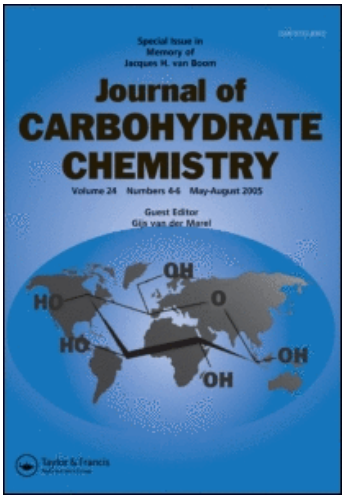
This article was downloaded by:
On: *23 January 2011*
Access details: *Access Details: Free Access*
Publisher *Taylor & Francis*
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Flexible Synthesis of Polyhydroxylated 2,2-Disubstituted Pyrrolidines

Frank Schieweck; Hans-Josef Altenbach

To cite this Article Schieweck, Frank and Altenbach, Hans-Josef(2000) 'Flexible Synthesis of Polyhydroxylated 2,2-Disubstituted Pyrrolidines', Journal of Carbohydrate Chemistry, 19: 4, 647 — 652
To link to this Article: DOI: 10.1080/07328300008544107
URL: http://dx.doi.org/10.1080/07328300008544107

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

J. CARBOHYDRATE CHEMISTRY, 19(4&5), 647–652 (2000)

COMMUNICATION

FLEXIBLE SYNTHESIS OF POLYHYDROXYLATED 2,2-DISUBSTITUTED PYRROLIDINES[1]

Frank Schieweck and Hans-Josef Altenbach*

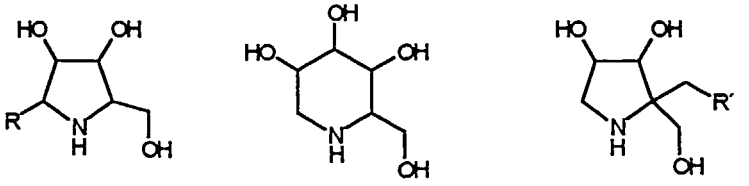
Department of Organic Chemistry, Bergische Universität-GH Wuppertal, D-42119 Wuppertal, Gaußstrasse 20, Germany

Received September 27, 1999 - Final Form February 7, 2000

Downloaded At: 07:27 23 January 2011

Many polyhydroxylated pyrrolidines and piperidines have attracted considerable attention because they have been shown to selectively inhibit the oligosaccharide processing enzymes by mimicking the transition state.[2] Especially their potential to exhibit antibacterial, antiviral[3] and cancerostatic activities[4] has led to a tremendous interest and demand for flexible synthetic strategies.

In our continuing work on the synthesis of sugar analogues[5] we were interested in the development of new types of polyhydroxylated pyrrolidines.



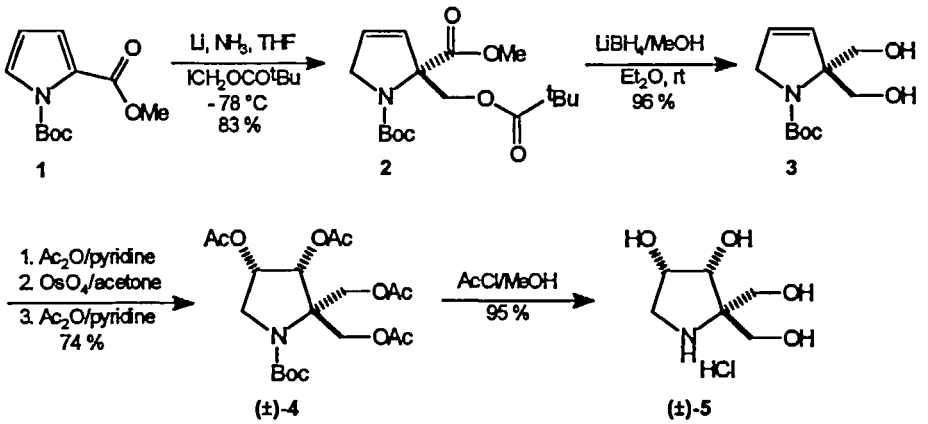
R = H, Alkyl, CH_2OH R' = OH, sugar moiety

While the 2,5-bis-hydroxymethyl pyrrolidines are well investigated and a large number of syntheses have been published so far,[6] the polyhydroxylated 2,2-disubstituted

Copyright © 2000 by Marcel Dekker, Inc. www.dekker.com

pyrrolidines are representatives of a hitherto unknown class of potential glycosidase inhibitors.[7] Herein, we wish to report a short and efficient *de novo* synthesis of 3,4-dihydroxy-2,2-bis-hydroxymethyl-pyrrolidine and a imino-*C*-disaccharide derivative. These systems can be prepared from the inexpensive *N*-Boc methyl pyrrole carboxylate **1**[8] by Birch reduction followed by a reductive alkylation protocol recently published by Donohoe et al.[9] Subsequent functionalisation of the double bond and deprotection led in a highly diastereoselective manner to the 2,2-disubstituted pyrrolidines in good to excellent yield.

Birch reduction of the pyrrole carboxylate **1** and subsequent alkylation with the C_1-synthon pivaloyl iodomethyl ester were best accomplished by the use of 2.15 equiv of lithium at -78 °C in NH_3/THF followed by the addition of 1.20 equiv of the iodomethyl ester after 30 mins. By this procedure the 2,2-disubstituted 2,5-dihydropyrrole **2** was isolated in 83% yield after flash chromatography. Due to the two preferred amide rotamers the ^{1}H NMR spectrum of **2** exhibited for the double bond three signals in a ratio of 0.7:0.3:1 at δ 6.00, 5.93 and 5.53 (dt, ^3J = 6.1 Hz, ^4J = 2.0 Hz) and the ^{13}C NMR spectrum revealed no methine carbon atom apart from the double bond but instead a new quaternary carbon atom.[10]



The diester **2** represents an ideal precursor for the synthesis of the *pro*-chiral diol **3**, a flexible building block for the synthesis of the anticipated pyrrolidine iminosugar. Reduction of **2** was performed by the use of lithium borohydride/methanol in 96% yield. The ^{1}H NMR spectrum of **3** showed for the *pro*-chiral methylene groups an AB system at δ 3.91 (J = 11.2 Hz) and a pseudo singlet δ 4.15 for the methylene protons next to the double bond. Catalytic cis-dihydroxylation of the corresponding diacetate with OsO_4/NMO

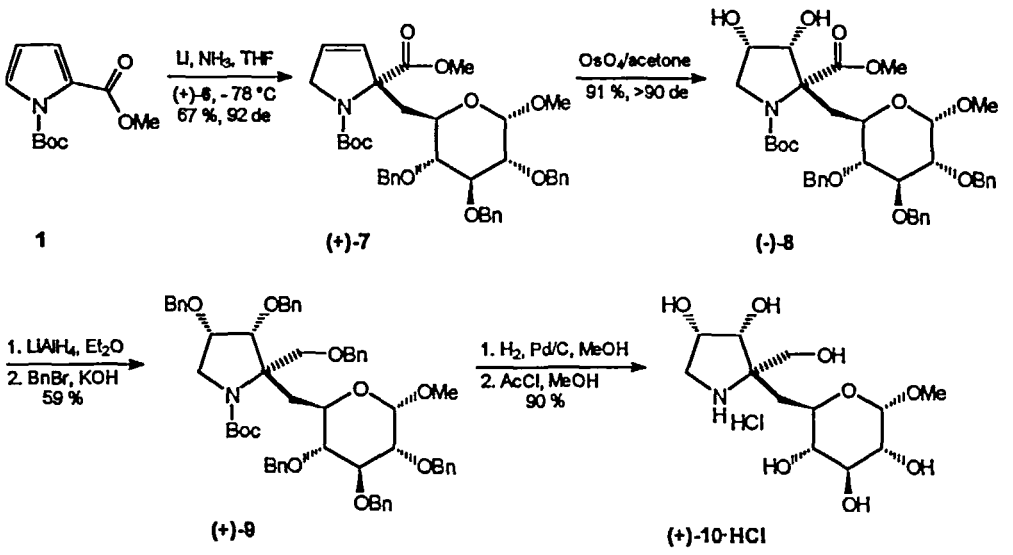
Downloaded At: 07:27 23 January 2011

in acetone/water followed by acetylation yielded the tetraacetate **4** as a colourless oil after flash chromatography. The two methine protons showed a broad ^{1}H NMR absorption between δ = 5.40 - 5.48, and mass spectrometry (EI, 70 eV) revealed a peak at *m/z* 371 (M^+ - AcOH). Acidic deprotection with acetyl chloride in methanol completed the synthesis of 3,4-dihydroxy-2,2-bis-hydroxymethyl-pyrrolidine *rac*-(**5**).[11] In the ^{1}H NMR spectrum (D_2O) of **5** the two protons at C-3 and C-4 showed a coupling constant of 4.6 Hz which is typical for a syn periplanar arrangement, and the four methylene protons of the side chains revealed two slightly shifted AB spinsystems at δ 3.87 (J = 12.2 Hz) and 3.79 (J = 12.2 Hz). High resolution mass spectrometry showed a significant base peak at *m/z* 164 (Calcd. for $C_6H_{14}NO_4$: 164.0923. Found: 164.0916).

In expansion of our methodology we investigated the synthesis of a 2,2-disubstituted iminosugar with a glucose moiety instead of the hydroxymethyl side chain by alkylation with an appropriate glucose halide.[12] Birch reduction of the pyrrole derivative **1** with 2.10 equiv of lithium followed by alkylation with 1.15 equiv of methyl 2,3,4-tri-*O*-benzyl-6-deoxy-6-iodo-α-D-glucopyranoside (**6**)[13] gave after flash chromatography **7**, $[\alpha]_D$ +25.9° ($CHCl_3$), in 67% yield[14] and 10% of the elimination product with an exocyclic double bond.[15] Especially remarkable was the diastereoselectivity of the reaction with a ratio of ≥95:5 as indicated by ^{1}H NMR spectroscopy.

Downloaded At: 07:27 23 January 2011

Compound **7** was then treated with a catalytic amount of OsO_4/NMO in acetone/water to give the cis-dihydroxylated derivative **8**. Investigation of the ^{1}H NMR showed a diastereomeric ratio of ≥95:5. The major isomer was isolated by flash chromatography, $[\alpha]_D$ -19.8° ($CHCl_3$), in 91% yield and was identified by NOESY NMR experiments to have the two hydroxyl groups trans to the bulky glucose moiety.[16] Reduction of the methyl ester was best accomplished with excess of LAH in diethyl ether and yielded the triol as a colourless foam, $[\alpha]_D$ +24.2° (MeOH), in 71% yield, mass spectrometry (EI, 70 eV) showed a peak at *m/z* 647 (M^+ - CH_3OH). Subsequent treatment of the triol with benzyl bromide/KOH in the presence of a phase transfer catalyst[17] afforded after flash chromatography the stable and easy to handle perbenzylated compound **9**, $[\alpha]_D$ +4.4° ($CHCl_3$), in 83% yield. The ^{1}H and ^{13}C NMR spectra are in good agreement with the proposed structure of **9**, mass spectrometry (EI, 70 eV) showed a peak at *m/z* 828 (M^+ - CH_2OBn) and the combustion analysis was consistent with the calcd mass for $C_{59}H_{67}NO_{10}$ (950.18): C, 74.58; H, 7.11; N, 1.47. Found: C, 74.50; H, 7.17; N, 1.56.



Downloaded At: 07:27 23 January 2011

Debenzylation of **9** was accomplished by hydrogenolysis using a catalytic amount of 10% palladium on charcoal in methanol (92% yield, $[\alpha]_D$ +54.4° (MeOH)). Deprotection of the carbamate was quantitatively achieved at 0°C by the *in situ* generation of HCl in methanol with acetyl chloride to give the desired disaccharide **10**, $[\alpha]_D$ +62.0° (MeOH). The significant ^{1}H NMR data of **10** (D_2O) were as follows: δ 4.76 (d, 1H, J = 3.6 Hz, CHOMe), 3.89 (AB, 2H, J = 12.3 Hz, CH_2O), 4.43 (d, 1H, J = 4.7 Hz, CH(OH)-Cq), 3.43 (s, 3H, OMe). The ^{13}C-{^{1}H} NMR of **10** showed twelve signals, one of them being a methyl group, three methylene and one quaternary carbon atom, and HRMS revealed a base peak at *m/z* 310 (M^+ + H): (Calcd for $C_{12}H_{24}O_8N$: 310.1502. Found: 310.1502).

In conclusion, the first synthesis of a polyhydroxylated 2,2-bis-hydroxymethyl pyrrolidine and its 2-hydroxymethyl-2→6-(methyl 6-deoxy-α-D-glucopyranoside) analogue (**5** and **10**) were achieved by reductive alkylation of the pyrrole methyl carboxylate **1** with pivaloyl iodomethyl ester or methyl 2,3,4-tri-*O*-benzyl-6-deoxy-6-iodo-α-D-glucopyranoside respectively. Subsequent functionalisation of the double bond and deprotection yielded the free iminosugars by a short and efficient synthetic sequence. Further studies are under current investigation employing the *pro*-chiral diol **3** as a flexible building block for the synthesis of other 2,2-disubstituted pyrrolidines.

ACKNOWLEDGMENT

This work was in part supported by a scholarship of the state Nordrhein Westfalen. The authors thank M. Braun for a sample of the methyl 2,3,4-tri-*O*-benzyl-6-deoxy-6-iodo-α-D-glucopyranoside and the Bayer AG, Wuppertal, for the high resolution mass spectrometry analysis.

REFERENCES AND NOTES

1. Presented as a poster at the *First Euroconference on Carbohydrates in Drug Research* (ECCDR-1), Sardinia, September 16-19, 1999.
2. a) T. D. Heightman, A. T. Vasella, *Angew. Chem.* **111**, 794 (1999); b) B. Winchester, G. W. J. Fleet, *Glycobiology* **2**, 199 (1992).
3. a) G. W. J. Fleet, A. Karpas, R. A. Dwek, L. E. Fellows, A. S. Tyms, S. Petursson, S. K. Namgoong, N. R. Ramsden, P. W. Smith, J. C. Son, F. Wilson, D. R. Witty, G. S. Jacob, T. W. Rademacher, *FEBS Lett.* **237**, 128 (1988); b) R. A. Gruters, J. J. Neefies, M. Tersmette, R. E. DeGroede, A. Tulp, H. G. Huisman, F. Miedema, H. L. Ploegh, *Nature* **330**, 74 (1987); c) D. A. Winkler, G. Holan, *J. Med. Chem.*, **32**, 2084 (1989).
4. a) K. Tsukamoto, A. Uno, S. Shimada, G. Imokaw, *Clin. Res.* **37A**, 722 (1989); b) J. W. Dennis, K. Koch, D. Becker, *J. Nat. Cancer Inst.* **81**, 1028 (1989); c) B. Woynaroska, H. Wilkiel, M. Sharma, N. Carpenter, G. W. J. Fleet, R. J. Bernacki, *Anticancer Res.* **12**, 161 (1992).
5. a) H.-J. Altenbach, G. Blanda, *Tetrahedron: Asymm.*, **9**, 1519 (1998); b) H.-J. Altenbach, D. J. Brauer, G. F. Merhof, *Tetrahedron*, **53**, 6019 (1997); c) H.-J. Altenbach, K. Himmeldirk, *Tetrahedron: Asymm.*, **6**, 1077 (1995).
6. For an overview see: a) S. G. Lee; Y.-J. Yoon, S. C. Shin, B. Y. Lee, S.-D. Cho, S. K. Kim, J.-H. Lee, *Heterocycles* **45**, 701 (1997); b) N. Ikota, *Heterocycles*, **36**, 2035 (1993); c) G. W. J. Fleet, P. W. Smith, *Tetrahedron Lett.*, **26**, 1469 (1985); d) Y. Le Merrer, L. Poitout, J.-C. Depezay, I. Dosbaa, S. Geoffroy, M.-J. Foglietti, *Bioorg. Med. Chem.*, **5**, 519 (1997).
7. To the best of our knowledge these systems represent a formerly unknown class of iminosugars. Similar structures are the corresponding γ-lactames and saturated 2,2-disubstituted pyrrolidine derivatives, see for example: a) R. Kuciak, W. Sas, *Tetrahedron Lett.*, **35**, 8647 (1994); b) Y. Kishida, A. Terada, *Chem. Pharm. Bull.*, **17**, 2417 (1969); c) M. Koszytkowska-Stawinska, W. Sas, *J. Chem. Res. (S)*, 298 (1998); d) T. Sheradsky, L. Yusupova, *Tetrahedron Lett.*, **36**, 7701 (1995); e) S. Toii, H. Okumoto, A. Genba, *Chem. Lett.*, 747 (1996).
8. a) J. W. Harbuck, H. Rapoport, *J. Org. Chem.*, **37**, 3618 (1972); b) T. J. Donohoe, P. M. Guyo, *J. Org. Chem.*, **61**, 7664 (1996).

Downloaded At: 07:27 23 January 2011

9. T. J. Donohoe, P. M. Guyo, R. L. Beddoes, M. Helliwell, *J. Chem. Soc., Perkin Trans. 1*, 667 (1998).
10. All ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz Bruker ARX 400 NMR spectrometer.
11. A. Nudelman, Y. Bechor, E. Falb, B. Fischer, B. A. Wexler, A. Nudelman, *Synthetic Commun.*, **28**, 471 (1998).
12. For the synthesis of pyrrolidine-based disaccharides see for example: a) K. Kraehenbuehl, S. Picasso, P. Vogel, *Helv. Chim. Acta*, **81**, 1439 (1998); b) I. McCart, A. Duréault, J.-C. Depezay, *Tetrahedron Lett.*, **39**, 4463 (1998); c) G. Mikkelsen, T. V. Christensen, M. Bols, I. Lundt, M. R. Sierks, *Tetrahedron Lett.*, **36**, 6541 (1995); d) K. Dax, M. Ebner, R. Peinsipp, A. E. Stütz, *Tetrahedron Lett.*, **38**, 225 (1997).
13. a) A. Lipták, P. Fügedi, P. Nánási, *Carbohydr. Res.*, **68**, 151 (1979); b) R. L. Whistler, A. K. M. Anisuzzaman, *Meth. Carbohydr. Chem.*, **8**; 227 (1980).
14. Significant spectral data for **7**: ^{1}H NMR ($CDCl_3$) (two amide rotamers in a ratio of 7:3) δ 5.98 (d, J = 6.1 Hz, C<u>H</u>=CH), 5.93 (d, J = 6.1 Hz, C<u>H</u>=CH), 5.45 (d, J = 6.1 Hz, CH=C<u>H</u>), 5.38 (d, J = 6.1 Hz, CH=C<u>H</u>), 4.49 (d, J = 3.5 Hz, C<u>H</u>OMe), 4.47 (d, J = 3.2 Hz, C<u>H</u>OMe), 3.95 (t, J = 9.2 Hz, C-3 glucose), 3.71 (s, CO_2<u>Me</u>) and 3.69 (s, CO_2<u>Me</u>). LRMS (EI, 70 eV): *m/z* 673 (M^+). Anal. Calcd for $C_{39}H_{47}NO_9$ (673.80): C, 69.52; H, 7.03; N, 2.08. Found: C, 69.30; H, 7.11; N, 2.04.
15. P. Letellier, R. Ralainirina, D. Beaupère, R. Uzan, *Tetrahedron Lett.*, **35**, 4555 (1994).
16. Anal. Calcd for $C_{39}H_{49}NO_{11}$ (707.82): C, 66.18; H, 6.98; N, 1.98. Found: C, 65.67; H, 6.80; N, 1.90.
17. D. Dubreuil, J. Cleophax, A. Loupy, *Carbohydr. Res.*, **252**, 149 (1994).

Downloaded At: 07:27 23 January 2011