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Carbohydrate Research 339 (2004) 1747–1751
Carbohydrate RESEARCH

The chemistry of castanospermine. Direct oxidation of the tetraacetate to the corresponding γ-lactam ☆

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Received 29 February 2004; accepted 13 May 2004
Available online 10 June 2004

Abstract—From the products of oxidation of tetra-*O*-acetylcastanospermine (**2**) with *N*-bromosuccinimide, only the γ-lactam **11** was isolated (19%). Treatment of this lactam with DBU in dichloromethane afforded the elimination product **12**, while deacetylation with sodium methoxide in methanol gave tetraol **13** together with diene **14**. The X-ray crystal structure of compound **13** is reported.

Keywords: Castanospermine; Lactam; Oxidation

1. Introduction

Castanospermine (**1**) is a polyhydroxy indolizidine alkaloid found in the seeds of *Castanospermum australe* and the pods of *Alexa leiopetala*. It and its derivatives show potent inhibitory effects on a range of glycosidases, and the consequences of these effects conceivably account for its activities against cancer and viruses as well as its anti-malarial, -diabetic, -inflammatory, and immunosuppressant properties.[2]

In previous parts of this series[1] the preparations of a large number of castanospermine derivatives from the natural product were reported, and the profound importance of the nitrogen atom on the chemical reactivities of compounds of this type was revealed. In particular, this atom has a major influence on nucleophilic displacement reactions undergone by compounds with a good leaving group at C-6 or C-8. As illustrated in Scheme 1 these reactions give products derived by nucleophilic displacement with retention of configuration at these centres, together with products of rearrangement reactions. These findings can be accounted for by invoking participation of the nitrogen atom to generate tricyclic aziridinium species that undergo nucleophilic attack at each of the carbon atoms of the three-membered rings. In this way, for example, the C-6 alcohol **3** reacts with diethylaminosulfur trifluoride (DAST) to give 6-fluoride **5** (49%) and the ring-contracted australine derivative **6** (19%) following attack by fluoride at C-6 and C-5, respectively, of intermediate **4**.[3] Likewise, with this reagent, C-8 alcohol **7** gives compounds **9** and **10** via the aziridinium ion **8**, nucleophilic attack in this case occurring at C-8 and C-8a, respectively.[4]

2. Results and discussion

In consequence of the findings illustrated in Scheme 1, it was of interest to us to obtain derivatives of castanospermine containing functionality that would alter the nucleophilicity of the nitrogen atom, and with this objective, we turned attention to the possibility of making lactam analogues by direct oxidation of tetraacetate **2**. γ-Lactams of castanospermine have been reported on several occasions as intermediates in the synthesis of the alkaloid and its derivatives,[5] and δ-lactam analogues have been similarly encountered,[6] but we are not aware of such compounds having been obtained previously by direct oxidation procedures.

☆ Part VI in a series. For Part V see Ref. 1.

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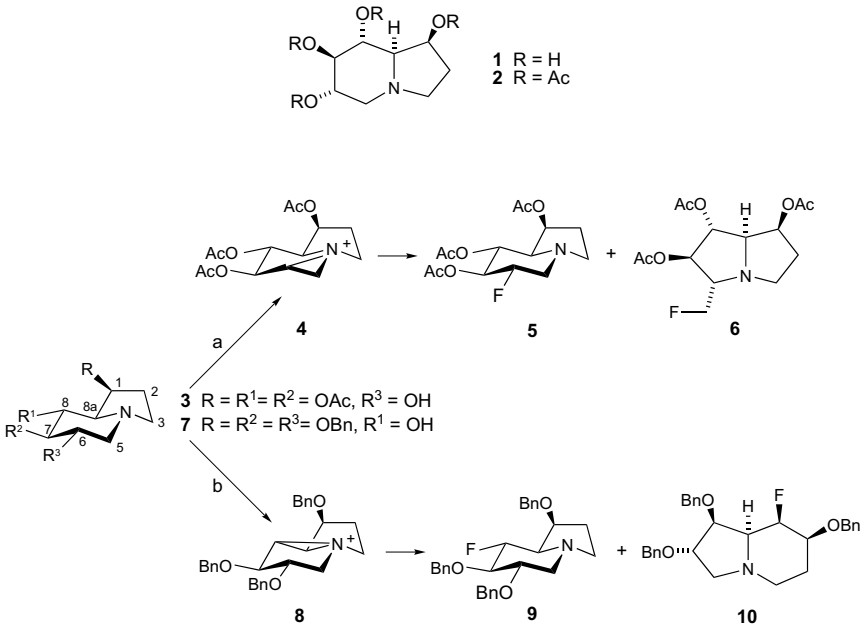
doi:10.1016/j.carres.2004.05.006

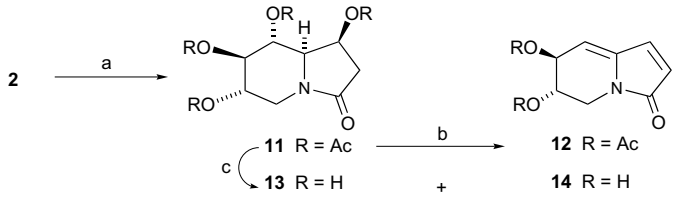


Scheme 1. Reagents and conditions: (a) DAST, CH_2Cl_2, 40 °C, 2 h; (b) DAST, CH_2Cl_2, rt, 50 h.

Oxidations of cyclic tertiary amines to amides with halogen-based reagents, including *N*-bromosuccinimide,[7] are well established,[8] if not commonly used conversions, and we now report that the crystalline γ-lactam **11** was obtained directly from castanospermine tetraacetate (**2**) in 19% yield, and as the only isolated product, following oxidation with *N*-bromosuccinimide in aqueous dioxane. The observed apparent selective reaction at C-3 of castanospermine tetraacetate would be expected whether carbenium-ion or free-radical formation controls the rate of its oxidation, since the generation of both species is favoured at carbon atoms bonded to heteroatoms within five- relative to six-membered rings.[9,10]

When lactam **11** was treated with DBU in dichloromethane the diene **12**, derived by loss of two molecules of acetic acid, was obtained in high yield, whereas treatment of product **11** with sodium methoxide in methanol gave the deacetylated tetraol **13** in 37% yield and, in addition, the diene **14**, isolated in 23% yield (Scheme 2).

The crystal structure of the castanospermine lactam **13** is shown in Figure 1 and the unit cell in Figure 2. Independent molecules are bound into a three-dimensional lattice by classical hydrogen bonds utilising all four hydroxyl protons (H···O 1.96–2.02 Å, O–H···O 163–174°).[11,12] Acceptor atoms are O-3 (with bonds from HO-7 and HO-1 of different molecules), O-6 and O-8 (with bonds to HO-8 and HO-6, of different molecules, respectively). The five-membered ring (N-4, C-8a, C-1–3) adopts a flattened envelope conformation [$Q(2)$ 0.247(3) Å, ϕ 113.0(6)°][13] with the flap atom C-1 0.393(4) Å from the plane of the other four, and the six-membered ring (N-4, C-5–8a) adopts a regular chair conformation with N-4, C-5, C-7, C-8 coplanar [±0.004(1) Å] and C-8a and C-6 −0.569(3) and 0.693(3) Å from the plane; Q, θ and ϕ are 0.535(3) Å, 9.1(3) and 124(2)°, respectively.[13] The substituents on this ring all adopt equatorial orientations. For the tetraacetate **11** of compound **13**, this ring conformation is retained in solution as is indicated by the large vicinal proton NMR coupling constants exhibited by H-5′, H-6, H-7, H-8 and H-8a.



Scheme 2. Reagents and conditions: (a) NBS, dioxane, H_2O, rt, 20 min; (b) DBU, CH_2Cl_2, rt, 24 h; (c) NaOMe, MeOH, rt, 30 min.

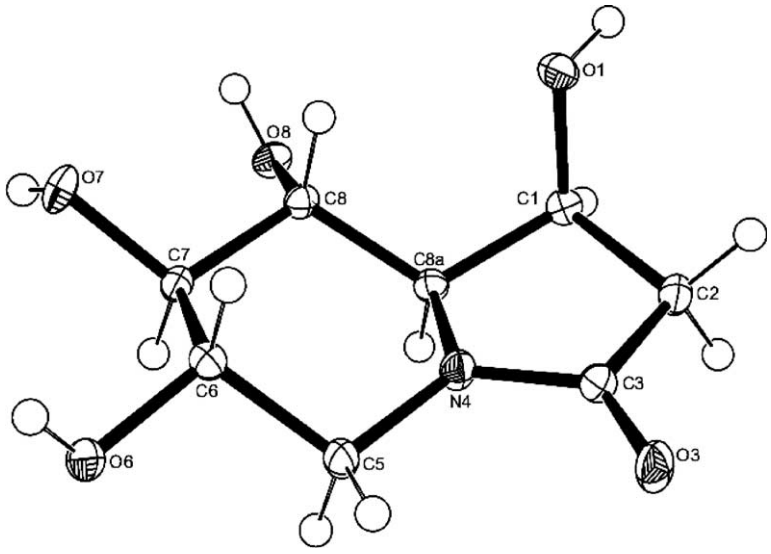


Figure 1. Crystal structure of compound **13** ($C_8H_{13}NO_5$).[17] Displacement ellipsoids are drawn at the 50% probability level. Hydrogen atoms have arbitrary radii.

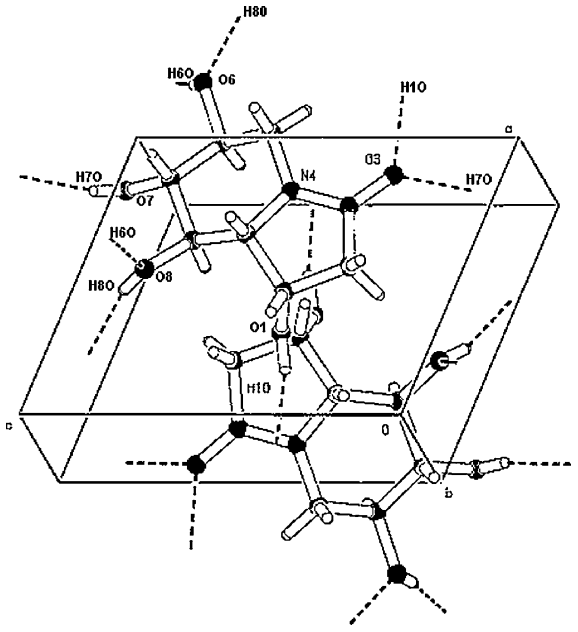


Figure 2. Unit cell contents of compound **13** viewed down the *b*-axis (approx); dashed lines represent hydrogen bonds. For clarity, only cell edges and the O, N and hydroxyl H atoms of the unique molecule are labelled.[11]

3. Experimental

3.1. General methods

NMR spectra were recorded on a Bruker AC-300 spectrometer at 300 MHz (^{1}H) or 75 MHz (^{13}C). High-resolution accurate mass determinations were performed on a VG70-250S spectrometer using chemical ionisation with isobutane. Melting points were measured on a Reichert hot stage microscope and are uncorrected. Elemental analyses were determined in the Campbell Microanalytical Laboratory of the University of Otago, Dunedin, New Zealand. Aluminum-backed silica gel sheets (E. Merck or Reidel de Haen) were used for thin-layer chromatography, and column chromatography was performed on silica gel (230–400 mesh, E. Merck). Chromatography solvents were distilled prior to use; 'hexanes' refers to a petroleum fraction boiling near 68 °C. Castanospermine was extracted from the dried seeds of *C. australe*.[4] All other chemicals were commercially available and were used without further purification.

3.2. (1*S*,6*S*,7*R*,8*R*,8a*R*)-1,6,7,8-Tetraacetoxyhexahydroindolizin-3-one (11)

A solution of tetra-*O*-acetylcastanospermine (**2**)[3] (5.0 g, 14.2 mmol) in 9:1 dioxane–water (22 mL) was stirred rapidly at room temperature while *N*-bromosuccinimide (6.3 g, 35.4 mmol) was added with the temperature being kept below 40 °C. After the addition was complete, the mixture was allowed to cool to room temperature. It was partitioned between CH_2Cl_2 (50 mL) and aq 1 M $Na_2S_2O_3$ (50 mL), and the organic phase was washed with satd aq $NaHCO_3$, dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography with 2:3 → 0:1 hexanes–EtOAc as eluant gave the crystalline title γ-lactam (1.1 g, 19%). Recrystallised from hexanes–EtOAc it had mp 184–185 °C. ^{1}H NMR ($CDCl_3$): δ 5.56 (t, 1H, *J* 5.7 Hz, H-1), 5.28 (t, 1H, *J* 9.6 Hz, H-8), 5.21 (t, 1H, *J* 9.3 Hz, H-7), 4.97 (m, 1H, H-6), 4.42 (dd, 1H, *J* 5.9, 12.8 Hz, H-5), 3.80 (dd, 1H, *J* 5.2, 9.3 Hz, H-8a), 2.78 (dd, 1H, *J* 5.8, 18.1 Hz, H-2), 2.68 (t, 1H, *J* 11.4 Hz, H-5′), 2.43 (d, 1H, *J* 18.1 Hz, H-2′), 2.08, 2.06, 2.04, 2.01 (4s, 12H, CH_3). ^{13}C NMR ($CDCl_3$): δ 171.2 (C-3), 170.1,

170.0, 169.5, 169.4 ($COCH_3$), 74.1 (C-7), 67.6 (C-6), 66.7 (C-8), 64.4 (C-1), 60.7 (C-8a), 40.6 (C-5), 38.4 (C-2), 20.9, 20.7, 20.6, 20.6 (CH_3). HRMS: Calcd for $C_{16}H_{22}NO_9$, m/z 372.1294; found, m/z 372.1279 (MH+). Anal. Calcd for $C_{16}H_{21}NO_9$: C, 51.75; H, 5.66; N, 3.77. Found: C, 51.6; H, 5.71; N, 4.05.

3.3. (6*S*,7*R*)-6,7-Diacetoxy-6,7-dihydroindolizin-3(5*H*)-one (12)

DBU (2.2 mL, 14.5 mmol) was added to a solution of tetraacetyllactam **11** (2.5 g, 6.7 mmol) in CH_2Cl_2. After 24 h the reaction mixture was washed with 1 M HCl and aq satd $NaHCO_3$, dried and concentrated under reduced pressure. Column chromatography of the residue using 1:2 hexanes–EtOAc as eluant gave the title compound (1.5 g, 6.0 mmol, 89%), mp 100–102 °C. ^{1}H NMR ($CDCl_3$): δ 7.02 (d, 1H, J 5.8 Hz, H-2), 6.28 (d, 1H, J 5.8 Hz, H-1), 5.58 (d, 1H, J 5.2 Hz, H-8), 5.32 (m, 1H, H-7), 5.23 (m, 1H, H-6), 4.07 (m, 1H, H-5), 3.61 (dd, 1H, J 2.9, 13.9 Hz, H-5′), 2.09, 2.05 (2s, 6H, $COCH_3$). ^{13}C NMR ($CDCl_3$): δ 169.7, 169.6, 169.0 ($COCH_3$, C-3), 141.5 (C-8a), 134.9 (C-1), 127.2 (C-2), 104.1 (C-8), 66.1 (C-6), 65.3 (C-7), 38.4 (C-5), 20.9 ($COCH_3$). HRMS: Calcd for $C_{12}H_{14}NO_5$, m/z 252.0872; found, m/z 252.0853 (MH^+). Anal. Calcd for $C_{12}H_{13}NO_5$: C, 57.4; H, 5.22; N, 5.58. Found: C, 57.5; H, 5.04; N, 5.65.

3.4. (1*S*,6*S*,7*R*,8*R*,8a*R*)-1,6,7,8-Tetrahydroxyhexahydroindolizin-3-one (13) and (6*S*,7*R*)-6,7-dihydroxy-6,7-dihydroindolizin-3(5*H*)-one (14)

Tetraacetoxylactam **11** (0.52 g, 1.4 mmol) was stirred in methanolic 0.2 M NaOMe (2 mL) until dissolved, and the solution was neutralised with HOAc. The solvent was removed under reduced pressure, and the syrupy residue was passed through a column of cation-exchange resin (Dowex 50 X-8, H^+). Concentration under reduced pressure, followed by column chromatography (4:1 EtOAc–MeOH) gave dihydroxydiene **14** (50 mg, 0.32 mmol, 23%): mp (MeOH) 194–195 °C. ^{1}H NMR (D_2O): δ 7.16 (d, 1H, J 5.8 Hz, H-2), 6.22 (d, 1H, J 5.8 Hz, H-1), 5.79 (d, 1H, J 4.7 Hz, H-8), 4.29 (t, 1H, J 4.6 Hz, H-7), 4.02 (m, 1H, H-6), 3.63 (m, 2H, H-5, -5′). ^{13}C NMR (D_2O): δ 174.3 (C-3), 141.2 (C-8a), 138.7 (C-1), 128.3 (C-2), 115.6 (C-8), 70.0, 68.6 (C-6, C-7), 42.9 (C-5). HRMS: Calcd for $C_8H_{10}NO_3$, m/z 168.0661; found, m/z 168.0652 (MH^+). Anal. Calcd for $C_8H_9NO_3$: C, 57.48; H, 5.45; N, 8.38. Found: C, 57.6; H, 5.51; N, 8.33.

Further elution with the same solvent gave tetraol **13** (100 mg, 0.52 mmol, 37%): mp 188–194 °C (EtOAc–MeOH). ^{1}H NMR (D_2O): δ 4.50 (t, 1H, J 5.3 Hz, H-1), 3.99 (m, 1H, H-5), 3.63 (m, 1H, H-7 or H-8), 3.43 (m, 3H, H-6, H-8 or H-7, H-8a), 2.78 (m, 1H, H-2), 2.58 (m, 1H, H-5′), 2.29 (d, 1H, J 17.9 Hz, H-2′). ^{13}C NMR (D_2O): δ 178.4 (C-3), 80.0, 70.9, 70.4, 67.3 (C-6, C-7, C-8, C-8a), 45.9 (C-5), 43.5 (C-2). HRMS: Calcd for $C_8H_{14}NO_5$, m/z 204.0872; found, m/z 204.0896 (MH^+). Anal. Calcd for $C_8H_{13}NO_5$: C, 47.3; H, 6.45; N, 6.89. Found: C, 47.2; H, 6.65; N, 7.03.

3.5. Crystal structure analysis of compound 13

Crystals of the compound **13** (molecular formula $C_8H_{13}NO_5$) were grown from EtOAc–methanol, M 203.08, monoclinic space group $P2_1$ (No 4),[14] $a = 6.673(2)$, $b = 8.859(3)$, $c = 8.459(3)$ Å, $\beta = 111.94(3)°$, $V = 449.7(3)$ Å^3, $Z = 2$, $D_c = 1.501$ g cm^{-3}, $F(000) = 216$, $\mu_{Mo} = 0.126$ mm^{-1}. Data were collected using ω:2θ scans at 143(2) K with a Nicolet R3m diffractometer with Mo Kα radiation (graphite monochromator, λ 0.71073 Å). The crystals were colourless prisms, $0.40 \times 0.25 \times 0.25$ mm; 1182 reflections were measured, 1096 unique ($5.2 < 2\theta < 55.0°$) of which 1020 'observed' reflections had $I > 2.5\sigma(I)$, $R_{int} = 0.028$. Corrections were applied for Lorentz and polarisation effects. No absorption correction was applied. The structure was solved by direct methods[15] and refined on F^2 using observed data.[16] Final R_1, wR_2 values were 0.033, 0.076 (observed data) and 0.036, 0.078 (all data). All hydrogen atoms were included but were not refined in calculated positions (0.97–1.0 Å as defined[16]) with constrained thermal isotropic parameters (1.2 times parent C, O or N equivalent values). Final max., min. residual electron densities were 0.305 and −0.195 e Å^{-3}.

4. Supplementary material

Crystallographic data (excluding structure factors) for compound **13** have been deposited with the Cambridge Crystallographic Centre as supplementary publications, No CCDC 221352. These data can be obtained, free of charge, through http://www.ccdc.cam.ac.uk/conts/retrieving.html or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 (1)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.

Acknowledgements

The work was funded by the New Zealand Foundation for Research, Science and Technology. Dr. Herbert Wong provided the NMR service and Professor Robin Ferrier assisted with the preparation of the manuscript.

References

1. Furneaux, R. H.; Gainsford, G. J.; Mason, J. M.; Tyler, P. C.; Hartley, O.; Winchester, B. G. *Tetrahedron* **1997**, *53*, 245–268.

2. Tyler, P. C.; Winchester, B. G. Synthesis and biological activity of castanospermine and close analogs. In *Iminosugars as Glycosidase Inhibitors*; Stũtz, A. E., Ed.; Wiley-VCH: Weinheim, 1999; pp 125–156.
3. Furneaux, R. H.; Gainsford, G. J.; Mason, J. M.; Tyler, P. C. *Tetrahedron* **1994**, *50*, 2131–2160.
4. Furneaux, R. H.; Gainsford, G. J.; Mason, J. M.; Tyler, P. C.; Hartley, O.; Winchester, B. G. *Tetrahedron* **1995**, *51*, 12611–12630.
5. (a) Bernotas, R. C.; Ganem, B. *Tetrahedron Lett.* **1984**, *25*, 165–168; (b) Setio, H.; Taneko, H.; Hashimoto, M. *Tetrahedron Lett.* **1985**, *26*, 4617–4620; (c) Ina, H.; Kibayashi, C. *J. Org. Chem.* **1993**, *58*, 52–61; (d) Leeper, F. J.; Howard, S. *Tetrahedron Lett.* **1995**, *36*, 2335–2338.
6. (a) Miller, S. A.; Chamberlin, A. R. *J. Am. Chem. Soc.* **1990**, *112*, 8100–8122; (b) Kim, N.-S.; Choi, J.-R.; Cha, J. K. *J. Org. Chem.* **1993**, *58*, 7096–7099; (c) Kim, N.-S.; Kang, C. H.; Cha, J. K. *Tetrahedron Lett.* **1994**, *35*, 3489–3492; (d) Overkleeft, H. S.; Pandit, U. K. *Tetrahedron Lett.* **1996**, *37*, 547–550.
7. Picot, A.; Lusinchi, X. *Synthesis* **1975**, 109–111.
8. Moriarty, R. M.; Vaid, R. K.; Duncan, M. P.; Ochiai, M. P.; Inenaga, M.; Nagao, Y. *Tetrahedron Lett.* **1988**; *29*, 6913–6916.
9. Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994. p 769.
10. Malatesta, V.; Ingold, K. U. *J. Am. Chem. Soc.* **1981**, *103*, 609–614.
11. Spek, A. L. *PLATON J. Appl. Crystallogr.* **2003**, *36*, 7–13.
12. Desiraju, G. R.; Steiner, T. *The Weak Hydrogen Bond in Structural Chemistry and Biology*; Oxford University Press: Oxford, 1999; pp 12–16.
13. Cremer, D.; Pople, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 1354–1358.
14. *International Tables for Crystallography*; Hahn, T., Ed.; Kluwer Academic: Dordrecht, 1995; 4th ed., Vol. A., Part I.7, pp 174–175.
15. Sheldrick, G. M. *Acta Crystallogr. Sect. A* **1990**, *46*, 467–473.
16. Sheldrick, G. M. SHELXL-97. Program for the Refinement of Crystal Structures and CIFTAB, Program for Publication of Structures, University of Gottingen, Germany, 1997.
17. Farrugia, L. J. *J. Appl. Crystallogr.* **1997**, *30*, 565.