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Application of the Blaise reaction: stereoselective synthesis of (4*R*)-*tert*-butyl 3-amino-4-trimethylsilyloxy-2-alkenoates from (*R*)-cyanohydrins[1]

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Abstract

O-Trimethylsilyl protected (*R*)-cyanohydrins **3** react with Reformatsky reagents from *tert*-butyl 2-bromoesters **4** and zinc dust (Blaise reaction) to give the corresponding addition products in high yields. Workup with an aqueous solution of NH_4Cl at low temperature gives (4*R*)-*tert*-butyl 3-amino-4-trimethylsilyloxy-2-alkenoates (*R*)-**5** without racemization. Hydrogenation of the alkenoates **5** to the corresponding *tert*-butyl β-amino-γ-hydroxyalkanoates **6**, resulting in a mixture of two diastereoisomers, was only possible under special hydrogenation conditions. With HCl in dichloromethane compounds **6** cyclize to the corresponding β-amino-γ-hydroxybutyrolactones **8**.

The (1*R*,2*S*)- and (1*S*,2*R*)-2-amino alcohols are easily accessible by addition of Grignard reagents to O-protected (*R*)- and (*S*)-cyanohydrins and subsequent hydrogenation.[2] Since Grignard reagents derived from α-halo ethers or silylmethyl chlorides for the preparation of an additional functional group in the 3-position of the amino alcohols gave no addition products with O-protected cyanohydrins,[3] the addition of vinylmagnesium bromide was applied.[3] Reductive ozonolysis of the primarily obtained 2-vinyl-2-amino alcohols resulted in the formation of (1*R*,2*S*)-2-amino-1,3-diols starting from (*R*)-cyanohydrins.[3]

In the present paper the results of the reaction of Reformatsky reagents, derived from 2-bromo esters and zinc, with O-protected (*R*)-cyanohydrins, a further example of the application of optically active cyanohydrins in stereoselective synthesis, are described.

The reaction of Reformatsky reagents with nitriles, known as the Blaise reaction,[4] has already been applied to racemic[5] as well as to optically active[6] O-protected cyanohydrins. In all cases workup under acidic conditions resulted in the formation of tetronic acids.[5,6] Under special reaction conditions, however, the intermediate β-amino-α,β-unsaturated esters could be isolated.[4d,7] In the case of the Blaise reaction with optically active cyanohydrins, this type of intermediate, not yet described in the literature,

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would be of interest for the stereoselective synthesis of β-amino-γ-hydroxy carboxylic acids and β-amino-γ-butyrolactones, respectively.

β-Amino-γ-hydroxy acids are main components in macrocyclic peptides or glycopeptides with antifungal, antibiotic[8] and gastroprotective[9] activity. β-Amino-γ-butyrolactones are key intermediates for the synthesis of pharmacologically important β-amino alcohols,[10] β-lactam antibiotics[11] and polyene macrolide antibiotics.[12] They are also of interest as phosphodiesterase inhibitors[13] and moreover they potentiate the action of adrenaline on blood pressure.[14] We therefore have investigated the Blaise reaction with O-protected (*R*)-cyanohydrins in detail in a more general way.

1. Preparation of (4*R*)-*tert*-butyl 3-amino-4-trimethylsilyloxy-2-alkenoates (*R*)-5 from (*R*)-cyanohydrins (*R*)-2

The Blaise reaction of racemic O-protected cyanohydrins, described by Krepski et al.,[5b] leads after hydrolysis with diluted sulfuric acid directly to tetronic acids. According to this described procedure we tried to synthesize (*R*)-tetronic acids starting from (*R*)-cyanohydrins. We did not, however, succeed in the isolation of the desired products after hydrolysis, neither with diluted sulfuric acid nor with aqueous HCl (10%). We therefore decided to optimize first the reaction conditions for this type of Reformatsky reaction.

Parameters such as solvent, state and activation of the zinc applied as well as the hydrolysis conditions were varied widely in the reaction of racemic 2-(trimethylsilyloxy)pentanenitrile **3b** with *tert*-butyl α-bromoacetate **4a**. Ethyl α-bromoacetate commonly used in Reformatsky reactions was replaced by the *tert*-butyl ester **4a** in order to minimize side-reactions of the organozinc compound. THF was retained as the most suitable solvent.

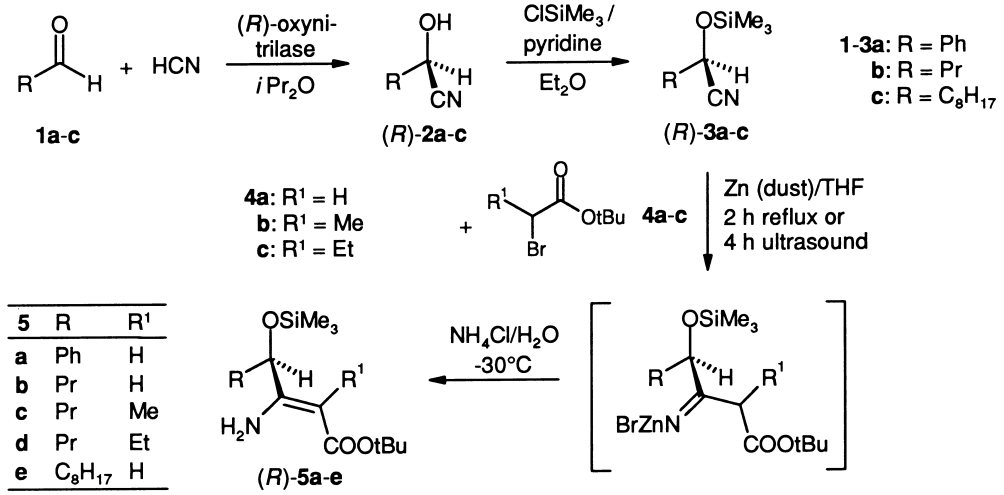
For hydrolysis, instead of mineral acid, we used a saturated solution of NH_4Cl as a mildly acidic medium at −30°C. Under these reaction conditions no lactonization occurred. We were able to isolate *tert*-butyl 3-amino-4-trimethylsilyloxy-2-heptenoate **5b** in 75% yield. By hydrolysis of the addition product with glacial acetic acid at −30°C, **5b** was isolated in 20% yield only. An interesting modification, using THF/trimethyl borate[15] as the solvent mixture instead of THF alone, gave **5b** in 45% yield.

Both zinc dust and granulated zinc, which differ in their surfaces, were investigated. After identical activations using 20% HCl and workup by hydrolysis with NH_4Cl, **5b** was obtained in comparable yields of 75% (granulated zinc) and 79% (zinc dust). In all further reactions zinc dust was applied. Zinc dust was activated not only by HCl but also by a solution of conc. HNO_3 in conc. H_2SO_4[16] and by copper(II) acetate solution.[17] With the HCl and H_2SO_4/HNO_3 activated zinc, respectively, **5b** was obtained in 79% yield. The yield by Zn–Cu activation was slightly less with 73%. We therefore used zinc activation with HCl for further reactions.

The results described so far show a strong dependence of the yield of **5** on hydrolysis conditions and workup. The influence of all other parameters we have varied, however, can be neglected.

Scheme 1 shows the Blaise reaction of optically active O-protected (*R*)-cyanohydrins (*R*)-**3** with *tert*-butyl 2-bromoalkanoates **4** under the optimized hydrolysis and workup conditions.

The (*R*)-cyanohydrins (*R*)-**2a**,**b** were already known,[2b] 2-hydroxydecanenitrile (*R*)-**2c** was prepared in 82% yield and 96% *ee* ($[\alpha]_D^{23}$=+10.3 (*c* 0.5, CH_2Cl_2)) by (*R*)-oxynitrilase [EC 4.1.2.10] catalyzed addition of HCN to aldehyde **1c**. The trimethylsilyl protecting group in (*R*)-**2a**–**c** was introduced without racemization according to a known procedure[2a] (see Experimental). The results of the addition of *tert*-butyl α-bromoalkanoates **4a**–**c** to racemic and to (*R*)-cyanohydrins **3a**–**c**, respectively, are summarized in Table 1.



5	R	R¹
a	Ph	H
b	Pr	H
c	Pr	Me
d	Pr	Et
e	C_8H_{17}	H

Scheme 1.

Table 1
tert-Butyl 3-amino-4-trimethylsilyloxy-2-alkenoates **5** by addition of Reformatsky reagents prepared from α-bromoesters **4** to cyanohydrins **3** and subsequent hydrolysis

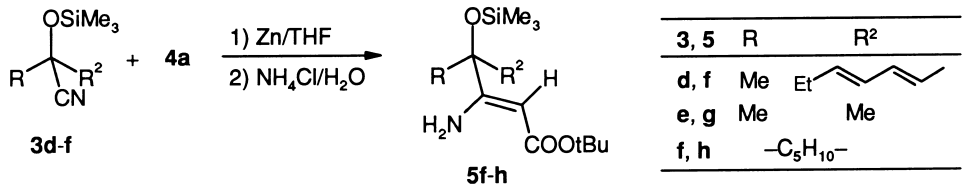
cyanohydrins **3**		α-bromo acids	enaminoesters **5**			
	ee (%)[a]	**4**		yield (%)	*ee* (%)[b]	$[\alpha]_D^{23}$ (*c*, CH_2Cl_2)
3a	-	**a**	**5a**	74	-	-
(*R*)-**3a**	>99	**a**	(*R*)-**5a**	54	>95	-80.5 (1.0)
3b	-	**a**	**5b**	79	-	-
(*R*)-**3b**	95	**a**	(*R*)-**5b**	83	94	-14.2 (1.0)
3b	-	**b**	**5c**	80	-	-
(*R*)-**3b**	99	**b**	(*R*)-**5c**	74	72	+3.1 (1.0)
3b	-	**c**	**5d**	80	-	-
(*R*)-**3b**	99	**c**	(*R*)-**5d**	70	76	+5.3 (0.9)
3c	-	**a**	**5e**	81	-	-
(*R*)-**3c**	96	**a**	(*R*)-**5e**	66	-[c]	-11.7 (0.6)

[a] *ee*-Values of starting cyanohydrins (*R*)-**2**. [b] Determined from underivatized **5** by GC on chiral β-cyclodextrin phases Chiraldex B-DA (**5a**) and Bondex-unβ-5.5-Et-105. [c] No separation of the enantiomers by GC or by ^{1}H NMR spectroscopy with shift reagents.

Table 1 shows that (4*R*)-*tert*-butyl 3-amino-4-phenyl-4-trimethylsilyloxy-2-butenoate **5a** and (4*R*)-*tert*-butyl 3-amino-4-trimethylsilyloxy-2-heptenoate **5b** could be isolated without racemization. In the reaction of (*R*)-**3b** with both *tert*-butyl α-bromopropionate **4b** and -butyrate **4c**, however, partial racemization was observed. Despite the bulky *tert*-butyl group, both esters **4b** and **4c** have the tendency to yield the corresponding β-keto esters.[18] It was therefore necessary to carry out the reactions at low temperature (10–15°C) under ultrasound. The aromatic cyanohydrin (*R*)-**3a** reacts with the bromoesters **4b**,**c** predominantly to give by-products which could not be separated from the corresponding α-alkylated enaminoesters.

The Blaise reaction was also applied to the racemic trimethylsilylated ketone cyanohydrins **3d–f** (Scheme 2).

The ketone cyanohydrins **3d–f** react with *tert*-butyl α-bromoacetate **4a** to give the corresponding



Scheme 2.

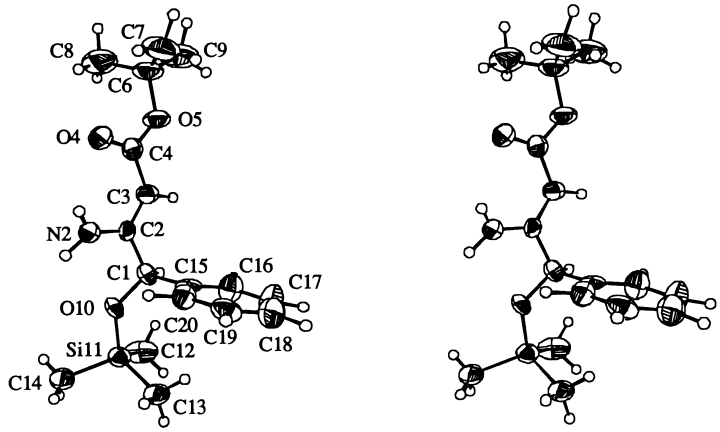


Fig. 1. ORTEP diagram of compound (*R*)-**5a**

enaminoesters **5f**,**g** in 77% yield and the enaminoester **5h** in 61% yield. We did not, however, succeed in the reaction of **3d**–**f** with *tert*-butyl α-bromopropionate **4b** or ethyl α-bromopropionate. In these cases a reaction to give the α-alkylated enaminoesters did not take place.

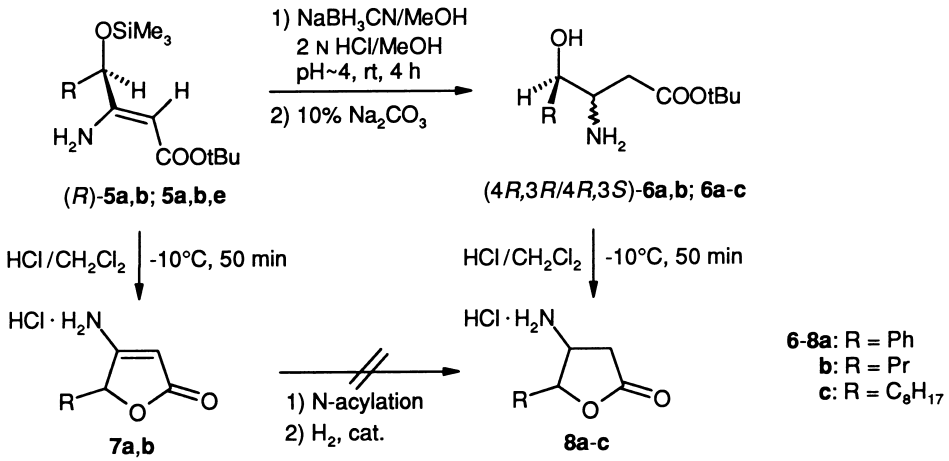
Our attempts to prepare (*R*)-**3d** by oxynitrilase catalyzed addition of HCN to (3*E*,5*E*)-octa-3,5-dien-2-one failed. This ketone was not accepted as a substrate by (*R*)-oxynitrilase. 3,5-Octadien-2-one was therefore reacted directly with cyanotrimethylsilane under ZnI_2 catalysis to yield racemic **3d** in 17% yield.

In all cases the Blaise reaction to give compounds **5** proceeded stereoselectively resulting in only one geometric isomer. The (*Z*)-configuration of **5a**–**d** was determined by comparison of ^{13}C–^{1}H coupled NMR spectra, and in the case of (*R*)-**5a** by X-ray crystallographic analysis[19] (Fig. 1).

2. Preparation of *tert*-butyl β-amino-γ-hydroxyalkanoates 6 and β-amino-γ-butyrolactones 8 from 2-alkenoates 5

β-Amino-γ-hydroxycarboxylates should be accessible by simple hydrogenation of the double bond in *tert*-butyl alkenoates **5**. Pd/C or Rh/Al_2O_3 catalyzed hydrogenation with H_2 at a higher temperature and pressure, successfully used for non-alkylated enaminoesters,[20] could not be applied due to the allyl– and benzyl–oxygen bonds in **5**, which are sensitive to hydrogenation. We therefore first studied suitable methods for the hydrogenation using racemic **5a**. We found that the application of $NaBH_4$ or KBH_4 in *tert*-butanol or ethanol as solvents did not lead to *tert*-butyl 3-amino-4-hydroxy-4-phenylbutanoate **6a** (see Scheme 3). Also the hydrogenation with aluminium hydride complexes such as sodium bis[2-methoxyethoxy]aluminium hydride or $LiAlH_4$ failed.

From these results we concluded that the nonpolar enamino system in **5** requires a stronger activation for the reaction with hydrides. One possibility for activation is the protonation of compounds **5** to



Scheme 3.

Table 2
Hydrogenation of *tert*-butyl 3-amino-4-trimethylsilyloxyalkenoates **5** to *tert*-butyl 3-amino-4-hydroxyalkanoates **6** and subsequent cyclization to γ-hydroxybutyrolactones **8**

enaminoester		diastereomeric β-amino-γ-hydroxyalkanoates **6**				γ-hydroxybutyrolactones	
	ee (%)		yield (%)	*ee* (%)[a]	ratio (%)[b]		yield (%)
5a	-	**a**	88	-	70 : 30	**8a**	49
(*R*)-**5a**	>95	**a**	80	>95	70 : 30	-	
5b	-	**b**	80	-	56 : 44	**8b**	44
(*R*)-**5b**	94	**b**	71	n.d.	60 : 40	-	
5e	-	**c**	80	-	50 : 50	**8c**	39

[a] Determined by GC after derivatization with pivaloyl chloride. [b] Determined by ^{1}H NMR spectroscopy; an assignment to *erythro* and *threo* was not possible.

the more reactive iminium salts.[21] Therefore a solution of **5a** in absolute methanol was acidified with methanolic HCl to pH ~4 (indicator: bromocresol green), and after addition of the hydrogenating agent $NaBH_3CN$ the pH value of the reaction mixture was fixed again at pH ~4 with methanolic HCl. In this way, the hydrogenated product **6a** could be isolated in 88% yield with a diastereomeric ratio of 70:30 after 4 hours reaction time, basic workup and separation of the indicator by chromatography on silica gel with CH_2Cl_2/NH_3 sat. methanol. With $NaBH_4$ in glacial acetic acid/THF[22] the yield of **6a** decreased to 20%.

Under the optimized reaction conditions described above, racemic **5b**,**e** and the optically active enaminoesters (*R*)-**5a**,**b** were hydrogenated (Scheme 3). The results are listed in Table 2.

As can be seen from Table 2, (*R*)-**5a** was hydrogenated without racemization to give **6a** in a diastereomeric ratio of 70:30. Since the use of the eluent CH_2Cl_2/NH_3 sat. methanol led to partial racemization in this case, the hydrogenation was carried out without the indicator bromocresol green. All attempts to separate the diastereomers of **6a**–**c** either by chromatographic methods or by recrystallization failed so far. An unambiguous assignment of both diastereomers to the *erythro* or *threo* configuration by X-ray analysis was therefore not possible. Also spectroscopic methods did not allow an assignment.

The selective introduction of an N-Boc or N-acetyl group in compounds **5** in order to activate the 'vinylogous amide' was very difficult in the case of **5a**. Besides the desired N-Boc substituted derivative, the O-acylated compound was formed, and unreacted **5a** was reisolated in 73% yield. The

acetylation of **5a** proceeded quantitatively but only undesired by-products were formed predominantly. The enaminoester **5b**, however, could be acetylated to the corresponding N,O-diacetyl derivative in 64% yield. Unfortunately, hydrogenation of this compound with $NaBH_4$ to **6b** failed.

As outlined in Scheme 3, two pathways appeared to offer an approach to the β-amino-γ-butyrolactones **8**. The enaminoesters **5a**,**b** could be cyclized in dichloromethane to the hydrochlorides of the unsaturated lactones **7a**,**b** with ca 80% crude yield at −10°C by passing HCl through the reaction mixture. Unfortunately both lactones **7a**,**b** were extremely unstable and decomposed completely during the conversion to N-acyl derivatives. Hydrogenation of **7** to give **8** was therefore not possible.

Under the same reaction conditions with HCl in dichloromethane, however, we succeeded in the preparation of β-amino-γ-butyrolactone hydrochlorides **8a**–**c** by cyclization of the racemic *tert*-butyl β-amino-γ-hydroxycarboxylates **6a**–**c** (Scheme 3, Table 2). The hydrochlorides **8** were obtained after recrystallization with 39–49% yield (not optimized). The butyrolactone hydrochloride **8a**[10,14] could not be isolated in an analytically pure form.

3. Experimental

3.1. Materials and methods

Avicel cellulose, cyanotrimethylsilane, ZnI_2 and sodium cyanoborohydride were purchased from Merck, nonanal and zinc dust from Fluka as well as granulated zinc (30 mesh) from Janssen Chimica. Racemic cyanohydrins **1** were prepared according to the literature,[23] *tert*-butyl 2-bromoesters **4** according to Pavlov et al.,[24] and 2-(trimethylsilyloxy)cyclohexanecarbonitrile **3f** according to Rasmussen.[25] Cyanohydrins **2** were silylated according to procedures described previously.[2a] All solvents were purified and dried as described in the literature. Blaise reactions were performed under an argon atmosphere (argon stream) in dried glassware. Melting points were determined on a Büchi SMP-20 and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC 250 F with TMS as an internal standard. Optical rotations were determined on a Perkin–Elmer polarimeter 241 LC. Preparative column chromatography was performed with glass columns of different sizes packed with silica gel S, grain size 0.032–0.063 mm (Riedel-de Haen). GC for determination of enantiomeric excess: (a) Carlo Erba HRGC 5300 Mega Series with FID, Carlo Erba Mega Series integrator, 0.4–0.5 bar or 0.36 bar hydrogen, column 20 m, phase OV 1701 or PS086 with 10% permethylated β-cyclodextrin or Bondex-unβ-5.5-Et-105 or pivaloyl bornamide; (b) Hewlett–Packard 5890 Series II with HP 7673 injector and FID, Software HP 3365 Series II ChemStation, Version A.03.21, hydrogen, column 30 m×0.32 mm, phase Chiraldex B-DA (ITC).

3.2. (R)-Oxynitrilase catalyzed preparation of (R)-cyanohydrins *2*

Performed according to a literature method.[2b,26] (*R*)-2-Hydroxydecanenitrile (*R*)-**2c**: colourless liquid, bp 77–80°C/0.001 torr; 96% *ee*, $[\alpha]_D^{23}$=+10.3 (*c* 0.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ=0.89 (broad t, *J*=6.6 Hz, 3H, CH_3), 1.27–1.53 (m, 12H, $(CH_2)_6$), 1.80–1.90 (m, 2H, CH_2), 2.33 (broad s, 1H, OH), 4.48 (t, *J*=6.7 Hz, 1H, CHCN).

3.3. (R)-2-(Trimethylsilyloxy)decanenitrile (R)-*3c*

Colourless liquid, bp 137–138°C/14 torr; $[\alpha]_D^{23}$=+39.4 (*c* 0.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ=0.21 (s, 9H, $Si(CH_3)_3$), 0.88 (broad t, *J*=6.4 Hz, 3H, CH_3), 1.20–1.50 (m, 12H, $(CH_2)_6$), 1.70–1.80 (m, 2H,

CH_2), 4.40 (t, *J*=6.6 Hz, 1H, CHCN). Anal. calcd for $C_{13}H_{27}NOSi$: C, 64.66; H, 11.27; N, 5.80. Found: C, 64.73; H, 11.17; N, 5.85.

*3.4. Preparation of (3E,5E)-2-methyl-2-(trimethylsilyloxy)octa-3,5-dienenitrile **3d***

To a solution of cyanotrimethylsilane (10.6 g, 106.8 mmol) and ZnI_2 (6 mg, 18.8 μmol) under an argon atmosphere, (3*E*,5*E*)-octa-3,5-dien-2-one[23b] (12 g, 96.6 mmol) was added dropwise. After stirring for 16 h at 50°C, the product was fractionally distilled three times *in vacuo* through a Spaltrohr® column to yield 3.7 g (17%) of the pure product as a light yellow liquid, bp 85°C/0.35 torr; ^{1}H NMR ($CDCl_3$): δ=0.21 (s, 9H, $Si(CH_3)_3$), 1.03 (t, *J*=7.4 Hz, 3H, CH_3), 1.65 (s, 3H, CH_3), 2.14 (dq, *J*=6.0, 7.4 Hz, 2H, CH_2), 5.51 (d, *J*=15.2 Hz, 1H, CH), 5.89 (dt, *J*=15.2, 5.9 Hz, 1H, CH), 6.02 (dd, *J*=9.6, 15.5 Hz, 1H, CH), 6.47 (dd, *J*=15.2, 9.6 Hz, 1H, CH). Anal. calcd for $C_{12}H_{21}NOSi$: C, 64.52; H, 9.47; N, 6.27. Found: C, 64.27; H, 9.49; N, 6.26.

3.5. Activation of zinc

Zinc dust was washed several times with 10% HCl followed by water (up to neutral pH), acetone and dry diethyl ether, and dried at 100°C *in vacuo*. This activated zinc was stored under an argon atmosphere in an exsiccator.

*3.6. Blaise reaction of O-silylated cyanohydrins **3a–c** with 2-bromoester **4a** to enaminoesters **5a,b,e**; general procedure*

To activated zinc dust (2 g, 30.6 mmol) in 7 ml THF under an argon atmosphere the respective cyanohydrin **3** (16.6 mmol) was added via syringe. This reaction mixture was heated to reflux, the heating was removed and a solution of **4a** (5 g, 25.6 mmol) in 7 ml THF was slowly added dropwise, so that the reaction mixture remained at reflux. After refluxing for a further 2 h followed by addition of 7 ml THF, the reaction mixture was cooled to −30°C, and a sat. solution of NH_4Cl was slowly added dropwise (temperature kept between −30 and −20°C). The reaction mixture was allowed to warm to room temperature, treated with 14 ml water and extracted with ethyl acetate. The combined extracts were dried ($MgSO_4$), concentrated, and the residue either distilled *in vacuo* or recrystallized from ethyl acetate (**5a**).

*3.7. Blaise reaction of **3b** with 2-bromoesters **4b,c** to enaminoesters **5c,d**; general procedure*

To activated zinc dust (1 g, 15.3 mmol) in 3.5 ml THF under an argon atmosphere, **3b** (1.4 g, 8.2 mmol) was added via syringe. Under ultrasound at 10–15°C, a solution of **4b** and **4c** (12.9 mmol), respectively, in 3.5 ml THF was slowly added dropwise. The reaction mixture was warmed to room temperature, and stirred for a further 4 h. Workup was performed as described above.

3.8. Determination of enantiomeric excess

(a) A quantity of acetic anhydride (50 μl) and 10 μl pyridine were added to a solution of 5 μl crude **2** in 200 μl dichloromethane. After heating to 60°C for between 2 and 3 h, the reaction mixture was filtered through a silica gel column (3×0.5 cm) with 3 ml dichloromethane. The enantiomeric excesses were determined directly from the filtrate by gas chromatography.

Physical and ^{1}H NMR data of compounds **5**

compd	bp (°C/Torr)	^{1}H NMR (250 MHz, $CDCl_3$, δ)
(*R*)-**5a**	mp 54-55.5°C	0.09 (s, 9 H, $Si(CH_3)_3$), 1.45 (s, 9 H, $C(CH_3)_3$), 4.52 (s, 1 H, 2-CH), 5.08 (s, 1 H, 4-CH), 7.28-7.40 (m, 5 H, Ph)
(*R*)-**5b**	85-86/0.001	0.12 (s, 9 H, $Si(CH_3)_3$), 0.90 (t, J = 7.1 Hz, 3 H, CH_3), 1.20-1.43 (m, 2 H, CH_2), 1.35 (s, 9 H, $C(CH_3)_3$), 1.50-1.69 (m, 2 H, CH_2), 4.04 (dd, J = 7.1, 4.8 Hz, 1 H, 4-CH), 4.38 (s, 1 H, 2-CH)
(*R*)-**5c**	69/0.005	0.12 (s, 9 H, $Si(CH_3)_3$), 0.92 (t, J = 7.0 Hz, 3 H, CH_3), 1.15-1.59 (m, 4 H, $(CH_2)_2$), 1.49 (s, 9 H, $C(CH_3)_3$), 1.65 (s, 3 H, 2-CH_3), 4.49 (dd, J = 3.1, 8.1 Hz, 1 H, 4-CH)
(*R*)-**5d**[a]	72-73/0.005	0.13 (s, 9 H, $Si(CH_3)_3$), 0.92 (t, J = 7.1 Hz, 3 H, CH_3), 0.98 (t, J = 7.2 Hz, 3 H, CH_3), 1.33-1.67 (m, 4 H, $(CH_2)_2$), 1.49 (s, 9 H, $C(CH_3)_3$), 1.98 (dq, J = 7.3, 14.5 Hz, 1 H, 2-C$H_a$$H_b$$CH_3$), 2.15 (dq, 1 H, $CH_a$$H_b$$CH_3$), 4.48 (dd, J = 2.3, 8.9 Hz, 1 H, 4-CH)
(*R*)-**5e**	130-132/0.001	0.12 (s, 9 H, $Si(CH_3)_3$), 0.88 (broad t, J = 6.4 Hz, 3 H, CH_3), 1.20-1.60 (m, 14 H, $(CH_2)_7$), 1.47 (s, 9 H, $C(CH_3)_3$), 4.00 (dd, J = 5.6, 6.4 Hz, 1 H, 4-CH), 4.40 (s, 1 H, 2-CH)
5f	-[b]	0.14 (s, 9 H, $Si(CH_3)_3$), 1.02 (t, J = 7.4 Hz, 3 H, CH_3), 1.46 (s, 9 H, $C(CH_3)_3$), 1.54 (s, 3 H, CH_3), 2.13 (dq, J = 7.4, 6.4 Hz, 2 H, CH_2), 4.37 (s, 1 H, 2-CH), 5.58 (d, J = 15.3 Hz, 1 H, CH=C*H*), 5.78 (dt, J = 6.4, 14.9 Hz, 1 H, CH_2C*H*=CH), 6.02 (dd, J = 10.2, 14.3 Hz, 1 H, CH_2CH=C*H*), 6.21 (dd, J = 10.0, 15.3 Hz, 1 H, CHC*H*=CH)
5g	80-81/0.09[c]	0.17 (s, 9 H, $Si(CH_3)_3$), 1.38 (s, 9 H, $C(CH_3)_3$), 1.44 (s, 6 H, 2 CH_3), 4.42 (s, 1 H, 2-CH)
5h	120/0.005	0.15 (s, 9 H, $Si(CH_3)_3$), 1.14-1.22 (m, 1 H, C$H_a$$H_b$), 1.47 (s, 9 H, $C(CH_3)_3$), 1.47-1.81 (m, 9 H, $(CH_2)_4CH_a$$H_b$), 4.57 (s, 1 H, 2-CH)

[a] 500 MHz spectrum. [b] Bulb-to-bulb distillation. [c] Mp 34-36°C.

Elemental analytical data of compounds **5**

	molecular formula (molecular weight)	calcd/found C	H	N		molecular formula (molecular weight)	calcd/found C	H	N
(*R*)-**5a**	$C_{17}H_{27}NO_3Si$	63.52	8.46	4.36	(*R*)-**5e**	$C_{19}H_{39}NO_3Si$	63.82	10.99	3.92
	(321.5)	63.49	8.44	4.27		(357.6)	63.85	11.06	3.66
(*R*)-**5b**	$C_{14}H_{29}NO_3Si$	58.49	10.17	4.87	**5f**	$C_{18}H_{33}NO_3Si$	63.67	9.80	4.13
	(287.5)	58.38	10.27	4.74		(339.5)	63.80	9.80	3.73
(*R*)-**5c**	$C_{15}H_{31}NO_3Si$	59.76	10.36	4.64	**5g**	$C_{13}H_{27}NO_3Si$	57.10	9.95	5.12
	(301.5)	59.75	10.47	4.33		(273.4)	57.27	9.97	5.01
(*R*)-**5d**	$C_{16}H_{33}NO_3Si$	60.91	10.54	4.44	**5h**	$C_{16}H_{31}NO_3Si$	61.30	9.97	4.47
	(315.5)	61.20	10.69	4.01		(313.5)	61.19	9.95	4.39

(b) A quantity of pivaloyl chloride (50 μl) was added to **6** (3 mg) in 300 μl pyridine. After standing at room temperature for 16 h, the reaction mixture was filtered through a silica gel column (3×0.5 cm) with 4 ml dichloromethane. The *ee* value was determined directly from the filtrate by gas chromatography.

3.9. Crystal structure analysis of (R)-5a

Crystal dimensions, 0.5×0.2×0.1 mm; formula, $C_{17}H_{27}NO_3Si$; formula weight, 321.46; crystal system, orthorhombic; space group, $P2_12_12_1$; a=8.0301(36), b=12.0643(84), c=19.9056(109) Å; α=β=γ=90°; V=1928.4(2) Å^3; Z=4; ρ(calcd)=1.10 g cm^{-3}; MoKα (λ=0.71073 Å); graphite monochromator; temperature 293 K; θ–2θ scan; 2θ scan limits, 2–48°; independent reflections, 1745; reflections observed $I>3\sigma(I)$, 894. The crystal structure was solved by the direct method.[19a] Full matrix least-squares refinement led to the final convergence with R=0.052 (R_w=0.050). The residual electron density was 0.44 e Å^{-3}. Complete data have been deposited at the Cambridge Crystallographic Data Centre.

3.10. Hydrogenation of enaminoesters (R)-5 to tert-butyl β-amino-γ-hydroxyalkanoates (R)-6; general procedure

A solution of **5** in dry methanol containing, with the exception of (*R*)-**5a**, bromocresol green as the indicator was acidified to pH ~4 with 2 N methanolic HCl. After addition of $NaBH_3CN$, the reaction mixture was again adjusted to pH ~4 with methanolic HCl and stirred for a further 4 h (pH control). After addition of sodium carbonate solution (10%), the aqueous phase was extracted several times with diethyl ether. The combined extracts were washed with sat. NaCl solution (up to pH 7), dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel with dichloromethane:NH_3 sat. methanol (10:1) (**6a**, (*R*)-**6b**), (7:1) (**6c**) and dichloromethane:methanol (5:1) ((*R*)-**6a**).

(*R*)-**6a**: White crystals, mp 88–106°C; dominant diastereomer: ^{1}H NMR ($CDCl_3$) δ=1.43 (s, 9H, $C(CH_3)_3$), 2.17 (dd, J=16.0, 9.4 Hz, 1H, CH_2), 3.37 (dd, J=16.0, 3.6 Hz, 1H, CH_2), 3.44 (ddd, J=9.4, 3.6, 5.0 Hz, 1H, CH–N), 4.36 (d, J=5.0 Hz, 1H, CH–O), 7.30–7.40 (m, 5H, Ph). Minor diastereomer: 1.44 (s, 9H, $C(CH_3)_3$), 2.12–2.50 (2dd, 2H, CH_2), 3.27 (ddd, J=9.0, 4.1, 6.3 Hz, 1H, CH–N), 4.40 (d, J=6.3 Hz, 1H, CH–O), 7.30–7.40 (m, 5H, Ph). Anal. calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.76; H, 8.44; N, 5.47.

(*R*)-**6b**: Colourless oil and white crystals; diastereomeric mixture: ^{1}H NMR ($CDCl_3$) δ=0.94 (broad t, 6H, $2CH_3$), 1.30–1.60 (m, 8H, $2CH_2CH_2$), 1.46 (s, 18H, $2C(CH_3)_3$), 1.90 (broad s, 3H, OH, NH_2), 2.24 (dd, J=9.5, 15.9 Hz, 1H, CH_2), 2.26 (dd, J=8.9, 15.7 Hz, 1H, CH_2), 2.44 (dd, J=15.8, 3.5 Hz, 1H, CH_2), 2.48 (dd, J=15.6, 4.1 Hz, 1H, CH_2), 2.96–3.04, 3.10–3.17 (2m, 2H, 2CH–N), 3.30–3.36, 3.49–3.55 (2m, 2H, 2CH–O). Anal. calcd for $C_{11}H_{23}NO_3$: C, 60.80; H, 10.67; N, 6.44. Found: C, 60.57; H, 10.64; N, 6.54.

6c: Wax-like white solid; diastereomeric mixture: ^{1}H NMR ($CDCl_3$) δ=0.87 (broad t, 6H, $2CH_3$), 1.21–1.66 (m, 28H, $2(CH_2)_7$), 1.46 (s, 18H, $2C(CH_3)_3$), 2.10 (broad s, 3H, OH, NH_2), 2.18–2.40 (2dd, 2H, $2CH_2$), 2.44 (dd, J=3.5, 16.0 Hz, 1H, CH_2), 2.48 (dd, J=4.1, 15.7 Hz, 1H, CH_2), 3.00 (ddd, J=4.1, 9.2, 5.3 Hz, 1H, CH–N), 3.18 (ddd, J=3.6, 9.6, 3.6 Hz, 1H, CH–N). Anal. calcd for $C_{16}H_{33}NO_3$: C, 66.85; H, 11.57; N, 4.87. Found: C, 66.86; H, 11.66; N, 4.73.

3.11. Preparation of β-amino-γ-butyrolactones 8; general procedure

HCl was passed through a solution of **6** (7.8 mmol) in 25 ml dry ethanol at −10°C for 40 min, and then the reaction mixture was stirred for a further 1 h without cooling. Ethanol was removed, and the remaining solid was dried *in vacuo* and recrystallized from ethanol or ethanol/diethyl ether.

8a·HCl: first fraction: 27% yield, 68% *de*, mp 229°C (dec); second fraction: 25% yield, 60% *de*, mp 220°C;[10,14] dominant *trans*-diastereomer: ^{1}H NMR (DMSO) δ=2.76 (dd, J=3.6, 18.5 Hz, 1H, CH_2), 3.25

(dd, *J*=8.5, 18.5 Hz, 1H, CH_2), 4.00–4.03 (m, 1H, CH–N), 5.75 (d, *J*=3.1 Hz, 1H, CH–O), 7.40–7.47 (m, 5H, Ph), 9.02 (broad s, 3H, NH_3^+). Minor diastereomer: 4.69 (broad d, *J*=7.2 Hz, 1H, CH–O).

8b·HCl: 44% yield, 22% *de*, mp 184; diastereomeric mixture: ^{1}H NMR (DMSO) δ=0.88–0.95 (2t, 6H, $2CH_3$), 1.20–1.80 (m, 8H, $2CH_2CH_2$), 2.65 (2dd, *J*=3.6, 18.4 Hz, 2H, $2CH_2$), 3.05–3.20 (2dd, 2H, $2CH_2$ interfered), 3.74–3.77 (m, 1H, CH–N), 4.06–4.12 (m, 1H, CH–N), 4.54–4.67 (m, 2H, 2CH–O), 8.80 (broad s, 6H, $2NH_3^+$). Anal. calcd for $C_7H_{13}NO_2$·HCl: C, 46.80; H, 7.85; N, 7.80; Cl, 19.73. Found: C, 46.90; H, 7.82; N, 8.01; Cl, 19.69.

8c·HCl: first fraction: 10% yield, 17% *de*, mp 190°C; second fraction: 29% yield, 43% *de*, mp 189°C; diastereomeric mixture: ^{1}H NMR (DMSO) δ=0.86 (broad t, 6H, $2CH_3$), 1.17–1.75 (m, 28H, $2(CH_2)_7$), 2.64 (2dd, *J*=3.9, 18.4 Hz, 2H, $2CH_2$), 3.04–3.19 (2dd, 2H, $2CH_2$ interfered), 3.72–3.78, 4.03–4.14 (2m, 2H, 2CH–N), 4.52–4.65 (m, 2H, 2CH–O), 8.75 (broad s, 6H, $2NH_3^+$). Anal. calcd for $C_{12}H_{23}NO_2$·HCl: C, 57.70; H, 9.68; N, 5.61; Cl, 14.19. Found: C, 57.39; H, 9.66; N, 5.45; Cl, 14.24.

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