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Cyclopentanes from *N*-amino-glyconolactams. A synthesis of mannostatin A

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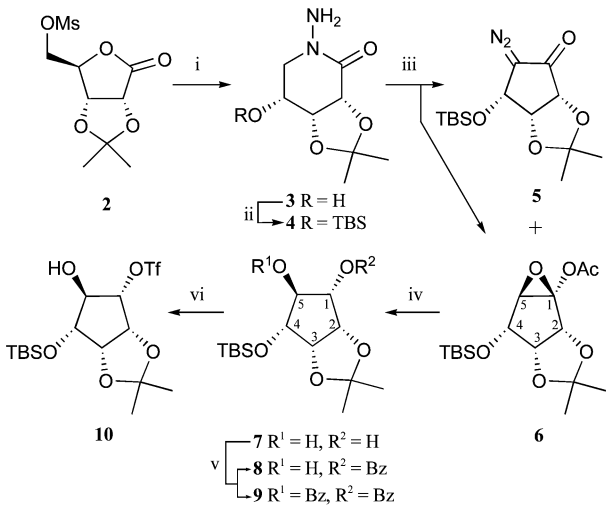
Oxidation of a *N*-amino-ribonolactam with lead tetraacetate yields two cyclopentanes; the major one was transformed into the α-mannosidase inhibitor mannostatin A.

Several highly functionalized cyclopentanes are strong glycosidase inhibitors; pertinent examples are mannostatin A (**1**) and B,[1] trehazolin, and allosamidine.[2] Carbohydrates are attractive starting materials for the synthesis of such highly functionalized cyclopentanes, and the methods for the transformation of monosaccharides and inositols into cyclopentanes have been reviewed.[2,3] In the context of our work on the inhibition of mannosidases[4] we required mannostatin A (**1**). This glycosidase inhibitor was isolated by Aoyagi and collaborators[1a,b] in 1989, and several syntheses of **1** have been reported.[2,5] Two use ribose[5b,f] as starting material and proceed *via* an aldolisation, and one starts from myo-inositol.[5a,h,i]

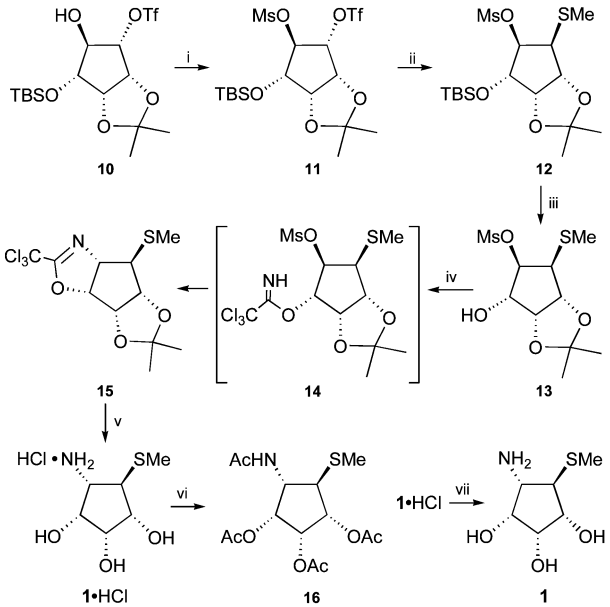
We considered the unexplored *N*-aminoglyconolactams[6] attractive starting materials for the synthesis of highly functionalized carbocyclic compounds. Oxidation of *N*-aminoglyconolactams should lead to *N*-acyl-1,1-diazenes that may lose nitrogen and cyclize. Indeed, sulfoximine precursors of *N*-aminopyrrolidinone-derived diazenes were thermally or photochemically transformed into cyclobutanones,[6d] while oxidation of an *N*-aminobutyrolactam with tBuOCl led to a cyclic *N*-acyl-1,1-diazene and hence to a pyridazinone.[6e]

The *N*-aminoribonolactam **4**† was chosen as starting material for the synthesis of mannostatin A (**1**). This *N*-aminolactam was prepared in two high-yielding steps from the known mesylate **2** that is available in a yield of 90% from D-ribonolactone (Scheme 1).[7] Oxidation of **4** with $Pb(OAc)_4$ in toluene gave a mixture of the acetoxyepoxide **6**† and the diazoketone **5**† that were isolated in 48 and 27% yield, respectively.

Reduction of **6** with $LiAlH_4$ gave the *trans*-diol **7**.† A H-bond between HO–C(1) and O–C(2) was evidenced by *J*(HCOH) of 9.7 Hz. It should enhance the nucleophilicity of C(1)OH and allow a regioselective acylation. Indeed, benzoylation of **7** by treatment with TMEDA and BzCl[8] at −40 °C gave a mixture of a monobenzoate **8** (71%), a dibenzoate **9** (7%), and recovered **7** (13%). Crystal structure analysis of the dibenzoate **9**‡ established the configuration of **7**, and further evidenced the structure of **6**.† Similarly to this benzoylation, triflation at −60 °C of **7** proceeded selectively to provide the monotriflate **10** (91%) which was mesylated to yield 99% of **11** (Scheme 2). Treating **11** with excess NaSMe in THF gave the mesyloxy thioether **12** (95%). Substitution of the mesyloxy group by azide did not proceed at r.t., and increasing the temperature led to elimination only. Desilylation of **12** at r.t. provided the alcohol **13**, besides the corresponding epoxide; desilylation at −30 °C yielded 99% of **13**. The trichloroacetimidate **14** was formed in high yield by treating **13** with trichloroacetonitrile in the presence of DBU. Cyclisation of isolated **14** in the presence of diisopropylethylamine provided **15** in a rather low yield, while treating the alcohol **13** and trichloroacetonitrile sequentially with DBU and diisopropylethylamine yielded 80% of the desired oxazoline **15**§ besides 13% of the trichloroacetamide **14**. Hydrolysis of **15** with HCl in MeOH afforded **1**·HCl.¶ Its ^1H and ^{13}C NMR spectra and its specific rotation are in agreement with published data.[1b,5] Acetylation of **1**·HCl provided the known tetraacetate **16**.¶ Its melting point and its ^1H and ^{13}C NMR data are in agreement with literature,[5] and its specific rotation corresponds to the highest published value.[5h] The free base **1**¶ was obtained by chromatography of **1**·HCl on Amberlite IR-120 (H^+) resin using 0.5 M aqueous ammonia as eluent. It inhibited jack bean α-mannosidase with IC_{50} = 48 nM (lit.[1c] IC_{50} = 70 nM).



Scheme 1 *Reagents and conditions*: i, $NH_2NH_2{\cdot}H_2O$, r.t., quant.; ii, TBSOTf, Py, 0–23 °C, 85%; iii, $Pb(OAc)_4$, toluene, **5** (27%), **6** (48%); iv, $LiAlH_4$, THF, 0 °C, 81%; v, BzCl, TMEDA, CH_2Cl_2, −40 °C, **8** (71%), **9** (7%); vi, Tf_2O, py, −60 °C, 91%.



Scheme 2 *Reagents and conditions*: i, Ms_2O, py, 0 °C, 99%; ii, NaSMe, 15-crown-5, THF, r.t., 95%; iii, TBAF, −30 °C, 99%; iv, Cl_3CCN, DBU, *o*-xylene, r.t., 3 h, then $(i\text{-Pr})_2NEt$, 110 °C, 14 h, **15** (80%) and **14** (13%); v, 7 M HCl/MeOH (1:1), r.t., 94–98%; vi, Ac_2O, py, 93%; vii, Amberlite IR-120 (H^+), 80%.

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To rationalise the conspicuous *endo*-orientation of the acetoxy group of **6**, we assume that **6** results from electrocyclisation of an acetoxy carbonyl ylide. This carbonyl ylide may be formed by nitrogen extrusion from an acetoxy 1,3,4-oxadiazoline. The formation of this oxadiazoline from **4** may begin with a well-precedented *N*-acetoxylation[9] that is followed by ring expansion to an *N*-acyldiazene, isomerisation, acetoxylation, and ring closure.[10] This reaction mechanism and the chemistry of the diazoketone **5** are under investigation.

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Notes and references

† All new compounds showed satisfactory spectroscopic and mass spectrometry data. Selected data of **4**: ^{1}H NMR (300 MHz, $CDCl_3$): 4.47 (d, J = 5.9, H–C(2)); 4.46 (s, exchanged with D_2O, NH_2); 4.39 (br. dd, J = 5.9, 1.9, addition of D_2O and irrad. at 3.41→sharp dd, J = 6.2, 2.5, H–C(3)); 4.12 (ddd, J = 9.3, 4.7, 2.5, H–C(4)); 3.76 (dd, J = 11.8, 9.3, H–C(5)); 3.41 (ddd, J = 11.8, 4.7, 1.25, H–C(5′)); 1.43, 1.39 (2s, Me_2C); 0.90 (s, Me_3C); 0.123, 0.112 (2s, 2 Me_2Si). ^{13}C NMR (75 MHz, $CDCl_3$): 166.4 (s, C=O); 111.2 (s, Me_2C); 76.7 (d, C(2)); 73.8 (d, C(3)); 65.7 (d, C(4)); 52.1 (d, C(5)); 27.2 (q, Me_2C); 26.0 (q, Me_3C); 25.6 (q, Me_2C); 18.5 (s, Me_3C); −4.35, −4.45 (q, Me_2Si). Anal. calc. for $C_{14}H_{28}N_2O_4Si$ (316.47): C 53.13, H 8.92, N 8.85; found: C 53.39, H 8.86, N 8.86%. **5**: IR ($CHCl_3$): 3019m, 2954w, 2932w, 2860w, 2102s, 1679s, 1472w, 1384w, 1375m, 1349m, 1326m, 1306w, 1255m, 1156m, 1133m, 1102m, 873m, 840m. ^{1}H NMR (300 MHz, $CDCl_3$): 5.33 (d, J = 5.3, H–C(2)); 4.62 (t, $J \approx$ 5.4, H–C(3)); 4.49 (d, J = 5.6, H–C(4)); 1.48, 1.39 (2s, Me_2C); 0.93 (s, Me_3C); 0.18, 0.16 (2s, Me_2Si). ^{13}C NMR (75 MHz, $CDCl_3$): 190.8 (s, C=O); 113.5 (s, Me_2C); 81.3 (d, C(2)); 76.3 (d, C(3)); 68.8 (d, C(4)); 27.4, 26.1 (2q, Me_2C); 25.8 (q, Me_3C); 18.5 (s, Me_3C); −4.3, −4.7 (2q, Me_2Si). Anal. calc. for $C_{14}H_{24}N_2O_4Si$ (312.44): C 53.82, H 7.74, N 8.97; found: C 53.91, H 7.65, N 8.89%. **6**: IR ($CHCl_3$): 3031w, 2952m, 2932m, 2858m, 1779s, 1472w, 1464w, 1438w, 1373m, 1251m, 1167m, 1136s, 1090s, 1018m, 973w, 866s, 839s. ^{1}H NMR (300 MHz, $CDCl_3$): 5.01 (dd, J = 5.3, 1.0, H–C(2)); 4.41 (td, $J \approx$ 5.4, 1.0, H–C(3)); 3.94 (d, J = 5.6, H–C(4)); 3.74 (t, J = 1.0, H–C(5)); 2.15 (s, OAc); 1.49, 1.36 (2s, Me_2C); 0.92 (s, Me_3C); 0.12 (s, Me_2Si). ^{13}C NMR (75 MHz, $CDCl_3$): 169.4 (s, C=O); 113.7 (s, Me_2C); 86.8 (s, C(1)); 81.4 (d, C(3)); 78.0 (d, C(2)); 69.6 (d, C(4)); 64.2 (d, C(5)); 26.9, 26.1 (2q of Me_2C, 3q of Me_3C); 21.2 (q, OAc); 18.8 (s, Me_3C); −4.3, −4.9 (2q, Me_2Si). ESI-MS: 345 ($[M + H]^+$); 362 ($[M + H_2O]^+$); 367 ($[M + Na]^+$); 383 ($[M + K]^+$). Anal. calc. for $C_{16}H_{28}O_6Si$ (344.48): C 55.79, H 8.19; found: C 55.82, H 8.21%. **7**: ^{1}H NMR (300 Hz, $CDCl_3$): 4.44, 4.41 (2t, $J \approx$ 5.8, H–C(2), H–C(3)); 3.88 (td, J = 8.7, 2.2, H–C(5)); 3.60 (dd, $J \approx$ 9.0, 5.0, H–C(4)); 3.59 (td, J = 10.0, 5.6, H–C(1)); 2.63 (d, J = 9.7, exchanged with D_2O, HO–C(1)); 2.46 (br.d, J = 2.2, exchanged with D_2O, HO–C(5)); 1.48, 1.32 (2s, Me_2C); 0.92 (s, Me_3C); 0.14, 0.10 (2s, Me_2Si). ^{13}C NMR (75 Hz, $CDCl_3$): 111.4 (s, Me_2C); 79.5 (d, C(5)); 77.6, 75.4 (2d, C(2) and C(3)); 74.4 (d, C(4)); 73.2 (d, C(1)); 25.9 (3q of Me_3C, 2q of Me_2C); 24.3 (2q of Me_2C); 18.4 (s, Me_3C); −4.55, −4.50 (2q, Me_2Si). HI-MALDI-MS: 327.1595 (7.3, $C_{14}H_{28}O_5SiNa$, $[M + Na]^+$, calc. 327.1604). For **5**, strong IR-bands at 2102 and 1679 cm^{-1} and a ^{13}C singlet at 190.8 ppm evidence the diazo and the carbonyl groups. For **6**, a strong IR band at 1779 cm^{-1}, a ^{1}H singlet at 2.15 ppm, and a ^{13}C singlet at 169.4 ppm evidence the acetoxy group. A dd at 5.01 ppm (J = 5.3, 1.0) and the td at 4.41 ppm ($J \approx$ 5.4, 1.0) were assigned to H–C(2) and H–C(3), respectively; a d (J = 5.6) resonating at higher fields (3.94 ppm) was assigned to H–C(4), geminal to the silyloxy group. A t at 3.74 ppm (J = 1.0) was assigned to H–C(5). A NOE (6.6%) between the dd at 5.01 ppm (H–C(2)) and the td at 4.41 ppm (H–C(3)) and a NOE (5.7%) between the td at 4.41 ppm (H–C(3)) and the d at 3.94 ppm (H–C(4)) evidence that (H–C(2)), (H–C(3)), and (H–C(4)) are *cis* to each other while a weak NOE of 2.8% between the d at 3.94 ppm (H–C(4)) and the t at 3.74 ppm (H–C(5)) evidences that (H–C(5)) is *trans* to (H–C(4)).

‡ Crystal data for **9**: $C_{28}H_{36}O_7Si$, M = 512.66, monoclinic, a = 6.3780(10), b = 19.449(5), c = 11.752(3) Å, V = 1420.4(6) Å^3, T = 293(2) K, space group $P2_1$, Z = 2, μ(Cu-K$_\alpha$) = 1.076 mm^{-1}, 2627 reflections measured, 2283 unique (R_{int} = 0.027). Flack = −0.10(7). *R1* = 0.0509. The final *wR*(F^2) was 0.1632 (all data). CCDC 202048. See http://www.rsc.org/suppdata/cc/b3/b301213a/ for crystallographic data in .cif or other electronic format.

§ Selected data of **15**: ^{1}H NMR (300 Hz, $CDCl_3$): 5.25 (ddd, J = 8.0, 5.9, 0.6, irrad. at 3.55→dd, J = 8.4, 5.9, H–C(4)); 4.82 (t, J = 5.6, H–C(3)); 4.61 (dd, J = 8.1, 2.2, irrad. at 3.55→d, J = 8.3, H–C(5)); 4.58 (dd, J = 5.6, 2.2, irrad. at 3.55→d, J = 5.6, H–C(2)); 3.58–3.51 (m, H–C(1)); 2.25 (s, MeS); 1.49, 1.33 (2s, Me_2C). ^{13}C NMR (75 Hz, $CDCl_3$): 162.1 (s, C=N); 112.9 (s, Me_2C), 86.4, 85.2, 80.3, 79.6 (4d, C(2), C(3), C(4), and C(5)); 53.1 (d, C(1)); 26.5, 24.4 (2q of Me_2C); 15.6 (q, MeS). ESI-MS: 346, 348, 350, 352 ($[M + H]^+$). Anal. calc. for $C_{11}H_{14}NO_3SCl_3$ (346.66): C 38.11, H 4.07, N 4.04, S 9.25, Cl 30.68; found: C 38.32, H 4.30, N 4.04, S 9.20, 30.61%.

¶ Selected data of **1**·HCl: $[\alpha]_D^{25}$ = +7.5 (c = 0.95, MeOH); $[\alpha]_D$ = +5.9 (c = 1.08, MeOH);[5d] selected data of **16**: m.p. 121.5–122.5 °C; m.p. 121 °C;[1b] m.p. 119–120 °C;[5b] m.p. 122–123 °C;[5h] m.p. 119–121 °C.[5i] $[\alpha]_D^{25}$ = +18.3 (c = 1.02, $CHCl_3$); $[\alpha]_D$ = +8.5 (c = 0.9, $CHCl_3$);[5b] $[\alpha]_D^{28}$ = +7.4 (c = 0.45, $CHCl_3$);[5i] $[\alpha]_D^{27}$ = +16 (c = 0.88, $CHCl_3$).[5h] Synthetic (+)-**1** inhibited jack bean α-D-mannosidase with IC_{50} = 48 nM; (*p*-nitrophenyl α-D-mannopyranoside, acetate buffer, pH 4.5).

1 (*a*) T. Aoyagi, T. Yamamoto, K. Kojiri, H. Morishima, M. Nagai, M. Hamada, T. Takeuchi and H. Umezawa, *J. Antibiot.*, 1989, **42**, 883; (*b*) H. Morishima, K. Kojiri, T. Yamamoto, T. Aoyagi, H. Nakamura and Y. Iitaka, *J. Antibiot.*, 1989, **42**, 1008; (*c*) J. E. Tropea, G. P. Kaushal, I. Pastuszak, M. Aoyagi, R. J. Molyneux and A. D. Elbein, *Biochemistry*, 1990, **29**, 10062.

2 Their chemistry has been reviewed, see: A. Berecibar, C. Grandjean and A. Siriwardena, *Chem. Rev.*, 1999, **99**, 779.

3 (*a*) A. D. Borthwick and K. Biggadike, *Tetrahedron*, 1992, **48**((4)), 571; (*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*) J. Marco-Contelles, C. Alhambra and A. Martínez-Grau, *Synlett*, 1998, 693; (*e*) P. I. Dalko and P. Sinaÿ, *Angew. Chem., Int. Ed.*, 1999, **38**, 773.

4 (*a*) A. Vasella, G. J. Davies and M. Böhm, *Curr. Opin. Chem. Biol.*, 2002, **6**, 619; (*b*) L. Remen and A. Vasella, *Helv. Chim. Acta*, 2002, **85**, 1118; (*c*) E. Lorthiois, M. Meyyappan and A. Vasella, *Chem. Commun.*, 2000, **29**, 1829; (*d*) C. V. Ramana and A. Vasella, *Helv. Chim. Acta*, 2000, **83**, 1599.

5 (*a*) S. Ogawa and Y. Yuming, *J. Chem. Soc., Chem. Commun.*, 1991, 890; (*b*) S. Knapp and T. G. M. Dhar, *J. Org. Chem.*, 1991, **56**, 4096; (*c*) B. M. Trost and D. L. Van Vranken, *J. Am. Chem. Soc.*, 1991, **113**, 6317; (*d*) S. B. King and B. Ganem, *J. Am. Chem. Soc.*, 1991, **113**, 5089; (*e*) B. M. Trost and D. L. Van Vranken, *J. Am. Chem. Soc.*, 1993, **115**, 444; (*f*) C. Li and P. L. Fuchs, *Tetrahedron Lett.*, 1994, **35**, 5121; (*g*) S. B. King and B. Ganem, *J. Am. Chem. Soc.*, 1994, **116**, 562; (*h*) S. Ogawa, H. Kimura, C. Uchida and T. Ohashi, *J. Chem. Soc., Perkin Trans. 1*, 1995, 1695; (*i*) S. Ogawa and Y. Yuming, *Bioorg. Med. Chem.*, 1995, **3**, 939; (*j*) R. Ling and P. S. Mariano, *J. Org. Chem.*, 1998, **63**, 6072.

6 For the formation of an *N*-aminoriburonolactam, see (*a*) R. R. Schmidt, K.-H. Jung and P. Hermentin, *Chem. Ber.*, 1978, **111**, 3311; (*b*) for leading references to the chemistry of non-carbohydrate derived *N*-aminolactams, see P. A. S. Smith, *Derivatives of Hydrazine and Other Hydronitrogens Having N–N Bonds*, The Benjing/Cummings Publishing, Massachusetts, 1983; (*c*) R. Braslau, M. O. Anderson, F. Rivera, A. Jimenez, T. Haddad and J. R. Axon, *Tetrahedron*, 2002, **58**, 5513; (*d*) R. D. Miller, P. Gölitz, J. Janssen and J. Lemmens, *J. Am. Chem. Soc.*, 1984, **106**, 7277; (*e*) R. D. Miller, P. Gölitz, J. Janssen and J. Lemmens, *J. Am. Chem. Soc.*, 1984, **106**, 1508.

7 (*a*) R. Bisaz, Ph.D, ETH-Zürich, 1975; (*b*) H. Kold, I. Lundt and C. Pedersen, *Acta Chem. Scand.*, 1994, **48**, 675.

8 G. Hu and A. Vasella, *Helv. Chim. Acta*, 2002, **85**, 4369.

9 (*a*) R. S. Atkinson and B. J. Kelly, *J. Chem. Soc., Chem. Commun.*, 1987, 1362; (*b*) R. S. Atkinson and B. J. Kelly, *J. Chem. Soc., Chem. Commun.*, 1989, 836; (*c*) R. S. Atkinson, M. J. Grimshire and B. J. Kelly, *Tetrahedron*, 1989, **45**, 1362.

10 (*a*) D. C. Iffland, L. Salisbury and Wm. R. Schafer, *J. Am. Chem. Soc.*, 1961, **83**, 747; (*b*) R. W. Hoffmann and H. J. Luthardt, *Tetrahedron Lett.*, 1966, 411; (*c*) W. A. F. Gladstone and R. O. C. Norman, *J. Chem. Soc. (C)*, 1966, 1531; (*d*) R. W. Hoffmann and H. J. Luthardt, *Chem. Ber.*, 1968, **101**, 3851; (*e*) R. W. Hoffmann and H. J. Luthardt, *Chem. Ber.*, 1968, **101**, 3861; (*f*) A. Stojiljkovic, N. Orbovic, S. Sredojevic and M. Lj. Mihailovic, *Tetrahedron*, 1970, **26**, 1101.