Pergamon

Tetrahedron Letters, Vol. 38, No. 33, pp. 5869-5872, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01306-3

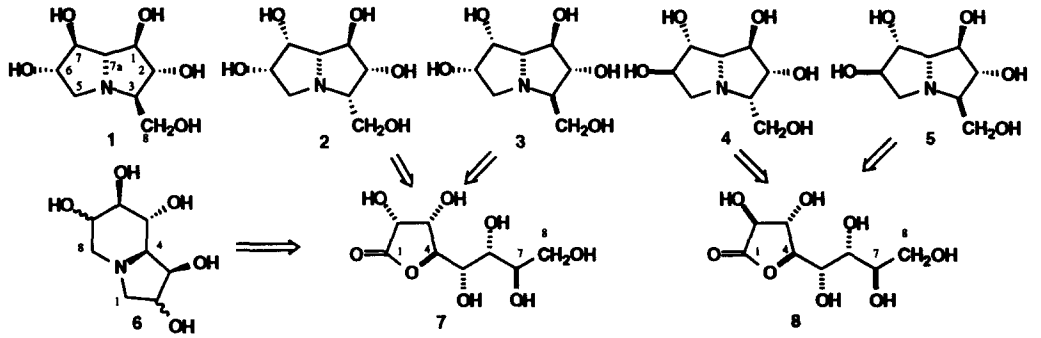
Synthesis of Casuarines [Pentahydroxylated Pyrrolizidines] by Sodium Hydrogen Telluride-Induced Cyclisations of Azidodimesylates

Andrew A. Bell,[a] Lea Pickering,[a] Alison A. Watson,[a,b] Robert J. Nash,[b] Yuan T. Pan,[c] Alan D. Elbein [c] and George W. J. Fleet[a]*

[a]Dyson Perrins Laboratory, Oxford Centre for Molecular Sciences, South Parks Road, Oxford OX1 3QY UK
[b]Institute of Grassland and Environmental Research, Plas Gogerddan, Aberystwyth, Cardiganshire SY23 3EB UK
[c]University of Arkansas for Medical Sciences, Department of Biochemistry & Molecular Biology, 4301 West Markham, Little Rock, Arkansas 72205, USA

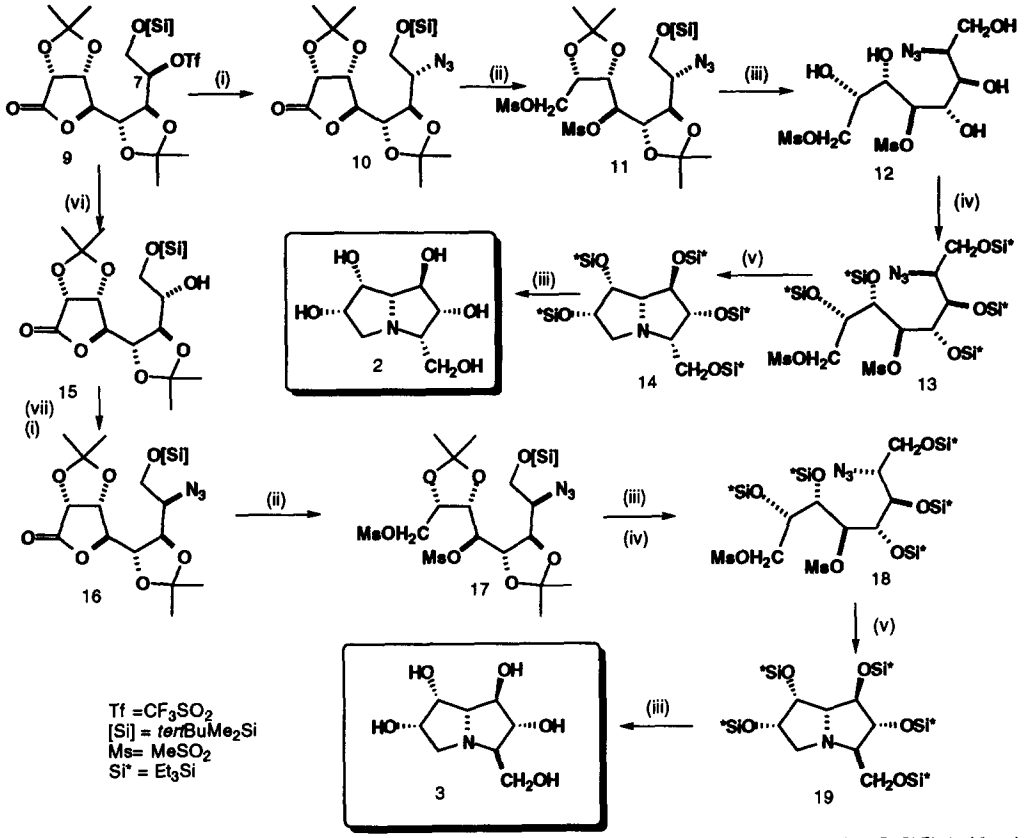
Abstract: The key step in the synthesis of four diastereomers of casuarine from eight carbon sugar lactones is the efficient reduction of open chain azidodimesylates by sodium hydrogen telluride [Suzuki-Takaoka reduction] to allow the formation of the pyrrolizidine nucleus by bicyclisation. This is the first report of the synthesis of such highly oxygenated pyrrolizidines.

A wide range of both naturally occurring[1] and synthetic[2,3] nitrogen analogues of carbohydrates cause inhibition of glycosidases and other enzymes[4] with the potential of controlling individual steps of carbohydrate metabolism.[5] Casuarine **1**,[6] the most highly oxygenated bicyclic sugar mimic yet isolated, and its 6-*O*-glucoside occur in the bark of *Casuarina equisetifolia* (Casuarinaceae) which has been prescribed for the treatment of cancer in Western Samoa. Casuarine also occurs as the major alkaloid both in the leaves and bark of *Eugenia jambolana* (Myrtaceae), traditionally used for treating diabetes in India, and also in an unidentified African plant reputed to be beneficial in treating AIDS patients.[7] Casuarine is a potent inhibitor of glucosidase I (72% inhibition at 5 μg/ml), being only slightly less active than castanospermine (82% inhibition at 5 μg/ml).[8] Casuarine **1**, however, has no effect on glycoprotein processing in cultured cells, probably due to its porr uptake; in contrast, castanospermine is effective at 50 - 100 μg/ml. Because of possible differences in absorbtion and activity in various cells, casuarine or its butanoylated derivatives may have interest in the study of possible approaches to the treatment of cancer and AIDS.[9] Although casuarine is the major isomer present, it is clear from examination of plant extracts that several other very highly oxygenated pyrrolizidines and related compounds are also present; in particular a diastereomer of casuarine occurs as a minor component in the African plants used by AIDS patients. The unambiguous synthesis of diastereomers of **1** may allow the determination of the structure of natural products in complex mixtures from which it would be very difficult to obtain pure samples, as well as giving samples for the unequivocal determination of the biological properties of such materials.



As yet, no reports of the synthesis of casuarine or of any of its diastereomers have appeared. The octonolactones **7** and **8**[10] have been used in the synthesis of the four diastereomeric hydroxycastanospermines **6** by joining C-1, C-4 and C-8 together by nitrogen.[11] This paper reports the synthesis of pure samples of the diastereomers of casuarine **2** - **5** from **7** and **8** by connecting together with nitrogen, with control of the stereochemistry by S_N2 reactions, C-1, C-4 and C-7. The key step in these syntheses required the reduction of protected azidodimesylates to the corresponding amines in order to construct both rings of the pyrrolizidine

nucleus efficiently and cleanly from an open chain precursor. While hydrogenation of the azides gave low yields, the Suzuki-Takaoka sodium hydrogen telluride reduction of azides,[12] followed by *in situ* treatment of the amines with sodium acetate, gave excellent yields of the bicyclic products.

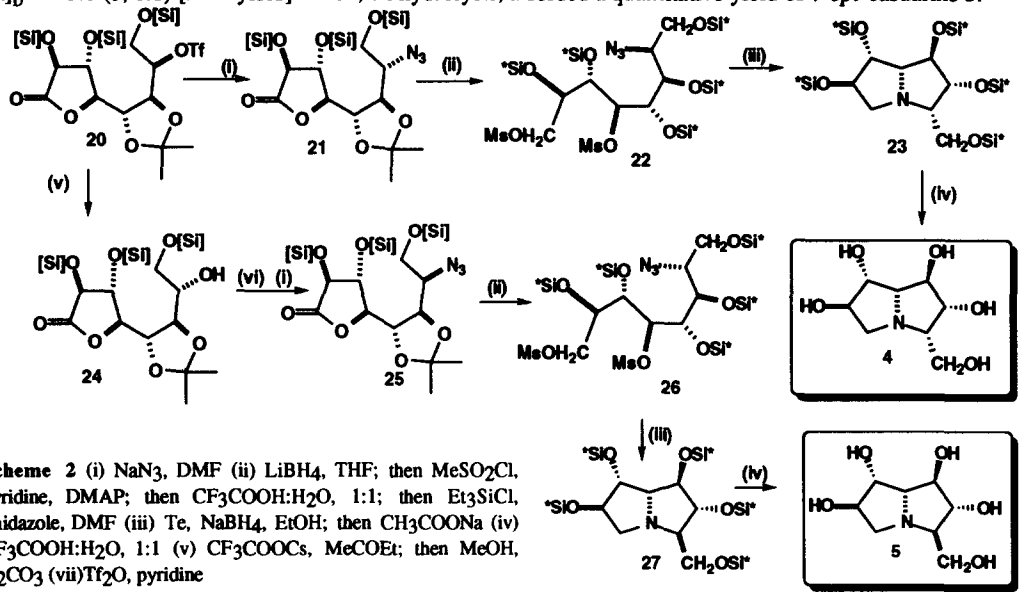


Scheme 1 (i) NaN_3, DMF (ii) $LiBH_4$, THF; then $MeSO_2Cl$, pyridine, DMAP (iii) $CF_3COOH:H_2O$, 1:1 (iv) Et_3SiCl, imidazole, DMF (v) Te, $NaBH_4$, EtOH; then CH_3COONa (vi) CF_3COOCs, MeCOEt; then MeOH, K_2CO_3 (vii) Tf_2O, pyridine, CH_2Cl_2

The ready availability[11] of the crystalline triflate [m.p. 80-81°C, $[\alpha]_D^{24}$ -12.2 (*c*, 0.72)][13] **9** allows manipulation of both the stereochemistry and functionalisation at C-7 of the octonolactone **7**. For the synthesis of 3,7-*diepi*-casuarine **2** reaction of the triflate **9** with sodium azide in DMF gave the inverted azide **10**, $[\alpha]_D^{23}$ +21.9 (*c*, 0.62) in 96% yield. Reduction of the lactone **10** with lithium borohydride in THF, followed by esterification of the resulting diol with methanesulfonyl chloride, gave the protected azidodimesylate **11**, $[\alpha]_D^{22}$ -15.5 (*c*, 0.97) in 80% yield. Reduction of **11** with palladium and hydrogen gave an aminomesylate; however, it was not possible to cyclise this aminomesylate since the resulting first pyrrolidine ring formed would contain a *trans*-acetonide, so that in this and all the other cases in this paper, it was necessary to remove the ketal protecting group prior to cyclisation. Subsequent removal of both the silyl and ketal protecting groups in **11** by acid hydrolysis afforded **12**, $[\alpha]_D^{23}$ -7.7 (*c*, 0.77, H_2O), in 90% yield. Hydrogenation of **12** with palladium black in water followed by treatment of the resulting amine with sodium acetate gave **2** in good 97% yield, but together with a small amount of an impurity [as judged by GC of the pertrimethylsilylated ethers]. In our hands, we were unable to remove this impurity. Although this reduction of **12** gave mostly one bicyclic product, that was not the case for some of the other isomers of **12** in this paper; so, in order to prepare pure samples of these very highly oxygenated and polar materials it was decided to protect all the hydroxyl groups in **12** as the corresponding triethylsilyl ethers. Accordingly, treatment of **12** with chlorotriethylsilane in DMF

in the presence of imidazole gave the pentatriethylsilyl ether **13**, $[\alpha]_D^{22}$ -7.8 (*c*, 0.97) in 45% yield. All attempts to reduce the fully protected azide **13** by catalytic hydrogenation proceeded in low yield, probably due to steric hindrance from the adjacent silyl ethers. However, reduction of **13** by the Suzuki-Takaoka sodium hydrogen telluride procedure, followed by treatment with sodium acetate in ethyl acetate, gave the doubly cyclised fully protected pyrrolizidine **14**, $[\alpha]_D^{23}$ -12.5 (*c*, 1.35) in 84% yield. Removal of the triethylsilyl ethers in **14** with aqueous trifluoroacetic acid and subsequent ion-exchange chromatography gave 3,7-*diepi*-casuarine **2**[14] in quantitative yield.

For the synthesis of **3**, it is necessary to introduce nitrogen with retention of configuration at C-7 of **7**. Reaction of the triflate **9** with cesium trifluoroacetate[15] in butanone, followed by methanol and potassium carbonate, gave the inverted alcohol **15**, $[\alpha]_D^{22}$ +1.4 (*c*, 0.74) [66% yield]. Esterification of the free hydroxyl group in **15** with triflic anhydride in dichloromethane in the presence of pyridine, followed by treatment with sodium azide in DMF, gave the azide **16**, $[\alpha]_D^{21}$ -6.8 (*c*, 0.91) [71% yield]. Reduction of the lactone **16**, with subsequent mesylation, gave the dimesylate **17**, $[\alpha]_D^{23}$ -28.1 (*c*, 0.16), in 69% yield. Removal of the protecting groups in **17** by acid hydrolysis, followed by pertriethylsilylation, afforded **18**, $[\alpha]_D^{22}$ -20.8 (*c*, 0.73), in 56% yield. Suzuki-Takaoka reduction and subsequent cyclisation of **18** gave the readily purified **19**, $[\alpha]_D^{22}$ +13.8 (*c*, 0.8) [92% yield] which, on hydrolysis, afforded a quantitative yield of 7-*epi*-casuarine **3**.[16]



Scheme 2 (i) NaN_3, DMF (ii) $LiBH_4$, THF; then $MeSO_2Cl$, pyridine, DMAP; then $CF_3COOH:H_2O$, 1:1; then Et_3SiCl, imidazole, DMF (iii) Te, $NaBH_4$, EtOH; then CH_3COONa (iv) $CF_3COOH:H_2O$, 1:1 (v) CF_3COOCs, MeCOEt; then MeOH, K_2CO_3 (vii)Tf_2O, pyridine

The synthesis of the two casuarine diastereomers from the lactone **8** is shown in Scheme 2. The triflate **20**, $[\alpha]_D^{22}$ +10.8 (*c*, 1.05), obtained in 95% yield by esterification of the corresponding alcohol with triflic anhydride in dichloromethane in the presence of pyridine, is the key intermediate in the synthesis of the pyrrolizidines **4** and **5** from **8**. Treatment of **20** with sodium azide in DMF afforded the azide **21**, $[\alpha]_D^{22}$ +33.7 (*c*, 2.13) in 86% yield. Reduction of **21** with lithium borohydride, subsequent mesylation, complete removal of the silyl ether and isopropylidene protecting groups by acid, and reprotection by pertriethylsilylation, gave the azido mesylate **22**, $[\alpha]_D^{22}$ +18.3 (*c*, 1.20) in an overall yield of 50% for the 4 steps. Sodium hydrogen telluride reduction of **22**, followed by treatment with sodium acetate, gave the fully protected bicycle **23**, $[\alpha]_D^{22}$ -28.3 (*c*, 1.06), in 89% yield. Deprotection of **23** with acid gave the casuarine diastereomer **4**[17] in quantitative yield. For the synthesis of 6,7-*diepi*casuarine **5**, the triflate **20** was treated with cesium trifluoroacetate in butanone to give, after work-up with basic methanol, the alcohol **24**, $[\alpha]_D^{21}$ +23.7 (*c*, 0.45) in 76% yield. Esterification of the free hydroxyl group in **24** with triflic anhydride, followed by displacement of the resulting triflate by sodium azide in DMF, afforded the azide **25**, $[\alpha]_D^{23}$ +8.9 (*c*, 1.56),

in 63% yield. Further elaboration of **25** by chemistry similar to that described for the epimer **21**, gave the azidomesylate **26**, $[\alpha]_D^{22}$+6.0 (*c*, 0.92), in an overall yield of 28%. Again, Suzuki-Takaoka reduction of **26** and subsequent cyclisation proceeded in high (83%) yield to give the fully protected bicycle **27**, $[\alpha]_D^{22}$-2.4 (*c*, 0.92), which on deprotection gave the fourth stereoisomer **5**[18] in quantitative yield.

In summary this paper provides the first report of the synthesis of stereoisomers of the very highly functionalised alkaloid, casuarine **1** which has relatively specific effects on glycosidases and in particular is a potent inhibitor of glucosidase I; the evaluation of the diastereomers synthesised here in a number of assays is in progress and will be compared with the properties of casuarine elsewhere.[19]

REFERENCES

1. Zeng, Y. C., Pan, Y. T., Asano, N., Nash, R. J., Elbein, A. D, *Glycobiology*, 1997, **7**, 297; Kato, A., Asano, N., Kizu, H., Matsui, K., Watson, A. A., Nash, R. J, *J. Nat. Prod.*, 1997, **60**, 312.
2. Asano, N., Kizu, H., Oseki, K., Tomioka, E., Matsui, K., Okamoto, M., Baba, M., *J. Med. Chem.*, 1995, **38**, 2439.
3. Davis, B., Bell, A. A.,Nash, R. J., Watson, A. A., Griffiths, R. C., Jones, M. G., Smith, C., and Fleet, G. W. J., *Tetrahedron Lett.*, 1996, **37**, 8565; Shilvock, J. P., Wheatley, J. R., Davis, B., Nash, R. J., Griffiths, R. C., Jones, M. G., Muller, M., Crook, S., Watkin, D. J., Smith, C., Besra, G. S., Brennan, P. J., and Fleet, G. W. J., *Tetrahedron Lett.*, 1996, **37**, 8569 and references therein.
4. Platt, F.M., Neises, G.R., Dwek, R.A., and Butters, T.D., *J. Biol. Chem.*, 1994, **269**, 8362; Qiao, L., Murray, B.W., Shimazaki, M., Schultz, J., Wong, C-H., *J. Am. Chem. Soc.*, 1996, **118**, 7653; C. A. Collyer, J. D. Goldberg, H. Viehmann, D. M. Blow, N. G. Ramsden, G. W. J. Fleet, F. J. Montgomery and P. Grice, *Biochemistry*, 1992, **31**, 12211.
5. Nash, R. J., Watson, A. A., Asano, N., *Alkaloids: Chemical & Biological Perspectives*, 1996, **11**, 346; Winchester, B., Fleet, G. W. J., *Glycobiology*, 1992, **2**, 199.
6. Nash, R. J., Thomas, P. I., Waigh, R. D., Fleet, G. W. J., Wormald, M. R., Lilley, P. M. D., Watkin, D. J., *Tetrahedron Lett.*, 1994, **35**, 7849.
7. Wormald, M. R., Nash, R. J., Watson, A. A., Bhadoria, B. K., Langford, R., Sims, M., and Fleet, G. W. J.,*Carbohydr. Lett.*, 1996, **2**, 169.
8. Pan, Y. T., Molyneux, R., Nash, R., Fleet, G. W. J., and Elbein, A. D., manuscript in preparation; Pan, Y. T., Nori, H., Saul, R., Sanford, B. A., Molyneux, R., and Elbein, A. D., *Biochemistry*, 1983, **22**, 3975.
9. Bridges, C. G., Ahmed, S. P., Kang, M. S., Nash, R. J., Porter, E. A., Tyms, A. S., *Glycobiology*, 1995, **5**, 249; Taylor, D.L., Nash, R., Fellows, L.E., Kang, M.S., and Tyms, A.S., *Antiviral Chemistry & Chemotherapy*, 1992, **3**, 273.
10. Bell, A. A., Nash, R. J., Fleet, G. W. J., *Tetrahedron: Asymmetry*, 1996, **7**, 595.
11. Bell, A. A., Pickering, L., Watson, A. A., Nash, R. J., Griffiths, R. C., Jones, M. G., Fleet, G. W. J., *Tetrahedron Lett.*, 1996, **37**, 8561 and unpublished work.
12. Suzuki, H., Takaoka, K., *Chemistry Lett.*, **1984**, 1733.
13. All new compounds in this paper, except where otherwise stated, were oils; all specific rotations [other than where stated] were determined at the concentration in chloroform indicated.
14. Selected data for 3,7-*diepi*-casuarine **2**: hygroscopic white solid (31mg, 100%). $[\alpha]_D^{23}$-26.3 (*c*, 0.61, H_2O); $\delta_H(D_2O)$: 3.10 (1H, app t, *J* 9.7 Hz, H-5), 3.20 (1H, dd, $J_{5',6}$ 6.6 Hz, $J_{5,5'}$ 9.3 Hz, H-5'), 3.50 (1H, app dt, *J* 4.5 Hz, $J_{3,8'}$ 7.5 Hz, H-3), 3.69 (1H, app t, *J* 3.6 Hz, H-7a), 3.91 (1H, dd, $J_{8,3}$ 7.5 Hz, $J_{8,8'}$ 12.3 Hz, H-8), 4.00 (1H, dd, $J_{8',3}$ 5.1 Hz, $J_{8',8}$ 12.3 Hz, H-8'), 4.16 (1H, app t, *J* 3.4 Hz, H-2), 4.24 (2H, m, H-6, H-7), 4.49 (1H, app t, *J* 2.7 Hz, H-1); $\delta_C(D_2O)$: 49.5, 56.9 (2 x t, C-5, C-8), 65.0, 70.0, 72.2, 74.0, 74.5, 78.0 (6 x d, C-1, C-2, C-3, C-6, C-7, C-7a).
15. For related work, see Kruizinga, W. H., Strijtveen, B., and Kellogg, R. M., *J. Org. Chem.*, 1981, **46**, 4321; Huffman, J. W., and Desai, R. C., *Syn. Commun.*, 1983, **13**, 553; Torisawa, Y., Okabe, H., and Ikegami, S., *Chem. Lett.*, **1984**, 1555; Lampe, D., and Potter, B. V. L., *Tetrahedron Lett.*, 1993, **34**, 2365.
16. Selected data for 7-*epi*-casuarine **3**: a hygroscopic white solid, $[\alpha]_D^{22}$+6.2 (*c*, 0.65, H_2O); $\delta_H(D_2O)$: 2.54 (1H, app t, *J* 9.7 Hz, H-5), 2.73 (1H, ddd, $J_{3,8'}$ 3.4 Hz, $J_{3,8}$ 6.6 Hz, $J_{3,2}$ 9.6 Hz, H-3), 3.16 (1H, dd, $J_{7a,7}$ 4.2 Hz, $J_{7a,1}$ 7.6 Hz, H-7a), 3.18 (1H, dd, $J_{5',6}$ 6.4 Hz, $J_{5',5}$ 9.5 Hz, H-5'), 3.50 (1H, dd, $J_{8,3}$ 6.6 Hz, $J_{8,8'}$ 11.9 Hz, H-8), 3.70 (1H, dd, $J_{8',3}$ 3.4 Hz, $J_{8',8}$ 11.8 Hz, H-8'), 3.75 (1H, app t, *J* 8.9 Hz, H-2), 4.07 (1H, app t, *J* 4.1 Hz, H-7), 4.15 (1H, ddd, $J_{6,7}$ 3.8 Hz, $J_{6,5'}$ 6.5 Hz, $J_{6,5}$ 9.6 Hz, H-6), 4.29 (1H, app t, *J* 7.9 Hz, H-1); $\delta_C(D_2O)$: 56.8 (t, C-5), 63.2 (t, C-8), 69.1 (d, C-7a), 70.6 (d, C-7), 71.7 (d, C-3), 73.9 (d, C-1), 75.5 (d, C-6), 78.6 (d, C-2).
17. Selected data for 3,6,7-*triepi*-casuarine **4**: a hygroscopic white solid: $[\alpha]_D^{22}$-20.1 (*c*, 0.93, H_2O); $\delta_H(D_2O)$: 2.79 (1H, d, $J_{5,5'}$ 11.4 Hz, H-5), 3.26 (1H, dd, $J_{5',6}$ 4.0 Hz, $J_{5',5}$ 11.4 Hz, H-5'), 3.32 (1H, app q, *J* 5.5 Hz, H-3), 3.55 (1H, app t, *J* 4.4 Hz, H-7a), 3.78 (1H, dd, $J_{8,3}$ 6.6 Hz, $J_{8,8'}$ 12.1 Hz, H-8), 3.89 (1H, dd, $J_{8',3}$ 5.2 Hz, $J_{8',8}$ 12.1 Hz, H-8'), 4.11 (2H, m, H-2, H-7), 4.21 (1H, m, H-6), 4.25 (1H, app t, $J_{2,3}$ 6 Hz, H-1); $\delta_C(D_2O)$: 52.4, 57.5 (2 x t, C-5, C-8), 64.6, 74.1, 74.5 , 74.7 , 77.7, 79.2 (6 x d, C-1, C-2, C-3, C-6, C-7, C-7a); $[\alpha]_D^{22}$+8.4 (*c*, 0.89, H_2O); $\delta_H(D_2O)$: 2.67 (1H, ddd, $J_{3,8'}$ 3.5 Hz, $J_{3,8}$ 6.6 Hz, $J_{3,2}$ 9.6 Hz, H-3), 2.85 (1H, dd, $J_{5,6}$ 4.2 Hz, $J_{5,5'}$ 12.0 Hz, H-5), 3.00 (1H, dd, $J_{5',6}$ 1.8 Hz, $J_{5',5}$ 11.9 Hz, H-5'), 3.36 (1H, dd, $J_{7a,7}$ 4.5 Hz, $J_{7a,1}$ 7.2 Hz, H-7a), 3.55 (1H, dd, $J_{8,3}$ 6.6 Hz, $J_{8,8'}$ 11.8 Hz, H-8), 3.73 (1H, dd, $J_{8',3}$ 3.5 Hz, $J_{8',8}$ 11.8 Hz, H-8'), 3.86 (1H, dd, $J_{2,1}$ 8.1 Hz, $J_{2,3}$ 9.6 Hz, H-2), 4.08 (1H, dd, $J_{7,6}$ 2.3 Hz, $J_{7,7a}$ 4.5 Hz, H-7), 4.23 (1H, app dt, *J* 2.1 Hz, $J_{6,5}$ 4.1 Hz, H-6); $\delta_C(D_2O)$: 59.0, 63.3 (2 x t, C-5, C-8), 69.6, 71.5 , 73.6 , 74.6 , 78.2, 79.5 (6 x d, C-1, C-2, C-3, C-6, C-7, C-7a).
18. Selected data for 6,7-*diepi*-casuarine **5**: a hygroscopic white solid: $[\alpha]_D^{22}$+8.4 (*c*, 0.89, H_2O); $\delta_H(D_2O)$: 2.67 (1H, ddd, $J_{3,8'}$ 3.5 Hz, $J_{3,8}$ 6.6 Hz, $J_{3,2}$ 9.6 Hz, H-3), 2.85 (1H, dd, $J_{5,6}$ 4.2 Hz, $J_{5,5'}$ 12.0 Hz, H-5), 3.00 (1H, dd, $J_{5',6}$ 1.8 Hz, $J_{5',5}$ 11.9 Hz, H-5'), 3.36 (1H, dd, $J_{7a,7}$ 4.5 Hz, $J_{7a,1}$ 7.2 Hz, H-7a), 3.55 (1H, dd, $J_{8,3}$ 6.6 Hz, $J_{8,8'}$ 11.8 Hz, H-8), 3.73 (1H, dd, $J_{8',3}$ 3.5 Hz, $J_{8',8}$ 11.8 Hz, H-8'), 3.86 (1H, dd, $J_{2,1}$ 8.1 Hz, $J_{2,3}$ 9.6 Hz, H-2), 4.08 (1H, dd, $J_{7,6}$ 2.3 Hz, $J_{7,7a}$ 4.5 Hz, H-7), 4.23 (1H, app t, *J* 7.7 Hz, H-1), 4.15 (1H, app dt, *J* 2.1 Hz, $J_{6,5}$ 4.1 Hz, H-6); $\delta_C(D_2O)$: 59.0, 63.3 (2 x t, C-5, C-8), 69.6, 71.5 , 73.6 , 74.6 , 78.2, 79.5 (6 x d, C-1, C-2, C-3, C-6, C-7, C-7a).

19. This work has been supported by graduate studentships from the Medical Research Council AIDS Committee, by an NIH grant NIH HL-17783, and by an EPSRC Post-doctoral Fellowship.

(*Received in UK* 23 *May* 1997; *revised* 24 *June* 1997; *accepted* 27 *June* 1997)