Annulation of β-aryl-α-nitro-α,β-enals and 2,2-dimethyl-1,3-dioxan-5-one: a one-step assembly of nitrocyclitols. Application to a short practical synthesis of (±)-7-deoxy-2-*epi*-pancratistatin tetraacetate†

Juan Carlos Ortiz,‡ Lidia Ozores,§ Fernando Cagide-Fagín and Ricardo Alonso*

Received (in Cambridge, UK) 6th June 2006, Accepted 31st July 2006
First published as an Advance Article on the web 31st August 2006
DOI: 10.1039/b606277f

A novel, highly stereocontrolled formal [3 + 3] annulation of β-aryl-α-nitro-α,β-enals with the enamine derived from 2,2-dimethyl-1,3-dioxan-5-one and pyrrolidine afforded protected nitrocyclitols with five newly created stereocentres and constituted the key step in a short, gram-scale synthesis of a pancratistatin analogue.

Polyhydroxylated cyclohexanes are present in a vast number of biologically and pharmacologically relevant compounds. They include inositol derivatives, which display a wide variety of crucial biological functions,[1] the conduritols[2] and the aminocyclitols,[3] which are attracting increasing attention for the treatment of diabetes, cancer, and viral and bacterial infections.[4] They also include a variety of complex natural products, such as the potential antitumoral agent pancratistatin (**1**, Fig. 1).[5–7] Not surprisingly, polyhydroxylated cyclohexanes were identified early as key synthetic targets.[8] However, most methods proposed hitherto for their preparation have been based on the carbocyclization of a carbohydrate derivative[2,3,9,10] and usually involve a considerable number of steps before and/or after the key cyclization step.[11] Herein we describe a novel route to cyclitols of type **8** that are assembled in a single step from β-aryl-α-nitro-α,β-enals **6** and commercial 2,2-dimethyl-1,3-dioxan-5-one (**7**), a protected form of 1,3-dihydroxyacetone (Table 1). The value of this approach is illustrated by the gram-scale preparation of a protected pancratistatin analogue (**2**, Fig. 1).

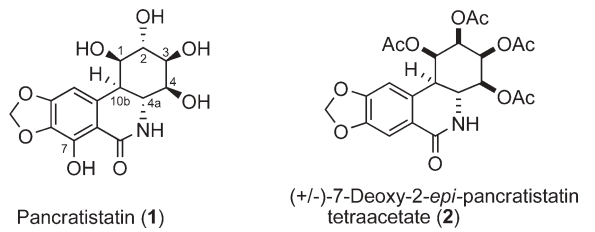


Fig. 1 Natural pancratistatin (**1**), and synthetic (±)-7-deoxy-2-*epi*-pancratistatin tetraacetate (**2**).

Departamento de Química Orgánica, Universidad de Santiago, 15782 Santiago de Compostela, Spain. E-mail: qoraa@usc.es; Fax: +34 981 595012; Tel: +34 981 547085

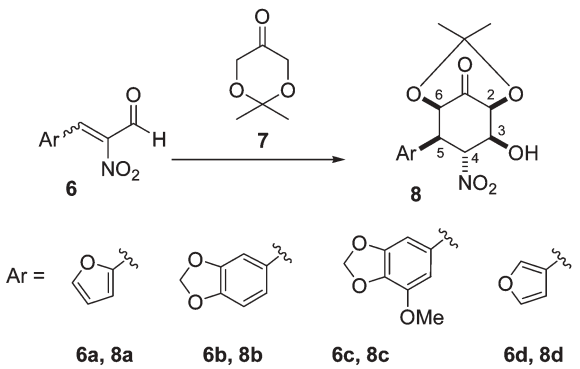
† Electronic supplementary information (ESI) available: NMR spectra for nitrocyclitols **8a–d**, intermediates **9** and **10**, and (±)-7-deoxy-2-*epi*-pancratistatin tetraacetate. See DOI: 10.1039/b606277f

‡ Currently at Sintenovo, Mexico.
§ Currently at the Max Planck Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, D-45470 Mülheim an der Ruhr, Germany.

Before addressing the reaction between **6** and **7** we checked the accessibility of the required β-aryl-α-nitro-α,β-enals **6**, a rare and essentially unexplored family of compounds.[12,13] After some experimentation we found that they can be prepared in gram quantities, and then isolated in pure, or essentially pure, form as inseparable *E–Z* mixtures, by a two-step reaction sequence involving condensation of aromatic aldehydes with 2-nitroethanol followed by oxidation with either Dess–Martin periodinane (DMP) or 2-iodoxybenzoic acid (IBX) (Scheme 1).[14]

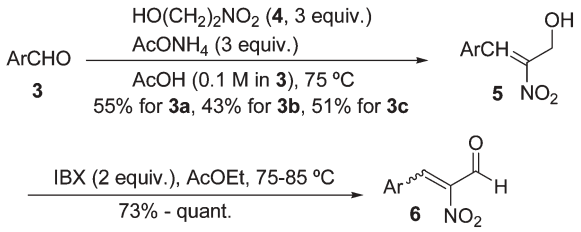
To investigate the annulation of nitroenals **6** with dioxanone **7**, we initially treated mixtures of **6a** (**6**, Ar = furyl) and **7** with a number of different acids and bases, with no success: either no reaction occurred or complex mixtures were obtained. However, addition of **6a** to a CH_3CN solution of the enamine formed from **7** and pyrrolidine, followed by hydrolysis, extraction and chromatography, gave,

Table 1 Annulation of nitroenals **6a–d** with dioxanone **7**[a]



Entry	6, amount/mg	Solvent, 7 : pyrr[b]	Additive equiv.	Yield 8[c]
1[d]	**6a**, 80	CH_3CN[d]	—	**8a** 24%
2	**6a**, 80	CH_3CN, 1 : 1	—	**8a** 27%
3	**6a**, 80	CH_3CN, 1 : 1	PPTS 1	**8a** 0%
4[e]	**6a**, 130	CH_3CN, 1 : 1	PPTS 0.2	**8a** 38%
5[e]	**6a**, 130	DMF, 1 : 1	PPTS 0.2	**8a** 38%
6	**6b**, 500	CH_3CN, 1 : 1	—	**8b** 25%
7	**6b**, 200	CH_3CN, 1 : 0.8	—	**8b** 25%
8[f,g]	**6b**, 100	DMF, 1 : 0.8	PPTS 0.2	**8b** 37%[g]
9[f]	**6b**, 1200	DMF, 1 : 0.8	PPTS 0.2	**8b** 42%
10[f,h]	**6c**, 150–400	DMF, 1 : 0.8	PPTS 0.2	**8c** 22–30%[h]
11[f]	**6c**, 1000	DMF, 1 : 0.8	PPTS 0.2	**8c** 30%
12[f]	**6d**, 300	DMF, 1 : 0.8	PPTS 0.2	**8d** 33%

[a] For a general annulation procedure see ref. 16. [b] Pyrrolidine. [c] Isolated yields. [d] In this case the enamine from **7** and pyrrolidine was isolated and then reacted with nitroenal **6a**. [e] The reaction was quenched after 10 min at 0 °C. [f] Quenching by addition of 5 : 1 EtOH–H_2O. [g] Average of 3 experiments with yields of 35%, 38% and 39%. [h] Four experiments.



Scheme 1 Two-step synthesis of β-aryl-α-nitro-α,β-enals **6**.

together with some dark material that remained attached to the column and some very minor unidentified eluates, a single major product (Table 1, entry 1). Its identification as the protected nitrocyclitol **8a** was confirmed by X-ray crystallography (Fig. 2),[15] and proved that the desired annulation was indeed feasible

Slightly better annulation yields were obtained when the enamine of **7** was not isolated, but generated *in situ* before addition of **6a** (entry 2). It was also found that although addition of a whole equivalent of pyridinium *p*-toluenesulfonate (PPTS) completely inhibited the process, addition of 0.2 equiv. was beneficial, increasing the yield of **8a** to 38% in both CH_3CN and DMF (entries 3–5).[16] We judged this yield to be satisfactory, considering that an easily purified complex product with five new stereogenic carbons had been formed in a single step from two achiral materials (one commercial and the other prepared in two steps from commercial aldehydes), and moved on to evaluate the annulation process with other α-nitroenals. The piperonal-derivative **6b** behaved similarly to its furyl analogue **6a** (compare for example entries 2 and 6). It was also observed that the amount of pyrrolidine could be reduced to 0.8 equiv. (entry 7); that yields were reproducible (entry 8, note *g*); and that the process could be scaled up to the gram level (entry 9). The annulation of nitroenals **6c** and **6d** was achieved with similar efficiencies (entries 10–12), the annulated products **8c** and **8d** being again easily purified as virtually the sole elutable products.

Finally, to demonstrate the potential of the new annulation procedure, we used it to carry out a gram-scale preparation of the protected pancratistatin analogue 7-deoxy-2-*epi*-pancratistatin tetraacetate (**2**). We chose a pancratistatin as our target because the relative configurations of C2, C3, C4, C5 and C6 of **8** match those of C3, C4, C4a, C10b and C1 of natural pancratistatin (**1**), a product with great antitumoral potential that is obtainable only in minute quantities from natural sources (screening at the U.S. National Cancer Institute was suspended because of scant supply)[5b] and for which no practical syntheses have been developed (despite considerable efforts).[5a,b] We chose to prepare a 7-deoxy pancratistatin because the absence of the 7-hydroxy group, which is known not to be essential for antitumoral activity,[5c] allows the use of inexpensive piperonal as starting aldehyde rather than expensive 5-methoxypiperonal. Finally, we chose to prepare a pancratistatin with *R* rather than *S* configuration at C2 because this would allow investigation of the influence of C2 configuration on the antitumoral activity of pancratistatins.

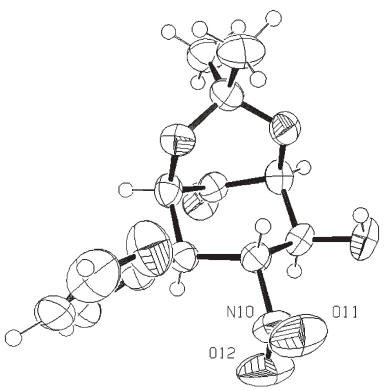
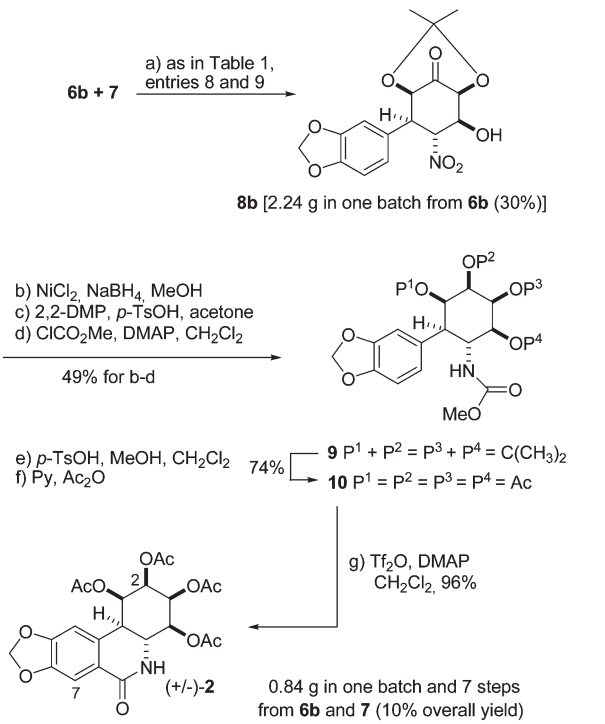


Fig. 2 Crystal structure of **8a** (50% probability ellipsoids for C, N and O; H's as fixed-size spheres).[15]

Following the synthetic plan indicated in Scheme 2, we began by preparing 2.24 g of nitrocyclitol **8b** in one-batch from α-nitroenal **6b**. We then simultaneously reduced the nitro group and the carbonyl (with complete stereocontrol),[17] protected the four hydroxyl groups as acetonides and converted the amino group into a methyl carbamate, thus forming **9**. Replacing the isopropylidene groups by acetyls gave **10**, and final cyclization[18] afforded 0.84 g of the desired product **2**, in seven steps and 10% overall yield from commercial dioxanone, **7**.[19]

In conclusion, β-aryl-α-nitro-α,β-enals, a family that has hitherto been largely overlooked, offer extraordinary promise for organic synthesis. The novel annulation process described in this paper allows their conversion, in one easy step and under very mild conditions, into crystalline and highly complex β-aryl-substituted nitrocyclitols that are easily isolated and which conformationally locked bridgehead structures facilitate further stereoselective transformations. It is expected that the new annulation will find wide acceptance for the preparation of compounds containing cyclitol units,[20] and that further advances may follow as the result of increased interest in the chemistry of α-nitroenals.

This work was supported by ERDF in collaboration with the Spanish Ministries of Science and Technology (under Project



Scheme 2 Gram-scale synthesis of (±)-7-deoxy-2-*epi*-pancratistatin tetraacetate (**2**) from nitroenal **6b** and commercial dioxanone **7**.

BQU2002-01176) and Education and Science (under Project CTQ2005-02338), and by the Xunta de Galicia through Project PGIDIT05BTF20901PR and through a fellowship awarded to L.O.

Notes and references

1 (*a*) B. V. L. Potter and D. Lampe, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1933; (*b*) K. Hinterding, D. Alonso-Díaz and H. Waldmann, *Angew. Chem., Int. Ed.*, 1998, **37**, 688; (*c*) R. L. Patterson, D. Boehning and S. H. Snyder, *Annu. Rev. Biochem.*, 2004, **73**, 437; (*d*) M. Bennett, S. M. N. Onnebo, C. Azevedo and A. Saiardi, *Cell. Mol. Life Sci.*, 2006, **63**, 552.

2 M. S. Gültekin, M. Çelik and M. Balci, *Curr. Org. Chem.*, 2004, **8**, 1159.

3 (*a*) T. Mahmud, *Nat. Prod. Rep.*, 2003, **20**, 137; (*b*) X. Chen, Y. Fan, Y. Zheng and Y. Shen, *Chem. Rev.*, 2003, **103**, 1955.

4 The aminocyclitol voglibose, for example, is already being prescribed for diabetics.

5 For the most recent comprehensive critical review of pancratistatins, see: (*a*) U. Rinner and T. Hudlicky, *Synlett*, 2005, 365–387. See also: (*b*) O. N. Nadein and A. Kornienko, *Org. Lett.*, 2004, **6**, 831; (*c*) U. Rinner, H. L. Hillebrenner, D. R. Adams, T. Hudlicky and G. R. Pettit, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 2911.

6 For the pharmacological potential and biological mode of action of pancratistatins, see: (*a*) S. Pandey, N. Kekre, J. Naderi and J. McNulty, *Artif. Cells, Blood Substitutes, Immobilization Biotechnol.*, 2005, **33**, 279; (*b*) A. McLachlan, N. Kekre, J. McNulty and S. Pandey, *Apoptosis*, 2005, **10**, 619; (*c*) N. Kekre, C. Griffin, J. McNulty and S. Pandey, *Cancer Chemother. Pharmacol.*, 2005, **56**, 29.

7 Other examples of natural products with polyhydroxylated cyclohexanes in their structure include: wailupemycins [(*a*) S. F. Kirsch and T. Bach, *Chem.–Eur. J.*, 2005, **11**, 7007]; hibarimicins [(*b*) K. Kim, U. S. M. Maharoof, J. Raushel and G. A. Sulikowski, *Org. Lett.*, 2003, **5**, 2777] and tetrodotoxins [(*c*) *Tetrodotoxin, Saxitoxin, and the Molecular Biology of the Sodium Channel*; C. Y. Kao, S. R. Levinson, Eds.; New York Academy of Sciences: New York, 1986; Vol. 479; (*d*) D. B. Tikhonov and B. S. Zhorov, *Biophys. J.*, 2005, **88**, 184; (*e*) S. L. Geffeney, E. Fujimoto, E. D. Brodie, III, E. D. Brodie and P. C. Ruben, *Nature*, 2005, **434**, 759].

8 W. Schmid and G. M. Whitesides, *J. Am. Chem. Soc.*, 1990, **112**, 9670.

9 For reviews see: (*a*) B. Fraser-Reid and R. Tsang, in *Strategies and Tactics in Organic Synthesis*, ed. T. Lindberg, 1989, vol. 2, 123–62; (*b*) R. J. Ferrier and S. Middleton, *Chem. Rev.*, 1993, **93**, 2779; (*c*) A. Martínez-Grau and J. Marco-Contelles, *Chem. Soc. Rev.*, 1998, **27**, 155; (*d*) P. I. Dalko and P. Sinay, *Angew. Chem., Int. Ed.*, 1999, **38**, 773(*e*) J. Zhou, G. Wang, L.-H. Zhang and X.-S. Ye, *Curr. Org. Chem.*, 2006, **10**, 625.

10 Representative sugar-carbocylization methods to prepare polyhydroxylated cyclohexanes include: cycloadditions [(*a*) T. Ishikawa, Y. Shimizy, T. Kudoh and S. Saito, *Org. Lett.*, 2003, **5**, 3879]; rearrangements [Ferrier: (*b*) C. Jaramillo, J.-L. Chiara and M. Martín-Lomas, *J. Org. Chem.*, 1994, **59**, 3135(*c*) P. Serrano, A. Llebaria, J. Vázquez, J. de Pablo, J. M. Anglada and A. Delgado, *Chem.–Eur. J.*, 2005, **11**, 4465]; [3,3] sigmatropic [(*d*) A. V. R. L. Sudha and M. Nagarajan, *Chem. Commun.*, 1998, 925]; Henry reaction [(*e*) R. C. Soengas, J. C. Estévez and R. J. Estévez, *Org. Lett.*, 2003, **5**, 4457]; Horner–Wadsworth–Emmons reaction [(*f*) H. Fukase and S. Horii, *J. Org. Chem.*, 1992, **57**, 3651(*g*) K. S. E. Tanaka, G. C. Winters, R. J. Batchelor, F. W. B. Einstein and A. J. Bennet, *J. Am. Chem. Soc.*, 2001, **123**, 998]; radical cyclization [(*h*) J. Marco-Contelles, C. Pozuelo, M. L. Jimeno, L. Martínez and A. Martínez-Grau, *J. Org. Chem.*, 1992, **57**, 2625(*i*) A. M. Gómez, E. Moreno, S. Valverde and J. C. López, *Eur. J. Org. Chem.*, 2004, 1830]; and ring-closing metathesis [(*j*) L. Hyldtoft, C. S. Poulsen and R. Madsen, *Chem. Commun.*, 1999, 2101; (*k*) C. S. Poulsen and R. Madsen, *J. Org. Chem.*, 2002, **67**, 4441].

11 Polyhydroxylated cyclohexanes and their derivatives have also been prepared from non-sugar precursors; representative examples include: the first one-pot chemo-enzymatic synthesis of a nitrocyclohexitol from γ-nitroaldehydes [(*a*) L. El Blidi, D. Crestia, E. Gallienne, C. Demuynck, J. Bolte and M. Lemaire, *Tetrahedron: Asymmetry*, 2004, **15**, 2951]; Diels–Alder-based approaches from pyrones [(*b*) K. Afarinkia and F. Mahmood, *Tetrahedron*, 1999, **55**, 3129], furane [(*c*) A. Baran, C. Kazaz, H. Seçen and Y. Sütbeyaz, *Tetrahedron*, 2003, **59**, 3643; (*d*) O. Arjona and J. Plumet, *Curr. Org. Chem.*, 2002, **6**, 571; (*e*) J. L. Aceña, O. Arjona, R. F. de la Pradilla, J. Plumet and A. Viso, *J. Org. Chem.*, 1994, **59**, 6419], and cyclopentadiene derivatives [(*f*) G. Mehta and S. S. Ramesh, *Chem. Commun.*, 2000, 2429]; methods based on the oxidation of benzenes [(*g*) K. Faber, *Pure Appl. Chem.*, 1997, **69**, 1613] and unsaturated cyclohexanes [(*h*) T. J. Donohoe, P. D. Hohnson, R. J. Pye and M. Keenan, *Org. Lett.*, 2005, **7**, 1275]; methods based on the derivatization of quinic acid [(*i*) C. González, M. Carballido and L. Castedo, *J. Org. Chem.*, 2003, **68**, 2248(*j*) T. M. Shing and V. W.-F. Tai, *J. Org. Chem.*, 1995, **60**, 5332] and inositols [(*k*) A. Krief, W. Dumont, D. Billen, J.-J. Letesson, P. Lestrate, P. J. Murphy and D. Lacroix, *Tetrahedron Lett.*, 2004, **45**, 1461]; and the preparation of diaminocyclitols from serine based on ring-closing metathesis [(*l*) X. Cong, Q.-J. Liao and Z.-J. Yao, *J. Org. Chem.*, 2004, **69**, 5314].

12 Hitherto, only one β-aryl-α-nitro-α,β-enal has been mentioned in the literature: 2-nitro-3-[2-(trifluoromethyl)phenyl]-2-propenal, which was named in a German patent [S. Goldmann, M. Bechem, Ger. Offen. (1994), DE 4222770 A1].

13 The only known β-heteroaryl-α-nitro-α,β-enals are three β-furyl-α-nitroenals prepared by nitration of β-furyl-2-propenals with N_2O_4 [A. I. Sitkin, V. I. Klimenko and A. L. Fridman, *Zh. Org. Khim.*, 1975, **11**, 2452].

14 Further details will be given in a forthcoming full paper.

15 (*a*) Crystallographic data for **8a**: $C_{13}H_{15}NO_7$, M = 297.26, orthorhombic, a = 18.300(4), b = 6.1987(18), c = 12.443(4) Å, U = 1411.5(7) Å^3, T = 293(2) K, space group $Pna2_1$, Z = 4, μ = 0.986 mm^{-1}, 1480 reflections measured, the final w$R(F_2)$ was 0.1382 (all data). CCDC 277671. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b606277f(*b*) Fig. 2 was prepared using Ortep-3 for Windows: L. J. Farrugia, *J. Appl. Crystallogr.*, 1997, **30**, 565.

16 *General annulation procedure.* 2,2-Dimethyl-1,3-dioxan-5-one (**7**), freshly distilled pyrrolidine and the solvent (dry CH_3CN or dry DMF) were sequentially introduced into an oven-dried reaction flask under Ar. If so indicated, PPTS was added after 10 min of stirring. After 1 h at rt and cooling to 0 °C, the appropriate α-nitroenal **6** (1 equiv.) was added to a final concentration of 0.1–0.2 M, either as a solid or as a solution in the same solvent. After additional stirring for 1 h at 0 °C and 1 h at rt, the reaction was quenched by addition of either 5 : 1 EtOH–H_2O or a 1 : 4 mixture of aqueous 0.1 N HCl and acetone, and stirring was continued at rt for 20 h or 1–2 h, respectively. Nitrocyclitols **8** were obtained by extraction and chromatography. Nitrocyclitol **8b**: Prepared according to the general annulation procedure using a solution of 2.75 g (21.15 mmol) of dioxanone **7** and 0.88 mL (16.92 mmol, 0.8 equiv.) of pyrrolidine in DMF (93 mL), 1.06 g (4.23 mmol, 0.2 equiv) of PPTS and a solution of crude nitroenal **6b** in DMF (45 mL) [**6b** was obtained as a 1.5 : 1 mixture of geometric isomers from the corresponding alcohol precursor (4.72 g, 21.16 mmol) and IBX (11.85 g, 42.23 mmol, 2 equiv.) in AcOEt (137 mL)]. After stirring for 1 h at 0 °C and 10 h at rt, quenching with 5 : 1 EtOH–H_2O (561 mL, stirring for 20 h), partial evaporation of the solvent, and extraction (Et_2O, 3 × 374 mL), chromatography (silica gel, 25% AcOEt–hexane) afforded **8b** as a pale yellow solid (2.236 g, 30%). Rf = 0.36 (25% EtOAc–hexane); mp = 203 °C (hexane/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.51 (s, 3H), 1.64 (s, 3H), 2.95 (bs, 1H), 3.11 (dd, J = 12, 1.2 Hz, 1H), 4.21 (bs, 1H), 4.34 (dd, $J \approx$ 1.5 Hz, 1H), 4.50 (dd, $J \approx$ 2.4 Hz, 1H), 5.30 (dd, J = 12, 11.6 Hz, 1H), 5.95 (s, 2H), 6.75 (m, 2H), 6.95 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.31, 28.36, 50.03, 76.15, 79.02, 79.18, 90.98, 99.94, 101.34, 108.50, 108.63, 122.42, 127.39, 148.09, 148.12, 205.43 ppm; IR ($CHCl_3$) 1733 (CO), 1556 (NO_2) cm^{-1}; LRMS (CI, CH_4) m/z (%) 379 [100, (M + 28)$^+$]; anal calcd for $C_{16}H_{17}NO_8$: C, 54.70; H, 4.88; N, 3.99; found: C, 55.05; H, 5.23; N, 3.97.

17 J. O. Osby and B. Ganem, *Tetrahedron Lett.*, 1985, **26**, 6413.

18 (*a*) M. G. Banwell, B. D. Bissett, S. Busato, C. J. Cowden, G. C. R. Hockless, J. W. Holman, R. W. Read and A. W. Wu, *J. Chem. Soc., Chem. Commun.*, 1995, 2551; (*b*) M. G. Banwell, C. J. Cowden and R. W. Gable, *J. Chem. Soc., Perkin Trans. 1*, 1994, 3515.

19 7-Deoxy-2-*epi*-pancratistatin (obtained from **2** by hydrolysis with K_2CO_3 in MeOH) is currently undergoing biological screening against the human large cell lung carcinoma cell line NCI-H460.

20 Subsequent derivatization of **8**, in particular through well-established reactions involving their NO_2 group (α-alkylations, condensations, eliminations, conversion of the NO_2 into methylene and keto groups, *etc*), should allow access to a variety of cyclitols, including non-amino cyclitols.