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Enantioselective modification of the Pomeranz–Fritsch–Bobbitt synthesis of tetrahydroisoquinoline alkaloids: synthesis of (–)-salsolidine and (–)-carnegine

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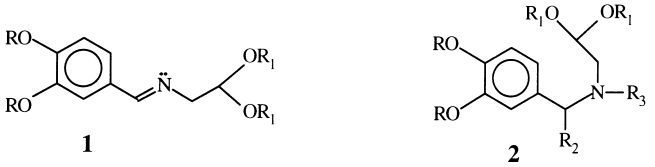
Abstract

(–)-Salsolidine **7** and (–)-carnegine **8** were prepared in 46 and 36% *e.e.*, respectively, by enantioselective addition of methyllithium to the Pomeranz–Fritsch imine **13** in the presence of ligands **9**–**12**, followed by acid-catalyzed cyclization and hydrogenolysis.

1. Introduction

The Bobbitt modification[1] of the traditional Pomeranz–Fritsch isoquinoline synthesis,[2] which enables the synthesis of 1,2,3,4-tetrahydroisoquinoline derivatives, involves benzylaminoacetaldehyde acetal **2** as the key intermediate (Scheme 1). This aminoacetal **2** is usually prepared from the classic Pomeranz–Fritsch imine **1** by in situ catalytic hydrogenation of the imine C=N double bond[1] or by addition of Grignard reagents.[3–6] Recently, this type of benzylaminoacetal intermediate **2** has been prepared from the corresponding benzyl alcohol on reaction with aminoacetaldehyde derivatives,[7–10] or by *N*-alkylation of benzylamine with bromoacetaldehyde acetal.[6]



$R = CH_3$, $R+R=CH_2$ R_2 = H, alkyl, aryl, benzyl
$R_1 = CH_3$, C_2H_5 R_3 = H, CH_3, Ts

Scheme 1.

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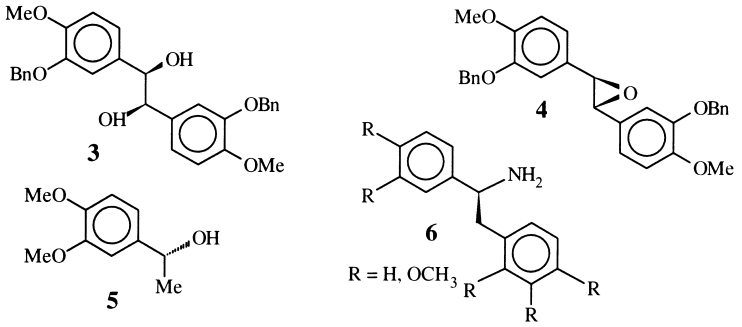
In the next step, intermediate **2** is cyclized in acidic solution to give unstable 1,2-dihydroisoquinoline, which may be reduced in situ to 1,2,3,4-tetrahydroisoquinoline (the Bobbitt modification[1]), or dehydrogenated, preferably via an *N*-tosyl derivative, to a fully aromatic system (the Jackson modification[11]).

Only a few examples of stereochemical modification of the Pomeranz–Fritsch–Bobbitt cyclization resulting in chiral non-racemic isoquinoline alkaloids have been repeorted.[6,8,9] This approach has been investigated much less frequently then the two other classic syntheses, the Bischler–Napieralski and the Pictet–Spengler ones, which have made important contributions to the many strategies available for stereoselective synthesis of isoquinoline alkaloids.[12]

In the published stereoselective Pomeranz–Fritsch–Bobbitt syntheses a source of the C-1 stereogenic center has already been present in the precursors of amine **2**. Thus, in the synthesis of (+)- and (–)-reticuline, Hirsenkorn[8] used alternatively optically active hydrobenzoin **3** or epoxide **4** and converted each into type **2** amines by aminolysis with *N*-methyl aminoacetaldehyde acetal. In Kaufman's[9] synthesis of (–)-salsolidine **7**, non-racemic benzyl alcohol **5** was treated with *N*-tosyl-aminoacetaldehyde acetal under Mitsunobu reaction conditions to give *N*-tosylated amine type **2**. Several optically active benzylamines, type **6**, alkylated with bromoacetaldehyde acetal, have been applied by Badia et al.[6] for the synthesis of a series of isopavine alkaloids (Scheme 2).



Scheme 2.

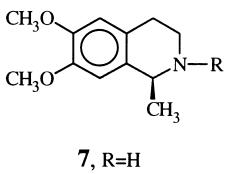
2. Results and discussion

Herein we report the enantioselective synthesis of isoquinoline alkaloids performed according to the Pomeranz–Fritsch–Bobbitt methodology based on the enantioselective addition of methyllithium to type **1** imines induced by ligands **9**–**12**, prior to isoquinoline cyclization. It should be mentioned that enantioselective addition of carbon nucleophiles to imines, recently reviewed by Denmark and Nicaise[13] and Enders and Reinhold,[14] has not been studied as intensively as that of the analogous reaction involving prochiral carbonyl compounds.

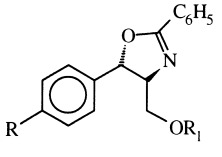
To achieve enantioselectivity in the addition step for the two isoquinoline alkaloids, salsolidine **7** and carnegine **8**, we have used non-racemic oxazolines **9**–**12**. These compounds were chosen not only because of the well-known efficiency of oxazolines in stereoselective transformations, both in the reactions based on chiral auxiliary and in asymmetric catalysis,[15–17] but also because they could be obtained from (1*S*,2*S*)-2-amino-1-aryl-1,3-propandiols (industrial waste products) which we have used successfully as a source and/or promoter of stereochemistry in many types of organic synthesis.[18,19]

The starting Schiff base **13** was obtained in good yield, as a single isomer, by condensation of veratraldehyde with aminoacetaldehyde dimethyl acetal in the usual manner.[18b] The *E*-configuration of **13** was established by ^{1}H NMR spectroscopy on the basis of NOESY spectrum, which showed through space interaction between H-1 and both the H-3 and OCH_3 group protons.

Ligands **10** and **12** were synthesized from the known (4*S*,5*S*)-oxazolines **9** and **11**, prepared easily from (+)-thiomicamine or (1*S*,2*S*)-2-amino-1-phenyl-1,3-propandiol, respectively, in reaction with benzonitrile, according to a known procedure.[18a] Compounds **9** and **11** were *O*-methylated with CH_3I–NaH in DMF to give *O*-methyl derivatives (4*S*,5*S*)-**10** and **12**,[20] respectively, in a satisfactory yield (Scheme 3).



7, R=H
8, R=CH_3



No	R	R_1
9	SCH_3	H
10	SCH_3	CH_3
11	H	H
12	H	CH_3

Scheme 3.

In order to optimize the reaction conditions of the key step, the enantioselective addition of MeLi to imine **13**, we have undertaken initial studies with the use of ligand **10** as a promoter (Table 1). Before addition of methyllithium the imine **13** was allowed to react with the catalyst for 30 min to 1 h (data in parentheses, Table 1). It was found that 2.5 equiv. of MeLi and 2.5–3.5 h reaction time (TLC monitoring) were necessary for conversion of imine **13** to amine **14**. Imine **13** was essentially unreactive toward MeLi at low temperatures in the absence of the ligands, indicating the catalytic activity of the latter compounds. Toluene, a solvent with a low coordination ability for organolithium reagents, was found to be superior to ethyl ether and THF (entries 5, 10, 11). The influence of temperature on enantioselectivity was also evaluated. The results in Table 1 show that the selectivity successively increased with lowering temperature from rt to –65°C (entries 13, 12, 7, 6, 5), while at –90°C no further increase was observed (entry 8). In the reactions carried out with substoichiometric quantities of **10** (0.1–0.5 equiv., entries 1 and 2), enantioselectivity was much lower than that in which 1.0–2.0 equiv. were used (entries 3 and 4); however, the best results (49% *e.e.*) were obtained in the presence of 2.6 equiv. of **10** (entry 5), a quantity applied by Tomioka et al.,[21] which was even better than with 3.0 equiv. (entry 9).

As a result of the above experiments we conclude that the optimum conditions for the addition step involve the use of: 2.5 equiv. of MeLi, toluene as a solvent, –65°C as the reaction temperature, 2.6 equiv. of the ligand and 1 h of interaction of the imine with the catalyst. The optimized conditions were applied in further studies in which other ligands **9**, **11** and **12** were used. Poor asymmetric induction (1–9%) was achieved with the use of ligands **9** and **11**; however, in the case of **12** the enantioselectivity reached 40%.

The enantiomeric excess of amine **14** was determined by integrating absorption bands of the acetal methoxy group protons split into two singlets at 3.31 and 3.36 ppm in the ^{1}H NMR spectrum recorded in the presence of 3 equiv. of TADDOL,[22] used as a solvating agent. Its (*S*)-configuration was established in the course of subsequent transformation of a sample of optically active amine **14** into (1*S*)-(–)-salsolidine **7** of known absolute stereochemistry.[23]

Table 1
Addition of methyllithium to imine **13** in the presence of ligand **10**

	Reaction conditions			amine **14**			
Entry	Ligand (equiv.)	Solvent	Temp.(°C)[a]	Y (%)[b]		*e.e.* (%)[c]	
1	0.1	toluene	- 65	43		7	
2	0.5	toluene	- 65	55	(44)[d]	23	(22)[d]
3	1.0	toluene	- 65	78		28	
4	2.0	toluene	- 65	85	(78)[d]	37	(34)[d]
5	2.6	toluene	- 65	85	(92)[d]	38	(49)[d]
6	2.6	toluene	- 42	85		33	
7	2.6	toluene	- 42→ - 20	81		15	
8	2.6	toluene	- 90		(14)[d]		(45)[d]
9	3.0	toluene	- 65		(78)[d]		(42)[d]
10	2.6	THF	- 65	no reaction			
11	2.6	Et_2O	- 60		(40)[d]		(14)[d]
12	2.6	toluene	0	56		8	
13	2.6	toluene	R.T.		(47)[d]		(8)[d]

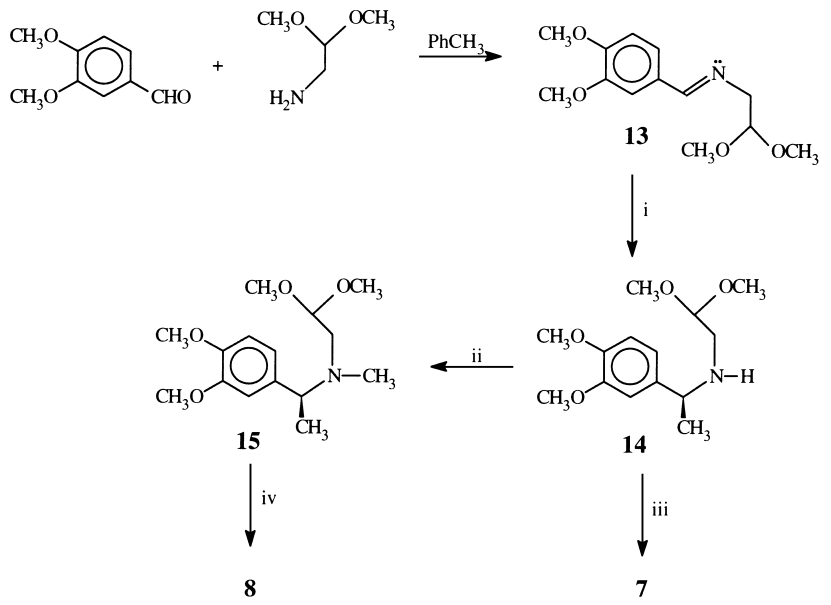
[a] (±) 2°C;
[b] determined by ^{1}H NMR of crude reaction products;
[c] *e.e.* established by ^{1}H NMR run in the presence of TADDOL[22];
[d] 1 h of preliminary interaction of imine **13** with ligand **10**.

For the synthesis of salsolidine **7**, amine **14** of 49% *e.e.* in 6N hydrochloric acid was subject to catalytic hydrogenolysis in the presence of 5% palladium on carbon at rt to afford levorotatory salsolidine **7**[23] in 57% yield and with 46% enantioselectivity (Scheme 4). In its ^{1}H NMR spectrum, recorded in the presence of 2 equiv. of TADDOL, the doublet of CH_3 group protons was split into two doublets from which the lower-field one (1.26 ppm), which was dominant, represented the (*S*)-(–)-enantiomer, since the other one (1.21 ppm) was earlier identified as belonging to the (*R*)-(+)-salsolidine.[18b]

In another series of experiments amine **14** showing 38% *e.e.* was first *N*-methylated with the $HCOH/CH_3COOH–NaBH_4$ system to give *N*-methyl derivative (–)-**15** in 86% yield and with 38% *e.e.*, before it was cyclized in the conditions employed for the synthesis of **7** to give (–)-carnegine **8** of known (*S*)-configuration[23] in 79% yield and 36% *e.e.* (Scheme 4).

3. Conclusion

The first enantioselective modification of the known Pomeranz–Fritsch–Bobbitt synthesis of tetrahydroisoquinoline alkaloids has been achieved. The concept of the synthesis is built upon enantioselective addition of organometallic reagents to the Pomeranz–Fritsch imine **13** prior to



Scheme 4. Reagents and conditions: (i) CH_3Li, toluene, –65°C, ligands **9**–**12**; (ii) HCHO, $CH_3COOH/NaBH_4$, EtOH; (iii) 6N HCl, 1 day, H_2/Pd–C; (iv) 6N HCl, 2 days, H_2/Pd–C

cyclization of the heterocyclic ring. The steric course of the addition step is controlled by oxazolines **9**–**12** used as external ligands. The most important points of the strategy employed are that the C-1 stereogenic center of the alkaloids is formed at an early stage of the synthesis, and no covalently bonded chiral auxiliary is involved. The enantiomeric excess achieved in the addition step leading to amine **14** was not lost during the synthesis of the alkaloids (–)-salsolidine **7** and (–)-carnegine **8**.

4. Experimental

4.1. General

Melting points: determined on a Koffler block and are uncorrected. IR spectra: Perkin–Elmer 180 in KBr pellets. NMR spectra: Varian Gemini 300, in $CDCl_3$, with TMS as internal standard. Mass spectra (EI): Joel D-100, 75 eV. Specific rotation: Perkin–Elmer polarimeter 243B at 20°C. Merck Kieselgel 60 (70–230 mesh) was used for column chromatography and Merck DC-Alufolien Kieselgel 60_{254} for TLC.

4.2. O-*Methylation of oxazoline* ***9***

To oxazoline **9**[18a] (13.16 g, 44 mmol) in DMF (128 ml), NaH (1.32 g, 55 mmol) was added portionwise at ice-bath temperature. The mixture was stirred at this temperature for 1 h before CH_3I (3.5 ml, 56 mmol) was introduced. The whole mixture was stirred at rt for 17 h, then poured onto ice and after rt was reached the solid was filtered off. It was washed with water and air-dried to give crude oxazoline **10**. An additional amount of **10** was obtained from the filtrate by

extraction with ethyl ether until the Dragendorff test was negative. The two bunches of the product were combined and recrystallized from ethyl ether to give 12.5 g (91%) of enantiomerically pure (4*S*,5*S*)-oxazoline **10**; m.p. 85.5–86.5°C; $[\alpha]_D = +60.5$ (*c* 0.5, CH_2Cl_2). IR cm^{-1}: 1645 (C=N); ^1H NMR δ: 2.47 (s, 3H, SCH_3), 3.43 (s, 3H, OCH_3), 3.60 (dd, J = 6.6, 9.6 Hz, 1H, C*H*HOCH_3), 3.73 (dd, J = 4.7, 9.6 Hz, 1H, CH*H*OCH_3), 4.31 (ddd, J = 6.9, 6.6, 4.7 Hz, 1H, C*H*N), 5.45 (d, J = 7.1 Hz, 1H, C*H*Ph), 7.23–7.54 (m, 7H, Ar*H*), 8.01–8.05 (m, 2H, Ar*H*); MS *m*/*z* (%): 313 (M^+, 37), 268 (70), 192 (73), 165 (100), 105 (50); found: C, 68.92; H, 6.06; N, 4.49. $C_{18}H_{19}NO_2S$ (313.11) requires: C, 68.98; H, 6.11; N, 4.47.

4.3. *Addition of CH_3Li to imine **13**. A typical procedure*

A mixture of imine **13**[18b] (0.127 g, 0.5 mmol) and ligand **10** (0.407 g, 1.3 mmol) in toluene (30 ml) was stirred under an argon atmosphere at –65°C for 1 h. CH_3Li (1.6 M solution in ether, 0.78 ml, 1.25 mmol) was then added and stirring was continued until the end of the reaction (ca. 2 h, TLC). The reaction mixture was quenched with 20% NH_4Cl at –65°C and, after rt was reached, phases were separated and the aqueous one was extracted with ethyl ether until the Dragendorff test was negative. The combined organic extracts were dried and the solvent was evaporated under reduced pressure. The residue was dissolved in methanol from which ligand **10** precipitated overnight at 0°C. It was filtered off, the filtrate was concentrated in vacuo, and the *e.e.* of the crude product was determined by ^1H NMR spectrum measured in the presence of 2 equiv. of TADDOL[22] by integration peaks at 3.31 and 3.36 ppm.

For further transformation the crude amine **14** was purified by column chromatography (crude **14**:silica gel, 1:10; toluene:ethyl ether, 99:1). TLC comparison with an authentic sample of racemic **14** and spectral characteristics of the oily base **14,** obtained in 92% yield, corresponded to the literature data.[18b]

4.4. *(S)-(–)-(2,2-Dimethoxyethyl)-[1-(3,4-dimethoxyphenyl)ethyl]*-N-*methylamine **15***

To a mixture composed of amine **14** (1.32 g, 4.91 mmol), glacial acetic acid (0.46 ml, 8 mmol) and aqueous formaldehyde (37%, 1.18 ml, 15.9 mmol) in ethanol (10 ml), sodium borohydride (1.26 g, 33.3 mmol) was added in portions over a 40 min period at ice-bath temperature. The solvent was then evaporated under reduced pressure and water was added, followed by extraction with ethyl ether until the Dragendorff test was negative. The organic extracts were dried and the solvent was evaporated to afford crude amine **15**. It was purified by column chromatography (crude **15**:silica gel, 1:10; toluene:ethyl ether, 9:1) to give 1.19 g yellow oil (86%); $[\alpha]_D$ = ca. –6.0 (*c* 0.7, CH_2Cl_2); ^1H NMR δ: 1.35 (d, J = 7.0 Hz, 3H, CCH_3), 2.30 (s, 3H, NCH_3), 2.38 (dd, J = 5.1, 13.2 Hz, 1H, C*H*HN), 2.60 (dd, J = 5.5, 13.2 Hz, 1H, CH*H*N), 3.28, 3.29 (2s, 3H each, OCH_3), 3.56 (q, J = 7.0 Hz, 1H, C*H*), 3.87, 3.89 (2s, 3H each, OCH_3), 4.44 (dd, J = 5.1, 5.5 Hz, 1H, C*H*), 6.78–6.94 (m, 3H, Ar*H*); MS *m*/*z* (%): 283 (M^+, 4), 252 (3), 165 (100), 75 (5), 28 (9); HRMS found: 283.1783; calcd for $C_{15}H_{25}NO_4$: 283.1782.

4.5. *(S)-(–)-Salsolidine 7*

Amine **14** (0.269 g, 1 mmol) (49% *e.e.*) was dissolved in 6N hydrochloric acid (5 ml) and the solution was stirred at rt for 26 h. It was then hydrogenated with hydrogen at 0.3 MPa in the presence of 5% palladium on carbon (0.27 g). When no more starting material was present in the

reaction mixture (TLC, 21 h) the catalyst was removed by filtration through a pad of Celite, the filtrate was basified with 20% NaOH and extracted with $CHCl_3$. After work-up the crude reaction product was purified by column chromatography (crude **7**:silica gel, 1:10; dichloromethane:methanol, 100:1) to give pure (–)-salsolidine **7** in 57% yield, identical with an authentic sample by TLC and spectral data comparison.[18b,23] Enantioselectivity (46%) was established by integration of absorption bands at 1.21 and 1.26 ppm in the ^{1}H NMR spectrum recorded in the presence of 2 equiv. of TADDOL.[22]

4.6. (S)-(–)-Carnegine **8**

Amine **15** (0.283 g, 1 mmol) (prepared from amine **14** showing 38% *e.e.*) was dissolved in 6N hydrochloric acid (10 ml) and stirred at rt for 48 h, then hydrogenated with hydrogen at 0.3 MPa in the presence of 5% palladium on carbon (0.28 g) (TLC, 20 h) and worked up as described above. After column chromatography (crude **8**:silica gel, 1:20; dichloromethane) pure (–)-carnegine **8** was obtained with 79% yield and 36% *e.e.* Enantiomeric composition was established by integration of absorption bands at 2.25 and 2.27 ppm in the ^{1}H NMR spectrum recorded in the presence of 2 equiv. of TADDOL.[22] It was identical with natural (–)-carnegine[23] in terms of spectral data and TLC comparison.

Acknowledgements

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