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The asymmetric synthesis of (*R*)-(+)- and (*S*)-(–)-*O*-methylbharatamine

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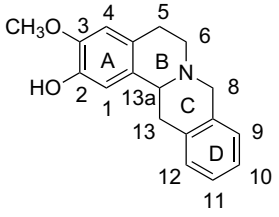
Abstract—The asymmetric syntheses of (*R*)-(+)- and (*S*)-(−)-*O*-methylbharatamine were performed using the lateral metallation strategy, in which (*R*)- and (*S*)-phenylalaninol were applied as chiral auxiliaries. The addition reaction of chiral *o*-toluamide carbanion to 6,7-dimethoxy-3,4-dihydroisoquinoline proceeded with a simultaneous cyclization reaction, giving both enantiomers of 2,3-dimethoxy-8-oxoberbine in good yield (76%) with high enantioselectivity (99% ee). Lithium aluminum hydride reduction of each enantiomer led to (*R*)-(+)- and (*S*)-(−)-*O*-methylbharatamine without loss of enantioselectivity.

1. Introduction

Bharatamine **1**, a protoberberine alkaloid, has been isolated in its racemic form from the seeds of *Alangium lamarackii* Thw. (Alangiaceae) in 1983 by Pakrashi et al.[1] Its structure as 2-hydroxy-3-methoxy-5,8,13,13a-tetrahydro-6*H*-dibenzo[*a*,*g*]quinolizine **1** elucidated on the basis of the spectral data analysis of the natural product was confirmed by an unequivocal synthesis.[1] Bharatamine **1** is a protoberberine alkaloid, which does not have the two oxygenated substituents at ring D, always present in this class of alkaloids. It has been postulated that compound **1** is biogenetically derived from loganin, a monoterpenoid precursor, on a plausible biogenetic route involving deacetylipecoside or its equivalent.[1] According to Shamma et al.,[2] bharatamine **1** has also been classified as an emetine type alkaloid because its lower half (C and D rings) is very probably of a terpenoidal origin. The *O*-methylated derivative of compound **1**, *O*-methylbharatamine **2**, served for many years as the model compound in designing new methods of synthesis of the protoberberine skeleton (Fig. 1).[3–12]



Bharatamine 1

Figure 1.

Until now, only racemic bharatamine **1** has been synthesized[13–17] with no synthesis of this protoberberine alkaloid in its optically active form being published. Among the different methods developed for the construction of a protoberberine skeleton, a growing interest in the lateral metallation methodology[18] has been observed over the last decade. In 1998, the regioselective addition–cyclization reaction of achiral *o*-tolyl oxazoline with 3,4-dihydroisoquinoline was applied by Singh[16] for the synthesis of racemic bharatamine **1**. Warrener et al.,[19] performed the asymmetric synthesis of 2,3-dimethoxy-8-oxoberbine **3** by incorporation of chiral amines into *o*-toluamides. Recently, an efficient enantioselective synthesis of lactam **3** based upon the (−)-sparteine-mediated addition of nonchiral *o*-toluamides to 3,4-dihydroisoquinoline has been reported by Liu.[20]

To continue our study on stereoselective syntheses of isoquinoline alkaloids,[21–25] including protoberberine system,[26] based on the addition of carbon nucleophiles to imines, we have performed the first asymmetric synthesis of (*R*)-(+)- and (*S*)-(−)-*O*-methylbharatamine **2**. Our concept of the asymmetric synthesis is based on

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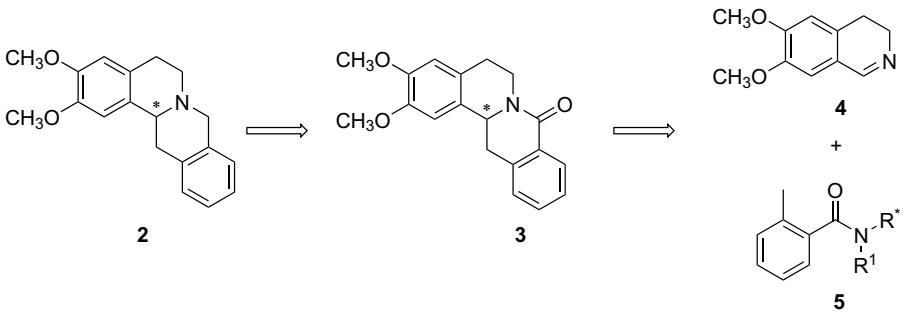


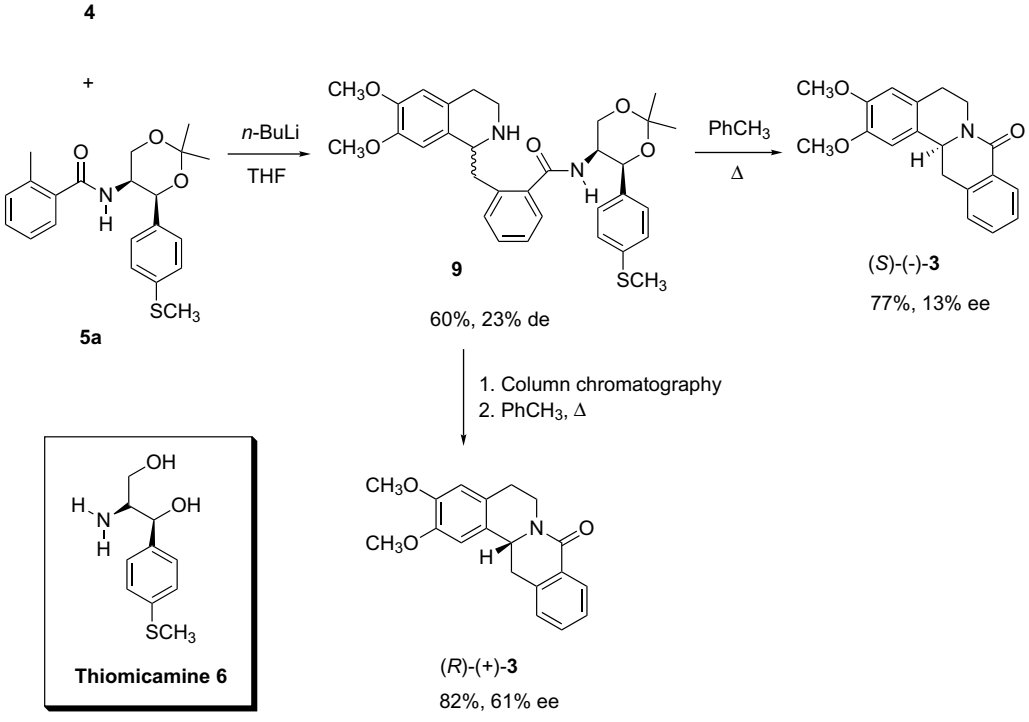
Scheme 1.

the lateral metallation methodology involving the addition of a carbon nucleophile derived from optically active *o*-toluamide **5** to 3,4-dihydroisoquinoline **4**. A new stereogenic center created at C-13a leads to the optically active 2,3-dimethoxy-8-oxoberbine **3**,[27] which is further transformed to *O*-methylbharatamine **2** by $LiAlH_4$ reduction. The retrosynthetic analysis of this synthesis is illustrated in Scheme 1.

2. Results and discussion

In our synthesis we have placed the chiral auxiliary in the amine part of the carbon nucleophile. For this purpose chiral amines, commercially available, enantiomerically pure, (+)-thiomicamine **6** and (*R*)- and (*S*)-phenylalaninol **7**, *ent*-**7** have been chosen. Thiomicamine **6**, an industrial waste product, has been used successfully by our research group, as a source or promoter of stereochemistry in many types of organic synthesis, including the enantioselective synthesis of isoquinoline alkaloids[21–25] and diastereoselective synthesis of protoberberine alkaloid,[26] as well. Our initial synthesis started with optically active amide **5a**, prepared from thiomicamine **6** and *o*-toluoyl chloride **8** as according to literature procedure.[26]

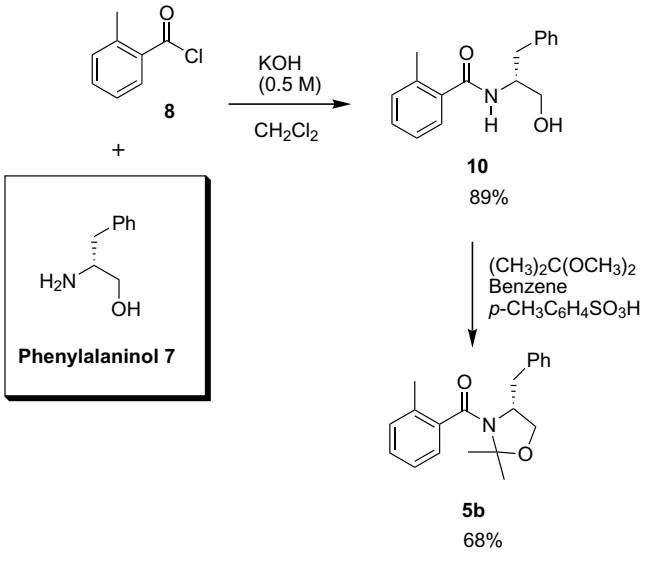
The reaction of lithiated *o*-toluamide **5a** with 6,7-dimethoxy-3,4-dihydroisoquinoline **4**[28] activated with boron trifluoride etherate[29] and subsequent work-up provided an addition product **9** as a diastereomeric mixture (23% de by ^1H NMR) in 60% yield. In the cyclization step, crude product **9** was heated in refluxing toluene to give the laevorotatory enantiomer (*S*)-(−)-**3** in 77% yield with 13% ee (by HPLC) along with recovered thiomicamine **6** (Scheme 2). The spectral data of lactam **3** corresponded to those reported for racemic (±)-**3** in literature.[30] Due to the low enantiomeric purity, this compound was used as our reference sample of 'racemic' amide **3** for the determination of the enantiomeric excess by HPLC.



Scheme 2.

In another experiment, crude product **9** was chromatographed on a silica gel column to give the diastereomerically enriched fractions of the more polar diastereomer, 78% de (HPLC), which was cyclized to afford the dextrorotatory 2,3-dimethoxy-8-oxoberbine **3** {$[\alpha]_D$ = +172.2 (*c* 0.6, chloroform)} in 82% yield. The enantiomeric excess of this compound, established by HPLC, was 61%. The absolute configuration of the product was postulated as (*R*) on the basis of the sign of the specific rotation, which corresponded to that reported for this compound by Ninomiya[31] and Warrener et al.[19] The synthesized dextrorotatory (*R*)-enantiomer was characterized on HPLC as that showing the shorter retention time in comparison with our reference 'racemic' sample of **3** with 13% ee.

To improve the diastereoselectivity of the addition step, we decided to prepare an amide without hydrogen at the nitrogen atom, which is supposed to be responsible for lowering the selectivity in such additions.[19] Therefore, we replaced (+)-thiomicamine **6** with both enantiomers of phenylalaninol, **7** and *ent*-**7** realizing a possibility of protection of NH and OH groups in the form of an oxazolidine ring. Thus, the reaction of (*R*)-phenylalaninol **7** with *o*-toluoyl chloride **8** gave amide **10** in 89% yield. The functional NH and OH groups in compound **10** were converted into oxazolidine derivative **5b**. This was prepared in 68% yield, in the reaction of amide **10** with 2,2-dimethoxypropane catalyzed by *p*-toluenesulfonic acid, in refluxing benzene under an argon atmosphere and followed by column chromatography purification (Scheme 3).

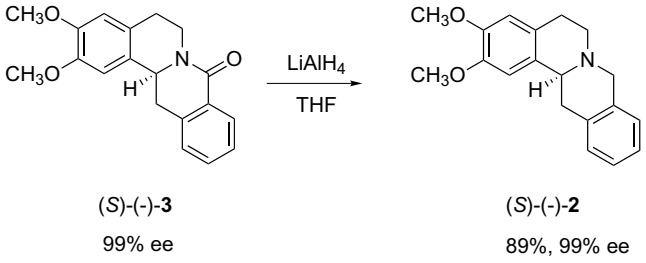


Scheme 3.

The carbanion was generated from oxazolidine **5b** with the aid of 1.1 equiv of *n*-butyllithium at −72 °C. After the addition of 6,7-dimethoxy-3,4-dihydroisoquinoline **4** and subsequent work-up, the cyclization product, dextrorotatory (*R*)-8-oxoberbine **3** was isolated in 67% yield with 92% ee (HPLC) along with the addition product, amine **11** (98% de). After recrystallization of (*R*)-**3** from diethyl ether/methanol, a sample of 2,3-dimethoxy-8-oxoberbine **3** with ee >99% was obtained, showing mp 169–171 °C, and $[\alpha]_D$ = +420.1 (*c* 0.359, chloroform), {lit.[19] $[\alpha]_D$ = +366.6 (*c* 0.359, chloroform), 96% ee}. Amine **11** was readily converted to lactam (*R*)-**3** (99% ee) under basic conditions (*n*-BuLi) providing an additional 9% of (*R*)-**3** (Scheme 4).

The same synthesis carried out with oxazolidine *ent*-**5b** incorporating (*S*)-phenylalaninol *ent*-**7**, and imine **4** led to (*S*)-8-oxoberbine **3** in 60% yield with 82% ee (HPLC) along with the addition product, amine *ent*-**11** (98% de). Recrystallization of (*S*)-**3** from diethyl ether/methanol led to pure 2,3-dimethoxy-8-oxoberbine **3** with ee >99%, mp 169–172 °C, and $[\alpha]_D$ = −413.8 (*c* 0.359, chloroform), {lit.[19] $[\alpha]_D$ = −372.4 (*c* 0.359, chloroform), 97% ee}. The cyclization reaction of *ent*-**11** provided an additional 11% of 8-oxoberbine (*S*)-**3** with 99% ee (Scheme 4).

Lithium aluminum hydride reduction of (*R*)-and (*S*)-2,3-dimethoxy-8-oxoberbine **3** led to (*R*)-and (*S*)-*O*-methylbharatamine **2**. The reaction was carried out in THF at reflux and no loss of enantioselectivity was observed (Scheme 5).



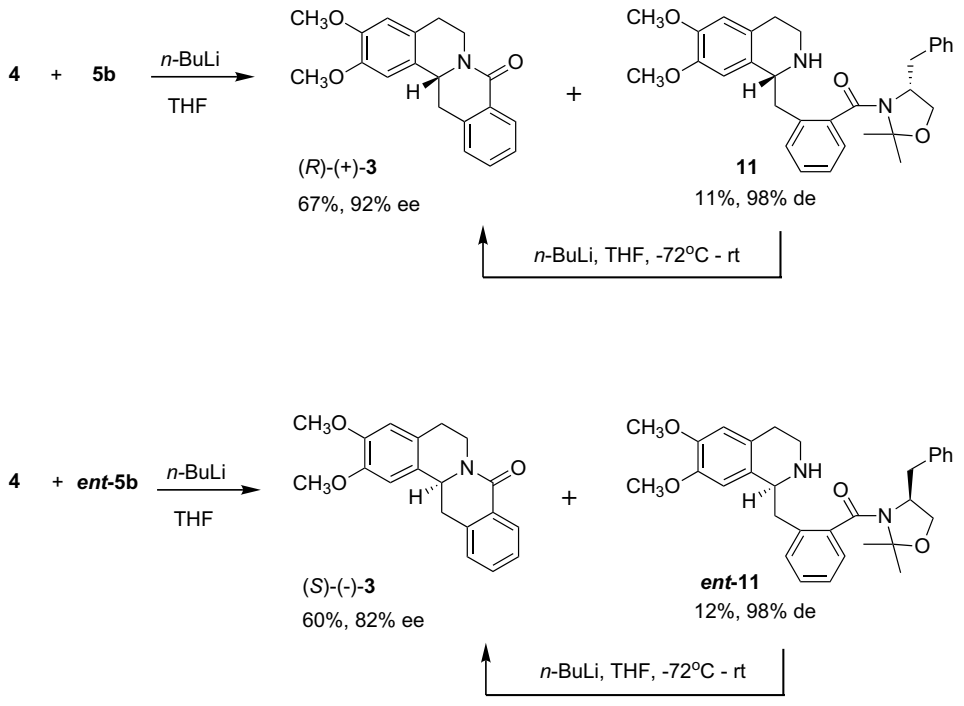
Scheme 5.

The reduction reaction of dextrorotatory lactam (*R*)-**3** (99% ee) led to dextrorotatory (*R*)-*O*-methylbharatamine **2** in 90% yield with >99% ee by HPLC, and $[\alpha]_D$ = +282.3 (*c* 0.32, chloroform). The free base (*R*)-(+)-**2** was converted to its hydrochloride salt with hydrochloric acid in methanol to give crystalline (*R*)-**2**·HCl, mp 223–225 °C (dec).

Laevorotatory lactam (*S*)-**3** (99% ee) was transformed to laevorotatory (*S*)-*O*-methylbharatamine **2** in 89% yield with >99% ee (HPLC), showing $[\alpha]_D$ = −285.5 (*c* 0.51, chloroform). The free base (*S*)-(−)-**3** was converted to its hydrochloride salt (*S*)-**2**·HCl, mp 206–207 °C (dec). The spectral data of our synthetic product **2** corresponded to those reported for racemic amine (±)-**2** in the literature.[6,7,12]

3. Conclusion

Herein, we have reported the first asymmetric synthesis of (*R*)-(+)- and (*S*)-(−)-*O*-methylbharatamine **2** obtained as enantiomerically pure compounds. The high enantioselectivity has been achieved in the addition reaction of *o*-toluamide **5b** and *ent*-**5b**, incorporating (*R*)- and (*S*)-phenylalaninol, **7** and *ent*-**7** as a chiral auxiliary,



Scheme 4.

respectively, to 3,4-dihydroisoquinoline **4**. This process was accompanied by simultaneous cyclization directly affording optically active lactams (*R*)-**3** and (*S*)-**3** in 67% and 60% yield, respectively. We would like to point out the simplicity of this process and the high enantioselectivity achieved. We were also able to isolate the addition product **11** (and *ent*-**11**, respectively), and convert it into enantiomerically pure lactam (*R*)-(+)-**3** [and (*S*)-(−)-**3**, respectively], which increased by ca. 10% the total yield of the product.

The key intermediates in the synthesis, lactams (*R*)-(+)-**3** and (*S*)-(−)-**3**, were obtained with high yield and with >99% ee. The enantiomeric excess was established by HPLC using a Chiracel OD-H column. The values of the specific rotation measured for both pure enantiomers with >99% ee reached $[\alpha]_D = +420.1$ (*c* 0.359, chloroform) for (*R*)-(+)-**3** and $[\alpha]_D = -413.8$ (*c* 0.359, chloroform) for (*S*)-(−)-**3**. These differ from those reported in literature:[19] $[\alpha]_D = +366.6$ (*c* 0.359, chloroform), and $[\alpha]_D = -372.4$ (*c* 0.359, chloroform), which were claimed to represent 96% ee for (*R*)-(+)-**3** and 97% ee for (*S*)-(−)-**3**, respectively.

4. Experimental

4.1. General

Melting points were determined on a Koffler block and are uncorrected. IR spectra: Bruker FT-IR IFS 113V. NMR spectra: Varian Gemini 300 in $CDCl_3$, with TMS as the internal standard. Mass spectra (EI): instrument AM D402. Optical rotations: Perkin–Elmer polarimeter 242B at 20 °C. Elemental analyses: Vario EL III. Merck Kieselgel 60 (70–230 mesh) was used for column chromatography and Merck DC-Alufolien Kieselgel 60_{254} for TLC. Analytical HPLC: Waters HPLC system with Mallinkrodt–Baker Chiracel OD-H column.

THF and diethyl ether were freshly distilled from $LiAlH_4$, benzene, and toluene—from sodium wire and acetone—from $KMnO_4$. Unless stated otherwise, all reagent were purchased from commercial sources and used without additional purification. 6,7-Dimethoxy-3,4-dihydroisoquinoline **4** was prepared as previously described.[28]

4.2. Addition product 9

Amide **5a**[26] (371 mg, 1 mmol) was dissolved in dry THF (5 mL) under an argon atmosphere and the mixture cooled to −72 °C. *n*-BuLi (1.6 M solution in hexanes, 1.4 mL) was introduced and the carbanion generated for 30 min at −72 °C. A solution of 6,7-dimethoxy-3,4-dihydroisoquinoline **4**[28] (191 mg, 1 mmol), activated with borontrifluoride etherate[29] (156 mg, 1.1 mmol) in dry THF (5 mL) was added and the mixture kept at −72 °C for 4 h and treated at this temperature with 20% aqueous NH_4Cl (6 mL). When the reaction mixture reached room temperature, the phases were separated and the aqueous one extracted with diethyl ether (3×10 mL). The combined organic extracts were dried and the solvents removed under reduced pressure to give a yellow foam of compound **9** (546 mg) with 23% de by ^1H NMR. The crude product **9** was purified by column chromatography (dichloromethane/methanol, 100:1 → 50:1) yielding diastereomerically enriched fractions (337 mg, 60% yield). IR (KBr) *v*: 3441, 3299 (NH amine,

amide), 1653 (C=O) cm^{-1}; ^1H NMR (more polar diastereoisomer **9**, 67% de) δ: 1.47, 1.54, 1.60 (3s, 6H, $C(CH_3)_2$), 1.75 (br s, 1H, NH, disappeared with D_2O), 2.32, 2.36 (2s, 3H, SCH_3), 2.55–2.95 (m, 5H, CH_2), 3.17, 3.28 (2dd, $J = 3.85$, 13.7 Hz, 1H, CH_2), 3.70, 4.16 (2dd, $J = 3.85$, 8.5 Hz, 1H, ArC*H*(NH)), 3.87, 3.88, 3.89, 3.90 (4s, 6H, OCH_3), 4.00 (dd, $J = 1.92$, 12.0 Hz, 1H, CH_2O), 4.32 (dd, $J = 1.92$, 12.0 Hz, 1H, CH_2O), 4.52 (dd, $J = 2.2$, 9.1 Hz, 1H, C*H*(NHCO)), 5.26 (d, $J = 2.2$ Hz, 1H, ArC*H*O), 6.55, 6.60, 6.69, 6.73 (4s, 2H, ArH isoquinoline ring), 6.95, 7.06 (2d, $J = 8.5$ Hz, 1H, ArH), 7.03–7.11 (m, 1H, ArH), 7.18–7.32 (m, 5H, ArH), 7.89, 8.25 (2d, $J = 8.8$ Hz, 1H, CONH, disappeared with D_2O); MS *m*/*z* (%): 562 (M^+, 3), 560 (M^+-2, 5), 308 (25), 307 (11), 306 (15), 305 (16), 292 (11), 264 (4), 193 (13), 192 (100), 176 (8), 152 (12), 118 (11), 90 (9); HRMS calcd for $C_{32}H_{36}N_2O_5S_2$ 560.23242. Found 560.23450.

4.3. Cyclization of addition product 9 to 5,6,13,13a-tetrahydro-2,3-dimethoxy-8*H*-dibenzo[*a*,*g*]quinolizin-8-one (2,3-dimethoxy-8-oxoberbine) 3

4.3.1. Cyclization of crude reaction product 9. Crude product **9** (453 mg, 0.7 mmol) was refluxed in dry toluene (15 mL) for 20 h. After cooling to room temperature, it was evaporated to dryness and the remaining oil purified by repeated column chromatography (dichloromethane) to yield pure 2,3-dimethoxy-8-oxoberbine **3** (193 mg, 77% yield) with 13% ee of the enantiomer with longer retention time by HPLC [hexane/propan-2-ol = 4:1, 0.5 mL/min; t_R 27.4, 32.0 min (major)]; mp 137–139 °C (diethyl ether), (lit.[4] mp 142 °C,[10] 140–141 °C,[12] 144–145 °C,[30] 136 °C); IR (KBr) *v*: 1653 (C=O) cm^{-1}; ^1H NMR δ: 2.75–2.83 (m, 1H, H-5), 2.94–3.03 (m, 3H, H-5, H-6, H-13), 3.23 (dd, $J = 3.6$, 15.7 Hz, 1H, H-13), 3.90 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.88 (dd, $J = 3.6$, 13.2 Hz, 1H, H-13a), 5.00–5.30 (m, 1H, H-6),), 6.71 (s, 1H, H-4), 6.73 (s, 1H, H-1), 7.26–7.29 (m, 1H, ArH), 7.38–7.50 (m, 2H, ArH), 8.15 (d, $J =$ 7.7 Hz, 1H, H-9); MS *m*/*z* (%): 309 (M^+, 100), 308 (81), 294 (40), 278 (32), 190 (19), 176 (11), 118 (54), 90 (59).

4.3.2. Cyclization of diastereomerically enriched 9. (*R*)-(+)-5,6,13,13a-Tetrahydro-2,3-dimethoxy-8*H*-dibenzo-[*a*,*g*]quinolizin-8-one (2,3-dimethoxy-8-oxoberbine) 3. The diastereomerically enriched **9** consisting mainly of the more polar diastereomer of **9** (TLC) diastereomeric ratio 8:1 (by HPLC), (201 mg, 0.36 mmol) was refluxed in dry toluene (10 mL) for 20 h. After cooling to room temperature, it was evaporated to dryness and the remaining oil (198 mg) dissolved in diethyl ether (30 mL) and extracted with 5% aqueous HCl (4 × 2 mL). The organic phase was dried and evaporated yielding pure 2,3-dimethoxy-8-oxoberbine **3** (90 mg, 82% yield) with 61% ee of the enantiomer with shorter retention time by HPLC [hexane/propan-2-ol = 4:1, 0.5 mL/min; t_R 27.4 min (major), t_R 32.0 min]; $[\alpha]_D = +172.2$ (*c* 0.6, chloroform). The acidic aqueous phase was alkalized with KOH pellets, reextracted with diethyl ether (3 × 10 mL), dried and evaporated to give an oil (66 mg), which consisted of thiomicamine **6**, according to TLC and HPLC analysis.

4.4. Synthesis of 2-*o*-toluamide-3-phenylpropanol

4.4.1. (2*R*)-2-*o*-Toluamide-3-phenylpropanol 10. To (*R*)-(−)-2-amino-3-phenylpropanol **7** (0.755 g, 5 mmol) dissolved in dichloromethane (60 mL) aqueous 0.5 M KOH solution (32.5 mL) was added and then *o*-toluoyl chloride **8** (0.77 g, 5 mmol) introduced dropwise with stirring at 0 °C. After 30 min, the cooling bath was removed and the stirring continued at room temperature for 1 h. The phases were separated and the aqueous one extracted with dichloromethane (3 × 20 mL). The combined organic phases were dried and the solvent removed under reduced pressure yielding a white precipitate of amide **10** (1.369 g, 89% yield); mp 125–127.5 °C (EtOH); $[\alpha]_D = +36.4$ (*c* 1.055, chloroform); IR (KBr) *v*: 3368, 3286 (OH, NH), 1640 (C=O) 1540 (NH) cm^{-1}; ^1H NMR δ: 2.31 (s, 3H, $ArCH_3$), 2.88–3.03 (m, 3H, $ArCH_2$, OH, 1H disappeared with D_2O), 3.64–3.81 (m, 2H, CH_2OH), 4.33–4.43 (m, 1H, C*H*(NH)), 6.05 (d, $J = 7.4$ Hz, 1H, NH, disappeared with D_2O), 7.10–7.37 (m, 9H, ArH); ^{13}C NMR δ: 19.7 (CH_3Ar), 37.0 (C-3), 53.1 (C-2), 64.4 (C-1), 125.6 (CH), 126.5 (CH), 126.6 (CH), 128.6 (2C, CH), 129.1 (2C, CH), 129.8 (CH), 130.8 (CH), 135.9 (C), 136.0 (C), 137.4 (C), 170.5 (C=O); MS *m*/*z* (%): 269 (M^+, 4), 238 (4), 178 (49), 119 (100), 91 (44); Anal. Calcd for $C_{17}H_{19}NO_2 \times 1/8\ H_2O$: C, 75.18; H, 7.14; N, 5.16. Found; C, 75.32; H, 7.03; N 4.98.

4.4.2. (2*S*)-2-*o*-Toluamide-3-phenylpropanol *ent*-10. The reaction was run in the same way as described in Section 4.4.1 using (*S*)-(−)-2-amino-3-phenylpropanol *ent*-**7** (2.265 g, 15 mmol), dichloromethane (200 mL), aqueous 0.5 M KOH solution (97.5 mL) and *o*-toluoyl chloride **8** (2.35 g, 15 mmol), yielding a white precipitate of amide *ent*-**10** (4.005 g, 99% yield); mp 124–127 °C; $[\alpha]_D = -36.0$ (*c* 1.13, chloroform).

4.5. Synthesis of 2,2-dimethyl-3-*o*-toluoyl-4-benzyloxazolidine

4.5.1. (4*R*)-2,2-Dimethyl-3-*o*-toluoyl-4-benzyloxazolidine 5b. To compound **10** (1.369 g, 5.09 mmol) in dry benzene (40 mL), 2,2-dimethoxypropane (8.50 g, 81.7 mmol) was added under an argon atmosphere followed by catalytic amounts of *p*-toluenesulfonic acid (0.25 g). The reaction mixture was stirred at reflux for 3.5 h and allowed to reach room temperature. Then the reaction mixture was washed with 1% aqueous NaOH solution (3 × 2 mL), dried and the solvent evaporated. The crude reaction product was chromatographed (dichloromethane and dichloromethane/methanol 200:1) to give the pure oxazolidine **5b** (1.074 g, 68% yield) as an oil; $[\alpha]_D = +32.6$ (*c* 1.115, chloroform); IR (film) *v*: 1642 (C=O) cm^{-1}; ^1H NMR δ: 1.72 (s, 3H, $C(CH_3)_2$), 1.87 (s, 3H, $C(CH_3)_2$), 2.36 (s, 3H, $ArCH_3$), 2.58–2.74 (m, 2H, $ArCH_2$), 3.62 (br s, 1H, C*H*(CH_2O)), 3.76–3.84 (m, 2H, CH_2O), 6.48–6.53 (m, 2H, ArH), 7.11–7.18 (m, 3H, ArH), 7.26–7.42 (m, 4H, ArH); ^{13}C NMR δ: 18.9 (CH_3Ar), 23.1 (*C*H_3C-2), 27.0 (*C*H_3C-2), 40.2 (*C*H_2Ph), 61.0 (C-4), 66.2 (C-5), 95.4 (C-2), 125.6 (CH), 125.9 (CH), 126.5 (CH), 128.5 (2C, CH), 128.8 (2C, CH), 128.9 (CH), 130.5 (CH), 137.4 (2C, C), 137.7 (C), 167.7

(C=O); MS *m*/*z* (%): 309 (M^+, 0.9), 218 (38), 119 (100), 91 (33); Anal. Calcd for $C_{20}H_{23}NO_2 \times 1/4H_2O$: C, 76.52; H, 7.55; N, 4.46. Found C, 76.74; H, 7.77; N, 4.43.

4.5.2. (4*S*)-2,2-Dimethyl-3-*o*-toluoyl-4-benzyloxazolidine *ent*-5b. The reaction was run in the same way as described in Section 4.5.1 using amide *ent*-**10** (2.138 g, 7.9 mmol), dry benzene (60 mL), 2,2-dimethoxypropane (13.43 g, 129 mmol) and *p*-toluenesulfonic acid (0.295 g). The crude reaction product was chromatographed (dichloromethane and dichloromethane/methanol 200:1) to give the pure oxazolidine *ent*-**5b** (1.731 g, 71% yield) as an oil; $[\alpha]_D = -31.8$ (*c* 0.99, chloroform).

4.6. Addition reaction of oxazolidine 5b (*ent*-5b) to imine 4

4.6.1. (*R*)-(+)-5,6,13,13a-Tetrahydro-2,3-dimethoxy-8*H*-dibenzo[*a*,*g*]quinolizin-8-one (2,3-dimethoxy-8-oxoberbine) 3 and addition product 11. Oxazolidine **5b** (309 mg, 1 mmol) was dissolved in dry THF (6 mL) under an argon atmosphere and the solution cooled to −72 °C. *n*-BuLi (1.6 M solution in hexanes, 0.7 mL) was added and the carbanion generated for 30 min at −72 °C. A solution of 6,7-dimethoxy-3,4-dihydroisoquinoline **4** (191 mg, 1 mmol) in dry THF (7 mL) was introduced dropwise and the mixture kept at −72 °C for 3 h, then treated at this temperature with 5% aqueous HCl solution (3 mL). When the reaction mixture reached room temperature, the phases were separated and the organic one extracted with 5% aqueous HCl (3 × 2 mL). The organic phase was dried and evaporated, yielding 2,3-dimethoxy-8-oxoberbine **3**, (208 mg, 67% yield) with 92% ee by HPLC [hexane/propan-2-ol = 4:1, 0.5 mL/min; t_R 27.4 min (major), t_R 32.0 min]. After recrystallization from diethyl ether/methanol, a sample of 2,3-dimethoxy-8-oxoberbine **3** with ee >99% was obtained, showing mp 169–171 °C, $[\alpha]_D$ = +428.1 (*c* 0.359, chloroform); {lit.[19] $[\alpha]_D$ = +366.6 (*c* 0.359, chloroform), 96% ee}.

The acidic aqueous phase was alkalized with KOH pellets, re-extracted with diethyl ether (3 × 10 mL), dried and evaporated to give an oil, consisting of addition product **11** with high diastereomeric purity (98% de) by HPLC [hexane/propan-2-ol = 4:1, 0.5 mL/min; t_R 37.0, 62.9 min (major)]. Amine **11** was purified by column chromatography (dichloromethane/methanol, 50:1 → 20:1) yielding pure amine **11** (56 mg, 11% yield). IR (film) *v*: 3416 (NH), 1631 (C=O) cm^{-1}; ^1H NMR *δ*: 1.73 (s, 3H, $C(CH_3)_2$), 1.93 (s, 3H, $C(CH_3)_2$), 2.45–2.83 (m, 5H, CH_2, NH, 1H disappeared with D_2O), 2.91–2.96 (m, 2H, CH_2), 3.03–3.27 (m, 2H, CH_2), 3,74–3.95 (m, 3H, CH, CH_2) 3.81 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.37 (br s, 1H, CH), 6.48–6.51 (m, 2H, ArH), 6.57 (s, 1H, ArH), 6.59–6.71 (m, 1H, ArH), 7.08–7.16 (m, 3H, ArH), 7.27–7.48 (m, 4H, ArH); MS *m*/*z* (%): 500 (M^+, 0.6), 310 (2), 206 (10), 193 (14), 192 (100), 148 (2), 118 (2).

4.6.2. *S*)-(–)-5,6,13,13a-Tetrahydro-2,3-dimethoxy-8*H*-dibenzo[*a*,*g*]quinolizin-8-one (2,3-dimethoxy-8-oxoberbine) 3 and addition product *ent*-11. The reaction was run in the same way as described in Section 4.6.1. using oxazolidine *ent*-**5b** (331 mg, 1.07 mmol), dry THF (17 mL), *n*-BuLi (0.74 mL), and 6,7-dimethoxy-3,4-dihydroisoquinoline **4** (200 mg, 1.05 mmol). Extractive work-up yielded (−)-2,3-dimethoxy-8-oxoberbine **3** (195 mg, 60% yield) with 82% ee by HPLC [hexane/propan-2-ol = 4:1, 0.5 mL/min; t_R 27.4, 32.0 min (major)]. After recrystallization from diethyl ether/methanol, a sample with >99% ee was obtained, mp 169–172 °C, $[\alpha]_D = -413.8$ (*c* 0.359, chloroform); {lit.[19] $[\alpha]_D$ = −372.4 (*c* 0.359, chloroform), 97% ee}.

Additionally amine *ent*-**11**, with high diastereomeric purity (98% de) by HPLC [hexane/propan-2-ol = 4:1, 0.5 mL/min; t_R 52.6 min (major), t_R 95.0 min] was obtained, which was further purified by column chromatography.

4.6.3. Cyclization of amine 11 to (*R*)-(+)-2,3-dimethoxy-8-oxoberbine 3. To a solution of pure amine **11** (56 mg, 0.11 mmol) in dry THF (10 mL), *n*-BuLi (1.6 M solution in hexanes, 0.08 mL) was added at −72 °C under an argon atmosphere. The reaction mixture was allowed to warm-up to ambient temperature and quenched by the addition of an aqueous solution of 5% HCl (2 mL). Extractive work-up yielded (+)-2,3-dimethoxy-8-oxoberbine **3** (17 mg, 50% yield) with 99% ee by HPLC. This provided an additional 9% yield of lactam **3**.

4.6.4. Cyclization of amine *ent*-11 to (*S*)-(–)-2,3-dimethoxy-8-oxoberbine 3. The reaction was run in the same way as described in Section 4.6.3 using amine *ent*-**11** (109 mg, 0.2 mmol), dry THF (20 mL) and *n*-BuLi (1.6 M solution in hexanes, 0.3 mL). Extractive work-up yielded (*S*)-(−)-2,3-dimethoxy-8-oxoberbine **3**, (35 mg, 57% yield) with >99% ee by HPLC. This provided an additional 11% yield of lactam **3**.

4.7. Reduction reaction of 8-oxoberbine 3 to 2,2-dimethoxy-5,8,13,13a-tetrahydro-6*H*-dibenzo[*a*,*g*]guinolizine (*O*-methylbharatamine) 2

4.7.1. (*R*)-(+)-*O*-Methylbharatamine 2. To a solution of (*R*)-(+)-**3** (70 mg, 0.23 mmol, >99% ee by HPLC) in dry THF (15 mL), $LiAlH_4$ (70 mg) was added portionwise with stirring. The mixture was refluxed for 30 min and left to reach ambient temperature. The excess of the reducing agent was decomposed with water (0.7 mL) and 20% aqueous NaOH solution (0.2 mL). The ether was decanted and the solid material extracted with diethyl ether (3 × 10 mL). The combined ether extracts were dried and evaporated to give a yellow oil, which was purified by column chromatography (dichloromethane). Pure (*R*)-(+)-*O*-methylbharatamine **2** (60 mg, 90% yield) was obtained with >99% ee by HPLC [hexane/propan-2-ol = 4:1, 0.5 mL/min; t_R 35.4 min]; $[\alpha]_D$ = +282.3 (*c* 0.32, chloroform). The free base **2** was converted to its hydrochloride salt with hydrochloric acid in methanol, mp 223–225 °C (dec).

4.7.2. (*S*)-(–)-*O*-Methylbharatamine 2. The reaction was run in the same way as described in Section 4.7.1 using (*S*)-(−)-**3** (60 mg, 0.19 mmol, >99% ee by HPLC),

dry THF (20 mL) and $LiAlH_4$ (60 mg). After work-up and column chromatography, pure (*S*)-(−)-*O*-methylbharatamine **2** (51 mg, 89% yield) was obtained with >99% ee by HPLC [hexane/propan-2-ol = 4:1, 0.5 mL/min; t_R 18.5 min]; $[\alpha]_D = -285.5$ (*c* 0.51, chloroform). IR (KBr) *v*: 2751, 1644, 1610, 1512 cm^{-1}; ^1H NMR δ: 2.60–2.70 (m, 2H, H-5, H-6), 2.91 (dd, $J = 11.2$, 16.1 Hz, 1H, H-13), 3.10–3.20 (m, 2H, H-5, H-6), 3.33 (dd, $J = 3.8$, 16.1 Hz, 1H, H-13), 3.63 (dd, $J = 3.8$, 11.2 Hz, 1H, H-13a), 3.75 (d, $J = 14.9$ Hz, 1H, H-8), 3.88 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.01 (d, $J = 14.9$ Hz, 1H, H-8), 6.63 (s, 1H, ArH isoquinoline ring), 6.76 (s, 1H, ArH, isoquinoline ring), 7.08–7.12 (m, 1H, ArH), 7.14–7.17 (m, 3H, ArH); ^{13}C NMR and DEPT and ^1H–^{13}C NMR COSY δ: 29.1 (C-5), 36.9 (C-13), 51.4 (C-6), 55.8 (OCH_3), 56.1 (OCH_3), 58.6 (C-8), 59.6 (C-13a), 108.4, 111.2 (C-1, C-4), 125.7 (C-9), 126.0 (C-10), 126.1 (C-11), 126.6, 129.6 (C-4a, C-13b), 128.6 (C-12), 134.2, 134.3 (C-8a, C-12a), 147.2, 147.3 (C-2, C-3); MS *m*/*z* (%): 295 (M^+, 77), 294 (100), 280 (13), 191 (11), 190 (26), 176 (10),105 (15), 104 (16).

Free base **2** was converted to its hydrochloride salt with hydrochloric acid in methanol, mp 206–207 °C (dec).

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