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ASYMMETRIC SYNTHESIS OF MALIC ACID-TYPE SYNTHONS VIA CHIRAL NOREPHEDRINE-DERIVED OXAZOLIDINES

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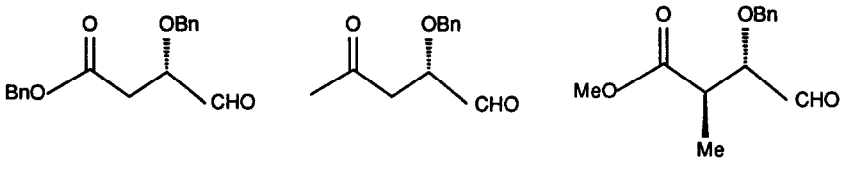
Abstract

Polyoxygenated C_4 synthons **5-7** are synthesized in enantiomerically pure form starting from ephedrine derived oxazolidines **2**, **4** and **13**. The 1,4-benzylate addition to **2** and **4**, the key step in the synthesis of **5** and **6**, proceeds cleanly with almost complete diastereoface selection. The key steps in the synthesis of target **7** are the nucleophilic epoxidation of aldehyde **13** and the lithium dimethyl cuprate epoxide opening, both of which proceed with high regio and stereocontrol. This route compares favorably with synthesis from malic acid, in that both enantiomers of ephedrine are available cheaply and it provides three differentiated oxygenated positions directly.

Malic acid has been extensively used as a C_4 chiron for the enantiospecific synthesis of several classes of compounds.[1] The naturally occurring (S) enantiomer is, in fact, a cheap source of chirality in a highly functionalized environment, its two carboxyl groups representing convenient synthetic handles for elongation. The (R) enantiomer is also available commercially, although at a much higher price, and a few asymmetric syntheses of it have been reported.[2] Interesting synthons with an additional stereocenter have been obtained

FIGURE 1



5 **6** **7**

through the *anti* specific C-3 alkylation of the hydroxy ester which is reported to proceed in moderate yield.[3, 1h] The use of these acids in synthesis requires, in all cases, a few preliminary steps to differentiate between the two carboxy termini. It would therefore be of great synthetic utility if, by asymmetric synthesis, one could obtain malic acid type chirons with the three oxygenated positions already differentiated, possibly in both the

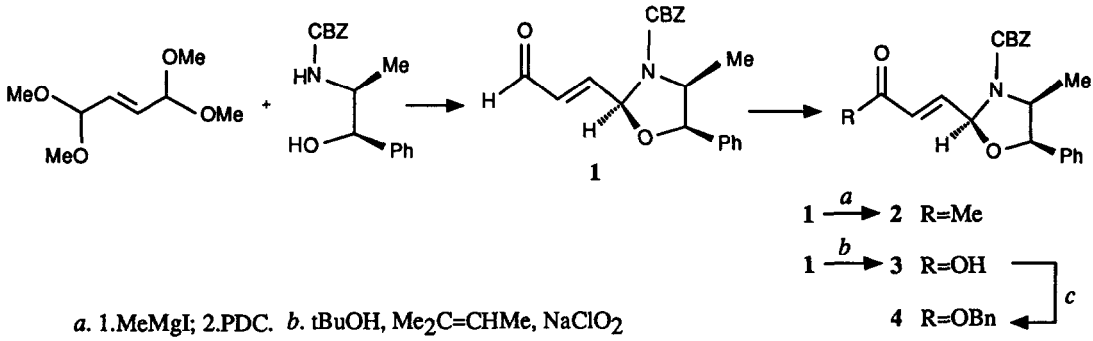
unsubstituted and 3-alkyl series. Enantiomerically pure oxazolidines **1-4**, which we recently developed as C_4 enantioselective Michael acceptors[4-7] could be suitable to achieve this goal, provided that a good stereocontrol in a formal 1,4-alkoxide addition can be obtained. Since **1-4** derive their chirality from ephedrine, available cheaply in both enantiomeric forms, they also potentially constitute an inexpensive access to the unnatural (R)-(+) malic acid series.

Here we report on our efforts which led to a practical synthesis of chirons **5-7** (Fig.1)

RESULTS AND DISCUSSION

Alkenyloxazolidines **1-4** are most conveniently prepared according to Scheme I by the cyclization of fumaraldehyde-bisdimethylacetal with N-protected (1R,2S) norephedrine in the presence of pyridinium tosylate as a catalyst. Hydrolysis of the acetal gave aldehyde **1**, the precursor for ketone **2**,[6] acid **3**[7] and ester **4** (Scheme I).

SCHEME I



a. 1.MeMgI; 2.PDC. *b*. tBuOH, Me_2C=CHMe, $NaClO_2$

c. 1.KOH, MeOH; 2.$PhCH_2Br$, CH_3CN, Bu_4NHSO_4

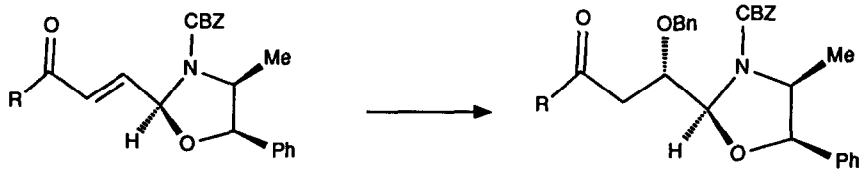
The formal 1,4-alkoxide addition to α,β-unsaturated carbonyl compounds is generally achieved with good stereocontrol by the two step sequence of alkoxymercuriation-demercuriation.[8] This reaction has been documented to proceed smoothly with high regioselectivity to afford the α-HgX β-OR adduct. In our case however, no oxymercuriation occurred on ester **4** even after prolonged exposure to $Hg(CF_3COO)_2$ and in the presence of a large excess of benzyl alcohol at room temperature. Increasing the temperature only led to decomposition.

We therefore turned our attention to the direct alkoxide Michael addition of which, to the best of our knowledge, there is only a scattering of examples of allylic stereocontrol reported in the chemical literature whereas *anti* selectivity up to 95% has been observed for some γ-alkoxy enoates in a kinetically controlled process.[9] We elected to use benzyl alcohol as the nucleophile for the addition (Scheme II) so that the resulting benzylether would serve as a readily removable protecting group for the derived hydroxyl function. Our results are reported in Table 1.

Ketone **2** reacts readily with Li and Na benzylate in a 2:1 $PhCH_2OH$:THF mixture at -50°C to give excellent yield of the addition product **8** as a single detectable isomer (Table 1, Entries 1, 2). Under these

conditions the less reactive ester **4** is recovered unaffected even after several days (Entry 3).Reaction occurs, albeit very slowly, at -30°C to give **9** with yield and selectivity comparable to the ketone case (Entry 4).[10] Further increase of temperature to R.T. leads to decomposition if the reaction is run in 2:1 $PhCH_2OH$:THF with $PhCH_2ONa$ (Entry 5) however, the reaction occurs smoothly and at a reasonable rate in pure $PhCH_2OH$ at R.T. (Entry 6). Under these conditions the best yield and selectivity are obtained with the more reactive K salt (Entry

SCHEME II

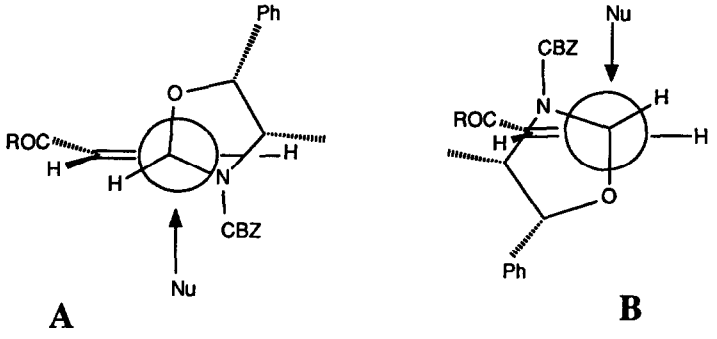


2 R = Me
4 R = OBn

8 R = Me
9 R = OBn

8) whereas the reaction is too sluggish to be practical when Li is employed as the counterion (Entry 7). Interestingly, the selectivity, which appears to be under kinetic control (Entries 8 and 9, 6 and 4), seems to be inversely related, or at best insensitive, to the coordinating ability of the cation (Entries 6, 7, 8, 11).

FIGURE 2



This is strongly suggestive of a mechanism of asymmetric induction that does not involve coordination phenomena. The stereochemical outcome of this reaction instead can be rationalized on the basis of MO considerations[11] using the transition structure models **A** and **B** (Fig.2); **A**, which leads to the experimentally observed products (vide infra) is favored over **B**, apparently for steric reasons.

TABLE I

Entry	Substrate	Reagents	Solvent	T	t	d.r.[a]	yield %
1	2	$PhCH_2OLi$	2:1 $PhCH_2OH$/THF	-50°C	18h	≥95:5	98
2	2	$PhCH_2ONa$	"	-50°C	18h	≥95:5	98
3	4	$PhCH_2ONa$	"	-50°C	18h	—	N.R.
4	4	$PhCH_2ONa$	"	-30°C	60h	≥95:5	85
5	4	$PhCH_2ONa$	"	RT	18h	—	—[b]
6	4	$PhCH_2ONa$	$PhCH_2OH$	RT	18h	94:6	65
7	4	$PhCH_2OLi$	"	RT	36h	93:7	30
8	4	$PhCH_2OK$	"	RT	18h	94:6	90
9	4	$PhCH_2OK$	2:1 $PhCH_2OH$/THF	-30°C	60h	≥95:5	80
10	4	$PhCH_2ONa$ DCH-18-c-6[c]	$PhCH_2OH$	RT	18h	—	—[b]
11	4	$PhCH_2ONa$ DCH-18-c-6[c]	"	- 5°C	24h	≥95:5	35[d]

a. Determined by ^1H and ^{13}C-NMR spectroscopy

b. Starting material decomposition

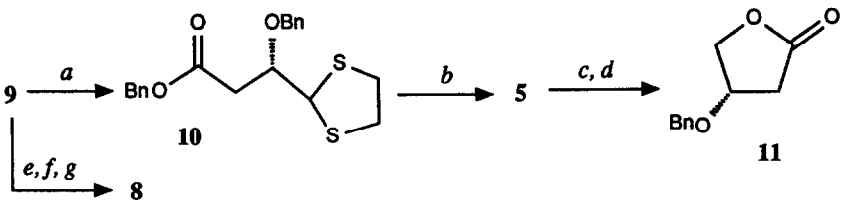
*c.*DCH-18-c-6: dicyclohexyl-18-crown-6

d. 35% of the starting material is recovered intact

The target malic acid derivative **5** was obtained from **9** by using our standard procedure to remove the chiral auxiliary (Scheme III).[4-7] For this purpose **9** was treated with 1,2-ethanedithiol in the presence of a catalytic amount of $BF_3.Et_2O$ in CH_2Cl_2 to smoothly release the optically pure (1R,2S)-N-carbobenzyloxy norephedrine together with dithiolane **10**. The latter was then submitted to thioacetal hydrolysis ($CaCO_3$/MeI/acetone/H_2O) and the (S)-3-benzyloxy succinaldehydic acid benzyl ester **5** was isolated in 75% yield.

The absolute configuration and the optical purity of **5** were determined by transformation into the known lactone **11** via reduction ($NaCNBH_3$/ AcOEt:AcOH 9:1) of the aldehydic function followed by PTSA catalized lactonization (Scheme III). The optical rotation of the thus obtained lactone is identical to that reported[12] for the 3-(S) enantiomer, showing that the alkoxide addition to **4** occurred from the substrate *si* face. The transformation of **9** into ketone **8** (see Scheme III) proved that this is also the case in the addition to **2** . From **8**, keto aldehyde **6** was obtained in 64% yield using the usual protocol after having first protected the carbonyl function (Scheme IV).

SCHEME III

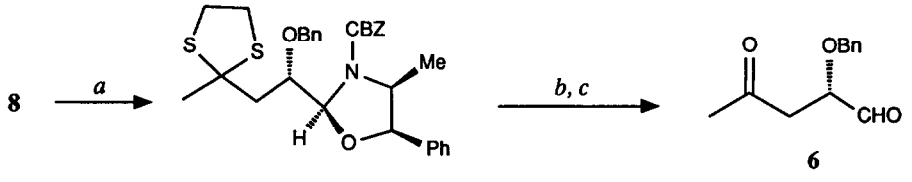


a. $HS(CH_2)_2SH$, $BF_3.Et_2O$, CH_2Cl_2; *b*. $CaCO_3$, MeI, H_2O, acetone;

c. $NaCNBH_3$, 9:1 AcOEt:AcOH; *d*. PTSA, benzene, RT overnight;

e. NaOH, MeOH; *f*. $(COCl)_2$, Py; *g*. Me_2CuLi.

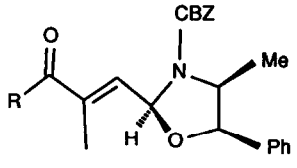
SCHEME IV



a.$HS(CH_2)_2SH$, ZnI_2, Et_2O; *b*. $HS(CH_2)_2SH$, $BF_3.Et_2O$, CH_2Cl_2; *c*. $CaCO_3$, MeI, H_2O, acetone.

In view of the good results obtained so far, the most straightforward way to achieve our second goal, the synthesis of 2-alkyl malic acid derivatives, seemed to be the benzylate addition to trisubstituted Michael acceptors such as **12a** and **12b** (Fig.3); no clean addition product however was obtained upon reaction of these substrates under the usual conditions.[13] We therefore turned our attention to the use of epoxyacid **14**, synthesized from **13** by the stereoselective nucleophilic epoxidation (KClO/ THF-H_2O) that we recently described (Scheme

FIGURE 3

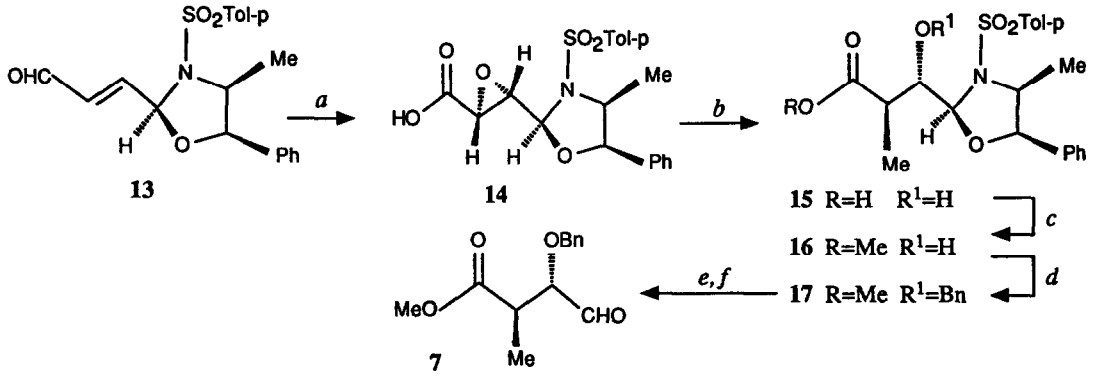


12 **a** R = Me

b R = OBn

V).[7] Transformation of **14** into the 2-methyl-3-hydroxy acid **15** was achieved by treatment with Me_2CuLi in Et_2O (Scheme V), a reaction that occurs in 79% yield with complete regio and stereocontrol. This is in agreement with Sharpless and Chong's observation[14] that the regioselectivity of organocuprate attack at the C-2 of a trans glycidic acid increases with the increase of the electron withdrawing character of the C-4 substituent. Acid **15** was then esterified under phase transfer conditions to the methyl ester **16**, from which ester **7** was obtained through O-benzylation, followed by the usual removal of the chiral auxiliary (Scheme V).

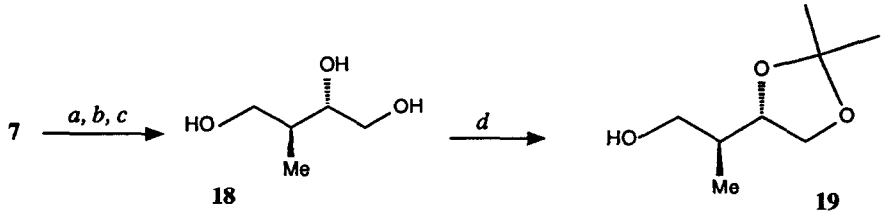
SCHEME V



a. KClO, THF, H_2O; *b*. Me_2CuLi, Et_2O, 0°C; *c*. KOH, MeOH, MeI, Bu_4NHSO_4, CH_3CN, RT;

d. $PhCH_2Br$, Ag_2O, Et_2O; *e*. $HS(CH_2)_2SH$, $BF_3.Et_2O$, CH_2Cl_2; *f*. $CaCO_3$,MeI, acetone, H_2O.

SCHEME VI



a. $NaCNBH_3$; *b*. H_2, Pd-C10%, MeOH-H_2O; *c*. $LiAlH_4$, THF; *d*. acetone, PTSA cat.

The absolute configuration and optical purity of **7** were established by transformation into the known (2S,3S)-3-methyl-1,2,4-butanetriol **18**[15] and its ketal **19**[16] (Scheme VI). For this purpose **7** was treated with $NaCNBH_3$, the crude reaction product being hydrogenated to remove the benzyl group and the resulting γ-lactone reduced with $LiAlH_4$ affording, after flash chromatography, butanetriol **18** in 74% overall yield with no intermediate purification. Triol **18** was in turn transformed into **19** by treatment with *p*-toluensulfonic acid in acetone. The optical rotation of both **18** and **19** was the same as that previously reported.[15,16]

CONCLUSIONS

Addition of alkoxides to oxazolidines **2** and **4** provides an effective way of synthesizing C-4 polyoxygenated synthons in enantiomerically pure form. This route compares favorably with the syntheses from malic acids[1,2] in that both enantiomers of ephedrine are available cheaply and in that it provides three differentiated oxygenated positions. Synthesis of 3-methyl malic acid derivatives, achievable only in modest yield by malic ester alkylation,[3] was also obtained through an epoxidation-nucleophilic opening process, in good yield and >99% e.e.[17]

EXPERIMENTAL SECTION

^{1}H-NMR spectra were recorded with a XL-200 or a Bruker WP-80, while ^{13}C-NMR spectra were recorded with a Varian XL-200 instrument in the FT mode with tetramethylsilane as internal standard. Optical rotations were measured in a 1-dm cell of 1-ml capacity by using a Perkin-Elmer 457 spectrophotometer. Silica gel 60 F_{254} plates (Merck) were used for analytical TLC, 270-400 mesh silica gel (Merck) for flash chromatography. Organic extracts were dried over Na_2SO_4 and filtered before removal of the solvent under reduced pressure. "Dry" solvents were distilled under N_2 just before use: tetrahydrofuran (THF) and diethyl ether were distilled from sodium metal in the presence of benzophenone, C_6H_6 from sodium metal, CH_2Cl_2 from CaH_2. All reactions employing dry solvents were run under a nitrogen (from liquid N_2) atmosphere.

(2S,4S,5R)-4-methyl-5-phenyl-3-carbobenzyloxy-2-[(E)-2-carboxy]ethyloxazolidine (3).

A solution of sodium chlorite (1.51g, 16.7 mmol) and sodium dihydrogenphosphate (2.30g, 16.7mmol) in water (38 ml) was added dropwise, over a 10 minute period, to the aldehyde **1** (1.95g, 5.56mmol) dissolved in tert-butyl alcohol (22 ml) and 2-methyl-2-butene (5 ml).

The pale yellow reaction mixture was stirred at room temperature overnight. Volatile components were removed under vacuum, the residue was dissolved in water (14 ml) and extracted with n-hexane (2x40 ml). The aqueous layer was acidified with HCl to pH 3 and extracted with CH_2Cl_2 (3x100 ml). The combined organic layers were washed with 100 ml of cold water, dried and the solvent evaporated under reduced pressure to give 1.60g (78.5%) of a solid which was not further purified. ^{1}H NMR (80MHz, $CDCl_3$+D_2O) δ 0.83 (d, 3H, J=7.0 Hz), 4.20-4.55 (m, 1H), 5.18 (s, 2H), 5.18 (d, 1H, 5.3Hz), 5.72 (d, 1H, J=5.3 Hz), 6.25 (d, 1H, J=15.8 Hz), 7.08 (dd, 1H, J=15.8 Hz, 5.3 Hz), 7.30 (s, 10H).

(2S,4S,5R)-4-methyl-5-phenyl-3-carbobenzyloxy-2-[(E)-2-carbobenzyloxy]ethyloxazolidine (4).

A methanolic solution of KOH (0.4 M; 10.2 ml) was added to a solution of acid **3** (1.50 g, 4.10 mmol) in MeOH (8 ml). After stirring at room temperature for 5 min. the solvent was evaporated. The potassium carboxylate was suspended in CH_3CN (41 ml); benzyl bromide (0.536 ml, 4.51 mmol) and tetrabutylammonium hydrogensulfate (70 mg, 0.205 mmol) were added and the reaction mixture was stirred at room temperature overnight.

The solvent was removed under vacuum and the crude product was purified by flash chromatography (n-hexane/AcOEt 85/15). Yield 96%.

$[\alpha]_D^{25}$-73.5° (c 0.99, $CHCl_3$); IR ($CHCl_3$) 1720, 1700, 1605, 1450, 1413 cm^{-1}; ^{1}H-NMR (80 MHz, $CDCl_3$) δ 0.83 (d, 3H, J=7.7 Hz), 4.10-4.60 (m,1 H),5.00-5.30 (m, 5H), 5.70 (d, 1H, J=5.6 Hz), 6.31 (d, 1H, J=16.1 Hz), 7.03 (dd, 1H, J=16.1 Hz, 5.6 Hz), 7.33 (s, 10H), 7.40 (s, 5H); ^{13}C-NMR (50.3 MHz,$CDCl_3$) selected data δ 16.1, 56.0, 66.6, 67.4, 81.8, 86.1, 153.1, 165.8; Anal.Calcd for $C_{28}H_{27}NO_5$: C,73.51; H,5.95; N,3.06. Found: C,73.48; H,5.88; N,3.00.

(2S,4S,5R)-4-methyl-5-phenyl-3-carbobenzyloxy-2-[(1S)-1-benzyloxy-2-carbobenzyloxy]-ethyloxazolidine (9).

1.1 ml of benzyl alcohol/THF (2:1) was added to a suspension of 60% NaH in mineral oil (46mg, 1.140 mmol) at RT. After 1 hour the reaction mixture was cooled at -30° and a solution of **4** (52 mg, 0.114 mmol) in 1.1 ml of benzyl alcohol/THF (2:1) was added. After stirring at -30°C for 60 hours the reaction was quenched with 1.7 M AcOH in THF (0.368 ml) and water (0.750 ml) and extracted with Et_2O (3x5 ml). The combined organic layers were dried, diethyl ether was evaporated and benzyl alcohol was removed by Kugelrohr distillation in vacuo. The oily residue was purified by flash chromatography (n-hexane/AcOEt 85/15) to give 55 mg (85%) of **9**.

$[\alpha]_D^{25}$-28.7° (c 0.68, $CHCl_3$); IR ($CHCl_3$) 1675, 1650, 1550, 1355, 1300 cm^{-1}; ^{1}H-NMR (200 MHz,$CDCl_3$) δ 0.78 (d, 3H, J=6.9 Hz), 2.70-3.00 (AB part of the ABX system, 2H), 4.30 (dq, 1H, J=6.9 Hz), 4.50-4.75 (m, 3H), 5.00-5.20 (m, 4H), 5.04 (d, 1H, J=6.9 Hz), 5.38 (d, 1H, J=2.4 Hz), 7.25-7.40 (m, 20H); ^{13}C-NMR (50.3 MHz,$CDCl_3$) selected data δ 16.5, 34.8, 56.3, 66.4, 67.4, 73.3, 76.5, 81.1, 88.6; Anal.Calcd for $C_{35}H_{35}NO_6$: C,74.32; H,6.24; N,2.48. Found: C,74.30; H,6.25; N,2.51.

(2S,4S,5R)-4-methyl-5-phenyl-3-carbobenzyloxy-2-[(1S)-1-benzyloxy-2-carbomethyl]-ethyloxazolidine (8).

1.0 ml of benzyl alcohol/THF (2:1) was added to a suspenion of 60% NaH in mineral oil (32.5 mg, 0.812 mmol) at R.T. After 1 hour the reaction mixture was cooled to -50°C and a solution of **2** (53 mg, 0.145 mol) in 0.4 ml of benzyl alcohol/THF (2:1) was added.

After stirring at -50°C for 18 hours the reaction was quenched with 0.478 ml of 1.7 M AcOH in THF, 3 ml of water were added and the temperature was raised to +25°C. After Et_2O extraction the organic layer was dried and the solvent evaporated; benzyl alcohol was removed by Kugelrohr distillation in vacuo. The oily residue was purified by flash chromatography (n-hexane/AcOEt 85/15) to give 67 mg (98%) of **8**. $[\alpha]_D^{25}$ -82.6° (c1.08, $CHCl_3$); IR ($CHCl_3$) 1700,1690,1605,1405,1400,1350,1325 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.80 (d, 3H, J=6.7 Hz),2.15 (s, 3H), 2.50-3.20 (m, 2H), 4.28 (dq, 1H, J= 6.7 Hz, 5.9 Hz), 4.49-4.70 (m, 1H), 4.67 (s, 2H), 5.08 (d, 1H, J=5.9 Hz), 5.18 (s, 2H), 5.39 (d, 1H, J= 2.6 Hz), 7.25 (s, 5H), 7.35 (s, 5H), 7.41 (s, 5H); ^{13}C-NMR (50.3 MHz $CDCl_3$) selected data δ 16.5, 30.9, 43.3, 56.5, 67.5, 73.4, 75.9, 81.2, 88.9, 154.4, 206.9; Anal.Calcd for $C_{29}H_{31}NO_5$: C,73.55; H,6.60; N,2.96. Found: C,73.60; H,6.58; N,2.90.

2-[(1S)-1-benzyloxy-2-carbobenzyloxy]-ethyl-1,3-dithiolane (10).

A solution of oxazolidine **9** (45 mg, 0.0796 mmol) in dry CH_2Cl_2 (0.7 ml) was treated with 1,2 ethanedithiol (0.067 ml, 0.796 mmol) and $BF_3.Et_2O$ (4µl, 0.0318 mmol). The reaction was allowed to stand for 7 hours at RT. The reaction mixture was quenched with a 5% $NaHCO_3$ aqueous solution and extracted with CH_2Cl_2. The organic layers were dried, filtered and the solvent was evaporated. The crude product was purified by flash chromatography (n-hexane/AcOEt 90/10) to give 22 mg (74%) of **10**.

^{1}H-NMR (80 MHz,$CDCl_3$) δ 2.70-2.90 (m, 2H), 3.20 (s, 4H), 3.90-4.15 (m, 1H), 4.68 (AB syst, 2H), 4.71 (d, 1H, J=6.7 Hz), 5.10 (s, 2H), 7.20-7.35 (m, 10H). Anal.Calcd for $C_{20}H_{22}O_3S_2$: C,64.14; H,5.92. Found: C,64.12; H,5.93.

Benzyl (3S)-3-benzyloxy-4-oxobutanoate (5).

A solution of the dithiolane **10** (118 mg, 0.316 mmol) in acetone/water 4/1 (1.6 ml) was treated with $CaCO_3$ (95 mg, 0.947 mmol) and MeI (0.197 ml, 31.6 mmol) and stirred for 12 hours at 60°C.

The reaction mixture was filtered through a celite pad and the filtrate was washed with a 5M $AcONH_4$ solution then with brine, dried and the solvent evaporated. The crude product was purified by flash chromatography (n-hexane/AcOEt 75/25) to give 70 mg (75%) of aldehyde **5**.

$[\alpha]_D^{25}$ -10.1° (c 0.50, $CHCl_3$); IR ($CHCl_3$) 1735, 1730, 1600, 1450 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.78 (m, 2H), 4.20 (m, 1H), 4.67 (s, 2H), 5.16 (s, 2H), 7.30 (s, 10H), 9.72 (d, 1H, J=1.0 Hz); Anal.Calcd for

$C_{18}H_{18}O_4$: C,72.47; H,6.08. Found: C,72.51; H,6.06.

(4S)-4-benzyloxy-dihydro-2 (3H)-furanone (11).

A solution of the aldehyde **5** (65 mg, 0.218 mmol)in AcOEt/AcOH 9:1 (1 ml) was treated with $NaCNBH_3$ (14 mg, 0.218 mol). After stirring for 20 min. the reaction mixture was quenched with a NH_4Cl saturated aqueous solution. The inorganic salts were filtered off and washed with AcOEt. The solvent was evaporated and the crude product, dissolved in C_6H_6 (1.0 ml), was treated with p-toluensulfonic acid (1 mg). After stirring overnight at RT, the reaction mixture was neutralized with K_2CO_3, filtered and the solvent evaporated. The oily residue was purified by flash chromatography (n-hexane/AcOEt 70/30) to give 33 mg (78%) of **11**.

$[\alpha]_D^{25}$ -28.7° (c 0.95, $CHCl_3$) (lit.[12] $[\alpha]_D^{25}$ -29° (c 1.0, $CHCl_3$); mp 70-71° (acetone);

^{1}H-NMR (80 MHz, $CDCl_3$) δ 2.65 (m, 2H), 4.34 (m, 3H), 4.52 (s, 2H), 7.30 (s, 5H); Anal.Calcd for $C_{11}H_{12}O_3$: C,68.74; H,6.29. Found: C,68.70; H,6.28.

(2S)-2-benzyloxy-4-oxopentanal (6).

The oxazolidine **8** (80 mg, 0.169 mmol) was dissolved in Et_2O (1.7 ml) and treated with ZnI_2 (54 mg, 0.169 mmol). After 5 min. 1,2 ethanedithiol (0.071 ml, 0.845 mmol) was added. After stirring for 2 hours the reaction mixture was quenched with water (1.0 ml) and extracted with Et_2O (3x2 ml). The combined organic layers were dried, filtered and the solvent was evaporated. The crude product was dissolved in CH_2Cl_2 (1.7 ml); 1,2 ethanedithiol (0.142 ml, 1.690 mmol) and $BF_3.Et_2O$ (0.010 ml, 0.0845 mol) were added. After stirring at RT overnight the reaction mixture was quenched with a 5% $NaHCO_3$ aqueous solution and extracted with CH_2Cl_2. The organic layers were dried, filtered and the solvent was evaporated. The oily residue was purified by flash chromatography n-hexane/AcOEt 80/20) to give 49 mg (81%) of the corresponding bis-dithiolane.

^{1}H-NMR (80 MHz, $CDCl_3$) δ 1.78 (s, 3 H), 2.30-2.45 (m, 2H), 3.15-3.30 (m, 4H), 3.30-3.45 (m, 4H), 4.10-4.30 (m, 1H), 4.50-4.80 (m, 2H), 4.88 (d, 1H, J=3.0 Hz); Anal.Calcd for $C_{16}H_{22}OS_4$: C,53.59; H,6.18. Found: C,53.50; H,6.21.

The bis-dithiolane was subsequentely hydrolyzed, as reported for **10**, but with a longer reaction time (36 h). The crude product was purified by flash chromatography (n-hexane/AcOEt 60/40) affording **6** (79%).

$[\alpha]_D^{25}$ -63.7° (c= 2.05; $CHCl_3$); IR ($CHCl_3$) 2920, 1720, 1600, 1360 cm^{-1}; ^{1}H-NMR (80 MHz, $CDCl_3$) δ 2.17 (s, 3H), 2.85 (d, 2H, J=5.4 Hz), 4.23 (ddd, 1H, J=1.0 Hz, 5.4 Hz, 5.4 Hz), 4.68 (s, 2H), 9.75 (d, 1H, J=1.0 Hz); ^{13}C-NMR (50.3 MHz, $CDCl_3$) selected data δ 30.4, 44.6, 73.4, 79.4, 137.1, 202.6, 204.6; Anal.Calcd for $C_{12}H_{14}O_3$: C,69.89; H,6.84. Found: C,69.81; H,6.79.

Transformation of 9 to 8.

A solution of ester **9** (450 mg, 0.796 mol) in 5 ml of MeOH was treated with a 1 N solution of NaOH (0.956 mmol) and stirred at room temperature for three days. The reaction mixture was acidified to pH=3 with 5% HCl and extracted with CH_2Cl_2. The extracts were dried, filtered and evaporated in vacuo to give the corresponding acid which was not further purified (yield 90%). A solution of this acid in C_6H_6 (1.5 ml) was treated with pyridine (0.117 ml, 1.423 mmol) and oxalyl chloride (0.123 ml, 1.423 mmol) at O°C. The reaction mixture was stirred overnight at room temperature. Volatile components and solvent were then removed under vacuum, the residue was dissolved in Et_2O (1.5 ml). This solution was added dropwise to a solution of Me_2CuLi in Et_2O at -78°C [The cuprate was prepared by adding MeLi (1.79 ml, 2.866 mmol, 1.6 M in Et_2O) to a suspension of CuI (273 mg, 1.432 mmol) in Et_2O (14 ml) at O°C and subsequent stirring 10 min].

The temperature was slowly raised to O°C then the reaction was quenched with a NH_4Cl saturated aqueous solution and extracted with Et_2O. The extracts were dried, filtered and evaporated in vacuo. The oily residue was purified by flash chromatography (hexane/AcOEt 85/15) to give 244 mg (65% overall yield) of **8**.

(2S,4S,5R)-4-methyl-5-phenyl-3-p-toluenesulfonyl-2-[(1S,2R)-1-hydroxy-2-carboxy]-propyloxazolidine (15).

19 ml (30.4 mmol) of a 1.6 M solution of MeLi in Et_2O was added to a suspension of CuI (2.95 g, 15.5 mmol) in Et_2O (45 ml) at 0°C. After 10 min a solution of the epoxy acid **14**[7] (2.08 g, 5.2 mmol) in THF (13 ml) was added dropwise under vigorous stirring at 0°C.

After 5 hours at 0°C the reaction mixture was acidified to pH=2 with 5% aqueous HCl. The resulting mixture was filtered through a celite pad and the filtrate was extracted with AcOEt. The organic layer was dried over sodium sulfate, filtered and the solvent evaporated. The residue was purified by flash chromatography

(AcOEt/MeOH 95/5) to give 1.71 g (79%) of **15**.

$[\alpha]_D^{25}$ -1.4° (c 0.98,$CHCl_3$); IR ($CHCl_3$) 3520, 1715, 1355, 1170 cm^{-1}; ^{1}H-NMR (200 MHz,$CDCl_3$+D_2O) δ 0.92 (d, 3H, J=7.1 Hz), 1.49 (d, 3H, J=8.0 Hz), 2.50 (s, 3H), 3.06-3.19 (dq, 1H, J=8.0 Hz, 2.8 Hz), 4.02-4.20 (m, 2H), 4.23 (d, 1H, J=5.7 Hz), 5.12 (d, 1H, J=6.0 Hz), 7.08-7.88 (m, 9H); ^{13}C-NMR (50.3 MHz, $CDCl_3$) selected data δ 15.7, 16.9, 21.4, 40.5, 58.8, 76.6, 81.4, 91.5, 181.6; Anal.Calcd for $C_{21}H_{25}NO_6S$: C,60.13; H,6.01; N,3.34. Found: C,60.10; H,6.03; N,3.33.

(2S,4S,5R)-4-methyl-5-phenyl-3-p-toluenesulfonyl-2-[(1S,2R)-1-hydroxy-2-carbomethoxy]-propyloxazolidine (16).

The acid **15** (2.0 g, 4.77 mmol) dissolved in MeOH (50 ml) was treated with a methanolic solution of KOH (0.4 M; 11.9 ml) and after 5 min. the solvent was evaporated. The potassium carboxylate was suspended in CH_3CN (50 ml); methyl iodide (0.90 ml, 14.3 mmol) and tetrabutylammonium hydrogensulfate (80 mg, 0.238 mmol) were added and the reaction mixture was stirred at room temperature overnight. The solvent was removed under vacuum and the oily residue purified by flash chromatography (benzene/iPr_2O 90/10) to give 1.90 g (92%) of **16**.

$[\alpha]_D^{25}$+28.3° (c 1.09, $CHCl_3$); IR ($CHCl_3$) 3495, 1720, 1350, 1160 cm^{-1}; ^{1}H-NMR (200 MHz $CDCl_3$+D_2O) δ 0.87 (d, 3H, J=6.6 Hz), 1.41 (d, 3H, J=7.1 Hz), 2.43 (s, 3H), 3.05 (dq, 1H, J=7.1 Hz, 3.0 Hz), 3.74 (s, 3H), 4.05-4.17 (m, 2H), 4.25 (d, 1H, J=5.3 Hz), 5.12 (d, 1H, J=5.3 Hz), 7.00-7.90 (m, 9H); ^{13}C-NMR (50.3 MHz, $CDCl_3$) selected data δ 14.5, 17.2, 21.6, 39.5, 51.7, 59.1, 77.1, 81.4, 92.0, 175.5; Anal.Calcd for $C_{22}H_{27}NO_6S$: C,60.95; H,6.28; N,3.23. Found: C,60.92; H,6.32; N,3.22.

(2S,4S,5R)-4-methyl-5-phenyl-3-p-toluenesulfonyl-2-[(1S,2R)-1-benzyloxy-2-carbomethoxy]-propyloxazolidine (17).

The oxazolidine **16** (1.62 g, 3.75 mmol) in diethyl ether (18 ml) was treated with benzyl bromide (0.67 ml, 5.63 mmol) and Ag_2O (868 mg, 3.75 mmol). The mixture was refluxed for 16 hours, then the inorganic salts were filtered off and washed with diethyl ether. The solvent was evaporated and the residue was purified by flash chromatography (n-hexane/AcOEt 80/20) to give 1.49 g (76%) of **17**.

$[\alpha]_D^{25}$ -36.8° (c 2.0, $CHCl_3$); IR ($CHCl_3$) 1730, 1355, 1165 cm^{-1}; ^{1}H-NMR (80 MHz, $CDCl_3$) δ 0.83 (d, 3H, J=6.8 Hz), 1.38 (d, 3H, J=7.4 Hz), 2.41 (s, 3H), 2.95-3.30 (m, 1H), 3.66 (s, 3H), 3.90-4.30 (m, 3H), 4.75 (AB system, 2H, J=12 Hz), 5.27 (d, 1H, J=5.1 Hz), 6.95-7.80 (m, 14H); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 13.7, 16.8, 21.7, 41.5, 51.7, 58.9, 74.4, 81.3, 82.7, 90.8, 138.3, 144.4, 174.5; Anal.Calcd for $C_{29}H_{33}NO_6S$: C,66.52; H,6.35; N,2.67. Found: C,66.55; H,6.32; N,2.71.

Methyl (2R,3S)-2-methyl-3-benzyloxy-4-oxobutanoate (7).

The dithiolane was obtained from **17** as reported above for **10** from **9**.

The crude product was purified by flash chromatography (n-hexane/Et_2O 80/20) (86%).

$[\alpha]_D^{25}$ -15.1° (c 2.45, $CHCl_3$); IR ($CHCl_3$) 3010, 2390, 1730 cm^{-1}; ^{1}H-NMR (80 MHz, $CDCl_3$) δ 1.20 (d, 3H, J=7.1 Hz), 2.97 (dq, 1H, J=7.1 Hz, 6.0 Hz), 3.10-3.24 (m, 4H), 3.64 (s, 3H), 3.76 (dd, 1H, J=6.0 Hz, 6.6 Hz), 4.74 (d, 1H, J=6.6 Hz), 4.75 (AB system, 2H, J=11.4 Hz), 7.19-7.40 (m, 5H); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 13.4, 38.5, 38.7, 44.2, 51.7, 55.3, 75.7, 86.2, 127.6, 127.8, 128.3, 138.3, 174.2; Anal.Calcd.for $C_{15}H_{20}O_3S_2$: C,57.66; H,6.45. Found: C,57.70; H,6.38.

The dithiolane was subsequentely hydrolyzed as reported above for **10**, with a shorter reaction time (8 hrs). The crude product was purified by flash chromatography (n-hexane/Et_2O 75/25) affording **7** (86%).

$[\alpha]_D^{25}$ -73.0° (c 1.24, $CHCl_3$); IR ($CHCl_3$) 1730,1450 cm^{-1}; ^{1}H-NMR (80 MHz, $CDCl_3$) δ 1.19 (d, 3H, J=7.3 Hz), 2.75-3.13 (1H, m), 3.68 (s, 3H), 3.84 (dd, 1H, J= 6.4 Hz, 1.7 Hz), 4.63 (2H, AB system, J=13.2 Hz), 7.15-7.45 (m, 5H), 9.66 (d, 1H, J=1.7 Hz); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 12.9, 41.8, 52.1, 73.6, 84.4, 128.2, 128.6, 137.0, 173.0, 202.5; Anal.Calcd for $C_{13}H_{16}O_4$: C,66.09; H,6.82. Found: C,66.07, H,6.88.

(2S,3S)-3-methyl-1,2,4-butanetriol (18).

$NaCNBH_3$ (140 mg, 2.24 mol) was added to a solution of **7** (530 mg, 2.24 mmol) in AcOEt/AcOH 9:1 (11 ml). After 20 min stirring the mixture was quenched with a saturated aqueous NH_4Cl solution. The inorganic salts were filtered off, washed with AcOEt and the solvent evaporated affording 526 mg of alcohol (98%). [^{1}H-NMR of the crude: (80 MHz, $CDCl_3$) δ 1.15 (d,3H,J=6.7 Hz), 2.21 (bs, 1H), 2.63-3.09 (m, 1H), 3.41-3.85 (m, 6H), 4.58 (s, 2H), 7.30 (s, 5H)].

The crude product (500 mg; 2.08 mol) was hydrogenated in the presence of a catalytic amount of 10% Pd-C in methanol for three hours, then the catalyst was filtered off and washed with hot methanol. Evaporation of the solvent afforded 229 mg (95%) of the lactone.

A solution of the crude lactone (225 mg, 1.94 mmol) in Et_2O/THF 1:1 (4.0 ml) was added to a suspension of lithium aluminum hydride (37 mg, 0.97 mmol) in Et_2O/THF 1:1 (4.0 ml) at 0°C. After 20 min stirring at 0°C, 37 µl of water, 37 µl of 10% aqueous NaOH and 111 µl of water were added in that order. The resulting mixture was stirred for 30 min at RT then the salts were filtered off and washed with THF. The solvent was evaporated and the residue purified by flash chromatography (n-hexane/AcOEt 1/2) to give 184 mg (79%) of **18**.

$[\alpha]_D^{25}$ -5.7° (c 0.5, $CHCl_3$). (lit [15] $[\alpha]_D^{25}$= +5.8° (c 1.00, $CHCl_3$) for the (2R,3R) enantiomer); IR ($CHCl_3$) 3300, 2900, 1455, 1220 cm^{-1}; ^{1}H-NMR (80 MHz, $CDCl_3$) δ 0.88 (d, 3H, J=7.3 Hz), 1.50-2.10 (m, 1H), 2.90 (bs, 2H), 3.00-3.35 (m, 1H), 3.40-4.00 (m, 4H), 4.50-4.60 (bs, 1H); Anal.Calcd for $C_5H_{12}O_3$: C,49.98; H,10.07. Found: C,49.95; H,10.10.

(2S,3S)-1,2-O-isopropylidene-3-methyl-1,2,4-butanetriol (19).

A solution of **18** (100 mg, 0.833 mmol) in acetone (3.5 ml) was treated with *p*-toluenesulfonic acid (6 mg) and stirred for 24 hr at RT. The mixture was then neutralized with K_2CO_3, filtered, and the solvent evaporated. The residue was purified by flash chromatography (n-hexane/AcOEt 70/30) to give 98 mg (74%) of **19**.

$[\alpha]_D^{25}$ +15.7° (c 0.521, C_6H_6) [lit[16] $[\alpha]_D^{25}$ +16.1° (c 2.3, C_6H_6)]; ^{1}H-NMR (80 MHz, $CDCl_3$+D_2O) δ 0.84 (d, 3H, J=7.0 Hz), 1.38 (s, 3H), 1.42 (s, 3H), 1.60-1.95 (m, 1H), 3.55-3.75 (m, 3H), 3.90-4.15 (m, 2H); ^{13}C-NMR (20.15 MHz, $CDCl_3$) δ 12.8, 25.5, 26.5, 39.2, 66.7, 68.4, 80.0, 109.1; Anal.Calcd for $C_8H_{16}O_3$: C,59.98; H,10.07. Found: C,59.94; H,10.03.

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