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Short stereoselective synthesis of (+)-crispine A via an *N*-sulfinyl Pictet–Spengler reaction

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ABSTRACT

We report the highly stereoselective synthesis of (*R*)-(+)-crispine A from the (*R*)-*N*-sulfinyl amine **1** by using a one-pot process involving the Pictet–Spengler reaction with 4-chlorobutanal, removal of the sulfinyl group by protonolysis of the N–S bond and in situ cyclization, with a 55% overall yield.

Alkoxy and hydroxy tetrahydroisoquinolines bearing a stereocenter at C-1 are the structural motif of many natural alkaloids with interesting biological properties. Representative natural products include compounds with a simple alkyl group at C-1, such as (+)-salsolidine and (+)-carnegine, as well as others bearing an additional five-membered ring (pyrroloisoquinoline alkaloids), such as (−)-trolline and (+)-crispine A (Fig. 1).

Among them, (+)-crispine A emerged as a target of great interest due to its high cytotoxic activity against various human cancer cell lines.[1,2] It was firstly isolated in 2002 from *Cardus crispus* by Zhao and co-workers.[2] The pharmacological interest of (+)-crispine A has prompted many groups to develop in its asymmetric synthesis over the last ten years. Many of the reported papers are not specifically oriented toward the synthesis of crispine A, but its preparation is reported as an example illustrating the validity of different synthetic methodologies. This is the case of catalytic hydrogenation methods applied to cyclic enamines[3] or iminium salts,[4] asymmetric allylation of cyclic imines,[5] and $Bi(OTf)_3$-catalyzed intramolecular 1,3-chirality transfer reactions.[6]

The enantioselective deprotonation of *N*-Boc pyrrolidine followed by Pd-catalyzed α-arylation[7] was also illustrated with a synthesis of (+)-crispine A, which, in turn, has been also described from chiral 1-cyanotetrahydroisoquinolines, obtained by electrochemical methods.[8] Most of these procedures involve the use of long sequences for preparing the starting materials required by the corresponding methodology, thus resulting in a moderate efficiency. A similar problem is detected in methods based on enzyme-catalyzed kinetic resolution.[9]

So far only two reported papers specifically describe the synthesis of (+)-crispine A. The first one[10] is based on the application of the highly diastereoselective *N*-acyliminium cyclization reaction[11] to the case of the crispine A, and has similar problems to those previously indicated. The second and most direct so far reported method involves the Pictet–Spengler reaction of 4-chloro-1,1-dimethoxybutane with the commercially available but expensive (*R*)-amino ester indicated in Scheme 1. It affords (+)-crispine A in a one-pot sequence of Pictet–Spengler reaction followed by decarboxylation.[12]

The main advantage of this procedure is the clever use of the Pictet–Spengler reaction, that allows the bis-cyclization affording the skeleton of (+)-crispine A in only one-step. However, its main drawbacks are the moderate control of the stereoselectivity exerted by the amino ester moiety (63% de) and the low yield (39%) of the two-step procedure required for decarboxylation. From these results we reasoned that the use of another easily removable and more efficient chiral auxiliary as stereocontroller, could provide a better method for obtaining (*R*)-(+)-crispine A. Taking into account that the sulfinamine group had been successfully used in the preparation of tetrahydro-β-carbolines[13a] and 1-alkyl tetrahydroisoquinolines[13b] by Pictet–Spengler reaction, we have investigated the role of this group in a similar

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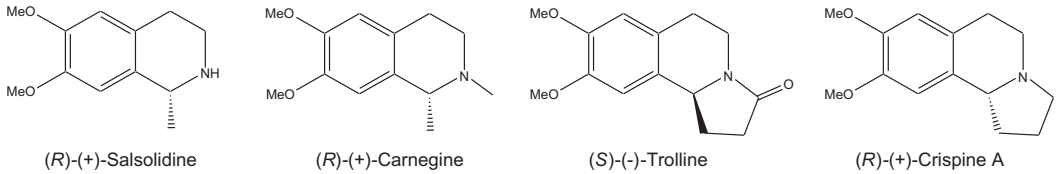
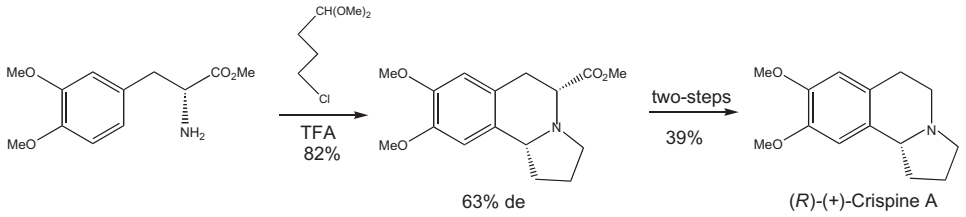
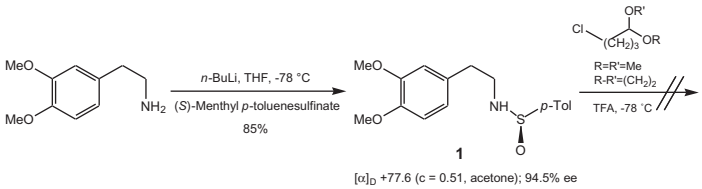


Figure 1. Examples of tetrahydroisoquinoline-derived natural products.



Scheme 1. Synthesis of (+)-crispine A via Pictet–Spengler reaction.[12]



Scheme 2. Synthesis and unsuccessful reactions of the *N*-sulfinyl amine **1**.

sequence to that shown in Scheme 1. In this Letter we describe the results obtained in this study, demonstrating that the sulfinamine allows the complete control of the stereoselectivity in the Pictet–Spengler reaction and is more easily removed than the CO_2Me group, thus providing a more efficient method for the asymmetric synthesis of (*R*)-(+)-crispine A.

The synthesis of (*R*)-*N*-*p*-tolylsulfinyl 2-(3,4-dimethoxy)phenyl ethylamine (**1**), used as the precursor of our sequence, was performed following the procedure reported by us,[14] consisting in the reaction of the 3,4-dimethoxyphenylethylamine with *n*-butyllithium (2 equiv) at −78 °C and the quick addition of the resulting anion to (*S*)-menthyl *p*-toluenesulfinate (Scheme 2). Under these conditions, the *N*-sulfinyl derivative **1** was obtained in 85% yield[15] (94.5% ee by chiral HPLC). Then, Pictet–Spengler reaction of **1** with different aldehyde surrogates was studied under a variety of conditions. First, we checked the conditions indicated in Scheme 1, consisting in the use of 4-chloro-1,1-dimethoxybutane as the coupling partner and protic acids (trifluoroacetic, acetic, or *p*-toluenesulfonic acids) as catalysts at low temperatures (−78 to 0 °C). In general, application of these reaction conditions resulted in the recovery of the starting material or hydrolysis of the nitrogen–sulfur bond of sulfinamide **1** (Scheme 2). Similar results were obtained starting from the cyclic acetal 2-(3-chloropropyl)-1, 3-dioxolane.

Then, we turned our attention to the use of Lewis acids. When sulfinamide **1** reacted under Pictet–Spengler conditions with the cyclic and acyclic acetals using $BF_3{\cdot}OEt_2$ as the catalyst no cyclized products could be isolated. However, the use of 4-chlorobutanal (4 equiv) in dry CH_2Cl_2 at −78 °C, using 2.2 equiv of $BF_3{\cdot}Et_2O$ as the catalyst afforded, after 2 h, a 90:10 diastereoisomeric mixture (as determined by ^1H NMR spectroscopic analysis of the crude) of the expected Pictet–Spengler product. A better result was observed by performing the reaction at −90 °C (Scheme 3), because only one diastereoisomer of compound **2** (>98% de) was obtained in 57% yield.[16] The optical purity of this compound (94.8% ee by chiral HPLC) was identical to that of the starting material **1**, which indicated that it was not affected under the used reaction conditions. Removal of the *p*-tolylsulfinyl chiral auxiliary group was accomplished in 88% yield using concentrated HCl in ethanol at 0 °C to produce exclusively (*R*)-(+)-crispine A[17] by cyclization in situ of the resulting aminochloro derivative (Scheme 3).

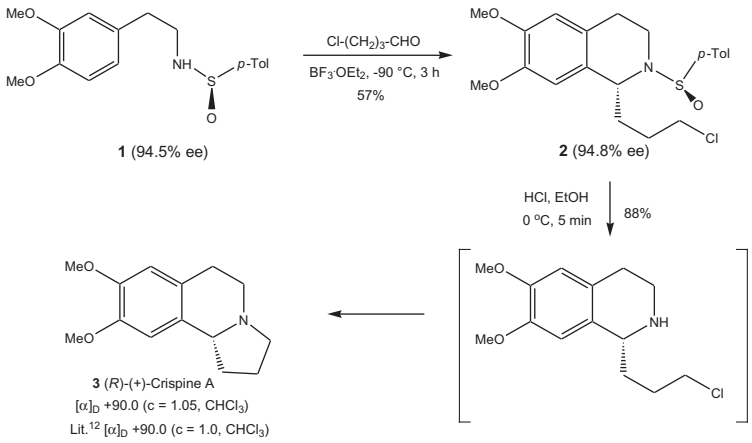
The absolute configuration of the obtained crispine was unequivocally established as (*R*) by comparison of its specific rotation with that reported in the literature for this enantiomer.[12]

It also allowed us to assign the same configuration to the benzylic carbon of intermediate **2**.

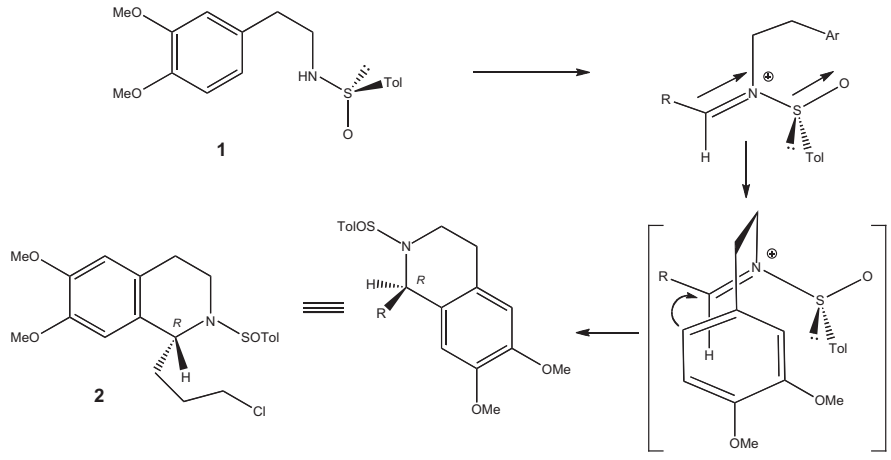
The role of the sulfinyl group in the stereoselectivity control of the Pictet–Spengler reaction can be rationalized by assuming that the approach of the nucleophilic ring to the iminium intermediate (formed by the reaction of the aldehyde with the amine) adopting its presumably most stable conformation (that minimizing the strong dipolar repulsions of the S–O and C=N^+ bonds) should take place to the *pro-R* face of the iminium, in order to avoid the strong steric interactions with the *p*-tolyl group oriented toward the *pro-S* face (Scheme 4).

Unfortunately the use of $BF_3{\cdot}OEt_2$ instead of TFA as the catalyst did not allow the in situ desulfinylation and subsequent cyclization resulting in the formation of (+)-crispine A in only one-step from **1**. However, we explored the conversion of sulfinamide **1** into **3** via a one-pot process involving asymmetric Pictet–Spengler reaction/hydrolysis/cyclization (Scheme 5). To our delight, this two-step one-pot procedure directly connecting the starting sulfinamide **1** with (*R*)-(+)-crispine A took place in 55% overall yield.[17]

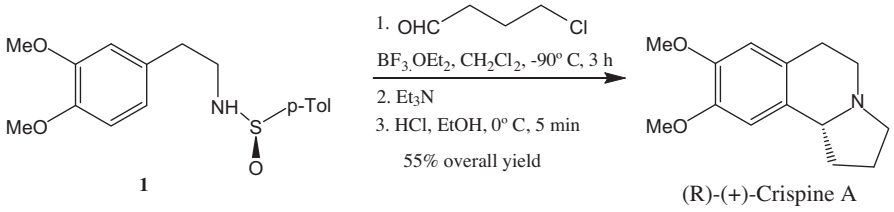
The shortest reported routes to (*R*)-crispine A are the three-step sequence (54% overall yield) from the known but hard to prepare methyl 2-(2-bromo-4,5-dimethoxyphenyl)acetate[7] and the three-step sequence (32% overall yield) from commercially available but expensive (*R*)-(−)-methyl 2-amino-3-(3,4-dimethoxyphenyl)propanoate.[12] Our approach proceeds in a two-step one-pot process (55% yield) starting from the *N*-sulfinyl derivative **1**,



Scheme 3. A two-step synthesis of **3** from the *N*-sulfinyl amine **1**.



Scheme 4. Mechanistic proposal for explaining the stereochemical results.



Scheme 5. One-pot synthesis of (*R*)-(+)-crispine A (**3**) from **1**.

or in a three-step sequence (43% overall yield) starting from commercially available and cheap 3,4-dimethoxy phenethylamine.

In summary, we have reported the highly stereoselective synthesis of (*R*)-(+)-crispine A from the *N*-sulfinyl amine **1** by using a one-pot process involving the Pictet–Spengler reaction with 4-chlorobutanal, removal of the sulfinyl group by protonolysis of the N–S bond and cyclization, with a 55% overall yield.

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Supplementary data

Supplementary data (^{1}H NMR and ^{13}C NMR spectra and CSP-HPLC data for compounds **1**–**3**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.01.121.

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15. *Compound* ***1***: To a stirred solution of *N*-(3,4-dimethoxy)phenethylamine (1.81 g, 10 mmol) in dry THF (40 mL) cooled at −78 °C a solution 2.1 M of *n*-BuLi in hexanes (20 mmol, 2 equiv) was added. The resulting mixture was stirred at −78 °C for 15 min and then added very quickly to a solution of (*S*)-menthyl *p*-toluenesulfinate (2.94 g, 10 mmol, 1 equiv) in THF (22 mL). The reaction mixture was allowed to warm to room temperature and stirred 1 h. Then it was quenched with a saturated aqueous solution of NH_4Cl (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were washed with water (3 × 40 mL), dried with sodium sulfate and concentrated. The residue was purified by flash chromatography over silica gel eluting with hexane/ethyl acetate 40:60 to produce **1** as a pale yellow oil (2.71 g, 85%), $[\alpha]_D$ +77.6 (*c* 0.51, acetone) [lit.[13] $[\alpha]_D$ + 66.9 (*c* 0.50, acetone)]. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.40 (s, 3H), 2.76 (t, *J* = 6.9 Hz, 2H), 3.01–3.12 (m, 1H), 3.30–3.40 (m, 1H), 3.84 (s, 3H), 3.85 (s, 3H), 4.09 (m, 1H), 6.65 (d, *J* = 1.8 Hz, 1H), 6.70 (dd, *J* = 2.1 and 8.1 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 7.28 and 7.53 (AA′BB′ system, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.27, 36.40, 42.27, 55.78, 55.90, 111.31, 111.96, 120.77, 125.89, 129.48, 130.87, 141.07, 141.16, 147.71, 148.99. The enantiomeric purity was determined by HPLC (Chiralpak IA, hexane/ethanol/triethylamine: 80:20:0.1, 1.0 mL/min, t_R (major) 9.2–9.4 min, t_R (minor) 12.4–12.7 min: 94.5% ee.
16. *Compound* ***2***: To a stirred solution of **1** (0.391 g, 1.22 mmol, 1 equiv) and 4-chlorobutanal (0.518 g, 4.88 mmol, 4 equiv) in dry CH_2Cl_2 (15 mL) cooled at −78 °C $BF_3{\cdot}Et_2O$ (0.381 g, 2.68 mmol, 2.2 equiv) was added and the resulting mixture was stirred at −90 °C for 3 h. Then, Et_3N (0.247 g, 2.44 mmol, 2 equiv) was added. The volatiles were evaporated to provide a crude residue that was judged to be a >98:2 mixture of diastereoisomers by ^{1}H NMR analysis. The residue was purified by flash chromatography over silica gel eluting with hexane/ethyl acetate 60:40 to give the major diastereoisomer **2** as a colorless oil (0.283 g, 57%). $[\alpha]_D$ +56.4 (*c* 1.07, $CHCl_3$), $[\alpha]_D$ +78.2 (*c* 1.05, acetone). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.50–1.60 (m, 1H), 1.70–1.93 (m, 3H), 2.42 (s, 3H), 2.53–2.64 (m, 1H), 2.80–2.94 (m, 1H), 3.36 (t, *J* = 6 Hz, 2H), 3.40–3.51 (m, 1H), 3.56–3.64 (m, 1H), 3.83 (s, 3H), 3.84 (s, 3H), 4.37 (dd, *J* = 3.3 and 9.0 Hz, 1H), 6.52 (s, 1H), 6.53 (s, 1H), 7.29 and 7.54 (AA′BB′ system, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.33, 28.10, 29.39, 34.13, 40.42, 44.62, 55.00, 55.79, 55.87, 109.29, 111.61, 125.34, 126.10, 129.40, 129.83, 140.71, 141.40, 147.45, 147.74. MS-FAB *m*/*z* 408 (33, M^++1), 330 (98), 314 (19), 268 (94), 205 (43), 191 (100), 154 (78), 136 (75), 89 (49), 77 (57). The enantiomeric purity was determined by HPLC (Chiralpak IA, heptane/ethanol/triethylamine: 90:10:0.1, 1.0 mL/min, t_R (major) 21.1–21.7 min, t_R (minor) 27.0–28.4 min: 94.8% ee.
17. *(R)-(+)-Crispine A (****3****)*: To a stirred solution of **2** (0.432 g, 1.06 mmol, 1 equiv) in EtOH (15 mL) cooled at 0 °C concentrated HCl (0.4 mL, 4.9 mmol, 4.6 equiv) was added. The resulting mixture was stirred at 0 °C for 5 min, then a saturated aqueous K_2CO_3 (6 mL) was added and the mixture was extracted with ethyl acetate (4 × 20 mL). The combined organic extracts were dried with sodium sulfate and evaporated. The residue was purified by flash chromatography over silica gel using ethyl acetate/methanol/triethylamine 85:14:1 as the eluent to give (*R*)-(+)-crispine A (**3**) as a colorless oil that solidifies on standing (0.217 g, 88%), mp 55–57 °C (lit. [6] mp 53–55 °C), $[\alpha]_D$ +90.0 (*c* 1.05, $CHCl_3$), [lit.[12] $[\alpha]_D$ +90.0 (*c* 1.0, $CHCl_3$)]. A sample was crystallized from acetone–hexane, mp 82–84 °C (lit. mp 86–88 °C), $[\alpha]_D$ + 90.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.65–1.78 (m, 1H), 1.79–2.02 (m, 2H), 2.26–2.37 (m, 1H), 2.51–2.77 (m, 3H), 2.96–3.12 (m, 2H), 3.14–3.22 (m, 1H), 3.41 (t, *J* = 8.1 Hz, 1H), 3.84 (s, 3H), 3.85 (s, 3H), 6.57 (s, 1H), 6.61 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.22, 28.03, 30.47, 48.34, 53.12, 55.89, 56.00, 62.93, 108.98, 111.44, 126.27, 131.06, 147.27, 147.38. The enantiomeric purity was determined by HPLC (chiralcel OJ, heptane/ethanol/triethylamine: 95/5/0.2, 0.8 mL/min, t_R (minor) 11.7 min, t_R (major) 12.7–12.9 min: 94.8% ee.

One-pot process: To a stirred solution of **1** (0.520 g, 1.63 mmol, 1 equiv) and 4-chlorobutanal (0.692 g, 6.52 mmol, 4 equiv) in dry CH_2Cl_2 (25 mL) cooled at −90 °C, $BF_3{\cdot}Et_2O$ (0.509 g, 3.58 mmol, 2.2 equiv) was added and the resulting mixture was stirred at −78 °C for 3 h. Then, Et_3N (0.362 g, 3.58 mmol, 2.2 equiv) was added and the volatiles were evaporated. The residue was dissolved in EtOH (25 mL), cooled at 0 °C and concentrated HCl (0.66 mL, 8.02 mmol, 4.92 equiv) was added. The resulting mixture was stirred at 0 °C for 5 min, then a saturated aqueous K_2CO_3 (10 mL) was added and the mixture was extracted with ethyl acetate (4 × 25 mL). The combined organic extracts were dried with sodium sulfate and evaporated. The residue was purified by flash chromatography over silica gel using ethyl acetate/methanol/triethylamine 85:14:1 as the eluent to give (*R*)-(+)-crispine A (**3**) as a white solid (0.207 g, 55%), mp 54–56 °C, $[\alpha]_D$ +89.2 (*c* 1.0, $CHCl_3$).