Synthesis of Enantiopure 1-Benzyl-2,3-disubstituted Piperazines from Enantiopure *p*-Toluenesulfinimines

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Abstract: The treatment of enantiopure *N*-sulfinyl-*N*′-benzyldiaminoalcohols with diethyl oxalate and sodium methoxide followed by reduction with BH_3 affords enantiopure 1-benzyl-2,3-disubstituted piperazines. A related sequence produces substituted monoketopiperazines in good yields.

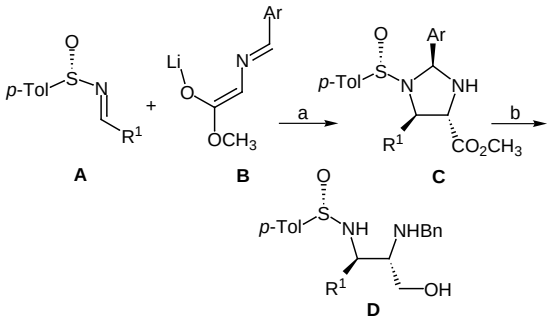
Key words: piperazines, amino alcohols, sulfinimines, chiral auxiliaries, asymmetric synthesis

The piperazine ring is truly ubiquitous in molecules involved in the regulation of a wide variety of biological processes. Indeed, the piperazine scaffold is found in HIV-protease inhibitors such as indinavir,[1] potent antiproliferative agents such as ectenaiscidin 743,[2] compounds acting at different membrane receptors such as arylpiperazines, powerful 5-HT_{1A} ligands,[3] as well as in some members of the dragmacines,[4] a family of marine natural products with a broad spectrum of biological activities. On the other hand, the structurally related mono- and diketopiperazines are gaining importance as farnesyl transferase inhibitors,[5] and as conformationally restricted peptidomimetics,[6] among several biological activities.[7] In addition, recent findings have revealed piperazines and diketopiperazines as efficient chiral ligands in asymmetric catalysis.[8]

Despite the increasing interest on these compounds, the existing routes to prepare chiral piperazines are scarce,[9] and not fully applicable to the straightforward synthesis of highly substituted derivatives. This is particularly true for non-symmetrical 2,3-disubstituted piperazines for which the simplest route entails reduction of 2,3-disubstituted diketopiperazines in turn prepared from the corresponding vicinal diamines. In fact, the synthesis of suitably substituted enantiopure vicinal diamines may be quite challenging,[10] and this severely limits the viability of this approach.

Within a program directed to the discovery of new therapeutically valuable piperazine derivatives,[11] and taking advantage of our previous experience in the asymmetric synthesis of non-symmetrical vicinal diamine derivatives,[12] we now disclose a straightforward entry to a new family of homochiral piperazines and ketopiperazines, with carbon and nitrogen atoms differently functionalized.

We have previously reported the asymmetric synthesis of enantiopure 1,3-imidazolidines **C** through the diastereoselective stepwise condensation between readily available *p*-tolylsulfinimines **A**,[13] and glycine iminoester enolates **B** in the presence of boron trifluoride.[12b] Under these conditions, enantiopure *p*-tolylsulfinimines display a moderate to high facial selectivity rendering the corresponding *N*-sulfinylimidazolidines in good to excellent diastereomeric excess. Ensuing reductive cleavage of the aminal moiety expediently transforms our 1,3-imidazolidines **C** into differentially protected vicinal diamines **D** in good yields. (Scheme 1). The availability of these substrates, along with the aforementioned relevance of piperazines prompted us to examine the transformation of a series of our vicinal diamines **1** into the corresponding ketopiperazines and piperazines.



Scheme 1 Synthesis of *N*-sulfinyldiaminoalcohols.[a] *Conditions*: (a) $BF_3{\cdot}OEt_2$, –78 ºC, THF, (60–93%); (b) $LiAlH_4$, Et_2O, r.t., (68–85%).

Our initial efforts to obtain homochiral diketopiperazines were focussed on substrates **1a**–**e**,[14] originally obtained from glycine-derived enolates (Scheme 2, R^2 = H). After testing different experimental conditions we found that the treatment of **1a** (R^1 = Et) with diethyl oxalate in CH_2Cl_2 afforded 2,3-diketopiperazine **2a** in moderate yields (60%), along with a small amount of morpholinedione **3a** derived from N,O ring closure. After chromatographic separation we observed that **3a** slowly converted into **2a** upon standing in a solution of MeOH, (5 days) and that a catalytic amount of NaOMe accelerated (1 h) this conversion. Substrates **1b** and **1c** paralleled this behavior, after removal of the diketopiperazine by filtration. Seek-

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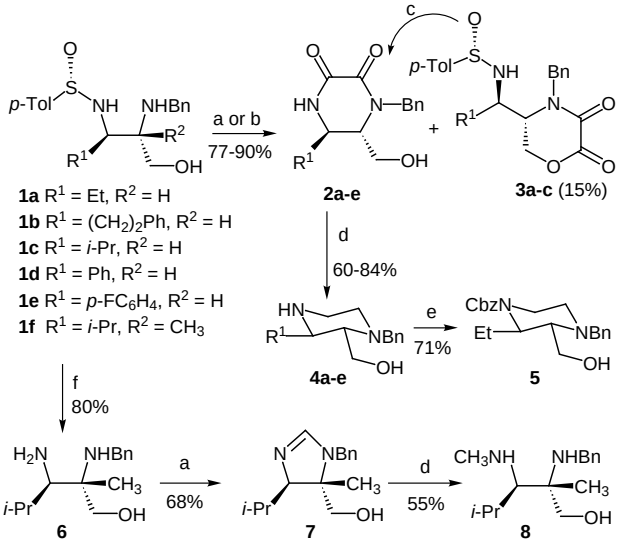
ing to increase the efficiency of the process, we added a solution of NaOMe in MeOH to the reaction mixture, and this promoted in situ nucleophilic displacement at sulfur, rendering methyl *p*-toluenesulfinate along with the desired diketopiperazine in excellent yields. This procedure was also satisfactorily extended to aromatic substrates (**1d** and **1e**) to produce diketopiperazines **2d** and **2e**.[15]

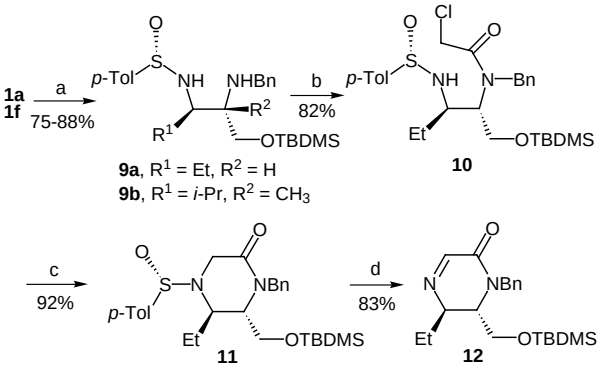
After considerable experimentation,[16] diketopiperazines **2a**–**e** were efficiently transformed into the corresponding enantiopure 2,3-disubstituted piperazines **4a**–**e** in good yields (60–84%), upon treatment with borane dimethyl sulfide complex.[17] These hydroxymethylpiperazines are amenable to selective protection at the secondary nitrogen as benzyloxycarbonyl derivatives as illustrated by the preparation of hydroxymethylpiperazine **5**.



Scheme 2 Synthesis of enantiopure hydroxymethylpiperazines and ketopiperazines.[a] *Conditions*: (a) $(CO_2Et)_2$, NaOMe, CH_2Cl_2, MeOH, r.t.; (b) i) $(CO_2Et)_2$, CH_2Cl_2, r.t.; ii) NaOMe, MeOH, r.t.; (c) NaOMe, MeOH, r.t.; (d) $BH_3{\cdot}SMe_2$, THF, reflux; (e) CbzCl, NaOH, CH_2Cl_2, r.t.; (f) TFA, MeOH, r.t.

To broaden the scope of these procedures we considered vicinal diamine **1f**, originally obtained from alanine (Scheme 2).[14] Unfortunately, the presence of a quaternary carbon in its skeleton ($R^2 = CH_3$) prevented any cyclization from taking place. Thus, when compound **1f** was treated with diethyl oxalate, cyclic derivatives **2** or **3** were not observed, even in the presence of NaOMe, instead labile open-chain acylated intermediates were detected. To enhance the nucleophilicity of the substrate we prepared desulfinylated diamine **6**, and the treatment of **6** with diethyloxalate (Scheme 2), surprisingly, afforded hydroxymethylimidazoline **7** (68%). Subsequent reductive cleavage of the imidazoline ring produced exclusively *N*-benzyl-*N*′-methyldiaminoalcohol **8** in fair yield (55%). The generality of these serendipitous findings remains to be tested.

To address the preparation of monoketopiperazines from our substrates,[18] the primary alcohol of **1a** and **1f** was protected uneventfully as a silyl ether in excellent yields, affording **9a** and **9b**, respectively (Scheme 3). Not unexpectedly, **9b** did not undergo N-acylation with $ClCH_2COCl$ under mild conditions, presumably due to the quaternary carbon hindering the amino moiety and, at this stage, no further efforts were conducted on this substrate. In contrast, **9a** underwent smooth acylation to give chloroacetamide **10** that cyclized to *N*-sulfinyl-*N*′-benzyl monoketopiperazine **11** in excellent yield, often accompanied by small amounts of a desulfinylated product, tentatively assigned as imine **12**, presumably derived from **11** by enolate formation and elimination of the sulfur moiety. Treatment of **11** with NaH in refluxing THF afforded an excellent yield of imine **12** that was fully characterized.[19] We believe that **11** and **12** hold considerable potential for further selective manipulations at 'C-5' and 'C-6'.



Scheme 3 Synthesis of monoketopiperazines.[a] *Conditions*: (a) TBDMSCl, imidazole, cat. DMAP, CH_2Cl_2, r.t., 90 min; (b) $ClCH_2COCl$, EtOAc, sat. $NaHCO_3$, (1:1), 0 ºC to r.t., 2 h; (c) Cs_2CO_3, DMF, 65 ºC, 2 h; (d) NaH, THF, 0 ºC to reflux, 1 h.

In summary, readily available enantiopure *N*-sulfinyl-*N*′-benzyl diaminoalcohols have been expediently transformed into a variety of homochiral 2,3-disubstituted piperazines with adequate functionalization for subsequent transformations. In addition, a simple entry to more functionalized monoketopiperazines from the same precursors has been outlined. We are currently exploring the scope, limitations and further developments of the methodology.

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(14) The preparation of **1a–c** and **1f** was carried out following the procedures described in ref.[12b]; details will be published soon in a full account on this chemistry.

(15) (a) The treatment of enantiopure *N*-sulfinyloxazolidinones with lithium alkoxides results in clean inversion at sulfur to produce enantiopure sulfinate esters. See: Evans, D. A.; Faul, M. M.; Colombo, L.; Bisaha, J. J.; Clardy, J.; Cherry, D. *J. Am. Chem. Soc.* **1992**, *114*, 5977. (b) Synthesis of (+)-(5*R*,6*S*)-1-benzyl-5-ethyl-6-hydroxymethylpiperazin-2,3-dione, **2a**. From **1a** (416 mg, 1.20 mmol) in anhyd CH_2Cl_2 (6 mL/mmol) at r.t., with diethyl oxalate (0.98 mL, 7.20 mmol, 6 equiv) and 0.5 equiv of a solution of NaOMe in MeOH (0.3 M, 2 mL, 0.60 mmol) a crude product was obtained after standard extractive isolation. Purification by washing thoroughly the crude product with 90% Et_2O–hexane and chromatography (5% MeOH–CH_2Cl_2) of the mother liquor afforded 250 mg (0.95 mmol, 79%) of **2a** as a white solid. Data of **2a**: mp: 90–92 °C. R_f = 0.25 (12:1 CH_2Cl_2–MeOH). $[\alpha]^{20}_D$ +166.5 (*c* 1.19, MeOH). ^{1}H NMR (CD_3OD, 400 MHz): δ = 0.75 (t, 3 H, *J* = 7.5 H), 1.33 (m, 1 H), 1.55 (m, 1 H), 3.52 (m, 1 H), 3.61 (ddd, 1 H, *J* = 7.6, 5.0, 1.1 Hz), 3.87 (dd, 1 H, *J* = 11.2, 7.6 Hz), 3.96 (dd, 1 H, *J* = 11.2, 5.0 Hz), 4.25 (d, 1 H, *J* = 14.2 Hz), 5.53 (d, 1 H, *J* = 14.2 Hz), 7.57 (m, 5 H). ^{13}C NMR (DMSO-d_6, 50 MHz): δ = 10.4, 28.2, 49.2, 50.6, 58.0, 61.0, 128.5, 129.3 (2 C), 129.6 (2 C), 137.5, 157.4, 157.8. IR(film): 3413, 2928, 1665, 1454, 1117, 1052, 757, 705 cm^{-1}. MS (ES): 297 $[M + Cl]^+$ (100%). Anal. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 63.85; H, 7.04; N, 10.49.

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(17) Synthesis of (–)-(2*S*,3*R*)-1-benzyl-3-ethyl-2-hydroxymethylpiperazine, **4a**. From **2a** (188 mg, 0.713 mmol) in anhyd THF (10 mL/mmol) with 9 equiv of $BH_3{\cdot}SMe_2$ in THF (2 M, 3.21 mL, 6.417 mmol), after refluxing for 7 h, removal of the solvent and sequential treatment with 4 equiv of a 0.4 M HCl (30 min at 100 °C) and 6 equiv of a 0.4 M solution of NaOH (90 min at 0 ºC) a crude product was obtained after standard extractive isolation. Purification by chromatography (0–20% MeOH–Et_2O) afforded 123 mg (0.525 mmol, 75%) of **4a** as a colorless oil. Data of **4a**:

R_f = 0.10 (40% MeOH–Et_2O). $[\alpha]^{20}_D$ –14.1 (*c* 0.91, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.92 (t, 3 H, *J* = 7.3 Hz), 1.48 (sept, 1 H, *J* = 7.6 Hz), 1.72 (m, 1 H), 2.19 (m, 1 H), 2.29 (dt, 1 H, *J* = 9.9, 3.0 Hz), 2.70 (m, 1 H), 2.78-2.96 (m, 3 H), 3.29 (d, 1 H, *J* = 13.3 Hz), 3.65 (dd, 1 H, *J* = 11.7, 1.6 Hz), 4.02 (d, 1 H, *J* = 13.3 Hz), 4.05 (dd, 1 H, *J* = 11.8, 3.2 Hz), 7.26 (m, 5 H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 10.3, 25.1, 43.1, 50.5, 58.3, 59.1, 63.3, 127.0, 128.3 (2 C), 128.7 (2 C), 138.4. IR(film): 3306, 3057, 3021, 2958, 1490, 1452, 1027, 739, 699 cm^{-1}. MS (ES): 235 $[M + 1]^+$ (100%).

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(19) Synthesis of (+)-(5*R*,6*S*,S_S)-1-benzyl-6-[(*t*-butyldimethylsilyloxy)methyl]-5-ethyl-4-(*p*-tolylsulfinyl)piperazin-2-one, **11**. From **10** (315 mg, 0.59 mmol) in DMF (6 mL, 10 mL/mmol) at r.t., with 1.8 equiv of Cs_2CO_3 (340 mg, 1.04 mmol) at 65 °C (2 h) a crude product was obtained after standard extractive isolation. Purification by chromatography on silica gel (0–30% Et_2O–CH_2Cl_2) afforded 269 mg (0.54 mmol, 92%) of **11** as a white foam. Data of **11**: R_f = 0.27 (10% Et_2O–CH_2Cl_2). $[\alpha]^{20}_D$ +61.1 (*c* 1.10, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.07 (s, 3 H), 0.10 (s, 3 H), 0.54 (t, 3 H, *J* = 7.5 Hz), 0.90 (s, 9 H), 1.33–1.42 (m, 1 H), 1.75–1.83 (m, 1 H), 2.39 (s, 3 H), 3.08 (d, 1 H, *J* = 17.7 Hz), 3.26 (ddd, 1 H, *J* = 8.3, 5.3, 1.5 Hz), 3.66 (dd, 1 H, *J* = 9.8, 8.5 Hz), 3.71 (dd, 1 H, *J* = 9.7, 5.3 Hz), 3.75 (ddd, 1 H, *J* = 10.2, 4.7, 1.5 Hz), 3.80 (d, 1 H, *J* = 17.7 Hz), 3.84 (d, 1 H, *J* = 14.3 Hz), 5.33 (d, 1 H, *J* = 14.3 Hz), 7.24-7.33 (m, 7 H), 7.47 (d, 2 H, *J* = 8.1 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = –5.3, –5.2, 10.3, 18.1, 21.3, 22.5, 25.8 (3 C), 39.7, 48.6, 57.8, 59.1, 62.4, 125.6 (2 C), 128.0, 128.8 (2 C), 128.9 (2 C), 129.8 (2 C), 136.6, 139.3, 141.8, 165.5. IR(film): 2963, 2855, 1732, 1646, 1435, 1260, 1090, 1018, 799 cm^{-1}. MS (ES): 501 $[M + 1]^+$ (100%), 502 $[M + 2]^+$, 503 $[M + 3]^+$, 523 $[M + Na]^+$. Synthesis of (+)-(5*R*,6*S*)-1-benzyl-6-(*t*-butyldimethylsilyloxymethyl)-5-ethyl-5,6-dihydro-1*H*-pyrazin-2-one, **12**. From a cold (0 °C) suspension of 4 equiv of NaH in anhyd THF (5 mL/mmol of NaH), with a solution of **11** (72 mg, 0.144 mmol) in THF (5 mL/mmol) after stirring at r.t. (1 h) and at reflux (1 h), a crude product was obtained after standard extractive isolation. Purification by chromatography on silica gel (30–80% Et_2O–hexane) afforded 43 mg (0.119 mmol, 83%) of **12** as a colorless oil. Data of **12**: R_f = 0.38 (80% Et_2O–hexane). $[\alpha]^{20}_D$ +188.3 (*c* 1.23, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz**)**: δ = 0.05 (s, 6 H), 0.54 (t, 3 H, *J* = 7.4 Hz), 0.86 (s, 9 H), 0.86–0.98 (m, 1 H), 1.40–1.49 (m, 1 H), 3.27 (ap t, 1 H, *J* = 6.5 Hz), 3.55 (dd, 1 H, *J* = 10.2, 6.9 Hz), 3.63 (dd, 1 H, *J* = 10.2, 5.8 Hz), 3.78 (dd, 1 H, *J* = 7.7, 5.5 Hz), 3.92 (d, 1 H, *J* = 14.3 Hz), 5.34 (d, 1 H, *J* = 14.3 Hz), 7.26–7.34 (m, 5 H), 7.70 (d, 1 H, *J* = 1.5 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = –5.6, –5.5, 10.2, 18.1, 25.8 (4 C), 48.4, 55.2, 59.4, 63.0, 128.1, 128.8 (2 C), 129.1 (2 C), 136.1, 155.1 (2 C). IR(film): 3400, 3030, 2929, 2857, 1674, 1632, 1454, 1361, 1258, 1101, 908, 838, 804, 779, 704 cm^{-1}. MS (ES): 361 $[M + 1]^+$ (100%), 743 $[2 M + Na]^+$.