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Enantiospecific synthesis of (*S*)-(−)-8-oxoxylopinine

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ABSTRACT

The enantiospecific synthesis of (*S*)-(−)-8-oxoxylopinine **1** was performed using a lateral metallation strategy, in which (*S*)-alaninol or (*S*)-phenylalaninol was applied as chiral auxiliary and building block. (4*S*)-3-(4,5-Dimethoxy-2-methylbenzoyl)-2,2,4-trimethyl-1,3-oxazolidine **12** was synthesized starting from veratraldehyde **13**. The addition reaction of benzylic anion generated in situ from chiral amide **12** into 6,7,-dimethoxy-3,4-dihydroisoquinoline **7a** proceeded with simultaneous cyclization leading to the protoberberine alkaloid with high enantioselectivity.

1. Introduction

8-Oxoxylopinine **1** can be considered as a precursor of xylopinine **2**, a protoberberine alkaloid.[1] There are several well-known methods described in the literature for the reduction of 8-oxoxylopinine **1** to xylopinine **2** both in the synthesis of the racemate[2] and in the stereoselective synthesis.[3]

To date, several syntheses of racemic 8-oxoxylopinine (±)-**1** have been published,[2] while three examples of the synthesis of non-racemic 8-oxoxylopinine **1** have been reported.[3] In 1997, Comins et al.[3a] used compound **3**, which contained a chiral auxiliary derived from (+)-*trans*-(α-cumyl)cyclohexyl chloroformate and vinyl ether derivative, 2-bromo-4,5-dimethoxy-1-(2-methoxyethenyl)benzene **3a**, as the aldehyde equivalent in the asymmetric Pictet–Spengler reaction. The intermediate chiral benzyltetrahydroisoquinoline (79% de) was further transformed into (*S*)-(−)-8-oxoxylopinine **1** (Fig. 1). A few years later Davis and Mohanty[3b] used enantiopure sulfinimine **4** and the laterally lithiated *o*-tolunitrile of **5** as substrates and next transformed the resulting cyano sulfinamide adduct into the protoberberine system (*S*)-(−)-**1**. In 2007, Iwao and Fukuda[3c] developed a synthesis of both enantiomers of protoberberine **1** and *ent*-**1** via the addition of laterally lithiated (*S*)-4-isopropyl-2-(*o*-tolyl)oxazoline **6** into 6,7-dimethoxy-3,4-dihydroisoquinoline **7a** to give diastereomeric adducts with modest diastereoselectivity. After their chromatographic separation and acid catalyzed lactamization, both enantiomeric alkaloids (*S*)-**1** and (*R*)-*ent*-**1** were obtained with 98% ee and 96% ee, respectively. These two last examples confirmed the usefulness of the lateral metallation methodology,[5] which proceeded with high regiochemical control for the synthesis of heterocyclic compounds including protoberberines.

2. Results and discussion

In continuation of our studies on stereoselective synthesis of isoquinoline alkaloids[6] based on the addition of chiral nucleophiles to imines, we have used the lateral metallation approach for the synthesis of protoberberine alkaloids.[7–9] Initially we performed the asymmetric synthesis of both enantiomers of 2,3-dimethoxy-8-oxoberbine **9** and 2,3-methylenedioxy-8-oxoberbine **10**, compounds which do not possess an oxygenated substituent on ring D. Oxazolidines **8** derived from commercially available aminoalcohols, (1*R*,2*R*)-norephedrine, or (*S*)- or (*R*)-phenylalaninol, respectively, were used as chiral auxiliaries and building blocks. The key step of the synthesis, in which a new stereogenic center at C13a was created, involved the addition of laterally lithiated chiral *o*-toluamide of type **8** into imine **7**. This addition proceeded stereoselectively and was accompanied by simultaneous cyclization to directly afford protoberberine alkaloids **9** or **10** (Fig. 2).

To apply the same methodology to the synthesis of 8-oxoxylopinine **1**,[3] a protoberberine alkaloid with oxygenated substituents at ring D, an amide with methoxy substituents in the aromatic ring was needed. Thus, we performed the synthesis of two homochiral *o*-toluamides (4*S*)-2,2-dimethyl-3-(4,5-dimethoxybenzoyl)-4-benzyl-1,3-oxazolidine **11** and (4*S*)-3-(4,5-dimethoxybenzoyl)-2,2,4-trimethyl-1,3-oxazolidine **12** starting with veratraldehyde **13** and commercially available amino alcohols: (*S*)-(−)-phenylalaninol and (*S*)-(+)-alaninol, respectively (Scheme 1). We have already published[10] the synthesis of oxazolidine **11**, which is based on the transformation of veratraldehyde **13** into carboxylic acid **14** and the reaction of its acid chloride with (*S*)-phenylalaninol, followed

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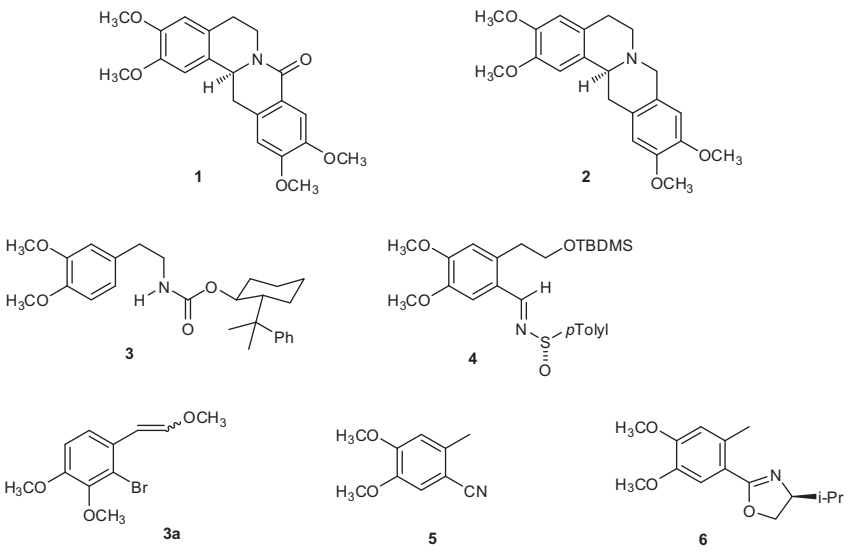


Figure 1. (*S*)-(−)-8-Oxoxylopinine **1**, (*S*)-(−)-xylopinine **2** and compounds used in its asymmetric synthesis.

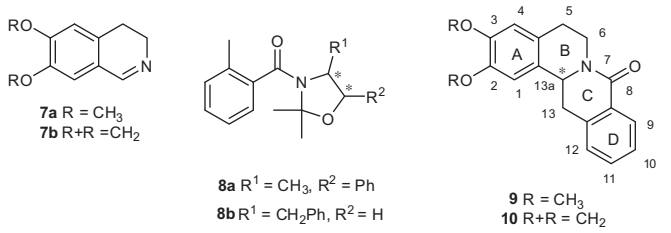
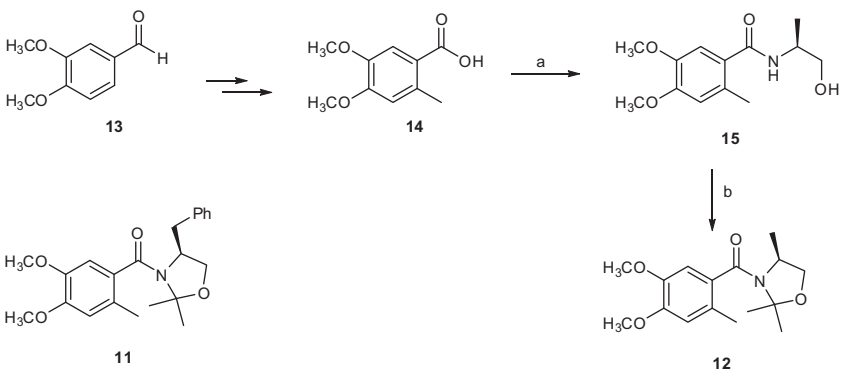


Figure 2. Starting compounds and products in asymmetric syntheses of 8-oxoberbines **9**, **10**.

by cyclization to afford the oxazolidine. According to the same procedure, the synthesis of (4*S*)-3-(4,5-dimethoxybenzoyl)-2,2,4-trimethyl-1,3-oxazolidine **12** was carried out, in which 2-methyl-4,5-dimethoxybenzoic acid **14** and (*S*)-(+)-alaninol were used as substrates (Scheme 1).

Acid **14** was obtained in its pure form from veratraldehyde **13** according to a literature procedure[10,11a] involving bromination, exchange of the bromine substituent for the methyl group and oxidation of the aldehyde group to a carboxylic acid. From acid **14**, the acid chloride was prepared in situ with thionyl chloride and then reacted with (*S*)-alaninol to give amide **15** in 70% yield. It was then recrystallized from methanol/diethyl ether to yield a crystalline compound with an mp of 133-135 °C and $[\alpha]_D^{20} = -5.9$ (*c* 0.97, $CHCl_3$); $[\alpha]_D^{20} = +6.4$ (*c* 1.2, MeOH). The low value of the specific rotation $[\alpha]_D$ measured for amide **15**, and the changes in sign of the specific rotation depending on the solvent used ($CHCl_3$ or MeOH) prompted us to undertake additional experiments to verify the enantiomeric purity of **15**. For this purpose, we prepared a sample of racemic compound (±)-**15** according to the same synthetic route as depicted in Scheme 1, using acid **14** and (±)-alaninol as substrates. A sample of racemic amide (±)-**15** was analyzed on HPLC Chiralcel OD-H column and the result was compared with a chromatogram of chiral amide **15** to confirm the enantiomeric purity of this compound. Next, homochiral compound **15** was transformed into the desired oxazolidine derivative **12**, prepared in 73% yield in the reaction with 2,2-dimethoxypropane (DMP), catalyzed by *p*-toluene sulfonic acid, in benzene at reflux and under an argon atmosphere. Pure oxazolidine **12** was obtained after column chromatography separation and crystallization from diisopropyl ether, mp 85–86 °C, $[\alpha]_D^{20} = +46.8$ (*c* 0.55, $CHCl_3$). For the sake of comparison, we prepared a sample of racemic compound (±)-**12** from (±)-**15** following the same synthetic route as depicted in Scheme 1. HPLC analysis confirmed the enantiomeric purity of chiral oxazolidine **12**. In addition, the correctness of the structures and purity of amide **15** and oxazolidine **12** obtained



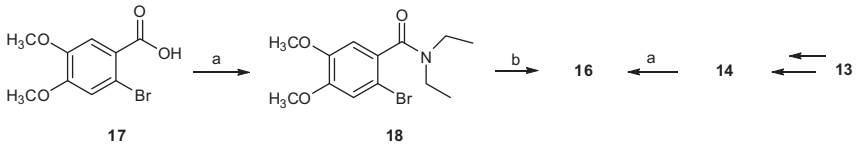
Reagents and conditions: (a) $SOCl_2$, (*S*)-Alaninol, 0.5 M KOH, CH_2Cl_2; (b) DMP, *p*-TsOH, PhH.

Scheme 1. Synthesis of oxazolidine **12**.

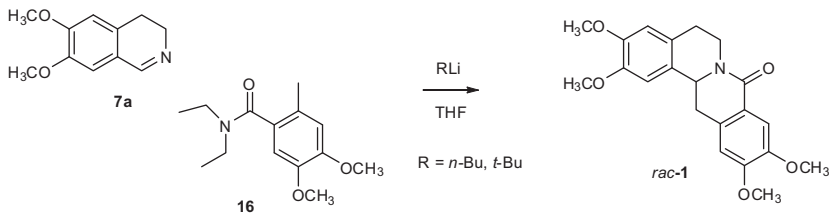
were confirmed by spectroscopic characteristics and elemental analysis. Since compounds **15** and **12** were prepared from (*S*)-(+)-alaninol, we were able to assign an (*S*) absolute configuration for the enantiomers. On HPLC analysis, amide **15** was characterized by a longer retention time, while oxazolidine **12** by a shorter retention time.

We started with the synthesis of racemic 8-oxoxylopinine (±)-**1** to obtain a sample for HPLC comparison, also employing the lateral metallation methodology. For this purpose, we tried to prepare *N*,*N*-diethyl-4,5-dimethoxy-2-methylbenzamide **16** from the commercially available 2-bromo-4,5-dimethoxybenzoic acid **17** (Scheme 2). The acid chloride of compound **17** was prepared in situ with thionyl chloride and treated with diethylamine to give amide **18** with 82% yield.[12] The bromine substituent in amide **18** was exchanged for a methyl group in the reaction with *n*-butyllithium and methyl iodide. However the crude product **16** needed purification by repeated column chromatography, finally supplying pure amide **16** in only 34% yield. Thus, we decided to prepare compound **16** starting with veratraldehyde **13**, via 2-methyl-4,5-dimethoxybenzoic acid **14**, which was converted into *N*,*N*-diethylamide **16** by treatment with diethylamine with 98% yield.

Crystallization from methanol/diethyl ether led to pure crystalline amide **16** showing an mp of 58–60 °C. The key step of the synthesis of 8-oxoxylopinine (±)-**1** was the addition of the benzylic anion generated from *N*,*N*-diethyl-4,5-dimethoxy-2-methylbenzamide **16** to the imine 6,7-dimetoxy-3,4-dihydroisoquinoline **7a** (Scheme 2). During this addition, a spontaneous cyclization to the protoberberine system took place. The carbanion was generated from amide **16** (1.3 equiv) with the aid of 1.5 equiv of *n*-butyllithium at −72 °C. After the addition of 6,7-dimethoxy-3,4-dihydroisoquinoline **7a** and subsequent work-up, the addition/cyclization product, racemic 8-oxoxylopinine (±)-**1** was isolated as a crystalline compound, mp 193–197 °C (lit.[4a] mp 191–192 °C) although with a low yield of 13%. Thus, we obtained a sample of (±)-**1** for confirmation of the correctness of its structure and evaluation of HPLC conditions for the determination of the enantiomeric excess of samples of **1**. We attempted to optimize the conditions of the addition using, for example, a higher excess of amide **16** (4 equiv), *t*-BuLi instead of *n*-BuLi for deprotonation of amide **16** or $BF_3{\cdot}Et_2O$ for the activation of imine **7a**, but these changes did not improve the yield of the final product.



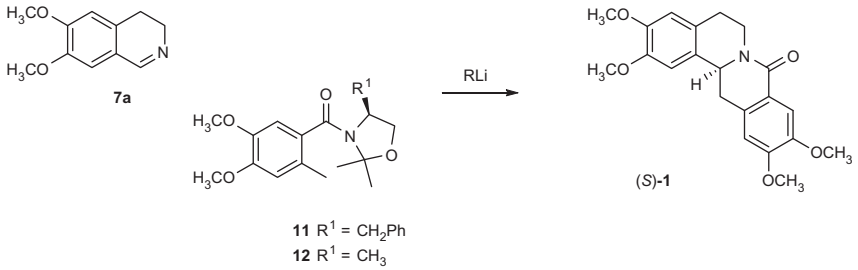
Reagents and conditions: (a) $SOCl_2$, $(CH_3CH_2)_2NH$, 0.5 M KOH, CH_2Cl_2; (b) *n*-BuLi, THF, CH_3I.



Scheme 2. Synthesis of (±)-8-oxoxylopinine **1**.

With this information in hand we carried out the asymmetric synthesis of **1** by the addition of the benzylic anion generated in situ from chiral amide **11**, in one series of experiments, or **12**, in another series of experiments, into 6,7-dimethoxy-3,4-dihydroisoquinoline **7a** (Scheme 3). In both series of experiments we checked the influence of different parameters on the stereoselectivity and yield of the addition step to 3,4-dihydroisoquinoline **7a**, in particular the types of bases used for the generation of the benzylic anion from amides **11** and **12**. We also examined different stoichiometries of the substrates, time of carbanion generation, and the presence of additive such as TMEDA.

Our attempts to deprotonate benzyloxazolidine **11** with *n*-BuLi, which was used successfully for the deprotonation of (4*S*)-4-benzyl-2,2-dimethyl-3-*o*-toluoyl-1,3-oxazolidine **8b**,[7] failed. Increasing the amounts of amide **11** to 2 equiv gave only trace amounts of the desired product **1** in the reaction mixture. Using *s*-BuLi or *s*-BuLi with the addition of TMEDA or a different molar ratio of *s*-BuLi to amide **11** did not lead to the formation of desired product



Scheme 3. Synthesis of (*S*)-(−)-8-oxoxylopinine **1**.

1. Finally, with *t*-BuLi (2 equiv) in THF 8-oxoxylopinine **1** was isolated with 74% ee and in 5% yield after column chromatography. It should be mentioned that the 4-benzyl group present in oxazolidine **8b** was proven to be a good chiral auxiliary in the synthesis of 8-oxoberbines **9** and **10** but for oxazolidine **11**, the presence of methoxy substituents in the aromatic ring made this process more complicated, which has also been reported by others.[13,14] This explained the low yield of racemic (±)-**1** obtained from amide **16**.

The process of the deprotonation of methyloxazolidine **12** was more effective than that of compound **11**. The addition of benzyl anion of **12** generated with *n*-BuLi (1.1 equiv) into 6,7-dimethoxy-3,4-dihydroisoquinoline **7a** (1 equiv) led to product **1** with 76% ee and in 5% yield. The use of 3 equiv of amide **12** under similar reaction conditions led to a product with lower ee (56%) and did not increase the chemical yield of the reaction. Using LDA for the deprotonation of amide **12** led to product **1** with 51% ee. The use of *s*-BuLi or *t*-BuLi increased the stereoselectivity of this process, affording product **1** with 90% ee and 84% ee, respectively. When *t*-BuLi was used, there was a smaller amount of by-products in the reaction mixture, which permitted a simpler isolation of pure alkaloid **1** from the reaction mixture with 13% yield. Enantiomerically pure 8-oxoxylopinine **1** was isolated from the crude reaction product by column chromatography and additionally crystallized from dichloromethane/diethyl ether. Recrystallization of the enantiomerically enriched product led first to a product with a lower ee but from the mother liquor, enantiomerically pure compound **1** was obtained (>99% ee), mp 194–197 °C (lit.[3a] mp 187–188 °C). The specific rotation measured was $[\alpha]_D^{20} = -301.8$ (*c* 0.115, $CHCl_3$), lit.[3b] $[\alpha]_D = -297.1$ (*c* 0.42, $CHCl_3$). HPLC analysis confirmed the high enantiomeric purity of **1**; only one peak corresponding to a longer retention time t_R of 35.18 min was present in the chromatogram. On the basis of a comparison of the sign of the specific rotation with the literature data, the (*S*)-absolute configuration of our synthetic compound **1** (characterized by a longer retention time in HPLC chromatogram) could be postulated.

3. Conclusions

Herein, we have reported on the enantiospecific synthesis of (*S*)-(−)-8-oxoxylopinine **1** using the lateral metallation methodology. The addition reaction of oxazolidine **11** or **12**, incorporating (*S*)-phenylalaninol or (*S*)-alaninol as the chiral auxiliary and building block, respectively, into 3,4-dihydroisoquinoline **7a** was accompanied by simultaneous cyclization to directly afford lactam (*S*)-**1**. Although the yield of (*S*)-(−)-**1** is low (13%), this is overcome somewhat by the simplicity of the process. The steric outcome of the synthesis made with (*S*)-alaninol or (*S*)-phenylalaninol as the chiral auxiliary was comparable with that of the reactions with other aminoalcohols, such as norephedrine and phenylalaninol, which have been used previously in the synthesis of 8-oxoberbines **9** and **10**. In conclusion, the configuration of the C4 stereogenic center in the oxazolidine ring turned out to be an important factor for the stereochemical outcome of the reaction. We also noticed that the absolute configuration of the newly created stereogenic center depends on the configuration of the C-4 atom in the oxazolidine ring. From oxazolidines **11** and **12** with a (4*S*)-configuration, a new stereogenic center with an (*S*) configuration in **1** was created, which is in agreement with our earlier experiments.[7–9]

4. Experimental

4.1. General

Melting points were determined on a Koffler block and are uncorrected. IR spectra: Bruker FT-IR IFS 113V. NMR spectra: Varian Gemini 300, with TMS as the internal standard. Mass spectra: Varian 4000 GC/MS. Optical rotations: Perkin–Elmer polarimeter 242B at 20 °C. Elemental analyses: Vario EL III. Merck DC-Alufolien Kieselgel 60_{254} was used for TLC and Kieselgel 60 (70–230 mesh ASTM) for column chromatography. Analytical HPLC: Waters HPLC system with Daicel Chiralcel OD-H column; flow rate: 0.5 mL/min. All compounds were purchased from Aldrich Chemical Co. and used as received. THF was freshly distilled from $LiAlH_4$, benzene, and toluene—from sodium wire.

4.2. (2*S*)-2-(4,5-Dimethoxy-2-methylbenzamide)-1-propanol 15

The acid chloride was prepared in situ from 2-methyl-4,5-dimethoxybenzoic acid **14** (2.596 g, 13.2 mmol) which was refluxed with $SOCl_2$ (9 mL) and a drop of DMF for 1 h. After the mixture was cooled to room temperature, the excess of $SOCl_2$ was removed in vacuo to afford a white precipitate. The acid chloride was dissolved in CH_2Cl_2 (25 mL) and then carefully added to a mixture of (*S*)-(+)-alaninol (0.992 g, 13.2 mmol) in CH_2Cl_2 (120 mL) and 0.5 M KOH (86 mL) at 0 °C. The mixture was stirred intensively for 1.5 h and then left overnight at room temperature. The phases were then separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). Combined extracts were dried over Na_2SO_4. The solvent was evaporated in vacuo to afford a light oil that quickly solidified. Pure product **15** was crystallized from MeOH/Et_2O yielding 2.34 g (70%) of white crystals. Mp 133–135 °C. $[\alpha]_D^{20} = -5.9$ (*c* 0.97, $CHCl_3$), $[\alpha]_D^{20} = +6.4$ (*c* 1.2, MeOH). IR (KBr) ν cm^{-1}: 3350 (NH), 3287 (OH), 1633 (C=O). ^1H NMR ($CDCl_3$) δ: 1.25 (d, J = 6.7 Hz, 3H, CH_3), 2.38 (s, 3H, $ArCH_3$), 3.31–3.34 (m, 1H, disappears on treatment with D_2O, OH) 3.59–3.61 (m, 1H, CH_2), 3.70–3.75 (m, 1H, CH_2), 3.84 (s, 3H, CH_3O), 3.87 (s, 3H, CH_3O), 4.17–4.22 (m, 1H, CH), 6.13 (d, J = 7.2 Hz, 1H, NH), 6.64 (s, 1H, ArH), 6.91 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$) δ: 17.00 (CH_3), 19.57 ($ArCH_3$), 48.05 (CH), 55.81 (CH_3O), 56.06 (CH_3O), 66.88 (CH_2), 110.60 (CH), 113.62 (CH), 127.89 (C), 128.66 (C), 146.59 (C), 149.94 (C), 170.28 (C=O). GCMS (t_R = 13.67 min), m/z (%): 253 (M^+, 5), 235 (43), 220 (49), 192 (15), 179 (100), 165 (10), 151 (20), 136 (10), 107 (10), 77 (15). Anal. Calcd for $C_{13}H_{19}NO_4 \times 1/3H_2O$: C, 60.22; H, 7.64; N, 5.40. Found: C, 60.41; H, 7.80; N, 5.42. HPLC for chiral **15** [hexane/propan-2-ol = 4:1] t_R = 21.57 - min. HPLC for (±)-**15** [hexane/propan-2-ol = 4:1] t_R = 18.73 min and t_R = 21.32 min.

4.3. (4*S*)-3-(4,5-Dimethoxy-2-methylbenzoyl)-2,2,4-trimethyl-1,3-oxazolidine 12

To amide **15** (1.999 g, 7.9 mmol) in dry benzene (110 mL), 2,2-dimethoxypropane (13.146 g, 126.4 mmol) and *p*-toluenesulfonic acid monohydrate (0.390 g, 2.1 mmol) were added and the mixture was refluxed for 2 h. Next the mixture was cooled to room temperature and washed with 1% NaOH. The organic phase was dried over Na_2SO_4 and the solvent was evaporated in vacuo. The crude product was chromatographed on silica gel (hexane/ethyl acetate 90:10, 80:20, and 75:35, v/v) yielding 1.69 g (73%) of product **12**. An analytical sample was crystallized from *i*-Pr_2O yielding white crystals, mp 85–86 °C; $[\alpha]_D^{20} = +46.8$ (*c* 0.55, $CHCl_3$). IR (KBr) ν cm^{-1}: 1629 (C=O). ^1H NMR ($CDCl_3$) δ: 1.03 (d, J = 6.3 Hz, 3H, CH_3), 1.70 (s, 3H, CH_3), 1.81 (s, 3H, CH_3), 2.27 (s, 3H, $ArCH_3$), 3.67 (d, J = 1.5 Hz, 2H, CH_2), 3.87 (s, 3H, CH_3O), 3.88 (s, 3H, CH_3O), 4.02–4.07 (m, 1H, CH), 6.68 (s, 1H, ArH), 6.73 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$) δ: 18.33 ($ArCH_3$), 20.54 (CH_3), 23.28 (CH_3), 26.92 (CH_3), 54.54 (CH), 55.82 (CH_3O), 56.10 (CH_3O), 69.60 (CH_2), 95.25 ($C(CH_3)_2$), 109.14 (CH), 113.14 (CH), 125.96 (C), 129.94 (C), 146.85 (C), 149.00 (C), 167.66 (C=O). GCMS (t_R = 17.39 min), m/z (%): 293 (M^+, 7), 235 (5), 220 (5), 179 (100), 151 (9), 136 (6), 120 (3), 107 (2), 93 (2). Anal. Calcd for $C_{16}H_{23}NO_4 \times 4/5H_2O$: C, 62.44; H, 8.06; N, 4.55. Found: C, 62.13; H, 8.25; N, 4.18. HPLC for

(+)-**12** [hexane/propan-2-ol = 9:1] t_R = 35.23 min HPLC for (±)-**12** [hexane/propan-2-ol = 9:1] t_R = 35.11 min and t_R = 51.23 min.

4.4. *N,N*-Diethyl-4,5-dimethoxy-2-bromobenzamide 18

The acid chloride was prepared in situ from 2-bromo-4,5-dimethoxybenzoic acid **17** (2.089 g, 8.0 mmol) refluxed with $SOCl_2$ (8 mL) and a drop of DMF for 1 h. After the mixture was cooled to room temperature, the excess of $SOCl_2$ was removed in vacuo to afford a white precipitate. The acid chloride was dissolved in CH_2Cl_2 (20 mL) and then carefully added to a mixture of diethylamine (0.585 g, 8.0 mmol) in CH_2Cl_2 (60 mL) and 0.5 M KOH (52 mL) at 0 °C. The mixture was then stirred intensively for 1.5 h. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). Organic phases were dried over Na_2SO_4. Solvent was evaporated in vacuo to afford a light yellow oil, which was crystallized from MeOH/Et_2O to afford 2.070 g crystals of pure product **18** (82%). Mp 103–104 °C (lit.[12] mp 104–105 °C). ^{1}H NMR δ (ppm): 1.08 (t, J = 7.2 Hz, 3H, CH_3), 1.27 (t, J = 7.1 Hz, 3H, CH_3), 3.19 (q, J = 7.1 Hz, 4H, CH_2), 3.86 (s, 3H, CH_3O), 3.88 (s, 3H, CH_3O), 6.76 (s, 1H, ArH), 7.00 (s, 1H, ArH). GCMS (t_R = 15.45 min) m/z (%): 316 (M^+, 35), 302 (8), 243 (100), 236 (48), 214 (8), 165 (13), 157 (8), 108 (10), 94 (5), 77 (12), 56 (7).

4.5. *N,N*-Diethyl-4,5-dimethoxy-2-methylbenzamide 16

4.5.1. Synthesis from *N,N*-diethyl-4,5-dimethoxy-2-bromobenzamide 18

Amide **18** (0.979 g, 3.1 mmol) was dissolved in dry THF (25 mL), after which *n*-BuLi (1.7 equiv, 1.6 M solution in hexanes, 3.3 mL, 5.28 mmol) was added at −72 °C under an argon atmosphere. The mixture was stirred for 10 min and then a solution of CH_3I was added (2.083 g, 14.7 mmol) in THF (10 mL). After stirring for 2.5 h, the mixture was allowed to warm up to −30 °C and 20% NH_4Cl was added. When the reaction mixture reached room temperature, the phases were separated. The aqueous phase was extracted with Et_2O (3 × 15 mL). The combined organic extracts were dried over Na_2SO_4. The solvents were evaporated in vacuo to afford an orange oil, which was chromatographed on silica gel (CH_2Cl_2/MeOH, 200:1 and 100:1, v/v) to give 0.266 g (34%) of pure product **16**.

4.5.2. Synthesis from 4,5-dimethoxy-2-methylbenzoic acid 14

The acid chloride was prepared in situ from 2-methyl-4,5-dimethoxybenzioc acid **14** (0.981 g, 5.0 mmol), which was refluxed with $SOCl_2$ (5 mL) and a drop of DMF for 1 h. After the mixture was cooled to room temperature, the excess $SOCl_2$ was removed in vacuo to afford a white precipitate of the acid chloride. The precipitate was dissolved in CH_2Cl_2 (15 mL) and then carefully added to a mixture of diethylamine (0.366 g, 5.0 mmol) in CH_2Cl_2 (50 mL) and 0.5 M KOH (32.5 mL) at 0 °C. The mixture was then stirred intensively for 2.5 h. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over Na_2SO_4. The solvent was evaporated in vacuo to afford a light yellow oil that solidified. Product **16** was crystallized from MeOH/Et_2O to afford 1.236 g crystals of pure amide **16** (98%). Mp 58–60 °C. In the literature, this compound was described as an oil.[11] ^{1}H NMR δ (ppm): 1.05 (t, J = 7.1, 3H, CH_3), 1.26 (t, J = 7.1, 3H, CH_3), 2.23 (s, 3H, $ArCH_3$), 3.16 (q, J = 7.1 Hz, 2H, CH_2), 3.84–3.90 (m, 2H, CH_2), 3.85 (s, 3H, CH_3O), 3.88 (s, 3H, CH_3O), 6.69 (s, 2H, ArH). GCMS (t_R = 13.25 min) m/z (%), 251 (M^+, 5), 236 (22), 179 (100), 151 (20), 136 (9), 93 (5), 78 (5).

4.6. 8-Oxoxylopinine 1: general procedure

Amide **16**, **11**, or **12** was dissolved in dry THF (15 mL for 0.7 mmol) under an argon atmosphere. The solution was cooled to −72 °C and R-Li was added. The resulting dark purple solution indicated the formation of the benzyl anion. The mixture was stirred for 3–25 min (depending on color changes) and treated with a solution of 6,7-dimethoxy-3,4-dihydroisoquinoline **7a** (1 equiv) in THF (7 mL for 0.7 mmol). After 1 h, the reaction mixture was quenched at −72 °C with 5% HCl. When the temperature of the reaction mixture reached room temperature, the phases were separated and the organic phase was washed a few times with 5% HCl until it became colorless. The organic phase was dried over Na_2SO_4. The solvent was evaporated in vacuo to afford an oil which was chromatographed on silica gel (hexane/ethyl acetate 73:30 and 60:40, v/v). The product was obtained as a light beige solid and crystallized from CH_2Cl_2/Et_2O. (±)-**1** mp 193–197 °C (lit.[4a] mp 191–192 °C) HPLC for (±)-**1** [hexane/propan-2-ol = 65:35] t_R = 33.60 min (*R*)-**1**, t_R = 39.31 min (*S*)-**1**. (*S*)-(−)-**1** mp 194–197 °C (lit.[3a] mp 187–188 °C); $[\alpha]_D^{20}$ = −301.8 (*c* 0.115, $CHCl_3$), lit.[3b] $[\alpha]_D$ = −297.1 (*c* 0.42, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ (ppm): 2.71–2.97 (m, 4H, CH_2), 3.15 (dd, J = 3.84, 15.66 Hz, 1H, CH_2), 3.90 (s, 3H, CH_3O), 3.91 (s, 3H, CH_3O), 3.95 (s, 3H, CH_3O), 3.96 (s, 3H, CH_3O), 4.84 (dd, J = 3.71, 13.46 Hz, 1H, CH_2), 4.97–5.00 (m, 1H, CH), 6.70 (s, 1H, ArH), 6.72 (s, 1H, ArH), 6.73 (s, 1H, ArH), 7.65 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$): δ (ppm): 29.22 (CH_2), 37.65 (CH_2), 38.65 (CH_2), 55.24 (CH), 55.89 (CH_3O), 56.02 (CH_3O), 56.08 (CH_3O), 56.10 (CH_3O), 108.70 (CH), 109.13 (CH), 110.68 (CH), 111.39 (CH), 121.62 (C), 127.30 (C), 127.71 (C), 130.94 (C), 147.87 (C), 147.93 (C), 148.17 (C), 151.85 (C), 164.69 (C=O). GCMS (t_R = 26.99 min), m/z (%): 369 (72, M), 354 (35), 338 (23), 207 (7), 178 (60), 150 (100), 107 (12), 77 (23). HPLC for (*S*)-**1** [hexane/propan-2-ol = 65:35] t_R = 35.18 min.

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