Pergamon

Tetrahedron Letters 41 (2000) 4819–4822

TETRAHEDRON LETTERS

A new entry to hydroxylated pyrrolizidines

John K. Gallos,* Vassiliki C. Sarli, Theocharis V. Koftis and Evdoxia Coutouli-Argyropoulou

Department of Chemistry, Aristotle University of Thessaloniki, Thessaloniki 540 06, Greece

Received 23 March 2000; accepted 4 May 2000

Abstract

A short and efficient synthesis of (1*R*,2*S*,5*R*,8*S*)-5-hydroxymethyl-1,2-dihydroxypyrrolizidine **1**, by hetero-Diels–Alder addition of a nitrosoalkene to a pent-4-enofuranoside derived from D-ribose, followed by reductive opening of the oxazine ring formed, is reported.

Keywords: glycosidase inhibitors; D-ribose; hetero-Diels–Alder reaction; pyrrolizidine alkaloids; hydrogenation.

Natural pyrrolizidine alkaloids represent a structurally diverse group of compounds that display a broad spectrum of biological activities.[1] Many of them exhibit specific glycosidase inhibition, thus being potential anticancer and antiviral agents. Further to necines (with a hydroxymethyl group at the C-1 position), the more recently discovered family of alexine, australine, casuarine and related compounds, possessing a hydroxymethyl group at the C-3 carbon of the pyrrolizidine skeleton, have become popular synthetic targets.[2] We now report an efficient synthesis of enantiomerically pure **1**, which represents a novel route to polyhydroxylated pyrrolizidine alkaloids (Fig. 1).

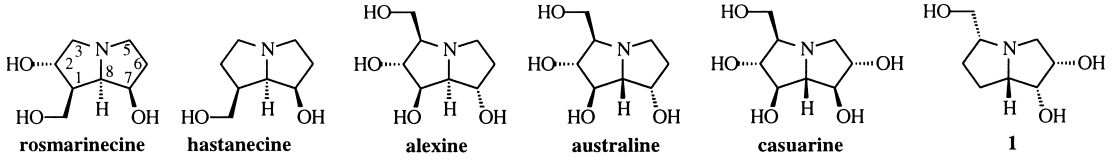


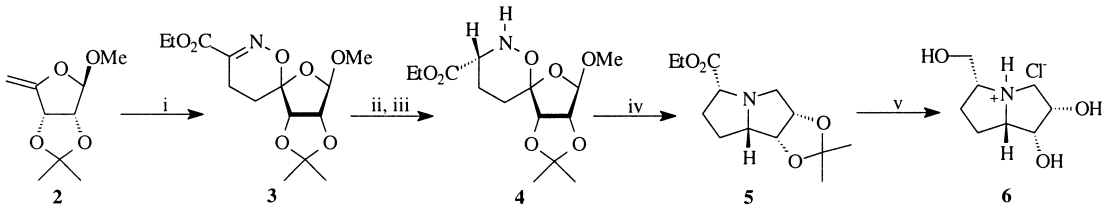
Figure 1.

Hetero-Diels–Alder addition of ethyl 2-nitrosoacrylate (prepared in situ from the oxime of ethyl bromopyruvate)[3] to pent-4-enofuranoside **2** (Scheme 1), readily available from D-ribose in three steps,[4] afforded cycloadduct **3** as a single diastereoisomer.[5] Although the absolute configuration

* Corresponding author. Fax: +31-997679; e-mail: igallos@chem.auth.gr

0040-4039/00/$ - see front matter
PII: S0040-4039(00)00732-2

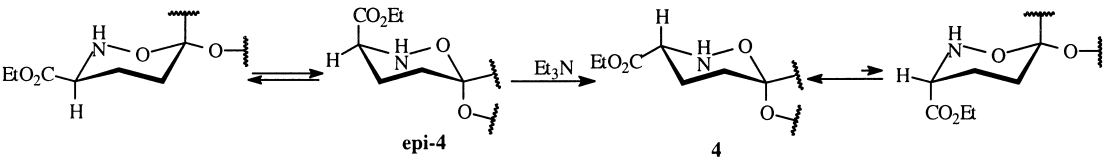
of the spiro-carbon in **3** could not be unequivocally assigned by the existing spectroscopic data, the given structure is the most probable, generated by the addition of the diene to the less hindered face of the double bond. Analogous structures have been assigned for the nitrile oxide cycloadducts to **2**.[4a]



Scheme 1. *Reagents and conditions*: (i) $BrCH_2C(NOH)CO_2Et$ (2 equiv.), aqueous Na_2CO_3 (5 equiv.), CH_2Cl_2, 20°C, 24 h, 64%; (ii) $NaCNBH_3$ (4 equiv.), AcOH glacial, 20°C, 24 h; (iii) $CHCl_3$, Et_3N (cat.), reflux, 30 min, 80%; (iv) Raney Ni, H_2, 1 atm, H_3BO_3 (20 equiv.), MeOH, $MgSO_4$, 20°C, 24 h, 64%; (v) $LiBH_4$ (5 equiv.), THF, 20°C, 24 h, then MeOH, HCl, 69%

Compound **3** was further reduced by $NaCNBH_3$ to a varying mixture of epimers depending upon the reaction time. Chromatographic separation of the mixture gave only the fast-moving product in pure form, the slow-moving one being always contaminated by the former, apparently because of partial isomerisation of the kinetic to the thermodynamic product either upon standing or in the column. Indeed, reflux of a solution of the mixture in $CHCl_3$ in the presence of Et_3N for 30 min caused quantitative conversion of the slow-moving to the fast-moving product.[5]

The absolute configuration of the newly formed stereocentre in product **4** was assigned in the next step. Having determined that the isolated product had the structure of **4**, the easy conversion of epi-**4** to **4** was explained, in which the oxazine ring adopting a chair-like conformation (Scheme 2) has the two *C*-substituents equatorial and the *O*-substituent axial, the last being favoured by the anomeric effect.

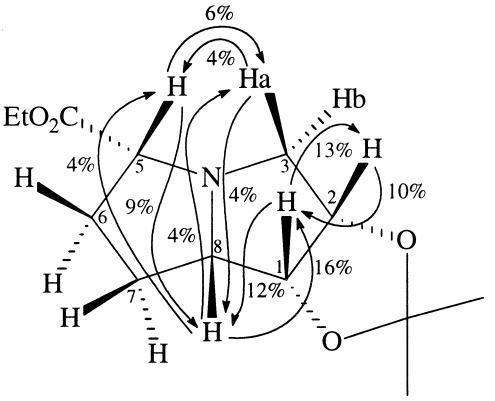


Scheme 2.

In the following step, Raney Ni hydrogenation of **4** in MeOH in the presence of 20 equivalents of H_3BO_3 gave **5** as the exclusive product in 64% yield (Scheme 1). It is apparent that the N–O bond cleavage by the hydrogenation triggered a sequence of tandem condensation–hydrogenation reactions, which led to **5**. Finally, reduction of the ester group in **5** with $LiBH_4$ in THF and further treatment with HCl yielded the desired pyrrolizidine as its hydrochloride **6**.[5]

The absolute configuration of the newly formed stereocentre in **5** was deduced from its ^1H NMR spectrum and the observed NOE enhancements. As depicted in Fig. 2, the mutual strong NOEs between 8-H and 1-H confirm their *cis*-arrangement. Furthermore, the significant NOEs observed among 3-Ha, 5-H and 8-H are indicative of their proximity, in agreement with the

proposed structure. The proton assignment in **5** was easily made by successive proton decouplings starting from the easily distinguishable signals of 1-H/2-H and 5-H protons.



5

Figure 2.

In conclusion, a new hydroxylated pyrrolizidine of the alexine family has been prepared from D-ribose in seven steps, utilising cheap and easily available reagents, applying simple and convenient methods. The high diastereoselectivity of the reductive cyclisation reaction is also worth noting. Further work in the synthesis of other pyrrolizidine or indolizidine analogues is in progress.

Acknowledgements

We are grateful to Dr. Alexandros E. Koumbis for the high resolution mass spectra.

References

1. (a) Rizk, A.-F. M. In *Naturally Occurring Pyrrolizidine Alkaloids*; CRC Press: Boca Raton, 1991. (b) Mattocks, A. R. In *Chemistry and Toxicology of Pyrrolizidine Alkaloids*; Academic Press: London, 1986. (c) Robins, D. J. *Nat. Prod. Rep.* **1990**, *7*, 377. (d) Robins, D. J. *Nat. Prod. Rep.* **1991**, *8*, 213. (e) Robins, D. J. *Nat. Prod. Rep.* **1992**, *9*, 313. (f) Robins, D. J. *Nat. Prod. Rep.* **1993**, *10*, 487. (g) Robins, D. J. *Nat. Prod. Rep.* **1994**, *11*, 613. (h) Liddell, J. R. *Nat. Prod. Rep.* **1996**, *13*, 187. (i) Liddell, J. R. *Nat. Prod. Rep.* **1997**, *14*, 653. (j) Liddell, J. R. *Nat. Prod. Rep.* **1998**, *15*, 363. (k) Liddell, J. R. *Nat. Prod. Rep.* **1999**, *16*, 499. (l) Hudlicky, T.; Seoane, G.; Price, J. D.; Gadamasetti, K. *Synlett* **1990**, 433. (m) Dai, W.-M.; Nagao, Y.; Fugita, E. *Heterocycles* **1990**, *30*, 1231. (n) Ibuka, T. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, 1987; Vol. 31, Chapter 6, p. 193. (o) Broggini, G.; Zecchi, G. *Synthesis* **1999**, 905. (p) Casiraghi, G.; Zanardi, F.; Rassu, G.; Pinna, L. *Org. Prep. Proced. Int.* **1996**, *28*, 641.
2. (a) Casiraghi, G.; Rassu, G.; Spanu, P. *Chemtracts: Org. Chem.* **1992**, *5*, 201, and references cited therein. (b) Denmark, S. E.; Martinborough, E. A. *J. Am. Chem. Soc.* **1999**, *121*, 3046. (c) Denmark, S. E.; Hurd, A. R. *Org. Lett.* **1999**, *1*, 1311. (d) de Vicente, J.; Arrayás, R. G.; Carretero, J. C. *Tetrahedron Lett.* **1999**, *40*, 6083, and references cited therein.

3. (a) Gilchrist, T. L.; Roberts, T. G. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1283. (b) Gilchrist, T. L. *Chem. Soc. Rev.* **1983**, *12*, 53. (c) Arnold, T.; Orschel, B.; Reissig, H.-U. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1033. (d) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1.
4. (a) Gallos, J. K.; Koftis, T. V.; Koumbis, A. E.; Moutsos, V. I. *Synlett* **1999**, 1289. (b) Hill, J. M.; Hutchinson, E. J.; Le Grand, D. M.; Roberts, S. M.; Thorpe, A. J.; Turner, N. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1483.
5. All new compounds gave spectral and analytical data consistent with the proposed structures. Compound **3**: oil, $[\alpha]_D$ +10.5 (*c* 1.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.34 (s, 3H), 1.36 (t, 3H, $J=6.7$ Hz), 1.49 (s, 3H), 1.86 (ddd, 1H, $J=13.3$, 11.6, 7.4 Hz), 2.17 (ddd, 1H, $J=13.3$, 7.3, 3.2 Hz), 2.57 (ddd, 1H, $J=14.7$, 11.6, 5.2 Hz), 2.70 (ddd, 1H, $J=14.7$, 7.4, 7.3 Hz), 3.30 (s, 3H), 4.33 (two dq as m, 2H), 4.73 (d, 1H, $J=5.9$ Hz), 4.93 (d, 1H, $J=5.9$ Hz), 5.06 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0, 18.4, 21.8, 24.7, 26.0, 55.1, 61.9, 83.3, 84.7, 108.1, 109.0, 112.9, 150.7, 163.2; HRMS (MALDI-FTMS) calcd ($C_{14}H_{21}NO_7Na$): 338.1210 (M+Na); found: 338.1220; σ: 3.0 ppm. Compound **4**: oil, $[\alpha]_D$ +46.3 (*c* 1.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.28 (t, 3H, $J=7.2$ Hz), 1.31 (s, 3H), 1.46 (s, 3H), 1.95 (m, 4H), 3.50 (s, 3H), 3.84 (br, 1H), 4.19 (q, 2H, $J=7.2$ Hz), 4.51 (d, 1H, $J=6.0$ Hz), 4.69 (d, 1H, $J=6.0$ Hz), 5.04 (s, 1H), 5.79 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 23.5, 24.8, 26.2, 27.2, 56.4, 58.5, 61.1, 83.6, 84.6, 108.5, 110.5, 112.7, 171.0; anal. calcd for $C_{14}H_{23}NO_7$: C, 52.99, H, 7.31, N, 4.41; found: C, 53.06, H, 7.46, N, 4.27. Compound **5**: oil, $[\alpha]_D$ +26.3 (*c* 0.34, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.28 (t, 3H, $J=7.1$ Hz), 1.34 (s, 3H), 1.55 (s, 3H), 1.63 (m, 1H), 1.94 (m, 1H), 2.26 (m, 2H), 2.52 (dd, 1H, $J=10.1$, 5.3 Hz), 2.83 (m, 1H), 2.97 (dd, 1H, $J=10.1$, 2.3 Hz), 3.22 (t, 1H, $J=8.0$ Hz), 4.19 (q, 2H, $J=7.1$ Hz), 4.51 (t, 1H, $J=5.1$ Hz), 4.86 (dt, 1H, $J=5.1$, 2.3 Hz); ^{13}C NMR ($CDCl_3$) δ 14.2, 21.2, 25.7, 26.5, 30.1, 53.6, 60.6, 61.4, 70.5, 77.6, 84.3, 112.7, 172.2; HRMS (MALDI-FTMS) calcd ($C_{13}H_{22}NO_4$): 256.1543 (M^++H); found: 256.1550; σ: 2.7 ppm. Compound **6**: oil, $[\alpha]_D$ –27.6 (*c* 0.4, MeOH); ^1H NMR (D_2O) δ 1.53 (m, 1H), 1.83 (m, 2H), 2.05 (m, 1H), 2.97 (t, 1H, $J=11.0$ Hz), 3.27 (dd, 1H, $J=9.9$, 6.1, Hz), 3.54 (m, 2H), 3.73 (d, 1H, $J=11.0$ Hz), 4.04 (m, 1H), 4.13 (m, 2H); ^1H NMR ($CDCl_3$/DMSO-d_6) δ 1.67 (m, 1H), 1.86 (m, 2H), 2.16 (m, 1H), 3.07 (m, 1H), 3.20 (m, 1H), 3.60 (m, 4H), 4.05 (m, 3H), 5.40 (br, 1H), 5.53 (br, 2H), 10.80 (br, 1H); ^{13}C NMR (DMSO-d_6) δ 23.1, 26.6, 47.3, 57.9, 65.0, 68.5, 69.4, 70.7; HRMS (MALDI-FTMS) calcd ($C_8H_{16}NO_3$): 174.1125 (M^++H); found: 174.1127l; σ: 1.1 ppm.