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(*S*)-(−)-α-Methylbenzylamine as an efficient chiral auxiliary in enantiodivergent synthesis of both enantiomers of *N*-acetylcalycotomine

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Abstract

(*S*)-(−)-α-Methylbenzylamine **2** was used as a chiral auxiliary in the enantiodivergent synthesis of simple isoquinoline alkaloids. The prochiral imine moiety in compound **4** was reduced with different reagents, giving diastereomeric amines **5a** or **5b**, which subsequently were transformed to either (*S*)-(−)-*N*-acetylcalycotomine **6** or (*R*)-(+)-*N*-acetylcalycotomine *ent*-**6** in good enantiomeric excess. ^{19}F NMR of its Mosher's acid ester was used to establish the purities of final compounds.

1. Introduction

(*S*)-(−)-α-Methylbenzylamine **2** and its enantiomer *ent*-**2**, appear to be ideal compounds for use as chiral auxiliaries or chiral building blocks.[1–3] Both enantiomers are inexpensively available in very high enantiomeric purity, which makes them attractive as stereodifferentiating agents even for large scale operations. Recently, (*S*)-(−)-α-methylbenzylamine **2** has been used as a chiral building block in the asymmetric synthesis of tetrahydro-β-carbolines.[1] This method afforded diastereomers of 1-substituted tetrahydro-β-carbolines in good diastereomeric enrichments. Enantiomerically pure ethyl 2-amino-1-cyclohexanecarboxylate was synthesized[2] via reductive amination of 2-oxo-cyclohexanecarboxylate with amine **2**. The same compound was also used for a five-step synthesis of novel enantiomerically pure *cis*- and *trans*-*N*-(propionyl)hexahydrobenzoxazolidin-2-ones.[3] Good diastereoselectivity, due to chiral induction originating from (*S*)-(−)-α-methylbenzylamine **2**, allowed the preparation of three pyrrolizidine and indolizidine alkaloids: (+)-tashiromine, (+)-laburnine and (−)-isoretronecanol.[4] On the other hand, (*R*)-(+)-α-methylbenzylamine *ent*-**2** served as a chiral building block in the synthesis

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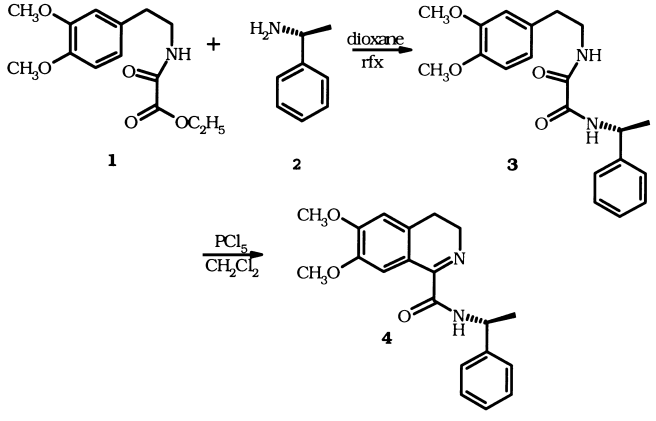
of (−)- and (+)-chinoin with an excellent enantioinduction[5] (ee>98%). Several examples of enantioselective elaboration of the quaternary carbon center in Michael-type additions with the use of (*S*)-(−)-α-methylbenzylamine **2** as chiral inducing agent have recently been presented.[6–8] Also, (+)-vincamine, an indole alkaloid showing a strong vasodilation activity, was prepared from (*S*)-(+)-2-ethyl-2-(2-methoxycarbonylethyl)cyclopentanone which had previously been obtained using (*R*)-(+)-α-methylbenzylamine *ent*-**2** as a chiral building block.[9] The above examples prompted us to explore the possibility of the application of (*S*)-(−)-α-methylbenzylamine **2** for the enantioselective synthesis of isoquinoline alkaloids.

2. Results and discussion

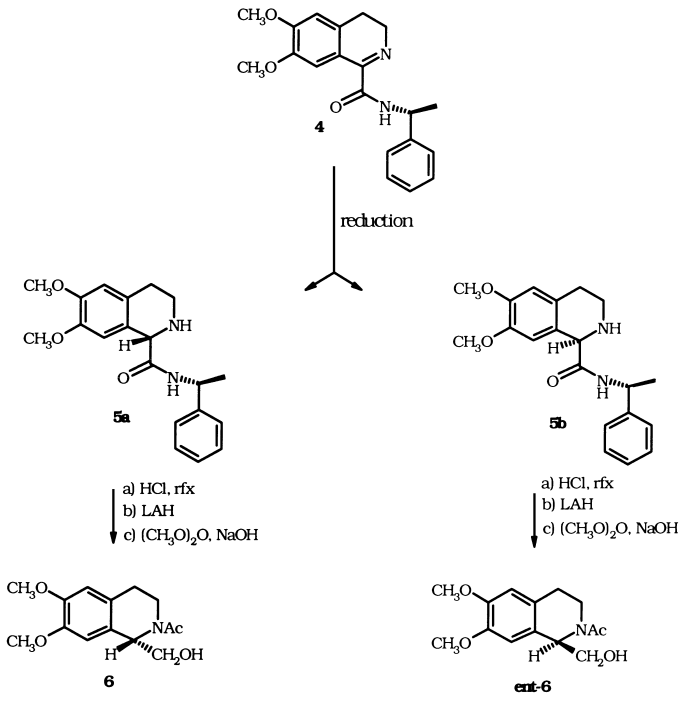
Our synthetic route (Scheme 1) started with the reaction of the known amide-ester **1**[10] with (*S*)-(−)-α-methylbenzylamine **2** in which amide **3** was obtained in quantitative yield. Subsequent Bischler–Napieralski[11] cyclization of amide **3** using PCl_5 under mild conditions gave imine **4** which, as its hydrochloride or as a free base, was subjected to reductions using different reagents (Scheme 2).



Scheme 1. Preparation of imine **4**

The ratios of diastereomeric amines thus formed were determined by HPLC analysis. Table 1 summarizes the stereochemical outcome of these reductions.

Relatively good diastereomeric enrichment (**5a**:**5b**=88:12) was obtained when imine **4** was treated with sodium borohydride at −78°C. Surprisingly, the ratio was reversed (**5a**:**5b**=9:91) when **4** was subjected to Wilkinson's hydrogenation conditions. It is noteworthy that the ratios obtained were relatively high, considering a 1,4-chirality transfer in **4**. Different reductions of the hydrochloride of **4** gave much poorer results. Fortunately, imine **4** appears to be stable enough to tolerate various reducing conditions. On the other hand, however, amines **5a** and **5b** decompose slowly and even though they could be effectively separated by column chromatography and fully characterized, they cannot be stored longer than a few days. In order to assign the relative stereochemistry on C(1) in **5** we wished to perform an X-ray structural analysis but despite considerable efforts we were unable to prepare derivatives giving suitable crystals for that purpose. In the search for such derivatives *N*-methylation of amines **5a** and **5b** was planned but application of the classical Eschweiler–Clarke procedure afforded oxazoloisoquinolinylidene derivatives **7a** and **7b**, respectively (Scheme 3). In both proton and carbon NMR spectra of **7a** and **7b** two components in the ratio of approximately 5:1 were detected, although they could not be chromatographically separated. On the basis of the relatively high shielding effect on the imine methyl



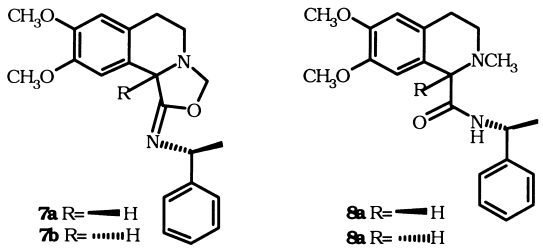
Scheme 2. Preparation of compounds **6** and *ent*-**6**

group, deshielding of H-8 aromatic protons and computer assisted energy estimations[12] we propose a *Z* geometry of the imine double bond. When sodium cyanoborohydride was applied as a reducing agent for **5a** and **5b**, amines **8a** and **8b** were obtained.

Table 1
Reduction of imine **4**

Entry)substrate	Reduction conditions	Ratio of diastereomers **5a** and **5b**
a)**4**xHCl	$NaCNBH_3/AcOH/CH_2Cl_2/0^oC$	49:51
b)**4**	$H_2/PtO_2/0^oC$	44:56
c)**4**xHCl	$H_2/PtO_2/0^oC$	42:58
d)**4**	$NaBH_4/EtOH/RT$	66:34
e)**4**	$NaBH_4/EtOH/-78^oC$	88:12
f)**4**xHCl	$NaBH_4/EtOH/HCl/-20^oC$	40:60
g)**4**	$H_2/RhCl(PPh_3)_3/100atm/RT$	9:91

Diastereomeric amines **5a** and **5b** could be effectively purified by careful column chromatography, and an X-ray structural measurement on the hydrochloride prepared from **5a** allowed us to assign the absolute stereochemistry (Fig. 1) of this derivative as (*S*)-C(1). This result was in accordance with further correlation of **5a** and **5b** with *N*-acetylcalycotomine **6** and *ent*-**6**. Thus, both amines **5a** and **5b** were subjected to hydrolysis using 18% HCl immediately followed by lithium aluminum hydride reduction



Scheme 3.

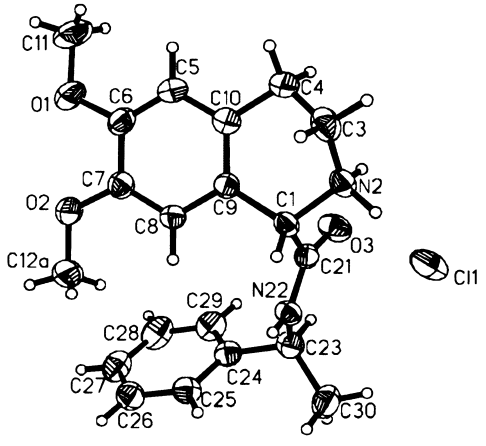


Figure 1. Perspective view of the X-ray crystal structure of **5a**·HCl

and *N*-acetylation with acetic anhydride/sodium hydroxide system. Finally, both enantiomers of *N*-acetylcalycotomine **6** and *ent*-**6** were obtained, respectively. The enantiomeric purities of **6a** and *ent*-**6** determined by ^{19}F NMR of their Mosher's acid esters gave the value of >98% ee for both compounds.

3. Experimental

Infrared (IR) spectra were obtained using a Nicolet Magna IR 500 spectrophotometer. NMR spectra were recorded on a Varian Gemini spectrometer operating at 200 MHz for ^{1}H NMR and at 50.3 MHz for ^{13}C NMR, and on a Varian Unity Plus spectrometer operating at 500 MHz for ^{1}H NMR and at 125 MHz for ^{13}C NMR. Tetramethylsilane (TMS) or solvents were used as internal standards. The ^{19}F NMR spectra were recorded on a Varian Unity plus-500 spectrometer with C_6F_6 as external reference. Chemical shifts are reported in ppm. Mass spectra were collected on an AMD 604 apparatus; high resolution mass spectra were acquired using LSIMS (positive ion mode). Optical rotations were measured on a Perkin–Elmer 247 MC polarimeter. TLC analyses were performed on Merck 60 silica gel glass plates and visualized using iodine vapor. Column chromatography was carried out at atmospheric pressure using silica gel 60 (230–400 mesh, Merck) and Al_2O_3(III). HPLC analyses were performed on a Knauer (model 64) apparatus with Eurochrom 2000 software using 4×250 mm silica (5 μm) column model Li-Chrosorb Si-60 (Knauer) with methyl chloride:methanol 98:2 (v/v) as eluent. For better separation the columns were cooled to 10°C. Melting points were determined on a Boetius hot-plate microscope and are uncorrected.

3.1. Preparation of amide **3**

A mixture of 10 g (82.6 mmol) of (*S*)-(−)-1-phenylethylamine **2**, 25.5 g (90.9 mmol) of compound **1**[7] and a catalytic amount of 4-dimethylaminopyridine was refluxed in 200 mL of dioxane for 3 h under argon. The product precipitated upon cooling. Filtration afforded amide **3** as a white solid in 88.5% yield. Mp 168–171°C, $[\alpha]_D^{23}$ −66.5 (*c* 1.05, $CHCl_3$). IR (KBr, cm^{-1}): 3290, 1650, 1520, 1275, 1245, 1155, 1140, 1030, 770, 700. ^{1}H NMR (500 MHz, $CDCl_3$): 7.84 (d, 1H, *J*=8.3 Hz, H-2′), 7.64 (apparent t, 1H, *J*=5.4 Hz, H-2), 7.26–7.35 (m, 5H, H-6′–H-10′), 6.79 (d, 1H, *J*=8.0 Hz, H-8), 6.72 (dd, 1H, J_1=8.0 Hz, J_2=2.0 Hz, H-9), 6.69 (d, 1H, *J*=2.0 Hz, H-5), 5.05 (dq, 1H, J_1=7.3 Hz, J_2=8.3 Hz, H-3′), 3.85 and 3.84 (two s, 3H each, 2×OCH_3), 3.53 (apparent q, 2H, *J*=6.8 Hz, 2H-3), 2.79 (t, 2H, *J*=6.8 Hz, H-4), 1.55 (d, 3H, *J*=7.3 Hz, 3H-4′). ^{13}C NMR (125 MHz, $CDCl_3$): 159.72, 158.82, 148.99, 147.73, 142.04, 130.56, 128.70, 127.60, 126.07, 120.54, 111.68, 111.32, 55.84, 55.78, 49.39, 40.98, 34.94, 21.68. EI 70eV 8 kV (%): 356 (19), 164 (100), 151 (27), 105 (12), 91 (2).

3.2. Preparation of imine **4**

To a stirred and cooled (0°C) solution of 10 g (28.1 mmol) of amide **3** in 120 mL of dry methylene chloride 14 g (67.1 mmol) of PCl_5 was added in five portions. After 3 h stirring the resulting red mixture was poured slowly into a suspension of 28.4 g (267.9 mmol) sodium bicarbonate. The organic layer was then separated, washed twice with brine and dried ($MgSO_4$). After evaporation, the red residue was subjected to column chromatography on silica gel. Elution with $CHCl_3$ gave imine **4** in 90% yield as an amorphous yellow solid.

$[\alpha]_D^{23}$ −39.9 (*c* 0.99, MeOH). IR (KBr, cm^{-1}): 3300, 2940, 2830, 1650, 1600, 1510, 1270, 1210, 1140, 1030, 700. ^{1}H NMR (500 MHz, $CDCl_3$): 8.00 (s, 1H, H-8), 7.85 (d, 1H, *J*=8.3 Hz, H-2′), 7.22–7.38 (m, 5H, H-6′–H-10′), 6.65 (s, 1H, H-5), 5.16–5.20 (m, 1H, H-3′), 3.89 and 3.89 (two s, 3H each, 2×OCH_3), 3.71 (t, 2H, *J*=6.8 Hz, 2H-3), 2.61 (t, 2H, *J*=6.8 Hz, H-4), 1.56 (d, 3H, *J*=6.8 Hz, 3H-4′). ^{13}C NMR (125 MHz, $CDCl_3$): 163.70, 158.31, 151.22, 147.19, 143.25, 131.91, 128.68, 127.30, 126.16, 119.39, 111.83, 109.74, 56.08, 55.91, 48.71, 47.16, 25.48, 22.14. EI 70eV 8 kV (%): 338 (29), 323 (9), 219 (10), 191 (100), 176 (10), 164 (18), 120 (36), 105 (8). For imine **4** hydrochloride: mp 147–150°C (methanol:ether), $[\alpha]_D^{23}$ −37.2 (*c* 0.84, $CHCl_3$). IR (KBr, cm^{-1}): 3400, 3150, 2650, 1670, 1550, 1340, 1280, 1210, 1150, 1040. ^{1}H NMR (500 MHz, $CDCl_3$): 10.06 (br s, 1H, H-2), 7.55 and 7.56 (two s, 1H each, H-2′ and H-8), 7.23–7.35 (m, 5H, H-6′–H-10′), 6.77 (s, 1H, H-5), 5.20–5.23 (m, 1H, H-3′), 3.99 (br s, 5H, OCH_3 and 2H-3), 3.70 (s, 3H, OCH_3), 3.10 (br s, 2H, 2H-4), 1.71 (d, 3H, *J*=6.8 Hz, 3H-4′). ^{13}C NMR (125 MHz, $CDCl_3$): 164.17, 158.31, 157.21, 148.55, 142.68, 134.79, 128.64, 127.40, 126.65, 115.68, 113.89, 110.80, 56.65, 56.05, 51.00, 41.22, 25.09, 21.97.

3.3. Preparation of diastereomeric amines **5a** and **5b**

3.3.1. Reduction a

A solution of 60 mg (0.161 mmol) of the hydrochloride of imine **4** in 5 mL of glacial acetic acid and 15 mL of methylene chloride was treated with 25 mg (0.398 mmol) of solid sodium cyanoborohydride at 0°C. After 1 h of stirring, addition of sodium bicarbonate solution and brine, extraction with chloroform (4×10 mL) and evaporation of solvent, 50 mg of an orange residue was obtained. The ratio of diastereomeric amines (**5a**:**5b**=49:51) was estimated with HPLC analysis.

3.3.2. Reduction b

A solution of 120 mg (0.355 mmol) of imine **4** in 10 mL of glacial acetic acid and 30 mL of dry THF was hydrogenated at atmospheric pressure over 10 mg of platinum(II) oxide at 0°C. After 16 h the hydrogen was replaced by argon, the catalyst was filtered off and the solution was carefully poured onto a suspension of 7 g of sodium bicarbonate in 100 mL of water. The water layer was then extracted with 4×20 mL of chloroform. The organic phase, after drying ($MgSO_4$) and evaporation, afforded the mixture of diastereomeric amines in the ratio **5a**:**5b**=44:56.

3.3.3. Reduction c

The hydrogenation was performed exactly as described above except that the hydrochloride of imine **4** was used. In this case a ratio of **5a**:**5b**=42:58 was obtained.

3.3.4. Reduction d

To a solution of 52 mg (0.139 mmol) of hydrochloride of imine **4** in 15 mL of ethanol 50 mg of sodium borohydride was added in two portions at 0°C. After 1 h of stirring at the same temperature ethanol was evaporated and 30 mL of brine was added. The water layer was then extracted with 4×15 mL of chloroform and the organic solution was dried ($MgSO_4$). Evaporation of solvent afforded the mixture of diastereomeric amines in the ratio **5a**:**5b**=66:34.

3.3.5. Reduction e

A sample of 2.4 g (0.063 mol) of sodium borohydride was poured into 25 mL of ethanol. After 1 h of stirring 5 mL of the resulting solution was slowly introduced into the mixture of 120 mg (0.355 mmol) of imine **4** in 30 mL of ethanol at −78°C. After 4 h of stirring at the same temperature a cooling-bath was removed and stirring was continued for 12 h. Subsequent evaporation of the solvent, addition of brine (30 mL) and extraction with chloroform afforded the mixture of diastereomeric amines in the ratio **5a**:**5b**=88:12.

3.3.6. Reduction f

A solution of sodium borohydride in absolute ethanol (5 mL) prepared as above was added dropwise at −20°C to a solution of 52 mg (0.139 mmol) of the hydrochloride of imine **4** in 50 mL of absolute ethanol, to which 1.6 mL of acetyl chloride had been added previously. The mixture was stirred for 1 h at −20°C and then allowed to warm to ambient temperature. The standard work-up of the reaction mixture gave rise to the formation of diastereomeric amines in the ratio **5a**:**5b**=40:60.

3.3.7. Reduction g

A solution of 60 mg (0.177 mmol) of imine **4** in 5 mL of degassed methylene chloride was hydrogenated over 15 mg of chlorotris(triphenylphosphine)rhodium(I) (Wilkinson's catalyst) under 100 atm of hydrogen during 24 h. The catalyst was removed by filtration through a pad of silica gel. HPLC analysis of this mixture revealed the presence of two components **5a**:**5b** in the ratio 9:91.

Both diastereomers could be separated by careful column chromatography on alumina (activity III) using 2% (v/v) methanol in chloroform as eluent. Analytical data of amine **5a**: mp 174–176°C, $[\alpha]_D^{23}$ −61.5 (*c* 0.94, $CHCl_3$). IR (KBr, cm^{-1}): 3310, 2940, 1640, 1520, 1230, 1120, 710. ^1H NMR (500 MHz, $CDCl_3$): 7.48 (br d, 1H, *J*=8.3 Hz, H-2′), 7.14–7.28 (m, 5H, H-6′–H-10′), 6.97 (s, 1H, H-8), 6.56 (s, 1H, H-5), 5.04–5.12 (m, 1H, H-3′), 4.49 (s, 1H, H-1), 3.76 and 3.85 (two s, 3H each, 2×OCH_3), 3.05 (apparent dd, 2H, J_1=6.8 Hz, J_2=5.8 Hz, 2H-3), 2.77 (dt, 1H, J_1=16.1 Hz, J_2=6.8 Hz, H-4_{eq}), 2.66 (dt, 1H, J_1=16.1 Hz, J_2=5.8 Hz, H-4_{ax}), 1.80 (br s, 1H, H-2), 1.48 (d, 3H, *J*=6.8 Hz, 3H-4′). ^{13}C NMR (125

MHz, $CDCl_3$): 172.09, 147.92, 147.04, 143.34, 128.48, 127.06, 126.53, 125.85, 124.26, 111.37, 110.53, 59.76, 55.81, 55.79, 48.44, 41.42, 28.80, 22.17. EI 70eV 8 kV (%): 340 (0.2), 323 (9), 192 (100), 176 (9), 148 (5), 131 (2), 105 (2).

Analytical data of amine **5b**: mp 148–150°C, $[\alpha]_D^{23}$ −30.8 (*c* 0.97, $CHCl_3$). IR (KBr, cm^{-1}): 3280, 2910, 1650, 1525, 1250, 1210, 1110, 770, 710. ^{1}H NMR (500 MHz, $CDCl_3$): 7.61 (br d, 1H, *J*=8.3 Hz, H-2′), 7.24–7.36 (m, 5H, H-6′–H-10′), 7.14 (s, 1H, H-8), 6.57 (s, 1H, H-5), 5.06–5.13 (m, 1H, H-3′), 4.47 (s, 1H, H-1), 3.86 and 3.87 (two s, 3H each, 2×OCH_3), 3.07 (apparent dd, 2H, J_1=5.4 Hz, J_2=5.9 Hz, 2H-3), 2.79 (dt, 1H, J_1=16.1 Hz, J_2=5.9 Hz, H-4_{eq}), 2.66 (dt, 1H, J_1=16.1 Hz, J_2=5.4 Hz, H-4_{ax}), 1.87 (br s, 1H, H-2), 1.42 (d, 3H, *J*=6.8 Hz, 3H-4′). ^{13}C NMR (125 MHz, $CDCl_3$): 171.95, 147.94, 147.13, 143.40, 128.65, 127.26, 126.62, 126.13, 124.43, 111.33, 110.66, 59.33, 55.94, 55.82, 48.49, 41.33, 28.87, 21.92. EI 70eV 8 kV (%): 340 (0.1), 192 (100), 176 (5), 148 (2), 105 (2).

3.4. *Preparation of* N-*methylamines* ***8a*** *and* ***8b***

A sample of 60 mg (0.176 mmol) of amines **5a** or **5b** in 6 mL of dry EtOH, containing 0.5 mL of glacial acetic acid and 1 mL of aqueous formaldehyde solution, was stirred at 0°C for 12 h. Sodium cyanoborohydride (80 mg) was then added in three portions during 30 min. After 15 min stirring at the same temperature the cooling-bath was removed and the mixture was stirred at room temperature for 20 min. Evaporation of the solvents, addition of 20% sodium bicarbonate solution and extraction with $CHCl_3$ afforded a colourless amorphous solid which was purified by column chromatography to give a white solid in 90% yield. Analytical data of *N*-methylamine **5a**: mp >260°C, $[\alpha]_D^{23}$ −27.8 (*c* 1.03, $CHCl_3$). IR (KBr, cm^{-1}): 3420, 3280, 2940, 2780, 1650, 1525, 1255, 1220, 1150, 1020, 710. ^{1}H NMR (500 MHz, $CDCl_3$): 7.15–7.24 (m, 4H, H-6′–H-10′ except H-8′), 7.03 and 7.01 (two br s, 2H, H-2′ and H-8′), 6.90 (s, 1H, H-8), 6.57 (s, 1H, H-5), 5.02–5.09 (m, 1H, H-3′), 3.85 (s, 3H, OCH_3), 3.83 (s, 1H, H-1), 3.68 (s, 3H, OCH_3), 3.00 (apparent t, 2H, *J*=11.0 Hz, 2H-3), 2.50–2.70 (m, 2H, 2H-4), 2.46 (s, 3H, 3H-2), 1.47 (d, 3H, *J*=7.0 Hz, 3H-4′). ^{13}C NMR (125 MHz, $CDCl_3$): 172.29, 147.86, 147.26, 143.26, 128.34, 126.91, 125.71, 125.29, 124.03, 110.84, 109.14, 70.27, 55.80, 55.75, 50.96, 48.11, 44.61, 28.71, 22.11. LSIMS (+) 8 kV (%): 377 $(M+Na)^+$ (2), 355 $(M+H)^+$ (19), 206 (100), 192 (12), 105 (12), 95 (14).

Analytical data of *N*-methylamine **8b**: Mp >260°C, $[\alpha]_D^{23}$ −11.2 (*c* 1.04, $CHCl_3$). IR (KBr, cm^{-1}): 3310, 2930, 2780, 1650, 1520, 1260, 1225, 1140, 1025, 825, 700, 560. ^{1}H NMR (500 MHz, $CDCl_3$): 7.24–7.36 (m, 6H, H-6′–H-10′ and H-2′), 7.11 (s, 1H, H-8), 6.57 (s, 1H, H-5), 5.02–5.11 (m, 1H, H-3′), 3.86 and 3.86 (two s, 3H each, 2×OCH_3), 3.79 (s, 1H, H-1), 2.98 (apparent dd, 2H, J_1=5.0 Hz, J_2=7.0 Hz, 2H-3), 2.63 (apparent d, 1H, *J*=16.0 Hz, H-4_{eq}), 2.52 (apparent dd, 1H, J_1=16.0 Hz, J_2=7.0 Hz, H-4_{ax}), 2.33 (s, 3H, 3H-2), 1.35 (d, 3H, *J*=7.0 Hz, 3H-4′). ^{13}C NMR (125 MHz, $CDCl_3$): 172.25, 147.86, 147.36, 143.36, 128.59, 127.23, 126.18, 125.50, 124.29, 110.78, 109.26, 69.85, 55.93, 55.77, 50.88, 48.25, 44.69, 28.77, 21.51. LSIMS (+) 8 kV (%): 377 $(M+Na)^+$ (7), 355 $(M+H)^+$ (39), 206 (100), 192 (6), 105 (7).

3.5. *Preparation of oxazoloisoquinolinylidene derivatives* ***7a*** *and* ***7b***

A solution of 100 mg (0.294 mmol) of amine **5a** or **5b** in 6 mL of formic acid and 1.5 mL of formaldehyde was refluxed for 1 h. After this period, 1 mL of formaldehyde solution was added and the mixture was refluxed for an additional 2 h. After evaporation of the solvents, 20% of a sodium bicarbonate solution was added and the water layer was extracted with 3×30 mL of chloroform. The organic layer was then dried ($MgSO_4$) and concentrated in vacuo affording an orange oil which was chromatographed on silica gel. Elution with 0.5% (v/v) methanol in chloroform gave the oxazoloisoquinolinylidene derivative

as a yellowish oil in 80% yield. Analytical data for compound **7a**: $[\alpha]_D^{23}$ −155.8 (*c* 0.98, $CHCl_3$). IR (KBr, cm^{-1}): 3350, 2930, 2850, 1700, 1520, 1230, 1225, 1125, 1020, 750, 700. ^1H NMR (500 MHz, $CDCl_3$): 7.22–7.36 (m, 5H, H-6′–H-10′), 7.14 (s, 1H, H-8), 6.57 (s, 1H, H-5), 5.39 (q, 1H, *J*=6.8 Hz, H-3′), 4.53 (d, 1H, *J*=7.8 Hz, H-2_{eq}), 3.93 and 3.85 (two s, 3H each, 2×OCH_3), 3.91 (s, 1H, H-1), 2.79 (d, 1H, *J*=7.8 Hz, H-2_{ax}), 2.75–2.84 (m, 2H, 2H-3), 2.67 (dt, 1H, J_1=14.7 Hz, J_2=4.4 Hz, H-4_{eq}), 2.57 (apparent dt, 1H, J_1=14.7 Hz, J_2=3.4 Hz, H-4_{ax}), 1.60 (d, 3H, *J*=6.8 Hz, 3H-4′). ^{13}C NMR (125 MHz, $CDCl_3$): 171.30, 148.15, 147.59, 139.56, 128.66, 127.78, 127.35, 126.98, 125.99, 110.79, 110.54, 64.96, 62.30, 55.96, 55.88, 49.31, 46.98, 26.92, 22.10. LSIMS (+) 8 kV (%): 353 $(M+H)^+$ (37), 247 (13), 205 (24), 192 (14), 123 (43), 109 (64), 95 (100).

Analytical data for compound **7b**: $[\alpha]_D^{23}$ −33.7 (*c* 1.01, $CHCl_3$). IR (KBr, cm^{-1}): 3360, 2940, 2840, 1710, 1510, 1450, 1425, 1375, 1230, 1125, 1025, 770, 705. ^1H NMR (500 MHz, $CDCl_3$): 7.23–7.39 (m, 5H, H-6′–H-10′), 7.15 (s, 1H, H-8), 6.59 (s, 1H, H-5), 5.39 (q, 1H, *J*=7.0 Hz, H-3′), 4.19 (d, 1H, *J*=7.0 Hz, H-2_{eq}), 4.13 (d, 1H, *J*=7.8 Hz, H-2_{ax}), 3.92 and 3.85 (two s, 3H each, 2×OCH_3), 3.90 (s, 1H, H-1), 2.86–2.98 (m, 2H, 2H-3), 2.70–2.84 (m, 2H, 2H-4), 1.54 (d, 3H, *J*=7.0 Hz, 3H-4′). ^{13}C NMR (125 MHz, $CDCl_3$): 171.00, 148.16, 147.65, 139.43, 128.79, 128.48, 127.85, 126.86, 125.77, 110.88, 110.34, 64.51, 61.92, 55.99, 55.88, 49.39, 46.59, 26.00, 22.69. LSIMS (+) 8 kV (%): 353 $(M+H)^+$ (50), 339 (6), 261 (16), 247 (28), 205 (50), 192 (28), 105 (80), 95 (100).

3.6. Preparation of N-*acetylcalycotomine* ***6***

A mixture of 340 mg (1 mmol) of amine **5a** and 10 mL of 18% HCl was refluxed for 8 h. After evaporation of the HCl solution, three portions of toluene (20 mL) were added and the mixture evaporated. The residue was additionally dried overnight in a vacuum dessicator over P_2O_5 and subsequently refluxed with 40 mL of absolute ethanol to which 1 mL of thionyl chloride had been added. Evaporation with toluene and drying were repeated and the residue was refluxed in 20 mL of dry THF with 350 mg of lithium aluminum hydride. After 2 h the reaction was quenched by the addition of 20% NaOH and the precipitate was filtered off. To the precipitate 50 mL of chloroform was added four times and the suspensions were heated under reflux for 15 min. The combined organic extracts were dried ($MgSO_4$) and evaporated leaving 240 mg of a yellow oil. This oil was dissolved in 30 mL of CH_2Cl_2 and 50 mL of 30% NaOH was added. After cooling to 0°C, 1.5 mL of acetic anhydride was added dropwise and the solution was stirred for 0.5 h. The water layer was then extracted with 3×30 mL portions of chloroform. The organic phase after drying ($MgSO_4$) and evaporation afforded an orange residue which was subjected to column chromatography on silica gel. Elution with 1.5% (v/v) methanol in chloroform gave 50 mg of *N*-acetylcalycotomine **6** as white crystals.

Mp 192–194°C, $[\alpha]_D^{23}$ −141 (*c* 0.9, MeOH). IR (KBr, cm^{-1}): 3330, 2950, 1610, 1525, 1470, 1440, 1360, 1260, 1230, 1120, 1060, 990, 790. Two conformers were observed in NMR spectra. Data for major conformer: ^1H NMR (500 MHz, $CDCl_3$): 6.71 (s, 1H, H-8), 6.63 (s, 1H, H-5), 5.63 (dd, 1H, J_1=8.8 Hz, J_2=3.9 Hz, H-1′), 3.91–3.96 (m, 2H, H-1′ and H-1), 3.86 and 3.86 (two s, 3H each, 2×OCH_3), 3.75–3.81 (m, 2H, 2H-3), 3.63–3.69 (m, 1H, H-4_{eq}), 2.79–2.91 (m, 1H, H-4_{ax}), 2.22 (s, 3H, NAc), 1.82 (br s, 1H, OH). Data for minor conformer: ^1H NMR (500 MHz, $CDCl_3$): 6.63 (s, 1H, H-8), 6.62 (s, 1H, H-5), 4.92 (dd, 1H, J_1=9.3 Hz, J_2=3.9 Hz, H-1), 4.74 (dd, 1H, J_1=12.7 Hz, J_2=4.9 Hz, H-1′), 3.87 and 3.86 (two s, 3H each, 2×OCH_3), 3.26 (br s, 1H, OH), 3.04 (td, 1H, J_1=12.7 Hz, J_2=3.9 Hz, H-1′), 2.79–2.91 (m, 3H, H-4_{eq} and 2H-3), 2.64 (br d, 1H, *J*=15.1 Hz, H-4_{ax}), 2.28 (s, 3H, NAc). ^{13}C NMR (125 MHz, $CDCl_3$, two stable conformers were present): 172.17, 170.89, 148.32, 148.16, 147.90, 147.60, 127.20, 126.31, 125.00, 124.28, 111.67, 111.17, 110.24, 109.82, 67.45, 65.10, 59.20, 56.06, 55.95, 55.26, 41.98, 34.86,

28.52, 27.85, 22.11, 21.99. LSIMS (+) 8 kV (%): 288 $(M+Na)^+$ (11), 266 $(M+H)^+$ (100), 248 (11), 234 (63), 222 (7), 206 (10), 192 (16), 176 (11), 95 (35).

3.7. *Determination of the enantiomeric composition of* N-*acetylcalycotomine* ***6***

A solution of 0.12 mL (1.4 mmol) of oxalyl chloride was added to a solution of 66 mg (0.28 mmol) of (*R*)-(+)-MTPA and 0.022 mL (0.28 mmol) of DMF in 12 mL of hexane. After 1 h the mixture was filtered and concentrated in vacuo and the residue was used without any further treatment. A solution of 20 mg (0.08 mmol) of (−)-*N*-acetylcalycotomine **6**, 1 mL of triethylamine and a catalytic amount of 4-dimethylaminopyridine in 3 mL of dichloromethane was treated with the above prepared Mosher's acid chloride in 3 mL of dichloromethane. The mixture was then stirred for 24 h at room temperature followed by washing with an aqueous solution of citric acid, sodium bicarbonate and brine. The water layer was extracted with two portions of chloroform and the combined extracts were dried ($MgSO_4$) and evaporated, and the residue was filtered through a pad of silica gel using $CHCl_3$ as eluent. The ^{19}F NMR spectrum was recorded on a Varian Unity plus-500 spectrometer with C_6F_6 as external reference. In the ^{19}F NMR spectrum, a pair of signals (due to the presence of stable conformers) were observed at −71.18 and −71.54 ppm (*S* enantiomer) with relative intensities 1.00:2.32; the *R* enantiomer was not observed.

3.8. *X-Ray crystallography*

A number of 1821 data from the θ range 2.75 through 73.32° were collected with the MACH-3 κ-axis diffractometer, using graphite monochromatized CuKα radiation. Unit cell parameters were obtained from the least-squares treatment performed for 15 reflections with $22.7 \leq 2\theta \leq 40.2°$. The orthorhombic space group was chosen based on lattice dimensions and symmetry of a diffraction pattern. The structure was solved using direct methods from the SHELXS-86 program[13] and refined by full matrix least-squares treatment based on F^2 using SHELXL-93 software.[14] All the hydrogen atoms were included in the calculated positions with isotropic displacement parameters taken as 1.2 times the isotropic equivalents for carbons or nitrogens they are bonded to (1.5 factor was applied for methyl hydrogens). Final *R* and *wR* were 0.0366 and 0.0960, respectively. The weights were $w=1/[\sigma^2(Fo^2)+(0.0527P)^2+0.2171P]$ where $P=(Fo^2+2Fc^2)/3$. GOF=1.035.

3.9. *Crystal data for compound* ***5a***

$C_{20}H_{25}ClN_2O_3$, M=376.87, space group $P2_12_12_1$, a=7.847(2) Å, b=8.052(2) Å, c=32.109(6) Å, V=2028.8(8) Å^3, Z=4, D_c=1.234 g cm^{-3}, F(000)=800 μ, (CuKα)=1.836 cm^{-1}.

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