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Asymmetric synthesis of (*R*)-(+)- and (*S*)-(−)-2,3-methylenedioxy-8-oxoberbine (gusanlung D)

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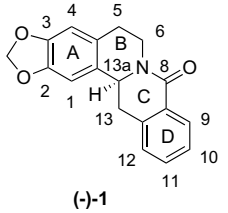
Abstract—The reaction of 6,7-methylenedioxy-3,4-dihydroisoquinoline with laterally lithiated *o*-toluamides in which the amine part derived from (1*S*,2*S*)-thiomicamine or (1*R*,2*S*)-2-amino-1-phenylpropanol, affording (*R*)-(+)- and (*S*)-(−)-2,3-methylenedioxy-8-oxoberbine in 77% and 64% yield, respectively, and with enantiomeric excess >99% is described. Physical and spectral data of the synthetic product differ from those reported for the natural alkaloid, gusanlung D.

1. Introduction

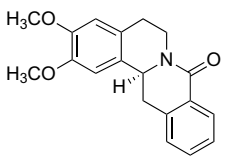
(−)-Gusanlung D isolated from *Acangelisia gusanlung* H. S. Lo, by Zhang et al.[1] in 1995 is the first optically active natural protoberberine alkaloid unoxygenated at ring D. Its structure as (*S*)-(−)-2,3-methylenedioxy-8-oxoberbine **1** was elucidated on the basis of spectral data analysis. Recently the synthesis of racemic amide **1** has been reported from three laboratories.[2–4] Herein we report the first asymmetric synthesis of compound **1**.

As a continuation of our study on stereoselective syntheses of isoquinoline alkaloids based on the addition of carbon nucleophiles to imines,[5] we extended this approach to the synthesis of the protoberberine system. The key step of the synthesis, in which a new stereogenic centre at C-13a was created, involved the addition of laterally metallated chiral *o*-toluamides to cyclic imines. The metallation methodology has been developed for the synthesis of racemic heterocyclic compounds, including protoberberines, and proceeded with high regiochemical control.[6,7] This feature coupled with the simultaneous cyclization of the addition product, offers a direct approach to the protoberberine skeleton and its related structures. It has been successfully applied to the asymmetric synthesis of unnatural 2,3-dimethoxy-8-oxoberbine **2** and ***ent*-2**,[8,9] as well as the naturally occurring (−)-xylopinine **3**.[10]

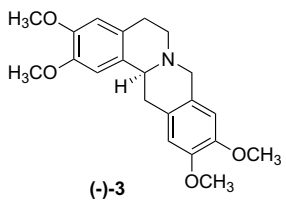
In our concept of the asymmetric synthesis of gusanlung D, an addition reaction of the carbon nucleophile, derived from optically active *o*-toluamide **4**, to 6,7-methylenedioxy-3,4-dihydroisoquinoline **5** was planned. The retrosynthetic analysis of this synthesis is shown in Scheme 1. The chiral auxiliary was placed at the carbon nucleophile, derived from commercially available,



(-)-1



(-)-2



(-)-3

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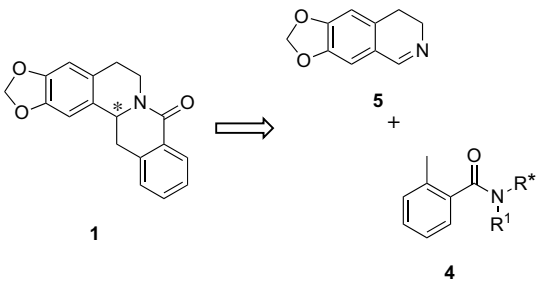
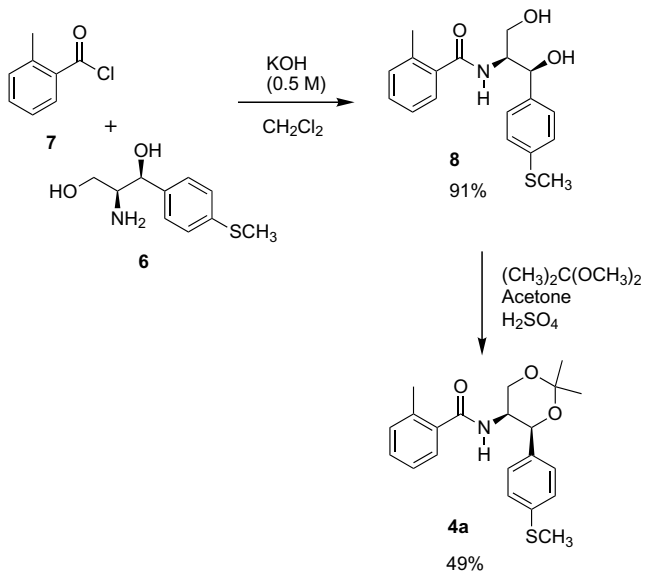


Scheme 1.

o-toluoyl chloride and enantiomerically pure (1*S*,2*S*)-2-amino-1-[4-(methylthio)phenyl]-1,3-propanediol and (1*R*,2*S*)-2-amino-1-phenylpropanol.

2. Results and discussion

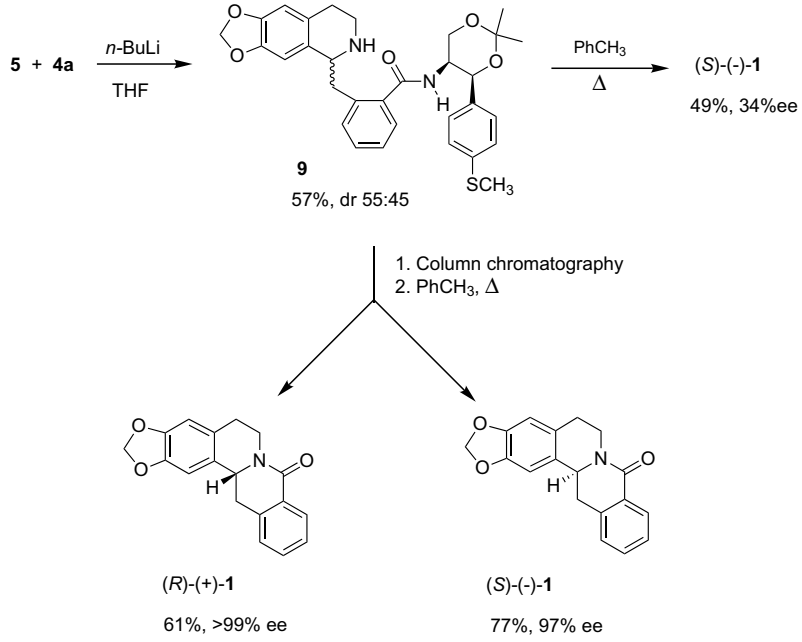
At first (1*S*,2*S*)-(+)-thiomicamine **6**, an industrial waste product, which has been used successfully by our research group as a source or promoter of stereochemistry in many types of organic syntheses, especially in enantioselective syntheses of isoquinoline alkaloids,[11–15] was chosen. In the reaction of thiomicamine **6** with *o*-toluoyl chloride **7**, amide **8** was obtained in 91% yield. The two hydroxyl groups in compound **8** were protected as a 1,3-*O*-isopropylidene derivative prepared in the reaction of diol **8** with 2,2-dimethoxypropane in dry acetone, catalyzed with concentrated sulfuric acid, giving compound **4a** in 49% yield, after column chromatography purification (Scheme 2).



Scheme 2.

Treatment of **4a** with *n*-butyllithium (2.2 equiv) in dry THF, at −72 °C for 30 min resulted in the formation of a deep brown coloured anion, which upon addition of 6,7-methylenedioxy-3,4-dihydroisoquinoline **5**[16] and subsequent work-up provided amine **9** as a diastereomeric mixture 55:45 (by HPLC) in 57% yield. The crude product **9**, when heated in refluxing toluene under an argon atmosphere, was cyclized to 2,3-methylenedioxy-8-oxoberbine **1** in 49% yield with 34% ee (by HPLC) (Scheme 3). This compound was used as our reference sample of 'racemic' amide **1** for further HPLC comparison and enantiomeric excess determination.

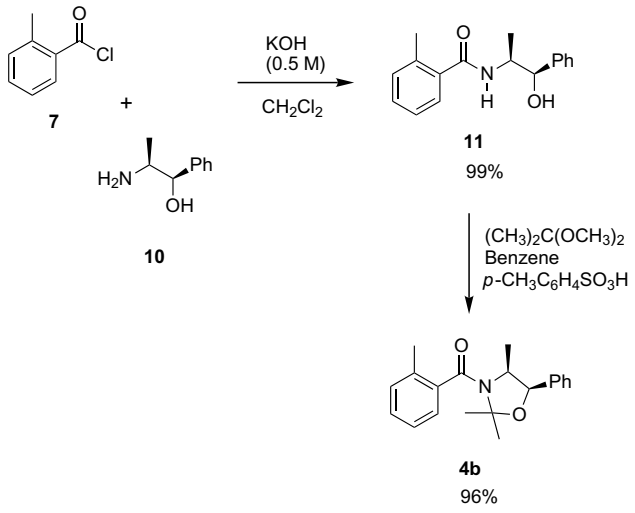
The two diastereoisomers of compound **9** could be separated by column chromatography on silica gel. When diastereomerically pure **9**, characterized by a shorter



Scheme 3.

retention time on HPLC, was cyclized in the same conditions as above, the laevorotatory enantiomer of amide **1**, showing a longer retention time, was formed (97% ee) in 77% yield. The cyclizaton of the diastereomer **9**, with longer retention time by HPLC, led to dextrorotatory 2,3-methylenedioxy-8-oxoberbine **1** in 61% yield. After recrystallization from methanol, a sample of (*R*)-(+)-**1** with >99% ee was obtained, showing mp 194–196 °C and $[\alpha]_D = +415.3$ (*c* 0.77, $CHCl_3$).

Since this initial study showed that the diastereoselectivity of the addition reaction of amide **4a** to imine **5** was rather low and that intermediate amine **9** had to be cyclized in the next step of the synthesis, we turned our attention to amides with other chiral auxiliaries. Thus, (1*R*,2*S*)-2-amino-1-phenylpropanol **10** was chosen and reacted with *o*-toluoyl chloride **7** to give the amide **11** in 99% yield. The functional NH and OH groups were protected as oxazolidine derivative **4b** prepared in 96% yield via reaction of **11** with 2,2-dimethoxypropane catalyzed by *p*-toluenesulfonic acid, in refluxing benzene under an argon atmosphere (Scheme 4).



Scheme 4.

The carbanion generated from compound **4b** with the aid of 1.1 M equiv of *n*-butyllithium, in reaction conditions similar as for amide **4a**, followed by addition of 6,7-methylenedioxy-3,4-dihydroisoquinoline **5** and subsequent work-up, afforded 8-oxoberbine (−)-**1**, isolated in 33% yield with 81% ee. Additionally, the secondary amine **12** was isolated in 31% yield as a diastereomeric mixture (Scheme 5).

The secondary amine **12** was cyclized to 8-oxoberbine **1** by addition of *n*-butyllitium to the THF solution of **12** at −72 °C, and then allowed to reach ambient temperature. Pure 8-oxoberbine **1**, with the same absolute configuration at C-13a, was isolated with 98% ee (Scheme 5). Therefore the total yield of compound **1** was 64%.

After recrystallization from methanol, a sample of 2,3-methylenedioxy-8-oxoberbine **1** with >99% ee was obtained, showing mp 195–197 °C (lit.[1] mp 250–251 °C) and $[\alpha]_D = -432.6$ (*c* 0.80, $CHCl_3$) {lit.[1] $[\alpha]_D = -345$ (*c* 0.018, $CHCl_3$)}.

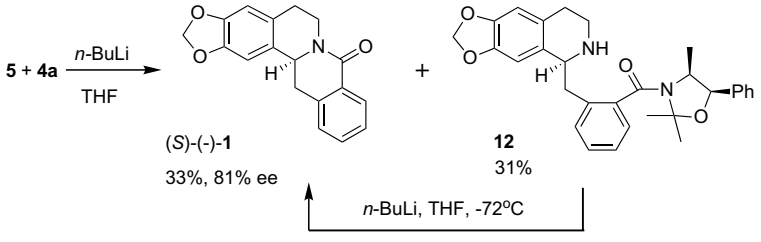
3. Conclusion

(*R*)-(+)- and (*S*)-(−)-2,3-Methylenedioxy-8-oxoberbines **1** prepared in the above described asymmetric synthesis were fully characterized by UV, IR, ^{1}H NMR, ^{13}C NMR, 2D NMR and MS spectra (Table 1). The enantiomeric excess was established by HPLC analysis using a Chiracel OD-H column. The absolute configuration of (+)- and (−)-**1** was postulated on the basis of the sign of their specific rotation, which corresponded to that reported for the other berbines, for example, 2,3-dimethoxy-8-oxoberbine **2**.[8,17,18] The synthesized laevorotatory (*S*)-enantiomer **1** was characterized on HPLC as that of a longer retention time, while the dextrorotatory (*R*)-enantiomer **1** as that of a shorter retention time, relative to that of the sample of **1** with 34% ee.

As shown in Table 1, the physical properties {mp, $[\alpha]_D$} and spectral data of our synthetic product **1** differ from those reported for natural gusanlung D, but are in line with those reported for racemic compound **1**.[2,4]

From our experience in the synthesis of 8-oxoberbines,[18,19] we have noticed that the main product could often be accompanied by dehydrolactam, for example, **13**.[4,20] In our synthesis, the presence of the concomitant compound **13** was difficult to notice by HPLC since its retention time was similar to that of (*S*)-(−)-enantiomer-**1**, which is illustrated in Figure 1.

However, these two compounds could be easily distinguished by UV spectra, as that of the dehydrolactam **13** showed a strong absorption at 330 nm.[21] In the UV spectrum of our pure 2,3-methylenedioxy-8-oxoberbine **1**, there was no absorption in this region.

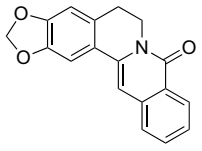


Scheme 5.

Table 1. The physical and IR, ^{1}H NMR and ^{13}C NMR, and MS data for synthetic compound (*S*)-(−)-**1** and natural gusanlung D

	Synthetic **1**		Gusanlung D	
Mp	195–197 °C (MeOH)		250–251 °C	
$[\alpha]_D$	−432.6 (*c* 0.80, $CHCl_3$)		−345 (*c* 0.018, $CHCl_3$)	
UV λ_{max}	209, 229, 289 nm		222, 273, 294, 320 nm	
IR ν (KBr)	1637 cm^{-1}		1650 cm^{-1}	
NMR	δ_H (300 MHz)	δ_C (75 MHz)	δ_H (300 MHz)	δ_C (75 MHz)
1	6.71 (s)	105.8	7.35 (s)	107.3
2		146.5[a]		135.0
3		146.7[a]		147.0
4	6.67 (s)	108.6	6.80 (s)	107.5
4a		128.8		126.5
5	2.70–2.80 (m)	29.6	2.70–3.40 (m)	29.7
	2.82–3.02 (m)			
6	2.82–3.02 (m)	38.7	2.70–3.40 (m)	42.0
	4.93–4.99 (m)		4.80 (m)	
8		164.5		162.0
8a		137.2		117.3
9	8.13 (d, 7.4)	128.6	8.07 (d, 8.0)	128.7[b]
10	7.34–7.40 (m)	127.3	7.29–7.41 (m)	127.9[b]
11	7.41–7.49 (m)	131.8	7.29–7.41 (m)	127.1[b]
12	7.24 (d, 7.4)	126.8	7.29–7.41 (m)	126.8[b]
12a		129.0		124.6
13	2.82–3.02 (m)	38.1	2.70–3.40 (m)	33.5
	3.18 (dd, 15.6, 3.7)			
13a	4.83 (dd, 13.3, 3.7)	55.2	3.95 (m)	49.4
13b		128.5		126.5
OCH_2O	5.96 (s)	101.1	6.20, 6.06 (2s)z	100.9
MS *m*/*z*	293, 276, 204, 174, 119, 118, 90		293, 248, 235, 204, 178	
HRMS	Calcd 293.1052, found 293.1034		Calcd 293.1047, found 293.1017	

[a,b]Interchangeable assignments.



13

In our opinion, there is the possibility that the isolated natural gusanlung D could be contaminated with a considerable amount of dehydrolactam **13**, due to the presence of the absorption band at 320 nm in the UV spectra (Table 1). However, a comparison of physical and NMR data published for gusanlung D with those published for compound **13**[4,20] and with our data for synthetic **1** did not lead to any constructive explanation of the differences in physical and spectral data for gusanlung D and (−)-**1**. As a result, the problem concerning the structure of the natural originated (−)-gusanlung D remains to be clarified.

4. Experimental

4.1. General

Melting points: determined on a Koffler block and are uncorrected. UV spectra: Jasco V-550. IR spectra: Bruker FT-IR IFS 113 V in KBr pellets. NMR spectra: Varian Gemini 300 in $CDCl_3$ (unless stated otherwise), 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 reagents were purchased from commercial sources and used without additional purification. 6,7-Methylenedioxy-3,4-dihydroisoquinoline **5** was prepared as previously described.[16]

4.2. (1*S*,2*S*)-2-*o*-Toluamide-1-[4-(methylthio)phenyl]-1,3-propanediol 8

To (1*S*,2*S*)-(+)-thiomicamine **6** (2.13 g, 10 mmol) suspended in dichloromethane[22] (135 mL) aqueous 0.5 M KOH (65 mL, 10 mmol) was added, then *o*-toluoyl chloride **7** (1.54 g, 10 mmol) introduced dropwise with stirring at 0 °C. After 30 min the cooling bath was removed and stirring continued at room temperature for 2 h. The resulting white precipitate of amide **8** was fil-

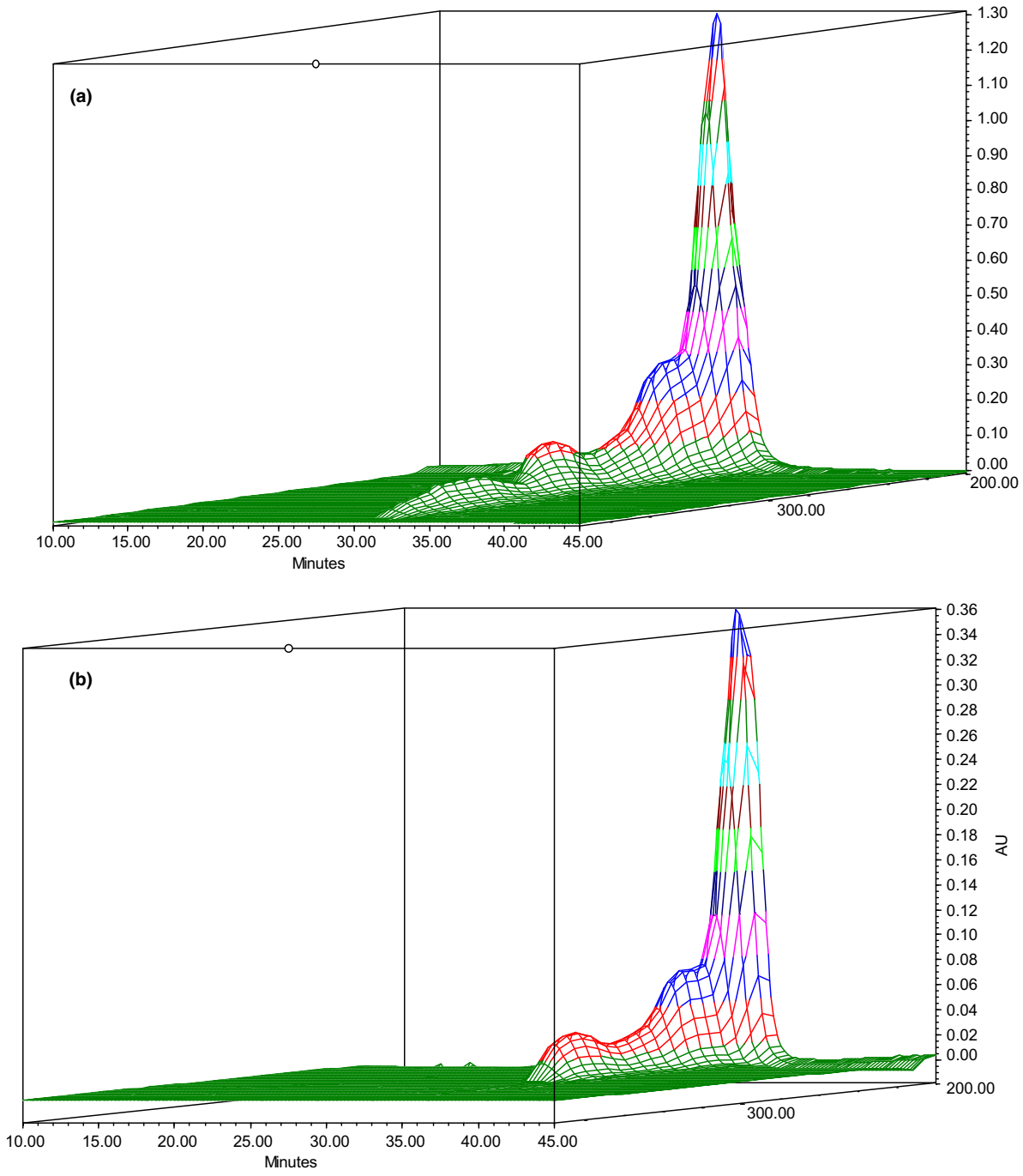


Figure 1. (a) 3D HPLC chromatogram of (*S*)-(−)-2,3-methylenedioxy-8-oxoberbine **1** contaminated with dehydrolactam **13**. (b) 3D HPLC chromatogram of pure (*S*)-(−)-**1**.

tered off (2.115 g). The phases from the filtrate were separated and the organic one was washed with water (3×10 mL) and brine (10 mL) and dried. After removal of organic solvent under reduced pressure an additional amount of amide **8** (1.04 g) was obtained. Recrystallization from diethyl ether/diisopropyl ether gave crystalline **8** (3.004 g, 91%); mp 125–126 °C; $[\alpha]_D = +84.7$ (*c* 1.005, MeOH); IR *v*: 3354 (OH, NH), 1616 (C═O), 1526 (NH) cm^{-1}; ^1H NMR δ: 2.21 (s, 3H, $ArCH_3$), 2.46 (s, 3H, SCH_3), 3.29 and 3.84 (br s, 1H each, OH, disappeared with D_2O), 3.89 (d, $J = 3.3$ Hz, 2H, CH_2O), 4.22–4.29 (m, 1H, C*H*NH), 5.05 (d, $J = 3.6$ Hz, 1H, C*H*(OH)), 6.52 (d, $J = 8.2$ Hz, 1H, NH(CO)), 7.12–7.30 (m, 8H, ArH); ^{13}C NMR (CD_3OD) δ: 16.0 (CH_3S), 19.7 (CH_3Ar), 58.4 (C-2), 62.7 (C-3), 72.3 (C-1), 126.5 (CH), 127.4 (2C, CH) 127.9 (3C, CH) 130.6 (CH), 131.5 (CH), 136.6 (C), 137.9 (C), 138.8 (C), 140.7 (C), 173.0 (C═O); MS *m*/*z* (%): 331 (M^+, 0.5), 161 (33), 153 (14), 152 (12), 119 (100), 91 (31); Anal. Calcd for $C_{18}H_{21}NO_3S \times \frac{1}{4}H_2O$: C, 64.36; H, 6.45; N, 4.17; S, 9.55. Found: C, 64.70; H, 6.10; N, 4.10; S, 9.33.

4.3. (1*S*,2*S*)-2-*o*-Toluamide-1-[4-(methylthio)phenyl]-1,3-*O*-isopropylidenepropane 4a

Amide **8** (2.94 g, 8.9 mmol) was dissolved in dry acetone (35 mL) after which 2,2-dimethoxypropane (5.44 g, 52 mmol) and concentrated sulfuric acid (0.35 mL) were added. Stirring was continued for 2 h. The solution was neutralized with 10% aqueous Na_2CO_3 (3 mL). Acetone was removed in vacuo and the remaining aqueous phase extracted with dichloromethane (3×10 mL). The combined organic extracts were dried and the solvents removed in vacuo yielding 3.282 g of a colourless oil, which was then purified by column chromatography (dichloromethane and dichloromethane/methanol; 200:1 → 100:1) to afford a pure oily compound **4a** (1.612 g, 49%). $[\alpha]_D = +119.8$ (*c* 1.065, $CHCl_3$); IR *v*: 3428 (NH), 1661 (C=O), 1296 (COC), 1199 (COC) cm^{-1}; ^1H NMR δ: 1.52 (s, 3H, $C(CH_3)_2$), 1.60 (s, 3H, $C(CH_3)_2$), 2.08 (s, 3H, $ArCH_3$), 2.45 (s, 3H, SCH_3), 3.99 (dd, $J = 1.92$, 12.1 Hz, 1H, CH_2O), 4.35 (dd, $J = 1.9$, 12.1 Hz, 1H, CH_2O), 4.46 (dddd, $J = 1.9$, 1.9, 1.9, 9.6 Hz, 1H, C*H*NH), 5.26 (d, $J = 1.9$ Hz, 1H, ArCHO), 6.34 (d, $J = 9.6$ Hz, 1H, NH), 7.02–7.05 (m, 1H, ArH), 7.09–7.14 (m, 2H, ArH), 7.22–7.32 (m, 5H, ArH); ^{13}C NMR δ: 16.2 (CH_3S), 18.6 (*C*H_3C), 19.3 (CH_3Ar), 29.8 (*C*H_3C), 46.2 (C-2), 64.7 (C-3), 71.6 (C-1), 99.6 (CH_3*C*), 125.5 (CH), 125.6 (2C, CH), 126.5 (CH), 126.6 (2C, CH), 129.6 (CH), 130.0 (CH), 135.3 (C), 135.8 (C), 136.1 (C), 137.5 (C), 169.2 (C=O); MS *m*/*z* (%): 371 (M^+, 1.3), 160 (29), 151 (50), 119 (100), 91 (35); Anal. Calcd for $C_{21}H_{25}NO_3S \times \frac{1}{2}H_2O$: C, 66.29; H, 6.89; N, 3.68; S, 8.43. Found: C, 66.50; H, 6.85; N, 3.58; S, 8.16.

4.4. Addition product 9

Amide **4a** (371 mg, 1 mmol) was dissolved in dry THF (10 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-methylenedioxy-3,4-dihydroisoquinoline **5**[16] (175 mg, 1 mmol) in dry THF (10 mL) was added and the mixture kept at −72 °C for 4 h and then 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 solvents removed under reduced pressure yielding a yellow foam (549 mg). HPLC analysis of the crude reaction product indicated the presence of two new compounds {diastereoisomers of amine **9** in a ratio 55:45 [hexane/propan-2-ol=9:1, 0.5 mL/min; t_R 53.2 min (major), t_R 56.9 min]} together with unreacted amide **4a** and imine **5**. The crude product was purified by column chromatography (dichloromethane/methanol, 50:1) yielding diastereomerically enriched and pure fractions of compound **9** (312 mg, 57%). The fraction containing pure diastereomer **9** with a shorter retention time (t_R 53.2 min) was isolated as a colourless solid (120 mg, 22% yield). Spectral data for pure diastereoisomer **9**: IR *v*: 1656 (C=O) cm^{-1}; ^1H NMR δ: 1.52 (s, 3H, $C(CH_3)_2$), 1.60 (s, 3H, $C(CH_3)_2$), 1.62 (br s, 1H, NH, disappeared with D_2O), 2.36 (s, 3H, SCH_3), 2.48–2.60 (m, 2H, CH_2), 2.67–2.85 (m, 2H, CH_2), 2.89–3.05 (m, 2H, CH_2), 3.97 (dd, $J = 1.9$, 12.1 Hz, 1H, CH_2O), 4.12 (dd, $J = 3.0$, 9.2 Hz, 1H, ArCHN), 4.32 (dd, $J = 1.9$, 12.1 Hz, 1H, CH_2O), 4.54 (dd, $J = 1.9$, 9.1 Hz, 1H, C*H*(NHCO)), 5.25 (d, $J = 1.9$ Hz, 1H, ArCHO), 5.97 (ABq, $J = 1, 4$ Hz, 2H, OCH_2O), 6.55 (s, 1H, ArH), 6.67 (s, 1H, ArH), 7.02–7.11 (m, 3H, ArH), 7.18–7.33 (m, 5H, ArH), 8.03 (d, $J = 9.1$ Hz, 1H, CONH, disappeared with D_2O); MS *m*/*z* (%): 546 (M^+, 0.6), 292 (6), 264 (2), 176 (100), 118 (6), 90 (3). The fraction containing pure diastereomer **9** with a longer retention time (t_R 56.9 min) was isolated as a colourless solid (80 mg, 15%); ^1H NMR (signals different from those for the first diastereoisomer **9**) δ: 1.47 (s, 3H, $C(CH_3)_2$), 1.60 (s, 3H, $C(CH_3)_2$), 1.80 (br s, 1H, NH, disappeared with D_2O), 2.33 (s, 3H, SCH_3), 3.68 (dd, $J = 3.0$, 9.2 Hz, 1H, ArCHN), 4.52 (dd, $J = 1.9$, 9.1 Hz, 1H, C*H*(NHCO)), 5.92 (ABq, $J = 1, 4$ Hz, 2H, OCH_2O), 6.53 (s, 1H, ArH), 6.71 (s, 1H, ArH), 7.86 (d, $J = 9.0$ Hz, 1H, CONH, disappeared with D_2O).

4.5. Cyclization of addition product 9 to 5,6,13,13a-tetrahydro-2,3-methylenedioxy-8H-dibenzo[*a*,*g*]quinolizin-8-one (2,3-methylenedioxy-8-oxoberbine) 1

4.5.1. Cyclization of crude reaction product. Crude product **9** (373 mg, 0.7 mmol) was refluxed under argon in dry toluene (15 mL) for 22 h. After cooling to room temperature, it was evaporated to dryness and the remaining oil (370 mg) dissolved in diethyl ether (30 mL) and extracted with 5% aqueous HCl (4×2 mL). The organic phase was dried and evaporated yielding 200 mg of an oil, which was purified by repeated column chromatography (dichloromethane) to yield pure 2,3-methylenedioxy-8-oxoberbine **1** (110 mg, 49%) with 34% ee of the enantiomer with a longer retention time by HPLC [hexane/propan-2-ol=4:1, 0.5 mL/min; t_R 28.4 min, t_R 30.0 min (major)]; mp 175–178 °C (diethyl ether). The acidic aqueous phase was alkalized with KOH pellets, reextracted with diethyl ether (3×10 mL), dried and evaporated to give a yellow oil (96 mg), which consisted of unreacted 6,7-methylenedioxy-3,4-dihydroisoquinoline **5** and thiomicamine **6**, according to TLC and HPLC analysis.

4.5.2. Cyclization of pure 9 with a shorter retention time. The fraction consisting of only one diastereomer of **9** with a shorter retention time (120 mg, 0.2 mmol) was refluxed under argon in dry toluene (10 mL) under the same conditions as that for crude product **9**. After work-up the neutral fraction, isolated as a yellow foam (45 mg, 77%), consisted of (−)-2,3-methylenedioxy-8-oxoberbine **1**, 97% ee (by HPLC), the enantiomer with longer retention time. From the amine fraction thiomicamine **6** (21 mg) was recovered.

4.5.3. Cyclization of pure 9 with longer retention time. (*R*)-(+)-5,6,13,13a-Tetrahydro-2,3-methylenedioxy-8H-dibenzo[*a*,*g*]quinolizin-8-one (2,3-methylenedioxy-8-oxoberbine) 1. The fraction consisting of the diastereomer **9** with a longer retention time (80 mg, 0.15 mmol)

was cyclized under the same conditions as described above. After work-up and recrystallization, pure dextrorotatory amide **1** (27 mg, 61%) was isolated with >99% ee, mp 194–196 °C (methanol); $[\alpha]_D = +415.3$ (*c* 0.77, $CHCl_3$).

4.6. (1*R*,2*S*)-2-*o*-Toluamide-1-phenylpropanol 11

To (1*R*,2*S*)-2-amino-1-phenylpropanol **10** (0.775 g, 5 mmol) dissolved in dichloromethane (67 mL) aqueous KOH (33 mL, 0.5 M) was added, and *o*-toluoyl chloride **7** (0.770 g, 5 mmol) then introduced dropwise at 0 °C. After 30 min, the cooling bath was removed and the mixture was stirred at room temperature. After 2 h, the reaction had gone to completion according to TLC analysis. The white precipitate of **11** was filtered off (1.338 g, 99%). An analytical sample was crystallized from dichloromethane/methanol/diethyl ether yielding crystalline **11**, mp 152–154 °C; $[\alpha]_D = -99.7$ (*c* 1.02, $CHCl_3$); IR *v*: 3379 (OH), 3281 (NH), 1637 (C=O) cm^{-1}; ^1H NMR δ: 1.12 (d, $J = 7.1$ Hz, 3H; $CHCH_3$), 2.44 (s, 3H, $ArCH_3$), 3.64 (br s, 1H, OH, disappeared with D_2O), 4.46–4.57 (m, 1H, $CHCH_3$), 4.93 (d, $J = 3.3$ Hz, 1H, CHOH), 5.92 (d, $J = 8.0$ Hz, 1H, NH, disappeared with D_2O), 7.16–7.41 (m, 9H, ArH); ^{13}C NMR δ: 14.8 (C-3), 19.8 (CH_3Ar), 51.3 (C-2), 76.5 (C-1), 125.6 (CH), 126.2 (2C, CH), 126.4 (CH), 126.6 (CH), 127.5 (CH), 128.1 (CH), 129.9 (CH), 130.9 (CH), 135.8 (C), 135.9 (C), 140.6 (C), 170.4 (C=O); MS *m*/*z* (%): 270 (M^+, 0.2), 163 (31); 162 (22), 119 (100), 91 (26); Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.78; H, 6.95; N, 5.13.

4.7. (4*S*,5*R*)-2,2,4-Trimethyl-3-*o*-toluoyl-5-phenyloxazolidine 4b

To compound **11** (1.076 g, 4 mmol) in dry benzene (50 mL), 2,2-dimethoxypropane (6.8 g, 65 mmol) was added under an argon atmosphere followed by catalytic amounts of *p*-toluenesulfonic acid (0.2 g). The reaction mixture was stirred at reflux for 2 h and allowed to reach room temperature. The reaction mixture was then 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 → 100:1) to give pure oxazolidine **4b** (1.192 g, 96%). Recrystallization from diethyl ether gave white crystals of **4b**; mp 117–119 °C; $[\alpha]_D = +22.9$ (*c* 0.995, $CHCl_3$); IR *v*: 1619 (C=O) cm^{-1}; ^1H NMR δ: 0.59 (d, $J = 6.6$ Hz, 3H, $CHCH_3$); 1.86 (s, 3H, $C(CH_3)_2$), 1.94 (s, 3H, $C(CH_3)_2$), 2.39 (s, 3H, $ArCH_3$), 3.79 (br s, 1H, CHN), 5.29 (d, $J = 4.9$ Hz, 1H, CHO), 7.22–7.38 (m, 9H, ArH); ^{13}C NMR δ: 16.4 (CH_3C-4), 18.9 (CH_3Ar), 23.8 (CH_3C-2), 27.5 (CH_3C-2), 58.4 (C-4), 78.5 (C-5), 94.6 (C-2), 125.6 (CH), 125.7 (CH), 126.0 (2C, CH), 127.7 (CH), 128.2 (2C, CH), 128.7 (CH), 130.3 (CH), 135.9 (2C, C), 137.6 (C), 167.7 (C=O); MS *m*/*z* (%): 294 ($M^+ - CH_3$, 10), 203 (51), 148 (36), 119 (100), 91 (45); Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.94; H, 7.13; N, 4.54.

4.8. (*S*)-(−)-5,6,13,13a-Tetrahydro-2,3-methylenedioxy-8H-dibenzo[*a*,*g*]quinolizin-8-one (2,3-methylenedioxy-8-oxoberbine) 1 and addition product 12

Oxazolidine **4b** (309 mg, 1 mmol) was dissolved in dry THF (10 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-methylene- dioxy-3,4-dihydroisoquinoline **5**[16] (175 mg, 1 mmol) in dry THF (8 mL) was introduced dropwise and the mixture kept at −72 °C for 3 h, then 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 solvents removed under reduced pressure yielding an oily product (484 mg). HPLC analysis of the crude reaction product indicated the presence of mainly one enantiomer of 2,3-methylenedioxy-8-oxoberbine **1** with a longer retention time, accompanied by the addition product **12** [hexane/propan-2-ol=4:1, 0.5 mL/min; t_R 36.8 min]. The crude product was dissolved in diethyl ether (30 mL) and extracted with 5% aqueous HCl (3×2 mL). The organic phase was dried and evaporated in vacuo yielding an oily product (119 mg), which was purified by column chromatography (dichloromethane) to give pure (−)-2,3-methylenedioxy-8-oxoberbine **1**, (98 mg, 33%) 81% ee by HPLC. Recrystallization from methanol furnish a sample of **1** with >99% ee, mp 195–197 °C, (lit.[1] mp 250–251 °C); $[\alpha]_D = -432.6$ (*c* 0.80, $CHCl_3$); {lit.[1] $[\alpha]_D = -345$ (*c* 0.018, $CHCl_3$)}; UV λ_{max} (MeOH): 209, 229, 289 nm; IR *v*: 1637 (C=O), 1330 (CN) cm^{-1}: ^1H NMR and 2D ^1H–^1H NMR COSY δ: 2.70–2.80 (m, 1H, H-5), 2.82–3.02 (m, 3H, H-5, H-6, H-13), 3.18 (dd, $J = 3.7$, 15.6 Hz, 1H, H-13), 4.83 (dd, $J = 3.7$, 13.3 Hz, 1H, H-13a), 4.93–4.99 (m, 1H, H-6), 5.96 (s, 2H, OCH_2O), 6.67 (s, 1H, H-4), 6.71 (s, 1H, H-1), 7.24 (d, $J = 7.4$ Hz, 1H, H-12), 7.34–7.40 (m, 1H, H-10), 7.41–7.49 (m, 1H, H-11), 8.13 (d, $J = 7.4$ Hz, 1H, H-9); ^{13}C NMR and DEPT and ^1H–^{13}C NMR COSY δ: 29.6 (C-5), 38.1 (C-13), 38.7 (C-6), 55.2 (C-13a), 101.1 (OCH_2O), 105.8 (C-1), 108.6 (C-4), 126.6 (C-12), 127.3 (C-10), 128.5 (C-13b), 128.6 (C-9), 128.8 (C-4a), 129.0 (C-12a), 131.8 (C-11), 137.2 (C-8a), 146.5, 146.9 (C-2, C-3), 164.5 (C-8); MS *m*/*z* (%): 293 (M^+, 47), 276 (17), 204 (6), 174 (15), 119 (26), 118 (69), 90 (100); HRMS calcd for $C_{18}H_{15}NO_3$ 293.1052, found 293.1034.

The acidic aqueous phase was alkalized with KOH pellets, reextracted with diethyl ether (3×10 mL), dried and evaporated to give a yellow oil (288 mg), which consisted mainly of one diastereoisomer of the addition product **12**, by HPLC [hexane/propan-2-ol=4:1, 0.5 mL/min; t_R 36.8 min]. The oily product was purified by chromatography (dichloromethane/methanol 100:1 → 50:1) to give pure **12** (151 mg, 31% yield). IR *v*: 1633 (C=O) cm^{-1}; ^1H NMR δ: 0.58 (d, $J = 5.8$ Hz, 3H, $CHCH_3$); 1.86 (s, 3H, $C(CH_3)_2$), 1.92 (s, 1H, NH, disappeared with D_2O) 2.00 (s, 3H, $C(CH_3)_2$), 2.61–2.79 (m, 2H, CH_2), 2.86–3.08 (m, 2H, CH_2), 3.12–3.19 (m, 2H, CH_2), 3.85–3.87 (br m, 1H, $CHNCH_3$), 4.33 (d, $J = 9.3$ Hz, 1H, ArCHN), 5.27 (d, $J = 4.4$ Hz, 1H,

CHO), 5.91 (d, $J = 1.4$ Hz, 2H, OCH_2O), 6.56 (s, 1H, ArH), 6.77 (s, 1H, ArH), 7.19–7.39 (m, 9H, ArH); MS m/z (%): 484 (M^+, 0.9), 292 (6), 264 (9), 176 (100), 118 (4), 91 (4). HRMS calcd for $C_{30}H_{32}N_2O_4$ 484.2362, found 484.2365.

4.9. Cyclization of amine 12 to (−)-5,6,13,13a-tetrahydro-2,3-methylenedioxy-8H-dibenzo[*a*,*g*]quinolizin-8-one (2,3-methylenedioxy-8-oxoberbine) 1

To a solution of amine **12** (49 mg, 0.1 mmol) in dry THF (10 mL) at −72 °C, *n*-BuLi (1.6 M solution in hexanes, 0.06 mL) was added 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 20% NH_4Cl. Extractive work-up yielded (−)-2,3-methylenedioxy-8-oxoberbine **1**, which was purified by column chromatography to give pure amide **1**, in 50% yield and with 98% ee by HPLC.

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