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# Synthesis of hexahydrochromeno[4,3-*b*]azepine derivatives

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**Abstract**—Synthesis of optically pure (6a*R*,11a*S*)-7,8,9,10,11,11a-hexahydro-5-oxa-11-azacyclohepta[*a*]naphthalen-6a-ylamine from 2-cyano-6-oxazolopiperidine is described via the CN(*R*,*S*) strategy. The lithium aluminium hydride involves a one-pot reduction and a ring-enlargement process. Absolute configuration of the tricyclic derivative is unambiguously established by X-ray crystal structure analyses. © 2003 Published by Elsevier Science Ltd.

## 1. Introduction

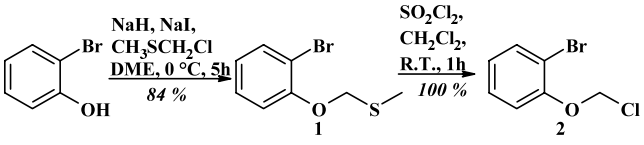
Several compounds owning the 3-aminochroman skeleton, synthesized in our laboratory, have shown a good affinity and a good selectivity toward the serotoninergic receptors 5-$HT_{1A}$ and 5-$HT_7$.[1] Due to the potential of 1,2-diamines[2] as medicinal agents, we were attracted to prepare compounds owning a 3-aminochromanic skeleton incorporating the 1,2-diamine functionality.

We report here the synthesis of (6a*R*,11a*S*)-7,8,9,10,11,11a-hexahydro-5-oxa-11-azacyclohepta[*a*]naphthalen-6a-ylamine derivatives achieved through the CN(*R*,*S*) strategy developed by Husson et al.[3]

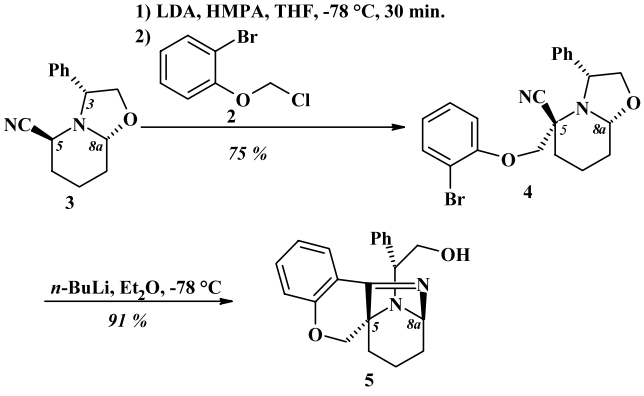
## 2. Results and discussion

The electrophile **2** was obtained in a two-step procedure starting from the commercially available 2-bromophenol. Then, action of sodium hydride on this phenol in solution in 1,2-dimethoxyethane followed by the addition of the chloromethylmethylsulfide led to the *O*,*S*-acetal **1** in 84% yield (Scheme 1). Compound **2** was obtained quantitatively from thiocompound **1** by action of sulfuryl chloride in dichloromethane at room temperature.

The stereoselective alkylation of the anion derived from (3*R*,5*S*,8a*R*)-2-cyano-6-phenyloxazolopiperidine **3**[4] with 1-bromo-2-(chloromethoxy)benzene **2** (LDA, THF, −78°C) led to the bromo derivative **4** (Scheme 2). This compound **4** was isolated as a single isomer in 75% yield after flash chromatography on silica gel. The absolute configuration at C-5 was (*S*) according to the CN(*R*,*S*) strategy.[3] Compound **4** was then involved in a




**Scheme 1.**




**Scheme 2.**

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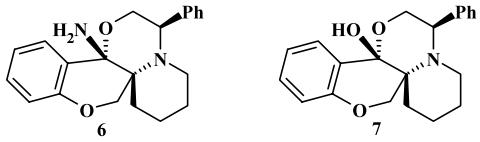
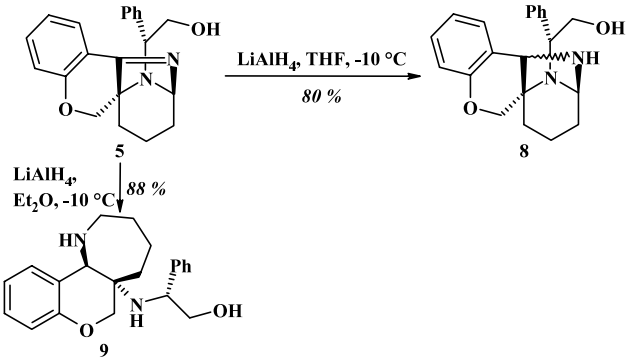
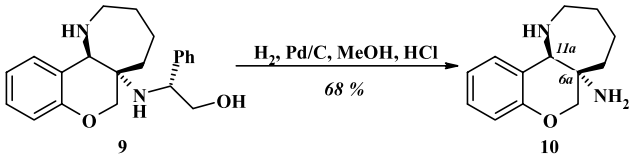


**Figure 1.** Reduction of imine **5** with $NaBH_3CN$.



**Scheme 3.**



**Scheme 4.**

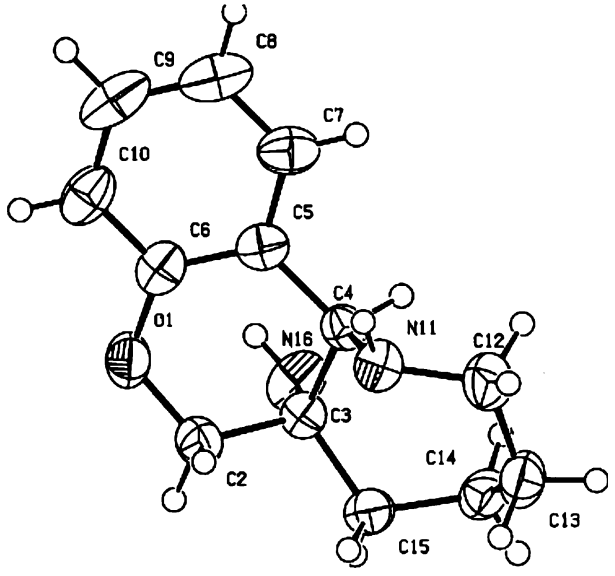


**Figure 2.** ORTEP diagram of diamine **10**.

halogen/metal exchange reaction using *n*-BuLi in THF at −78°C. The lithiated intermediate led to a single isomer of imine **5**, isolated in 91% yield.

According to the literature,[5] the formation of compound **5** can be explained by the attack of an intermediate imine salt on the potential iminium ion at C-8a. A narrow triplet, attributed to the bridgehead proton, was observed at $\delta$ 5.03 ($J=2.1$ Hz) in the $^1$H NMR spectrum of compound **5**.

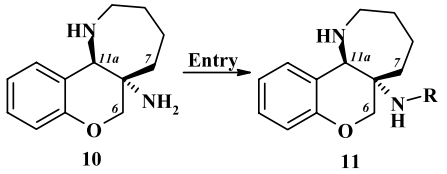
As shown in our previous paper,[1f] reduction of imine **5** with sodium cyanoborohydride in acidic conditions afforded hemiaminal **6** and/or hemiacetal **7** according to the chosen solvent (Fig. 1).

Different results were observed when the reduction of imine **5** was performed with lithium aluminium hydride. Although we still noticed an important influence of the solvent choice. Indeed, as shown in Scheme 3, when the reaction was performed in THF at −10°C, only reduction of the imine moiety into its corresponding amine function occurred, leading to a 65/35[6] diastereoisomeric mixture of compound **8** in 80% yield. On the other hand, when this sequence was realized in $Et_2O$ at −10°C, only diaminoalcohol **9**[7] was isolated in 88% yield. Such ring enlargement was recently discovered and explained by Husson et al. in a less constrained system.[8]

Finally, we had to cleave the chiral appendage. Thus, treatment of compound **9** under classical hydrogenolysis conditions furnished the desired diamine **10**[9] in 68% yield (Scheme 4).

The structure of the diamino derivative **10** was unambiguously established using X-ray crystallography (Fig. 2). The spatial group ($P2_1$) indicated that there is only one isomer. This result can be used, in conjunction with the previous datum concerning C-5 of compound **5**, to establish the (6a*R*,11a*S*) absolute configuration of **10**.

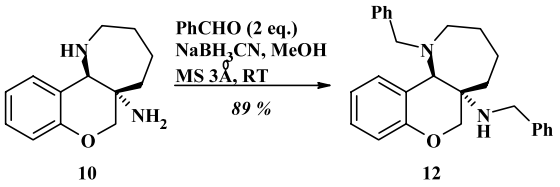
A preliminary study of the reactivity of the 1,2-diamino derivative **10** was achieved (Scheme 5). Thus, when **10** was treated with 1 equiv. of acetic anhydride in pyridine, only the amide **11a** was formed (Table 1, entry 1). With regard to the sulfonylation, two cases were considered. When the reaction was performed in methylene chloride with triethylamine and using 1 equiv. of sulfonyl chloride derivatives, a separable mixture of monosulfonamides on both positions was obtained in moderate yield. On the other hand, when the reaction was realized in pyridine using 1 equiv. of 4-bromoben-



**Scheme 5.**

**Table 1.** Synthesis of amide **11a** and sulfonamide **11b**

| Entry | Conditions | R | **11** |
|---|---|---|---|
| 1 | $Ac_2O$, pyridine | Ac | **11a** 87% |
| 2 | 4-$BrC_6H_4SO_2Cl$, pyridine | 4-$BrC_6H_4SO_2$ | **11b** 81% |




10 12

**Scheme 6.**

zenesulfonyl chloride only the mono-sulfonamide **11b** was isolated (entry 2).

Such results enlighten the influence of the experimental conditions on the behaviour of both amine centres towards these reactions. But at the present time, no explanation of this reactivity difference can be founded.

In order to prove the structure of compound **11**, the $^1$H NMR data of each compound could be consider. Indeed, the H-11a signal of compound **10** ($\delta = 3.29$ ppm) is very close to compounds **11** ($\delta = 3.39$ ppm). Moreover, the influence of the amide or sulphonyl group on the primary amine involves a downfield shift of one H-6 proton and one H-7 proton of compounds **11**. Let us take for example, the case of the amide **11a**. H-6 protons of this compound represent two doublets at $\delta = 3.83$ and $\delta = 4.66$ ppm. While for compound **10**, H-6 protons represent two doublet at $\delta = 3.31$ and $\delta = 3.64$ ppm. The same analysis can be carried out for the H-7 protons. Indeed, a H-7 proton of compound **11a** is moved of $\delta = 1.80$ ppm to $\delta = 2.59$ ppm. These observations indicate us that it is the primary amine function which reacts under these condition. For sulfonamide **11b**, the same remarks were observed.

A reductive amination of amine **10** was although performed. Benzaldehyde, molecular sieves, and sodium cyanoborohydride were added in a solution of **10** in methanol (Scheme 6). A separable mixture of mono- and dialkylated compounds was obtained when 1 equiv. of the aldehyde was used. On the other hand, when 2 equiv. of the reactant were used, only dialkylated derivative **12** was generated in 89% yield.

## 3. Conclusion

In conclusion, synthesis of (6a*R*,11a*S*)-7,8,9,10,11,11a-hexahydro-5-oxa-11-azacyclohepta[*a*]naphthalen-6a-ylamine **10** was performed in four steps via the CN(*R*,*S*) strategy in 41% overall yield, starting from the 2-cyano-6-phenyloxazolopiperidine **3**. The key step involved an one-pot reduction and a ring-enlargement process occurring in a highly regio- and stereoselective way. The absolute configuration of diamine **10** was unambiguously established by X-ray crystallography (Fig. 2). A preliminary study of the reactivity of this new diamine was realized.

## Supplementary Material

Analytical data for compounds **1**, **2**, **4**–**12** (this material is available from the author) and description of crystallographic methods. Further crystallographic data for the structure **10** have been deposited with the Cambridge Crystallographic Centre as supplementary publication number CCDC-205276. Copy of data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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## References

1. (a) Podona, C.; Guardiola-Lemaître, B.; Caignard, D.-H.; Adam, G.; Pfeiffer, B.; Renard, P.; Guillaumet, G. *J. Med. Chem.* **1994**, *37*, 1779–1793; (b) Usse, S.; Pavé, G.; Guillaumet, G.; Viaud-Massuard, M.-C. *Tetrahedron: Assymmetry* **2001**, *12*, 1689–1694; (c) Rezaie, R.; Joseph, B.; Bremner, J. B.; Delagrange, P.; Kopp, C.; Misslin, R.; Pfeiffer, B.; Renard, P.; Guillaumet, G. *J. Pharm. Pharmacol.* **2001**, *53*, 959–968; (d) Comoy, C.; Marot, C.; Podona, T.; Baudin, M.-L.; Morin-Allory, L.; Guillaumet, G.; Pfeiffer, B.; Caignard, D.-H.; Renard, P.; Rettori, M.-C.; Adam, G.; Guardiola-Lemaître, B. *J. Med. Chem.* **1996**, *39*, 4285–4298; (e) Usse, S.; Guillaumet, G.; Viaud, M. C. *J. Org. Chem.* **2000**, *65*, 914–917; (f) Pavé, G.; Léger, J.-M.; Jarry, C.; Viaud-Massuard, M.-C.; Guillaumet, G. *J. Org. Chem.* **2003**, *68*, 1401–1408.
2. Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580–2627 and references cited therein.
3. Husson, H.-P.; Royer, J. *J. Chem. Soc. Rev.* **1999**, *28*, 383–394 and references cited therein.
4. Bonin, M.; Grierson, D. S.; Royer, J.; Husson, H.-P. *Org. Synth.* **1992**, *70*, 54–58.
5. Froelich, O.; Desos, P.; Bonin, M.; Quirion, J.-C.; Husson, H.-P. *J. Org. Chem.* **1996**, *61*, 6700–6705.
6. Ratio determined by $^1$H NMR.
7. *Typical procedure for imine reduction. Preparation of* ***9***: to a suspension of $LiAlH_4$ (0.36 g, 9.6 mmol) at −10°C in diethylether (30 mL), imine **7** (0.4 g, 1.2 mmol) was added portionwise. After stirring for 18 h, the solution was hydrolyzed by NaOH (1N, 0.4 mL) and water (1.2 mL). The mixture was stirred again for 18 h and filtrated through celite pad. After concentration, the residue was purified by flash chromatography ($SiO_2$, $CH_2Cl_2$/MeOH 98:2) to furnish diaminoalcohol **9** as a white foam in 88% yield (0.36 g).
8. Cutri, S.; Bonin, M.; Micouin, L.; Froelch, O.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **2000**, *41*, 1179–1182.
9. Diamine (−)-**10**. Colourless crystal. mp = 74°C. MS: 219 $(M+1)^+$, 202 $(M-NH_2)^+$; $[\alpha]_D^{20} = -151$ (*c* 1.0, $CHCl_3$). $^1$H NMR (250 MHz, $CDCl_3$) ($\delta$, ppm; *J*, Hz): 1.31–1.87 (m,

9H), 2.94 (td, 1H, $J=12.2$, 2.8), 3.27 (d, 1H, $J=2.2$), 3.27–3.34 (m, 1H), 3.64 (dd, 1H, $J=10.7$, 2.2), 3.91 (d, 1H, $J=10.7$), 6.85 (d, 1H, $J=8.1$), 6.91 (td, 1H, $J=8.1$, 1.3), 7.12–7.22 (m, 2H); $^{13}$C NMR (62.5 MHz, $CDCl_3$, $\delta$, ppm): 20.8, 32.2, 37.1, 52.7, 53.0, 65.0, 70.8, 116.2, 120.7, 123.4, 128.2, 130.7, 152.8. Anal. calcd for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.28; H, 8.34; N, 12.97%.