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Preparation of enantiomerically pure *cis*- and *trans*-*N*-(propionyl)hexahydrobenzoxazolidin-2-ones

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Abstract: A high-yield, five-step synthesis of novel enantiomerically pure *cis*- and *trans*-*N*-(propionyl)-hexahydrobenzoxazolidin-2-ones **5a–d** from cyclohexene oxide and (*S*)-α-methylbenzylamine is described. The highly diastereoselective benzylation of **5b** is also described. © 1997 Elsevier Science Ltd

Introduction

Interest in the synthesis of 4- and 5-substituted oxazolidin-2-ones is well known. The use of enantiomerically pure oxazolidin-2-one derivatives as chiral auxiliaries in asymmetric synthesis was first reported by Evans *et al.*[1] The functionalization at nitrogen of oxazolidin-2-ones by means of electrophiles such as acid chlorides followed by chemical modification of the side chain, and by hydrolysis of the *N*-acylated-oxazolidin-2-ones under mild conditions made the employment of enantiopure cyclic carbamates a widely used procedure in enantioselective methodology.[2–6] Furthermore, several synthetic oxazolidinones have exhibited strong antibacterial activity.[7] Nevertheless, the preparation of the starting oxazolidinones is generally limited to the availability of the enantiomerically pure β-aminoalcohols[8a] or to the resolution of the racemic oxazolidinones. Alternatively, transition metal-catalyzed asymmetric synthesis of the chiral carbamates is also applicable.[8b]

We report here the synthesis of both pairs of enantiomeric hexahydrobenzoxazolidin-2-ones **4a–d** from the diastereoisomeric mixture of (1*R*,2*R*,1′*S*)- and (1*S*,2*S*,1′*S*)-2-[*N*-(α-methylbenzyl)amino]cyclohexanols **1a** and **1b**. Compounds **1a**, **1b** and **4d** have been previously reported[9,10] (Schemes 1 and 3). We also report the use of **4b** as effective chiral auxiliary for the stereoselective benzylation of propionic acid (Scheme 4).

Results

Diastereoisomeric aminoalcohols **1a** and **1b** were prepared by the opening of cyclohexene oxide with (*S*)-α-methylbenzylamine in presence of lithium perchlorate in refluxing acetonitrile.[9d] The diastereoisomeric mixture was derivatized at nitrogen with methyl chloroformate and the resulting diastereoisomeric carbamates **2a, b** were then separated by flash chromatography (Scheme 1). The isolated carbamates were purified by recrystallization or vacuum distillation. Optical rotations were measured and the products were further characterized by ^{1}H, ^{13}C NMR, I.R. and mass spectra, and microanalyses (see Experimental part).

Carbamates **2a** and **2b** were cyclized under basic conditions with conservation of configuration by treatment with sodium hydride in THF to give the diastereoisomeric *trans*-*N*-(*S*)-α-methylbenzyl-

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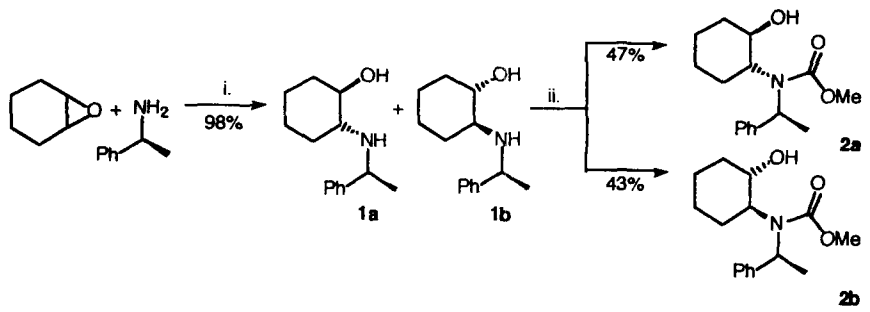
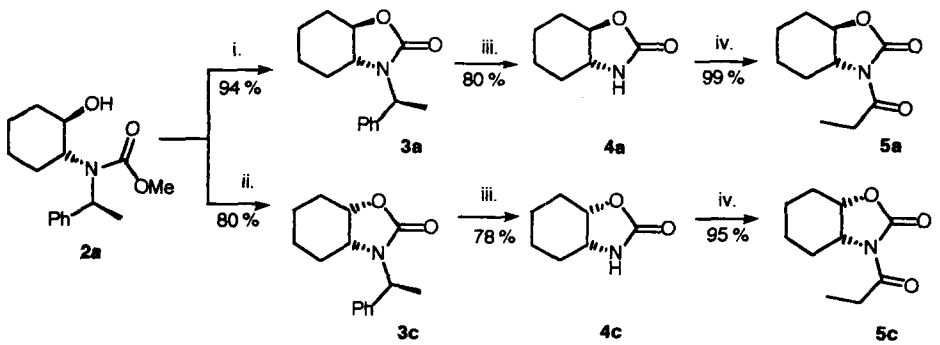


Conditions: (i) $LiClO_4/CH_3CN$/reflux,18 h. (ii) 1. $ClCO_2Me$/NaH/THF/reflux, 2.5 h. 2. Flash chromatography.

Scheme 1.

oxazolidin-2-ones **3a** and **3b** (94 and 95% yield). Inversion of the configuration at the C(1) stereogenic center was achieved by mesylation of carbamates **2a** and **2b** followed by in situ cyclization under basic conditions in refluxing toluene, to give *cis*-*N*-(*S*)-α-methylbenzyl-oxazolidin-2-ones **3c** and **3d** (80 and 84% yield, respectively). Birch hydrogenolysis with lithium in liquid ammonia removed the methylbenzyl group from compounds **3a–d** and provided oxazolidin-2-ones **4a–d**, respectively (75–80% yield). Finally, **4a–d** were *N*-acylated by treatment with *n*-butyllithium at 0°C, followed by addition of propionyl choride at −78°C to generate the *N*-propionyl derivatives **5a–d** (83–99% yield)[2a] (Schemes 2 and 3). Optical rotations were measured and the products were further characterized by ^1H, ^{13}C NMR, I.R. and mass spectra, and microanalyses (see Experimental part).



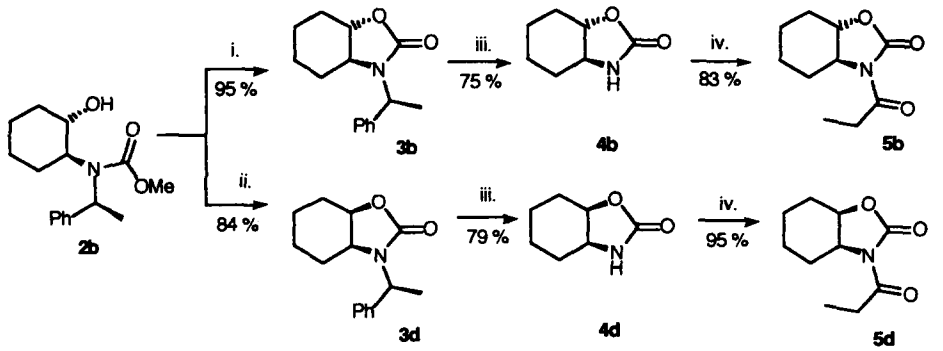
Conditions: (i) NaH/THF, reflux, 6 h. (ii) 1. $MeSO_2Cl$/Py/toluene, r. t., 24 h; 2. reflux, 8 h. (iii) Li/NH_3/THF, -40°C, 1 h; (iv) 1. *n*-BuLi/THF, 0°C, 30 min; 2. EtCOCl, -78°C, 1 h.

Scheme 2.

The alkylation of **5b** with benzyl bromide was performed in order to probe the potential of oxazolidi-2-ones **4** in asymmetric synthesis (Scheme 4). Enolate **5b**-Na was prepared by means of NaHMDS, at −78°C in THF, and alkylation performed at −30°C→rt, using 3 equiv. of benzyl bromide. High resolution ^1H NMR spectra showed a single benzylated product **6b** (thus, ds>98%), whose configuration was determined by chemical correlation. The yield of the isolated pure α-benzylated product, **6b**, after flash chromatography, was 32%.

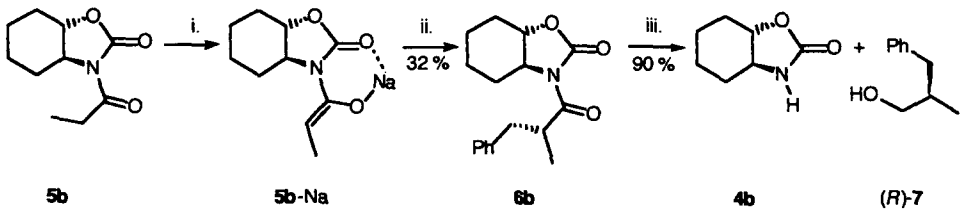
Reduction of **6b** with $LiAlH_4$ afforded (*R*)-2-benzyl-1-propanol, **7** {$[\alpha]_D$=+10.9 (c=2.0, C_6H_6), lit.[3a] $[\alpha]_D$=+11.1 (c=1.25, C_6H_6)} in 90% yield.

In conclusion, the efficient preparation of both pairs of enantiomers of *cis*- and *trans*-hexahydrobenzoxazolidinones **4a–d** is described. Preliminary demonstration of the application of **4a–d** as chiral auxiliaries is also presented.



Conditions: (i) NaH/THF, reflux, 4.5 h. (ii) 1. $MeSO_2Cl$/Py/toluene, r. t., 24 h; 2. reflux, 8 h. (iii) Li/NH_3/THF, -40°C, 1 h. (iv) 1. *n*-BuLi//THF, 0°C, 30 min, 2. EtCOCl, -78°C, 1 h.

Scheme 3.



Conditions: (i) NaHMDS (2 equiv.) /THF/- 78°C, 45 min. (ii) $BrCH_2Ph$ (3quiv.)/THF/- 78 → - 30°C, 4h 3. r.t. , 2h. (iii) $LiAlH_4$/THF/25°C, 3h.

Scheme 4.

Experimental section

Melting points were taken using a Mel-Temp apparatus and are uncorrected. ^1H NMR spectra were measured at 200 MHz on a Varian Gemini-200 spectrometer. ^{13}C NMR spectra were recorded at 67.8 MHz on a JEOL-270 instrument, in $CDCl_3$ or $(CD_3)_2SO$ solution with tetramethylsilane (TMS) as an internal standard. Chemical shifts are given as δ values (ppm) and coupling constants *J* are given in Hz. Optical rotations $[\alpha]_D$ were measured at ambient temperature in 0.1 dm cells, using a Perkin–Elmer 241 spectrophotometer. FT-I.R. spectra were recorded on a GBC Instrument. Mass spectra were recorded on a Hewlett–Packard 5989 A.

All reagents were purchased from Aldrich Chemical Co. THF and toluene were dried over Na/benzophenone (under argon) until the blue color of the benzophenone ketyl persisted, at this point the THF and toluene were distilled and handled by means of syringes and cannulas.

The *n*-BuLi was titrated prior to its use.[11] Flasks, stirring bars, and hypodermic needles used for the generation of organometallic compounds were dried for ca. 12 h at 120°C and allowed to cool in a desiccator over anhydrous calcium sulfate. Reagent quality solvents were used without further purification. Analytical TLC plates and silica gel (230–400 mesh) were purchased from Merck.

*(1*R,2R,*1'*S)- *and (1*S,2S,*1'*S)-2-N-*[(α-Methylbenzyl)amino]cyclohexanol (**1a** and **1b**)*

In a dry two-necked flask provided with addition funnel, condenser and magnetic stirrer was placed with stirring under argon an equimolar mixture of cyclohexene oxide (4.0 g, 41 mmol) and anhydrous lithium perchlorate (4.4 g, 41 mmol) in freshly dried acetonitrile (ca. 40 mL) until complete dissolution of the lithium perchlorate. The reaction mixture was cooled in an ice–water bath to 0°C before the dropwise addition of (*S*)-α-methylbenzylamine (5.3 mL, 41 mmol). The resulting solution was then

heated to reflux for 18 h. Water (25 mL) was added to the reaction and the organic phase was extracted with CH_2Cl_2 (3×25 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* affording a diastereoisomeric mixture of β-aminoalcohols **1a**:**1b** as a yellow colored oil in a 55: 45 ratio; yield: 8.8 g (98%). $[\alpha]_D$=−39.7 (c=1.0, EtOH), $[\alpha]_D$=−36.0 (c=1.0, MeOH).

*(1R,2R,1′S)- and (1S,2S,1′S)-2-[*N*-(Carbomethoxy)-*N*-(α-methylbenzyl)]amino-1-cyclohexanol (**2a** and **2b**)*

In a dry two-necked flask fitted with condenser, addition funnel and magnetic stirrer, the diastereoisomeric mixture **1a–b** (5.0 g, 23 mmol) and NaH (0.55 g, 23 mmol) was dissolved in THF (25 mL) under argon. The resulting solution was cooled to 0°C before the dropwise addition of methyl chloroformate (1.8 mL, 23 mmol). The reaction mixture was heated to reflux until no starting β-aminoalcohol was detected by TLC (2.5 h). At this point the reaction was quenched with water (25 mL), and extracted with CH_2Cl_2 (3×25 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford a diastereoisomeric mixture of carbamates as a yellow colored oil; yield: 6.0 g (94%). Separation of the crude diastereoisomeric mixture was accomplished by flash chromatography (petroleum ether/ethyl acetate, 5:1).[12]

*(1R,2R,1′S)-**2a***

3.0 g (47.0%) as white crystals, mp 132–133°C, $[\alpha]_D$=−81.2 (c=1.0, EtOH).

$C_{16}H_{23}NO_3$ (277.3) calc. 69.28% C, 8.36% H; found 69.15% C, 8.59% H.

^{1}H NMR (DMSO-d_6/TMS) (T=120°C): 0.9 (m, 1H), 1.1 (m, 3H), 1.5 (m, 3H), 1.6 (d, 3H, *J*=7), 1.9 (m, 1H), 3.1 (m, 1H), 3.5 (s, 3H), 3.8 (m, 1H), 5.1 (q, 1H *J*=7), 7.3 (m, 5H).

^{13}C NMR (DMSO-d_6/TMS) (T=120°C): 17.3, 23.6, 24.6, 28.9, 35.1, 50.6, 52.7, 61.2, 67.8, 125.9, 126.4, 127.2, 142.1, 155.2.

Mass (*m/z*): 277 (molecular ion), 218, 180, 178, 140, 105 (base peak), 79, 59, 41.

I.R. (cm^{-1}) 1676.2.

*(1S,2S,1′S)-**2b***

3.0 g (43.0%) as white crystals, mp 56–57°C, $[\alpha]_D$=−2.9 (c=1.0, EtOH).

$C_{16}H_{23}NO_3$ (277.3) calc. 69.28% C, 8.36% H; found 69.34% C, 8.44% H.

^{1}H NMR ($CDCl_3$/TMS): 1.1 (m, 2H), 1.2 (m, 1H), 1.6 (d, 3H, *J*=7), 1.7 (m, 3H), 1.9 (m, 1H), 3.4 (m, 1H), 3.5 (s, 3H), 3.7 (m, 1H), 4.7 (q, 1H, *J*=7), 7.1 (t, 1H *J*=7), 7.3 (t, 2H, *J*=7), 7.5 (d, 2H, *J*=7).

^{13}C NMR ($CDCl_3$/TMS): 24.8, 26.1, 30.6, 35.3, 52.7, 54.3, 62.4, 70.4, 127.8, 128.0, 129.0, 141.3, 158.9.

Mass (*m/z*): 277 (molecular ion), 218, 180, 178, 140, 105 (base peak), 79, 59, 41.

I.R. (cm^{-1}) 1680.1.

*N-[(S)-α-Methylbenzyl]hexahydrobenzoxazolidin-2-ones (**3a–d**); general procedure*

Method A (for *trans*-(4*R*,5*R*,1′*S*)- and (4*S*,5*S*,1′*S*)-*N*-(α-methylbenzyl)-hexahydrobenzoxazolidin-2-ones, **3a** and **3b**): In a dry flask fitted with condenser and magnetic stirrer, under argon, compound **2** (1.0 g, 3.6 mmol) and NaH (0.10 g, 4.3 mmol) were suspended in THF (30 mL). The mixture was heated to reflux until no more carbamate **2a** or **2b** was detected by TLC (6 and 4.5 h, respectively). The reaction was quenched with water (25 mL) and the organic layer was extracted with CH_2Cl_2 (3×25 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude products were purified by flash chromatography (petroleum ether/ethyl acetate, 3:1) to provide pure diastereoisomers **3a** and **3b**.

*(4R,5R,1′S)-**3a***

0.83 g (94.0%) as white crystals, mp 69–70°C, $[\alpha]_D$=+5.4 (c=1.0, EtOH).

$C_{15}H_{19}NO_2$ (245.3) calc. 73.44% C, 7.81% H; found 73.78% C, 7.86% H.

^1H NMR ($CDCl_3$/TMS): 0.9 (dq, 1H, *J*=12, 3), 1.3 (m, 3H), 1.6 (m, 2H), 1.7 (d, 3H, *J*=7), 1.8 (m, 1H), 2.2 (m, 1H), 3.2 (dt, 1H, *J*=11, 3), 3.8 (dt, H, *J*=11, 3), 5.1 (q, 1H, *J*=7), 7.3 (m, 5H).

^{13}C NMR ($CDCl_3$/TMS): 15.2, 23.3, 23.4, 28.2, 28.6, 51.3, 61.2, 80.7, 126.7, 127.1, 128.0, 141.0, 159.2.

Mass (*m/z*): 245 (molecular ion), 186, 164 (base peak), 140, 120, 105, 77, 51, 42.

I.R. (cm^{-1}) 1749.5.

*(4S,5S,1′S)-**3b***

0.84 g (95.0%) as white crystals, mp 105–106°C, $[\alpha]_D$=−80.0 (c=1.1, EtOH).

$C_{15}H_{19}NO_2$ (245.3) calc. 73.44% C, 7.81% H; found 73.65% C, 8.08% H.

^1H NMR ($CDCl_3$/TMS): 1.1 (m, 1H), 1.4 (m, 3H), 1.6 (d, 3H, *J*=7), 1.8 (m, 2H), 2.1 (m, 2H), 2.8 (dt, 1H, *J*=11, 3), 3.8 (dt, 1H,*J*=11, 3), 5.3 (q, 1H, *J*=7), 7.3 (m, 5H).

^{13}C NMR ($CDCl_3$/TMS): 18.7, 24.0, 24.1 28.8, 30.2, 52.5, 61.9, 81.2, 127.9, 128.3, 129.1, 139.3, 159.8.

Mass (*m/z*): 245 (molecular ion), 186, 164, 140, 120, 105 (base peak), 77, 51, 42.

I.R. (cm^{-1}) 1745.5.

Method B (for *cis*-(4*R*,5*S*,1′*S*)- and (4*S*,5*R*,1′*S*)-*N*-(α-methylbenzyl)hexahydrobenzoxazolidin-2-ones, **3c** and **3d**): In a two-necked flask provided with an addition funnel, condenser and a magnetic stirrer, under argon, compound **2** (1.0 g, 3.6 mmol) and dry pyridine (2 mL) were dissolved in dry toluene (20 mL). To the ice-cooled mixture was added dropwise a mixture of methanesulfonyl chloride (1.4 g, 12.3 mmol, 0.94 mL) in dry toluene (5 mL). The reaction mixture was stirred at rt until no more carbamate **2** was detected by TLC (ca. 24 h), and then the in situ mesylated compound was heated to reflux for 8 h to give the desired products. The cool reaction mixture was poured over ice cooled 1N HCl (30 mL) and the organic layer was extracted with CH_2Cl_2 (3×25 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude products were purified by flash chromatography (petroleum ether/ethyl acetate, 5:1) to provide pure diastereoisomers **3c** or **3d**.

*(4R,5S,1′S)-**3c***

0.71g (80.0%) as white crystals, mp 51–52°C, $[\alpha]_D$=−9.0 (c=3.0, EtOH).

$C_{15}H_{19}NO_2$ (245.3) calc. 73.44% C, 7.81% H; found 73.82% C, 8.04% H.

^1H NMR ($CDCl_3$/TMS): 1.0 (m, 1H), 1.2 (m, 3H), 1.4 (m, 2H), 1.7 (d, 3H, *J*=7), 1.9 (m, 2H), 3.7 (q, 1H, *J*=6), 4.4 (q, 1H, *J*=5), 5.1 (q, 1H, *J*=7), 7.4 (m, 5H).

^{13}C NMR ($CDCl_3$/TMS): 17.8, 19.9, 20.5, 27.4, 27.7, 52.1, 54.0, 74.2, 127.8, 128.2, 128.9, 141.9, 158.9.

Mass (*m/z*): 245 (molecular ion), 230, 186, 164, 140, 120, 105 (base peak), 91, 77, 51, 42.

I.R. (cm^{-1}) 1734.1.

*(4S,5R,1′S)-**3d***

0.74 g (84.0%) as white crystals, mp 73–74°C, $[\alpha]_D$=+25.6 (c=1.0, EtOH).

$C_{15}H_{19}NO_2$ (245.3) calc. 73.44% C, 7.81% H; found 73.74% C, 8.12% H.

^1H NMR ($CDCl_3$/TMS): 1.1 (m, 1H), 1.5 (m, 3H), 1.6 (d, 3H, *J*=7), 1.8 (m, 2H), 2.1 (m, 2H), 3.3 (q, 1H, *J*=6), 4.3 (q, 1H, *J*=4), 5.2 (q, 1H, *J*=7), 7.4 (s, 5H).

^{13}C NMR ($CDCl_3$/TMS): 19.0, 19.9, 21.2, 27.4, 29.9, 52.7, 53.9, 74.5, 127.7, 128.2, 129.2, 140.5, 158.7.

Mass (*m/z*): 245 (molecular ion), 230, 186, 164, 140, 120, 105 (base peak), 91, 77, 51, 42.

I.R. (cm^{-1}) 1735.2.

*3H-Hexahydrobenzoxazolidin-2-ones (**4a–d**); general procedure*

In a dry two-necked flask, provided with a magnetic stirrer and a trap filled with dry ice/acetone, 30 mL of liquified ammonia was collected. The flask was mantained at −40°C before the addition, under an argon stream, of lithium shot (0.088 g, 12.6 mmol). To the deep blue reaction mixture was added a solution of **3** (0.44 g, 1.8 mmol) in THF (20 mL). The mixture was stirred at −40°C for 1 h and then was quenched with NH_4Cl (0.661 g, 12.6 mmol) allowed to warm to rt, and shaken overnight. Water (25 mL) and 1M HCl was added until pH=7. The organic layer was extracted with CH_2Cl_2 (3×25 mL), dried with anhydrous Na_2SO_4, filtered and evaporated. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 2:1) obtaining **4a, b, c, d**, respectively.

*(4R,5R)-**4a***

0.20 g (80.0%) as white crystals, mp 134–135°C, $[\alpha]_D$=+6.0 (c=1.0, EtOH).
$C_7H_{11}NO_2$ (141.2) calc. 59.55% C, 7.86% H; found 59.47% C, 8.02% H.

*(4S,5S)-**4b***

0.19 g (75.0%) as white crystals, mp 132–134°C, $[\alpha]_D$=−5.9 (c=1.0, EtOH).
$C_7H_{11}NO_2$ (141.2) calc. 59.55% C, 7.86% H; found 59.44% C, 8.13% H.
^1H NMR ($CDCl_3$/TMS): 1.6 (m, 6H), 2.1 (m, 1H), 2.2 (m, 1H), 3.3 (dt, 1H, *J*=11, 2), 3.9 (dt, 1H, *J*=11, 3), 5.6 (br, 1H, NH).
^{13}C NMR ($CDCl_3$/TMS): 24.0, 24.2, 29.0, 29.6, 61.4, 84.3, 160.5.
Mass (*m/z*): 141 (molecular ion), 112, 98, 96, 82, 69, 56 (base peak), 41, 28.
I.R. (cm^{-1}) 1747.9.

*(4R,5S)-**4c***

0.20 g (78.0%) as white crystals, mp 92–93°C, $[\alpha]_D$=−28.6 (c=1.0, EtOH).
$C_7H_{11}NO_2$ (141.2) calc. 59.55% C, 7.86% H; found 59.32% C, 7.82% H.

*(4S,5R)-**4d***

0.20 g (79.0%) as white crystals, mp 90–92°C, $[\alpha]_D$=+28.3 (c=1.0, EtOH).
$C_7H_{11}NO_2$ (141.2) calc. 59.55% C, 7.86% H; found 59.57% C, 8.17% H.
^1H NMR ($CDCl_3$/TMS): 1.3 (m, 1H), 1.6 (m, 4H), 1.9 (m, 3H), 3.7 (q, 1H, *J*=6), 4.6 (dt, 1H, *J*=6, 5), 5.9 (br, 1H, NH).
^{13}C NMR ($CDCl_3$/TMS): 19.9, 20.3, 27.2, 29.1, 52.2, 76.5, 161.1.
Mass (*m/z*): 141 (molecular ion), 112, 98, 96, 82, 68, 56, 41, 28 (base peak).
I.R. (cm^{-1}) 1732.2.

*N-(Propionyl)hexahydrobenzoxazolidin-2-ones (**5a–d**); general procedure*

A dry two-necked flask provided with magnetic stirrer, a dropping funnel and a low-temperature thermometer, was charged with a mixture of **4** (0.14 g, 1.0 mmol) in THF (10 mL) under argon. The solution was cooled to 0°C in an ice bath before the dropwise addition of a precooled solution of *n*-BuLi (0.65 mL, 1.6 M in hexane). After 30 min. the mixture was cooled at −78°C with an acetone/dry ice bath, and then a precooled solution of propionyl chloride (0.09 g, 1.0 mmol) in THF (5 mL) was added dropwise. The reaction mixture was stirred and allowed to warm up to rt and quenched with a saturated aqueous solution of NH_4Cl (5 mL). Water (25 mL) was added and the organic material was extracted with CH_2Cl_2 (3×25 mL), dried with anhydrous Na_2SO_4, filtered and evaporated. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 5:1) to give compounds **5a, b, c, d**, respectively.

*(4R,5R)-**5a***

0.19 g (99.0%) as white crystals, mp 109–110°C, $[\alpha]_D$=−93.0 (c=1.0, $CHCl_3$).

$C_{10}H_{15}NO_3$ (197.2) calc. 60.89% C, 7.67% H; found 61.13% C, 7.86% H

(4S,5S)-5b

0.16 g (83.0%) as white crystals, mp 109°C, $[\alpha]_D$=+96.3 (c=1.0, $CHCl_3$).

$C_{10}H_{15}NO_3$ (197.2) calc. 60.89% C, 7.67% H; found 60.80% C, 7.76% H.

^1H NMR ($CDCl_3$/TMS): 1.2 (t, 3H, *J*=7), 1.5 (m, 3H), 1.6 (m, 1H), 1.9 (m, 2H), 2.2 (m, 1H), 2.8 (dq, 1H, *J*=18, 7), 2.9 (m, 1H), 3.0 (dq, 1H, *J*=18, 7), 3.6 (dt, 1H, *J*=11, 3), 3.9 (dt, 1H, *J*=11, *J*=3).

^{13}C NMR ($CDCl_3$/TMS): 8.8, 24.0, 24.2, 29.0, 29.4, 30.4, 63.6, 81.8, 157.6, 176.8.

Mass (*m/z*): 197 (molecular ion), 169, 152, 142, 112, 97, 81, 74, 57 (base peak), 29.

I.R. (cm^{-1}) 1790.8, 1695.5.

(4R,5R)-5c

0.19 g (95.0%) as an oil, $[\alpha]_D$=−112.3 (c=1.0, $CHCl_3$).

$C_{10}H_{15}NO_3$ (197.2) calc. 60.89% C, 7.67% H; found 61.21% C, 7.92% H.

(4S,5S)-5d

0.19 g (95.0%) as an oil, $[\alpha]_D$=+112.1 (c=1.0, $CHCl_3$).

$C_{10}H_{15}NO_3$ (197.2) calc. 60.89% C, 7.67% H; found 61.03% C, 7.95% H.

^1H NMR ($CDCl_3$/TMS): 1.1 (m, 3H), 1.2 (m, 2H), 1.6 (m, 4H), 2.2 (m, 2H), 2.8 (m, 2H), 4.3 (m, 1H), 4.5 (m, 1H).

^{13}C NMR ($CDCl_3$/TMS): 8.7, 19.5, 21.2, 26.7, 27.5, 29.5, 54.1, 74.8, 154.3, 174.2.

Mass (*m/z*): 197 (molecular ion), 169, 152, 142, 112, 97, 81, 74, 57 (base peak), 29.

I.R. (cm^{-1}) 1793.9, 1685.5.

(4S,5S,2'R)-trans-N-*[2'-Benzyl-propionyl]-hexahydrobenzoxazolidin-2-one (**6b**)*

A dry two-necked flask provided with magnetic stirrer, a dropping funnel and a low-temperature thermometer, was charged with a mixture of **5b** (0.50 g, 0.25 mmol) in THF (5 mL) under argon. The solution was cooled to −78°C in an acetone/dry ice bath before the dropwise addition of a precooled solution of NaHMDS (1M, hexane, 0.50 mmol). After 45 min at −78°C a precooled solution of benzyl bromide (0.13 g, 0.75 mmol) in THF (5 mL) was added dropwise. The reaction mixture was stirred and allowed to warm up to −30°C during 4 h, then was allowed to warm up to rt for 2 h more and quenched with a saturated solution of NH_4Cl (5 mL). Water (25 mL) was added and the organic material was extracted with CH_2Cl_2 (3×25 mL), dried with anhydrous Na_2SO_4, filtered and evaporated. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 4:1) to yield 0.24 g (32%) of compound **6b**, as white crystals, mp 62–63°C, $[\alpha]_D$=−50.7 (c=1.0, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$/TMS) δ: 0.9 (m, 1H), 1.0 (m, 1H), 1.1 (d, 3H), 1.8 (m, 2H), 2.2 (m, 1H), 2.6 (m, 1H), 2.8 (dd, 1H), 2.9 (dd, 1H), 3.4 (m, 2H), 4.0 (q, 1H), 7.2–7.3 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ: 17.1, 23.6, 23.8, 28.2, 40.5, 41.5, 63.0, 63.8, 81.2. 126.5, 128.0, 129.0, 139.9, 154.3, 178.5.

Mass (*m/z*): 287 (molecular ion), 243, 228, 174, 142, 118 (base peak), 91, 74, 55, 41.

I.R. (cm^{-1}) 1784.3, 1701.3.

$C_{17}H_{21}NO_3$ (287.4) calc. 71.05% C, 7.37% H; found 70.97% C, 7.40% H.

(R)-2-Benzyl-1-propanol [(R)-7]

A dry two-necked flask provided with magnetic stirrer and a dropping funnel was charged with a mixture and $LiAlH_4$ (13 mg, 0.70 mmol) in THF (5 mL) under argon. The solution was cooled to 0°C in an ice water bath before the dropwise addition of a precooled solution of **6b** (100 mg, 0.35 mmol) in THF (5 mL). The reaction mixture was stirred and allowed to warm up to rt for 3 h and quenched with a saturated solution of NH_4Cl (5 mL). Water (25 mL) was added and the organic material was extracted with CH_2Cl_2 (3×25 mL), dried with anhydrous Na_2SO_4, filtered and evaporated, to

afford (*R*)-**7** in 95% crude yield. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 6:1) to give (*R*)-**7** (0.04 g, 90%) $[\alpha]_D$=+10.9 (c=2.0, C_6H_6) [lit.[3a] $[\alpha]_D$=+11.1 (c=1.25, C_6H_6)].

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12. The ^1H and ^{13}C NMR spectra at room temperature present more signals than expected because carbamates **2a** and **2b** are present in dynamic equilibria with their rotamers.

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