Pergamon

Tetrahedron Letters 41 (2000) 1583–1587

TETRAHEDRON
LETTERS

Synthesis of enantiopure protected 3-hydroxy-4-amino pyrroline *N*-oxides

Stefano Cicchi, Paola Ponzuoli, Andrea Goti and Alberto Brandi *

Dipartimento di Chimica Organica 'U. Schiff', Università di Firenze, Centro di Studio C.N.R. sulla Chimica e la Struttura dei Composti Eterociclici e loro Applicazioni, Via G. Capponi 9, I-50121, Firenze, Italy

Received 4 October 1999; accepted 16 December 1999

Abstract

The synthesis of new five-membered enantiopure cyclic nitrones bearing protected *cis* vicinal amino and hydroxy functionalities is reported. The key step was a Mitsunobu reaction, which allowed placement of an azido group, with inversion of configuration, at the reacting centre. Cycloaddition of the novel nitrones to but-3-en-1-ol followed by simple elaboration of the adducts readily afforded protected amino dihydroxy indolizidines.

Keywords: nitrones; pyrrolidines; Mitsunobu reactions; cycloadditions.

Many indolizidine alkaloids act as powerful and selective inhibitors of glycosidases.[1] This biological activity has promoted considerable interest in the synthesis of these compounds and their analogues. Castanospermine, swainsonine, lentiginosine and their analogues are the most common targets of synthetic efforts (Fig. 1).[2]

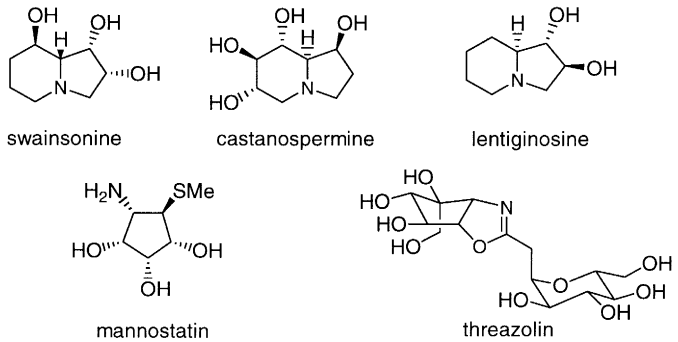


Fig. 1.

* Corresponding author. Fax: +0552476964; e-mail: brandi@chimorg.unifi.it (A. Brandi)

0040-4039/00/$ - see front matter
PII: S0040-4039(99)02335-7

Other natural products such as mannostatin[3] or threazolin[4] possess a similar activity towards glycosidases. Their common and most relevant feature is the presence of a *cis* vicinal aminoalcohol or -alkoxy functionality. This substitution pattern seems to play an important role in many biological processes since it is present in other active compounds.[5] Moreover, it is also necessary to form an oxazolidine that appears essential for biological activity.[6]

The introduction of this substitution pattern in a class of compounds, such as indolizidines, which already show inhibitory activity towards glycosidases becomes, then, an important synthetic goal for further bioactivity studies.

A useful approach to the synthesis of the indolizidine skeleton is offered by the 1,3 dipolar cycloaddition of five-membered cyclic nitrones **1** to but-3-en-1-ol **2** followed by simple transformations (Fig. 2).[7] In this communication we report the synthesis of new enantiopure five-membered cyclic nitrones **3** and **4** via a Mitsunobu reaction as the key step (Fig. 3). The new nitrones with a protected *cis* vicinal aminoalcohol functionality have been used in the synthesis of protected amino substituted dihydroxy indolizidines.

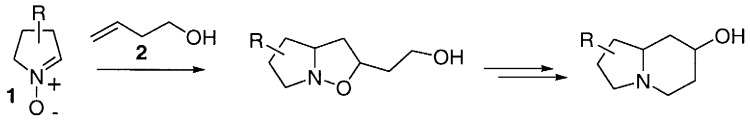


Fig. 2.

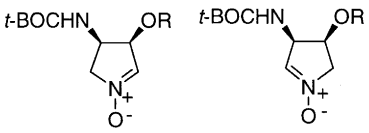
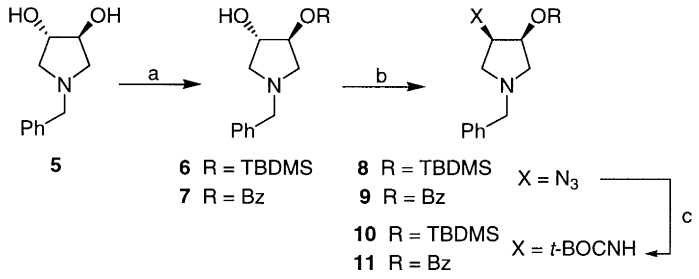


Fig. 3.

Commercially available (3*S*,4*S*)-*N*-benzyl-3,4-dihydroxypyrrolidine **5**, upon reaction with a substoichiometric amount of TBDMSCl or BzCl, afforded derivatives **6** and **7**, respectively, in quantitative yields, considering recycling of side products (Scheme 1).

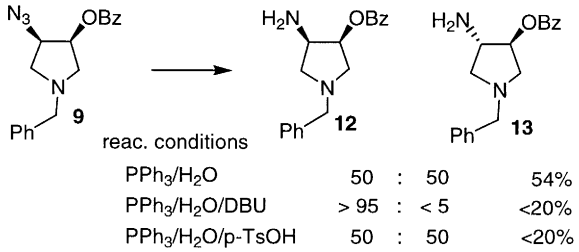


Scheme 1. (a) TBDMSCl (0.6 equiv.), imidazole, DMF (**6**, 60%) or benzoyl chloride (0.9 equiv.), NEt_3 (**7**, 90%); (b) DEAD, diphenylphosphorylazide, PPh_3 (**8**, 95%; **9**, 91%); (c) (i) H_2, Pd/C; (ii) $(t\text{-BOC})_2O$, NEt_3 (**10**, 63%; **11**, 45%)

The introduction of nitrogen at C4 with inversion of configuration was achieved by a Mitsunobu reaction with diphenylphosphorylazide, diethylazodicarboxylate and triphenylphosphine. Compounds **6** and **7** gave the azido derivatives **8** and **9** in excellent yield,[8] as single diastereoisomers. The inversion of configuration at C4 was ascertained by ^1H NMR analysis ($J_{H3–H4}$=6.3 Hz consistent with a *cis* relationship).[9]

However, reduction of the azido group in **9** to an amine under the standard conditions proved somewhat troublesome.

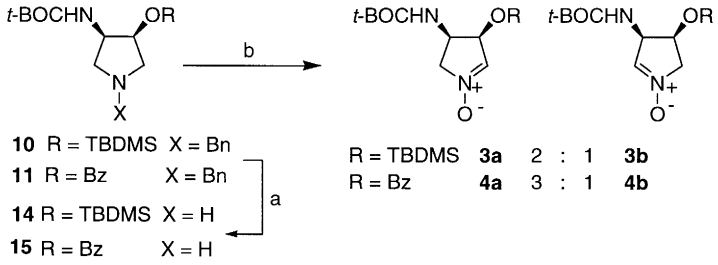
Under Staudinger conditions (PPh_3/H_2O)[10] **9** gave a mixture of two compounds in an equimolar ratio. Spectroscopic analysis allowed their characterization as amines **12** and **13**, with differing configuration at C4 (Scheme 2). Addition of an equimolar amount of a strong base such as DBU drove the reaction exclusively towards amine **12** that was, however, recovered in low yield. On the other hand, addition of *p*-toluenesulfonic acid had no effect on the ratio. A possible neighbouring group participation by the ring nitrogen atom cannot be ruled out although the experiment with *p*-toluenesulfonic acid and previous reports on similar substrates exclude this hypothesis in our case.[11] The benzoate group, in contrast to TBDMSO, might favour the deprotonation of the intermediate phosphorimine, causing the partial epimerization of the C-4 centre.



Scheme 2.

However, catalytic hydrogenation with Pd/C, gave the desired *cis* amines in good yield, and these were transformed into the corresponding crystalline *t*-BOC amides **10** and **11** (Scheme 1).[12]

X-Ray analysis of **11** confirmed the *cis* relationship of the substituents. Apparently the *cis*-benzoyloxy group induced the epimerization of the vicinal stereocentre during reduction of the azide. In fact, reduction of azido derivative **8** with the Staudinger method proceeded smoothly to the desired *cis* amine. Finally, debenzylation of *N*-benzyl pyrrolidines **10** and **11** afforded the secondary amines **14** and **15**, which were oxidized to the desired nitrones with *C*-phenyl-*N*-benzenesulfonyloxaziridine. As already reported for similar substrates, this reagent was the only one able to perform the oxidation without extensive decomposition of the pyrrolidine skeleton.[9,13] The oxidation reactions afforded, as expected, mixtures of regioisomeric nitrones whose structures were unambiguously assigned on the basis of their ^{1}H NMR spectra (Scheme 3).

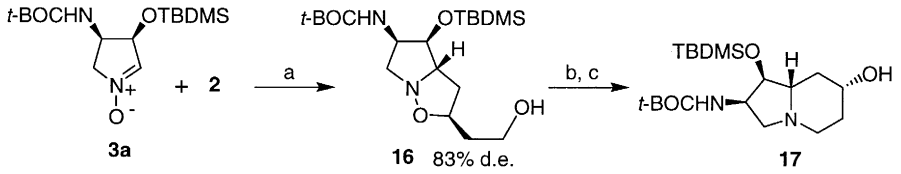


Scheme 3. (a) H_2, $Pd(OH)_2/C$, MeOH (95%); (b) *N*-benzenesulfonyl-*C*-phenyloxaziridine, rt, 2 h (**3a**–**b**, 50%; **4a**–**b**, 52%).

Although the effect is limited, the regioselectivity is higher for the benzoyloxy derivative confirming previous results obtained in the oxidation of 3-substituted *N*-hydroxypyrrolidines with mercury oxide and other oxidants.[14]

The cycloadditon of these nitrones to but-3-en-1-ol **2** afforded bicyclic isoxazolidines which were transformed into indolizidines.[9,14,15] The reaction with nitrone **3a**, easily separated from the regioisomer

by flash column chromatography, is reported in Scheme 4. The cycloaddition proceeded smoothly with complete regioselectivity and high stereoselectivity (d.e. 83%) (Scheme 4). The major cycloadduct **16** derives from an *anti–exo* approach of the dipolarophile to the nitrone.[13,15]



Scheme 4. (a) Benzene, 60°C, 3 days (89%); (b) methansulfonyl chloride, NEt_3, CH_2Cl_2, rt, 1 h; (c) Pd/C 5%, H_2 (1 atm), 12 h then Ambersep 700 (**17**, 65%)

Compound **16** was transformed into the target indolizidine by mesylation of the hydroxyl functionality followed by cyclization to the isoxazolidinium salt which underwent N–O bond cleavage to the desired indolizidine **17** by catalytic hydrogenation.[16]

In conclusion, the efficient synthesis of enantiopure, diversely functionalized, five-membered cyclic nitrones, useful synthons of amino polyhydroxy indolizidines, has been accomplished. Further applications are under investigation.

Acknowledgements

The authors thank M.U.R.S.T.-Cofin98 (Nuove Metodologie e Strategie di Sintesi di Composti di Interesse Biologico) for financial support. Dr. Cristina Faggi and Dr. Annalisa Guerri are acknowledged for X-ray crystallographic analysis. Degussa A.G. is gratefully acknowledged for a generous gift of enantiopure (3*S*,4*S*)-*N*-benzyl-3,4-dihydroxypyrrolidine **5**.

References

1. Elbein, A. D.; Molyneux, R. J. *In Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley-Interscience: New York, 1987; Vol. 5, chap. 1.
2. (a) Goti, A.; Cicchi, S.; Cordero, F. M.; Fedi, V.; Brandi, A. *Molecules* **1999**, *4*, 1–12, and references cited therein. (b) Elbein, A. D. *Ann. Rev. Biochem.* **1987**, *56*, 497–534. (c) Cossy, J.; Vogel, P. In *Studies in Natural Product Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: New York, 1993; Vol. 12, p. 275.
3. Aoyagi, T.; Yamamoto, T.; Koijiri, K.; Morishima, H.; Nagai, M.; Hamada, M.; Takeuchi, T.; Umezawa, H. *J. Antibiot*. **1989**, *42*, 883–889.
4. Nakayama, T.; Amachi, T.; Murao, S.; Sakai, T.; Shin, T.; Kenny, P. T. M.; Iwashita, T.; Zagroski, M.; Komura, H.; Nomoto, K. *J. Chem. Soc., Chem. Commun.* **1991**, 919–921.
5. Knapp, S. *Chem. Soc. Rev*. **1999**, *28*, 61–72, and references cited therein.
6. Ogawa, S. *Eur. Pat.* EP 0 713 873 A2, 1996.
7. (a) Tufariello, J. J.; Tegeler, J. J. *Tetrahedron Lett.* **1976**, 4037–4040. (b) Tufariello, J. J. *Acc. Chem. Res.* **1979**, *12*, 396–403.
8. Hughes, D. L. *Org. React*. **1992**, *42*, 335–669.
9. Cicchi, S.; Nunes Jr., J.; Goti, A.; Brandi, A. *Eur. J. Org. Chem*. **1998**, 419–421.
10. Knouzi, N.; Vaultier, Carrié, R. *Bull. Chem. Soc. Fr.* **1985**, 815–819.
11. Roesn, T.; Fesik, S. W.; Chu, D. T. W.; Pernet, A. G. *Synthesis* **1988**, 40–44.
12. For analogous racemic substrates, see: Naito, T.; Kakagawa, K.; Nakamura, T.; Kasei, A.; Ninomiya, I.; Kiguchi, T. *J. Org. Chem*. **1999**, *64*, 2003–2009.
13. McCaig, A. E.; Wightman R. H. *Tetrahedron Lett*. **1993**, *34*, 3939–3942.
14. Goti, A.; Cicchi, S.; Fedi, V.; Nannelli, L.; Brandi, A. *J. Org. Chem*. **1997**, *62*, 3119–3125.
15. Cicchi, S.; Goti, A.; Brandi, A. *J. Org. Chem*. **1995**, *60*, 4743–4748.

16. All new compounds were fully characterized: **3a**: $[\alpha]_D^{20}$=32.3 (*c* 0.82, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 6.82 (d, J=1.1 Hz, 1H), 5.16 (d, J=8.1 Hz, 1H), 4.83 (d, J=6.6 Hz, 1H), 4.56 (m, 1H), 4.07 (dd, J=13.9, 7.7 Hz, 1H), 3.91 (dd, J=13.9, 6.9 Hz, 1H), 1.42 (s, 9H), 0.89 (s, 9H), 0.1 (s, 3H), 0.09 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 155.1 (s), 134.0 (d), 80.1 (s), 71.12 (d), 65.8 (d), 48.4 (t), 28.2 (q, 3C), 25.5 (q, 3C), 18.1 (s), −4.8 (q), −5.2 (q); MS (70 eV): *m/z* 330 [M^+]; anal. calcd for $C_{15}H_{30}N_2O_4Si$: C, 54.51; H, 9.15; N, 8.48. Found: C, 54.27; H, 9.48; N, 8.18. **3b**: $[\alpha]_D^{20}$=−20.1 (*c* 0.82, $CHCl_3$); m.p. 96–97°C; ^{1}H NMR ($CDCl_3$): δ 6.76 (s, 1H), 5.07 (s, 1H), 4.55 (m, 1H), 4.10 (ddd, J=14.3, 4.8, 1.8 Hz, 1H), 3.75 (d, J=14.3 Hz, 1H), 1.43 (s, 9H), 0.88 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 154.9 (s), 133.5 (d), 80.4 (s), 71.12 (d), 69.9 (d), 67.7 (d), 55.2 (t), 28.2 (q, 3C), 25.5 (q, 3C), 17.9 (s), −5.0 (q), −5.3 (q); MS (70 eV): *m/z* 274 [M^+−56]; anal. calcd for $C_{15}H_{30}N_2O_4Si$: C, 54.51; H, 9.15; N, 8.48. Found: C, 54.76; H, 9.05; N, 8.85. **17**: $[\alpha]_D^{20}$=−40.6 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 5.15 (d, J=7.0 Hz, 1H), 4.08 (q, J=7.3 Hz, 1H), 3.82 (t, J=7.0 Hz, 1H), 3.66–3.43 (m, 2H), 2.96 (dt, J=11.4, 2.6 Hz, 1H), 2.18 (dt, J=11.4, 2.2 Hz, 1H), 2.04–1.82 (m, 4H), 1.60–1.35 (m, 2H), 1.40 (s, 9H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 155.6 (s), 79.1 (s), 74.6 (d), 69.3 (d), 67.7 (d,), 61.2 (d), 49.8 (t), 49.2 (t), 38.0 (t), 34.6 (t), 28.3 (q, 3C), 25.7 (q, 3C), 18.0 (s), −5.0 (q), −5.1 (q); MS (70 eV): *m/z* 387 [M^+]; anal. calcd for $C_{19}H_{38}N_2O_4Si$: C, 59.03; H, 9.91; N, 7.25. Found: C, 58.88; H, 10.19; N, 7.46.