PICTET-SPENGLER REACTION OF BIOGENIC AMINES WITH (2*R*)-*N*-GLYOXYLOYLBORNANE-10,2-SULTAM. ENANTIOSELECTIVE SYNTHESIS OF (*S*)-(+)-*N*-METHYLCALYCOTOMINE AND (*R*)-(+)-XYLOPININE

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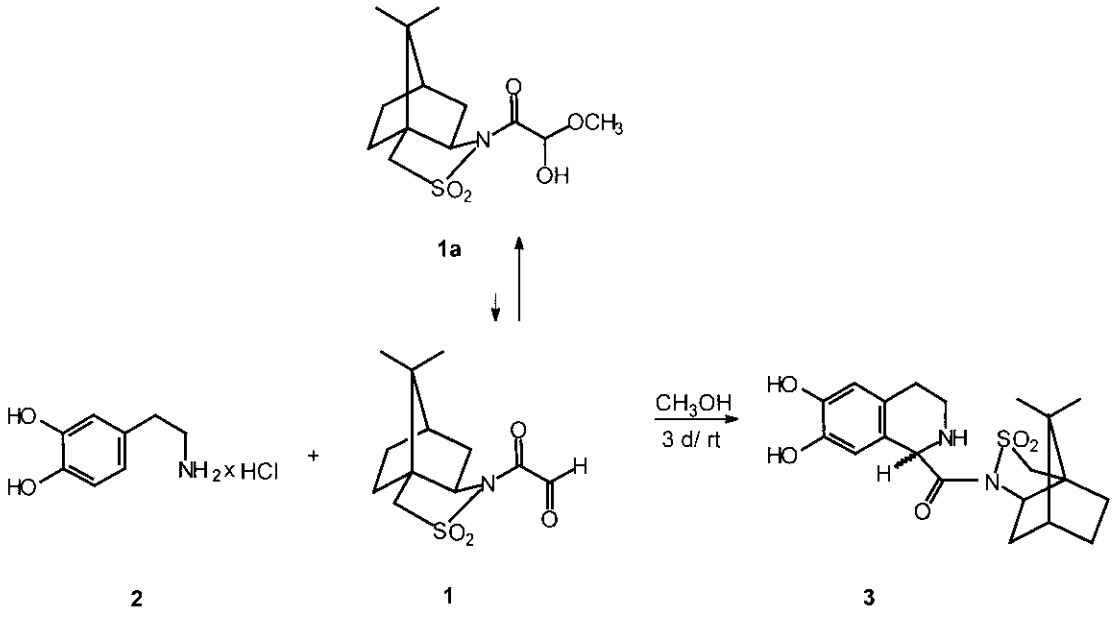
Abstract- The Pictet-Spengler reaction of (2*R*)-*N*-glyoxyloylbornane-10,2-sultam with dopamine hydrochloride gave the condensation product, which was further converted into (*S*)-(+)-*N*)-methylcalycotomine and (*R*)-(+)-xylopinine of high enantiomeric purity.

The Pictet-Spengler reaction[1,2] has played an important role in the syntheses of isoquinoline[3] and indole alkaloids.[4] For over fifty years from its discovery in 1911,[1] the reaction served mainly as a tool for the construction of racemic isoquinolines and β-carbolines. During the last two decades several new procedures have been developed that allowed efficient chirality transfer into the target molecules. Chiral auxiliary or chiral building block approaches were mainly explored. Those chiral auxiliary mediated Pictet-Spengler condensations involved the use of, among others, nonracemic sulfoxides,[5] (1*S*)-(-)-β-pinene,[6] or *N*-protected amino acids.[7] On the other hand amino acids,[4,8] terpenoids,[9] carbohydrates[10] or hydroxy acids[11] have also been applied as chiral building blocks.

Recently,[12] we turned our attention to bornane-10,2-sultam, a camphor derivative introduced to asymmetric synthesis by Oppolzer[13] and proven to be one of the most versatile and effective stereocontrollers known. Bornane-10,2-sultam can be transformed into its *N*-glyoxyloyl derivative (**1**)[14] which in turn may serve as a chiral building block in the Pictet-Spengler condensation.

Indeed, we found that the reaction of **1** with dopamine hydrochloride (**2**) in boiling methanol gave the

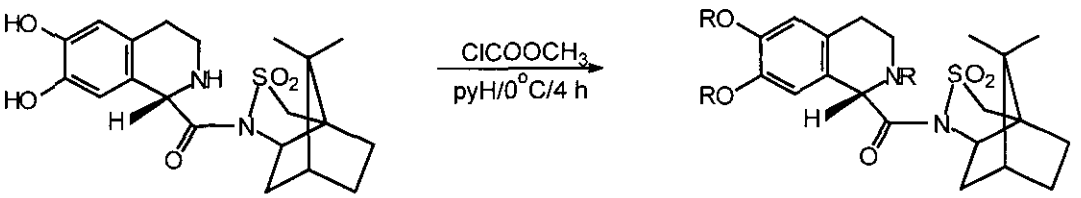
condensation product (**3**) in 25-30% yield. Relatively low chemical yield was caused mainly by unstability of **3** and its troublesome isolation from decomposition products. However, when the reaction was carried out in methanol at room temperature for 72 h with the use of a hemiacetal form (**1a**)[14] of **1**, the complete conversion of substrates was observed and the product (**3**) was isolated as a mixture of diastereomers. Their ratio was estimated on the basis of ^{1}H NMR (500 MHz) of the crude reaction mixture and it was further confirmed to be 89:11 by HPLC analysis of the peracetyl derivative of **3**. Several solvents and their mixtures were investigated and even better diastereodifferentiation (93:7) was obtained when methanol-water mixture was used.



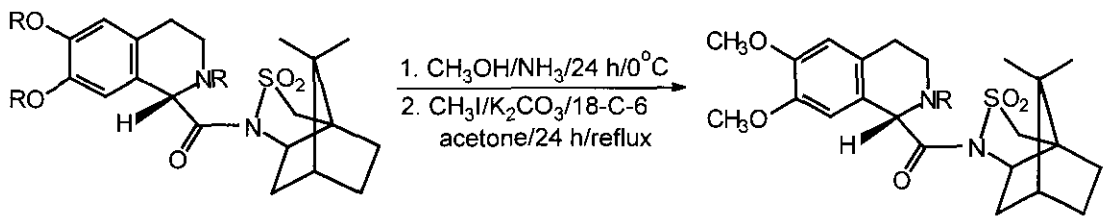
The isolation of **3** in the pure form and in good chemical yield was difficult due to its fast air oxidation and extensive decomposition at temperatures above 25°C. Compound (**3**) therefore, was converted into stable and chromatographically separable diastereomers of *per*-amide ester derivative, using methyl chloroformate in pyridine. The predominant component (**4**) was finally isolated in 90% yield. Subsequent treatment of **4** with ammonia in methanol at 0°C and immediate etherification of phenolic hydroxyl groups of the unstable intermediate with methyl iodide in the presence of potassium carbonate, allowed the formation of dimethoxy compound (**5**) in good yield.

Strong electrophilic character of the carbonyl group attached to sultam moiety was then utilized to perform its facile reduction with lithium aluminum hydride and also to the extension of this protocol to the preparation of more complex isoquinoline alkaloids by the introduction of the aromatic substituent. Thus, the reaction of **5** with LAH, accompanied by simultaneous reduction of the carbamate moiety to *N*-

methyl group and the reductive cleavage of *C*-sultam bond, gave directly (*S*)-(+)-*N*-methylcalycotomine (**6**) of known absolute configuration[15] in 91% yield.

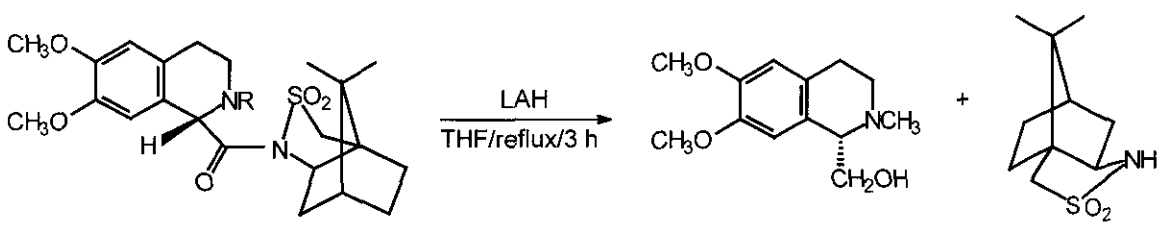


3a **4** R=$COOCH_3$



4 R=$COOCH_3$ **5** R=$COOCH_3$

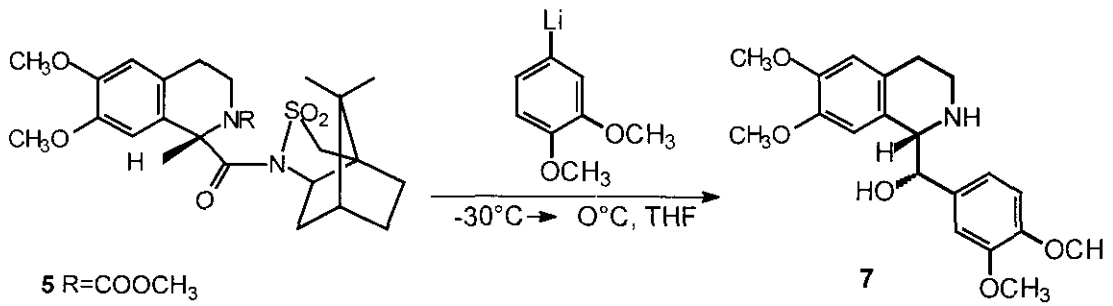
The enantiomeric composition of **6** was established by ^{1}H-NMR experiment with 0.1 eq of Eu(hfc)$_3$. The integration of differentiated aromatic signals gave the ratio 96:4, which corresponds to 92% ee. This value was in accordance with our earlier estimations based on optical rotation measurements.[16] During a work up of the reaction mixture we were also able to recover the sultam in 96% yield, without any loss of the optical purity.



5 R=$COOCH_3$ **6**

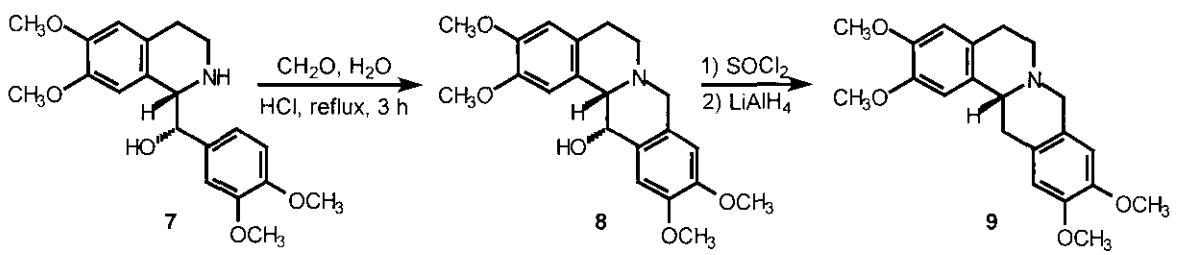
The above results prompted us to extend the procedure for the preparation of 1-aryl-tetrahydroisoquinolines. For this purpose we chose 3,4-dimethoxyphenyllithium as a nucleophile in the reaction with compound (**5**). In several attempts however, we found this reaction giving complex mixture of unstable products. After a considerable efforts we discovered that when the solution of compound (**5**)

was introduced into a large (10 eq) excess of an organometallic reagent with a simultaneous addition to CO-sultam and carbamate carbonyls took place accompanied also by the removal of the sultam moiety. Accordingly, *threo*-hydroxynorlaudanosine (7) was isolated in 74% yield (based on **5**).



5 R=$COOCH_3$ **7**

It is noteworthy that this addition took place with the complete diastereoselectivity. Using HPLC and ^1H NMR analysis of the crude reaction mixture we were able to indicate the presence of only *threo*-hydroxy compound (**7**) with no detectable contamination with the *erythro*-congener. Standard conditions for the Mannich reaction of **7** with formaldehyde brought about the formation of **8** in 78% yield.



7 **8** **9**

Enantiomeric modification of **8** (**ent-8**) has already been prepared[17,18] and claimed to be virtually homochiral but it's optical purity was not established by an absolute method. Our earlier findings based solely on optical rotation measurements have now been proven to be correct within an experimental error with the use of ^{19}F NMR of its Mosher's acid ester of **8** (prepared from (*R*)-(+)-MTPA;[19] the cross reference was obtained from **rac-8**[17]). *Threo*-α-hydroxyprotoberberine (**8**) was then subjected to our modified deoxygenation procedure[17] to afford *R*-(+)-xylopinine (**9**)[20] in 88% yield. Despite considerable efforts (HPLC on chiral columns, chiral lanthanide NMR shift reagents), we were unable to determine the absolute enantiomeric composition of the final product. However, the latter possessed $[\alpha]^{23}_D$ +277° (*c* 0.28, $CHCl_3$) and this value is quite close to the reported highest rotation $[\alpha]^{23}_D$ -283° (*c* 0.32, $CHCl_3$) given by Meyers[21] for **ent-9**. Furthermore, the spectroscopic data for our final product (**9**) were identical to

the literature values.[17,21] Thus, we may conclude that the deoxygenation procedure gives no observable decomposition or racemization even with labile compounds.

Finally, we have shown herein that (2*R*)-*N*-glyoxyloylbornane-10,2-sultam (**1a**) may serve as a versatile and effective chiral inducing agent also in isoquinoline alkaloid chemistry.

ACKNOWLEDGMENT

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EXPERIMENTAL

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. Chemical shifts are reported in (δ) ppm. MS were collected on AMD 604 apparatus; high resolution MS were acquired using LSIMS (positive ion mode). Optical rotation was 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). Elemental analyses were performed in a Microanalytical Laboratory of the Institute for Organic Chemistry, Polish Academy of Sciences, Warsaw. HPLC analyses were performed on a Knauer (model 64) apparatus with Eurochrom 2000 software using 4 mm x 250 mm silica (5μm) column. Chiral HPLC analyses were done using a ChiraSep (DNBPG) column from Merck with hexane / 2-propanol 95:5 (v/v) or ChiraDex column (Merck) with methanol / water 4:1 (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.

Condensation of dopamine hydrochloride (2) with (1a):

A solution of 3.37 g (17.82 mmol) of dopamine hydrochloride (**2**) in 4 mL of demineralized water and 6.00 g (19.80 mmol) of hemiacetal of (2*R*)-*N*-glyoxyloylbornane-10,2-sultam (**1a**) in 35 mL of methanol was stirred at rt for 3 days under argon atmosphere. After completion of the reaction (TLC) methanol was evaporated and the residue was taken up into 30 mL of chloroform. Anhydrous magnesium sulfate was added (2.0 g) and after 15 min of stirring the mixture was filtered and concentrated. Column chromatography (silica gel, 99:1 chloroform/methanol) afforded compound (**3**) (4.13 g, 57 %) as a brown amorphous solid: ^{1}H-NMR ($CDCl_3$, δ, 500 MHz): 6.91 (1H, s), 6.83 (1H, s), 4.82 (1H, br t, J=10.9 Hz), 4.06 (1H, br t, J=5.4 Hz), 4.00 - 3.83 (2H, m), 3.51 - 3.40 (2H, m), 2.98 - 2.92 (2H, dt, J_1=17.5 Hz, J_2=5.4 Hz), 1.91 - 1.75 (5H, m), 1.51 - 145 (1H, m), 1.31 - 1.25 (1H, m), 1.16 (3H, s), 1.00 (3H, s). Integration of

two singlets at 1.15 and 1.08, that probably corresponds to traces of the second diastereomer, gave the value of 86% de for **3a**. This value was further confirmed by HPLC analysis of the peracetyl derivative of **3**. Anal. Calcd for $C_{20}H_{26}N_2O_5S$: C: 59.10, H: 6.45, N: 6.89, S: 7.89. Found: C: 59.85, H: 6.25, N: 7.26, S: 7.22. All other analytical data were the same as described earlier.[12]

Preparation of compound (4):

To a stirred solution of 3.80 g (9.35 mmol) of compound (**3**) in 75 mL of chloroform containing 6.04 g (76.4 mmol) of dry pyridine at 0°C, a solution of 3.61 g (38.2 mmol) of methyl chloroformate in 5 mL of chloroform was added dropwise over the period of 5 min. The reaction mixture was the allowed to warm to rt and was stirred for 4 h. After this period, solvents were evaporated *in vacuo*, the residue was dissolved in diluted acetic acid (200 mL, 5% aqueous), and the solution was extracted with toluene (3 x 70 mL). The combined organic extracts were washed with 5% solution of $NaHCO_3$, water, dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography of the residue (silica gel, 99.5:0.5 chloroform/methanol) afforded compound (**4**) (5.42 g, 90%) as colourless foam: $[\alpha]^{23}_D$ -1.2° (*c* 1.11, $CHCl_3$), ^{1}H-NMR ($CDCl_3$, δ, 500 MHz): 7.13 (1H, s), 7.10 (1H, s), 6.14 (1H, s), 4.23 - 4.16 (1H, m), 3.91 - 3.86 (2H, m), 3.87 and 3.89 (two s, 3H each), 3.73 (3H, s), 3.57 - 3.43 (2H, ABq, J=10.1 Hz), 3.24 - 3.17 (1H, m), 2.79 (1H, br t, J=15.6 Hz), 1.95 -1.81 (3H, m), 1.76 - 1.61 (2H, m), 1.49 - 1.39 (1H, m), 1.36 - 1.26 (1H, m), 0.91 (3H, s), 0.88 (3H, s). LSIMS (+) NBA 8 kV *m/z* (%): 280 (8.8), 294 (6.5), 338 (100), 366 (8.2), 581 $(M + H)^+$ (13.5), 603 $(M + Na)^+$, 1183 $(2M + Na)^+$. LSIMS HR: calcd for $C_{26}H_{33}N_2O_{11}S$ $(M + H)^+$: 581.1805, found: 581.1800.

Preparation of compound (5):

To a solution of 3.00 g (5.17 mmol) of compound (**4**) in 100 mL of dry methanol 10 drops of 25 % aq. ammonia were added at 0°C and the reaction mixture was stirred at this temperature for 24 h (with TLC monitoring). After this period the solvent was evaporated to dryness *in vacuo* and the residue was additionally dried in a vacuum dessicator over phosphorous pentoxide overnight. The mixture was then dissolved in 200 mL of dry acetone, 5 g of anhydrous potassium carbonate, 10 mg of 18-crown-6 and 3.2 mL (51.4 mmol) of methyl iodide were added all at once, operating under strictly anhydrous conditions. The resulting mixture was refluxed for 24 h under argon atmosphere. After this period the solution was filtered, the residue washed with anhydrous ether and combined filtrate and washings were evaporated *in vacuo*. Column chromatography (silica gel, 99:1 chloroform/methanol) afforded compound (**5**) (1.98 g, 78%) as an amorphous white solid, $[\alpha]^{23}_D$ - 3.8° (*c* 1.26, $CHCl_3$), ^{1}H-NMR ($CDCl_3$, δ, 500 MHz): 7.28(1H, s), 6.65 (1H, s), 5.99 (1H, s), 4.23 - 4.19 (1H, m), 3.88 - 3.81 (2H,m), 3.82 and 3.84 (two s, 3H each), 3.73 (3H, s), 3.53 (2H, ABq, J=13.3 Hz), 3.39 - 3.31 (1H, m), 3.19 (1H, t, J=15.4 Hz), 1.93 - 1.71 (5H, m), 1.57 - 1.42 (2H, m), 1.26 (3H, s), 0.93 (3H, s). LSIMS (+) NBA 8 kV *m/z* (%): 250 (100), 493 (M

+ H)$^+$ (17.6), 515 (M + Na)$^+$ (26.5). LSIMS HR: calcd for $C_{24}H_{32}N_2O_7NaS$ (M + Na)$^+$ 515.1828, found 515.1828.

Preparation of (*S*)-(+)-*N*-methylcalycotomine (6):

To a solution of 250 mg (0.51 mmol) of compound (**5**) in 30 mL of dry tetrahydrofuran 150 mg (2.1 mmol) of lithium aluminum hydride was carefully added. The mixture was then refluxed for 3 h. After cooling to rt 0.5 mL of sodium hydroxide solution (11%, aqueous) was added dropwise. The resulting suspension was filtrated and washed several times with hot THF. The combined filtrate and washings were evaporated *in vacuo* and the residue subjected to column chromatography (silica gel, 95:5 chloroform/methanol) to afford (*S*)-(+)-*N*-methylcalycotomine (**6**) (110 mg, 91%) as a colourless oil: $[\alpha]^{23}_D$ +50.4° (*c* 0.67, $CHCl_3$), lit.,[12] $[\alpha]^{23}_D$ +55° (*c* 0.4, $CHCl_3$), *CI MS m/z (%): 238 (32, M$^+$ +1), 206* (100, M$^+$ -CH_2OH), ^{1}H-NMR ($CDCl_3$, δ, 200 MHz): 6.61 (1H, s), 6.57 (1H, s), 3.82 and 3.83 (2x3H, two s), 3.75 (1H, m), 3.52 (2H, m), 3.13 (2H, m), 2.81 (2H, m), 2.54 (3H, s). Upon addition of 0.1 eq of Eu(hfc)$_3$ signals at 6.61 and 6.57 ppm gave two pairs of signals: 6.70 and 6.68 ppm (major), and 6.61 and 6.60 ppm (minor), the integration of which gave the ratio 96:4 that corresponds to 92% ee.

Preparation of (*S*)-3,4-dimethoxyphenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl-methanol ((-)-*threo*-hydroxynorlaudanosine) (7):

A stirred solution of 2.33 mL (18.2 mmol) of freshly distilled 4-bromoveratrole in 40 mL of dry tetrahydofuran was treated dropwise with 10.0 mL of 1.6 M n-butyllithium (10.0 mmol) in hexane at –78°C. After 1 h stirring a solution of compound (**5**) (979 mg, 1.99 mmol) in 5 mL of THF was added dropwise at the same temperature. The reaction mixture was then stirred for 1 h at the same temperature and the cooling bath was removed and the mixture was allowed to reach rt. After decomposition with 1 mL of methanol, the contents of the flask was evaporated under reduced pressure and the residue was dissolved in 20 mL of chloroform. The organic layer was washed with 20 mL of water, from which bornane-10, 2-sultam could be quantitatively recovered by acidification and extraction procedure. The remaining organic layer was dried ($MgSO_4$) and evaporated to leave an oil which was then subjected to column chromatography on silica gel using chloroform-methanol-25% aq. ammonia (97:3:0.01 v/v) as eluent. Compound (**7**) was isolated as yellowish crystalline mass (530 mg, 74%). ^{1}H NMR spectrum of the crude product revealed the presence of only *threo* diastereomer of **7**. Recrystallization from ethanol gave an analytical sample having mp 199-201°C, $[\alpha]^{23}_D$ –95.7° (*c* 2.12, $CHCl_3$); for **ent-7** lit.,[18] mp 197-199°C, $[\alpha]^{23}_D$ +94.5° (*c* 1.33, $CHCl_3$). All spectral data were the same as previously described.[18]

Preparation of (13*S*,13a*S*)-2,3,10,11-tetramethoxy-5,8,13,13a-tetrahydro-6*H*-isoquino[3,2-*a*]isoquinolin-13-ol (8):

The Mannich condensation of (-)-*threo*-hydroxynorlaudanosine (**7**) with formaldehyde[18] (37%, aqueous)

afforded the title 13-hydroxyprotoberberine derivative (**8**) in 78% yield.[18] mp 150-152°C, $[\alpha]^{23}_D$ +298.1° (*c* 1.32, $CHCl_3$); for **ent-8** lit.,[18] mp 150-152°C, $[\alpha]^{23}_D$ –299.1° (*c* 2.61, $CHCl_3$). A sample of **8** was subjected to determination of enantiomeric composition by the use of ^{19}F NMR. Thus, oxalyl chloride (0.12 mL 1.4 mmol) was added to the solution of (*R*)-(+)-MTPA (66 mg, 0.28 mmol) in 12 mL of anhydrous hexanes containing 0.022 mL (0.28 mmol) of DMF and after 3 h of stirring at rt the mixture was filtered, concentrated *in vacuo*, dissolved in 3 mL of dichloromethane and introduced to the solution of compound (**8**) (31 mg, 0.084 mmole) in the mixture of 1 mL (0.726 g) triethylamine and 3 mL of dichloromethane. The resulting mixture was stirred for 24 h at rt and then washed with 5% citric acid, 5% sodium bicarbonate and brine. The organic layer was dried over $MgSO_4$, concentrated and the residue was filtered through a pad of silica gel. The resulting solution was concentrated and the residue was subjected to ^{19}F NMR with C_6F_6 as internal standard. Integration of signals at –76.2 and -75.7 ppm gave value >96% ee.

Preparation of *R*-(+)-xylopinine (9)

The conversion of *threo*-α-hydroxyprotoberberine (**8**) into *R*-(+)-xylopinine (**9**) was accomplished by the use of an deoxygenation method previously described by us.[17] Now we found that doubling the amounts of reagents towards *threo*-α-hydroxyprotoberberine (**8**) used gave better yield of the final alkaloid together with less decomposition products formed. Thus, *R*-(+)-xylopinine (**9**) was obtained in the form of white crystals in 88% yield. mp 178-180°C (from methanol), $[\alpha]^{23}_D$ +277.2° (*c* 0.28, $CHCl_3$); for **ent-9** lit.,[21] mp 179-180°C, $[\alpha]^{23}_D$ –283.1° (*c* 0.32, $CHCl_3$). All the spectral data were the same as those in the literature[17,21]. Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.77; H, 6.59; N, 3.75.

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