

Tetrahedron Letters 40 (1999) 4597-4600

TETRAHEDRON LETTERS

Synthesis of Polycyclic Indolic Structures

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Received 2 February 1999; revised 9 April 1999; accepted 12 April 1999

Abstract

We report the development of routes for the synthesis of three types of polycyclic indolic compounds, all possessing a tetrahydro- β -carboline sub-structure to which an additional 5- or 6-membered heterocycle is attached across the 1,2-positions of ring C; all three routes involve a Pictet-Spengler reaction as a key step, which can be used to control the stereochemistry of up to 5 chiral centres. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: indoles, polycyclic heterocyclic compounds, Pictet-Spengler reactions

Polycyclic indolic compounds continue to be the targets of extensive synthetic interest, partly because there are many biologically active natural products of this type, and also because the polycyclic frameworks lead to relatively rigid structures that might be expected to show substantial selectivity in their interaction with enzymes or receptors. For example, there have been over 2000 synthetic and medicinal papers on yohimbines 1a, and over 1500 on reserpines 1b in the 1990s alone. The reserpines and yohimbines primarily display cardiovascular and CNS activity; reserpine 2 is mainly used as a psychotic drug [1] or to treat hypertension [2], whilst the yohimbine alkaloid ajmalicine 3 is the strongest inhibitor known of cytochrome P-450 2D6 [3], and is produced commercially on a large scale [4]. Synthesis of yohimbines in general [5], and of reserpine [6] and ajmalicine [7] derivatives in particular, continues apace.



1b: X = carbon, reserpine skeleton One specific sub-structure that is

One specific sub-structure that is part of our current research programme is illustrated in Figure 1, and exemplified by structures 4-6 (c.f. compounds 7a-c, which were prepared by Lehmann *et al.* in 1994 [8] in racemic form). We report herein three independent routes to compounds of structural types 4-6, all starting from L-tryptophan, and providing access to a wide range of polycyclic indole targets in homochiral form.



In our first approach, we targetted the [6,5,6,5,6] ring system 4. Cook had previously shown that the condensation of L-tryptophan methyl ester (Trp-OMe) with 2-oxoglutaric acid could, under appropriate conditions, lead to Pictet-Spengler reaction, decarboxylation and lactamisation in a one pot reaction, generating 8 [9]. Similarly, when we used 2-carboxybenzaldehyde under conditions of refluxing toluene, we obtained the pentacyclic target 12 in 77% yield, as a 40:60 *cis:trans* mixture of diastereoisomers. Deprotonation at C(1) was found to be easy, due to the aromatic stabilisation of the anion; for example, alkylation with excess base/iodomethane gave the dimethylated product 13, notably as a single diastereoisomer, and with no alkylation at C(3) (Scheme 1).



Next, we targetted the [6,5,6,6,6] oxa system 5. For our targets, we hoped to condense 2-hydroxybenzaldehyde with Trp-OMe in a Pictet-Spengler reaction, but this reaction did not proceed under the typical mild conditions for the Mannich process, presumably because mesomeric stabilization of the aldehyde by the *o*-hydroxy group reduced its reactivity so much; indeed, Cook has reported that only fully aromatized products are formed from this reaction under various conditions [9].

We discovered, however, that if the reactants were stirred in dichloromethane with catalytic TFA in the presence of molecular sieves, then the imine 14 could be isolated in high yield. Subsequent acidification (excess TFA at -5°C) triggered cyclization in high yield, furnishing 15a/b in a 4:1 cis:trans ratio; the cis selectivity was in accordance with our previous work in this area [10], whilst room temperature reaction led to a 1:1 cis:trans ratio. After separating the stereoisomers of 15a/b by chromatography, treatment with triphosgene gave the desired pentacyclic targets 16a or 16b, although the yield from the cis-isomer 15a was much higher. Alternatively, the imine 14 could be treated directly with triphosgene giving stereomerically pure 16a, although the yield was poor (Scheme 2).



Scheme 2 Synthesis of the second type of target 5.

Finally, we wished to gain access to the [6,5,6,6] aza system 6. In previous studies, we had found that methyl 4-oxobutanoate underwent the Pictet-Spengler reaction to generate the adduct 19, presumably via the mechanism outlined in Scheme 3 [11]. If the enamine 17 were to attack an imine instead of an aldehyde, then the desired products should be readily accessed.



Scheme 3 Reaction of Trp-OMe with methyl 4-oxobutanoate [11].

To test the principle, (3,4-dimethoxyphenyl)ethanal was reacted with Trp-OMe, with the hope that the imine and enamine might be generated in equilibrium under acid catalysed conditions. This must presumably have been the case, for the Pictet-Spengler reaction generated adduct 22 as a single diastereoisomer (Scheme 4); reaction of 22 with triphosgene (Scheme 5) yielded 24 with the [6,5,6,6] system required, and allowed us to assign the stereochemistry as shown on Figure 2 (key J values and n.O.e.s are indicated).







It was notable that the expected [10] cis control in the Pictet-Spengler reaction (bond a for 20/21 in Scheme 4) actually led to complete diastereocontrol in this case. Molecular modelling indicated that there was considerable conformational flexibility in the final target 24, but the stereochemistry is consistent with a well defined 6-membered transition state as shown in Scheme 4 (structures 20/21, indicated by dotted bonds a,b,c) in which all substituents occupy equatorial positions of a chair-like intermediate. In general, if the Pictet-Spengler reaction proceeds *via* an imine/enamine equilibrium that lies substantially to the latter, trapping with a range of electrophiles should allow the rapid construction of complex indolic systems with complete stereochemical control.

In summary, we have developed routes to three types of polycyclic indolic systems (4-6), in all cases with high diastereocontrol; by starting from L-tryptophan, homochiral products of the yohimbine stereochemistry were accessed, whilst starting from Dtryptophan would allow entry to the epimeric reserpine series, and the methodologies should be applicable to a wide range of related targets.

We thank Dr. A.S.F. Boyd for NMR spectra; Dr. R. Ferguson for mass spectra; David de Leiris for additional studies; Zeneca Agrochemicals for funding.

References

- 2 Recent review: Siepmann M, Kirch W. Medizinische Klinik 1998;93;733.
- 3 Strobl GR, Vonkruedener S, Stöckigt J, Guengerich FP, Wolff T. J. Med. Chem. 1993;36:1136.
- 4 Fulzele DP, Heble MR. J. Biotech. 1994;35;1.
- 5 For example: a) Lee AWM, Chan WH, Mo T. Tetrahedron Lett. 1997;38:3001. b) Wender PA, Smith TE. J. Org. Chem.
- 1996;61:824. c) Lock R, Waldmann H. Tetrahedron Lett. 1996;37:2753. d) Aube J, Ghosh S, Tanol M. J. Am. Chem. Soc.
- 1994;116:9009. e) Jung YS, Mariano PS. Tetrahedron Lett. 1993;34:4611. f) Yamaguchi R, Hamasaki T, Sasaki T, Ohta T,
- Utimoto K, Kozima S, Takaya H. J. Org. Chem. 1993;58:1136. g) Waldmann H, Braun M, Weymann M, Gewehr M. Tetrahedron 1993;49:397. h) Gomezpardo D, Dangelo J. Tetrahedron Lett. 1992;33:6637. i) Meyers AI, Highsmith TK, Buonora PT. J. Org.
- Chem. 1991;56:2960. j) Baxter EW, Labaree D, Ammon HL, Mariano PS. J Am. Chem. Soc. 1990;112:7682.
- 6 For example:a) Mehta G, Reddy DS. J. Chem. Soc., Perkin Trans. 1 1998:2125. b) Hanessian S, Pan JW, Carnell A, Bouchard H, Lesage L. J Org. Chem. 1997;62:465. c) Chu CS, Liao CC, Rao PD. Chem. Commun. 1996:1537. d) Gomez AM, Lopez JC, Fraser-Reid B. J Org. Chem. 1995;60:3859. e) Gomez AM, Lopez JC, Fraser-Reid B. J Org. Chem. 1994;59:4048.
- 7 For example: a) Logers M, Overman LE, Welmalker GS. J. Am. Chem. Soc. 1995;1 17:9139. b) Martin SF, Clark CW, Corbett JW. J. Org. Chem. 1995;60:3236. c) Honda T, Haze N, Ishige H, Masuda K, Naito K, Suzuki Y. J. Chem. Soc., Perkin Trans. 1

1993:539. d) Hanessian S, Faucher AM. J. Org. Chem. 1991;56:2947.

8 Lehmann J, Nieger M, Witt T. Heterocycles 1994;38:511.

- 9 Soerens D, Sandrin J, Ungemach F, Mokry P, Wu GS, Yamanaka E, Hutchins L, DiPierro M, Cook JM. J. Org. Chem. 1979;44:535.
- 10 Bailey PD, Hollinshead SP, McLay NR, Morgan KM, Palmer SJ, Prince SN, Reynolds CD, Wood SD. J. Chem. Soc., Perkin Trans. 1 1993:431.
- 11 Bailey PD, McLay NR. J. Chem. Soc., Perkin Trans. 1 1993:441.

¹ Recent review: Bennett MR. J. Psychopharm. 1998;12:289.