35. Optically Pure Isoproterenol Analogues with Side Chains Containing an Amide Bond: Synthesis and Biological Properties

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(6. I. 88)

The isoproterenol analogues **4a** and **4b**, synthesized as mixtures of diastereoisomers, were shown to possess very potent β-adrenoceptor agonistic activity. Therefore, the four possible diastereoisomers of **4a** have been synthesized and tested for inotropic activity. The (6*R*,2′*R*)-diastereoisomer turned out to be the most interesting one. Consequently, also (6*R*,2′*R*)-**4b** has been prepared and tested. For the diastereoselective synthesis, three variants have been elaborated: *i*) coupling of epoxides **12** with amines **27** *(Scheme 6)*; *ii*) coupling of the activated glycol **17** with the amine **22** *(Scheme 8)*; *iii*) diastereoselective hydrogenation of the amino ketone **31** *(Scheme 7)*. Both (6*R*,2′*R*)-**4a** and (6*R*,2′*R*)-**4b** show long lasting positive inotropic activity after intravenous as well as oral administration and are at least three times as potent as *rac*-isoproterenol. In the anesthetized dog, a good separation of positive inotropic and positive chronotropic effects is observed. In conscious dogs, however, heart rate and contractile force increase to the same extent (possibly due to reflex tachycardia).

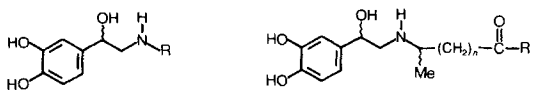
1. Introduction. – Within the scope of studies [1–9], the final objective of which is to improve the therapeutic index of drugs by covalent conjugation to carrier molecules, particularly to peptides, *Goodman* and *Melmon* and their coworkers investigated numerous compounds which have the skeleton of isoproterenol (**2**) and can be described by the general formula **3** *(Scheme 1)* [1–4][7–9]. These compounds were synthesized starting from *rac*-norepinephrine (**1**) by reductive amination and, therefore, obtained as mixtures of diastereoisomers. Separation into pure components could not be achieved [1]. In comparison with **2** in four *in-vitro* test systems, the preparations **4a** and **4b** attracted particular attention as very potent β-adrenoceptor agonists [1][4]. This activity was confirmed in the guinea-pig left atria model as well as in various *in-vivo* tests [2][4] *(cf. Chapt. 3)*. These biological findings prompted us to study optically pure stereoisomers of **4a** and **4b**.

First, the four diastereoisomers of **4a** were synthesized and biologically evaluated. Since (6*R*,2′*R*)-**4a** turned out to be by far the most interesting compound; subsequently, of the more complex structure **4b**, only the (6*R*,2′*R*)-isomer was prepared and biologically studied.

In the following, we report on our synthetic work *(Chapt. 2)* and on the pharmacological investigation of the optically pure stereoisomers mentioned in comparison to the corresponding mixtures of racemic diastereoisomers *(Chapt. 3)*.

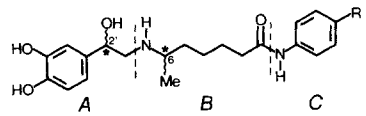
2. Synthesis. – 2.1. *Strategy* (*Scheme 1*). The structure of the target molecules **4** and the position of their centers of chirality suggest a synthetic strategy, in which electrophilic

Scheme 1



1 R = H *rac*-Norepinephrine
2 R = $CHMe_2$ Isoproterenol

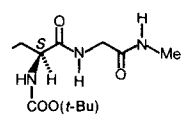
3



A B C

4a R = CF_3

4b R =

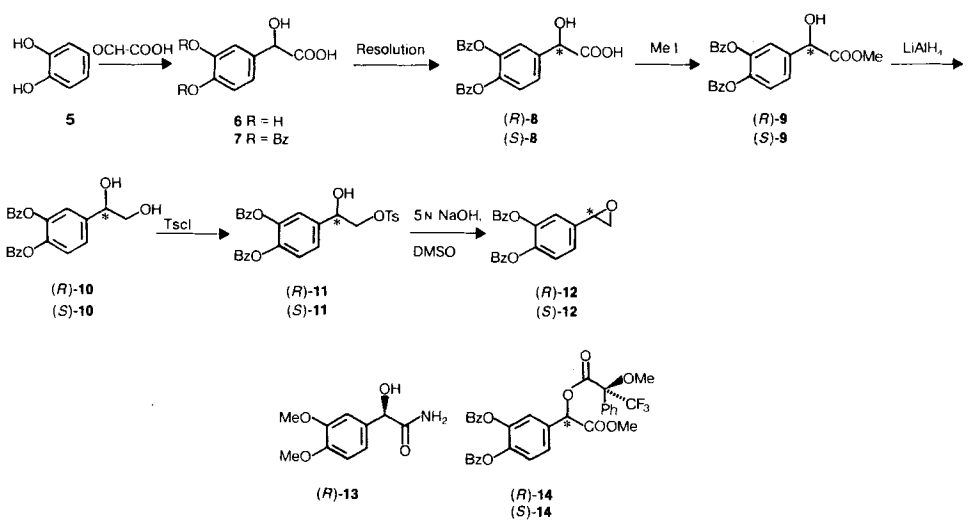


•: Centre of chirality

building blocks **A** and nucleophilic buildings blocks (amines) **B** or **BC**, corresponding to the partial structure ***A***, ***B***, and ***BC*** in formula **4**, respectively, are combined by nucleophilic substitution.

This principle was applied in three variants: *i*) with the epoxides (*R*)-**12** and (*S*)-**12** as **A** and the amines (*R*)-**27** and (*S*)-**27** as **BC** *(Chapt. 2.4, Scheme 6)*; *ii*) with the activated 1,2-diol derivative (*R*)-**17** as **A** and the amine (*R*)-**22** as **B** *(Chapt. 2.6, Scheme 8)*; *iii*) with the achiral bromoketone **30** as **A** and the amine (*R*)-**27** as **BC** *(Chapt. 2.5, Scheme 7)*.

Scheme 2



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6 R = H
7 R = Bz

(*R*)-**8**
(*S*)-**8**

(*R*)-**9**
(*S*)-**9**

(*R*)-**10**
(*S*)-**10**

(*R*)-**11**
(*S*)-**11**

(*R*)-**12**
(*S*)-**12**

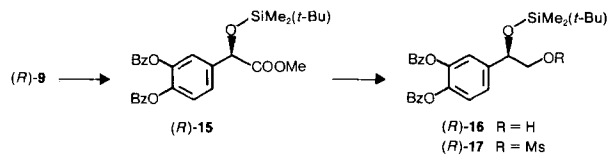
(*R*)-**13**

(*R*)-**14**
(*S*)-**14**

*: Centre of chirality as defined by (*R*) or (*S*)

Bz = $PhCH_2$

Scheme 3



2.2. *Synthesis of the Building Blocks* **A**. The optically pure epoxides **12** were prepared as outlined in *Scheme 2*. The racemic trihydroxy acid **6** is fairly well available [10]. The corresponding dibenzyl derivative **7** [11] was resolved into the antipodes with (+)- and (−)-ephedrine. The epoxide ring closure was performed *via* the tosylates **11** (65% yield from **8**). To establish the absolute configuration of the compounds, the (−)-acid (*R*)-**8** was transformed without racemization into the dimethoxy-mandelamide (*R*)-**13**. The latter is correlated with (*R*)-norepinephrine [12][13]. The optical purity of the hydroxy ester **9** was proved by forming the corresponding *Mosher* ester **14**.

The mesylate (*R*)-**17** was synthesized from the hydroxy ester (*R*)-**9** according to *Scheme 3*. DIBAH is a suitable reagent for the reduction of (*R*)-**15**. (With $LiAlH_4$, the silyl group is shifted to a certain extent to the primary oxygen function.)

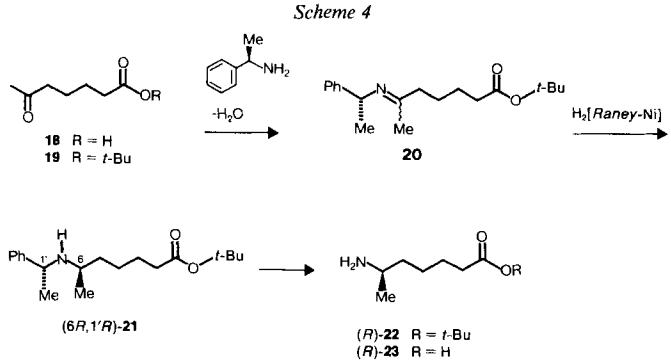
The bromo ketone **30** [14] *(cf. Scheme 7)* was prepared by bromination of 3',4'-bis(benzyloxy)acetophenone with trimethyl(phenyl)ammonium perbromide.

2.3. *Synthesis of the Building Blocks* **B** *and* **BC**. The synthesis of the optically pure amino ester (*R*)-**22** is shown in *Scheme 4*. From the keto ester **19**, obtained from the acid **18**, and (*R*)-α-methylbenzylamine, the imine **20** was formed. Hydrogenation of **20** with *Raney*-Ni yielded the (6*R*,1'*R*)-amino-ester **21** (*cf.* [15]) as the main product (with *ca.* 70% d.e.). The pure (*R*,*R*)-diastereoisomer was obtained by crystallization of the hydrochloride. Hydrogenolysis in the presence of Pd/C catalyst gave (*R*)-**22**. The (*R*)-amino acid **23**, obtained from (*R*)-**22** with anhydrous HCl, is, according to its specific rotation and all other physical data, identical with the compound described in [16].

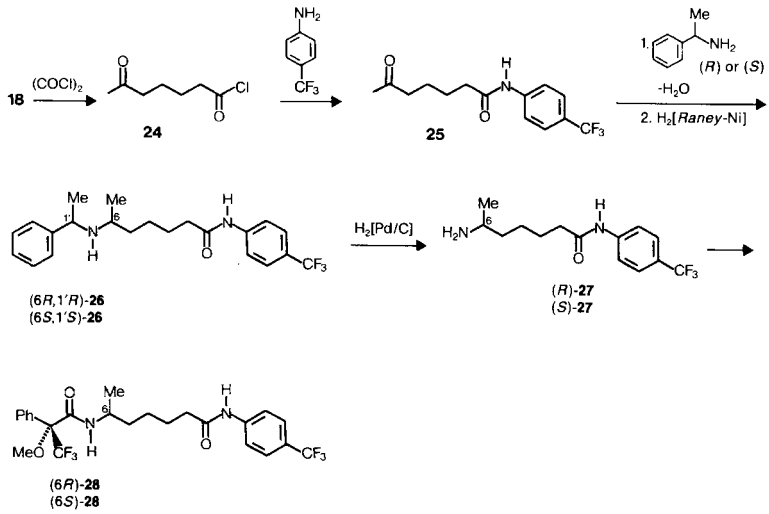
The amines (*R*)- and (*S*)-**27** were prepared in analogy to **22** as indicated in *Scheme 5*. Their optical purity was proved by transformation into the corresponding *Mosher* amides **28**.

2.4. *Synthesis of the Optically Pure Diastereoisomers* **4a** *from the Epoxides (*R*)- and (*S*)-***12***.* If DMSO was used as solvent and CO_2 rigorously excluded, the condensation of

Scheme 4



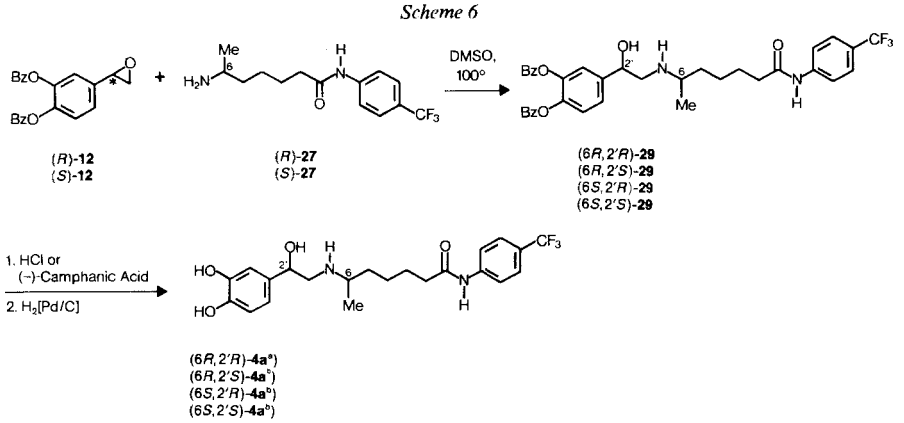
Scheme 5



the epoxides **12** with the amines **27** *(Scheme 6)* afforded the desired diastereoisomers of **29** as main products. Under the conditions mentioned, attack of the amines on the benzylic position of the epoxides was widely suppressed (isomer ratio 4:1, isolation of pure **29** by chromatography). Diastereoisomers **29** were smoothly debenzylated by hydrogenolysis in presence of 1 equiv. of acid. Deoxygenation of the 2'-position was not observed. All four diastereoisomers of **4a** were first prepared as (amorphous) hydrochlorides, but turned out to be unstable in this form even at −20°. Their salts with (−)-camphanic acid, however, were stable. Both, free base as well as camphanate of (6*R*,2'*R*)-**4a** are crystalline compounds.

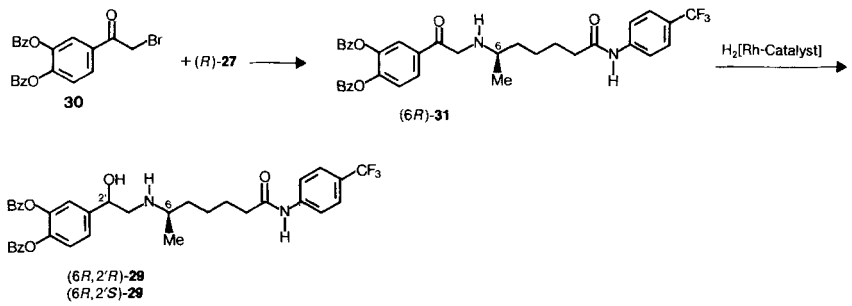
2.5. *Synthesis of the Diastereoisomers (6*R,2'R*)-***4a*** *and (6*R,2'S*)-***4a*** *from the Phenacyl Bromide* **30**. The amino ketone (*R*)-**31** was obtained by reaction of the bromo ketone

Scheme 6



a) Isolated as free base and as salts of HCl and (−)-camphanic acid.
b) Isolated as salts of HCl and (−)-camphanic acid.

Scheme 7

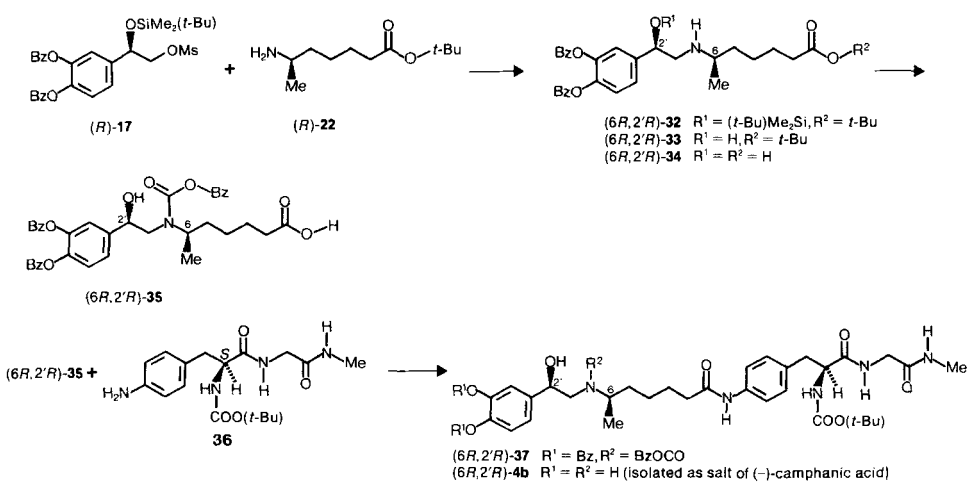


30 with an excess of (*R*)-**27** and isolated as hydrochloride in 65% yield *(Scheme 7)*. Diastereoselective hydrogenation of (*R*)-**31** could be performed making use of the methods published by *Kumada* and coworkers [17]. To suppress debenzylation, the hydrogenations were run in presence of 10 mol-equiv. of Et_3N. The stereochemical outcome of the reaction strongly depended on solvent and catalyst. With the cationic [Rh-(*S*)-(*R*)-BPPFOH]ClO_4[1]) complex in MeOH, predominantly (6*R*,2′*S*)-**29** was formed; with the neutral complex [RhCl-(*S*)-(*R*)-BPPFOH][1]) in AcOEt, in contrast, pure (6*R*,2′*R*)-**29** (87.4% yield) was obtained. This procedure allows the preparation of (6*R*,2′*R*)-**4a** on a large scale.

2.6. *Synthesis of (6*R,2′R*)-***4b***. In **4b**, the partial structure ***C*** is multifunctional. For this compound, therefore, the synthetic scheme **A** + **B**→**AB**; **AB** + **C**→**ABC** was chosen.

Since in the synthesis of **4a** the condensation of the epoxides **12** with the amines **27** was not completely regioselective, the protected and activated glycol (*R*)-**17** was prepared, as already described in *Chapt. 2.2.* The amino ester (*R*)-**22** *(Chapt. 2.3)* as

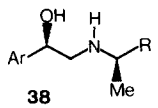
Scheme 8



[1]) Nomenclature according to [17]; for IUPAC nomenclature, see *Exper. Part.*

building block **B** and the mesylate (*R*)-**17** as **A** were combined, in presence of *Hünig*'s base at 120°, to the **AB** molecule (6*R*,2'*R*)-**32** in 65% yield *(Scheme 8)*. The silyl protecting group was removed with Bu_4NF in $MeCN/H_2O$ (→(6*R*,2'*R*)-**33**), the *t*-Bu by alkaline saponification (→(6*R*,2'*R*)-**34**). Subsequently, the NH group was blocked by benzyloxycarbonylation (→(6*R*,2'*R*)-**35** (26% from **32**)). After activation of the COOH group in **35** by forming the mixed anhydride with isobutyl chloroformate, compund **36** [3], as building block **C**, was attached (→(6*R*,2'*R*)-**37**). Finally, the protecting groups were removed by catalytic hydrogenolysis. Compound (6*R*,2'*R*)-**4b** was isolated as amorphous salt with (−)-camphanic acid (69% yield from (6*R*,2'*R*)-**35**).

3. Pharmacology[2]). – To elaborate possible relationships between configuration and biological activity, first we compared the optically pure diastereoisomers of **4a** as the freshly prepared hydrochlorides in *in-vitro* tests *(Table 1)*. They were found to differ markedly with regard to their affinity to β-adrenoceptors. In the [^{3}H]dihydroalprenolol binding assay [19], the (6*R*,2'*R*)-isomer was roughly 500 times more active than its antipode (6*S*,2'*S*)-**4a** and 40 times more active than *rac*-isoproterenol (**2**). The (6*R*,2'*S*)-isomer had 1/10 the potency of **4a**, but five times that of its antipode (6*S*,2'*R*)-**4a**. About the same order of potencies of the isomers was observed for increasing myocardial



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contractile force in isolated guinea-pig left atria. That β-adrenoceptor ligands with an absolute configuration as depicted in formula **38** show higher affinity to β-adrenoceptors than their isomers with one or both chiral centers inverted has been described earlier [15][20]. The camphanates of the isomers **4a** are clearly more active in the guinea-pig model than the hydrochlorides. In the same test, also the phosphate of (6*R*/*S*,2'*R*/*S*)-**4a**[3]) [1] shows remarkably high activity. (6*R*/*S*,2'*R*/*S*)-**4b**·H_3PO_4[3]) and (6*R*,2'*R*)-**4b**·(−)-camphanic acid show a similar potency in isolated guinea-pig left atria as (6*R*/*S*,2'*R*/*S*)-**4a**·H_3PO_4[3]) and (6*R*,2'*R*)-**4a**·HCl *(Table 2)*.

The isoproterenol analogues **4** produced pronounced haemodynamic effects in anaesthetized open-chest dogs after intravenous administration *(Tables 1* and *2)*. The (6*R*,2'*R*)-isomers are clearly more active than *rac*-isoproterenol (**2**) and, in contrast to that compound, display a favorably dissociated pattern of activities inasmuch as heart rate was increased only weakly at doses almost doubling myocardial contractile force ($d(LVP)/dt_{max}$). Moreover, they were found to have a duration of action of several hours, while the effect of isoproterenol lasts for a few minutes only. The most surprising feature of these compounds is their oral activity in conscious dogs, which contrasts markedly with orally poorly active isoproterenol. All isomers of **4** prepared increased myocardial force ($d(LVP)/dt_{max}$) in a dose-dependent manner from 10 to 100 μg/kg p.o. However, the dissociation between inotropic and chronotropic activity, which was observed after i.v. injection, was almost lost after oral administration to conscious dogs, probably due to reflex tachycardia, occurring in response to the decreased peripheral resistance.

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[2]) A more detailed account of our pharmacological studies with **4** will be published elsewhere. Methods have been described in [18].

[3]) Mixture of four possible diastereoisomers.

Table 1. In-vitro *and* in-vivo (*i.v.* and *p.o.*) *Effects of* rac-*Isoproterenol* (**2**), *(6* R/S,*2'* R/S*)*-**4a** · H_3PO_4, *and the Four Pure Isomers of* **4a** *on Myocardial Contractility and Heart Rate in Guinea-Pig Left Atria, Anaesthetized Open-Chest, and Chronically-Instrumented, Conscious Dogs.* [^{3}H]Dihydroalprenolol binding of **2** and of the isomers of **4a**.

	[^{3}H]Dihydroalprenolol binding K_i [nM]	Guinea-pig left atria tension development EC_{50} [nM]	Anaesthetized open-chest dog								Cardiac performance conscious dog				
			Dose [μg/kg] *i.v.*	d(*LVP*)/dt_{max}[a])		HR[b])		CO[c])		TPR[d])		Dose [μg/kg] *p.o.*	d(*LVP*)/dt_{max}[a])		HR[b])	
				Δ[%]	DOA[e])	Δ[%]	DOA[e])	Δ[%]	DOA[e])	Δ[%]	DOA[e])		Δ[%]	DOA[f])	Δ[%]	DOA[f])
rac-Isoproterenol (**2**)	285	77	0.1[h])	40	5	46	5	17	5	−51	5	900[i])	–	–	50	–
			0.3[h])	54	5	53	5	27	5	−55	5					
			1.0[h])	64	5	59	5	26	5	−52	5					
			3.0[h])	60	10	72	10	28	10	−57	10					
(6*R*/*S*,2'*R*/*S*)-**4a** · H_3PO_4[j])		2.5	0.05	80	120	16	>200	–	–	–	–	10	− 9	> 8	− 22	8
			0.15	60	–	10	–	–	–	–	–	30	+ 62	8	+ 45	3
(6*R*,2'*R*)-**4a** · HCl	7.2	6.2	0.001[g])	6	> 20	0	20	5	10	−10	10	10[g])	+ 4	8	0	8
			0.003[h])	30	>120	3	30	36	120	−25	120	30[h])	+ 42	> 4	20	3
			0.01[h])	64	>120	10	>120	24	160	−29	120	50[h])	+ 95	> 8	+ 73	6
			0.03[g])	77	>240	26	>240	34	120	−38	120	100[g])	+112	8	+100	8
(6*R*,2'*R*)-**4a** · (−)-camphanic acid	2.9	0.5	0.01[h])	64	60	5	30	31	30	−30	45	10[h])	22	7	30	1
			0.1[h])	93	120	28	120	61	60	−58	120	100[h])	82	21	84	6
(6*S*,2'*R*)-**4a** · HCl	370	160	0.1[g])	38	20	6	30	15	10	−35	10	10	+ 6	3	− 10	8
			0.3[g])	67	> 20	9	20	–	–	–	–	30	− 3	8	− 21	8
			1.0[g])	100	30	19	30	–	–	–	–	100	+ 33	3	+ 14	3
			3.0[g])	100	60	27	< 20	88	30	−69	60					
(6*S*,2'*R*)-**4a** · (−)-camphanic acid		13														
(6*R*,2'*S*)-**4a** · HCl	68.2	170	0.01[g])	14	10	0	–	–	–	–	–	10	− 9	< 6	− 13	< 6
			0.03[g])	57	60	8	60	–	–	–	–	30	+ 13	> 8	− 13	> 8
			0.1[g])	53	> 60	14	< 60	–	–	–	–	100	+ 44	< 6	+ 21	< 6
			0.3[g])	59	>120	31	>120	77	30	−64	60					
			1.0[g])	29	120	62	120	69	30	−65	60					
(6*R*,2'*S*)-**4a** · (−)-camphanic acid		14														
(6*S*,2'*S*)-**4a** · HCl	3500	1100	1.0[g])	31	10	3	10	17	3	−24	3	10	+ 3	8	− 10	8
			3.0[g])	63	60	10	30	36	6	−48	6	30	–	–	–	–
												100	+ 11	< 2	+ 8	< 2
(6*S*,2'*S*)-**4a** · (−)-camphanic acid		150														

[a]) d(*LVP*)/dt_{max} [mm Hg/s]: Max. rate of rise of left ventricular pressure. [b]) HR [beats/min]: Heart rate. [c]) CO [ml/min/10 kg]: Cardiac output. [d]) TPR [dyn · s/cm^5]: Total peripheral vascular resistance. [e]) DOA [min]: Duration of action. [f]) DOA [h]: Duration of action. [g]) Results based on a single experiment. [h]) Results based on at least four experiments. [i]) Data reported in [21]. [j]) Mixture of four possible diastereoisomers.

Table 2. In-vitro *and* in-vivo (*i.v.* and *p.o.*) *Effects of (6*R/S, *2'*R/S*)-***4b*** · H_3PO_4 *and (6*R,*2'*R*)-***4b*** · (−)-Camphanic Acid on Myocardial Contractility and Heart Rate in Guinea-Pig Left Atria, Anaesthetized Open-Chest and Chronically-Instrumented, Conscious Dogs*

	Guinea-pig left atria tension development EC_{50} [nM]	Anaesthetized open-chest dog									Cardiac performance conscious dog				
		Dose [μg/kg] *i.v.*	$d(LVP)/dt_{max}$[a])		HR[b])		CO[c])		TRP[d])		Dose [μg/kg] *p.o.*	$d(LVP)/dt_{max}$[a])		HR[b])	
			Δ[%]	DOA[e])	Δ[%]	DOA[e])	Δ[%]	DOA[e])	Δ[%]	DOA[e])		Δ[%]	DOA[f])	Δ[%]	DOA[f])
(6*R*/*S*,2'*R*/*S*)-**4b** · H_3PO_4[g])	4.3	0.03	37	60	8	> 60	19	> 60	−23	> 60	10	21	3	13	> 2
		0.1	90	120	25	>120	37	120	−38	120	20	27	6	16	3
											30	121	8	71	8
(6*R*,2'*R*)-**4b** · (−)-camphanic acid	2.9	–	–	–	–	–	–	–	–	–	3	22	> 6	− 7	6
		–	–	–	–	–	–	–	–	–	10	128	> 8	101	6

[a–f]) See Footnotes of *Table 1*.

[g]) Mixture of four possible diastereoisomers.

The skillful assistance of *A. Binggeli, R. Preiswerk, R. Huber, J.P. Parys, U. Sprecher*, and *A. Meili* is acknowledged. The authors thank also Drs. *W. Arnold, A. Dirscherl, G. Englert, M. Grosjean, W. Vetter*, and Mr. *Meister* for spectroscopic determinations and microanalyses, Dr. *W. Burkard* for binding assays.

Experimental Part

General. Reagent-grade solvents (*Fluka, Merck*) were dried over molecular sieves. All reactions were performed in closed systems with a slight Ar overpressure. Evaporation means removal of solvent by use of a *Büchi* rotary evaporator at 40–50°/*in vacuo* (20–400 Torr) followed by evaporation at 10^{-2} Torr. Crystalline substances in all cases were dried *in vacuo* (< 0.1 Torr). Column chromatography was carried out by using silica gel *60* (0.04–0.063 mm; *Merck*) and 0.3–1.0 bar Ar pressure. GC: *Varian 3700, SE 54* column (20 m). M.p.: uncorrected; *Büchi 510*. $[\alpha]_D^{20}$: *Perkin Elmer 241* polarimeter, *c* in g/100 ml. IR spectra: *Nicolet-7199-FT-IR* spectrophotometer; in cm^{-1}. ^{1}H-NMR spectra: *Varian-A-60-D* (60 MHz) and *EM-390* (90 MHz); *Bruker-Spectrospin-WP-80-CW* (80 MHz), *HX-90/15* (90 MHz), *AS-250* (250 MHz), *HX-270* (270 MHz), *WM-400* (400 MHz), δ values in ppm relative to internal or external TMS; coupling constants (*J*) in Hz. MS: *MS 9* updated with a *Finnigan ZAB* console, data system *SS 200, VG Altrincham* (EI:70 eV); *MS 902*, fast-atom gun *Kratos*, data system *2050, VG Altrincham* (FAB, Xe-atom 6 keV, thioglycerol matrix (*Fluka*)); *m/z* (intensity in % of the base peak (100%)).

1. *(±)-2-[3,4-Bis(benzyloxy)phenyl]-2-hydroxyethanoic Acid* (**7**). A 50% aq. soln. of glyoxylic acid (138 ml, 1 mol) was added within 30 min below 32° to a soln. of catechol (220 g, 2 mol) and NaOH (120 g, 3 mol) in H_2O (1.2 l). The resulting mixture was stirred at r.t. for 24 h, acidified to pH 2.5 with 6N aq. HCl (450 ml) and extracted with Et_2O (3 × 1 l) to remove unreacted catechol. The aq. soln. was evaporated at 80° *in vacuo*. The residue was evaporated from toluene (2 × 1 l), heated under reflux in a mixture of acetone (2.5 l) and MeOH (0.25 l) and filtered hot. The residue was heated again under reflux in a mixture of acetone and MeOH (2.5 l of each) and filtered. The combined filtrates were evaporated giving crude (±)-*2-(3,4-dihydroxyphenyl)-2-hydroxyethanoic acid* **6** (130 g) as amorphous solid, which was used without further purification.

$PhCH_2Cl$ (100 g, 0.79 mol) was added within 1 h to a mixture of crude **6** (130 g), anh. K_2CO_3 (115 g, 0.83 mol) and KI (7.6 g, 0.046 mol) in abs. MeOH (2.7 l) heated under reflux. K_2CO_3 (115 g, 0.83 mol) was added and additional $PhCH_2Cl$ (100 g, 0.79 mol) within 3 h. After the addition of a third portion of K_2CO_3 (115 g, 0.83 mol), the mixture was refluxed for 18 h, evaporated, suspended in H_2O (2 l), acidified with conc. HCl (0.44 l), and extracted with AcOEt (2 × 2 l). The org. phase was washed with brine, dried (Na_2SO_4), and evaporated. The residue was crystallized from AcOEt/petroleum ether and subsequently from acetone/H_2O: 107.8 g (29.6%) of **7**. M.p. 137–138° ([11]: 137°). ^{1}H-NMR (80 MHz, (D_6)DMSO): 4.96 (*s*, 1 H); 5.11 (*s*, 2 H); 5.14 (*s*, 2 H); 7.04 (*m*, 2 H); 7.22 (*m*, 1 H); 7.43 (br. *m*, 10 H); OH, COOH br. Anal. calc for $C_{22}H_{20}O_5$ (364.40): C 72.51, H 5.53; found: C 72.19, H 5.60.

2. *(R)-2-[3,4-Bis(benzyloxy)phenyl]-2-hydroxyethanoic Acid* ((*R*)-**8**). Compound **7** (100 g, 0.275 mol) and (−)-ephedrine (25 g, 0.151 mol) were dissolved in AcOEt (1.3 l) at 50°. When the crystallization progressed and the soln. reached r.t., Et_2O (1.3 l) was added to complete the crystallization. The crystals were collected by filtration and recrystallized twice from MeCN: (*R*)-**8**-(−)-ephedrine salt (44.0 g + 6.4 g from recrystallized mother liquors, 69.2%). M.p. 131–133°. $[\alpha]_D^{20} = -43.2°$ (*c* = 1.0, MeOH). Anal. calc. for $C_{32}H_{35}NO_6$ (529.63): C 72.57, H 6.66, N 2.64; found: C 72.46, H 6.64, N 2.60.

The (*R*)-**8**-(−)-ephedrine salt (50.4 g, 0.0952 mol) was suspended in AcOEt (700 ml), 2N HCl (350 ml) was added and the mixture stirred intensively for 5 min. The org. phase was separated, the aq. soln. extracted with a second portion of AcOEt (700 ml), the combined AcOEt solns. were washed with brine, dried (Na_2SO_4), evaporated, and the residue crystallized from AcOEt/petroleum ether: 30.0 g (86.5%) (*R*)-**8**. M.p. 105°. $[\alpha]_D^{20} = -72.0°$ (*c* = 1.0, MeOH). IR (KBr): 3360, 1715, 1520. ^{1}H-NMR (80 MHz, (D_6) DMSO): identical to that of **7**. MS: 364 (3, $M^{+\cdot}$), 181 (5), 91 (100). Anal. calc. for $C_{22}H_{20}O_5$ (364.40): C 72.51, H 5.53; found: C 72.44, H 5.57.

3. *(S)-2-[3,4-Bis(benzyloxy)phenyl]-2-hydroxyethanoic Acid* ((*S*)-**8**). Analogously to *2* from **7** and (+)-ephedrine.

*Data of (S)-***8***-(+)-Ephedrine Salt.* M.p. 131–133°. $[\alpha]_D^{20} = +43.1°$ (*c* = 1.0, MeOH). Anal. calc. for $C_{32}H_{35}NO_6$ (529.63): C 72.57, H 6.66, N 2.64; found: C 72.54, H 6.58, N 2.52.

*Data of (S)-***8**. M.p. 105–106°. $[\alpha]_D^{20} = +70.6°$ (*c* = 1.0, MeOH). IR (KBr): 3450, 1730, 1520. ^{1}H-NMR and MS: identical to those of (*R*)-**8**. Anal. calc. for $C_{22}H_{20}O_5$ (364.40): C 72.51, H 5.53; found: C 72.55, H 5.76.

4. *Methyl (R)-2-[3,4-Bis(benzyloxy)phenyl]-2-hydroxyethanoate* ((*R*)-**9**). MeI (200 ml, 3.2 mol) was added, within 15 min at r.t., to a mixture of (*R*)-**8** (106 g, 0.291 mol), K_2CO_3 (254 g, 1.84 mol) in acetone (2.0 l) and the mixture was refluxed for 1 h. The K salts were filtered off, the filtrate evaporated, poured into ice-water (1 l) and extracted with AcOEt (1.5 and 1 l). The org. phase was washed with sat. $NaHCO_3$-soln. and brine, dried (Na_2SO_4),

evaporated, and the residue recrystallized from CH_2Cl_2/Et_2O/hexane: 102 g (92.6%) (*R*)-**9**. M.p. 90–91°. $[\alpha]_D^{20} = -70.4°$ (*c* = 1.0, MeOH). IR (KBr): 3440, 1745, 1520, 1270, 1240. ^{1}H-NMR (60 MHz, $CDCl_3$): 3.25 (br., 1 H); 3.69 (*s*, 3 H); 5.07 (*s*, 1 H); 5.15 (*s*, 4 H); 6.92 (*m*, 2 H); 7.01 (*m*, 1 H); 7.37 (*m*, 10 H). MS: 378 (10, $M^{+\cdot}$), 319 (2), 287 (3), 227 (2), 91 (100). Anal. calc. for $C_{23}H_{22}O_5$ (378.4): C 73.00, H 5.86; found: C 73.07, H 5.81.

5. *Methyl (S)-2-[3,4-Bis(benzyloxy)phenyl]-2-hydroxyethanoate* ((S)-**9**). Analogously to *4* from (*S*)-**8**.

*Data of (S)-***9**. M.p. 91–92°. $[\alpha]_D^{20} = +69.6°$ (*c* = 1.0, MeOH). IR, ^{1}H-NMR, MS identical to those of (*R*)-**8**. Anal. calc. for $C_{23}H_{22}O_5$ (378.42): C 73.00, H 5.86; found: C 72.92, H 5.86.

6. *(R)-1-[3,4-Bis(benzyloxy)phenyl]-1,2-ethanediol* ((*R*)-**10**). Compound (*R*)-**9** (100 g, 0.264 mol), dissolved in THF (800 ml), was added within 30 min at r.t. to a suspension of $LiAlH_4$ (20 g, 0.53 mol) in THF (250 ml). After stirring for 30 min at r.t, H_2O (390 ml) was added below 10°; the resulting suspension was filtered, the filtrate partially evaporated, poured into aq. 2N NaOH (250 ml) of 0°, and extracted with AcOEt (2 × 1 l). The org. phase was washed with brine, dried (Na_2SO_4), and evaporated, giving crude (*R*)-**10** (92 g, 100%). A small portion was recrystallized from CH_2Cl_2/hexane, giving pure (*R*)-**10**. M.p. 76–78°. $[\alpha]_D^{20} = -15.2°$ (*c* = 1.0, MeOH). IR (KBr): 3390, 1530, 1280. ^{1}H-NMR (80 MHz, $CDCl_3$): 2.83 (*s*, 2 H); 3.58 (*m*, 2 H); 4.64 (*dd*, *J* = 7, 4.5, 1 H); 5.13 (*s*, 4 H); 6.89 (*m*, 2 H); 7.00 (*m*, 1 H); 7.40 (*m*, 10 H). MS: 350 (2, $M^{+\cdot}$), 319 (5), 91 (100). Anal. calc. for $C_{22}H_{22}O_4$ (350.41): C 75.41, H 6.33; found: C 75.30, H 6.37.

7. *(S)-1-[3,4-Bis(benzyloxy)phenyl]-1,2-ethanediol* ((*S*)-**10**). Analogously to *6* from (*S*)-**9**.

*Data of (S)-***10**. M.p. 76–78°. $[\alpha]_D^{20} = +14.6°$ (*c* = 1.0, MeOH). IR, ^{1}H-NMR, MS identical to those of (*R*)-**10**. Anal. calc. for $C_{22}H_{22}O_4$ (350.41): C 75.41, H 6.33; found: C 75.39, H 6.41.

8. *(R)-2-[3,4-Bis(benzyloxy)phenyl]-2-hydroxyethyl* p-*Toluenesulfonate* ((*R*)-**11**). Compound (*R*)-**10** (83.0 g, 0.237 mol), dissolved in toluene/Et_2O (4:1, 325 ml), was added, within 30 min at 5°, to a soln. of TsCl (49.0 g, 0.257 mol) in toluene (130 ml) and pyridine (24 ml, 0.297 mol). The mixture was stirred at 5° for 96 h, diluted with a mixture of CH_2Cl_2 and Et_2O (1:1, 340 ml), the crystalline pyridine hydrochloride was filtered off, the filtrate was evaporated, and the residue chromatographed on silica gel (1 kg) with toluene and toluene/AcOEt (9:1), affording (*R*)-**11** (84 g, 70%) as a viscous oil. $[\alpha]_D^{20} = -18.4°$ (*c* = 0.50, MeOH). IR (film): 3510, 1600, 1515, 1360, 1270, 1180. ^{1}H-NMR (80 MHz, (D_6)DMSO): 2.38 (*s*, 3 H); 3.96 (*d*, *J* = 5.5, 2 H); 4.66 (*t*, *J* = 5.5, 1 H); 5.01 (*s*, 2 H); 5.08 (*s*, 2 H); 6.69–7.05 (*m*, 3 H); 7.24 (*d*, *J* = 8.5, 2 H); 7.36 (*m*, 10 H); 7.66 (*d*, *J* = 8.5, 2 H); OH br. MS: 486 (33, $M^{+\cdot} - H_2O$), 181 (63), 91 (100).

9. *(S)-2[3,4-Bis(benzyloxy)phenyl]-2-hydroxyethyl* p-*Toluenesulfonate* ((S)-**11**). Analogously to *8* from (S)-**10**.

*Data of (S)-***11**. ^{1}H-NMR identical to that of (*R*)-**11**.

10. *(R)-1,2-Bis(benzyloxy)-4-oxiranylbenzene* ((*R*)-**12**). Aq. NaOH soln. (5N, 80 ml) was added, within 15 min between 0° and 5°, to (*R*)-**11** (137.5 g, 0.272 mol), dissolved in DMSO (165 ml). The mixture was stirred for 75 min at 5°, poored into ice-water, and extracted with a mixture of hexane/Et_2O 1:1 (1 l, 2 × 0.5 l). The org. phase was washed with H_2O, dried ($MgSO_4$), and evaporated, affording (*R*)-**12** (94.2 g, > 100%) as an oil. $[\alpha]_D^{20} = -10.5°$ (*c* = 1.0, $CHCl_3$). IR (film): 1610, 1590, 1515, 1270, 1020. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.71 (*dd*, *J* = 2.5, 5, 1 H); 3.08 (*dd*, *J* = 4, 5, 1H); 3.76 (*dd*, *J* = 2.5, 4, 1H); 5.15 (*m*, 4 H); 6.80–6.92 (*m*, 3 H); 7.20–7.50 (*m*, 10 H). MS: 332 (4, $M^{+\cdot}$), 241 (3), 181 (6), 91 (100).

11. *(S)-1,2-Bis(benzyloxy)-4-oxiranylbenzene* ((S)-**12**). Analogously to *10* from (*S*)-**11**.

*Data of (S)-***12**. ^{1}H-NMR identical to that of (*R*)-**12**.

12. *(R)-2-(3,4-Dimethoxyphenyl)-2-hydroxyethanamide* ((*R*)-**13**). Compound (*R*)-**8** (1.00 g, 2.74 mmol) was hydrogenated for 1.5 h at r.t. and normal pressure in MeOH/H_2O (20:1; 21 ml) in the presence of 5% Pd/C (0.2 g). The catalyst was removed by filtration and the soln. evaporated; the residue (0.58 g) was dissolved in toluene, evaporated again, dissolved in MeOH (20 ml), and treated with etheral CH_2N_2 soln. (110 ml, *ca.* 30 mmol CH_2N_2). The mixture was allowed to stand at r.t. for 20 h. Excess CH_2N_2 was removed by slight heating; the mixture was then evaporated, the residue (0.64 g) dissolved in MeOH (10 ml), and the mixture saturated with NH_3 (gas) at 0° for 1 h, stirred at 0° for 6 h, saturated again with NH_3 (gas), allowed to reach r.t. over night, evaporated, and the residue crystallized twice from AcOEt: (*R*)-**13** (0.314 g, 54%). M.p. 135–136°. $[\alpha]_D^{20} = -114°$ (*c* = 0.45, $CHCl_3$). ([12]: M.p. 135–136°. $[\alpha]_D^{20} = -115.4°$ (*c* = 0.45, $CHCl_3$)). IR (KBr): 1660, 1515, 1235, 1150. ^{1}H-NMR (250 MHz, (D_6)DMSO): 3.73 (*s*, 6 H); 4.76 (*d*, *J* = 5, 1 H); 5.88 (*d*, *J* = 5, 1 H); 6.90 (*m*, 2 H); 7.01 (*s*, 1 H); 7.13, 7.37 (2 s, 1 H each, NH_2). MS: 211 (14, $M^{+\cdot}$), 167 (100). Anal. calc. for $C_{10}H_{13}NO_4$ (211.22): C 56.87, H 6.20, N 6.63; found: C 56.67, H 6.10, N 6.57.

13. *(R)-3,4-Bis(benzyloxy)-α-(methoxycarbonyl)benzyl (S)-3,3,3-Trifluoro-2-methoxy-2-phenylproprionate* ((1'*R*)-**14**). 4-(Dimethylamino)pyridine (33.1 mg, 0.271 mmol) and (*R*)-**9** (41.4 mg, 0.109 mmol) were added to a soln. of (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropionyl chloride [22] (68.5 mg, 0.271 mmol) in DMF (1 ml). The mixture was stirred at r.t. for 30 min (100% conversion according to TLC) and diluted with Et_2O (50 ml). The org.

phase was washed with 3N HCl (2 × 10 ml), sat. $NaHCO_3$ soln. (10 ml), brine (10 ml), dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel (3 g) with CH_2Cl_2/hexane (1:1), affording (1'*R*)-**14** (56.3 mg, 87%) with ≥ 98% d.e. (^{1}H-NMR). ^{1}H-NMR (250 MHz, $CDCl_3$): 3.49 (*m*, 3 H); 3.69 (*m*, 3 H); 5.11 (*s*, 2 H); 5.16 (*s*, 2 H); 5.98 (*s*, 1 H); 6.89–7.02 (*m*, 3 H); 7.29–7.48 (*m*, 13 H); 7.59 (*m*, 2 H). MS: 594 (6, M^+), 503 (2), 189 (9), 91 (100).

14. *(S)-3,4-Bis(benzyloxy)-α-(methoxycarbonyl)benzyl (S)-3,3,3-Trifluoro-2-methoxy-2-phenylpropionate* ((1'*S*)-**14**). Analogously to *13* from (*S*)-**9**; ≥ 98% d.e. (^{1}H-NMR). ^{1}H-NMR (250 MHz, $CDCl_3$): 3.65 (*m*, 3 H); 3.71 (*m*, 3 H); 5.07 (*s*, 2 H); 5.15 (*s*, 2 H); 5.98 (*s*, 1 H); 6.83–6.95 (*m*, 3 H); 7.28–7.45 (*m*, 13 H); 7.61 (*m*, 2 H). MS: 594 (6, M^+), 503 (2), 189 (9), 91 (100).

15. *Methyl (R)-2-[3,4-Bis(benzyloxy)phenyl]-2-[(*tert*-butyl)dimethylsilyloxy]ethanoate* ((*R*)-**15**). Compound (*R*)-**9** (30.5 g, 80.6 mmol), dissolved in DMF (27 ml), was added to a soln. of (*t*-Bu)Me_2SiCl (18.8 g, 125 mmol) and 4-(dimethylamino)pyridine (20.1 g, 164 mmol) in DMF (45 ml) within 15 min below 23°. The mixture was stirred at r.t. for 1.5 h, poured into ice-water (200 ml), acidified to pH 3 with dil. HCl soln., and extracted with Et_2O (200 ml, 2 × 100 ml). The org. phase was dried ($MgSO_4$) and evaporated, affording (*R*)-**15** (42.5 g, > 100%). A sample (1.5 g) was recrystallized from MeOH, giving pure (*R*)-**15** (1.1 g). M.p. 50–51°. $[\alpha]_D^{20} = -54.6°$ (*c* = 1.0, MeOH). IR (thin film): 1755, 1510, 1255. ^{1}H-NMR (80 MHz, $CDCl_3$): 0.03 (*s*, 3 H); 0.11 (*s*, 3 H); 0.94 (*s*, 9 H); 3.69 (*s*, 3 H); 5.19 (*s*, 2 H); 5.21 (*s*, 2 H); 5.20 (br., 1 H); 6.98 (*m*, 2 H); 7.15 (*m*, 1 H); 7.42 (*m*, 10 H). MS: 435 (35, $M^+ - C_4H_9$), 433 (7), 91 (100). Anal. calc. for $C_{29}H_{36}O_5Si$ (492.69): C 70.70, H 7.37; found: C 70.99 H 7.54.

16. *(R)-2-[3,4-Bis(benzyloxy)phenyl]-2-[(*tert*-butyl)dimethylsilyloxy]ethanol* ((*R*)-**16**). DIBAH (166 ml of a 1.2M soln. in toluene, 199 mmol) was added, within 20 min between −20 and −30°, to a soln. of (*R*)-**15** (41 g, max. 77.8 mmol) in Et_2O (400 ml). The mixture was stirred at the same temp. for 2.5 h, cooled to −70°, treated with H_2O (200 ml), stirred at r.t. for 30 min, and filtered. The org. phase was separated, the aq. phase extracted with AcOEt (2 × 100 ml), the combined org. phase dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel (450 g) with CH_2Cl_2/hexane (1:1) and CH_2Cl_2, affording (*R*)-**16** (33.8 g, 93%) as a yellowish oil. $[\alpha]_D^{20} = -37.7°$ (*c* = 1.0, MeOH). IR (thin film): 3450, 1510, 1260. ^{1}H-NMR (80 MHz, $CDCl_3$): −0.15 (*s*, 3 H); 0.02 (*s*, 3 H); 0.88 (*s*, 9 H); 1.82 (*s*, 1 H); 3.50 (*d*, *J* = 6, 2 H); 4.65 (*t*, *J* = 6, 1 H); 5.15 (*m*, 4 H); 6.88 (*m*, 2 H); 6.96 (*m*, 1 H); 7.38 (*m*, 10 H). MS: 433 (10, $M^+ - CH_2OH$); 407 (1), 91 (100). Anal. calc. for $C_{28}H_{36}O_4Si$ (464.68): C 72.37, H 7.81; found: C 71.81, H 8.02.

17. *2-[3,4-Bis(benzyloxy)phenyl]-2-[(*tert*-butyl)dimethylsilyloxy]ethyl Methanesulfonate* ((*R*)-**17**). Et_3N (10.2 ml, 73.2 mmol) was added to a soln. of (*R*)-**16** (13.94 g, 30.0 mmol) in CH_2Cl_2 (70 ml). The mixture was cooled to −70° and MsCl (3.2 ml, 41 mmol) added below −60°. The mixture was stirred at −70° for 1.5 h, poured into ice-water, and extracted with CH_2Cl_2. The org. phase was dried (K_2CO_3) and evaporated, affording (*R*)-**17** (16.3 g, 100%) as yellowish oil. $[\alpha]_D^{20} = -38.5°$ (*c* = 1.0, MeOH). IR (thin film): 1510, 1360, 1260, 1180. ^{1}H-NMR (80 MHz, $CDCl_3$): −0.09 (*s*, 3 H); 0.05 (*s*, 3 H); 0.87 (*s*, 9 H); 2.82 (*s*, 3 H); 4.08 (*d*, *J* = 6, 2 H); 4.85 (*t*, *J* = 6, 1 H); 5.16 (*s*, 4 H); 6.90 (*m*, 2 H); 6.98 (*m*, 1 H); 7.39 (*m*, 10 H). MS: 446 (1, $M^+ - CH_3SO_3H$), 433 (2), 91 (100). Anal. calc. for $C_{29}H_{38}O_6SSi$ (542.76): C 64.18, H 7.06; found: C 63.97, H 7.22.

18. tert-*Butyl 6-Oxoheptanoate* (**19**). A mixture of **18** (398.4 g, 2.76 mol) [23], conc. H_2SO_4 (28 ml, 0.5 mol), and 2-methylpropene (1.2 l, condensed at −30°) in CH_2Cl_2 (2.4 l) was stirred in a glass autoclave at r.t. for 96 h. The mixture was then poured into a cold sat. $NaHCO_3$ soln. (2 l) and extracted with CH_2Cl_2. The org. phase was dried ($MgSO_4$) and evaporated, giving crude **19** (498.4 g, 90%) as a yellowish oil. ^{1}H-NMR (60 MHz, $CDCl_3$): 1.46 (*s*, 9 H); 1.38–1.90 (*m*, 4 H); 2.15 (*s*, 3 H); 2.08–2.66 (*m*, 4 H).

19. tert-*Butyl (R)-6-[(R)-(α-Methylbenzyl)amino]heptanoate Hydrochloride* ((6*R*,1'*R*)-**21**·HCl). Compound **19** (498.4 g, 2.49 mol), (*R*)-α-methylbenzylamine (286.5 g, 2.36 mol), TsOH·H_2O (9.8 g, 0.052 mol), and toluene (3.5 l) were heated under reflux with a H_2O separator for 12 h. The solvent was removed under reduced pressure (oil pump), the residue dissolved in MeOH (7 l), and the mixture hydrogenated in the presence of *Raney*-Ni (80 g) and H_2 (10 bar) for 24 h at r.t. The catalyst was removed by filtration, the filtrate evaporated, the residue dissolved in AcOEt (2 l), and treated with HCl in EtOH (4M, 550 ml). The crystalline masse formed was collected by filtration and recrystallized from AcOEt, giving (6*R*,1'*R*)-**21**·HCl (307 g, 38.0%). M.p. 156–157° with 96.6% d.e. (GC of the free base). $[\alpha]_D^{20} = +39.5°$ (*c* = 1.0, MeOH). IR (KBr): 1720, 1160. ^{1}H-NMR (90 MHz, (D_6)DMSO): 1.40 (*s*, 9 H); 1.45 (*d*, *J* = 7, 3 H); 1.90 (*d*, *J* = 7, 3 H); 1.30–2.00 (*m*, 6 H); 2.14 (*t*, *J* = 7, 2 H); 2.77 (br., 1 H); 4.35 (br., 1 H); 7.33–7.83 (*m*, 5 H); 9.88 (br., 2 H). MS: 306 (1, M^+ + H), 290 (7), 234 (24), 148 (83), 105 (89), 44 (100). Anal. calc. for $C_{19}H_{32}ClNO_2$ (341.92): C 66.74, H 9.43, N 4.10, Cl 10.37; found: C 66.41, H 9.52, N 4.08, Cl 10.41.

20. tert-*Butyl (R)-6-Aminoheptanoate Hydrochloride* ((*R*)-**22**·HCl). Compound (6*R*,1'*R*)-**21**·HCl (200 g, 0.585 mol) was hydrogenated in EtOH (3 l) in the presence of 5% Pd/C (25 g) at 60° and 10 bar H_2 for 24 h. The catalyst was removed by filtration, the filtrate evaporated and recrystallized from EtOAc/hexane, affording

(*R*)-**22**·HCl (126.8 g, 91.2%). M.p. 109–111°. $[\alpha]_D^{20} = +3.8°$ (*c* = 1.0, MeOH). IR (KBr): 1730, 1170. ^{1}H-NMR (60 MHz, (D_6)DMSO): 1.22 (*d*, *J* = 7, 3 H); 1.43 (*s*, 9 H); 1.00–1.70 (*m*, 6 H); 2.02–2.35 (*m*, 2 H); 3.10 (*m*, 1 H); 8.13 (br., 3 H). Anal. calc. for $C_{11}H_{24}ClNO_2$ (237.77): C 55.57, H 10.17, N 5.89; found: C 55.49, H 10.19, N 5.85.

21. *(R)-6-Aminoheptanoic Acid* ((*R*)-**23**). A soln. of (*R*)-**22**·HCl (71.3 g, 0.300 mol) in CH_2Cl_2 (0.75 l) was treated with dry HCl (gas) for 30 min and stirred at r.t. for 1 h. The crystalline mass formed was collected and recrystallized from EtOH/Et_2O, affording (*R*)-**23**·HCl (43.4 g, 79.6%). M.p. 159–162°. $[\alpha]_D^{20} = +3.8°$ (*c* = 1.0, MeOH). IR (KBr): 1720. ^{1}H-NMR (60 MHz, (D_6)DMSO): 1.20 (*d*, *J* = 7, 3 H); 1.43 (*m*, 6 H); 2.25 (*m*, 2 H); 3.08 (br., 1 H), 8.3 (br., 4 H). Anal. calc. for $C_7H_{16}ClNO_2$ (181.66): C 46.28, H 8.88, N 7.71; found: C 46.61, H 8.78, N 7.66.

(*R*)-**23**·HCl (8.69 g, 47.8 mmol), dissolved in H_2O (160 ml), was chromatographed on *Amberlite IRA* 93 (free base) (120 g (dry weight)) affording (*R*)-**23** (5.37 g, 77.4%). M.p. 221–223° (MeOH/H_2O/Et_2O). ([16]: 215–217°). $[\alpha]_D^{20} = +2.0°$ (*c* = 5.191; *c* = 1.0, H_2O) ([16]: $[\alpha]_D^{20} = +2.4°$ (*c* = 5.0, H_2O)). IR (KBr): 1640, 1550, 1400. ^{1}H-NMR (60 MHz, D_2O): 1.30 (*d*, *J* = 7, 3 H); 1.53 (*m*, 6 H); 2.22 (*m*, 2 H); 3,33 (*m*, 1 H). MS: 130 (1, $M^+ - CH_3$), 44 (100). Anal. calc. for $C_7H_{15}NO_2$ (145.20): C 57.90, H 10.41, N 9.65; found: C 57.64, H 10.48, N 9.61.

22. *6-Oxoheptanoyl Chloride* (**24**). DMF (1 drop) and oxalyl chloride (264 ml, 3.07 mol) were added at r.t. to a soln. of **18** (291 g, 2.02 mol) [23] in benzene (1.8 l). The mixture was stirred at r.t. (1 h) and 50° (1 h). Evaporation of the benzene and distillation afforded **24** (261.9 g, 79.7%). B.p. 85–90° (1.5 mbar). ^{1}H-NMR (60 MHz, $CDCl_3$): 1.63 (*m*, 4 H); 2.13 (*s*, 3 H); 2.47 (*m*, 2 H); 2.90 (*m*, 2 H). Anal. calc. for $C_7H_{11}ClO_2$ (162.62): C 51.70, H 6.82; found: C 51.50, H 6.56.

23. *6-Oxo-*N*-[4-(trifluoromethyl)phenyl]heptanamide* (**25**). Compound **24** (242.8 g, 1.49 mol) in DMF (250 ml) was added, within 40 min between 25 and 30°, to a soln. of 4-(trifluoromethyl)aniline (240.6 g, 1.49 mol), 4-(dimethylamino)pyridine (60.2 g, 0.49 mol), and Et_3N (116.3 g, 1.15 mol) in DMF (600 ml). The mixture was stirred at r.t. for 90 min, poured into H_2O (1.6 l), acidified with conc. aq. HCl soln. (40 ml), and extracted with $CHCl_3$ (2 l, 2 × 0.5 l). The combined org. extracts were dried ($MgSO_4$), evaporated, and the residue recrystallized from CH_2Cl_2, affording **25** (335.8 g, 78.4%). M.p. 138° ([1]: 139–140°). IR (KBr): 1700. ^{1}H-NMR (60 MHz, $CDCl_3$): 1.72 (*m*, 4 H); 2.18 (*s*, 3 H); 2.50 (*m*, 4 H); 7.55 (*d*, *J* = 10, 2 H); 7.69 (*d*, *J* = 10, 2 H); 7.93 (br., 1 H), MS: 287 (11, M^+), 203 (13), 161 (92), 43 (100). Anal. calc. for $C_{14}H_{16}NO_2F_3$ (287.28): C 58.53, H 5.61, N 4.88; found: C 58.24, H 5.59, N 4.77.

24. *(R)-6-[(R)-(α-Methylbenzyl)amino]-*N*-[4-(trifluoromethyl)phenyl]heptanamide* ((6*R*,1'*R*)-**26**). Compound **25** (335 g, 1.17 mol), (*R*)-α-methylbenzylamine (141.8 g, 1.17 mol), TsOH·H_2O (4.8 g, 25 mmol), and toluene (3.2 l) were refluxed (H_2O separator) for 10 h. The solvent was removed under reduced pressure (oil pump), the residue dissolved in MeOH (3.3 l) and the mixture hydrogenated in the presence of *Raney*-Ni (90 g) and H_2 (15 bar) for 24 h at r.t. The catalyst was removed by filtration and the filtrate evaporated. The residue was dissolved in $CHCl_3$ (2 l), the soln. treated with MsOH (76 ml, 1.17 mol), diluted with Et_2O (1 l), and the suspension cooled to −10°. The crystals formed were collected by filtration and recrystallized from MeOH/Et_2O, giving (6*R*,1'*R*)-**26**·MsOH (192 g, 33.6%). M.p. 210–212°. $[\alpha]_D^{20} = +32.7°$ (*c* = 1.0, MeOH). IR (KBr): 1705, 1610, 1540, 1330. ^{1}H-NMR (80 MHz, (D_6)DMSO): 1.21 (*d*, *J* = 7, 3 H); 1.58 (*d*, *J* = 7, 3 H); 1.05–1.80 (*m*, 6 H); 2.39 (*t*, *J* = 6, 2 H); 2.44 (*s*, 3 H); 2.90 (br., 1 H); 4.55 (br., 1 H); 7.54 (*m*, 5 H); 7.66 (*d*, *J* = 9, 2 H); 7.89 (*d*, *J* = 9, 2 H); 8.78 (br., 2 H); 10.31 (*s*, 1 H). Anal. calc. for $C_{23}H_{31}F_3N_2O_4S$ (488.57): C 56.54, H 6.40, N 5.73; found: C 56.46, H 6.62, N 5.76.

A small sample was transformed into (6*R*,1'*R*)-**26**. M.p. 61–63° ($CHCl_3$); d.e. ≥ 98% (^{1}H-NMR). $[\alpha]_D^{20} = +63.9°$ (*c* = 1.0, MeOH). IR (KBr): 1680, 1340, 1120. ^{1}H-NMR (270 MHz, $CDCl_3$): 0.96 (*d*, *J* = 6.5, 3 H); 1.31 (*d*, *J* = 6.5, 3 H); 1.24–1.60 (*m*, 5 H); 1.70 (*m*, 2 H); 2.35 (*t*, *J* = 7.5, 2 H); 2.53 (*m*, 1 H); 3.87 (*q*, *J* = 7, 1 H); 7.18–7.36 (*m*, 5 H); 7.55 (*d*, *J* = 9, 2 H); 7.57 (*s*, 1 H); 7.64 (*d*, *J* = 9, 2 H). MS: 377 (19, $M^+ - CH_3$), 148 (70), 105 (100). Anal. calc. for $C_{22}H_{27}F_3N_2O$ (392.47): C 67.33, H 6.93, N 7.14; found: C 66.98, H 6.95, N 7.32.

25. *(S)-6-[(S)-(α-Methylbenzyl)amino]-*N*-[4-(trifluoromethyl)phenyl]heptanamide* ((6*S*,1'*S*)-**26**). Analogously to *24* from **25** and (*S*)-α-methylbenzylamine.

*Data of (6*S*,1'*S*)-**26**·MsOH.* M.p. 208–210°. $[\alpha]_D^{20} = -33°$ (*c* = 1.0, MeOH). ^{1}H-NMR identical to that of (6*R*,1'*R*)-**26**.

*Data of (6*S*,1'*S*)-**26**.* M.p. 60–62°; d.e. ≥ 98% (^{1}H-NMR). $[\alpha]_D^{20} = -64.5°$ (*c* = 1.0, MeOH). ^{1}H-NMR identical to that of (6*R*,1'*R*)-**26**. Anal. calc. for $C_{22}H_{27}F_3N_2O$ (392.47): C 67.33, H 6.93, N 7.14; found: C 67.07, H 6.94, N 7.18.

26. *(R)-6-Amino-*N*-[4-(trifluoromethyl)phenyl]heptanamide* ((*R*)-**27**). Compound (6*R*,1'*R*)-**26**·MsOH (191.9 g, 0.393 mol) was hydrogenated in EtOH (4 l) in the presence of 5% Pd/C (30 g) at 60° and 4 bar H_2 for 30 h. The catalyst was removed by filtration, the filtrate evaporated, and the residue recrystallized from EtOH/Et_2O, affording (*R*)-**27**·MsOH (133.6 g, 88.4%). M.p. 162–164°. $[\alpha]_D^{20} = +1.3°$ (*c* = 1.0, MeOH). IR (KBr): 1670, 1530, 1320. ^{1}H-NMR (80 MHz, (D_6)DMSO): 1.04–1.84 (*m*, 6 H); 1.16 (*d*, *J* = 6.5, 3 H); 2.38 (*s*, 3 H); *ca.* 2.40 (*m*, 2 H);

3.20 (*m*, 1 H); 7.42–8.00 (br., 3 H); 7.60 (*d*, *J* = 9, 2 H); 7.85 (*d*, *J* = 9, 2 H); 10.31 (*s*, 1 H). Anal. calc. for $C_{15}H_{23}F_3N_2O_4S$ (384.41): C 46.87, H 6.03, N 7.29; found: C 46.55, H 6.27, N 7.15.

A small sample was transformed into (*R*)-**27** (aq. NaOH, extraction with $CHCl_3$/i-PrOH 4:1) with m.p. 71–73° ($CHCl_3$/hexane). $[\alpha]_D^{20} = -1.5°$ (*c* = 1.0, MeOH). IR ($CHCl_3$): 1690, 1320. ^{1}H-NMR (80 MHz, $CDCl_3$): 1.06 (*d*, *J* = 7, 3 H); 1.20–1.94 (*m*, 8 H); 2.42 (*t*, *J* = 7, 2 H); 2.91 (*m*, 1 H); 7.57 (*d*, *J* = 9, 2 H); 7.66 (*d*, *J* = 9, 2 H); 8.09 (br., 1 H). MS: 288 (1, M^+), 161 (13), 44 (100). Anal. calc. for $C_{14}H_{19}F_3N_2O$ (288.31): C 58.32, H 6.64, N 9.72; found: C 58.60, H 6.63, N 9.69.

27. *(S)-6-Amino-*N*-[4-(trifluoromethyl)phenyl]heptanamide* ((*S*)-**27**). Analogously to *26* from (6*S*,1′*S*)-**26**·MsOH.

*Data of (S)-***27**·*MsOH*. M.p. 160–162°. $[\alpha]_D^{20} = -1.1°$ (*c* = 1.0, MeOH). IR, ^{1}H-NMR identical to that of (*R*)-**27**. Anal. calc. for $C_{15}H_{23}F_3N_2O_4S$ (384.41): C 46.87, H 6.03, N 7.29, F 14.83, S 8.34; found: C 46.53, H 6.26, N 7.17, F 14.73, S 8.38.

*Data of (S)-***27**. M.p. 70–71° ($CHCl_3$/hexane). $[\alpha]_D^{20} = +1.4°$ (*c* = 1.0, MeOH). IR, ^{1}H-NMR, MS identical to those of (*R*)-**27**. Anal. calc. for $C_{14}H_{19}F_3N_2O$ (288.31): C 58.32, H 6.64, N 9.72; found: C 58.26, H 6.60, N 9.73.

28. *(R)-6-[(R)-3,3,3-Trifluoro-2-methoxy-2-phenylpropionamido]-*N*-[4-(trifluoromethyl)phenyl]heptanamide* ((6*R*,2′*R*)-**28**). Et_3N (0.063 ml, 0.46 mmol) and (*R*)-**27** (64.3 mg, 0.223 mmol) in CH_2Cl_2 (1.0 ml) were added to a soln. of (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropionyl chloride [22] (110 mg, 0.435 mmol) in CH_2Cl_2 (0.5 ml). The mixture was stirred at r.t. for 1 h (100% conversion according to TLC) and diluted with AcOEt (50 ml). The org. phase was washed with 3N HCl (2 × 10 ml), sat. $NaHCO_3$ soln. (10 ml), brine (10 ml), dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel (3 g) with CH_2Cl_2/hexane 1:1 and CH_2Cl_2, affording (6*R*,2′*R*)-**28** (85 mg, 76%) with ⩾ 95% d.e. (^{1}H-NMR). ^{1}H-NMR (90 MHz, $CDCl_3$): 1.19 (*d*, *J* = 6.5, 3 H); 1.29–1.93 (*m*, 6 H); 2.34 (*t*, *J* = 7, 2 H); 3.35 (*q*, *J* = 1.3, 3 H); 4.04 (*m*, 1 H); 6.84 (*d*, *J* = 9, 1 H); 7.31–7.66 (*m*, 9 H); 8.22 (*s*, 1 H). MS: 504 (5, M^+), 272 (100).

29. *(S)-6-[(R)-3,3,3-Trifluoro-2-methoxy-2-phenylpropionamido]-*N*-[4-(trifluoromethyl)phenyl]heptanamide* ((6*S*,2′*R*)-**28**). Analogously to *28* from (*S*)-**27**.

*Data of (6*S,2′R*)-***28**. ⩾ 95% d.e. (^{1}H-NMR). ^{1}H-NMR (90 MHz, $CDCl_3$): 1.21 (*d*, *J* = 6.5, 3 H); 1.26–1.90 (*m*, 6 H); 2.26 (*t*, *J* = 7, 2 H); 3.38 (*q*, *J* = 1.5, 3 H); 4.04 (*m*, 1 H); 6.73 (*d*, *J* = 9, 1 H); 7.24–7.69 (*m*, 9 H); 7.88 (*s*, 1 H). MS: 504 (4, M^+), 272 (100).

30. *(R)-6-{(R)-[2-[3,4-Bis(benzyloxy)phenyl]-2-hydroxyethyl]amino}-*N*-[4-(trifluoromethyl)phenyl]-heptanamide* ((6*R*,2′*R*)-**29**). *a*) (*R*)-**12** (8.3 g, 25 mmol) and (*R*)-**27**, freshly prepared from 11.53 g (30 mmol) of (*R*)-**27**·MsOH according to *26* (all operation in Ar atmosphere) in DMSO (60 ml), were stirred and heated to 100° for 23 h. The mixture was poured into ice-water (300 ml) and extracted with $CHCl_3$ (300, 200, 150 ml). The org. phase was dried ($MgSO_4$), evaporated, and the residue chromatographed on silica gel (300 g) with CH_2Cl_2/i-PrOH (4:1), affording (6*R*,2′*R*)-**29** (6.3 g, 41%). M.p. 145–147° (MeOH/Et_2O); d.e. ⩾ 98% (^{1}H-NMR).

b) (*R*)-**31**·HCl (1.0 g, 1.53 mmol), Et_3N (1.51 g, 15 mmol), (*S*)-(*R*)-BPPFOH[1]) ((1*S*)-2-[(*S*)-1-hydroxyethyl]-1,1′-bis(diphenylphosphino)ferrocene[4])) [17] (9.0 mg, 0.015 mmol), and [Rh(cyclooctadiene)Cl]$_2$ (3.8 mg, 0.0075 mmol) were dissolved in AcOEt (300 ml) (exclusion of O_2, all operations in glove-box) and hydrogenated in a 500-ml autoclave at 27°/50 bar H_2 for 120 h and at 40°/50 bar H_2 for 70 h. Et_3N·HCl was filtered off, the filtrate evaporated, the residue suspended in Et_2O (40 ml) and aq. NH_3 (25%, 5 ml), the suspension stirred at r.t. for 30 min, filtered, and the crystals washed with Et_2O affording pure (6*R*,2′*R*)-**29** (0.83 g, 87.4%). M.p. 146–147°; ⩾ 98% d.e. (^{1}H-NMR). Extraction of the filtrate with H_2O (60 ml) and evaporation to dryness gave (6*R*,2′*R*)-**29** (0.11 g, 11.6%). M.p. 143–145°; d.e. *ca.* 70% (^{1}H-NMR).

*Data of (6*R,2′R*)-***29**. $[\alpha]_D^{20} = +0.7°$ (*c* = 1.0, MeOH). IR (KBr): 1665, 1530, 1330. ^{1}H-NMR (400 MHz, (D_6)DMSO): 0.943 (*d*, *J* = 6, 3 H); 1.18–1.55 (*m*, 5 H); 1.58 (*m*, 2 H); 2.34 (*t*, *J* = 7.5, 2 H); 2.55 (*m*, 3 H); 4.47 (*m*, 1 H); 5.10 (*s*, 2 H); 5.11 (*s*, 2 H); 5.18 (br., 1 H); 6.84 (*dd*, *J* = 8.5, 2, 1 H); 6.97 (*d*, *J* = 8.5, 1 H); 7.05 (*d*, *J* = 2, 1 H); 7.26–7.48 (*m*, 10 H); 7.65 (*d*, *J* = 8.5, 2 H); 7.80 (*d*, *J* = 8.5, 2 H); 10.24 (*s*, 1 H). MS: 511 (3, $M^+ - (Ph{-}CH_2 + H_2O)$), 301 (52), 91 (100). Anal. calc. for $C_{36}H_{39}F_3N_2O_4$ (620.71): C 69.66, H 6.33, N 4.51; found: C 69.55, H 6.30, N 4.52.

31. *(R)-6-{(S)-[2-[3,4-Bis(benzyloxy)phenyl]-2-hydroxyethyl]amino}-*N*-[4-(trifluoromethyl)phenyl]-heptanamide* ((6*R*,2′*S*)-**29**). Analogously to *30a* from (*S*)-**12** and (*R*)-**27**.

*Data of (6*R,2′S*)-***29**. M.p. 142–144° (MeOH). $[\alpha]_D^{20} = +9.8°$ (*c* = 1.0, MeOH). IR (KBr): 1670, 1530, 1510, 1330. ^{1}H-NMR (400 MHz, (D_6)DMSO): 0.920 (*d*, *J* = 6, 3 H); 1.18–1.53 (*m*, 5 H); 1.59 (*m*, 2 H); 2.35 (*t*, *J* = 7.5, 2 H); 2.43–2.68 (*m*, 3 H); 4.46 (*m*, 1 H); 5.10 (*s*, 2 H); 5.11 (*s*, 2 H); 5.20 (br., 1 H); 6.84 (*dd*, *J* = 8.5, 2, 1 H); 6.97 (*d*, *J* = 8.5, 1 H); 7.05 (*d*, *J* = 2, 1 H); 7.38–7.50 (*m*, 10 H); 7.65 (*d*, *J* = 8.5, 2 H); 7.81 (*d*, *J* = 8.5, 2 H); 10.25 (*s*, 1 H).

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[4]) Systematic nomenclature according to [24], p. 424, and [25].

MS: 602 (3, $M^{+\cdot} - H_2O$), 511 (7), 301 (59), 91 (100). Anal. calc. for $C_{36}H_{39}F_3N_2O_4$ (620.71): C 69.66, H 6.33, N 4.51; found: C 69.58, H 6.43, N 4.48.

32. *(S)-6-{(R)-[2-[3,4-Bis(benzyloxy)phenyl]-2-hydroxyethyl]amino}-N-[4-(trifluoromethyl)phenyl]-heptanamide* ((6*S*,2′*R*)-**29**). Analogously to *30a* from (*R*)-**12** and (*S*)-**27**.

*Data of (6*S,2′R*)-***29***. M.p. 143–145° (MeOH/hexane). $[\alpha]_D^{20} = -10.3°$ (*c* = 1.0, MeOH). IR, ^{1}H-NMR, MS identical to those of (6*R*,2′*S*)-**29**. Anal. calc. for $C_{36}H_{39}F_3N_2O_4$ (620.71): C 69.66, H 6.33, N 4.51; found: C 69.49, H 6.35, N 4.48.

33. *(S)-6-{(S)-[2-[3,4-Bis(benzyloxy)phenyl]-2-hydroxyethyl]amino}-N-[4-(trifluoromethyl)phenyl]-heptanamide* ((6*S*,2′*S*)-**29**). Analogously to *30a* from (*S*)-**12** and (*S*)-**27**.

*Data of (6*S,2′S*)-***29***. M.p. 144–146° (MeOH/hexane). $[\alpha]_D^{20} = -0.5°$ (*c* = 1.0, MeOH). IR, ^{1}H-NMR, MS identical to those of (6*R*,2′*R*)-**29**. Anal. calc. for $C_{36}H_{39}F_3N_2O_4$ (620.71): C 69.66, H 6.33, N 4.51; found: C 69.59, H 6.60, N 4.55.

34. *(R)-6-{(R)-[2-(3,4-Dihydroxyphenyl)-2-hydroxyethyl]amino}-N-[4-(trifluoromethyl)phenyl]heptanamide* ((6*R*,2′*R*)-**4a**). *a*) (6*R*,2′*R*)-**29** (1.5 g, 2.42 mmol) was hydrogenated for 30 min at r.t. and normal pressure in MeOH (60 ml) and 3.1M HCl in AcOEt (0.74 ml, 2.30 mmol) in the presence of 5% Pd/C (0.3 g). The catalyst was removed by filtration and the soln. evaporated, affording (6*R*,2′*R*)-**4a**·HCl as a slightly colored amorphous solid (1.15 g, 100%). $[\alpha]_D^{20} = -17.7°$ (*c* = 1.0, MeOH). IR (KBr): 1670, 1600, 1530, 1325. ^{1}H-NMR (80 MHz, (D_6)DMSO): 1.23 (*d*, *J* = 6, 3 H); 1.08–1.94 (*m*, 6 H); 2.46 (*m*, 2 H); 2.85–3.50 (*m*, 3 H); 4.88 (br., 1 H); 6.00 (br., 1 H); 6.57–6.92 (*m*, 3 H); 7.68 (*d*, *J* = 8.5, 2 H); 7.94 (*d*, *J* = 8.5, 2 H); 8.96 (br., 4 H); 10.59 (*s*, 1 H).

*Data of (6*R,2′R*)-***4a*** (prepared by treating (6*R*,2′*R*)-**4a**·HCl in EtOH with a stoichiometric amount of KOH in EtOH and removing the KCl formed by filtration). M.p. 144–146° (MeOH/Et_2O; dec.). $[\alpha]_D^{20} = -3.9°$ (*c* = 1.0, MeOH). IR (KBr): 1675, 1600, 1530, 1490, 1330. ^{1}H-NMR (270 MHz, (D_6)DMSO): 0.95 (*d*, *J* = 6.5, 3 H); 1.30 (*m*, 4 H); 1.58 (*m*, 2 H); 2.34 (*t*, *J* = 7, 2 H); 2.53 (*m*, 3 H); 4.38 (*t*, *J* = 6, 1 H); 6.55 (*dd*, *J* = 8, 2, 1 H); 6.65 (*d*, *J* = 8, 1 H); 6.73 (*d*, *J* = 2, 1 H); 7.66 (*d*, *J* = 8.5, 2 H); 7.81 (*d*, *J* = 8.5, 2 H); OH, NH br. FAB-MS: 441 ($[M + H]^+$). Anal. calc. for $C_{22}H_{27}F_3N_2O_4$ (440.46): C 59.99, H 6.18, N 6.36; found: C 59.93, H 6.37, N 6.31.

b) (6*R*,2′*R*)-**29** (3.1 g, 5.0 mmol) and (1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylic acid ((−)-camphanic acid, 1.0 g, 5.0 mmol) dissolved in MeOH (100 ml) were hydrogenated for 1 h at r.t. and normal pressure in the presence of 5% Pd/C (0.6 g). The catalyst was removed by filtration, the filtrate evaporated, and the residue recrystallized from i-PrOH/AcOEt, affording (6*R*,2′*R*)-**29**·(−)-camphanic acid (2.9 g, 91%). M.p. 107–110° (dec.). $[\alpha]_D^{20} = -17.0°$ (*c* = 1.0, MeOH). IR (KBr): 1760, 1600, 1325. ^{1}H-NMR (270 MHz, (D_6)DMSO): 0.81 (*s*, 3 H); 0.95 (*s*, 3 H); 0.99 (*s*, 3 H); 1.17 (*d*, *J* = 6.5, 3 H); 1.20–1.90 (*m*, 10 H); 2.37 (*m*, 3 H); 2.80–3.00 (*m*, 2 H); 3.13 (br., 1 H); 4.75 (*m*, 1 H); 6.62 (*dd*, *J* = 8, 2, 1 H); 6.72 (*d*, *J* = 8, 1 H); 6.80 (*d*, *J* = 2, 1 H); 7.66 (*d*, *J* = 9, 2 H); 7.83 (*d*, *J* = 9, 2 H); 9.11 (br., 4 H); 10.39 (*s*, 1 H). FAB-MS: 441 ($[M$(base) + H$]^+$). Anal. calc. for $C_{33}H_{41}F_3N_2O_8$ (638.68): C 60.18, H 6.47, N 4.39; found: C 59.92, H 6.19, N 4.35.

35. *(R)-6-{(S)-[2-(3,4-Dihydroxyphenyl)-2-hydroxyethyl]amino}-N-[4-(trifluoromethyl)phenyl]heptanamide* ((6*R*,2′*S*)-**4a**). Analogously to *34* from (6*R*,2′*S*)-**29**.

*Data of (6*R,2′S*)-***4a***·HCl*. Amorphous solid. $[\alpha]_D^{20} = +26.2°$ (*c* = 1.0, MeOH). IR (KBr): 1670, 1600, 1530, 1325. ^{1}H-NMR (80 MHz, (D_6)DMSO): 1.26 (*d*, *J* = 6, 3 H); 1.12–2.00 (*m*, 6 H); 2.43 (*m*, 2 H); 3.01 (*m*, 3 H); 4.85 (br., 1 H); 5.93 (br., 1 H); 6.57–6.94 (*m*, 3 H); 7.67 (*d*, *J* = 8.5, 2 H); 7.92 (*d*, *J* = 8.5, 2 H); 8.26–9.36 (br., 4 H); 10.52 (*s*, 1 H).

*Data of (6*R,2′S*)-***4a***·(−)-Camphanic Acid*. ^{1}H-NMR (270 MHz, (D_6)DMSO): 0.81 (*s*, 3 H); 0.95 (*s*, 3 H); 1.00 (*s*, 3 H); 1,21 (*d*, *J* = 6.5, 3 H); 1.28–1.93 (*m*, 10 H); 2.37 (*m*, 3 H); 2.80–3.04 (*m*, 2 H); 3.16 (*m*, 1 H); 4.75 (*m*, 1 H); 6.63 (*dd*, *J* = 8, 2, 1 H); 6.71 (*d*, *J* = 8, 1 H); 6.81 (*d*, *J* = 2, 1 H); 7.65 (*d*, *J* = 9, 2 H); 7.82 (*d*, *J* = 9, 2 H); 9.0 (br. 4 H); 10.38 (*s*, 1 H). FAB-MS: 441 ($[M$(base) + H$]^+$).

36. *(S)-6-{(R)-[2-(3,4-Dihydroxyphenyl)-2-hydroxyethyl]amino}-N-[4-(trifluoromethyl)phenyl]heptanamide* ((6*S*,2′*R*)-**4a**). Analogously to *34* from (6*S*,2′*R*)-**29**.

*Data of (6*S,2′R*)-***4a***·HCl*. Amorphous solid. $[\alpha]_D^{20} = -26.2°$ (*c* = 1.0, MeOH). IR, ^{1}H-NMR identical to those of (6*R*,2′*S*)-**4a**·HCl.

*Data of (6*S,2′R*)-***4a***·(−)-Camphanic Acid*. ^{1}H-NMR (270 MHz, (D_6)DMSO): 0.81 (*s*, 3 H); 0.95 (*s*, 3 H); 0.99 (*s*, 3 H); 1.21 (*d*, *J* = 6.5, 3 H); 1.25–1.93 (*m*, 10 H); 2.37 (*m*, 3 H); 2.80–3.04 (*m*, 2 H); 3.15 (br., 1 H); 4.74 (*m*, 1 H); 6.63 (*dd*, *J* = 8, 2, 1 H); 6.71 (*d*, *J* = 8, 1 H); 6.80 (*d*, *J* = 2, 1 H); 7.65 (*d*, *J* = 9, 2 H); 7.82 (*d*, *J* = 9, 2 H); 9.13 (br., 4 H); 10.38 (*s*, 1 H). FAB-MS: 441 ($[M$(base) + H$]^+$).

37. *(S)-6-{(S)-[2-(3,4-Dihydroxyphenyl)-2-hydroxyethyl]amino}-N-[4-(trifluoromethyl)phenyl]heptanamide* ((6*S*,2′*S*)-**4a**). Analogously to *34* from (6*S*,2′S)-**29**.

*Data of (6*S,2′S*)-***4a***·HCl*. Amorphous solid. $[\alpha]_D^{20} = +16.8°$ (*c* = 1.0, MeOH). IR, ^{1}H-NMR identical to those of (6*R*,2′*R*)-**4a**·HCl.

*Data of (6S,2'S)-***4a**·*(−)-Camphanic Acid.* ^{1}H-NMR (270 MHz, (D_6)DMSO): 0.80 (*s*, 3 H); 0.95 (*s*, 3 H); 0.99 (*s*, 3 H); 1.81 (*d*, *J* = 6.5, 3 H); 1.25–1.92 (*m*, 10 H); 2.25–2.45 (*m*, 3 H); 2.80–3.04 (*m*, 2 H); 3.15 (br., 1 H); 4.76 (*m*, 1 H); 6.63 (*dd*, *J* = 8, 2, 1 H); 6.72 (*d*, *J* = 8, 1 H); 6.80 (*d*, *J* = 2, 1 H); 7.65 (*d*, *J* = 9, 2 H); 7.83 (*d*, *J* = 9, 2 H); 9.13 (br., 4 H); 10.39 (*s*, 1 H). FAB-MS: 441 ($[M(\text{base}) + H]^+$).

38. *3',4'-Bis(benzyloxy)-2-bromoacetophenone* (**30**). Trimethylphenylammonium bromide dibromide (36.9 g, 98.2 mmol) was added within 10 min below 21° to a soln. of 3',4'-bis(benzyloxy)acetophenone [14] (30.8 g, 92.7 mmol) in THF (190 ml). After 30 min stirring at r.t., H_2O (930 ml) was added, the mixture cooled to 3° and filtered. The crystalline mass was dissolved in CH_2Cl_2, dried ($MgSO_4$), and the soln. evaporated. The residue was chromatographed on silica gel (520 g) with toluene/hexane 6:4 and toluene, affording **30** (29.7 g, 77.9%). M.p. 92° (EtOH/CH_2Cl_2) ([14]: 92–93°). IR (KBr): 1660. ^{1}H-NMR (80 MHz, $CDCl_3$): 4.28 (*s*, 2 H); 5.14 (*s*, 2 H); 5.18 (*s*, 2 H), 6.89 (*dm*, *J* = 8.5, 1 H); 7.20–7.50 (*m*, 11 H); 7.53 (*s*, 1 H). MS: 412 (7, M^+), 410 (7, M^+), 91 (100). Anal. calc. for $C_{22}H_{19}BrO_3$ (411.30): C 64.25, H 4.66, Br 19.43; found: C 64.48, H 4.77, Br 19.17.

39. *(R)-6-{[3,4-Bis(benzyloxy)phenacyl]amino}-*N*-[4-(trifluoromethyl)phenyl]heptanamide Hydrochloride* ((6*R*)-**31**·HCl). A soln. of **30** (15.0 g, 36.5 mmol) in THF (90 ml) was added, at 0° within 15 min, to a soln. of (*R*)-**27** (31.5 g, 109 mmol) in THF (120 ml). The mixture was stirred at r.t. for 5 min and at 50° for 5 min, cooled to 0°, treated with 4N HCl (54 ml), evaporated partially, diluted with H_2O (150 ml), and cooled to 0°. The crystals formed were collected by filtration, dissolved in EtOH/CH_2Cl_2 1:1 (0.5 l) and treated with H_2O (0.5 l) and NaCl (150 g). The mixture was stirred at r.t. for 18 h and extracted with CH_2Cl_2 (4 × 0.5 l); the combined CH_2Cl_2 extracts were dried ($MgSO_4$), evaporated, and the residue recrystallized from MeOH/Et_2O, affording (6*R*)-**31**·HCl (14.7 g, 65.1%). M.p. 197–200°. (*R*)-**27**·MsOH (21.3 g, 76% of the excess used) could be recovered from the first mother liquor (extraction with CH_2Cl_2/i-PrOH 4:1 at pH 14; treatment with MsOH, recrystallization).

*Data of (6*R*)-***31***·HCl.* $[\alpha]_D^{20} = +3.1°$ (*c* = 1.0, MeOH). IR (KBr): 1675, 1605, 1325. ^{1}H-NMR (80 MHz, (D_6)DMSO): 1.28 (*d*, *J* = 6.5, 3 H); 1.11–1.94 (*m*, 6 H); 2.45 (*m*, 2 H); 3.23 (br., 1 H); 4.69 (br., 2 H); 5.24 (*s*, 2 H); 5.30 (*s*, 2 H); 7.18–7.98 (*m*, 17 H); 9.03 (br., 2 H); 10.56 (*s*, 1 H). MS: 618 (3, M^+ (base)), 301 (100), 91 (78). Anal. calc. for $C_{36}H_{38}ClF_3N_2O_4$ (655.16): C 66.00, H 5.85, N 4.28, Cl 5.41; found: C 66.11, H 6.04, N 4.31, Cl 5.47.

40. tert-*Butyl (*R*)-6-{(*R*)-[2-[3,4-Bis(benzyloxy)phenyl]-2-[(*tert*-butyl)dimethylsilyloxy]ethyl]amino}-heptanoate* ((6*R*,2'*R*)-**32**). Compound (*R*)-**22** (freshly prepared from 6.54 g, (27.5 mmol) of (*R*)-**22**·HCl (analogously to *26*) and (*R*)-**17** (13.57 g, 25.0 mmol) in *N*,*N*-diisopropylethylamine (17.5 ml) were stirred and heated under reflux for 23 h. The cooled mixture was poured into ice-water (200 ml) and extracted with CH_2Cl_2 (3 × 200 ml); the org. phase was dried (K_2CO_3), evaporated, and the residue chromatographed on silica gel (200 g) with CH_2Cl_2 and 0–5% i-PrOH, affording (6*R*,2'*R*)-**32** (10.6 g, 65.4%) as yellowish oil. ^{1}H-NMR (60 MHz, $CDCl_3$): −0.20 (*s*, 3 H); 0.00 (*s*, 3 H); 0.63–1.67 (*m*, 7 H); 0.87 (*s*, 9 H); 0.99 (*d*, *J* = 6, 3 H); 1.43 (*s*, 9 H); 2.02–2.83 (*m*, 5 H); 4.67 (*t*, *J* = 6, 1 H); 5.13 (*s*, 4 H); 6.90 (*m*, 3 H); 7.37 (*m*, 10 H).

41. tert-*Butyl (*R*)-6-{(*R*)-[2-[3,4-Bis(benzyloxy)phenyl]-2-hydroxyethyl]amino}heptanoate* ((6*R*,2'*R*)-**33**). Compound (6*R*,2'*R*)-**32** (12.0 g, 18.5 mmol), Bu_4NCl (15.8 g, 53.3 mmol), KF (3.0 g, 51.6 mmol), H_2O (2.0 ml), and MeCN (80 ml) were stirred and heated under reflux for 3 h. The mixture was cooled, poured into ice-water (250 ml), and extracted with AcOEt (3 × 200 ml). The org. phase was dried (K_2CO_3), evaporated, and the residue chromatographed on silica gel (100 g) with CH_2Cl_2 and 0–5% i-PrOH, affording (6*R*,2'*R*)-**33** (7.9 g, 80%) as yellowish oil. $[\alpha]_D^{20} = -3.7°$ (*c* = 1.0, MeOH). IR (thin film): 1725, 1510, 1260, 1150. ^{1}H-NMR (80 MHz, $CDCl_3$): 1.07 (*d*, *J* = 6, 3 H); 1.20–1.75 (*m*, 6 H); 1.44 (*s*, 9 H); 2.21 (*m*, 2 H); 2.50–3.01 (*m*, 3 H); 3.14 (*s*, 2 H); 4.64 (*dd*, *J* = 8, 4, 1 H); 5.13 (*s*, 2 H); 5.15 (*s*, 2 H); 6.90 (*m*, 2 H); 7.03 (*m*, 1 H); 7.23–7.57 (*m*, 10 H). MS: 534 (0.5, $[M + H]^+$), 442 (9), 214 (79), 158 (100), 91 (> 100). Anal. calc. for $C_{33}H_{43}NO_5 \cdot 0.2\ H_2O$ (537.31): C 73.77, H 8.14, N 2.61; found: C 73.67, H 8.15, N 2.58.

42. *(*R*)-6-{(*R*)-[2-[3,4-Bis(benzyloxy)phenyl]-2-hydroxyethyl]amino}heptanoic Acid* ((6*R*,2'*R*)-**34**). Compound (6*R*,2'*R*)-**33** (7.50 g, 14.0 mmol), KOH (powder, 86%) (0.94 g, 14.4 mmol), dicyclohexyl-18-crown-6 (0.53 g, 1.4 mmol), and toluene (150 ml) were stirred and heated under reflux for 5.5 h. The mixture was then evaporated, diluted with H_2O, acidified with aq. HCl to pH 1, and extracted with CH_2Cl_2/i-PrOH 4:1 (4 × 200 ml). The org. phase was dried ($MgSO_4$), evaporated, and the residue chromatographed on silica gel (120 g) with CH_2Cl_2 and 0–50% i-PrOH, affording (6*R*,2'*R*)-**34**·HCl (5.3 g, 73%) as amorphous solid. A small amount of (6*R*,2'*R*)-**34**·HCl was extracted into $CHCl_3$ at pH 6; drying of the $CHCl_3$ phase, evaporation, and crystallization gave (6*R*,2'*R*)-**34**. M.p. 140–141° (MeOH/Et_2O). $[\alpha]_D^{20} = -16.4°$ (*c* = 1.0, MeOH). IR (KBr): 1560, 1515, 1390, 1270. ^{1}H-NMR (250 MHz, (D_6)DMSO): 0.98 (*d*, *J* = 6, 3 H); 1.14–1.55 (*m*, 6 H); 2.14 (*t*, *J* = 7, 2 H); 2.64 (*m*, 3 H); 4.55 (*t*, *J* = 6, 1 H); 5.10 (*s*, 2 H); 5.11 (*s*, 2 H); 4.50–6.00 (br., 3 H); 6.83 (*dd*, *J* = 8, 2, 1 H); 6.96 (*d*, *J* = 8, 1 H); 7.06 (*d*, *J* = 2, 1 H); 7.25–7.51 (*m*, 10 H). MS: 459 (1, $M^+ - H_2O$), 158 (100), 91 (80). Anal. calc. for $C_{29}H_{35}NO_5$ (477.60): C 72.93, H 7.39, N 2.93; found: C 72.84, H 7.42, N 2.81.

43. *(R)-6-{(R)-[N-(Benzyloxycarbonyl)][2-[3,4-Bis(benzyloxy)phenyl]-2-hydroxyethyl]amino}heptanoic Acid* ((6*R*,2′*R*)-**35**). Benzyl chloroformate (90%) (5.10 ml, 32 mmol) was added, within 15 min below 5°, to a stirred soln. of (6*R*,2′*R*)-**34**·HCl (4.35 g, 8.46 mmol) in H_2O (75 ml) and 4N NaOH (10.15 ml, 40.6 mmol). The mixture was then intensively stirred for 16 h at 0–5°. The suspension was acidified to pH 3–4 with dil. HCl, extracted with CH_2Cl_2 (3 × 100 ml), the org. phase dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel (150 g) with toluene, toluene/AcOEt (9:1 and 3:1) and AcOEt, affording (6*R*,2′*R*)-**35** (2.3 g, 44%) as oil. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.11 (*d*, *J* = 6, 3 H); 1.05–1.70 (*m*, 7 H); 2.24 (*m*, 2 H); 3.03 (*m*, 1 H); 3.52 (*m*, 1 H); 4.05 (*m*, 1 H); 4.78 (*m*, 1 H); 5.15 (*m*, 6 H); 6.89 (*m*, 2 H); 7.05 (*m*, 1 H); 7.22–7.48 (*m*, 15 H); HOOC, br. FAB-MS: 594 ($[M + H]^+ - H_2O$).

44. tert-*Butyl* N-{(S)-{[4-[(R)-6-[[(R)-N-(*Benzyloxycarbonyl*)][2-[3,4-bis(benzyloxy)phenyl]-2-hydroxyethyl]amino]heptanamido]phenyl]methyl}{[(N-methylcarbamoyl)methyl]carbamoyl}methyl}carbamate ((6*R*,2′*R*)-**37**). Isobutyl chloroformate (95%) (0.547 ml, 3.97 mmol) was added, within 5 min at −20°, to a stirred soln. of (6*R*,2′*R*)-**35** (2.3 g, 3.76 mmol) and Et_3N (0.573 ml, 4.11 mmol) in THF (7.0 ml). After 1 h at −20°, **36** [3] (1.44 g, 4.11 mmol) in DMF (7.0 ml) was added within 5 min at −20°. The mixture was stirred at −20° for 0.5 h and at r.t. for 20 h, poured into H_2O, and extracted with CH_2Cl_2 (3 × 50 ml). The org. phase was dried (K_2CO_3), evaporated, and the residue chromatographed on silica gel (200 g) with AcOEt and 0–5% i-PrOH, affording (6*R*,2′*R*)-**37** (2.85 g, 80.3%) as oil. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.07 (*d*, *J* = 6, 3 H); 1.13–2.39 (*m*, 8 H); 1.41 (*s*, 9 H); 2.73 (*d*, *J* = 5, 3 H); 2.98 (*m*, 2 H); 3.19 (*m*, 1 H); 3.47 (*m*, 1 H); 3.81 (*m*, 2 H); 4.00 (*m*, 1 H); 4.17 (*q*, *J* = 6, 1 H); 4.81 (*m*, 1 H); 5.12 (*m*, 7 H); 6.63 (br., 2 H); 6.87 (br., 2 H); 7.05 (br., 1 H); 7.05 (*d*, *J* = 8, 2 H); 7.22–7.60 (*m*, 19 H).

45. tert-*Butyl* N-{(S)-{[4-[(R)-6-[(R)-[2-(3,4-Dihydroxyphenyl-2-hydroxyethyl]amino]heptanamido]-phenyl]methyl}{[(N-methylcarbamoyl)methyl]carbamoyl}methyl}carbamate (1*S*,4*R*)-4,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate (1:1) ((6*R*,2′*R*)-**4b**·(−)-Camphanic Acid). Compound (6*R*,2′*R*)-**37** (1.06 g, 1.12 mmol) and (1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylic acid ((−)-camphanic acid; 0.22 g, 1.12 mmol) dissolved in MeOH (20 ml) were hydrogenated for 1 h at r.t. and normal pressure in the presence of 5% Pd/C (0.2 g). The catalyst was removed by filtration and the filtrate evaporated, affording (6*R*,2′*R*)**4b**·(−)-camphanic acid (0.80 g, 86%) as amorphous solid. ^{1}H-NMR (270 MHz, (D_6)DMSO): 0.82 (*s*, 3 H); 0.96 (*s*, 3 H); 1.00 (*s*, 3 H); 1.19 (*d*, *J* = 6.5, 3 H); 1.32 (*s*, 1.32 (*s*, 9 H); 1.10–1.94 (*m*, 9 H); 2.25–2.40 (*m*, 3 H); 2.59 (*d*, *J* = 5, 3 H); 2.70 (*m*, 1 H); 2.81–3.05 (*m*, 3 H); 3.17 (br., 1 H); 3.53–3.75 (*m*, 2 H); 4.10 (*m*, 1 H); 4.77 (*m*, 1 H); 6.63 (*dd*, *J* = 8, 2, 1 H); 6.71 (*d*, *J* = 8, 1 H); 6.79 (*d*, *J* = 2, 1 H); 7.04 (*d*, *J* = 8, 1 H); 7.15 (*d*, *J* = 8, 2 H); 7.48 (*d*, *J* = 8, 2 H); 7.59 (*m*, 1 H); 8.27 (*t*, *J* = 6, 1 H); 8.0–9.8 (br., 5 H); 9.89 (*s*, 1 H). FAB-MS: 630 ([*M*(base) + H]$^+$).

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