# Asymmetric Catalysis, 131[+]
# Naproxen Derivatives by Enantioselective Decarboxylation

**Henri Brunner*[a] and Peter Schmidt[a]**

**Keywords:** Naproxen / Asymmetric catalysis / Decarboxylation / Alkaloids / Epicinchonaalkaloid amides

A new catalytic method to synthesize the important anti-inflammatory agent naproxen [(*S*)-**1**] which has to be used as the (*S*) enantiomer, involves the enantioselective decarboxylation of the 6-methoxynaphth-2-yl derivative **2** of 2-cyanopropionic acid. Compound **2** was stirred in THF at 15 °C with catalytic amounts of chiral bases, which abstracted the carboxyl proton. After decarboxylation, reprotonation of the anion of **6** afforded the enantiomerically enriched naproxen nitrile **6**, which may be hydrolyzed to naproxen. A variety of bases were screened, and cinchona alkaloids were found to give the best enantioselectivities. Thus, with quinidine **10**, up to 34% *ee* was obtained for (*S*)-**6**. The enantiomeric excess could be increased by turning to amides of 9-amino-9-deoxyepicinchona alkaloids. The most successful 2-ethoxybenzamide **31a** of 9-amino-9-deoxyepicinchonine **11** gave up to 71.9% *ee* (*S*)-**6**. Cyclic ethers like THF were suitable solvents, and at a temperature of 15 °C, conversion was quantitative within 24 h in most cases. For high enantioselectivities, 5–10 mol-% of chiral base was sufficient, and the catalyst could be fully recycled after decarboxylation. The model compound 2-cyano-2-phenylpropionic acid (**40**) was decarboxylated with base **31a** to the (*S*) enantiomer of the corresponding nitrile **41** with 60% *ee*.

## Introduction

Naproxen is the international nonproprietary name for (*S*)-2-(6-methoxynaphth-2-yl)propionic acid (Figure 1).[1] It belongs to the group of nonsteroidal anti-inflammatory drugs (NSAID). It was first synthesized by Syntex and has been on the market as a prescription drug since 1972, first as the free acid and later as the sodium salt.[2] The production of naproxen was estimated in 1992 to be about 1000 tons per year. After the patent had expired in 1988 (1993 in the USA), a generic market developed in many countries. Early 1994, the Food and Drug Administration of the United States approved naproxen sodium in a lower dosage as a nonprescription pain reliever; this led to an increasing demand for new production methods for naproxen.

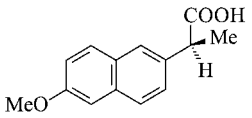
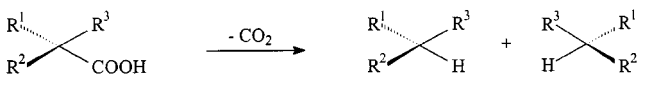



Figure 1. Naproxen, (*S*)-**1**

2-Aryl-substituted propionic acids, such as naproxen, exist in two enantiomeric forms. The (*S*) enantiomer of **1** is about 28 times more effective than the (*R*) enantiomer.[2] For that reason, it is exclusively (*S*)-**1** which is sold and applied. Early production of naproxen involved the synthesis of the racemate, followed by resolution.[3] The resolving agent (−)-cinchonidine was replaced by the more effective *N*-alkyl-D-glucamines.[3] Because of the increasing interest in optically pure 2-arylpropionic acids, strategies have been developed to produce the desired enantiomers directly by asymmetric synthesis.[4,5] Industrial manufacturing methods leading to naproxen include the Zambon process,[6] the catalytic asymmetric hydrocyanation of 6-methoxy-2-vinylnaphthalene (Du Pont),[7,8] and the asymmetric hydrogenation of 2-(6-methoxynaphth-2-yl)propenoic acid (Monsanto).[9−11] In addition, (*S*)-**1** has been prepared by biochemical techniques, such as enantioselective hydrolysis of naproxen derivatives.[12−14] Recently, naproxen diisopropylamide was synthesized in high optical yield by catalytic asymmetric protonation of the corresponding amide enolate.[15,16]

Our approach to the synthesis of 2-aryl-substituted propionic acids is to decarboxylate suitably substituted malonic acids and their monoesters as well as cyanoacetic acids (Scheme 1).




$R^3$ = COOH, COOR, CN

Scheme 1. Decarboxylation of malonic acids, their monoesters and cyanoacetic acids

[+] Part 130: H. Brunner, S. Stefaniak, M. Zabel, *Synthesis*, in press.

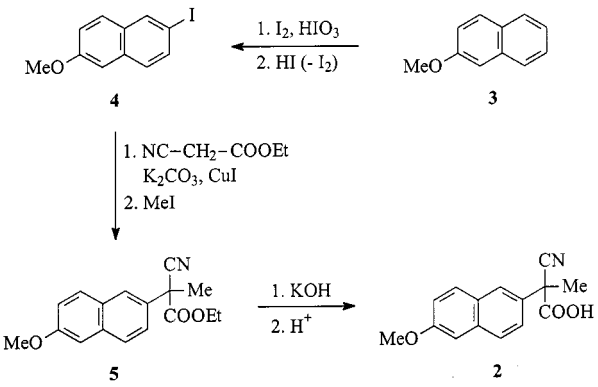
[a] Institut für Anorganische Chemie der Universität, 93040 Regensburg, Germany
Fax: (internat.) + 49-(0)941/943-4439
E-mail: henri.brunner@chemie.uni-regensburg.de

  1434−193X/00/0611−2119 $ 17.50+.50/0 

In the presence of optically active auxiliaries, the decarboxylation of these prochiral substrates should be enantioselective. Already in 1904, Marckwald obtained low enantiomerically enriched 2-methylbutyric acid by heating the brucine salt of ethyl(methyl)malonic acid.[17,18] Until the mid 1980s, few reports had been devoted to enantioselective decarboxylation, all with unsatisfactory results.[19,20] In 1986, Toussaint et al. published the decarboxylation of malonic acids under mild conditions in the presence of $Cu_2O$. Monocarboxylic acids were obtained in nearly quantitative yields and a catalytic cycle involving copper(I) was postulated.[21] The use of a combination of CuCl and cinchona alkaloids led to optical inductions in the resulting monocarboxylic acids.[22] The highest enantiomeric excess of 27% in the decarboxylation of methyl(phenyl)malonic acid was achieved with a substrate/cinchonine/CuCl molar ratio of 1:1.4:0.7. Later it was shown that the amount of CuCl could be reduced significantly, and an increase in the alkaloid concentration raised the optical induction to 36% *ee*.[23] However, only a marginal enantiomeric excess could be obtained with catalytic amounts of alkaloid.[23] After the role of copper(I) in the decarboxylation of malonic acids had been minimized,[23,24,25] further investigations proved that the reaction is not copper(I)-catalyzed, but is induced by bases.[26,27] Thus, decarboxylations with CuCl are much slower than those with $Cu_2O$, which contains the more basic oxide anion. Alkaloids as bases without any additives were able to initiate the decarboxylation. In the decarboxylation of the monoethyl ester of methyl(phenyl)malonic acid, a catalytic amount of alkaloid was sufficient to obtain a reasonable enantiomeric excess. With 10 mol-% cinchonine in THF, 33.8−34.5% *ee* ethyl (*S*)-2-phenylpropionate could be obtained.[26] Enzymatic decarboxylation of 2-(6-methoxynaphth-2-yl)-2-methylmalonic acid, to produce naproxen, has also been attempted. However, only the undesired (*R*)-**1** could be isolated in over 95% *ee*.[28,29] In this paper, we report on our studies concerning the enantioselective decarboxylation of 2-cyano-2-(6-methoxynaphth-2-yl)-propionic acid (**2**).[30,31] The resulting optically active nitrile may then be hydrolyzed to naproxen.[32]

## Synthesis of the Substrate

2-Cyano-2-(6-methoxynaphth-2-yl)propionic acid (**2**) was chosen as the substrate for decarboxylation, because it may be prepared more efficiently than the corresponding malonic acid and its monoethyl ester (Scheme 2). As starting material, readily available 2-methoxynaphthalene (**3**) was used. For the formation of **2**, a halogen substituent in the 6-position had to be introduced first. Published procedures were followed, and **3** was iodinated twice in the 2- and 6-positions, to give the diiodo compound in situ. The halogen substituent *ortho* to the methoxy group was removed by the addition of hydriodic acid, leading to 2-iodo-6-methoxynaphthalene (**4**).[33,34] Disubstitution was necessary because monohalogenation leads exclusively to substitution in the

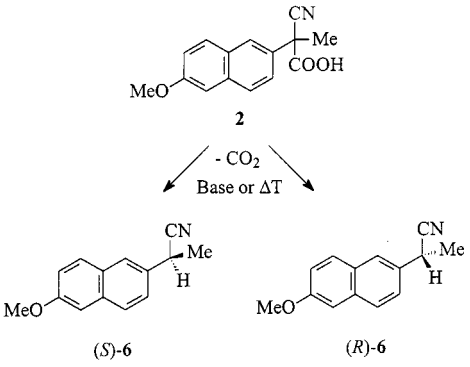



Scheme 2. Preparation of the substrate **2**

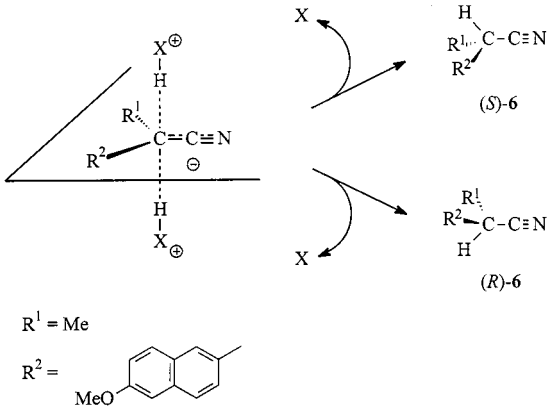
Aryl halides react with carbon nucleophiles, such as anions of active methylene compounds, to form carbon−carbon bonds.[35,36] This copper(I)-catalyzed coupling reaction is best carried out with aryl iodides. Frequently, a stoichiometric amount of copper(I) salt is necessary for reasonable yields.[37] Miura et al. found that the reaction of aryl iodides with certain active methylene compounds proceeds catalytically if DMSO is used as the solvent.[38] Thus, **4** was heated in DMSO with ethyl cyanoacetate and $K_2CO_3$ as base, in the presence of 10 mol-% CuI. After treatment with methyl iodide, the resulting ethyl 2-cyano-2-(6-methoxynaphth-2-yl)propionate (**5**) could be isolated in 70% yield.[38] Under the same reaction conditions, we observed no conversion with diethyl malonate as coupling reagent. After ester hydrolysis of **5**, the substrate 2-cyano-2-(6-methoxynaphth-2-yl)propionic acid (**2**) was obtained in 90% yield. Compound **2** is very sensitive towards decarboxylation. Loss of $CO_2$ occurs immediately if the compound is dissolved in DMSO or acetone. In pure diethyl ether, THF, and dichloromethane, **2** is stable at room temperature for at least 24 hours.

## Enantioselective Decarboxylation of 2

Decarboxylation of **2** leads to 2-(6-methoxynaphth-2-yl)-propionitrile (**6**) which exists in two enantiomeric forms (Scheme 3). If **2** is decarboxylated thermally, a racemic mixture of **6** is obtained.




Scheme 3. Decarboxylation of **2**, leading to nitrile **6**



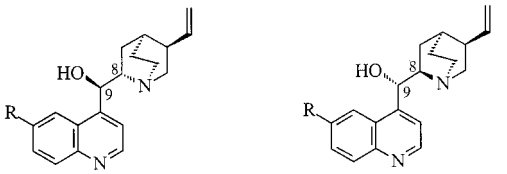

Scheme 4. Protonation of the planar ketenimine anion from the top face or the bottom face, leading to the different enantiomers of nitrile **6**

In the decarboxylation of the anion of **2**, a prochiral intermediate, a planar ketenimine anion, is formed (Scheme 4). An acidic compound $[X-H]^+$ may protonate the carbanionic carbon atom, leading to nitrile **6**. With optically active species $[X-H]^+$, *si* and *re* face protonation should take place at different rates and the enantiomers should be obtained in different quantities. Alkaloids or other nitrogen bases promote the decarboxylation of **2** by abstracting the carboxylic acid proton. In the protonation of the resulting ketenimine anion, the conjugate acids $[X-H]^+$ should act as chiral proton donors.

The enantioselective decarboxylation was carried out by stirring of 170 mg of **2** and 10 mol-% of an optically active base in 10 mL of abs. THF at 15 °C under nitrogen. After 24 h, the solvent was evaporated and the residue was dissolved in ether. The bases were separated and recycled by extraction of the ether phase with dilute hydrochloric acid. The ether was removed and conversion was determined by $^1$H-NMR spectroscopy. Then the reaction product **6** was isolated by column chromatography on silica gel. In most cases, decarboxylation was complete within 24 h. The enantiomeric excess of **6** was determined by gas chromatography.

## Screening of Bases

Previous papers report the use of cinchona alkaloids as suitable bases for the enantioselective decarboxylation.[22,23,26] Thus, the commercially available cinchona alkaloids cinchonidine (**7**), quinine (**8**), cinchonine (**9**) and quinidine (**10**) were applied as catalysts (Figure 2).




R = H: cinchonidine **7**
R = OMe: quinine **8**

R = H: cinchonine **9**
R = OMe: quinidine **10**

Figure 2. The cinchona alkaloids **7**–**10**

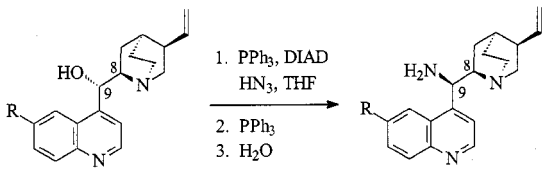
Table 1. Enantiomeric excess of **6** obtained with different bases in the decarboxylation of **2**

| Entry | Base | *ee* [%][a] of **6** | Config. |
|---|---|---|---|
| 1 | **7** | 5.0; 6.0 | (*R*) |
| 2 | **8** | 11.5; 12.7 | (*R*) |
| 3 | **9** | 15.8; 16.5 | (*S*) |
| 4 | **10** | 33.1; 34.0 | (*S*) |
| 5 | **11** | 2.2; 2.3 | (*S*) |
| 6 | **12** | 2.9; 2.9 | (*R*) |
| 7 | **13** | 48.6; 50.9; 51.1 | (*S*) |

[a] Quantitative conversion according to the $^1$H-NMR spectra; enantiomeric excess determined by GC on a Restek Rt-β DEX cst column.

Cinchonidine (**7**) and quinine (**8**) provided (*R*)-**6** in optical yields up to 12.7% *ee* (entries 1,2; Table 1). In contrast, cinchonine (**9**) gave around 16% *ee* (entry 3) and quinidine (**10**) (entry 4) gave up to 34.0% *ee* of the desired (*S*)-**6**. Thus, simultaneous inversion at the carbon atoms C8 and C9 led to a change in the configuration of the decarboxylation product **6**. This is not surprising, as the diastereomers in pairs **7**/**9** and **8**/**10** behave almost like enantiomers.[39,40] Compared to **9**, **10** has an additional methoxy group attached at the quinoline system. This structural detail resulted in an increase in the optical induction, by about 17%. Alkaloids not containing the cinchona alkaloid structure, such as strychnine, brucine and sparteine, were less successful. Even the alkaloid (−)-*N*-methylephedrine, containing the β-amino alcohol structure like that of the cinchona alkaloids, gave only marginal optical inductions.[30,31] Therefore, derivatives of cinchona alkaloids, such as esters and tosylates, have been tested, but the enantiomeric excess of 34.0% obtained with quinidine **10** could not be exceeded.[30,31]

Published procedures were followed to replace the hydroxy group of **9** with an amino function, with simultaneous inversion at C9; this led to 9-amino-9-deoxyepicinchonine (**11**) (Scheme 5).[41,42] We carried out the reaction with **10** similarly and obtained the corresponding 9-amino-9-deoxyepiquinidine (**12**). The key step is a Mitsunobu reaction that leads to the C9-azido compound by an $S_N2$ mechanism. To avoid the isolation of the azide, the reduction was performed in situ, according to Staudinger's method, by adding triphenylphosphane followed by hydrolysis of the intermediate aminophosphorane.[43]




R = H: cinchonine **9**
R = OMe: quinidine **10**

R = H: 9-amino(9-deoxy)epicinchonine **11**
R = OMe: 9-amino(9-deoxy)epiquinidine **12**

Scheme 5. Preparation of the 9-amino-9-deoxyepicinchona alkaloids **11** and **12**

With the free amines **11** and **12**, only low optical inductions were obtained (entries 5, 6; Table 1). Surprisingly, however, the benzamide of **11**, *N*-(9-deoxyepicinchonine-9-

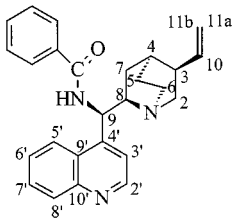
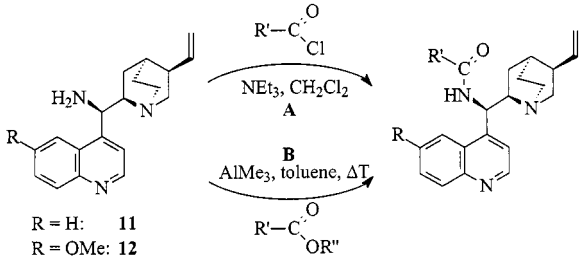


Figure 3. *N*-(9-Deoxyepicinchonine-9-yl)benzamide (**13**)

yl)benzamide[43] (**13**) (Figure 3), induced an enantiomeric excess of up to 51.1% *ee* (entry 7); this indicates that amide **13** is a new leading structure, which gives better optical yields in the enantioselective decarboxylation reaction than the other bases tested before.

## Amides of 11 and 12 as Catalysts

By varying the amide substituents, we tried to increase the enantiomeric excess in the decarboxylation of **2**. For the synthesis of the amides, two methods were applied. Besides the well-known condensation of amines with acid chlorides (method A, Scheme 6), amides were formed by the reaction of amines with trimethylaluminum and carboxylic acid esters (method B).[44] Method B proved to be advantageous, because carboxylic acids too sensitive to give acid chlorides without decomposition can be used as their methyl/ethyl esters, and side products were not observed. In contrast, if the conversion was carried out according to method A, purification by transforming the base into the hydrochloride followed by recrystallization was necessary. The commercial cinchona alkaloids contain small amounts of their dihydro derivatives, which are difficult to separate. However, after the amide formation, it is possible to separate the dihydro compound by column chromatography. Although this purification step decreased the yields considerably, it was carried out in all cases to obtain the pure bases.




Scheme 6. Preparation of amides from amines **11** and **12** and either carboxylic acid chlorides (method A) or trimethylaluminum and carboxylic acid esters (method B)

Most alkaloid derivatives were synthesized with amine **11**, because the Mitsunobu reaction gave **11** in higher yields than **12** and cinchonine (**9**) leading to **11** is less expensive than quinidine (**10**) leading to **12** (Scheme 5). Figure 4 shows all synthesized amides **14a**−**22a**, **24a**−**26a**, **28a**−**31a**, and **31b** from the carboxylic acid chlorides **c** by method A and **23a**, **27a**, **30b**, and **32a**−**35a** from the carboxylic acid esters **d** by method B. The results with all of these bases that gave the desired (*S*) enantiomer of **6** are summarized in Table 2. Compared to the benzamide **13** (entry 7, Table 1), the cyclohexylamide **14a** (entry 8, Table 2) resulted in an enantiomeric excess decrease of about 10%. The 3-phenylpropyl derivative **15a** (entry 9) performed similarly, and the diphenylacetamide **16a** (entry 10) gave slightly better results. The base **17a** contains the (1*S*)-(−)-camphanic acid moiety, which is used for separating racemic alcohols and amines. However, **17a** gave enantiomeric excesses below 10% (entry 11). The coumarin-3-carboxylic acid amide **18a** induced up to 24.3% *ee* (entry 12) and the α-methylcinnamic acid amide **19a** gave up to 51% *ee* (entry 13). Thus, bases with aliphatic or olefinic substituents attached to the amide carbon atom were not able to raise the enantiomeric excess above the 51.1% obtained with the benzamide **13**.

Table 2. Enantiomeric excess of **6** obtained in the decarboxylation of **2** with amides **a** of **11** and **b** of **12**

| Entry | Base | *ee* (*S*) [%][a] of **6** |
|---|---|---|
| 8 | **14a** | 41.0; 41.4 |
| 9 | **15a** | 41.8; 42.3 |
| 10 | **16a** | 43.5; 44.3 |
| 11 | **17a** | 8.8; 9.2 |
| 12 | **18a** | 22.7; 24.3 |
| 13 | **19a** | 50.5; 51.0 |
| 14 | **20a** | 31.3; 32.3 |
| 15 | **21a** | 53.5; 54.1 |
| 16 | **22a** | 41.4; 41.7 |
| 17 | **23a** | 41.6; 43.5 |
| 18 | **24a** | 53.4; 54.0 |
| 19 | **25a** | 45.7; 46.3 |
| 20 | **26a** | 42.2; 43.9 |
| 21 | **27a** | 49.5; 50.4 |
| 22 | **28a** | 42.3; 42.6 |
| 23 | **29a** | 48.1; 48.6 |
| 24 | **30a** | 61.8; 62.2; 63.1; 64.5 |
| 25 | **30b** | 63.1; 64.6 |
| 26 | **31a** | 66.9; 67.1; 70.1; 70.4 |
| 27 | **31b** | 60.3; 61.6 |
| 28 | **32a** | 64.8; 65.5; 70.4; 70.9 |
| 29 | **33a** | 34.0; 34.9 |
| 30 | **34a** | 34.6; 35.0 |
| 31 | **35a** | 23.4; 24.0 |

[a] Quantitative conversion according to the $^1$H-NMR spectra except entry 17 (78 and 80% conversion) and entry 29 (82 and 85% conversion); enantiomeric excess determined by GC on a Restek Rt-β DEX cst column.

To vary the aromatic substituents at the amide carbon atom, the naphthamides of **11** were synthesized first of all. Slightly better optical inductions than with the benzamide **13** were achieved with the 2-naphthamide **21a** (entry 15), whereas with the 1-naphthamide **20a** (entry 14) the enantioselectivity dropped significantly. The ferrocenylcarboxylic acid amide **22a** (entry 16) and the 2-indolcarboxylic acid amide **23a** (entry 17) gave somewhat more than 40% *ee*. The 2-furancarboxamide **24a** afforded up to 54.0% *ee* (entry 18). For investigating the influence of different functional groups on the enantiomeric excess, substituted benzoic acid derivatives were used as amide components. Compared to the benzamide **13** (entry 7), the base **25a** with additional *tert*-butyl groups in the 3- and 5-positions gave less optical induction, around 46% (entry 19), similar to the 2-fluorobenzamide **26a** with an enantiomeric excess of up to 43.9%

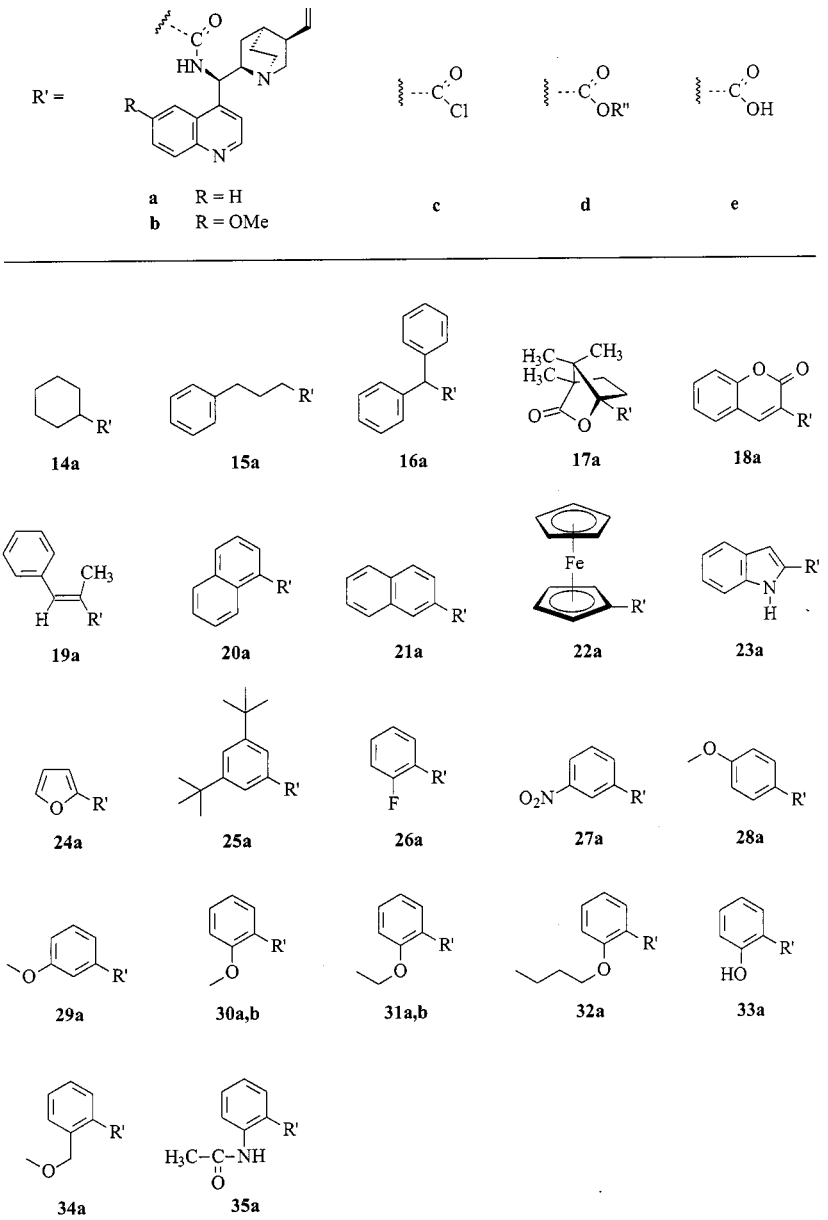



Figure 4. Amides **a** of **11** and **b** of **12**, synthesized according to method A or B, and the carboxylic acid chlorides **c**, carboxylic esters **d**, and carboxylic acids **e**

(entry 20). The results obtained with the 3-nitrobenzamide **27a** (entry 21) were almost identical to that of the unsubstituted benzamide **13**. To study the effect of the same functional group in the *ortho*, *meta*, or *para* position of the phenyl moiety, the three methoxybenzamides **28a**−**30a** were synthesized. The 3-methoxybenzamide **29a** (entry 23) with 48.6% *ee* was superior to the 4-methoxybenzamide **28a** (entry 22) with 42.6% *ee*. However, the best results were achieved with the 2-methoxybenzamide **30a**, which gave 61.8−64.5% *ee* (entry 24). As functional groups in the *ortho* position seemed to be the most successful, the 2-ethoxybenzamide **31a** was synthesized and tested, revealing the highest optical inductions of 66.9−70.4% (entry 26) so far. The 2-butoxybenzamide **32a** with a longer alkoxy chain showed similar, although less reproducible results (entry 28). With the 2-hydroxybenzamide **33a**, the enantioselectivity decreased to 34.0% *ee* (entry 29), probably due to the additional hydroxy proton, which may act as an undesired proton source in the reprotonation of the ketenimine anion. In contrast to the 2-alkoxybenzamides, the 2-(methoxymethyl) derivative **34a**, in which the oxygen atom is not directly bonded to the aromatic ring, yielded only about 35% *ee* (entry 30). The 2-(acetamido)benzamide derivative **35a**, as another variant with a functional group in the 2-position, gave only 24% *ee* (entry 31).

All amides tested so far were synthesized with the amine component 9-amino-9-deoxyepicinchonine (**11**). As pointed out earlier, the enantiomeric excess increased when methoxy-substituted quinidine (**10**) was used instead of unsubstituted cinchonine (**9**). We were interested to find out if the same effect would show up if amides of 9-amino-9-deoxyepiquinidine (**12**) were used as catalysts instead of 9-amino-

9-deoxyepicinchonine (**11**). We therefore synthesized the 2-methoxybenzamide **30b** and 2-ethoxybenzamide **31b** from the quinidine derivative **12**. With the 2-methoxybenzamides **30a** and **30b** analogous results were achieved (entries, 24, 25), whereas the enantiomeric excess obtained with **31b** as the base (entry 27) was about 10% lower than with the corresponding 2-ethoxybenzamide **31a** (entry 26). Thus, in the amide series, an additional methoxy group at the quinoline system did not lead to higher enantioselectivity.

## Testing of Additional Bases

Figure 5 shows additional bases which were tested in the enantioselective decarboxylation reaction. The dihydro alkaloid **36** (entry 32; Table 3), synthesized by hydrogenation of the vinyl derivative **31a**, gave optical inductions comparable to that of the parent compound **31a**; this shows that the double bond is not significant for high enantioselectivity. The cinchona alkaloids and the derivatives discussed in this paper contain two basic nitrogen atoms, the quinoline and the quinuclidine nitrogen atom. As the quinuclidine nitrogen atom is the much more basic one, it should act as proton acceptor and donor exclusively. To find out about the influence of the quinoline nitrogen atom, the mono(arene) *N*-oxide **37** was prepared and tested. The optical inductions obtained with the nonoxidized and oxidized compounds **36** and **37** were basically identical (entries 32, 33). Thus, it can be ruled out that the quinoline nitrogen atom has a significant influence on enantioselective decarboxylation. In contrast to benzamide **13** of **11**, the corresponding phthalimide **38** supplied a nearly racemic decarboxylation product **6**, with a slight excess of the (*R*) enantiomer (entry 34).

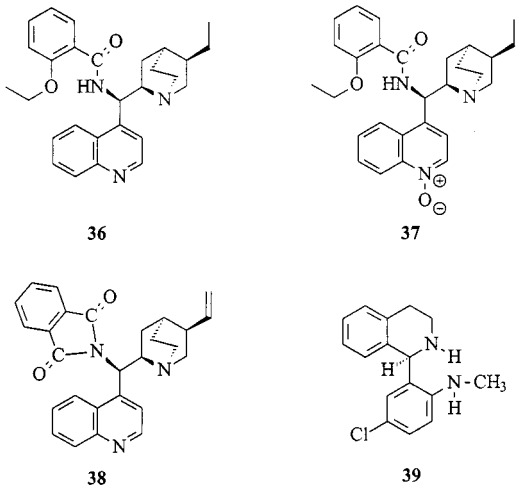



Figure 5. Additional bases tested in the decarboxylation of **2**

Table 3. Enantiomeric excess of **6** obtained in the decarboxylation of **2** with the bases **36**−**39**

| Entry | Base | *ee* [%][a] of **6** | Config. |
|---|---|---|---|
| 32 | **36** | 69.4; 70.3 | (*S*) |
| 33 | **37** | 67.8; 70.5 | (*S*) |
| 34 | **38** | 2.4; 2.7 | (*R*) |
| 35 | **39** | 5.7; 5.8 | (*S*) |

[a] Quantitative conversion according to the $^1$H-NMR spectra; enantiomeric excess determined by GC on a Restek Rt-β DEX cst column.

Compound **39** was used as a base, because the asymmetric protonation of the lithium salt of naproxen diisopropylamide with **39** had given 97% *ee*.[15,16] However, in the enantioselective decarboxylation of **2**, **39** induced less than 6% *ee* (entry 35).

## Variation of the Reaction Conditions and Kinetic Investigations

To increase the enantiomeric excess of around 70% obtained under standard reaction conditions with the 2-alkoxybenzamides of 9-amino-9-deoxyepicinchonine (**11**) and their derivatives **36** and **37**, the reaction conditions were varied, starting with the temperature (Table 4). Thus, the benzamide **13** was stirred with **2** at 5 °C instead of at 15 °C in the standard reaction. As only poor conversions were observed (TLC monitoring) after 15 h, the reaction was continued for 144 h to give complete conversion. Decrease of the temperature to 5 °C resulted in a slightly higher optical induction, of 53.5% (entry 36), than at 15 °C (48.6−51.1% *ee*, entry 7). Analogous tests with the 2-methoxybenzamide **30a** revealed no significant change in the optical induction (entries 24, 37), whereas the enantiomeric excess decreased to 64% with the corresponding 2-ethoxybenzamide **31a** (entries 26, 38). At 10 °C, the enantioselectivities induced by base **31a** were comparable to the results obtained under standard conditions (entries 26, 39); at 20 °C they were a little lower (entries 26, 40). Altogether, the experiments confirm an optimum reaction temperature of 15 °C.

Table 4. Variation of the reaction temperature in the decarboxylation of **2**

| Entry[a] | Base | *T* [°C] | *ee* (*S*) [%][b] of **6** | *t* [h] |
|---|---|---|---|---|
| 36 | **13** | 5 | 53.5 | 144 |
| 37 | **30a** | 5 | 63.5; 65.0 | 95.5 |
| 38 | **31a** | 5 | 63.9; 64.2 | 117 |
| 39 | **31a** | 10 | 66.9; 68.2 | 24 |
| 40 | **31a** | 20 | 65.2; 65.3 | 24 |

[a] Apart from different reaction temperatures and reaction times, the catalyses were carried out according to the standard procedure. − [b] Quantitative conversion according to the $^1$H-NMR spectra after the indicated reaction time; enantiomeric excess determined by GC on a Restek Rt-β DEX cst column.

Subsequently, the standard procedure was modified by changing the base concentration (Table 5). Almost the same optical inductions were obtained with 5 instead of 10 mol-% of **31a**; this indicates that the reaction proceeds with the same enantioselectivity with lower amounts of catalyst (entries 26, 41). On the other hand, an equimolar ratio of substrate **2** and base **31a** did not raise the enantiomeric excess (entries 26, 42). Thus, catalytic amounts of base are sufficient for highly enantioselective decarboxylation.

Table 5. Variation of the base concentration in the decarboxylation of **2**

| Entry[a] | Base | Base concentration [mol-%][b] | *ee* (*S*) [%][c] of **6** |
|---|---|---|---|
| 41 | **31a** | 5 | 66.0; 69.2 |
| 42 | **31a** | 100 | 68.7; 70.5 |

[a] Apart from different base concentrations, the catalyses were carried out according to the standard procedure. – [b] The base concentration is specified in mol-% base in relation to substrate **2**. – [c] Quantitative conversion according to the $^1$H-NMR spectra after 24 h; enantiomeric excess determined by GC on a Restek Rt-β DEX cst column.

For a further optimization of the enantioselective decarboxylation reaction, the quantity and nature of the solvent were changed (Table 6). When **2** was stirred with **31a** in 5 mL instead of in 10 mL (standard) of THF, somewhat lower optical inductions were obtained (entries 26, 43), whereas the results with 20 mL of THF resembled those obtained under standard conditions (entries 26, 44). The addition of one drop of water to the standard 10 mL of THF containing **30a** as a base decreased the enantiomeric excess to 60% (entry 45). The use of argon or air instead of nitrogen as the protective gas proved not to be relevant for the enantioselectivity (entries 26, 46, 47). However, to ensure anhydrous conditions, the catalyses were carried out under nitrogen. In diethyl ether as solvent, base **13** was only partially soluble and after 40 h an optical induction of 25.6% at 23% conversion was obtained (entry 48). Although complete conversion occurred within 20 h in the solvent $CH_3CN$ (clear solution), the enantiomeric excess was only 15.2% *ee* (entry 49). Both **2** and **13** were readily soluble in $CH_2Cl_2$, but even after 40 h reaction time, no decarboxylation was observed (entry 50). Due to the low conversion after 15 h in the reaction of **2** and **13** in dioxane, the temperature was raised to 25 °C. After 49 h, the enantiomeric excess of 55.9% at 91% conversion was 5% *ee* higher than in THF (entries 7, 51). Two of the most successful bases, **30a** and **31a**, were tested in dioxane as well. After complete conversion, almost identical optical inductions of around 66% *ee* were found. Compared to the results obtained in THF, that stands for a higher enantiomeric excess with **30a** (entries 24, 52) and a somewhat lower optical induction with **31a** (entries 26, 53). In tetrahydropyran**,** the enantioselectivity of **31a** was similar to (entry 54) and in 1,3-dioxolane (entry 55) it was lower than in THF (entry 26) or dioxane (entry 51). Because base **31a** was insoluble in furan, the decarboxylation was carried out in a 1:1 mixture of furan and THF; this gave a slight decrease in enantiomeric excess compared to in pure THF (entries 26, 56). Thus, besides THF, other cyclic ethers such as dioxane and tetrahydropyran are suitable solvents for the enantioselective decarboxylation reaction. However, optical inductions could not be increased significantly above 70% *ee*.

Table 6. Variation of solvent quantity and solvent type in the decarboxylation of **2**

| Entry[a] | Base | Solvent | *ee* (*S*) [%][b] of **6** | *t* [h] |
|---|---|---|---|---|
| 43 | **31a** | 5 mL THF | 64.8; 67.3 | 24 |
| 44 | **31a** | 20 mL THF | 68.5; 71.9 | 24 |
| 45 | **30a** | 10 mL THF + 0.025 mL $H_2O$ | 58.9; 60.7 | 24 |
| 46 | **31a** | THF under argon | 67.4; 70.7 | 24 |
| 47 | **31a** | THF p.a., distilled, not $N_2$-saturated | 66.7; 70.7 | 24 |
| 48 | **13** | $Et_2O$ | 25.6 | 40 |
| 49 | **13** | $CH_3CN$ | 15.2 | 20 |
| 50 | **13** | $CH_2Cl_2$ | – | 40 |
| 51 | **13** | 1,4-dioxane | 55.9 | 49 |
| 52 | **30a** | 1,4-dioxane | 65.2; 67.4 | 70 |
| 53 | **31a** | 1,4-dioxane | 65.8; 67.2 | 70 |
| 54 | **31a** | tetrahydropyran | 67.0; 70.9 | 24 |
| 55 | **31a** | 1,3-dioxolane | 57.2; 57.3 | 24 |
| 56 | **31a** | 5 mL THF + 5 mL furan | 63.5; 67.3 | 24 |

[a] Apart from different solvents and solvent quantities, the catalyses were carried out according to the standard procedure except entry 51, where the temperature was raised during the reaction (see text). – [b] Quantitative conversion according to the $^1$H-NMR spectra after the indicated reaction time except entry 48 (23% conversion), entry 50 (no conversion), entry 51 (91% conversion) and entry 56 (87 and 89% conversion); enantiomeric excess determined by GC on a Restek Rt-β DEX cst column.

Not only the decarboxylation product **6**, but also the substrate **2** contains an asymmetric carbon atom. It seemed to be interesting to find out if the decarboxylation of enantiomerically enriched **2** would affect the optical induction in the product **6**. In earlier studies, the ammonium salt of (–)-2-cyanobutyric acid was decarboxylated thermally in various solvents.[45] The configuration of the product and the enantiomeric excess was dependent on the solvent; this was explained with diastereomeric transition states formed by asymmetric solvation or an intimate ion pair.[45] Due to the sensitivity of the cyanopropionic acid **2** towards decarboxylation, resolution of **2** was not attempted. However, it was possible to separate ester **5** into its enantiomers by HPLC. Fractions of 95% *ee* (+)-**5** (first fraction) and 91% *ee* (–)-**5** (second fraction) were obtained.[46] The absolute configurations are unknown. The enantiomerically enriched esters were hydrolyzed to the corresponding acids and the raw materials (without recrystallization) were decarboxylated with base **31a** under standard conditions. The 67.2% *ee* (first fraction) and 64.3% *ee* (second fraction) of (*S*)-**6** were slightly lower than with the racemic substrate **2**. However, after decarboxylation of the recrystallized acids **2**, the enantioselectivities of 66.9% *ee* (first fraction) and 69.9% *ee* (second fraction) did not differ from that of the catalyses carried out with racemic **2**.

A kinetic study was carried out to investigate whether or not the enantioselectivity remains constant during decarboxylation (Figure 6). Aliquots from a twelvefold standard reaction with base **31a** were analyzed after every hour. The

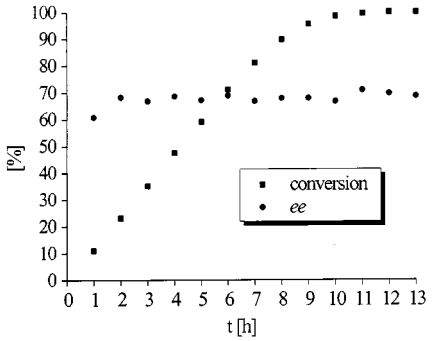


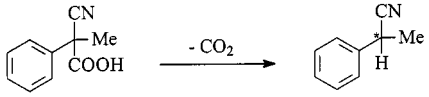

Figure 6. Kinetics of the decarboxylation of **2** with base **31a**

enantioselectivity did not change with time, although the optical induction after one hour seemed a little lower than what it was later.

The plot conversion vs. time was linear for a reaction time of 6 h; this indicates zero-order behavior of acid **2**, with a rate constant of 11.80 $s^{-1}$. Then, the rate decreased. Conversion was complete after a reaction time of 12 h.

## Enantioselective Decarboxylation of 40

The model compound of **2**, 2-cyano-2-phenylpropionic acid (**40**),[38] was decarboxylated, giving 2-phenylpropionitrile (**41**) (Scheme 7). The reaction was carried out with 148 mg of **40**, according to the standard decarboxylation procedure of **2**.




**40** **41**

Scheme 7. Decarboxylation of **40** leading to nitrile **41**

Cinchonine (**9**) led to slightly lower optical inductions in **41** (entry 57; Table 7) than in the naproxen derivative **6** (entry 3; Table 1). Similarly, the 2-alkoxybenzamides **31a**, **32a** and **30b** all gave around 60% *ee* of (*S*)-**41** (entries 58−60).

Table 7. Enantiomeric excess of **41** obtained in the decarboxylation of **40** with **9** and amides **a** of **11** and **b** of **12**

| Entry | Base | *ee* [%][a] of **41** | Config. |
|---|---|---|---|
| 57 | **9** | 12.9; 13.0; 13.2 | (*S*) |
| 58 | **31a** | 60.0; 60.2 | (*S*) |
| 59 | **32a** | 59.5; 59.6 | (*S*) |
| 60 | **30b** | 59.6; 61.1 | (*S*) |

[a] Quantitative conversion according to the $^1$H-NMR spectra; enantiomeric excess determined by GC on a Restek Rt-β DEX cst column.

## Attempted Decarboxylation of 2 with Pyruvate Decarboxylase

An approach to investigate the enantioselective decarboxylation of **2** induced by pyruvate decarboxylase isolated from *Saccharomyces cerevisiae* was undertaken. The cyanopropionic acid **2** proved to be stable for two days in phosphate or citrate buffer (pH = 6.0). The rate of the decarboxylation of pyruvate decreased exponentially with increasing concentration of **2**, which can be defined as a classical reversible inhibitor, because the inhibitory effect is not time-dependent. A plot of pyruvate concentration vs. pyruvate decarboxylation indicates a strong rate decrease with increasing inhibitor concentration. Therefore, **2** acts as a non-competitive inhibitor of pyruvate decarboxylase. Thus, pyruvate decarboxylase does not accept the cyanopropionic acid **2** as a substrate for decarboxylation.

## Conclusion

A new method for synthesizing naproxen derivatives by enantioselective decarboxylation with catalytic amounts of bases, with chiral bases giving optical induction, was established. Thus, 2-cyano-2-(6-methoxynaphth-2-yl)propionic acid (**2**) was decarboxylated with 10 mol-% of cinchona alkaloids as bases, of which quinidine (**10**) afforded the highest enantiomeric excess, of up to 34%. Amides of 9-amino-9-deoxyepicinchonine (**11**) gave improved optical inductions. The best enantioselectivity was obtained with **31a**, the 2-ethoxybenzamide of **11**, which gave up to 71.9% *ee* of (*S*)-**6**. A decrease to 5 mol-% of **31a** did not lower the enantioselectivity considerably, demonstrating the catalytic nature of the reaction. A kinetic study proved that the enantiomeric excess remained constant during the reaction period. As the same enantioselectivity was obtained with enantiomerically enriched **2** and with racemic **2**, the enantioselectivity-determining step must be the protonation of the anion formed in the decarboxylation. The decarboxylation of the model compound 2-cyano-2-phenylpropionic acid (**40**) with the 2-alkoxybenzamide derivatives of **11** gave 60% *ee* in the product **41**. Thus, the enantioselective decarboxylation reaction of substituted 2-cyanopropionic acids is a simple and straightforward reaction. Catalytic amounts of an optically active base are sufficient for obtaining good enantioselectivities; in addition, the catalyst may be fully recycled by extraction.

## Experimental Section

**General Remarks:** NMR spectra: Bruker AC 250 and Bruker ARX 400 (internal TMS). − EI mass spectra: Finnigan MAT 311 A; CI mass spectra: Finnigan MAT 95. − GC: Hewlett−Packard HP 5890 series II equipped with a column Rt-β DEX cst (30 m length, 0.32 mm inner diameter, from Restek); GC integration: Spectra Physics SP 4270 integrator. − Infrared spectra: Beckman IR 4240 and Perkin−Elmer Paragon 1000PC. − Optical rotations: Perkin−Elmer polarimeter 241 (1-dm cell). − Melting points: Büchi SMP 20 (uncorrected values). − For numbering of the alkaloid derivatives see Figure 3.

The carboxylic acid chlorides **14c**−**16c**, **19c**−**21c**, **25c**, and **29c**−**31c** were obtained by reflux of the corresponding acids **e** with distilled $SOCl_2$ for 2 h, followed by distillation in vacuo. For **18c**

and methyl 2-chlorocarbonylbenzoate, the crude acid chloride was used after removal of $SOCl_2$. Compounds **7**, **9**, **14e**, **16e**, **17c**, **20e**, **24c**, **28c**, **30e**, **33d**, $NaN_3$, monomethyl phthalate, $PdCl_2$, and diisopropyl azodicarboxylate were purchased from Merck; **8**, **10**, **29e**, and trimethylaluminum ($c \approx 2$ M in toluene or hexane) were obtained from Fluka; **15e**, **18e**, **19e**, **21e**, **23d**, **25e**, **26c**, **27d**, **30d**, and 3-chloroperoxybenzoic acid were supplied by Aldrich and were used without purification.

Compounds **4**,[33] **5**,[38] **11**,[41,42] **22c**,[47,48] **32d**,[49] **34e**,[50,51] **35d**[52] and the ethyl ester of **40**[38] were prepared as described in the literature. Ester **34d** was synthesized from the silver salt of acid **34e** by esterification with MeI. Diamine **39** was obtained from 1-[5-chloro-2-(methylamino)phenyl]-1,2,3,4-tetrahydroisoquinoline tartrate, purchased from Aldrich.[15] All the standard-condition catalyses were carried out with dried, distilled solvents under nitrogen.

**2-Cyano-2-(6-methoxynaphth-2-yl)propionic Acid (2):** Ethyl 2-cyano-2-(6-methoxynaphth-2-yl)propionate[33,38] (**5**) (5.00 g, 17.6 mmol) was suspended in a solution of KOH (4.95 g, 88.2 mmol) in water (50 mL) and EtOH (12.5 mL). After the mixture was stirred for 24 h, the alcohol was removed in vacuo at room temp. Water was added to fully dissolve the potassium salt and the solution was saturated with NaCl. The water phase was extracted four times with ether (ether extracts discarded) and was then acidified with 2 N $H_2SO_4$ at 0 °C. The product was isolated by being extracted with ether three times; the organic layer was decolorized with charcoal and was dried with $Na_2SO_4$. After the solvent was removed at room temp, the resulting solid was dissolved in ether. Addition of hexane and cooling to −30 °C afforded **18** (4.05 g, 90%) as colorless crystals, m.p. 139−141 °C (dec., $-CO_2$). − IR (KBr): $\tilde{\nu}$ = 2260 (C≡N), 1725 $cm^{-1}$ (C=O). − $^1H$ NMR ($CDCl_3$): δ = 7.97 (d, $^4J$ = 2.0 Hz, 1 H, *H1*), 7.78 (d, $^3J$ = 8.8 Hz, 1 H, *H4*), 7.77 (d, $^3J$ = 9.0 Hz, 1 H, *H8*), 7.55 (dd, $^3J$ = 8.8 Hz, $^4J$ = 2.0 Hz, 1 H, *H3*), 7.20 (dd, $^3J$ = 9.0 Hz, $^4J$ = 2.4 Hz, 1 H, *H7*), 7.13 (d, $^4J$ = 2.4 Hz, 1 H, *H5*), 6.94 (br. s, 1 H, COO*H*), 3.93 (s, 3 H, OC*H*$_3$), 2.06 (s, 3 H, C*H*$_3$). − MS (EI, 70 eV); *m*/*z* (%): 211 $[M - CO_2]^+$ (92). − $C_{15}H_{13}NO_3$ (255.3): calcd. C 70.58, H 5.13, N 5.49; found C 70.56, H 5.16, N 5.51.

**2-Cyano-2-phenylpropionic Acid (40):** Ethyl 2-cyano-2-phenylpropionate[38] (20.00 g, 98.4 mmol) was hydrolyzed in a solution of KOH (16.5 g, 294 mmol) in water (200 mL) and EtOH (50 mL), according to the method for the saponification of **5**. The crude product was purified by filtration through $SiO_2$ with ether. Concentration of the ether solution and addition of pentane gave the title compound at −30 °C as colorless crystals (12.4 g, 72%), m.p. 97−100 °C (dec., $CO_2$). − IR (KBr): $\tilde{\nu}$ = 2240 (C≡N), 1710 $cm^{-1}$ (C=O). − $^1H$ NMR ($CDCl_3$): δ = 7.60−7.52 (m, 2 H, Ar-*H*), 7.48−7.36 (m, 3 H, Ar-*H*), 7.17 (br. s, 1 H, COO*H*), 1.99 (s, 3 H, C*H*$_3$). − MS (CI, $NH_3$); *m*/*z* (%): 193 $[M + NH_4]^+$ (12). − $C_{10}H_9NO_2$ (175.2): calcd. C 68.56, H 5.18, N 8.00; found C 68.43, H 5.22, N 7.96.

**9-Amino-9-deoxyepiquinidine (12):** A solution of hydrazoic acid[53] in benzene (96 mL, 93.1 mmol, 0.97 mol/l) was added at 10 °C under nitrogen to a stirred mixture of quinidine (**10**) (25.0 g, 77.1 mmol) and triphenylphosphane (24.3 g, 92.6 mmol) in abs. THF (400 mL). After 5 min, the reaction mixture was cooled to −5 to −10 °C, and diisopropyl azodicarboxylate (DIAD; 16.5 mL, 17.1 g, 84.8 mmol) in abs. THF (80 mL) was added dropwise. The mixture was stirred for 4 h at room temp. Then triphenylphosphane (20.2 g, 77.1 mmol) in abs. THF (80 mL) was added in one portion. The mixture was heated at 45 °C until gas evolution ceased (approx. 5 h). Water (8 mL) was added and the solution was stirred for another 4 h. The solvents were removed and the residue was dissolved in $CH_2Cl_2$ and 2 N HCl (1:1, 500 mL). After the mixture was vigorously shaken, the aqueous phase was separated and washed with $CH_2Cl_2$ (2 × 100 mL). The water was removed under reduced pressure and the hydrochloride was recrystallized from methanol. The free base was obtained after the salt was dissolved in water, which was neutralized with $Na_2CO_3$ and extracted with $CH_2Cl_2$. Evaporation of the dried ($Na_2CO_3$) organic solvent yielded a yellow residue which was purified by distillation (240 °C, 0.01 Torr) to give a slightly yellow oil (11.5 g, 46%). − $[\alpha]_D^{22}$ = 69 ($c$ = 2.51, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3370, 3290 $cm^{-1}$ (N−H). − $^1H$ NMR ($CDCl_3$): δ = 8.75 (d, $^3J$ = 4.5 Hz, 1 H, *H2′*), 8.03 (d, $^3J$ = 9.2 Hz, 1 H, *H8′*), 7.61 (br. s, 1 H, *H5′*), 7.53 (d, $^3J$ = 4.5 Hz, 1 H, *H3′*), 7.38 (dd, $^3J$ = 9.2 Hz, $^4J$ = 2.7 Hz, 1 H, *H7′*), 5.96−5.82 (m, $^3J$ = 17.1 Hz, $^3J$ = 10.6 Hz, $^3J$ = 6.5 Hz, 1 H, *H10*), 5.12−5.04 (m, 2 H, *H11a*, *H11b*), 4.68 (d, $^3J$ = 9.9 Hz, 1 H, *H9*), 3.97 (s, 3 H, OC*H*$_3$), 3.10−2.90 (m, 5 H, *H2*, *H6*, *H8*), 2.33−2.22 (m, 1 H, *H3*), 2.15 (s, 2 H, N*H*$_2$), 1.61−1.51 (m, 3 H, *H4*, *H5*), 1.19−1.10 (m, 1 H, *H7a*), 1.00−0.88 (m, 1 H, *H7b*). − $^{13}C$ NMR ($CDCl_3$): δ = 157.6 (*C6′*), 147.8 (*C2′*), 147.5 (*C4′*), 144.7 (*C10′*), 140.8 (*C10*), 131.8 (*C8′*), 128.7 (*C9′*), 121.5 (*C7′*), 119.9 (*C3′*), 114.4 (*C11*), 101.6 (*C5′*), 62.4 (*C8*), 55.4 (O*C*H$_3$), 51.8 (*C9*), 49.5 (*C2*), 47.5 (*C6*), 39.4 (*C3*), 27.6 (*C4*), 26.7 (*C5*), 25.0 (*C7*). − MS (EI, 70 eV); *m*/*z* (%): 323 $[M]^+$ (59). − $C_{20}H_{25}N_3O$ (323.4): calcd. C 74.27, H 7.79, N 12.99; found C 73.85, H 7.87, N 12.84.

**General Procedure for the Preparation of the Amides "a" of 11 and "b" of 12**

**Variant A (Amides from Carboxylic Acid Chlorides and Amines):** The 9-amino-9-deoxyepicinchona alkaloid was dissolved in $CH_2Cl_2$ and 7 mL of abs. triethylamine. The carboxylic acid chloride in 4 mL of $CH_2Cl_2$ was added dropwise at 0 °C. After the reaction mixture was stirred for 10 h at room temperature, the organic phase was diluted with $CH_2Cl_2$, washed three times with a half-concentrated $Na_2CO_3$ solution, dried with $Na_2CO_3$ and the solvent was removed.

In most cases, for purification, the hydrochloride was formed: The base was stirred with a fivefold excess of HCl in ethanol for 10 h. The solvent was removed and the hydrochloride was recrystallized. The base was liberated when the salt was dissolved in water, an excess of $Na_2CO_3$ solution was added, and extraction with $CH_2Cl_2$ occurred. Chromatography on silica gel with MeOH as eluent was carried out (column 40 × 6 cm). For further details, see the individual compounds (if filtration through $Al_2O_3$ is described, a Pasteur pipette filled with the adsorbent was used).

**Variant B (Amides from Carboxylic Acid Esters and Amines):** The 9-amino-9-deoxyepicinchona alkaloid was dissolved in abs. toluene under nitrogen. The stirred mixture was treated with a 1.2-fold molar amount of a solution of $AlMe_3$ in toluene or hexane and stirring was continued for 15 min at room temp. (evolution of $CH_4$). Then, a 1.1-fold molar amount (with respect to the alkaloid) of carboxylic acid ester dissolved in toluene was added and the mixture was heated at 80 °C for 10 h. Water (1 mL) was added to the cold solution (gas evolution). Then the mixture was diluted with toluene, filtered, washed with a diluted $Na_2CO_3$ solution, dried ($Na_2CO_3$), and the solvent was removed. For further purification (chromatography) see Variant A.

***N*-(9-Deoxyepicinchonin-9-yl)cyclohexylcarboxamide (14a):** Variant A was followed, with 9-amino-9-deoxyepicinchonine (**11**) (1.00 g, 3.41 mmol) in $CH_2Cl_2$ (18 mL) and cyclohexanecarbonyl chloride (**14c**) (733 mg, 5.00 mmol). The hydrochloride was dissolved in hot MeOH (3 mL) and was treated with acetone (100 mL). Cooling to

−30 °C gave a solid which was recrystallized. The free base was dissolved in ether and filtered through $Al_2O_3$. Colorless powder (630 mg, 46%), m.p. 69−70 °C. − $[\alpha]_D^{22}$ = 196 (*c* = 0.89, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3255 (N−H), 1535 $cm^{-1}$ (amide). − $^1H$ NMR ($CDCl_3$): δ = 8.85 (d, $^3J$ = 4.6 Hz, 1 H, *H2′*), 8.36 (dd, $^3J$ = 8.6 Hz, $^4J$ = 0.8 Hz, 1 H, *H5′*), 8.11 (dd, $^3J$ = 8.4 Hz, $^4J$ = 1.0 Hz, 1 H, *H8′*), 7.73−7.66 (m, 1 H, *H7′*), 7.60−7.53 (m, 1 H, *H6′*), 7.38 (d, $^3J$ = 4.6 Hz, 1 H, *H3′*), 7.04 (br. s, 1 H, CON*H*), 5.91 (ddd, $^3J$ = 17.1 Hz, $^3J$ = 10.5 Hz, $^3J$ = 6.6 Hz, 1 H, *H10*), 5.21 (br. s, 1 H, *H9*), 5.16 (td, $^3J$ = 10.5 Hz, $^3J$ = 1.5 Hz, $^4J$ = 1.5 Hz, 1 H, *H11a*), 5.12 (td, $^3J$ = 17.1 Hz, $^3J$ = 1.5 Hz, $^4J$ = 1.5 Hz, 1 H, *H11b*), 3.00−2.90 (m, 4 H, quinuclidine-*H*), 2.82−2.73 (m, 1 H, quinuclidine-*H*), 2.36−2.24 (m, 1 H, *H3*), 2.20−2.09 (m, 1 H, cyclohexyl-*H*), 1.79−1.10 (m, 14 H, *H4*, *H5*, *H7a*, cyclohexyl-*H*), 0.98−0.87 (m, 1 H, *H7b*). − MS (EI, 70 eV); *m*/*z* (%): 403 $[M]^+$ (47). − $C_{26}H_{33}N_3O$ (403.6): calcd. C 77.38, H 8.24, N 10.41; found C 76.96, H 8.51, N 10.17.

***N*-(9-Deoxyepicinchonin-9-yl)-4-phenylbutyramide (15a):** Variant A was followed, with 9-amino-9-deoxyepicinchonine (**11**) (1.00 g, 3.41 mmol) in $CH_2Cl_2$ (18 mL) and 4-phenylbutyric acid chloride (**15c**) (913 mg, 5.00 mmol). The base was dissolved in ether and filtered through $Al_2O_3$. Colorless powder (830 mg, 55%), m.p. 53−55 °C. − $[\alpha]_D^{22}$ = 180 (*c* = 0.51, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3380 (N−H), 1655, 1515 $cm^{-1}$ (amide). − $^1H$ NMR ($CDCl_3$): δ = 8.85 (d, $^3J$ = 4.5 Hz, 1 H, *H2′*), 8.36 (d, $^3J$ = 8.5 Hz, 1 H, *H5′*), 8.12 (dd, $^3J$ = 8.4 Hz, $^4J$ = 1.1 Hz, 1 H, *H8′*), 7.74−7.67 (m, 1 H, *H7′*), 7.62−7.55 (m, 1 H, *H6′*), 7.38 (d, $^3J$ = 4.5 Hz, 1 H, *H3′*), 7.29−7.11 (m, 5 H, phenyl-*H*), 6.89 (br. s, 1 H, CON*H*), 5.91 (ddd, $^3J$ = 17.1 Hz, $^3J$ = 10.5 Hz, $^3J$ = 6.5 Hz, 1 H, *H10*), 5.29 (br. d, 1 H, *H9*), 5.16 (td, $^3J$ = 10.5 Hz, $^3J$ = 1.5 Hz, $^4J$ = 1.5 Hz, 1 H, *H11a*), 5.11 (td, $^3J$ = 17.1 Hz, $^3J$ = 1.5 Hz, $^4J$ = 1.5 Hz, 1 H, *H11b*), 3.01−2.79 (m, 5 H, *H2*, *H6*, *H8*), 2.58 (t, 2 H, $^3J$ = 7.5 Hz, PhC$H_2$C$H_2$C$H_2$CO), 2.34−2.14 (m, 3 H, *H3*, C$H_2$), 1.95−1.80 (m, 2 H, C$H_2$), 1.64−1.25 (m, 4 H, *H4*, *H5*, *H7a*), 0.98−0.87 (m, 1 H, *H7b*). − MS (EI, 70 eV); *m*/*z* (%): 439 $[M]^+$ (93). − $C_{29}H_{33}N_3O$ (439.6): calcd. C 79.24, H 7.57, N 9.56; found C 78.84, H 7.77, N 9.46.

***N*-(9-Deoxyepicinchonin-9-yl)-2,2-diphenylacetamide (16a):** Variant A was followed, with 9-amino-9-deoxyepicinchonine (**11**) (1.00 g, 3.41 mmol) in $CH_2Cl_2$ (18 mL) and diphenylacetyl chloride (**16c**) (1.15 g, 4.99 mmol). The hydrochloride was dissolved in hot MeOH (4 mL) and was precipitated by the addition of ethyl acetate. After being cooled at −30 °C, a solid was obtained, which was recrystallized. The free base was dissolved in ether and filtered through $Al_2O_3$. Concentration and addition of hexane at −30 °C gave colorless crystals (380 mg, 23%), m.p. 82−84 °C. − $[\alpha]_D^{22}$ = 183 (*c* = 1.04, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3300 (N−H), 1645, 1520 $cm^{-1}$ (amide). − $^1H$ NMR ($CDCl_3$): δ = 8.82 (d, $^3J$ = 4.5 Hz, 1 H, *H2′*), 8.26 (br. d, $^3J$ = 8.4 Hz, 1 H, *H5′*), 8.12 (dd, $^3J$ = 8.5 Hz, $^4J$ = 0.9 Hz, 1 H, *H8′*), 7.73−7.66 (m, 1 H, *H7′*), 7.55−7.49 (m, 1 H, *H6′*), 7.30−7.15 (m, 12 H, *H3′*, CON*H*, phenyl-*H*), 5.89 (ddd, $^3J$ = 17.1 Hz, $^3J$ = 10.5 Hz, $^3J$ = 6.5 Hz, 1 H, *H10*), 5.24 (br. s, 1 H, *H9*), 5.15 (td, $^3J$ = 10.5 Hz, $^3J$ = 1.5 Hz, $^4J$ = 1.5 Hz, 1 H, *H11a*), 5.09 (td, $^3J$ = 17.1 Hz, $^3J$ = 1.5 Hz, $^4J$ = 1.5 Hz, 1 H, *H11b*), 4.93 (s, 1 H, *H*C−CO), 2.92−2.66 (m, 5 H, *H2*, *H6*, *H8*), 2.30−2.21 (m, 1 H, *H3*), 1.62−1.25 (m, 4 H, *H4*, *H5*, *H7a*), 0.98−0.79 (m, 1 H, *H7b*). − MS (EI, 70 eV); *m*/*z* (%): 487 $[M]^+$ (54). − $C_{33}H_{33}N_3O$ (487.6): calcd. C 81.28, H 6.82, N 8.62; found C 81.15, H 7.10, N 8.61.

**(1*S*)-*N*-(9-Deoxyepicinchonin-9-yl)camphanamide (17a):** Variant A was followed, with 9-amino-9-deoxyepicinchonine (**11**) (1.00 g, 3.41 mmol) in $CH_2Cl_2$ (18 mL) and (1*S*)-camphanoyl chloride (**17c**) (900 mg, 4.15 mmol). The base was dissolved in toluene and filtered through $Al_2O_3$. Colorless solid (970 mg, 60%), m.p. 168−170 °C. − $[\alpha]_D^{22}$ = 151 (*c* = 0.61, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3420, 3380 (N−H), 1795 (C=O, camphane), 1680, 1515 $cm^{-1}$ (amide). − $^1H$ NMR ($CDCl_3$): δ = 8.88 (d, $^3J$ = 4.5 Hz, 1 H, *H2′*), 8.34 (d, $^3J$ = 8.3 Hz, 1 H, *H5′*), 8.14 (dd, $^3J$ = 8.4 Hz, $^4J$ = 1.0 Hz, 1 H, *H8′*), 7.80−7.66 (m, 2 H, *H7′*, CON*H*), 7.63−7.57 (m, 1 H, *H6′*), 7.40 (d, $^3J$ = 4.5 Hz 1 H, *H3′*), 5.93 (ddd, $^3J$ = 17.1 Hz, $^3J$ = 10.5 Hz, $^3J$ = 6.5 Hz, 1 H, *H10*), 5.40 (br. s, 1 H, *H9*), 5.15 (td, $^3J$ = 10.5 Hz, $^3J$ = 1.5 Hz, $^4J$ = 1.5 Hz, 1 H, *H11a*), 5.10 (td, $^3J$ = 17.1 Hz, $^3J$ = 1.5 Hz, $^4J$ = 1.5 Hz, 1 H, *H11b*), 3.11−2.68 (m, 5 H, *H2*, *H6*, *H8*), 2.38−2.21 (m, 2 H, *H3*, camphane-*H*), 1.11 (s, 3 H, camphane-C$H_3$), 1.04 (s, 3 H, camphane-C$H_3$), 0.99 (s, 3 H, camphane-C$H_3$), 1.93−0.85 (m, 8 H, *H4*, *H5*, *H7*, 3 camphane-*H*). − MS (EI, 70 eV); *m*/*z* (%): 473 $[M]^+$ (17). − $C_{29}H_{35}N_3O_3$ (473.6): calcd. C 73.54, H 7.45, N 8.87; found C 73.33, H 7.51, N 8.75.

***N*-(9-Deoxyepicinchonin-9-yl)coumarin-3-carboxamide (18a):** Variant A was followed, with 9-amino-9-deoxyepicinchonine (**11**) (1.00 g, 3.41 mmol) in $CH_2Cl_2$ (20 mL) and coumarin-3-carbonyl chloride (**18c**) (1.04 g, 5.00 mmol). The hydrochloride was dissolved in MeOH and precipitated at −30 °C by addition of acetone. The free base was dissolved in $CH_2Cl_2$ and filtered through $Al_2O_3$. Ether was added to the concentrated solution; after approx. 2 weeks at −30 °C, **18a** was obtained as colorless crystals (110 mg, 7%), m.p. 182−184 °C. − $[\alpha]_D^{22}$ = 266 (*c* = 0.31, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3320 (N−H), 1720 (C=O, coumarin), 1660, 1570, 1530 $cm^{-1}$ (amide). − $^1H$ NMR ($CDCl_3$): δ = 9.75 (br. s, 1 H, CON*H*), 8.89 (d, $^3J$ = 4.6 Hz, 1 H, *H2′*), 8.72 (s, 1 H, *H4′′*), 8.44 (d, $^3J$ = 8.4 Hz, 1 H, *H5′*), 8.14 (dd, $^3J$ = 8.3 Hz, $^4J$ = 1.2 Hz, 1 H, *H8′*), 7.76−7.55 (m, 4 H, *H6′*, *H7′*, coumarin-*H*), 7.49 (d, $^3J$ = 4.6 Hz, 1 H, *H3′*), 7.40−7.28 (m, 2 H, coumarin-*H*), 5.92 (ddd, $^3J$ = 17.0 Hz, $^3J$ = 10.7 Hz, $^3J$ = 6.4 Hz, 1 H, *H10*), 5.67 (br. s, 1 H, *H9*), 5.14 (td, $^3J$ = 10.7 Hz, $^3J$ = 1.5 Hz, $^4J$ = 1.5 Hz, 1 H, *H11a*), 5.12 (td, $^3J$ = 17.0 Hz, $^3J$ = 1.5 Hz, $^4J$ = 1.5 Hz, 1 H, *H11b*), 3.20−2.92 (m, 5 H, *H2*, *H6*, *H8*), 2.35−2.25 (m, 1 H, *H3*), 1.65−1.46 (m, 4 H, *H4*, *H5*, *H7a*), 1.04−0.89 (m, 1 H, *H7b*). − MS (EI, 70 eV); *m*/*z* (%): 465 $[M]^+$ (46). − $C_{29}H_{27}N_3O_3$ (465.6): calcd. C 74.82, H 5.85, N 9.03; found C 74.62, H 5.84, N 8.74.

***N*-(9-Deoxyepicinchonin-9-yl)-α-methylcinnamamide (19a):** Variant A was followed, with 9-amino-9-deoxyepicinchonine (**11**) (1.00 g, 3.41 mmol) in $CH_2Cl_2$ (18 mL) and α-methylcinnamoyl chloride (**19c**) (813 mg, 4.50 mmol). The hydrochloride was dissolved in hot MeOH and precipitated at −30 °C by the addition of acetone. The free base was dissolved in ether and was filtered through $Al_2O_3$. Addition of hexane to the concentrated solution and storage at −30 °C afforded a colorless solid (660 mg, 44%), m.p. 70−72 °C. − $[\alpha]_D^{22}$ = 301 (*c* = 0.70, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3290 (N−H), 1650, 1515 $cm^{-1}$ (amide). − $^1H$ NMR ($CDCl_3$): δ = 8.88 (d, $^3J$ = 4.5 Hz, 1 H, *H2′*), 8.42 (d, $^3J$ = 8.5 Hz, 1 H, *H5′*), 8.14 (dd, $^3J$ = 8.3 Hz, $^4J$ = 1.1 Hz, 1 H, *H8′*), 7.75−7.69 (m, 1 H, *H7′*), 7.64−7.58 (m, 1 H, *H6′*), 7.53 (br. s, 1 H, CON*H*), 7.47 (d, $^3J$ = 4.5 Hz, 1 H, *H3′*), 7.37 (q, $^4J$ = 1.4 Hz, 1 H, *H*C=CCH$_3$), 7.37−7.25 (m, 5 H, phenyl-*H*), 5.94 (ddd, $^3J$ = 17.1 Hz, $^3J$ = 10.5 Hz, $^3J$ = 6.5 Hz, 1 H, *H10*), 5.34 (br. d, 1 H, *H9*), 5.18 (td, $^3J$ = 10.5 Hz, $^3J$ = 1.5 Hz, $^4J$ = 1.5 Hz, 1 H, *H11a*), 5.13 (td, $^3J$ = 17.1 Hz, $^3J$ = 1.5 Hz, $^4J$ = 1.5 Hz, 1 H, *H11b*), 3.12−2.81 (m, 5 H, *H2*, *H6*, *H8*), 2.37−2.27 (m, 1 H, *H3*), 2.09 (d, $^4J$ = 1.4 Hz, 3 H, HC=CC$H_3$), 1.67−1.33 (m, 4 H, *H4*, *H5*, *H7a*), 1.03−0.92 (m, 1 H, *H7b*). − MS (EI, 70 eV); *m*/*z* (%): 437 $[M]^+$ (42). − $C_{29}H_{31}N_3O$ (437.6): calcd. C 79.60, H 7.14, N 9.59; found C 79.43, H 7.39, N 9.29.

***N*-(9-Deoxyepicinchonin-9-yl)naphthalene-1-carboxamide (20a):** Variant A was followed, with 9-amino-9-deoxyepicinchonine (**11**) (1.00 g, 3.41 mmol) in $CH_2Cl_2$ (18 mL) and naphthalene-1-carbonyl chloride (**20c**) (953 mg, 5.00 mmol). The hydrochloride was dissolved in hot MeOH (4 mL) and was precipitated at −30 °C by the addition of acetone (100 mL). The free base was filtered through $Al_2O_3$ with ether, concentrated, and crystallized after addition of petroleum ether (40−60 °C) at −30 °C. Colorless solid (540 mg, 35%), m.p. 105−107 °C. − $[\alpha]_D^{22}$ = 145 (*c* = 0.43, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3280 (N−H), 1650, 1515 $cm^{-1}$ (amide). − $^1H$ NMR ($CDCl_3$): δ = 8.92 (d, $^3J$ = 4.5 Hz, 1 H, *H2′*), 8.51 (d, $^3J$ = 8.5 Hz, 1 H, *H5′*), 8.24 (br. s, 1 H, CON*H*), 8.17 (dd, $^3J$ = 8.4 Hz, $^4J$ = 1.2 Hz, 1 H, *H8′*), 7.91−7.81 (m, 2 H, naphthyl-*H*), 7.78−7.72 (m, 1 H, *H7′*), 7.67−7.61 (m, 2 H, *H6′*, naphthyl-*H*), 7.54 (d, $^3J$ = 4.5 Hz, 1 H, *H3′*), 7.56−7.42 (m, 4 H, naphthyl-*H*), 5.98 (ddd, $^3J$ = 17.1 Hz, $^3J$ = 10.5 Hz, $^3J$ = 6.6 Hz, 1 H, *H10*), 5.57 (br. s, 1 H, *H9*), 5.20 (td, $^3J$ = 10.5 Hz, $^3J$ = 1.5 Hz, $^4J$ = 1.5 Hz, 1 H, *H11a*), 5.16 (td, $^3J$ = 17.1 Hz, $^3J$ = 1.5 Hz, $^4J$ = 1.5 Hz, 1 H, *H11b*), 3.16−2.90 (m, 5 H, *H2*, *H6*, *H8*), 2.37−2.28 (m, 1 H, *H3*), 1.69−1.38 (m, 4 H, *H4*, *H5*, *H7a*), 1.09−0.98 (m, 1 H, *H7b*). − MS (EI, 70 eV); *m*/*z* (%): 447 [$M^+$] (23). − $C_{30}H_{29}N_3O$ (447.6): calcd. C 80.51, H 6.53, N 9.39; found C 80.23, H 6.65, N 9.26.

***N*-(9-Deoxyepicinchonin-9-yl)naphthalene-2-carboxamide (21a):** Variant A was followed, with 9-amino-9-deoxyepicinchonine (**11**) (900 mg, 3.07 mmol) in $CH_2Cl_2$ (20 mL) and naphthalene-2-carbonyl chloride (**21c**) (1.00 g, 5.25 mmol). The hydrochloride was dissolved in MeOH/EtOH (1:10) and was precipitated at −30 °C after the addition of acetone. The free base was dissolved in ether and was crystallized after the addition of petroleum ether (40−60 °C) at −30 °C. Colorless solid (310 mg, 23%), m.p. 116−118 °C. − $[\alpha]_D^{22}$ = 316 (*c* = 0.79, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3277 (N−H), 1636, 1533, 1508 $cm^{-1}$ (amide). − $^1H$ NMR ($CDCl_3$): δ = 8.89 (d, $^3J$ = 4.5 Hz, 1 H, *H2′*), 8.49 (d, $^3J$ = 8.5 Hz, 1 H, *H5′*), 8.32 (br. s, 1 H, naphthyl-*H*), 8.15 (dd, $^3J$ = 8.3 Hz, $^4J$ = 1.3 Hz, 1 H, *H8′*), 8.01 (br. s, 1 H, CON*H*), 7.95−7.82 (m, 4 H, naphthyl-*H*), 7.76−7.70 (m, 1 H, *H7′*), 7.66−7.59 (m, 1 H, *H6′*), 7.55 (d, $^3J$ = 4.5 Hz, 1 H, *H3′*), 7.56−7.50 (m, 2 H, naphthyl-*H*), 5.95 (ddd, $^3J$ = 17.1 Hz, $^3J$ = 10.5 Hz, $^3J$ = 6.5 Hz, 1 H, *H10*), 5.47 (br. d, $^3J$ = 10.3 Hz, 1 H, *H9*), 5.19 (td, $^3J$ = 10.5 Hz, $^3J$ = 1.4 Hz, $^4J$ = 1.4 Hz, 1 H, *H11a*), 5.16 (td, $^3J$ = 17.1 Hz, $^3J$ = 1.4 Hz, $^4J$ = 1.4 Hz, 1 H, *H11b*), 3.20−2.83 (m, 5 H, *H2*, *H6*, *H8*), 2.38−2.28 (m, 1 H, *H3*), 1.69−1.39 (m, 4 H, *H4*, *H5*, *H7a*), 1.09−0.97 (m, 1 H, *H7b*). − MS (EI, 70 eV); *m*/*z* (%): 447 [$M]^+$ (22). − $C_{30}H_{29}N_3O$ (447.6): calcd. C 80.51, H 6.53, N 9.39; found C 80.16, H 6.38, N 9.21.

***N*-(9-Deoxyepicinchonin-9-yl)ferrocenecarboxamide (22a):** Variant A was followed, with 9-amino-9-deoxyepicinchonine (**11**) (1.25 g, 4.26 mmol) in $CH_2Cl_2$ (20 mL) and ferrocenecarbonyl chloride (**22c**) (1.06 g, 4.27 mmol). A small amount of charcoal was added to a solution of the base in $CH_2Cl_2$; this was followed by filtration and removal of the solvent. Orange crystals were obtained at −30 °C when a solution of the product in ether/$CH_2Cl_2$ (1:1) was covered with a layer of pentane (1.58 g, 73%), m.p. 193−194 °C. − $[\alpha]_D^{22}$ = 110 (*c* = 0.42, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3240 (N−H), 1630, 1540, 1520 $cm^{-1}$ (amide). − $^1H$ NMR ($CDCl_3$): δ = 8.87 (d, $^3J$ = 4.5 Hz, 1 H, *H2′*), 8.45 (d, $^3J$ = 8.5 Hz, 1 H, *H5′*), 8.13 (dd, $^3J$ = 8.3 Hz, $^4J$ = 1.2 Hz, 1 H, *H8′*), 7.75−7.68 (m, 1 H, *H7′*), 7.65−7.58 (m, 1 H, *H6′*), 7.49 (d, $^3J$ = 4.5 Hz, 1 H, *H3′*), 7.33 (br. s, 1 H, CON*H*), 5.94 (ddd, $^3J$ = 17.1 Hz, $^3J$ = 10.5 Hz, $^3J$ = 6.5 Hz, 1 H, *H10*), 5.34 (br. s, 1 H, *H9*), 5.17 (td, $^3J$ = 10.5 Hz, $^3J$ = 1.5 Hz, $^4J$ = 1.5 Hz, 1 H, *H11a*), 5.12 (td, $^3J$ = 17.1 Hz, $^3J$ = 1.5 Hz, $^4J$ = 1.5 Hz, 1 H, *H11b*), 4.71−4.66 (m, 2 H, ferrocene-*H*), 4.32 (t, $^3J$ = 1.9 Hz, 2 H, ferrocene-*H*), 4.14 (s, 5 H, ferrocene-*H*), 3.20−2.84 (m, 5 H, *H2*, *H6*, *H8*), 2.37−2.27 (m, 1 H, *H3*), 1.68−1.34 (m, 4 H, *H4*, *H5*, *H7a*), 1.05−0.94 (m, 1 H, *H7b*). − MS (EI, 70 eV); *m*/*z* (%): 505 [$M]^+$ (31). − $C_{30}H_{31}FeN_3O$ (505.4): calcd. C 71.29, H 6.18, N 8.31; found C 71.19, H 6.39, N 8.28.

***N*-(9-Deoxyepicinchonin-9-yl)indole-2-carboxamide (23a):** Variant B was followed, with 9-amino-9-deoxyepicinchonine (**11**) (1.28 g, 4.36 mmol) in toluene (15 mL) and ethyl indole-2-carboxylate (**23d**). The base was dissolved in $CH_2Cl_2$ and filtered through $Al_2O_3$. Recrystallization from ether afforded a colorless solid (560 mg, 29%), m.p. 165−167 °C. − $[\alpha]_D^{22}$ = 358 (*c* = 0.34, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3280 (N−H), 1640, 1540, 1515 $cm^{-1}$ (amide). − $^1H$ NMR ($CDCl_3$): δ = 10.05 (br. s, 1 H, N*H*), 8.81 (d, $^3J$ = 4.5 Hz, 1 H, *H2′*), 8.45 (dd, $^3J$ = 8.7 Hz, $^4J$ = 0.8 Hz, 1 H, *H5′*), 8.17 (dd, $^3J$ = 8.4 Hz, $^4J$ = 1.1 Hz, 1 H, *H8′*), 8.04 (br. s, 1 H, N*H*), 7.76−7.69 (m, 1 H, *H7′*), 7.62−7.50 (m, 2 H, *H6′*, indole-*H*), 7.48 (d, $^3J$ = 4.5 Hz 1 H, *H3′*), 7.10−6.99 (m, 2 H, indole-*H*), 6.86 (br. s, 1 H, indole-*H*), 6.67−6.62 (m, 1 H, indole-*H*), 5.95 (ddd, $^3J$ = 17.2 Hz, $^3J$ = 10.5 Hz, $^3J$ = 6.4 Hz, 1 H, *H10*), 5.49 (br. d, 1 H, *H9*), 5.19 (td, $^3J$ = 10.5 Hz, $^3J$ = 1.4 Hz, $^4J$ = 1.4 Hz, 1 H, *H11a*), 5.13 (td, $^3J$ = 17.2 Hz, $^3J$ = 1.4 Hz, $^4J$ = 1.4 Hz, 1 H, *H11b*), 3.18−2.85 (m, 5 H, *H2*, *H6*, *H8*), 2.38−2.28 (m, 1 H, *H3*), 1.70−1.38 (m, 4 H, *H4*, *H5*, *H7a*), 1.06−0.94 (m, 1 H, *H7b*). − MS (EI, 70 eV); *m*/*z* (%): 436 [$M]^+$ (100). − $C_{28}H_{28}N_4O$ (436.6): calcd. C 77.04, H 6.46, N 12.83; found C 76.50, H 6.61, N 12.67.

***N*-(9-Deoxyepicinchonin-9-yl)furan-2-carboxamide (24a):** Variant A was followed, with 9-amino-9-deoxyepicinchonine (**11**) (1.00 g, 3.41 mmol) in $CH_2Cl_2$ (18 mL) and furan-2-carbonyl chloride (**24c**) (653 mg, 5.00 mmol). The base was dissolved in $CH_2Cl_2$ and was filtered through $Al_2O_3$. Colorless solid (980 mg, 74%), m.p. 197−199 °C. − $[\alpha]_D^{22}$ = 317 (*c* = 0.38, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3260 (N−H), 1640 $cm^{-1}$ (amide). − $^1H$ NMR ($CDCl_3$): δ = 8.87 (d, $^3J$ = 4.6 Hz, 1 H, *H2′*), 8.41 (dd, $^3J$ = 8.4 Hz, $^4J$ = 0.9 Hz, 1 H, *H5′*), 8.13 (dd, $^3J$ = 8.4 Hz, $^4J$ = 1.0 Hz, 1 H, *H8′*), 7.75−7.69 (m, 2 H, *H7′*, CON*H*), 7.64−7.57 (m, 1 H, *H6′*), 7.47 (d, $^3J$ = 4.6 Hz, 1 H, *H3′*), 7.47 (dd, $^3J$ = 1.8 Hz, $^4J$ = 0.9 Hz, 1 H, furan-*H*), 6.98 (dd, $^3J$ = 3.5 Hz, $^4J$ = 0.9 Hz, 1 H, furan-*H*), 6.45 (dd, $^3J$ = 3.5 Hz, $^4J$ = 1.8 Hz, 1 H, furan-*H*), 5.92 (ddd, $^3J$ = 17.1 Hz, $^3J$ = 10.6 Hz, $^3J$ = 6.4 Hz, 1 H, *H10*), 5.45 (br. d, 1 H, *H9*), 5.17 (td, $^3J$ = 10.6 Hz, $^3J$ = 1.5 Hz, $^4J$ = 1.5 Hz, 1 H, *H11a*), 5.12 (td, $^3J$ = 17.2 Hz, $^3J$ = 1.5 Hz, $^4J$ = 1.5 Hz, 1 H, *H11b*), 3.17−2.84 (m, 5 H, *H2*, *H6*, *H8*), 2.36−2.26 (m, 1 H, *H3*), 1.79−1.26 (m, 4 H, *H4*, *H5*, *H7a*), 1.04−0.93 (m, 1 H, *H7b*). − MS (EI, 70 eV); *m*/*z* (%): 387 [$M]^+$ (31). − $C_{24}H_{25}N_3O_2$ (387.5): calcd. C 74.39, H 6.50, N 10.84; found C 74.17, H 6.65, N 10.76.

**3,5-Di-*tert*-butyl-*N*-(9-deoxyepicinchonin-9-yl)benzamide (25a):** Variant A was followed, with 9-amino-9-deoxyepicinchonine (**11**) (1.00 g, 3.41 mmol) in $CH_2Cl_2$ (18 mL) and 3,5-di-*tert*-butylbenzoyl chloride (**25c**) (1.07 g, 4.23 mmol). The hydrochloride was dissolved in MeOH and was precipitated at −30 °C by the addition of ether. Recrystallization of the free base from ether afforded a colorless solid (780 mg, 45%), m.p. 209−210 °C. − $[\alpha]_D^{22}$ = 242 (*c* = 0.30, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3320 (N−H), 1630, 1535, 1520 $cm^{-1}$ (amide). − $^1H$ NMR ($CDCl_3$): δ = 8.87 (d, $^3J$ = 4.5 Hz, 1 H, *H2′*), 8.42 (dd, $^3J$ = 8.5 Hz, $^4J$ = 1.0 Hz, 1 H, *H5′*), 8.13 (dd, $^3J$ = 8.3 Hz, $^4J$ = 1.2 Hz, 1 H, *H8′*), 7.88 (br. s, 1 H, CON*H*), 7.75−7.68 (m, 1 H, *H7′*), 7.63 (d, $^4J$ = 1.8 Hz, 2 H, phenyl-*H*), 7.64−7.60 (m, 1 H, *H6′*), 7.56 (t, $^4J$ = 1.8 Hz, 1 H, phenyl-*H*), 7.52 (d, $^3J$ = 4.5 Hz 1 H, *H3′*), 5.94 (ddd, $^3J$ = 17.1 Hz, $^3J$ = 10.6 Hz, $^3J$ = 6.5 Hz, 1 H, *H10*), 5.41 (br. d, 1 H, *H9*), 5.17 (td, $^3J$ = 10.6 Hz, $^3J$ = 1.5 Hz, $^4J$ = 1.5 Hz, 1 H, *H11a*), 5.12 (td, $^3J$ = 17.1 Hz, $^3J$ = 1.5 Hz, $^4J$ = 1.5 Hz, 1 H, *H11b*), 3.16−2.82 (m, 5 H, *H2*, *H6*, *H8*), 2.37−2.27 (m, 1 H, *H3*), 1.68−1.25 (m, 4 H, *H4*, *H5*, *H7a*), 1.33

(s, 18 H, *tert*-butyl-*H*), 1.07−0.94 (m, 1 H, *H7b*). − MS (EI, 70 eV); *m*/*z* (%): 509 $[M]^+$ (37). − $C_{34}H_{43}N_3O$ (509.7): calcd. C 80.12, H 8.50, N 8.24; found C 79.90, H 8.47, N 8.19.

***N*-(9-Deoxyepicinchonin-9-yl)-2-fluorobenzamide (26a):** Variant A was followed, with 9-amino-9-deoxyepicinchonine (**11**) (1.00 g, 3.41 mmol) in $CH_2Cl_2$ (18 mL) and 2-fluorobenzoyl chloride (**26c**) (793 mg, 5.00 mmol). The hydrochloride was dissolved in $CH_2Cl_2$ and was precipitated by the addition of acetone. The free base was filtered through $Al_2O_3$ with ether. Recrystallization from ether gave colorless crystals (590 mg, 42%), m.p. 163−164 °C. − $[\alpha]_D^{22}$ = 294 (*c* = 0.48, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3420 (N−H), 1660, 1510 $cm^{-1}$ (amide). − $^1H$ NMR ($CDCl_3$): δ = 8.88 (d, $^3J$ = 4.5 Hz, 1 H, *H2′*), 8.43 (dd, $^3J$ = 8.4 Hz, $^4J$ = 0.8 Hz, 1 H, *H5′*), 8.29 (br. d, 1 H, CON*H*), 8.14 (dd, $^3J$ = 8.5 Hz, $^4J$ = 1.0 Hz, 1 H, *H8′*), 7.92 (dd, $^3J$ = 7.9 Hz, $^4J$ = 1.9 Hz, 1 H, phenyl-*H*), 7.75−7.69 (m, 1 H, *H7′*), 7.64−7.58 (m, 1 H, *H6′*), 7.50 (d, $^3J$ = 4.5 Hz 1 H, *H3′*), 7.49−7.40 (m, 1 H, phenyl-*H*), 7.21−7.08 (m, 2 H, phenyl-*H*), 5.94 (ddd, $^3J$ = 17.1 Hz, $^3J$ = 10.6 Hz, $^3J$ = 6.5 Hz, 1 H, *H10*), 5.46 (br. s, 1 H, *H9*), 5.17 (td, $^3J$ = 10.6 Hz, $^3J$ = 1.5 Hz, $^4J$ = 1.5 Hz, 1 H, *H11a*), 5.12 (td, $^3J$ = 17.1 Hz, $^3J$ = 1.5 Hz, $^4J$ = 1.5 Hz, 1 H, *H11b*), 3.15−2.83 (m, 5 H, *H2*, *H6*, *H8*), 2.36−2.26 (m, 1 H, *H3*), 1.67−1.34 (m, 4 H, *H4*, *H5*, *H7a*), 1.03−0.87 (m, 1 H, *H7b*). − MS (EI, 70 eV); *m*/*z* (%): 415 $[M]^+$ (55). − $C_{26}H_{26}FN_3O$ (415.5): calcd. C 75.16, H 6.31, N 10.11; found C 74.88, H 6.49, N 10.03.

***N*-(9-Deoxyepicinchonin-9-yl)-3-nitrobenzamide (27a):** Variant B was followed, with 9-amino-9-deoxyepicinchonine (**11**) (1.55 g, 5.28 mmol) in toluene (13 mL) and ethyl 3-nitrobenzoate (**27d**). The base was dissolved in $CH_2Cl_2$ and filtered through $Al_2O_3$. Concentration, and addition of aqueous ether gave slightly yellow crystals at −30 °C (1.04 g, 44%), m.p. 130−132 °C. − $[\alpha]_D^{22}$ = 267 (*c* = 0.61, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3290 (N−H), 1650, 1535 $cm^{-1}$ (amide). − $^1H$ NMR ($CDCl_3$): δ = 8.88 (d, $^3J$ = 4.5 Hz, 1 H, *H2′*), 8.64−8.62 (m, 1 H, phenyl-*H*), 8.42 (d, $^3J$ = 8.5 Hz, 1 H, *H5′*), 8.37−8.32 (m, 1 H, phenyl-*H*), 8.17−8.12 (m, 2 H, *H8′*, phenyl-*H*), 8.01 (br. s, 1 H, CON*H*), 7.78−7.71 (m, 1 H, *H7′*), 7.67−7.58 (m, 2 H, *H6′*, phenyl-*H*), 7.49 (d, $^3J$ = 4.5 Hz 1 H, *H3′*), 5.94 (ddd, $^3J$ = 17.1 Hz, $^3J$ = 10.5 Hz, $^3J$ = 6.5 Hz, 1 H, *H10*), 5.44 (br. d, 1 H, *H9*), 5.20 (td, $^3J$ = 10.5 Hz, $^3J$ = 1.5 Hz, $^4J$ = 1.5 Hz, 1 H, *H11a*), 5.13 (td, $^3J$ = 17.1 Hz, $^3J$ = 1.5 Hz, $^4J$ = 1.5 Hz, 1 H, *H11b*), 3.20−2.80 (m, 5 H, *H2*, *H6*, *H8*), 2.39−2.29 (m, 1 H, *H3*), 1.71−1.36 (m, 4 H, *H4*, *H5*, *H7a*), 1.10−0.98 (m, 1 H, *H7b*). − MS (EI, 70 eV); *m*/*z* (%): 442 $[M - H_2O]^+$ (30). − $C_{26}H_{26}N_4O_3$ $H_2O$ (460.5): calcd. C 67.81, H 6.13, N 12.17; found C 67.46, H 6.28, N 12.05.

***N*-(9-Deoxyepicinchonin-9-yl)-4-methoxybenzamide (28a):** Variant A was followed, with 9-amino-9-deoxyepicinchonine (**11**) (1.00 g, 3.41 mmol) in $CH_2Cl_2$ (18 mL) and 4-methoxybenzoyl chloride (**28c**) (853 mg, 5.00 mmol). The hydrochloride was recrystallized from methanol. Filtration of the free base through $Al_2O_3$ with $CH_2Cl_2$ gave a colorless solid (780 mg, 54%), m.p. 135−137 °C. − $[\alpha]_D^{22}$ = 297 (*c* = 0.64, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3300 (N−H), 1640, 1510 $cm^{-1}$ (amide). − $^1H$ NMR ($CDCl_3$): δ = 8.86 (d, $^3J$ = 4.6 Hz, 1 H, *H2′*), 8.45 (d, $^3J$ = 8.3 Hz, 1 H, *H5′*), 8.13 (dd, $^3J$ = 8.4 Hz, $^4J$ = 1.1 Hz, 1 H, *H8′*), 7.77 (d, $^3J$ = 8.9 Hz, 2 H, phenyl-*H*), 7.80−7.66 (m, 2 H, *H7′*, CON*H*), 7.63−7.57 (m, 1 H, *H6′*), 7.49 (d, $^3J$ = 4.6 Hz 1 H, *H3′*), 6.91 (d, $^3J$ = 8.9 Hz, 2 H, phenyl-*H*), 5.93 (ddd, $^3J$ = 17.2 Hz, $^3J$ = 10.5 Hz, $^3J$ = 6.5 Hz, 1 H, *H10*), 5.40 (br. d, 1 H, *H9*), 5.17 (td, $^3J$ = 10.5 Hz, $^3J$ = 1.5 Hz, $^4J$ = 1.5 Hz, 1 H, *H11a*), 5.12 (td, $^3J$ = 17.2 Hz, $^3J$ = 1.5 Hz, $^4J$ = 1.5 Hz, 1 H, *H11b*), 3.83 (s, 3 H, $OCH_3$), 3.13−2.80 (m, 5 H, *H2*, *H6*, *H8*), 2.36−2.26 (m, 1 H, *H3*), 1.77−1.36 (m, 4 H, *H4*, *H5*, *H7a*), 1.04−0.93 (m, 1 H, *H7b*). − MS (EI, 70 eV); *m*/*z* (%): 427 $[M]^+$ (23). − $C_{27}H_{29}N_3O_2$ (427.6): calcd. C 75.85, H 6.84, N 9.83; found C 75.60, H 7.04, N 9.72.

***N*-(9-Deoxyepicinchonin-9-yl)-3-methoxybenzamide (29a):** Variant A was followed, with 9-amino-9-deoxyepicinchonine (**11**) (1.50 g, 5.11 mmol), in $CH_2Cl_2$ (25 mL) and 3-methoxybenzoyl chloride (**29c**) (1.50 g, 8.79 mmol). The hydrochloride was dissolved in hot methanol and precipitated at −30 °C by the addition of acetone (100 mL). Filtration of the free base through $Al_2O_3$ with ether gave a colorless solid (1.09 g, 50%), m.p. 81−83 °C. − $[\alpha]_D^{22}$ = 281 (*c* = 0.52, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3300 (N−H), 1650, 1520 $cm^{-1}$ (amide). − $^1H$ NMR ($CDCl_3$): δ = 8.86 (d, $^3J$ = 4.5 Hz, 1 H, *H2′*), 8.44 (d, $^3J$ = 8.2 Hz, 1 H, *H5′*), 8.13 (dd, $^3J$ = 8.5 Hz, $^4J$ = 1.0 Hz, 1 H, *H8′*), 7.91 (br. s, 1 H, CON*H*), 7.73−7.69 (m, 1 H, *H7′*), 7.63−7.59 (m, 1 H, *H6′*), 7.48 (d, $^3J$ = 4.5 Hz 1 H, *H3′*), 7.38−7.30 (m, 3 H, phenyl-*H*), 7.03−7.00 (m, 1 H, phenyl-*H*), 5.93 (ddd, $^3J$ = 17.1 Hz, $^3J$ = 10.6 Hz, $^3J$ = 6.5 Hz, 1 H, *H10*), 5.40 (br. s, 1 H, *H9*), 5.16 (td, $^3J$ = 10.6 Hz, $^3J$ = 1.4 Hz, $^4J$ = 1.4 Hz, 1 H, *H11a*), 5.13 (td, $^3J$ = 17.1 Hz, $^3J$ = 1.4 Hz, $^4J$ = 1.4 Hz, 1 H, *H11b*), 3.78 (s, 3 H, $OCH_3$), 3.10−2.82 (m, 5 H, *H2*, *H6*, *H8*), 2.34−2.28 (m, 1 H, *H3*), 1.67−1.36 (m, 4 H, *H4*, *H5*, *H7a*), 1.02−0.95 (m, 1 H, *H7b*). − MS (EI, 70 eV); *m*/*z* (%): 427 $[M]^+$ (27). − $C_{27}H_{29}N_3O_2$ (427.6): calcd. C 75.85, H 6.84, N 9.83; found C 75.82, H 6.92, N 9.57.

***N*-(9-Deoxyepicinchonin-9-yl)-2-methoxybenzamide (30a):** Variant A was followed, with 9-amino-9-deoxyepicinchonine (**11**) (1.00 g, 3.41 mmol), in $CH_2Cl_2$ (18 mL) and 2-methoxybenzoyl chloride (**30c**) (853 mg, 5.00 mmol). The hydrochloride was dissolved in a hot mixture of methanol (0.5 mL) and ethanol (4 mL) and was precipitated at −30 °C by the addition of acetone (100 mL). Filtration of the free base through $Al_2O_3$ (ether), concentration and addition of hexane afforded a colorless solid at −30 °C (700 mg, 48%), m.p. 83−84 °C. − $[\alpha]_D^{22}$ = 318 (*c* = 0.45, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3370, 3300 (N−H), 1655, 1510 $cm^{-1}$ (amide). − $^1H$ NMR ($CDCl_3$): δ = 9.31 (br. s, 1 H, CON*H*), 8.86 (d, $^3J$ = 4.5 Hz, 1 H, *H2′*), 8.45 (dd, $^3J$ = 8.5 Hz, $^4J$ = 0.9 Hz, 1 H, *H5′*), 8.13 (dd, $^3J$ = 8.4 Hz, $^4J$ = 1.0 Hz, 1 H, *H8′*), 7.99 (dd, $^3J$ = 8.2 Hz, $^4J$ = 1.8 Hz, 1 H, phenyl-*H*), 7.74−7.67 (m, 1 H, *H7′*), 7.62−7.55 (m, 1 H, *H6′*), 7.48 (d, $^3J$ = 4.5 Hz 1 H, *H3′*), 7.45−7.38 (m, 1 H, phenyl-*H*), 7.02−6.96 (m, 2 H, phenyl-*H*), 5.94 (ddd, $^3J$ = 17.1 Hz, $^3J$ = 10.5 Hz, $^3J$ = 6.6 Hz, 1 H, *H10*), 5.49 (br. d, 1 H, *H9*), 5.16 (td, $^3J$ = 10.5 Hz, $^3J$ = 1.5 Hz, $^4J$ = 1.5 Hz, 1 H, *H11a*), 5.11 (td, $^3J$ = 17.1 Hz, $^3J$ = 1.5 Hz, $^4J$ = 1.5 Hz, 1 H, *H11b*), 4.00 (s, 3 H, $OCH_3$), 3.15−2.91 (m, 5 H, *H2*, *H6*, *H8*), 2.36−2.25 (m, 1 H, *H3*), 1.67−1.25 (m, 4 H, *H4*, *H5*, *H7a*), 1.01−0.90 (m, 1 H, *H7b*). − MS (EI, 70 eV); *m*/*z* (%): 427 $[M]^+$ (24). − $C_{27}H_{29}N_3O_2$ (427.6): calcd. C 75.85, H 6.84, N 9.83; found C 75.84, H 6.98, N 9.81.

***N*-(9-Deoxyepiquinidin-9-yl)-2-methoxybenzamide (30b):** Variant B was followed, with 9-amino-9-deoxyepiquinidine (**12**) (1.00 g, 3.09 mmol) in toluene (10 mL) and ethyl 2-methoxybenzoate (**30d**). The base was dissolved in ether/$CH_2Cl_2$ (2:1) and was filtered twice through $Al_2O_3$. Colorless solid (560 mg, 40%), m.p. 94−96 °C. − $[\alpha]_D^{22}$ = 335 (*c* = 0.37, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3380, 3310 (N−H), 1660, 1515 $cm^{-1}$ (amide). − $^1H$ NMR ($CDCl_3$): δ = 9.28 (br. s, 1 H, CON*H*), 8.71 (d, $^3J$ = 4.7 Hz, 1 H, *H2′*), 8.03 (dd, $^3J$ = 7.8 Hz, $^4J$ = 1.9 Hz, 1 H, phenyl-*H*), 8.01 (d, $^3J$ = 9.2 Hz, 1 H, *H8′*), 7.69 (d, $^3J$ = 2.7 Hz, 1 H, *H5′*), 7.43 (d, $^3J$ = 4.7 Hz, 1 H, *H3′*), 7.45−7.33 (m, 2 H, *H7′*, phenyl-*H*), 7.03−6.95 (m, 2 H, phenyl-*H*), 5.95 (ddd, $^3J$ = 17.7 Hz, $^3J$ = 10.1 Hz, $^3J$ = 6.2 Hz, 1 H, *H10*), 5.47 (br. d, 1 H, *H9*), 5.17−5.09 (m, 2 H, *H11a*, *H11b*), 3.98 (s, 3 H, $OCH_3$), 3.96 (s, 3 H, $OCH_3$), 3.16−2.98 (m, 5 H, *H2*, *H6*, *H8*), 2.37−2.27 (m, 1 H, *H3*), 1.70−1.69 (m, 1 H, *H4*), 1.59−1.18 (m, 3 H, *H5*, *H7a*), 1.09−0.97 (m, 1 H, *H7b*). − MS (EI, 70 eV); *m*/*z*

(%): 457 $[M]^+$ (16). − $C_{28}H_{31}N_3O_3$ (457.6): calcd. C 73.50, H 6.83, N 9.18; found C 73.21, H 7.11, N 8.98.

***N*-(9-Deoxyepicinchonin-9-yl)-2-ethoxybenzamide (31a):** Variant A was followed, with 9-amino-9-deoxyepicinchonine (**11**) (1.00 g, 3.41 mmol) in $CH_2Cl_2$ (18 mL) and 2-ethoxybenzoyl chloride (**31c**) (830 mg, 4.51 mmol). The base was filtered through $Al_2O_3$ ($CH_2Cl_2$). Two recrystallizations from ether gave colorless crystals (830 mg, 55%), m.p. 137−138 °C. − $[\alpha]_D^{22}$ = 343 (*c* = 1.13, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3350 (N−H), 1705, 1580 $cm^{-1}$ (amide). − $^1H$ NMR ($CDCl_3$): δ = 9.26 (br. s, 1 H, CON*H*), 8.86 (d, $^3J$ = 4.6 Hz, 1 H, *H2′*), 8.48 (dd, $^3J$ = 8.5 Hz, $^4J$ = 1.0 Hz, 1 H, *H5′*), 8.12 (dd, $^3J$ = 8.4 Hz, $^4J$ = 1.1 Hz, 1 H, *H8′*), 8.03 (dd, $^3J$ = 8.0 Hz, $^4J$ = 1.9 Hz, 1 H, phenyl-*H*), 7.74−7.68 (m, 1 H, *H7′*), 7.67−7.56 (m, 1 H, *H6′*), 7.47 (d, $^3J$ = 4.6 Hz, 1 H, *H3′*), 7.42−7.35 (m, 1 H, phenyl-*H*), 6.99−6.93 (m, 2 H, phenyl-*H*), 5.94 (ddd, $^3J$ = 17.1 Hz, $^3J$ = 10.5 Hz, $^3J$ = 6.5 Hz, 1 H, *H10*), 5.53 (br. d, 1 H, *H9*), 5.16 (td, $^3J$ = 10.5 Hz, $^3J$ = 1.5 Hz, $^4J$ = 1.5 Hz, 1 H, *H11a*), 5.11 (td, $^3J$ = 17.1 Hz, $^3J$ = 1.5 Hz, $^4J$ = 1.5 Hz, 1 H, *H11b*), 4.23 (q, $^3J$ = 7.0 Hz, 2 H, $OCH_2CH_3$), 3.16−3.04 (m, 1 H, *H8*), 3.01−2.94 (m, 4 H, *H2*, *H6*), 2.31−2.27 (m, 1 H, *H3*), 1.61 (t, $^3J$ = 7.0 Hz, 3 H, $OCH_2CH_3$), 1.66−1.45 (m, 3 H, *H4*, *H5*), 1.39−1.33 (m, 1 H, *H7a*), 0.97−0.86 (m, 1 H, *H7b*). − MS (EI, 70 eV); *m*/*z* (%): 441 $[M]^+$ (39). − $C_{28}H_{31}N_3O_2$ (441.6): calcd. C 76.16, H 7.08, N 9.52; found C 76.05, H 7.27, N 9.54.

***N*-(9-Deoxyepiquinidin-9-yl)-2-ethoxybenzamide (31b):** Variant A was followed, with 9-amino-9-deoxyepiquinidine (**12**) (1.00 g, 3.09 mmol) in $CH_2Cl_2$ (18 mL) and 2-ethoxybenzoyl chloride (**31c**) (738 mg, 4.00 mmol). The base was dissolved in ether and filtered through $Al_2O_3$. Concentration and cooling to −30 °C gave a colorless solid (690 mg, 47%), m.p. 127−128 °C. − $[\alpha]_D^{22}$ = 357 (*c* = 0.82, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3320 (N−H), 1650, 1510 $cm^{-1}$ (amide). − $^1H$ NMR ($CDCl_3$): δ = 9.26 (br. s, 1 H, CON*H*), 8.71 (d, $^3J$ = 4.6 Hz, 1 H, *H2′*), 8.06 (dd, $^3J$ = 7.8 Hz, $^4J$ = 1.8 Hz, 1 H, phenyl-*H*), 8.01 (d, $^3J$ = 9.2 Hz, 1 H, *H8′*), 7.71 (d, $^3J$ = 2.7 Hz, 1 H, *H5′*), 7.42 (d, $^3J$ = 4.6 Hz, 1 H, *H3′*), 7.40−7.34 (m, 2 H, *H7′*, phenyl-*H*), 6.99−6.93 (m, 2 H, phenyl-*H*), 5.95 (ddd, $^3J$ = 17.0 Hz, $^3J$ = 10.8 Hz, $^3J$ = 6.2 Hz, 1 H, *H10*), 5.53 (br. s, 1 H, *H9*), 5.15−5.10 (m, 2 H, *H11a*, *H11b*), 4.21 (q, $^3J$ = 7.0 Hz, 2 H, $OCH_2CH_3$), 3.97 (s, 3 H, $OCH_3$), 3.08−2.92 (m, 5 H, *H2*, *H6*, *H8*), 2.33−2.27 (m, 1 H, *H3*), 1.70−1.65 (m, 1 H, *H4*), 1.57 (t, $^3J$ = 7.0 Hz, 3 H, $OCH_2CH_3$), 1.54−1.47 (m, 2 H, *H5*), 1.42−1.34 (m, 1 H, *H7a*), 1.02−0.95 (m, 1 H, *H7b*). − MS (EI, 70 eV); *m*/*z* (%): 471 $[M]^+$ (32). − $C_{29}H_{33}N_3O_3$ (471.6): calcd. C 73.86, H 7.05, N 8.91; found C 74.02, H 7.11, N 8.86.

**2-Butoxy-*N*-(9-deoxyepicinchonin-9-yl)benzamide (32a):** Variant B was followed, with 9-amino-9-deoxyepicinchonine (**11**) (922 mg, 3.14 mmol), in toluene (12 mL) and ethyl 2-butoxybenzoate[49] (**32d**). Filtration of the base through $Al_2O_3$ with ether gave a colorless solid (690 mg, 47%), m.p. 53−56 °C. − $[\alpha]_D^{22}$ = 320 (*c* = 0.84, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3370 (N−H), 1650, 1510 $cm^{-1}$ (amide). − $^1H$ NMR ($CDCl_3$): δ = 9.17 (br. s, 1 H, CON*H*), 8.86 (d, $^3J$ = 4.5 Hz, 1 H, *H2′*), 8.49 (d, $^3J$ = 8.5 Hz, 1 H, *H5′*), 8.12 (dd, $^3J$ = 8.4 Hz, $^4J$ = 0.9 Hz, 1 H, *H8′*), 8.04 (dd, $^3J$ = 7.9 Hz, $^4J$ = 1.9 Hz, 1 H, phenyl-*H*), 7.73−7.68 (m, 1 H, *H7′*), 7.62−7.57 (m, 1 H, *H6′*), 7.46 (d, $^3J$ = 4.5 Hz 1 H, *H3′*), 7.42−7.35 (m, 1 H, phenyl-*H*), 6.99−6.93 (m, 2 H, phenyl-*H*), 5.94 (ddd, $^3J$ = 17.1 Hz, $^3J$ = 10.5 Hz, $^3J$ = 6.5 Hz, 1 H, *H10*), 5.58 (br. s, 1 H, *H9*), 5.16 (td, $^3J$ = 10.5 Hz, $^3J$ = 1.3 Hz, $^4J$ = 1.3 Hz, 1 H, *H11a*), 5.12 (td, $^3J$ = 17.1 Hz, $^3J$ = 1.3 Hz, $^4J$ = 1.3 Hz, 1 H, *H11b*), 4.16 (t, $^3J$ = 6.8 Hz, 2 H, $OCH_2CH_2CH_2CH_3$), 3.15−2.94 (m, 5 H, *H2*, *H6*, *H8*), 2.34−2.24 (m, 1 H, *H3*), 2.07−1.87 (m, 2 H, $OCH_2CH_2CH_2CH_3$), 1.69−1.30 (m, 6 H, *H4*, *H5*, *H7a*, $OCH_2CH_2CH_2CH_3$), 1.09 (t, $^3J$ = 7.3 Hz, 3 H, $OCH_2CH_2CH_2CH_3$), 0.98−0.86 (m, 1 H, *H7b*). − MS (EI, 70 eV); *m*/*z* (%): 469 $[M]^+$ (39). − $C_{30}H_{35}N_3O_2$ (469.6): calcd. C 76.73, H 7.51, N 8.95; found C 76.61, H 7.42, N 8.94.

***N*-(9-Deoxyepicinchonin-9-yl)-2-hydroxybenzamide (33a):** Variant B was followed, with 9-amino-9-deoxyepicinchonine (**11**) (1.03 g, 3.51 mmol), in toluene (13 mL) and methyl 2-hydroxybenzoate (**33d**). Filtration of the base through $Al_2O_3$ with $CH_2Cl_2$ and two recrystallizations from ether afforded a colorless solid (450 mg, 31%), m.p. 199−201 °C (dec.). − $[\alpha]_D^{22}$ = 302 (*c* = 0.79, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3400−2600 (O−H), 3280 (N−H), 1655, 1515 $cm^{-1}$ (amide). − $^1H$ NMR ($CDCl_3$): δ = 8.88 (d, $^3J$ = 4.6 Hz, 1 H, *H2′*), 8.38 (dd, $^3J$ = 8.7 Hz, $^4J$ = 1.0 Hz, 1 H, *H5′*), 8.16 (dd, $^3J$ = 8.4 Hz, $^4J$ = 1.1 Hz, 1 H, *H8′*), 8.19−8.00 (br. s, 1 H, CON*H*), 7.78−7.71 (m, 1 H, *H7′*), 7.66−7.60 (m, 1 H, *H6′*), 7.55 (dd, $^3J$ = 7.9 Hz, $^4J$ = 1.4 Hz, 1 H, phenyl-*H*), 7.47 (d, $^3J$ = 4.6 Hz, 1 H, *H3′*), 7.41−7.34 (m, 1 H, phenyl-*H*), 6.93−6.85 (m, 2 H, phenyl-*H*), 5.94 (ddd, $^3J$ = 17.1 Hz, $^3J$ = 10.5 Hz, $^3J$ = 6.5 Hz, 1 H, *H10*), 5.35 (br. d, 1 H, *H9*), 5.20 (td, $^3J$ = 10.5 Hz, $^3J$ = 1.4 Hz, $^4J$ = 1.4 Hz, 1 H, *H11a*), 5.13 (td, $^3J$ = 17.1 Hz, $^3J$ = 1.4 Hz, $^4J$ = 1.4 Hz, 1 H, *H11b*), 3.07−2.78 (m, 5 H, *H2*, *H6*, *H8*), 2.39−2.29 (m, 1 H, *H3*), 1.70−1.39 (m, 4 H, *H4*, *H5*, *H7a*), 1.07−0.97 (m, 1 H, *H7b*). − MS (EI, 70 eV); *m*/*z* (%): 413 $[M]^+$ (100). − $C_{26}H_{27}N_3O_2$ (413.5): calcd. C 75.52, H 6.58, N 10.16; found C 75.15, H 6.72, N 10.11.

***N*-(9-Deoxyepicinchonin-9-yl)-2-(methoxymethyl)benzamide (34a):** Variant B was followed, with 9-amino-9-deoxyepicinchonine (**11**) (1.80 g, 6.13 mmol), in toluene (8 mL) and methyl 2-(methoxymethyl)benzoate[50,51] (**35d**). The base was dissolved in ether and filtered through $Al_2O_3$. Concentration, addition of pentane and cooling to −30 °C gave a colorless powder (810 mg, 30%), m.p. 90−92 °C. − $[\alpha]_D^{22}$ = 177 (*c* = 0.37, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3250 (N−H), 1630, 1540, 1510 $cm^{-1}$ (amide). − $^1H$ NMR ($CDCl_3$): δ = 8.90 (d, $^3J$ = 4.5 Hz, 1 H, *H2′*), 8.49 (dd, $^3J$ = 8.4 Hz, $^4J$ = 0.9 Hz, 1 H, *H5′*), 8.14 (dd, $^3J$ = 8.3 Hz, $^4J$ = 1.2 Hz, 1 H, *H8′*), 8.14 (br. s, 1 H, CON*H*), 7.77−7.70 (m, 1 H, *H7′*), 7.68−7.60 (m, 2 H, *H6′*, phenyl-*H*), 7.49 (d, $^3J$ = 4.5 Hz, 1 H, *H3′*), 7.44−7.31 (m, 3 H, phenyl-*H*), 5.93 (ddd, $^3J$ = 17.1 Hz, $^3J$ = 10.5 Hz, $^3J$ = 6.5 Hz, 1 H, *H10*), 5.65 (br. s, 1 H, *H9*), 5.16 (td, $^3J$ = 10.5 Hz, $^3J$ = 1.5 Hz, $^4J$ = 1.5 Hz, 1 H, *H11a*), 5.14 (td, $^3J$ = 17.1 Hz, $^3J$ = 1.5 Hz, $^4J$ = 1.5 Hz, 1 H, *H11b*), 4.61, 4.52 ($d_{AB}$, $^2J$ = 11.6 Hz, 2 H, $CH_2OCH_3$), 3.37 (s, 3 H, $CH_2OCH_3$), 3.20−2.88 (m, 5 H, *H2*, *H6*, *H8*), 2.34−2.24 (m, 1 H, *H3*), 1.66−1.45 (m, 3 H, *H4*, *H5*), 1.37−1.26 (m, 1 H, *H7a*), 1.07−0.96 (m, 1 H, *H7b*). − MS (EI, 70 eV); *m*/*z* (%): 441 $[M]^+$ (39). − $C_{28}H_{31}N_3O_2$ (441.6): calcd. C 76.10, H 7.08, N 9.52; found C 75.87, H 7.11, N 9.48.

**2-(Acetylamino)-*N*-(9-deoxyepicinchonin-9-yl)benzamide (35a):** Variant B was followed, with 9-amino-9-deoxyepicinchonine (**11**) (1.20 g, 4.09 mmol), in toluene (7 mL) and methyl 2-(acetamido)-benzoate (**34d**). The base was dissolved in $CH_2Cl_2$ and filtered through $Al_2O_3$. Recrystallization from ether gave a colorless solid (690 mg, 37%), m.p. 105−107 °C. − $[\alpha]_D^{22}$ = 187 (*c* = 0.29, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3300 (N−H), 1690, 1645, 1520 $cm^{-1}$ (amide). − $^1H$ NMR ($CDCl_3$): δ = 10.89 (br. s, 1 H, CON*H*), 8.90 (d, $^3J$ = 4.5 Hz, 1 H, *H2′*), 8.56 (dd, $^3J$ = 8.4 Hz, $^4J$ = 0.8 Hz, 1 H, *H5′*), 8.40 (dd, $^3J$ = 8.4 Hz, $^4J$ = 0.5 Hz, 1 H, phenyl-*H*), 8.17 (dd, $^3J$ = 8.4 Hz, $^4J$ = 1.1 Hz, 1 H, *H8′*), 7.99 (br. s, 1 H, CON*H*), 7.78−7.72 (m, 1 H, *H7′*), 7.66−7.60 (m, 2 H, *H6′*, phenyl-*H*), 7.49 (d, $^3J$ = 4.5 Hz 1 H, *H3′*), 7.50−7.43 (m, 1 H, phenyl-*H*), 7.14−7.08 (m, 1 H, phenyl-*H*), 5.96 (ddd, $^3J$ = 17.1 Hz, $^3J$ = 10.5 Hz, $^3J$ = 6.5 Hz, 1 H, *H10*), 5.32 (br. d, 1 H, *H9*), 5.19 (td, $^3J$ = 10.5 Hz, $^3J$ = 1.4 Hz, $^4J$ = 1.4 Hz, 1 H, *H11a*), 5.13 (td, $^3J$ = 17.1 Hz, $^3J$ = 1.4 Hz, $^4J$ = 1.4 Hz, 1 H, *H11b*), 3.11−2.74 (m, 5 H, *H2*, *H6*, *H8*),

2.40−2.27 (m, 1 H, *H3*), 2.04 (s, 3 H, C*H*$_3$), 1.70−1.33 (m, 4 H, *H4*, *H5*, *H7a*), 1.06−0.95 (m, 1 H, *H7b*). − MS (EI, 70 eV); *m*/*z* (%): 454 [M]$^+$ (56). − $C_{28}H_{30}N_4O_2$ (454.6): calcd. C 73.98, H 6.65, N 12.33; found C 73.88, H 6.73, N 12.26.

***N*-(9-Deoxyepidihydrocinchonin-9-yl)-2-ethoxybenzamide (36):** *N*-(9-Deoxyepicinchonin-9-yl)-2-ethoxybenzamide (**30a**) (1.00 g, 2.26 mmol) was dissolved in a mixture of water (10 mL) and conc. HCl (0.6 mL), then $PdCl_2$ (11.8 mg, 0.07 mmol) was added. After being stirred for 1 h under hydrogen pressure (30 bar), the base was liberated by the addition of an excess of $Na_2CO_3$ solution and extraction with $CH_2Cl_2$ (3 × 50 mL). After drying ($Na_2CO_3$) and removal of the solvent, the resulting solid was dissolved in ether/$CH_2Cl_2$ (10:1) and filtered through a Pasteur pipette filled with $Al_2O_3$. Addition of pentane to a solution of the base in ether gave **36** at −30 °C as a colorless solid (710 mg, 71%), m.p. 126−127 °C. − $[\alpha]_D^{22}$ = 321 (*c* = 0.61, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3350 (N−H), 1650, 1510 cm$^{-1}$ (amide). − $^1$H NMR ($CDCl_3$): δ = 9.30 (br. s, 1 H, CON*H*), 8.86 (d, $^3J$ = 4.5 Hz, 1 H, *H2′*), 8.50 (d, $^3J$ = 8.5 Hz, 1 H, *H5′*), 8.13 (dd, $^3J$ = 8.3 Hz, $^4J$ = 1.1 Hz, 1 H, *H8′*), 8.03 (dd, $^3J$ = 8.1 Hz, $^4J$ = 1.9 Hz, 1 H, phenyl-*H*), 7.74−7.67 (m, 1 H, *H7′*), 7.63−7.57 (m, 1 H, *H6′*), 7.48 (d, $^3J$ = 4.5 Hz, 1 H, *H3′*), 7.41−7.34 (m, 1 H, phenyl-*H*), 6.98−6.92 (m, 2 H, phenyl-*H*), 5.51 (br. s, 1 H, *H9*), 4.23 (q, $^3J$ = 7.0 Hz, 2 H, OC*H*$_2$CH$_3$), 3.11−2.85 (m, 5 H, *H2*, *H6*, *H8*), 2.63−2.55 (m, 1 H, *H3*), 1.61 (t, $^3J$ = 7.0 Hz, 3 H, OCH$_2$C*H*$_3$), 1.66−1.22 (m, 6 H, *H4*, *H5*, *H7a*, *H10*), 0.94−0.84 (m, 1 H, *H7b*), 0.89 (t, $^3J$ = 7.1 Hz, 3 H, *H11*). − MS (EI, 70 eV); *m*/*z* (%): 443 [M]$^+$ (40). − $C_{28}H_{33}N_3O_2$ (443.6): calcd. C 75.82, H 7.50, N 9.47; found C 75.67, H 7.55, N 9.47.

***N*-(9-Deoxy-1′-oxyepidihydrocinchonin-9-yl)-2-ethoxybenzamide (37):** *N*-(9-Deoxyepidihydrocinchonin-9-yl)-2-ethoxybenzamide (**36**) (1.45 g, 3.27 mmol), and 3-chloroperoxybenzoic acid (3.45 g, 20.0 mmol) were dissolved in $CHCl_3$ (50 mL) and stirred for 5 d at room temperature. After being filtered and diluted with 100 mL $CHCl_3$, the organic phase was washed with a half-concentrated $Na_2CO_3$ solution (4 × 50 mL) and then dried ($Na_2CO_3$). The residue was purified by chromatography on silica with MeOH (column 30 × 2.5 cm). Filtration through a Pasteur pipette filled with $Al_2O_3$ gave the *N*,*N*′-dioxide (950 mg, 61%), of which 800 mg (1.68 mmol) was dissolved in MeOH (25 mL). Then, $SO_2$ gas was passed through the solution for 3 h, followed by removal of the solvent. After the residue was dissolved in $CH_2Cl_2$, the organic phase was washed with half-concentrated $Na_2CO_3$ solution (3 × 50 mL) and water (1 × 50 mL), the solution was concentrated to approx. 5 mL and filtered through $Al_2O_3$. Two recrystallizations from ether gave 320 mg (41%, with respect to the *N*,*N*′-dioxide) of colorless **37**, m.p. 181−182 °C. − $[\alpha]_D^{22}$ = 321 (*c* = 0.29, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3380 (N−H), 1650, 1570 cm$^{-1}$ (amide). − $^1$H NMR ($CDCl_3$): δ = 9.31 (br. s, 1 H, CON*H*), 8.83 (dd, $^3J$ = 8.3 Hz, $^4J$ = 1.7 Hz, 1 H, *H8′*), 8.54−8.45 (m, 1 H, *H5′*), 8.48 (d, $^3J$ = 6.4 Hz, 1 H, *H2′*), 8.02 (dd, $^3J$ = 8.0 Hz, $^4J$ = 1.9 Hz, 1 H, phenyl-*H*), 7.80−7.68 (m, 2 H, *H6′*, *H7′*), 7.43−7.35 (m, 1 H, phenyl-*H*), 7.38 (d, $^3J$ = 6.4 Hz, 1 H, *H3′*), 7.00−6.94 (m, 2 H, phenyl-*H*), 5.40 (br. s, 1 H, *H9*), 4.29−4.17 (m, 2 H, OC*H*$_2$CH$_3$), 3.08−2.86 (m, 5 H, *H2*, *H6*, *H8*), 2.59−2.51 (m, 1 H, *H3*), 1.60 (t, $^3J$ = 7.0 Hz, 3 H, OCH$_2$C*H*$_3$), 1.63−1.22 (m, 6 H, *H4*, *H5*, *H7a*, *H10*), 1.02−0.91 (m, 1 H, *H7b*), 0.90 (t, $^3J$ = 7.1 Hz, 3 H, *H11*). − MS (EI, 70 eV); *m*/*z* (%): 459 [M]$^+$ (7). − $C_{28}H_{33}N_3O_3$ (459.6): calcd. C 73.18, H 7.24, N 9.14; found C 73.15, H 7.29, N 9.14.

***N*-(9-Deoxyepicinchonin-9-yl)phthalimide (38):** Variant A was followed, with 9-amino-9-deoxyepicinchonine (**11**) (1.00 g, 3.41 mmol), in $CH_2Cl_2$ (18 mL) and methyl 2-(chlorocarbonyl)benzoate (1.19 g, 5.99 mmol). The hydrochloride was dissolved in hot methanol (12 mL) and precipitated at −30 °C by addition of acetone (100 mL). Recrystallization of the free base from methanol gave colorless crystals (790 mg, 55%), m.p. >250 °C. − $[\alpha]_D^{22}$ = 21 (*c* = 0.33, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 1710 cm$^{-1}$ (imide). − $^1$H NMR ($CDCl_3$): δ = 8.97 (d, $^3J$ = 4.6 Hz, 1 H, *H2′*), 8.51 (d, $^3J$ = 8.5 Hz, 1 H, *H5′*), 8.14 (dd, $^3J$ = 8.3 Hz, $^4J$ = 1.2 Hz, 1 H, *H8′*), 8.00 (d, $^3J$ = 4.6 Hz, 1 H, *H3′*), 7.80−7.61 (m, 6 H, *H7′*, *H6′*, phthalyl-*H*), 5.84 (ddd, $^3J$ = 17.2 Hz, $^3J$ = 10.4 Hz, $^3J$ = 6.6 Hz, 1 H, *H10*), 5.12 (td, $^3J$ = 10.4 Hz, $^3J$ = 1.4 Hz, $^4J$ = 1.4 Hz, 1 H, *H11a*), 5.07 (td, $^3J$ = 17.2 Hz, $^3J$ = 1.4 Hz, $^4J$ = 1.4 Hz, 1 H, *H11b*), 3.08−2.79 (m, 5 H, *H2*, *H6*, *H8*), 2.28−2.22 (m, 1 H, *H3*), 1.68−1.44 (m, 4 H, *H4*, *H5*, *H7a*), 1.09−1.04 (m, 1 H, *H7b*). − MS (EI, 70 eV); *m*/*z* (%): 423 [M]$^+$ (65). − $C_{27}H_{25}N_3O_2$ (423.5): calcd. C 76.57, H 5.95, N 9.92; found C 76.49, H 6.04, N 9.88.

**Enantioselective Decarboxylation of 2-Cyano-2-(6-methoxynaphth-2-yl)propionic Acid (2) (Standard Procedure):** 2-Cyano-2-(6-methoxynaphth-2-yl)propionic acid (**2**) (170 mg, 0.67 mmol) and 10 mol-% of optically active base were stirred in abs. THF (10 mL) under nitrogen for 24 h at 15 °C. After removal of the solvent, the residue was dissolved in ether (50 mL) and the base was separated by being shaken with 2 N HCl (50 mL). The organic phase was washed with water (2 × 50 mL) and dried with $Na_2SO_4$. The conversion was determined by $^1$H-NMR analysis (decarboxylation was quantitative in most cases). Chromatography on silica with ether/petroleum ether (40−60 °C) (2:1) afforded the pure product **6** as a colorless solid. The enantiomeric excess was determined by GC.

**Enantioselective Decarboxylation of 2-Cyano-2-phenylpropionic Acid (40) (Standard Procedure):** The reaction was carried out with 148.0 mg (0.84 mmol) of 2-cyano-2-phenylpropionic acid (**40**) according to the decarboxylation of **2** which gave the product **41** as a colorless oil.

**GC Conditions:** 30-m Rt-β DEX cst fused silica capillary column (0.32 mm inner diameter, from Restek), injector temp. 260 °C, detector temp. 260 °C [flame ionisation]; **6** (**41**): column temp. 177 °C (120 °C), $H_2$ pressure 1.0 bar (0.7 bar), retention times for the enantiomers [(*S*)/(*R*)] 24.5/25.5 min (6.7/7.3 min). − $^1$H NMR: Approx. 10 mg dissolved in 0.8 mL of $CDCl_3$, conversion determined by comparison of the singlet of **2** (**40**) at δ = 2.06 (1.99) with the doublet of **6** (**41**) at δ = 1.71 (1.65).

## Acknowledgments

Generous financial support by the Bayerischer Forschungsverbund Katalyse (FORKAT II) and the Hermann-Schlosser-Stiftung (Degussa−Hüls AG) are gratefully acknowledged. We thank Dr. Chris Welch (Regis Technologies Inc., U.S.A.) for the separation of the enantiomers of ester **5** by HPLC. We are grateful to Prof. Dr. Gerhard Hübner and Jonathan Müller (Institut für Biochemie, Martin-Luther-Universität Halle-Wittenberg, Germany) for carrying out the decarboxylation experiments with pyruvate decarboxylase.

[1] C. Giordano, M. Villa, S. Panossian, *Naproxen: Industrial Asymmetric Synthesis*, in *Chirality in Industry* (Eds.: A. N. Collins, G. N. Sheldrake, J. Crosby), Wiley, New York, **1992**, p. 303.

[2] I. T. Harrison, B. Lewis, P. Nelson, W. Rooks, A. Roszkowski, A. Tomolonis, J. H. Fried, *J. Med. Chem.* **1970**, *13*, 203.

[3] G. P. Stahly, R. M. Starrett, *Production Methods for Chiral Non-steroidal Anti-inflammatory Profen Drugs*, in *Chirality in Industry II* (Eds.:A. N. Collins, G. N. Sheldrake, J. Crosby), Wiley, New York, **1997**, p. 22.

[4] J.-P. Rieu, A. Boucherle, H. Cousse, G. Mouzin, *Tetrahedron* **1986**, *42*, 4095 and references therein.
[5] H. R. Sonawane, N. S. Bellur, J. R. Ahuja, D. G. Kulkarni, *Tetrahedron: Asymmetry* **1992**, *3*, 163 and references therein.
[6] C. Giordano, G. Castaldi, S. Cavicchioli, M. Villa, *Tetrahedron* **1989**, *45*, 4243.
[7] T. V. Rajan Babu, A. L. Casalnuovo, *J. Am. Chem. Soc.* **1992**, *114*, 6265.
[8] A. L. Casalnuovo, T. V. Rajan Babu, T. A. Ayers, T. H. Warren, *J. Am. Chem. Soc.* **1994**, *116*, 9869.
[9] T. Ohta, H. Takaya, M. Kitamura, K. Nagai, R. Noyori, *J. Org. Chem.* **1987**, *52*, 3174.
[10] Monsanto Corp. (S. A. Laneman, A. S. C. Chan), US-Pat. 5144050 (Sept. 01, 1992) [*Chem. Abstr.* **1993**, *118*, 147783w].
[11] K. T. Wan, M. E. Davis, *Nature* **1994**, *370*, 449.
[12] Q.-M. Gu, C.-S. Chen, C. J. Sih, *Tetrahedron Lett.* **1986**, *27*, 1763.
[13] F. Effenberger, B. W. Graef, S. Oßwald, *Tetrahedron: Asymmetry* **1997**, *8*, 2749.
[14] M. García, C. del Campo, E. F. Llama, J. M. Sánchez-Montero, J. V. Sinisterra, *Tetrahedron* **1993**, *49*, 8433.
[15] E. Vedejs, N. Lee, S. T. Sakata, *J. Am. Chem. Soc.* **1994**, *116*, 2175.
[16] E. Vedejs, A. W. Kruger, *J. Org. Chem.* **1998**, *63*, 2792.
[17] W. Marckwald, *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 349.
[18] W. Marckwald, *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 1368.
[19] J. Kenyon, W. A. Ross, *J. Chem. Soc.* **1952**, 2307.
[20] L. Verbit, T. R. Halbert, R. B. Patterson, *J. Org. Chem.* **1975**, *40*, 1649.
[21] O. Toussaint, P. Capdevielle, M. Maumy, *Synthesis* **1986**, 1029.
[22] O. Toussaint, P. Capdevielle, M. Maumy, *Tetrahedron Lett.* **1987**, *28*, 539.
[23] H. Brunner, M. Kurzwart, *Monatsh. Chem.* **1992**, *123*, 121.
[24] D. J. Darensbourg, M. W. Holtcamp, B. Khandelwal, J. H. Reibenspies, *Inorg. Chem.* **1994**, *33*, 531.
[25] D. J. Darensbourg, M. W. Holtcamp, B. Khandelwal, K. K. Klausmeyer, J. H. Reibenspies, *Inorg. Chem.* **1995**, *34*, 2389.
[26] H. Brunner, J. Müller, J. Spitzer, *Monatsh. Chem.* **1996**, *127*, 845.
[27] F. Hénin, J. Muzart, M. Nedjma, H. Rau, *Monatsh. Chem.* **1997**, *128*, 1181.
[28] K. Miyamoto, H. Ohta, *J. Am. Chem. Soc.* **1990**, *112*, 4077.
[29] K. Miyamoto, H. Ohta, *Biocatalysis* **1991**, *5*, 49.
[30] P. Schmidt, Diplomarbeit, Universität Regensburg, **1997**.
[31] P. Schmidt, Dissertation, Universität Regensburg, **1999**.
[32] E. K. A. Wolber, C. Rüchardt, *Chem. Ber.* **1991**, *124*, 1667.
[33] W. B. Smith, *J. Org. Chem.* **1985**, *50*, 3649.
[34] In the literature, the reduction of **4** is performed by the addition of hydriodic acid and heating to 65 °C. However, we were not able to remove the halogen substituent at this temperature. Therefore, we carried out the reaction at an oil-bath temperature of 110 °C, at which conversion occurred.
[35] J. Lindley, *Tetrahedron* **1984**, *40*, 1433.
[36] H. Suzuki, Q. Yi, J. Inoue, K. Kusume, T. Ogawa, *Chem. Lett.* **1987**, 887.
[37] R. Ugo, P. Nardi, R. Psaro, D. Roberto, *Gazz. Chim. Ital.* **1992**, *122*, 511.
[38] K. Okuro, M. Furuune, M. Miura, M. Nomura, *J. Org. Chem.* **1993**, *58*, 7606.
[39] G. D. H. Dijkstra, R. M. Kellogg, H. Wynberg, J. S. Svendsen, I. Marko, K. B. Sharpless, *J. Am. Chem. Soc.* **1989**, *111*, 8069.
[40] G. D. H. Dijkstra, R. M. Kellogg, H. Wynberg, *J. Org. Chem.* **1990**, *55*, 6121.
[41] H. Brunner, J. Bügler, B. Nuber, *Tetrahedron: Asymmetry* **1995**, *6*, 1699.
[42] H. Brunner, J. Bügler, *Bull. Soc. Chim. Belg.* **1997**, *106*, 77.
[43] M. Vaultier, N. Knouzi, R. Carrié, *Tetrahedron Lett.* **1983**, *24*, 763.
[44] A. Basha, M. Lipton, S. M. Weinreb, *Tetrahedron Lett.* **1977**, 4171.
[45] D. J. Cram, P. Haberfield, *J. Am. Chem. Soc.* **1961**, *83*, 2354.
[46] The separation was carried out by Dr. Chris Welch, Regis Technologies Inc., Morton Grove, Illinois, U.S.A. with a preparative HPLC column (*S*,*S*) Whelk-O 1 CSP (21.1 mm × 25 cm); mobile phase = 20% 2-propanol/hexane; flow rate = 20 mL/min; detection = UV 350 nm; run time = 16 min; injection: 350 mg/mL in $CH_2Cl_2$ each time; total amount separated: 3.5 g. The enantiopurity of the pooled fractions was determined on a column (*R*,*R*) Whelk-O 1 CSP (4.6 mm × 25 cm); mobile phase = 20% 2-propanol/hexane; flow rate = 2.0 mL/min; detection = UV 254 nm; run time = 5.6 min. First fraction collected: 95% *ee* ($[\alpha]_D^{22} = +30.1$, $c = 0.60$, $CHCl_3$); Second fraction collected: 91% *ee* ($[\alpha]_D^{22} = -26.1$, $c = 0.54$, $CHCl_3$).
[47] P. C. Reeves, *Org. Synth. Coll. Vol.* **1988**, *VI*, 625.
[48] P. L. Pauson, W. E. Watts, *J. Chem. Soc.* **1963**, 2990.
[49] W. J. Coates, B. Connolly, D. Dhanak, S. T. Flynn, A. Worby, *J. Med. Chem.* **1993**, *36*, 1387.
[50] P. R. Jones, *J. Org. Chem.* **1958**, *23*, 1386.
[51] L. L. McCoy, D. Mal, *J. Org. Chem.* **1984**, *49*, 939.
[52] A. Kar, H. C. Gugnani, U. A. Madumere, *Pharmazie* **1980**, *35*, 466.
[53] H. Wolff, *Org. React.* **1946**, *III*, 327.

Received December 21, 1999
[O99682]