Enantioselective Synthesis of α-Alkylmalates as the Pharmacophoric Group of Several Natural Alkaloids and Glycosides

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A general enantioselective synthesis of α-alkylmalates found in *Cephalotaxus* and *Orchidaceae* species is described. This preparation is based upon Seebach's procedure for the alkylation of D-malic acid with self-regeneration of stereogenic centers. Reaction of the dioxolanone **8a** with LiHMDS and allyl halides as well as benzyl bromide gave **10** and **14**, respectively, which could be transformed into enantiopure α-alkylmalates **13**, **15**, **18** and **19**. In addition, enantiopure furans of type **20** have been prepared.

Introduction

Enantiopure α-alkylmalates are important parts of *Cephalotaxus*[1] and some *Orchidaceae* alkaloids[2] as well as of *Orchidaceae* glycosides[3] and other biological active compounds.[4] In most cases, the bioactivity of these natural products is closely related to the α-alkylmalate moiety. Thus, cephalotaxine (**1**) which do not contain this group shows almost no bioactivity, whereas several malate esters of **1**, called harringtonines **2** and **3** with either a 2-(3-methylbutyl)malate or a 2-(4-methylpentyl)malate moiety and the corresponding hydroxylated compounds, are highly active antileukaemic agents. Deoxyharringtonine (**2d**) with an IC_{50} = 7.5 ng/mL is the most potent of these compounds and homoharringtonine **2g** is currently in phase 3 in clinical trials. Moreover, homoharringtonine (**2g**) has recently been demonstrated as the only compound under investigation capable of inducing a high rate of complete haematological remission in patients with chronic myelogenous leukaemia resistant to all existing chemotherapies including interferon α (Scheme 1).[5] 2-Benzylmalic acid is a component of phalaenopsin T and phalaenopsin La **4**, as well as of neoharringtonine (**2b**). Methyl 2-isobutylmalate is found in comucervine **5** (Scheme 2) and benzyl 2-isobutylmalate in the *Orchidaceae* glycosides **6**, such as dactylorhin A, dactylorhin C, dactylorhin E and militarine. Free 2-isobutylmalic acid has been obtained by enzymatic hydrolysis of militarine (**6a**) (Scheme 3).

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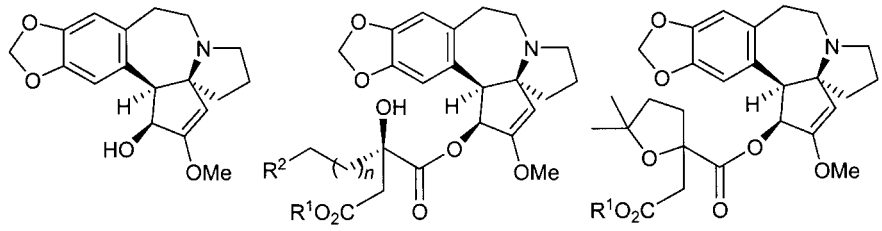
In the past, several methods for the synthesis of individual α-alkylmalates have been developed,[6] but there is no general enantioselective procedure available for the synthesis of this important class of compounds.

Here, we report a general enantioselective synthesis of α-alkylmalates as found in *Cephalotaxus* alkaloids **2** and **3**, *Orchidaceous* alkaloids **4** and **5**, and *Orchidaceae* glycosides **6**. The preparation is based upon Seebach's procedure[7] for the alkylation of D-malic acid with self-regeneration of stereogenic centres. The described method represents a substantial improvement over the published procedures and represents a general entry to α-alkyl-α-hydroxy acids.

Results

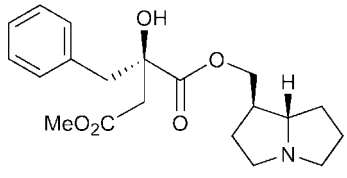
Acid-catalyzed acetalization of pivalaldehyde with enantiopure D-(+)-malic acid (**7**) furnishes the *cis*-acetal **8a** in 92% yield, which is thermodynamically more stable than the corresponding *trans* diastereomer. Esterification of **8a** using methyl iodide in the presence of K_2CO_3 in DMF as solvent led quantitatively to the ester **8b**. It was anticipated that the α-carbonyl H atom being located *trans* to the bulky *tert*-butyl group in **8a** or **8b** can easily be removed to give a chiral lithium enolate, which can then be alkylated with retention of configuration. The final step would be the hydrolysis of the acetal moiety to give the desired enantiopure α-alkylmalic acid. However, the introduction of a side chain in **8a** and **8b**, respectively, turned out to be more difficult. The allylation of the dioxolanone **8a** with dimethylallyl bromide (**9a**) in the presence of one equiv. of LDA in THF was unsuccessful, and after work up only unchanged starting material was recovered. Using two equiv. of LDA in THF the *O*-allylated compound **11** was the main product (60%) along with the desired compound **10a** in only 10% yield. Furthermore, reaction of the methyl ester **8b** in presence of



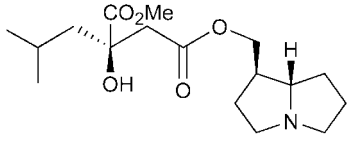
1 2 3

Compound No.	*n*	R^1	R^2	Alkaloid
2a	0	H	$CH(CH_3)_2$	Nordeoxyharringtonic acid
2b	0	Me	$CH_2C_6H_5$	Neoharringtonine
2c	1	H	$CH(CH_3)_2$	Deoxyharringtonic acid
2d	1	Me	$CH(CH_3)_2$	Deoxyharringtonine
2e	1	Me	$C(OH)(CH_3)_2$	Harringtonine
2f	2	H	$C(OH)(CH_3)_2$	5'-De-*O*-methylharringtonine
2g	2	Me	$C(OH)(CH_3)_2$	Homoharringtonine
2h	2	Me	$CH(CH_3)_2$	Homodeoxyharringtonine
3	-	Me	-	Anhydroharringtonine

Scheme 1. Cephalotaxus alkaloids.

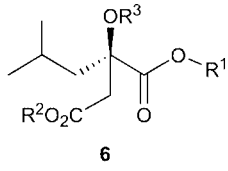


Phalaenopsin T, phalaenopsin La **4**



Comucervine **5**

Scheme 2. Orchidaceae alkaloids.



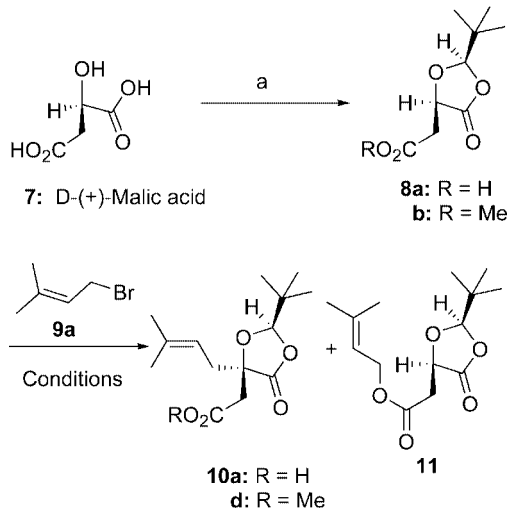
6

6	R^1	R^2	R^3	Glycoside
a	$CH_2C_6H_4$(*p*-O-Glc)	$CH_2C_6H_4$(*p*-O-Glc)	H	Militarine
b	$CH_2C_6H_4$(*p*-O-Glc)	$CH_2C_6H_4$(*p*-O-Glc)	Glc	Dactylorhin A
c	H	H	Glc	Dactylorhin C
d	$CH_2C_6H_4$(*p*-O-Glc)	H	Glc	Dactylorhin E

Scheme 3. Orchidaceae glycosides.

one or two equiv. of LDA or LiHMDS gave only low amounts of the desired **10d**. However, good results were obtained in the allylation of acetal **8a** using two equiv. of LiHMDS in THF and dimethylallyl bromide (**9a**) to give **10a** in 74% yield (Scheme 4). The ^1H NMR spectrum of **10a** displays a doublet of doublet at δ = 5.17 ppm for the olefinic proton and two doublets at δ = 2.50 ppm for the allylic protons.

Using the described conditions, **8a** was also allylated with 5-bromo-2-methyl-3-pentene[8] (**9b**) and 3-bromo-2-methyl-1-propene (**9c**) to furnish the substituted dioxolanones **10b** and **10c** in good yields. It is worthy to note that for the synthesis of homoharringtonine **2g** and related



Scheme 4. Reagents: a) 1.7 equiv. pivalaldehyde, cat. *p*TsOH, cat. H_2SO_4, pentane, reflux, 92%.

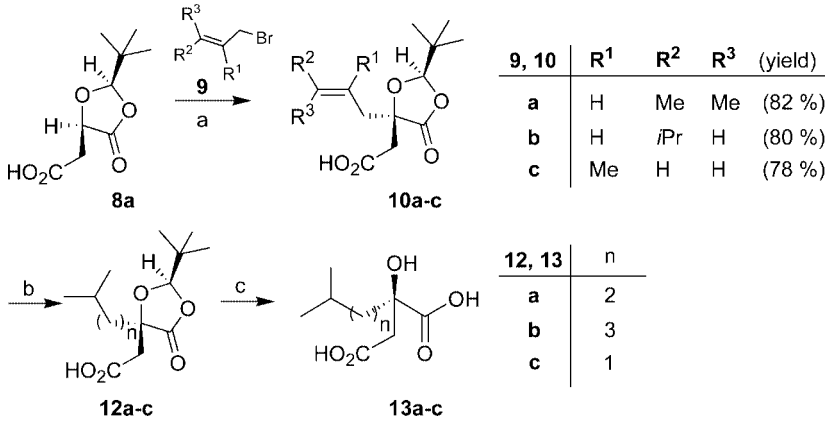
compounds, 5-bromo-2-methyl-2-pentene can not be used as alkylating agent due to its low reactivity, whereas employing 5-bromo-2-methyl-3-pentene (**9b**) not only gives good results in the introduction of the side chain but also allows the introduction of the necessary hydroxy group by an allylic oxidation using SeO_2 in the presence of a peroxide.[9]

For the synthesis of the desired α-alkylmalates **13a**–**c** the allylated dioxolanone **10a**–**c** were subjected to catalytic hydrogenation with platinum oxide in ethyl acetate as solvent to afford the alkyldioxolanone **12a**–**c** which were hydrolyzed using 50% H_2SO_4 in dioxane (1:5) at 60 °C for 24 h (Scheme 5). For the obtained α-isobutylmalic acid (**13c**) an $[\alpha]_D^{20}$ = –9.8 (*c* = 0.51, MeOH) was measured, which is higher than that recorded for the natural compound with $[\alpha]_D^{20}$ = –8.4 (*c* = 0.51, MeOH).[3]

In a similar way, the 2-benzylated malates **15a** and **15b** were obtained from **8a** using benzyl bromide as alkylating agent followed by acid cleavage of the obtained acetal **14** either in dioxane or methanol to give **15a** or **15b** in very good overall yields in two steps (Scheme 6).

For the synthesis of harringtonine, homoharringtonine and similar compounds, it was necessary to provide α-alkylmalate monoesters. For this purpose compounds **10a** and **10b** were esterified using MeI in the presence of K_2CO_3 and DMF as solvent at room temp. for 3 h to furnish the ester **16a** and **16b** in quantitative yield. Hydrogenation of **16a** and **16b** in ethyl acetate using PtO_2 as a catalyst gave the ester **17a** and **17b** in 95% and 90% yield, respectively. However, hydrolysis of the acetal functionality under the so far best conditions using 50% H_2SO_4 in dioxane (1:5) at 60 °C for 5 h, as well as under a variety of other acidic conditions, gave only the corresponding malic acid derivatives **13a** and **13b** as the sole products in high yield. The problem was finally solved by heating **17a** and **17b** with a suspension of silica gel in MeOH/H_2O at 60 °C for 2 days (Scheme 7).

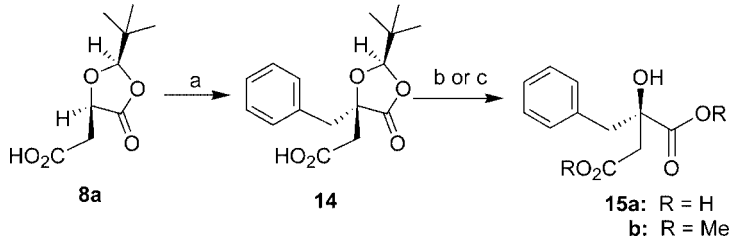
Several cephalotaxus alkaloids such as harringtonine (**2e**) and homoharringtonine (**2g**) contain a 2-(hydroxyalkyl)-malate moiety. For the synthesis of this group we applied an oxymercuration–demercuration procedure or an oxidation



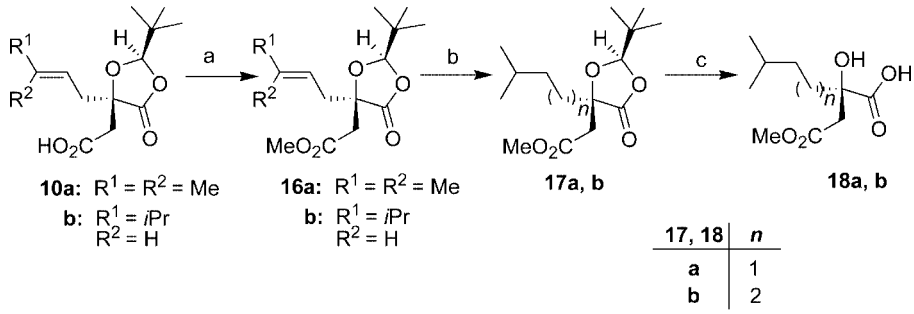
9, 10	R^1	R^2	R^3	(yield)
a	H	Me	Me	(82 %)
b	H	*i*Pr	H	(80 %)
c	Me	H	H	(78 %)

12, 13	n
a	2
b	3
c	1

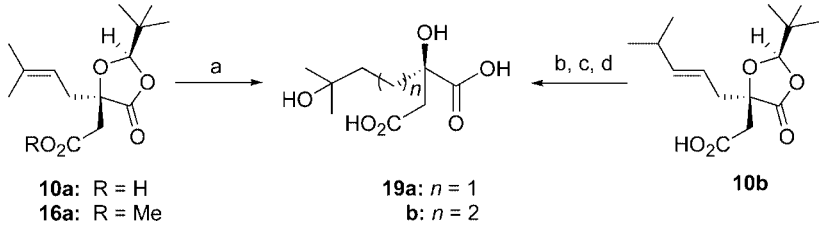
Scheme 5. Reagents: a) 2 equiv. LiHMDS, THF/hexane –78 °C, 1 h, then **9**; b) H_2, PtO_2, EtOAc; c) 50% H_2SO_4, dioxane (1:5), 60 °C, 24 h.



Scheme 6. Reagents: a) 2 equiv. LiHMDS, THF/hexane, –78 °C, 1 h, then benzyl bromide, 87%; b) 50% H_2SO_4, dioxane (1:5), 60 °C, 24 h; c) 50% H_2SO_4, MeOH, 60 °C, 6 h.



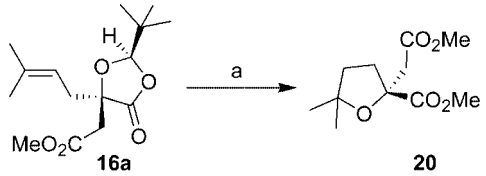
Scheme 7. Reagents: a) MeI, K_2CO_3, DMF, 3 h, quant.; b) H_2, PtO_2, EtOAc, 95%; c) SiO_2, MeOH/H_2O (6:1), 60 °C, 48 h.



Scheme 8. Reagents: a) i. $Hg(OAc)_2$, NaOH, THF/H_2O (1:5) 5 h, ii. $NaBH_4$, NaOH, room temp., 12 h, 86%; b) SeO_2, $tBuO_2H$; c) H_2, PtO_2, EtOAc; d) 50% H_2SO_4, dioxane, 60 °C, 6 h, 44% over three steps.

with SeO_2/peroxide. Treatment of **10a** with $Hg(OAc)_2$ and NaOH in THF/H_2O followed by reductive work up led to **19a** in 86% overall yield. Under the same conditions, the methyl ester **16a** also led to **19a**. For the synthesis of **19b**, which corresponds to the side chain of homoharringtonine (**2g**), we performed a direct insertion of oxygen into the terminal allylic carbon–hydrogen bond of **10b** in 44% overall yield by using a stoichiometric amount of SeO_2 in the presence of *tert*-butyl hydroperoxide followed by catalytic reduction and hydrolysis of the intermediate acetal using 50% H_2SO_4 in dioxane (1:5) at 60 °C for 6 h (Scheme 8).

For the synthesis of the furan moiety of anhydroharringtonine (**3**), we anticipated that the furan ring could be formed using conditions for the acid-catalyzed cleavage of the intermediate acetal such as **16a**, which would allow to stabilize a carbocation formed by protonation of the olefinic double bond. Indeed, treatment of the acetal **16a** with 50% H_2SO_4 in MeOH instead of dioxane at 60 °C for 4 h provided the tetrahydrofuran derivative **20** in 87% yield (Scheme 9).



Scheme 9. Reagents: a) 50% H_2SO_4, MeOH, 60 °C, 6 h, 79%.

Conclusions

2-Alkylmalates are important parts of several natural products and are responsible for their bioactivity in many cases. In this paper we have described a straight forward and flexible synthesis of these compounds with very high enantiopurity using a diastereoselective allylation of chiral dioxolanes obtained from D-(+)-malic acid according to the procedure developed by Seebach as the key step.

Experimental Section

Standart Methods: All reactions were performed in flame-dried glassware under argon. Unless otherwise noted, all reagents obtained from commercial sources were used without further purification. All solvents were dried by standard methods. Thin-layer chromatography was performed on precoated silica gel SIL G/UV_{254} plates (Macherey–Nagel), and silica gel 32–63 (0.032–0.064 mm) (Merck) was used for column chromatography. Melting points were measured with a Mettler FP61 apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded with a Varian XL 200, VXR 200 and VXR 500 or a Bruker AMX-300 with tetramethylsilane (TMS) as internal standard in [D]chloroform and [D_6]acetone. Chemical shifts are reported relative to the standard ppm value for the solvent used. The multipicities of the ^{13}C NMR peaks were determined with the APT pulse sequence.

(2*R*,4*R*)-(2-*tert*-Butyl-5-oxo-1,3-dioxolan-4-yl)acetic Acid (8a): To a suspension of D-(+)-malic acid (**7**) (4.0 g, 30 mmol) and pivalaldehyde (5.7 mL, 52 mmol, 1.7 equiv.) in pentane (50 mL), *p*TsOH (0.5 g) and concd. H_2SO_4 (1 drop) was added. The mixture was heated under reflux for 6 h with azeotropic removal of water. The resulting suspension was filtered and the solid dissolved in CH_2Cl_2 and washed with 8% aqueous H_3PO_4 (2×20 mL). The combined organic phases were dried with $MgSO_4$, the solvent removed under vacuo and the residue purified by column chromatography. Crystallization from Et_2O gave **8a** (5.7 g, 28 mmol, 92%) as colorless crystals. R_f = 0.41 (PE/EtOAc, 4:1). M.p. 107–108 °C (Et_2O). $[\alpha]_D^{20}$ = +2.8 (*c* = 1.3, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3123, 2983 (br), 1772, 1484 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.98 [s, 9 H, $C(CH_3)_3$] 2.83 (dd, *J* = 17.2, 7.2 Hz, 1 H, 6-H_1), 3.02 (dd, *J* = 17.2, 3.9 Hz, 1 H, 6-H_1), 4.66 (dq, *J* = 1.2, 3.9 Hz, 1 H, 4-H_1), 5.19 (s,

1 H, 2-H_1), 11.0 (br. s, 1 H, 7-H_1) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.42 [$C(CH_3)_3$], 34.25 [$C(CH_3)_3$], 35.39 (C-6), 71.43 (C-4), 109.9 (C-2), 172.1 (C-7), 175.2 (C-5) ppm. $C_9H_{14}O_5$ (202.12): calcd. C 53.46, H 6.98; found C 53.32, H 6.76.

General Procedure I – Esterification: To a stirred solution of the acid **8a**, **10b** or **10c** (3.6 mmol) and anhydrous K_2CO_3 (562 mg, 4.0 mmol, 1.1 equiv.) in DMF (5 mL) was added methyl iodide (0.25 mL, 4.0 mmol, 1.1 equiv.) at 0 °C over a period of 30 min. The reaction was quenched after 4 h by addition of water (15 mL) and the resulting solution extracted with Et_2O. After drying with $MgSO_4$ the solvent was removed under vacuo and purified by column chromatography.

Methyl (2*R*,4*R*)-(2-*tert*-Butyl-5-oxo-1,3-dioxolan-4-yl)acetate (8b): According to general procedure I, **8a** (727 mg, 3.6 mmol) was transformed to give **8b** in quant. yield (778 mg, 3.6 mmol) as an oil. R_f = 0.41 (PE/EtOAc, 8:1). $[\alpha]_D^{20}$ = +1.0 (*c* = 1.3, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 2964, 1485, 1439, 1411 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 [s, 9 H, $C(CH_3)_3$], 2.69 (dd, *J* = 16.2, 7.2 Hz, 1 H, 6-H_1), 2.86 (dd, *J* = 17.4, 3.6 Hz, 1 H, 6-H_1), 3.69 (s, 3 H, CH_3), 4.59 (dq, *J* = 3.6, 1.5 Hz, 1 H, 4-H_1), 5.10 (d, *J* = 1.5 Hz, 1 H, 2-H_1) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.42 [$C(CH_3)_3$], 33.98 [$C(CH_3)_3$], 35.21 (C-6), 52.00 (CH_3), 71.51 (C-4), 109.5 (C-2), 169.2 (C-7), 172.1 (C-5) ppm. $C_{10}H_{16}O_5$ (216.23): calcd. C 55.55, H 7.46; found C 55.32, H 7.36.

General Procedure II – Alkylation: To a stirred solution of **8a** (1.01 g, 5.0 mmol) in THF (60 mL) a solution of LiHMDS (21 mL, 10.5 mmol, 2.1 equiv., 0.5 M in THF) in THF/hexane (3:1) was added at –78 °C and stirred for 1 h. After addition of the allyl bromide (10 mmol) over a period of 30 min the temperature was raised to –10 °C over a period of 3 h. The resulting solution was partitioned between EtOAc and 1 N HCl and extracted with EtOAC. The combined organic phases were dried with $MgSO_4$, the solvent removed under vacuo and the residue purified by column chromatography.

(2*R*,4*R*)-[2-*tert*-Butyl-4-(3-methylbut-2-enyl)-5-oxo-1,3-dioxolan-4-yl]acetic Acid (10a): According to General Procedure II **8a** was alkylated with 4-bromo-2-methyl-2-butene (**9a**) (1.42 g, 10 mmol, 2.0 equiv.) to give **10a** (1.12 g, 4.1 mmol, 82%) as an oil. R_f = 0.25 (PE/EtOAc, 4:1). $[\alpha]_D^{20}$ = –44.0 (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 2972, 1801, 1709, 1439 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 [s, 9 H, $C(CH_3)_3$], 1.63 (s, 3 H, 12-H_3), 1.74 (s, 3 H, 11-H_3), 2.50 (d, *J* = 9.0 Hz, 2 H, 8-H_2), 2.83 (s, 2 H, 6-H_2), 5.16 (m, 2 H, 2-H_1, 9-H_1), 8.19 (br. s, 1 H, 7-H_1) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.05 (C-12), 23.63 [$C(CH_3)_3$], 25.99 (C-11), 32.45 (C-8), 34.30 [$C(CH_3)_3$], 39.48 (C-6), 80.58 (C-4), 108.5 (C-2), 115.6 (C-9), 138.0 (C-10), 173.9 (C-7), 174.7(C-5) ppm. $C_{14}H_{22}O_5$ (270.32): calcd. C 62.20, H 8.20; found C 62.29, H 8.18.

(2*R*,4*R*)-[2-*tert*-Butyl-4-(4-methylpent-2-enyl)-5-oxo-1,3-dioxolan-4-yl]acetic Acid (10b): According to General Procedure II **8a** was alkylated with 5-bromo-2-methyl-3-pentene (**9b**) (1.63 g, 10 mmol, 2.0 equiv.). After recrystallization from ether/pentane **10b** (0.99 g, 4.0 mmol, 80%) was obtained as a crystalline white solid. R_f = 0.27 (PE/EtOAc, 4:1). M.p. 64–65 °C (PE/EtOAc). $[\alpha]_D^{20}$ = –38.5 (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 2959, 1798, 1704, 1483 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 [s, 9 H, $C(CH_3)_3$], 0.96, 0.94 each (s, 3 H, 12-, 13-H_3), 2.67 (sept, *J* = 6.6 Hz, 1 H, 10-H_1), 2.46 (t, *J* = 16.8 Hz, 2 H, 8-H_1), 2.78 (AB system, *J* = 16.2 Hz, 2 H, 6-H_2), 5.17 (s, 1 H, 2-H_1), 5.32 (m, 1 H, 9-H_1), 5.57 (dd, *J* = 15.0, 7.2 Hz, 1 H, 10-H_1), 10.6 (br. s, 1 H, 7-H_1) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.14 (C-13), 22.20 (C-12), 23.57 [$C(CH_3)_3$], 31.16 (C-11), 34.32 [$C(CH_3)_3$], 37.21 (C-8), 39.60 (C-6), 80.14 (C-4), 108.4 (C-2), 118.2 (C-9), 144.5 (C-10), 173.6 (C-7), 174.9 (C-5) ppm. $C_{15}H_{24}O_5$ (248.35): calcd. C 63.36, H 8.51; found C 63.37, H 8.48.

(2*R*,4*R*)-[2-*tert*-Butyl-4-(2-methylprop-2-enyl)-5-oxo-1,3-dioxolan-4-yl]acetic Acid (10c): According to General Procedure II **8a** was alkylated with 3-bromo-2-methyl-1-propene (**9c**) (1.35 g, 10 mmol, 2.0 equiv.) to give of **10a** (1.01 g, 3.9 mmol, 78%) as an oil. R_f = 0.21 (PE/EtOAc, 4:1). $[\alpha]_D^{20}$ = –57.8 (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 2966, 1799, 1721, 1485 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 [s, 9 H, $C(CH_3)_3$], 1.83 (s, 3 H, 11-H_3), 2.50 (AB system, *J* = 16.8 Hz, 2 H, 8-H_1), 2.87 (AB system, *J* = 16.2 Hz, 2 H, 6-H_2), 4.88 (s, 1 H, 10-H_1), 5.02 (t, *J* = 1.6 Hz, 1 H, 10-H_1), 5.19 (s, 1 H, 2-H_1), 8.19 (br. s, 1 H, 7-H_1) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.63 [$C(CH_3)_3$], 23.73 (C-11), 34.19 [$C(CH_3)_3$], 39.25 (C-8), 40.39 (C-6), 80.39 (C-4), 108.1 (C-2), 117.5 (C-10), 138.9 (C-9), 174.7 (C-5), 173.9 (C-7) ppm. $C_{13}H_{20}O_5$ (256.30): calcd. C 60.92, H 7.87; found C 60.93, H 7.82.

(2*R*,4*R*)-[4-Benzyl-2-*tert*-butyl-5-oxo-1,3-dioxolan-4-yl]acetic Acid (14): According to General Procedure II **8a** was alkylated with benzyl bromide (1.71 g, 10 mmol, 2.0 equiv.). After recrystallization from ether/pentane **14** (1.27 g, 4.3 mmol, 87%) was obtained as a crystalline white solid. R_f = 0.31 (PE/EtOAc, 4:1). M.p. 140–141 °C (PE/EtOAc). $[\alpha]_D^{20}$ = –67 (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3300, 2962, 1798, 1703 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 [s, 9 H, $C(CH_3)_3$], 2.80 (AB system, *J* = 16 Hz, 2 H, 8-H_1), 3.06 (AB system, *J* = 14 Hz, 2 H, 6-H_2), 4.59 (s, 1 H, 2-H_1), 7.25 (m, 2 H, Ar-H_2), 7.30 (ddd, *J* = 10.5, 5.1, 1.8 Hz, 3 H, Ar-H_3), 10.2 (br. s, 1 H, 7-H_1) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.46 [$C(CH_3)_3$], 34.23 [$C(CH_3)_3$], 39.98 (C-6), 40.12 (C-8), 80.79 (C-4), 108.7 (C-2), 127.7 (C-14), 128.7 (C-12, C-13), 130.4 (C-10, C-11), 133.7 (C-9), 173.8 (C-7), 174.5 (C-5) ppm. $C_{16}H_{20}O_5$ (292.33): calcd. C 65.74, H 6.90; found C 65.71, H 6.89.

General Procedure III – Catalytic Hydrogenation: A solution of the alkene (10 mmol) in EtOAc was stirred with $PtO_2 \cdot H_2O$ (10 mol%) for 4 h under H_2. After filtration through celite the solvent was removed under vacuo and the residue purified by column chromatography.

(2*R*,4*R*)-[2-(*tert*-Butyl)-4-(3-methylbutyl)-5-oxo-1,3-dioxolan-4-yl]-acetic Acid (12a): According to General Procedure III alkene **10a** (2.70 g, 10 mmol, 2.0 equiv.) was hydrogenated to afford **12a** (2.72 g, 10 mmol, quant.) as an oil. R_f = 0.29 (PE/EtOAc, 4:1). $[\alpha]_D^{20}$ = –33.6 (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 2957, 1800, 1704, 1450 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (s, 3 H, 12-H_3), 0.91 (s, 3 H, 11-H_3), 0.98 [s, 9 H, $C(CH_3)_3$], 1.30 (m, 2 H, 9-H_2), 1.55 (sept, *J* = 6.6 Hz, 1 H, 10-H_1), 1.81 (tt, *J* = 8.7, 2.4 Hz, 2 H, 8-H_2), 2.85 (AB system, *J* = 16 Hz, 2 H, 6-H_2), 5.17 (s, 1 H, 2-H_1), 8.19 (br. s, 1 H, 7-H_1) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.30 (C-12), 22.42 (C-11), 23.63 [$C(CH_3)_3$], 28.17 (C-10), 31.70 (C-8), 32.09 (C-9), 34.43 [$C(CH_3)_3$], 39.50 (C-6), 80.19 (C-4), 108.3 (C-2), 174.0 (C-7),174.6 (C-5) ppm. $C_{14}H_{24}O_5$ (272.34): calcd. C 61.74, H 8.88; found C 62.01, H 8.71.

(2*R*,4*R*)-[2-(*tert*-Butyl)-4-(4-methylpentyl)-5-oxo-1,3-dioxolan-4-yl]-acetic Acid (12b): According to General Procedure III alkene **10b** (2.84 g, 10 mmol 2.0 equiv.) was hydrogenated to afford **12b** (2.74 g, 9.5 mmol, 95%) as a solid. R_f = 0.31 (PE/EtOAc, 4:1). M.p. 75–76 °C (PE/EtOAc). $[\alpha]_D^{20}$ = –27.3 (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3486, 2956, 1800, 1705 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83 (s, 3 H, 13-H_3), 0.85 (s, 3 H, 12-H_3), 0.91 [s, 9 H, $C(CH_3)_3$], 1.17 (quat., *J* = 6.6 Hz, 2 H, 8-H_2), 1.25–1.68 (m, 3 H, 9-H_2, 11-H_1), 1.76 (t, *J* = 8.2 Hz, 2 H, 10-H_1), 2.83 (s, 2 H, 6-H_2), 5.15 (s, 1 H, 2-H_1), 10.7 (br. s, 1 H, 7-H_1) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.09 (C-9), 22.40 (C-13), 22.44 (C-12), 23.56 [$C(CH_3)_3$], 27.62 (C-11), 33.82 (C-10), 34.35 [$C(CH_3)_3$], 38.71 (C-8), 39.51 (C-6),

80.18 (C-4), 108.3 (C-2), 174.1 (C-7), 174.8 (C-5) ppm. $C_{15}H_{26}O_5$ (286.37): calcd. C 62.91, H 9.15; found C 62.84, H 9.26.

(2*R*,4*R*)-[2-(*tert*-Butyl)-4-(2-methylpropyl)-5-oxo-1,3-dioxolan-4-yl]-acetic Acid (12c): According to General Procedure III alkene **10c** (2.56 g, 10 mmol) was hydrogenated to afford **12a** (2.53 g, 9.8 mmol, 98%) as an oil. R_f = 0.27 (PE/EtOAc, 4:1). $[\alpha]_D^{20}$ = –25.3 (c = 1.0, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 2962, 1798, 1722, 1484 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.95 (s, 9 H, $C(CH_3)_3$), 0.98 (d, J = 6.0 Hz, 3 H, 11-H_3), 1.01 (d, J = 6.0 Hz, 3 H, 10-H_3), 1.68 (dd, J = 6.0, 2.1 Hz, 2 H, 8-H_2), 1.89 (sept, J = 6.0 Hz, 1 H, 9-H_1), 2.92 (AB system, J = 10.2 Hz, 2 H, 6-H_2), 5.15 (s, 1 H, 2-H_1), 10.7 (br. s, 1 H, 7-H_1) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.85 (C-11), 23.53 [$C(CH_3)_3$], 24.09 (C-9), 24.52 (C-10), 34.14 [$C(CH_3)_3$], 39.20 (C-8), 40.60 (C-6), 80.37 (C-4), 107.7 (C-2), 174.5 (C-7), 174.5 (C-5) ppm. $C_{13}H_{22}O_5$ (258.31): calcd. C 60.45, H 8.58; found C 60.39, H 8.47.

General Procedure IV – Cleavage of Acetals: 50% H_2SO_4 (2 mL) was added to a solution of the dioxolone (5.4 mmol) in dioxane (10 mL). After stirring at 60 °C for 24 h, the solvent was removed under vacuo and water (15 mL) was added. The aqueous phase was extracted with EtOAc (3 × 100 mL), the combined organic phases were dried with Mg_2SO_4, the solvent was removed under vacuo and the residue purified by column chromatography.

(2*R*)-2-Hydroxy-2-(3-methylbutyl)succinic Acid (13a): According to General Procedure IV acetal **12a** (1.47 g, 5.4 mmol) was cleaved to give **13a** (0.95 g, 4.7 mmol, 86%) as a solid. R_f = 0.24 (PE/EtOAc, 1:1). M.p. 127–128 °C (PE/EtOAc). $[\alpha]_D^{20}$ = –12.4 (c = 0.5, MeOH). IR (MeOH): $\tilde{\nu}$ = 3569, 2963 (br), 1714, 1430 cm^{-1}. ^1H NMR (300 MHz, C_3D_6O): δ = 0.86 (d, J = 6.6 Hz, 3 H, 9-H_3), 0.88 (d, J = 6.6 Hz, 3 H, 8-H_3), 1.10 (ddd, J = 21.6, 9.6, 5.4 Hz, 1 H, 6-H_1), 1.38 (ddd, J = 13.2, 6.6, 5.4 Hz, 1 H, 6-H_1), 1.51 (sept, J = 6.6 Hz, 1 H, 7-H_1), 1.60–1.80 (m, 2 H, 5-H_2), 2.79 (AB system, J = 16.2 Hz, 2 H, 3-H_2), 10.5 (br. s, 2 H, 1-H_1, 4-H_1). ^{13}C NMR (75 MHz, C_3D_6O): δ = 22.74 (C-9), 22.81 (C-8), 28.82 (C-7), 32.81 (C-6), 37.98 (C-5), 43.79 (C-3), 75.39 (C-2), 172.3 (C-4), 176.4 (C-1) ppm. $C_9H_{16}O_5$ (204.22): calcd. C 52.93, H 7.90; found C 52.76, H 7.86.

(2*R*)-2-Hydroxy-2-(4-methylpentyl)succinic Acid (13b): According to General Procedure IV acetal **12b** (1.54 g, 5.3 mmol) was cleaved to give **13b** (0.98 g, 4.5 mmol, 83%) of **13c** as a solid. R_f = 0.25 (PE/EtOAc, 1:1). M.p. 90–91 °C (PE/EtOAc). $[\alpha]_D^{20}$ = –11.4 (c = 1.0, MeOH). IR (MeOH): $\tilde{\nu}$ = 3486, 2956 (br), 1706, 1461 cm^{-1}. ^1H NMR (300 MHz, C_3D_6O): δ = 0.83 (s, 3 H, 10-H_3), 0.85 (s, 3 H, 9-H_3), 1.10–1.30 (m, 4 H, 5-H_2, 6-H_1), 1.40–1.70 (m, 3 H, 7-H_2, 8-H_1), 2.79 (AB system, J = 16.5 Hz, 2 H, 3-H_2), 8.19 (br. s, 2 H, 1-H_1, 4-H_1) ppm. ^{13}C NMR (C_3D_6O): δ = 21.69 (C-7), 22.72 (C-10), 22.82 (C-9), 28.44 (C-8), 39.58 (C-6), 40.21 (C-5), 43.71 (C-3), 75.40 (C-2), 172.4 (C-4), 176.5 (C-1) ppm. $C_{10}H_{18}O_5$ (218.24): calcd. C 55.03, H 8.31; found C 54.89, H 7.99.

(2*R*)-2-Hydroxy-2-(2-methylpropyl)succinic Acid (13c): According to General Procedure IV acetal **12c** (1.39 g, 5.4 mmol) was cleaved to give **13a** (0.86 g, 4.5 mmol, 83%) as a solid. R_f = 0.22 (PE/EtOAc, 1:1). M.p. 105–106 °C (PE/EtOAc). $[\alpha]_D^{20}$ = –9.8 (c = 0.51, MeOH). IR (MeOH): $\tilde{\nu}$ = 3544, 2960 (br), 1715, 1438 cm^{-1}. ^1H NMR (300 MHz, C_3D_6O): δ = 1.01 (d, J = 6.6 Hz, 3 H, 8-H_3), 1.09 (d, J = 6.6 Hz, 3 H, 7-H_3), 1.68 (ddd, J = 23.0, 14.0, 5.7 Hz, 2 H, 5-H_1), 1.87 (sept, J = 6.6 Hz, 1 H, 6-H_1), 2.79 (AB system, J = 16.5 Hz, 2 H, 3-H_2), 10.5 (br. s, 2 H, 1-H_1, 4-H_1) ppm. ^{13}C NMR (75 MHz, C_3D_6O): δ = 23.95 (C-8), 24.64 (C-6), 24.73 (C-7), 44.29 (C-3), 48.29 (C-5), 75.51 (C-2), 172.4 (C-4), 176.8 (C-1) ppm. $C_8H_{14}O_5$ (190.20): calcd. C 50.52, H 7.42; found C 50.42, H 7.38.

(2*R*)-2-Benzyl-2-hydroxysuccinic Acid (15a): According to General Procedure IV acetal **14** (1.54 g, 5.4 mmol) was cleaved to give **15a** (0.72 g, 4.3 mmol, 61%) as an oil. R_f = 0.27 (PE/EtOAc, 1:1). $[\alpha]_D^{20}$ = –17.5 (c = 1.0, MeOH). IR (MeOH): $\tilde{\nu}$ = 3030, 2960 (br), 1716, 1469 cm^{-1}. ^1H NMR (300 MHz, C_3D_6O): δ = 2.84 (AB system, J = 16.5 Hz, 2 H, 5-H_2), 3.32 (AB system, J = 13.5 Hz, 2 H, 3-H_2), 7.20–7.32 (m, 5 H, Ar-H), 9.82 (br. s, 2 H, 1-H_1, 4-H_1) ppm. ^{13}C NMR (C_3D_6O): δ = 43.01 (C-5), 45.54 (C-3), 75.51 (C-2), 127.4 (C-9), 128.5 (C-8, C-10), 131.3 (C-7, C-11), 136.5 (C-6), 172.2 (C-4), 175.8 (C-1) ppm. $C_{11}H_{12}O_5$ (224.21): calcd. C 58.93, H 5.39; found C 58.88, H 5.31.

Dimethyl (2*R*)-2-Benzyl-2-hydroxysuccinate (15b): 50% H_2SO_4 (2 mL) was added to a solution of dioxolone **14** (1.54 g, 5.4 mmol) in MeOH (10 mL). After stirring at 60 °C for 6 h, the solvent was removed under vacuo. To the residue water (25 mL) was added and the aqueous phase extracted with EtOAc (3 × 100 mL). The combined organic phases were dried with $MgSO_4$, the solvent removed under vacuo, and the residue was purified by column chromatography to give **15b** (1.14 g, 5.2 mmol, 86%) as an oil. R_f = 0.27 (PE/EtOAc, 1:10). $[\alpha]_D^{20}$ = –12.4 (c = 0.5, MeOH). IR (MeOH): $\tilde{\nu}$ = 3569, 2963 (br), 1714, 1430 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.87 (AB system, J = 16.2 Hz, 2 H, 3-H_2), 2.98 (AB system, J = 13.5 Hz, 2 H, 3-H_2), 3.65 (s, 3 H, OMe), 3.74 (s, 3 H, OMe), 7.16–7.32 (m, 5 H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 42.75 (C-5), 45.20 (C-3), 51.80 (C–OMe), 52.68 (C–OMe), 75.76 (C-2), 127.1 (C-9), 128.1 (C-8, C10), 130.1 (C-7, C-11), 134.7 (C-6), 171.0 (C-4), 174.6 (C-1) ppm. $C_{13}H_{16}O_5$ (252.27): calcd. C 61.90, H 6.39; found C 62.19, H 6.41.

Methyl (2*R*,4*R*)-[2-*tert*-Butyl-4-(3-methylbut-2-enyl)-5-oxo-1,3-dioxolan-4-yl]acetate (16a): According to General Procedure I **10b** (1.0 g, 3.6 mmol) was transformed to give **16a** (1.05 g, 3.6 mmol, quant.) as a colorless oil. R_f = 0.53 (PE/EtOAc, 20:1). $[\alpha]_D^{20}$ = –38.5 (c = 1.0, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 2964, 1801, 1799, 1748 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 [s, 9 H, $C(CH_3)_3$], 1.58 (s, 3 H, 13-H_3), 1.68 (s, 3 H, 12-H_3), 2.45 (d, J = 8.1 Hz, 2 H, 9-H_2), 2.75 (s, 2 H, 6-H_2), 3.59 (s, 3 H, OMe), 5.12 (s, 1 H, 2-H_1), 5.12 (tt, J = 8.1, 1.5 Hz, 1 H, 10-H_1) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.90 (C-13), 23.49 [$C(CH_3)_3$], 25.85 (C-12), 32.46 (C-9), 34.06 [$C(CH_3)_3$], 39.62 (C-6), 51.79 (C-8), 80.60 (C-4), 108.2 (C-2), 137.6 (C-11), 115.7 (C-10), 168.7 (C-7), 173.8 (C-5) ppm. $C_{15}H_{24}O_5$ (284.35): calcd. C 63.36, H 8.51; found C 63.45, H 8.59.

Methyl (2*R*,4*R*)-[2-*tert*-Butyl-4-(4-methylpent-2-enyl)-5-oxo-1,3-dioxolan-4-yl]acetate (16b): According to General Procedure I **10c** (1.02 g, 3.6 mmol) was transformed to give **16b** (1.07 g, 3.6 mmol, quant.) as an colorless oil. R_f = 0.59 (PE/EtOAc, 20:1). $[\alpha]_D^{20}$ = –34.5 (c = 1.0, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 2960, 1801, 1748, 1485 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.85 [s, 9 H, $C(CH_3)_3$], 0.63 (s, 3 H, 14-H_3), 0.96 (s, 3 H, 13-H_3), 2.25 (sept, J = 6.6 Hz, 1 H, 12-H_1), 2.45 (d, J = 15.4 Hz, 2 H, 9-H_2), 2.88 (s, 2 H, 6-H_2), 3.63 (s, 3 H, OMe), 5.16 (s, 1 H, 2-H_1), 5.32 (m, 1 H, 11-H_1), 5.52 (dd, J = 15.4, 3.2 Hz, 1 H, 10-H_1). ^{13}C NMR ($CDCl_3$): δ = 22.10 (C-14), 22.16 (C-13), 23.51 [$C(CH_3)_3$], 31.11 (C-12), 34.15 [$C(CH_3)_3$], 37.27 (C-9), 39.77 (C-6), 51.85 (C-8), 80.24 (C-4), 108.2 (C-2), 118.3 (C-10), 144.2 (C-11), 168.7 (C-7), 173.7 (C-5) ppm. $C_{16}H_{26}O_5$ (298.38): calcd. C 64.41, H 8.78; found C 64.36, H 8.87.

Methyl (2*R*,4*R*)-[2-*tert*-Butyl-4-(3-methylbutyl)-5-oxo-1,3-dioxolan-4-yl]acetate (17a): According to General Procedure III alkene **16a** (2.84 g, 10 mmol) was hydrogenated to afford **17a** (2.72 g, 9.5 mmol, 95%) as an oil. R_f = 0.25 (PE/EtOAc, 10:1). $[\alpha]_D^{20}$ = –18.6 (c = 1.0, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 2959, 1801, 1749, 1485 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.86 (s, 3 H, 13-H_3) 0.88 (s, 3 H, 12-H_3), 0.93 [s, 9 H, $C(CH_3)_3$], 1.15–1.40 (m, 2 H, 10-H_2), 1.52 (sept, J = 6.6 Hz, 1 H, 11-H_1), 1.78 (tt, J = 8.7, 2.4 Hz, 2 H, 9-H_2), 2.79 (s, 2 H, 6-H_2), 3.64 (s, 3 H, 8-H_3), 5.13 (s, 1 H, 2-

H_1). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.30 (C-13), 22.35 (C-12), 23.53 [$C(CH_3)_3$], 28.08 (C-11), 31.71 (C-9), 31.99 (C-10), 34.43 [$C(CH_3)_3$], 39.59 (C-6), 51.88 (C-8), 80.25 (C-4), 108.1 (C-2), 168.8 (C-7), 174.0 (C-5) ppm. $C_{15}H_{26}O_5$ (286.37): calcd. C 62.91, H 9.15; found C 63.11, H 9.25.

Methyl (2*R*,4*R*)-[2-*tert*-Butyl-4-(4-methylpentyl)-5-oxo-1,3-dioxolan-4-yl]acetate (17b): According to General Procedure III alkene **16b** (2.98 g, 10 mmol) was hydrogenated to afford **17b** (2.70 g, 9.0 mmol, 90%) as an oil. R_f = 0.27 (PE/EtOAc, 10:1). $[\alpha]_D^{20}$ = –34.5 (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 2960, 1801, 1748, 1485 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.82 (s, 3 H, 14-H_3), 0.84 (s, 3 H, 13-H_3), 0.96 [s, 9 H, $C(CH_3)_3$], 1.19 (quat., *J* = 6.6 Hz, 2 H, 8-H_2), 1.25–1.68 (m, 3 H, 9-H_2, 12-H_1), 1.76 (t, *J* = 8.2 Hz, 2 H, 11-H_1), 2.83 (s, 2 H, 6-H_2), 3.69 (s, 3 H, OMe), 5.14 (s, 1 H, 2-H_1) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.09 (C-10), 22.40 (C-14), 22.44 (C-13), 23.56 [$C(CH_3)_3$], 27.62 (C-12), 33.82 (C-11), 34.35 [$C(CH_3)_3$], 38.71 (C-9), 39.51 (C-6), 51.88 (C–OMe), 80.18 (C-4), 108.3 (C-2), 174.1 (C-7), 174.8 (C-5) ppm. $C_{16}H_{28}O_5$ (300.39): calcd. C 63.97, H 9.40; found C 64.19, H 9.31.

General Procedure V – Selective Acetal Cleavage: To a solution of **17a** or **17b** (10 mmol) in MeOH/H_2O (6:1, 35 mL) was added Silica gel (200–400 mesh, 60 Å, 3.0 g, Aldrich) and the mixture stirred for 48 h. After filtration the silica gel was washed with MeOH, the solvent removed under vacuo and the residue dissolved in H_2O. The aqueous phase was extracted with CH_3Cl, the combined organic phases were dried with $MgSO_4$ and purified by column chromatography.

4-Methyl (2*R*)-2-Hydroxy-2-(3-methylbutyl)succinate (18a): According to General Procedure V **17a** (2.86 g, 10 mmol) was cleaved to give **18a (**1.28 g, 5.9 mmol, 59%) as an oil. R_f = 0.25 (PE/EtOAc, 4:1). $[\alpha]_D^{20}$ = –25.9 (*c* = 1.0, CH_3Cl). IR (CH_3Cl): $\tilde{\nu}$ = 3569, 2963 (br), 1714, 1430 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.86 (d, *J* = 6.6 Hz, 3 H, 10-H_3), 0.88 (d, *J* = 6.6 Hz, 3 H, 9-H_3), 1.10 (ddd, *J* = 21.6, 9.6, 5.4 Hz, 1 H, 7-H_1), 1.38 (ddd, *J* = 13.2, 6.6, 5.4 Hz, 1 H, 7-H_1), 1.55 (sept, *J* = 6.6 Hz, 1 H, 8-H_1), 1.60–1.80 (m, 2 H, 6-H_2), 2.79 (AB system, *J* = 16.2 Hz, 2 H, 3-H_2), 3.63 (s, 3 H, OMe), 8.19 (br. s, 1 H, 1-H_1) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.74 (C-10), 22.78 (C-9), 28.79 (C-8), 32.78 (C-7), 37.89 (C-6), 43.87 (C-3), 51.98 (C–OMe), 75.39 (C-2), 172.3 (C-4), 176.4 (C-1) ppm. $C_{10}H_{18}O_5$ (218.25): calcd. C 55.03, H 8.31; found C 54.95; H, 8.19.

4-Methyl (2*R*)-2-Hydroxy-2-(4-methylpentyl)succinicate (18b): According to General Procedure V **17b** (3.0 g, 10 mmol) was cleaved to give **18b** (1.2 g, 5.3 mmol, 53%) as an oil. R_f = 0.27 (PE/EtOAc, 4:1). $[\alpha]_D^{20}$ = –22.3 (*c* = 1.0, CH_3Cl). IR (CH_3Cl): $\tilde{\nu}$ = 3569, 2964 (br), 1715, 1429 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.86 (d, *J* = 6.6 Hz, 3 H, 10-H_3), 0.89 (d, *J* = 6.6 Hz, 3 H, 9-H_3), 1.36–1.58 (m, 4 H, 7-H_2, 8-H_2), 1.51 (sept, *J* = 6.6 Hz, 1 H, 9-H_1), 1.60–1.80 (m, 2 H, 6-H_2), 2.65 (AB system, *J* = 16.2 Hz, 2 H, 3-H_2), 3.66 (s, 3 H, OMe), 10.2 (br. s, 1 H, 1-H_1) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.74 (C-11), 22.78 (C-10), 27.32 (C-8), 28.79 (C-9), 32.78 (C-7), 37.89 (C-6), 43.83 (C-3), 52.01 (C–OMe), 75.49 (C-2), 172.8 (C-4), 176.4 (C-1) ppm. $C_{11}H_{20}O_5$ (232.27): calcd. C 56.88, H 8.68; found C 56.79, H 8.59.

(2*R*)-2-Hydroxy-2-(3-hydroxy-3-methylbutyl)succinic Acid (19a): To a solution of mercury acetate (0.4 g, 2.4 mmol 2.0 equiv.) in H_2O/THF (1:1, 2 mL) **10a** or **16** (1.2 mmol) was added and the mixture stirred at room temp. for 12 h. NaOH (1 mL, 3.0 M) was added followed by $NaBH_4$ (1 mL, 0.5 M in 3.0 M NaOH). After decantation from the mercury the solution was extracted with diethyl ether, the aqueous phase neutralised with concd. HCl and extracted with EtOAc (3 × 50 mL). The combined organic phases were dried with $MgSO_4$ and the residue purified by column chromatography to give **19a** (0.22 g, 1.0 mmol, 83%) of as solid. R_f = 0.25 (PE/EtOAc, 4:1). M.p. 124–125 °C (PE/EtOAc). $[\alpha]_D^{20}$ –5.8 (*c* = 1.0, MeOH). IR (MeOH): $\tilde{\nu}$ = 3345, 2975 (br), 1722, 1372 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.32 (s, 3 H, 10-H_3), 1.34 (s, 3 H, 9-H_3), 1.88 (dt, *J* = 7.5, 1.5 Hz, 2 H, 4-H_2), 1.18 (quat., *J* = 6.6 Hz, 1 H, 5-H_1), 2.45 (quat., *J* = 6.6 Hz, 1 H, 5-H_1), 2.93 (AB system, *J* = 16.6 Hz, 2 H, 3-H_2), 10.2 (br. s, 2 H, 1-H_1, 4-H_1) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.19 (C-9), 28.71 (C-8), 36.11 (C-6), 37.45 (C-5), 43.72 (C-3), 83.43 (C-7), 85.52 (C-2), 175.3 (C-4), 177.7 (C-1) ppm. $C_9H_{16}O_6$ (220.22): calcd. C 49.09, H 7.32; found C 49.19, H 7.47.

(2*R*)-2-Hydroxy-2-(4-hydroxy-4-methylpentyl)succinic Acid (19b): To a suspension of SeO_2 (14 mg, 0.125 mmol, 2.5 mol%) in CH_2Cl_2 (3 mL), 90% *tert*-butyl hydroperoxide (1 mL) was added and the mixture stirred for 0.5 h at 25 °C (water bath). **10b** (1.42 g, 5 mmol) was added over a period of 15 min, and the mixture was stirred for 48 h at 25 °C. After removal of the solvent under vacuo the residue was dissolved in acetic acid/Me_2S (1:1, 2 mL) and stirred at 30 °C for 4 h. H_2O was added, the mixture was extracted with CH_3Cl, and the combined organic phases were dried with $MgSO_4$. The solvent was removed under vacuo, the residue was dissolved in EtOAc and hydrogenated with $PtO_2 \cdot H_2O$ as catalyst for 4 h. After filtration through a pad of Celite and concentration under reduced pressure the residue was dissolved in dioxane (10 mL) and 50% H_2SO_4 (2 mL) was added. After stirring at 60 °C for 6 h, the solvent was evaporated under vacuo. Water (15 mL) was added and the aqueous phase extracted with EtOAc (3 × 100 mL); the solvent removed under vacuo, and the residue was purified by column chromatography to give **19b** (0.52 g, 2.2 mmol, 44%) as a solid. R_f = 0.25 (PE/EtOAc, 4:1). M.p = 135–136 °C (PE/EtOAc). $[\alpha]_D^{20}$ = –5.8 (*c* = 1.0, MeOH). IR (MeOH): $\tilde{\nu}$ = 3349, 2977 (br), 1723, 1375 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.32 (s, 3 H, 10-H_3), 1.34 (s, 3 H, 9-H_3), 1.88 (m, 2 H, 6-H_2), 2.41 (m, 2 H, 7-H_1), 2.45 (m, 2 H, 5-H_2), 2.91 (AB system, *J* = 16.1 Hz, 2 H, 3-H_2), 10.2 (br. s, 2 H, 1-H_1, 4-H_1) ppm. ^{13}C NMR ($CDCl_3$): δ = 12.33 (C-6), 30.12 (C-10), 30.21 (C-9), 36.24 (C-5), 41.98 (C-3), 46.72 (C-7), 68.43 (C-8), 78.52 (C-2), 177.3 (C-4), 179.6 (C-1) ppm. $C_{10}H_{18}O_6$ (234.25): calcd. C 51.27, H 7.75; found C 52.19, H, 7.67.

Methyl (2*R*)-2-(Methoxycarbonylmethyl)-5,5-dimethyl-tetrahydrofuran-2-carboxylate (20): According to General Procedure IV acetal **16** (2.84 g, 10 mmol) was cleaved to give **20** (1.82 g, 7.9 mmol, 79%) as an oil. R_f = 0.25 (PE/EtOAc, 10:1). $[\alpha]_D^{20}$ = –1.0 (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 2972, 1742, 1437, 1166 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.24 (s, 3 H, 12-H_3), 1.33 (s, 3 H, 11-H_3), 1.75–1.95 (m, 2 H, 4-H_2), 2.16 (dt, *J* = 13.2, 7.5 Hz, 1 H, 3-H_1), 2.44 (ddd, *J* = 10.5, 7.5, 6.0 Hz, 1 H, 3-H_1), 2.86 (AB system, *J* = 15.6 Hz, 2 H, 5-H_2), 3.67 (s, 3 H, 8-H_3), 3.77 (s, 3 H, 10-H_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.07 (C-12), 28.85 (C-11), 35.28 (C-4), 37.58 (C-3), 43.75 (C-6), 51.63 (C-10), 52.32 (C-8), 83.67 (C-5), 84.00 (C-2), 170.3 (C-7), 174.2 (C-9) ppm. $C_{11}H_{18}O_5$ (230.26): calcd. C 57.38, H 7.88; found C 57.27, H 7.79.

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[1] For reviews see: a) L. Huang, Z. Xue, in *The Alkaloids* (Ed.: A. Brossi), Academic Press: New York, **1984**, *23*, 157–223; b) T. Hudlicky, L. D. Kwart, J. W. Reed, in *Alkaloids: Chemical*

and Biological Perspectives (Ed.: S. W. Pelletier), John Wiley & Sons: New York, **1987**, *5*, 639–690; c) M. A. Jalil Miah, T. Hudlicky, J. W. Reed, in *The Alkaloids* (Ed.: G. A. Cordell), Academic Press: New York, **1998**, *51*, 199–264.

[2] a) S. Brandange, S. Josephson, S. Vallen, *Acta Chem. Scand.* **1974**, *28*, 153–156; b) S. Brandange, S. Josephson, S. Vallen, *Acta Chem. Scand.* **1973**, *27*, 3668–3672; c) S. Brandange, I. Granelli, B. Luning, C. Moberg, E. Sjostrand, *Acta Chem. Scand.* **1972**, *26*, 2558–2560; d) S. Brandange, B. Luning, *Acta Chem. Scand.* **1969**, *23*, 1151–1154; e) B. Luning, H. Trankner, S. Brandange, *Acta Chem. Scand.* **1966**, *20*, 2011.

[3] H. Kizu, E. Kaneko, T. Tomimori, *Chem. Pharm. Bull.* **1999**, *47*, 1618–1625.

[4] a) M. Zer, J. Shuster, L. Hamer, K. Adachi, T. Dezwaan, S.-C. Lo, M. V. Montenegro-Chamorro, S. Frank, B. Darveaux, S. Mahanty, R. Heiniger, A. Skalchunes, H. Pan, R. Tarpey, PCT Int. Appl. **2003**, WO 2003046130; b) B. Siedle, R. Murillo, O. Hucke, A. Labahn, I. Merfort, *Pharmazie* **2003**, *58*, 337–339; c) H. Toshima, *Yuki Gosei Kagaku Kyokaishi* **2001**, *59*, 1121–1129; d) G. Blay, I. Fernandez, P. Formentin, B. Monje, J. R. Pedro, R. Ruiz, *Tetrahedron* **2001**, *57*, 1075–1081; e) G. Ma, D. R. J. Palmer, *Tetrahedron Lett.* **2000**, *41*, 9209–9212; f) H. Toshima, M. Saito, T. Yoshihara, *Bioscience, Biotechnology, and Biochemistry* **1999**, *63*, 1934–1941; g) H. Toshima, M. Saito, T. Yoshihara, *Bioscience, Biotechnology, and Biochemistry* **1999**, *63*, 964–967; h) Z.-C. Li, J.-Q. Xu, *Molecules* **1998**, *3*, 31–34; i) T. Tanaka, H. Suda, H. Naganawa, M. Hamada, T. Takeuchi, T. Aoyagi, H. Umezawa, *J. Antibiotics* **1984**, *37*, 682–684; j) W. Heller, C. Tamm, *Helvetica Chimica Acta* **1975**, *58*, 974–979.

[5] For reviews on homoharringtonine in clinical trials: a) H. M. Kantarjian, M. Talpaz, V. Santini, A. Murgo, B. Cheson, S. M. O' Brien, *Cancer* **2001**, *92*, 1591–1605; most recent results: b) E. Hitt, *Lancet Oncol.* **2002**, *3*, 259; c) S. M. O' Brien, M. Talpaz, J. Cortes, J. Shan, F. J. Giles, S. Federl, D. Thomas, G. Garcia-Manero, S. Mallard, M. Beth, C. Koller, S. Kornblau, M. Andreeff, A. Murgo, M. Keating, H. M. Kantarjian, *Cancer* **2002**, *94*, 2024–2032; d) B. Scappini, F. Onida, H. M. Kantarjian, L. Dong, S. Vertovesek, M. J. Keating, M. Beran, *Cancer* **2002**, *94*, 2653–2662; e) S. Sinha, S. Jain, *Prog. Drug Res.* **1994**, *42*, 53–132; f) D. C. Zhou, R. Zittoun, J. P. Marie, *Bull. Cancer* **1995**, *82*, 987–995.

[6] Synthesis of the homoharrigtonine side chain: a) L. Keller, F. Dumas, J. d′Angelo, *Eur. J. Org. Chem.* **2003**, *13*, 2488–2497; b) Q. Zhang, R. Wen, *Huaxue Shiji* **2000**, *22*, 325–330; c) Y. Wang, Y. Li, X. Pan, S. Li, W. Huang, *Huaxue Xuebao* **1985**, *43*, 161–167; d) S. Hiranuma, M. Shibata, T. Hudlicky, *J. Org. Chem.* **1983**, *48*, 5321–5326; e) S. Hiranuma, T. Hudlicky, *Tetrahedron Lett. Tetrahedron. Lett.* **1982**, *23*, 3431–3434; f) Y. Li, X. Pan, W. Huang, W. Hwang, Y. Wang, Y. Li, *Huaxue Xuebao* **1981**, *39*, 937–939; synthesis of homoharringtonine: g) T. R. Kelly, J. C. McKenna, P. A. Christenson, *Tetrahedron Lett.* **1973**, *36*, 3501–3504; h) Z. Xue, L. Xu, D. Chen, L. Huang, *Yaoxue Xuebao* **1981**, *16*, 752–756; i) J. Auerbach, T. Ipaktchi, S. M. Weinreb, *Tetrahedron Lett.* **1973**, *46*, 4561–4564; j) K. L. Mikolajczak, R. G. Powell, C. R. Smith Jr., *Tetrahedron* **1972**, *28*, 1995–2001. Isobutylmaleate (glycoside); k) A. Gitterman, R. J. Parry, R. F. Dufresne, D. D. Sternbach, M. D. Cabelli, *J. Am. Chem. Soc.* **1980**, *102*, 2074–2081; l) R. J. Parry, D. D. Sternbach, M. D. Cabelli, *J. Am. Chem. Soc.* **1976**, *98*, 6380–6382; m) S. Brandange, S. Josephson, S. Vallen, *Acta Chem. Scand.* **1974**, *28*, 153–156; n) S. Brandange, S. Josephson, S. Vallen, *Acta Chem. Scand.* **1973**, *27*, 3668–3672.

[7] a) D. Seebach, R. Naef, G. Calderari, *Tetrahedron* **1984**, *40*, 1313–1324; b) G. Ma, D. R. J. Palmer, *Tetrahedron Lett.* **2000**, *41*, 9209–9212.

[8] a) H. Kaga, K. Goto, T. Takahashi, M. Hino, T. Tokuhashi, K. Orito, *Tetrahedron* **1996**, *52*, 8451–8470; b) A. J. Bloodworth, R. J. Curtis, M. Spencer, N. A. Tallant, *Tetrahedron* **1993**, *49*, 2729–2750; c) D. Jacoby, J. P. Celerier, H. Petit, G. Lhommet, *Synthesis* **1990**, *4*, 301–304.

[9] K. B. Sharpless, M. A. Umbreit, *J. Am. Chem. Soc.* **1977**, *99*, 5526–5528.

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