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Diastereoselective Pomeranz–Fritsch–Bobbitt synthesis of (*S*)-(−)-*O*-methylbharatamine using (*S*)-*N*-*tert*-butanesulfinimine as a substrate

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Abstract—The protoberberine-type alkaloid, (*S*)-(−)-*O*-methylbharatamine, has been synthesized in six steps involving the addition of laterally lithiated *o*-toluamide to (*S*)-*N*-*tert*-butanesulfinimine as the crucial process. The target alkaloid was obtained in 24.4% overall yield with 88% ee.

1. Introduction

The synthesis of chiral non-racemic isoquinoline alkaloids using the Bobbitt modification of the Pomeranz–Fritsch methodology involves aminoacetals of types **1**–**3** as key intermediates[1] (Fig. 1). They are then subjected to cyclization by treatment with acids followed by reduction (catalytic hydrogenation or $NaBH_4$ reduction) to afford the 1,2,3,4-tetrahydroisoquinoline core.

So far, both enantiomers of aminoacetal **1** were used in the synthesis of (*S*)-(−)- and (*R*)-(+)-salsolidine and (*S*)-(−)-carnegine. In the enantioselective synthesis, compound (*S*)-**1** (R = H, R′ = CH_3) was prepared from classic 'Pomeranz–Fritsch' imine **4** (R′ = CH_3) by the addition of methyl lithium in the presence of external inductors of chirality of an oxazoline-type[2] (Fig. 1). In the diastereoselective synthesis, chiral imines **5** were used as substrates. Imine **5a** afforded benzylamine (*S*)-**1** (R = H, R′ = Et)

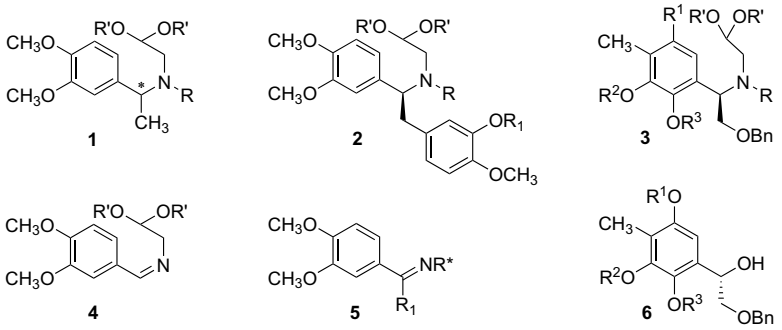

Figure 1.

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when subjected to a series of transformations involving the addition of methylmagnesium bromide, removal of the chiral auxiliary from the addition product and *N*-alkylation with the bromoacetaldehyde acetal; this was further cyclized to (*S*)-(−)-salsolidine.[3] The enantiomer (*R*)-**1** (R = H, R′ = Et) was obtained by hydride reduction of imine **5b** and transformed into (*R*)-(+)-salsolidine according to the same reaction scheme.[4]

In a similar fashion, chiral imine **5c**, incorporating (*S*)-phenylglycinol,[5–7] was converted into several aminoacetals of type **2**, differing in substituents in the aromatic rings. These were then transformed into benzylisoquinolines,[5] isopavines,[6] and (+)-glaucine.[7]

Aminoacetals of type **3**, which were prepared from the corresponding benzyl alcohols **6** (R^1, R^2, R^3 = alkyl, allyl) (Fig. 1) either by treatment with *N*-tosylated aminoacetaldehyde acetal to give the corresponding **3** (R = Ts),[8] or via azidolysis, catalytic hydrogenation and reaction with glyoxal monoacetal to give the corresponding compound **3** (R = H),[9,10] were used as important building blocks in the synthesis of β-adrenergic receptor antagonist MY336-a[8] as well as of ecteinascidin 743[9] and cribrostatin IV.[10]

Herein, we report the synthesis of (*S*)-(−)-*O*-methylbharatamine **14**, a protoberberine alkaloid, by applying chiral (*S*)-*N*-*tert*-butanesulfinimine *ent*-**5a** and *o*-toluamide **8** as building blocks.

2. Results and discussion

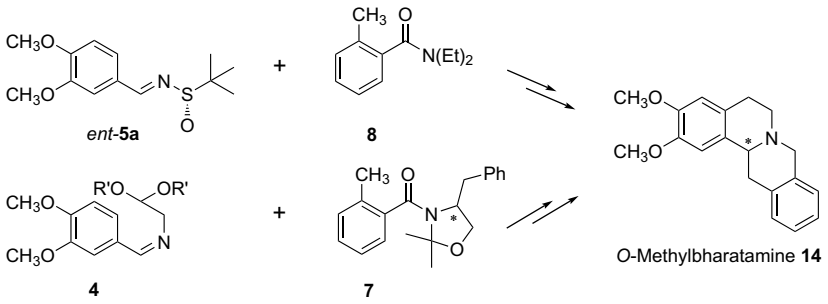
As a contribution to our study on the stereoselective modification of the Pomeranz–Fritsch–Bobbitt synthesis of isoquinoline alkaloids, in a previous paper,[11] we have described the synthesis of both enantiomers of *O*-methylbharatamine **14** of good enantiomeric purity, using achiral imine **4** and both enantiomers of *o*-toluamide **7** as substrates (Scheme 1). Herein, we report on a complementary diastereoselective synthesis of (*S*)-(−)-*O*-methylbharatamine **14**, starting with chiral sulfinaldimine *ent*-**5a** and achiral *o*-toluamide **8** (Scheme 1).

Chiral sulfimines are known to be excellent substrates for the asymmetric synthesis of amines and their derivatives;[12–14] however, only in a few cases[3,4,15–19] have they found application in the syntheses of isoquinoline alkaloids. Ellman et al.,[15] using *N*-*tert*-butanesulfinimine as a substrate performed the synthesis of pavine and isopavine-type alkaloids, in the eight-step reaction sequence, by applying the Pomeranz–Fritsch cyclization as the final step. Davis et al.[16–19] via the addition of laterally lithiated *o*-toluamides, *o*-tolunitriles and phthalide to chiral *N*-*p*-toluenesulfinimines obtained several mono- and disubstituted tetrahydroisoquinolines, which are important building blocks for alkaloid synthesis,[16–18] for example, for (*S*)-(−)-xylopinine.[19]

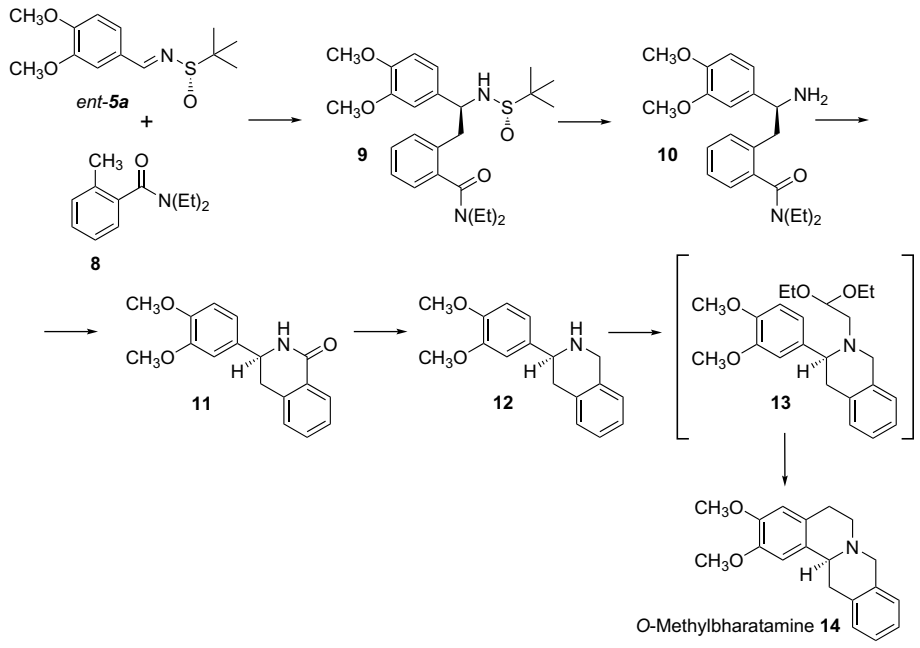
In our synthesis (*S*)-sulfinaldimine *ent*-**5a** was used as a chiral starting material (Scheme 2). It was prepared by the condensation of 3,4-dimethoxybenzaldehyde with (*S*)-*tert*-butanesulfinamide in the presence of $Ti(OEt)_4$, according to Ellman's procedure,[20] in 91% yield, mp 77–78 °C, $[\alpha]_D = +19.8$, showing spectral characteristics corresponding to those of the (*R*)-enantiomer, **5a** (lit.[3] mp 77–78 °C, $[\alpha]_D = -19.1$).

The addition of laterally lithiated *N*,*N*-diethyl-*o*-toluamide **8** to the sulfinimine C=N double bond was the key step of the synthesis. The amide carbanion was best generated with *t*-BuLi at −72 °C affording addition product **9** as an oil in 93% yield, $[\alpha]_D = -18.3$. The diastereoselectivity of this step could not be established either by chiral HPLC analysis, run under various conditions, or by ^{1}H NMR spectroscopy (amide functionalities). The (*S*)-configuration of sulfinamide **9** was finally postulated at the end of the synthesis on the basis of the negative sign of the specific rotation of the target alkaloid, *O*-methylbharatamine **14**, for which the (*S*)-configuration had been previously established.[21] It also could be deduced from a transition state postulated by Davis et al.[16] for a similar reaction, in which the lithium cation of the lithiated *o*-toluamide was chelated to the sulfinimine and amide oxygen atoms to form a less crowded chair-like six-membered system with the carbanion approaching from the less hindered *Si* site (Fig. 2).

Removal of the *N*-sulfinyl auxiliary from sulfinamide **9** occurred with concentrated hydrochloric acid in methanol at room temperature for 1 h. Amine **10** was isolated as an oil (93%) and characterized as its hydrochloride salt, **10·HCl**, mp 189–191 °C, $[\alpha]_D = +36.6$.



Scheme 1.



Scheme 2.

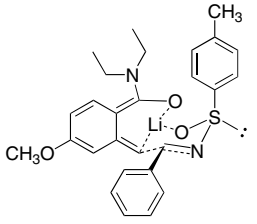


Figure 2.

In the next step of the synthesis, amine **10**, upon treatment with 1 equiv of *n*-BuLi in THF at −70 °C, cyclized easily into isoquinolone **11** in 96% yield and with 85% ee (by HPLC analysis). Attempts to increase ee by crystallization failed, for example, a sample crystallized from ethyl acetate showed only 72% ee (mp 149–150 °C, $[\alpha]_D = -76.2$).

Crude isoquinolone **11** of 85% ee was then reduced with boron reducing agents, $BH_3{\cdot}S(CH_3)_2$ or $BH_3{\cdot}THF$ in THF. Better yields (85% vs 66%) were obtained with the latter reagent in reaction carried out at reflux for 28 h, giving pure tetrahydroisoquinoline **12**, mp 123–125 °C, $[\alpha]_D = -83.0$. Its *N*-alkylation with bromoacetaldehyde in DMF/sodium hydride led to aminoacetal **13**, which could not be isolated in pure form because of its instability during both crystallization and chromatographic separation. Therefore crude **13** was used in the final step of the synthesis in which it was treated with 5 M hydrochloric acid for 12 h at room temperature and then reduced with sodium borohydride/TFA in methylene chloride, producing (*S*)-(−)-*O*-methylbharatamine **14**, $[\alpha]_D = -264.5$ (lit.[21] $[\alpha]_D = -285.5$ for a sample of 99% ee) in 38% yield. The negative sign of the specific rotation indicated an (*S*) configuration of the product synthesized **14**, while HPLC analysis established the enantiomeric excess to be 88%.

3. Conclusion

In conclusion, the asymmetric synthesis of (*S*)-(−)-*O*-methylbharatamine **14** from readily available chiral sulfinaldimine *ent*-**5a** and *o*-toluamide **8** is described. The key process, during which a new stereogenic center was created, involved the addition of laterally lithiated *o*-toluamide to the imine C=N double bond. The final step of the synthesis, the formation of the protoberberine ring system was accomplished via a Pomeranz–Fritsch–Bobbitt cyclization/reduction to afford the target alkaloid in 24.4% overall yield and with enantiomeric excess of 88%.

4. Experimental

4.1. General

Melting points: determined on a Koffler block and are uncorrected. IR spectra: Perkin–Elmer 180 in KBr pellets. NMR spectra: Varian Gemini 300, with TMS as internal standard. Mass spectra (EI): instrument AM D402. Specific rotation: Perkin–Elmer polarimeter 243B at 20 °C. Analytical HPLC: Waters HPLC system with Mallinkrodt-Baker Chiralcel OD-H column. Merck DC-Alufolien Kieselgel 60_{254} was used for TLC. Merck Kieselgel 60 (70–230 mesh) was used for column chromatography. THF was freshly distilled from $LiAlH_4$. 3,4-Dimethoxybenzaldehyde, $Ti(OEt)_4$, *tert*-butanesulfinamide, *t*-BuLi, *n*-BuLi, $BH_3{\cdot}S(CH_3)_2$, $BH_3{\cdot}THF$, bromoacetaldehyde diethyl acetal and TFA were purchased from Aldrich and used as received.

4.2. (*S*)-(+)-*N*-(3,4-Dimethoxybenzylidene)-2-methylpropanesulfinamide *ent*-5a

To a solution of 3,4-dimethoxybenzaldehyde (332 mg, 2 mmol) and (*S*)-*tert*-butanesulfinamide (242 mg, 2 mmol) in anhydrous THF (4 ml), $Ti(OEt)_4$ (0.84 ml, 4 mmol) was added. The mixture was heated at reflux for 4 h under an argon atmosphere. Water (5 ml) was added with rapid stirring and the reaction mixture was filtered through a pad of Celite® and the filter cake was washed with CH_2Cl_2. The phases were separated, the organic solution washed with brine, dried over Na_2SO_4, and the solvents were evaporated. The residue was crystallized from *i*-Pr_2O to give pure *ent*-**5a**, mp 77–78 °C, $[\alpha]_D = +19.8$ (*c* 0.57, CH_2Cl_2). Additional amounts (total yield 91%) were obtained from mother liquors after silica gel column chromatography with CH_2Cl_2. The spectral characteristics of *ent*-**5a** corresponded to that of **5a**.[3]

4.3. Addition of *o*-toluamide 8 to sulfinimine *ent*-5a

o-Toluamide **8** (132 mg, 0.69 mmol) was dissolved in dry THF (3 ml) under an argon atmosphere and the solution cooled to −72 °C. *tert*-BuLi (1.7 M solution in pentane, 0.4 ml, 0.69 mmol) was added and the carboanion (red) was generated for 10 min at −72 °C. A solution of imine *ent*-**5a** (80 mg, 0.29 mmol) in THF (1 ml) was introduced dropwise and, after 40 min, 20% NH_4Cl (3 ml) was added at this low temperature. When the solution was warmed-up to room temperature, the phases were separated and the aqueous one was extracted with Et_2O (3 × 5 ml). The combined organic extracts were dried over Na_2SO_4 and the solvents were evaporated to yield a yellow oil, from which, after silica gel column chromatography with CH_2Cl_2/MeOH (100:0.3), oily **9** (89 mg, 93%) was eluted, $[\alpha]_D = -18.3$ (*c* 0.95, MeOH). IR (KBr) cm^{-1}: 3243, 1613, 1518. ^{13}C NMR ($CDCl_3$) δ: 12.89, 14.06, 22.44, 22.74, 39.24, 41.95, 43.05, 55.87, 55.92, 60.94, 110.16, 111.07, 118.67, 125.35, 126.43, 128.95, 129.70, 135.37, 136.85, 148.16, 148.91, 171.03. FAB-MS *m*/*z* (%): 461 (M^++H). Anal. Calcd for $C_{25}H_{36}N_2SO_4$: C, 65.18; H, 7.88; N, 6.09; S, 6.95. Found: C, 65.23; H, 7.95; N, 6.06; S, 7.01.

4.4. (*S*)-(+)-*N*,*N*-Diethyl-2-[2-amino-2-(3,4-dimethoxyphenyl)ethyl]benzamide hydrochloride 10·HCl

Sulfinamide **9** (577 mg, 1.25 mmol) was dissolved in MeOH (7.6 ml) and the solution was cooled to 0 °C. Concentrated hydrochloric acid (0.23 ml, 2.77 mmol) was added and the reaction mixture stirred at room temperature for 1 h. The solvent was evaporated, water (5 ml) added and the mixture extracted with Et_2O. Phases were separated and the aqueous one was basified with solid NaOH and extracted with CH_2Cl_2 until the Dragendorff test was negative. The organic solution was dried over Na_2SO_4 and the solvent evaporated to leave oily **10** (416 mg, 93%). It was characterized as the hydrochloride salt, **10·HCl**, mp 189–191 °C, $[\alpha]_D = +36.6$ (*c* 1.14, EtOH). IR (KBr) cm^{-1}: 2905. ^1H NMR (DMSO-d_6) δ: 0.93 (t, $J = 6$ Hz, 3H, CH_2CH_3), 1.19 (t, $J = 6.8$ Hz, 3H, CH_2CH_3), 2.88, 3.04, 3.55 (3m, 6H, 3 × CH_2), 3.70 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 4.51 (dd, $J = 6$ Hz, 9 Hz, 1H, CH_2CH), 6.84–7.23 (m, 7H, ArH), 8.71 (s, 3H, disappears on treatment with D_2O, NH_3^+). ^{13}C NMR (DMSO-d_6) δ: 12.86, 13.74, 38.32, 42.20, 54.66, 55.48, 55.61, 111.07, 111.32, 120.13, 125.47, 126.68, 128.50, 129.47, 130.37, 132.55, 137.35, 148.66, 148.78, 169.21. EI MS *m*/*z* (%): 356 (M^+−HCl, 2), 190 (6), 166 (100), 139 (5), 124 (6). Anal. Calcd for $C_{21}H_{29}ClN_2O_3 \cdot 1/2H_2O$: C, 62.74; H, 7.53; N, 6.97. Found: C, 62.78; H, 7.61; N, 6.82.

4.5. (*S*)-(−)-3-(3,4-Dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinolone 11

To the addition product **10** (53 mg. 0.15 mmol) dissolved in THF (3 ml), *n*-BuLi (1.6 M solution in hexanes, 0.09 ml, 0.15 mmol) was added at −70 °C. After 20 min, 20% NH_4Cl (2 ml) was added at this low temperature. When the solution reached room temperature, the phases were separated, and the aqueous one extracted with Et_2O (3 × 10 ml). The combined organic extracts were dried over Na_2SO_4 and the solvent evaporated to give **11** (41 mg, 96%) in 85% ee [HPLC hexane/2-propanol 85:15; 0.5 ml/min; $t_R = 55$ min (major), $t_R = 63$ min (minor)]. Recrystallization from EtOAc afforded crystalline **11** (72% ee), mp 149–150 °C, $[\alpha]_D = -76.2$ (*c* 0.28, MeOH). IR (KBr) cm^{-1}: 3339, 1662. ^1H NMR ($CDCl_3$) δ: 3.08 (dd, $J = 4.6$ Hz, 15.6 Hz, 1H, $CHHCH$), 3.20 (dd, $J = 11.3$ Hz, 15.3 Hz, 1H, $CHHCH$), 3.88 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.80 (dd, $J = 4.6$ Hz, 11.5 Hz, 1H, CH_2CH), 6.1 (s, 1H, disappears on treatment with D_2O, NH), 6.84–7.49 (m, 6H, ArH), 8.11 (d, 1H, ArH). ^{13}C NMR ($CDCl_3$) δ: 37.64, 55.88, 55.91, 55.96, 109.13, 111.16, 118.77, 127.24, 127.28, 127.98, 128.26, 132.47, 133.36, 137.63, 148.95, 149.26, 166.29. EI MS *m*/*z* (%): 283 (M^+, 64), 252 (48), 224 (5), 164 (7), 146 (7), 118 (100). Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.05, H, 6.05, N, 4.95. Found: C, 71.74, H, 5.98, N, 4.75.

4.6. (*S*)-(−)-3-(3,4-Dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline 12

4.6.1. Reduction with $BH_3 \cdot S(CH_3)_2$. In a distillation set supplied with a Vigreux column and a receiver containing 30% hydrogen peroxide, a solution of compound **11** (102 mg, 0.35 mmol) of 85% ee in THF (10 ml) was placed. Then $BH_3 \cdot S(CH_3)_2$ (0.25 ml, 1.25 mmol) was added and the mixture was kept at 65 °C for 4 h under a strong stream of argon. It was then cooled to 0 °C, treated slowly with 10% hydrochloric acid (4 ml) and warmed to 65 °C for 0.5 h. Then, at room temperature, 20% NaOH (5 ml) was added, phases were separated and the basic solution extracted with Et_2O (4 × 5 ml). The organic extracts were washed with 10% hydrochloric acid (10 ml), and the phases were separated. The organic extract was dried over Na_2SO_4 and concentrated to give the starting compound **11** (45 mg, 44%). The aqueous layer was basified with 20% NaOH and re-extracted with Et_2O (3 × 10 ml) to give, after drying over Na_2SO_4 and solvent evaporation, pure **12** (63 mg, 66%).

4.6.2. Reduction with $BH_3 \cdot THF$. To compound **11** (292 mg, 1.03 mmol) of 85% ee in dry THF (11 ml), $BH_3 \cdot THF$ (1 M solution in THF, 3 ml, 3 mmol) was added

and the mixture heated at reflux for 15 h under an argon atmosphere. After that time, an additional amount of the reducing agent (3 ml, 3 mmol) was introduced and heating continued for 13 h. This was then cooled to room temperature and 10% hydrochloric acid (6 ml) added dropwise. The mixture was heated at 65 °C for 1 h, then basified with 20% NaOH and extracted with Et_2O (4×10 ml). The organic phase was treated with 15% hydrochloric acid (3×6 ml) and the acidic aqueous phase was basified with 20% NaOH and extracted with CH_2Cl_2 (5×10 ml). The organic solution was dried over Na_2SO_4 and the solvent evaporated yielding pure **12** (237 mg, 85%), mp 123–125 °C, $[\alpha]_D = -83.0$ (*c* 1.17, CH_2Cl_2). IR (KBr) cm^{-1}: 3262, 2929, 2787, 1517. ^1H NMR ($CDCl_3$) δ: 1.92 (s, 1H, disappears on treatment with D_2O, NH), 2.97 and 2.99 (2s, 2H, CH_2CH), 3.88 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.96 (dd, $J = 6.3$ Hz, 8.8 Hz, 1H, CHN), 4.23 (m, 2H, CH_2N), 6.84–7.26 (m, 7H, ArH). ^{13}C NMR ($CDCl_3$) δ: 37.88, 49.32, 55.91, 55.94, 58.41, 109.48, 110.94, 118.53, 125.73, 126.05, 126.15, 128.92, 134.67, 134.70, 136.87, 148.09, 148.97. EI MS *m*/*z* (%): 269 (M^+, 26), 252 (12), 238 (13), 179 (6), 165 (15), 151 (20), 130 (17), 104 (100). Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.80, H, 7.11, N, 5.20. Found: C, 75.54, H, 6.95, N, 5.05.

4.7. (*S*)-*N*-(2,2-Diethoxyethyl)-3-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline 13

To a solution of tetrahydroisoquinoline **12** (110 mg, 0.4 mmol) in DMF (4 ml), NaH (60% dispersion in mineral oil, 160 mg, 4 mmol) was added and the suspension heated at 153 °C for 1 h under an argon atmosphere. Bromoacetaldehyde diethyl acetal (0.3 ml, 2 mmol) was added and heating was continued for 6 h. After cooling to room temperature, the reaction mixture was poured onto ice (28 g) and extracted with Et_2O (4×10 ml). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to give crude **13** (240 mg) which could not be purified because of it is instability, thus it was used as such in the final step of the synthesis.

4.8. (*S*)-(−)-*O*-Methylbharatamine 14

A solution of the crude amino acetal **13** (240 mg) in 5 M hydrochloric acid (3.4 ml) was stirred for 12 h at room temperature. The mixture was basified with 20% NaOH and extracted with CH_2Cl_2 (4×10 ml). The combined organic extracts were dried and the solvent evaporated. The oily residue (166 mg) was dissolved in CH_2Cl_2 (16 ml) and treated with $NaBH_4$ (151 mg, 4 mmol) followed by the dropwise addition of TFA (3 ml, 38 mmol) in CH_2Cl_2 (6 ml) at 0 °C. The mixture was stirred at room temperature for 6 h, then the solvent and TFA were removed under reduced pressure. To the resulting slurry water (3 ml) and 20% NaOH were added and the mixture was extracted with CH_2Cl_2 (3×10 ml). The organic extracts were dried over Na_2SO_4 and the solvent was evaporated to yield an oily residue (100 mg), from which pure (*S*)-(−)-*O*-methylbharatamine **14** (45 mg, 38%) of 88% ee [HPLC hexane/2-propanol 90:10; 0.5 ml/min; $t_R = 24$ min (major), $t_R = 50$ min (minor)] was isolated by silica gel column chromatography with CH_2Cl_2. $[\alpha]_D = -264.5$ (*c* 0.55, $CHCl_3$), lit.[21] for a sample of (*S*)-(−)-**14** showing 99% ee: $[\alpha]_D = -285.5$ (*c* 0.51, $CHCl_3$). Spectral characteristics of our sample corresponded to those of the literature for (*S*)-(−)-**14**.[21]

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