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Enantioselective synthesis of benzocyclic α,α-dialkyl-amino acids: new insight into the solvent dependent stereoselectivity of the TMSCN addition to phenylglycinol derived imines

Ralf Warmuth,* Tamara E. Munsch, Robert A. Stalker, Bing Li and Alicia Beatty†

Department of Chemistry, Kansas State University, Manhattan, KS 66506-3701, USA

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Abstract—Different benzocycloalkane-1-amino-1-carboxylic acids **1a–e** have been synthesized via an asymmetric Strecker reaction using (*S*)-α-methylbenzylamine and (*R*)-phenylglycinol as chiral auxiliaries. The Zn^{2+}-catalyzed addition of HCN to (*S*)-α-methylbenzylamine derived ketimines of 1-tetralone (**8a**) and 1-benzosuberone (**8b**) yielded mixtures of diastereomeric aminonitriles (1*S*,1′*S*)-**10a**/(1*R*,1′*S*)-**10a** (10:1 ratio) and (1*R*,1′*S*)-**10b**/(1*S*,1′*S*)-**10b** (56:44 ratio), respectively. These aminonitriles are converted to amino acids **1a**,**b** in two steps. The addition of TMSCN to the (*R*)-phenylglycinol derived ketimines of **8a**, **8b**, 1-indanone (*8c*), 7-fluoro-1-tetralone (*8d*), 7-fluoro-1-benzosuberone (*8e*) yielded mixtures of diastereomeric trimethylsilylated aminonitriles (1*S*,1′*R*)-**14a–e**/(1*R*,1′*R*)-**14a–e**. The addition proceeded with diastereofacial selectivities ranging from 1:2.9 to 1:25. The selectivity was found to be temperature and solvent dependent. The diastereomeric ratio (dr) of aminonitriles (1*S*,1′*R*)-**14a**/(1*R*,1′*R*)-**14a** increased in different solvents in the order methanol<methanol/CH_2Cl_2 (1:2.5)<THF<toluene<$CHCl_3$<CH_2Cl_2. In the pure THF, toluene, $CHCl_3$, or CH_2Cl_2 kinetic product mixtures were formed, whereas the presence of methanol led to thermally equilibrated product mixtures. This solvent dependent change of the product dr is interpreted with a change in the TMSCN addition mechanism. Hydrolysis of the aminonitrile mixtures (1*S*,1′*R*)-**14a–c**/(1*R*,1′*R*)-**14a–c** and oxidative cleavage of the auxiliary yielded **1a–c**, which showed the (*S*)-configuration as the major isomer.

1. Introduction

The α-helix and the 3_{10}-helix are important secondary structures which occur in proteins and polypeptides. When removed from their natural context, however, most helices partially or completely unfold into random coils. Different strategies have been developed in order to affect the helix-coil transition of short peptides.[1] These include the covalent attachment of nucleation sites or templates to the N-terminus of the peptide,[2] the covalent linkage of amino acid side chains,[3] ligand and metal interactions,[4] or the incorporation of α,α-disubstituted glycines into the peptide backbone.[5–7]

In particular, α-aminoisobutyric acid (Aib), 1-aminocycloalkane-1-carboxylic acid (Ac_nc, n=3–9, 12), and the benzannulated derivative of Ac_6c (**1a**) have proven to be superb in stabilizing short helical peptides (Chart 1).[5,6,8]

Among the natural amino acids, alanine is ranked as the strongest α-helix former. However, a recent investigation by Daniel Kemp and co-workers has revealed that the helical propensity of alanine in alanine-rich peptides varies widely and is strongly context dependent.[9] An important factor for the stability of such alanine-rich α-helices is the positioning of polar amino acids (lysine, arginine, glutamate, glutamine) in the peptide sequence. In addition, the packing of their flexible side chain bearing the polar group with respect to the helix barrel results in local hydrophobic and electrostatic stabilization.

We are interested in the synthesis of various conformationally constrained lysine derivatives of the general type **2**. Incorporation of such lysine derivatives into a helical peptide, will align the polar protonated amino group in a very precise orientation relative to the overall macroscopic dipole moment of the helix. Host–guest studies using such derivatives are expected to further support Kemp's conclusions.

For the synthesis of lysine derivatives **2**, we decided to introduce the amino acid moiety via an asymmetric Strecker-type reaction from a corresponding benzocycloalkanone. Here, we report an investigation of this type of asymmetric Strecker reaction and, in particular, on the effects of solvent on the diastereofacial selectivity of the TMSCN addition to (*R*)-phenylglycinol derived ketimines.

Keywords: asymmetric Strecker reaction; dialkyl-amino acid; solvent effect.

* Corresponding author. Tel.: +785-532-6665; fax: +785-532-6666; e-mail: warmuth@ksu.edu

† Present address: Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, Indiana, USA.

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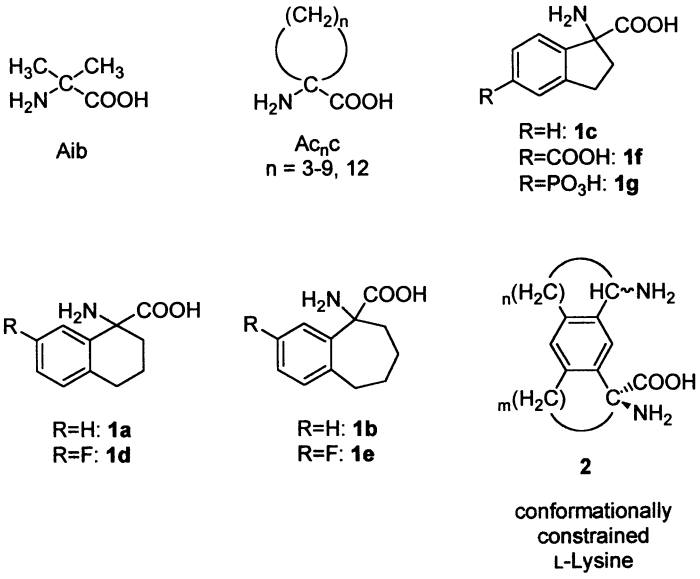
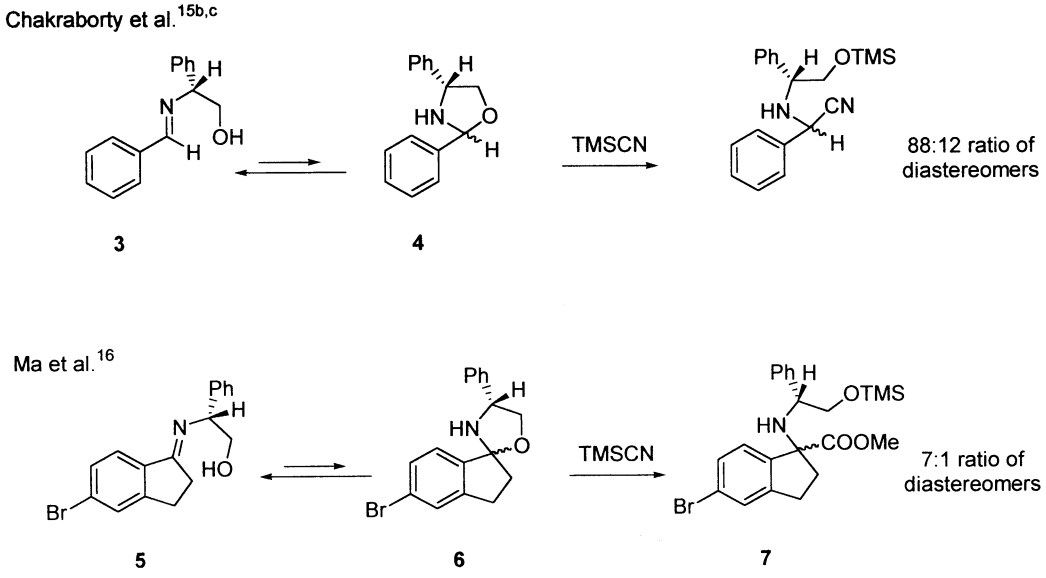


Chart 1.

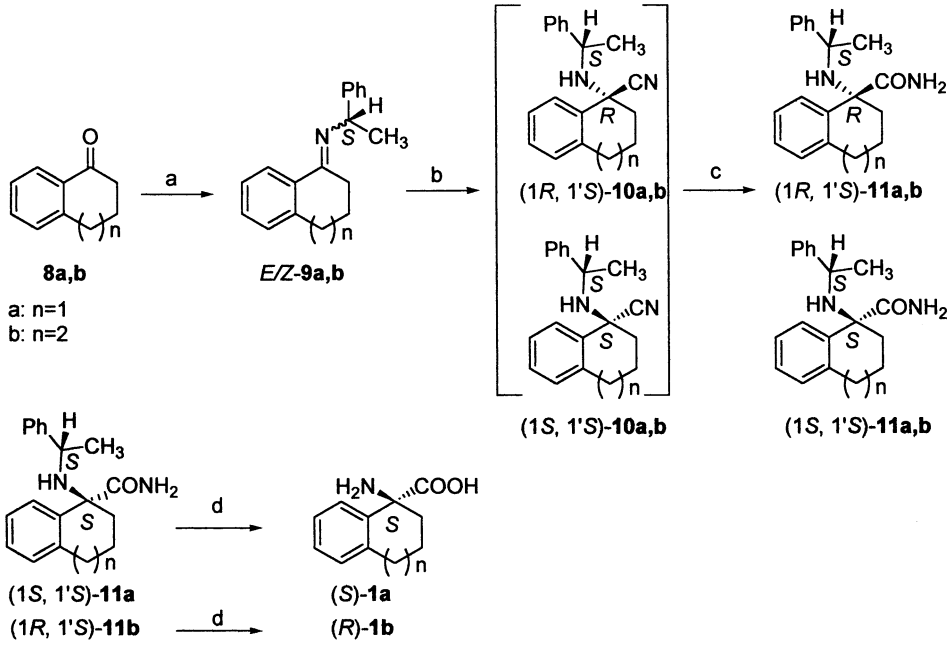
2. Results and discussion

The asymmetric Strecker reaction is one of the most important methods for the synthesis of chiral α-amino acids and α,α-dialkyl-amino acids.[10–15] In recent years, highly efficient catalysts have been developed, in particular for the asymmetric synthesis of α-phenylamino acids, which in most reported cases give excellent enantiomeric excesses.[12] A second, more traditional approach is the use of enantiopure chiral amino-auxiliaries, that, after the successful Strecker reaction, can be chemically modified to yield the free amino acids. Among those, α-methylbenzylamine and phenylglycinol have proven to be excellent and have been widely used to synthesize natural and unnatural α-amino acids as well as α,α-dialkyl amino acids from various aldehydes and ketones.[13–15] Recently, Chakraborty et al. reported the highly diastereoselective addition of TMSCN to a variety of α-phenylglycinol derived benzaldimines **3**.[13b,c] Product diastereomeric ratios (dr) of up to 90:10 were obtained. The failure to observe a higher dr was attributed in part to the presence of 5–10% of diastereomeric 1,3-oxazolidines **4**, which might be in an equilibrium with **3**. While our investigation of the asymmetric Strecker synthesis of **1a–e** was in progress, Ma et al. reported the asymmetric synthesis of the indane-amino acid derivatives **1f–g**.[15] Ma's successful synthesis of **1f–g** was the first example of asymmetric synthesis of cyclic α-alkyl-α-aryl amino acid via the Strecker reaction (Scheme 1).

The key step in the multi-step reaction sequence toward **1f–g** was the TMSCN addition to the (*R*)-phenylglycinol derived indanone imine **5**, which gave the two isomeric aminonitriles **7** in an excellent 7:1 ratio.[15] Ma et al. also



Scheme 1.



Scheme 2. a: (*S*)-α-methylbenzylamine, *p*-TsOH, benzene, reflux, 2 days; b: HCN, cat. ZnI_2, CH_2Cl_2, 0°C; c: conc. H_2SO_4/hexanes/CH_2Cl_2 (2:1:1); 3.5 days; r.t.; d: H_2/Pd/C; MeOH/1 M HCl aq (1:1); 24 h.

reported the presence of an imine/1,3-oxazolidine (**6**) mixture. In order to avoid the formation of 1,3-oxazolidines, which might be a disadvantage of phenylglycinol derived imines, we initiated our investigation on the asymmetric synthesis of **1a–e** by using (*S*)-α-methylbenzylamine as the chiral amino auxiliary, which lacks the ability to cyclize.

2.1. (*S*)-α-Methylbenzylamine as chiral auxiliary for the asymmetric Strecker reaction

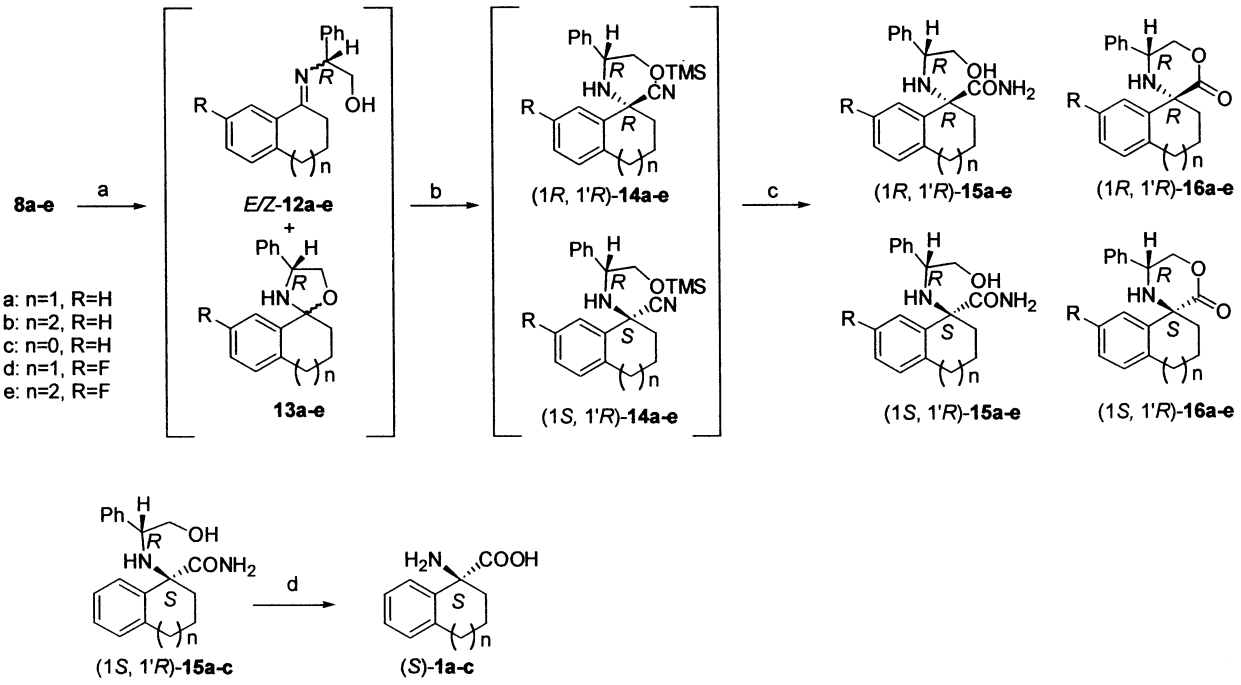
In a general procedure of this Strecker reaction, the intermediate *E*-imine (*E*-**9a**) is first formed by refluxing tetralone (**8a**) and 1.1 equiv. (*S*)-α-methylbenzylamine in the presence of catalytic amounts of *p*-tolylsulfonic acid under constant azeotropic removal of water (Scheme 2).[16] Addition of 2.5 equiv. HCN to a cooled solution of *E*-**9a** in dichloromethane in the presence of catalytic amounts of ZnI_2 (0.1 mol%) afforded a 10:1 mixture of the diastereomeric aminonitriles **10a** (83% yield) as determined by ^{1}H NMR. Attempts to isolate or separate both the aminonitriles led to the quantitative decomposition in agreement with similar observations by Frahm et al.[11g] Hydrolysis of both aminonitriles was possible using a protocol developed by Frahm et al. for the hydrolysis of dialkylaminonitriles.[11g] The slow addition of conc. H_2SO_4 to a cold solution of the crude aminonitriles in hexane/dichloromethane, which was then stirred for 3–5 days, afforded a 10:1 mixture of the desired diastereomeric amides **11a** (Table 1).

Application of the same reaction sequence to benzosuberone **8b** afforded a 44:55 mixture of the diastereomeric amides **11b**. The low observed diastereomeric excess is most likely a result of the formation of both *E*-**9b** and *Z*-**9b** (44:55) in the initial condensation of **8b** with α-methylbenzylamine. The assignment of the major isomer to *Z*-**9b** is based on ROESY experiments and is consistent with molecular mechanics calculations (MM2* with $CHCl_3$ solvent force field),[17–19] which predict a lower conformational energy for *Z*-**9b** as compared to *E*-**9b** (ΔE_{calc}= 0.35 kcal mol^{-1}; ΔG_{exp}(353 K)=0.2 kcal mol^{-1}). The fact that the observed imine ratio and the dr for **10b** and for **11b** are virtually identical suggests that the TMSCN

Table 1. Asymmetric Strecker reaction of ketones **8a** and **8b** with (*s*)-α-methylbenzylamine and HCN

Ketone	*E*/*Z*-imine ratio[a] 9	Ratio of diastereo. aminonitriles[b] (*S*,*S*)-**10a**, **b**: (*R*,*S*)-**10a**, **b**	Yield (%)	Ratio of diastereo. amides[c,d] (*S*,*S*)-**11a**, **b**: (*R*,*S*)-**11a, b**	Yield (%)
8a	>40:1[e]	n.d.[f]	83	10:1	86
8b	46:54	44:56[g]	62	44:55	50

[a] Determined from the relative integrals of the quartets assigned to the methine protons of both isomers in the ^{1}H NMR spectrum.
[b] In CH_2Cl_2 at 0°C in the presence of 0.1 mol% anhydrous ZnI_2.
[c] Determined from the relative integrals of the quartets assigned to the benzylic methine protons of (1*S*,1′*S*)-**11a**(**b**) and (1*R*,1′*S*)-**11a**(**b**), respectively in the ^{1}H NMR spectrum of the crude reaction mixture.
[d] Conc. H_2SO_4/hexane/CH_2Cl_2 (2:1:1), 3.5 days.
[e] *Z*-isomer could not be detected by ^{1}H NMR spectroscopy.
[f] n.d.: not determined.
[g] Determined from the relative integrals of the quartets assigned to the benzylic methine protons of (1*S*,1′*S*)-**10b** and (1*R*,1′*S*)-**10b**, respectively in the ^{1}H NMR spectrum of the crude reaction mixture.



Scheme 3. a: (*R*)-phenylglycinol, toluene, reflux, 6 h; b: TMSCN, CH_2Cl_2, 0°C; c: conc. H_2SO_4/hexanes (1:1); 3–5 days; r.t.; d: 1. $Pb(OAc)_4$, MeOH/CH_2Cl_2 (1:2) 1 h. 2. 6M HCl aq reflux 3 h. 3. EtOH, propylene oxide, reflux, 20 min.

addition to each isomeric imine proceeds with high diastereofacial selectivity.

Separation of both diastereomeric amide mixtures **11a** and **11b** was possible using standard column chromatrography, though with great difficulty. Catalytic hydrogenation of the major isomers of **11a** and **11b** followed by hydrolysis afforded quantitatively the corresponding amino acids **1a** and **1b**, respectively.

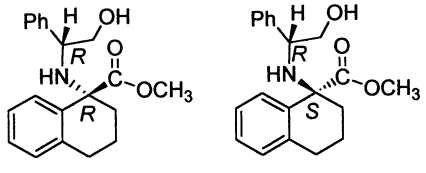
The Zn^{2+}-catalyzed TMSCN addition to the chiral (*S*)-α-methylbenzylamine derived tetralone-imine **8a** proceeds with higher diastereofacial selectivity (10:1) as compared to the 7:1 ratio reported by Ma et al. for the reaction of **5**.[15] In order to compare both chiral amino auxiliaries, we investigated this asymmetric Strecker method.

2.2. (*R*)-Phenylglycinol as chiral auxiliary for the asymmetric Strecker reaction

In a typical procedure (Scheme 3), a solution of the tetralone **8a** and (*R*)-phenylglycinol in toluene was heated at reflux under argon for 6 h, to give a reaction mixture comprised predominately of the *E*-imine *E*-**12a** (80–90%) along with a small amount of ring-closed 1,3-oxazolidines **13a** and unreacted **8a** (<5%). The *Z*-imine *Z*-**12a** was not found in the reaction mixture. Further heating led only to an increased amount of the undesired 1,3-oxazolidines. Addition of a catalytic amount (10 mol%) of *p*-TSA and/or substitution of xylene for toluene substantially shortened the reaction time (<2 h). Attempts to purify **12a** by crystallization or flash column chromatography were unsuccessful.

The reaction of this mixture with TMSCN (2 equiv.) in CH_2Cl_2 at 0°C for 1 h gave two new compounds in a 14:1 ratio (96% conversion). We assign these two compounds to the diastereomeric aminonitriles (1*R*,1′*R*)-**14a** and (1*S*,1′*R*)-**14a**. The assignment is based on the similar observation by other groups for related systems,[14,15] and on the outcome of the subsequent hydrolysis of this reaction mixture. Treatment of a hexane solution of the aminonitriles **14a** with precooled conc. H_2SO_4 at −10°C for 3 h, followed by gradual warming to room temperature and prolonged stirring at ambient temperature resulted in a mixture of the corresponding diastereomeric aminoamides **15a** and a small amount of the diastereomeric lactone **16a** (Table 2). If the crude aminonitrile mixture **14a** was hydrolyzed as described and the crude hydrolysis products were treated with a saturated solution of ammonia in methanol (24 h, rt) in order to convert lactones **16a** to the corresponding aminoamides **15a**, the latter showed an identical dr as observed for **14a**.

Since the hydrolysis of ketimine derived aminonitriles has always been difficult due to their thermal lability,[11g,12k] we undertook a more systematic investigation of alternative methods that are less time-consuming than the Frahm procedure.[11g] Refluxing the crude aminonitrile (**14a**) mixture in conc. HCl (2 h) followed by Fischer esterification (MeOH, conc. H_2SO_4 cat., reflux, 2 h) afforded the diastereomeric methyl esters **17a** (14:1 ratio) accompanied with small amounts of lactone **16a** (80% total yield).



Ma's direct methanolysis protocol using methanolic HCl afforded **7** in low yield (25%), with a large quantity of

Table 2. Asymmetric Strecker reaction of ketones **8a–e** with (*R*)-phenylglycinol and TMSCN

Entry	Ketone	Ratio[a] **12**:**13**	Ratio [b] (1*S*,1′*R*)-**14**:(1*R*,1′*R*)-**14**	Ratio[a] (1*S*,1′*R*)-**15**:(1*R*,1′*R*)-**15**	Yield[c] **15** (%)	Yield[c] **16** (%)	Ratio (1*S*,1′*R*)-**16**:(1*R*,1′*R*)-**16**	Recovered ketone (%)
1	**8a**	86:14[d,e]	14:1[a]	14:1	85	4	[f]	3
2	**8b**	[g]	3.4:1	3.2:1	29	23	3.7:1	2
3	**8c**	>40:1[d]	9.5:1[h]		0[i]	75[i]	[f]	0
4	**8c**	>40:1[d]	9.5:1[h]	10:1	54[j]	27[j]	[f]	0
5	**8d**	89:11[d,k]	11:1[a]	10:1	74	4	[f]	11
6	**8e**	[g]	2.9:1	1.7:1	27	7	12:1	31

[a] Determined from the integrals of the 1′ methine proton signals of the products in the ^{1}H NMR spectrum of the reaction mixture after >95% conversion.
[b] The reaction was carried out in CH_2Cl_2 at 0°C using 1.5–2 mol equiv. TMSCN per mol imine.
[c] Yield of isolated product (mixture).
[d] Only *E*-imine was detected.
[e] 10:4 ratio of diastereomeric 1,3-oxazolidines **13a**.
[f] Only the diastereoisomer (1*S*,1′*R*-)-**16a**,**c**,**d**.
[g] Complex mixture of *E*-**12**, *Z*-**12**, and two diastereomeric 1,3-oxazolidines (1*S*,1′*R*)-**13** and (1*R*,1′*R*)-**13**.
[h] Determined from the integrals of the N–*H* proton signals of the products in the ^{1}H NMR spectrum of the reaction mixture.
[i] Aminonitrile hydrolysis was carried out for 5 days.
[j] Aminonitrile hydrolysis was carried out for 3 days.
[k] 7:4 ratio of diastereomeric 1,3-oxazolidines **13d**.

tetralone recovered from the reaction mixture.[15] However, **17a** was obtained quantitatively when a dichloromethane solution of **14a** (14:1 mixture of diastereomers) was saturated with HCl gas followed by the addition of a small amount of methanol (17 vol%).

Application of the above general Strecker procedure to **8b–e** gave the corresponding amides **15b–e** accompanied with small amounts of lactones **16b–e** in good yields and diastereomeric product ratios (Table 2). We further confirmed the dr of the TMSCN additions by converting a small sample of the crude aminonitrile hydrolysis products (**15** and **16**) completely to the lactones **16a–e** via extensive reflux in toluene; the resulting lactones were examined by either analytical HPLC or ^{1}H NMR spectroscopy. In all TMSCN additions, the major isomer had the (*S*)-configuration as determined by X-ray crystallographic analysis of the corresponding isolated lactones except for lactones **16b** and **16d**, where suitable crystals could not be obtained, and assignment of absolute stereochemistry was performed by comparison of their ^{1}H NMR spectra with those of **16e** and **16a**, respectively.

The chiral auxiliary can be readily cleaved by standard procedures.[14b,c,15,20] Thus, treatment of (1*S*,1′*R*)-**15a–c** with lead tetraacetate in dichloromethane/methanol, followed by hydrolysis with refluxing 6 M HCl afforded the amino acid hydrochlorides (*S*)-**1a–c**·HCl, which were converted to (*S*)-**1a–c** with propylene oxide in ethanol (60–72% yield). A comparison of the optical rotation of these products with those obtained from the catalytic hydrogenation of the major isomer of **11a** and **11b** allowed us to determine the stereochemical outcome of the Strecker reaction using (*S*)-α-methylbenzylamine. The configuration of the major amides are (1*S*,1′*S*)-**11a** and (1*R*,1′*S*)-**11b**. The opposite configuration of the major isomer (1*R*,1′*S*)-**11b** as compared to the major isomer (1*S*,1′*S*)-**11a**, is consistent with the 45:55 (*E*/*Z*) ratio of **9b** and with our suggestion that, the addition to each isomeric imine **9b** proceeds with high diastereofacial selectivity.

In the case of the five- and six-membered rings, the diastereomeric product ratios are excellent, whereas the reaction with the seven-membered ring ketones **8b**,**e** gave lower diastereofacial selection due to the presence of a complex mixture of isomeric imines *E*/*Z*-**12b**,**e** and 1,3-oxazolidines **13b**,**e**. However, we noticed that while the amides **15e** were formed in a low 1.7:1 diastereomeric ratio, the dr of isolated lactones **16e** after the reaction of **14e** with H_2SO_4 was substantially higher (12:1). Thus, we could obtain reasonable quantities of lactone (1*S*,1′*R*)-**16e** and amide (1*R*,1′*R*)-**15e** via a kinetic separation. In order to test whether the outcome of this kinetic separation could be improved by varying the reaction conditions, we measured the rate of lactonization of **15b** in tetrachloroethane-d_2 at various temperatures by ^{1}H NMR spectroscopy. At all temperatures, first order kinetics were observed for both diastereomers. An Arrhenius plot (Fig. 1) provided the activation energies E_a((1*S*,1′*R*) isomer)=24 kcal mol^{-1} and E_a((1*R*,1′*R*) isomer)=26 kcal mol^{-1} and *A* values of 1×10^{12} s^{-1} and 5×10^{12} s^{-1} for the (1*S*,1′*R*) and (1*R*,1′*R*) isomers, respectively. Unfortunately, the difference in activation energies is very small. Thus, only a slight increase in the dr can be expected if the lactonization is carried out below room temperature.

2.3. Solvent and temperature effect

The selectivity of the TMSCN addition could be further

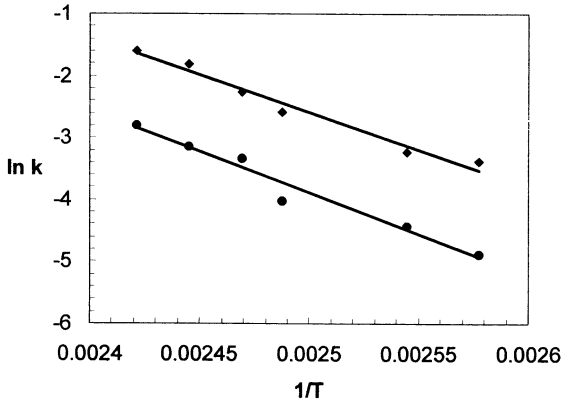


Figure 1. Arrhenius plot for thermal cyclization of (1*S*,1′*R*) (◆) and (1*R*,1′*R*) (●) **15b**.

Table 3. Solvent and temperature dependence of the TMSCN addition to imine **12a**

Entry	Solvent	T (°C)	Reaction time	Composition[a] (%)			Ratio of diastereomeric aminonitriles[b] (1*S*,1′*R*)-**14a**:(1*R*,1′*R*)-**14a**
				12a	**14a**	**18a**	
1	CH_2Cl_2[c]	25	1 h	–	85	15	12.5:2
2	CH_2Cl_2[c]	0	1 h	–	96	4	14:01
3	CH_2Cl_2[d]	0	1 h	–	96	4	6.3:1
4	CH_2Cl_2[c]	−10	4.5 h	–	96	4	21:01
5	CH_2Cl_2[e]	−10	2.5 h	–	90	10	19:01
6	CH_2Cl_2[c]	−26	40 h	–	96	4	25:1
7	$CHCl_3$[c]	0	1 h	–	85	15	11.5:1
8	Toluene[c]	0	9 h	–	85	15	9:1
9	THF[c]	0	25 h	–	85	15	6.3:1
10	CH_2Cl_2/MeOH[c] (2.5:1)	25	18 h	12	88	–	3.5:1
11	MeOH[c]	25	5 days	10	90	–	2:1[f]

[a] Determined from the relative integrals of multiplets assigned to the methylene protons of the ((*R*)-2′-hydroxy-1′-phenylethyl)-group of **18a**, (1*S*,1′*R*)-**14a**, and (1*R*,1′*R*)-**14a**, respectively in the ^{1}H NMR spectrum of the crude reaction mixture after the indicated reaction time.
[b] Determined from the relative integrals of multiplets assigned to the methylene protons of the ((*R*)-2′-hydroxy-1′-phenylethyl)-group of (1*S*,1′*R*)-**14a** and (1*R*,1′*R*)-**14a**, respectively in the ^{1}H NMR spectrum of the crude reaction mixture.
[c] 2 equiv. TMSCN were added to 0.19–0.28 M **12a** in the given solvent (mixture).
[d] 2 equiv. Et_4NCN were added to 0.26 M **18a**·HCl in CH_2Cl_2. The TMS–iminium hydrochloride **18a**·HCl was prepared by the reaction of **12a** with 1.1 equiv. TMSCl in CH_2Cl_2 at 0°C for 40 min followed by the removal of excess TMSCl and the solvent.
[e] **18a** (0.34 M) was dissolved in a CH_2Cl_2 solution containing 2 equiv. of TMSCN and 2 equiv. of methanol. The TMS–imine **18a** was prepared by the addition of 2 equiv. TMSCN to **12a** in THF at 0°C. After 10 min, the solvent, HCN and excess TMSCN are pumped off leaving **18a** as yellowish oil.
[f] Ratio of desilylated aminonitriles.

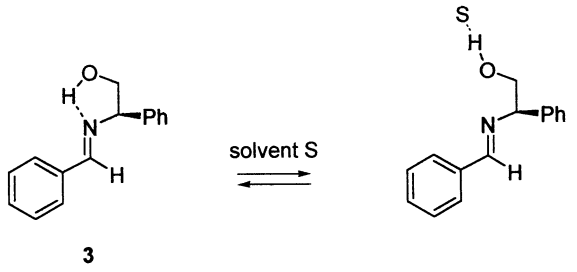
Table 4. Temperature dependence of the TMSCN addition to imine **12c**

Entry	Solvent	T (°C)	Reaction time (h)	Conversion[a] (%)	Ratio of diastereomeric aminonitriles[b] (1*S*,1′*R*)-**14c**: (1*R*,1′*R*)-**14c**
1	CH_2Cl_2	0	3	93	9.5:1
2	CH_2Cl_2	−10	8	90	10.5:1
3	CH_2Cl_2	−26	23	93	11.5:1

2 equiv. TMSCN were added to 0.25–0.28 M **12c** in the CH_2Cl_2 at the given temperature.
[a] Determined from the relative integrals of the multiplets assigned to the methine protons of the ((*R*)-2′-hydroxy-1′-phenylethyl)-group of (1*S*,1′*R*)-**14c**, (1*R*,1′*R*)-**14c**, and the TMS–imine **18c** formed from **12c**, respectively in the ^{1}H NMR spectrum of the crude reaction mixture after the indicated reaction time.
[b] Determined from the relative peak heights of the singlets assigned to the N–*H* protons of (1*S*,1′*R*)-**14c**, and (1*R*,1′*R*)-**14c**, respectively in the ^{1}H NMR spectrum of the crude reaction mixture after the indicated reaction time.

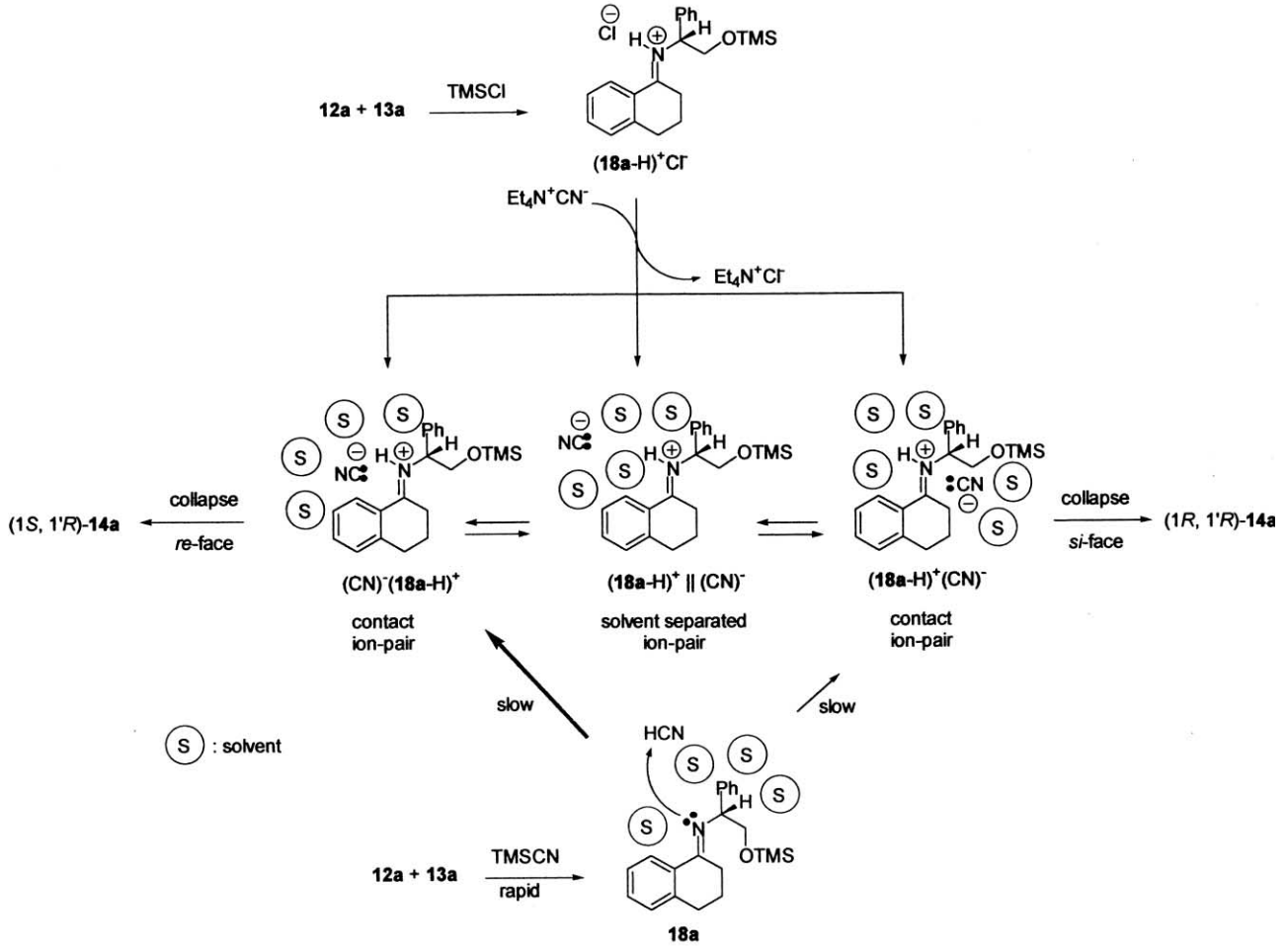
improved by lowering the temperature (Tables 3 and 4). Whereas, the dr improved only slightly for **12c** (Table 4), a two-fold increase of the dr was observed for the addition to **12/13a** upon lowering the temperature from 25 to −26°C. The solvent, however, had a much stronger effect on the observed selectivity (Table 3, entries 1, 7–11). Remarkable solvent effects had earlier been observed by other groups for phenylglycinol and α-methylbenzylamine derived aldemines and ketimines and are characteristic for asymmetric Strecker syntheses.[11f,g,13a,14b,c] Chakraborthy et al. explained the change of the diastereofacial selectivity for **3** upon changing the solvent with the formation or disruption of an intramolecular hydrogen bond between the OH-group and the imine electron lone pair (Scheme 4).[14b] This hydrogen bond was postulated to conformationally lock the phenyl substituent in place which shields more efficiently the *si* face. Conclusive evidence for such a hydrogen bond, however, could not be obtained. For **12/13a** the selectivity as well as the rate of the TMSCN addition increases in the order methanol < methanol/CH_2Cl_2 (1:2.5)<THF<toluene<$CHCl_3$<CH_2Cl_2. Though the lowest selectivity is clearly observed in the most polar solvent, the selectivity is not simply a measure of the solvent polarity which decrease in the order methanol>methanol/CH_2Cl_2 (1:2.5)>CH_2Cl_2>$CHCl_3$>THF>toluene.

A careful NMR investigation gave further insight into the mechanism and the role of the solvent on the diastereofacial selectivity. When **12a/13a** was reacted with 2 equiv. TMSCN in THF at 0°C for 10 min followed by the removal of all volatile components, the ^{1}H NMR spectrum indicated complete conversion to the silylated imine **18a** with only traces (<2%) of **14a** formed. When the course of this reaction in dichloromethane was monitored by periodically removing samples and examining the products by ^{1}H NMR, only **18a** (85%) and **14a** (15%) could be detected after 30 s. At subsequent times, the ratio of **18a** to **14a** had decreased to reach about 1:20 after 1 h. In order to



3

Scheme 4.



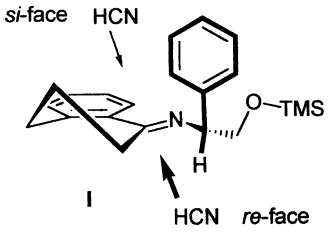
Scheme 5.

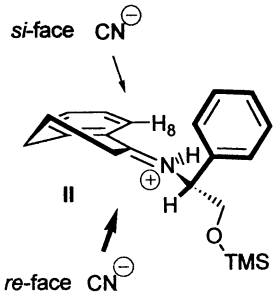
rationalize these observations, we propose the following general mechanism (Scheme 5).

Both **12a** and **13a** react rapidly with TMSCN to yield **18a** and HCN, followed by the slower addition of HCN to **18a** which is initiated by the protonation of the imine electron lone pair to form a contact ion pair (**18a**-H)$^+$CN$^-$.[21] The contact ion pair either collapses to **14a** or forms a solvent-separated ion pair (**18a**-H)$^+$||CN$^-$.

The extent of solvent separated ion pair formation obviously depends strongly on the chosen solvent and plays a key role to rationalize the observed solvent effects. Based on this mechanism, we group solvents in three categories (A–C):

(A) In solvents, such as dichloromethane and chloroform, which are very weakly iminium ion solvating, the contact ion pair (**18a**-H)$^+$CN$^-$, once formed, immediately collapses to product. The high preference for an attack of HCN from the *re*-face in these solvents can be rationalized by a Felkin–Anh model **I** in which the phenyl substituent lies almost perpendicular to the plane of the imine bond.[22] This reactive conformation **I** is supported by molecular mechanics calculations. The observed diastereomeric product ratio reflects the difference in activation energies for protonation of **18a** by HCN from the *re*- or the *si*-face.





(B) In solvents, such as tetrahydrofuran or toluene, which allow for a better solvation of the iminium ion (**18a**-H)$^+$ via lone pair–cation or π–cation interactions,[23] the initially formed contact ion pair dissociates completely or to some extent to a solvent separated ion pair (**18a**-H)$^+$||CN$^-$.

Table 5. Room temperature epimerization of (1*S*,1′*R*)-**14a**/(1*R*,1′*R*)-**14a** (14:1 ratio)

Entry	Solvent	Final reaction ratio (1*S*,1′*R*)-**14a**:(1*R*,1′*R*)-**14a**	Time
1	CD_3OD/CD_2Cl_2 (1:2)	3.8:1	45 min
2	CD_3OD	3.5:1	<5 min
		2.6:1[a]	5 days
3	$CDCl_3$	3.5:1	2 weeks

[a] Ratio of desilylated aminonitriles.

Again, the observed diastereomeric product ratio reflects now the difference in activation energies for nucleophilic attack of CN^- from either the *re*- or the *si*-face of (**18a**-H)$^+$. The preferred nucleophilic attack can be again explained by assuming a Felkin–Anh transition state model **II**. Even though the positioning of the phenyl substituent, with respect to the imine double bond, might be identical in **I** and **II**, steric interactions between the iminium proton and H-8 (see **II**) will tilt the iminium bond out of the plane of the fused aryl ring. As a consequence, we expect a different diastereofacial selectivity for the reaction with (**18a**-H)$^+$ as compared to **18a**. This interpretation was supported by the following observation (Table 3, entry 3 and Scheme 5). When we prepared (**18a**-H)$^+Cl^-$ in CH_2Cl_2 via the addition of 1 equiv. of TMSCl to **12a/13a**, and subsequently added 2 equiv. of $NEt_4{}^+CN^-$ at 0°C, the observed diastereomeric product ratio (1*S*,1′*R*)-**14a**:(1*R*,1′*R*)-**14a**=6.3:1 was identical to the ratio observed in THF for the addition of TMSCN to **12a/13a** (Table 3, entry 9).

(C) In polar, protic solvents such as small alcohols or in the presence of a polar, protic co-solvent, which is able to solvate anions and cations, a thermodynamic diastereomeric product mixture is obtained. In these solvents, the reactivity of the cyanide ion is very low and the epimerization of the products **14a** is faster than their formation. This is supported by epimerization studies (Table 5). Epimerization is very slow in nonpolar solvents. However, in the presence of methanol, epimerization leads rapidly to the thermodynamic product mixture of about 3.5:1.

It is likely that this mechanistic model is also true for the addition of TMSCN or HCN to other phenylglycinol or α-methylbenzylamine derived ketimines or aldimines, in which similar drastic changes in the diastereofacial selectivity have been observed upon changing the solvent from category A to B to C.[13a,14b]

2.4. What is the role of 1,3-oxazolidines on the stereochemistry of the addition of TMSCN to phenylglycinol derived ketimines and aldimines?

Finally, we would like to address this important issue.[14b,15] According to our NMR investigations, the amount of **13a** has no influence on the selectivity in the addition of TMSCN to **12a/13a** mixtures. Prior to the attack of HCN or CN^-, **12a** and **13a** are quantitatively converted to **18a** independent of the **12a/13a** ratio. Even though (1*R*,1′*R*)-**13a** and (1*S*,1′*R*)-**13a** could form *Z*-**18a** and also *E*-**18a** upon reacting with TMSCN, the rate constants leading to *Z*-**18a** should be orders of magnitude smaller as compared to the rate constants leading to *E*-**18a** in light of the large energy difference between *Z*-**18a** and *E*-**18a** (5.2 kcal mol^{-1} based on molecular mechanics calculations: MM2* with $CHCl_3$-solvent force field). However, the situation is certainly different for imines, which are formed as a mixture of *E*- and *Z*-isomers, such as *E*/*Z*-**12b**. Here, different 1,3-oxazolidine formation rates from the *E*- and *Z*-isomers might dictate the ratio of *Z*-imine **12b** to *E*-imine **12b** during the high temperature reaction of phenylglycinol with the corresponding ketone. This might explain why the observed diastereomeric ratios (1*R*,1′*R*)-**14b**:(1*S*,1′*R*)-**14b** and (1*R*,1′*R*)-**14e**:(1*S*,1′*R*)-**14e** are much larger than the ratio (1*S*,1′*S*)-**10b**:(1*R*,1′*S*)-**10b**. (Table 1 and 2).

3. Conclusion

In summary, we have reported an improved asymmetric Strecker methodology which allows for the facile synthesis of a range of benzocyclic amino acids in good yields and high diastereoselectivity, using easily accessible aryl ketones as starting materials. Our mechanistic analysis of the addition of TMSCN to (*R*)-phenylglycinol derived ketimines shows that this addition proceeds through different mechanisms if the solvent is changed. The fate of the TMS–iminium-cyanide contact ion pair (**18**-H)$^+CN^-$, which is generated via the protonation of the initially formed TMS–imine **18** by HCN, is important. This contact ion pair either collapses to the aminonitrile, which shows a diastereomeric product ratio that is primarily determined by the facial selectivity for the protonation of **18** by HCN, or, alternatively, in solvents that strongly interact with the iminium ion (**18**-H)$^+$, the contact ion pair dissociates to a solvent separated ion pair (**18**-H)$^+\|CN^-$, which shows its own facial selectivity for the collapse to products. We believe that our interpretation of the solvent dependent diastereoselectivity is also important for the understanding of similar, sometimes dramatic solvent effects in related TMSCN or HCN additions to (*R*)-phenylglycinol and (*S*)-α-methylbenzylamine derived imines.

4. Experimental

4.1. General

1-Indanone, 1-tetralone, 1-benzosuberone and 8-fluoro-1-benzosuberone were obtained from Aldrich Chemical Company, and were distilled under reduced pressure prior to use when necessary. 7-Fluoro-α-tetralone was synthesized from fluorobenzene and succinnic anhydride in three steps.[24,25] Dichloromethane, methanol and tetrahydrofuran were freshly distilled from calcium hydride, magnesium methoxide or benzophenone ketyl respectively, under an

inert atmosphere. All other reagents were used without further purification. All reactions were conducted under an argon atmosphere unless otherwise stated. ^{1}H- and ^{13}C-NMR spectra were obtained using a 400 MHz Varian FT NMR spectrometer or a Varian 200 MHz FT NMR spectrometer. Spectra were referenced to the residual $CHCl_3$, $CHDCl_2$, THF-d_7, CHD_2OD, $CHD_2S(O)CD_3$, or 1,1,2,2,-tetrachloroethane-d_1, signals at δ 7.27, 5.32, 3.58, 3.31, 2.50 or 5.96, respectively. MALDI-TOF mass spectra were obtained on an IonSpec HiRes MALDI mass spectrometer. FAB-MS were determined on a ZAB SE instrument with 3-nitrobenzyl alcohol (NOBA) matrix from the mass spectrometry laboratory at the University of Kansas, Lawrence, Kansas. CHN analyses were obtained from Desert Analytics, Tucson, Arizona. Gravity chromatography was performed on Bodman silica gel (70–230 mesh). HPLC was performed on Rainin Varian Dual Pump System.

4.2. X-Ray crystallography

Crystalline samples of lactones were placed in inert oil, mounted on a glass pin, and transferred to the cold gas stream of the diffractometer. Crystal data were collected and integrated using a Bruker SMART 1000 system, with graphite monochromated MoKα (λ=0.71073 Å) radiation at 173 K, except (1*S*,1′*R*)-**16e**, in which data was collected at 203 K. The structures were solved by direct methods using SHELXS-97 and refined using SHELXL-97 (Sheldrick, G. M., University of Göttingen). Nonhydrogen atoms were found by successive full matrix least squares refinement on F^2 and refined with anisotropic thermal parameters. Hydrogen atom positions were located from difference Fourier maps, and a riding model with fixed thermal parameters [u_{ij}=1.2U_{ij}(eq) for the atom to which they are bonded], was used for subsequent refinements.

4.3. Molecular modeling

Conformational searches were performed with MacroModel version 6.5 on a Silicon Graphics workstation using either MM2* or the AMBER* force fields.[18,26] Solution phase calculations were performed using the GB/SA continuum model for chloroform.[19] Conformational searches were performed using the systematic Monte Carlo method[17] for 2000 starting structures. Duplicate conformations and those with an energy greater than 50 kJ mol^{-1} above the global minimum were discarded.

4.4. General procedure for the asymmetric Strecker reaction using (*S*)-α-methylbenzylamine (*Procedure A*)

A solution of ketone **8** (8.61 mmol), (*S*)-α-methylbenzylamine (8.64 mmol), and *p*-toluenesulfonic acid (0.05 mmol) in benzene (7.5 mL) was heated to reflux. The formed water was collected in a Dean–Stark trap. After 24 h, an additional 1 mmol of (*S*)-α-methylbenzylamine was added and refluxed for another 24 h. The solvent was removed in vacuo, the crude imine **9** (0.21 mmol) was taken up in anhydrous CH_2Cl_2 (13 mL). The solution was cooled to 0°C, and to it was added drop wise trimethylsilyl cyanide (5.2 mmol) followed by ZnI_2 (8 mg) and methanol (0.21 mL, 5.2 mmol). The reaction mixture was allowed to stir at 0°C for 2 h. The solvent was evaporated in vacuo to give an oil, which was dissolved in hexanes/CH_2Cl_2 ((1:1), 6 mL) and cooled to −12°C. To this solution, conc. H_2SO_4 (6 mL) was added drop wise. The resulting two-phase mixture was allowed to warm gradually to room temperature, and was stirred for 3.5 days. The reaction mixture was poured onto ice (20 g). This was covered with ethyl acetate (20 mL) and basified with conc. NH_3 to pH 9–10. The organic phase was separated and the aqueous phase was extracted with ethyl acetate (4×20 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated in vacuo to give the crude amides **11**. The diastereomeric (1*S*,1′*R*)-**11** and (1*S*,1′*S*)-**11** ratio was determined by ^{1}H NMR spectroscopy from the relative integration of the multiplets assigned to the benzylic methine protons of both diastereomers. The crude amides **11** were purified by column chromatography (SiO_2, eluting with hexanes/EtOAc (2:1)).

4.4.1. Compound *E*-9a. (71% crude yield); colorless solid after crystallization from hexane at −26°C; (60% yield) mp 38°C; $[\alpha]^{24}_{D}$=+117° (*c* 1.14 CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 8.40 (1H, dd, *J*=7.2, 2.0 Hz), 7.50 (2H, d, *J*=7.2 Hz), 7.39–7.22 (5H, m), 7.15 (1H, dd, *J*=6.8, 1.2 Hz), 4.90 (1H, q, *J*=6.5 Hz), 2.82–2.79 (2H, m), 2.74–2.65 (1H, m), 2.57–2.50 (1H, m), 1.99–1.85 (2H, m), 1.56 (3H, d, *J*=6.5 Hz); δ_C (100.56 MHz, $CDCl_3$) 162.86, 146.79, 140.67, 135.40, 129.80, 128.56, 128.51, 126.92, 126.68, 126.54, 126.34, 58.71, 30.06, 27.93, 25.50, 22.99; HR-FABMS *m/z* 250.161 (M+H$^+$) (calcd for $C_{18}H_{20}N$, 250.163).

4.4.2. Compound *Z*-9b/*E*-9b. (55:45 ratio); yellow oil; (87% yield); δ_H (400 MHz, $CDCl_3$) 7.51–7.06 (9H, m; *Z*-**9b**), 7.51–7.06 (9H, m, *E*-**9b**), 4.87 (1H, q, *J*=6.6 Hz; *Z*-**9b**), 4.51 (1H, br s; *E*-**9b**), 2.83–2.63 (4H, m; *Z*-**9b**, *E*-**9b**), 2.50–2.43 (4H, m; *Z*-**9b**, *E*-**9b**), 1.59 (3H, d, *J*=6.6 Hz; *Z*-**9b**), 1.34 (3H, br s; *E*-**9b**); δ_C (100.56 MHz, $CDCl_3$; 58°C) 172.45 (br), 171.38, 146.29, 146.15 (br), 142.45, 139.65, 139.17, 138.62, 129.45, 128.85, 128.54, 128.44, 128.35, 127.99, 126.71, 126.67, 126.62, 126.59, 126.53, 125.84, 125.5 (br), 60.75, 58.91, 40.72, 35.73 (br), 32.70, 30.24, 30.06, 27.49, 26.17, 25.46, 24.77 (br), 23.51; HR-FABMS *m/z* 264.175 (M+H$^+$) (calcd for $C_{19}H_{22}N$, 264.179); HR-FABMS *m/z* 264.175 (M+H$^+$) (calcd for $C_{19}H_{22}N$, 264.179).

4.4.3. Compound (1*R*,1′*S*)-10a/(1*S*,1′*S*)-10a. (1:10 ratio) δ_H (400 MHz, $CDCl_3$) 7.61–7.05 (9H, m; (1*R*,1′*S*)-**10a**, (1*S*,1′*S*)-**10a**), 4.28 (1H, q, *J*=6.7 Hz; (1*S*,1′*S*)-**10a**), 4.20–4.12 (1H, m; (1*R*,1′*S*)-**10a**), 2.85–2.64 (3H, m; (1*R*,1′*S*)-**10a**, (1*S*,1′*S*)-**10a**), 1.97–1.66 43H, m; (1*R*,1′*S*)-**10a**, (1*S*,1′*S*)-**10a**), 1.48–1.43 (3H, m; (1*R*,1′*S*)-**10a**, (1*S*,1′*S*)-**10a**).

4.4.4. Compound (1*R*,1′*S*)-10b/(1*S*,1′*S*)-10b. (56:44 ratio) δ_H (400 MHz, $CDCl_3$) 7.80 (1H, dd, *J*=6.4, 2.4 Hz; (1*R*,1′*S*)-**10b**), 7.65 (1H, d, *J*=7.2 Hz; (1*S*,1′*S*)-**10b**), 7.53–6.93 (8H, m; (1*R*,1′*S*)-**10b**), 7.53–6.93 (7H, m; (1*S*,1′*S*)-**10b**), 6.75 (1H, d, *J*=6.8 Hz; (1*S*,1′*S*)-**10b**), 3.96–3.93 (1H, m; (1*R*,1′*S*)-**10b**), 3.91–3.89 (1H, m; (1*S*,1′*S*)-**10b**), 3.55 (1H, t, *J*=12.6 Hz; (1*R*,1′*S*)-**10b**), 3.21 (1H, t, *J*=13.0 Hz; (1*S*,1′*S*)-**10b**), 2.80–1.31 (8H, m; (1*R*,1′*S*)-**10b**, (1*S*,1′*S*)-**10b**), 1.47 (3H, d, *J*=6.4 Hz; (1*S*,1′*S*)-**10b**), 1.14 (3H, d, *J*=6.8 Hz; (1*R*,1′*S*)-**10b**).

4.4.5. Compound (1*S*,1′*S*)-11a/(1*R*,1′*S*)-11a. (10:1 ratio) δ_H (400 MHz, $CDCl_3$) 7.31–6.98 (m, 9H, (1*R*,1′*S*)-**11a**; 10H (1*S*,1′*S*)-**11a**), 6.57 (1H, br s; (1*R*,1′*S*)-**11a**), 5.97 (1H, br s; (1*S*,1′*S*)-**11a**), 5.79 (1H, br s; (1*R*,1′*S*)-**11a**), 3.82 (1H, q, *J*=6.7 Hz; (1*S*,1′*S*)-**11a**), 3.71–3.70 (1H, m; (1*R*,1′*S*)-**11a**), 2.87–2.69 (2H, m; (1*R*,1′*S*)-**11a**, (1*S*,1′*S*)-**11a**), 2.41–2.34 (1H, m; (1*R*,1′*S*)-**11a**, (1*S*,1′*S*)-**11a**), 2.11–1.22 (4H, m; (1*R*,1′*S*)-**11a**, (1*S*,1′*S*)-**11a**), 1.28–1.27 (3H, m; (1*R*,1′*S*)-**11a**, (1*S*,1′*S*)-**11a**).

4.4.6. Compound (1*S*,1′*S*)-11a. Colorless oil; $[\alpha]^{24}_D$= −36.0° (*c* 1.47, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.31–6.98 (10H, m), 5.90 (1H, br s), 3.82 (1H, q, *J*=6.8 Hz), 2.83–2.75 (2H, m), 2.41–2.34 (1H, m), 2.11–2.04 (1H, m), 1.90–1.83 (2H, m), 1.85–1.68 (1H, m), 1.26 (3H, d, *J*=6.8 Hz); δ_C (100.56 MHz, $CDCl_3$) 179.84, 147.40, 137.82, 137.07, 129.55, 128.68, 128.52, 127.73, 126.81, 126.52, 126.11, 64.95, 53.80, 31.68., 29.77, 29.41, 19.43; MALDI HRMS *m/z* (M+Na^+) 317.168 (calcd for $C_{19}H_{22}N_2ONa$, 317.167).

4.4.7. Compound (1*R*,1′*S*)-11b. Colorless oil; $[\alpha]^{24}_D$= −19.3° (*c* 0.69, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.58–7.57 (1H, d), 7.26–7.12 (7H, m), 7.01–6.99 (1H, m), 6.84 (1H, br s), 5.56 (1H, br s), 3.64 (1H, q, *J*=6.4 Hz), 2.73–2.60 (2H, m), 2.30–2.23 (1H, m), 2.14 (1H, br s), 1.92–1.84 (1H, m), 1.89 (1H, br s), 1.70–1.59 (3H, m), 1.28 (3H, d, *J*=6.4 Hz); δ_C (100.56 MHz, $CDCl_3$) 179.09, 147.56, 142.83, 139.70, 131.33, 129.98, 128.60, 127.92, 126.88, 126.53, 126.30, 70.87, 53.86, 37.24, 35.84, 26.92, 26.50, 24.74; MALDI HRMS *m/z* (M+Na^+) 331.176 (calcd for $C_{20}H_{24}N_2ONa$, 331.183).

4.4.8. Compound (1*S*,1′*S*)-11b. Colorless oil; $[\alpha]^{24}_D$= −69.4° (*c* 0.9, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.55–7.52 (1H, m), 7.35–7.18 (7H, m), 7.12–7.10 (1H, m), 6.37 (1H, br s), 5.18 (1H, br s), 3.84 (1H, q, *J*=6.6 Hz), 2.86–2.84 (2H, m), 2.37–2.31 (1H, m), 1.90–1.68 (6H, m), 1.17 (3H, d, *J*=6.6 Hz); δ_C (100.56 MHz, $CDCl_3$) 178.78, 147.97, 142.42, 140.41, 131.26, 129.62, 128.72, 127.97, 126.87, 126.60, 126.34, 70.36, 53.53, 36.40, 36.06, 27.15, 26.65, 25.10; MALDI HRMS *m/z* 331.176 (M+Na^+) (calcd for $C_{20}H_{24}N_2ONa$, 331.178).

4.4.9. (*S*)-1-Amino-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (1a) via catalytic hydrogenation of (1*S*,1′*S*)-11a (*Procedure B*). Dissolved (1*S*,1′*S*)-**11a** (47.5 mg; 0.162 mmol) in methanol/1N HCl aq (1:1) (3 mL) and added palladium on charcoal hydrogenation catalyst (10 mg; 5% Pd on C). Purged solution for 2 min with H_2 gas and stirred under a hydrogen atmosphere (1 bar) for 24 h. Degassed solution, filtered through a pad of Celite 545, washed with 3 mL of methanol and concentrated. Took up residue in 6N HCl (5 mL), and refluxed for 3 h. Concentrated and dried at vacuum pump. Dissolved residue in ethanol (2 mL), added 200 μL propylene oxide and refluxed for 20 min. Removed solvent under vacuo. Purified crude amino acid by reverse phase column chromatography on a Beckman Ultrasphere RP18-250×10 column with water as eluant (3 mL min^{-1}; UV-detection at 254 nm) to obtain *S*-**1a** as a white solid (26 mg; 83% yield). mp 240°C (Lit: 244–245°C for *rac*-**1a**);[27] $[\alpha]^{24}_D$=+41.8° (*c* 1.35, MeOH); δ_H (400 MHz, CD_3OD) 7.42 (1H, d, *J*=7.2 Hz), 7.29–7.15 (3H, m), 2.96–2.82 (2H, m), 2.58–2.45 (1H, m), 2.18–2.04 (2H, m), 1.92–1.78 (1H, m); δ_H (400 MHz, $CD_3S(O)CD_3$) 7.92 (3H, br s), 7.38 (1H, d, *J*=7.6 Hz), 7.2–7.05 (3H, m), 2.8–2.65 (2H, m), 2.30 (1H, t, *J*=7.2 Hz), 2.1–1.7 (3H, m); δ_C (100.56 MHz, CD_3OD) 176.69, 139.39, 135.18, 130.90, 129.81, 128,85, 127.88, 63.35, 33.58, 30.33, 20.04; HR-FAB MS *m/z* 192.102 (M+H^+) (calcd for $C_{11}H_{14}NO_2$, 192.103).

4.4.10. (*S*)-1-Aminobenzocycloheptane-1-carboxylic acid (1b). (*S*)-**1b** was synthesized from (1*S*,1′*S*)-**11b** via application of procedure B, except that the crude (*S*)-**1b** was purified by crystallization from ethanol. (86% yield) mp 268°C; $[\alpha]^{24}_D$=+39.9° (*c* 0.026, MeOH); δ_H (400 MHz, CD_3OD, D_2O (1:1)) 7.33–7.16 (4H, m), 3.3–3.0 (1H, m), 2.93–2.86 (1H, m), 2.6–2.53 (1H, m), 2.12–2.05 (1H, m), 2.0–1.86 (1H, m), 1.86–1.76 (3H, m); δ_H (400 MHz, $CD_3S(O)CD_3$) 7.86 (3H, br s) 7.35–7.30 (1H, m), 7.15–7.05 (3H, m), 3.18–3.10 (1H, m), 2.8–2.65 (1H, m), 2.48–2.35 (1H, m), 1.85–1.55 (5H, m); δ_C (100.56 MHz, CD_3OD, D_2O (1:1)) 176.96, 143.56, 137.47, 132.78, 130.10, 129.97, 127.96, 69.78, 34.75, 34.73, 27.10, 23.55; HR-FAB MS *m/z* 206.116 (M+H^+) (calcd for $C_{12}H_{16}NO_2$, 206.118).

4.5. General procedure for the asymmetric Strecker reaction using (*R*)-2-phenylglycinol (*Procedure C*)

To a stirred solution of aryl ketone **8** (6 mmol) in xylenes (12 mL) was added (*R*)-2-phenylglycinol (6.6 mmol) and *p*-toluenesulfonic acid (0.5 mol%). The resulting mixture was heated to reflux and maintained there until ^{1}H NMR spectroscopy showed no ketone remaining (3–8 h). Solvent was removed in vacuo, and the resulting crude imine **12** was taken up in anhydrous CH_2Cl_2 (6 mL). The solution was cooled to 0°C, and to it was added drop wise trimethylsilyl cyanide (12 mmol). The reaction mixture was allowed to stir at 0°C for 1–2 h, by which time ^{1}H NMR spectroscopy showed complete consumption of the imine. The solvent was evaporated in vacuo to give the two diastereomeric aminonitriles **14** as an oil.

4.6. General procedure for the hydrolysis of the aminonitrile 14a–e (*Procedure D*)

The crude aminonitriles **14** (*Procedure C*) were dissolved in hexane (12 mL) and cooled to −10°C. Ice-cold conc. H_2SO_4 (12 mL) was slowly added to this reaction. The resulting two-phase mixture was allowed to warm gradually to room temperature, and was stirred for 5 days. The hexane layer was decanted, and the acidic layer was poured onto ice (10 g). This was then cooled in an ice bath, covered with ethyl acetate (20 mL) and basified with conc. NH_3 to pH 9–10. The organic phase was separated and the aqueous phase was extracted with ethyl acetate (5×20 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated in vacuo to give the crude hydroxyaminoamide **15**, along with a small amount of lactone **16**. The diastereomeric excess of the reaction was determined by converting the amide to the lactone, as described below. The crude hydroxyaminoamide products were purified by column chromatography (SiO_2, eluting with petroleum ether/EtOAc (5:1), then EtOAc/MeOH (10:1)).

4.7. General procedure for lactone synthesis (*Procedure E*)

A small amount of the crude hydroxyaminoamide **15** was dissolved in toluene and heated to reflux until ^{1}H NMR spectroscopy revealed complete conversion to the corresponding lactone **16**. Solvent was evaporated in vacuo to give the crude product, which was then washed through a small pad of silica with ethyl acetate, to remove excess amino alcohol. The diastereomeric excess of the reaction was then determined by a combination of ^{1}H NMR spectroscopy and HPLC analysis of the crude lactone mixtures (Luna-SiO_2 column 250×4.6 mm (Phenomenex), eluant 0.2% THF, 1 mL min^{-1}, UV-detection at 254 nm). Isolation of the individual diastereomers was achieved either by column chromatography (SiO_2, eluting with petroleum ether/ethyl acetate (7:1)) or HPLC (Luna-SiO_2 column 250×10 mm (Phenomenex), eluant 0.2% THF/CH_2Cl_2, 5 mL min^{-1}, UV-detection at 254 nm).

4.7.1. Compounds *E*-12a/13aA/13aA′. (86:10:4 ratio) solid; δ_H (400 MHz, $CDCl_3$) 8.41 (1H, d, J=7.6 Hz; *E*-**12a**), 7.65 (1H, d, J=7.2 Hz; **13aA**′), 7.61 (1H, d, J=8.8 Hz; **13aA**), 7.53–6.98 (8H, m; *E*-**12a**, **13aA**, **13aA**′), 4.80 (1H, m; *E*-**12a**, **13aA**′), 4.60–4.50 (1H, m; **13aA**, **13aA**′), 4.48–4.44 (1H, t, J=8.0 Hz; **13aA**), 3.97–3.86 (2H, m; *E*-**12a**; 1H, m, **13aA**, **13aA**′), 3.82–1.73 (7H, m; *E*-**12a**, **13aA**, **13aA**′); δ_C (400 MHz, $CDCl_3$) *E*-**12a**: 167.68, 141.39, 141.05, 134.73, 130.32, 128.70, 128.68, 127.57, 127.34, 126.53, 126.17, 69.13, 65.33, 29.92, 29.22, 22.74.

4.7.2. Compounds *E*-12b/13b. δ_H (400 MHz, $CDCl_3$) 7.86–7.78 (0.09H, m), 7.78–7.70 (0.18H, m), 7.56 (0.38H, dd, J=6.6, 2.2 Hz), 7.50–6.95 (8.35H, m), 4.96 (0.04 H, dd, J=10.5, 4.0 Hz), 4.81 (0.38H, dd, J=8.0, 4.4 Hz), 4.67–4.34 (0.32H, m), 4.39 (0.09H, t, J=7.6 Hz), 4.30–4.21 (0.36H, m), 4.11–3.64 0.94H, m), 4.03 (0.38H, dd, J=10.8, 8.0 Hz), 3.89 (0.38H, dd, J=10.8, 4.4 Hz), 3.55 (0.09H, dd, J=10.8, 8.8 Hz), 3.42–3.25 (0.2H, m), 3.15–1.33 (8.8H, m).

4.7.3. Compound *E*-12c. White solid (75% yield), mp 147°C (Ether/Hexane); $[\alpha]^{24}_D$=+53.5° (*c* 0.99, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 8.00 (1H, d, J=7.6 Hz), 7.42–7.23 (8H, m), 4.67 (1H, dd, J=8.4, 4.2 Hz), 4.06 (1H, dd, J=10.8, 8.4 Hz), 3.91 (1H, dd, J=10.8, 4.2 Hz), 3.6–2.9 (1H, br s), 2.64–2.56 (2H, m), 2.38–2.16 (2H, m); δ_C (100.56 MHz, $CDCl_3$) 178.10, 150.80, 140.66, 139.10, 131.58, 128.71, 127.77, 127.45, 126.79, 125.43, 123.82, 69.81, 68.89, 29.13, 27.88; HR-FAB MS *m*/*z* 252.138 ($M+H^+$) (calcd for $C_{17}H_{18}NO$, 252.139).

4.7.4. Compounds 12d/13dA/13dA′. (89:7:4 ratio) oil; δ_H (400 MHz, $CDCl_3$) 8.08 (1H, dd, J=10.4, 2.4 Hz; **12d**), 7.37–7.03 (7H, m; **12d**; 8H, m; **13dA**, **13dA**′), 4.81 (1H, m; **12d**, **13dA**), 4.62–4.51 (1H, m; **13dA**, **13dA**′), 4.98–4.93 (1H, m; **13dA**′), 4.10–3.59 (2H, m; **12d**), 4.10–3.59 (1H, m; **13dA**, **13dA**′), 2.80–1.81 (7H, m; **12d**, **13dA**, **13dA**′).

4.7.5. Compounds *E*-12e/Z-12e/13e. (Complex mixture) oil; δ_H (400 MHz, $CDCl_3$) 7.54 (0.18H, dd, J=10.8, 2.9 Hz), 7.47 (0.36H, dd, J=10.8, 2.8 Hz), 7.43–6.78 (7.43H, m), 4.79 (0.25H, dd, J=8.0, 4.4 Hz), 4.60–4.42 (0.21H, m), 4.38 (0.18H, dd, J=7.2, 7.2 Hz), 4.29–4.15 (0.72H, m), 4.00 (0.25H, dd, J=10.8, 8.0 Hz), 3.89 (0.25H, dd, J=10.8, 4.4 Hz), 4.05–3.84 (0.21H, m), 3.84–3.62 (0.93H, m) 3.35–3.18 (0.46H, m), 3.00–1.30 (8.54H, m).

4.7.6. Compounds (1*S*,1′*R*)-14a/(1*R*,1′*R*)-14a. (14:1 ratio); δ_H (400 MHz, $CDCl_3$) 7.59–7.13 (9H, m; (1*S*,1′*R*)-**14a**, (1*R*,1′*R*)-**14a**), 4.27 (1H, dd, J=9.6, 4.0 Hz; (1*S*,1′*R*)-**14a**), 4.10–4.04 (1H, m; (1*R*,1′*R*)-**14a**), 3.68 (1H, dd, J=10.4, 4.4 Hz; (1*S*,1′*R*)-**14a**), 3.60 (1H, dd, J=10, 4.0 Hz; (1*R*,1′*R*)-**14a**), 3.43 (1H, m; (1*S*,1′*R*)-**14a**, (1*R*,1′*R*)-**14a**), 2.80–2.65 (2H, m; (1*S*,1′*R*)-**14a**, (1*R*,1′*R*)-**14a**), 2.59 (1H, br s; (1*S*,1′*R*)-**14a**), 2.44 (1H, br s; (1*R*,1′*R*)-**14a**), 1.92–1.72 (3H, m; (1*S*,1′*R*)-**14a**, (1*R*,1′*R*)-**14a**), 1.42–1.39 (1H, m; (1*S*,1′*R*)-**14a**, (1*R*,1′*R*)-**14a**), 0.16 (9H, s; (1*S*,1′*R*)-**14a**), 0.09 (9H, s; (1*R*,1′*R*)-**14a**); (1*S*,1′*R*)-**14a:** δ_C (100.56 MHz, $CDCl_3$) 141.79, 136.94, 135.82, 129.97, 128.93, 128.55, 127.87, 127.86, 127.70, 127.11, 122.44, 67.18, 63.15, 59.16, 33.53, 28.99, 17.12, −0.32.

4.7.7. Compounds (1*S*,1′*R*)-14b/(1*R*,1′*R*)-14b. (3.4:1 ratio); δ_H (400 MHz, $CDCl_3$) 7.74 (1H, d, J=6.8 Hz; (1*S*,1′*R*)-**14b**), 7.54–6.91 (8H, m; (1*S*,1′*R*)-**14b**, (1*R*,1′*R*)-**14b**), 6.78–6.76 (1H, m; (1*R*,1′*R*)-**14b**), 4.01–3.97 (1H, m; (1*R*,1′*R*)-**14b**), 3.76–3.74 (1H, m; (1*S*,1′*R*)-**14b**), 3.66–3.46 (2H, m; (1*S*,1′*R*)-**14b**, (*1R*,*1′R*)-**14b**), 3.36 (1H, t, J=11.8 Hz; (1*R*,1′*R*)-**14b**), 3.34 (1H, t, J=12.8 Hz; (1*S*,1′*R*)-**14b**), 2.84–1.28 (7H, m; (1*S*,1′*R*)-**14b**, (1*R*,1′*R*)-**14b**), 2.72 (1H, br s; (1*R*,1′*R*)-**14b**), 2.56 (1H, br s; (1*S*,1′*R*)-**14b**), 0.16 (9H, br s; (1*R*,1′*R*)-**14b**), 0.04 (9H, br s; (1*S*,1′*R*)-**14b**).

4.7.8. Compounds (1*S*,1′*R*)-14c/(1*R*,1′*R*)-14c. (10:1 ratio); δ_H (400 MHz, $CDCl_3$) 7.50–7.16 (9H, m; (1*S*,1′*R*)-**14c**, (1*R*,1′*R*-**14c**), 4.25 (1H, dd, J=9.2, 4.2 Hz; (1*S*,1′*R*)-**14c**), 4.12–4.04 (1H, m; (1*R*,1′*R*)-**14c**), 3.69 (1H, dd, J=10.4, 4.2 Hz; (1*S*,1′*R*)-**14c**), 3.64–3.61 (1H, m; (1*R*,1′*R*)-**14c**), 3.50–3.45 (1H, m; (1*S*,1′*R*)-**14c**), 3.43–3.38 (1H, m; (1*R*,1′*R*)-**14c**), 3.18–3.01 (2H, m; (1*R*,1′*R*)-**14c**), 2.94–2.73 (2H, m; (1*S*,1′*R*)-**14c**), 2.66 (1H, br s; (1*S*,1′*R*)-**14c**), 2.62–2.39 (2H, m; (1*R*,1′*R*)-**14c**), 2.51 (1H, br s; (1*R*,1′*R*)-**14c**), 2.03–1.86 (2H, m; (1*S*,1′*R*)-**14c**), 0.15 (9H, s; (1*S*,1′*R*)-**14c**), 0.12 (9H, s; (1*R*,1′*R*)-**14c**).

4.7.9. Compounds (1*S*,1′*R*)-14d/(1*R*,1′*R*)-14d. (11:1 ratio); δ_H (400 MHz, $CDCl_3$) 7.42–6.80 (8H, m; (1*S*,1′*R*)-**14d**, (1*R*,1′*R*)-**14d**), 4.23 (1H, dd, J=4.2, 9.6 Hz; (1*S*,1′*R*)-**14d**), 4.05 (1H, dd, J=4.2, 8.8 Hz; (1*R*,1′*R*)-**14d**), 3.70 (1H, dd, J=4.2, 10.8 Hz; (1*S*,1′*R*)-**14d**), 3.61 (1H, dd, J=4.2, 10.4 Hz; (1*R*,1′*R*)-**14d**), 3.47 (1H, dd, J=8.8, 10.4 Hz; (1*R*,1′*R*)-**14d**), 3.43 (1H, dd, J=9.6, 10.8 Hz; (1*S*,1′*R*)-**14d**), 2.86–2.42 (2H, m; (1*S*,1′*R*)-**14d**, (1*R*,1′*R*)-**14d**), 2.58 (1H, br s; (1*S*,1′*R*)-**14d**), 2.53 (1H, br s; (1*R*,1′*R*)-**14d**), 2.20–1.66 (3H, m; (1*S*,1′*R*)-**14d**, (1*R*,1′*R*)-**14d**), 1.44–1.40 (1H, m; (1*S*,1′*R*)-**14d**, (1*R*,1′*R*)-**14d**), 0.20 (9H, s; (1*R*,1′*R*)-**14d**), 0.17 (9H, s; (1*S*,1′*R*)-**14d**.

4.7.10. Compounds (1*S*,1′*R*)-14e/(1*R*,1′*R*)-14e. (2.8:1 ratio); δ_H (400 MHz, $CDCl_3$) 7.52 (1H, dd, J=10.4, 2.4 Hz; (1*S*,1′*R*)-**14e**), 7.41–6.92 (7H, m; (1*S*,1′*R*)-**14e**), 7.41–6.92 (6H, m; (1*R*,1′*R*)-**14e**), 6.65–6.57 (2H, m; (1*R*,1′*R*)-**14e**), 4.02 (1H, dd, J=8.8, 3.6 Hz; (1*R*,1′*R*)-**14e**),

3.80–3.78 (1H, m; (1*S*,1′*R*)-**14e**), 3.68–3.46 (2H, m; (1*S*,1′*R*)-**14e**, (1*R*,1′*R*)-**14e**), 3.35 (1H, dd, *J*=13.2, 13.2 Hz; (1*R*,1′*R*)-**14e**), 3.28–3.16 (1H, m; (1*S*,1′*R*)-**14e**), 2.90–1.25 (7H, m; (1*S*,1′*R*)-**14e**, (1*R*,1′*R*)-**14e**), 2.75 (1H, br s; (1*S*,1′*R*)-**14e**), 2.59 (1H, br s; (1*R*,1′*R*)-**14e**), 0.17 (9H, br s; (1*R*,1′*R*)-**14e**), 0.06 (9H, br s; (1*S*,1′*R*)-**14e**).

4.7.11. *N*-[(*R*)-2′-Hydroxy-1′-phenylethyl]-(*S*)-1-amino-1,2,3,4,-tetrahydronaphthalene-1-carboxamide ((1*S*,1′*R*)-15a). White solid; mp 67°C; $[\alpha]^{24}_{D}=-3.7°$ (*c* 1.0, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 7.35–7.21 (7H, m), 7.18–7.14 (1H, m), 7.09–7.05 (2H, m), 5.88 (1H, br s), 4.02–3.98 (1H, m), 3.61–3.44 (3H, m), 2.75–2.70 (2H, m), 2.22–2.15 (2H, m), 2.05–1.98 (1H, m), 1.52–1.46 (2H, m); δ_C (100.56 MHz, $CDCl_3$) 179.82 (s), 137.64 (s), 129.72 (d), 128.60 (d), 128.06 (d), 128.00 (d), 127.47 (d), 127.30 (d), 126.47 (d), 67.88 (t), 65.40 (s), 60.79 (d), 31.89 (t), 29.75 (t), 18.58 (t); MALDI HRMS *m*/*z* 333.1582 ($M+Na^+$) (calcd for $C_{19}H_{22}N_2NaO_2$, 333.1579).

4.7.12. *N*-[(*R*)-2′-Hydroxy-1′-phenylethyl]-(*S*)-1-amino-1,2,3,4,-tetrahydronaphthalene-1-carboxamide ((1*R*,1′*R*)-15a). White solid; mp 123 °C; $[\alpha]^{24}_{D}=-105°$ (*c* 1.73 CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 7.48–7.46 (1H, m), 7.26–7.10 (7H, m), 7.01–6.99 (1H, m); 6.40 (1H, br s), 6.08 (1H, br s), 3.71 (1H, dd, *J*=8.4, 4.6 Hz), 3.47 (1H, dd, *J*=10.8, 4.6 Hz), 3.43–3.38 (1H, m), 2.94 (1H, br s), 2.75–2.59 (3H, m), 2.02–1.73 (4H, m); δ_C (100.56 MHz, $CDCl_3$) 179.88, 143.29, 139.25, 136.18, 129.66, 128.99, 128.56, 128.03, 127.20, 126.93, 126.34, 68.08, 65.48, 59.59, 35.06, 29.64, 19.88; HR-FAB MS *m*/*z* 311.176 ($M+H^+$) (calcd for $C_{19}H_{22}N_2O_2$, 311.176).

4.7.13. *N*-[(*R*)-2′-Hydroxy-1′-phenylethyl]-(*S*)-1-amino-benzocycloheptane-1-carboxamide ((1*S*,1′*R*)-15b). Oil; $[\alpha]^{24}_{D}=-36.8°$ (*c* 1.08 CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 7.57–7.55 (1H, m), 7.28–7.22 (4H, m), 7.21–7.16 (1H, m), 7.15–7.11 (2H, m), 7.07–7.02 (1H, m), 6.63 (1H, br s), 6.08 (1H, br s), 4.00–3.97 (1H, m), 3.65 (1H, br s), 3.50–3.46 (1H, m), 3.33 (1H, br t, *J*=9.8 Hz), 2.94–2.88 (1H, m), 2.77–2.72 (1H, m), 2.44 (1H, br s), 2.21–2.16 (1H, m), 1.64–1.49 (5H, m); δ_C (50 MHz, $CDCl_3$) 179.43 (s), 143.56 (s), 142.29 (s), 141.06 (s), 131.01 (d), 128.54 (d), 128.48 (d), 128.04 (d), 127.36 (d), 127.25 (d), 126.37 (d), 70.33 (s), 67.66 (t), 59.87 (d), 34.87 (t), 34.48 (t), 26.86 (t), 24.22 (t); MALDI HRMS *m*/*z* 347.1747 ($M+Na^+$) (calcd for $C_{20}H_{24}N_2NaO_2$, 347.1735).

4.7.14. *N*-[(*R*)-2′-Hydroxy-1′-phenylethyl]-(*R*)-1-amino-benzocycloheptane-1-carboxamide ((1*R*,1′*R*)-15b). Colorless solid; mp 178°C; $[\alpha]^{24}_{D}=-33.6°$ (*c* 2.0, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 7.38–7.17 (3H, m), 7.13–6.97 (4H, m), 6.84–6.82 (2H, m), 6.69–6.67 (1H, m), 6.06 (1H, br s), 3.76 (1H, dd, *J*=6.7, 6.7 Hz), 3.53–3.52 (2H, m), 2.57–2.51 (1H, m), 2.33–2.18 (2H, m), 1.96–1.46 (7H, m); δ_C (50 MHz, CD_3OD) 183.7, 144.3, 143.5, 140.7, 132.0, 131.8, 128.6, 128.4, 127.9, 127.4, 126.4, 72.4, 68.2, 62.1, 40.4, 36.8, 28.5, 25.8; MALDI HRMS *m*/*z* 347.1746 ($M+Na^+$) (calcd for $C_{20}H_{24}N_2NaO_2$, 347.1735).

4.7.15. *N*-[(*R*)-2′-Hydroxy-1′-phenylethyl]-(*S*)-1-amino-7-fluoro-1,2,3,4,-tetrahydronaphthalene-1-carboxamide ((1*S*,1′*R*)-15d). Foam; $[\alpha]^{24}_{D}=-6.2°$ (*c* 0.6, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 7.88 (1H, br s), 7.24–7.14 (5H, m), 7.05 (1H, dd, *J*=10.2, 2.6 Hz), 6.98–6.88 (1H, m), 6.86–6.79 (1H, m), 6.25 (1H, br s), 4.10–3.60 (1H, br s), 3.90 (1H, dd, *J*=9.5, 4.0 Hz),3.54–3.50 (1H, m), 3.42–3.36 (1H, m), 2.64–2.61 (2H, m), 2.26–2.14 (1H, m), 1.97–1.88 (1H, m), 1.50–1.30 (2H, m); δ_C (50 MHz, $CDCl_3$) 179.21 (s), 161.23 (d, $^1J_{CF}$=244 Hz), 142.72 (s), 139.40 (d, $^3J_{CF}$=6.1 Hz), 133.28 (d, $^4J_{CF}$=3.1 Hz), 131.00 (dd, $^3J_{CF}$=7.6 Hz), 128.69 (d), 127.59 (d), 127.18 (d), 115.17 (dd, $^2J_{CF}$= 21.0 Hz), 114.56 (dd, $^2J_{CF}$=21.7 Hz), 67.88 (t), 65.27 (s), 60.45 (d), 31.36 (t), 29.07 (t), 18.65 (t); MALDI HRMS *m*/*z* 351.1501 ($M+Na^+$) (calcd for $C_{19}H_{21}FN_2NaO_2$, 351.1485).

4.7.16. *N*-[(*R*)-2′-Hydroxy-1′-phenylethyl]-1-(*S*/*R*)-amino-8-fluorobenzocycloheptane-1-carboxamide ((1*S*,1′*R*)/(1*R*,1′*R*)-15e). Obtained as a mixture of diastereomers (60:40 ratio) after column chromatography; δ_H (400 MHz, $CDCl_3$) 7.44–7.41 (0.6H, m), 7.33–7.22 (3.8H, m), 7.19–7.16 (0.4H, m), 7.12–7.04 (1.6H, m), 6.92–6.86 (1.4H, m), 6.71–6.61 (0.6H, m), 6.44 (0.6H, br s), 5.78 (0.4H, br s), 5.58 (0.6H, br s), 4.06–4.03 (0.6H, m), 3.83–3.80 (0.4H, m), 3.61–3.46 (2.0H, m), 3.25 (0.4H, br s), 2.92–2.77 (1.4H, m), 2.61–2.24 (3.2H, m), 1.96–1.46 (5.0H, m); δ_C (50 MHz, $CDCl_3$) 179.6, 177.9, 161.6 (d, J_{CF}=242 Hz), 161.2 (d, J_{CF}=241.5 Hz), 143.2, 141.8, 138.9 (d, J_{CF}= 3.1 Hz), 138.1, (d, J_{CF}=3.1 Hz), 132.5 (d, J_{CF}=7.5 Hz), 128.8, 128.2, 127.6, 127.4, 127.1, 127.0, 117.6 (d, J_{CF}= 22.8 Hz), 116.0 (d, J_{CF}=23.0 Hz), 114.5 (d, J_{CF}=20.1 Hz), 114.3 (d, J_{CF}=20.5 Hz), 70.8, 69.9, 67.8, 67.7, 60.5, 59.9, 39.0, 35.2, 34.8, 34.5, 27.2, 27.0, 25.0, 24.5; MALDI HRMS *m*/*z* 365.1650 ($M+Na^+$) (calcd for $C_{20}H_{23}FN_2NaO_2$, 365.1642).

4.7.17. (1,3′*S*)-1,2,3,4-Tetrahydronaphthalene-1-spiro-3′-[(5′*R*)-5′-phenyl-2′,3′,5′,6′-tetrahydro-1′,4′-oxazin-2′-one] ((1,3′*S*,5′*R*)-16a). Colorless solid; mp 118°C $[\alpha]^{24}_{D}$+ 99.3° (*c* 0.15 CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 7.55–7.53 (1H, m), 7.50–7.47 (2H, m), 7.43–7.35 (3H, m), 7.30–7.23 (2H, m), 7.16–7.14 (1H, m), 4.61–4.50 (3H, m), 2.97–2.80 (2H, m), 2.53–2.46 (1H, m), 2.39–2.34 (1H, m), 2.08–2.01 (2H, m, m), 1.93–1.85 (1H, m); δ_C (50 MHz, $CDCl_3$) 173.12 (s), 138.64 (s), 137.72 (s), 137.61 (s), 129.46 (d), 129.32 (d), 129.10 (d), 128.83 (d), 128.01 (d), 127.28 (d), 126.73 (d), 76.17 (t), 63.17 (s), 52.49 (d), 33.88 (t), 29.32 (t), 18.52 (t); Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 78.0; H, 6.1; N, 4.8.

4.7.18. (1,3′*S*)-Benzocycloheptan-1-spiro-3′-[(5′*R*)-5′-phenyl-2′,3′,5′,6′-tetrahydro-1′,4′-oxazin-2′-one] ((1,3′*S*,5′*R*)-16b). Oil; $[\alpha]^{24}_{D}$+68.3° (*c* 0.53 CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 7.38–7.16 (9H, m), 4.51–4.49 (1H, m), 4.34–4.24 (2H, m), 3.59–3.52 (1H, m), 2.83 (1H, dd, *J*=14.2, 7.3 Hz), 2.36–2.32 (2H, m), 2.20 (1H, br s), 1.95–1.87 (3H, m), 1.58–1.52 (1H, m); δ_C (50 MHz, $CDCl_3$) 173.46 (s), 143.26 (s), 142.12 (s), 139.23 (s), 131.88 (d), 128.92 (d), 128.39 (d), 128.15 (d), 127.32 (d), 127.14 (d), 126.72 (d), 72.44 (t), 67.27 (s), 55.37 (d), 35.93 (t), 35.12 (t), 27.77 (t), 24.23 (t); MALDI HRMS *m*/*z* 330.1465 ($M+Na^+$) (calcd for $C_{20}H_{21}NNaO_2$, 330.148).

4.7.19. (1,3′*R*)-Benzocycloheptan-1-spiro-3′-[(5′*R*)-5′-phenyl-2′,3′,5′,6′-tetrahydro-1′,4′-oxazin-2′-one] ((1,3′*R*,5′*R*)-16b). Solid; mp 103°C; $[\alpha]^{24}_{D}=-95.2°$ (*c* 0.21

CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 7.38–7.29 (5H, m), 7.22–7.18 (3H, m), 7.15–7.13 (1H, m), 4.49 (1H, *A*BX, *J*=10.8, 4.4 Hz), 4.31 (1H, A*B*X, *J*=10.8, 10.8 Hz), 4.00 (1H, AB*X*, *J*=10.8, 4.4 Hz), 3.22 (1H, t, *J*=13.7 Hz), 2.77–2.72 (1H, m), 2.48–2.40 (1H, m), 2.30–2.26 (2H, m), 2.05–1.93 (3H, m), 1.57–1.48 (1H, m); δ_C (50 MHz, $CDCl_3$) 172.12, 141.87, 139.76, 138.68, 132.36, 129.39, 129.09, 128.58, 128.13, 127.04, 126.23, 17.12, 68.87, 51.57, 37.89, 36.82, 28.14, 25.32; MALDI HRMS *m/z* 330.1465 ($M+Na^+$) (calcd for $C_{20}H_{21}NNaO_2$, 330.1475).

4.7.20. (1,3′*S*)-Indan-1-spiro-3′-[(5′*R*)-5′-phenyl-2′,3′,5′,6′-tetrahydro-1′,4′-oxazin-2′-one] ((1,3′*S*,5′*R*)-16c). Oil; $[\alpha]^{24}_D$+128.0° (*c* 0.77 CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 7.50–7.44 (3H, m), 7.38–7.32 (3H, m), 7.30–7.23 (3H, m), 4.54–4.49 (1H, m), 4.53–4.42 (2H, m), 3.22–3.14 (1H, m), 3.06–2.98 (2H, m), 2.20–2.13 (1H, m), 1.95 (1H, br s); δ_C (50 MHz, $CDCl_3$) 171.36 (s), 144.70 (s), 144.15 (s), 137.83 (s), 129.13 (d), 129.06 (d), 128.86 (d), 127.25 (d), 127.10 (d), 125.05 (d), 124.45 (d), 75.90 (t), 72.37 (s), 54.35 (d), 42.44(t), 30.63(t); Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.57; H, 6.06; N, 5.12.

4.7.21. (1,3′*S*)-7-Fluoro-1,2,3,4-tetrahydronaphthalene-1-spiro-3′-[(5′*R*)-5′-phenyl-2′,3′,5′,6′-tetrahydro-1′,4′-oxazin-2′-one] ((1,3′*S*,5′*R*)-16d). Colorless solid; mp 161°C; $[\alpha]^{24}_D$+99.0° (*c* 0.31 CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 7.49–7.47 (2H, m), 7.42–7.34 (3H, m), 7.29 (1H, dd, *J*=9.9, 2.7 Hz), 7.09 (1H, dd, *J*=8.4, 5.9 Hz), 6.94 (1H, ddd, *J*=8.4, 8.4, 2.7 Hz), 4.60–4.55 (1H, m), 4.53–4.48 (2H, m), 2.90–2.73 (2H, m), 2.56–2.50 (1H, ddd, *J*=13.5, 10.4, 3.1 Hz), 2.29–2.22 (1H, m), 2.10–1.99 (2H, m), 1.87–1.79 (1H, m); δ_C (50 MHz, $CDCl_3$) 172.11 (s, C-2′), 161.34 (d, J_{CF}=244 Hz, C-7), 140.12 (d, J_{CF}=6.5 Hz, C-14a), 137.47 (s, Ph), 133.29 (d, J_{CF}=3.4 Hz, C-16a), 130.76 (dd, J_{CF}=7.6 Hz, C-5), 129.12 (d, Ph), 128.96 (d, Ph), 127.33 (d, Ph), 115.47 (dd, J_{CF}=21.4 Hz, C-6 and C-8), 76.09 (t, C-6′), 63.12 (s, C-1,3′), 52.58 (d, C-5′), 34.02 (t, C-4), 28.70 (t, C-2), 18.80 (t, C-3); MALDI HRMS *m/z* 334.1231 ($M+Na^+$) (calcd for $C_{19}H_{18}FNNaO_2$, 334.1219).

4.7.22. (1,3′*S*)-8-Fluorobenzocycloheptan-1-spiro-3′-[(5′*R*)-5′-phenyl-2′,3′,5′,6′-tetrahydro-1′,4′-oxazin-2′-one] ((1,3′*S*,5′*R*)-16e). Colorless solid; mp 126°C; $[\alpha]^{24}_D$+55.4° (*c* 0.54 CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 7.37–7.29 (5H, m), 7.16 (1H, dd, *J*=10.7, 2.6 Hz, 9-H), 7.14 (1H, dd, *J*=8.2, 6.1 Hz, 6-H), 6.90 (1H, ddd, *J*=10.8, 8.2, 2.6 Hz, 7-H), 4.53–4.46 (1H, m), 4.36–4.26 (2H, m), 3.43–3.37 (1H, m), 2.93–2.88 (1H, m), 2.37–2.34 (2H, m), 2.20 (1H, br s), 1.90–1.82 (3H, m), 1.58–1.53 (1H, m); δ_C (50 MHz, $CDCl_3$) 172.60, 161.42 (J_{CF}=244 Hz, C-8), 143.98 (J_{CF}=5.7 Hz, C-15a), 138.76, 138.64 (J_{CF}=3.1 Hz, C-11a), 133.12 (J_{CF}=7.6 Hz, C-6), 129.04, 128.61, 127.32, 114.90 (J_{CF}=14.1 Hz, C-7 or 9), 114.47 (J_{CF}=11.1 Hz, C-9 or 7), 72.95, 67.21, 54.97, 35.67, 34.15, 27.66, 23.72; MALDI HRMS *m/z* 348.1391 ($M+Na^+$) (calcd for $C_{20}H_{20}FNNaO_2$, 348.1376). Anal. Calcd for $C_{20}H_{20}FNO_2$: C, 73.83; H, 6.20; N, 4.30. Found: C, 73.72; H, 6.23; N, 4.46.

4.7.23. (1,3′*R*)-8-Fluorobenzocycloheptan-1-spiro-3′-[(5′*R*)-5′-phenyl-2′,3′,5′,6′-tetrahydro-1′,4′-oxazin-2′-one] ((1,3′*R*,5′*R*)-16e). Colorless oil; $[\alpha]^{24}_D$=−79.2° (*c* 0.77 CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 7.39–7.30 (5H, m), 7.09 (1H, dd, *J*=8.1, 6.1 Hz, 6-H), 6.95 (1H, dd, *J*=10.5, 2.6 Hz, 9-H), 6.89 (1H, ddd, *J*=8.1, 8.1, 2.6 Hz, 7-H), 4.54 (1H, dd, *J*=10.8, 4.2 Hz, 5′-H), 4.34 (1H, dd, *J*=10.8, 10.8 Hz, 6′-H_a), 4.02 (1H, dd, *J*=10.8, 4.2 Hz, 6′-H_e), 3.14 (1H, br t, *J*=13.7 Hz), 2.76–2.72 (1H, m), 2.48–2.24 (3H, m), 2.03–1.93 (3H, m), 1.49–1.45 (1H, m); δ_C (50 MHz, $CDCl_3$) 171.48 (s, C-2′), 160.96 (d, J_{CF}=245 Hz, C-8), 141.92 (d, J_{CF}=5.7 Hz, C-15a), 138.34 (s, Ph), 137.51 (d, J_{CF}=3.4 Hz, C-11a), 133.60 (dd, J_{CF}=7.6 Hz, C-6), 129.13 (d, Ph), 128.67 (d, Ph), 126.96 (d, Ph), 116.85 (dd, J_{CF}=23.3 Hz, C-7 or C-9), 114.32 (dd, J_{CF}=20.2 Hz, C-7 or C-9), 75.39 (t, C-6′), 68.56 (s, C-1,3′), 51.67 (d, C-5′), 37.84 (t, C-2 or C-5), 36.07 (t, C-2 or C-5), 28.13 (t, C-3 or C-4), 25.22 (t, C-3 or C-4); MALDI HRMS *m/z* 348.1370 ($M+Na^+$) (calcd for $C_{20}H_{20}FNNaO_2$, 348.138).

4.7.24. Synthesis of *N*-[(*R*)-2′-hydroxy-1′-phenylethyl]-(*S*)-1-amino-benzocyclopentane-1-carboxamide ((1*S*,1′*R*)-15c) via aminolysis of (1*S*,1′*R*)-16c. A solution of **16c** (26.5 mg, 0.095 mmol) in 2 mL methanol is cooled to 0°C and is purged with dry ammonia for 10 min and left standing for 24 h at room temperature. Evaporation off the solvent yields quantitatively **15c** as a colorless oil. $[\alpha]^{24}_D$=+27.4° (*c* 1.26CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 8.00 (1H, br s), 7.30–7.10 (8H, m), 7.06 (1H, dt, *J*=8.5, 1.6 Hz), 6.49 (1H, br s), 4.43 (1H, br s), 3.85 (1H, dd, *J*=9.6, 4.0 Hz), 3.51 (1H, dd, *J*=11.2, 4.0 Hz), 3.33 (1H, dd, *J*=9.6, 11.2 Hz), 2.95–2.80 (1H, m), 2.75–2.60 (1H, m), 2.62–2.52 (1H, m), 2.2 (1H, br s), 1.85 (1H, m); δ_C (100.56 MHz, $CDCl_3$) 179.09 (s), 145.28 (s), 144.24 (s), 143.05 (s), 128.67 (d), 128.61(d), 127.44(d), 126.97(d), 126.68(d), 125.05(d), 123.63(d), 74.39 (s), 67.68 (t), 61.68 (d), 35.27 (t), 31.24 (t); MALDI HRMS *m/z* 319.146 ($M+Na^+$) (calcd for $C_{18}H_{20}N_2NaO_2$, 319.142).

4.7.25. Synthesis of methyl ester 17a (*Procedure F*). The crude TMSCN addition adduct **14a** (prepared from 0.20 mmol **8a** via *Procedure C*) was stirred in dry CH_2Cl_2 (5 mL at −18°C); HCl gas was purged into the solution for 15 min. Then methanol (1 mL) was added to the solution, HCl gas was further bubbled for 20 min. The cold bath was removed, and the resulting solution was stirred at room temperature for 12 h. The excess HCl gas and CH_2Cl_2 were evaporated off to dryness, and the residue was dissolved in ethyl acetate (5 mL). The solution was washed with sat. $NaHCO_3$ (5 mL), the aqueous solution was extracted with ethyl acetate twice (2×5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography of the residue on silica gel (elution with 15% ethyl acetate in *n*-hexane) gave (1*S*,1′*R*)-**17a**, a colorless oil (97% yield based on **14a**). $[\alpha]^{24}_D$=+2.46° (*c* 0.53, THF); δ_H (400 MHz, $CDCl_3$) 7.29–7.17 (7H, m), 7.11 (2H, t, *J*=6.4 Hz), 4.03 (1H, br s), 3.90 (1H, dd, *J*=4.4, 10 Hz), 3.71 (3H, s), 3.64 (1H, dd, *J*=4.4, 10.8 Hz), 3.43 (1H, dd, *J*=10, 10.8 Hz), 2.72 (2H, dd, *J*=4.8, 7.6 Hz), 2.38 (1H, br s), 2.16 (1H, ddd, *J*=3.2, 11.2, 14.4 Hz), 1.87 (1H, ddd, *J*=2.8, 6.0, 9.2 Hz), 1.64–1.53 (1H, m), 1.49–1.40 (1H, m); δ_C (50.28 MHz, $CDCl_3$) 178.16, 143.21, 137.27, 136.84, 129.83, 128.41, 127.98, 127.24, 127.20, 126.86, 126.54, 68.18, 65.64, 61.59, 53.03, 30.86, 29.86, 18.44; HR-FABMS *m/z* ($M+H^+$) 326.178 (calcd for $C_{20}H_{23}NO_3$, 326.176).

4.7.26. Synthesis of (*S*)-1-aminobenzocyclopentane-1-carboxylic acid 1c (*Procedure G*).[28] A solution of (1*S*,1′*R*)-**15c** (175 mg, 0.59 mmol) in dry CH_2Cl_2 (2 mL) and dry MeOH (1 mL) is cooled to 0°C under argon. Lead (IV) acetate (263 mg) is added. The solution is stirred at 0°C for 1 h and quenched by the addition of phosphate buffer (0.2 M, pH 7, 6 mL). After stirring at room temperature for 15 min, the solution is diluted with CH_2Cl_2 (10 mL) and filtered through celite. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2×10 mL). The combined organic layers are dried over magnesium sulfate, filtered and concentrated. The remaining yellowish oil is taken up in HCl (6N, 20 mL) and heated to reflux for 3 h. After cooling to room temperature, the solution is extracted with CH_2Cl_2 (3×10 mL) and concentrated to leave the amino acid hydrochloride as a slightly yellowish solid. This solid was taken up in ethanol/propylene oxide (5/0.4 mL, respectively) and heated to reflux for 20 min. The solvent is evaporated and the residue purified by reversed phase HPLC (Beckman Ultrasphere, RP 18, 250×10 mm; water as eluant; 3 mL min^{-1}; detection at 254 nm) to yield (*S*)-**1c** as a white solid (65 mg, 62% yield). Mp 247°C; $[\alpha]^{24}_D$=+103.7° (*c* 0.96, MeOH); δ_H (400 MHz, CD_3OD) 7.45 (1H, d, *J*=7.6 Hz), 7.36–7.21 (3H, m), 3.26–3.10 (2H, m), 2.92–2.82 (1H, m), 2.3–2.2 (1H, m); δ_H (400 MHz, $CD_3S(O)CD_3$) 8.07 (3H, br s), 7.37 (1H, d, *J*=7.2 Hz), 7.3–7.16 (3H, m), 3.09–32.91 (2H, m), 2.66 (1H, ddd, *J*=12.9, 8.7, 4.9 Hz), 2.00 (1H, ddd, *J*=12.9, 8.7, 6.9 Hz); δ_C (100.6 MHz, CD_3OD) 175.95, 146.21, 142.55, 130.69, 128.29, 126.34, 124.77, 71.50, 36.25, 31.92; HR-FABMS *m/z* 178.085 ($M+H^+$) (calcd for $C_{10}H_{12}NO_2$, 178.089).

4.7.27. Synthesis of (*S*)-1-amino-1,2,3,4,-tetrahydronaphthalene-1-carboxylic acid 1a. Application of procedure G to (1*S*,1′*R*)-**15a** afforded (*S*)-**1a** in 60% yield: $[\alpha]^{24}_D$=+42.8 (*c* 0.9, MeOH).

4.7.28. Synthesis of (*S*)-1-aminobenzocycloheptane-1-carboxylic acid 1b. Application of procedure G to (1*S*, 1′*R*)-**15b** afforded (*S*)-**1b** in 72% yield: $[\alpha]^{24}_D$=+41.8 (*c* 0.83, MeOH).

4.8. General procedure for epimerization studies

Aminonitrile **14a** was prepared from 1-tetralone **8a** as described in the general procedure for the asymmetric Strecker reaction, except that imine *E*-**12a** was washed with several portions of water to remove excess (*R*)-2-phenylglycinol and dried ($MgSO_4$) prior to TMSCN addition. The diastereomeric ratio of the resulting aminonitrile **14a** was determined by ^1H NMR spectroscopy in $CDCl_3$. For the epimerization studies, 10 mg of aminonitrile was dissolved in an appropriate solvent or solvent mixture (total volume of sample 0.6 mL), and the epimerization was monitored by integration of the 1′-benzylic methine signals in the ^1H NMR spectrum.

4.9. General procedure for kinetic studies

A 1:1 mixture of (1*S*,1′*R*)-**15b** and (1*R*,1′*R*)-**15b** (10 mg) was dissolved in 1,1,2,2-tetrachloroethane-d_2 (0.7 mL) in an NMR tube equipped with a Teflon seal. The solution was heated to a constant temperature under an argon atmosphere, and was monitored by integration of the 1′-benzylic methine ^1H NMR signals of (1*S*,1′*R*)-**15b** and (1*R*,1′*R*)-**15b**, and the 5′-methine and 6′-methylene ^1H NMR signals of lactones (1*S*,1′*R*)-**16b** and (1*R*,1′*R*)-**16b**.

4.9.1. Preparation of TMS–imine 18a (*Procedure H*). A solution of the **12a/13b** mixture (86:14; 80.5 mg, 0.30 mmol) in dry THF (1 mL) is cooled to 0°C under argon. TMSCN (80 μL, 2 equiv.) is added. The reaction mixture is stirred for 10 min at 0°C. The solvent is pumped off at 0°C using an oil-pump leaving the crude TMS–imine **18a** as a yellowish oil. This imine was used for the mechanistic studies by NMR without further purification. δ_H (400 MHz, $CDCl_3$) 8.40 (1H, dd, *J*=7.2, 1.2 Hz), 7.49 (2H, d, *J*=7.6 Hz), 7.33–7.21 (5H, m), 7.13 (1H, d, *J*=7.2 Hz), 4.88 (1H, t, *J*=6.4 Hz), 3.92–3.86 (2H, m), 2.85–2.78 (3H, m), 2.50–2.42 (1H, m), 1.94–1.85 (2H, m), 0.01 (9H, s); δ_C (100.56 MHz, $CDCl_3$) 164.79, 142.42, 140.84, 135.40, 129.85, 128.56, 128.48, 128.00, 127.24, 126.52, 125.44, 69.59, 65.87, 30.16, 28.64, 23.06, −0.16.

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