

0040-4039(95)02237-6

A Formal Synthesis of Castanospermine using an Olefin Metathesis Cyclisation Reaction as a Key Step

Herman S. Overkleeft and Upendra K. Pandit*

Organic Chemistry Laboratory, University of Amsterdam, Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands.

Abstract: The formal synthesis of castanospermine (1) starting from tetrabenzylgluconolactam (3) is described. Olefin metathesis cyclisation reaction of dialkene 9, derived from 3, leads to indolizidinone 10, which can be used as a key intermediate for the synthesis of castanospermine (1) and its analogues.

Introduction. (+)-Castanospermine (1) (Scheme 1) is a member of a large family of polyhydroxylated alkaloids which are analogues of monosaccharides in which the ring oxygen is replaced by a nitrogen atom¹. It is a structural analogue of glucopyranoside (2, R=H) and, thus, is a potent inhibitor of several α - and β -glycosidases². Since the isolation of 1 from *Castanospermum australe*³ and *Alexa leiopetala*³ b castanospermine (1) has been the subject of extensive synthetic efforts which have resulted in several total syntheses of the parent molecule 1 and its structural analogues⁴.



Scheme 1

In connection with a programme on the development of new azasugars as potential glycosidase inhibitors, we have reported a facile general synthesis of sugar lactams⁵. Thus, gluconolactam (4) was synthesised from tetrabenzylglucopyranose (2, R=Bn) in a 4 step sequence via tetrabenzylgluconolactam (3) (Scheme 1) and is available in our laboratory on a multigram scale^{5.6}. We now describe the formal synthesis of 1 starting from 3 via the application of an olefin metathesis cyclisation reaction⁷ in the critical step of the synthetic sequence.

Synthesis. In Scheme 2 the transformation of gluconolactam 3 to dialkene 8 is outlined. N-allylation of lactam 3 was accomplished with allyl bromide, using two-phase conditions with tetrabutylammonium iodide as a phase transfer catalyst, to give 5 in 93% yield. Selective deprotection of the primary alcohol function by treatment with ferric chloride and acetic anhydride and subsequent hydrolysis of the resulting acetate gave alcohol 6, which was oxidised to aldehyde 7 with the Dess Martin periodane⁸, in 80% overall yield. Treatment of this aldehyde with methyl (triphenylphosphoranylidene)acetate gave the Wittig product 8 in 85% yield⁹.



a allyl bromide, KOH (50% aq)/methylene chloride 1:1, TBAI(cat); 93% b Ac₂O, FeCl₃; then NH₃, MeOH c Dess Martin periodane; 80% d Ph₃P=CHCO₂Me; 85%

Scheme 2

The dialkene 8 was subsequently allowed to undergo a metathesis cyclisation reaction with the ruthenium carbene complex 9 as a catalyst⁷ (Scheme 3). It may be noted that since the development of this ruthenium complex and the related molybdenum carbene complex^{7b}, the olefin metathesis cyclisation reaction has aroused a great deal of attention. The syntheses of several oxygen¹⁰ and nitrogen^{11,12} containing heterocycles, including pyrrolidines, pyrrolizidines and indolizidines (using this method) have been published recently. In our own laboratory, a metathesis-mediated closure of a 13-membered ring, in a strategy for preparing the ABCD ring system of the alkaloid manzamine A, was achieved recently¹³.



Scheme 3

The cyclisation of dialkene 8 (catalyst 9, 5% w/w, toluene, 110°) in which one of the reacting alkenes consists of an α - β -unsaturated ester is unprecedented in literature¹⁴. Although this reaction was much slower than that of the corresponding substrate with two terminal olefines⁹, the cyclisation was accomplished yielding 70% of the bicyclic lactam 10¹⁵. The double bond was oxidised, using a catalytic amount of osmium tetroxide with Nmethyl morfoline N-oxide as the cooxidant¹⁶, to form a mixture of diols, which was subsequently transformed into a mixture of sulphites¹⁷ 11 (55%). Oxidation of this mixture gave, after separation on silicagel, the sulphates 12 and 13, almost quantitatively, in a ratio of 1:5. The transformation to the sulphates has been chosen because epoxidation of the double bond in 10 gave unsatisfactory results. Cyclic sulphates can be regarded as chemical equivalents of epoxides which are generally more reactive towards nucleophiles¹⁸. Such a building block has been succesfully used as an intermediate for the synthesis of azasugar pyrrolidines¹⁹. The relative configuration of the sulphates 12 and 13 has been established by NOE experiments (Scheme 4) showing that the major isomer 13 has the stereochemistry corresponding with castanospermine (1). Irradiation of H5 gave a positive effect on H6 and *vice versa*; proving these protons to be on the same side of the bicyclic framework. From analogous experiments performed on the minor isomer 12, proximity of the protons H4 and H6 is evidenced; as would be expected in structure 12.



Scheme 4

Finally, the cyclic sulphate was treated with sodium borohydride in dimethyl acetamide to yield a monosulphate¹⁷, which gave lactam 14 upon hydrolysis. In the reduction step, the product resulting from attack of the hydride from the sterically less hindered side is formed exclusively (98%; Scheme 5).



Scheme 5

All spectroscopic data for 14 are in agreement with those described in the literature^{4a,20} for this compound. The transformation of 14 to the title compound (1) has been accomplished by reducing the lactam to the amine, followed by hydrogenolysis of the benzyl ethers^{4a}.

In conclusion, a new synthesis of castanospermine (1) has been devised. The precursor lactam 15 is synthesised in 11 steps starting from tetrabenzyl gluconolactam (3) in an overall yield of 19%. The olefin metathesis cyclisation reaction has been shown to be a useful method in the synthesis of natural occurring heterocycles. The bicyclic systems 10 and 13 are expected to be useful synthons for the synthesis of new analogues of castanospermine (1).

REFERENCES AND NOTES

Satisfactory spectroanalytical data were obtained for all new compounds.

- 1. For a review on azasugars see: Winchester, B.; Fleet, G. W. J. Glycobiology 1992, 48, 319-388.
- 2. Sinnot, M. L. Chem. Rev. 1990, 90, 1171-1202.
- (a) Hohenschutz, L. D.; Bell, E. A.; Jewess, P. J.; Leworthy, D. P.; Pryce, R. J.; Arnold, E.; Clardy, J. Phytochemistry 1981, 20, 811. (b) Nash, R. J.; Fellows, L. E.; Dring, J. V.; Stirton, C. H.; Carter, D.; Hegarty, M. P.; Bell, E. A. Phytochemistry 1988, 27, 1403.
- 4. For example: (a) Miller, S. A.; Chamberlin, A. R. J. Am. Chem. Soc. 1990, 112, 8100-8112.
 (b) Hamana, H.; Ikota, N.; Ganem, B. J. Org. Chem 1987, 52, 5492-5494. (c) Ina, H.; Kibayashi, C. J. Org. Chem. 1993, 58, 52-61. (d) Gerspacher, M.; Rapoport, H. J. Org. Chem. 1992, 57, 3700.
- (a) Overkleeft, H. S.; van Wiltenburg, J.; Pandit, U. K. *Tetrahedron Lett.* 1993, 34, 2527-2528
 (b) Overkleeft, H. S.; van Wiltenburg, J.; Pandit, U. K. *Tetrahedron* 1994, 50, 4215-4224.

- 6. (a) Jpn. Kokai Tokkyo Koho, 80,105,666 to Nippon Shinyaku Co. (CA: 1981, 94, 103124e).
 (b) Hoos, R.; Naughton, A. B.; Vasella, A. Helv. Chim. Acta 1992, 75, 1802-1807.
- (a) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. J. Am. Chem. Soc. 1993, 115, 9856-9857.
 (b) Fu, G. C.; Grubbs, R. H. J. Am. Chem. Soc. 1992, 114, 7324-7325.
- 8. For a procedure for the preparation of the Dess Martin periodane, see: Ireland, R. E.; Liu, L. J.Org. Chem. 1993, 58, 2899.
- 9. The aldehyde was reacted with other phosphorous ylids such as Ph₃P=CH₂ and Ph₃P=CHC₆H₅. These reactions gave unsatisfactory yields because of competitive elimination reactions due to the acidity of the C2-proton. The results of these reactions and the cyclisation of the corresponding products will be discussed elsewhere.
- 10. Miller, S. J.; Kim, S-H.; Chen, Z-R.; Grubbs, R. H. J. Am. Chem. Soc. 1995, 117, 2108-2109.
- 11. Martin, S. F.; Liao, Y.; Chen, H-J.; Pätzel, M.; Ramser, M. Tetrahedron Lett. 1994, 35, 6005-6008.
- 12. Huwe, C. M.; Bleichert, S. Tetrahedron Lett. 1995, 36, 1621-1624.
- 13. Borer, B. C.; Deerenberg, S.; Bieräugel, H.; Pandit, U. K. *Tetrahedron Lett.* **1994**, *35*, 3191-3194.
- 14. See for an example on substituent effects on the alkyne moiety on an enyne metathesis: Kinoshima, A.; Mori, M. Synlett 1994, 1020-1022.
- 15. **10**: v_{max} : 3060, 3000, 2900, 2880, 1670, 1620, 1500, 690. ¹H NMR (400 MHz, C₆D₆): δ 3.34 (dd, 1H; J = 5.8 and 9.8 Hz), 3.80 (m, 1H), 4.01 (dd, 1H; J = 5.8 and 3.1 Hz), 4.22 (d, 1H; J = 3.1 Hz), 4.29-4.39 (m, 3H), 4.50 (d, 1H; J = 11.7 Hz), 4.53-4.58 (m, 1H), 4.61 (d, 1H; J = 11.8 Hz), 4.73 (d, 1H; J = 11.8 Hz), 4.94 (d, 1H; J = 11.8 Hz), 5.17-5.20 (m, 1H; J = 6.2 Hz), 5.59-5.63 (m, 1H; J = 6.3 Hz), 7.0-7.4 (m, 15H). ¹³C NMR (APT,100 MHz, C₆D₆): δ 53.4 64.6 73.0 73.1 73.9 80.6 84.7 84.9 127.5 128.5 128.7 128.8 128.9 129.0 129.2 129.3 131.4 138.9 139.0 139.4 167.2. HRMS (EI⁺): calculated for C₂₉H₂₉NO₄: 455.2097; found: 455.2061.
- 16. See for a review on catalytic asymmetric dihydroxylation: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. Chem. Rev. 1994, 94, 2483-2547.
- 17. Gao, Y.; Sharpless, K. B. J. Am. Chem. Soc. 1988, 110, 7538-7539.
- 18. See for a review on cyclic sulphates as epoxide like synthons: Lohray, B. B. Synthesis 1992, 1035-1052.
- van der Klein, P. A. M.; Filemon, W.; Broxterman, H. J. G.; van der Marel, G. A.; van Boom, J. H. Synth. Commun. 1992, 22, 1763-1771.
- 20. $15: \alpha_D = 152^{\circ}(c = 0.004)$ (Lit^{4a} $\alpha_D(546) = 151.9^{\circ}$). v_{max} : 3560, 3500-3400, 3060, 2980, 1655 (lactam), 690. ¹H NMR (400 MHz, CDCl₃): δ 1.03 (bs, 1H), 1.90-1.95 (m, 2H), 3.43 (dd, 1H; J = 2.9 and 9.5 Hz), 3.48 (m, 1H), 3.59 (m,1H), 3.76 (dd, 1H; J = 9.0 and 9.3 Hz), 3.94 (dd, 1H; J = 7.1 and 8.9 Hz), 4.03 (d, 1H; J = 7.1 Hz), 4.25 (bs, 1H), 4.71 (d, 1H; J = 11.7 Hz), 4.74-4.87 (m, 4H), 5.16 (d, 1H; J = 11.1 Hz), 7.25-7.50 (m, 15H). ¹³C NMR (APT,100 MHz, CDCl₃): δ 31.4 43.2 63.8 70.3 73.7 74.2 74.4 74.4 80.3 83.9 127.8 128.0 128.3 128.4 128.4 128.6 128.7 130.0 138.0 138.1 167.7 (both proton- and ¹³C NMR are in accordance with those given in literature^{4a}).

(Received in UK 27 September 1995; revised 21 November 1995; accepted 24 November 1995)