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Tetrahedron: *Asymmetry* 18 (2007) 557–561
Tetrahedron: *Asymmetry*

Total synthesis of (*R*)-(+)-salsolidine by hydride addition to (*R*)-*N*-*tert*-butanesulfinyl ketimine

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Received 19 January 2007; accepted 29 January 2007
Available online 27 February 2007

Abstract—(*R*)-(+)-Salsolidine **1** of high enantiomeric purity was synthesized using the Pomeranz–Fritsch–Bobbitt methodology, in which the reduction ($NaBH_4$, DIBAL-H) of *N*-*tert*-butanesulfinyl ketimine, derived from 3,4-dimethoxyacetophenone, was the key step. The synthesis was completed in a sequence of reactions involving the removal of the chiral auxiliary, *N*-alkylation with 2,2-diethoxyethyl bromide and final cyclization/hydrogenolysis.

1. Introduction

Chiral non-racemic *N*-sulfinimines are versatile precursors for the asymmetric synthesis of amines, providing easy access to chiral building blocks for the construction of nitrogen-containing natural products and biologically active compounds. The increasingly significant role of *N*-sulfinimines as substrates in asymmetric synthesis, in particular that of sulfinimines developed by Davis et al.[1] and Ellman et al.,[2] has been reported in several review articles.[1–3]

Among the many types of transformations of *N*-sulfinimines, the diastereoselective 1,2-addition of nucleophilic reagents to the imine double bond to afford α-branched chiral *N*-sulfinyl-protected amines is one of the most popular methods for the preparation of this class of amines. An important factor of this chemistry is the possibility of controlling the steric course of the addition to access the amine with a desired configuration of the newly generated α-stereogenic center.

From a synthetic point of view, the synthesis of α-substituted amines with a tertiary α-carbon can be accomplished in two ways: either by the addition of organometallic reagents (preferably RMgX, RLi) to *N*-sulfinyl aldimines, or by hydride reduction of the corresponding *N*-sulfinyl ketimines (Fig. 1).

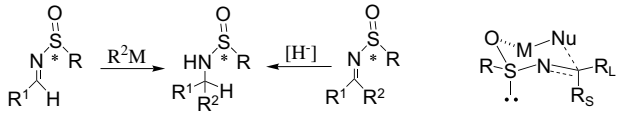

Figure 1.

Surprisingly, not many examples concerning the 1,2-addition of hydride ions to *N*-sulfinyl ketimines have been reported in the literature,[4–12] which is in significant contrast to a large number of reactions involving *N*-sulfinyl aldimines and organometallic reagents.[1–3]

In the majority of experiments concerning the hydride reduction of *N*-sulfinyl ketimines, efforts have been made to access any of the diastereomeric reduction products using the same enantiomer of either (*R*)- or (*S*)-sulfinimine. One solution to this problem was the appropriate selection of the reducing agents. In the reduction of ketimines, the following pairs of reductors have been shown to give products with a reversal of diastereselectivity: L-Selectride versus $NaBH_4$,[5–7] L-Selectride versus DIBAL-H,[8–10] L-Selectride versus 9BBN,[10] catecholborane versus $LiBHEt_3$.[11,12] Another possibility was to introduce an additional chelating agent to the reduction system[9] or to vary the reaction conditions.[7–9]

Another concept that allowed both diastereomeric amines to be obtained in this type of synthesis was based on the reversal of the order of introduction of the substituents to C-α. Such an approach was applied by Ellman et al.[13]

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doi:10.1016/j.tetasy.2007.01.033

in the synthesis of bisabolene derivatives: one diastereomeric addition product was obtained in the reaction of an *N*-sulfinyl aldimine with an organometallic reagent, while the other by a hydride reduction of the corresponding *N*-sulfinyl ketimine. However, this strategy can be applied only when both types of reactions proceed via a transition state in which both nucleophilic species are delivered from the same face of the C=N double bond. Such a situation exists in the additions of Grignard reagents to aldimines on the one hand and $NaBH_4$ or DIBAL-H reduction of ketimines on the other. In both cases, a six-membered chelated cyclic transition state has been proposed (Fig. 1). In this model, the metal is coordinated to the sulfinyl oxygen while the sulfur substituent and the larger group on the imine moiety are in pseudo-equatorial positions, thus forcing the nucleophile to approach from the less hindered site, which is that occupied by the larger substituent, securing a high degree of diastereoselectivity.

Herein we report the synthesis of (*R*)-(+)-salsolidine **1**, performed by the Pomeranz–Fritsch–Bobbitt methodology, in which hydride addition to *N*-*tert*-butanesulfinyl ketimine was the key step. This synthesis was undertaken as being complementary to the previous one,[14] in which Grignard addition to *N*-*tert*-butanesulfinyl aldimine afforded the enantiomeric (*S*)-(−)-salsolidine *ent*-**1**.

2. Results and discussion

Our stereoselective modifications of the Pomeranz–Fritsch–Bobbitt synthesis of isoquinoline alkaloids performed so far, involved as the crucial step, the enantioselective[15,16] and diastereoselective[17] addition of carbon nucleophiles to a prochiral 'Pomeranz–Fritsch imine' and further elaboration to the tetrahydroisoquinoline ring system by acid-catalyzed cyclization/hydrogenolysis of the chiral addition products (Scheme 1). In this way (*S*)-(−)-salsolidine and (*S*)-(−)-carnegine with moderate enantiomeric excess (46% and 36%)[15,16] and both enantiomers of *O*-methylbharatamine were prepared with satisfactory ee (73% and 88%).[17]

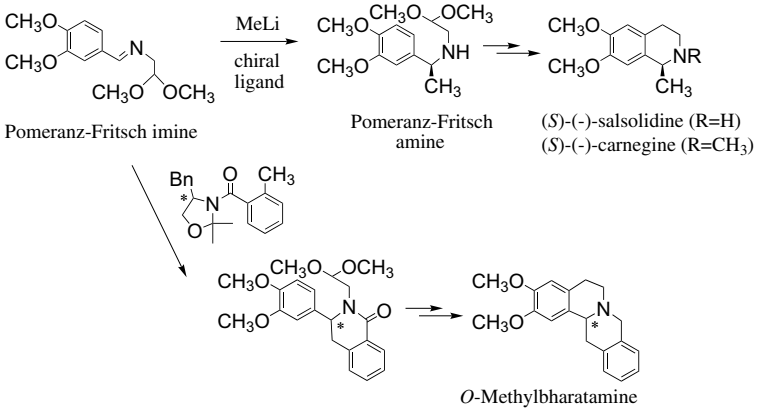
Recently, as a continuation of this study, being interested in the synthetic potential of chiral *N*-sulfinylimines, we performed the diastereoselective synthesis of (*S*)-(−)-salsolidine *ent*-**1** of high enantiomeric purity (98% ee) applying as the key step the addition of methyl magnesium bromide to the corresponding (*R*)-*tert*-butanesulfinyl aldimine.[14]

Herein we report the synthesis of the enantiomeric (*R*)-(+)-salsolidine **1** performed by reduction (DIBAL-H or $NaBH_4$) of (*R*)-*tert*-butanesulfinyl ketimine **2** (Scheme 2).

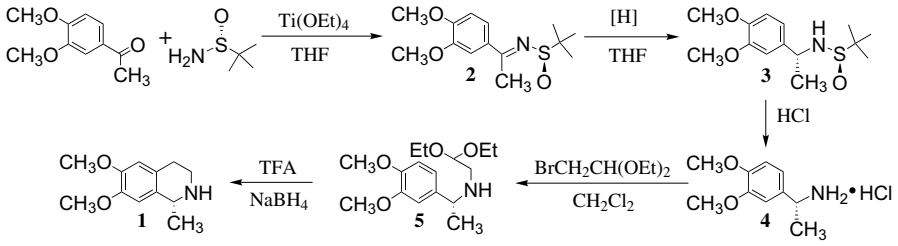
The synthesis was initiated by condensation of 3,4-dimethoxyacetophenone with (*R*)-*tert*-butanesulfinyl amide in the presence of Ti(IV) salts according to the Ellman procedure.[18] Depending on the reaction conditions and the ratio of the reagents used (Table 1), oily ketimine **2**, $[\alpha]_D = +22.2$, isolated as a single isomer, was produced in yields ranging from 0% with $Ti(OiPr)_4$ (entry 1) to 79% (entry 4) when in the reaction a mixture of sulfinamide/ketone/$Ti(OEt)_4$ at the ratio: 0.91/1/1.97 in THF was heated at reflux for 14 h.

Ketimine **2** was then used in the key step of the synthesis, in the hydride addition to the imine C=N double bond. Since we were interested in obtaining access to the enantiomeric α-substituted amine **3** from the same *N*-sulfinyl chiral directing group as used in the Grignard addition,[14] $NaBH_4$ or DIBAL-H seemed to be the reagent of choice. To optimize the reaction conditions, several experiments using these reagents were carried out with the results shown in Table 2.

In most cases, sulfinamide **3** was prepared in satisfactory yield (except for entry 4) and diastereoselectivity, irrespective of the reducing agent used, $NaBH_4$ or DIBAL-H, taking into account a reasonable compromise between the yield and diastereoselectivity. Moreover, in all cases, the diastereomer characterized by a shorter retention time (HPLC) was produced as the major isomer. Reduction products from three experiments (entries 1, 2, and 5) were combined and recrystallized from isopropyl ether/hexane to afford sulfinamide **3** with 98:2 dr, mp 79–81 °C, $[\alpha]_D = -36.3$ which was used in the next step of the synthesis. Compound **3** could be also prepared in the one-pot procedure reported by Ellman et al.,[7,19] with a less satisfactory diastereoselectivity (ca. 70:30 dr).



Scheme 1.



Scheme 2.

Table 1. Condensation of 3,4-dimethoxyacetophenone with (*R*)-*t*-butanesulfinamide

Entry	*t*-BuSONH$_2$ (mmol)	Ketone (mmol)	Ti(OR)$_4$ (mmol)	THF (ml)	Time of reaction at reflux (h)	Yield (%)
1	1	1	Ti(O*i*Pr)$_4$ (2.5)	3	4	0
2	1.79	3.58	Ti(OEt)$_4$ (3.58)	7	13	24
3	2	2	Ti(OEt)$_4$ (4)	8	10	28
4	0.91	1	Ti(OEt)$_4$ (1.97)	2	14	79

Table 2. Reduction (DIBAL-H, NaBH$_4$) of sulfinyl ketimine[a] **2**

Entry	**2** (mmol)	Reducting agent (mmol)	Temperature (°C)	Time (h)	Yield (%)	dr[b] (%)
1	1	DIBAL-H (2.3)	−22	0.45	89 (Crude)	95:5
2	1	DIBAL-H (2.3)	−68	1.5	87	98:2
3	1	NaBH$_4$ (4)	−40	120	90	93:7
4	1	NaBH$_4$ (4)	−35 → −17	24	58	92:8
5	1	NaBH$_4$ (4)	−50[c] → rt	24	83 (Crude)	96:4

[a] THF as solvent.
[b] After column chromatography. Evaluated by HPLC: Chiralcel OD-H, *i*PrOH/hexane 10:90, 0.5 ml/min. The retention time of the minor diastereoisomer was the same as that of the starting ketimine **2**.
[c] No reaction at −50 °C.

Upon treatment of sulfinamide **3** with hydrochloric acid at 0 °C, followed by stirring of the mixture at rt for 2h, the primary amine **4** was isolated as a hydrochloride salt, **4**·HCl, mp 202–203 °C, $[\alpha]_D = +5.8$ (lit.[14] for *ent*-**4**·HCl mp 201–203 °C, $[\alpha]_D = -6.9$), in 89% yield. The (*R*)-configuration of the new stereocenter in **3** and **4** was deduced only at the end of the synthesis on the basis of the positive sign of the specific rotation of the target alkaloid, (+)-salsolidine **1** for which the (*R*)-configuration had been previously established.[20]

Amine **4** was then alkylated with bromoacetaldehyde acetal/potassium carbonate in acetonitrile at reflux to give the 'Pomeranz–Fritsch amine' **5**, oil, $[\alpha]_D = +28.0$, in moderate yield (58%).

The tetrahydroisoquinoline nitrogen-containing ring was closed by a one-pot two-step procedure involving sequential treatment of aminoacetal **5** with 6 M hydrochloric acid for 20 h followed by NaBH$_4$/TFA reduction to afford (+)-salsolidine **1** in 58% yield with 95.5% ee.

3. Conclusion

The diastereoselectivity of the Pomeranz–Fritsch–Bobbitt synthesis of isoquinoline alkaloid (*R*)-(+)-salsolidine **1**, was accomplished in the key step, by using a (*R*)-*tert*-butanesulfinyl chiral auxiliary attached to the nitrogen atom of ketimine **2**. The target alkaloid was obtained in 20% overall yield and with 95.5% ee, in a five-step reaction sequence. The result is similar to that reached in our previous synthesis[14] of the enantiomeric (*S*)-(−)-salsolidine *ent*-**1** in which methyl magnesium bromide was added to the corresponding (*R*)-*tert*-butanesulfinyl aldimine. The synthesis described here, and the previous one,[14] are examples illustrating the opportunity to prepare the desired enantiomeric addition product using the same chiral auxiliary, by choosing the proper synthetic strategy, either the 'Grignard' or 'hydride' approach.

4. Experimental

4.1. General

Melting points: determined on a Koffler block and are not corrected. IR spectra: Perkin–Elmer 180 in KBr pellets. NMR spectra: Varian Gemini 300, with TMS as internal standard. Mass spectra (EI): instrument AM D402. Specific rotation: Perkin–Elmer polarimeter 243B at 20 °C. Analytical HPLC: Waters HPLC system with Mallinkrodt–Baker Chiralcel OD-H column. Merck DC-Alufolien Kieselgel 60$_{254}$ were used for TLC. Merck Kieselgel 60 (70–230 mesh) were used for column chromatography.

THF was freshly distilled from LiAlH$_4$. Ti(O*i*Pr)$_4$ was purchased from Fluka. Ti(OEt)$_4$, *tert*-butanesulfinamide,

$NaBH_4$, and DIBAL-H were purchased from Aldrich and used as received.

4.2. (*R*)-(+)-*N*-[1-(3,4-Dimethoxyphenylethylidene)]-2-methylpropanesulfinamide 2

To a solution of 3,4-dimethoxyacetophenone (180 mg, 1 mmol) and *tert*-butanesulfinamide (110 mg, 0.9 mmol) in anhydrous THF (2 ml), $Ti(OEt)_4$ (0.41 ml, 1.97 mmol, technical grade, ~20% Ti) was added. The mixture was heated at 60–70 °C for 14 h under an argon atmosphere. Water (5 ml) was added on rapid stirring, then the reaction mixture was filtered through a pad of Celite®, the filter cake was washed with CH_2Cl_2 and the phases were separated. The organic phase was washed with brine, dried over Na_2SO_4, and the solvent was evaporated. The crude reaction product was purified by silica gel column chromatography with CH_2Cl_2/MeOH (100:0.2). Yield: 79%; green oil; $[\alpha]_D = +22.2$ (*c* 1.12, $CHCl_3$). IR (KBr), *ν* (cm^{-1}): 1567, 1517, 1272. ^1H NMR ($CDCl_3$): *δ* 1.32 (s, 9H, $C(CH_3)_3$), 2.74 (s, 3H, $CH_3C{=}N$), 3.92 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 6.88 (d, $J = 8.5$ Hz, 1H, Ar*H*), 7.46 (dd, $J = 2$ Hz, $J = 8.5$ Hz, 1H, Ar*H*), 7.58 (d, $J = 2$ Hz, 1H, Ar*H*). ^{13}C NMR ($CDCl_3$): 19.6, 22.5, 55.8, 55.9, 57.18, 109.6, 109.9, 121.3, 131.3, 148.6, 152.2, 175.4. EI MS *m*/*z* (%): 283 (M^+, 1), 267 (0.7), 227 (73), 179 (100), 164 (25). Anal. Calcd for $C_{14}H_{21}NSO_3$: C, 58.97; H, 7.25; N, 4.67; S, 11.57. Found: C, 59.34; H, 7.42; N, 4.95; S, 11.29.

4.3. (*R*,*R*)-(−)-*N*-[1-(3,4-Dimethoxyphenylethyl)]-2-methylpropanesulfinamide 3

4.3.1. Reduction with $NaBH_4$. A solution of ketimine **2** (39 mg, 0.14 mmol) in 0.3 ml of THF was cooled to −40 °C. Sodium borohydride (22 mg, 0.14 mmol) was then added and the reaction mixture stirred at −40 °C for 120 h. MeOH (2 ml) was added at −40 °C, followed by brine (3 ml) at room temperature. The reaction mixture was extracted three times with ethyl ether, and the combined organic extracts were dried over Na_2SO_4. The solvent was evaporated to give 36 mg of colorless oil. The crude product was purified by silica gel column chromatography with CH_2Cl_2/MeOH (100:0.25). Yield: 90%, dr: 93:7.

4.3.2. Reduction with DIBAL-H. A solution of ketimine **2** (30 mg, 0.1 mmol) in THF (1 ml) under an argon atmosphere was cooled to −68 °C and DIBAL-H (1 M solution in hexane, 0.23 ml, 0.23 mmol in 0.5 ml of THF) was then added. The reaction mixture was stirred at −68 °C for 1.5 h, then, when room temperature was reached, the solvents were evaporated. The residue was treated with 10% NaOH (3 ml) and extracted three times with ethyl ether. The combined organic extracts were dried over Na_2SO_4 and the solvent was evaporated to provide 36 mg of colorless oil. The crude product was purified by silica gel column chromatography with CH_2Cl_2/MeOH (100:0.25). Yield: 87%, dr: 98:2. $[\alpha]_D = -36.3$ (*c* 0.32, $CHCl_3$); mp 79–81 °C (from iPr_2O/hexane). IR (KBr), *ν* (cm^{-1}): 2974, 1520, 1266, 1063. ^1H NMR ($CDCl_3$): *δ* 1.24 (s, 9H, $C(CH_3)_3$), 1.51 (d, $J = 6.3$ Hz, 3H, CH_3CH), 3.37 (br s, 1H, N*H*), 3.88 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.47–4.53 (m, 1H, $CHCH_3$), 6.82–6.92 (m, 3H, Ar*H*). ^{13}C NMR ($CDCl_3$): 22.70, 22.75, 53.84, 55.43, 55.99, 110.26, 111.38, 118.56, 136.61, 148.59, 149.10. EI MS *m*/*z* (%): 285 (M^+, 0.6), 229 (6), 213 (2), 179 (2), 165 (100), 150 (5). Anal. Calcd for $C_{14}H_{23}NSO_3$: C, 58.92; H, 8.13; N, 4.91; S, 11.21. Found: C, 58.94; H, 8.15; N, 4.88; S, 10.95.

4.4. (*R*)-(+)-1-(3,4-Dimethoxyphenyl)ethylamine hydrochloride 4·HCl

Sulfinamide **3** (100 mg, 0.35 mmol) was dissolved in EtOH (2 ml) and the solution was cooled to 0 °C. Concentrated HCl (0.1 ml) was added and the reaction mixture was stirred at room temperature for 2 h then saturated K_2CO_3 (7 ml) was added and the reaction mixture was extracted twice with ethyl acetate. The combined organic extracts were dried over Na_2SO_4 and the solvent was evaporated. To the crude reaction product 3% solution of HCl in MeOH (2 ml) was added and after 1 h the solvents were evaporated. The residue was washed a few times with ethyl acetate and dried in air providing a white solid (68 mg, 89% yield); mp 202–203 °C, $[\alpha]_D = +5.8$ (*c* 0.86, MeOH). Its spectral characteristics corresponded to that of (*S*)-(−)-enantiomer.[14]

4.5. (*R*)-(+)-*N*-(2,2-Diethoxyethyl)-1-(3,4-dimethoxyphenyl)ethylamine 5

To a solution of amine **4** (45 mg, 0,24 mmol) prepared from the amine hydrochloride **4**·HCl by treatment with 20% NaOH, in MeCN (2 ml), anhydrous K_2CO_3 (56 mg, 0.4 mmol) was added followed by 2-bromo-1,1-diethoxyethane (0.27 mmol, 0.04 ml). The reaction mixture was heated under an argon atmosphere at 82 °C for 25 h. On heating, two additional amounts of K_2CO_3 and 2-bromo-1,1-diethoxyetane were added. After completion of the reaction, the mixture was filtered off and the solvent evaporated providing 200 mg of an oil, which was purified by silica gel column chromatography with CH_2Cl_2/MeOH (100:0.6). Yield: 58%; $[\alpha]_D = +28.0$ (*c* 0.66, $CHCl_3$). Its spectral characteristics corresponded to that of (*S*)-(−)-enantiomer.[14]

4.6. (*R*)-(+)-Salsolidine 1

A solution of aminoacetal **5** (40 mg, 0.13 mmol) and 5 M aqueous HCl (1.3 ml) was stirred overnight at rt. The mixture was basified with 20% aqueous NaOH and extracted five times with dichloromethane. The combined organic extracts were dried over Na_2SO_4 and evaporated to give a solid (25 mg), which was dissolved in dichloromethane (6 ml) and cooled to 0 °C. To this solution, $NaBH_4$ (66 mg, 1,7 mmol) was added along with slow introduction of trifluoroacetic acid (0.93 ml, 12.2 mmol) in dichloromethane (2 ml). The reaction mixture was stirred at rt for 24 h, then the solvent was removed under reduced pressure. The resultant precipitate was dissolved in water (4 ml), basified with 20% aqueous NaOH and extracted three times with dichloromethane. The organic extract was dried over Na_2SO_4 and evaporated to provide 25 mg of a yellow oil which was purified by silica gel chromatography with CH_2Cl_2/MeOH (100:0.6). Yield: 58%, ee: 95.5% (HPLC:

Chiralcel OD-H, *i*PrOH/hexane 20:80, 0,5 ml/min). $[\alpha]_D = +51.0$ (*c* 1.0, EtOH), lit.[20] $[\alpha]_D = +59.5$ (*c* 0.9, EtOH).

Acknowledgements

This work was supported by a research Grant from the State Committee for Scientific Research for 2003–2006 (KBN Grant No. 4T09A 07824).

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