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Charles Felix Manful
Marquette University

William A. Donaldson
Marquette University, william.donaldson@marquette.edu

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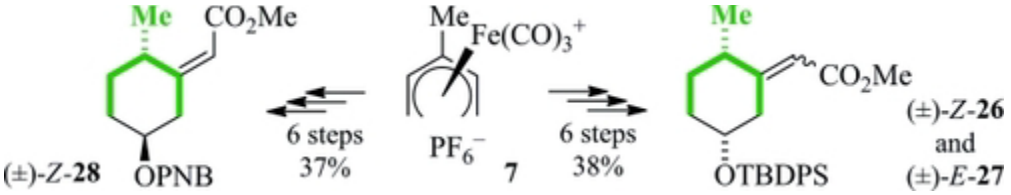
Charles F. Manful
Department of Chemistry, Marquette University, Milwaukee, WI
William A. Donaldson
Department of Chemistry, Marquette University, Milwaukee, WI

Graphical Abstract

The reaction of (3-methylpentadienyl)Fe(CO)$_3^+$ cation (**7**) with stabilized carbon nucleophiles affords cyclohexenones. Reaction of **7** with a non-racemic C2 chiral nucleophile dihydrotachysterol analogs proceeds with good diastereoselectivity. Issues in diastereoselectivity in approaches to synthons for the A-ring of the tachysterols from these cyclohexenones are reported.

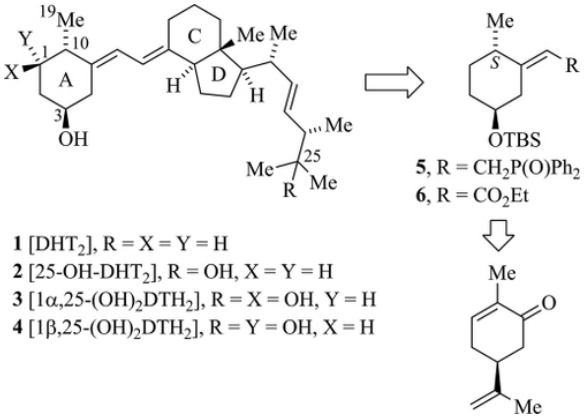


Abstract

The reaction of tricarbonyl(3-methylpentadienyl)iron(1+) cation (**7**) with stabilized carbon nucleophiles affords 4-methyl-5-substituted cyclohexenones. Reaction of **7** with sodium bis[(+)-2-phenylcyclohexyl]malonate afforded a mixture of diastereomers (*de* = 60 %); the diastereomeric allylic alcohols resulting from Luche reduction of this mixture were separable by column chromatography. Issues in diastereoselectivity in approaches to synthons for the A-ring of the tachysterols from these cyclohexenones are reported.

Introduction

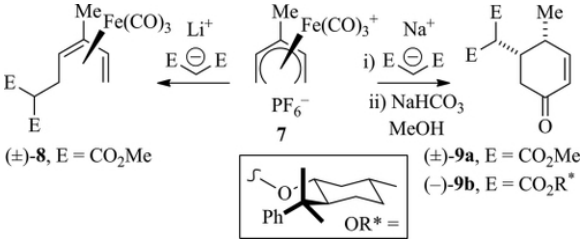
Dihydrotachysterol$_2$ (DHT$_2$, **1**, Scheme **1**) is one of several by-products of irradiation of ergosterol. This steroid raises serum levels of calcium and is orally administered for the treatment of parathyroid tetany, renal osteodystrophy and hypothyroidism.[1] The structure of **1** was eventually confirmed by preparation from (5*E*)-vitamin D$_2$.[2a] This as well as other means of semi-synthesis by reduction of the 10,19-olefin invariably produce mixtures of the desired 10*S*- and unnatural 10*R*-diastereomers.[2,3] In vivo metabolism of DHT$_2$ in rats produces 25-hydroxydihydrotachysterol$_2$, 1α,25-dihydroxy- and 1β,25-dihydrotachysterol$_2$ (**2**–**4** respectively).[4] The metabolite 25-OH-DHT$_2$ (**2**) is more active than **1** in binding to the chick intestinal receptor for 1α,25-dihydroxy vitamin D$_3$, and thus **2** "could be responsible for the therapeutic effectiveness" of **1**.[3] Of the two triol metabolites the 1α-stereoisomer **3** exhibits good binding to the mammalian vitamin D receptor [VDR], while **4** showed poor binding. It has been speculated "... that 1α,25-dihydroxylated DHTs represent promising analogs worthy of study for cell differentiation as well as calcemic properties."[4b] Total syntheses[5] of **1** and **2** have been accomplished by coupling the chiral phosphine oxide **5** with an appropriate CD ketone via the Lythgoe olefination strategy.[6] The phosphine oxide **5** is prepared from enoate **6** (4 steps) which is in turn prepared[5] from expensive (*S*)-carvone.[7]



Scheme 1 Dihydrotachysterols and retrosynthetic dissection.

We have previously reported that the regioselectivity for attack by malonate nucleophiles on the (3-methylpentadienyl)Fe(CO)$_3^+$ cation **7** is dependent on the nature of the counterion; reaction with the lithium salt gives a (diene)iron product (±)-**8** while reaction with the sodium salt gives a 4,5-disubstituted cyclohexenone product (±)-**9a** (Scheme **2**).[8] Furthermore, reaction of **7** with sodium bis[(–)-8-phenylmenthyl]malonate gave a

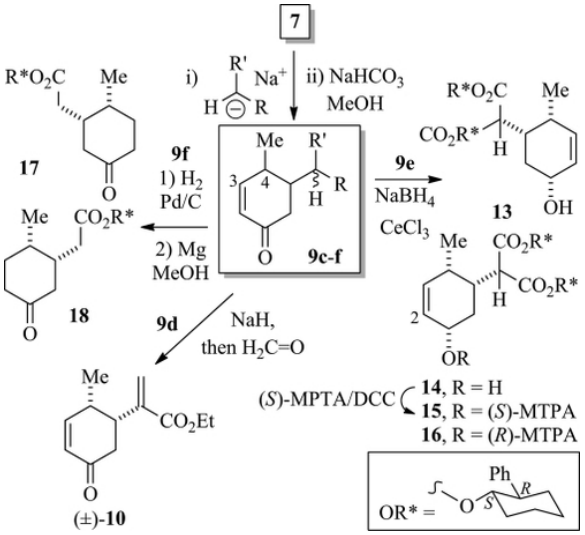
single diastereomer (–)-**9b**. We herein report our studies toward application of this methodology towards preparation of A-ring synthons for dihydrotachysterol.[9–11]



Scheme 2 Reaction of (3-methylpentadienyl)Fe(CO)$_3^+$ cation **7** with malonate nucleophiles (ref.**8**).

Results and Discussion

The reaction of (pentadienyl)iron cation **7** with sodium methyl phenylsulfonylacetate, followed by work-up with sodium hydrogen carbonate gave a mixture of diastereomeric cyclohexenones (±)-**9c**/**c'** which were partially separable by column chromatography (Scheme **3**, Table **1**). In a similar fashion, reaction of **7** with sodium triethyl phosphonylacetate gave a mixture of diastereomeric cyclohexenones (±)-**9d**/**d'**. While it was not possible to separate the mixture of **9d**/**d'**, Horner–Emmons olefination of the mixture gave a single product (±)-**10**.



Scheme 3 Preparation of 4-methyl-5-substituted-cyclohexenones **9c**–**f** (MPTA = α-methoxy-α-trifluoromethylphenylacetic acid).

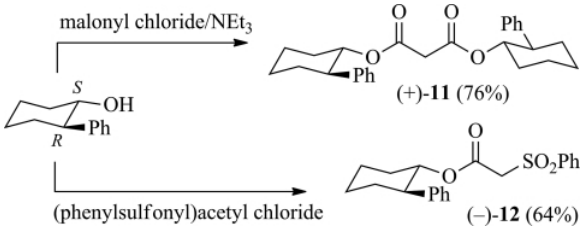
Table 1. Addition of stabilized carbon nucleophiles to pentadienyl cation **7**.

R	R'	Product (yield)	Product (yield)
CO_2Me	SO_2Ph	(±)-**9c**/**c'** (72 %)	–
CO_2Et	$P(O)(OEt)_2$	(±)-**9d**/**d'** (84 %)	(±)-**10** (98 %)
CO_2R^*[a]	CO_2R^*	**9e**/**9e'** (60 %, 1:5)	**13**/**14** (86 %, 1:5)
CO_2R^*	SO_2Ph	**9f** (87 %, 3:3:3:1)	**17**/**18** (52 %, 3:2)

[a] (R* = 1*S*,2*R*-phenylcyclohexyl).

The cyclohexenones **9c** and **9d** were assigned as the *cis*-stereoisomer based on their NMR spectroscopic data. The signals at ca. δ = 6.95–7.05 (dd, 1 H) for each were assigned to the H3 olefinic proton. The H3-H4 coupling constant for each (ca. 6 Hz) are similar to those observed for (±)-**9a** and (–)-**9b**, and these are consistent with the couplings reported for *cis*-4,5-dimethylcyclohexenone.[12]

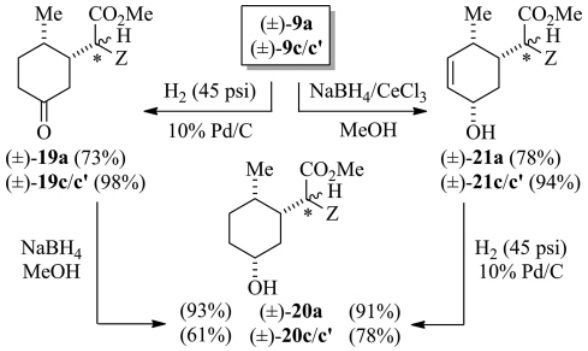
The absolute configuration of (–)-**9b** is opposite to that desired for the A-ring of the tachysterols. While (–)-8-phenylmenthol is commercially available, preparation of the pseudoenantiomer (1*S*,2*R*,*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexanol is laborious.[13] For this reason, we decided to explore an alternative chiral auxilary for this transformation. Toward this end, reaction of (1*S*,2*R*)-phenylcyclohexanol (prepared from 1-phenylcyclohexene)[14] with malonyl chloride or phenylsulfonylacetyl chloride gave the corresponding esters (+)-**11**[15] or (–)-**12** respectively (Scheme **4**). Reaction of **7** with the sodium salt of (+)-**11** gave a mixture of two diastereomers **9e**/**9e'** in a 1:5 ratio as determined by ^{1}H NMR spectroscopy (Scheme **3**, Table **1**). Attempted separation of this mixture was unsuccessful. Luche reduction[16] of this mixture gave a separable mixture of two allylic alcohols **13** and **14**. Assignment of the absolute configuration at the carbinol carbon of **14** was based on the ^{1}H NMR chemical shifts of the alkenyl proton (H^2) of the derived (*S*)- and (*R*)-Mosher's esters **15** and **16** (δ = 5.42 and 5.32 ppm respectively). These relative chemical shifts are consistent with an (*S*)-stereochemical assignment at C1.[17] These results might be anticipated since the (1*S*,2*R*)-phenylcyclohexyl auxiliary is known to direct the generation of asymmetric centers with an absolute configuration opposite to that obtained when using the 8-phenylmenthyl auxiliary.[18]



Scheme 4 Preparation of optically active nucleophiles.

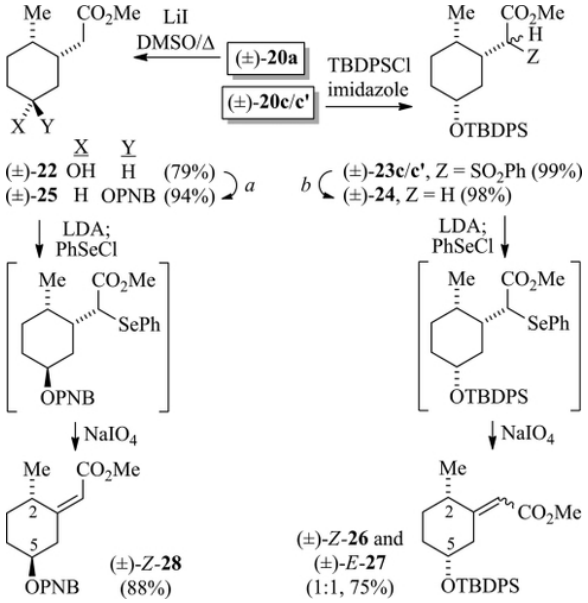
Reaction of **7** with the sodium salt of (–)-**12** gave a mixture of four diastereomers **9f** (Scheme **3**, Table **1**). Catalytic hydrogenation of this mixture, followed by reductive desulfonylation gave a mixture of diastereomeric cyclohexanones **17** and **18** (ca. 3:2 ratio). Since attempted separation of this mixture was unsuccessful and since the diastereomers were produced in a nearly equimolar ratio, the relative configuration of each was not determined. The low diastereoselectivity observed for the addition of the anion derived from C_1 symmetric (–)-**12** [as compared to the C2 anion derived from (+)-**11**] might be attributed to multiple orientations possible for this nucleophile as well as the ability of this nucleophile to react from either the *si*- or the *re*-face.

Elaboration of the cyclohexenones (±)-**9a** or (±)-**9c**/**c'** to a dihydrotachysterol A-ring fragment was attempted (Scheme **5**). To this end, catalytic hydrogenation of **9a** gave the cyclohexanone (±)-**19a**. Hydride reduction of **19a** gave the cyclohexanol (±)-**20a**. Alternatively, this same cyclohexanol could be prepared by (*i*) Luche reduction of **9a** to afford the cyclohexenol (±)-**21a**, followed by (*ii*) hydrogenation. In a similar fashion, processing of the diastereomeric mixture of phenylsulfonylacetates **9c**/**c'** along the same reaction conditions gave (±)-**19c**/**c'**, (±)-**20c**/**c'** and (±)-**21c**/**c'**, respectively (Scheme **5**). While **19c**–**21c** were isolated as a mixture of diastereomers at the indicated carbon (*), a clean sample of one or both diastereomers was isolated for **20c**/**c'** and **21c**/**c'** after careful column chromatography. The relative configuration about the cyclohexyl ring of **20a** and **20c** were assigned on the basis of their ^{1}H NMR spectroscopic data. In particular, the signal for the alcohol methine proton of each exhibited two large couplings (**20a**: δ = 3.60, tt, *J* = 2.8, 10.3 Hz; **20c**: δ = 3.58, tt, *J* = 4.6, 11.1 Hz). These large couplings are consistent with axial-axial couplings indicating that the hydroxy group occupies an equatorial orientation in each. The signal for the alcohol methine proton of **20c'** is relatively broad but it appears at a similar chemical shift (δ = 3.68–3.57, m) indicative of an equatorial orientation for the alcohol functionality in this diastereomer as well. While the diastereomeric mixtures could be separated by careful column chromatography in certain cases, it proved more convenient to carry these mixtures forward.



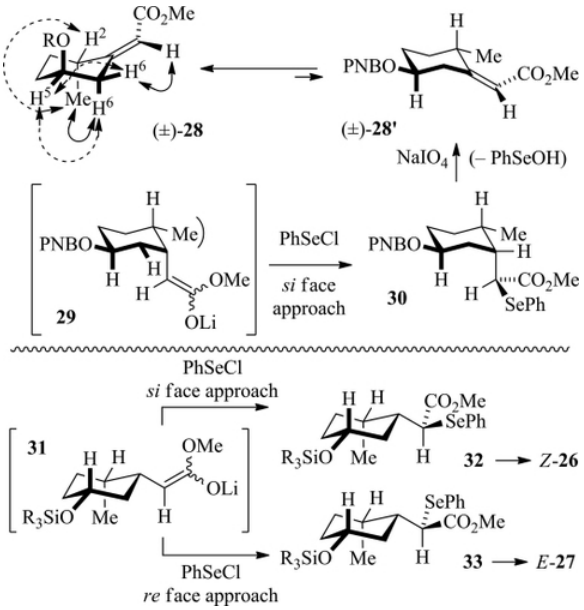
Scheme 5 Attempted syntheses of dihydrotachysterol A ring fragments.

While Krapcho decarbomethoxylation[19] of **20a** gave the ester (±)-**22**, the attempted reductive desulfonylation of **20c/c'** was unsuccessful (Scheme **6**). Toward this end, reaction of **20c/c'** with *tert*-butyldiphenylsilyl chloride afforded the silyl ether (±)-**23c/c'** as a mixture of diastereomers. Notably, reductive desulfonylation of the mixture of diastereomers **23c/c'** gave (±)-**24** as a single diastereomer. Alternatively, reaction of **22** with *p*-nitrobenzoic acid under Mitsunobu conditions[20] gave the PNB ester (±)-**25** with inversion of configuration at the carbinol carbon. Handschuh and Voelter reported that treatment of methyl 17-hydroxy-3-oxo-α-(phenylsulfonyl)-androst-4-ene-6-acetate with base proceeded via elimination to afford the 6-carboxymethylene derivative.[21] Unfortunately, in our hands treatment of the mixture of (±)-**23c/c'** under similar reaction conditions gave a complex mixture of unidentified products. Alternatively, Posner[22a] reported the preparation of A-ring synthons for vitamin D analogs via elimination of in situ generated α-sulfoxide esters, while the groups of Ito[22b] and Crich[22c] reported the preparation of carboxymethylene cyclohexanones via the elimination of α-selenoxide esters. Following these precedents, deprotonation of (±)-**24**, followed by reaction with phenylselenyl chloride gave a mixture of diastereomeric α-phenylselenyl esters which upon oxidation with sodium periodate gave a mixture of *E*-**26** and *Z*-**27**. Attempted separation of this mixture was unsuccessful. The structural assignment for these stereoisomers was based on their ^{1}H NMR spectroscopic data. In particular, the pair of singlets at δ = 5.73 (s, 1 H) and δ = 5.36 (s, 1 H) ppm were assigned to the α-olefinic protons, while the pair of multiplets at δ = 4.05 (m, 1 H) and δ = 3.98 (s, 1 H) ppm were assigned to the 5-H protons.



Scheme 6 Generation of enoates via α-selenation/elimination (reagents: *a: p*-nitrobenzoic acid/diethyl azodicarboxylate/PPh_3, *b:* Mg/MeOH).

In contrast, α-deprotonation of (±)-**25**, followed by reaction with phenylselenyl chloride and subsequent oxidative elimination of phenylselenic acid afforded only the enoate (±)-*Z*-**28**. The structural assignment for **28** was based on its ^{1}H NMR spectroscopic data (Scheme **7**). In particular, the singlet at δ = 5.61 ppm was assigned to the α-olefinic proton, while the multiplet at δ = 5.44 ppm was assigned to 5-H. The assignment of this latter signal was further supported by COSY crosspeaks with the signals for 6-H_{ax} and 6-H_{eq} (δ = 2.78 and 2.46 ppm respectively). Finally assignment of the broad multiplet at δ = 4.25–4.15 ppm to 2-H was aided by a COSY crosspeak with the 2-Me doublet at δ = 1.22 ppm. The lack of any NOESY crosspeaks between the α-olefinic proton signal (δ = 5.61 ppm) and the signals for 2-Me or 2-H, and the appearance of a crosspeak with 6-H_{eq} (δ = 2.46 ppm) lead to the assignment of the *Z*-stereochemistry for the exocyclic olefin. Enoate **28** exists predominantly in the 2-Me/OPNB diaxial conformer as evidenced by (*i*) the narrow half-width of the signal for 5-H (1/2W = 7.4 Hz) indicative of a lack of axial–axial couplings, (*ii*) a NOESY crosspeak between the signal for 2-Me and 6-H_{ax}, and (*iii*) the relatively large downfield shift for 2-H due to the deshielding anisotropy of the Z-enoate functionality. The higher energy of the 2-Me/OPNB diequatorial conformer (±)-**28'** is due to the 1,3-allylic strain[23] between the ester substituent and 2-Me present in this conformer; this strain is absent in the 2-Me/OPNB diaxial conformer **28**. A similar methyl axial conformational preference has been reported for (*Z*)-(2-methylcyclohexylidene)acetic acid.[24]



Scheme 7 Structure of (±)-*Z*-**28**. Dashed arrows signify COSY interactions, solid double-headed arrows signify NOESY interactions. Rationale for the stereochemical outcome of the a-phenylselenation/elimination sequence for **24** and **25**.

Exclusive formation of the *Z*-stereoisomer is rationalized in the following manner. Electrophilic attack of phenylselenyl chloride on the ester enolate **29** derived from **25** occurs preferentially on the *si*-face opposite to the steric bulk of the 2-Me substituent to afford the α-selenyl ester **30**. Oxidation of **30** leads to an α-selenyl oxide, which undergoes a *syn*-elimination to generate **28'**, which undergoes a chair-chair inversion the more stable conformer **28**. Attempts to isomerize (±)-**28** to the presumably more stable *E*-isomer using either acid, iodine or photochemically were unsuccessful. In contrast, since the C2-methyl substituent occupies an axial orientation in the ester enoate **31** derived from **24**, phenylselenyl chloride can approach equally well from either the *si*- or the *re*-face to form the a-phenylseleno esters **32** and **33** respectively. Oxidation and concerted *syn*-elimination of **32** affords *Z*-**26**, while oxidation and concerted *syn*-elimination of **33** affords *Z*-**27**.

Conclusions

The preparation of 3-methyl-4-substituted cyclohexenones by reaction of (3-methylpentadienyl)$Fe(CO)_3^+$ cation with stabilized carbon nucleophiles has been extended to phenylsulfonylacetates and triethyl phosphonoacetates. Use of the chiral nucleophile sodium bis[(+)-2-phenylcyclohexyl]malonate led to a diastereomerically enriched cyclohexenone which possesses the opposite absolute configuration about the cyclohexenone ring compared to our previously reported results. Finally, functional group manipulation of the cyclohexenones (±)-**9a** and (±)-**19c/c'** illustrate issues in controlling the stereoselective formation of the C5-C-6 olefin in synthons which could be used for the synthesis of DHT_2 analogs.

Experimental Section

Methyl 2-(3'-Methyl-6'-oxo-1'-cyclohexen-4'-yl)-2-(phenylsulfonyl)acetate (±)-9c/c': To a stirring suspension of NaH (33 mg, 0.82 mmol) in freshly distilled THF (13 mL) under N_2 at 0 °C was added dropwise methyl phenylsulfonylacetate. The reaction mixture was stirred at this temperature for 1 h. Salt **7** (200 mg, 0.546 mmol) was added in one portion and the mixture stirred at room temperature for 2 h. The reaction was diluted with CH_2Cl_2 (13 mL) and saturated $NaHCO_3$/MeOH (26 mL) and stirred at room temperature for 24 h. The reaction was finally quenched with water and the organic components extracted into CH_2Cl_2, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate, 4:1) to afford a mixture of two diastereomeric cyclohexenones **9c** and **9c'** (ca. 1:1, 126 mg, 72 %) as a yellow oil along with a trace amount of iron diene products. The mixture of diastereomers could be partially separated by subjecting the mixture to a second chromatographic purification and isolation of the leading and trailing fractions.

9c/9c': IR (neat): $\tilde{\nu}$ = 1743, 1678, 1327, 1149 cm^{-1}. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.7 and 196.6 (C1), 165.9 and 165.8 (CO_2R), 155.5, 154.2, 137.5, 134.83, 134.78, 129.43, 129.39, 129.35, 128.2, 127.9, 74.1 and 72.3 [*C*H(SO_2Ph)CO_2Me], 53.22 and 53.17 (OMe), 36.6, 36.4, 36.2, 31.8, 31.7, 12.4 and 12.3 (4-Me) ppm. HRMS (ESI): calcd. for $C_{16}H_{18}O_5SNa$ 345.0767, found 345.0772.

9c: ^1H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 7.6 Hz, 2 H, ArH), 7.72 (t, *J* = 7.4 Hz, 1 H, ArH), 7.60 (t, *J* = 7.6 Hz, 2 H, ArH), 7.07 (dd, *J* = 5.8, 10.4 Hz, 1 H, 3-H), 5.99 (d, *J* = 10.4 Hz, 1 H, 2-H), 4.15 [d, *J* = 9.6 Hz, 1 H, C*H*(SO_2Ph)CO_2Me], 3.47 (s, 3 H, OMe), 3.25–3.15 (m, 2 H), 2.41 (dd, *J* = 13.4, 16.8 Hz, 1 H, 6-H), 2.13 (dd, *J* = 3.6, 16.8 Hz, 1 H, 6'-H), 1.23 (d, *J* = 6.4 Hz, 3 H, 4-Me) ppm.

9c': (300 MHz, $CDCl_3$, deconvoluted from mixture of **9c/c'**): ^1H NMR: δ = 7.55–7.95 (m, 5 H, ArH), 6.92 (dd, *J* = 6.3, 9.9 Hz, 1 H, 3-H), 5.97 (d, *J* = 9.9 Hz, 1 H, 2-H), 4.10 [d, *J* = 11.7 Hz, 1 H, C*H*(SO_2Ph)CO_2Me], 3.52 (s, 3 H, OMe), 3.24–3.18 (m, 1 H), 3.12–3.00 (m, 1 H), 2.52 (dd, *J* = 13.5, 17.1 Hz, 1 H, 6-H), 2.42–2.32 (m, 1 H, 6'-H), 1.04 (d, *J* = 6.9 Hz, 3 H, 3-Me) ppm.

Triethyl 2-(2-Methyl-5-oxocyclohex-3-en-1-yl)phosphonoacetate (±)-9d/d': To an ice-cold stirring suspension of NaH (13.5 mg, 0.546 mmol) in dry THF (10 mL) was added triethyl phosphonoacetate (0.122 mg, 0.546 mmol). The mixture was stirred at 0 °C for 10–15 min. Solid cation **7** (0.20 g, 0.55 mmol) was added in one portion and the reaction mixture stirred for 2 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 and saturated methanolic $NaHCO_3$ (10 mL each) and stirred overnight at room temperature. Water (20 mL) was added and the mixture extracted several times with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (SiO_2, diethyl ether/hexanes 0 → 50 % gradient) to afford **9d/d'** as a yellowish oil (164 mg, 84 %) as well as an unquantified trace of (diene)iron complex. IR (neat): $\tilde{\nu}$ = 1736, 1680, 1258 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.99 (dd, *J* = 6.1, 10.1 Hz, 1 H, 3-H), 5.92 (d, *J* = 6.1 Hz, 1 H, 2-H), 4.32–4.03 (m, 6 H, OC*H*$_2$CH$_3$), 3.08–2.73 (m, 5 H), 1.37–1.19 (m, 9 H, OCH$_2$C*H*$_3$), 1.10 (d, *J* = 6.7 Hz, 3 H, 4-Me) ppm. HRMS (ESI): calcd. for $C_{12}H_{25}O_6PNa$ 355.1285, found 355.1281.

Ethyl 2-(2-Methyl-5-oxocyclohex-3-en-1-yl)propenoate (±)-10: To an ice-cold stirring suspension of NaH (43 mg, 0.11 mmol) in dry THF (5 mL) was added a mixture of diastereomers **9d**/**d'** (40 mg, 0.11 mmol). The mixture was stirred at 0 °C for 30 min, and paraformaldehyde (3.2 mg, 0.11 mmol) added. The reaction mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with H_2O (10 mL) and extracted several times with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (SiO_2, diethyl ether/hexanes, 0 → 25 % gradient) to afford (±)-**10** as a pale yellow oil (20 mg, 98 %). IR (neat): = 1714, 16 cm^{-1}83cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02 (dd, *J* = 4.1, 9.5 Hz, 1 H, 3-H), 6.39 (s, 1 H, C=C*H*$_2$), 5.99 (d, *J* = 9.5 Hz, 1 H, 2-H), 5.48 (s, 1 H, C=C*H*$_2$), 4.22 (q, *J* = 7.5 Hz, 2 H, OC*H*$_2$CH$_3$), 3.54–3.41 (m, 1 H), 2.94–2.81 (m, 1 H), 2.66–2.53 (m, 1 H), 2.39–2.28 (m, 1 H), 1.31 (t, *J* = 7.1 Hz, 3 H, OCH$_2$C*H*$_3$), 0.88 (d, *J* = 6.6 Hz, 3 H, 4-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.3 (C1), 168.0 (CO_2R), 155.6, 140.9, 127.6, 125.3, 60.9 (O*C*H$_2$CH$_3$), 38.1, 37.1, 32.1, 14.2 (OCH$_2$*C*H$_3$), 12.6 (4-Me) ppm. HRMS (ESI): calcd. for $(C_{12}H_{16}O_6)_2Na$ 439.2100, found 439.2091.

Bis[(1*S*,2*R*)-2-phenylcyclohexyl] Malonate (+)-11: To a stirring solution of (1*S*,2*R*)-2-phenylcyclohexanol (360 mg, 2.03 mmol) in freshly distilled CH_2Cl_2 at 0 °C was added triethylamine (206 mg, 2.03 mmol). The reaction mixture was stirred under N_2 at 0 °C for 1 h. Malonyl dichloride (143 mg, 1.02 mmol) was added dropwise over a 5 min period, and the mixture was stirred at 0 °C for 30 min and at room temperature for 24 h. The solvent was evaporated under a N_2 stream and the residue purified by column chromatography (SiO_2, hexanes/ethyl acetate = 5:1) to afford (+)-**11** (208 mg, 76 %) as a colorless solid, m.p. 114–116 °C. $[\alpha]_D^{20}$ = +13.5 (*c* = 0.0169, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.15 (m, 10 H, ArH), 4.98 (dt, *J* = 4.2, 10.6 Hz, 2 H, 1-H), 2.80 [s, 2 H, C*H*$_2$(CO$_2$R*)$_2$], 2.63 (dt, *J* = 3.5, 11.6 Hz, 2 H, 2-H), 2.17–2.08 (m, 2 H), 2.00–1.75 (m, 6 H), 1.65–1.30 (m, 8 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8 (CO_2Me), 142.9 (Ar), 128.4 (Ar), 127.6 (Ar), 126.5 (Ar), 77.0 (*C*HOR), 49.4, 41.5, 33.9, 32.0, 25.8, 24.7 ppm. HRMS (ESI): calcd. for $C_{27}H_{32}O_4Na$ 443.2193, found 443.2193.

(1*S*,2*R*)-2-Phenylcyclohexyl (Phenylsulfonyl)acetate (–)-12: To (phenylsulfonyl)acetic acid (100 mg, 0.499 mmol) under N_2 was added dropwise oxalyl chloride (78 mg, 0.62 mmol). The mixture was stirred at room temperature for 1 h, and then the excess oxalyl chloride was removed under vacuum. The crude acid chloride was dissolved in benzene (5 mL), and (1*S*,2*R*)-2-phenylcyclohexanol (105 mg, 0.599 mmol) was added in one portion. The mixture was heated at reflux for 48 h. After this time, the solvent was evaporated under vacuum and the residue purified by column chromatography (ethyl acetate/hexanes, 0 → 20 % gradient) to afford (–)-**12** (115 mg, 64 %) as a viscous oil. $[\alpha]_D^{20}$ = –5.1 (*c* = 0.0049, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67 (dd, *J* = 1.2, 8.1 Hz, 2 H, ArH), 7.57 (dt, *J* = 1.2, 8.1 Hz, 1 H, ArH), 7.44 (dt, *J* = 1.2, 8.1 Hz, 2 H, ArH), 7.19–6.97 (m, 5 H, ArH), 4.86 (dt, *J* = 4.2, 10.5 Hz, 1 H, 1-H), 3.76 (d, *J* = 14.4 Hz, 1 H, SC*H*H'CO$_2$R*), 3.70 (d, *J* = 14.4 Hz, 1 H, SCH*H'*CO$_2$R*), 2.51 (dt, *J* = 3.7, 11.6 Hz, 1 H, 2-H), 2.00–1.92 (m, 1 H), 1.87–1.62 (m, 3 H), 1.50–1.15 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.7 (CO$_2$R*), 142.6, 138.8, 134.3, 129.3, 128.7, 128.5, 127.6, 126.8, 78.7 (*C*HOR), 60.9 (S*C*H$_2$CO$_2$R*), 49.4, 33.9, 32.0, 25.7, 24.8 ppm. HRMS (ESI): calcd. for $C_{20}H_{22}O_4SNa$ 381.1131, found 381.1127.

Bis[(1*S*,2*R*)-2-phenylcyclohexyl] 2-(3-Methyl-6-oxo-1-cyclohexen-4-yl)propanedioate (9e/9e'): To a stirring suspension of NaH (48 mg, 1.1 mmol) in freshly distilled THF (10 mL) under N_2 at 0 °C was added dropwise a solution of (+)-**11** (320 mg, 0.761 mmol) in THF (3 mL). The reaction mixture was stirred at 0 °C for 1 h, and then solid cation **7** (418 mg, 1.14 mmol) was added in one portion. The reaction mixture was stirred for 2 h at 0 °C and then diluted with CH_2Cl_2 (13 mL) and saturated $NaHCO_3$/MeOH (15 mL). The mixture was stirred at room temperature for 24 h. The reaction was quenched with water (20 mL), extracted several times with CH_2Cl_2, and the combined extracts were dried (Na_2SO_4) and concentrated. Purification of the residue by column chromatography (SiO_2, ethyl acetate/hexanes, 0 → 25 % gradient) gave an inseparable mixture of two diastereomeric cyclohexenones **9e** and **9e'** (241 mg, 0.455 mmol, 1:5 ratio, 60 % total) as a colorless solid, m.p. 144–146 °C. HRMS (ESI): calcd. for $C_{34}H_{40}O_5Na$ 551.2768, found 551.2757.

9e: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.08 (m, 10 H, Ph), 6.67 (dd, *J* = 6.3, 10.2 Hz, 1 H, 3-H), 5.78 (d, *J* = 9.9 Hz, 1 H, 2-H), 5.00 (dt, *J* = 4.5, 10.8 Hz, 1 H), 4.95 (dt, *J* = 4.5, 10.5 Hz, 1 H), 2.79 (d, *J* = 11.7 Hz, 1 H, C*H*E_2), 2.66 (dt, *J* = 3.3, 11.1 Hz, 1 H, 6-H), 2.56 (dt, *J* = 3.6, 11.1 Hz, 1 H, 6'-H), 2.40–1.10 (m, 20 H), 0.17 (d, *J* = 6.9 Hz, 3 H, 4-Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.4 (C=O), 167.0 (CO_2R), 166.6 (CO_2R), 155.4 (C-3), 143.2, 142.7, 128.7, 128.6, 128.5, 127.7, 127.6, 127.5, 127.1, 126.7, 77.8 (C-2'), 54.7 [*C*H(CO_2R*)$_2$], 49.7, 49.5, 36.1, 36.0, 34.4, 34.2, 32.2, 31.9, 30.6, 25.8, 24.8, 11.5 (4-Me) ppm.

Bis[(1*S*,2*R*)-2-phenylcyclohexyl] 2-[(3*S*,4*R*,6*S*)-6-Hydroxy-3-methyl-1-cyclohexen-4-yl]propanedioate (+)-14 and Bis[(1*S*,2*R*)-2-phenylcyclohexyl] 2-[(3*R*,4*S*,6*R*)-6-Hydroxy-3-methyl-1-cyclohexen-4-yl]propanedioate (–)-13: To the mixture of chiral cyclohexenones (**9e**/**9e'**, 100 mg, 0.189 mmol) in MeOH (10 mL) at 0 °C was added $CeCl_3 \cdot 7H_2O$ (149 mg, 0.400 mmol). The mixture was stirred vigorously until homogeneous (ca. 15 min). Solid $NaBH_4$ (29 mg, 0.76 mmol) was added in small portions and stirring continued at room temperature for 3 h. The reaction was quenched with water, extracted with diethyl ether, dried ($MgSO_4$) and concentrated. Purification of the residue by flash column chromatography (SiO_2, ethyl acetate/hexanes, 0 → 40 % gradient) to afforded two isomeric cyclohexenols (–)-**13** (less polar, 21 mg, colorless oil) and (+)-**14** (more polar, 65 mg, colorless oil) in 86 % overall yield.

(+)-14: $[\alpha]_D^{20}$ = +20.6 (*c* = 0.00156, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.10 (m, 10 H, ArH), 5.38–5.35 (narrow m, 2 H, CH=CH), 5.12 (dt, *J* = 4.5, 10.5 Hz, 1 H, C*H*OR), 5.03 (dt, *J* = 4.2, 10.8 Hz, 1 H, C*H'*OR), 3.47 (dd, *J* = 6.3, 9.3 Hz, 1 H, C*H*OH), 2.78 [d, *J* = 12.3 Hz, 1 H, C*H*(CO_2R*)$_2$], 2.70 (dt, *J* = 3.9, 11.7 Hz, 1 H), 2.61 (dt, *J* = 3.9, 11.7 Hz, 1 H), 2.14–1.20 (m, 19 H), 0.80 (dt, *J* = 9.9, 12.6 Hz, 1 H), 0.62 (dd, *J* = 6.3, 11.1 Hz, 1 H), 0.06 (d, *J* = 7.5 Hz, 3 H, 2-Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.8 (CO_2R*), 167.1 (CO_2R*), 143.8, 143.1, 134.5, 128.76, 128.74, 128.5, 127.8, 127.6, 126.7, 126.3, 76.6, 76.5, 67.8, 55.8, 49.6, 49.5, 35.4, 34.9, 34.6, 32.1, 32.0, 30.7, 30.0, 25.9, 24.9, 24.8, 13.9 (2-Me) ppm. A satisfactory HRMS spectrum was not obtained for this compound.

(–)-13: $[\alpha]_D^{20}$ = –31 (*c* = 0.0014, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.10 (m, 10 H, ArH), 5.35 (d, *J* = 10.2 Hz, 1 H, CH=CH), 5.24 (ddd, *J* = 1.4, 5.0, 10.1 Hz, 1 H, CH=CH), 5.08–4.93 (m, 2 H), 3.85 (dt, *J* = 1.2, 7.9 Hz, 1 H), 2.77 [d, *J* = 12.0 Hz, 1 H, C*H*(CO_2R*)$_2$], 2.67 (dt, *J* = 3.3, 11.4 Hz, 1 H), 2.60 (dt, *J* = 3.2, 11.6 Hz, 1 H), 2.10–1.70 (m, 9 H), 1.58–1.10 (m, 11 H), 0.60–0.49 (m, 1 H), 0.47 (d, *J* = 7.2 Hz, 3 H, 2-Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.1 (CO_2Me), 167.2 (CO_2Me), 143.7, 143.2, 134.9, 128.7, 128.3, 128.0, 127.5, 126.6, 126.4, 77.0, 67.8, 55.9, 49.8, 49.4, 35.6, 34.9, 34.4, 32.1, 32.0, 30.4, 29.8, 25.9, 25.85, 24.8, 14.3 (2-Me) ppm. A satisfactory HRMS spectrum was not obtained for this compound.

***S*-(–)-(α)-MTPA Ester 15:** To a solution of (+)-**14** (15 mg, 0.028 mmol) in freshly distilled THF (3 mL) was added *S*-(–)-(α)-MTPA (26 mg, 0.11 mmol). The mixture was homogenized and then DCC (23 mg, 0.11 mmol) and DMAP (0.5 mg, 0.004 mmol) were added successively with stirring. After 4 h the reaction mixture was heated at reflux for 12 h. Upon completion consumption of the starting material the solvent was removed under a stream of N_2. The product was purified by column chromatography (SiO_2, ethyl acetate/hexanes, 0 → 40 % gradient) to afford **15** as a colorless oil quantitatively. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58–7.16 (m, 15 H, ArH), 5.49 (dd, *J* = 5.2, 6.4 Hz, 1 H, 3-H), 5.42 (d, *J* = 7.0 Hz, 1 H, 2-H), 5.13–4.95 (m, 3 H), 3.56 (s, 3 H, OMe), 2.71 [d, *J* = 7.4 Hz, 1 H, C*H*(CO_2R*)$_2$], 2.66–2.60 (m, 2 H), 2.17–1.65 (m, 10 H), 1.54–0.89 (m, 10 H), 0.00 (d, *J* = 7.5 Hz, 3 H, 4-Me) ppm.

***R*-(+)-(α)-MTPA 16:** Esterification of (+)-**14** (15 mg, 0.028 mmol) with *R*-(+)-(α)-MTPA (26 mg, 0.11 mmol) was carried out in a fashion similar to the reaction of (+)-**14** with (*S*)-MTPA. The product was purified by (SiO_2, ethyl acetate/hexanes, 0 → 40 % gradient) to afford **16** as a colorless solid quantitatively, m.p. 130–132 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56–7.14 (m, 15 H, ArH), 5.57 (dd, *J* = 5.4, 6.0 Hz, 1 H, 3-H), 5.32 (d, *J* = 6.8 Hz, 1 H, 2-H), 5.16–4.85 (m, 3 H), 3.57 (s, 3 H, OMe), 2.78–2.56 (d & m, 3 H), 2.16–1.65 (m, 10 H), 1.47–0.89 (m, 10 H), 0.00 (d, *J* = 7.4 Hz, 3 H, 4-Me) ppm.

(1*S*,2*R*)-2-Phenylcyclohexyl 2-(2-Methyl-4-oxocyclohexyl)acetate (17 and 18): To a stirred suspension of NaH (83 mg, 2.1 mmol) in freshly distilled THF (34 mL) under N_2 at 0 °C was added dropwise (–)-**12** (542 mg, 1.51 mmol). The reaction mixture was stirred for 1 h, and then solid cation **7** (500 mg, 1.37 mmol) was added in one portion. The mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was diluted with CH_2Cl_2 (34 mL) and saturated $NaHCO_3$/MeOH (44 mL) and stirred at room temperature for 24 h. The reaction mixture was quenched with water, extracted several times with CH_2Cl_2, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 4:1) to afford an inseparable mixture of four diastereomeric cyclohexenones (ca. 1:3:3:3 ratio) (560 mg, 87 %) as a pale oil. This mixture was used in the next step without further characterization. Catalytic hydrogenation of the mixture of isomeric cyclohexenones (182 mg, 0.388 mmol) in MeOH in the presence of 10 % Pd/C was carried out in a fashion similar to the preparation of **19a**. Purification of the residue by column chromatography (SiO_2, acetone/hexanes, 0 → 20 % gradient) gave an inseparable mixture of four diastereomeric cyclohexanones (ca. 3:3:3:1 ratio) as a colorless foamy solid (141 mg, 78 %). This mixture was used in the next step without further characterization. Reductive desulfonylation of the mixture of diastereomeric cyclohexanones (145 mg, 0.309 mmol) in MeOH with added activated Mg (54.2 mg, 2.25 mmol) was carried out in a fashion similar to the preparation of **24**. Purification of the residue by column chromatography (hexanes/ethyl acetate = 4:1) gave an inseparable mixture of two diastereomers **17** and **18** (ca. 3:2 ratio) (68 mg, 0.21 mmol, 67 %) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25–7.05 (m, 5H ArH), 4.95 (dt, *J* = 4.2, 10.6 Hz, 1 H, C*H*OR), 2.65–2.52 (m, 1 H), 2.25–1.18 (m, 18 H), 0.79 and 0.65 (2 × d, *J* = 6.9 Hz, 3 H, 2-Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.9 (C=O), 171.8 (CO_2R*), 171.4 (CO_2R*), 143.4, 143.3, 129.0, 128.65, 128.59, 128.55, 127.71, 127.66, 126.71, 126.67, 77.4, 76.3, 50.09, 50.06, 43.9, 43.6, 38.3, 38.2, 37.95, 37.88, 37.5, 37.0, 34.36, 34.34, 32.58, 32.53, 31.7, 31.24, 31.17, 30.8, 30.3, 29.91, 19.87, 26.0, 24.9, 13.4 (2-Me), 12.8 (2-Me) ppm. HRMS (ESI): calcd. for $C_{21}H_{28}O_3Na$ 351.1931, found 351.1926.

Dimethyl 2-(2-Methyl-5-oxocyclohexyl)propanedioate (±)-19a: The cyclohexenone (±)-**9a** (112 mg, 0.467 mmol) was dissolved in methanol (10 mL) and the resultant solution transferred into a small heavy-walled hydrogenation flask. Palladium on activated carbon (10 % w/w, 15 mg) was added and the flask was connected to a Parr hydrogenation apparatus. The reaction mixture was maintained under H_2 (45 psi) and stirred for 24 h after which the pressure was released and the solvent removed. The residue was suspended in ethyl acetate and filtered through a pad of celite. The filter bed was washed several times with ethyl acetate and the extracts concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, ethyl acetate/hexanes, 15 → 30 % gradient) to afford (±)-**19a** as a pale yellow oil (82 mg, 73 %). IR (neat): $\tilde{\nu}$ = 1735, 1666 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.76 (s, 3 H, OMe), 3.74 (s, 3 H, OMe), 3.40 [d, *J* = 10.8 Hz, 1 H, C*H*(CO_2Me)$_2$], 2.72 (ddt, *J* = 3.5, 5.6, 11.1 Hz, 1 H), 2.53–2.01 (m, 5 H), 1.97–1.85 (m, 2 H), 1.07 (d, *J* = 6.9 Hz, 3 H, 4-Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 209.4, 168.42, 168.36, 55.3, 53.0, 52.9, 40.9, 40.7, 36.4, 31.6, 28.7, 11.9 (2-Me) ppm. HRMS (ESI): calcd. for ($C_{12}H_{18}O_5$)$_2$Na 507.2201, found 507.2210.

Dimethyl 2-(5-Hydroxy-2-methylcyclohex-3-en-1-yl)propandioate (±)-21a: The reduction of (±)-**9a** (33 mg, 0.14 mmol) under Luche conditions in methanol (2.5 mL) with $CeCl_3 \cdot 7H_2O$ (57 mg, 0.15 mmol) and $NaBH_4$ (25 mg, 0.65 mmol) was carried out in a fashion similar to the reduction of **9e**/**9e'**. Purification of the residue by flash chromatography (SiO_2, diethyl ether/hexanes, 0 → 75 % gradient) to afford (±)-**21a** as a pale yellow oil (26 mg, 78 %). IR (neat): $\tilde{\nu}$ = 3404, 1735 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.70 (ddd, *J* = 1.8, 5.0, 10.2 Hz, 1 H, CH=CH), 5.61 (br. d, *J* = 10.2 Hz, 1 H, CH=CH), 4.32 (br. t, *J* = 8.1 Hz, 1 H, C*H*OH), 3.75 (s, 3 H, OMe), 3.73 (s, 3 H, OMe), 3.38 [d, *J* = 11.4 Hz, 1 H, C*H*(CO_2Me)$_2$], 2.57 (dddd, *J* = 2.1, 5.1, 11.8, 13.5 Hz, 1 H), 2.33 (br. q, *J* = 6.0 Hz, 1 H), 1.77 (br. dd, *J* = 6.2, 11.8 Hz, 1 H), 1.68 (br. s, 1 H), 1.36 (dt, *J* = 9.9, 12.6 Hz, 1 H), 0.90 (d, *J* = 6.9 Hz, 3 H, 2-Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.3 (*C*O_2Me), 168.5 (*C*O_2Me), 134.6 (CH=CH), 129.9 (CH=CH), 68.2 (*C*HOH), 55.2 [*C*H(CO_2Me)$_2$], 52.9 (OMe), 52.8 (OMe), 36.3, 31.3, 30.8, 14.6 (2-Me) ppm. HRMS (ESI): calcd. for ($C_{12}H_{18}O_5$)$_2$Na 507.2201, found 507.2213.

Dimethyl 2-(5-Hydroxy-2-methylcyclohexyl)propandioate (±)-20a: Catalytic hydrogenation of (±)-**21a** (56 mg, 0.23 mmol) in methanol in the presence of 10 % Pd/C under N_2 (45 psi) was carried out in a fashion similar to the reduction of (±)-**9a**. The residue was suspended in ethyl acetate (10 mL) and filtered through a pad of celite. The filter bed was washed several times with ethyl acetate and the extracts concentrated under reduced pressure to afford (±)-**20a** as a colorless oil (52 mg, 91 %). IR (neat): $\tilde{\nu}$ = 3471, 2910, 1675, 1448 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.73 (s, 3 H, OMe), 3.72 (s, 3 H, OMe), 3.74–3.70 (m, 1 H, 5-H), 3.30 [d, *J* = 8.7 Hz, 1 H, C*H*$(CO_2Me)_2$], 2.31 (tt, *J* = 3.6, 11.4 Hz, 1 H), 1.89 (tdd, *J* = 3.6, 7.6, 10.8 Hz, 1 H), 1.70 (dd, *J* = 3.6, 8.0 Hz, 1 H), 1.57–1.52 (m, 1 H), 1.45–1.20 (m, 5 H), 0.89 (d, *J* = 5.4 Hz, 3 H, 2-Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.3 (CO_2Me), 168.9 (CO_2Me), 70.7 (C-5), 55.7 [*C*H$(CO_2Me)_2$], 52.7 (OMe), 39.6, 33.7, 31.0, 29.5, 28.4, 12.2 (2-Me) ppm. A satisfactory HRMS spectrum was not obtained for this compound.

Hydride reduction of **19a** (36 mg, 0.15 mmol) with $NaBH_4$ in methanol afforded **20a** (31 mg, 93 %).

Methyl 2-(5-Hydroxy-2-methylcyclohexyl)acetate (±)-22: To a stirring solution of (±)-**20a** (40 mg, 0.17 mmol) in DMSO (10 mL) was added LiI (70 mg, 1.4 mmol) and H_2O (70 mg, 3.9 mmol). The reaction mixture was stirred at room temperature until all the inorganic salts had dissolved and then heated to reflux at 150 °C for 24 h. After completion the reaction mixture was cooled to room temperature, diluted with water and extracted with CH_2Cl_2. The combined organic extracts were washed with 10 % aqueous HCl (15 mL) followed by saturated aqueous $NaHCO_3$ (38 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford (±)-**22** as a colorless oil (23 mg, 79 %). ^1H NMR (300 MHz, $CDCl_3$): δ = 3.68 (s, 3 H, OMe), 3.68–3.58 (m, 1 H, 5-H), 2.34–2.17 (m, 2 H), 2.14–2.00 (m, 1 H), 1.87–1.20 (m, 8 H), 0.86 (d, *J* = 8.1 Hz, 3 H, 2-Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.8 (CO_2Me), 70.8 (C-5), 51.8 (OMe), 38.8, 36.1, 36.0, 30.8, 30.4, 29.8, 12.5 (2-Me) ppm. HRMS (ESI): calcd. for $C_{10}H_{18}O_3Na$ 209.1148, found 209.1148.

Methyl 2-(2′-Methyl-5′-oxocyclohexyl)-2-(phenylsulfonyl)acetate (±)-19c/c′: Hydrogenation of the mixture of diastereomeric cyclohexenones **9c/c′** (378 mg, 1.17 mmol) in MeOH (20 mL) in the presence of 10 % Pd/C under H_2 (45 psi) was carried out in a fashion similar to the hydrogenation of **9a**. Purification of the residue by flash column chromatography (SiO_2, ethyl acetate/hexanes, 0 → 80 % gradient) gave an inseparable mixture of **19c/19c′** as a pale oil (370 mg, 98 %). **19c/c′:** ^1H NMR (400 MHz, $CDCl_3$): δ = 7.87–7.95 (m, 2 H, ArH), 7.68–7.75 (m, 1 H, ArH), 7.55–7.64 (m, 2 H, ArH), 4.04 and 4.08 [d, *J* = 10.4, and d, *J* = 10.8 Hz, 1 H total, C*H*$(SO_2Ph)CO_2Me$], 3.40 and 3.54 (2 × s, 3H total, OMe), 2.80–3.12 (m, 1 H), 2.70–2.80 (m, 1 H), 2.25–2.50 (m, 3 H), 1.80–2.10 (m, 3 H), 1.08 and 1.19 (d, *J* = 7.2, and d, *J* = 7.2 Hz, 3H total, 2-Me) ppm. HRMS (ESI): calcd. for $C_{16}H_{20}O_5SNa$ 347.0924, found 347.0921.

Methyl 2-(6′-Hydroxy-3′-methyl-1-cyclohexen-4′-yl)-2-(phenylsulfonyl)acetate (±)-21c/c′: Hydride reduction of the mixture of diastereomeric cyclohexenones **9c/c′** (83 mg, 0.26 mmol) in methanol with $CeCl_3 \cdot 7H_2O$ (97 mg, 0.26 mmol) and $NaBH_4$ (10 mg, 0.28 mmol) was carried out in a fashion similar to the preparation of **21a**. Purification of the residue by flash column chromatography (SiO_2, ethyl acetate/hexanes, 5 % → 20 % gradient) afforded a mixture of diastereomers **21c/21c′** (ca. 3:4 ratio) as a pale yellow oil (78 mg, 94 % yield). Careful rechromatography of this mixture gave a pure sample of each diastereomer. The relative stereochemical assignments of these diastereomers was arbitrary.

21c: ^1H NMR (300 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 7.8 Hz, 2 H, ArH), 7.69 (t, *J* = 7.5 Hz, 1 H, ArH), 7.58 (t, *J* = 7.5 Hz, 2 H, ArH), 5.76 (ddd, *J* = 1.2, 4.5, 10.2 Hz, 1 H), 5.60 (d, *J* = 10.2 Hz, 1 H), 4.35–4.25 (br. m, 1 H, C*H*OH), 4.09 [d, *J* = 9.6 Hz, 1 H, C*H*$(SO_2Ph)CO_2Me$], 3.49 (s, 3 H, OMe), 2.80–2.68 (m, 2 H), 1.70–1.55 (m, 2 H), 1.44 (dt, *J* = 10.2, 12.3 Hz, 1 H), 1.07 (d, *J* = 6.6 Hz, 3 H, 3-Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7 (CO_2Me), 138.2, 134.60, 134.57, 129.4, 129.3, 73.1 [*C*H$(SO_2Ph)CO_2Me$], 68.3 (*C*HOH), 53.0 (OMe), 35.6, 31.5, 31.2, 14.8 (2-Me) ppm. HRMS (ESI): calcd. for $C_{16}H_{20}O_5SNa$ 347.0924, found 347.0921.

21c′: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 7.8 Hz, 2 H, ArH), 7.68 (t, *J* = 7.5 Hz, 1 H, ArH), 7.58 (t, *J* = 7.5 Hz, 2 H, ArH), 5.61 (s, 2 H, CH=CH), 4.32–4.23 (br. m, 1 H, C*H*OH), 4.04 [d, *J* = 11.7 Hz, 1 H, C*H*(SO_2Ph)CO_2Me], 3.47 (s, 3 H, OMe), 2.72 (dd, *J* = 5.2, 12.1 Hz, 1 H), 2.57 (ddt, *J* = 1.8, 4.5, 11.4 Hz, 1 H), 2.15–2.00 (m, 2 H), 1.53 (dt, *J* = 10.3, 12.7 Hz, 1 H), 0.89 (d, *J* = 6.9 Hz, 3 H, 3-Me) ppm.

Methyl 2-[5′-Hydroxy-2′-methylcyclohexyl]-2-(phenylsulfonyl)acetate (±)-20c/c′: Catalytic hydrogenation of the diastereomeric mixture of cyclohexenols **21c**/**c′** (35 mg, 0.11 mmol) in MeOH with H_2 in the presence of 10 % Pd/C catalyst was carried out in a fashion similar as the reduction of cyclohexenone **9a**. The residue was purified by flash column chromatography (SiO_2, ethyl acetate/hexanes, 30 → 50 % gradient) to afford a mixture of diastereomeric cyclohexanols **20c**/**c′** (27 mg, 78 %) as a pale yellow oil. Careful rechromatography of this mixture gave a pure sample of each diastereomer. The relative stereochemical assignments of these diastereomers was arbitrary.

20c: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 7.8 Hz, 2 H, ArH), 7.67 (t, *J* = 7.2 Hz, 1 H, ArH), 7.56 (t, *J* = 7.6 Hz, 2 H, ArH), 4.03 [d, *J* = 9.6 Hz, 1 H, C*H*(SO_2Ph)CO_2Me], 3.58 (tt, *J* = 4.6, 11.1 Hz, 1 H, C*H*OH), 3.45 (s, 3 H, OMe), 2.55–2.44 (m, 2 H), 1.80–1.23 (m, 7 H), 0.98 (d, *J* = 7.2 Hz, 3 H, 2-Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8 (CO_2Me), 138.1 (Ph), 134.5 (Ph), 129.4 (Ph), 129.3 (Ph), 73.6 [*C*H(SO_2Ph)CO_2Me], 70.7 (*C*HOH), 52.9 (OMe), 38.6, 33.4, 30.9, 29.4, 28.5, 12.1 (2-Me) ppm. HRMS (ESI): calcd. for $C_{12}H_{22}O_5SNa$ 349.1080, found 349.1080.

20c′: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 7.5 Hz, 2 H, ArH), 7.67 (t, *J* = 7.8 Hz, 1 H, ArH), 7.56 (t, *J* = 7.5 Hz, 2 H, ArH), 4.00 [d, *J* = 11.7 Hz, 1 H, C*H*(SO_2Ph)CO_2Me], 3.68–3.57 (m, 1 H, C*H*OH), 3.42 (s, 3 H, OMe), 2.52 (br. d, *J* = 12.0 Hz, 1 H), 2.45 (td, *J* = 3.3, 12.0 Hz, 1 H), 1.80–1.35 (m, 7 H), 0.87 (d, *J* = 6.9 Hz, 3 H, 2-Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6 (CO_2Me), 138.1 (Ph), 134.4 (Ph), 129.3 (Ph), 129.2 (Ph), 75.0 [*C*H(SO_2Ph)CO_2Me], 70.3 (*C*HOH), 52.9 (OMe), 38.4, 33.5, 30.7, 29.4, 28.8, 12.4 (2-Me) ppm.

Hydride reduction of the mixture of diastereomeric cyclohexanones **19c**/**c′** (168 mg, 0.484 mmol) with $NaBH_4$ in methanol afforded the same mixture of **20c**/**c′** (103 mg, 61 %).

Methyl 2-[5′-(*tert*-Butyldiphenylsilyl)oxy-2′-methylcyclohexyl]-2-(phenylsulfonyl)acetate (±)-23c/c′: To a solution of diastereomeric cyclohexanols **20c**/**c′** (435 mg, 1.33 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added imidazole (182 mg, 2.67 mmol). The reaction mixture was stirred under N_2 for 15 min. Solid *tert*-butyldiphenylsilyl chloride (561 mg, 2.00 mmol) was added slowly with vigorous stirring. After addition was complete the mixture was stirred at room temperature overnight and quenched with water. The resulting mixture was extracted several times with Et_2O, and the combined extracts dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (SiO_2, acetone/hexanes, 5 → 20 % gradient) to afford a mixture of protected cyclohexanols **23c**/**c′** (744 mg, 99 %) as a pale yellow oil. This mixture was partially separable by careful rechromatography.

23c: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75–7.35 (m, 15 H, ArH), 3.96 [d, *J* = 11.4 Hz, 1 H, C*H*(SO_2Ph)CO_2Me], 3.55–3.45 (s & m, 4H total, C*H*OSi and OMe), 2.47 (br. d, *J* = 12.9 Hz, 1 H), 2.20–2.15 (m, 1 H), 1.63–1.20 (m, 6 H), 1.08 (s, 9 H, *t*Bu), 0.87 (d, *J* = 7.2 Hz, 3 H, 2-Me) ppm.

23c′: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85–7.30 (m, 15 H, ArH), 3.97 [d, *J* = 10.5 Hz, 1 H, C*H*(SO_2Ph)CO_2Me], 3.65–3.53 (m, 1 H, C*H*OSi), 3.30 (s, 3 H, OMe), 2.45–2.20 (m, 2 H), 1.20–1.65 (m, 6 H), 1.02 (s, 9 H, *t*Bu), 0.97 (d, *J* = 6.9 Hz, 3 H, 2-Me) ppm.

23c/c′: ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.9 (CO_2Me), 167.8 (CO_2Me), 139.6, 139.3, 137.06, 137.00, 136.90, 136.86, 135.64, 135.60, 135.54, 135.44, 135.36, 131.03, 131.00, 130.41, 130.38, 130.30, 130.27, 129.0, 128.9, 128.7, 76.1, 74.3, 73.7, 73.3, 53.3 (OMe), 53.2 (OMe), 40.0, 39.9, 34.9, 34.4, 31.8, 31.7, 30.7, 30.5, 30.4, 29.7,

27.7, 27.6, 20.1 (Si*t*Bu), 20.0 (Si*t*Bu), 12.6 (2-Me), 12.5 (2-Me) ppm. HRMS (ESI): calcd. for $C_{32}H_{40}O_5SiSNa$ 587.2258, found 587.2256.

Methyl 2-[5'-(*tert*-Butyldiphenylsilyl)oxy-2'-methylcyclohexyl]acetate (±)-24: To a solution of diastereomeric silyl ethers **23c**/**c'** (68 mg, 0.12 mmol) in MeOH (10 mL) was added Mg (21 mg, 0.87 mmol). The reaction mixture was stirred at 50 °C until gas evolution started at which stage the heating source was removed and stirring continued at room temperature. Additional Mg (21 mg, 6X) was added at 50 °C successively until all starting material had been consumed as indicated by TLC. The solvent was evaporated and the mixture redissolved in CH_2Cl_2. The mixture was filtered, washed (brine), dried ($MgSO_4$) and concentrated to give (±)-**24** as a single diastereomer (52 mg, quantitative). This compound was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75–7.70 (m, 4 H, Ph), 7.40–7.35 (m, 6 H, Ph), 3.70–3.62 (s & m, 4H total, OMe & C*H*OSi), 2.26 (dd, *J* = 7.8, 15.0 Hz, 1 H, CH_2CO_2Me), 2.20 (dd, *J* = 8.1, 15.0 Hz, 1 H, CH_2CO_2Me), 2.00–1.85 (m, 1 H), 1.79–1.30 (m, 7 H), 1.09 (s, 9 H, *t*Bu), 0.88 (d, *J* = 7.5 Hz, 3 H, 2-Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.6 (*C*O_2Me), 135.96, 135.94, 135.93, 134.89, 134.76, 129.6, 127.7, 127.6, 72.2 (CHOSi), 51.5 (OMe), 38.6, 36.3, 36.0, 30.6, 30.3, 30.1, 27.2, 19.3 (*t*Bu), 12.6 (2-Me) ppm. HRMS (ESI): calcd. for $C_{26}H_{36}O_3SiNa$ 447.2326, found 447.2324.

3-(2-Methoxy-2-oxoethyl)-4-methylcyclohexyl 4-Nitrobenzoate (±)-25: To a mixture of (±)-**22** (27 mg, 0.15 mmol), *p*-nitrobenzoic acid (99.3 mg, 0.594 mmol) and triphenylphosphine (156 mg, 0.594 mmol), under N_2, was added freshly distilled THF (5 mL). The mixture was stirred at room temperature until homogeneous (ca. 15 min). The reaction mixture was cooled to 0 °C and a solution of diethyl azodicarboxylate (259 mg, 0.594 mmol, 40 wt.-% solution in toluene) was added slowly over 10 min. The mixture was stirred vigorously at 0 °C for 30 min after which the cold bath was removed and stirring continued at room temperature for 24 h. Upon completion of the reaction as indicated by TLC the solvent was evaporated under an N_2 stream and the residue was purified by column chromatography (SiO_2, ethyl acetate/hexanes, 0 → 40 % gradient) to afford (±)-**25** (46 mg, 94 %) as a pale oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.30 and 8.22 ppm (AA'BB', J_{AB} = 9.2 Hz, 4H total, ArH), 5.30–5.22 (m, 1 H, C*H*OPNB), 3.68 (s, 3 H, CO_2Me), 2.55–2.45 (m, 1 H), 2.35 (dd, *J* = 6.7, 15.2 Hz, 1 H, C*H*H'CO_2Me), 2.24 (dd, *J* = 8.7, 15.3 Hz, 1 H, CH*H'*CO_2Me), 1.99–1.64 (m, 6 H), 1.48–1.38 (m, 1 H), 0.94 (d, *J* = 7.2 Hz, 3 H, 2-Me) ppm. ^{13}C NMR ([D_6]DMSO, 75 MHz): δ = 172.8 (CO_2Me), 163.6 ($ArCO_2R$), 150.2 (Ar), 135.6 (Ar), 130.6 (Ar), 124.0 (Ar), 71.3 (C-4), 51.3 (OMe), 35.7, 32.7, 31.6, 30.9, 27.2, 26.1, 13.6 (2-Me) ppm. HRMS (ESI): calcd. for $C_{17}H_{21}NO_6Na$ 358.1261, found 358.1260.

Methyl 5-(*tert*-Butyldiphenylsilyloxy)-2-methylcyclohexylideneacetate (±)-*Z*-26 and (±)-*E*-27: To a stirring solution of LDA in heptanes (0.08 mL, 2.0 M, 0.2 mmol) in dry THF (2 mL) at –78 °C was added dropwise a solution of (±)-**24** (30 mg, 0.071 mmol) in dry THF (2 mL). The mixture was stirred at –78 °C under N_2 for 30 min. A solution of phenylselenyl chloride (27 mg, 0.14 mmol) in dry THF (0.5 mL) was added dropwise rapidly with vigorous stirring. The reaction mixture was slowly warmed to room temperature and stirred for 24 h under N_2. The reaction was quenched with water and the resulting mixture was extracted several times with Et_2O. The combined extracts were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate, 20:1) to afford a mixture of two diastereomeric phenylseleno compounds (38 mg, 92 %) as a bright green oil. To a stirring solution of the phenylseleno compounds (27 mg, 0.046 mmol) in MeOH (3 mL) was added $NaIO_4$ (23 mg, 0.11 mmol). The mixture was stirred vigorously under N_2 overnight. The reaction was quenched with water. The resulting mixture was extracted several times with Et_2O, and the combined extracts washed with saturated $NaHCO_3$, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate = 20:1) to afford an inseparable mixture of unsaturated esters (±)-*Z*-**26** and (±)-*E*-**27** (ca. 1:1) (15 mg, 77 %) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52–7.64 (m, 4 H, Ph), 7.50–7.33 (m, 6 H), 5.74 (s, 0.5 H), 5.36 (d, *J* = 1.5 Hz, 0.5 H), 4.05–3.98 (m, 0.5 H), 3.90–3.80 (m, 0.5 H), 3.65 and 3.64 (2 × s, 3H total), 2.57 (dd, *J* = 2.7, 14.1

Hz, 0.5 H), 2.45 (dt, *J* = 0.9, 12.3 Hz, 0.5 H), 2.26–2.18 (m, 0.5 H), 2.16 (dd, *J* = 5.0, 13.3 Hz, 0.5 H), 1.78–1.50 (m, 5 H), 1.13 and 1.12 (d, *J* = 7.2, and d, *J* = 6.3 Hz, 3H total), 1.07 and 1.04 (2 × s, 9H total) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.6 (CO_2Me), 166.9 (CO_2Me), 164.7, 163.6, 136.1, 136.0, 135.9, 134.9, 134.53, 134.5, 134.3, 129.9, 129.8, 129.7, 128.8, 128.77, 127.7, 114.3, 113.7, 73.2 (C-5), 71.2 (C-5), 51.1 (OMe), 42.9, 39.3, 36.8, 32.2, 31.2, 30.3, 29.8, 29.6, 27.2, 27.1, 19.4, 19.3, 18.6, 18.4 ppm. HRMS (ESI): calcd. for $C_{26}H_{34}O_3SiNa$ 445.2169, found 445.2168.

Methyl 2-Methyl-5-(*p*-nitrobenzoyloxy)-*Z*-cyclohexylideneacetate (±)-28: To a stirring solution of LDA (2.0 M in heptane, 0.26 mL, 1.3 mmol) in dry THF (1 mL) at –78 °C was added dropwise a solution of the crude (±)-**27** (35 mg, 0.10 mmol) in dry THF (2 mL). The mixture was stirred at –78 °C under N_2 for 30 min. A solution of PhSeCl (40 mg, 0.21 mmol) in dry THF (0.5 mL) was added dropwise rapidly with vigorous stirring. The reaction mixture was slowly warmed to room temperature and stirred for 24 h under N_2. The solvent was evaporated under an N_2 stream and the residue purified by column chromatography (SiO_2, ethyl acetate/hexanes, 0 → 20 % gradient) the crude phenylseleno compound (46 mg, 90 %) as green oil. Owing to the susceptibility of the latter to slow oxidation by air the crude compound was used without further purification. To a stirring solution of the crude phenylseleno compound (15 mg, 0.031 mmol) in MeOH (2 mL) was added $NaIO_4$ (13 mg, 0.61 mmol). The mixture was stirred vigorously under N_2 for 6 d. The reaction was quenched with water. The resulting mixture was extracted several times with Et_2O, dried ($MgSO_4$) and concentrated under a N_2 stream. The residue was purified by column chromatography (SiO_2, diethyl ether/hexanes, 0 → 10 % gradient) to afford (±)-Z-**28** as a pale yellow oil (10 mg, 98 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.29 and 8.16 ppm (AA'BB', J_{AB} = 8.4 Hz, 4H total, ArH), 5.61 (s, 1 H, C=C*H*CO_2Me), 5.44 (m, 1/2width = 7.4 Hz, 1 H, C*H*OPNB), 4.25–4.15 (br. m, 1 H, 2-H), 3.71 (s, 3 H, OMe), 2.78 (td, *J* = 2.4, 15.3 Hz, 1 H, 6-H), 2.46 (br. d, *J* = 15.0 Hz, 1 H, 6'-H), 2.07–1.89 (m, 4 H), 1.22 (d, *J* = 7.5 Hz, 3 H, 2-Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6 (*C*O_2Me), 164.1 (Ar*C*O_2R), 162.2 (C-1), 150.8 (Ar), 136.1 (Ar), 130.9 (Ar), 123.8 (Ar), 116.0 (C=*C*HCO_2Me), 73.0 (C-5), 51.2 (OMe), 36.8, 30.4, 27.4, 24.5, 18.2 (2-Me) ppm. HRMS (ESI): calcd. for $C_{17}H_{19}NO_6Na$ 356.1105, found 356.1104.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H and/or ^{13}C NMR spectra of compounds **9c**/**9c'**, **9d**/**9d'**, **9e**/**9e'**, **10**–**16**, **17**/**18**, **19a**, **19c**/**c'**, **20a**, **20c**, **20c'**, **21a**, **21**, **21c**, **22**, **23c**, **23c'**, **24**–**28**.

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