Biocatalytic Organic Synthesis of Optically Pure (S)-Scoulerine and Berbine and Benzylisoquinoline Alkaloids

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ABSTRACT: A chemoenzymatic approach for the asymmetric total synthesis of the title compounds is described that employs an enantioselective oxidative C–C bond formation catalyzed by berberine bridge enzyme (BBE) in the asymmetric key step. This unique reaction yielded enantiomerically pure (R)-benzylisoquinoline derivatives and (S)-berbines such as the natural product (S)-scoulerine, a sedative and muscle relaxing agent. The racemic substrates rac-1 required for the biotransformation were prepared in 4–8 linear steps using either a Bischler–Napieralski cyclization or a C1–C9 alkylation approach. The chemoenzymatic synthesis was applied to the preparation of fourteen enantiomerically pure alkaloids, including the natural products (S)-scoulerine and (R)-reticuline, and gave overall yields of up to 20% over 5–9 linear steps.

INTRODUCTION

Benzylisoquinolines and berbines are two closely related classes of alkaloids encompassing more than 100 known structures. Both alkaloid families are associated with a broad range of biological activities: Many 1-benzyl-1,2,3,4-tetrahydroisoquinolines act as antispasmodic or hypotensive and some, such as norcoclaurine, coclaurine, and N-methylcoclaurine, possess anti-HIV activity in vitro. Berbines show diverse biological activities such as analgesic, sedative, hypnotic, or anti-inflammatory effects, and the non-natural derivative l-chloroscoulerine is currently investigated as a novel treatment of schizophrenia. In addition, tetrahydroisoquinolines have recently been employed as chiral ligands for metal-catalyzed transfer-hydrogenation.

Because of their biological significance, benzylisoquinolines and berbines have been targets for organic synthesis for a long time, and their asymmetric synthesis has been achieved by many different strategies. However, a large number of steps and harsh reaction conditions are often required, resulting in limited overall yields and ee values. Furthermore, among the published procedures only few catalytic processes are found, with metal-catalyzed asymmetric hydrogenation, intramolecular allylic amination or amidation, and various metal- or organocatalyzed asymmetric alkylation reactions representing the most notable exceptions. Despite the impressive progress in these areas, enantiomerically pure (ee > 99%) substances are rarely obtained. On the other hand, optically pure benzylisoquinoline and berbine alkaloids are produced by a number of plants belonging mainly to the Berberidaceae and Papaveraceae families. However, isolation of the natural products is cumbersome, and biotransformations using plant cell cultures afford minute amounts only. The production of benzylisoquinolines and related alkaloids from the morphine and sanguinarine pathways using recombinant enzymes in Escherichia coli and Saccharomyces cerevisiae has recently been reported, but conversions were rather low (<15%) in these fermentative processes and product isolation was not reported. In addition, this approach is limited to a small number of target molecules and is therefore not as flexible as chemical and biocatalytic synthetic methods.

Biocatalytic steps in organic synthesis have already proven to be an efficient, highly stereoselective and flexible option in the preparation of many target compounds. Of special interest are C–C bond-forming enzymes to set up the carbon framework of the organic molecules. Berberine bridge enzyme (BBE) represents an outstanding biocatalyst enabling an aerobic oxidative C–C bond formation transforming benzylisoquinolines to berbines. BBE catalyzes the first committed step in the benzophenanidine, protobberine, and protopine biosynthesis pathways in plants as it converts (S)-reticuline to (S)-scoulerine by intramolecular C–C coupling, forming the so-called “berberine bridge” (Scheme 1).

This transformation takes place via oxidative C–H activation of the substrate’s N-methyl group at the expense of molecular oxygen, a reaction unparalleled in organic synthesis. BBE from Eschscholzia californica (California poppy) has been heterologously expressed in Pichia pastoris, and its X-ray crystal structure and molecular mechanism have been solved.

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Recently, it has been shown that BBE accepts also non-natural substrates, whereby it transforms exclusively the (S)-enantiomer of racemic benzylisoquinolines to optically pure (S)-berbines. Since this reaction represents a highly enantioselective kinetic resolution, it provides access to the remaining optically pure (R)-substrates as well.19

In the present paper, we demonstrate the broad applicability of the enzyme to establish a novel synthetic route to optically pure (S)-berbines and (R)-benzylisoquinolines, including the first asymmetric total synthesis of naturally occurring (S)-scoulerine.

RESULTS AND DISCUSSION

The synthesis of racemic 1-substituted tetrahydroisoquinolines 1 usually relies on one out of three different strategies: (i) formation of the C1–C8a bond of the isoquinoline core employing either the Pictet–Spengler20 or the Bischler–Napieralski21 cyclization, (ii) alkylation at position C1 of the isoquinoline via nucleophilic or electrophilic activation,22 and (iii) formation of the C4–C4a bond by a Pomeranz–Fritsch reaction (Scheme 2).23 The first two approaches are particularly appealing since the target molecule is disconnected at central bonds leading to simple starting materials. We focused first on the Bischler–Napieralski cyclization of amides 3a–g, since it offers a broad scope and mild reaction conditions. Therefore, the N-methylphenethylamines 4a–g and phenylacetic acid derivatives 5a and 5f were needed for synthesis of the amides 3a–g used as educts in the cyclization reaction.

Although N-methyl-(3,4-dimethoxyphenyl)ethyamine (N-methylhomoveratrylamine) 4a as well as N-methylphenethylamine 4g were commercially available, all other phenethylamines had to be synthesized. Compounds 4b–d were prepared from the corresponding phenylacetic acid derivatives 6b–d via conversion into the N-methylamides 7b–d followed by reduction (Scheme 3). The latter transformation was first attempted employing LiAlH4 as reducing agent; however, only incomplete conversion was achieved even with a 3-fold excess of LiAlH4 and prolonged reaction time under reflux heating (48 h). Fortunately, borane proved to be more efficient: the reduction of 7b with BH3·THF led to full conversion as judged by TLC and GC–MS, giving 4b in 72% isolated yield.

Compound 4e was obtained starting from cheap and readily available vanillin 8.24 Benzylation followed by Henry-reaction with nitromethane and LiAlH4-reduction afforded the primary amine derivative 9 in 47% overall yield (Scheme 3). In a first trial, the amine 9 was reacted with acid chloride 5a to give the corresponding amide. N-Methylation of this compound was attempted following a published procedure,25 but unfortunately alkylation occurred not only at the nitrogen but also on the R-carbon of the amide, giving an undesired dimethylated product in 72% yield. In a second trial, cyclization of the secondary amide formed from 9 and 5a led to the desired tetrahydroisoquinoline; however, N-methylation employing methyl iodide in the presence of sodium hydride and triethylamine26 did not lead to any conversion. Finally, the third attempt was successful: the monomethylation of 9 was performed prior to amide formation via conversion into a carbamate and LiAlH4 reduction, giving the desired N-methylphenethylamine derivative 4e in 66% yield.

For the preparation of the phenylacetic acid building blocks two different approaches were investigated. Compound 5a was obtained from 3-hydroxyphenylacetic acid by selective monobenzylation.

Scheme 1. C–C Bond Formation Leading to (S)-Scoulerine Catalyzed by Berberine Bridge Enzyme (BBE)

![Scheme 1](attachment:image1.png)

Scheme 2. Strategies for the Construction of 1-Substituted 1,2,3,4-Tetrahydroisoquinolines

![Scheme 2](attachment:image2.png)
of the dianion.\textsuperscript{27} 3-Benzyloxy-4-methoxyphenylacetic acid \textit{5f} was also obtained by this method, requiring the commercially accessible acid \textit{12} as starting material. Alternatively, \textit{5f} was synthesized from isovanillin \textit{10} in a three-step sequence involving one-carbon homologation via the \(\alpha\)-trichloromethylcarbinol \textit{11} (Scheme 4).\textsuperscript{28}

With the required building blocks (4 and 5) in hand, amide coupling was performed. The carboxylic acids 5 were converted
into the corresponding acyl chlorides using oxalyl dichloride in toluene and connected with the amines under Schotten–Baumann conditions. Amides 3a–g were obtained in yields ranging from 63% to 97%. The best results were generally obtained when the acyl chloride was applied in slight excess.

Next, the Bischler–Napieralski cyclization of these amides was investigated to obtain the corresponding racemic tetrahydroisoquinolines 1. A broad range of reagents, employed in a wide variety of solvents, has been reported to effect this transformation.21

Table 1. Overall Yields of Chemical Route to Racemic Tetrahydroisoquinolines rac-1a–g

| Product | Structure | Steps (linear) | Overall Yield [%] |
|---------|-----------|----------------|-------------------|
| rac-1a  | ![Structure](image1) | 5 (5) | 40 |
| rac-1b  | ![Structure](image2) | 8 (6) | 42 |
| rac-1c  | ![Structure](image3) | 8 (6) | 28 |
| rac-1d  | ![Structure](image4) | 8 (6) | 43 |
| rac-1e  | ![Structure](image5) | 10 (8) | 21 |
| rac-1f  | ![Structure](image6) | 10 (8) | 16 |
| rac-1g  | ![Structure](image7) | 5 (4) | 33 |

Cyclization of 3a employing PCl5 in chloroform at room temperature followed by NaBH4-reduction afforded the desired tetrahydroisoquinoline, albeit only in 13% yield. The best results were obtained using phosphorus oxychloride in refluxing acetonitrile, followed by NaBH4-reduction in methanol. This sequence gave the tetrahydroisoquinolines in yields of 85–97%. Only the cyclization of 3g failed under these conditions, most likely owing to the lack of electron-donating substituents on the aromatic ring of the original amine building block. Although the Bischler–Napieralski reaction of nonactivated arenes is described in literature,21 no conversion was achieved in our case even under the most forcing reaction conditions employed (P2O5 in tetralin at 206 °C). Consequently, we had to change our strategy for the synthesis of 1g. Alkylation of a C1-lithiated tetrahydroisoquinoline derivative appeared promising and lithiation of tetrahydroisoquinoline carbamates employing t-BuLi has previously been described.22 Carbamate 14 and 3-benzyloxybenzyl bromide 16 were prepared and reacted following the published procedure to give the desired C–C coupling product in 29% yield (Scheme 5). By slightly changing the reaction conditions, i.e., higher temperature during the alkylation stage (see Experimental Section), this value could be improved to 51%, which approaches the reported yields obtained with less hindered nucleophiles.22 The alkylated carbamate was converted into the N-methyltetrahydroisoquinoline by LiAlH4 reduction. This represents an improvement on the original report, where this transformation was achieved in a two-step deprotection/reductive amination sequence. In our case the carbamate moiety serves a triple purpose: it protects the nitrogen atom, directs the lithiation, and serves as precursor of the N-methyl group.

The synthesis of racemic tetrahydroisoquinolines 1a–g (summarized in Table 1) was completed by hydrogenolytic cleavage of the benzyl ether protective groups, which proceeded quantitatively and generally gave the target compounds without the need for chromatographic purification. For instance, racemic

Table 2. Yields of BBE-Catalyzed Oxidative Kinetic Resolution via C–C Bond Formation

| entry | Substrate | c [%] a | yield (S)-2 [%] b | ee (S)-2 [%] c | yield (R)-1 [%] b | ee (R)-1 [%] c | E d |
|-------|-----------|--------|------------------|---------------|------------------|---------------|-----|
| 1     | rac-1a'   | 50     | 42               | >97           | 50               | >97           | >200|
| 2     | rac-1b'   | 50     | 36               | >97           | 36               | >97           | >200|
| 3     | rac-1c'   | 50     | 39               | >97           | 47               | >97           | >200|
| 4     | rac-1d'   | 50     | 31               | >97           | 46               | >97           | >200|
| 5     | rac-1e    | 50     | 22               | >97           | 49               | >97           | >200|
| 6     | rac-1f    | 50     | 47               | >97           | 37               | >97           | >200|
| 7     | rac-1g    | 50     | 46               | >97           | 49               | >97           | >200|

a Determined by HPLC on an achiral stationary phase. b Isolated yield (maximum theoretical yield = 50%). c Determined by HPLC on a chiral stationary phase. d Determined from the ee of substrate and product. e Kinetic resolution from ref 19.
reticuline rac-1f, as the most complex structure, was obtained with 16% overall yield, while the most efficient synthesis in terms of yield was achieved for rac-1d and rac-1b with 43% and 42% isolated overall yield, respectively.

Finally, the racemic tetrahydroisoquinolines rac-1a–g were subjected to enantioselective oxidative ring closure catalyzed by BBE, leading to the untouched optically pure (R)-substrates and the optically pure (S)-berbine products 2a–g via kinetic resolution (Table 2). The reaction was performed employing 1 g/L BBE, 5 g/L catalase, and 20 g/L substrate in a toluene/buffer (70:30) biphasic mixture. Under these conditions, substrate solubility is not an issue. Maximum conversion (50%) was achieved within 24 h in all cases, and the enantiomerically pure products (ee > 97%, HPLC) were obtained in good to excellent yields (Table 2). For instance, the kinetic resolution of racemic reticuline rac-1f yielded optically pure (R)-reticuline (R)-1f and optically pure (S)-scoulerine (S)-2f in 37% and 47% isolated yield.

### CONCLUSION

The combination of chemical synthesis of racemic 1-benzyl-1,2,3,4-tetrahydroisoquinolines with biocatalytic enantioselective intramolecular oxidative C–C coupling by BBE provided a new and efficient synthetic route to enantiomerically pure benzylisoquinoline and berbine alkaloids. The racemic substrates for BBE were prepared by two different pathways: either via Bischof–Napieralski cyclization or by alkylation of Boc-protected tetrahydroisoquinoline. BBE-catalyzed kinetic resolution proceeded with excellent enantioselectivity (E > 200), affording optically pure products in all cases. The overall chemoenzymatic synthesis resulted in yields of up to 20% for the benzylisoquinolines and 17% for the berbinens, which represents a competitive alternative to the conventional asymmetric syntheses of these compounds. In particular, this novel synthetic route enabled the first asymmetric total synthesis of naturally occurring (S)-scoulerine, a sedative and muscle-relaxing agent, yielding 230 mg (7.4%) of the enantiomerically pure alkaloid over 9 linear steps.

### EXPERIMENTAL SECTION

**Synthesis of Amides 7b–d.** A literature procedure was adapted for our purpose: A solution of phenylacetic acid derivative 6b–d (20.0 mmol), oxalyl chloride (2.89 g, 22.8 mmol) and one drop of DMF in dry toluene (50 mL) was stirred at room temperature for 1 h. The ice bath was removed and stirring was continued overnight. The mixture was stirred for 20 h at room temperature under argon atmosphere. The solution was filtered through Celite and washed with CH2Cl2 (3×20 mL). The combined organic phases were washed with 2 N HCl solution (100 mL), saturated NaHCO3 solution (100 mL), and water (100 mL) and dried over Na2SO4. Evaporation of the solvent under reduced pressure yielded 30.5 g of a yellow solid. TLC (petroleum ether/EtOAc = 1/1): Rf = 0.20. The 1H and 13C NMR as well as MS data are in accordance with literature.19

(3,4-Methylenedioxy)phenyl-N-methylacetamide (7d). Yield: 3.68 g (95%) as a pale yellowish solid. Mp: 100–101 °C (lit.15 99–101 °C). TLC (petroleum ether/EtOAc = 1/1): Rf = 0.20. The 1H and 13C NMR as well as MS data are in accordance with literature.19

Reduction of Amides 7b–d Giving Amines 4b–d. A literature procedure was adapted for our purpose: BH3·THF (1.0 M in THF; 100 mL, 100 mmol) was added to a solution of amide 7b–d (17.4–20.0 mmol) in anhydrous THF (100 mL) and the mixture was gently refluxed for 18 h under an argon atmosphere. The solution was allowed to cool to room temperature, and 6 N HCl solution (20 mL) was cautiously added. After stirring for 30 min, the resulting solution was concentrated under reduced pressure, basified by addition of 2 M NaOH solution (100 mL), and saturated with NaCl. The product was extracted into EtOAc (3×30 mL), and the combined organic phases were washed with brine, dried over Na2SO4, and evaporated under reduced pressure to give the crude product as a yellowish liquid. Flash chromatography (silica; CH2Cl2/MethOH/NH3(aq) = 90/9/1) afforded the pure amine 4b–d.

**N-Methyl-3-methoxyphenethylamine (4b).** Yield: 2.23 g (72%) as a pale yellowish solid. TLC (CH3Cl2/MethOH/NH3(aq) = 90/9/1): Rf = 0.21. The 1H and 13C NMR as well as MS data are in accordance with literature.33

**N-Methyl-3,4,5-trimethoxyphenethylamine (4c).** Yield: 3.54 g (78%) as a pale yellowish liquid, which crystallized upon standing to a pale yellowish solid. Mp: 175–177 °C (lit.35 178–180 °C). TLC (CH3Cl2/MethOH/NH3(aq) = 90/9/1): Rf = 0.37. The 1H and 13C NMR as well as MS data are in accordance with literature.33

**N-Methyl-3,4-methylenedioxyphenethylamine (4d).** Yield: 1.81 g (58%) as a pale yellowish solid. TLC (CH3Cl2/MethOH/NH3(aq) = 90/9/1): Rf = 0.20. The 1H and 13C NMR as well as MS data are in accordance with literature.33

**4-Benzylxy-3-methoxybenzaldehyde.** K2CO3 (20.1 g, 0.146 mol) and benzyl bromide (22.5 g, 0.132 mol) were added to a solution of vanillin (18.4 g, 0.301 mol), and NH4OAc (18.4 g, 0.239 mol) in AcOH (220 mL) was refluxed for 5 h. The mixture was poured into ice water (300 mL), followed by addition of CH2Cl2 (150 mL) to dissolve the precipitate. The phases were separated and the aqueous phase was extracted with CH2Cl2 (3×50 mL). The combined organic phases were washed with 2 N HCl solution (100 mL), saturated NaHCO3 solution (100 mL), and water (100 mL) and dried over Na2SO4. Evaporation of the solvent under reduced pressure yielded 30.5 g of a yellow solid. Recrystallization from ethanol gave 4-benzylxy-3-methoxybenzaldehyde (28.1 g, 89%) as a white solid. Mp: 61–63 °C (lit.36 61–62 °C). TLC (petroleum ether/EtOAc = 3/1): Rf = 0.62. The 1H and 13C NMR as well as MS data are in accordance with literature.36

**4-Benzylxy-3-methoxy-β-nitrostyrene.** A solution of 4-benzylxy-3-methoxybenzaldehyde (22.7 g, 0.094 mol), nitromethane (18.4 g, 0.301 mol), and NH2OAc (18.4 g, 0.239 mol) in AcOH (220 mL) was refluxed for 5 h. The mixture was poured into ice water (300 mL), followed by addition of CH2Cl2 (150 mL) to dissolve the precipitate. The phases were separated and the aqueous phase was extracted with CH2Cl2 (3×50 mL). The combined organic phases were washed with water (100 mL), half-saturated Na2CO3 solution (50 mL), and brine (50 mL), dried over Na2SO4, and evaporated under reduced pressure to give 21.4 g of a brown solid. Recrystallization from ethanol gave 4-benzylxy-3-methoxy-β-nitrostyrene (18.1 g, 68%) as a yellow solid. Mp: 119–121 °C (lit.37 124–125 °C). TLC (petroleum ether/EtOAc = 3/1): Rf = 0.47. The 1H and 13C NMR as well as MS data are in accordance with literature.36

**4-Benzylxy-3-methoxyphenethylamine (9).** To a suspension of LiAlH4 (8.05 g, 212 mmol) in dry THF (120 mL) under argon was added dropwise a solution of 4-benzylxy-3-methoxy-β-nitrostyrene (12.0 g, 42.0 mmol) in dry THF (80 mL) over 1 h. The reaction...
mixture was refluxed for 16 h, then diluted with THF (100 mL), and cooled to 0 °C on an ice bath. To the vigorously stirred mixture were added water (8 mL), 15% NaOH solution (8 mL), and water (24 mL), the ice bath was removed, and stirring was continued for 1 h at room temperature. The resulting suspension was filtered through Celite, washed with THF, and evaporated under reduced pressure. The residue was dissolved in 10% HCl solution (20 mL) and washed with ether; afterward the aqueous layer was made basic and extracted with ether (3 × 50 mL). The combined organic phases were washed with water (20 mL) and brine (20 mL), dried over K2CO3 and evaporated under reduced pressure to give 5.06 g (99%) of ethyl 4-benzyloxy-3-methoxyphenethylcarbamate as a yellow liquid that crystallized upon standing to a yellowish solid. Mp: 63–65 °C (lit.36 59–61 °C). TLC (CH2Cl2/MeOH/NH3(aq) = 90/9/1): Rf = 0.27. The 1H and 13C NMR as well as MS data are in accordance with literature.36

Ethyl 4-Benzyl-3-methoxyphenethylcarbamate. A literature procedure39 was adapted for our purpose: To a solution of 4-benzyloxy-3-methoxyphenethylamine 9 (4.00 g, 15.5 mmol) in dichloromethane (120 mL) were added triethylamine (1.75 g, 17.3 mmol) and ethyl chloroformate (2.01 g, 18.4 mmol), and the mixture was stirred for 3 h at room temperature. Water (100 mL) was added, the phases were separated, and the aqueous phase was extracted with CH2Cl2 (2 × 30 mL). The combined organic phases were dried over Na2SO4 and evaporated under reduced pressure to give 5.06 g (99%) of ethyl 4-benzyloxy-3-methoxyphenethylcarbamate as a yellow liquid that crystallized upon standing to a yellowish solid. Mp: 80–81 °C. TLC (ether/EtOAc = 3/1): Rf = 0.23. 1H NMR (CDCl3, 300 MHz): δ 1.24 (3H, t, J = 7.1 Hz, OCH2CH3), 2.75 (2H, t, J = 7.1 Hz, Ar-CH2CH2-N), 3.41 (2H, dt, J = 6.6 Hz, J5 = 6.5 Hz, Ar-CH2CH2-N), 3.89 (3H, s, OCH3), 4.12 (2H, q, J = 7.2 Hz, OCH2CH3), 4.71 (1H, br s, NH), 5.15 (2H, s, PhCH2O), 6.66–6.86 (3H, m, Ar), 7.31–7.47 (5H, m, Ar).13C NMR (CDCl3, 75 MHz): δ 40.5, 56.1, 71.1, 111.9, 115.3, 122.2, 125.6, 127.5, 127.9, 128.5, 137.0, 148.2, 149.1, 177.7.

Method A. A literature procedure28,43 was adapted for our purpose: To a stirred solution of isovanillin 10 (20.0 g, 0.131 mol) in ethanol (120 mL) were added K2CO3 (20.1 g, 0.145 mol) and benzyl bromide (22.5 g, 0.131 mol). The mixture was stirred for 2 h at room temperature under argon atmosphere. The solution was filtered through Celite and washed with CH2Cl2 (5 × 100 mL), and the solvent was evaporated under reduced pressure. The residue was taken up in CH2Cl2 (200 mL), washed with 5% NaOH solution (100 mL), and dried over K2CO3. Evaporation of the solvent under reduced pressure yielded 31.3 g of a yellow solid. Recrystallization from ethanol gave 3-benzyloxy-4-methoxybenzaldehyde (29.2 g, 91%) as a white solid. Mp: 62–63 °C (lit.42 61–62 °C). TLC (ether/EtOAc = 3/1): Rf = 0.29. The 1H and 13C NMR data are in accordance with literature.44 MS (EI, 70 eV): m/z = 242 (M+1, 13), 91 (100), 65 (9).

A solution of 3-benzyloxy-4-methoxybenzaldehyde (29.0 g, 0.120 mol) and chloroform (35 mL) in DMF (120 mL) under argon atmosphere was cooled to −10 °C on an ice/NaCl bath. A solution of KOH (8.88 g, 0.158 mol) in methanol (30 mL) was added dropwise over 30 min and the resulting mixture was stirred for 2 h at −10 °C. The reaction was quenched with 1 N hydrochloric acid (270 mL) and stirred for an additional 30 min at −10 °C. Afterward, the mixture was allowed to warm to room temperature, toluene (100 mL) was added, and the phases were separated. The aqueous phase was extracted with toluene (2 × 100 mL), and the combined organic phases were washed with water (30 mL) and brine (30 mL) and dried over Na2SO4. Evaporation of the solvent under reduced pressure gave 42.9 g (97%) of 1-(3-benzyloxy-4-methoxyphenethyl)−2,2,2-trichloroethanol 11 as a yellowish solid, which was used in the next step without further purification. TLC (petroleum ether/EtOAc = 3/1): Rf = 0.53.1H NMR (CDCl3, 300 MHz): δ 3.71 (1H, br s, OH), 3.91 (3H, s, OCH3), 5.09 (1H, s, CH−OH), 5.21 (2H, s, PhCH2O), 6.89 (1H, d, J = 8.7 Hz, Ar), 7.14–7.21 (2H, m, Ar), 7.26–7.46 (5H, m, Ar).13C NMR (CDCl3, 75 MHz): δ 55.9, 71.0, 84.1, 103.4, 110.6, 111.5, 112.6, 127.3, 127.9, 128.5, 137.0, 147.1, 150.5. MS (EI, 70 eV): m/z = 360 (M+1, 1), 243 (36), 91 (100).

Diphenyl disilene (36.9 g, 0.118 mol) was dissolved in deoxygenated ethanol (300 mL; purged with argon for 1 h). NaBH4 (9.0 g, 0.238 mol) was added in portions over 30 min, upon which the previously orange solution turned colorless. The resulting mixture was stirred for 30 min at room temperature before addition of NaI (40.8 g, 0.113 mol) followed by NaOH (27.1 g, 0.667 mol). The reaction was then stirred for 18 h at 40 °C. The solvent was evaporated under reduced conditions.
pressure, and the solid residue was dissolved in water (200 mL). The pH of the solution was adjusted to 1.0 by addition of conc hydrochloric acid, and the product was extracted into EtOAc (5 × 100 mL). The combined organic phases were dried over Na2SO4, and the solvent was evaporated under reduced pressure to give an orange solid, which was recrystallized from petroleum ether/acetone to afford $\text{Sf}$ (11.0 g, 31%) as an off-white solid. The spectroscopic and chromatographic data are identical to those of $\text{Sf}$ obtained by method A.

Synthesis of Amides 3a–g. A literature procedure65 was adapted for our purpose: A solution of phenylacetic acid derivative 5a or 5f (10.5–12.0 mmol), oxalyl chloride (1.95 g, 15.4 mmol), and one drop of DMF in dry toluene (40 mL) was stirred at room temperature under argon for 1 h. The solvent was evaporated under reduced pressure to give the acyl chloride (quant), which was used without further purification. The amine 4a–g (10.0–13.5 mmol) was dissolved in CHCl3 (30 mL). A 3% NaOH solution (150 mL) was added, and the mixture was cooled to 0°C on an ice bath. A solution of the crude phenylacetyl chloride derivative (10.6–12.8 mmol) in chloroform (20 mL) was added dropwise over 1 h to the vigorously stirred mixture. The ice bath was removed, and stirring was continued for 16 h at room temperature. The phases were separated, and the aqueous phase was extracted with CHCl3 (50 mL). The combined organic phases were washed with dilute HCl solution (100 mL) and then water (100 mL) and dried over Na2SO4. Evaporation of the solvent under reduced pressure yielded the crude amide 3a–g, which was purified by flash chromatography (silica; petroleum ether/EtOAc = 1/1). The product is obtained as a mixture of rotamers, to which NMR signals are assigned based on the peak ratios.

Yield: 2.39 g (76%) as an off-white solid. Ratio trans/cis = 1.14/1. Mp: 126–127°C. TLC (petroleum ether/EtOAc = 1/1): $R_f$ = 0.64. MS (EL, 70 eV): $m/z$ = 525 (M+, 3), 240 (22), 149 (11), 105 (14), 91 (100). HRMS: calcd for C32H33NO4: 495.2410; found 495.2411.

Yield: 2.79 g (68%) as a pale yellowish liquid. Ratio trans/cis = 1.05/1. Mp: 126–127°C. TLC (petroleum ether/EtOAc = 1/1): $R_f$ = 0.37. The 1H and 13C NMR as well as MS data are in accordance with literature.19 HRMS: calcd for C32H33NO4: 495.2410; found 495.2409.

Yield: 2.58 g (68%) as a pale yellowish liquid. Ratio trans/cis = 1.05/1. Mp: 126–127°C. TLC (petroleum ether/EtOAc = 1/1): $R_f$ = 0.37. The 1H and 13C NMR as well as MS data are in accordance with literature.19 HRMS: calcd for C32H33NO4: 495.2410; found 495.2409.

Yield: 2.30 g (63%) as a pale yellowish liquid. Ratio trans/cis = 1.05/1. Mp: 126–127°C. TLC (petroleum ether/EtOAc = 1/1): $R_f$ = 0.37. The 1H and 13C NMR as well as MS data are in accordance with literature.19 HRMS: calcd for C32H33NO4: 495.2410; found 495.2409.

Yield: 2.54 g (68%) as a pale yellowish liquid. Ratio trans/cis = 1.05/1. Mp: 126–127°C. TLC (petroleum ether/EtOAc = 1/1): $R_f$ = 0.37. The 1H and 13C NMR as well as MS data are in accordance with literature.19 HRMS: calcd for C32H33NO4: 495.2410; found 495.2409.

Yield: 2.58 g (68%) as a pale yellowish liquid. Ratio trans/cis = 1.05/1. Mp: 126–127°C. TLC (petroleum ether/EtOAc = 1/1): $R_f$ = 0.37. The 1H and 13C NMR as well as MS data are in accordance with literature.19 HRMS: calcd for C32H33NO4: 495.2410; found 495.2409.
1-(3-Benzxyloxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline. Yield: 2.87 g (98%) as a yellowish liquid. TLC (CHCl₃/MeOH/NH₄OH = 90/9/1): Rf = 0.75. The 1H and 13C NMR as well as MS data are in accordance with literature. HRMS: calculated for C₂₆H₂₈NO₃ [(M + H)⁺ 507.2410]; found 507.2435.

1-(3-Benzxyloxybenzyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline. Yield: 2.54 g (98%) as a pale yellowish liquid. TLC (CHCl₃/MeOH/NH₄OH = 90/9/1): Rf = 0.61. The 1H and 13C NMR as well as MS data are in accordance with literature. HRMS: calculated for C₂₆H₂₈NO₃ [(M + H)⁺ 507.2435]; found 507.2438.

1-(3-Benzxyloxybenzyl)-6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline. Yield: 2.89 g (85%) as a pale yellow viscous liquid. TLC (CHCl₃/MeOH/NH₄OH = 90/9/1): Rf = 0.75. The 1H and 13C NMR as well as MS data are in accordance with literature. HRMS: calculated for C₂₆H₂₈NO₃ [(M + H)⁺ 507.2435]; found 507.2438.

1-(3-Benzxyloxybenzyl)-6,7-dimethylenedioxy-2-methyl-1,2,3,4-tetrahydroisoquinoline. Yield: 4.36 g (88%) as a pale yellow liquid. TLC (CHCl₃/MeOH/NH₄OH = 90/9/1): Rf = 0.76. The 1H and 13C NMR as well as MS data are in accordance with literature. HRMS: calculated for C₂₆H₂₈NO₃ [(M + H)⁺ 507.2435]; found 507.2438.

1-(3-Benzxyloxybenzyl)-6,7-dimethylenedioxy-2-methyl-1,2,3,4-tetrahydroisoquinoline. Yield: 3.59 g (97%) as a pale yellow liquid. TLC (CHCl₃/MeOH/NH₄OH = 90/9/1): Rf = 0.76. The 1H and 13C NMR as well as MS data are in accordance with literature. HRMS: calculated for C₂₆H₂₈NO₃ [(M + H)⁺ 507.2435]; found 507.2438.

1-(3-Benzxyloxybenzyl)-7-benzoxyloxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline. Yield: 4.36 g (88%) as a pale yellow liquid. TLC (CHCl₃/MeOH/NH₄OH = 90/9/1): Rf = 0.76. The 1H and 13C NMR as well as MS data are in accordance with literature. HRMS: calculated for C₂₆H₂₈NO₃ [(M + H)⁺ 507.2435]; found 507.2438.

1-(3-Benzxyloxybenzyl)-7-benzoxyloxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline. Yield: 1.98 g (97%) as a yellowish liquid. TLC (CHCl₃/MeOH/NH₄OH = 90/9/1): Rf = 0.56. The 1H NMR (CDCl₃, 300 MHz): δ 2.47 (3H, s, NCH₃), 2.50–2.58 (1H, m, CH₂), 2.66–2.83 (3H, m, CH₃), 2.97–3.12 (2H, m, CH₂), 3.15 (1H, dd, J₁ = 6.9 Hz, J₂ = 5.2 Hz, CH), 3.85 (3H, s, OCH₃), 3.86 (3H, s, OCH₃), 4.38 (1H, t, J₁ = 12.3 Hz, PhCH₂O), 4.87 (1H, t, J₁ = 12.3 Hz, Ar), 5.07 (2H, s, Ph-CH₂O), 6.10 (1H, Ar), 6.55–6.57 (2H, m, Ar), 6.64 (1H, J₁ = 19.7 Hz, Ar), 6.77 (1H, J₁ = 8.2 Hz, Ar), 7.26–7.38 (8H, m, Ar). The 13C NMR (CDCl₃, 75 MHz): δ 25.8, 34.0, 42.7, 47.2, 55.9, 56.0, 64.6, 70.8, 70.9, 111.4, 116.3, 116.7, 116.9, 117.4, 119.4, 130.4, 146.8, 147.5, 148.0. MS (EI, 70 eV): m/z = 507 [(M + H)⁺], 527 [(M + Na)⁺].

**Tert-Butyl 3-(3-Benzxyloxybenzyl)-3,4-dihydro-2(1H)-isoquinolinecarboxylate (17).** A literature procedure was adapted for our purpose: A solution of tert-butyl 3,4-dihydro-2(1H)-isoquinolinecarboxylate 14 (2.33 g, 10.0 mmol) and tetramethylethylene-diamine (1.22 g, 10.5 mmol) in anhydrous THF under argon atmosphere was cooled to –78 °C. Tert-butyl lithium solution (1.7 M in pentane; 62 mL, 10.5 mmol) was added dropwise over 30 min, resulting in a deep red solution, which was stirred at –78 °C for 30 min. A solution of 3-benzxyloxybenzyl bromide (5.277 g, 10.0 mmol) in anhydrous THF (10 mL) was added dropwise over 30 min. The mixture was then stirred for 3 h, during which time the temperature was allowed to rise to –50 °C. The resulting yellow suspension was quenched with saturated NH₄Cl solution (10 mL). Water (30 mL) was added, the phases were separated, and the aqueous phase was treated with tert-butyl methyl ether (2 × 20 mL). The combined organic phases were dried over Na₂SO₄, and the solvent was evaporated under reduced pressure to give 5.52 g of an orange liquid. Flash chromatography (silica; petroleum ether → petroleum ether/EtOAc = 95/5) afforded 17 (2.21 g, 51%) as a colorless liquid. TLC (petroleum ether/ EtOAc = 3/1): Rf = 0.59. MS (EI, 70 eV): m/z = 429 [(M⁺, c₁), 232 (16), 176 (57), 132 (100), 91 (38)]. HRMS: calculated for C₂₆H₂₈NO₃ [(M + H)⁺ 429.2304]; found 429.2333. The product is obtained as a mixture of rotamers (ratio cis/trans = 2/1), to which NMR signals are assigned based on the peak intensities as well as the DEPT, COSY, and HSQC spectra.

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mixture, the ice bath was removed, and stirring was continued for 1 h at room temperature. The resulting suspension was filtered through Celite, washed with THF, dried over Na2SO4 and evaporated under reduced pressure to give 2.89 g of a yellow liquid. Flash chromatography (silica; CH2Cl2/MeOH/NH3 (aq) = 98/1/1) afforded 18 (2.09 g, 74%) as a yellowish liquid. TLC (CH2Cl2/MeOH/NH3 (aq) = 90/9/1); Rf = 0.56. 1H NMR (CDCl3, 300 MHz): δ = 2.54 (3H, s, NCH3), 2.67−2.83 (2H, m, CH2), 2.88−2.98 (2H, m, CH2), 3.14−3.27 (2H, m, CH2), 3.87 (1H, t, J = 6.2 Hz, CH2), 5.04 (2H, s, PhCH2O), 6.78−6.89 (4H, m, Ar), 7.06−7.24 (4H, m, Ar), 7.36−7.46 (5H, m, Ar). 13C NMR (CDCl3, 75 MHz): δ = 26.1, 41.5, 42.9, 47.1, 65.0, 69.9, 112.4, 116.2, 112.4, 122.6, 124.5, 126.0, 127.6, 127.9, 128.0, 128.6, 128.8, 129.0, 134.4, 137.3, 137.9, 141.7, 158.6. MS (EI, 70 eV); m/z = 342 [(M−H)+, <1], 146 (100), 131 (6), 91 (10). HRMS: calcld for C19H22NO3 [(M−H)+] 342.1585; found 342.1581.

Hydrogenolytic Deprotection Affording Tetrahydroisoquinolines 1a−g. A literature procedure24 was adapted for our purpose: A mixture of benzyl-protected tetrahydroisoquinoline (5.75−9.16 mmol), Pd 10% on activated charcoal (0.20 mmol), and dry methanol (50 mL) was stirred under H2 atmosphere (balloon) for 16 h. The mixture was filtered through Celite, washed with methanol (100 mL), and evaporated under reduced pressure. The residue was dissolved in CH2Cl2 (30 mL) and washed with half-saturated NaHCO3 solution (40 mL). The organic phase was dried over Na2SO4 and evaporated under reduced pressure to afford pure 1a−g.

1-(3-Hydroxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (1a). Yield: 2.07 g (98%) as an off-white solid foam. Mp: 127−128 °C (lit.19 135 °C). TLC (CH2Cl2/MeOH/NH3 (aq) = 90/9/1); Rf = 0.53. The 1H and 13C NMR as well as MS data are in accordance with literature.19,50 HRMS: calcld for C19H22NO3 [(M+H)+] 312.1600; found 312.1598.

1-(3-Hydroxybenzyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (1b). Yield: 1.53 g (94%) as an off-white solid foam. Mp = 113−116 °C. TLC (CH2Cl2/MeOH/NH3 (aq) = 90/9/1); Rf = 0.51. The 1H and 13C NMR as well as MS data are in accordance with literature.19 HRMS: calcld for C19H22NO4 [(M−H)+] 328.1504; found 328.1503.

1-(3-Hydroxybenzyl)-6-methylenedioxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (1c). Yield: 1.87 g (84%) as a highly viscous yellowish liquid. TLC (CH2Cl2/MeOH/NH3 (aq) = 90/9/1); Rf = 0.51. The 1H and 13C NMR as well as MS data are in accordance with literature.19 HRMS: calcld for C19H22NO3 [(M−H)+] 324.1584; found 324.1571.

Reticuline (1f). Yield: 0.90 g (70%) as an off-white solid foam. Mp: 83−84 °C. TLC (CH2Cl2/MeOH/NH3 (aq) = 90/9/1); Rf = 0.29. The NMR data are in accordance with literature.54 MS (EI, 70 eV); m/z = 328 [(M−H)+, <1], 192 (100), 177 (21). HRMS: calcld for C19H22NO3 [(M−H)+] 328.1549; found 328.1571.

BBE-Catalyzed Kinetic Resolution of 1a−g59. Substrate 1a−g (500 mg, 1.5−2.0 mmol) was dissolved in toluene (17.5 mL) and buffer (7.5 mL, 10 mM Tris-HCl, pH 9.0, 10 mM MgCl2) containing BBE (1.5 mL enzyme solution, final concentration = 1 g/L = 0.0117 mM) and crude catalase (125 mg, final concentration 5 g/L). The mixture was shaken in a light-shielded round-bottom flask (50 mL) at 200 rpm and 40 °C for 24 h. The reaction was stopped by phase separation, followed by extraction of the aqueous phase with ethyl acetate (3 × 10 mL). The combined organic phases were dried over Na2SO4 and evaporated under reduced pressure to give the crude product. Flash chromatography (silica; a−f, CH2Cl2/MeOH/NH3 (aq) = 98/3/1; g, CH2Cl2/MeOH/NH3 (aq) = 98/1/1) afforded pure (S)-g and (R)-1a−g.

(5S)-2,3-Dimethoxy-9-hydroxyberbine (5a). Yield: 249 mg (52%) as an off-white solid. Mp: 90−95 °C. TLC (CH2Cl2/MeOH/NH3 (aq) = 90/9/1); Rf = 0.78. [α]D20 = −273.4 (CHCl3, c = 1.0); lit.34 (R) +176 (MeOH, c = 0.34). The 1H and 13C NMR as well as MS data are in accordance with those obtained for the racemic compound. HRMS: calcld for C20H20NO4 341.1623; found 341.1622.

(R)-6,7-Dimethoxy-1-(3-hydroxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (1a). Yield: 249 mg (50%) as an off-white solid. Mp: 151−153 °C. TLC (CH2Cl2/MeOH/NH3 (aq) = 90/9/1); Rf = 0.53. [α]D20 = −109.4 (CHCl3, c = 1.0). The 1H and 13C NMR as well as MS data are in accordance with those obtained for the racemic compound. HRMS: calcld for C20H24NO4 [(M−H)+] 312.1600; found 312.1601.

(5S)-2,3-Dimethoxy-9-hydroxyberbine (5a). Yield: 177 mg (36%) as an off-white solid. Mp: 192−195 °C. TLC (CH2Cl2/MeOH/NH3 (aq) = 90/9/1); Rf = 0.56. [α]D20 = −280.6 (CHCl3, c = 0.5). The 1H and 13C NMR as well as MS data are in accordance with literature.19 HRMS: calcld for C19H20NO4 281.1416; found 281.1415.

(R)-6,7-Dimethoxy-1-(3-hydroxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (1a). Yield: 181 mg (36%) as a highly viscous yellow liquid. TLC (CH2Cl2/MeOH/NH3 (aq) = 90/9/1); Rf = 0.45. [α]D20 = −763.4 (CHCl3, c = 0.63). The 1H and 13C NMR as well as MS data are in accordance with those obtained for the racemic compound. HRMS: calcld for C19H20NO4 [(M−H)+] 312.1600; found 312.1614.
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(5)-9-Hydroxy-2,3-methylendioxyberbine (5)-2d. Yield: 155 mg (31%) as an off-white solid foam. Mp: 177–180 °C. TLC (CHCl3/MeOH/NH3(aq) = 90/9/1): Rf = 0.50. 1H NMR (CDCl3, c = 0.63). The 1H and 13C NMR as well as MS data are in accordance with those obtained for the racemic compound. HRMS: calculated for C19H21NO4 [(M + H)+]; 327.1471; found 327.1490.

Determination of Absolute Configuration.

The NMR data are in accordance with literatures.50

Preparation of Racemic Reference Samples for Chiral HPLC Analysis.

Yield: 232 mg (47%) as an off-white solid foam. Mp: 165–167 °C. TLC (CHCl3/MeOH/ NH3(aq) = 90/9/1): Rf = 0.63. 1H NMR (CDCl3, c = 0.28); lit.50 Rf = 0.31. The 1H and 13C NMR as well as MS data are in accordance with those obtained for the racemic compound. HRMS: calculated for C19H22NO4 [(M + H)+] 328.1549; found 328.1600. The NMR data are in accordance with literature.50

Enzyme Expression and Purification.

Yield: 182 mg (37%) as an off-white solid foam. Mp: 177–180 °C. TLC (CDCl3/MeOH/ NH3(aq) = 90/9/1): Rf = 0.39. 1H NMR (CDCl3, c = 0.36); lit.50 Rf = +43 (MeOH, c = 0.5). The 1H and 13C NMR as well as MS data are in agreement with those obtained for the racemic compound. HRMS: calculated for C19H21NO3 [(M + H)+] 298.1443; found 298.1453. The NMR data are in accordance with literature.50

(5)-Scoleline (5)-2f. Yield: 323 mg (47%) as an off-white solid foam. Mp: 194–195 °C. TLC (CHCl3/MeOH/ NH3(aq) = 90/9/1): Rf = 0.49. 1H NMR (CDCl3, c = 0.27); lit.51 Rf = –315 (MeOH, c = 0.11). The 1H NMR (CDCl3 300 MHz): δ = 2.55–2.70 (2H, m, CH2), 2.83 (1H, dd, J1 = 15.9 Hz, J2 = 11.4 Hz, CH2), 3.11–3.38 (3H, m, CH3), 3.49–3.57 (2H, m, N=CH-2=CH+), 3.87 (3H, s, OCH3), 3.88 (3H, s, OCH3), 4.25 (1H, d, J1 = 15.6 Hz, N=CH2-Ar), 6.61 (1H, s, Ar), 6.68 (1H, d, J = 8.3 Hz, Ar), 6.75 (1H, d, J = 8.3 Hz, Ar), 6.84 (1H, s, Ar).13C NMR (CDCl3 75 MHz): δ = 29.2 (CH3), 36.3 (CH3), 51.6 (CH2), 53.5 (CH2), 55.9 (CH2), 56.2 (CH2), 59.2 (CH2), 109.0 (CH), 110.6 (CH), 111.4 (CH), 119.3 (CH), 121.2 (C), 126.1 (C), 141.5 (C), 143.9 (C), 144.0 (C), 145.1 (C). MS (EI, 70 eV): m/z = 237 (M+, 55), 310 (8), 178 (100), 176 (32), 165 (13), 150 (48), 135 (27), 107 (16). HRMS: calculated for C20H21NO3 [M+H]+ 327.1471; found 327.1490.

(5)-Reticine (5)-1f. Yield: 182 mg (37%) as an off-white solid foam. Mp: 74–75 °C. TLC (CHCl3/MeOH/ NH3(aq) = 90/9/1): Rf = 0.29. 1H NMR (CDCl3, c = 0.26); lit.52 Rf = –55 (EtOH, c = 0.44). The 1H and 13C NMR as well as MS data are in agreement with those obtained for the racemic compound. HRMS: calculated for C20H21NO4 [(M+H)+] 328.1549; found 328.1600. The NMR data are in accordance with literature.24

(5)-9-Hydroxyberbine (5)-2g. Yield: 230 mg (46%) as an off-white solid foam. Mp: 103–104 °C. TLC (CHCl3/MeOH/ NH3(aq) = 90/9/1): Rf = 0.58. 1H NMR (CDCl3, c = 1.0). The 1H NMR (CDCl3 300 MHz): δ = 2.55–2.71 (2H, m, CH2), 2.86 (1H, dd, J1 = 16.3 Hz, J2 = 11.5 Hz, CH2), 3.10–3.20 (2H, m, CH2), 3.26 (1H, dd, J1 = 16.5 Hz, J2 = 3.7 Hz, CH2), 3.46 (1H, d, J = 15.6 Hz, N=CH2-Ar), 3.62 (1H, dd, J1 = 11.2 Hz, J2 = 3.3 Hz, CH), 3.69 (1H, d, J = 15.6 Hz, N=CH2-Ar), 6.21 (1H, d, J = 7.9 Hz, Ar), 6.58 (1H, d, J = 7.6 Hz, Ar), 6.78 (1H, t, J = 7.8 Hz, Ar), 7.04–7.21 (3H, m, Ar).13C NMR (DMso-d6 75 MHz): δ = 29.1 (CH2), 36.2 (CH2), 51.3 (CH3), 53.6 (CH2), 59.4 (CH), 112.5 (CH), 120.5 (CH), 121.8 (C), 125.5 (CH2), 126.1 (CH2), 126.3 (CH), 126.8 (CH), 128.9 (CH), 134.4 (C), 135.9 (C), 137.5 (C), 152.4 (C). MS (EI, 70 eV): m/z = 251 (M+, 70), 132 (100), 130 (50), 130 (32), 91 (27). HRMS: calculated for C19H17NO5 251.1310; found 251.1308.
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