α-Amino Acid Derivatives by Enantioselective Decarboxylation[‡]

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The methodology of enantioselective decarboxylation was applied to 2-aminomalonic acid derivatives in order to obtain enantio-enriched amino acid derivatives. Full conversion was achieved stirring racemic *N*-acetylated 2-aminomalonic hemiesters in THF at 70 °C with 10 mol % of a chiral base for 24 h. The catalyst may be recycled. Whereas the commercially available cinchona alkaloids gave poor results, benzamide and benzenesulfonamide derivatives of 9-amino(9-deoxy)epicinchonine turned out to be effective catalysts. The best result was obtained with 2-*N*-acetylamino-2-ethoxycarbonyl-3-phenylpropionic acid as the starting material and *N*-(9-deoxyepicinchonine-9-yl)-4-methoxybenzamide as the chiral base to give ethyl *N*-acetyl-L-phenylalaninate in 70% *ee*.

Introduction

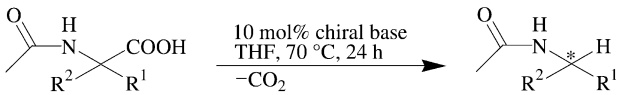
It was in 1904 when Marckwald reported on the first enantioselective decarboxylation reactions.[1,2] In the following decades, only few publications followed, all with disappointing results.[3,4] In 1986 Toussaint revitalized interest in enantioselective decarboxylation reactions, using copper(I) salts and cinchona alkaloids.[5,6] Later it was shown that the reaction was not copper(I)-catalyzed, but base-catalyzed.[7−10] Recently, we applied the enantioselective decarboxylation with substoichiometric amounts of chiral bases as catalysts in the synthesis of derivatives of Naproxen® with up to 72% *ee*.[11,12] Parallel to these studies, Hénin and Muzart prepared optically active linear and cyclic ketones via palladium-induced cascade reactions including enantioselective decarboxylation steps.[13−17] The group of Kim tried to get optically active β-hydroxyisobutyric acid by enantioselective decarboxylation.[18]

The synthesis of amino acids, proteinogenic and non-proteinogenic of both configurations, continues to be a challenge, although there are many synthetic approaches available. Not taking into account enzymatic processes, enantioselective catalytic decarboxylation has rarely been used to obtain enantio-enriched amino acids. A preparative approach to optically active amino acids by enantioselective decarboxylation was based on stoichiometric amounts of *trans*-dichlorocobalt(III) complexes.[19−21] In this paper, we report on our studies concerning the decarboxylation of *N*-acetylaminomalonic acid derivatives. Using different cinchona alkaloid bases, this methodology was set up for alanine derivatives. Varying the substituents we also arrived at valine and phenylalanine derivatives.[22,23]

Results and Discussion

Diethyl 2-*N*-acetylaminomalonate, commercially available and important in industrial amino acid synthesis,[23] was the precursor for the synthesis of substrates **1**, **2**, **3** and **4**. Hemiesters **1**,[25] **2**, **3**[26] were synthesized first by alkylation with the appropriate alkyl halide and second by partial saponification. Diacid **4** was prepared by full saponification. Cyanopropionic acid **5** was prepared analogously by starting from ethyl 2-*N*-acetylamino-2-cyanopropionate.[27]

The catalytic decarboxylation of the racemic substrates **1**−**5** (prochiral in case of **4**) afforded the corresponding amino acid derivatives **6**−**10** (Scheme 1). Standard reactions were carried out with 10 mol % optically active base in abs. THF at 70 °C under nitrogen. After 24 h the reactions were stopped by cooling and evaporating the solvent at room temp. The residue was dissolved in diluted hydrochloric acid



	1, 6	2, 7	3, 8	4, 9	5, 10
R^1	COOEt	COOEt	COOEt	COOH	CN
R^2	Me	$CH(CH_3)_2$	CH_2Ph	Me	Me

Scheme 1. Decarboxylation of **1**−**5** leading to amino acid derivatives **6**−**10**

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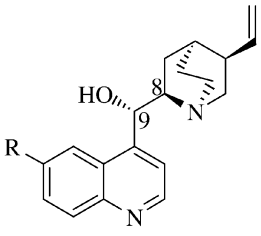
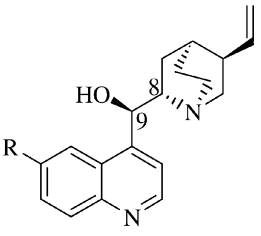
and extracted with ethyl acetate. The base stayed in the water phase and could be recycled. The organic layer was evaporated and the conversion was determined by ^{1}H NMR spectroscopy. Usually, conversion was quantitative. The enantiomeric excess of the products was determined by GC.

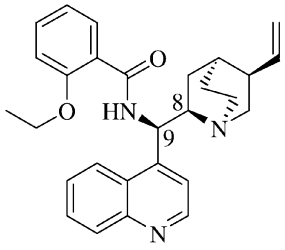
In order to find suitable reaction conditions for the catalysis, the parameters reaction temperature and time were varied, using the commercially available cinchona alkaloid cinchonine **11** (Scheme 2) in the solvent THF, which had been the best solvent for the decarboxylations in the Naproxen® system.[11,12]



R = H: cinchonine **11**
R = OMe: quinidine **13**



R = H: cinchonidine **12**
R = OMe: quinine **14**



N-(9-deoxyepicinchonine-9-yl)-2-ethoxybenzamide **15**

Scheme 2. Optically active bases **11**−**15**

At 15 °C no decarboxylation of 2-*N*-acetylamino-2-ethoxycarbonylpropionic acid (**1**) with 10 mol % cinchonine (**11**) occurred within 3 days (Table 1, Entry 1). Increasing the temperature to 35 °C increased the conversion after 3 days to 65% (Table 1, Entry 2). Higher temperatures shortened the reaction times improving the enantiomeric excess slightly (Table 1, Entries 3−7). Therefore, as standard conditions 70 °C in refluxing THF were chosen.

The results with the cinchona alkaloids **11**−**14** under standard conditions are given in Entries 7−10 of Table 1. Obviously, the configurations at positions 8 and 9 of the cinchona alkaloid and the presence or absence of the methoxy group in 6′-position of the quinoline ring determine the direction of induction. With respect to positions 8 and 9, cinchonine (**11**) and cinchonidine (**12**) as well as quinidine (**13**) and quinine (**14**) are mirror image isomers. Consequently, cinchonine (**11**) and cinchonidine (**12**) (Table 1, Entries 7 and 8) as well as quinidine (**13**) and quinine (**14**) (Table 1, Entries 9 and 10) gave different configurations of product **6**. On the other hand, the pairs cinchonine (**11**)**/** quinidine (**13**) and cinchonidine (**12**)**/**quinine (**14**) have the same configurations at position 8 and 9. They just differ in the absence or presence of a methoxy group in the quinoline system. Surprisingly, the components of the pairs afforded opposite configurations in product **6**. *N*-(9-Deoxyepicinchonine-9-yl)-2-ethoxybenzamide (**15**), the best base in the Naproxen® system,[11,12] gave better enantioselectivities than the commercially available alkaloids (Table 1, Entry 11).

Base **15** was also tested with the starting materials 2-*N*-acetylamino-2-methylmalonic acid (**4**) and 2-*N*-acetylamino-2-cyanopropionate (**5**) (Table 1, Entries 12 and 13). As 2-*N*-acetylamino-2-ethoxycarbonylpropionic acid (**1**) (Table 1, Entry 11) gave much better results, further catalyses were carried out with hemiester **1** as the starting material.

In addition to THF, other solvents were tested in the decarboxylation of **1** with 10 mol % **15** (Table 1, Entries 14

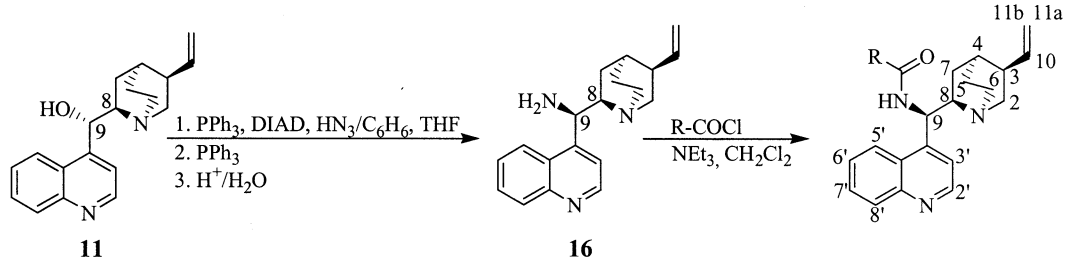
Table 1. Variation of temperature, reaction time, base and solvent in the decarboxylation of substrates **1**, **4** and **5**

Entry	Substrate	Base (10 mol %)	Solvent	*T* [°C]	*t* [h]	Product	Conv. [%]	*ee* [%]	Config.
1	**1**	**11**	THF	15	72	**6**	0	–	–
2	**1**	**11**	THF	35	72	**6**	65	7.2	D
3	**1**	**11**	THF	50	24	**6**	60	n.d.[a]	D
4	**1**	**11**	THF	50	48	**6**	96	n.d.[a]	D
5	**1**	**11**	THF	50	72	**6**	100	8.7; 7.7	D
6	**1**	**11**	THF	60	72	**6**	100	8.7	D
7	**1**	**11**	THF	70	24	**6**	100	9.6; 9.0; 9.0	D
8	**1**	**12**	THF	70	24	**6**	100	4.8; 5.0	L
9	**1**	**13**	THF	70	24	**6**	100	4.2; 4.0	L
10	**1**	**14**	THF	70	24	**6**	100	5.6; 6.2	D
11	**1**	**15**	THF	70	24	**6**	100	18.4; 18.6	L
12	**4**	**15**	THF	70	24	**9**	100	8.1; 11.9	L
13	**5**	**15**	THF	70	24	**10**	100	0.7; 4	n.d.[a]
14	**1**	**15**	MeCN	70	24	**6**	100	2.7; 2.1	L
15	**1**	**15**	dioxane	70	24	**6**	100	19.3; 19.6	L

[a] Not determined.

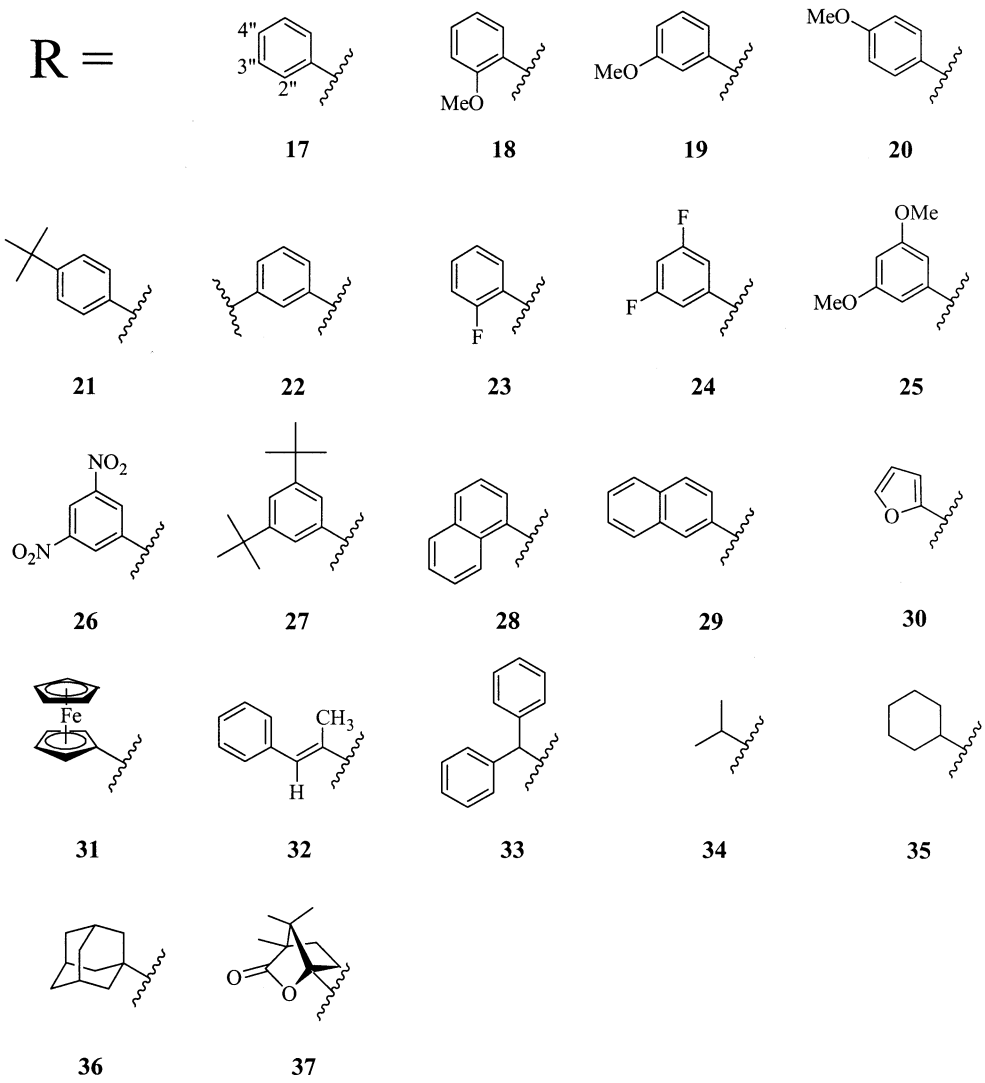
and 15). Acetonitrile had turned out to be a suitable solvent for enantioselective decarboxylations in recent publications.[9,13−16] However, in the decarboxylation of **1** the enantiomeric excess decreased dramatically (Table 1, Entry 14). Dioxane gave similar results as THF (Table 1, Entry 15). In diethyl ether both, starting material **1** and base **15** were almost insoluble.

Since benzamides of the cinchona alkaloids had been the best bases in decarboxylation reactions of the Naproxen® system,[11,12] in addition to benzamide **15** the amides **17**−**37** were screened as catalysts in the decarboxylation of hemiester **1**. The amides were prepared in two steps, illustrated in Scheme 3. In the first step, 9-amino(9-deoxy)epicinchonine (**16**) was prepared from cinchonine via a Mitsunobu reaction leading to an inversion at C-9.[28,29] Amine **16** was converted into amides **17**−**37** using the appropriate acid chlorides analogous to the literature.[11] Amides **21**, **24**, **25** and **36** included water affecting elemental analyses but



11 **16**

R =



17 **18** **19** **20**

21 **22** **23** **24** **25**

26 **27** **28** **29** **30**

31 **32** **33** **34** **35**

36 **37**

Scheme 3. Preparation of amides **17**−**37** of 9-amino(9-deoxy)epicinchonine (**16**)

Table 2. Decarboxylation of **1** with cinchona alkaloid derivatives **17**−**45** (THF, T = 70 °C, t = 24 h, 100% conversion)

Entry	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Base (10 mol %)	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**
ee [%] of **6**, L-config.	48.2; 51.6	16.7; 19.3	52.0; 52.2	49.9; 52.2	53.9; 54.2	43.8; 44.4	26.5; 29.6	53.9; 54.2	52.1; 53.7	49.6; 50.8	58.0; 59.6	29.3; 35.7	44.1; 39.9	44.5; 46.7	53.2; 54.0
Entry	16	17	18	19	20	21	22	23	24	25	26	27	28	29	
Base (10 mol %)	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**41**	**42**	**43**	**44**	**45**	
ee [%] of **6**, L-config.	42.3; 49.8	24.6; 26.8	24.5; 24.7	24.0; 25.8	8.0; 6.0	4.2; 4.9	53.9; 55.6	51.0; 52.7	2.5; 3.6	0.8; 2.4	28.2; 32.5	17.2; 18.0	6.5; 6.7	20.4; 22.1	

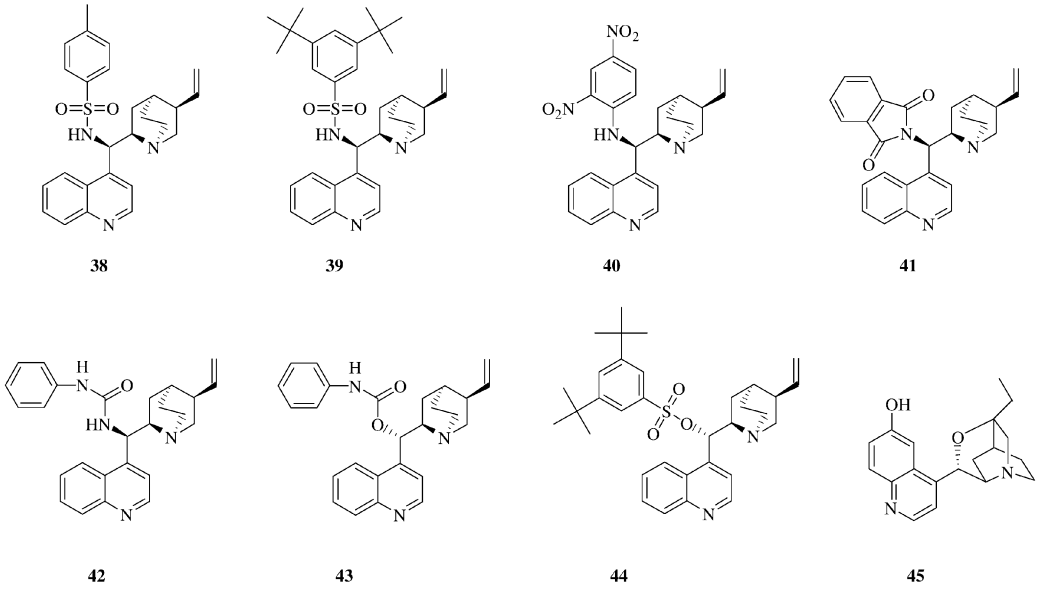
showing up in the ^{1}H NMR spectra. Compounds **23**, **28**−**35**, **37** (and **41**) were available from the previous study.[11]

In the decarboxylation of hemiester **1** to the acetylated alanine ester **6**, the unsubstituted benzamide **17** gave promising results with about 50% *ee* (Table 2, Entry 1). The *ortho*-, *meta*- and *para*-methoxy-substituted benzamides **18**−**20** were tested to see whether there were steric and electronic effects. In fact, the *ortho*-substituted derivative **18** afforded only about 18% *ee* (Table 2, Entry 2) compared to the *meta*- and *para*-substituted derivatives **18** and **19** with about 52% *ee* (Entries 3 and 4) indicating steric hindrance of *ortho*-substituents. This was corroborated by the low enantioselectivities of the *ortho*-ethoxy derivative **15** and the *ortho*-fluoro derivative **23** (Table 1, Entry 11; Table 2, Entry 7).

21 with a *tert*-butyl group in *para*-position gave 54% *ee* (Table 2, Entry 5) and the dibenzamide **22**[29] 44% *ee* (Table 2, Entry 6). Compounds **24**, **25**, **26**, containing strongly electron-withdrawing and electron-attracting substituents in 3,5-position led to an enantiomeric excess in a range between 50 and 54% *ee* (Table 2, Entries 8−10), showing that there was no pronounced inductive effect. *N*-(9-Deoxyepicinchonine-9-yl)-3,5-di-*tert*-butylbenzamide (**27**) afforded the best result (59% *ee*) in this series (Table 2, Entry 11). As expected on the basis of the steric hindrance argument, the 1-naphthyl derivative **28** gave a lower *ee* than the 2-naphthyl derivative **29** (Table 2, Entries 12 and 13). The 2-furanylamide **30** and the ferrocenylamide **31** provided similar results as the parent benzamide **17** (Table 2, Entries 14 and 15).

Amides **32**−**37** lacking the aromatic substituent were much less efficient in the decarboxylation of **1**. While the α-methylcinnamic acid amide **32** yielded about 45% *ee* (Table 2, Entry 16), the aralkyl and alkyl derivatives **33**−**37** afforded only low enantioselectivities (Table 2, Entries 17−21) including the adamantane derivative **36** and the (1*S*)-(−)-camphanic acid derivative **37** in which even group R was chiral.

In addition, compounds **38**−**45** (Scheme 4) were tested in the decarboxylation of hemiester **1**. Similar to the phenyl- and di-*tert*-butylphenyl-substituted benzamides **17** and **27**, the corresponding sulfonamides **38** and **39**, derived from 9-amino(9-deoxy)epicinchonine (**16**), afforded 55 and 52% *ee* (Table 2, Entries 22 and 23). The complex ^{1}H NMR spectrum of **38** simplified at 110 °C in $C_2D_2Cl_4$ (see Exp. Sect.). Amine **40** and phthalimide **41** gave poor results (Table 2, Entries 24 and 25), whereas the urea derivative **42** led to 30% *ee* (Table 2, Entry 26). The carbamate and sulfonate esters **43** and **44** of cinchonine achieved only low enantiose-



Scheme 4. Compounds **38**−**45**

lectivities as did compound **45**, a successful catalyst in the Baylis−Hillman reaction (Table 2, Entries 27−29).[30]

The screening was extended to the decarboxylation of **2** affording valine derivative **7**. With the unsubstituted benzamide **17** 15% *ee* was obtained (Table 3, Entry 1). Again the *ortho*-methoxy-substituted base **18** gave a bad result, in this case a racemate (Table 3, Entry 2), whereas the *meta*- and *para* derivatives **19** and **20** matched the unsubstituted benzamide **17** with about 13% *ee* (Table 3, Entries 3 and 4).

Table 3. Decarboxylation of **2** and **3** with different bases (THF, T = 70 °C, t = 24 h, 100% conversion)

Entry	Substrate	Base (10 mol %)	Product	*ee* [%] L-config.
1	**2**	**17**	**7**	14.2; 15.6
2	**2**	**18**	**7**	*rac*
3	**2**	**19**	**7**	9.7; 13.2
4	**2**	**20**	**7**	11.8; 13.7
5	**2**	**27**	**7**	48.0
6	**3**	**17**	**8**	65.7; 69.0
7	**3**	**18**	**8**	37.1; 37.8
8	**3**	**19**	**8**	63.7; 65.4
9	**3**	**20**	**8**	69.3; 71.1
10	**3**	**21**	**8**	67.3; 69.1
11	**3**	**27**	**8**	65.8; 67.7
12	**3**	**38**	**8**	62.4; 63.6
13	**3**	**39**	**8**	64.1; 64.7

An unexpected increase to 48% enantiomeric excess was observed with *N*-(9-deoxyepicinchonine-9-yl)-3,5-di-*tert*-butylbenzamide (**27**) (Table 3, Entry 5), also the best base in the system **1** → **6**.

Enantioselectivities were much higher in the decarboxylation of **3** to give ethyl *N*-acetylphenylalaninate **8**. The unsubstituted benzamide **17** afforded 67% *ee* (Table 3, Entry 6). Again, the *ortho*-substituted methoxybenzamide **18** gave only 38% *ee* (Table 3, Entry 7), whereas the *meta*- and *para*-substituted methoxybenzamides **19** and **20** achieved 65% and 70% *ee* (Table 3, Entries 8 and 9). With **21** and **27** close to 70% *ee* were obtained (Table 3, Entries 10 and 11). The sulfonamides **38** and **39** resulted in 63% and 65% *ee* (Table 3, Entries 12 and 13).

With **15**, the effect of varying the amount of catalyst in the decarboxylation of hemiester **1** was tested (Table 4, Entries 1−8). Increasing the amount of **15** gave rise to an increase of the enantiomeric excess, reaching 41.5% *ee* with 60 mol % base (Table 4, Entry 7). Use of a stoichiometric amount of base did not improve the results (Table 4, Entry 8). In contrast, with **27** the enantiomeric excess could not be improved with higher amounts of base (Table 4, Entries 9 and 10). A decrease of the reaction temperature to 30 °C made the reaction sluggish. After 18 days there was only 85% conversion with decreased enantioselectivity (Table 4, Entry 11).

A kinetic study of the decarboxylation of **1** was performed with base **27**, which had been the most successful catalyst in the system **1** → **6**. The twelvefold standard reaction was analyzed taking samples each hour. Conversion

Table 4. Variation of catalyst concentration and temperature in the decarboxylation of **1** to give **6**. 100% conversion in all cases except for Entry 11 with 85% conversion

Entry	Base	mol % base	Temp. [°C]	Time [h]	*ee* [%] L-config.
1	**15**	5	70	24	8.1
2	**15**	10	70	24	18.5
3	**15**	20	70	24	23.5
4	**15**	30	70	24	27.7
5	**15**	40	70	24	31.2
6	**15**	50	70	24	34.4
7	**15**	60	70	24	41.5
8	**15**	100	70	24	42.4
9	**27**	30	70	24	62.8
10	**27**	60	70	24	60.2
11	**27**	10	30	432	53.6

was almost complete after 12 h (Figure 1). At the beginning of the catalysis the enantiomeric excess of ethyl *N*-acetylalaninate (**6**) was a little lower. After 5 h it reached 60% *ee* and stayed constant then. A similar observation had been made in the Naproxen® system.[11] This is in contradiction to a computational study recently published in this journal,[30] denying a two-step decarboxylation/protonation mechanism and suggesting a concerted mechanism according to which each enantiomer of the starting material transforms into its own product enantiomer. In such a case, kinetic resolution should occur. This was not observed, neither in the Naproxen® system[11] nor in the present study. Moreover, in the Naproxen® system it had been shown that both enantiomers of the resolved starting material 2-cyano-2-(6-methoxynaphth-2-yl)propionic acid gave the same product enantioselectivity of about 68% *ee*, which is incompatible with a concerted mechanism. Thus, we continue to favor the two-step decarboxylation/protonation mechanism via planar intermediates, such as the enolate of ethyl *N*-acetylalaninate in the decarboxylation of **1**, and their stereoselective protonation.

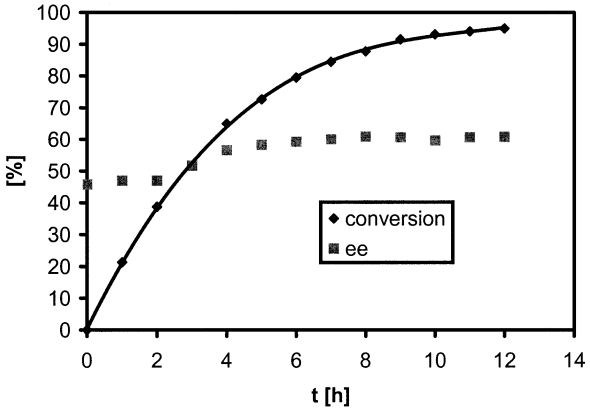


Figure 1. Kinetics of the decarboxylation of **1**→**6** with base **27**

Conclusion

The enantioselective decarboxylation methodology was extended to amino acid derivatives (10 mol % catalyst,

THF, 70 °C, 100% conversion). The best catalysts, epicinchonine benzamides and benzenesulfonamides (lacking *ortho*-substituents!) afforded 60% *ee* in the decarboxylation **1** → **6** and 70% *ee* in the decarboxylation **3** → **8**.

Experimental Section

General: ^{1}H NMR: Bruker AC 250, Bruker Avance 300 and Bruker Avance 400. EI MS: Finnigan MAT 311 A, CI and FD MS: Finnigan MAT 95. Only the most intense peak of a cluster is given. GC: Hewlett−Packard HP 5890 series II and Thermoquest 8130−10, Spectra Physics SP 4270 integrator. IR: Beckman IR 4240. Optical rotations: Perkin−Elmer polarimeter 241 (1-dm cell), measurement at room temp. Melting points: Büchi SMP 20 (uncorrected). Elemental analysis: Vario EL III.

The precursors for the substrates diethyl 2-*N*-acetylamino-2-methylmalonate[25], diethyl 2-*N*-acetylamino-2-isopropylmalonate,[32] diethyl 2-*N*-acetylamino-2-benzylmalonate[33] and ethyl 2-*N*-acetylamino-2-cyanopropionate[27] and the substrates 2-*N*-acetylamino-2-ethoxycarbonylpropionic acid (**1**)[25] and 2-*N*-acetylamino-2-ethoxycarbonyl-3-phenylpropionic acid (**3**)[26] were prepared according to the literature. 3,5-Dimethoxybenzoyl chloride was obtained by refluxing the corresponding acid for 2 h in $SOCl_2$, followed by bulb-to-bulb distillation in vacuo. 4-*tert*-Butylbenzoyl chloride**,** 3,5-difluorobenzoyl chloride, 3,5-dinitrobenzoyl chloride and 1-adamantanecarboxylic acid chloride were purchased from ACROS. Compounds **16, 17, 22** (ref.[29]) and **15**, **18**, **19**, **20**, **27** (ref.[11]) were prepared as described. Furthermore, 3,5-di-*tert*-butylbenzenesulfonyl chloride[34] and (3*R*,8*R*,9*S*)-10,11-dihydro-3,9-epoxy-6′-hydroxycinchonane (**45**)[30] were synthesized as described.

2-*N*-Acetylamino-2-ethoxycarbonyl-3-methylbutyric Acid (2): Diethyl 2-*N*-acetylamino-2-isopropylmalonate[32] (4.96 g, 19.1 mmol) was dissolved in EtOH (10 mL). A solution of KOH (1.28 g, 19.4 mmol) in water (1.3 mL) and EtOH (5.2 mL) was added dropwise. After stirring for 48 h at room temp., the solvents were removed in vacuo at room temp. The aqueous solution of the residue was washed 3 × with EtOAc to remove the starting material from the product. The water phase was acidified with half-concentrated HCl at 0 °C. The precipitating product was extracted 3 × with EtOAc. The organic layers were dried with Na_2SO_4 adding charcoal to remove a pink color. Evaporation of the organic solvent yielded **2** as a colorless solid (1.5 g, 34%), m.p. 130−132 °C (dec., ↑ CO_2). IR (KBr): $\tilde{\nu}$ = 3360 (N−H), 1780 cm^{-1} (C=O). ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 0.84, 0.87 [2 d, ^3J = 6.9 Hz, 6 H, CH(CH_3)$_2$], 1.11 (t, ^3J = 7.1 Hz, 3 H, CH$_2$CH_3), 1.89 (s, 3 H, COCH_3), 2.40−2.57 [m, 1 H, CH(CH$_3$)$_2$], 3.93−4.17 (m, 2 H, CH_2CH$_3$), 7.94 (s, 1 H, NH), 13.27 (br. s, 1 H, COOH) ppm. MS (CI, NH_3): *m*/*z* (%) = 188.1 (100) [MH − CO_2]. $C_{10}H_{17}NO_5$ (231.3): calcd. C 51.94, H 7.41, N 6.06; found C 52.10, H 7.25, N 6.20.

2-*N*-Acetylamino-2-methylmalonic Acid (4): Diethyl 2-*N*-acetylamino-2-methylmalonate[25] (5.0 g, 21.6 mmol) was added to a solution of KOH (4.90 g, 87.0 mmol) in EtOH (20 mL) and water (10 mL). After stirring for 6 d at room temp., the solvents were removed at room temp. in vacuo. Workup as described for **2**. For purification, the crude product was dissolved in THF, precipitated with PE 40/60 and stored at −30 °C. Colorless solid (0.74 g, 20%), m.p. 135 °C (dec., ↑ CO_2). IR (KBr): $\tilde{\nu}$ = 3350 (N−H), 1750 cm^{-1} (C=O). ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 1.51 (s, 3 H, CH_3), 1.86 (s, 3 H, COCH_3), 8.02 (s, 1 H, NH), 12.98 (br. s, 2 H, COOH) ppm. MS (CI, NH_3): *m*/*z* (%) = 129.9 (100) [M − COOH]. $C_6H_9NO_5$ (175.1): calcd. C 41.15, H 5.18, N 8.00; found C 40.58, H 5.16, N 7.53.

2-*N*-Acetylamino-2-cyanopropionic Acid (5): To a suspension of ethyl 2-*N*-acetylamino-2-cyanopropionate[27] (1.00 g, 5.43 mmol) in EtOH (2.8 mL), KOH (0.91 g, 16.2 mmol) dissolved in water (11 mL) was added at 0 °C. After stirring at room temp. for 10 h, workup was as for **4**, except that 2 N HCl was used for acidification and the product did not precipitate. Dissolution in THF, precipitation with PE 40/60 and storage at −30 °C gave **5** (170 mg, 20%) as a colorless solid, m.p. 125−128 °C (dec., ↑ CO_2). IR (KBr): $\tilde{\nu}$ = 3340 (N−H), 1730 cm^{-1} (C=O). ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 1.69 (s, 3 H, CH_3), 1.93 (s, 3 H, COCH_3), 8.99 (s, 1 H, NH), 13.80 (br. s, 1 H, COOH) ppm. MS (CI, NH_3): *m*/*z* (%) = 130.0 (100) [M + NH_4 − CO_2]. $C_6H_8N_2O_3$ (156.1): calcd. C 46.15, H 5.16, N 17.94; found C 46.19, H 5.25, N 17.56.

General Procedure for the Synthesis of the Amides of 9-Amino(9-deoxy)epicinchonine (16): 16 was dissolved in the given amount of CH_2Cl_2 and NEt_3. Then a solution of the appropriate benzoyl chloride in CH_2Cl_2 was added dropwise at 0 °C. After stirring at room temp. for 10 h, the reaction mixture was diluted with CH_2Cl_2 and washed 3 × with half-concentrated Na_2CO_3 solution, dried with Na_2CO_3 and the solvents were evaporated. All the amides were purified by chromatography on silica gel with MeOH as eluent. Further details are given for the individual compounds.

***N*-(9-Deoxyepicinchonine-9-yl)-4-*tert*-butylbenzamide (21): 16** (908 mg, 3.09 mmol), CH_2Cl_2 (16 mL), NEt_3 (6.4 mL) and 4-*tert*-butylbenzoyl chloride (755 mg, 3.84 mmol), CH_2Cl_2 (4 mL). After dissolution in Et_2O the product was precipitated with PE 40/60 and stored at −30 °C. Colorless solid (390 mg, 28%), m.p. 122−124 °C. $[\alpha]_D$ = 266 (*c* = 0.53, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3280 (N−H), 1640, 1515 cm^{-1} (amide). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.90−1.10 (m, 1 H, H^{b}7), 1.32 (s, 9 H, CH_3), 1.19−1.71 (m, 4 H, H4, H5, H^{a}7), 2.23−2.38 (m, 1 H, H3), 2.76−3.17 (m, 5 H, H2, H6, H8), 5.12 (td, ^3J = 17.2, ^2J = 1.5, ^4J = 1.5 Hz, 1 H, H11b), 5.17 (td, ^3J = 10.6, ^2J = 1.5, ^4J = 1.5 Hz, 1 H, H11a), 5.38 (br. d, 1 H, H9), 5.93 (ddd, ^3J = 17.1, ^3J = 10.6, ^3J = 6.5 Hz, 1 H, H10), 7.45 (d, ^3J = 8.7 Hz, 2 H, H3′′, H5′′), 7.49 (d, ^3J = 4.6 Hz, 1 H, H3′), 7.55−7.65 (m, 1 H, H6′), 7.67−7.75 (m, 1 H, H7′), 7.75 (d, ^3J = 8.7 Hz, 2 H, H2′′, H6′′), 7.90 (s, 1 H, NH), 8.13 (dd, ^3J = 8.4, ^4J = 1.2 Hz, 1 H, H8′), 8.45 (dd, ^3J = 8.5, ^4J = 1.0 Hz, 1 H, H5′), 8.86 (d, ^3J = 4.6 Hz, 1 H, H2′) ppm. MS (EI, 70 eV): *m*/*z* (%) = 161.3 (100) [4-*tert*-butylbenzoyl], 453.6 (38) [M]. $C_{30}H_{35}N_3O$ (453.6)·1.2H_2O: calcd. C 75.82, H 7.93, N 8.84; found C 75.45, H 8.17, N 8.84.

***N*-(9-Deoxyepicinchonine-9-yl)-3,5-difluorobenzamide (24): 16** (848 mg, 2.89 mmol), CH_2Cl_2 (15 mL), NEt_3, (6 mL) and 3,5-difluorobenzoyl chloride (748 mg, 4.24 mmol), CH_2Cl_2 (4 mL). Recrystallization from Et_2O. Colorless solid (326 mg, 26%), m.p. 134−137 °C. $[\alpha]_D$ = 243 (*c* = 0.54, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3320 (N−H), 1640, 1515 cm^{-1} (amide). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.95−1.09 (m, 1 H, H^{b}7), 1.30−1.71 (m, 4 H, H4, H5, H^{a}7), 2.25−2.41 (m, 1 H, H3), 2.89−3.18 (m, 5 H, H2, H6, H8), 5.12 (td, ^3J = 17.6, ^2J = 1.7, ^4J = 1.7 Hz, 1 H, H11b), 5.18 (td, ^3J = 10.8, ^2J = 1.7, ^4J = 1.7 Hz, 1 H, H11a), 5.36 (br. d, 1 H, H9), 5.93 (ddd, ^3J = 17.1, ^3J = 10.6, ^3J = 6.4 Hz, 1 H, H10), 6.93 (tt, $^3J_{H4'',F}$ = 8.6, ^4J = 2.3 Hz, 1 H, H4′′), 7.27−7.34 (m, 2 H, H2′′), 7.46 (d, ^3J = 4.4 Hz, 1 H, H3′), 7.56−7.67 (m, 1 H, H6′), 7.68−7.79 (m, 1 H, H7′), 7.87 (br. s, 1 H, NH), 8.15 (dd, ^3J = 8.3, ^4J = 1.2 Hz, 1 H, H8′), 8.39 (d, ^3J = 7.9 Hz, 1 H, H5′), 8.88 (d, ^3J = 4.4 Hz, 1 H, H2′) ppm. MS (EI, 70 eV): *m*/*z* (%) = 136.3 (100) [quinuclidine], 433.1 (10) [M]. $C_{26}H_{25}F_2N_3O$ (433.5)·2.2H_2O: calcd. C 69.22, H 6.57, N 9.31; found C 68.94, H 6.09, N 9.16.

***N*-(9-Deoxyepicinchonine-9-yl)-3,5-dimethoxybenzamide (25): 16** (590 mg, 2.01 mmol), CH_2Cl_2 (12 mL), NEt_3 (4.1 mL) and 3,5-dimethoxybenzoyl chloride (522 mg, 2.60 mmol), CH_2Cl_2 (3 mL). The hydrochloride was formed by stirring with an excess of ethanolic HCl for 10 h. After removal of the solvent, the hydrochloride was dissolved in MeOH, precipitated with acetone and stored at −30 °C. Then the free base was liberated by dissolving the hydrochloride in water, adding an excess of Na_2CO_3 solution and extraction with CH_2Cl_2. The free base was chromatographed and afterwards recrystallized from Et_2O. Colorless solid (330 mg, 36%), m.p. 123−125 °C. $[\alpha]_D$ = 267 (*c* = 0.52, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3340 (N−H), 1645, 1515 cm^{-1} (amide). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.91−1.07 (m, 1 H, H^b7), 1.46−1.73 (m, 4 H, H4, H5, H^a7), 2.24−2.38 (m, 1 H, H3), 2.76−3.15 (m, 5 H, H2, H6, H8), 3.79 (s, 6 H, OCH_3), 5.12 (td, ^3J = 17.3, ^2J = 1.5, ^4J = 1.5 Hz, 1 H, H11b), 5.18 (td, ^3J = 10.6, ^3J = 1.4, ^2J = 1.4 Hz, 1 H, H11a), 5.93 (ddd, ^3J = 17.2, ^3J = 10.6, ^3J = 6.4 Hz, 1 H, H10), 6.57 (t, ^4J = 1.8 Hz, 1 H, H4′′), 6.95 (d, ^4J = 2.2 Hz, 2 H, H2′′), 7.48 (d, ^3J = 4.4 Hz, 1 H, H3′), 7.55−7.66 (m, 1 H, H6′), 7.67−7.77 (m, 1 H, H7′), 7.90 (br. s, 1 H, NH), 8.13 (dd, ^3J = 8.4, ^4J = 1.0 Hz, 1 H, H8′), 8.47 (d, ^3J = 8.0 Hz, 1 H, H5′), 8.87 (d, ^3J = 4.7 Hz, 1 H, H2′) ppm. MS (EI, 70 eV): *m*/*z* (%) = 165.2 (100) [3,5-dimethoxybenzoyl], 457.2 (45) [M]. $C_{28}H_{31}N_3O_3$ (457.6)·H_2O: calcd. C 70.71, H 6.99, N 8.84; found C 70.30, H 6.94, N 8.76.

***N*-(9-Deoxyepicinchonine-9-yl)-3,5-dinitrobenzamide (26):** As the acid chloride is almost insoluble in CH_2Cl_2, $CHCl_3$ was used for this batch. **16** (500 mg, 1.70 mmol), $CHCl_3$ (9 mL), NEt_3 (3.5 mL) and 3,5-dinitrobenzoyl chloride (575 mg, 2.49 mmol), $CHCl_3$ (20 mL). Purification via the hydrochloride as described for **25**, but precipitation was done with Et_2O instead of acetone. Yellow-brown solid (190 mg, 23%), m.p. 196−199 °C. $[\alpha]_D$ = 236 (*c* = 0.51, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3320 (N−H), 1660, 1640, 1540 cm^{-1} (amide). ^1H NMR (250 MHz, $CDCl_3$): δ = 0.77−0.97 (m, 1 H, H^b7), 0.97−1.76 (m, 4 H, H4, H5, H^a7), 2.27−2.42 (m, 1 H, H3), 2.73−3.28 (m, 5 H, H2, H6, H8), 5.14 (td, ^3J = 17.2, ^2J = 1.5, ^4J = 1.5 Hz, 1 H, H11b), 5.21 (td, ^3J = 10.5, ^2J = 1.4, ^4J = 1.4 Hz, 1 H, H11a), 5.46 (br. s, 1 H, H9), 5.94 (ddd, ^3J = 17.1, ^3J = 10.5, ^3J = 6.5 Hz, 1 H, H10), 7.46 (d, ^3J = 4.4 Hz, 1 H, H3′), 7.61−7.71 (m, 1 H, H6′), 7.71−7.81 (m, 1 H, H7′), 8.14 (dd, ^3J = 8.5, ^4J = 1.2 Hz, 1 H, H8′), 8.38 (dd, ^3J = 8.4, ^4J = 0.8 Hz, 1 H, H5′), 8.87 (d, ^3J = 4.4 Hz, 1 H, H2′), 8.93 (d, ^4J = 2.1 Hz, 2 H, H2′′, H6′′), 9.13 (t, ^4J = 2.1 Hz, 1 H, H4′′) ppm. MS (EI, 70 eV): *m*/*z* (%) = 136.3 (100) [quinuclidine], 487.1 (14) [M]. $C_{26}H_{25}N_5O_5$ (487.5): calcd. C 64.06, H 5.17, N 14.47; found C 63.74, H 5.60, N 14.40.

***N*-(9-Deoxyepicinchonine-9-yl)-adamantanecarboxamide (36): 16** (1.07 g, 3.66 mmol), CH_2Cl_2 (18 mL), NEt_3 (7 mL) and 1-adamantanecarboxylic acid chloride (884 mg, 4.45 mmol), CH_2Cl_2 (4 mL). Colorless solid (910 mg, 55%), m.p. 80−82 °C. $[\alpha]_D$ = 192 (*c* = 0.51, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3360 (N−H), 1650, 1510 cm^{-1} (amide). ^1H NMR (250 MHz, $CDCl_3$): δ = 0.79−1.05 (m, 1 H, H^b7), 1.29−1.91 (m, 19 H, H4, H5, H^a7, adamantane-H), 2.20−2.39 (m, 1 H, H3), 2.64−2.81 (m, 1 H, H2), 2.85−3.08 (m, 4 H, H2, H6, H8), 5.09 (br. s, 1 H, H9), 5.10 (td, ^3J = 17.3, ^2J = 1.5, ^4J = 1.5 Hz, 1 H, H11b), 5.16 (td, ^3J = 10.6, ^2J = 1.5, ^4J = 1.5 Hz, 1 H, H11a), 5.92 (ddd, ^3J = 17.1, ^3J = 10.4, ^3J = 6.6 Hz, 1 H, H10), 7.37 (d, ^3J = 4.8 Hz, 1 H, H3′), 7.50−7.61 (m, 1 H, H6′), 7.64−7.74 (m, 1 H, H7′), 8.10 (dd, ^3J = 8.5, ^4J = 1.0 Hz, 1 H, H8′), 8.35 (dd, ^3J = 8.7, ^4J = 0.8 Hz, 1 H, H5′), 8.84 (d, ^3J = 4.4 Hz, 1 H, H2′) ppm. MS (FD, CH_2Cl_2): *m*/*z* (%) = 455.5 (100) [M]. $C_{30}H_{37}N_3O$ (455.6)·1/3 H_2O: calcd. C 78.06, H 8.22, N 9.10; found C 78.27, H 8.45, N 8.45.

***N*-(9-Deoxyepicinchonine-9-yl)-4-methylbenzenesulfonamide (38): 16** (960 mg, 3.27 mmol), *p*-toluenesulfonyl chloride (938 mg, 4.92 mmol) and K_2CO_3 (540 mg, 3.90 mmol) were stirred in CH_2Cl_2 (20 mL) at room temp. for 10 h. The reaction mixture was diluted with CH_2Cl_2, K_2CO_3 was removed by filtration and the solution was washed 3 × with saturated Na_2CO_3 solution. Chromatography on SiO_2 with EtOAc/MeOH (9:1). Colorless solid (460 mg, 31%), m.p. 190−192 °C. $[\alpha]_D$ = 52 (*c* = 0.51, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3440 (N−H), 1390, 1330, 1170 cm^{-1} (sulfonamide). ^1H NMR (250 MHz, $CDCl_3$): δ = 0.71−0.93 (m, 1 H, H^b7), 1.08−1.68 (m, 4 H, H4, H5, H^a7), 2.35 (s, 3 H, CH_3), 2.13−2.42 (m, 1 H, H3), 2.62−2.97 (m, 3.7 H, H2, H6, H8), 3.17−3.31 (m, 0.3 H, H8), 4.20 (br. d, ^3J = 10.7 Hz, 0.3 H, H11b), 4.82−4.96 (m, 1.7 H, H9, H11b), 5.12 (td, ^3J = 10.6, ^2J = 1.4, ^4J = 1.4 Hz, 1 H, H11a), 5.76 (ddd, ^3J = 17.2, ^3J = 10.6, ^3J = 5.8 Hz, 1 H, H10), 6.83 (d, ^3J = 8.1 Hz, 0.6 H, H3′′, H5′′), 7.07 (d, ^3J = 8.0 Hz, 1.4 H, H3′′, H5′′), 7.17 (d, ^3J = 4.3 Hz, 0.3 H, H3′), 7.33 (d, ^3J = 8.4 Hz, 0.6 H, H2′′, H6′′), 7.39−7.46 (m, 2.4 H, H2′′, H3′, H6′′, H7′), 7.55−7.64 (m, 1 H, H6′), 7.68−7.77 (m, 0.7 H, H7′), 7.98 (d, ^3J = 8.4 Hz, 0.3 H, H8′), 8.04 (d, ^3J = 8.5 Hz, 0.7 H, H8′), 8.10 (dd, ^3J = 8.5, ^4J = 0.9 Hz, 0.7 H, H5′), 8.41 (d, ^3J = 8.4 Hz, 0.3 H, H5′), 8.71 (d, ^3J = 4.6 Hz, 0.7 H, H2′), 8.74 (d, ^3J = 4.2 Hz, 0.3 H, H2′) ppm. ^1H NMR (400 MHz, $C_2D_2Cl_4$, 110 °C): δ = 0.77−0.92 (m, 1 H, H^b7), 1.12−1.23 (m, 1 H, H^a7), 1.37−1.64 (m, 3 H, H4, H5), 2.15−2.31 (m, 1 H, H3), 2.24 (s, 3 H, CH_3), 2.43−2.57 (m, 1 H, H2), 2.76−3.12 (m, 4 H, H2, H6, H8), 4.75 (br. s, 1 H, H9), 4.95 (td, ^3J = 17.4, ^3J = 1.5, ^2J = 1.5 Hz, 1 H, H11b), 5.12 (td, ^3J = 10.6, ^2J = 1.4, ^4J = 1.4 Hz, 1 H, H11a), 5.76 (ddd, ^3J = 17.3, ^3J = 10.7, ^3J = 5.9 Hz, 1 H, H10), 6.92 (d, ^3J = 7.9 Hz, 2 H, H3′′, H5′′), 7.21−7.38 (m, 1 H, H3′), 7.33 (d, ^3J = 8.3 Hz, 2 H, H2′′, H6′′), 7.43−7.54 (m, 1 H, H6′), 7.57−7.68 (m, 1 H, H7′), 8.03 (d, ^3J = 8.4, ^4J = 0.3 Hz, 1 H, H8′), 8.06−8.20 (m, 1 H, H5′), 8.68 (d, ^3J = 4.5 Hz, 1 H, H2′) ppm. MS (EI, 70 eV): *m*/*z* (%) = 136.3 (100) [quinuclidine], 447.1 (17) [M]. $C_{26}H_{29}N_3O_2S$ (447.6): calcd. C 69.77, H 6.53, N 9.39; found C 69.20, H 6.92, N 9.32.

***N*-(9-Deoxyepicinchonine-9-yl)-3,5-di-*tert*-butylbenzenesulfonamide (39): 16** (650 mg, 2.22 mmol), 3,5-di-*tert*-butylbenzenesulfonyl chloride (962 mg, 3.33 mmol) and K_2CO_3 (360 mg, 2.60 mmol) in CH_2Cl_2 (20 mL) were stirred at room temp. for 10 h. The reaction mixture was diluted with CH_2Cl_2 and K_2CO_3 was filtered off. The organic layer was washed 3 × with saturated Na_2CO_3 solution. The crude product was chromatographed on SiO_2 with MeOH. Colorless solid (340 mg, 28%), m.p. 95−98 °C. $[\alpha]_D$ = 57 (*c* = 0.55, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3420 (N−H), 1370, 1335, 1170 cm^{-1} (sulfonamide). ^1H NMR (250 MHz, $CDCl_3$): δ = 0.65−0.88 (m, 1.7 H, H^a7, H^b7), 0.94−1.01 (m, 0.3 H, H^a7), 1.04−1.66 (m, 3 H, H4, H5), 1.3 (s, 18 H, CH_3), 2.11−2.34 (m, 1 H, H3), 2.58−2.78 (m, 4.7 H, H2, H6, H8), 3.13−3.34 (m, 0.3 H, H8), 4.12 (d, ^3J = 10.7 Hz, 1 H, H11b), 4.75−4.92 (m, 2 H, H9, H11b), 5.00−5.11 (m, 1 H, H11a), 5.71 (ddd, ^3J = 17.3, ^3J = 10.7, ^3J = 5.4 Hz, 1 H, H10), 7.11 (d, ^3J = 4.3 Hz, 0.3 H, H3′), 7.36−7.40 (m, 0.3 H, H4′′), 7.41−7.53 (m, 3.4 H, H2′′, H3′, H3′′, H4′′), 7.53−7.63 (m, 1 H, H6′), 7.66−7.76 (m, 1 H, H7′), 8.01 (d, ^3J = 8.5 Hz, 0.3 H, H8′), 8.06 (d, ^3J = 8.1 Hz, 0.7 H, H8′), 8.08 (dd, ^3J = 8.4, ^4J = 0.8 Hz, 0.7 H, H5′), 8.53 (d, ^3J = 8.3 Hz, 0.3 H, H5′), 8.72 (d, ^3J = 4.6 Hz, 0.7 H, H2′), 8.74 (d, ^3J = 4.5 Hz, 0.3 H, H2′) ppm. MS (FD, CH_2Cl_2): *m*/*z* (%) = 545.6 (100) [M]. $C_{33}H_{43}N_3O_2S$ (545.8): calcd. C 72.62, H 7.94, N 7.70; found C 72.20, H 8.00, N 7.44.

***N*-(9-Deoxyepicinchonine-9-yl)-2,4-dinitrophenylamine (40): 16** (510 mg, 1.74 mmol) and fluoro-2,4-dinitrobenzene (324 mg, 1.74 mmol) were stirred in CH_2Cl_2 (15 mL) at room temp. for 10 h. A yellow powder precipitated. The solvent was removed in vacuo

and the residue was recrystallized from Et_2O. Intensely yellow powder (400 mg, 50%). m.p. 200−202 °C. $[\alpha]_D$ = 652 (*c* = 0.51, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3440, 3280 cm^{-1} (N−H). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.87−1.08 (m, 1 H, H^b7), 1.34−1.79 (m, 4 H, H4, H5, H^a7), 2.28−2.45 (m, 1 H, H3), 2.65−2.84 (m, 1 H, H2), 2.95−3.22 (m, 4 H, H2, H6, H8), 5.13 (td, ^3J = 17.3, ^2J = 1.5, ^4J = 1.5 Hz, 1 H, H11b), 5.21 (br. td, 1 H, H 11a), 5.94 (ddd, ^3J = 17.2, ^3J = 8.8, ^3J = 6.3 Hz, 1 H, 1 H, H10), 6.26 (br. s, 1 H, H9), 7.51 (d, ^3J = 4.5 Hz, 1 H, H3′), 7.65−7.93 (m, 3 H, H2′′, H6′, H7′), 7.85 (d, ^3J = 8.8 Hz, 1 H, H5′′), 8.23 (d, ^3J = 7.8 Hz, 1 H, H8′), 8.33 (dd, ^3J = 8.6, ^4J = 0.6, 1 H, H5′), 8.90 (d, ^3J = 4.4 Hz, 1 H, H2′), 9.09 (d, ^4J = 2.7 Hz, 1 H, H3′′), 9.84 (br. s, 1 H, NH) ppm. MS (EI, 70 eV): *m*/*z* (%) = 136.1 (100) [quinuclidine], 459.1 (30) [M]. $C_{25}H_{25}N_5O_4$ (459.5): calcd. C 65.35, H 5.48, N 15.24; found C 65.02, H 5.49, N 14.99.

***N*-(9-Deoxyepicinchonine-9-yl)-*N*′-phenylurea (42): 16** (276 mg, 0.94 mmol) was heated to 60 °C with phenylisocyanate (10 mL, 91.5 mmol) for 10 min. After further 15 min at room temp. the precipitate was collected, washed with PE 40/60 and recrystallized from Et_2O. Colorless solid (180 mg, 46%), m.p. 217−218 °C. $[\alpha]_D$ = 193 (*c* = 0.29, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3280 (N−H), 1690, 1510 cm^{-1} (amide). ^1H NMR (250 MHz, $CDCl_3$): δ = 0.80−0.97 (m, 1 H, H^b7), 1.15−1.68 (m, 4 H, H4, H5, H^a7), 2.19−2.36 (m, 1 H, H3), 2.77−3.06 (m, 5 H, H2, H6, H8), 5.10 (td, ^3J = 14.7, ^2J = 1.5, ^4J = 1.5 Hz, 1 H, H11b), 5.15 (td, ^3J = 14.7, ^2J = 1.5, ^4J = 1.5 Hz, 1 H, H11a), 5.30 (br. d, 1 H, H9), 5.89 (ddd, ^3J = 17.1, ^3J = 10.5, ^3J = 6.6 Hz, 1 H, H10), 6.28 (br. s, 1 H, RNH), 6.90−7.04 (m, 1 H, PhNH), 7.13−7.32 (m, 5 H, Ph-H), 7.47 (d, ^3J = 4.6 Hz, 1 H, H3′), 7.54−7.66 (m, 1 H, H6′), 7.67−7.77 (m, 1 H, H7′), 8.14 (dd, ^3J = 8.4, ^4J = 1.1 Hz, 1 H, H8′), 8.40 (dd, ^3J = 8.6, ^4J = 0.9 Hz, 1 H, H5′), 8.88 (d, ^3J = 4.6 Hz, 1 H, H2′) ppm. MS (EI, 70 eV): *m*/*z* (%) = 136.1 (100) [quinuclidine], 412.0 (5) [M]. $C_{26}H_{28}N_4O$ (412.5): calcd. C 75.70, H 6.84, N 13.58; found C 75.52, H 6.86, N 13.48.

Cinchonine-9-yl Phenylcarbamate (43):[35] Cinchonine (1.50 g, 5.10 mmol) was heated to 80 °C in phenylisocyanate (10 mL, 91.5 mmol) for 10 h. The excess of phenylisoyanate was removed in vacuo. The residue was stirred in boiling Et_2O, cooled to −30 °C and collected. Colorless solid (530 mg, 25%), m.p. 190−191 °C. $[\alpha]_D$ = 53 (*c* = 0.54, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3440 (N−H), 1730 cm^{-1} (amide). ^1H NMR (250 MHz, $CDCl_3$): δ = 1.16−1.31 (m, 1 H, H^b7), 1.41−1.97 (m, 4 H, H4, H5, H^a7), 2.20−2.34 (m, 1 H, H3), 2.61−2.90 (m, 2 H, H2, H6), 3.24−3.41 (m, 1 H, H8), 5.08 (td, ^3J = 9.7, ^2J = 1.5, ^4J = 1.5 Hz, 1 H, H11b), 5.12 (td, ^3J = 8.9, ^2J = 1.4, ^4J = 1.4 Hz, 1 H, H11a), 6.03 (ddd, ^3J = 17.1, ^3J = 10.5, ^3J = 7.2 Hz, 1 H, H10), 6.57 (d, ^3J = 8.0 Hz, 1 H, Ph-H), 6.82 (br. s, 1 H, H9), 7.05 (t, ^3J = 7.2 Hz, 1 H, Ph-H), 7.19−7.39 (m, 3 H, Ph-H), 7.44 (d, ^3J = 4.5 Hz, 1 H, H3′), 7.54−7.64 (m, 1 H, H6′), 7.66−7.78 (m, 1 H, H7′), 8.13 (dd, ^3J = 8.4, ^4J = 0.7 Hz, 1 H, H8′), 8.25 (d, ^3J = 8.5, ^4J = 0.9 Hz, 1 H, H5′), 8.89 (d, ^3J = 4.5 Hz, 1 H, H2′) ppm. MS (EI, 70 eV): *m*/*z* (%) = 136.1 (100) [quinuclidine], 413.1 (33) [M]. $C_{26}H_{27}N_3O_2$ (413.5): calcd. C 75.52, H 6.58, N 10.16; found C 75.00, H 6.49, N 10.27.

Cinchonine-9-yl 3,5-Di-*tert*-butylbenzenesulfonate (44): Cinchonine (424 mg, 1.40 mmol) and NaH (40.8 mg, 1.70 mmol) were refluxed in THF (10 mL) for 2 h. The mixture was cooled to 0 °C, 3,5-di-*tert*-butylbenzenesulfonyl chloride (500 mg, 1.73 mmol) in THF (10 mL) was added dropwise. After refluxing for 10 h, the solvent was removed. The residue was taken up in 2 N HCl and the aqueous phase was washed 3 × with Et_2O. After making basic with 2 N NaOH, the aqueous phase was extracted 3 × with Et_2O. The combined organic layers were dried with Na_2SO_4 and the solvents evaporated. The slightly brown powder was washed with MeOH and recrystallized from Et_2O. Colorless solid (300 mg, 39%), m.p. 180−182 °C. $[\alpha]_D$ = 40 (*c* = 0.54, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1370, 1360, 1190 cm^{-1} (S=O). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.07 (s, 18 H, CH_3), 1.79−2.01 (m, 5 H, H4, H5, H^a7, H^b7), 2.19−2.33 (m, 1 H, H3), 2.54−3.40 (m, 5 H, H2, H6, H8), 5.06−5.17 (m, 2 H, H11a, H11b), 5.98 (ddd, ^3J = 16.5, ^3J = 10.8, ^3J = 7.6 Hz, 1 H, H10), 7.14 (m, 1 H, H3′), 7.32 (t, ^4J = 1.8 Hz, 1 H, H4′′), 7.35−7.42 (m, 2 H, H2′′), 7.50−7.58 (m, 1 H, H6′), 7.61−7.69 (m, 1 H, H7′), 7.99 (dd, ^3J = 8.5, ^4J = 0.9 Hz, 1 H, H5′), 8.61 (d, ^3J = 4.5 Hz, 1 H, H2′) ppm. MS (DCI, NH_3): *m*/*z* (%) = 279.6 (100) [cinchonine − OH], 547.4 (12) [MH]. $C_{33}H_{42}N_2O_3S$ (546.8): calcd. C 72.49, H 7.74, N 5.12; found C 72.25, H 7.59, N 5.17.

Enantioselective Decarboxylation of 1−5 (Standard Procedure): The substrates **1**−**5** (0.74 mmol) were stirred with 10 mol % optically active base in abs. THF (9 mL) under nitrogen for 24 h at 70 °C. Conversion was monitored with TLC (SiO_2 plates) using EtOAc as eluent. Compounds **1**−**10** were made visible heating with molybdatophosphoric acid.

The solvent was removed at room temp. and the residue was dissolved in EtOAc (25 mL). 2 N HCl (15 mL) was added in order to remove the base as the hydrochloride. After extraction with EtOAc (3×25 mL), the organic layer was dried with Na_2SO_4 and the solvents evaporated at room temp.

^1H NMR conversion control in [D_6]DMSO: The singlet of the acetyl group of the starting material was compared to that of the product, for **1/6**: δ = 1.86/1.82 ppm, **2/7**: 1.89/1.86 ppm, **3/8**: 1.92/1.78 ppm, **4/9**: 1.86/1.81 ppm, **5/10**: 2.08/1.85 ppm.

GC conditions: Samples with incomplete conversion have to be chromatographed on SiO_2 with EtOAc in order to remove the starting material. For **6, 9** and **10**: Column Restek Rt-β DEX cst (30 m length, 0.32 mm i.d.), injector temp. 260 °C, detector temp. 260 °C (flame ionisation); ethyl *N*-acetylalaninate (**6**): column temp. 115 °C, H_2 pressure 0.7 bar, retention times for enantiomers D/L 10.9/11.7 min; *N*-acetylalanine (**9**): column temp. 170 °C, H_2 pressure 1.4 bar, retention times for enantiomers D/L 5.6/8.7 min; *N*-acetylalaninenitrile (**10**) column temp. 170 °C, H_2 pressure 0.7 bar, retention times 6.3/11.8 min.

For ethyl *N*-acetylvalinate (**7**): Column Macherey−Nagel Lipodex-E (50 m length, 0.25 mm i. d.), injector temp. 260 °C, detector temp. 260 °C (flame ionisation); column temp. 125 °C, He pressure 2 bar, retention times for enantiomers D/L 25.2/27.0 min.

For ethyl *N*-acetylphenylalaninate **(8)**: Column Chrompack Chirasil-Val-L (25 m length, 0.25 mm i. d.), injector temp. 260 °C, detector temp. 260 °C (flame ionisation); column temp. 155 °C, He pressure 1.2 bar, retention times for enantiomers D/L 12.0/13.6 min.

The assignment optical rotation/configuration is based on enantiomerically enriched samples of **6,**[36] **7,**[37] **8**[38] and **9.**[39]

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