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

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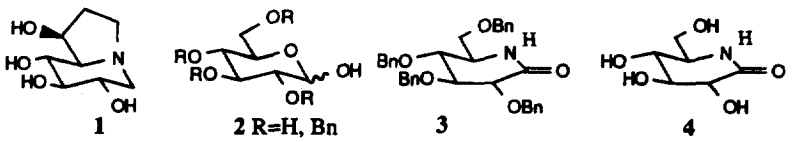
Abstract: **The formal synthesis of castanospermine (1) starting from tetrabenzylgluconolactam (3) is described. Olefin metathesis cyclisation reaction of dialkene 9, derived from 3, leads to indolizidinone 10, which can be used as a key intermediate for the synthesis of castanospermine (1) and its analogues.**

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 atom[1]. It is a structural analogue of glucopyranoside (**2**, R=H) and, thus, is a potent inhibitor of several α- and β-glycosidases[2]. Since the isolation of **1** from *Castanospermum australe*[3a] and *Alexa leiopetala*[3b] 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 analogues[4].

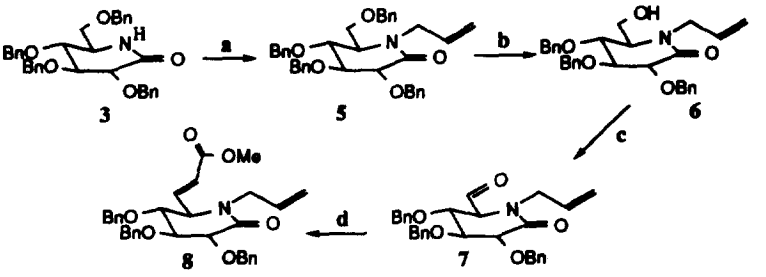


1 **2** R=H, Bn **3** **4**

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 lactams[5]. 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 reaction[7] in the critical step of the synthetic sequence.

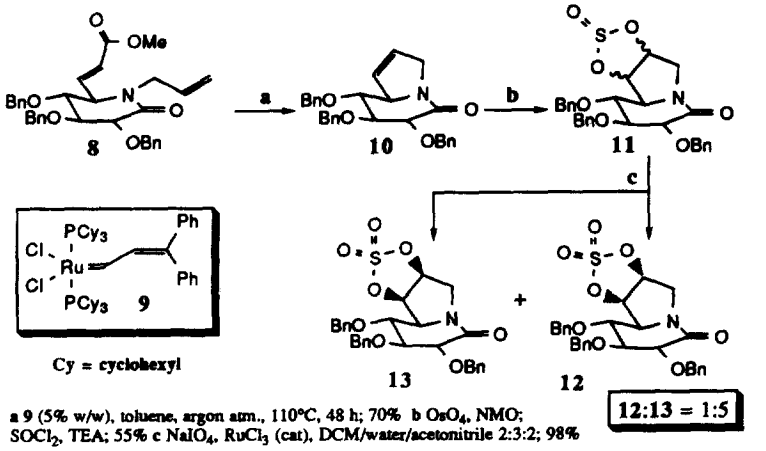
Synthesis. In **Scheme 2** the transformation of gluconolactam **3** to dialkene **8** is outlined. N-allylation of lactam **3** was accomplished with allyl bromide, using two-phase conditions with tetrabutylammonium iodide as a phase transfer catalyst, to give **5** in 93% yield. Selective deprotection 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 periodane[8], in 80% overall yield. Treatment of this aldehyde with methyl (triphenylphosphoranylidene)acetate gave the Wittig product **8** in 85% yield[9].



a allyl bromide, KOH (50% aq)/methylene chloride 1:1, TBAI(cat); 93% b Ac_2O, $FeCl_3$; then NH_3, MeOH c Dess Martin periodane; 80% d $Ph_3P{=}CHCO_2Me$; 85%

Scheme 2

The dialkene **8** was subsequently allowed to undergo a metathesis cyclisation reaction with the ruthenium carbene complex **9** as a catalyst[7a] (**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 oxygen[10] 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 recently[13].

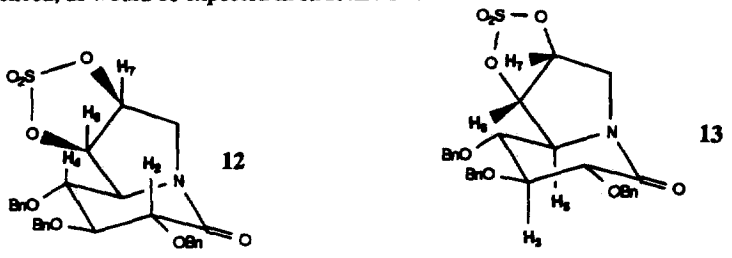


a **9** (5% w/w), toluene, argon atm., 110°C, 48 h; 70% b OsO_4, NMO; $SOCl_2$, TEA; 55% c $NaIO_4$, $RuCl_3$ (cat), DCM/water/acetonitrile 2:3:2; 98%

Scheme 3

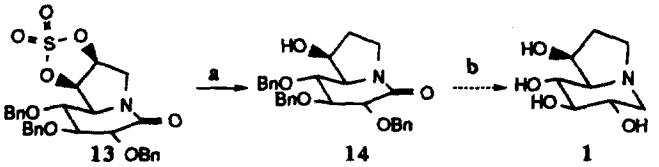
The cyclisation of dialkene **8** (catalyst **9**, 5% w/w, toluene, 110°) in which one of the reacting alkenes consists of an α-β-unsaturated ester is unprecedented in literature[14]. Although this reaction was much slower than that of the corresponding substrate with two terminal olefines[9], the cyclisation was accomplished yielding 70% of the bicyclic lactam **10**[15]. The double bond was oxidised, using a catalytic amount of osmium tetroxide with N-methyl morfoline N-oxide as the cooxidant[16], to form a mixture of diols, which was subsequently transformed into a mixture of sulphites[17] **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 nucleophiles[18]. Such a building block has been succesfully used as an intermediate for the synthesis of azasugar pyrrolidines[19].

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 monosulphate[17], 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**).



a $NaBH_4$, DMAC, then H_2SO_4 (20% aq), Et_2O; 98% b BH_3DMS; H_2, Pd/C[4a]

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**).

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Satisfactory spectroanalytical data were obtained for all new compounds.

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9. The aldehyde was reacted with other phosphorous ylids such as $Ph_3P{=}CH_2$ and $Ph_3P{=}CHC_6H_5$. 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.
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15. **10**: ν_{max}: 3060, 3000, 2900, 2880, 1670, 1620, 1500, 690. ^{1}H NMR (400 MHz, C_6D_6): 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). ^{13}C NMR (APT,100 MHz, C_6D_6): 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 $C_{29}H_{29}NO_4$: 455.2097; found: 455.2061.
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20. **15**: α_D=152° (c = 0.004) (Lit[4a] α_D(546) = 151.9°). ν_{max}: 3560, 3500-3400, 3060, 2980, 1655 (lactam), 690. ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (APT,100 MHz, $CDCl_3$): 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 ^{13}C NMR are in accordance with those given in literature[4a]).

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