Functionalised (±)-Cephalotaxine Analogues

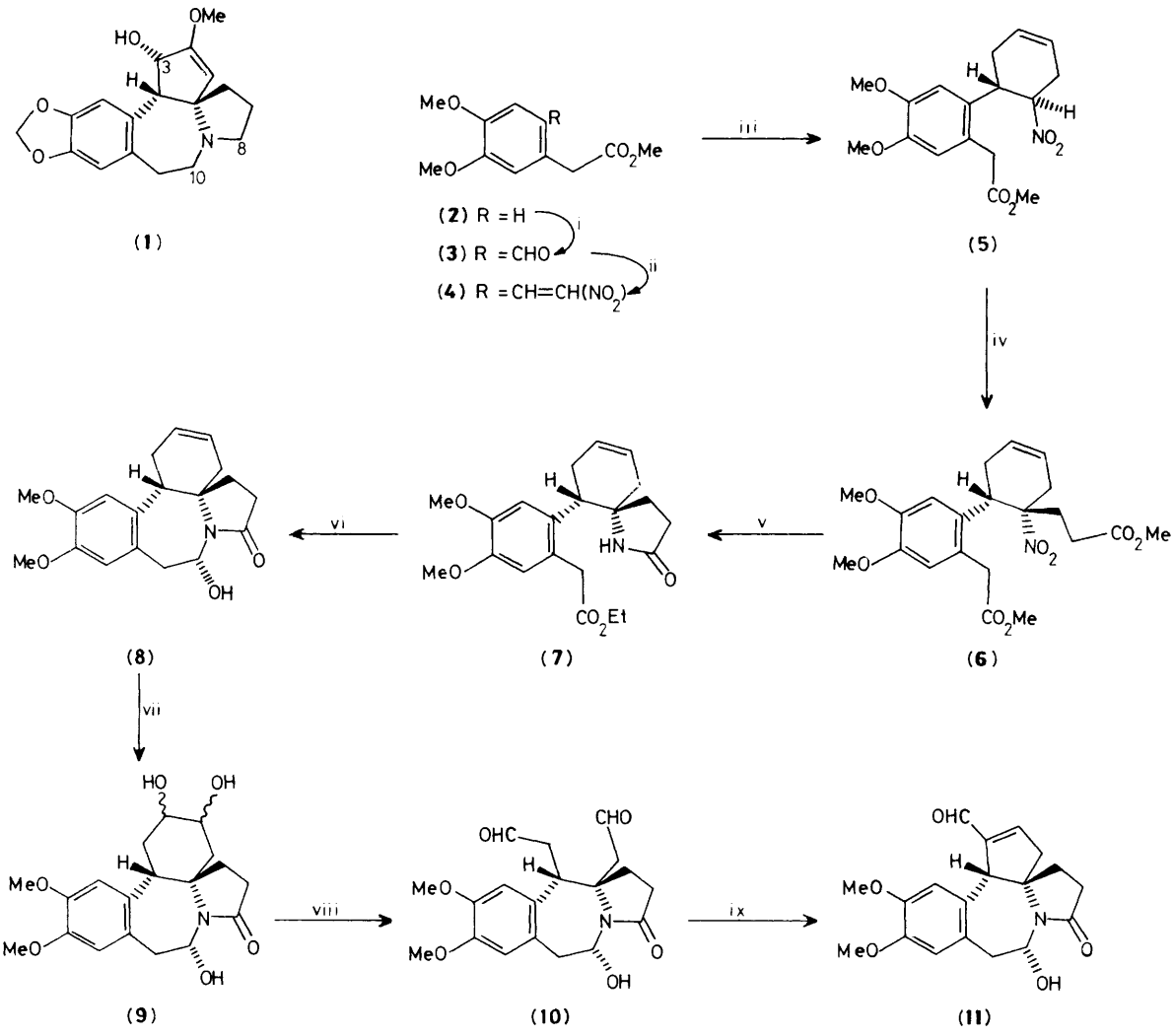
Martin R. Bryce* and John M. Gardiner

Department of Chemistry, University of Durham, South Road, Durham DH1 3LE, U.K.

A novel approach to functionalised analogues of Cephalotaxine is described; the fused azaspirocyclic skeleton (**11**) has been constructed stereospecifically in nine steps (overall yield 15%) starting from 3,4-dimethoxy-carbomethoxymethyl-benzene.

The alkaloid Cephalotaxine (**1**) is attracting keen attention due to antileukaemic properties of C-3 ester derivatives (Harringtonines) which are currently undergoing phase II clinical trials.[1] Five syntheses of (±)-Cephalotaxine (**1**) have been reported, three of them very recently.[2] Interest is now turning towards modified ring systems, *e.g.* with methoxy groups replacing the methylenedioxy ring A,[2c] and more highly substituted analogues: notably, hydroxy- and oxo-derivatives have been identified as important targets.[2d] We now describe a novel, stereospecific approach to this family of alkaloids that provides oxidised analogues of (**1**), that are suitable for further elaboration into a wide range of derivatives (Scheme 1).

3,4-Dimethoxy-carbomethoxymethyl-benzene (**2**) was formylated by reaction with α,α-dichloromethyl methyl ether in the presence of aluminium trichloride to yield compound (**3**), which was converted into the nitro-alkene (**4**) on reaction with the nitromethane anion. Cycloaddition of butadiene, derived from butadiene sulphone, to compound (**4**) afforded nitrocyclohexene derivative (**5**). Michael addition of methyl acrylate to the anion of compound (**5**) occurred stereospecifically, owing to the steric bulk of the aryl group, and yielded a single product (**6**), which had the relative stereochemistry indicated.[3] Nitro-diester (**6**) was then reductively cyclised, using zinc in ethanolic hydrochloric acid, to furnish spiro-γ-lactam (**7**), with concomitant *trans*-esterification of the ester group. The lactam carbonyl absorption (ν_{max} 1690 cm^{-1}) was consistent with γ-lactam structure (**7**), rather than the isomeric ε-lactam structure. Treatment of lactam-ester (**7**) with di-isobutyl aluminium hydride yielded the benzazepinol deriva-



Scheme 1. *Reagents, conditions, and % yields*: i, Cl_2HCOMe, $AlCl_3$, CH_2Cl_2, −10 °C → room temp., 85%; ii, $MeNO_2$, K_2CO_3, $MeNH_3^+Cl^-$, MeOH, 20 °C, 74%; iii, butadiene sulphone, hydroquinone, PhMe, 135 °C, 74%; iv, CH_2=$CHCO_2Me$, Triton B, tetrahydrofuran–t-butanol, 20 °C, 87%; v, Zn, HCl, EtOH, reflux, 90%; vi, Diisobutylaluminium hydride (DIBAL-H), CH_2Cl_2–PhMe, −78 °C → room temp., 91%; vii, OsO_4, *N*-methylmorpholine oxide, t-butanol–acetone, room temp., 66%; viii, HIO_4, MeOH, 3 h, 85% (crude); ix, basic Al_2O_3 column, eluent $CHCl_3$, 68% [from (**9**)].

tive (**8**) [ν_{max} 3280 (OH, sharp) and 1670 (C=O) cm^{-1}]. All spectroscopic and t.l.c. evidence indicated the cyclised product (**8**) to be of a single relative stereochemistry. Single crystal *X*-ray analysis confirmed structure (**8**),[4] which, due to the earlier stereospecific Michael addition [(**5**) → (**6**)], has the correct relative stereochemistry at the spiro centre that is required for Cephalotaxine analogues. Furthermore, the cyclisation step (**7**) → (**8**), is stereospecific in construction of the new stereocentre.

In principle, many methods are available for conversion of the cyclohexene ring of (**8**) into a cyclopentene or cyclopentane ring. We have achieved this contraction by hydroxylation of compound (**8**) using osmium tetraoxide-*N*-methylmorpholine oxide[5] to yield *cis*-diol (**9**) (relative stereochemistry of the hydroxylation unconfirmed) followed by periodate cleavage of diol (**9**) to afford dialdehyde (**10**) [$\delta_H(CDCl_3)$ 9.8 (2H, s, CHO)]. Product (**10**) was not purified, but passed directly down a column of basic alumina to yield a single product for which analytical and spectroscopic data were consistent with structure (**11**): notably, $\delta_C(CDCl_3)$, 200.1 and 177.1 (aldehyde and lactam C=O, respectively); $\delta_H(CDCl_3)$, 9.82 (1H, s, CHO), 5.41 [1H, m, *J* 7.6 Hz, -C*H*=C(CHO)], 3.40 [1H, m, benzylic H]; ν_{max} 3280 (OH, sharp), 1690 (α,β-unsaturated aldehyde), 1670 (lactam C=O) cm^{-1}. Decisive evidence in favour of product (**11**) over the possible isomeric aldol product is provided by the n.m.r. spectroscopic data for the benzylic proton which has shifted significantly downfield by 0.6 p.p.m. in compound (**11**) [*cf.* δ_H 2.8 (1 Ht, *J* 7.7 Hz) for compound (**8**)] consistent with the aldehyde and alkene functionality on the adjacent carbon. Furthermore, the benzylic proton in compound (**11**) shows only long range couplings with no coupling observed to an adjacent hydrogen [*cf.* data for compound (**8**)]. Regioselectivity in the intramolecular aldol reaction of dialdehyde (**10**), in favour of product (**11**) is clearly expected from steric considerations of compound (**10**), and from literature precedents for related dialdehyde systems.[6]

In conclusion, we have established efficient methodology for the stereospecific construction of the fused azaspirocyclic

skeleton of Cephalotaxine bearing oxygenated functionality at C-8 and C-10. The overall yield for the nine-step conversion of compound (**2**) into compound (**11**) is 15%. The way is now open to attach the ester side-chain, which is responsible for the biological activity of Harringtonine, to new positions, *e.g.* C-10 of the Cephalotaxine skeleton.

We thank the North of England Cancer Research Campaign for the award of a studentship (to J. M. G.).

Received, 29th December 1988; Com. 8/05024D

References

1 T. Hudlicky, L. D. Kwart, and J W. Reed, 'Alkaloids: Chemical and Biological Perspectives,' ed. S. W. Pelletier, Wiley, New York, 1987, vol. 5, 639; P. J. O'Dwyer, S. A. King, D. F. Hoth, M. Suffness, and B. Leyland-Jones, *J. Clin. Oncol.*, 1986, **4**, 1563; J. A. Neidhart, D. C. Young, E. Kraut, B. Howinstein, and E. N. Metz, *Cancer Res.*, 1986, **46**, 967; C. T. C. Tan, E. Luks, D. M. Bacha, P. Steinherz, L. Steinherz, and A. Mondora, *Cancer Treat. Rep.*, 1987, **71**, 1245.

2 (a) S. M. Weinreb and J. Auerbach, *J. Am. Chem. Soc.*, 1975, **97**, 2503; (b) M. F. Semmelhack, B. P. Chong, R. D. Stauffer, T. D. Rogerson, A. Chong, and L. D. Jones, *ibid.*, 1975, **97**, 2507; (c) S. Yasuda, T. Yamada, and M. Hanaoka, *Tetrahedron Lett.*, 1986, **27**, 2023; (d) T. P. Burkholder and P. L. Fuchs, *J. Am. Chem. Soc.*, 1988, **110**, 2341; (e) M. E. Kuehne, W. E. Bormann, W. H. Parsons, T. D. Spitzer, J. F. Blount, and J. Zubieta, *J. Org. Chem.*, 1988, **53**, 3439.

3 *Cf.* M. R. Bryce, J. M. Gardiner, M. B. Hursthouse, and R. L. Short, *Tetrahedron Lett.*, 1987, **28**, 577; R. K. Hill, S. Sawada, M. G. Bock, and J. R. Greene, *Heterocycles*, 1987, **25**, 515.

4 Structure solved by P. Bates and M. B. Hursthouse. Details will be published separately.

5 V. Van Rheenen, R. C. Kelly, and D. Y. Cha, *Tetrahedron Lett.*, 1976, 1973.

6 T. Harayama, M. Ohtani, M. Oki, and Y. Inubushi, *J. Chem. Soc., Chem. Commun.*, 1974, 827.