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Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 3859

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PAPER

Diastereoselective alkylation reactions of 1-methylcyclohexa-2,5-diene-1-carboxylic acid†

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Received 27th January 2012, Accepted 22nd March 2012
DOI: 10.1039/c2ob25211b

Published on 23 March 2012 on http://pubs.rsc.org | doi:10.1039/C2OB25211B
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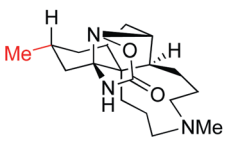
The deprotonation and alkylation of 1-methylcyclohexa-2,5-diene-1-carboxylic acid has been investigated under a range of conditions. In all cases, the formation of compounds **14** was found to be completely stereoselective, although compound **14c** was formed as an impurity when alkyl iodides were used as electrophiles, and doubly-alkylated compounds **17** were formed in some cases when alkyl bromides were used.

Introduction

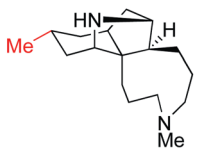
Cyclohexa-1,4-dienes are versatile intermediates in synthetic organic chemistry, most commonly prepared by various permutations of the Birch reduction.[1] In particular, with appropriate substitution patterns the two double bonds are either enantiotopic (achiral cyclohexadienes) or diastereotopic (chiral cyclohexadienes) and therefore their elaboration can lead to the formation of one or more new stereogenic centres[2] using either inter-[3] or intramolecular[4] transformations.

The desymmetrisation reactions of cyclohexa-1,4-dienes have significant potential in target synthesis, particularly where a quaternary stereogenic centre is introduced by way of a Birch reduction/alkylation approach. For example, we have recently demonstrated a synthetic approach to the cores of the complex lycopodium alkaloids lycoposerramine A (**1**)[5] and lycoposerramine S (**2**),[6] and model studies towards the core of cladiellin diterpenes such as 7-deacetoxyalcyonin acetate (**3**).[7]

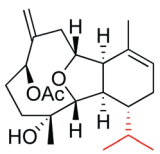
There is still one major challenge to be addressed in the development of this methodology. On each of the structures in Fig. 1, a substituent is highlighted in red. This substituent is attached to the carbon that was the 4-position in the benzoic acid precursor. If this substituent is present at the start (R^1 in structure **4**), the



1, lycoposerramine A



2, lycoposerramine S



3, 7-deacetoxyalcyonin acetate

Fig. 1 Complex targets to which cyclohexadiene desymmetrisation methodology has been applied.

Birch reduction/alkylation proceeds with little or no stereocontrol[6,8] (Scheme 1, route (a)) to form **5** (the only exception to this is if both R^1 and R^2 are very bulky[9]). However, late introduction of this substituent can require multiple steps and functional group interconversions (Scheme 1, route (b)).

Early introduction of R^1 is preferable, since the desymmetrisation process to form **6** can proceed with the selective formation of four stereogenic centres in a single step, controlled by a stereogenic substituent R^3. In fact, by using a desymmetrisation process which gives reaction at both cyclohexadiene double-bonds, it is possible to form six contiguous stereogenic centres with complete stereoselectivity in a single step, demonstrating the power of this approach.[10]

The ideal method therefore features the stereoselective formation of compounds such as **5**. An alternative method for the formation of such compounds would be the deprotonation and alkylation of a compound of general structure **8**. In 1976,

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†Electronic supplementary information (ESI) available: Experimental procedures; copies of ^1H and ^{13}C NMR spectra for all new compounds; details of computational methods. CCDC 854352. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25211b

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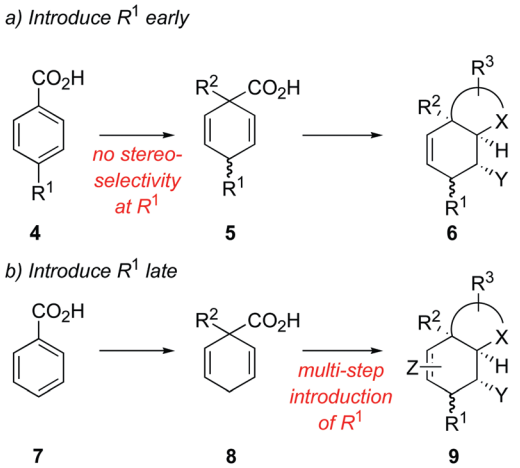
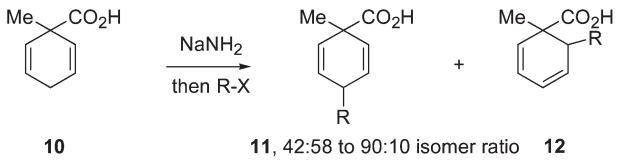
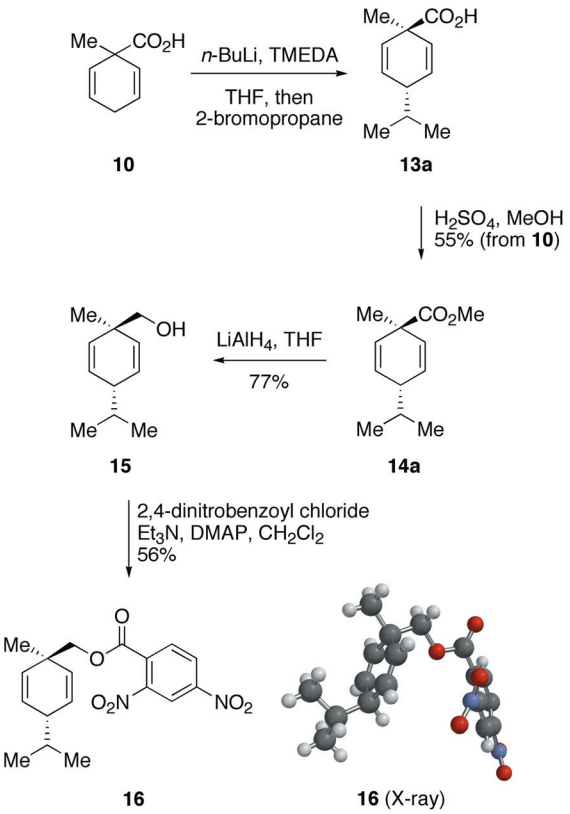


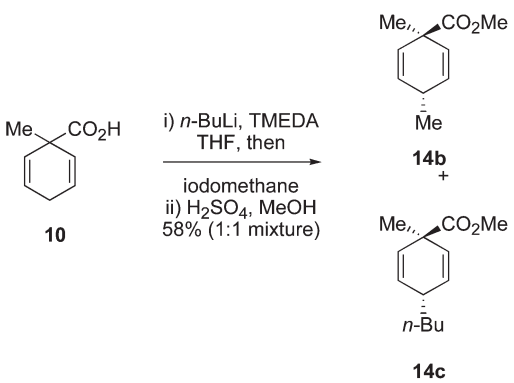
Scheme 1 Difficulties in introducing substituents at the 4-position of 1-alkylcyclohexa-2,5-diene-1-carboxylic acids, either early or late in a synthetic sequence.



Scheme 2 Reported alkylation of 1-methylcyclohexa-2,5-diene-1-carboxylic acid.[9]



Scheme 3 Synthesis and stereochemical determination of compound **13a**.



Scheme 4 Methylation of 1-methylcyclohexa-2,5-diene-1-carboxylic acid.

Zhurkovich and Ioffe reported[11] that the deprotonation of compound **10** with sodium amide followed by alkylation with a range of alkyl halides gave good yields but only moderate and variable stereoselectivity in the formation of the 1,4-dienes **11** (Scheme 2). *The stereochemical outcome of these reactions was not proven.*[12] Alkylation at the 2-position was also observed resulting in formation of the conjugated diene **12**. A number of groups have reported the direct deprotonation/alkylation of cyclohexa-1,4-diene itself,[13] while various other substituted cyclohexa-1,4-dienes have been directly alkylated[14] although these reactions do not have the opportunity for stereocontrol. The only asymmetric variant that we are aware of is the silver BINAP-mediated addition of cyclohexadienylstannanes to aldehydes.[15]

Results and discussion

In an effort to establish the levels of stereoselectivity that are achievable, and determine the stereochemical outcome, we therefore reinvestigated the alkylation of 1-methylcyclohexa-2,5-diene-1-carboxylic acid **10**. Deprotonation of this compound with *n*-BuLi/TMEDA followed by alkylation with 2-bromopropane gave a high yield of a single diastereoisomer of product **13a** (Scheme 3), which was characterised after conversion into the corresponding methyl ester **14a** (55% yield over 2 steps).

The stereochemistry of the compound was confirmed by reduction of the ester to the alcohol and preparation of the 2,4-dinitrobenzoate ester **16** (X-ray structure as shown in Scheme 3). This stereochemical outcome is the same as suggested by Zhurkovich and Ioffe, although the present conditions give much higher levels of both stereocontrol and regiocontrol.

When iodomethane was used as electrophile, the reaction also gave a single diastereoisomer of the desired product **14b**. Unfortunately this was contaminated with approximately equal amounts of the corresponding butylated product **14c** (Scheme 4). This is presumably formed by exchange of excess *n*-butyllithium with the iodomethane, even though only a slight excess (2.2 equivalents) of butyllithium was used, and could be attributed to possible presence of the corresponding carboxylate salt in carboxylic acid **10**. Any amount of this salt would mean that

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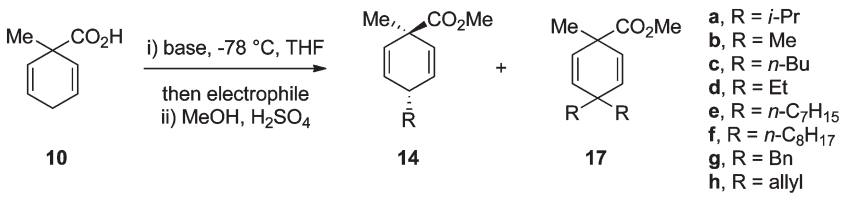
effectively a larger excess of butyllithium was being used. However, attempts to reduce the number of equivalents of butyllithium led to incomplete alkylation, while initial deprotonation with NaH followed by the use of a single equivalent of *n*-BuLi led to the formation of complex mixtures of products. Despite extensive experimentation, we have been unable to establish reaction conditions that lead to complete alkylation to give a single product in this case. Other methyl electrophiles (methyl triflate, dimethyl sulfate) gave very poor results (low yields or complex mixtures of products). LDA and LIDAKOR (LDA and potassium *t*-butoxide) were less effective as bases, giving 53% and 37% yields respectively after esterification. In each case only one diastereoisomer was formed, along with a small amount of unreacted starting material (as the methyl ester). Careful examination of NMR spectra strongly suggest that the same stereoisomer is formed as when *n*-butyllithium is used as base. Using the same alkyl residue in the electrophile and alkyllithium would seem to be a logical approach for avoiding the formation of mixtures of products. Unfortunately methyllithium/TMEDA is ineffective as a base, with starting material being recovered almost quantitatively.

The scope of the reaction was next probed with a range of electrophiles (Table 1). Similar complications were observed with other primary alkyl iodides. With iodoethane (entry 6) an approximately 1 : 1 mixture of products was obtained. With iodoheptane, significantly less of the butyl product **14c** was obtained, and the pure heptyl product **14e** was obtained in 54% yield after esterification (entry 8). Alkyl bromides do not give the same problem, with none of the butyl product **14c** being observed. For example, with bromoethane, the desired product **14e** was obtained as a single stereoisomer in 51% yield after esterification (entry 10). With alkyl bromides, it is also possible to obtain doubly-alkylated products **17**, and these were formed in very small quantities in most reactions (entries 7, 9) although they were readily removed during purification. These compounds become the major products when an excess of the base/electrophile is used (entry 12).

The reaction is, as shown by the examples in Table 1, quite general. In all cases, only a single stereoisomer can be observed/isolated, and of the reactions we have tried, the only electrophile that has failed is ethyl 2-bromoacetate, this giving a complex mixture of products.

When stabilised organolithium reagents react with electrophiles, the stereochemical outcome is strongly dependant on the nature of the electrophile. For example, alkyl halides tend to give inversion, while carbonyl electrophiles tend to give retention. Therefore, the observed outcome is consistent with a directed lithiation followed by alkylation with inversion.[16] DFT calculations with Gaussian 09[17] at the wB97XD/6-311++G(2df,2p)/B3LYP/6-31+G* level comparing the relative stabilities of metalated 1-methylcyclohexadienyl-1-carboxylates indicated that, neither the 'annelated' intermediate **18** nor the 'bridged' isomer **19** are local minima. Both were minimised to an identical structure, corresponding to η_5 coordination of the lithium to the cyclohexadienyl ligand. Saturation of the Li coordination spheres by THF or TMEDA molecules is favoured. Including thermal contributions and standard state corrections, the free energy of complexation of four THF molecules at −78 °C is −46.9 kcal mol^{-1}. Complexation of two molecules of TMEDA (structure **20**, Fig. 2) is even more favourable at −51.5 kcal mol^{-1}, therefore this should be considered to be the dominant complex of the lithiated cyclohexadiene. The presence of strongly interacting ligands that block the upper face provides a clear explanation for the observed stereoselectivity.

Table 1 Summary of results



Entry	Base[a]	Electrophile	Yields (products)
1	*n*-BuLi/TMEDA	2-Bromopropane	55% (**14a**)
2	*n*-BuLi/TMEDA	Iodomethane	58% (1 : 1 **14b** : **14c**)
3	LDA	Iodomethane	53% (**14b**)[b]
4	LIDAKOR	Iodomethane	37% (**14b**)[b]
5	*n*-BuLi/TMEDA	1-Bromobutane	64% (**14c**) + 4% (**17c**)
6	*n*-BuLi/TMEDA	Iodoethane	43% (1 : 1 **14d** : **14c**)
7	*n*-BuLi/TMEDA	Bromoethane	51% (**14d**)[c]
8	*n*-BuLi/TMEDA	1-Iodoheptane	53% (**14e**)
9	*n*-BuLi/TMEDA	1-Bromooctane	43% (**14f**)[d]
10	*n*-BuLi/TMEDA	Benzyl bromide	77% (**14g**)
11	*n*-BuLi/TMEDA	Allyl bromide	54% (**14h**)
12	*n*-BuLi/TMEDA[e]	Bromoethane	48% (**17d**)

[a] 2.2 equivalents of *n*-BuLi and TMEDA were used unless otherwise stated. [b] The products from these reactions were contaminated by approximately 20% of the methyl ester of compound **10**. [c] Small but variable amounts of the double alkylation product **17d** were observed in NMR spectra of the crude reaction mixtures. These were readily removed during purification. [d] A small amount of the double-alkylation product **17f** was observed, but this was not obtained pure. [e] *n*-BuLi (5.0 equiv.), TMEDA (2.5 equiv.), bromoethane (3.0 equiv.).

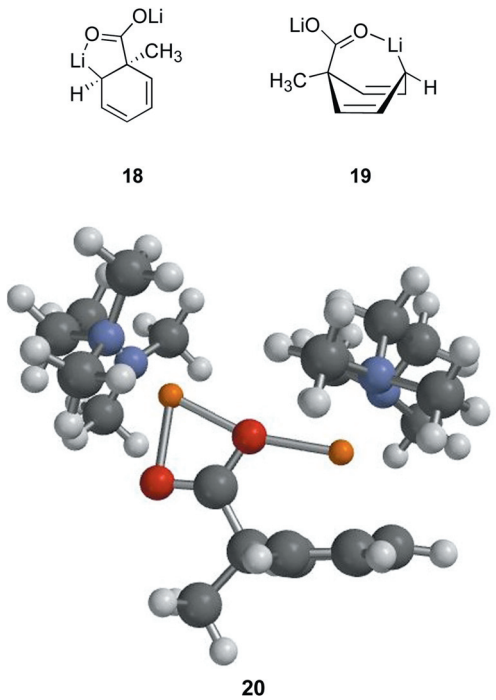


Fig. 2 Structure of the double-lithiated dianion (TMEDA complex) derived from compound **10**.

Conclusions

In conclusion, deprotonation of 1-methylcyclohexa-2,5-diene-1-carboxylic acid **10** with *n*-BuLi in the presence of TMEDA, followed by alkylation, offers a direct and highly diastereoselective route to the corresponding 4-substituted products in which the alkyl group introduced is *trans* to the carboxylic acid. This is complementary to the results of van Bekkum in which a 4-substituted benzoic acid is reductively alkylated. In that case, where any selectivity is observed, the alkyl group and the carboxylic acid are preferentially *cis*.

Experimental section

General procedure for the alkylation of 1-methylcyclohexa-2,5-diene-1-carboxylic acid (10)

A solution of *n*-butyllithium (2.0 M in cyclohexane, 1.99 mL, 3.98 mmol) was added to 1-methylcyclohexa-2,5-diene-1-carboxylic acid (**6**) (0.25 g, 1.81 mmol) in THF (10 mL) at −78 °C. TMEDA (0.59 mL, 3.98 mmol) was then added and the solution stirred for 30 minutes. The electrophile (for number of equivalents see individual compounds below) was added and the reaction stirred for 10 minutes at −78 °C, then allowed to warm to room temperature and stirred for a further 1 h. The reaction was quenched with 2 M hydrochloric acid (5 mL) and the product extracted into CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, concentrated *in vacuo* and the residue re-dissolved in methanol (10 mL). Concentrated sulfuric acid (0.05 mL) added and the resulting solution stirred at 25 °C for 17 h. The methanol was removed *in vacuo* and saturated aqueous $NaHCO_3$ solution (5 mL) added. The organic material was extracted into CH_2Cl_2 (3 × 20 mL), which was then dried over $MgSO_4$, and concentrated *in vacuo*. The crude products were purified as described below.

(1*r*,4*r*)-Methyl 4-isopropyl-1-methylcyclohexa-2,5-dienecarboxylate (14a)

Prepared according to the general procedure, using 14.5 mmol of 1-methylcyclohexa-2,5-diene-1-carboxylic acid (**10**), and using 2-bromopropane (1.5 mL, 15.9 mmol, 1.1 equiv.) as electrophile. Purification by flash column chromatography (9 : 1 hexane–diethyl ether) gave the *title compound* (1.55 g, 55%) as a colourless oil (Found: MH^+, 195.1377. $C_{12}H_{19}O_2$ requires M, 195.1385); ν_{max}. (neat) 2961, 2875, 1734, 1250 and 1114 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 5.83 (2H, dd, *J* 10.4, 2.0, 2 × alkene CH), 5.70 (2H, dd, *J* 10.4, 3.1, alkene CH), 3.69 (3H, s, OCH_3), 2.67 (1H, app. dtt, *J* 4.0, 3.1, 2.0, CH═CH–C*H*), 1.77 (1H, septet of doublets, *J* 6.9, 4.0, CH–C*H*$(CH_3)_2$), 1.32 (3H, s, CH_3) and 0.89 (6H, d *J* 6.9, 2 × CH_3); δ_C (500 MHz; $CDCl_3$) 175.8 (C═O), 129.4 (CH), 127.7 (CH), 52.3 (CH_3), 44.7 (C), 41.6 (CH), 32.0 (CH), 27.6 (CH_3) and 19.3 (CH_3); *m*/*z* (APCI) 195 (MH^+, 100) and 115 (34).

(1*r*,4*r*)-Methyl 1,4-dimethylcyclohexa-2,5-dienecarboxylate (14b)

Prepared according to the general procedure, using 3.6 mmol of 1-methylcyclohexa-2,5-diene-1-carboxylic acid (**10**), and using iodomethane (0.46 mL, 7.7 mmol, 2.1 equiv.) as electrophile. Purification by flash column chromatography (9 : 1 hexane–diethyl ether) gave the *title compound* (0.39 g, 58%) as a pale yellow oil, approximately 1 : 1 ratio of **14b** : **14c** with spectroscopic data in line with those from the individual compounds as given below.

(1*r*,4*r*)-Methyl 1,4-dimethylcyclohexa-2,5-dienecarboxylate (14b) using LDA as base

A solution of *n*-butyllithium (2.0 M in cyclohexane, 2.80 mL, 5.60 mmol) was added to a solution of diisopropylamine (0.81 mL, 5.60 mmol) in THF (10 mL) at −78 °C. After stirring for 30 minutes, 1-methylcyclohexa-2,5-diene-1-carboxylic acid (**10**) (0.25 g, 1.81 mmol) in THF (2 mL) was added and the resulting solution stirred for a further 30 minutes before addition of iodomethane (0.56 mL, 9.05 mmol). The solution was then stirred for 10 minutes at −78 °C, allowed to warm to room temperature and stirred for a further 1 h. The reaction was quenched with 2 M hydrochloric acid (5 mL), and the product extracted into CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, concentrated *in vacuo* and the residue re-dissolved in methanol (10 mL). Concentrated sulfuric acid (0.05 mL) added and the resulting solution stirred at 25 °C for 17 h. The methanol was removed *in vacuo* and the reaction quenched with saturated aqueous $NaHCO_3$ solution (5 mL). The organic material was extracted into CH_2Cl_2 (3 × 20 mL), which was then dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash column chromatography (9 : 1 hexane–diethyl ether) gave the *title compound* (0.16 g, 53%) as a colourless oil as an inseparable 4 : 1 mixture of **14b** and the methyl ester of

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unreacted acid **10** (Found: MH^+, 167.1075. $C_{10}H_{15}O_2$ requires M, 167.1072); ν_{max}. (neat) 2956, 1733, 1248, 1116 and 733 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 5.67–5.65 (4H, m, alkene CH), 3.68 (3H, s, CH_3O), 2.78–2.70 (1H, m, CH), 1.33 (3H, s, CH_3) and 1.08 (3H, d, *J* 7.3, CH_3); δ_C (500 MHz; $CDCl_3$) 175.7 (C═O), 131.0 (CH), 127.8 (CH), 52.3 (CH_3), 44.3 (C), 30.4 (CH), 27.9 (CH_3) and 21.8 (CH_3); *m*/*z* (APCI) 167 (MH^+, 100%).

(1*r*,4*r*)-Methyl 1,4-dimethylcyclohexa-2,5-dienecarboxylate (14b) using LIDAKOR as base

A solution of *n*-butyllithium (2.0 M in cyclohexane, 1.53 mL, 3.05 mmol) was added to a solution of potassium *tert*-butoxide (0.36 g, 3.19 mmol) in THF (7 mL) at −78 °C, followed by di-isopropylamine (0.45 mL, 3.19 mmol) and left to stir for 30 minutes. 1-Methylcyclohexa-2,5-diene-1-carboxylic acid (**10**) (0.20 g, 1.45 mmol) in THF (1 mL) was added and stirred for a further 30 minutes before iodomethane (0.45 mL, 7.25 mmol) was added, stirred for 10 minutes at −78 °C and then 1 h at 25 °C. The reaction was quenched with 2 M hydrochloric acid (5 mL), and the product extracted into CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, concentrated *in vacuo* and the residue re-dissolved in methanol (10 mL). Concentrated sulfuric acid (0.04 mL) added and the resulting solution stirred at 25 °C for 17 h. The methanol was removed *in vacuo* and the reaction quenched with saturated aqueous $NaHCO_3$ solution (5 mL). The organic material was extracted into CH_2Cl_2 (3 × 20 mL), which was then dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash column chromatography (9 : 1 hexane–diethyl ether) gave the *title compound* (90 mg, 37%) as a colourless oil as an inseparable 4 : 1 mixture of **14b** and the methyl ester of unreacted acid **10**. Spectroscopic data are as above.

(1*r*,4*r*)-Methyl 4-butyl-1-methylcyclohexa-2,5-dienecarboxylate (14c) and methyl 4,4-dibutyl-1-methylcyclohexa-2,5-dienecarboxylate (17c)

Prepared according to the general procedure using bromobutane (0.21 mL, 1.99 mmol, 1.1 equiv.) as electrophile. Purification by flash column chromatography (20 : 1 hexane–diethyl ether) gave the di-butyl compound **17c** (20 mg, 4%) as a pale yellow oil, and mono-butyl compound **14c** (240 mg, 64%) as a colourless oil.

Data for compound **17c**: Found: MH^+, 265.2178. $C_{17}H_{29}O_2$ requires M, 265.2168; ν_{max}. (neat) 2956, 2929, 1735, 1238, 1112 and 800 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 5.77 (2H, d, *J* 10.2, 2 × alkene CH), 5.39 (2H, d, *J* 10.2, alkene CH), 3.67 (3H, s, CH_3O), 1.31 (3H, s, CH_3), 1.31–1.00 (12H, m, 6 × CH_2) and 0.85 (3H, t, *J* 7.0, CH_3) and 0.83 (3H, t, *J* 7.0, CH_3); δ_C (500 MHz; $CDCl_3$) 175.8 (C═O), 133.4 (CH), 128.5 (CH), 52.2 (CH_3), 44.6 (C), 41.6 (CH_2), 41.2 (C), 41.2 (CH_2), 27.4 (CH_2), 27.4 (CH_3), 27.1 (CH_2), 23.4 (CH_2), 23.4 (CH_2), 14.2 (CH_3) and 14.2 (CH_3); *m*/*z* (ES) 265 (MH^+, 100%), 205 (14) and 146 (14).

Data for compound **14c**: Found: M^+, 208.1464. $C_{13}H_{20}O_2$ requires M, 208.1458; ν_{max}. (neat) 2956, 2931, 2873, 1733, 1248, 1117, 796 and 734 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 5.81–5.69 (4H, m, alkene CH), 3.68 (3H, s, CH_3O), 2.76–2.67 (1H, m, CH), 1.45–1.38 (2H, m, CH_2), 1.33 (3H, s, CH_3), 1.32–1.19 (4H, m, 2 × CH_2) and 0.89 (3H, t, *J* 6.9, CH_3); δ_C (500 MHz; $CDCl_3$) 175.8 (C═O), 129.6 (CH), 128.4 (CH), 52.3 (CH_3), 44.5 (C), 35.4 (CH), 35.4 (CH_2), 28.6 (CH_2), 27.8 (CH_3), 23.0 (CH_2) and 14.2 (CH_3); *m*/*z* (ES) 208 (M^+, 20%), 164 (18), 149 (100), 121 (25), 105 (68) and 93 (78).

(1*r*,4*r*)-Methyl 4-ethyl-1-methylcyclohexa-2,5-dienecarboxylate (14d)

Prepared according to the general procedure using bromoethane (0.15 mL, 1.99 mmol, 1.1 equiv.) as electrophile. Purification by flash column chromatography (50 : 1 hexane–diethyl ether) gave the *title compound* (165 mg, 51%) as a pale yellow oil (Found: MH^+, 181.1230. $C_{11}H_{17}O_2$ requires M, 181.1229); ν_{max}. (neat) 3023, 2965, 2931, 2875 and 1736 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 5.79 (2H, dd, *J* 10.3, 1.9, alkene CH), 5.71 (2H, dd, *J* 10.3, 3.1, alkene CH), 3.68 (3H, s, CH_3O), 2.73–2.67 (1H, m, CH), 1.47 (2H, qd, *J* 7.4, 6.0, CH_2), 1.33 (3H, s, CH_3) and 0.87 (3H, t, *J* 7.4, CH_3); δ_C (500 MHz; $CDCl_3$) 175.8 (C═O), 129.2 (CH), 128.7 (CH), 52.4 (CH_3), 44.4 (C), 36.4 (CH), 28.1 (CH_2), 27.8 (CH_3) and 10.5 (CH_3); *m*/*z* (APCI) 181 (MH^+, 100%) and 115 (62).

(1*r*,4*r*)-Methyl 4-heptyl-1-methylcyclohexa-2,5-dienecarboxylate (14e)

Prepared according to the general procedure using 1-iodoheptane (0.59 mL, 3.62 mmol, 2.0 equiv.) as electrophile. Purification by flash column chromatography (9 : 1 hexane–diethyl ether) gave the *title compound* (240 mg, 53%) as a clear oil (Found: M^+, 250.1936. $C_{16}H_{26}O_2$ requires M, 250.1933); ν_{max}. (neat) 3026, 2955, 2927, 2856, 1735, 1240, 1114, 795 and 733 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 5.79–5.70 (4H, m, 4 × alkene CH), 3.68 (3H, s, CH_3O), 2.74–2.67 (1H, m, CH), 1.45–1.36 (2H, m, CH_2), 1.33 (3H, s, CH_3), 1.33–1.20 (10H, m, 5 × CH_2), and 0.88 (3H, t, *J* 7.0, CH_3); δ_C (500 MHz; $CDCl_3$) 175.6 (C═0), 129.5 (CH), 128.2 (CH), 52.2 (CH_3), 44.3 (C), 35.6 (CH_2), 35.2 (CH), 31.9 (CH_2), 29.8 (CH_2), 29.2 (CH_2), 27.6 (CH_3), 26.2 (CH_2), 22.6 (CH_2) and 14.1 (CH_3); *m*/*z* (EI) 250 (M^+, 20%), 191 (100), 105 (80) and 91 (97).

(1*r*,4*r*)-Methyl 1-methyl-4-octylcyclohexa-2,5-dienecarboxylate (14f)

Prepared according to the general procedure using 1-bromo-octane (0.35 mL, 1.99 mmol, 1.1 equiv.) as electrophile. Purification by flash column chromatography (9 : 1 hexane–diethyl ether) gave the *title compound* (226 mg, 43%) as a colourless oil (Found: MH^+, 265.2164. $C_{17}H_{29}O_2$ requires M, 265.2168); ν_{max}. (neat) 2954, 2926, 2855, 1734, 1240, 1114, 734 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 5.76 (2H, dd, *J* 10.4, 1.5, alkene CH), 5.73 (2H, dd, *J* 10.4, 2.5, alkene CH), 3.68 (3H, s, CH_3), 2.74–2.68 (1H, m, CH), 1.44–1.36 (2H, m, CH_2), 1.32 (3H, s, CH_3), 1.32–1.20 (12H, m, 7 × CH_2) and 0.87 (3H, t, *J* 6.8, CH_3); δ_C (500 MHz; $CDCl_3$) 175.8 (C═O), 129.6 (CH), 128.4 (CH), 52.3 (CH_3), 44.5 (C), 35.8 (CH_2), 35.4 (CH), 32.0 (CH_2), 30.0 (CH_2),

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29.7 (CH_2), 29.5 (CH_2), 27.8 (CH_3), 26.4 (CH_2), 22.8 (CH_2) and 14.2 (CH_3); *m/z* (APCl) 265 (MH^+, 100%). Earlier fractions contained approximately 20% of the double-octyl compound **17f**, but this was not sufficiently pure for characterisation purposes.

(1*r*,4*r*)-Methyl 4-benzyl-1-methylcyclohexa-2,5-dienecarboxylate (14g)

Prepared according to the general procedure using benzyl bromide (0.43 mL, 3.62 mmol, 2.0 equiv.) as electrophile. Purification by flash column chromatography (50 : 1 hexane–diethyl ether) gave the *title compound* (340 mg, 77%) as a colourless oil (Found: MH^+, 243.1393. $C_{16}H_{19}O_2$ requires M, 243.1385); ν_{max}. (neat) 3028, 2928, 1732, 1242, 1114, 726 and 701 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.28 (2H, app. tt, *J* 7.0, 1.4, aromatic CH), 7.19 (1H, app. tt, *J* 7.3, 1.4, aromatic CH), 7.17–7.13 (2H, m, aromatic CH), 5.78–5.70 (4H, m, alkene CH), 3.66 (3H, s, OCH_3), 3.05–2.99 (1H, m, C*H*Ph), 2.71 (2H, d, J 7.0, CH_2) and 1.14 (3H, s, CH_3); δ_C (500 MHz; $CDCl_3$) 175.6 (C═O), 139.3 (C), 129.5 (2 × CH), 128.9 (2 × CH), 128.7 (2 × CH), 128.2 (2 × CH), 126.3 (CH), 52.4 (CH_3), 44.5 (C), 42.4 (CH_2), 37.3 (CH) and 27.5 (CH_3); *m/z* (TOF AP^+) 284 (MH^+ + CH_3CN, 38%), 243 (MH^+, 100) and 115 (40).

(1*r*,4*r*)-Methyl 4-allyl-1-methylcyclohexa-2,5-dienecarboxylate (14h)

Prepared according to the general procedure using allyl bromide (0.31 mL, 3.62 mmol, 2.0 equiv.) as electrophile. Purification by flash column chromatography (20 : 1 hexane–diethyl ether) gave the *title compound* (0.19 g, 54%) as a colourless oil (Found: M − H, 191.1075. $C_{12}H_{15}O_2$ requires M, 191.1072); ν_{max}. (neat) 2953, 1732, 1244, 1115 and 734; δ_H (400 MHz; $CDCl_3$) 5.82–5.70 (5H, m, alkene CH), 5.08–5.01 (2H, m, alkene CH_2), 3.69 (3H, s, OCH_3), 2.83–2.76 (1H, m, CH), 2.18 (2H, app. t, *J* 6.8, CH_2) and 1.33 (3H, s, CH_3); δ_C (500 MHz; $CDCl_3$) 175.6 (C═O), 135.9 (CH), 128.9 (CH), 128.7 (CH), 116.8 (CH_2), 52.4 (CH_3), 44.4 (C), 40.1 (CH_2), 35.2 (CH) and 27.7 (CH_3); *m/z* (TOF MS EI^+) 191 (M^+ − H, 32%), 151 (93), 107 (78), 91 (98) and 84 (100).

((1*r*,4*r*)-4-Isopropyl-1-methylcyclohexa-2,5-dienyl)methanol (15)

A solution of (1*r*,4*r*)-methyl 4-isopropyl-1-methylcyclohexa-2,5-dienecarboxylate (**14a**) (1.00 g, 5.15 mmol) in THF (2 mL) was added to a suspension of $LiAlH_4$ (0.27 g, 7.22 mmol) in THF (50 mL). The reaction was stirred at 25 °C for 1 h, then quenched with 15% aqueous NaOH solution (0.19 mL) and water (0.6 mL), stirred for 30 minutes, then dried over Na_2SO_4 and filtered before removing the solvent under reduced pressure to give the *title compound* (0.66 g, 77%) as an essentially-pure colourless oil (Found: MH^+, 167.1433. $C_{11}H_{19}O$ requires M, 167.1430); ν_{max}. (neat) 3366, 3011, 2957, 2928, 2871, 1464, 1384 and 1366 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 5.78 (2H, dd, *J* 10.4, 3.2, alkene CH), 5.51 (2H, dd, *J* 10.4, 2.0, alkene CH), 3.33 (2H, d, *J* 6.1, CH_2OH), 2.69–2.65 (1H, m, CH═CH–C*H*), 1.76 (1H, septet of doublets, *J* 6.9, 4.1, C*H*$(CH_3)_2$), 1.36 (1H, t, *J* 6.1, OH), 0.99 (3H, s, CH_3) and 0.89 (6H, d, *J* 6.9, 2 × CH_3); δ_C (500 MHz; $CDCl_3$) 131.9 (CH), 129.5 (CH), 71.0 (CH_2), 42.1 (CH), 39.9 (C), 32.1 (CH), 24.8 (CH_3) and 19.3 (CH_3); *m/z* (ES) 167 (MH^+, 21%), 149 (100) and 115 (56).

((1*r*,4*r*)-4-Isopropyl-1-methylcyclohexa-2,5-dienyl)methyl 2,4-dinitrobenzoate (16)

A solution of 2,4-dinitrobenzoyl chloride (0.14 g, 0.60 mmol) in CH_2Cl_2 (1 mL) was added to ((1*r*,4*r*)-4-isopropyl-1-methylcyclohexa-2,5-dienyl)methanol (**15**) (0.10 g, 0.60 mmol) in CH_2Cl_2 (10 mL). Triethylamine (0.08 mL, 0.60 mmol) and 4-DMAP (10 mg) were then added and the solution stirred for 24 h. The reaction was quenched with water (5 mL), extracted with CH_2Cl_2 (3 × 15 mL) and dried over Na_2SO_4. Recrystallisation from 1 : 1 hexane–ethyl acetate gave the *title compound* (0.12 g, 56%) as beige crystals (Found: MH^+, 361.1392. $C_{18}H_{21}N_2O_6$ requires M, 361.1394); ν_{max}. (neat) 2959, 1738, 1538, 1349 and 1284 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.74 (1H, d, *J* 2.2, aromatic CH), 8.51 (1H, dd, *J* 8.4, 2.2, aromatic CH), 7.92 (1H, d, *J* 8.4, aromatic CH), 5.69 (2H, dd, *J* 10.4, 3.2, alkene CH), 5.55 (2H, dd, *J* 10.4, 2.0, alkene CH), 4.15 (2H, s, CH_2O), 2.62–2.58 (1H, m, C*H*), 1.75 (1H, septet of doublets, *J* 6.9, 3.9, C*H*$(CH_3)_2$), 1.09 (3H, s, CH_3) and 0.88 (6H, d, *J* 6.9, 2 × CH_3); δ_C (500 MHz: $CDCl_3$) 131.6 (CH), 130.8 (2 × CH), 128.7 (2 × CH), 127.4 (CH), 119.7 (CH), 74.2 (CH_2), 42.0 (CH), 37.6 (C), 32.1 (CH), 25.3 (CH_3) and 19.3 (CH_3) (The ester and aromatic quaternary carbon atoms are not evident, presumably due to slow relaxation. The reasons for this are not entirely clear); *m/z* (ES) 361 (MH^+, 50%), 163 (18) and 115 (100).

Selected crystallographic data: $C_{18}H_{20}N_2O_6$, FW = 360.36, *T* = 150 K, λ = 0.71073 Å, triclinic, $P\bar{1}$, *a* = 7.6377(3) Å, *b* = 7.8225(3) Å, *c* = 32.1299(10) Å, α = 93.748(2)°, β = 91.221(2)°, γ = 109.094(2)°, *V* = 1808.28(11) $Å^3$, *Z* = 4, ρ(calc) = 1.324 Mg m^{-3} , crystal size = 0.30 × 0.20 × 0.12 mm^3, reflections collected = 8271, independent reflections = 6414, *R*(int) = 0.0393, parameters = 476, $R_1[I > 2\sigma(I)]$ = 0.0706, w$R_2[I > 2\sigma(I)]$ = 0.1381, R_1 (all data) = 0.1050, wR_2 (all data) = 0.1588. Full crystallographic data for this compound have been deposited with the CCDC, reference number 854352.

Methyl 4,4-diethyl-1-methylcyclohexa-2,5-dienecarboxylate (17d)

A solution of *n*-butyllithium (2.0 M in cyclohexane, 4.52 mL, 9.05 mmol) was added to 1-methylcyclohexa-2,5-dienecarboxylic acid (**10**) (0.25 g, 1.81 mmol) in THF (10 mL) at −78 °C. TMEDA (0.68 mL, 4.53 mmol) was then added and the solution stirred for a further 30 minutes. Bromoethane (0.41 mL, 5.43 mmol) was added, the solution was stirred for 10 minutes at −78 °C, allowed to warm to room temperature and stirred for a further 1 h. The reaction was quenched with 2 M hydrochloric acid (5 mL) and the organic material extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the crude alkylated carboxylic acid. This was then dissolved in methanol (10 mL), concentrated sulfuric acid (0.05 mL) added and the resulting solution stirred at 25 °C for 17 h. The solvent was removed *in vacuo*, saturated $NaHCO_3$ solution (5 mL) added and the product

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extracted into CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification by flash column chromatography (20 : 1 hexane–diethyl ether) gave the *title compound* (181 mg, 48%) as a pale yellow oil (Found: M^+, 208.1469. $C_{13}H_{20}O_2$ requires M, 208.1463); ν_{max}. (neat) 2964, 2928, 1734 and 1241 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 5.83 (2H, d, *J* 10.3, 2 × alkene CH), 5.32 (2H, d, *J* 10.3, 2 × alkene CH), 3.67 (3H, s, CH_3O), 1.34 (2H, q, *J* 7.5, CH_2), 1.33 (2H, q, *J* 7.5, CH_2), 1.32 (3H, s, CH_3), 0.73 (3H, t, *J* 7.5, CH_3) and 0.72 (3H, t, *J* 7.5, CH_3); δ_C (500 MHz; $CDCl_3$) 175.8 (C═O), 132.5 (CH), 129.3 (CH), 52.2 (CH_3), 44.6 (C), 42.1 (C), 34.0 (CH_2), 33.5 (CH_2), 27.5 (CH_3), 9.5 (CH_3) and 9.2 (CH_3); *m*/*z* (EI) 208 (M^+, 15%), 207 (17), 179 (100), 149 (90) and 107 (100).

Acknowledgements

The authors would like to thank Dr Robert Jenkins, Mr Robin Hicks and Mr David Walker for technical assistance, and Astra-Zeneca and EPSRC for financial support. We are grateful to Dr Yulia Rabenkova for the translation of reference 11.

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