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ALLYLIC STEREOCENTER DIRECTED ASYMMETRIC CONJUGATE ADDITION OF CUPRATES IN THE PRESENCE OF TRIMETHYLCHLOROSILANE. ENANTIOSELECTIVE SYNTHESIS OF 2-ALKYL-4-BENZYLOXYBUTANAL AND 2-ALKYL-4-OXOPENTANAL.

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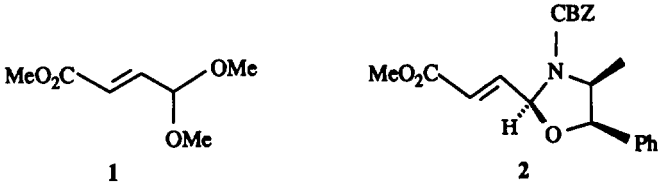
Abstract: Cuprate reagents in the presence of trimethylchlorosilane add with excellent π-face selectivity and yield to α,β-unsaturated ketone and aldehyde bearing in γ-position a masked aldehyde represented by the C-2 of a norephedrine-derived oxazolidine. The title compounds are obtained in high enantiomeric excess after removal of the chiral auxiliary and of the protective group.

We already reported [1,2] on the cyclization between the N-CBZ-norephedrine 3 and a series of dimethylacetals (e.g. 1) in the presence of pyridinium tosylate as acidic catalyst, to give the 2-alkenyloxazolidine 2 with a constant preference for the cis-isomer (Fig 1). Cuprate reagent conjugate additions to 2 occurred with excellent regio and stereoselectivity (diastereomeric ratio >95:5).[1,2]

FIGURE 1



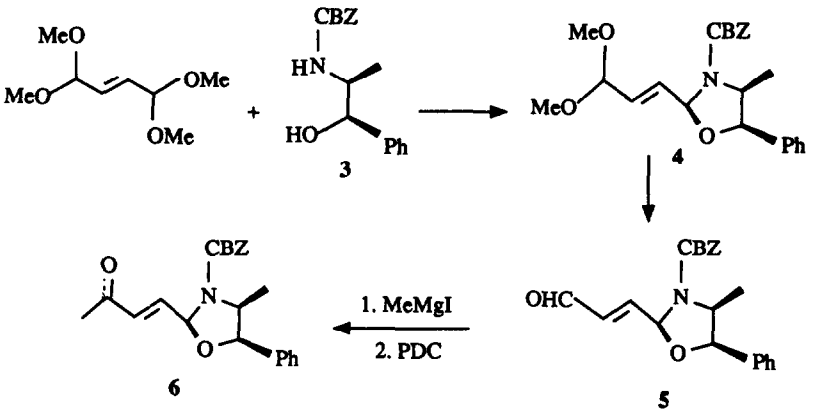
1 2

CBZ = Carbobenzyloxy

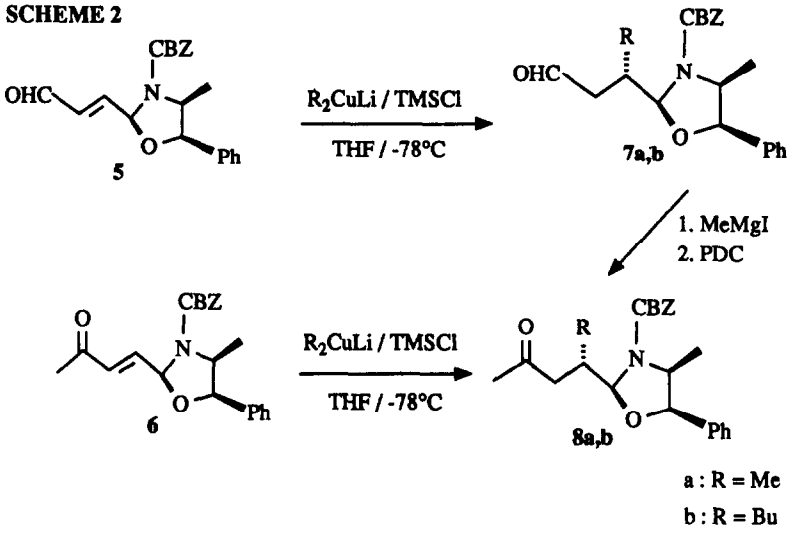
As the concluding study regarding π-face differentiation induced by a norephedrine-derived oxazolidine, we examine conjugate addition of cuprate reagents to unsaturated aldehyde 5 and ketone 6.

The α,β-unsaturated aldehyde 5[3] can be easily prepared on a large scale from one of the two commercially available N-CBZ-norephedrine enantiomers (i.e. 1R,2S) and fumaraldehyde bisdimethylacetal in the presence of pyridinium tosylate in benzene solution, followed by treatment with Amberlyst-15 in aqueous-acetone (Scheme 1).[4] The α,β-unsaturated ketone 6 is obtained from 5 through condensation with methyl magnesium iodide and subsequent oxidation with pyridinium dichromate (Scheme 1).

SCHEME 1



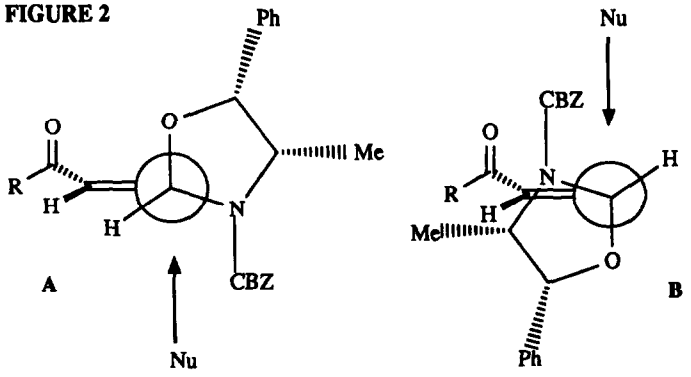
SCHEME 2



a : R = Me

b : R = Bu

FIGURE 2



R = H, Me

The results of the R_2CuLi additions to oxazolidines 5 and 6 are collected in Table I. When the reaction was performed without TMSCl (trimethylchlorosilane) (entry 1,3 and 5, Table I), we observed prevalently 1,2-cuprate addition and aldehyde (or ketone) autocondensation products. These undesidered products can be minimized by trapping the intermediate enolates as silylenol ethers. Infact, the best results were obtained when the reactions were carried out in THF in the presence of TMSCl (Entry 2,4,6 and 7, Table I). This behaviour was in accordance to

TABLE I. Cuprate Addition to 5 and 6.

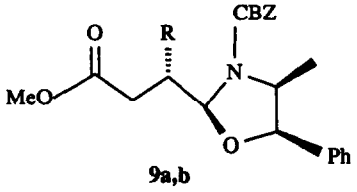
Entry	Oxazolidine	R	Product	Reaction Conditions	Y%	Conf.	Diast. Ratio[a]
1	5	Me	7a	$Me_2CuLi/Et_2O/-78^oC$	12	S	95/5
2	5	Me	7a	$Me_2CuLi/THF/Me_3SiCl/-78^oC$	77	S	95/5
3	5	Bu	7b	$Bu_2CuLi/Et_2O/-78^oC$	10		
4	5	Bu	7b	$Bu_2CuLi/THF/Me_3SiCl/-78^oC$	65	S	88/12
5	6	Me	8a	$Me_2CuLi/Et_2O/-78^oC$	20	S	95/5
6	6	Me	8a	$Me_2CuLi/THF/Me_3SiCl/-78^oC$	80	S	95/5
7	6	Bu	8b	$Bu_2CuLi/THF/Me_3SiCl/-78^oC$	80	S	95/5

a)Determined by ^{1}H-NMR and/or ^{13}C-NMR on the crude product.

the observation that the reaction between TMSCl and R_2CuLi is very slow, while the 1,4-addition of R_2CuLi to an enal or to an enone and O-silylation of the resulting enolates are fast processes and occur cleanly and with high yield.[5a-e,6] The configuration of the adducts 7a-b and 8a-b has been determined transforming the aldehyde adduct 7a-b into the corresponding methylketone 8a-b (1.MeMgI 2.PDC) identical to the compound obtained by the direct addition of cuprate to α,β-unsaturated ketone 6 (Scheme 2).

Aldehyde oxazolidine 7a-b has in turn been transformed into the corresponding methylester 9a-b (1.Ag_2O; 2.CH_2N_2)of known absolute configuration (Figure 3).[1,2]

FIGURE 3

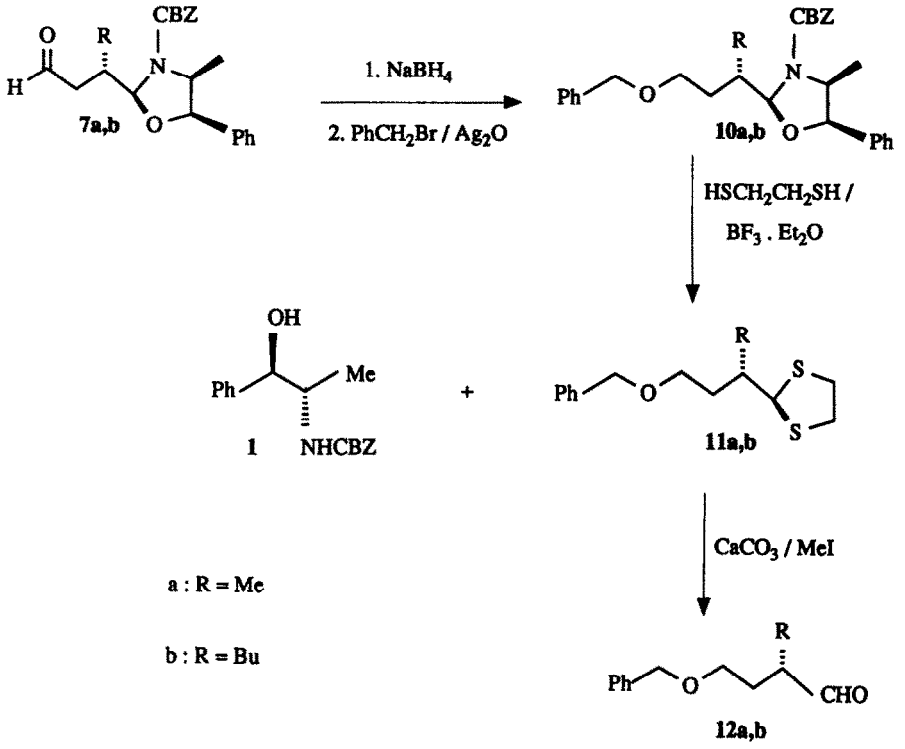


9a,b

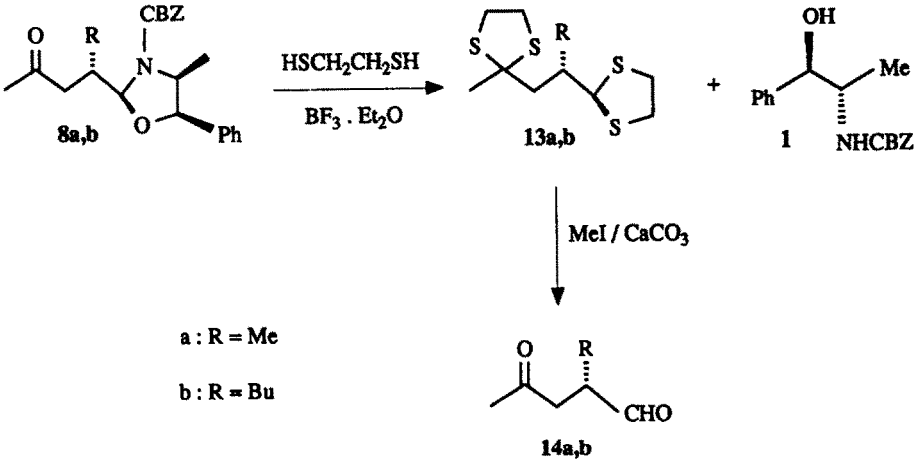
Although the mechanism of cuprate reagents conjugate addition is still an open question, convincing recent evidence shows the reversible formation of a cuprate-substrate (d-π^*) complex and a $Cu^{III}\beta$-adduct in the initial step.[5a,7,8] However, the presence of TMSCl in the reaction medium can irreversibly trap the latter intermediate thereby shifting the rate determining step from the reductive elimination level to the earlier d,π^* complexation stage.[5a]

Analogously to the already mentioned [1,2] oxazolidine 4, cuprate additions to oxazolidine 5 and 6 always occurred from the substrate si face; moreover the same selectivity was observed regardless of the presence or absence of TMSCl. It follows that the postulated kinetic β-adduct must be the more accessible (d-π^* complexation

SCHEME 3



SCHEME 4



as r.d.s.) or the faster reacting diastereomer (reductive-elimination as r.d.s.).[9]

Accordingly, the stereochemical outcome of these additions can be rationalized using the transition structure models A and B (Fig.2).

The very electronegative allylic substituent (oxygen) is aligned "anti" to the forming bond in both A and B, so that the withdrawal of electrons from the π-system can be maximized (Felkin-Anh model).[10a]

When the σ^*_{C-O} orbital is aligned "anti" to the forming bond, its overlap with the HOMO of the transition state, consisting of a mixture of the nucleophile HOMO and the electrophile LUMO, is increased, and stabilization is maximized.[10b]

A is favored over B, apparently for steric reasons.[1-3,5e]

For synthetic purposes, adduct 7a-b was transformed into the corresponding alcohol and protected as O-benzylderivative 10a-b . A straightforward non destructive removal of the chiral auxiliary, performed by treating 10a-b with $HSCH_2CH_2SH/BF_3.Et_2O$ in CH_2Cl_2, smoothly released the intact auxiliary 1 together with the corresponding dithiolane 11a-b. The dithiolane 11a-b was purified by flash chromatography and submitted to standard thioacetal hydrolysis ($CaCO_3/MeI/H_2O/Me_2CO$) to give the known chiron (S)-2-methyl-4-benzyloxybutanal 12a (e.e.)0.99) and (S)-2-n-butyl-4-benzyloxybutanal 12b (Scheme 3).

12b has been proved to be optically pure by reduction of aldehydic function and ^1H and ^{19}F NMR analysis of the corresponding Mosher's ester 15 (Scheme 5).[11]

The useful chiron 12a was already prepared by C.J.Sih and coworkers by chemical degradation of (R)-(+)-Pulegone or by enzymatic methods.[12]

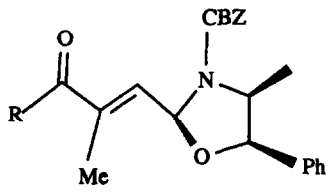
Similarly, the oxazolidine 8a-b was submitted to the standard deprotection protocol(1.$HSCH_2CH_2SH/BF_3Et_2O$ 2.$CaCo_3/MeI/H_2O/Me_2CO$) affording, respectively, 2-methyl-4-oxopentanal 14a and 2-n-butyl-4-oxopentanal 14b in high chemical and optical yields (Scheme 4).

Unfortunately, when the Michael acceptors are trisubstituted, such as compounds 16a and 16b, any attempt of conjugate addition (R_2CuLi, $RCu.BF_3$ in ET_2O or in THF, -78°/+25°C, also in the presence of TMSCl, 1-18h) fail.

FIGURE 4

a : R = OMe

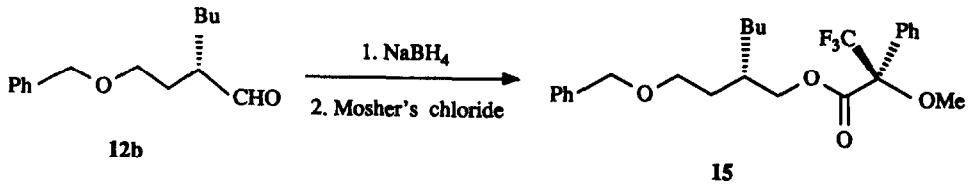
b : R = H



16a,b

In conclusion, the addition of cuprate reagents to oxazolidines 5 and 6 occurs with excellent and predictable π-face selectivity which has been rationalized on the basis of experimental evidence as well as MO considerations.

SCHEME 5



12b 15

The adducts obtained from the conjugate additions can be transformed into 2-alkyl-4-benzyloxybutanal and 2-alkyl-4-oxopentanal in high e.e. % by a simple procedure that allows the recovering of the intact chiral auxiliary.

This approach through 2-alkenyloxazolidines, included α,β unsaturated ester 2,[1,2] constitutes a general and mild procedure for the preparation of the very sensitive α-alkyl aldehydes bearing in γ position a keto, or a carboalkoxy group, or a precursor of another aldehyde group such as the benzyloxy group.

EXPERIMENTAL SECTION

^{1}H-NMR spectra were recorded with 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 cells of 1-ml capacity by using a Perkin-Elmer 241 polarimeter. IR spectra were recorded with 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.

Synthesis of N-Carbobenzyloxy-norephedrine 3.

N-CBZ-norephedrine 3 was obtained by using (1R,2S)-norephedrine and carbobenzyloxy chloride under standard Schotten-Baumann conditions. The crude product was used without further purification in the subsequent cyclization. Yield 98%; mp 111-113 C; $[\alpha]_D^{25}$=-38.7°(c=1.5, $CHCl_3$); 1H-NMR ($CDCl_3$)δ : 1.05 (3H, d, J=6.9 Hz); 1.53 (1H, bs); 2.50-3.10 (1H, m); 3.90-4.40 (1H, m); 4.90 (1H, d, J=3.2 Hz); 5.13 (2 H, s); 7.35 (10H, s). IR ($CHCl_3$) ν :3610, 3460, 1710, 1500, 1450 cm^{-1}. (Found C,71.8; H,6.79; N,5.00; $C_{17}H_{19}NO_3$ requires C,71.6; H,6.71; N,4.91).

Synthesis of oxazolidine 5.

A solution of fumaraldehyde bisdimethylacetal (440 mg, 2.5 mmol) in dry benzene (10 ml) was treated with N-CBZ-(1R,2S)-norephedrine (285 mg, 1.0 mmol) and pyridinium tosylate (75 mg, 0.3 mmol).
The mixture was refluxed for 40 minutes placing a bypassed dropping funnel filled with 4 A molecular sieves between the flask and the reflux condenser. The mixture was cooled, the solvent evaporated under reduced pressure and the exceeding fumaraldehyde bisdimethylacetal was recovered by distillation (b.p.=35 C/0.2 mm Hg). The oxazolidine 4 was purified by flash chromatography (hexane/AcOEt 80/20) (overall yield 85%). The dimethyl acetal was dissolved in acetone-water (54:1; 10 ml) and treated with Amberlyst-15 (91mg).[3,4] After stirring for 3 hours at room temperature the resin was filtered off and the solvent evaporated under reduced pressure to give 5 in 85% yield.

5: $[\alpha]_D^{25}$=-93.3° (c=1.03; $CHCl_3$). IR ($CHCl_3$) ν: 1695, 1415, 1355, 1340 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.80 (3H, d, J=6.7 Hz); 4.38 (1H, dq, J=6.7, 5.2 Hz); 5.17 (2H, s); 5.20 (1H, d, J=5.2 Hz); 5.79 (1H, d, J=4.7 Hz); 6.28-7.00 (2 H, m); 7.30 (10H, s); 9.62 (1H, d, J=8.0 Hz). ^{13}C-NMR ($CDCl_3$) selected data δ: 16.1; 55.9; 67.4; 82.0; 85.8; 153.1; 193.1 (Found C,71.82; H,6.06; N,3.99; $C_{21}H_{21}NO_4$ requires C,71.78; H,6.02; N,3.98).

Synthesis of ketone 6

Aldehyde 5 (351 mg, 1 mmol), was dissolved in dry Et_2O (5 ml) and treated with 2.1 ml of a 0.95 M solution of MeMgI in Et_2O at 0°C. After 20 min the reaction was quenched with a saturated aqueous NH_4Cl solution. The organic layer was separated, dried and the solvent evaporated under reduced pressure. The crude product was dissolved in 5 ml of dry CH_2Cl_2, PDC (639 mg; 1.7 mmol) and glacial AcOH (113 μl) were added. After 3.5 hours, the solution was diluted with 5 ml of Et_2O, and the salts were filtered off and washed with Et_2O. The solvent was evaporated under reduced pressure. Flash chromatography (hexane/AcOEt 70/30) yielded ketone 6 (overall yield 78%).
6: $[\alpha]_D^{25}$ = -79.3° (c=1.10; $CHCl_3$). IR ($CHCl_3$) ν: 1700, 1680, 1415, 1355, 1340, cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.83 (3H, d, J=7.3 Hz); 2.27 (3H, s); 4.36 (1H, dq, J=7.3, 2.6 Hz); 5.17 (2H, s); 5.19 (1H, d, J=2.6 Hz); 5.69 (1H, d, J=4.7 Hz); 6.40 (1H, d, J=16.0 Hz); 6.77 (1H, dd, J=16.0 Hz); 7.35 (10 H, s). ^{13}C-NMR ($CDCl_3$) selected data δ: 16.1; 27.4; 55.9; 67.4; 81.9; 86.4; 153.1; 198.1. (Found C,72.31; H6.39; N,3.89; $C_{22}H_{23}NO_4$ requires C,72.31; H,6.34; N,3.83).

Preparation of R_2CuLi species.

Me_2CuLi was prepared by MeLi (2 mmol, 1.5 M in Et_2O) addition to a suspension of CuI (1.0 mmol) in dry THF or Et_2O (10 ml) at 0°C and subsequent stirring for 10 min.
Bu_2CuLi was prepared by BuLi addition (2 mmol, 1.5 M in hexane) to a suspension of CuI (1.0 mmol) in dry THF or Et_2O (10 ml) at -25° C and subsequent stirring for 10 min.

Cuprate additions to oxazolidines 5 and 6. General procedure.

A solution of R_2CuLi (1.0 mmol) (obtained as above reported) at -78° C was treated with Me_3SiCl (5 mmol) and the appropriate oxazolidine 5 or 6 (1 mmol) dissolved in dry THF (10 ml). After 30 min at -78° C the mixture was treated with glacial AcOH (0.4 ml) and the temperature was made to rise to +25° C, then 10 ml of Et_2O were added and the reaction was quenched with a saturated aqueous NH_4Cl solution. After Et_2O extraction, the organic layer was dried and the solvent evaporated under reduced pressure. The crudes products were checked by ^{1}H and ^{13}C NMR analyses in order to determine the diastereomeric ratios (see Table I).
7a: Flash chromatography (hexane/AcOEt 80/20). $[\alpha]_D^{25}$ = -81.6° (c=1.00; $CHCl_3$). IR ($CHCl_3$) ν: 1720, 1695, 1410, 1355, 1345 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.80 (3H, d, J= 7.0 Hz); 1.20 (3H, d, J=7.0 Hz); 2.30-2.70 (2H, m); 2.70-3.10 (1H, m); 4.10-4.50 (1H, m); 5.05 (1H, d, J=6.0 Hz); 5.13 (1H, d, J=2.7 Hz); 5.18 (2H, s); 7.30 (5H, s); 7.39 (5H, s). ^{13}C-NMR ($CDCl_3$) selected data: δ: 16.3; 30.8; 44.2; 56.5; 67.1; 80.6; 92.1; 154.2; 202.0. (Found C,71.95; H,6.89; N,3.84; $C_{22}H_{25}NO_4$ requires C,71.91; H,6.86; N,3.81).
7b: Flash chromatography (hexane/AcOEt 85/15). $[\alpha]_D^{25}$ = -46.7° (c=0.750; $CHCl_3$). IR($CHCl_3$) ν: 1725, 1700, 1605, 1495, 1410, 1350 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.65-1.00 (5H, m); 1.00-1.80 (7H, m); 2.20-2.70 (2H, m); 2.70-3.00 (1H, m); 4.10-4.50 (1H, m); 5.03 (1H, d, J=6.2 Hz); 5.18 (2H,s); 5.22 (1H, d, J=2.2 Hz); 7.30 (5H, s); 7.39 (5H, s); 9.73 (1H, dd, J=2.0, 2.9 Hz). ^{13}C-NMR ($CDCl_3$) selected data: δ: 14.0; 16.4; 22.7; 29.4; 30.9; 35.4; 42.8; 56.5; 67.2; 80.8; 90.9; 154.2; 203.0. (Found C,73.28; H,7.60; N,3.38; $C_{25}H_{31}NO_4$ requires C,73.32; H,7.63; N,3.42).
8a: Flash chromatography (hexane/AcOEt 80/20). $[\alpha]_D^{25}$ =-71.1° (c=1.40; $CHCl_3$). IR ($CHCl_3$) ν: 1700, 1605, 1495, 1410, 1355, 1345 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.79 (3H, d, J=7.2 Hz); 1.08 (3H, d, J=7.2 Hz); 2.11 (3H, s); 2.15-2.75 (2H, m); 2.70-3.15 (1H, m); 4.10-4.50 (1H, m); 5.00 (1H, d, J=6.0 Hz); 5.11 (1H, d, J=3.0 Hz); 5.18 (2H, s); 7.30 (5H, s); 7.37 (5H, s). ^{13}C-NMR ($CDCl_3$) selected data: δ:16.0, 16.4, 30.1,

32.1, 44.4, 56.5, 67.2, 80.6, 92.4, 154.2, 208.2. (Found C, 72.50; H,7.18; N,3.73; $C_{23}H_{27}NO_4$ requires C,72.42; H,7.13; N,3.67).
8b: Flash chromatography (hexane/AcOEt 85/15). $[\alpha]_D^{25}$ =-63.8° (c=0.78; $CHCl_3$). IR ($CHCl_3$) ν: 1700, 1605, 1495, 1410, 1355, 1350 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.80 (3H, d, J=7.1 Hz); 0.82 (3H, t, J=4.0 Hz); 1.10-1.80 (6H, m); 2.10 (3H, s); 2.15-3.05 (3H, m); 4.29 (1H, dq, J=5.9, 7.1 Hz); 5.00 (1H, d, J=5.9 Hz); 5.17 (2H, s); 5.22 (1H, d, J=2.4 Hz); 7.30 (5H, s); 7.36 (5H, s). ^{13}C-NMR ($CDCl_3$) selected data: δ : 14.0, 16.5, 22.8, 29.3, 30.0, 30.9, 36.0, 43.2, 56.4, 67.2, 80.5, 90.9, 154.2, 208.3. (Found C,73.79; H,7.89; N,3.39; $C_{26}H_{33}NO_4$ requires C,73.73; H,7.85; N,3.31.

Transformation of 7a,b in 8a,b

8a,b were obtained from 7a,b as reported above for oxazolidine 6 from 5.

Transformation of 7a,b in 9a,b

A solution of aldehyde 7a,b (1 mmol) in dioxane-water (1:1; 5 ml) was treated with $AgNO_3$ (2.0 mmol) and 7N KOH solution (1.7 ml).
After stirring for 2h, the reaction mixture was acidified to pH=3 with 4N HCl solution, concentrated, and extracted with CH_2Cl_2. The organic extracts were dried, and the solvent evaporated under reduced pressure. The crude products, dissolved in Et_2O (3 ml), were treated with CH_2N_2. To give esters 9a,b.

Synthesis of oxazolidine 10a,b

Aldehyde 7a,b (1 mmol) dissolved in MeOH (3 ml) was added to $NaBH_4$ (1 mmol) in MeOH (3 ml) at 0°C. After 20 min stirring, the mixture was acidified to pH=3 with 1N HCl, concentrated and extracted with CH_2Cl_2. The organic extracts were dried and the solvent evaporated under reduced pressure.
The crude product was dissolved in dry Et_2O (5 ml) and treated with $PhCH_2Br$ (1.5 mmol) and Ag_2O (1.1 mmol). After refluxing for 3 hours, the reaction mixture was cooled to room temperature. The inorganic salts were filtered off and washed with Et_2O. The solvent was evaporated under reduced pressure and the benzyl ether 10a,b purified by flash chromatography.
10a: Flash chromatography (hexane/AcOEt 80/20). (88% overall yield). ^{1}H-NMR ($CDCl_3$): δ: 0.98 (3H, d, J=5.3 Hz); 1.26 (3H, d, J=5.4 Hz); 1.50-2.30 (2H, m); 2.40-2.80 (1H, m); 3.50-3.90 (2H, m); 4.30-4.55 (1H, m); 4.70 (2H, s); 5.15 (1H, d, J=5.2 Hz); 5.26 (1H, d, J=2.7 Hz); 5.31 (2H, s); 7.20-7.40 (15H, m). (Found C,75 70; H,7.19; N,3.09; $C_{29}H_{33}O_4N$ requires C,75.79; H,7.24; N,3.05).
10b: Flash chromatography (hexane/AcOEt 83/17).(80% overall yield). ^{1}H-NMR ($CDCl_3$) δ: 0.75-1.05 (6H, m); 1.15-2.50 (9H, m);3.30-3.70 (2H, m); 4.15-4.50 (1H, m); 4.50 (2H, s); 5.04 (1H, d, J=4.3 Hz); 5.17 (2H, s); 5.25 (1H, d, J=1.7 Hz); 7.35 (15H, s). (Found C,76.56; H,7.78; N,2.83; $C_{32}H_{39}O_4N$ requires C,76.61; H,7.84; N,2.79).

Synthesis of dithiolanes 11a,b

A solution of oxazolidine 10a,b (1 mmol) in dry CH_2Cl_2 (8 ml), was treated with 1,2 ethanedithiol (10 mmol) and $BF_3.Et_2O$ (0.4 mmol). The reaction was allowed to stand for 24 hours at room temperature. The mixture was quenched with a 5% aqueous $NaHCO_3$ solution and extracted with Ch_2Cl_2. The organic layers were dried, filtered and the solvent evaporated. The resulting dithiolane 11a,b was purified by flash chromatography.
11a: Flash chromatography (petrolether/Et_2O 90/10). (87% yield). ^{1}H-NMR ($CDCl_3$) δ : 1.05 (3H, d, J=7.7 Hz); 1.40-2.10 (3H,m); 3.19 (4H,s); 3.40-3.75 (2H,m); 4.49 (2H,s); 4.57 (1H, d, J=5.8 Hz); 7.30 (5H,s). (Found C,62.71; H,7.57; S,23.93; $C_{14}H_{20}OS_2$ requires C,62.64; H,7.51; S,23.89).
11b: Flash chromatography (hexane/Et_2O 97/3). (95% yield). ^{1}H-NMR ($CDCl_3$) δ: 0.821-0.91 (3H, m); 1.22-2.00 (9H, m); 3.10-3.28 (4H, m); 3.49-3.58 (2H, m); 4.43-4.58 (2H, m); 4.72 (1H, d, J=5.2 Hz); 7.25-7.35 (5H, m). (Found C,65.68; H,8.37; S,20.60; $C_{17}H_{26}OS_2$ requires C,65.76; H,8.44; S,20.65).

Synthesis of (S)-2-methyl-4-benzyloxybutanal 12a and (S)-2-n butyl-4-benzyloxybutanal 12b

A solution of the dithiolane 11a,b (1 mmol) in acetone/water 4/1 (2 ml) was treated with $CaCO_3$ (3 mmol) and MeI (10 mmol) and stirred for 12 hours at 60°C. The resulting mixture was filtered on a celite pad and the filtrate was washed with a 5 M $AcONH_4$ solution, then with brine; dried and the solvent evaporated. The crude was purified by flash chromatography.

12a: Flash chromatography (petrolether/Et_2O 83/17). (90% yield). $[\alpha]_D^{25}$ =+15.6° (c=1.00; $CHCl_3$)(lit.[12a] $[\alpha]_D^{25}$ =+15.8°(c=3.01; $CHCl_3$)). IR ($CHCl_3$) ν : 1725, 1450, 1360, 1095 cm^{-1}. ^{1}H-NMR ($CDCl_3$)δ : 1.10 (3H, d, J=7.1 Hz); 1.60-2.20 (2H,m); 2.45-2.62 (1H, m); 3.47-3.58 (2H, m); 4.47 (2H, s); 7.30 (5H, s); 9.65 (1H, d, J=2.0 Hz). ^{13}C-NMR ($CDCl_3$)δ : 13.3; 30.8; 43.7; 67.4; 73.0; 127.6; 128.4; 138.2; 204.6. (Found C,74.91; H,8.33; $C_{12}H_{16}O_2$ requires C,74.97; H,8.39).

12b: Flash chromatography (petrolether/Et_2O 95/5). (87% yield). $[\alpha]_D^{25}$ = -2.6° (c=1.10; $CHCl_3$). IR ($CHCl_3$) ν: 1723, 1602, 1452, 1364 cm^{-1}. ^{1}H-NMR $CDCl_3$)δ : 0.84-0.91 (3H,m); 1.37-2.19 (8H, m); 2.34-2.48 (1H, m); 3.40-3.54 (2H, m); 4.46 (2H, s); 7.22-7.48 (5H, m); 9.58 (1H, d, J=2.5 Hz). ^{13}C-NMR ($CDCl_3$)δ: 13.9; 22.8; 28.6; 29.2; 29.4;49.4; 67.9; 73.1; 127.7; 128.4; 138.3; 204.8. (Found C,76.95; H,9.51; $C_{15}H_{22}O_2$ requires C,76.88; H,9.46).

Synthesis of bis-dithiolanes 13a,b

13a,b was obtained from 8a,b as reported for 11a,b, with a longer reaction time (36h).

13a: Flash chromatography (petrolether/Et_2O 90/10). (88% yield). ^{1}H-NMR ($CDCl_3$)δ : 1.22 (3H, d, J=6.7 Hz); 1.78 (3H, s); 1.75-2.48 (3H, m); 3.19 (4H, s); 3.33 (4H, s); 4.73 (1H, d, J=4.0 Hz). (Found C,45.09; H,6.83; S,48.15; $C_{10}H_{18}S_4$ requires C,45.07; H,6.81; S,48.12).

13b: Flash chromatography (hexane/AcOEt 97/3). (90% yield). ^{1}H-NMR ($CDCl_3$)δ : 0.70-1.80 (9H, m); 1.77 (3H, s); 1.80-2.44 (3H, m); 3.17 (4H, s); 3.33 (4H, s); 4.98 (1H, d, J=2.7 Hz). (Found C,50.65; H,7.89; S,41.6; $C_{13}H_{24}S_4$ requires C,50.6; H,7.84; S,41.6).

Synthesis of (S)-2-methyl-4-oxopentanal 14a and (S)-2-n-butyl-4-oxopentanal 14b

The bis-dithiolane 13a,b was hydrolized as reported for 11a,b, with a longer reaction time (24 h).

14a: Flash chromatography (petrolether/Et_2O 1/1). (95% yield). $[\alpha]_D^{25}$ = -40.8° (c=1.00, $CHCl_3$). IR ($CHCl_3$) ν :1725, 1710, 1360 cm^{-1}. ^{1}H-NMR ($CDCl_3$)δ : 1.17 (3H, d, J=7.4 Hz); 2.19 (3H, s); 2.30-3.00 (2H, m); 5.07 (1H, m); 9.68(1H, s). ^{13}C-NMR ($CDCl_3$)δ : 13.5; 30.1; 41.6; 44.0; 203.1; 206.2. (Found C,62.9; H,8.78; $C_6H_{10}O_2$ requires C,63.14; H,8.83).

14b: Flash chromatography (petrolether/Et_2O 75/25). (92% yield). $[\alpha]_D^{25}$ = -96.4° (c=1.18, $CHCl_3$). IR ($CHCl_3$) ν :1720, 1715, 1365 cm^{-1}. ^{1}H-NMR ($CDCl_3$)δ : 0.70-1.00 (3H, m); 1.05-1.60 (6H, m); 2.18 (3H, s); 2.25-3.05 (3H, m); 9.68 (3H, m). ^{13}C-NMR ($CDCl_3$)δ : 13.8, 22.7, 28.3, 29.1, 30.1, 42.2, 46.8, 203.5, 206.8.(Found C,69.23; H,10.32; $C_9H_{16}O_2$ requires C,69.19; H,10.32).

Synthesis of Mosher's ester 15.

Aldehyde 12b (46 mg, 0.197 mmol) dissolved in MeOH (2 ml) was added to $NaBH_4$ in MeOH (2 ml) at 0°C. After 30 min stirring the mixture was concentrated under reduced pressure and acidified to pH=3 with 0.1 N HCl. After CH_2Cl_2 extraction, the organic layer was dried and the solvent evaporated under reduced pressure. The crude product and Mosher's chloride (55 mg, 0.217 mmol) were mixed with carbon tetrachloride (0.5 ml) and dry pyridine (7 drops). After 30 min, water (1 ml) was added and the reaction mixture extracted with ether. The ether solution, after

washing successively with dilute hydrochloric acid, saturated sodium carbonate solution, and water, was dried and the solvent evaporated under reduced pressure. The crude product was analyzed by ^{1}H- and ^{19}F-NMR spectroscopy.
15: ^{1}H-NMR ($CDCl_3$) δ:0.80-1.00 (3H, m); 1.10-2.00 (9H, m); 3.40 (2H, d, J=5.6 Hz); 3.52 (3H, m); 4.25 (2H, d, J=6.0 Hz); 4.44 (2H, s); 7.10-7.50 (10H,m).

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