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Stereoselective Synthesis of (1*R*,2*S*)-2-Amino-1,3-diols from (*R*)-Cyanohydrins[#,1]

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Abstract: Vinyl substituted (1*R*,2*S*)-amino alcohols **5** were obtained by addition of vinyl magnesium bromide to the corresponding cyanohydrin *O*-trimethylsilyl ethers (*R*)-**2**. The *O*- and *N*-protected vinyl amino alcohols **6** were ozonized at -78°C in methanol yielding (1*R*,2*S*)-2-amino-1,3-diols **7** in high enantiomeric and diastereomeric excesses. For purification, compounds **7** in some cases were acetylated to give the derivatives (1*R*,2*S*)-**8**. Racemic **6a** was converted by oxidative ozonolysis at -78°C in methanolic NaOH solution to the corresponding methyl *N*-acetyl-β-hydroxy propanoate **9a**. The configuration of (1*R*,2*S*)-**8a** was confirmed by x-ray crystallographic analysis.

(1*R*,2*S*)- and (1*S*,2*R*)-2-amino alcohols are accessible in high diastereomeric excesses by addition of Grignard reagents to *O*-protected (*R*)- or (*S*)-cyanohydrins and subsequent hydrogenation.[3] Only alkyl and aryl magnesium halides have been used until now as organometallic compounds in this reaction.[3,4]
By this route, the preparation of 2-amino-1,3-diols or β-hydroxy-α-amino acids, with defined sterical configurations, should also be possible by using the appropriate organometallic compounds.
(1*R*,2*S*)-2-Amino-1,3-diols are components of sphingosines and dihydrosphingosines;[5] they are also main structural elements of chloramphenicols,[6] representing important broad-spectrum antibiotics. α-Amino-β-hydroxy carboxylic acids are naturally occuring amino acids which are often found as components in cyclopeptides with antibiotic properties.[7,8] The preparation of α-amino-β-hydroxy carboxylic acids, starting from (*R*)-cyanohydrins, has already been described in the literature, but only α-alkyl or α-aryl derivatives can be obtained by the published procedure.[9]

In the present paper we report on the synthesis of (1*R*,2*S*)-2-amino-1,3-diols **7** starting from (*R*)-*O*-trimethylsilylated cyanohydrins **2** which are easily accessible by (*R*)-oxynitrilase [EC 4.1.2.10] catalyzed addition of HCN to the corresponding aldehydes and subsequent silylation.[3a,b]

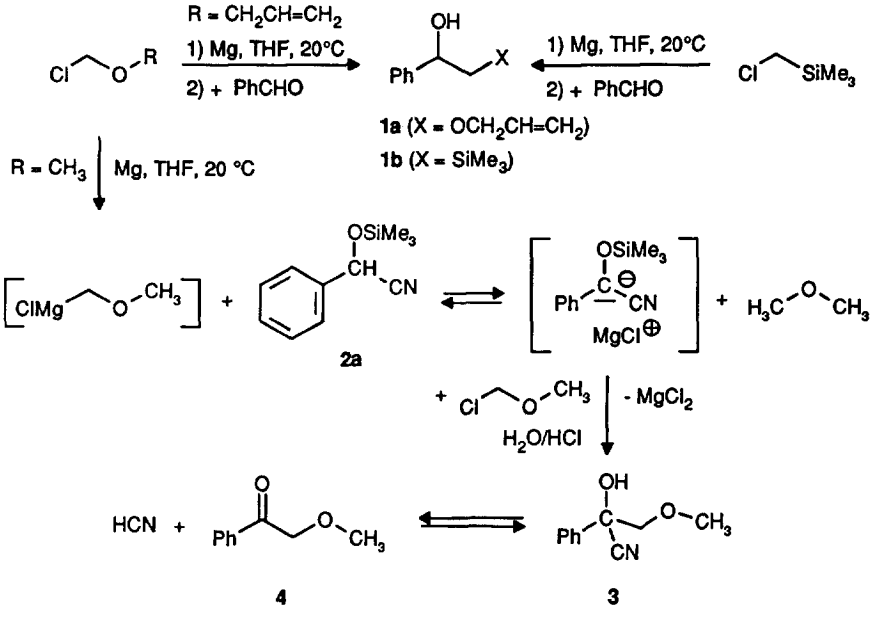
In analogy to the preparation of 2-amino alcohols via addition of organometallic compounds to *O*-protected cyanohydrins,[3,4] Grignard compounds derived from α-halo ethers[10] or silyl methyl chlorides[11] should be applicable for the synthesis of 2-amino-1,3-diols **7**. Therefore we have investigated the addition of both types of Grignard reagents to *O*-trimethylsilyl-protected mandelonitrile **2a**.
By reacting methoxy methyl magnesium chloride, prepared in situ at 20°C from α-halo ethers,[10] with **2a**, no addition of the Grignard reagent to the cyano group occured. In contrast the Grignard reacts as a base giving deprotonation of **2a** and further reaction of the anion of **2a** with α-chloromethyl methyl ether yields meth-

oxymethyl mandelonitrile **3** and methoxyacetophenone **4** in a ratio of 2:1 (Scheme 1).

Under these mild conditions, Grignard compounds derived from trimethylsilyl or dimethyl(phenyl)silyl methyl chlorides did not react with **2a** at all. At higher temperature only decomposition was observed.

With benzaldehyde instead of **2a** Grignard compounds from α-chloromethyl allyl ether[12] and trimethylsilyl methyl chloride, respectively, also prepared in situ, reacted to the corresponding addition products **1a** and **1b**, which were isolated in 43% and 25% yield, respectively, proving the formation of the Grignard reagent takes place (Scheme 1).

Scheme 1



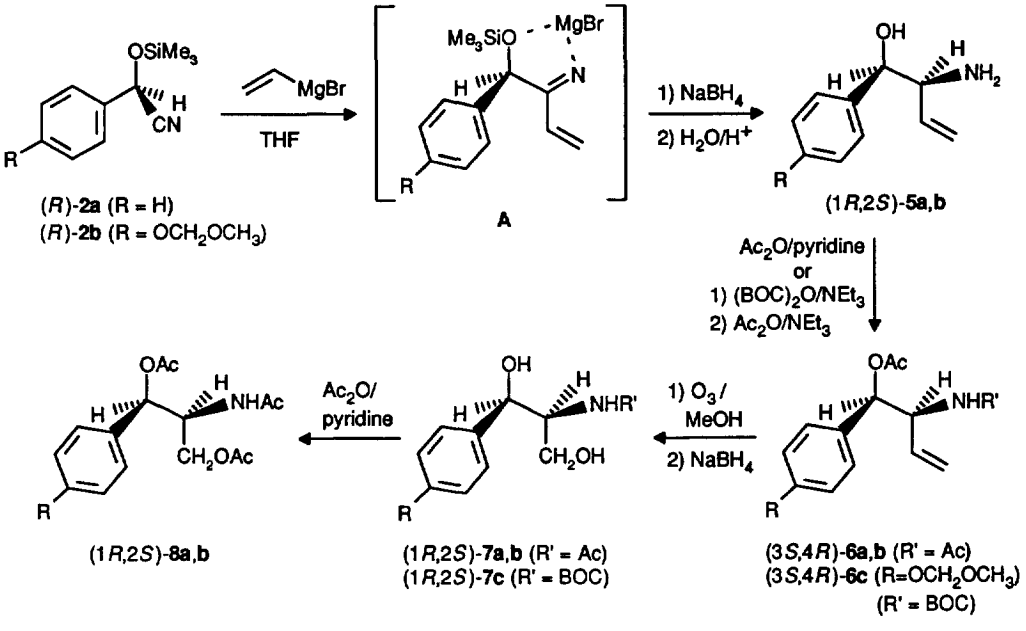
The introduction of a vinyl group via Grignard addition to the nitrile function of cyanohydrins, subsequent ozonolysis[13] followed by reductive work up[14] would offer an alternative route to 2-amino-1,3-diols. We have therefore investigated this synthetic route.

First the reaction conditions of the addition of vinyl Grignard to racemic[15] *O*-trimethylsilylated mandelonitrile **2a** have been optimized (Table 1). Then we have applied the optimal reaction conditions in the reaction of the *O*-protected (*R*)-cyanohydrins (*R*)-**2a** and (*R*)-**2b** with the vinyl Grignard. In Scheme 2 the preparation of (1*R*,2*S*)-2-amino-1,3-diols **7**, starting from chiral *O*-trimethylsilylated cyanohydrins (*R*)-**2**, via Grignard addition, subsequent ozonolysis and hydrogenation is summarized.

The vinyl substituted *erythro*-amino alcohols (1*R*,2*S*)-**5a,b** were obtained by addition of vinyl magnesium bromide[16] to the cyanohydrin *O*-trimethylsilyl ethers (*R*)-**2a,b** at -30°C followed by hydrogenation with $NaBH_4$ at -50°C in analogy to a procedure described[3a] (Scheme 2, Table 1). The methoxymethyl protecting

group, introduced according to Ref.,[17] is particularly advantageous since the (*R*)-oxynitrilase accepts the *O*-protected aldehyde as substrate in the enzyme catalyzed cyanohydrin formation, and furthermore the protecting group is stable under the conditions of the follow-up reactions.

Scheme 2



It is assured that *O*-protected chiral cyanohydrins react with alkyl and aryl Grignard reagents without any racemization.[3a] The hydrogenation of the imino intermediates with $NaBH_4$ proceeds highly diastereoselective to give *erythro*-2-amino alcohols.[3a]

The addition of the vinyl Grignard reagent to the *O*-protected (*R*)-cyanohydrins **2a** and **b** to the primary intermediate **A** (Scheme 2) proceeds also without any racemization at C1. The subsequent hydrogenation of **A** with $NaBH_4$ affords, as confirmed by x-ray analysis of compound (1*R*,2*S*)-**8a** (Figure 1), the *erythro*-2-amino alcohols (1*R*,2*S*)-**5a** and **b** with reasonable diastereomeric excesses (Table 1).

Table 1. (1*R*,2*S*)-Amino Alcohols **5** from *O*-Trimethylsilyl Protected Cyanohydrins **2** with Vinyl Magnesium Bromide and Subsequent Hydrogenation with $NaBH_4$

2	*ee* [%][a]	**5**	Yield [%][b]	*de* [%][c]	Yield [%][d]	*ee* [%]	$[\alpha]_D^{20}$ (*c*, solvent)
(*R*,*S*)-**2a**	-	**5a**	83	77.4	10	-	-
(*R*,*S*)-**2b**	-	**5b**	58	81.0	33	-	-
(*R*)-**2a**	99	(1*R*,2*S*)-**5a**	77	77.4	11	99	-54.0 (0.5, H_2O)
(*R*)-**2b**	94	(1*R*,2*S*)-**5b**	55	81.0	30	>90	-34.4 (0.5, EtOH)

[a] *ee*-Values of the starting cyanohydrins. [b] Crude products. [c] Determined from crude products by GC. [d] After conversion to hydrochlorides and recrystallization (**5a**) or chromatography on silica gel with EtOH,NH_3 sat./ethyl acetate (1:4) (**5b**).

To prevent the hydroxyl and the amino group in compounds **5** from oxidation during ozonolysis both groups were acetylated. The diacetyl derivatives **6a** and **b** were obtained in 21-34% yield referred to the starting cyanohydrin **2** (Table 2). **6c** was prepared from **5b** by introduction of the BOC protecting group[18] on the amino function and subsequent acetylation of the OH group (Scheme 2, Table 2).

Table 2. *N*- and *O*-Protected Vinyl Compounds **6** from 2-Amino Alcohols **5**

5	*ee* [%]	**6**	Yield [%][a]	*de* [%][b]	mp [°C]	$[\alpha]_D^{20}$ (*c*, CH_2Cl_2)
5a	-	**6a**	21	96.5	105-107	-
5b	-	**6b**	34	-	-	-
5b	-	**6c**	40[c]	98.7	79-80	-
(1*R*,2*S*)-**5a**	99	(3*S*,4*R*)-**6a**	27	95.6	137-138.5	-92.4 (1.00)
(1*R*,2*S*)-**5b**	>90	(3*S*,4*R*)-**6b**	84[c]	-	-	-81.4 (0.43)

[a] Referred to **2**. [b] Determined by GC. [c] Referred to **5b**.

The protected vinyl amino alcohols (3*S*,4*R*)-**6** were ozonized at -78°C in methanol. The advantage of methanol as solvent is the formation of an addition product of the carbonyl oxide, evolved in the ozonolysis, with methanol to give α-methoxyhydroperoxide.[13] So in methanol the formation of byproducts is prevented. The reaction was accomplished by hydrogenation with $NaBH_4$ to yield the (1*R*,2*S*)-2-amino-1,3-diols **7** (Scheme 2, Table 3).

An important factor of ozonolysis concerning the yields is the time of ozonization. In case of racemic **6a** the time of ozonization was varied within 2-6 min. After 3:30 minutes the signals of the vinyl group could not be detected any more by ^1H NMR spectroscopy. After acetylation of **7a** the product **8a** was isolated in 47% yield in this case. However, by increasing the time of ozonization to 5:30 minutes the yield of **8a** was diminished to 38% yield.

Table 3. Ozonolysis of Vinyl Amino Alcohols **6** at -78°C in Methanol and Subsequent Hydrogenation with $NaBH_4$ to (1*R*,2*S*)-2-Amino-1,3-propanediols **7**

Educts	Ozonolysis		Hydrogena-	Products			
6	Flow O_2/h	Time [min]	tion Time [h]	**7**	Yield [%]	*de* [%][a]	mp [°C]
6a	32 l	3:30	20	**7a**	74[b]	not determ.	-
6b	33-35 l	6:00	20	**7b**	76[b]	not determ.	-
6b[c]	32 l	7:00	19.5	**7b**	43	>99.9	112-113.5
6c	32 l	3:38	20	**7c**	63	not determ.	135-137
(3*S*,4*R*)-**6a**	20-60 l	5:07	17	(1*R*,2*S*)-**7a**	74[b]	not determ.	-
(3*S*,4*R*)-**6b**	32 l	5:40	20	(1*R*,2*S*)-**7b**	29	>99.9	105-107

[a] Determination by capillary gas chromatography and ^{13}C NMR spectroscopy; only one diastereomer could be proved. [b] Crude products. [c] 3 mmol preparation.

The 2-amino-1,3-diols **7b** and **c** could be purified by recrystallization. (1*R*,2*S*)-**7b** was isolated in 29% yield

based on (3*S*,4*R*)-**6b** with a *de*-value >99.9% and 96.3%*ee* ($[\alpha]_D^{20}$ = -20 (*c* 0.5, CH_2Cl_2)). As expected, the more bulky BOC protecting group in **7c** effects an increase of chemical yield to 63% compared with **7b** (43%) (Table 3). Only one diastereomer of **7b** could be detected either by gas chromatography or by ^{13}C NMR spectroscopy (Table 3). For isolation the *N*-acetyl-1,3-diol **7a** was acetylated to the triacetyl compound **8a** which could be purified by chromatography on silica gel. (1*R*,2*S*)-**8a** was obtained in 42% chemical yield with >99.9%*de* and >99.9%*ee* ($[\alpha]_D^{23}$ = -22 (*c* 1.0, CH_2Cl_2)). **7b** was acetylated to **8b** which was received after purification in 35% yield with a *de*-value of >99.9%. Also for the compounds **8a** and **8b** only one diastereomer was detected.

With the known configuration at C1 the stereochemistry of **8a** could be determined by x-ray crystallographic analysis:[19] crystal dimension, 0.7 x 0.3 x 0.15 mm; formula, $C_{15}H_{19}NO_5$; formula weight, 293.32; crystal system, monoclinic; space group, C2; a=24.4900(58), b=5.3917(13), c=11.7931(22) Å, α=90°, β=90.85(2)°, γ=90°, V=1557.0(6) $Å^3$; Z=4; ρ(calcd)=1.25 g/cm^3; Mo-Kα (λ=0.71073); graphite monochromator; temperature, 293 K; θ - 2θ scan; 2θ scan limits, 2 - 55°; independent reflections, 2009; reflections observed $F_0 \geq 3\sigma(F_0)$, 1118. The crystal structure was solved by the direct method.[19a] Full matrix least-squares refinement[19b] led to the final convergence with R=0.052 (R_w=0.054).

The crystal structure of **8a** shows, as expected from previous results,[3a] unambiguously the (1*R*,2*S*)-configuration (Figure 1). Thus, the crystal structure confirms the stereoselective hydrogenation of the vinyl addition product to yield the *erythro*-2-amino alcohols **5**. Their follow-up reactions (acetylation and ozonolysis) proceed without change at the stereogenic centers C1 and C2.

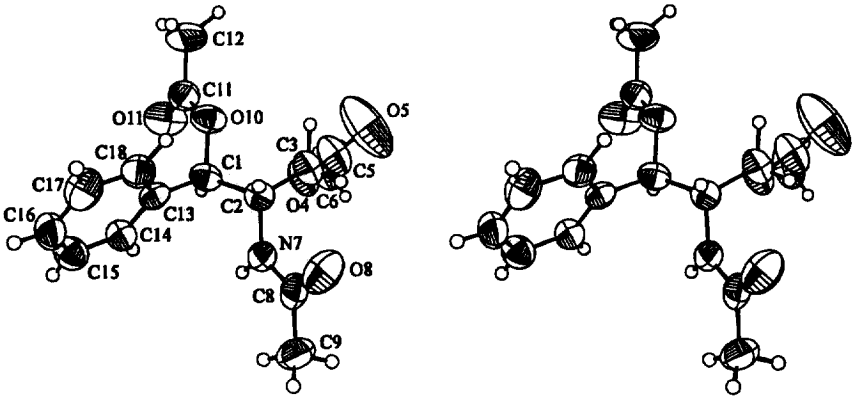


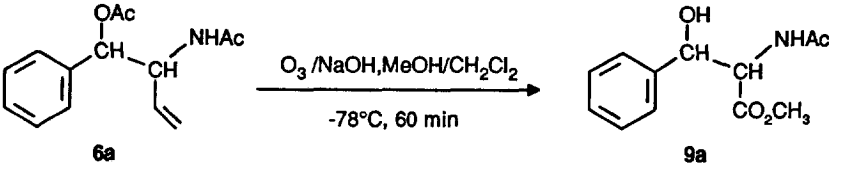
Figure 1. ORTEP diagram of compound (1*R*,2*S*)-**8a**

As mentioned in the introduction, the synthesis of β-hydroxy-α-amino acids, starting from optically active cyanohydrins, has been described by Brussee.[9a] In a Strecker-type reaction the imine intermediates, obtained by addition of alkyl or aryl Grignard compounds to *O*-protected (*R*)-cyanohydrins, were reacted with

potassium cyanide in methanol yielding α-alkyl or α-aryl substituted β-hydroxy-α-aminonitriles which should be transformed to the corresponding β-hydroxy-α-amino acids.[9]

We have now investigated the ozonolysis of protected vinyl amino alcohols **6** in order to get β-hydroxy-α-amino acids which are not substituted in α-position by alkyl or aryl groups. According to a procedure described in the literature[20] the reaction of *erythro*-**6a** (*de* 93.2%) was carried out at -78°C in methanolic NaOH with dichloromethane as cosolvent yielding methyl 2-acetamido-3-hydroxy-3-phenylpropanoate (**9a**) (Scheme 3).

Scheme 3



6a **9a**

Probably due to elimination of the *O*-acetyl group during ozonolysis, *erythro*-**9a** could be isolated after chromatography only in 15% yield with a *de*-value of 95.4%.

Experimental

Materials and Methods: Avicel cellulose was purchased from Merck, trimethylsilyl methyl chloride from Fluka. Racemic cyanohydrins were prepared according to Ref.,[15] chloromethyl methyl ether according to Ref.[21] and chloromethyl allyl ether according to Ref.[22] All solvents were purified and dried as described in the literature. Melting points were determined on a Büchi SMP 20 and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker ACF 250 with TMS as internal standard. Optical rotations were performed in a Perkin-Elmer polarimeter 241 LC. Ozone generation: Fischer ozone generator 502. Preparative column chromatography was performed with glass columns of different size packed with silica gel 60, grain size 0.040-0.063 mm (Merck). GC for determination of enantiomeric and diastereomeric excess: a) Carlo Erba Fractovap 4160 with FID, Spectra Physics minigrator, 0.5 bar hydrogen, column 30 m, phase PS086, column 25 m, phase OV 1701; b) Carlo Erba HRGC 5300 Mega Series with FID, Carlo Erba Mega Series integrator, 0.4 bar hydrogen, column 20 m, phase polydimethylsiloxane with 3.5% valeroyl-L-valin-(R)-bornylamide, Amid-DEX III, PS086 with 10% permethylated β-cyclodextrin; c) Hewlett Packard 5890 Series II with FID, 0.42 bar hydrogen, column 30 m, phase Chiraldex BT-A (ICT).

Preparation of compounds **1**: A catalytic amount of $HgCl_2$ was added to Mg (5 or 10 mmol), covered with THF (2 ml), and the mixture was refluxed. At room temperature α-chloromethyl ally ether (2.5 mmol) or trimethylsilyl methyl chloride (10 mmol) was added followed by benzaldehyde (5 or 10 mmol) after the formation of the Grignard reagent had started. The temperature was kept at 20-30°C by addition of THF and

carefully cooling. After stirring for 2 h (**1a**) or 1 h (**1b**) the mixture was hydrolyzed with sat. NH_4Cl solution (**1a**) or 10% HCl (**1b**) and extracted with ethyl acetate. The combined extracts were dried ($NaSO_4$), concentrated, and the residue chromatographed on silica gel with dichloromethane/ethyl acetate (9:1) (**1a**) or petroleum ether/ethyl acetate (9:1) (**1b**) to give **1a** and **b** in 43 and 25% yield, respectively.

Conversion of methoxy methyl magnesium chloride with **2a**: **2a** (10 mmol) was added at 20°C to a solution of methoxy methyl magnesium chloride (prepared from 40 mmol Mg and halo ether as described above). After stirring for 2 h the mixture was cooled to -50°C and $NaBH_4$ (10.6 mmol) and methanol (15 ml) were added. The mixture was stirred for 4 h, then hydrolyzed with 10% HCl, extracted with diethyl ether and the combined extracts were dried ($MgSO_4$). Evaporation and chromatography on silica gel with petroleum ether/ethyl acetate (7:3) afforded a 2:1 mixture of **3** and **4**.

Vinyl amino alcohols **5**: An ice-cooled solution of vinyl bromide (136.6 mmol) in THF (55 ml) was added via syringe to Mg (136.6 mmol) covered with THF (35 ml) under argon, and then the reaction mixture was refluxed for 30-60 min according to Ref.[16] THF (95 ml) was added and the solution of the Grignard reagent cooled to -30°C. Then **2** (68.3 mmol) was added via syringe to the solution, and the reaction mixture stirred at room temperature for 16 h [(*R*,*S*)-**2a**, (*R*)-**2a,b**] or 7 h [(*R*,*S*)-**2b**]. At -50°C solid $NaBH_4$ (136.6 mmol) was added followed by methanol (100 ml), the mixture stirred for 4 h and allowed to warm to room temperature (8.5 h). After hydrolysis with 10% HCl the aqueous phase was extracted with diethyl ether, set to pH 10 with NaOH and extracted with ethyl acetate. (In case of **5b**, the reaction mixture was diluted with diethyl ether and hydrolyzed with cooling with ice-cold 10% HCl). The combined ethyl acetate extracts were dried ($MgSO_4$) and concentrated. Compounds **5** were reacted without further purification.

Preparation of compounds **6** *and* **8**: Acetic anhydride (5 mmol) was added dropwise at 0°C to a solution of **5** or **7** (1.5 mmol) and *p*-dimethylaminopyridine (10 mol% referred to **5** or **7**) in pyridine (1.2 ml), the reaction mixture was stirred at room temperature for 17-21 h (for **5**), 25 h (for (1*R*,2*S*)-**7a**) or 48-63 h (for **7a,b**), hydrolyzed with ice and extracted with ethyl acetate. The combined extracts were washed with 10% HCl to remove pyridine, in case of **6b** and **8b** additionally with 10% $NaHCO_3$ solution and water, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel with ethyl acetate/petroleum ether (9:1) or ethyl acetate/acetone (15:1).

Preparation of Compound **6c**: Acetic anhydride was slowly added to an ice-cooled mixture of *N-tert*-butoxycarbonyl-1-(4-methoxymethoxyphenyl)-3-buten-1-ol [prepared from **5b** (1.7 g, 7.6 mmol) and di-*tert*-butyl dicarbonate (1.7 g, 7.6 mmol) in NEt_3 (2.1 ml, 15.2 mmol) and dichloromethane (5.4 ml) according to Ref.,[18] chromatographed on silica gel with ethyl acetate/petroleum ether (1:1.5), washed with diethyl ether/petroleum ether; 1.14 g (47%) white crystals, mp 82-84°C], NEt_3 and *p*-dimethylaminopyridine in dichloromethane, and the mixture stirred for 21 h. It was hydrolyzed with ice and extracted with chloroform. The combined extracts were dried ($MgSO_4$), evaporated, and the residue chromatographed on silica gel with ethyl acetate/petroleum ether (1:1.5) and recrystallized from ethyl acetate/petroleum ether to give **6c**.

Ozonolysis: Ozone was passed through a solution of **6** (2 mmol) in absolute methanol (20 ml) at -78°C within the given time (Table 3). The reaction mixture was washed with oxygen to remove the excess of ozone, then solid $NaBH_4$ (5 mmol) was added and after 2.5 h the stirred mixture was allowed to warm to room temperature (Table 3). The volatile compounds were removed *in vacuo*, the residue taken up in NH_4Cl solution and extracted with ethyl acetate. The combined extracts were dried ($MgSO_4$), concentrated and the product **7** was either recrystallized from ethyl acetate/petroleum ether or directly acetylated to give **8**.

^1H NMR Data of Compounds **5-8** (250 MHz, $CDCl_3$, δ)

5a[a]	4.99-5.22 (m, 3 H, CH=C*H*$_2$, C*H*NH_2), 5.62-5.77 (m, 1 H, C*H*=CH_2), 6.16 (d, *J*=4.2 Hz, 1 H, C*H*OH), 7.22-7.39 (m, 5 H, Ph), 8.39 (s, 3 H, NH_3)
5b	1.58-2.04 (broad s, 3 H, OH, NH_2), 3.47 (s, 3 H, CH_3O), 3.52-3.54 (m, 1 H, C*H*NH_2), 4.33 (d, *J*=6.7 Hz, 1H, threo C*H*OH), 4.53 (d, *J*=5.6 Hz, 1 H, C*H*OH), 5.14-5.22 (m, 4 H, CH_2O, CH=C*H*$_2$), 5.72-5.85 (m, 1 H, C*H*=CH_2), 7.00 (dd, J_1=6.7, J_2=2.0 Hz, 2 H, Ph), 7.26 (dd, 2 H, Ph)
6a	1.99, 2.14 (2 s, 6 H, CH_3), 4.92-5.00 (m, 1 H, C*H*NH), 5.07-5.19 (m, 2 H, CH=C*H*$_2$), 5.61 (broad d, *J*=8.5 Hz, 1 H, NH), 5.70-5.84 (m, 1 H, C*H*=CH_2), 5.89 (d, *J*=4.0 Hz, 1 H, C*H*OAc), 7.20-7.38 (m, 5 H, Ph)
6b	1.98, 2.12 (2 s, 6 H, CH_3), 3.47 (s, 3 H, CH_3O), 4.90-4.98 (m, 1 H, C*H*NH), 5.09-5.21 (m, 4 H, CH_2O, CH=C*H*$_2$), 5.59 (broad d, *J*=9.4 Hz, 1 H, NH), 5.70-5.84 (m, 1 H, C*H*=CH_2), 5.84 (d, *J*=4.2 Hz, 1 H, C*H*OAc), 7.01 (dd, J_1=6.6, J_2=2.0 Hz, 2 H, Ph), 7.24 (dd, 2 H, Ph)
6c	1.43 [s, 9 H, C(CH_3)$_3$], 2.11 (s, 3 H, CH_3), 3.47 (s, 3 H, CH_3O), 4.49-4.65 (broad m, 2 H, NH, C*H*NH), 5.10-5.20 (m, 4 H, CH_2O, CH=C*H*$_2$), 5.68-5.80 (m, 2 H, C*H*OAc, C*H*=CH_2), 7.00 (broad dd, J_1=6.7, J_2=2.0 Hz, 2 H, Ph), 7.23 (broad dd, 2 H, Ph)
7b	2.04 (s, 3 H, CH_3), 2.73 (broad dd, J_1=3.8, J_2=7.3 Hz, 1 H, CH_2OH), 3.32 (broad d, *J*=5.1 Hz, 1 H, CHO*H*), 3.48 (s, 3 H, CH_3O), 3.55-3.64 (m, 1 H, C*H*$_2$OH), 3.80-3.87 (ddd, J_1=3.5, J_2=11.4 Hz, 1 H, C*H*$_2$OH), 4.00-4.10 (m, 1 H, C*H*NH), 5.01 (broad dd, *J*=4.3 Hz, 1 H, C*H*OH), 5.17 (s, 2 H, CH_2O), 6.37 (broad d, *J*=8.0 Hz, 1 H, NH), 7.04 (dd, J_1=6.7, J_2=2.0 Hz, 2 H, Ph), 7.32 (broad d, 2 H, Ph)
7c	1.44 [s, 9 H, C(CH_3)$_3$], 2.51-2.56 (m, 1 H, C*H*NH), 3.08 (broad d, 1 H, OH), 3.48 (s, 3 H, CH_3O), 3.57-3.66 (m, 1 H, C*H*$_2$OH), 3.76-3.86 (m, 2 H, OH, C*H*$_2$OH), 4.99 (broad s, 1 H, C*H*OH), 5.17 (s, 2 H, CH_2O), 5.35 (broad d, 1 H, NH), 7.03 (dd, J_1=6.7, J_2=2.0 Hz, 2 H, Ph), 7.31 (broad d, 2 H, Ph)
8a	1.91, 2.04, 2.13 (3 s, 9 H, CH_3), 3.98 (dd, J_1=4.1, J_2=11.5 Hz, 1 H, C*H*$_2$OAc), 4.35 (dd, J_1=6.3, J_2=11.5 Hz, 1 H, C*H*$_2$OAc), 4.65-4.75 (m, 1 H, C*H*NH), 5.63 (d, *J*=9.1 Hz, 1 H, NH), 5.89 (d, *J*=5.7 Hz, 1 H, C*H*OAc), 7.28-7.43 (m, 5 H, Ph)
8b	1.91, 2.05, 2.10 (3 s, 9 H, CH_3), 3.47 (s, 3 H, CH_3O), 3.98 (dd, J_1=11.6, J_2=4.0 Hz, 1 H, C*H*$_2$OAc), 4.34 (dd, J_1=11.6, J_2=6.2 Hz, 1 H, C*H*$_2$OAc), 4.63-4.73 (m, 1 H, C*H*NH), 5.17 (s, 2 H, CH_2O), 5.58 (broad d, *J*=9.3 Hz, 1 H, NH), 5.86 (d, *J*=6.0 Hz, 1 H, C*H*OAc), 7.02 (dd, J_1=6.7, J_2=2.0 Hz, 2 H, Ph), 7.26 (dd, 2 H, Ph)

[a] Hydrochloride in DMSO-d_6.

Elemental Analytical Data of Compounds **5-8**

	Molecular Formula (Mol. Weight)	Calcd./Found C	H	N	Cl		Molecular Formula (Mol. Weight)	Calcd./Found C	H	N
5a	$C_{10}H_{13}NO \cdot HCl$	60.15	7.07	7.01	17.75	**7b**	$C_{13}H_{19}NO_5$	57.98	7.11	5.20
	(199.7)	59.89	6.96	6.90	17.56		(269.3)	57.87	7.08	5.11
5b	$C_{12}H_{17}NO_3$	64.55	7.67	6.27		**7c**	$C_{16}H_{25}NO_6$	58.70	7.70	4.28
	(223.3)	64.32	7.78	6.06			(327.4)	58.60	7.80	4.19
6a	$C_{14}H_{17}NO_3$	68.00	6.93	5.66		**8a**	$C_{15}H_{19}NO_5$	61.42	6.53	4.78
	(247.3)	67.77	6.98	5.48			(293.3)	61.38	6.54	4.75
6b	$C_{16}H_{21}NO_5$	62.53	6.89	4.56		**8b**	$C_{17}H_{23}NO_7$	57.78	6.56	3.96
	(307.4)	62.23	7.08	4.54			(353.4)	57.89	6.59	3.98
6c	$C_{19}H_{27}NO_6$	62.45	7.45	3.83						
	(365.4)	62.33	7.33	3.81						

Derivatization of **5** *and* **7** *for de and ee determination by capillary gc*: a) Pivaloyl chloride (50 µl) was added to **5** (2 mg) or **7** (3 mg) in pyridine (200 µl), and after 4-6 h at room temperature the reaction mixture was filtered through a silica gel column (0.5x6 cm) with dichloromethane as eluent. The diastereomeric excess was determined directly from the filtrate.

b) A mixture of **5** (1 mg) in dichloromethane (100 µl) and trifluoroacetic anhydride (100 µl) was heated to 70°C for 2 h. After evaporation the residue was taken up in dichloromethane (2 ml) and chromatographed.

c) To a solution of **5** (1 mg) in dichloromethane (150 µl) a solution of 1% pyridine in dichloromethane (250 µl) was added followed by a sat. solution of phosgene in toluene (30 µl). After 1 h the excess of reagent and solvent was removed with N_2 and the residue taken up in dichloromethane (500 µl), washed three times with H_2O (1 ml) and dried (mol. sieve 4 Å).

Oxidative ozonolysis to compound **9a** *according to Ref.*[20]: At -78°C ozone (flow 28 l O_2/h) was passed through a stirred solution of **6a** (2 mmol, *de* 93.2%) in abs. dichloromethane (16 ml) and 2.5 M methanolic NaOH (4 ml) within 60 min (until blue color of ozone). Diethyl ether (20 ml) and water (10 ml) were added, the reaction mixture allowed to warm to room temperature and extracted with diethyl ether. The combined extracts were dried ($MgSO_4$), concentrated, and the residue chromatographed twice on silica gel with ethyl acetate/petroleum ether (5:1 and 3:1) to give **9a** (15%) as white crystals, mp 119-121°C, *de* 95.4%. ^{1}H NMR ($CDCl_3$): δ = 2.03 (s, 3 H, CH_3), 3.74 (s, 3 H, CH_3O), 4.50 (broad s, 1 H, OH), 5.27 (broad s, 1 H, C*H*OH), 5.02 (dd, J_1=6.9, J_2=3.4 Hz, 1 H, C*H*NH), 6.25 (d, J=6.1 Hz, 1 H, NH), 7.20-7.37 (m, 5 H, Ph).

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References and Notes

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