



Enantioselective Synthesis of Fully Protected *anti* 3-Amino-2-Hydroxy Butyrates

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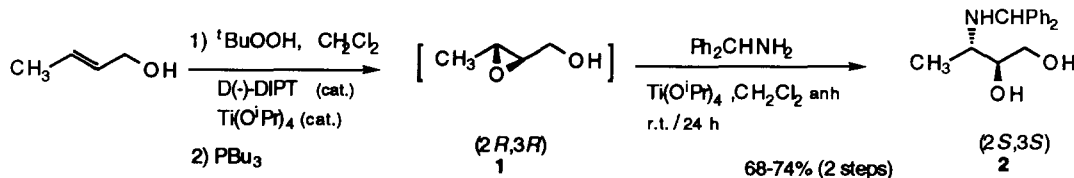
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Abstract: An efficient enantioselective synthesis of fully protected *anti* 3-amino-2-hydroxybutyrates has been developed. Starting from enantiomerically enriched *anti* *N*-diphenylmethyl-3-amino-1,2-butanediol, after a change in the nitrogen protecting group, the primary alcohol was protected by regioselective reduction of the corresponding *p*-methoxybenzylidene acetal. Formation of the oxazolidine and deprotection of the primary alcohol followed by oxidation afforded protected α -hydroxy- β -amino acids in good yield. Since the source of asymmetry is a catalytic Sharpless epoxidation, both enantiomeric series are available and the methodology developed here is expected to be of broad applicability.

Homochiral amino acids are nowadays the subject of an enormous interest. Besides the simple α - and β -amino acids, the more functionalized amino hydroxy acids have emerged as key components for a variety of protease inhibitors¹ and other new generation pharmaceuticals².

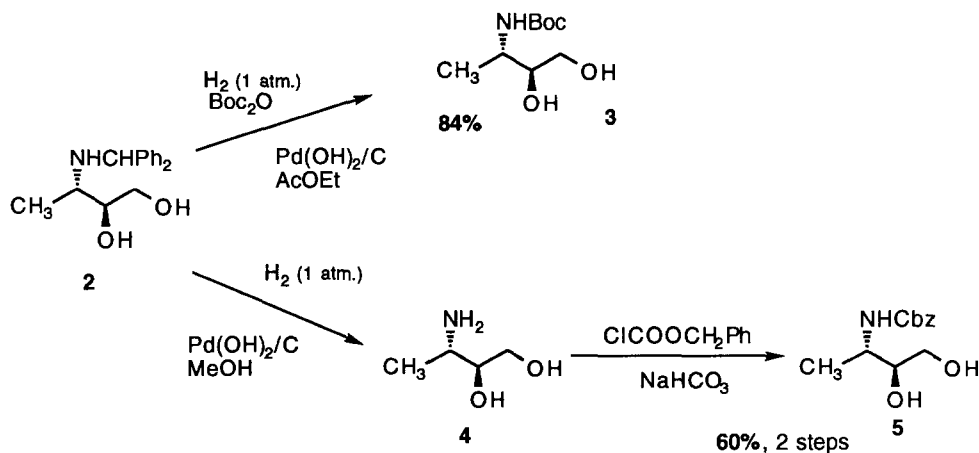
For the β -amino- α -hydroxy acids, numerous examples of interesting bioactivity are known among both the *syn* and the *anti* stereoisomers. Despite of the efforts devoted in recent years to the diastereo and enantioselective synthesis of these substances, broad scope methodologies for such purposes are still lacking. To fill this gap, we report in the present paper the synthesis of highly enantio-enriched *anti* 3-amino-2-hydroxybutyrates starting from (*E*)-crotyl alcohol and using a catalytic Sharpless epoxidation as the source of asymmetry. Given the known broad applicability of this procedure³, it can be anticipated that the methodology presented here can be readily extended to the preparation of a big variety of *anti*- α -hydroxy- β -amino acids in scalemic or homochiral form.

We have previously reported the regioselective ring opening of chiral epoxy alcohols by primary amines⁴. Application of this methodology to *in situ* generated (2*R*, 3*R*)-2-hydroxymethyl-3-methyloxirane **1** allows the preparation of multigram amounts of (2*S*, 3*S*)-3-benzhydrylamino-1,2-butanediol **2** of 92% enantiomeric excess (Scheme 1). Benzhydryl aminodiols like **2** have proved to be valuable starting materials for the preparation of α -amino acids^{5a,b}, β -amino acids^{5c}, azetidines^{5d}, aziridines^{5d} and terminal aminoalkyl epoxides^{5e}.



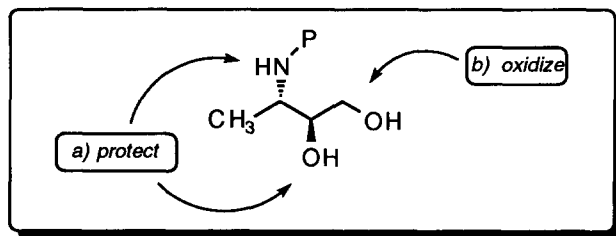
Scheme 1

The benzhydryl group in **2** serves mainly to control the regioselectivity of the ring opening process and to facilitate the purification of the product. Once these ends were secured, the benzhydryl group was changed to the more convenient *tert*-butoxycarbonyl or benzyloxycarbonyl, as depicted in Scheme 2. Hydrogenolysis of **2** in ethyl acetate in the presence of an slight excess of di-*tert*-butyl dicarbonate directly led to the *N*-Boc derivative **3** in 84% yield. The *N*-Cbz derivative **5**, in turn, was prepared by a two step procedure involving hydrogenolysis to (2*S*,3*S*)-3-amino-1,2-butanediol **4** and subsequent reaction with benzyl chloroformate in the presence of sodium hydrogen carbonate.



Scheme 2

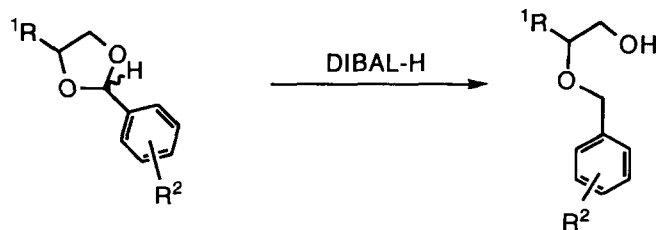
The strategy for the conversion of aminodiols **3/5** into the final amino acids was *a priori* simple: Selective protection of the secondary hydroxyl group, facilitated by the adjacent amino functionality, followed by oxidation of the primary alcohol would directly lead to the target molecules.



However, all attempts at selective and simultaneous protection of the amino group and the secondary alcohol failed completely. For instance, treatment of **3** with carbonyldiimidazole in the presence of *N*-methylmorpholine⁶ afforded exclusively the cyclic carbonate instead of the desired *N*-Boc oxazolidone. In a similar way, treatment of **5** with NaH in THF ⁷ did not induce a selective intramolecular attack of the secondary alcohol to the carbamate moiety.

The failure of the forementioned procedures led to the consideration of methodologies based on the formation of acetals on the glycol system followed by regioselective reduction. In fact, it has been reported in

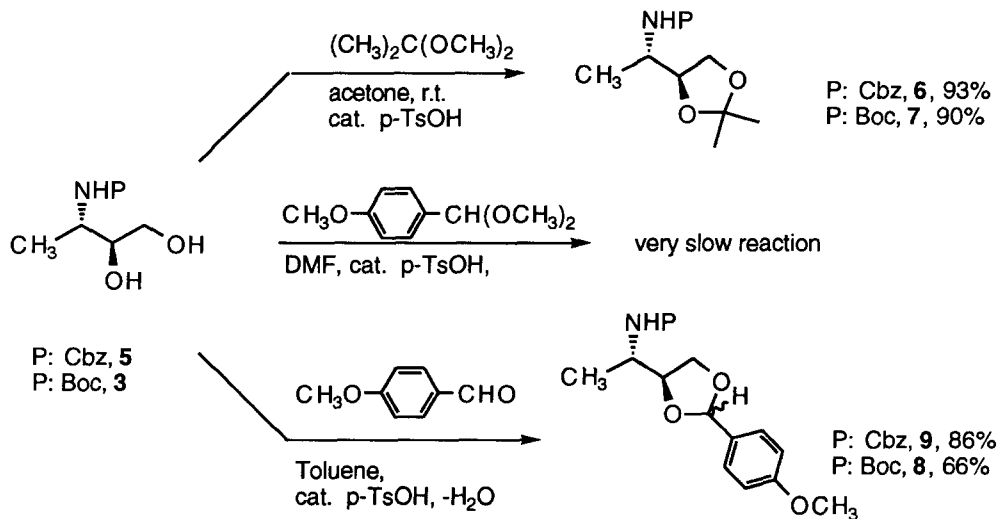
several instances the regioselective cleavage of acetals derived from aromatic aldehydes and terminal glycols⁸. The major product arising from such protocols is a 2-benzyloxy-1-alkanol, as shown in Scheme 3.



Scheme 3

Bearing in mind the convenience of an orthogonal protection Scheme, we decided to convert **3/5** into the corresponding *p*-methoxybenzaldehyde acetals; the subsequent reduction would then lead to *p*-methoxybenzyl ethers which can be readily deprotected under oxidative conditions.

In order to determine optimal reaction conditions, **3/5** were first acetylated with 2,2-dimethoxypropane in acetone, leading to the corresponding 2,2-dimethyldioxolanes **6** and **7** in very high yield. Unfortunately, the analogous reaction with *p*-methoxybenzaldehyde dimethyl acetal proceeded only sluggishly. Notwithstanding, the desired *p*-methoxybenzaldehyde acetals **8** and **9** could be finally obtained by direct acetylation in toluene at reflux using a Dean-Stark device.



Scheme 4

The reductive cleavage of **8/9** was studied under a variety of reaction conditions. Our results are summarized in Table 1.

Table 1. Reductive cleavage of aminoacetals **8** and **9**.

P: Boc, **8**
 P: Cbz, **9**,

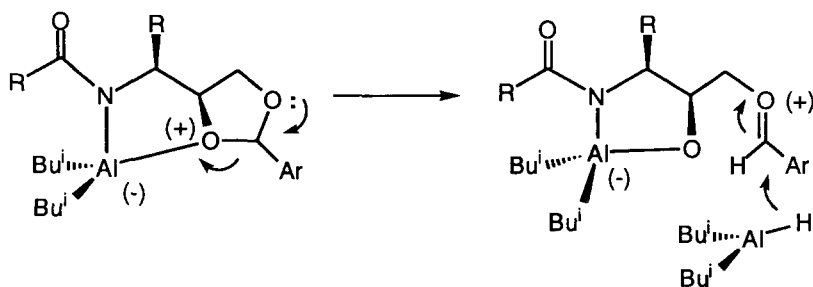
P: Boc, **10**
 P: Cbz, **12**

P: Boc, **11**
 P: Cbz, **13**

Entry	Substrate	Reducing Agent	Reaction Conditions	Yield (Conversion)	10/11 or 12/13
a	8	NaBH ₃ CN (CH ₃) ₃ SiCl	CH ₃ CN r.t., 45 min	71% (100%)	30 / 70 ^a
b	8	DIBAL-H	CH ₂ Cl ₂ -68°C, 7h	70% (63%)	<5 / >95 ^a
c	9	Et ₃ SiH TiCl ₄	CH ₂ Cl ₂ -68°C, 20 min	9% (100%) ^c	0 / 100 ^a
d	9	NaBH ₃ CN (CH ₃) ₃ SiCl	CH ₃ CN r.t., 45 min	72% (100%)	35 / 65 ^a
e	9	DIBAL-H	CH ₂ Cl ₂ 0°C, 6h	68% (100%)	16 / 84 ^b
f	9	DIBAL-H	CH ₂ Cl ₂ -68°C, 6h	68% (90%)	4 / 96 ^b

^aRatio determined by ¹H NMR. ^b Ratio determined by HPLC. ^c Major process is acetal hydrolysis

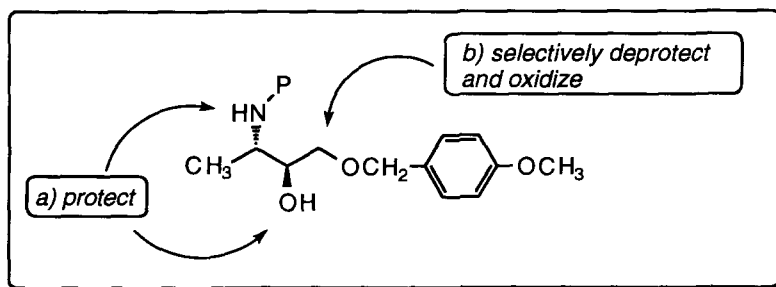
As it can be readily seen, the reductive cleavage of **8/9** can be performed with excellent regioselectivity (DIBAL-H, low temperature, entries b and f), but the major products are the secondary alcohols **11/13**, instead of the expected primary alcohols. The observed regioselectivity can be attributed to a directing effect exerted by the nitrogen of the vicinal carbamate group. A similar result has been observed by Takano^{8b} in benzylidene acetals with a vicinal alcohol or ether group.



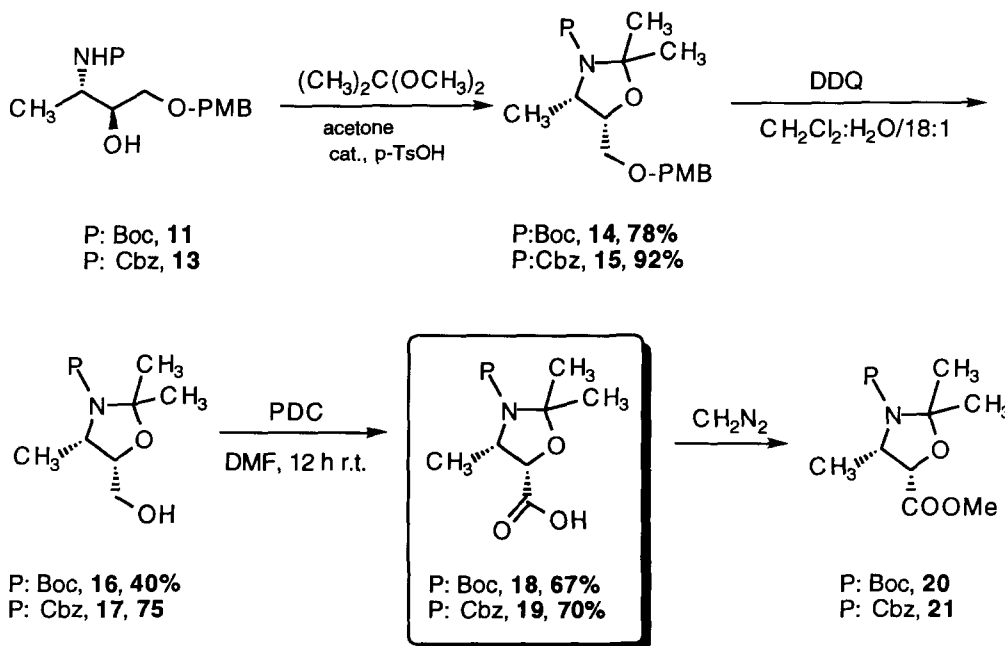
Scheme 5

Even working under reaction conditions ($\text{NaBH}_3\text{CN}/(\text{CH}_3)_3\text{SiCl}$) known to afford⁹ preferently the primary alcohol in similar cases, only a marginal increase in the **10/12** amounts was recorded.

In view of the results of the reductive cleavage, the original synthetic strategy was slightly modified: The secondary hydroxy group in **11/13** could be now easily protected and a subsequent selective cleavage of the PMB ether followed by oxidation should provide ready access to the α -hydroxy- β -amino acids.



The simultaneous protection of the N-H and OH functionalities was readily achieved by acid catalyzed treatment of **11/13** with 2,2-dimethoxypropane in acetone¹⁰ (Scheme 6). This procedure afforded 2,2-dimethyloxazolidines **14/15** in high yields.



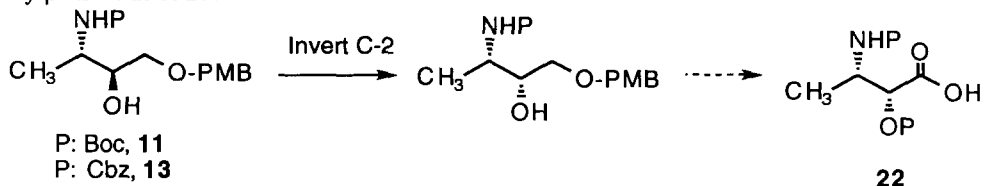
Scheme 6

Oxidative cleavage of the *p*-methoxybenzyl ethers was first studied on **15** with cerium ammonium nitrate in acetonitrile-water mixtures.¹¹ (4*S*,5*S*)-*N*-Benzyloxycarbonyl-5-hydroxymethyl-2,2,4-trimethyloxazolidine was obtained in low yield (29%) along with (2*S*,3*S*)-3-benzyloxycarbonylamino-1,2-butanediol **5** arising from oxazolidine hydrolysis. More satisfactory results were obtained when dichlorodicyanobenzoquinone was

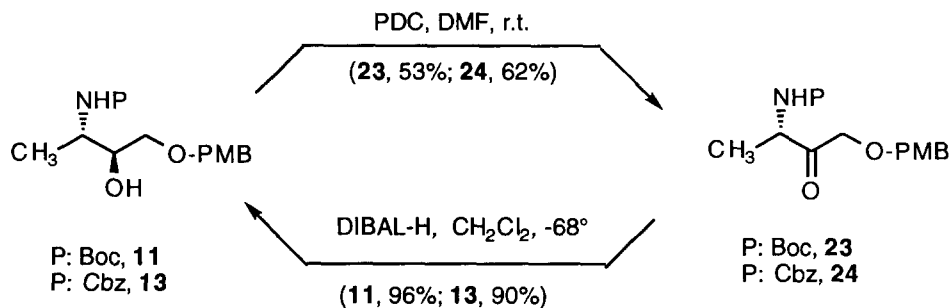
employed as the oxidant in 18:1 dichloromethane-water.¹² Under these conditions, the primary alcohols **16/17** were obtained in fair to good yield. It is to be mentioned that a concomitant partial hydrolysis of the oxazolidine moiety in **14** (or **16**) could not be completely suppressed.

Final conversion of **16/17** into the fully protected *anti*- α -hydroxy- β -amino acids **18/19** was achieved in good yield (65-70%) by oxidation with pyridinium dichromate in DMF. In order to facilitate chromatographical purification, **18/19** can be converted into the corresponding methyl esters **20/21** by treatment with diazomethane in diethyl ether.

Intermediates **11/13** were subjected to preliminary evaluation as precursors of the diastereomeric *syn*- α -hydroxy- β -amino acids **22**.



We devoted some effort to the key step in this sequence, i.e., the inversion of configuration at C2. An attempted Mitsunobu reaction on **13**, using *p*-nitrobenzoic acid as a nucleophile¹² did not proceed at all. As a less direct alternative, an oxidation/reduction sequence was also studied (Scheme 7)



Scheme 7

The oxidation of **11/13** with PDC in DMF cleanly provided (*S*)-3-alkoxycarbonylamino-1-*p*-methoxybenzyloxy-2-butanones **23/24**. The reduction of these ketones with DIBAL-H at low temperature took place with very high yields and excellent diastereoselectivities. Unfortunately, however, the observed stereoselectivity was opposite to the desired one, the process leading back to the *anti* series. Since this problematic has found a satisfactory solution in our laboratories through the use of related methodology,¹⁴ this strategy was abandoned at this point.

In summary, we have developed an asymmetric approach to fully protected *anti*-3-amino-2-hydroxybutyrates starting from (*E*)-crotyl alcohol. Since the source of asymmetry in the synthesis is a catalytic Sharpless epoxidation, both enantiomeric series are equally available at will, by merely selecting the configuration of the tartrate ester employed in the process. Moreover, given the large number of epoxy alcohols available in high enantiomeric purity from the Sharpless protocol, the methodology presented here is highly promising in terms of applicability. Work along these lines is in progress in our laboratories and will be reported in due course.

EXPERIMENTAL SECTION.

General Methods. Optical rotations were measured at room temperature on a Perkin-Elmer 141 polarimeter (Concentration in g/100 mL). Melting points were determined on a Gallenkamp apparatus and have not been corrected. Infrared spectra were recorded on a Perkin-Elmer 681, or on a Nicolet 510 FT-IR. NMR spectra were acquired on Varian XL-200 or Varian-Unity-300 instruments. ^1H -NMR were obtained at 200 or 300 MHz (s=singlet, d=doublet, t=triplet, q=quartet, dt= double triplet, m=multiplet and b=broad). ^{13}C -NMR were obtained at 50.3 MHz or 73.4 MHz. Carbon multiplicities have been assigned by distortionless enhancement by polarization transfer (DEPT) experiments. Mass spectra were recorded on a Hewlett-Packard 5890 instrument. Elemental analyses were performed on a Perkin Elmer 240 instrument. Chromatographic separations were carried out using NEt_3 pre-treated (2.5% v/v) SiO_2 (70-230 mesh) and eluting with hexanes/ethyl acetate mixtures of increasing polarity. Chromatographic analyses were performed on a Hewlett-Packard 1050 HPLC instrument equipped with Nucleosil 120 C18 (20 cm) or a Chiracel ODR (25 cm) columns.

(2S, 3S)-3-amino-1,2-butanediol 4.

To a solution of del (2S,3S)-3-benzhydrylamino-1,2-butanediol **2** (30 g 0.11 mol) in MeOH (530 mL) were added 1.9 g of Palladium hydroxide over C (20%) and the stirred mixture was hydrogenated at atmospheric pressure. The reaction was monitored by TLC. The mixture was filtered through Celite and evaporated under vacuum. The residue was washed with hexane and dried azeotropically with toluene yielding 11.6 g (quantitative yield) of **4** as an oil.

$[\alpha]_D = -5.9$ ($c=1.9$, MeOH). IR (film) $\nu_{\text{max.}}$ =3300 (b), 2980, 2920, 1600, 1465, 1450, 1380, 1080, 1030, 890 cm^{-1} . ^1H -NMR (200 MHz, CD_3OD , $\text{TMS}_{\text{int.}}$) δ =1.01 (d, $J=6.6\text{ Hz}$, 3H), 2.82 (dt, $J=13\text{ Hz}$, $J=6.6\text{ Hz}$, 1H), 3.59-3.35 (m, 3H) ppm. ^{13}C -NMR (50 MHz, CD_3OD) δ =18.0 (CH_3), 49.8 (CH), 64.7 (CH_2), 76.7 (CH) ppm.

(2S, 3S)-3-benzyloxycarbonylamino-1,2-butanediol 5.

To 2.05 g (19.52 mmol) of (2S,3S)-3-amino-1,2-butanediol **4** were added 300 mL of warm water (ca. 50°C), 4.1 g of NaHCO_3 and 3.3 mL (23.4 mmol) of benzyl chlorocarbonate. The mixture was vigorously stirred during 4 hours at room temperature and extracted thrice with methylene chloride and thrice with ethyl acetate. The combined organic layers were dried over MgSO_4 and concentrated. The crude product (3.88 g) was crystallized from ethyl ether/hexane yielding 1.85 g of (2S,3S)-3-benzyloxycarbonylamino-1,2-butanediol **5** as a white solid. The mother liquor was concentrated and purified by flash chromatography affording additional 0.9 g of **5** (total yield, 60%).

$[\alpha]_D = 2.7$ ($c=2.1$, MeOH). mp: $78-84^\circ\text{C}$. IR (KBr) $\nu_{\text{max.}}$ =3420, 3330, 2930, 1690, 1550, 1330, 1280, 1250, 1070, 1020, 700 cm^{-1} . ^1H -NMR (200 MHz, CD_3OD , $\text{TMS}_{\text{int.}}$) δ =1.15 (d, $J=6.7\text{ Hz}$, 3H), 3.4-3.6 (m, 1H), 3.54 (s, 2H), 3.6-3.8 (m, 1H), 5.06 (s, 2H), 7.30 (s, b, 5H) ppm. ^{13}C -NMR (50 MHz, CD_3OD) δ =16.0 (CH_3), 49.4 (CH), 64.5 (CH_2), 67.3 (CH_2), 75.7 (CH), 128.7 (CH), 128.9 (CH), 129.4 (CH), 138 (C), 158 (C) ppm. MS (EI) m/e =239 (M^+ , 0.05%), 208 ($\text{M}^+-\text{CH}_3\text{O}$, 0.31%), 178 ($\text{M}^+-\text{C}_2\text{H}_5\text{O}_2$, 10%), 134 (7.3%), 107 (2.5%), 105 (1.1%), 91 (C_7H_7^+ , 100%). Anal. Calcd. for $\text{C}_{12}\text{H}_{17}\text{NO}_4$: C, 60.22; H, 7.16; N, 5.86. Found: C, 59.93; H, 7.11; N, 5.80.

(2S, 3S)-3-tert-butoxycarbonylamino-1,2-butanediol 3.

A solution of (2S,3S)-3-benzhydrylamino-1,2-butanediol **2** (44.8 g, 0.16 mol) and Boc_2O (47 g, 0.21 mol, 1.3 eq.) in ethyl acetate (300 mL) was added *via* cannula to a stirred suspension of $\text{Pd}(\text{OH})_2/\text{C}$ (4.5 g) in ethyl acetate (75 mL). The mixture was hydrogenated at atmospheric pressure until no starting material could be

observed by TLC, filtered through Celite and evaporated. The crude oil was crystallized from ethyl ether/hexane. 24.1 g of (2*S*,3*S*)-3-*tert*-butoxycarbonylamino-1,2-butanediol were obtained in two crops as a white solid. The mother liquor was concentrated and purified by flash chromatography affording additional 4.2 g (total yield, 84%).

$[\alpha]_D = -5.8$ ($c=1$, CHCl₃), mp: 74–75°C. IR (KBr) $\nu_{\max} = 3400$ (b), 3360, 2970, 2940, 1680, 1530, 1370, 1320, 1250, 1170, 1050, 630 cm⁻¹. ¹H-NMR (200 MHz, CDCl₃, TMS_{int.}) $\delta = 1.24$ (d, $J=6.7$ Hz, 3H), 1.44 (s, 9H), 3.03 (b, 2H, hydroxyls), 3.3 (m, 1H), 3.64 (m, 3H), 4.7 (m, 1H) ppm. ¹³C-NMR (50 MHz, CDCl₃) $\delta = 16.8$ (CH₃), 28.3 (CH₃), 47.9 (CH), 63.2 (CH₂), 75.3 (CH), 80.0 (C), 156.5 (C) ppm. MS (EI) $m/e = 205$ (M⁺, 0.09%), 144 (M⁺-C₂H₅O₂, 35%), 132 (M⁺-^tBu, 12%), 88 (C₄H₉O₂⁺, 37%), 57 (^tBu⁺, 100%). Anal. Calcd. for C₉H₁₉NO₄: C, 52.65; H, 9.13; N, 6.82. Found: C, 52.58; H, 9.43; N, 6.72.

(2*S*, 3*S*)-1,2-*p*-methoxybenzyliden-3-benzyloxycarbonylamino-1,2-butanediol 9.

A solution of (2*S*,3*S*)-3-benzyloxycarbonylamino-1,2-butanediol **5** (3.79 g, 15.8 mmol), *p*-methoxybenzaldehyde (3.2 g, 24 mmol) and 30 mg of *p*-toluenesulfonic acid in toluene (150 ml) was refluxed in a Dean-Stark apparatus. The reaction was monitored by TLC. After 17 hours, the solution was washed with 10% NaOH, and the organic layer extracted with dichloromethane. The combined organic phases were dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by flash chromatography yielding 4.8 g of **9** (86% yield) as a white solid. The product is a 1:2.5 mixture of diastereomers A and B, epimers in the acetalic carbon.

IR (KBr) $\nu_{\max} = 3300$, 1680, 1615, 1550, 1515, 1300, 1250, 1070, 1030 cm⁻¹. ¹H-NMR (200 MHz, CDCl₃, TMS_{int.}) (A: major diastereomer, B: minor diastereomer) $\delta = 1.19$ γ 1.26 (2d, A $J=6.9$ Hz, B $J=7.2$ Hz, 3H), 3.77 (s, 3H), 3.8–4.2 (m, 4H), 5.10 (s, 2H), 5.1–5.3 (m, 1H), 5.69 (A, s, 1H), 5.9 (B, s, 1H), 6.88 (d, $J=8.4$, 2H), 7.40 (d, $J=8.4$, 2H), 7.33 (s, b, 5H) ppm.

¹³C-NMR (50 MHz, CDCl₃) (A: major diastereomer, B: minor diastereomer) $\delta = 15.6$ (A, CH₃), 16.6 (B, CH₃), 49.0 (CH), 55.2 (CH₃), 66.6 (CH₂), 67.4 (CH₂), 67.8 (CH₂), 78.6 (A, CH), 78.9 (B, CH), 104.1 (B, CH), 104.2 (A, CH), 113.7 (CH), 127.7 (CH), 128.0 (CH), 128.4 (CH), 130 (C), 138 (C), 154 (C), 160 (C) ppm. MS (EI) $m/e = 357$ (M⁺, 0.25%), 266 (M⁺-C₇H₇, 1.5%), 179 (C₁₀H₁₁O₃⁺, 30%), 178 (M⁺-C₁₀H₁₁O₃, 2.6%), 135 (C₈H₇O₂⁺, 26%), 121 (C₈H₉O⁺, 32%), 108 (8%), 91 (C₇H₇⁺, 100%). Anal. Calcd. for C₂₀H₂₃NO₅: C, 67.20; H, 6.49; N, 3.92. Found: C, 67.30; H, 6.49, N, 3.86.

(2*S*, 3*S*)-1,2-*p*-methoxybenzyliden-3-*tert*-butoxycarbonylamino-1,2-butanediol 8.

A solution of (2*S*,3*S*)-3-*tert*-butoxycarbonylamino-1,2-butanediol **3** (3.7 g, 18 mmol), *p*-methoxybenzaldehyde (3.7 g, 27 mmol) and 30 mg of *p*-toluenesulfonic acid in toluene (150 ml) was refluxed in a Dean-Stark apparatus. The reaction was monitored by TLC. After 28 hours, the solution was washed with 10% NaOH, and the organic layer extracted with dichloromethane. The combined organic phases were dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by flash chromatography yielding 3.9 g of **8** (66% yield) as a white solid. The product is a 1:1.5 mixture of diastereomers A and B, epimers in the acetalic carbon.

IR (KBr) $\nu_{\max} = 3480$, 2980, 2940, 1695, 1620, 1530, 1255, 1175, 1070, 1035 cm⁻¹. ¹H-NMR (200 MHz, CDCl₃, TMS_{int.}) (A: major diastereomer, B: minor diastereomer) $\delta = 1.22$ (d d, A γ B, $J=7.5$ Hz, $J=6.9$ Hz, 3H), 1.44 (s, 9H), 3.81 (s, 3H), 3.9–4.1 (s, 2H), 4.1–4.3 (m, 2H), 4.6–4.8 (m, 1H), 5.72 (A, s, 1H), 5.9 (B, s, 1H), 6.90 (d, $J=8.5$, 2H), 7.42 (d, $J=8.7$, 2H) ppm. ¹³C-NMR (50 MHz, CDCl₃) (A: major diastereomer, B: minor diastereomer) $\delta = 15.7$ (A, CH₃), 16.8 (B, CH₃), 28.3 (CH₃), 48.3 (CH), 55.2 (CH₃), 67.5 (A, CH₂), 67.8 (B, CH₂), 78.8 (A, CH), 79.3 (B, CH), 104.2 (B, CH), 104.3 (A, CH), 113.7 (CH), 127.7 (B, CH),

128.1 (A, CH), 129 (C), 130 (C), 132 (C), 155 (C), 160 (C) ppm. MS (EI) $m/e=323$ (M^+ , 0.64%), 179 ($C_{10}H_{11}O_3^+$, 67%), 144 ($M^+-C_{10}H_{11}O_3$, 25%), 135 (98%), 121 ($C_8H_9O^+$, 100%), 88 (32%). Anal. Calcd. for $C_{17}H_{25}NO_5$: C, 63.12; H, 7.80; N, 4.33. Found: C, 63.08; H, 7.82; N, 4.35.

Reduction of (2*S*, 3*S*)-1,2-*p*-methoxybenzyliden-3-benzyloxycarbonylamino-1,2-butanediol 9.

To a solution of (2*S*, 3*S*)-1,2-*p*-methoxybenzyliden-3-benzyloxycarbonylamino-1,2-butanediol **9** (0.22 g, 0.62 mmol) in CH_2Cl_2 (4.5 mL) at $-68^\circ C$, was added DIBAL-H (3.2 mL, 3.2 mmol, 20% in hexanes). The reaction was monitored by TLC. After 6 hours, methanol (1.5 mL) was added, the solution was washed with 10% NaOH, and the organic layer extracted with diethyl ether. The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography yielding 0.14 g of **13** (68% yield, >95% regioselectivity) as a white solid, along with 20 mg of starting material (90% conversion).

$[\alpha]_D=-2.2$ ($c=1.8$, $CHCl_3$). Mp: $89-92^\circ C$. IR (KBr) $\nu_{max}=3430, 3330, 2920, 1695, 1615, 1525, 1515, 1465, 1350, 1250, 1110, 1040, 1015\text{ cm}^{-1}$. 1H -NMR (200 MHz, $CDCl_3$, $TMS_{int.}$) $\delta=1.13$ (d, $J=6.6$ Hz, 3H), 2.4-2.6 (m, b, 1H), 3.4-3.6 (m, 3H), 3.7-3.9 (m, 1H), 3.80 (s, 3H), 4.46 (s, 2H), 5.09 (s, 2H), 5.1-5.3 (m, 1H), 6.87 (d, $J=8.7$, 2H), 7.24 (d, $J=8.4$, 2H), 7.35 (s, b, 5H) ppm. ^{13}C -NMR (50 MHz, $CDCl_3$) $\delta=15.7$ (CH_3), 48.1 (CH), 55.2 (CH_3), 66.6 (CH_2), 71.2 (CH_2), 72.3 (CH), 73.1 (CH_2), 113.8 (CH), 128.0 (CH), 128.4 (CH), 129.3 (CH), 129.6 (C), 138 (C), 156.0 (C), 160 (C) ppm. MS (EI) $m/e=359$ (M^+ , 0.03%), 268 ($M^+-C_7H_7$, 0.45%), 178 ($M^+-C_{10}H_{13}O_3$, 1.7%), 132 (28%), 121 ($C_8H_9O^+$, 67%), 91 ($C_7H_7^+$, 100%). Anal. Calcd. for $C_{20}H_{25}NO_5$: C, 66.82; H, 7.01; N, 3.90. Found: C, 66.74; H, 7.01; N, 3.84.

Reduction of (2*S*, 3*S*)-1,2-*p*-methoxybenzyliden-3-*tert*-butoxycarbonylamino-1,2-butanediol 8.

To a solution of (2*S*, 3*S*)-1,2-*p*-methoxybenzyliden-3-*tert*-butoxycarbonylamino-1,2-butanediol **8** (240 mg, 0.75 mmol) in dichloromethane (5 mL) at $-60^\circ C$, was added DIBAL-H (1.9 mL, 1.9 mmol, 20% in hexanes). The reaction was monitored by TLC. After 7 hours, methanol (1.5 mL) was added, the solution was washed with 10% NaOH, and the organic layer extracted with diethyl ether. The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography yielding 0.11 g of **11** (70% yield, >95% regioselectivity) as an oil, along with 90 mg of starting material (63% conversion).

$[\alpha]_D=-9$ ($c=3.9$, $CHCl_3$). IR (film) $\nu_{max}=3400$ (b), 2970, 2920, 1720, 1700, 1685, 1610, 1510, 1365, 1250, 1170, 1080, 1035 cm^{-1} . 1H -NMR (200 MHz, $CDCl_3$, $TMS_{int.}$) $\delta=1.08$ (d, $J=6.6$ Hz, 3H), 1.42 (s, 9H), 2.9-3.0 (s, b, 1H), 3.4-3.6 (m, 3H), 3.7-3.8 (m, 1H), 3.78 (s, 3H), 4.45 (s, 2H), 5-5.1 (m, 1H), 6.86 (d, $J=8.6$ Hz, 2H), 7.23 (d, $J=8.6$ Hz, 2H) ppm. ^{13}C -NMR (50 MHz, $CDCl_3$) $\delta=15.7$ (CH_3), 28.3 (CH_3), 48.5 (CH), 55.1 (CH_3), 71.4 (CH_2), 72.6 (CH), 73.0 (CH_2), 79.2 (C), 113.7 (CH), 129.3 (CH), 129.8 (C), 155.6 (C), 159.2 (C) ppm. MS (EI) $m/e=325$ (M^+ , 0.17%), 269 ($M^+-C_4H_9$, 2.3%), 144 ($M^+-C_{10}H_{13}O_3$, 3.6%), 138 (17%), 132 (19%), 121 ($C_8H_9O^+$, 100%), 91 ($C_7H_7^+$, 6.3%), 88 (18%).

(4*S*, 5*S*)-*N*-benzyloxycarbonyl-5-(4-methoxybenzyloxymethyl)-2,2,4-trimethyloxazolidine (15).

To a solution of (2*S*, 3*S*)-1-*p*-methoxybenzyloxy-3-benzyloxycarbonylamino-2-butanol **13** (0.28 g, 0.78 mmol), in acetone (9 mL) were added acetone dimethyl acetal (0.29 mL 2.3 mmol) and *p*-toluenesulfonic acid (catalytic amounts). The reaction was monitored by TLC. After 15 hours, the solution was washed with 10%

NaOH, and the organic layer extracted with dichloromethane. The combined organic phases were dried over MgSO_4 and concentrated *in vacuo*. The residue (0.4 g) was purified by flash chromatography yielding 0.3 g of **15** (92% yield) as an oil.

$[\alpha]_D = -16$ ($c=2.0$, CDCl_3). IR (film) $\nu_{\text{max.}}=2930, 2980, 2880, 1700, 1610, 1510, 1400, 1350, 1250, 1100, 1065, 1030 \text{ cm}^{-1}$. $^1\text{H-NMR}$ (200 MHz, CDCl_3 , $\text{TMS}_{\text{int.}}$) $\delta=1.10$ (d, $J=6.5$ Hz, 3H), 1.58 (s, 3H), 1.66 (s, 3H), 3.4-3.7 (m, 2H), 3.80 (s, 3H), 4.0-4.2 (m, 1H), 4.2-4.4 (q, 1H), 4.43 (d, 1H), 4.51 (d, 1H), 5.13 (s, 2H), 6.81 (d, $J=8.4$ Hz, 2H), 7.27 (d, $J=8.5$ Hz, 2H), 7.35 (s, b, 5H) ppm. $^{13}\text{C-NMR}$ (50 MHz, CDCl_3) Major rotamer $\delta=14.6$ (CH_3), 23.8 (CH_3), 27.9 (CH_3), 54.4 (CH), 55.2 (CH_3), 66.4 (CH_2), 67.7 (CH_2), 73.3 (CH_2), 75.2 (CH), 94 (C), 113.8 (CH), 127.8 (CH), 128.0 (CH), 128.5 (CH), 129.5 (CH), 137 (C), 152 (C), 159 (C) ppm. Minor rotamer $\delta=13.8$ (CH_3), 25.1 (CH_3), 28.2 (CH_3), 67.0 (CH_2), 67.8 (CH_2), 75.0 (CH) ppm. MS (EI) $m/e=399$ (M^+ , 0.21%), 384 (M^+-CH_3 , 0.75%), 340 ($\text{M}^+-\text{C}_3\text{H}_7\text{O}$, 2.4%), 222 ($\text{C}_{13}\text{H}_{18}\text{O}_3$, 4%), 136 (5.1%), 121 ($\text{C}_8\text{H}_9\text{O}^+$, 41%), 91 (C_7H_7^+ , 100%).

(4S, 5S)-N-tert-butoxycarbonyl-5-(4-methoxybenzyloxymethyl)-2,2,4-trimethyloxazolidine 14.

To a solution of (2S,3S)-1-*p*-methoxybenzyloxy-3-*tert*-butoxycarbonylamino-2-butanol (**11**) (0.10 g, 0.35 mmol), in acetone (5 mL) were added acetone dimethyl acetal (0.17 mL 1.4 mmol) and *p*-toluenesulfonic acid (catalytic amounts). The reaction was monitored by TLC. After 18 hours, the solution was washed with 10% NaOH, and the organic layer extracted with dichloromethane. The combined organic phases were dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography yielding 0.10 g of **14** (78% yield) as an oil.

$[\alpha]_D = -15.3$ ($c=2.8$, CHCl_3). IR (film) $\nu_{\text{max.}}=2980, 2940, 2880, 1695, 1615, 1515, 1465, 1455, 1390, 1370, 1305, 1250, 1175, 1100, 1070, 1035, 870, 850, 820 \text{ cm}^{-1}$. $^1\text{H-NMR}$ (200 MHz, CDCl_3 , $\text{TMS}_{\text{int.}}$) Major rotamer $\delta=1.05$ (d, b, $J=6.2$ Hz, 3H), 1.44 (s, 9H), 1.52 (s, 3H), 1.60 (s, 3H), 3.4-3.7 (m, 2H), 3.79 (s, 3H), 3.8-4.1 (m, 1H), 4.2 (q, 1H), 4.4 (d, 1H), 4.6 (d, 1H), 6.87 (d, $J=8.7$, 2H), 7.25 (d, $J=8.5$, 2H) ppm. Minor rotamer $\delta=1.47$ (s, 9H), 1.49 (s, 3H), 1.56 (s, 3H) ppm. $^{13}\text{C-NMR}$ (50 MHz, CDCl_3) Major rotamer $\delta=14.3$ (CH_3), 23.8 (CH_3), 28.1 (CH_3), 28.4 (CH_3), 54.4 (CH), 55.1 (CH_3), 67.7 (CH_2), 73.2 (CH_2), 74.8 (CH), 79.2 (C), 94 (C), 113.7 (CH), 129.5 (CH), 129.7 (C), 151.4 (C), 159.2 (C) ppm. Minor rotamer $\delta=13.7$ (CH_3), 24.91 (CH_3), 28.2 (CH_3), 67.8 (CH_2), 79.3 (C), 93 (C), 129.4 (CH), 151.6 (C) ppm. MS (EI) $m/e=365$ (M^+ , 0.43%), 350 (M^+-CH_3 , 0.33%), 250 ($\text{M}^+-\text{C}_5\text{H}_9\text{NO}_2$, 5.2%), 136 (5.6%), 121 ($\text{C}_8\text{H}_9\text{O}^+$, 100%), 115 ($\text{C}_5\text{H}_9\text{NO}_2^+$, 5.8%), 91 (C_7H_7^+ , 3.7%).

(4S, 5S)-N-benzyloxycarbonyl-5-hydroxymethyl-2,2,4-trimethyloxazolidine 17.

To a solution of oxazolidine **15** (0.15 g, 0.37 mmol) in dichloromethane (15 mL) were added H_2O (0.8 mL) and 2,3-dichloro-5,6-dicyanoquinone (DDQ) (0.1 g, 0.45 mmol). The reaction was stirred at room temperature, until no starting material could be detected by TLC (2 hours). The mixture was filtered and the residue washed with dichloromethane. The combined organic phases were dried over MgSO_4 and the solvents evaporated *in vacuo* yielding 0.17 g of an oil that was purified by chromatography. Oxazolidine **17** was obtained (79 mg, 76% yield) as an oil along with (2S,3S)-1,2-propyliden-3-benzyloxycarbonylamino-1,2-butanediol **7** (9 mg).

$[\alpha]_D = -3.6$ ($c=2.3$, CHCl_3). IR (film) $\nu_{\text{max.}}=3440$ (b), 2980, 2930, 1705, 1690, 1410, 1355, 1110, 1070-1050, 1020 cm^{-1} . $^1\text{H-NMR}$ (200 MHz, CDCl_3 , $\text{TMS}_{\text{int.}}$) $\delta=1.11$ (d, b, $J=6.6$ Hz, 3H), 1.56 (s, 3H), 1.64 (s, 3H), 2.3-2.5 (m, b, 1H), 3.6-3.9 (m, 2H), 4.0-4.1 (m, 2H), 4.15-4.25 (m, 1H), 5.12 (s, 2H), 7.35 (s, b, 5H)

ppm. ^{13}C -NMR (50 MHz, CDCl_3) Major rotamer δ =15.1 (CH_3), 24.0 (CH_3), 27.4 (CH_3), 54.4 (CH), 61.3 (CH_2), 66.8 (CH_2), 77.2 (CH), 94.0 (C), 128.1 (CH), 128.3 (CH), 128.8 (CH), 138 (C), 151 (C) ppm. Minor rotamer δ =14.2 (CH_3), 25.3 (CH_3), 28.1 (CH_3), 67.3 (CH_2), 54.8 (CH), 77.3 (CH), 93.5 (C) ppm. MS (EI) m/e =279 (M^+ , 0.04%), 264 (M^+-CH_3 , 8.0%), 220 ($\text{M}^+-\text{C}_3\text{H}_7\text{O}$, 3.3%), 111 (5.6%), 91 (C_7H_7^+ , 100%).

(4S, 5S)-N-tert-butoxycarbonyl-5-hydroxymethyl-2,2,4-trimethyloxazolidine 16.

To a solution of oxazolidine **14** (0.42 g, 1.14 mmol) in dichloromethane (17 mL) were added H_2O (1 mL) and 2,3-dichloro-5,6-dicyanoquinone (DDQ) (0.29 g, 1.25 mmol). The reaction was stirred at room temperature, until no starting product could be detected by TLC (3.5 hours). The mixture was filtered and the residue washed with dichloromethane. The combined organic phases were dried over MgSO_4 and the solvents evaporated *in vacuo* yielding an oil that was purified by chromatography. Oxazolidine **16** was obtained (30 mg, 40% yield) as an oil along with small amounts of (2S,3S)-1,2-propyliden-3-tert-butoxycarbonylamino-1,2-butanediol **7** and (2S,3S)-1,2-*p*-methoxybenzyliden-3-tert-butoxycarbonylamino-1,2-butanediol **8**.

$[\alpha]_D$ =-1.2 (c =2.1, CHCl_3). IR (film) ν_{max} =3450 (b), 2980, 2940, 1700, 1390, 1380, 1255, 1180, 1120, 1075, 1050 cm^{-1} . ^1H -NMR (200 MHz, CDCl_3 , TMS_{int}) δ =1.11 (d, J =6.3 Hz, 3H), 1.47 (s, 9H), 1.52 (s, b, 3H), 1.61 (s, b, 3H), 2.4-2.6 (m, b 1H) 3.6-3.9 (m, 2H), 3.9-4.1 (m, 1H), 4.1-4.2 (m, b, 1H) ppm. ^{13}C -NMR (50 MHz, CDCl_3) Major rotamer δ =14.7 (CH_3), 23.8 (CH_3), 27.3 (CH_3), 28.4 (CH_3), 54.2 (CH), 61.2 (CH_2), 76.6 (CH) ppm. Minor rotamer δ =14.0 (CH_3), 24.9 (CH_3) ppm.

(3S, 5S)-N-benzyloxycarbonyl-2,2,4-trimethyloxazolidin-5-carboxylic acid 19.

To a stirred solution of pyridinium dichromate (1.1 g, 3.6 mmol) in DMF (2.3 mL) was added (4S,5S)-N-benzyloxycarbonyl-5-hydroxymethyl-2,2,4-trimethyloxazolidine **17** (0.2 g, 0.7 mmols). The reaction was monitored by TLC. When no starting material could be detected, NaHCO_3 saturated aqueous solution (25 mL) and hexanes (25 mL) were added to the reaction. The organic layer was separated. The aqueous phase was washed with ether, carefully acidified with concentrated hydrochloric acid and extracted with ether. The combined ethereal phases were dried over MgSO_4 and concentrated, yielding 0.14 g of (3S,5S)-N-benzyloxycarbonyl-2,2,4-trimethyloxazolidin-5-carboxylic acid as a white solid (70% yield). The product can be purified by crystallization from dichloromethane/hexane mixtures.

$[\alpha]_D$ =-18.4 (c =1.2, CHCl_3). Mp: 105-110°C. IR (KBr) ν_{max} =3000 (b), 1735, 1650, 1440, 1360, 1255, 1240, 1220, 1135, 1110, 1085, 875, 765, 695, 655 cm^{-1} . ^1H -NMR (200 MHz, CDCl_3 , TMS_{int}) δ =1.23 (d, b, J =5.8 Hz, 3H), 1.58 (s, b, 3H), 1.73 (s, b, 3H), 4.3-4.5 (m, 1H), 4.72 (d, J =5.9, 1H), 5.15 (s, 2H), 7.36 (s, b, 5H), 7.5-7.8 (m, b, 1H) ppm. ^{13}C -NMR (50 MHz, CDCl_3) Major rotamer δ =15.7 (CH_3), 23.9 (CH_3), 27.1 (CH_3), 54.0 (CH), 66.9 (CH_2), 75.5 (CH), 95 (C), 127.9 (CH), 128.2 (CH), 128.6 (CH), 171.6 (C) ppm. Minor rotamer δ =14.8 (CH_3), 25.1 (CH_3), 28.0 (CH_3), 54.8 (CH), 67.4 (CH_2), 75.3 (CH) ppm. MS (EI) m/e =239 (M^+ , 1%), 278 (M^+-CH_3 , 100%), 234 ($\text{M}^+-\text{C}_3\text{H}_7\text{O}$, 54%).

Anal. Calcd. for $\text{C}_{15}\text{H}_{19}\text{NO}_5$: C, 61.41; H, 6.53; N, 4.78;. Found: C, 61.02; H, 6.52; N, 4.79.

Methyl (3S, 5S)-N-benzyloxycarbonyl-2,2,4-trimethyloxazolidin-5-carboxylate 21.

A solution of diazomethane in ethyl ether was added dropwise to a solution of acid **19** (20 mg) in ether until the yellow color of the diazomethane solution was maintained during several minutes. The solution was then concentrated *in vacuo* and purified by chromatography yielding 15 mg of **21** (71% yield).

^1H -NMR (200 MHz, CDCl_3 , TMS_{int}) δ =1.15 (d, b, J =5.9 Hz, 3H), 1.58 (s, b, 3H), 1.73 (s, b, 3H), 3.80 (s, 3H), 4.3-4.5 (m, 1H), 4.68 (d, J =5.5Hz, 1H), 5.13 (s, 2H), 7.36 (s, b, 5H) ppm.

(3*S*, 5*S*)-*N*-*tert*-butoxycarbonyl-2,2,4-trimethyloxazolidin-5-carboxylic acid 18.

To a stirred solution of pyridinium dichromate (1.3 g, 4.3 mmol) in DMF (3 mL) was added (4*S*,5*S*)-*N*-*tert*-butoxycarbonyl-5-hydroxymethyl-2,2,4-trimethyloxazolidine **16** (0.21 g, 0.86 mmol). The reaction was monitored by TLC. When no starting material could be detected, NaHCO₃ saturated aqueous solution (25 mL) and hexanes (25 mL) were added to the reaction. The organic layer was separated. The aqueous phase was washed with ether, carefully acidified with concentrated hydrochloric acid and extracted with ether. The combined ethereal phases were dried over MgSO₄ and concentrated, yielding 0.15 g of (3*S*,5*S*)-*N*-*tert*-butoxycarbonyl-2,2,4-trimethyloxazolidin-5-carboxylic acid as an oil (67% yield).

[α]_D=-22.5 (*c*=1.4, CHCl₃). IR (film) ν_{max} =3150 (b), 2980, 2930, 1765, 1740, 1700, 1455, 1380, 1370, 1300, 1255, 1220, 1175, 1150, 1130, 1110, 1080, 1045, 1020, 875 cm⁻¹. ¹H-NMR (200 MHz, CD₃Cl, TMS_{int.}) δ =1.21 (dd (rotamers), *J*=6.2 Hz, *J*=6.1 Hz, 3H), 1.46 (s, 9H), 1.53 (s, 3H), 1.67 (s, 3H), 4.1-4.4 (m, 1H), 4.68 (d, *J*=5.8, 1H), 8.7-9.0 (m, b, 1H) ppm. ¹³C-NMR (50 MHz, CDCl₃) Major rotamer δ =15.5 (CH₃), 23.9 (CH₃), 27.2 (CH₃), 28.4 (CH₃), 54.2 (CH), 75.3 (CH), 80.3 (C), 94.7 (C), 171.8 (C) ppm. Minor rotamer δ =14.8 (CH₃), 25.0 (CH₃) ppm.

MS (EI) *m/e*: 244(M⁺-CH₃, 30%), 188 (M⁺-CH₃-C₄H₈, 100%), 144 (M⁺-CH₃-C₄H₈-CO₂, 78%)

Methyl (3*S*, 5*S*)-*N*-*tert*-butoxycarbonyl-2,2,4-trimethyloxazolidin-5-carboxylate 20 .

A solution of diazomethane in ethyl ether was added dropwise to a solution of acid **18** (50 mg) in ether until the yellow color of the diazomethane solution is maintained during several minutes. The solution was then concentrated *in vacuo* and purified by chromatography yielding 35 mg of **20** (67% yield). ¹H-NMR (200 MHz, CD₃Cl, TMS_{int.}) δ =1.14 (d, b, *J*=5.9 Hz, 3H), 1.48 (s, 9H), 1.53 (s, 3H), 1.68 (s, 3H), 3.81 (s, 3H), 4.1-4.4 (m, 1H), 4.65 (d, 1H) ppm.

(3*S*)-1-*p*-methoxybenzyloxy-3-benzyloxycarbonylamino-2-butanone 24.

To a stirred solution of pyridinium dichromate (0.36 g, 1.2 mmol) in DMF (0.7 mL) was added (2*S*,3*S*)-1-*p*-methoxybenzyloxy-3-benzyloxycarbonylamino-2-butanol **13** (85 mg, 0.23 mmols). The reaction was monitored by TLC. When no starting material could be detected, water (7 mL) and ether (7 mL) were added to the reaction. The organic layer was separated and the aqueous phase was extracted with ether. The combined ethereal phases were dried over MgSO₄ and concentrated, yielding an oil that was purified by chromatography yielding 53 mg of (3*S*)-1-*p*-methoxybenzyloxy-3-benzyloxycarbonylamino-2-butanone as an oil (62% yield).

IR (film) ν_{max} =3350, 2950, 1730, 1715, 1620, 1520, 1460, 1255, 1070, 1035, 615 cm⁻¹. ¹H-RMN (200 MHz, CD₃Cl, TMS_{int.}) δ =1.33 (d, *J*=7.1 Hz, 3H), 3.80 (s, 3H), 4.16 (s, b, 2H), 4.52 (d, *J*=3.5 Hz, 2H), 4.4-4.7 (m, 1H), 5.09 (s, 2H), 5.5-5.6 (m, 1H), 6.88 (d, *J*=8.7 Hz, 2H), 7.27 (d, *J*=8.7 Hz, 2H), 7.34 (s, ample, 5H) ppm.

¹³C-RMN (50 MHz, CD₃Cl) δ =17.8 (CH₃), 52.8 (CH), 55.2 (CH₃), 66.8 (CH₂), 72.4 (CH₂), 73.1 (CH₂), 113.9 (CH), 128.0 (CH), 128.1 (CH), 128.4 (CH), 128.7 (CH), 129.6 (CH), 138 (C), 156 (C), 160 (C), 207 (C) ppm.

(3*S*)-1-*p*-methoxybenzyloxy-3-*tert*-butoxycarbonylamino-2-butanone 23.

To a stirred solution of pyridinium dichromate (0.49 g, 1.6 mmol) in DMF (1 mL) was added (2*S*,3*S*)-1-*p*-methoxybenzyloxy-3-*tert*-butoxycarbonylamino-2-butanol **11** (0.11 g, 0.32 mmol). The reaction was monitored by TLC. When no starting material could be detected, water (7 mL) and ether (7 mL) were added to the reaction. The organic layer was separated and the aqueous phase was extracted with ether. The combined ethereal

phases were dried over MgSO_4 and concentrated, yielding an oil that was purified by chromatography yielding 56 mg of (3*S*)-1-*p*-methoxybenzyloxy-3-*tert*-butoxycarbonylamino-2-butanone as an oil (53% yield).

IR (film) ν_{max} =3350, 2970, 2930, 1720, 1705, 1615, 1510, 1370, 1250, 1170, 1065, 1035 cm^{-1} . ^1H -RMN (200 MHz, CD_3Cl , TMS_{int}) δ =1.31 (d, J =7.1 Hz, 3H), 1.43 (s, 9H), 3.81 (s, 3H), 4.18 (s, ample, 2H), 4.53 (d=3.2 Hz, 2H), 4.4-4.6 (m, 1H), 5.2-5.3 (m, 1H), 6.89 (d, J =8.7 Hz, 2H), 7.28 (d, J =8.7 Hz, 2H) ppm. ^{13}C -RMN (50 MHz, CD_3Cl) δ =17.7 (CH_3), 28.2 (CH_3), 52.4 (CH), 55.2 (CH_3), 72.4 (CH_2), 73.0 (CH_2), 80 (C), 113.8 (CH), 129.6 (CH), 155.0 (C), 159.3 (C), 159.4 (C), 207.7 (C) ppm.

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