Acta Crystallographica Section E
Structure Reports Online
ISSN 1600-5368

3,7,7a-Tri-*epi*-casuarine pentaacetate

Francesco Punzo,[a]*‡ David J. Watkin,[b] Jeroen Van Ameijde,[c] Graeme Horne,[c,d] George W. J. Fleet,[c] Mark R. Wormald[e] and Robert J. Nash[d]

[a]Dipartimento di Scienze Chimiche, Facoltà di Farmacia, Università di Catania, Viale A. Doria 6, 95125 Catania, Italy, [b]Department of Chemical Crystallography, Chemical Research Laboratory, Mansfield Road, Oxford OX1 3TA, England, [c]Department of Organic Chemistry, Chemical Research Laboratory, Mansfield Road, Oxford OX1 3TA, England, [d]MNLPharma Limited, Institute of Grassland and Environmental Research, Aberystwyth SY23 3EB, Dyfed, Wales, and [e]Glycobiology Institute, Department of Biochemistry, Oxford University, South Parks Road, Oxford OX1 3QU, England

‡ Visiting Scientist at the Department of Chemical Crystallography, Chemical Research Laboratory, Mansfield Road, Oxford OX1 3TA, England

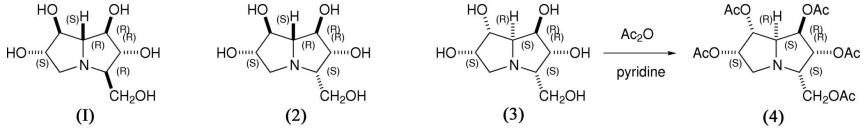
Correspondence e-mail: fpunzo@unict.it

Received 25 January 2006
Accepted 31 January 2006

The relative stereochemistry at six contiguous centres in an analogue of the natural product casuarine, *viz*. 3,7,7a-tri-*epi*-casuarine pentaacetate, $C_{18}H_{25}NO_{10}$, has been established by an analysis of a crystalline pentaacetate.

Comment

The structure of casuarine, (1) (see scheme) (Nash *et al.*, 1994), also isolated as its 6-α-D-glucoside (Wormald *et al.*, 1996), has been determined by X-ray crystallography. The crystal structure of 3-*epi*-casuarine, (2), has also been reported (Newton *et al.*, 2004). Only two syntheses of casuarine have been published to date (Denmark & Hurd, 2000; Izquierdo *et al.*, 2005). Casuarine, with six contiguous stereogenic centres, is a potent α-glucosidase inhibitor and is the most heavily oxygenated of the polyhydroxylated alkaloids which can be viewed as sugar mimics (Asano *et al.*, 2000; Winchester & Fleet, 1992). Synthetic studies on the epimers of casuarine are scant, and none of the stereoisomers reported significantly inhibited any glycosidase (Bell et al., 1997). Nonetheless, some casuarine analogues have promise as vaccine adjuvants and as potential candidates for viral disease and non-cytotoxic cancer therapies (Nash *et al.*, 2004).



(I) (2) (3) (4)

As part of a structure–activity investigation of the stereoisomers of casuarine, the tri-*epi* casuarine (3) was prepared by a route which did not define the relative configuration at two centres. Although (3) has not been crystallized, peracetylation by acetic anhydride in pyridine gave the crystalline pentaacetate, (4), the crystal structure of which is reported in this paper (Fig. 1 and Table 1).

This study firmly establishes the relative configuration at all six stereogenic centres. The absolute configuration of (4) is determined by the use of D-glucose as the starting material in the synthesis. A combination of crystal structures and NMR studies have established solid-state and solution conformations of a number of stereoisomers of the less oxygenated alexines (Wormald *et al.*, 1998; Kato *et al.*, 2003) which may be used to rationalize their biological activity. Similar structural studies on the stereoisomers of casuarine may permit the development of rationales for their novel biological activities. The crystal packing, represented in Fig. 2, highlights long-range interactions between the acetate fragments that are both non-polar, *i.e.* between methyl groups, and polar, *i.e.* between O atoms.

Key indicators

Single-crystal X-ray study
T = 120 K
Mean σ(C–C) = 0.003 Å
R factor = 0.039
wR factor = 0.091
Data-to-parameter ratio = 11.7

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

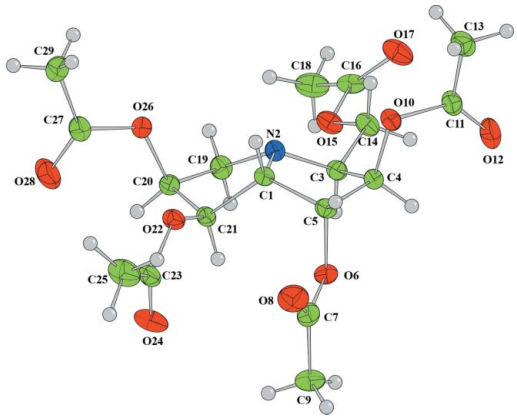


Figure 1
The molecular structure of (4), showing displacement ellipsoids drawn at the 50% probability level.

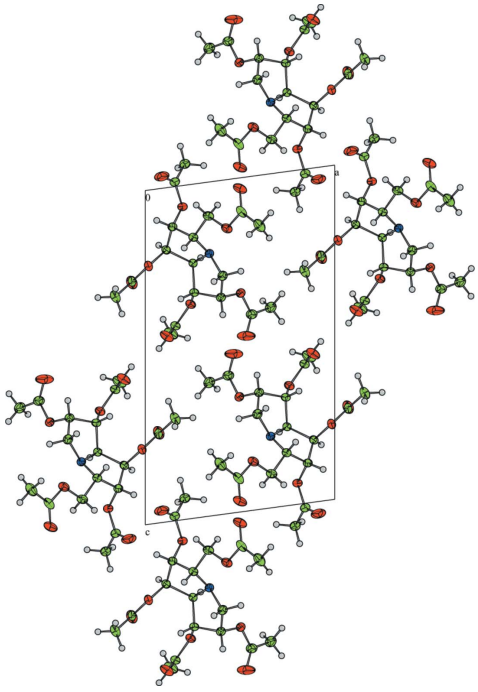


Figure 2
Packing diagram of (4), viewed down the *b* axis.

Experimental

Compound (4) was crystallized by dissolving it in cyclohexane, adding ethanol (in an approximate ratio of 9:1), and allowing slow competitive evaporation of the two solvents until clear colourless crystals formed.

Crystal data

$C_{18}H_{25}NO_{10}$
M_r = 415.40
Monoclinic, $P2_1$
a = 9.8357 (3) Å
b = 5.9443 (2) Å
c = 17.2146 (6) Å
β = 97.6513 (12)°
V = 997.51 (6) Å^3
Z = 2
D_x = 1.383 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 2338 reflections
θ = 5–30°
μ = 0.11 mm^{-1}
T = 120 K
Needle, colourless
0.30 × 0.10 × 0.10 mm

Data collection

Nonius KappaCCD diffractometer
ω scans
Absorption correction: multi-scan (*DENZO*/*SCALEPACK*; Otwinowski & Minor, 1997)
T_{min} = 0.99, T_{max} = 0.99
5106 measured reflections
3067 independent reflections
2513 reflections with $I > 2\sigma(I)$
R_{int} = 0.017
θ_{max} = 30.0°
$h = -13 \rightarrow 13$
$k = -8 \rightarrow 7$
$l = -24 \rightarrow 24$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.039
$wR(F^2)$ = 0.091
S = 0.94
3067 reflections
263 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F^2) + (0.04P)^2 + 0.2P]$, where $P = [\max(F_o^2,0) + 2F_c^2]/3$
$(\Delta/\sigma)_{max}$ <0.001
$\Delta\rho_{max}$ = 0.33 e Å^{-3}
$\Delta\rho_{min}$ = −0.35 e Å^{-3}
Extinction correction: Larson (1970), equation 22
Extinction coefficient: 1.8 (4) × 10^2

Table 1
Selected geometric parameters (Å, °).

C1—N2	1.486 (2)	C11—C13	1.491 (3)
C1—C5	1.540 (3)	C14—O15	1.448 (2)
C1—C21	1.517 (3)	O15—C16	1.351 (2)
N2—C3	1.466 (2)	C16—O17	1.208 (3)
N2—C19	1.477 (2)	C16—C18	1.483 (3)
C3—C4	1.528 (3)	C19—C20	1.513 (3)
C3—C14	1.508 (3)	C20—C21	1.523 (3)
C4—C5	1.525 (3)	C20—O26	1.456 (2)
C4—O10	1.448 (2)	C21—O22	1.432 (2)
C5—O6	1.453 (2)	O22—C23	1.363 (2)
O6—C7	1.357 (3)	C23—O24	1.197 (3)
C7—O8	1.197 (3)	C23—C25	1.490 (3)
C7—C9	1.493 (4)	O26—C27	1.355 (2)
O10—C11	1.355 (2)	C27—O28	1.193 (3)
C11—O12	1.200 (3)	C27—C29	1.482 (3)
N2—C1—C5	106.11 (15)	O12—C11—C13	126.35 (19)
N2—C1—C21	104.58 (15)	C3—C14—O15	107.24 (15)
C5—C1—C21	118.30 (16)	C14—O15—C16	114.62 (16)
C1—N2—C3	108.97 (14)	O15—C16—O17	122.2 (2)
C1—N2—C19	108.76 (15)	O15—C16—C18	112.17 (18)
C3—N2—C19	116.67 (16)	O17—C16—C18	125.6 (2)
N2—C3—C4	103.27 (16)	N2—C19—C20	105.06 (17)
N2—C3—C14	113.92 (16)	C19—C20—C21	101.52 (15)
C4—C3—C14	112.75 (15)	C19—C20—O26	108.48 (16)
C3—C4—C5	103.33 (15)	C21—C20—O26	109.03 (16)
C3—C4—O10	111.18 (15)	C20—C21—C1	103.69 (16)
C5—C4—O10	106.33 (16)	C20—C21—O22	114.18 (16)
C1—C5—C4	103.08 (15)	C1—C21—O22	110.11 (16)
C1—C5—O6	111.65 (15)	C21—O22—C23	117.04 (16)
C4—C5—O6	104.60 (16)	O22—C23—O24	122.9 (2)
C5—O6—C7	116.67 (17)	O22—C23—C25	110.27 (19)
O6—C7—O8	123.5 (2)	O24—C23—C25	126.8 (2)
O6—C7—C9	110.9 (2)	C20—O26—C27	117.07 (16)
O8—C7—C9	125.6 (2)	O26—C27—O28	122.8 (2)
C4—O10—C11	116.98 (16)	O26—C27—C29	112.16 (18)
O10—C11—O12	122.9 (2)	O28—C27—C29	125.1 (2)
O10—C11—C13	110.71 (19)		

In the absence of significant anomalous scattering effects, Friedel pairs were merged, and the absolute configuration was assigned from the known configuration of the starting material. H atoms were seen in a difference density synthesis. Those attached to C atoms were repositioned geometrically. The H atoms were initially refined with soft restraints on the bond lengths and angles to regularize their geometry, after which they were included with riding constraints, with C—H = 0.93–0.98 Å and with U_{iso}(H) values in the range 1.2–1.5U_{eq} of the carrier atom.

Data collection: *COLLECT* (Nonius, 2001); cell refinement and data reduction: *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *CAMERON* (Watkin *et al.*, 1996); software used to prepare material for publication: *CRYSTALS*.

References

Altomare, A., Cascarano, G., Giacovazzo G., Guagliardi A., Burla M. C., Polidori, G. & Camalli, M. (1994). *J. Appl. Cryst.* **27**, 435.

Asano, N., Nash, R. J., Molyneux, R. J. & Fleet, G. W. J. (2000). *Tetrahedron Asymmetry*, **11**, 1645–1680.

Bell, A. A., Pickering, L., Watson, A. A., Nash, R. J., Pan, Y. T., Elbein, A. D. & Fleet, G. W. J. (1997). *Tetrahedron Lett.* **38**, 5869–5872.

Betteridge, P. W., Carruthers, J. R., Cooper, R. I., Prout, K. & Watkin, D. J. (2003). *J. Appl. Cryst.* **36**, 1487.

Denmark, S. E. & Hurd, A. R. (2000). *J. Org. Chem.* **65**, 2875–2886.

Izquierdo, I., Plaza, M. T., Juan, A. & Tamayo, J. A. (2005). *Tetrahedron*, **61**, 6527–6533.

Kato, A., Kano, E., Adachi, I., Molyneux, R. J., Watson, A. A., Nash, R. J., Fleet, G. W. J., Wormald, M. R., Kizu, H., Ikeda, K. & Asano, N. (2003). *Tetrahedron Asymmetry*, **14**, 325–331.

Larson, A. C. (1970). *Crystallographic Computing,* edited by F. R. Ahmed, S. R. Hall & C. P. Huber, pp. 291–294. Copenhagen: Munksgaard.

Nash, R. J., Thomas, P. I., Waigh, R. D., Fleet, G. W. J., Wormald, M. R., Lilley, P. M. Q. & Watkin, D. J. (1994). *Tetrahedron Lett.* **35**, 7849–7852.

Nash, R. J., Watson, A. A. & Evinson, E. L. (2004). PCT Int. Appl. 2004, WO2004064715.

Newton, C., van Ameijde, J., Fleet, G. W. J., Nash, R. J. & Watkin, D. J. (2004). *Acta Cryst.* E**60**, o1463–o1464.

Nonius (2001). *COLLECT*. Nonius BV, Delft, The Netherlands.

Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, *Macromolecular Crystallography*, Part A, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.

Watkin, D. J., Prout, C. K. & Pearce, L. J. (1996). *CAMERON*. Chemical Crystallography Laboratory, Oxford, England.

Winchester, B. & Fleet, G. W. J. (1992). *Glycobiology*, **2**, 199–210.

Wormald, M. R., Nash, R. J., Hrnicar, P., White, J. D., Molyneux, R. J. & Fleet, G. W. J. (1998). *Tetrahedron Asymmetry*, **9**, 2549–2558.

Wormald, M. R., Nash, R. J., Watson, A. A., Bhadoria, B. K., Langford, R., Sim, M. & Fleet, G. W. J. (1996). *Carbohydr. Lett.* **2**, 169–174.