] $MgBr_2{\cdot}OEt_2$ was used as Lewis acid except entries 2, 4, 7, 9 and 11, for which $MgBr_2$ was used. [c] The reactions without Lewis acid showed no diastereoselectivity. [d] For definition of St, see Scheme 2.

suitable for the calculations because the interaction between the bromine atom and the R^2 group is an important factor controlling the chelate ring conformation.

(2-1) Conformational analysis of the radical intermediates 51–53 (R^2 = H). In the reactions of hydroxy esters **1**, **2**, **7** and **8** (R^2 = H), the diastereoselectivity depended largely on the size of the alkyl radicals (R^3), but the size and geometry of the R^1 groups hardly affected the selectivity. The poor influence of R^1 on the selectivity presents a striking contrast to that of the corresponding methoxymethyl ethers (MOMO) **4**, **5**, **9** and **10** and benzyl ethers **6**, **11** and **12** (*vide infra*). For the conformational analysis, we therefore chose simpler methyl ester intermediate models **46A**–**46D** having an isopropyl group as R^1 instead of the phenyl group or the steroidal skeleton, and a methoxycarbonyl group instead of the ethoxycarbonyl group. The CONFLEX calculations of the models **46A**–**46D** generated 38 lowest energy conformers within 8.8 kcal mol^{-1}, 41 lowest energy conformers within 4.0 kcal mol^{-1}, 19 lowest energy conformers within 5.5 kcal mol^{-1} and 66 lowest energy conformers within 4.0 kcal mol^{-1}, respectively.[14] The PM3 calculations for each of the searched conformers gave the global minimum energy conformer **46A-1** (not shown, see the corresponding ethyl ester **51A-1** in Fig. 2) together with five low energy conformers within 2.5 kcal mol^{-1} of the global minimum energy structure. These conformers differ in geometries of the propyl and methoxy groups. The lowest energy conformers for the diastereomers **46B**–**46D** were 5.3, 3.2 and 3.8 kcal mol^{-1} higher in energy than the global minimum energy conformer **46A-1** was, respectively, and therefore the participation of these low-energy conformers to the diastereoselectivity is ignored.

Table 2 Diastereoselectivity in the radical reactions of α-methylene-γ-oxycarboxylic acid esters **6**, **60** and **61** with isopropyl or *tert*-butyl iodide in the presence of $MgBr_2{\cdot}OEt_2$.

Entry	Substrate	R′	Yield(%)	*syn* : *anti*
1	**60**	Pr^i	95	5.6 : 1
2	**6**	Pr^i	86	15 : 1
3	**61**	Pr^i	99	17 : 1
4	**60**	Bu^t	95	1.6 : 1
5	**6**	Bu^t	82	3.8 : 1
6	**61**	Bu^t	97	5.4 : 1

The conformational analysis of the low-energy structures including **46A-1** suggests that the geometry of the ester moiety would largely affect the selectivity. In fact, the diastereoselectivity in the reactions of benzyloxy esters **6**, **60** and **61** has been shown to depend on the bulk of the alkoxy group in the ester moiety (see Scheme 3 and Table 2). Based on these observations, we examined newly the analysis of low-energy conformers of ethyl ester **51A**, an intermediate model for the addition reactions to γ-hydroxy esters **1** and **2**. Similar calculations for **51A** as described above gave the global minimum energy conformer **51A-1** and two low-energy conformers **51A-2** and **51A-3** within 2.50 kcal mol^{-1} of the global minimum energy structure (Fig. 2, **51A-3** is not shown). The three conformers have an ester group with *E*-geometry (dihedral angle O=C–O–C = −163.2° for **51A-1** and 175.4° for **51A-2**), and both the ethoxy group in the ester moiety and the propyl group attached to the radical centre shield the outside face of the radical centre. The arrangement around the magnesium ion is not congested because of the presence of a small hydrogen atom as R^2. The H-atom or allyl transfer would, therefore, occur preferentially

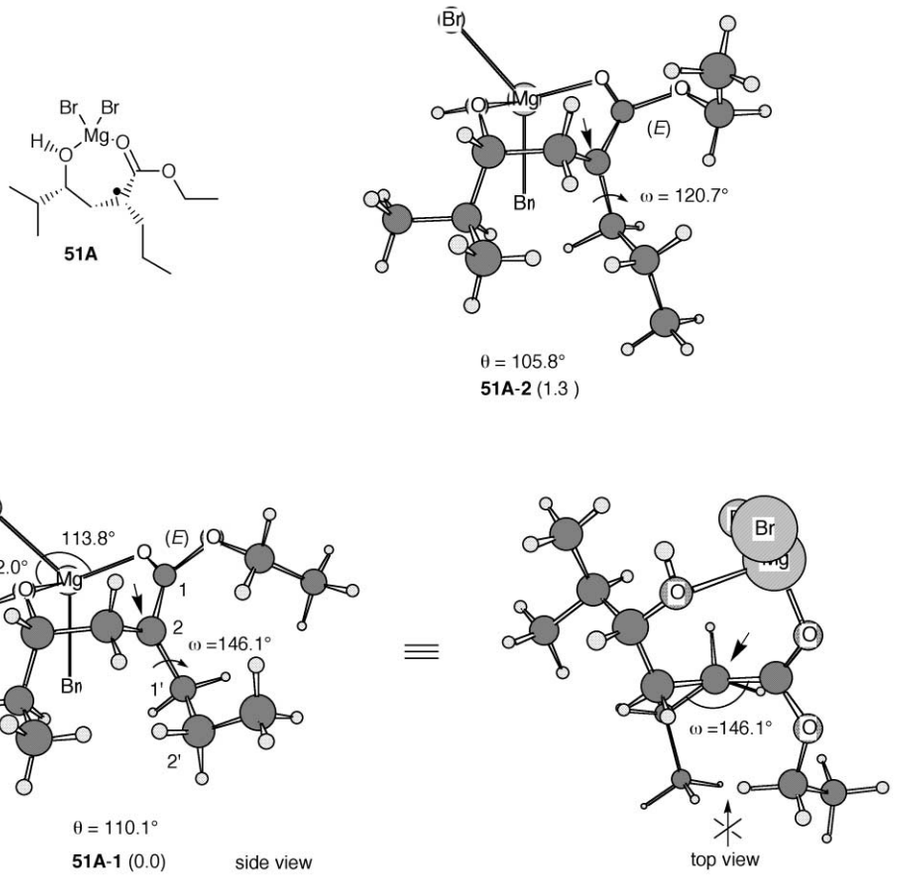
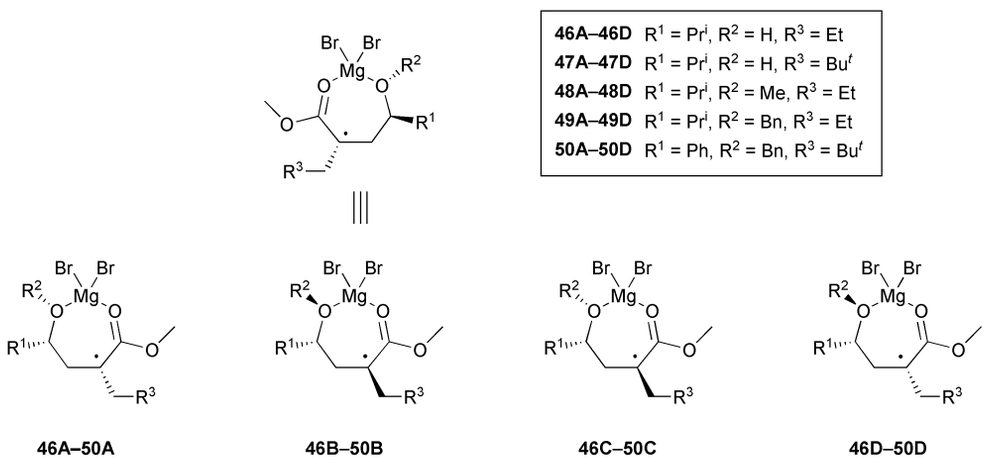
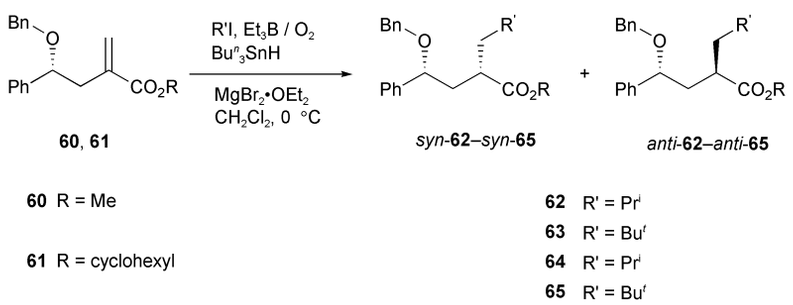


Fig. 2 Low-energy structures **51A-1** and **51A-2** (relative energy/kcal mol^{-1}) of chelated radical intermediate model **51A**.



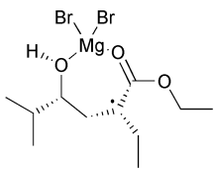
from the less hindered inside face of seven-membered heterocyclic intermediates **51A-1**–**51A-3** to give the *syn*-adduct. Although a linear C ··· H ··· Sn geometry is preferable in the intermolecular H-atom transfer from Bu^n_3SnH, a slight deviation from linearity may be allowed.[5c,15]

The low-energy conformers of **52A**, an intermediate model in the methyl radical addition to γ-hydroxy esters, were also exhaustively searched. The *syn*-selectivities in the reaction of **7** and **8** with methyl iodide were higher in comparison to those with ethyl iodide (entries 13 *vs.* 14 and entries 17 *vs.* 18). The higher *syn*-selectivity in the former reaction is attributed to the higher shielding of the outside face of radical centre by the



Scheme 3 Radical reactions of methyl and cyclohexyl α-methylene-γ-oxycarboxylates **60** and **61** with alkyl iodides in the presence of $MgBr_2$·OEt_2.

methyl group (= R^3) in the radical intermediate **52A-1** (not shown). The dihedral angle (ω) C1–C2–C1′–C2′ of **51A-1** is 146.1°, whereas that of **52-1** is 110.7°, *i.e.*, the CH_2–CH_3 bond is perpendicular to the radical face and the methyl group shields the outside face of the radical centre more effectively.



52A

The search of low-energy conformers of the methyl ester radical intermediates **47A**–**47D** (R^1 = Pr^i, R^2 = H, R^3 = Bu^t), intermediate models in the addition of *tert*-butyl radical, gave the global minimum energy conformer **47A-1** (not shown). The PM3 calculations for the structures obtained by replacing the methoxy group of the low-energy conformers of **47A** with ethoxy group gave low-energy conformers **53-1**–**53A-3** (Fig. 3).[16] The *anti*-selectivities in the reactions of **1**, **2**, **7** and **8** with *tert*-butyl iodide (see entries 16 and 20 in Table 1) are rationalised on the basis of the conformational analysis of **53A-1**–**53A-3** which have an ester group with *Z*-geometry (dihedral angle O=C–O–C = 6.2° for **53A-1**, 7.4° for **53A-2** and 1.2° for **53A-3**) and the dihedral angle (ω) C1–C2–C1′–C2′ of about −150°. In these structures neither the ethoxy group of the ester moiety nor the neopentyl group attached to the radical centre shields the radical face of the intermediates. The tin reagent therefore approaches preferentially from the exposed face of the radical centre in **53A-1**–**53A-3** to give the *anti*-adduct (shown by an arrow in Fig. 3).

The radical intermediates mentioned above have a sharply folded seven-membered chelate ring. The ring fold angle θ (deg) of the radical intermediates is shown in Figs. 2 and 3. The ring fold angle θ is defined to be the angle formed by the radical centre (C_2), the midpoint m_1 between C_1 and C_3, and the midpoint m_2 between the carbonyl oxygen atom and C_4 (Fig. 4).

(2-2) Conformational analysis of the radical intermediates 54–56 (R^2 = Me). The successive CONFLEX and PM3 calculations for methyl ethers **48A**–**48D** (R^1 = Pr^i, R^2 = Me, R^3 = Et) gave the global minimum energy conformer and 6 low-energy conformers within 2.0 kcal mol^{-1} of the global minimum energy structure (not shown), which were derived from **48B**. The structure of **48A** is not the energetically favoured arrangement because of the larger steric repulsion between the isopropyl and bulky methyl groups compared to that between the isopropyl group and the smaller hydrogen atom in **46A**.

On the bases of these results, **54** (R^1 = Ph, R^2 = Me, R^3 = Et) was chosen as an intermediate model in the ethyl radical addition to γ-methoxy ester **3**. The calculations for **54B** gave the global minimum energy structure **54B-1** and a low energy conformer **54B-2** which is 1.3 kcal mol^{-1} higher in energy than the global minimum structure (Fig. 5). In the conformer **54B-1**, both the ethoxy group with *E*-geometry and the propyl group attached to the radical centre shield the outside face of the radical centre. In contrast, the ethoxy group with *Z*-geometry in the structure **54B-2** does not shield the radical centre and would allow allyl transfer from the outside face of the radical centre. However, the contribution of the conformer **54B-2** is

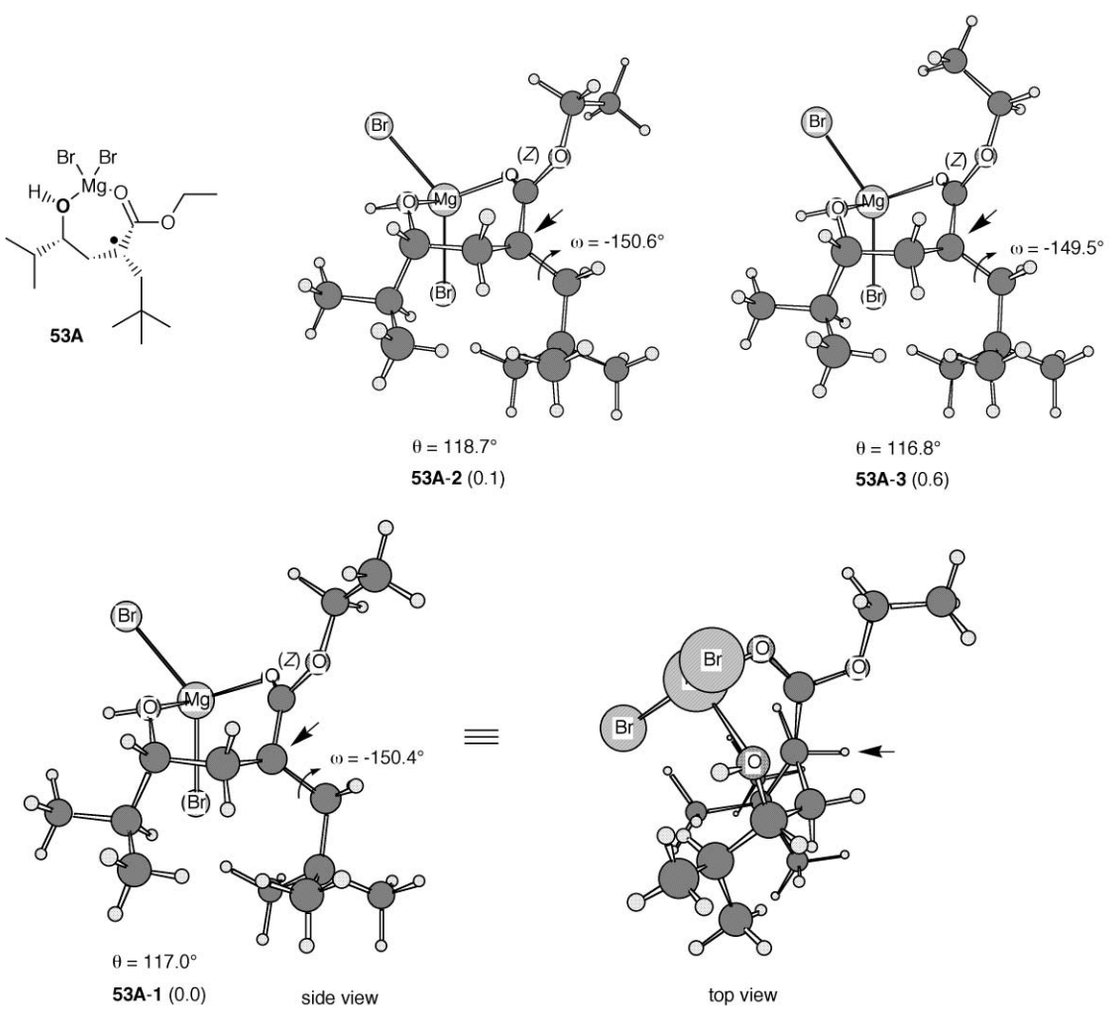
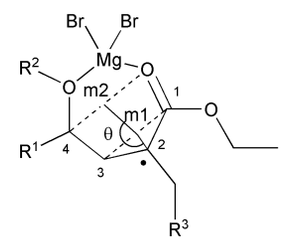


Fig. 3 Low-energy structures **53A-1**–**53A-3** (relative energy/kcal mol^{-1}) of chelated radical intermediate model **53A**.

not expected because of the low population. The high *syn*-selectivity in the allylation of **3** (Table 1, entry 4), therefore, can not be readily explained from the calculations.

The PM3 calculations for the structure obtained by replacing the isobutyl group of the global minimum energy structure of **55B** with a neopentyl group gave the global minimum energy structure **56B-1** as shown in Fig. 5.[17] Both the ethoxy group with *E*-geometry and the neopentyl group attached to the radical centre in **56B-1** shield the outside face of the radical centre and the H-atom transfer to the intermediate may proceed preferentially from the less hindered opposite face and afford *anti*-**17** predominantly.

(2-3) Conformational analysis of the radical intermediates 57 and 58 (R^2 = MOM). The high *syn*-selectivity in the reaction of MOM ether **5** with ethyl iodide and allyltributyltin affording **19** (Table 1, entry 9) can be explained as a result of the allyl transfer from the outside face of the sharply folded chelate ring in the global minimum energy conformer **57B-1** (Fig. 6). Neither the ethoxy group (*Z*-geometry) nor the propyl group attached to the radical centre (ω = 53.5°) shields the outside face of radical centre, whereas the opposite face is shielded by the congested arrangement around the magnesium ion.



θ (deg) = ring fold angle C2–m1–m2

Fig. 4 Definition of ring folding angle θ.

The *syn*-selectivities in the reactions of MOM ethers **4**, **9** and **10** with methyl, ethyl or isopropyl iodide were lower than the corresponding selectivities of **5** (Table 1, entries 6–9, 21, 22 and 24–26). The lower selectivity in the allylation reaction of **4** is attributed to the CH_2–CH_2CH_3 bond perpendicular to the radical face (dihedral angle $\omega = -93.8°$) and the shielding of the radical face by the ethyl group in the global minimum energy structure bearing an ethoxy group with *Z*-geometry (not shown). The calculations also show the presence of a conformer with nearly the same energy, but in the conformer the radical centre is shielded by the ethoxy group with *E*-geometry.

The steric interactions between the substituent R^1 and the methoxymethyl group (or benzyl group in the case of compounds **6**, **11** and **12**) regulate the conformation of the remote ethoxy group of the ester moiety and the CH_2R^3 group attached to the radical centre. In the case of hydroxy esters **1**, **2**, **7** and **8**, however, the substituents R^1 had virtually no effect on the selectivity because of the weaker interactions between R^1 and the small hydrogen atom (= R^2) (*vide supra*).

The *anti*-selectivity in the reaction of MOM ethers **9** and **10** with *tert*-butyl iodide is inferred from the conformational analysis of the global minimum energy structure **58B-1** (Fig. 7). The structures of **58B-2** and **58B-3** differ from **58B-1** only in the geometry of the ethoxy group. The front side of the radical centre in **58B-1** is completely shielded by the *tert*-butyl group and consequently the H-atom transfer may proceed from the less hindered back side of the radical centre to give the *anti*-product.

(2-4) Conformational analysis of the radical intermediates 59 and 66–69 (R^2 = Bn). The combined CONFLEX and PM3 calculations for the methyl ester **49B** (R^1 = Pr^i, R^2 = Bn, R^3 = Et) gave the global minimum energy conformer having a ring conformation similar to that of **59B-1** in Fig. 8. The lowest-

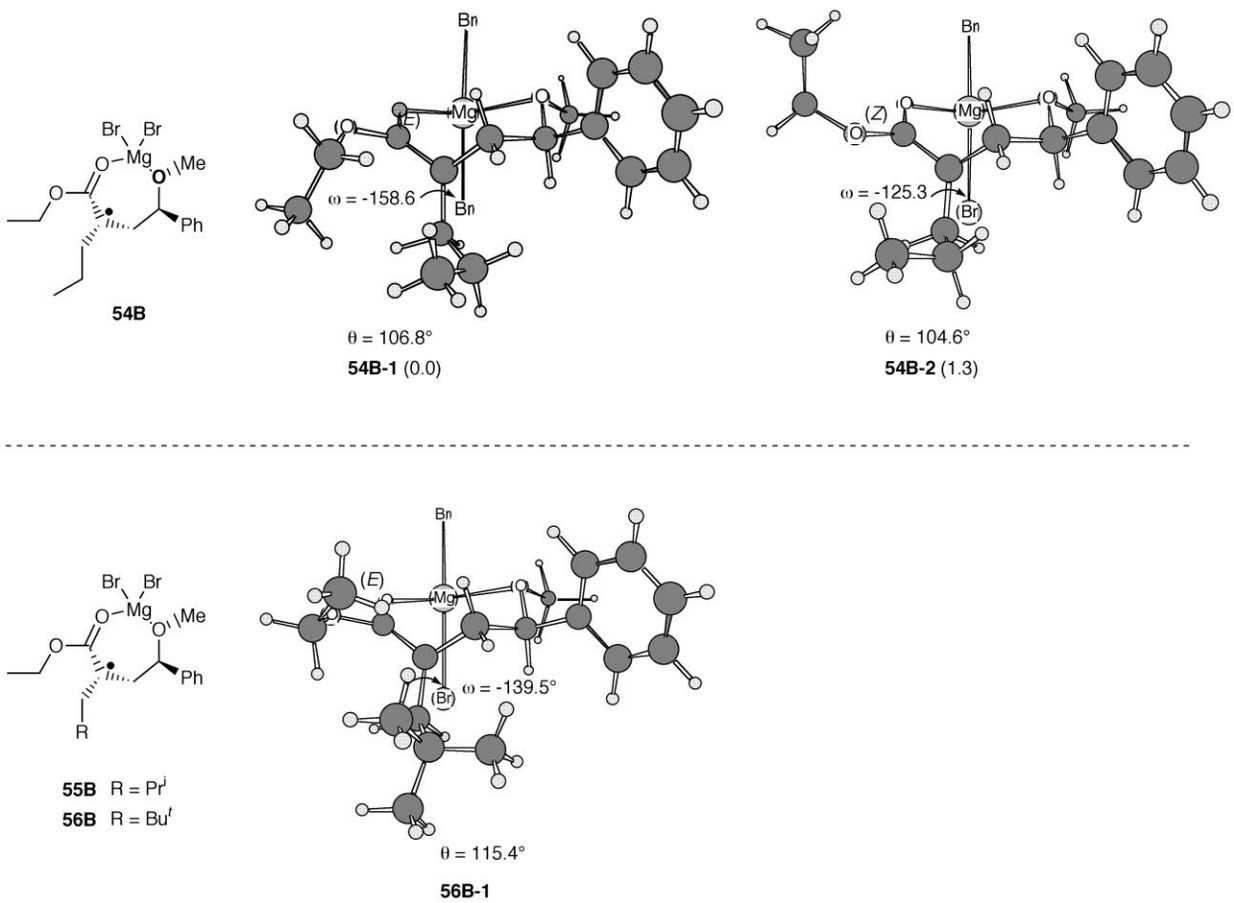


Fig. 5 Low-energy structures **54B-1** and **54B-2** of chelated radical intermediate model **54B** (relative energy/kcal mol^{-1}), and the global minimum structure **56B-1** of chelated radical intermediate **56B**.

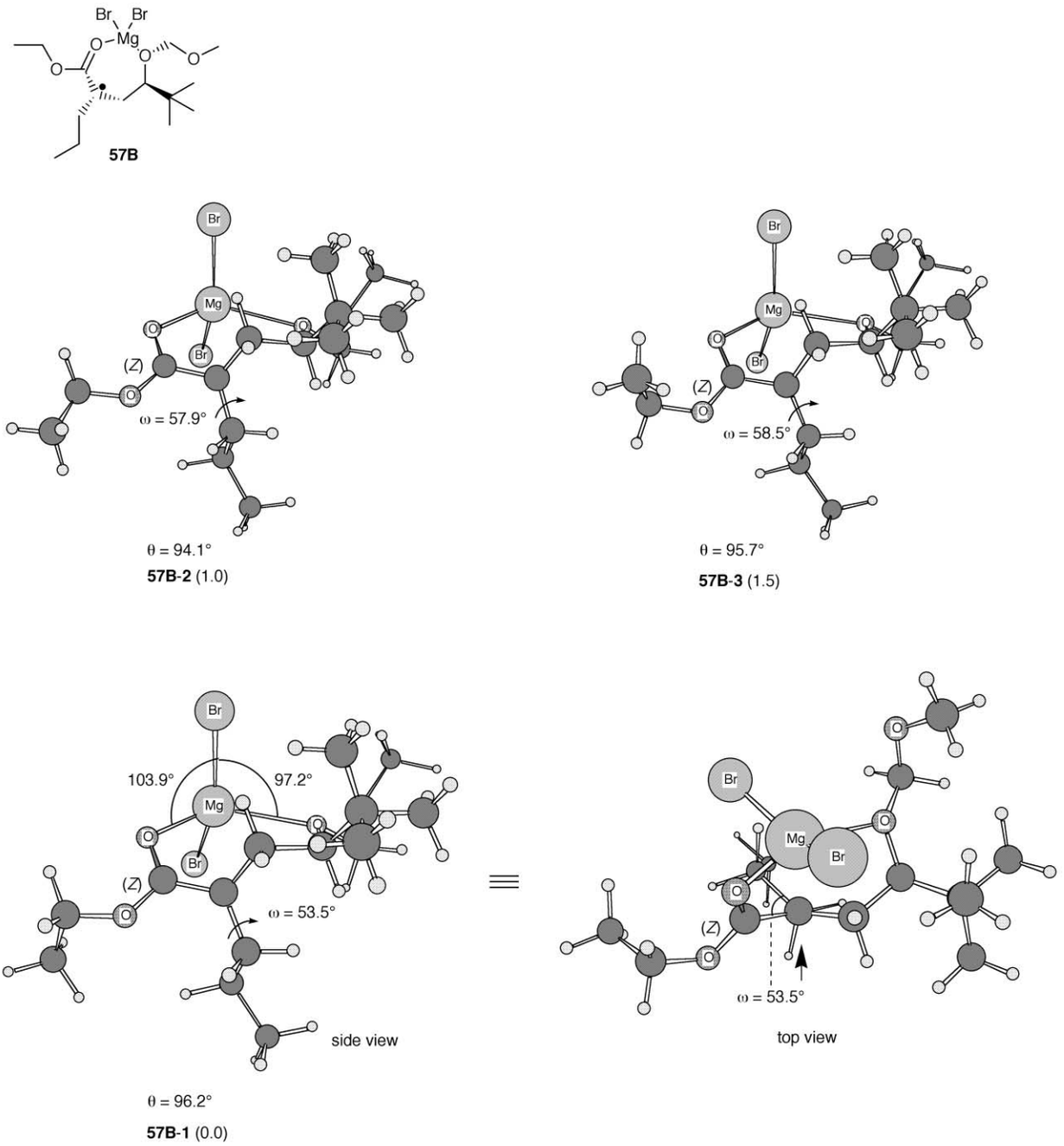


Fig. 6 Low-energy structures **57B-1**–**57B-3** (relative energy/kcal mol^{-1}) of chelated radical intermediate model **57B**.

energy conformer **49A-1** obtained by the calculations for the methyl ester **49A** is 1.07 kcal mol^{-1} higher in energy than the global minimum structure, and therefore the contribution from the conformer can be ignored. The structure **49A-1** is not the energetically favoured arrangement because of the large steric repulsion between the isopropyl and bulky benzyl groups.

Fig. 8 shows the three low-energy conformers **59B-1**–**59B-3** in which the two benzene rings adopt a quasi-parallel conformation. The π–π interaction between the benzene rings may dominate the conformation of **59B**.[18] The origin of the high *syn*-selectivity in the isopropyl radical addition to the benzyl ether **6** (entry 10, see also entry 11) can be rationalised as follows. The energy difference between the conformers **59B-1** and **59B-2** was very small (0.2 kcal mol^{-1}). The outside face of the radical centre in **59B-1** is shielded by the ethoxy group and therefore the exposed outside face of **59B-2** is subjected to the H-atom transfer, affording selectively *syn*-**22**.

The reaction of benzyloxy esters **6**, **11** and **12** with *tert*-butyl iodide gave predominantly the *syn*-adducts **24**, **35** and **45**, respectively (Table 1, entries 12, 31 and 33), in contrast to the γ-hydroxy, γ-methoxy and γ-methoxymethoxy esters affording selectively the *anti*-adducts. The calculations combined with CONFLEX and PM3 for methyl ester **50B** (R^1 = Ph, R^2 = Bn, R^3 = Bu^t), an intermediate model in *tert*-butyl radical addition, gave the global minimum energy structure, whereas the structures of the methyl ester **50A** were less stable and their contributions to the diastereoselectivity are ignored. The calculations for the intermediate model in the addition of *tert*-butyl radical to **6** (R^1 = Ph, R^2 = Bn) also gave the global minimum energy structure similar to **59B-2**. The preferential H-atom transfer from the less hindered outside face of the chelate intermediate gives a *syn*-adduct selectively. The shielding of the outside face of the seven-membered chelate ring by the substituent R^3 increases in the order of Et, Pr^i and Bu^t, and consequently the *syn*-selectivity decreased in the same order (Table 1, entries 10, 12 and 29–31).

The chelation-controlled reaction of ethyl ester **6** with isopropyl iodide gave the adducts in a ratio of *syn* : *anti* = 15 : 1

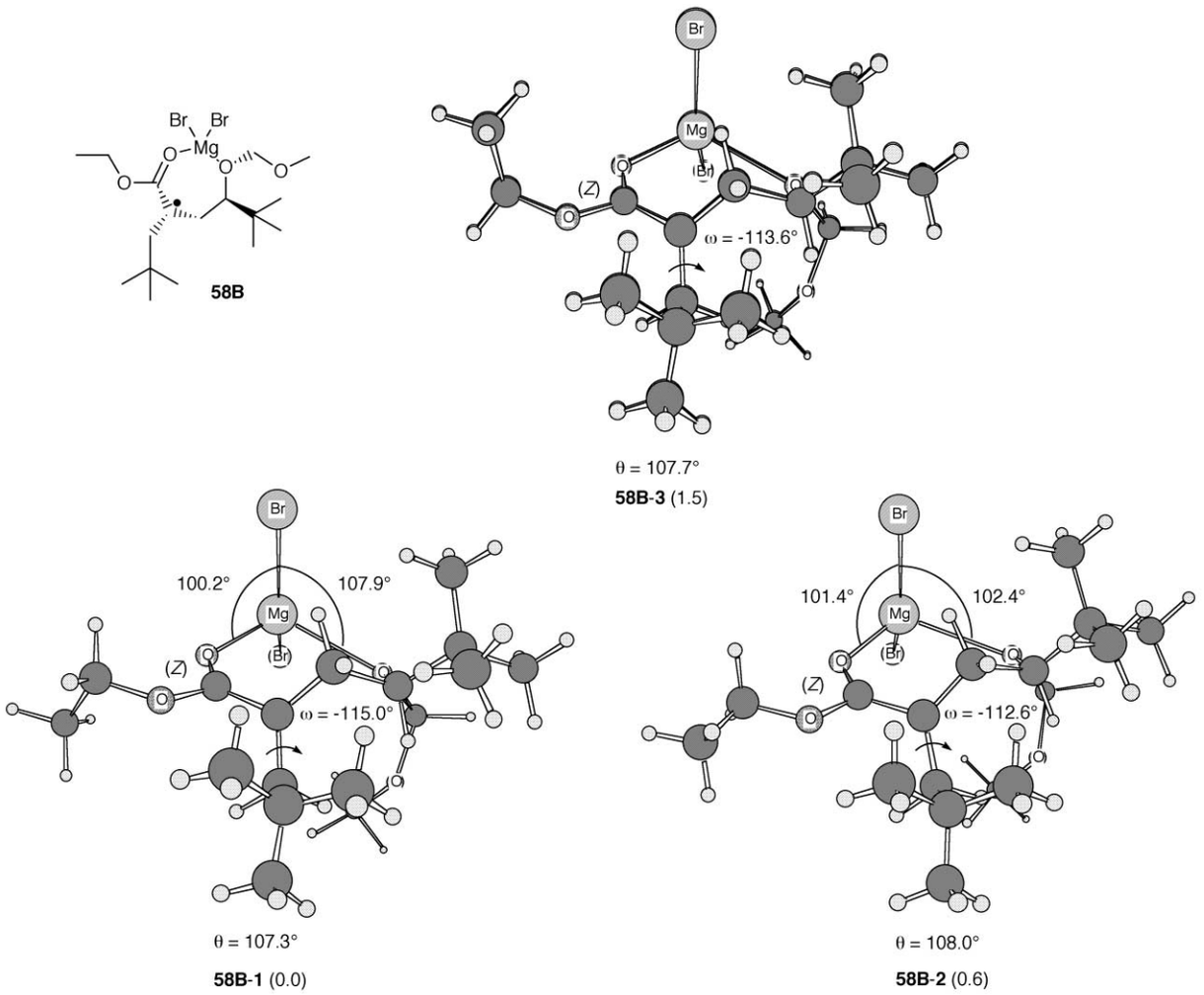


Fig. 7 Low-energy structures **58B-1**–**58B-3** (relative energy/kcal mol^{-1}) of chelated radical intermediate model **58B**.

(Table 1, entry 10), whereas the corresponding reaction of methyl ester **60** was lower in selectivity (*syn* : *anti* = 5.6 : 1) (Scheme 3 and Table 2). The difference in selectivity is due to the geometry of the isobutyl group attached to the radical centre. The dihedral angles C1–C2–C1′–C2′ (= ω) of the low-energy conformers **66B-1** ($\omega = -112.4°$) and **66B-2** ($\omega = -96.3°$) (Fig. 9) show that the isopropyl group shields the outside face of the radical centre, but that of **59B-2** ($\omega = 143.9°$) does not (Fig. 8). The cyclohexyl ester **61** showed higher *syn*-selectivity in the addition of isopropyl and *tert*-butyl radicals. The substrates **60** and **61** were prepared from ethyl ester **6**. The hydrolysis of ethyl ester **6** with sodium hydroxide in ethanol and the subsequent esterification of the resulting carboxylic acid with methanol (or cyclohexanol) in the presence of Ph_3P and diisopropyl azodicarboxylate[19] gave methyl ester **61** in 74% yield (or cyclohexyl ester **62** in 39% yield).

The diastereoselectivities of the steroidal γ-benzyloxy-α-methylenecarboxylic acid esters **11** and **12** strikingly depend on the configuration at C-22 (*i.e.*, the γ-position) and the bulk of alkyl radical R^3 (Table 1, entries 28–33). The addition of an ethyl radical to (22*R*)-22-benzyloxy derivative **11** performed in the presence of $MgBr_2{\cdot}OEt_2$ gave solely *syn*-adduct **33** (entry 29), whereas the addition of a methyl radical to the same substrate **11** gave *syn*-**32** and *anti*-**32** without diastereoselectivity (entry 28). The remarkable difference in selectivity is rationalised on the conformational analysis of the radical intermediate models **67B** and **68B** comprising the steroidal C and D rings and side chains. The A and B rings are ignored because the corresponding substrates having the A and B rings of brassinolides showed similar diastereoselectivities.[20]

The search for low-energy structures of **67B**, an intermediate model in the reaction of **11** with ethyl iodide, showed eleven conformers within 2.0 kcal mol^{-1} of the global minimum energy structure **67B-1** (Fig. 10). The sharply folded conformers having an ethoxy group with *Z*-geometry differ in dihedral angles C1–O–C–C and C1–C2–C1′–C2′. The high *syn*-selectivity is rationalised on the basis of the absence of shielding of the outside face of the radical centre by the ethoxy and the propyl groups. The exposed radical face is subjected to H-atom transfer as indicated by an arrow in Fig. 10.

The poor selectivity in the reaction of **11** with methyl iodide (entry 28) may be due to the presence of the global minimum energy structure **68B-1** (not shown), where the ethoxy group with *E*-geometry shields the outside face of the radical centre. The less stable conformers having an ethoxy group with *Z*-geometry would gave preferentially the *syn*-adduct **32**, but the contribution of these conformers is not expected because of their lower population.

The conformational analysis of the model **69B** showed that the poor diastereoselectivity in the reaction of (22*S*)-22-benzyloxy derivative **12** arises from the shielding of the outside face of the radical centre by the ethoxy group having *E*-geometry.

Studies on the effects of substituents at the δ-position and their geometry on the diastereoselectivity (*i.e.*, double asymmetric induction) are now in progress.

Conclusion

The aforementioned combination of CONFLEX and PM3 studies has provided a reasonably satisfactory rationale for the

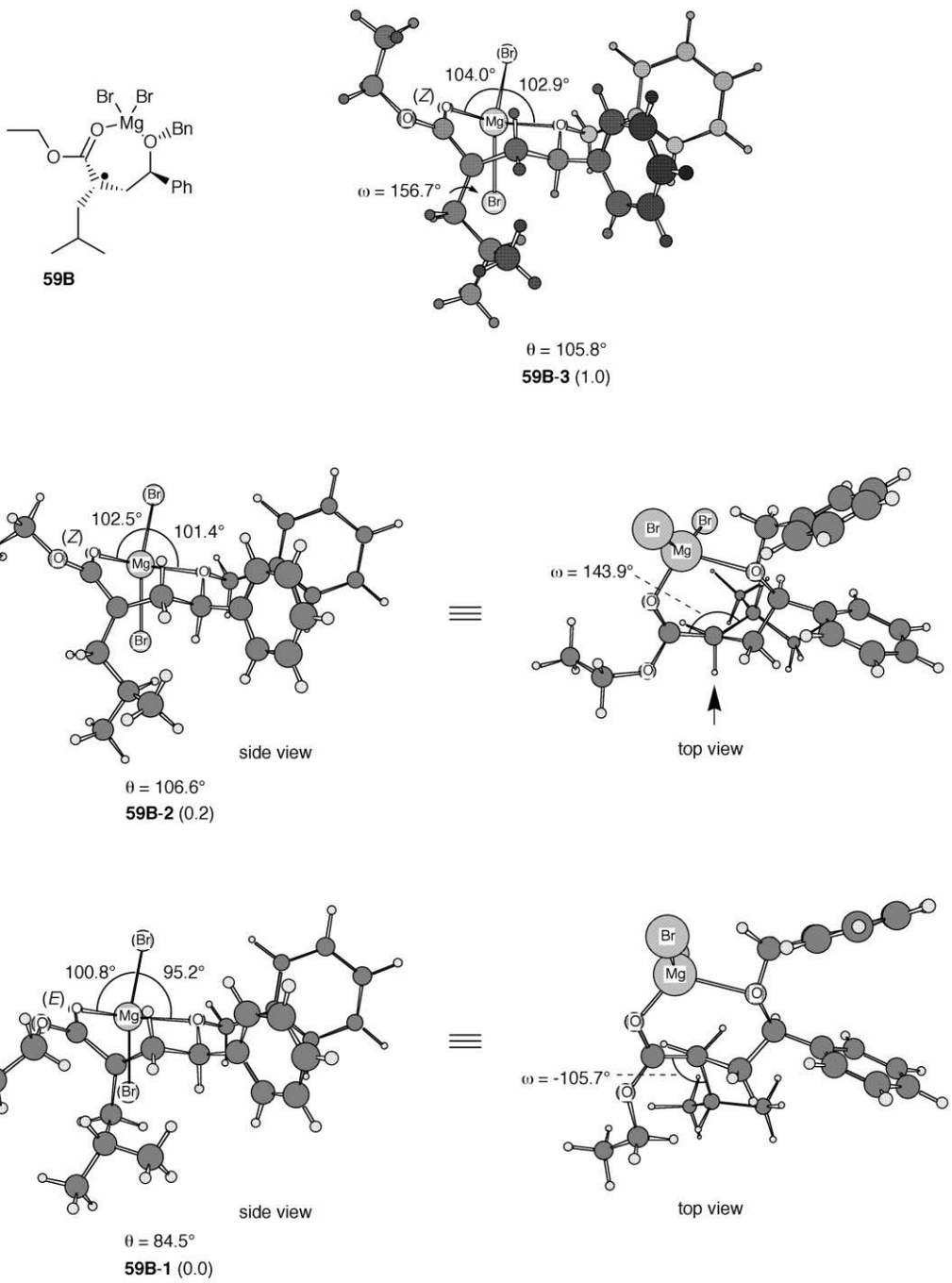


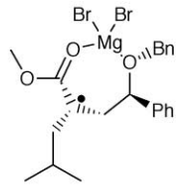
Fig. 8 Low-energy structures **59B-1**–**59B-3** (relative energy/kcal mol^{-1}) of chelated radical intermediate model **59B**.

outcome of the diastereoselectivity in radical reactions of α-methylene-γ-oxycarboxylic acid esters with alkyl iodide performed in the presence of Lewis acids. The sense of diastereoselectivity depends principally on the conformations of the sharply folded seven-membered chelate ring and the dihedral angle O=C–O–C of the ester moiety. The H-atom or allyl transfer reaction to the radical intermediate bearing an ethoxy group with *Z*-geometry (dihedral angle *ca.* 0°) occurs predominantly on the exposed outside face of the radical centre, whereas the ethoxy group with *E*-geometry (dihedral angle *ca.* 180°) shields the outside face of the radical centre and lowers the diastereoselectivity. The diastereoselectivity depends also on the conformation of the CH_2R^3 group attached to the radical centre. The agreement between theory and experiment is reasonable for the γ-hydroxy, γ-methoxymethoxy and γ-benzyloxy esters but the agreement is less satisfactory for the γ-methoxy esters. The analysis of low-energy conformers of chelated radical intermediates would be a powerful tool to predict the diastereoselectivity in chelation-controlled radical reactions of acyclic systems.

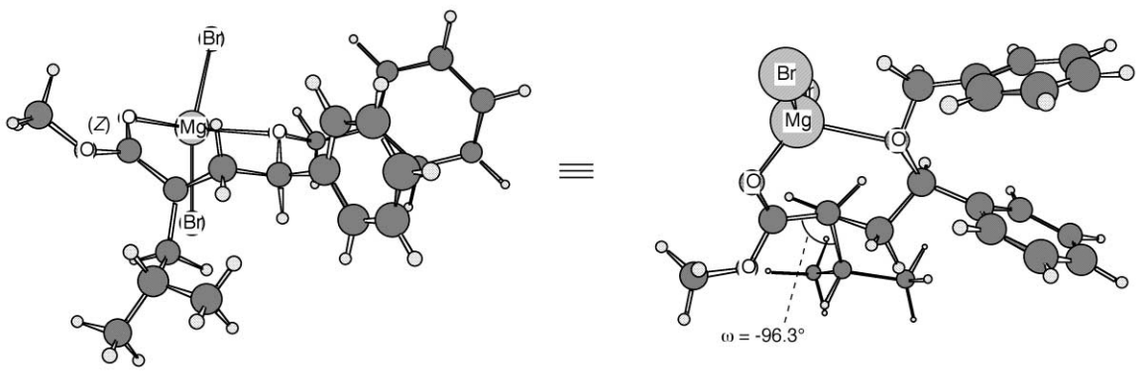
Experimental

Exhaustive searches of low-energy conformers of the chelated radical intermediates were performed with the program CONFLEX using the MM2 force field for energy minimisation followed by semi-empirical molecular orbital calculations (PM3) of the resulting conformers using the Hamiltonian implemented in MOPAC 6.0. Calculations using the CAChe™ 4.1 system (1999) from Oxford Molecular Ltd. were performed on an Apple Macintosh G3 platform.

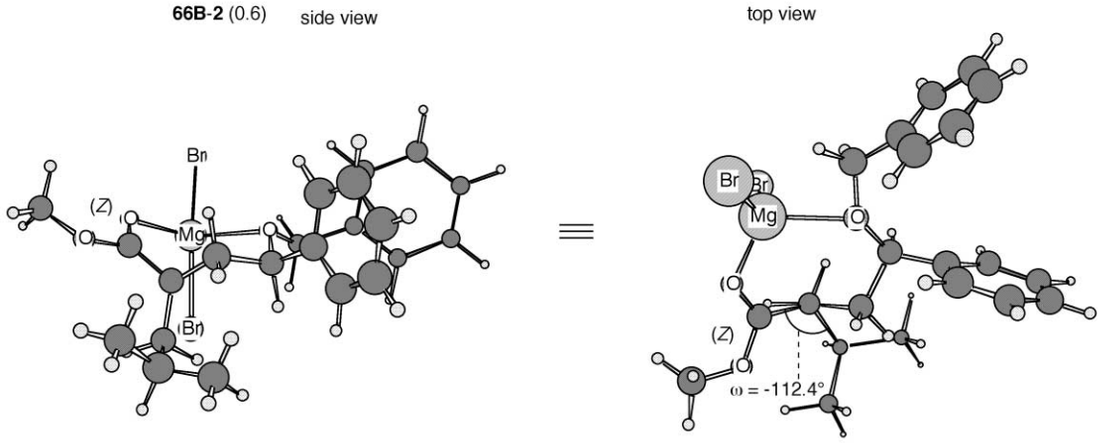
For the preparation of **1**–**6** and the reaction conditions of radical reactions, and the analytical instrumentation, see ref. 4*c*. Spectral data of compounds **1**–**6**, **13**–**24**, **29**, **31**, **40**, **42** and **60**–**65** are shown below.



66B



66B-2 (0.6) side view top view



66B-1 (0.0) side view top view

Fig. 9 Low-energy structures **66B-1**–**66B-3** (relative energy/kcal mol^{-1}) of chelated radical intermediate model **66B**.

Ethyl 2-(2-hydroxy-2-phenylethyl)propenoate 1

δ_H (270 MHz) 7.39–7.26 (5H, m, Ph), 6.24 (1H, s, =C*H*H), 5.60 (1H, s, =CH*H*), 4.88 (1H, dd, *J* 8.6 and 4.0, CH), 4.23 (2H, q, *J* 7.3, $CO_2CH_2CH_3$), 2.79 (1H, dd, *J* 14.0 and 8.6, C*H*H), 2.68 (1H, dd, *J* 14.0 and 4.0, CH*H*) and 1.32 (3H, t, *J* 7.3, $CO_2CH_2CH_3$); δ_C (67.8 MHz) 167.52, 143.82, 137.05, 128.23, 128.00, 127.34, 125.61, 73.14, 61.06, 42.56 and 14.25; *m*/*z* 220 (M^+, 15%), 114 (99), 107 (100) and 77 (38).

Ethyl 2-(2-hydroxy-3,3-dimethylbutyl)propenoate 2

δ_H (270 MHz) 6.25 (1H, d, *J* 1.3, =C*H*H), 5.66 (1H, s, =CH*H*), 4.21 (2H, m, $CO_2CH_2CH_3$), 3.33 (1H, ddd, *J* 10.2, 4.6 and 2.0, CH), 2.65 (1H, dt, *J* 13.5 and 2.0, C*H*H), 2.19 (1H, ddd, *J* 13.5, 10.2 and 0.7, CH*H*), 2.09 (1H, d, *J* 4.6, OH), 1.31 (3H, t, *J* 7.3, $CO_2CH_2CH_3$) and 0.95 (9H, s, Bu^t); δ_C (67.8 MHz) 167.64, 138.77, 126.88, 78.51, 60.92, 35.17, 35.02, 25.67 and 14.21; *m*/*z* 143 ($M^+ - C_4H_9$, 52%), 114 (91) and 97 (100).

Ethyl 2-(2-methoxy-2-phenylethyl)propenoate 3

δ_H (270 MHz) 7.37–7.24 (5H, m, Ph), 6.17 (1H, d, *J* 1.5, =C*H*H), 5.50 (1H, d, *J* 1.2, =CH*H*), 4.35 (1H, dd, *J* 8.0 and 5.6, CH), 4.19 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 3.21 (3H, s, OCH_3), 2.76 (1H, dd, *J* 14.2 and 8.1, C*H*H), 2.62 (1H, dd, *J* 14.2 and 5.6, CH*H*) and 1.30 (3H, t, *J* 7.1, $CO_2CH_2CH_3$); δ_C (67.8 MHz) 166.88, 141.45, 136.96, 128.21, 127.49, 127.17, 126.55, 82.29, 60.63, 56.79, 40.96 and 14.28; *m*/*z* 234.1271 (M^+. $C_{14}H_{18}O_3$ requires 234.1256), 157 (13%), 121 (100), and 77 (39).

Ethyl 2-(2-methoxymethoxy-2-phenylethyl)propenoate 4

δ_H (270 MHz) 7.33–7.29 (5H, m, Ph), 6.19 (1H, s, =C*H*H), 5.55 (1H, s, =CH*H*), 4.81 (1H, dd, *J* 8.3 and 5.3, CH), 4.50 (2H, s, OCH_2O), 4.21 (2H, q, *J* 7.3, $CO_2CH_2CH_3$), 3.30 (3H, s, OCH_3), 2.79 (1H, ddd, *J* 11.0, 8.3 and 1.0, C*H*H), 2.70 (1H, ddd, *J* 11.0, 5.3 and 1.0, CH*H*) and 1.31 (3H, t, *J* 7.3, $CO_2CH_2CH_3$); δ_C (67.8 MHz) 167.72, 141.32, 128.18, 127.52, 127.39, 126.68, 94.08, 76.42, 60.63, 55.45, 40.92 and 14.26; *m*/*z* 219 ($M^+ - C_2H_5O$, 36%), 203 (57), 151 (100) and 129 (75).

Ethyl 2-(2-methoxymethoxy-3,3-dimethylbutyl)propenoate 5

δ_H (270 MHz) 6.19 (1H, s, =C*H*H), 5.64 (1H, s, =CH*H*), 5.01 (1H, d, *J* 8.5, OC*H*HO), 4.54 (1H, d, *J* 8.5, OCH*H*O), 4.22 (2H, q, *J* 6.9, $CO_2CH_2CH_3$), 3.41 (1H, dd, *J* 9.6 and 2.3, CH), 3.31 (3H, s, OCH_3), 2.71 (1H, dd, *J* 14.0 and 2.3, C*H*H), 2.25 (1H, dd, *J* 14.0 and 9.6, CH*H*), 1.31 (3H, t, *J* 6.9, $CO_2CH_2CH_3$) and 0.95 (9H, s, Bu^t); δ_C (67.8 MHz) 166.81, 138.55, 126.79, 98.32, 85.55, 60.47, 56.02, 35.53, 34.93, 26.28 and 14.22; *m*/*z* 187.0985 ($M^+ - C_4H_9$. $C_9H_{15}O_4$ requires 187.0970), 131 (93%) and 57 (59).

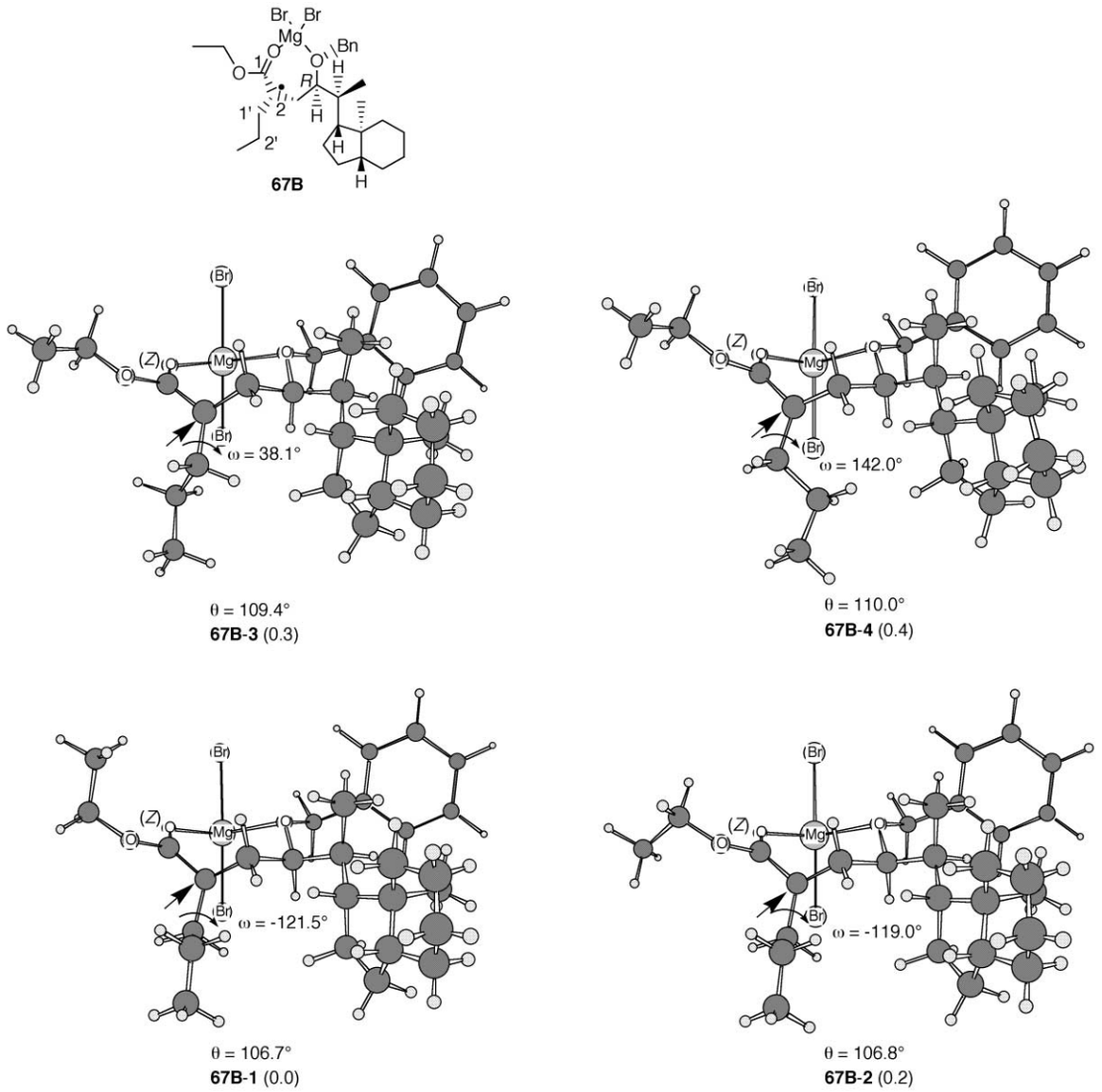
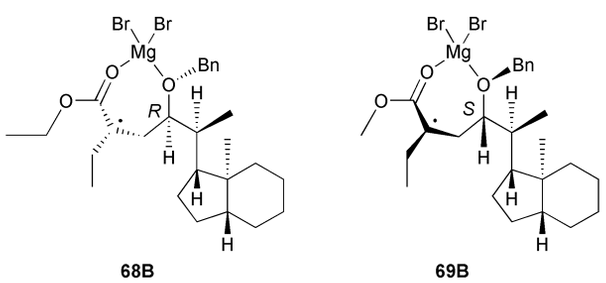


Fig. 10 Low-energy structures **67B-1**–**67B-4** (relative energy/kcal mol^{-1}) of chelated radical intermediate model **67B**. An additional four low-energy structures have been observed within 1.0 kcal mol^{-1} of global minimum energy structure **67B-1**.



Ethyl 2-(2-benzyloxy-2-phenylethyl)propenoate 6

δ_H (270 MHz) 7.30 (10H, m, 2 × Ph), 6.18 (1H, d, *J* 1.6, =C*H*H), 5.52 (1H, s, =CH*H*), 4.55 (1H, dd, *J* 8.2 and 4.9, CH), 4.46 (1H, d, *J* 11.9, OC*H*HPh), 4.25 (1H, d, *J* 11.9, OCH*H*Ph), 4.13 (2H, q, *J* 6.9, $CO_2CH_2CH_3$), 2.82 (1H, dd, *J* 13.8 and 8.2, C*H*H), 2.67 (1H, dd, *J* 13.8 and 4.9, CH*H*) and 1.25 (3H, t, *J* 6.9, $CO_2CH_2CH_3$).

Ethyl 2-(2-hydroxy-2-phenylethyl)-4-methylpentanoates 13

syn-**13**: δ_H (270 MHz) 7.35–7.24 (5H, m, Ph), 4.70 (1H, dt, *J* 9.3 and 3.4, CH), 4.15 (2H, m, $CO_2CH_2CH_3$), 2.77 (1H, m, 2-H), 2.25 (1H, d, *J* 3.2, OH), 2.00 (1H, ddd, *J* 13.5, 10.3 and 3.4, C*H*H), 1.84 (1H, ddd, *J* 13.5, 9.3 and 3.9, CH*H*), 1.59 (2H, m, CH_2Pr^i), 1.29 (1H, m, $CH(CH_3)_2$), 1.28 (3H, t, *J* 7.3, $CO_2CH_2CH_3$), 0.90 (3H, d, *J* 6.6, CH_3) and 0.87 (3H, d, *J* 6.4, CH_3); *anti*-**13**: δ_H (270 MHz) 7.36–7.27 (5H, m, Ph), 4.68 (1H, dt, *J* 9.3 and 3.4, CH), 4.14 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 2.50 (1H, m, 2-H), 2.17 (1H, dt, *J* 13.9 and 8.3, C*H*H), 2.07 (1H, br s, OH), 1.77 (1H, dt, *J* 13.9 and 5.1, CH*H*), 1.55 (2H, m, CH_2Pr^i), 1.29 (1H, m, $CH(CH_3)_2$), 1.27 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 0.88 (3H, d, *J* 6.6, CH_3) and 0.83 (3H, d, *J* 6.4, CH_3).

Ethyl 2-(2-hydroxy-3,3-dimethylbutyl)-2-propylpent-4-enoate 14

syn-**14**: ν_{max} (film/cm^{-1}) 3525, 1713, 1640, 1479, 1467, 1365, 1204, 1127, 1078, 916 and 738; δ_H (270 MHz) 5.78–5.63 (1H, m, CH_2=C*H*), 5.09–5.03 (2H, m, =CH_2), 4.12 (2H, m, $CO_2CH_2CH_3$), 3.29 (1H, septet, *J* 3.3, CH), 2.38 (2H, dd, *J* 1.0 and 7.3, CH_2CH=CH_2), 1.84 (1H, d, *J* 5.9, OH), 1.80–1.50 (4H, m, CH_2 and $CH_2CH_2CH_3$), 1.26 (3H, t, *J* 7.3, $CO_2CH_2CH_3$), 1.33–1.18 (2H, m, $CH_2CH_2CH_3$), 0.92 (3H, t, *J* 7.3, CH_3), 0.88 (9H, s, Bu^t); δ_C (67.8 MHz) 177.65, 139.92, 117.80, 77.19, 75.95, 60.51, 47.85, 40.58, 37.58, 35.35, 35.19, 25.64, 16.95, 14.76 and 14.32; *m*/*z* 252.2108 ($M^+ - H_2O$. $C_{16}H_{28}O_2$ requires 252.2090), 213 ($M^+ - C_4H_9$, 94%), 167 (39), 139 (58) and 121 (100).

Ethyl 2-(2-methoxy-2-phenylethyl)-4-methylpentanoates 15

syn-**15**: δ_H (270 MHz) 7.37–7.26 (5H, m, Ph), 4.05 (1H, dt, *J* 9.3 and 3.9, CH), 4.14 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 3.20 (3H, s, OCH_3), 2.78 (1H, m, 2-H), 1.86 (1H, m, C*H*H), 1.58 (2H, m, CH_2Pr^i), 1.20 (1H, m, $CH(CH_3)_2$), 1.28 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 0.90 (3H, d, *J* 6.6, CH_3) and 0.87 (3H, d, *J* 6.6, CH_3). *anti*-**15**: δ_H (270 MHz) 7.37–7.26 (5H, m, Ph), 4.05 (1H, dd, *J* 9.3 and 3.9, CH), 4.14 (2H, q, *J* 7.1, $CO_2CH_2CH_3$), 3.16 (3H, s, OCH_3), 2.43 (1H, m, 2-H), 2.16 (1H, m, C*H*H), 1.65 (1H, m, CH*H*), 1.51 (2H, m, CH_2Pr^i), 1.20 (1H, m, $CH(CH_3)_2$), 1.28 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 0.87 (3H, d, *J* 6.4, CH_3) and 0.81 (3H, d, *J* 6.4, CH_3). **15**: *m*/*z* 278.1866 (M^+. $C_{17}H_{26}O_3$ requires 278.1882), 263 (23%), 135 (73), 121 (100) and 77 (57).

Ethyl 2-(2-methoxy-2-phenylethyl)-2-propylpent-4-enoates 16

ν_{max} (film)/cm^{-1} 1729, 1640, 1494, 1455, 1368, 1182, 1107, 1038, 916, 755 and 701; *syn*-**16**: δ_H (400 MHz) 7.36–7.24 (5H, m, Ph), 5.78–5.67 (1H, m, CH_2=C*H*), 5.09 (1H, br d, *J* 5.3, =CH), 5.04 (1H, s, =CH), 4.15–4.00 (3H, m, CH and $CO_2CH_2CH_3$), 3.10 (3H, s, OCH_3), 2.43 (1H, dd, *J* 7.6, 14.3, CH_2CH=C*H*), 2.38 (1H, dd, *J* 14.3 and 7.6, CH_2CH=C*H*), 2.14 (1H, dd, *J* 15.0 and 9.8, C*H*H), 1.75 (1H, dd, *J* 15.0 and 3.4, CH*H*), 1.71–1.54 (2H, m, $CH_2CH_2CH_3$), 1.26 (3H, t, *J* 7.3, $CO_2CH_2CH_3$), 1.33–1.19 (2H, m, $CH_2CH_2CH_3$), 0.92 (3H, t, *J* 7.3, CH_3); *syn*-**16**: δ_C (67.8 MHz) 176.14, 142.62, 133.98, 128.27, 127.39, 126.37, 117.79, 80.79, 60.14, 56.52, 47.86, 44.59, 39.36, 35.83, 17.02, 14.77, 14.38; *anti*-**16**: δ_C (67.8 MHz 176.25, 142.60, 133.98, 128.23, 127.37, 126.29, 118.04, 80.46, 60.11, 56.60, 47.40, 45.04, 38.27, 36.40, 17.31, 14.62, 14.34. **16**: *m*/*z* 289.1813 ($M^+ - CH_3$. $C_{18}H_{25}O_3$ requires 289.1804), 231 (29%), 199 (100), 135 (86), 121 (100), 104 (61) and 91 (86).

Ethyl 2-(2-methoxy-2-phenylethyl)-4,4-dimethylpentanoates 17

syn-**17**: δ_H (400 MHz) 7.34–7.27 (5H, m, Ph), 4.13 (2H, m, $CO_2CH_2CH_3$), 3.99 (1H, m, CH), 3.20 (3H, s, OCH_3), 2.78 (1H, m, 2-H), 1.82 (2H, m, CH_2Bu^t), 1.81 (2H, m, CH_2), 1.28 (3H, t, *J* 7.0, $CO_2CH_2CH_3$) and 0.88 (9H, s, Bu^t). *anti*-**17**: δ_H (400 MHz) 7.34–7.27 (5H, m, Ph), 4.13 (2H, m, $CO_2CH_2CH_3$), 4.10 (1H, m, CH), 3.16 (3H, s, OCH_3), 2.53 (1H, m, 2-H), 2.12 (1H, dt, *J* 13.7 and 8.5, C*H*H), 1.82 (2H, m, CH_2Bu^t), 1.61 (1H, ddd, *J* 13.7 6.3 and 4.7, CH*H*), 1.28 (3H, t, *J* 7.0, $CO_2CH_2CH_3$) and 0.85 (9H, s, Bu^t). **17**: *m*/*z* 277 ($M^+ - CH_3O$, 13%), 135 (99), 121 (100) and 77 (17).

Ethyl 2-(2-methoxymethoxy-2-phenylethyl)-4-methylpentanoates 18

syn-**18**: δ_H (400 MHz) 7.34–7.27 (5H, m, Ph), 4.50 (3H, m, CH and OCH_2O), 4.14 (2H, m, $CO_2CH_2CH_3$), 3.37 (3H, s, OCH_3), 2.80 (1H, m, 2-H), 1.98 (1H, ddd, *J* 14.0, 10.4 and 3.7, C*H*H), 1.85 (1H, ddd, *J* 14.0, 9.8 and 4.0, CH*H*), 1.55 (2H, m, CH_2Pr^i), 1.28 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 1.25 (1H, m, $CH(CH_3)_2$), 0.90 (3H, d, *J* 6.4, CH_3) and 0.88 (3H, d, *J* 6.4, CH_3); *anti*-**18**: δ_H (400 MHz) 7.34–7.27 (5H, m, Ph), 4.50 (3H, m, CH and OCH_2O), 4.14 (2H, m, $CO_2CH_2CH_3$), 3.34 (3H, s, OCH_3), 2.45 (1H, m, 2-H), 2.24 (1H, dt, *J* 13.7 and 8.2, C*H*H), 1.73 (1H, dt, *J* 13.7 and 5.8, CH*H*), 1.55 (2H, m, CH_2Pr^i), 1.27 (3H, t, *J* 7.1, $CO_2CH_2CH_3$), 1.25 (1H, m, $CH(CH_3)_2$), 0.87 (3H, d, *J* 6.4, CH_3) and 0.81 (3H, d, *J* 6.4, CH_3). **18**: *m*/*z* 263.1605 ($M^+ - C_2H_5O$. $C_{16}H_{23}O_3$ requires 263.1647), 217 (100%), 151 (75).

Ethyl 2-(2-methoxymethoxy-2-phenylethyl)-2-propylpent-4-enoates 19

ν_{max} (film)/cm^{-1} 1729, 1456, 1194, 1153, 1033, 919 and 702; δ_H (270 MHz) 7.32–7.25 (5H, m, Ph), 5.77–5.62 (1H, m, CH_2=C*H*), 5.10 (1H, br d, *J* 4.6, =CH), 5.05 (1H, s, =CH), 4.69 (1H, dd, *J* 3.6 and 9.9, CH for *anti*-**19**), 4.62 (1H, dd, *J* 4.3 and 8.9, CH for *syn*-**19**), 4.40 (2H, s, CH_2OCH_3), 4.13–3.91 (2H, m, $CO_2CH_2CH_3$), 3.31 (3H, s, OCH_3), 2.41 (2H, d, *J* 7.3, CH_2CH=CH_2), 2.24 (1H, dd, *J* 14.5 and 8.9, C*H*H), 1.85 (1H, dd, *J* 14.5 and 4.3, CH*H*), 1.77–1.52 (2H, m, $CH_2CH_2CH_3$), 1.23 (5H, t, *J* 7.3, $CO_2CH_2CH_3$, $CH_2CH_2CH_3$) and 0.90(3H, t, *J* 7.3, CH_3); *syn*-**19**: δ_C (67.8 MHz) 175.84, 142.01, 133.59, 128.12, 127.47, 126.85, 117.84, 94.17, 75.14, 60.01, 56.18, 47.58, 43.58, 38.99, 35.77, 16.84, 14.59 and 14.22, *anti*-**19**: δ_C (67.8 MHz) 176.04, 142.13, 133.65, 128.15, 127.44, 126.70, 118.03, 94.29, 74.94, 60.01, 56.31, 47.14, 44.06, 38.23, 36.15, 17.11, 14.46 and 14.25. **19**: *m*/*z* 289.1790 ($M^+ - CH_2OCH_3$. $C_{18}H_{25}O_3$ requires 289.1803), 243 (70%), 199 (100), 151 (99), 105 (70) and 91 (45).

Ethyl 2-isobutyl-4-methoxymethoxy-5,5-dimethylhexanoates 20

syn-**20**: δ_H (400 MHz) 4.67 (1H, d, *J* 6.7, OC*H*HO), 4.66 (1H, d, *J* 6.7, OCH*H*O), 4.16 (1H, dq, *J* 14.4 and 7.3 CO_2CHCH_3) 4.15 (1H, dq, *J* 14.4 and 7.3 CO_2CHCH_3), 3.41 (3H, s, OCH_3), 2.98 (1H, dd, *J* 9.8 and 1.5, CH), 2.75 (1H, m, 2-H), 1.86 (1H, ddd, *J* 14.0 11.6 and 1.5, C*H*H), 1.58 (2H, m, CH_2Pri), 1.41 (1H, ddd, *J* 14.0, 9.8 and 3.1, CH*H*), 1.26 (3H, t, *J* 7.3, $CO_2CH_2CH_3$), 0.90 (6H, m, 2 × CH_3) and 0.89 (9H, s, Bu^t); Representative signals for *anti*-**20**: δ_H (400 MHz) 3.40 (3H, s, OCH_3), 3.07 (1H, dd, *J* 8.5 and 2.8, CH) and 2.64 (1H, m, 2-H). **20**: *m*/*z* 243 ($M^+ - C_2H_5O$, 12%), 231 (100) and 57 (30).

Ethyl 2-(2-methoxymethoxy-3,3-dimethylbutyl)-2-propylpent-4-enoates 21

syn-**21**: δ_H (270 MHz) 5.77–5.61 (1H, m, CH_2=C*H*), 5.08–5.02 (2H, m, =CH_2), 4.57 (2H, dd, *J* 11.5 and 6.3, OCH_2O), 4.16–4.04 (2H, m, $CO_2CH_2CH_3$), 3.34 (3H, s, OCH_3), 3.05 (1H, dd, *J* 10.2 and 2.0, CH), 2.36 (2H, septet, *J* 7.3, CH_2CH=CH_2), 1.91 (1H, dd, *J* 14.5 and 10.6, C*H*H), 1.68–1.44 (3H, m, C*H*H and $CH_2CH_2CH_3$), 1.32–1.14 (2H, m, $CH_2CH_2CH_3$), 1.25 (3H, t, *J* 7.3, $CO_2CH_2CH_3$), 0.90 (9H, s, Bu^t), 0.97–0.84 (3H, m, CH_3); *anti*-**21**: δ_H (270 MHz) 5.77–5.61 (1H, m, CH_2=C*H*), 5.13–5.07 (2H, m, =CH_2), 4.56 (2H, dd, *J* 11.2 and 6.3, OCH_2O), 4.16–4.04 (2H, m, $CO_2CH_2CH_3$), 3.33 (3H, s, OCH_3), 3.15 (1H, dd, *J* 10.6 and 2.0, CH), 2.54–2.41 (2H, m, CH_2CH=CH_2), 1.97 (1H, dd, *J* 14.5 and 10.6, C*H*H), 1.68–1.44 (3H, m, CH*H* and $CH_2CH_2CH_3$), 1.32–1.14 (2H, m, $CH_2CH_2CH_3$), 1.25 (3H, t, *J* 7.3, $CO_2CH_2CH_3$), 0.90 (9H, s, Bu^t), 0.97–0.84 (3H, m, CH_3); *syn*-**21**: δ_C (67.8 MHz) 176.27, 133.93, 117.67, 99.77, 86.27, 59.94, 56.07, 47.28, 39.52, 37.60, 35.69, 35.03, 26.58, 16.69, 14.77 and 14.36; *anti*-**21**: δ_C (67.8 MHz)176.32, 133.69, 118.04, 99.82, 86.07, 59.87, 55.98, 46.67, 38.76, 37.85, 35.73, 35.56, 26.58, 17.17, 14.59 and 14.35. **21**: ν_{max} (film)/cm^{-1} 1729, 1641, 1464, 1365, 1205, 1156, 1040, 918 and 735; *m*/*z* 283.2254 ($M^+ - OCH_3$. $C_{17}H_{31}O_3$ requires 283.2273), 269 ($M^+ - CH_3OCH_2O$, 5%), 257 ($M^+ - C_4H_9$, 79), 225 (18), 195 (25), 183 (43), 151 (53), 123 (24) and 45 (100).

Ethyl 2-(2-benzyloxy-2-phenylethyl)-4-methylpentanoates 22

syn-**22**: δ_H (400 MHz) 7.32 (10H, m, 2 × Ph), 4.41 (1H, d, *J* 11.3, C*H*HPh), 4.30 (1H, dd, *J* 9.5 and 4.0, CH), 4.24 (1H, d, *J* 11.3, CH*H*Ph), 4.08 (1H, dq, *J* 14.0 and 7.0, CO_2CHCH_3), 4.05 (1H, dq, *J* 14.0 and 7.0, CO_2CHCH_3),2.85 (1H, m, 2-H), 1.96 (1H, ddd, *J* 14.0, 10.0 and 4.0, C*H*H), 1.88 (1H, ddd, *J* 14.0, 9.5 and 4.3, CH*H*), 1.56 (2H, m, CH_2Pr^i), 1.26 (1H, m, $CH(CH_3)_2$), 1.23 (3H, t, *J* 7.3, $CO_2CH_2CH_3$), 0.89 (3H, d, *J* 6.4, CH_3) and 0.87 (3H, d, *J* 6.4, CH_3); *anti*-**22**: δ_H (400 MHz) 7.32 (10H, m, 2 × Ph), 4.40 (1H, d, *J* 11.5, C*H*HPh), 4.33 (1H, dd, *J* 8.5 and 5.5, CH), 4.22 (1H, d, *J* 11.6, CH*H*Ph), 4.11 (1H, dq, *J* 14.0 and 7.0, CO_2CHCH_3), 4.01 (1H, dq, *J* 14.0 and 7.0, CO_2CHCH_3), 2.49 (1H, m, 2-H), 2.24 (1H, dt, *J* 14.0 and 8.5, C*H*H), 1.70 (1H, dt, *J* 14.0 and 5.5, CH*H*), 1.52 (2H, m, CH_2Pr^i), 1.26 (1H, m, $CH(CH_3)_2$), 1.18 (3H, t, *J* 7.3, $CO_2CH_2CH_3$), 0.85 (3H, d, *J* 6.4, CH_3) and 0.79 (3H, d, *J* 6.4, CH_3).

Ethyl 2-(2-benzyloxy-2-phenylethyl)-2-propylpent-4-enoates 23

ν_{max} (film)/cm^{-1} 1729, 1641, 1494, 1456, 1209, 1095, 915, 735 and 701; δ_H (270 MHz) 7.38–7.24 (10H, m, Ph), 5.75–5.64 (1H, m, CH_2=C*H*), 5.04 (1H, s, =CH), 5.00 (1H, br d, *J* 4.3, =CH), 4.42 (1H, dd, *J* 9.6 and 3.3, CH for *anti*), 4.36 (1H, dd, *J* 9.6 and 3.3, CH for *syn*), 4.30 (1H, d, *J* 11.2, PhC*H*HO), 4.16 (1H, d, *J* 11.2, PhCH*H*O), 3.96–3.87 (2H, m, $CO_2CH_2CH_3$), 2.37 (2H, d, *J* 7.6, CH_2CH=CH_2), 2.23 (1H, dd, *J*, 14.5 and 9.6, C*H*H), 1.78 (1H, dd, *J*, 14.5 and 3.3, CH*H*), 1.66–1.48 (2H, m, $CH_2CH_2CH_3$), 1.27–1.18 (2H, m, $CH_2CH_2CH_3$), 1.14 (3H, t, *J* 7.3, $CO_2CH_2CH_3$); *syn*-**23**: δ_C (67.8MHz) 175.91, 142.57, 137.89, 133.80, 128.24, 128.18, 127.89, 127.37, 127.20, 126.44, 117.85, 77.85, 70.40, 59.95, 47.74, 44.68, 39.30, 35.80, 16.91, 14.56 and 14.11; *anti*-**23** δ_C (67.8MHz) 175.98, 142.57, 137.94, 133.85, 127.92, 128.07, 127.85, 127.35, 127.22, 126.37, 117.64, 78.22, 70.47, 59.90, 47.21, 44.10, 38.22, 36.37, 17.12, 14.45 and 14.14. **23**: *m*/*z* 289.1786 ($M^+ - C_7H_7$. $C_{18}H_{25}O_3$ requires 289.1804), 243 (24%), 199 (51), 155 (26) and 91 (100).

Ethyl 2-(2-benzyloxy-2-phenylethyl)-4,4-dimethylpentanoates 24

syn-**24**: δ_H (400 MHz) 7.34 (10H, m, 2 × Ph), 4.39 (1H, d, *J* 11.3, C*H*HPh), 4.25 (1H, d, *J* 11.3, CH*H*Ph), 4.26 (1H, m, CH), 4.07 (2H, m, $CO_2CH_2CH_3$), 2.85 (1H, m, 2-H), 1.92 (2H, m, CH_2), 1.76 (2H, m, CH_2Bu^t), 1.23 (3H, t, *J* 7.3, $CO_2CH_2CH_3$) and 0.89 (9H, s, Bu^t); *anti*-**24**: δ_H (400 MHz) 7.34 (10H, m, 2 × Ph), 4.38 (1H, d, *J* 11.6, C*H*HPh), 4.32 (1H, dd, *J* 8.6 and 5.2, CH), 4.24 (1H, d, *J* 11.6, CH*H*Ph), 4.07 (2H, m, $CO_2CH_2CH_3$), 2.52 (1H, m, 2-H), 2.22 (1H, dt, *J* 13.8 and 8.2, C*H*H), 1.67 (1H, dt, *J* 13.8 and 5.8, CH*H*), 1.76 (2H, m, CH_2Bu^t), 1.18 (3H, t, *J* 7.3, $CO_2CH_2CH_3$) and 0.82 (9H, s, Bu^t).

Compounds 29

ν_{max} (film)/cm^{-1} 3065, 3030, 1728, 1588, 1181, 1150, 1102, 1089, 821, 800, 795 and 738; δ_H (270 MHz) 7.69–7.32 (10H, m, 2 × Ph), 5.12 (1H, s, 6-H), 4.67 (1H, d, *J* 7.0, OC*H*HO), 4.55 (1H, d, *J* 7.0. OCH*H*O), 4.14 (2H, m, CH_2CH_3), 3.53 (1H, m, 3-H), 3.43 (1H, m, 22-H), [3.37 (*syn*) and 3.36 (*anti*), (3H, s each, OCH_3)], 2.57 (1H, m, 24-H), 1.26 (3H, t, *J* 7.3, CH_2CH_3), 1.06 (9H, s, $C(CH_3)_3$), 0.98 (3H, s, 10-CH_3), 0.91 (3H, d, *J* 5.1, 20-CH_3), 0.88 (3H, t, *J* 6.8, CH_3) and 0.65 (3H, s, 13-CH_3); δ_C (100.4 MHz) 176.3, 141.3, 135.7, 134.8, 129.4, 127.4, 121.0, 95.7 (*syn*), 95.5 (*anti*), 77.9 (*syn*), 77.7 (*anti*), 73.2, 60.1, 56.2, 55.7, 52.7, 50.0, 43.7, 42.6, 42.4 (*syn*), 41.9 (*anti*), 39.7, 38.4, 37.2, 36.4, 35.9, 31.8, 29.1, 27.0, 24.3, 22.6, 21.0 (*syn*), 20.6 (*anti*), 19.4, 19.1, 14.0, 12.5 and 11.8. *m*/*z* 685.4254 ($M^+ - C_4H_9$. $C_{43}H_{61}O_5Si$ requires 685.4288.) and 199 (100%).

Compounds 31

ν_{max} (film)/cm^{-1} 3070, 3047, 1731, 1644, 1146, 1102, 1085, 1042, 825, 800, 799 and 734; δ_H (400 MHz) 7.68–7.36 (10H, m, 2 × Ph), 5.12 (1H, s, 6-H), 4.64 (1H, d, *J* 6.8, OC*H*HO), 4.57 (1H, d, *J* 6.8. OCH*H*O), 4.12 (2H, m, CH_2CH_3), 3.50 (2H, m, 3-H and 22-H), [3.40 (*syn*) and 3.37 (*anti*), (3H, s each, OCH_3)], [2.69 (*syn*) and 2.48 (*anti*), (1H, m each, 24-H), 1.25 (3H, t, *J* 7.2, CH_2CH_3), 1.06 (9H, s, $C(CH_3)_3$), 0.98 (3H, s, 10-CH_3), 0.92 (3H, d, *J* 7.0, 20-CH_3), 0.88 (9H, s, $C(CH_3)_3$) and 0.67 (3H, s, 13-CH_3); δ_C (67.8 MHz) 177.9, 141.3, 135.7, 134.8, 129.4, 127.4, 121.0, 95.3 (*syn*), 95.3 (*anti*), 77.1 (*syn*), 77.9 (*anti*), 73.2, 60.1, 56.3, 55.7, 52.6, 50.0, 45.7, 42.6, 42.4, 39.6, 38.8, 37.2, 36.4, 33.7, 31.8, 31.6, 30.9, 30.7, 29.5, 27.5 (*syn*), 27.0 (*anti*), 24.4, 22.6, 21.0, 19.1, 14.1, 12.5 and 11.8. *m*/*z* 727.4724 ($M^+ - C_4H_9$. $C_{46}H_{67}O_5Si$ requires 727.4758) and 199 (100%).

Compounds 40

ν_{max} (film)/cm^{-1} 3072, 3032, 1734, 1590, 1174, 1150, 1083, 1037, 822, 798 and 740; δ_H (270 MHz) 7.73–7.32 (10H, m, 2 × Ph), 5.12 (1H, d, *J* 4.6, 6-H), 4.61 (2H, m, O-CH_2-O), 4.13 (2H, m, CH_2CH_3), 3.53 (1H, m, 3-H), 3.46 (1H, m, 22-H), [3.37 (*syn*) and 3.35 (*anti*), (3H, s each, OCH_3)], 2.48 (1H, m, 24-H), 1.25 (3H, t, *J* 7.3, CH_2CH_3), 1.06 (9H, s, $C(CH_3)_3$), 0.98 (3H, s, 10-CH_3), 0.87 (3H, t, *J* 6.5, CH_3) and [0.67 (*syn*) and 0.65 (*anti*) (3H, s each, 13-CH_3); δ_C (100.4 MHz) 176.2, 141.3, 135.7, 134.8, 129.4, 127.4, 121.6, 96.8 (*syn*), 96.0 (*anti*), 80.0 (*syn*), 9.0 (*anti*), 73.2, 60.1, 56.6, 55.7, 52.3, 50.0, 44.4, 42.3, 40.1, 39.8, 37.2, 36.4, 35.9, 35.4, 31.6, 28.2, 27.0 (*syn*), 26.5 (*anti*), 24.4, 22.6, 21.0 (*syn*), 20.5 (*anti*), 19.4, 19.1, 14.0, 12.7 and 11.6; *m*/*z* 685.4315 ($M^+ - C_4H_9$. $C_{43}H_{61}O_5Si$ requires 685.4288), 217 (22%) and 199 (100).

Compounds 42

ν_{max} (film)/cm^{-1} 3071, 3040, 1734, 1645, 1109, 1088, 1037, 859, 805 and 737; δ_H (270 MHz) 7.73–7.32 (10H, m, 2 × Ph), 5.12 (1H, d, *J* 4.9, 6-H), 4.62 (2H, s, O-CH_2-O), 4.12 (2H, q, *J* 7.3, CH_2CH_3), 3.53 (1H, m, 3-H), 3.47 (1H, m, 22-H), [3.37 (*syn*) and 3.35 (*anti*), (3H, s each, OCH_3)], 2.55 (1H, m, 24-H), 1.25 (3H, t, *J* 7.3, CH_2CH_3), 1.05 (9H, s, $C(CH_3)_3$), 0.98 (3H, s, 10-CH_3), 0.91 (3H, d, *J* 6.5, 20-CH_3), 0.89 (6H, d, *J* 6.8, 2 × CH_3) and [0.67 (*anti*) and 0.64 (*syn*), (3H, s each, 13-CH_3); δ_C (100.4 MHz) 176.5, 141.3, 135.7, 134.8, 129.4, 127.4, 121.1, 96.8 (*syn*), 96.1 (*anti*), 79.9 (*syn*), 78.3 (*anti*), 73.2, 60.1, 56.6, 55.7, 52.2, 50.0, 42.4, 42.3, 40.8 (*syn*), 40.7 (*anti*),, 39.8, 38.7, 37.2, 36.4, 35.2, 31.8, 31.6, 28.1, 27.9 (*syn*), 27.0 (*anti*), 2635, 26.1, 24.4, 23.1, 22.6, 22.2, 21.0, 19.4, 19.1, 13.5, 12.7 and 11.6; *m*/*z* 713.4578 ($M^+ - C_4H_9$. $C_{45}H_{65}O_5Si$ requires 713.4601) and 199 (100%).

Methyl 2-(2-benzyloxy-2-phenylethyl)propenoate 60

Hydrolysis of the ester **6** with 2.1 equiv. of sodium hydroxide in refluxing ethanol gave the corresponding carboxylic acid in 98% yield. To a solution of the carboxylic acid (400 mg, 1.4 mmol) and triphenylphosphine (1.12 g, 4.27 mmol) in dry THF (10 cm^3) were added methanol (95 μl) and diisopropyl azodicarboxylate (40% in toluene; 0.77 cm^3, 1.4 mmol). The mixture was stirred at room temperature for 5 h. After evaporation of the solvent, the residue was chromatographed on silica gel (hexane–ethyl acetate, 60 : 1 to 20 : 1) to give the methyl ester **60** (311 mg, 75%) as an oil. δ_H (400 MHz) 7.36–7.23 (10H, m, Ph), 6.17 (1H, d, *J* 1.6, =C*H*H), 5.53 (1H, s, =CH*H*), 4.54 (1H, m, CH), 4.45 (1H, d, *J* 12.0, OC*H*HPh), 4.25 (1H, d, *J* 12.0, OCH*H*Ph), 3.68 (3H, s, CH_3), 2.82 (1H, dd, *J* 14.0 and 8.8, C*H*H) and 2.67 (1H, dd, *J* 14.0 and 4.8, CH*H*); δ_C (100.4 MHz) 167.4, 141.6, 138.3, 136.7, 128.3, 128.2, 127.7, 127.6, 127.5, 127.3, 126.7, 79.7, 70.4, 51.8 and 41.1; *m*/*z* 205.0857 ($M^+ - C_7H_7$. $C_{12}H_{13}O_3$ requires 205.0865), 197 (29%), 105 (14) and 91 (100)

Cyclohexyl 2-(2-benzyloxy-2-phenylethyl)propenoate 61

Compound **61** was prepared following the procedures described for **60**. δ_H (400 MHz) 7.38–7.23 (10H, m, 2 × Ph), 6.18 (1H, s, =C*H*H), 5.49 (1H, s, =CH*H*), 4.78 (1H, m, CO_2CH), 4.57 (1H, dd, *J* 14.0 and 8.0, CH), 4.45 (1H, d, *J* 12.0, OC*H*HPh), 4.24 (1H, d, *J* 12.0, OCH*H*Ph), 2.82 (1H, dd, *J* 14.0 and 8.0, C*H*H) and 2.65 (1H, dd, *J* 14.0 and 4.8, CH*H*) and 1.79–1.18 (10H, m, cyclohexyl); δ_C (100.4 MHz) 166.3, 141.7, 138.3, 137.4, 128.3, 128.2, 127.6, 127.5, 127.3, 127.2, 126.7, 79.7, 70.4, 41.3, 31.5, 31.4, 25.4 and 23.7; *m*/*z* 287.1607 ($M^+ - C_6H_5$. $C_{18}H_{23}O_3$ requires 287.1647), 197 (45%), 181 (39), 105 (12) and 91 (100).

Methyl 2-(2-benzyloxy-2-phenylethyl)-4-methylpentanoates 62

syn-**62**: δ_H (400 MHz) 7.36–7.26 (10H, m, 2 × Ph), 4.42 (1H, d, *J* 11.6, C*H*HPh), 4.28 (1H, dd, *J* 9.6 and 4.0, CH), 4.22 (1H, d, *J* 11.6, CH*H*Ph), 3.57 (3H, s, CO_2CH_3), 2.86 (1H, m, 2-H), 1.92 (2H, m, C*H*H), 1.53 (2H, m, CH_2Pr^i), 1.24 (1H, m, $CH(CH_3)_2$), 0.88 (3H, d, *J* 6.4, $CH(CH_3)_2$) and 0.86 (3H, d, *J* 6.4, $CH(CH_3)_2$); *anti*-**62**: δ_H (400 MHz) 7.36–7.26 (10H, m, 2 × Ph), 4.39 (1H, d, *J* 11.2, C*H*HPh), 4.33 (1H, dd, *J* 8.8 and 5.2, CH),

4.21 (1H, d, *J* 11.2, CH*H*Ph), 3.54 (3H, s, CO_2CH_3), 2.53 (1H, m, 2-H), 2.24 (1H, dt, *J* 14.0 and 8.8, C*H*H), 1.70 (1H, dt, *J* 14.0 and 5.2, CH*H*), 1.53 (2H, m, CH_2Pr^i), 1.24 (1H, m, $CH(CH_3)_2$), 0.85 (3H, d, *J* 6.4, $CH(CH_3)_2$) and 0.80 (3H, d, *J* 6.4, $CH(CH_3)_2$); *syn*-**62**: δ_C (100.4 MHz) 176.7, 142.1, 138.2, 128.4, 128.2, 127.8, 127.5, 127.4, 126.4, 79.4, 70.7, 51.3, 42.3, 41.6, 40.2, 26.1, 22.9 and 22.3; *anti*-**62**: δ_C (100.4 MHz) 176.62, 141.8, 138.2, 128.4, 128.1, 127.8, 127.7, 127.3, 126.7, 79.9, 70.4, 51.3, 41.8, 41.4, 41.1, 26.0, 23.0 and 22.0. **62**: *m*/*z* 263.1631 ($M^+ - C_6H_5$. $C_{16}H_{23}O_3$ requires 263.1647), 249 (35%), 233 (39), 217 (94), 197 (31), 117 (19), 105 (68), 91 (100) and 77 (36).

Methyl 2-(2-benzyloxy-2-phenylethyl)-4,4-dimethylpentanoates 63

syn-**63**: δ_H (400 MHz) 7.36–7.29 (10H, m, 2 × Ph), 4.40 (1H, d, *J* 11.2, C*H*HPh), 4.23 (1H, d, *J* 11.2, CH*H*Ph), 4.22 (1H,dd, *J* 11.2 and 6.8, CH), 3.58 (3H, s, OCH_3), 2.86 (1H, m, 2-H), 1.91 (2H, m, CH_2), 1.76 (2H, m, CH_2Bu^t) and 0.87 (9H, s, Bu^t); *anti*-**63**: δ_H (400 MHz) 7.36–7.29 (10H, m, 2 × Ph), 4.38 (1H, d, *J* 10.0, C*H*HPh), 4.33 (1H,dd, *J* 8.4 and 4.4, CH), 4.22 (1H, d, *J* 10.0, CH*H*Ph), 3.52 (3H, s, OCH_3), 2.57 (1H, m, 2-H), 2.22 (1H, dt, *J* 13.6 and 8.8, C*H*H), 1.76 (2H, m, CH_2Bu^t), 1.67 (1H, dt, *J* 13.6 and 6.0, CH*H*) and 0.82 (9H, s, Bu^t); *syn*-**63**: δ_C (100.4 MHz) 177.5, 142.0, 138.2, 128.4, 128.2, 127.9, 127.6, 127.4, 126.5, 79.6, 70.8, 51.4, 47.0, 44.0, 38.8, 30.9 and 29.4; *anti*-**63**: δ_C (100.4 MHz) 177.4, 141.8, 138.2, 128.4, 128.1, 127.7, 127.6, 127.3, 126.7, 79.8, 70.4, 51.4, 46.3, 43.5, 39.4, 30.8 and 29.4. **63**: *m*/*z* 263.11678 ($M^+ - C_7H_7$. $C_{16}H_{23}O_3$ requires 263.1647), 231 (42%), 197 (25), 144 (20), 105 (12) and 91 (100).

Cyclohexyl 2-(2-benzyloxy-2-phenylethyl)-4-methylpentanoates 64

syn-**64**: δ_H (400 MHz) 7.36–7.26 (10H, m, 2 × Ph), 4.78 (1H, m, CO_2CH), 4.40 (1H, d, *J* 11.2, C*H*HPh), 4.33 (1H, dd, *J* 9.2 and 3.6, CH), 4.25 (1H, d, *J* 11.2, CH*H*Ph), 2.87 (1H, m, 2-H), 1.90 (2H, m, C*H*H), 1.85–1.19 (13H, m, cyclohexyl and $CH_2CH(CH_3)_2$), 0.90 (3H, d, *J* 6.0, $CH(CH_3)_2$) and 0.87 (3H, d, *J* 6.0, $CH(CH_3)_2$); *anti*-**64**: δ_H (400 MHz) 7.36–7.26 (10H, m, 2 × Ph), 4.78 (1H, m, CO_2CH), 4.40 (1H, d, *J* 11.6, C*H*HPh), 4.33 (1H, dd, *J* 9.2 and 3.6, CH), 4.20 (1H, d, *J* 11.6, CH*H*Ph), 2.42 (1H, m, 2-H), 2.25 (1H, m, C*H*H), 1.85–1.19 (14H, m, cyclohexyl and $CH_2CH(CH_3)_2$), 0.84 (3H, d, *J* 6.5, $CH(CH_3)_2$) and 0.78 (3H, d, *J* 6.5, $CH(CH_3)_2$); *syn*-**64**: δ_C (100.4 MHz) 175.6, 142.4, 138.4, 128.3, 128.2, 127.8, 127.5, 127.4, 126.3, 80.0, 72.1, 71.0, 42.4, 42.0, 40.7, 31.8, 31.7, 26.1, 25.4, 23.8, 23.1 and 22.1; *anti*-**64**: δ_C (100.4 MHz) 175.6, 141.8, 138.3, 130.2, 128.2, 127.7, 127.3, 126.8, 126.3, 79.4, 70.2, 65.8, 41.8, 41.2, 41.1, 31.7, 31.6, 26.0, 25.4, 23.8, 22.7 and 22.0. **64**: *m*/*z* 281.1871 ($M^+ - CO_2C_6H_{11}$. $C_{21}H_{31}O_3$ requires 281.1906), 197 (91%), 173 (14), 130 (13), 105 (15) and 91 (100).

Cyclohexyl 2-(2-benzyloxy-2-phenylethyl)-4,4-dimethylpentanoates 65

syn-**65**: δ_H (400 MHz) 7.35–7.30 (10H, m, 2 × Ph), 4.78 (1H, m, CO_2CH), 4.39 (1H, d, *J* 11.2, C*H*HPh), 4.30 (1H,m, CH), 4.29 (1H, d, *J* 11.2, CH*H*Ph), 2.87 (1H, m, 2-H), 1.91–1.19 (14H, m, 7 × CH_2) and 0.89 (9H, s, Bu^t); *anti*-**65**: δ_H (400 MHz) 7.35–7.30 (10H, m, 2 × Ph), 4.66 (1H, m, CO_2CH), 4.30 (1H,m, CH), 4.28 (1H, d, *J* 11.6, C*H*HPh), 4.21 (1H, d, *J* 11.6, CH*H*Ph), 2.41 (1H, m, 2-H), 2.23 (1H, m, C*H*H), 1.91–1.19 (13H, m, CH*H* and 6 × CH_2) and 0.81 (9H, s, Bu^t); *syn*-**65**: δ_C (100.4 MHz) 176.5, 142.3, 138.4, 128.4, 128.2, 127.8, 127.5, 127.4, 126.3, 80.0, 72.3, 71.1, 46.9, 44.4, 39.3, 31.9, 31.6, 31.0, 29.6, 25.4 and 23.9; *anti*-**65**: δ_C (100.4 MHz) 176.3, 141.1, 138.2, 128.4, 128.2, 127.8, 127.7, 127.3, 126.8, 79.3, 70.3, 65.8, 46.1, 43.4, 39.4, 31.6, 31.4, 30.9, 29.5, 23.9 and 15.3. **65**: *m*/*z* 331.2292 ($M^+ - C_7H_7$. $C_{21}H_{31}O_3$ requires 331.2273), 232 (14%), 212 (19), 197 (27), 105 (19) and 91 (100).

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