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ASYMMETRIC SYNTHESIS OF 2,3-DIMETHOXY-8-OXOBERBINE, PRECURSOR OF *O*-METHYLBHARATAMINE

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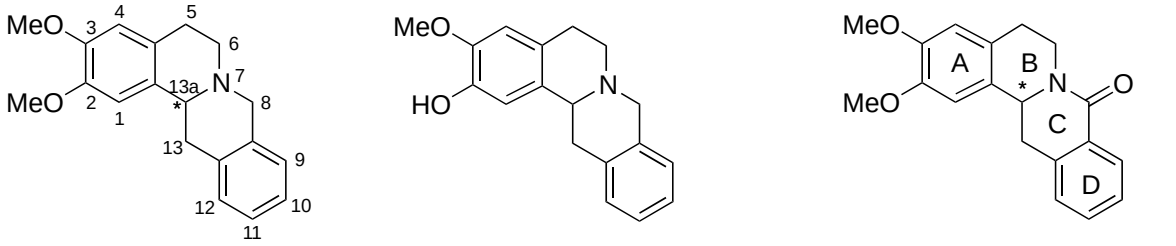
Abstract – The enantiospecific and enantioselective syntheses of 2,3-dimethoxy-8-oxoberbine were performed using the lateral metallation methodology. In the enantiospecific synthesis (4*S*)-2,2,4-trimethyl-3-(*o*-toluoyl)-oxazolidine incorporating (*S*)-alaninol as the chiral auxiliary was applied. The addition reaction of benzylic anion generated in situ from chiral oxazolidine into 6,7-dimethoxy-3,4-dihydroisoquinoline led to the protoberberine with high enantiomeric excess. Enantioselective synthesis of 2,3-dimethoxy-8-oxoberbine was performed with achiral 2,2-dimethyl-3-(*o*-toluoyl)oxazolidine in the presence of chiral ligands. Among them (–)-sparteine and (+)-sparteine surrogate turned out to be the most efficient ones.

INTRODUCTION

O-Methylbharatamine **1** is an *O*-methylated derivative of naturally occurring alkaloid bharatamine **2**, isolated in 1983, by Pakrashi[1] from the seeds of *Alangium lamarckii* Thw. (Alangiaceae) as a racemate. It is the first example of the protoberberine alkaloid unoxygenated at ring D (Figure 1). *Alangium lamarckii* is a small tree growing in the tropical region of South India on the coast of Malabar. The root, root bark, seeds and leaves of the plant are used in the Indian medicine,[2,3] showing antihelmenthic, purgative, antidiabetics, emetic properties and antibacterial, analgesic, anti-inflammatory, and antifungal activities.

Since 1960, berbine, of *O*-methylbharatamine structure **1**, was the model compound in designing new methods for the synthesis of protoberberine skeleton. Its first synthesis in the racemic form was reported by Huffman and Miller[4] in 1960. In stereoselective version, the synthesis of 8-oxo derivative, e.g. 2,3-dimethoxy-8-oxoberbine **3a**, was proposed by Ninomiya *et al*.[5] in 1983 and until now this compound is a model structure in evaluation of new methods of asymmetric synthesis. Among different methods developed for the construction of a protoberberine skeleton, the lateral metallation methodology[6] has been frequently used. Warrener *et al.*[7] performed in 1997 the asymmetric synthesis of

2,3-dimethoxy-8-oxoberbine **3a** by addition chiral *o*-toluamides type **5a** to 3,4-dihydroisoquinoline **4a** (Figure 2). In 2003 a complementary synthesis via (–)-sparteine **6** mediated addition of lithiated nonchiral *o*-toluamides type **5b**,**c** to 3,4-dihydroisoquinoline **4a** leading to enantiomerically enriched **3a** has been reported by Liu.[8]



O-methylbharatamine **1** bharatamine **2** 2,3-dimethoxy-8-oxoberbine **3a**

Figure 1. Protoberberine derivatives

Our study on stereoselective synthesis of protoberberine system[9-16] is based on the addition of carbon nucleophiles to imines in which the chiral auxiliary was placed either in *o*-toluamide or in imine derivatives. The addition of a carbon nucleophile derived from optically active oxazolidine derivatives **7a**,**b** to 3,4-dihydroisoquinolines **4** led to the optically active 8-oxoberbines **3** (Figure 2, Scheme 1).[11,12] The addition of chiral *o*-toluamides **7b**, with (4*S*)- or (4*R*)-absolute configuration, to acyclic imine **8**, the so-called Pomeranz-Fritsch imine, followed by Pomeranz-Fritsch-Bobbitt cyclization/reduction gave protoberberine (*S*)-**1** with 88% ee and (*R*)-**1** with 73% ee, respectively.[13] In another approach a complementary synthesis of **1** started with chiral sulfinamide **9** and achiral *o*-toluamide **5c**, was also performed to give (*S*)-**1** with 88% ee.[15]

In 2005 Wills *et al.*[17] published the synthesis of enantiomerically enriched *O*-methylbharatamine **1** involving ketoaldehyde **10** as the key intermediate (Figure 2). Compound **10** was transformed to tetrahydroprotoberberine (*S*)-**1** with 50% ee by one-pot sequence involving amine deprotection, intramolecular C=N bond formation and subsequent asymmetric reduction promoted by chiral ruthenium catalyst. Iwao *et al.*[18] in 2007 reported the addition of laterally lithiated chiral 2-(*o*-tolyl)oxazoline **11** to 3,4-dihydroisoquinoline **4a**, which proceeded in modest diastereoselectivity. They tried to perform this reaction in the presence of chiral diamines such as 2,2-bis[(*S*)-4-isopropyl-2-oxazolin-2-yl]propane, (1*R*,2*R*)-*N*,*N*,*N'*,*N'*-tetramethyl-1,2-cyclohexanediamine or (–)-sparteine **6**, however, diastereomeric ratio of addition products was not improved. Diastereomeric addition products after column chromatography separation were further transformed into *O*-methylbharatamine (*S*)-**1** and (*R*)-**1**, *via* 2,3-dimethoxy-8-oxoberbine (*S*)-**3a** and (*R*)-**3a** respectively.

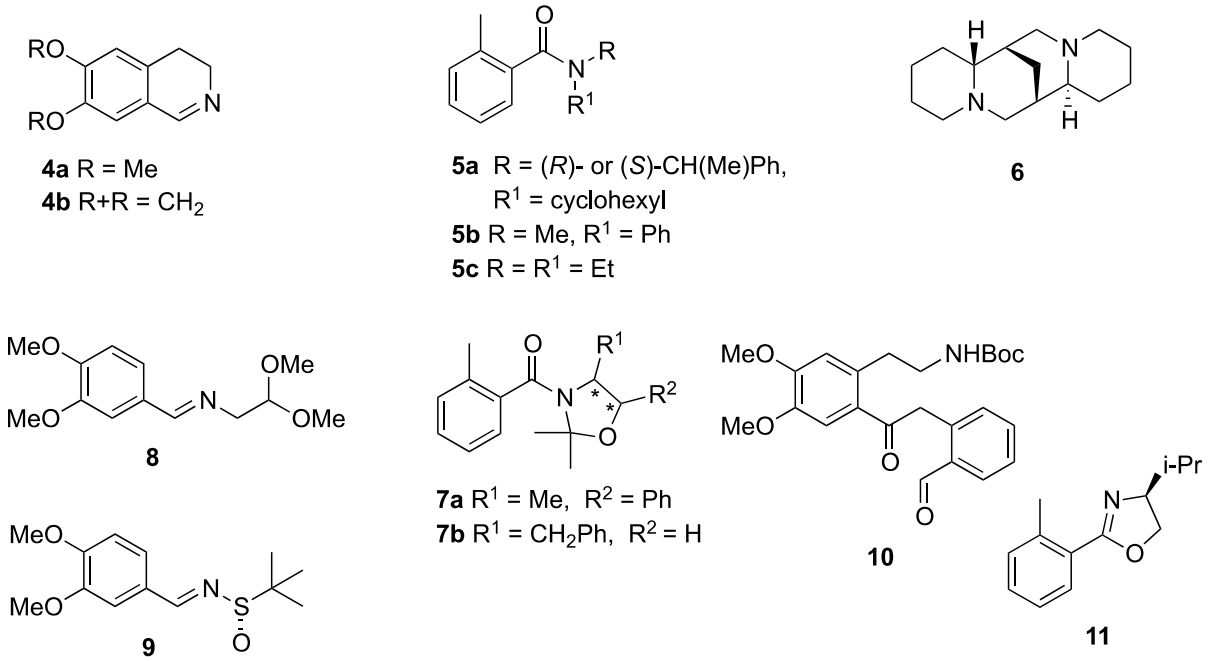


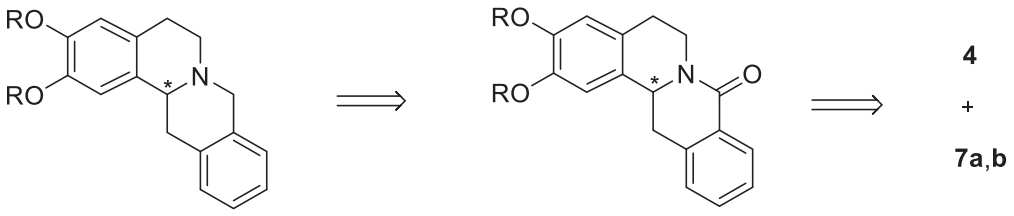
Figure 2. Key compounds for the synthesis of *O*-methylbharatamine **1** and 8-oxoberbines **3**

RESULTS AND DISCUSSION

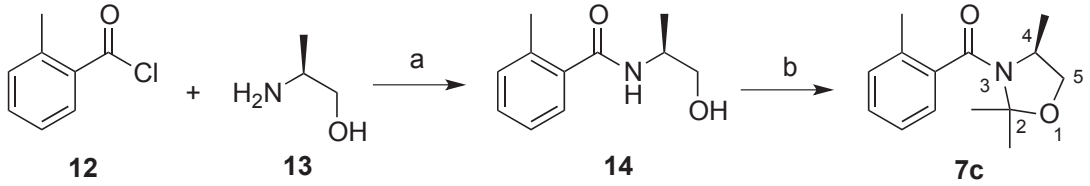
At the beginning of our study on the stereoselective synthesis of protoberberine system we used commercially available chiral 2-aminopropanols: (1*R*,2*S*)-norephedrine[11] and (*R*)- and (*S*)-phenylalaninol[12,13] as chiral auxiliaries in the preparation of the oxazolidine part of *o*-toluamides **7a**,**b**. During addition of benzyl anion generated from **7a**,**b** to 3,4-dihydroisoquinolines **4** a new stereogenic center was created at C-13a and accompanied by simultaneous cyclization leading to the optically active 8-oxoberbines **3a**,**b** with 81-92% ee. After single recrystallization enantiomerically pure lactam **3a** (with >99% ee, HPLC) was further transformed to *O*-methylbharatamine **1** without loss of enantioselectivity. The retrosynthetic analysis of our syntheses performed is illustrated in Scheme 1.

To study further the influence of the size of C-4 substituent in oxazolidine ring on stereoselectivity of the addition step, we prepared oxazolidine **7c** with a methyl group at C-4, using (*S*)-alaninol **13** as chiral auxiliary. We wanted to compare the steric outcome of the reaction with that obtained when compounds **7a**,**b** were used. Our synthesis began with the reaction of (*S*)-alaninol **13** with *o*-toluoyl chloride **12** leading to hydroxyamide **14** in 90% yield, which was converted into oxazolidine derivative **7c** under the action of 2,2-dimethoxypropane in 53% yield (Scheme 2).

The carbanion generated from oxazolidine **7c** with the aid of *n*-BuLi at –72 ºC was added to 6,7-dimethoxy-3,4-dihydroisoquinoline **4a**. After subsequent work-up of the reaction mixture, a cyclization product, laevorotatory (*S*)-8-oxoberbine **3a** was isolated in 63% yield with 87% ee (HPLC) along with the amine **15**, produced as a single diastereomer in 19% yield (Scheme 3).



Scheme 1. Retrosynthesis of protoberberine system

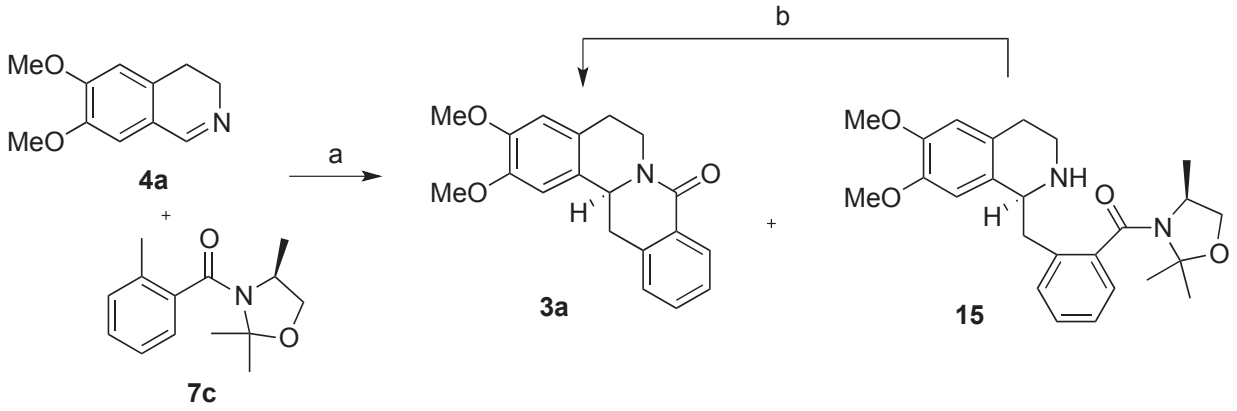


Reagents and conditions: (a) 0.5 M KOH, CH_2Cl_2; (b) $Me_2C(OMe)_2$, PhH, *p*-$MeC_6H_4SO_3H$

Scheme 2. Synthesis of oxazolidine **7c**

Amine **15** was readily converted to lactam **3a** (95% ee) under basic conditions (*n*-BuLi) providing an additional 11% of (*S*)-**3a**. After recrystallization of lactam **3a** from methanol/diethyl ether, pure (*S*)-2,3-dimethoxy-8-oxoberbine **3a** with >99% ee (HPLC) was obtained, showing mp 169–172 ºC; $[\alpha]_D$ –413.8 (*c* 0.359, $CHCl_3$); {lit.[7] $[\alpha]_D$ –372.4 (*c* 0.359, $CHCl_3$)}. Transformation of lactam (*S*)-**3a** leading to (*S*)-*O*-methylbharatamine **1** in 89% yield with 99% ee (HPLC) has been reported by us previously.[12] Thus the above presented synthesis is the formal synthesis of (*S*)-*O*-methylbharatamine **1**.

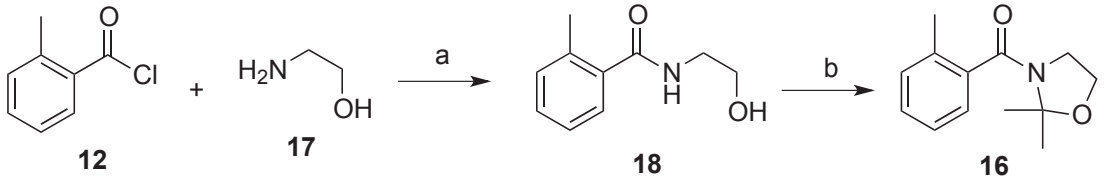
The steric outcome of the synthesis performed using (*S*)-alaninol **13** as the chiral auxiliary turned out to be comparable with that of the reactions with other amino alcohols, (1*R*,2*S*)-norephedrine and (*R*)- and (*S*)-phenylalaninol, used in our previous experiments.[11-13] Thus, the size of substituent at C-4 does not seem to have remarkable influence on the stereoselectivity observed in addition/cyclization reaction. However, the configuration of C-4 stereogenic center in oxazolidine ring turned out to be an important factor for the stereochemical outcome of the reaction. E.g. from *o*-toluamides **7** showing (4*S*) configuration formation of a new stereogenic center with (*S*) configuration at C-13a in compounds **3** and **1** was observed.[11-13] From *o*-toluamides **7** with (4*R*) configuration protoberberines **3** and **1** with (*R*) configuration at C-13a were formed.[12,13]



Reagents and conditions: (a) *n*-BuLi, THF, –72 °C; (b) *n*-BuLi, THF, –72 °C - rt

Scheme 3. Synthesis of (*S*)-2,3-dimethoxy-8-oxoberbine **3a**

Satisfactory results in diastereoselective approach to 8-oxoberberines **3a**,**b**[11-13,16] using chiral amides **7a-c** containing oxazolidine ring prompted us to use achiral oxazolidine type **16** in enantioselective synthesis carried out in the presence of external chirality inductor. Thus the second part of our study was devoted to enantioselective synthesis of 2,3-dimethoxy-8-oxoberbine **3a**. Besides oxazolidine **16** we have chosen *o*-toluamide **5c** as the reference compound. *N*,*N*-Diethylamide **5c** was obtained in the reaction of *o*-toluoyl chloride **12** with diethylamine in 61% yield. ^{1}H-NMR spectrum of pure amide **5c** was in agreement with literature data.[19,20] The synthesis of oxazolidine **16** was performed starting from *o*-toluoyl chloride **12** and ethanolamine **17** to give *N*-(2-hydroxyethyl)-2-methylbenzamide **18**[21] in 77% yield (Scheme 4). Hydroxyamide **18** was converted into oxazolidine **16** using 2,2-dimethoxypropane in acetone in the presence of *p*-toluenesulfonic acid in 45% yield. The correct structure of compound **16** was confirmed by spectral data analysis corresponding to those published by Taylor's group.[22]



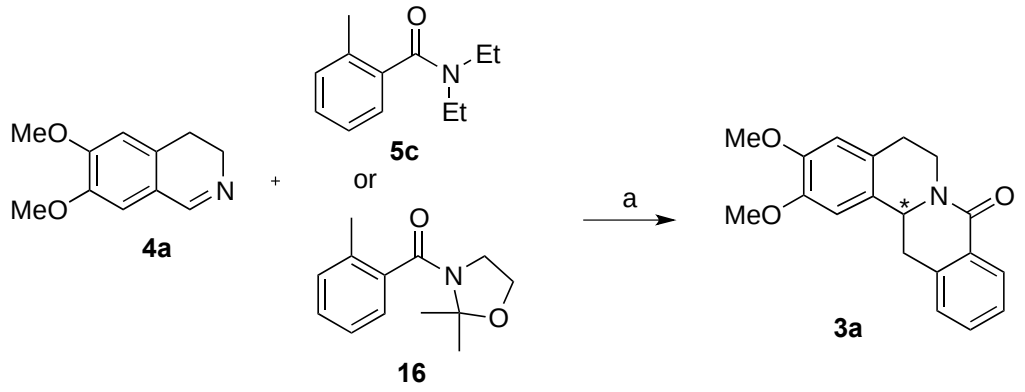
Reagents and conditions: (a) 0.5 M KOH, CH_2Cl_2; (b) $Me_2C(OMe)_2$, Me_2CO, *p*-$MeC_6H_4SO_3H$

Scheme 4. Synthesis of oxazolidine **16**

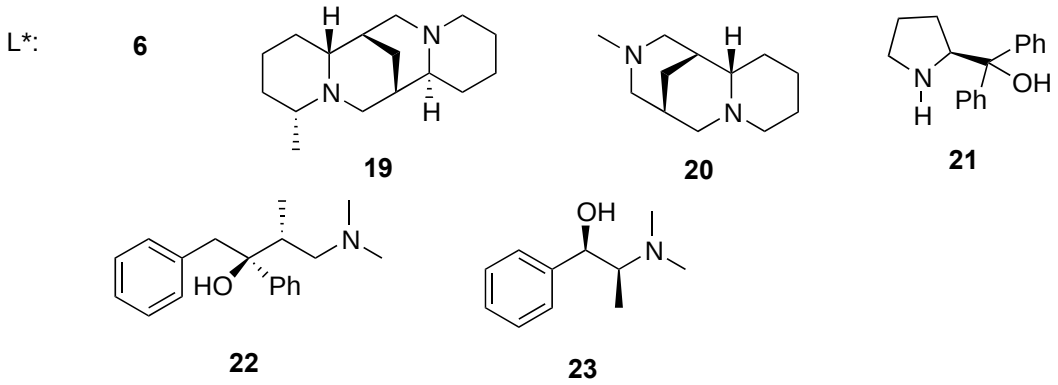
To establish the reaction conditions for the enantioselective synthesis of 8-oxoberbine **3a** at first we performed the synthesis of racemic compound (±)-**3a** using oxazolidine **16** or *o*-toluamide **5c** and 3,4-dihydroisoquinoline **4a** as starting compounds. The carbanion was generated from amide **5c** or **16**

with the aid of *n*-BuLi at –72 ºC in dry THF and then 6,7-dimethoxy-3,4-dihydroisoquinoline **4a** was added. A spontaneous cyclization of the addition product to 2,3-dimethoxy-8-oxoberbine (±)-**3a** took place in both cases. The yield of the reaction performed with oxazolidine **16** was comparable to that obtained with *N*,*N*-diethylamide **5c**.

In enantioselective synthesis we planned to investigate the effectiveness of quinolizidine and amino alcohol derivatives as external inductors of chirality. For this purpose (–)-sparteine **6**, (–)-2-methylsparteine **19**, (+)-sparteine surrogate **20**, (*S*)-(–)-α,α-dihpenyl-2-pyrrolidinemethanol **21**, (2*S*,3*R*)-(+)-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol **22** and (1*R*,2*S*)-(–)-2-dimethylamino-1-phenylpropanol **23** were chosen (Scheme 5).



Reagents and conditions: (a) *n*-BuLi, THF, - 72 °C, L*



Scheme 5. Enantioselective synthesis of 2,3-dimethoxy-8-oxoberbine **3a**

Pioneering studies on the external ligand-mediated asymmetric reaction of organolithium with imines were performed by Tomioka *et al*.[23] (–)-sparteine **6** has been applied as an external ligand in the asymmetric addition of organolithium compounds to acyclic[24-27] and cyclic imines.[28] In 2001 Snieckus and Derdau[29] published (–)-sparteine-mediated lateral metallation of amide **5c** and its reaction with acyclic imines leading to chiral tetrahydroisoquinolones. Two years later Liu reported (–)-sparteine-mediated lateral metallation of *o*-toluamides type **5b**,**c** and its reaction with cyclic imine,

6,7-dimethoxy-3,4-dihydroisoquinoline **4a**, leading to enantiomerically enriched 2,3-dimethoxy-8-oxoberbine **3a**.[8]

Our first experiment was started with the reaction carried out in the conditions described by Liu,[8] using *o*-toluamide **5c**, 3,4-dihydroisoquinoline **4a** and (–)-sparteine **6**. A solution of (–)-sparteine **6** in dry toluene was cooled to –72 ºC and *n*-BuLi was added. Stirring was continued for 20 min and then a solution of amide **5c** was added dropwise. After 25 min a solution of 3,4-dihydroisoquinoline **4a** was added at –72 ºC. After subsequent work-up of the reaction mixture a product (*S*)-**3a** was isolated in 52% yield with 40% ee (HPLC), (Table1, entry 1). The enantioselectivity of our experiment was similar to the result obtained by Liu (37% yield and 37% ee).[8] The reaction with oxazolidine **16** was carried out in the conditions described above and product (*S*)-**3a** was isolated with 57% ee (HPLC), (Table 1, entry 2). The (*S*) absolute configuration of our product was additionally confirmed on the basis of the sign of the specific optical rotation measured $[\alpha]_D$ –243.4 (*c* 0.475, $CHCl_3$).

Table 1. Enantioselective addition of *o*-toluamides **5c**, **16** to 3,4-dihydroisoquinoline **4a** performed in the presence of chiral ligand

Entry	Amide	Ligand (equiv)	Solvent	*n*-BuLi (equiv)	Yield (%)	Ee (configuration)
1	**5c**	**6** (1.2)	PhMe	1.0	52	40% (*S*)
2	**16**	**6** (1.2)	PhMe	1.0	61	57% (*S*)
3	**16**	**19** (1.2)	THF	1.0	51	racemate
4	**16**	**19** (1.2)	PhMe	1.0	0	no product
5	**16**	**20** (1.2)	PhMe	1.0	66	62% (*R*)
6	**5c**	**21** (1.0)	PhMe	4.4	47	4%
7	**16**	**21** (1.0)	PhMe	4.4	48	6% (*R*)
8	**5c**	**22** (1.2)	THF	3.3	50	15% (*R*)
9	**16**	**22** (1.2)	THF	3.3	49	6%
10	**5c**	**23** (1.2)	PhMe	3.3	52	9% (*R*)
11	**5c**	**23** (1.2)	THF	3.3	46	racemate
12	**16**	**23** (1.2)	THF	3.3	50	3%[a]

[a] racemic within error of method

The next ligand tested was (–)-2-methylsparteine **19**.[30] The reaction performed with oxazolidine **16** and 3,4-dihydroisoquinoline **4a** in THF in the presence of (–)-2-methylsparteine **19** led to racemic **3a**. Using toluene as the solvent we did not observe formation of product **3a** (Table 1, entries 3, 4). Next we used (+)-sparteine surrogate **20** as a new ligand. This compound has been evaluated by O'Brien group[31] and

used in such asymmetric transformations as desymmetrization[32] or lithiation.[33-35] To the best of our knowledge so far this compound has not been used as a ligand/catalyst in enantioselective addition of carbon nucleophile to imine. The reaction of oxazolidine **16** and 3,4-dihydroisoquinoline **4a** performed in the presence of (+)-sparteine surrogate **20** in toluene led to the opposite enantiomer (*R*)-**3a** in 56% yield with 62% ee (HPLC), (Table 1, entry 5). In further experiments we used amino alcohols as chiral ligand. The addition reaction of *o*-toluamide **5c** or **16** in toluene to imine **4a**, performed in the presence of (*S*)-(−)-α,α-diphenyl-2-pyrrolidinemethanol **21** led to rather racemic product **3a** with 4% ee and 6% ee, respectively, (Table 1, entries 6, 7). The use of (2*S*,3*R*)-(+)-4-dimethylamino-1,2-diphenyl-3-methyl--2-butanol **22** as the external inductor of chirality in THF led to lactam (*R*)-**3a** with 15% ee in the case of amide **5c** and with 6% ee in the case of oxazolidine **16** (Table 1, entries 8, 9). The reaction performed with (1*R*,2*S*)-(−)-2-dimethylamino-1-phenylpropanol **23** in toluene led to lactam (*R*)-**3a** with 9% ee (Table 1, entry 10). The same reaction carried out in THF led to racemic **3a** in the case of amide **5c** and in the case of oxazolidine **16** as well (Table 1, entries 11, 12).

In conclusion, we have reported on the enantiospecific and enantioselective syntheses of 2,3-dimethoxy-8-oxoberbine **3a** using the lateral metallation methodology. In the enantiospecific synthesis, the addition reaction of new chiral oxazolidine **7c**, incorporating (*S*)-alaninol **13** as the chiral auxiliary, into 3,4-dihydroisoquinoline **4a**, was accompanied by simultaneous cyclization to afford lactam (*S*)-**3a** as the major product along with addition product **15**. Amine **15** was readily converted to lactam **3a** under basic conditions providing an additional amount of (*S*)-**3a**. After single recrystallization enantiomerically pure (*S*)-2,3-dimethoxy-8-oxoberbine **3a** was obtained (>99% ee, HPLC). The steric outcome of the synthesis performed with (*S*)-alaninol **13** as the chiral auxiliary turned out to be comparable with that of the reactions with the other amino alcohols, norephedrine and phenylalaninol, used in our previous experiments.[11,12,16] Enantioselective synthesis of **3a** was performed with new achiral oxazolidine **16** or *o*-toluamide **5c** and 3,4-dihydroisoquinoline **4a** in the presence of chiral ligands leading to 2,3-dimethoxyberbine **3a**. The effectiveness of quinolizidine derivatives **6**, **19**, **20** and amino alcohol derivatives **21**-**23** as external inductors of chirality has been tested. Among them (–)-sparteine **6** and (+)-sparteine surrogate **20** turned out to be the most efficient ones and led to enantiomerically enriched product (*S*)-**3a** and (*R*)-**3a** with 57% and 62% ee, respectively. To the best of our knowledge (+)-sparteine surrogate **20** has been tested successfully for the first time as a chiral ligand in the enantioselective addition of benzyl anion derived from oxazolidine **16** to cyclic imine **4a**.

EXPERIMENTAL

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: AM D402.

Optical rotations: Perkin-Elmer polarimeter 242B at 20 ºC. Analytical HPLC: Waters HPLC system with Chiralcel OD-H column (250 x 4.6 mm), flow rate 0.5 mL/min. Merck DC-Alufolien Kieselgel 60_{254} were used for TLC and Kieselgel 60 (70-230 mesh ASTM) for column chromatography. All compounds were purchased from Aldrich Chemical Co. and used as received. THF was freshly distilled from $LiAlH_4$, benzene – from sodium wire. Imine **4a** was prepared as previously described.[28]

***N*-[(*S*)-2-Hydroxy-1-methylethyl]-2-methylbenzamide (14)**

To (*S*)-(+)-alaninol **13** (0.23 g, 3mmol) dissolved in CH_2Cl_2 (35 mL), 0.5 M KOH (18 mL) was added and then *o*-toluolyl chloride **12** (0.45 g, 3 mmol) was introduce dropwise on stirring at 0 ºC. After 30 min the cooling bath was removed and the stirring continued at room temperature for 24 h. The phases were separated and the aqueous one was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over Na_2SO_4 and the solvent removed under reduced pressure yielding amide **14** as white solid (0.54 g, 90% yield); mp 90–92 ºC (Et_2O); $[\alpha]_D$ –9.3 (*c* 0.82, $CHCl_3$); IR (KBr) 3359, 3372, 1637, 1540 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (d, *J* = 6.8 Hz, 3H), 2.37 (s, 3H), 3.47–3.53 (m, 1H), 3.63 (s broad, 1H, disappears on treatment with D_2O), 3.62–3.69 (m, 1H), 4.08–4.16 (m, 1H), 6.31 (d, *J* = 7.3 Hz, 1H, disappears on treatment with D_2O), 7.10–7.30 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$,) δ 16.9, 19.6, 47.8, 66.4, 125.6, 126.7, 129.8, 130.8, 135.7, 136.2, 170.7; MS *m/z* 193 (M^+, 2), 162 (11), 136 (16), 119 (100), 91 (36), 65 (13); HRMS (EI): calcd for $C_{11}H_{15}NO_2$ 193.1103, found 193.1104.

(4*S*)-2,2,4-Trimethyl-3-(*o*-toluoyl)oxazolidine (7c)

To amide **14** (0.54 g, 2.8 mmol) in dry benzene (20 mL), 2,2-dimethoxypropane (3.20 g, 31.8 mmol) was added under an argon atmosphere followed by addition of a catalytic amount of *p*-toluenesulfonic acid (0.10 g). The reaction mixture was stirred at reflux for 3 h and left to reach room temperature. Then the reaction mixture was washed with 1% NaOH (3 x 2 mL), dried over Na_2SO_4 and the solvent was evaporated. The crude reaction product was chromatographed on silica gel (CH_2Cl_2 and CH_2Cl_2/MeOH, 200:1, v/v) to give the pure oxazolidine **7c** (0.35 g, 54% yield) as an oil; $[\alpha]_D$ +59.3 (*c* 0.98, $CHCl_3$); IR (film) 1635 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.01 (d, *J* = 6.50 Hz, 3H), 1.70 (s, 3H), 1.82 (s, 3H), 2.32 (s, 3H), 3.64–3.67 (m, 2H), 4.01–4.05 (m, 1H), 7.16–7.30 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.7, 20.4, 23.2, 26.9, 54.5, 69.6, 95.3, 125.7, 128.7, 130.4, 136.3, 137.7, 167.8; MS *m/z* 233 (M^+, 2), 218 (49), 119 (100), 91 (24); HRMS (EI): calcd for $C_{14}H_{19}NO_2$ 233.1416, found 233.1423.

Addition reaction of oxazolidine 7c to imine 4a

Oxazolidine **7c** (233 mg, 1 mmol) was dissolved in dry THF (6 mL) under an argon atmosphere and the solution was cooled to –72 ºC. *n*-BuLi (1.6 M solution in hexanes, 0.7 mL) was added and the carbanion generated for 30 min at –72 ºC. A solution of 6,7-dimethoxy-3,4-dihydroisoquinoline **4a** (191 mg, 1 mmol) in dry THF (7 mL) was introduced dropwise and the mixture was kept at –72 ºC for 3 h, then treated at this temperature with 5% HCl (3 mL). When the reaction mixture reached room temperature,

the phases were separated and the organic one extracted with 5% HCl (3 x 2 mL). The organic phase was dried over Na_2SO_4 and the solvent evaporated yielding 2,3-dimethoxy-8-oxoberbine **3a** (194 mg, 63%) with 87% ee by HPLC [hexane/propan-2-ol = 4:1, t_R = 29.3 min (minor), t_R = 33.4 min (major)]. After recrystallization from Et_2O/MeOH a sample of 2,3-dimethoxy-8-oxoberbine **3a** with 99% ee was obtained, showing mp 169–172 ºC; $[\alpha]_D$ –413.8 (*c* 0.359, $CHCl_3$); {lit.[7] $[\alpha]_D$ –372.4 (*c* 0.359, $CHCl_3$)}. The spectral characteristics of our sample corresponded to the literature data for (*S*)-(–)-**3a**.[12]

The acidic aqueous phase was alkalized with KOH pellets, re-extracted with Et_2O (3 x 10 mL), dried over Na_2SO_4 and the solvent evaporated to give an oil, which was chromatographed on silica gel (CH_2Cl_2 and CH_2Cl_2/MeOH, 100:1 → 50:1, v/v) to give the pure addition product **15** (82 mg, 19% yield)) as a single diastereomer by HPLC [hexane/propan-2-ol = 4:1, t_R = 43.0 min]; IR (film) 1630 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.99 (d, *J* = 6.3 Hz, 3H), 1.72 (s, 3H), 1.87 (s, 3H), 2.00 (s, 1H disappears on treatment with D_2O), 2.69–2.87 (m, 2H), 2.91–3.02 (m, 2H), 3.09 (dd, *J* = 3.8, 13.7 Hz, 1H), 3.16–3.23 (m, 1H) 3.63 (dd, *J* = 1.1, 8.8 Hz, 2H), 3.79 (s, 3H), 3.85 (s, 3H), 3.97–4.02 (m, 1H), 4.32 (dd, *J* = 3.3, 9.1 Hz, 1H), 6.59 (s, 1H), 6.65 (s, 1H), 7.27–7.38 (m, 4H); MS *m/z* 424 (M^+, 1.3), 279 (14), 193 (14), 192 (100), 149 (48), 57 (19).

Cyclization of amine 15 to (*S*)-2,3-dimethoxy-5,6,13,13a-tetrahydro-8*H*-dibenzo[*a*,*g*]quinolizin-8-one (3a)

To a solution of pure amine **15** (82 mg, 0.19 mmol) in dry THF (10 mL) *n*-BuLi (1.6 M solution in hexanes, 0.13 mL) was added at –72 ºC under an argon atmosphere. The reaction mixture was allowed to warm-up to ambient temperature and quenched by the addition of 5% HCl (2 mL). Extractive work up yielded (*S*)-(–)-2,3-dimethoxyberbine **3a** (35 mg, 59% yield) with 95% ee by HPLC.

***N*,*N*-Diethyl-*o*-toluamide (5c)**

To a solution of diethylamine (0.730 g, 10 mmol) in CH_2Cl_2 (80 mL), 0.5 M KOH (65 mL) was added and the mixture was cooled to 0 ºC. The toluoyl chloride **12** (1.544 g, 10 mmol) was carefully added to the mixture. The reaction mixture was stirred intensively for 2 h at 0 ºC and next at room temperature for 1 h. Phases were separated. The aqueous one was extracted with CH_2Cl_2 (3 x 30 mL). Combined extracts were dried over Na_2SO_4. The solvent was evaporated affording colorless oil that was chromatographed on silica gel (CH_2Cl_2/MeOH, 100:1, v/v) to yield 1.22 g (64%) of pure product **5c**. ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (t, *J* = 7.1 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 2.29 (s, 3H), 3.14 (q, *J* = 7.1 Hz, 2H), 3.43–3.77 (m, 2H), 7.14–7.29 (m, 4 H). The ^1H-NMR spectrum of pure amide **5c** was in agreement with literature data.[19,20]

***N*-(2-Hydroxyethyl)-2-methylbenzamide (18)**

To a solution of ethanolamine **17** (1.220 g, 20 mmol) in CH_2Cl_2 (160 mL), 0.5 M KOH (130 mL) was added and the mixture was cooled to 0 ºC. Then *o*-toluoyl chloride **12** (3.390 g, 22.0 mmol) was carefully

added to the mixture. The mixture was stirred vigorously for 3 h. Phases were separated. The aqueous one was extracted with CH_2Cl_2 (4 x 30 mL). Combined extracts were dried over Na_2SO_4. Solvent was evaporated yielding 2.741 g (77%) of amide **18** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 3H), 2.76 (s, 1H, disappeared with D_2O), 3.51–3.57 (m, 2H), 3.69–3.79 (m, 2H), 6.44 (s, 1H), 7.14–7.35 (m, 4H); MS *m/z* 179 (M^+, 11), 161 (9), 146 (5), 136 (15), 119 (100), 91 (50). The spectra of amide **17** are in agreement with literature data.[21]

2,2-Dimethyl-3-(*o*-toluoyl)oxazolidine (16)

To *N*-(2-hydroxyethyl)-2-methylbenzamide **18** (1.88 g, 10.5 mmol) in dry acetone (60 mL) 2,2-dimethoxypropane (17.47 g, 168.0 mmol) was added followed by *p*-toluenesulfonic acid (0.52 g). The mixture was stirred at room temperature. After 4 h the reaction mixture was quenched with 10% Na_2CO_3 (10 mL). Acetone was evaporated and the product was extracted with CH_2Cl_2 (3 x 25 mL). The organic phase was dried over Na_2SO_4 and solvent was evaporated. Crude product was chromatographed on silica gel (CH_2Cl_2 and CH_2Cl_2/MeOH, 200:1, v/v) yielding 1.024 g (45%) of pure oily product **16**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.75 (s, 6H), 2.33 (s, 3H), 3.28 (t, *J* = 6.3 Hz, 2H), 3.94 (t, *J* = 6.3 Hz, 2H), 7.14–7.35 (m, 4 H); MS *m/z* 219 (M^+, 2), 204 (20), 188 (0,4), 161 (4), 146 (0,6), 133 (1), 119 (100), 91 (29). The spectra of oxazolidine **16** are in agreement with literature data.[22]

General procedure for addition of amide (5c, 16) to 3,4-dihydroisoquinoline 4a in the presence of chiral external ligand

The ligand (1.2 equiv) was dissolved in dry THF or toluene (10 mL for 0.96 mmol) under argon atmosphere. The solution was cooled to –72 ºC and *n*-BuLi (1.6 M solution in hexanes, 1.2 equiv) was added and reaction mixture was stirred for 20 min. Then the solution of amide **5c** or oxazolidine **16** (1 equiv) in an appropriate solvent (7 mL for 0.8 mmol) was added dropwise and the reaction mixture was stirred at –72 ºC for next 25 min. Next a solution of 6,7-dimethoxy-3,4-dihydroisoquinoline **4a** (1 equiv) in an appropriate solvent (7 mL for 0.8 mmol) was added. The reaction progress was controlled on TLC. The reaction mixture was quenched at –72 ºC with 5% HCl. When the reaction mixture reached room temperature, the phases were separated and the organic one was extracted with 5% HCl (3 x 2 mL). The organic phase was dried over Na_2SO_4 and the solvent evaporated to give 2,3-dimethoxy-8-oxoberberine **3a**. An analytical sample was crystallized from Et_2O affording white crystals of **3a**, mp 169–172 ºC. The spectral characteristics of our sample corresponded to those of the literature data for (*S*)-(–)-**3a**.[12]

$[\alpha]_D$ –243.4 (*c* 0.475, $CHCl_3$) was measured for a sample of (*S*)-**3a** with 57% ee obtained in reaction performed with oxazolidine **16** and imine **4a** in the presence of (–)-sparteine **6**, HPLC [hexane/propan-2-ol = 4:1, (*R*)-**3a**: t_R = 28.6 (minor), (*S*)-**3a**: t_R = 32.8 min (major)].

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