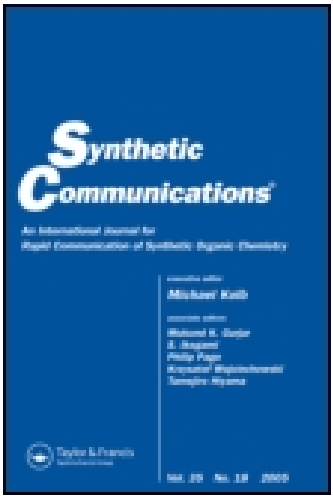


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Regiocontrolled C-8 Acylation of Castanospermine

Nelson G. Landmesser [a], Hon-Chung Tsui [b], Chi-Hsin R. King [a] & Leo A. Paquette [b]

[a] Hoechst Marion Roussel, Inc., 2110 East Galbraith Road, Cincinnati, Ohio, 45215

[b] Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio, 43210

Published online: 21 Aug 2006.

To cite this article: Nelson G. Landmesser, Hon-Chung Tsui, Chi-Hsin R. King & Leo A. Paquette (1996) Regiocontrolled C-8 Acylation of Castanospermine, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 26:11, 2213-2221, DOI: 10.1080/00397919608003581

To link to this article: http://dx.doi.org/10.1080/00397919608003581

SYNTHETIC COMMUNICATIONS, 26(11), 2213-2221 (1996)

REGIOCONTROLLED C-8 ACYLATION OF CASTANOSPERMINE

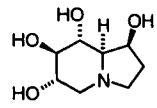
Nelson G. Landmesser,*[a] Hon-Chung Tsui,[b] Chi-Hsin R. King,[a]
and Leo A. Paquette[b]

[a]Hoechst Marion Roussel, Inc., 2110 East Galbraith Road, Cincinnati, Ohio 45215 and [b]Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

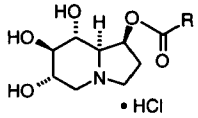
Abstract: A convenient route to previously unknown 8-acylated castanospermines is illustrated by synthesis of the butyryl derivative.

The indolizidine alkaloid castanospermine (**1**)[1] is recognized to be a potent inhibitor of several important glucosidase enzymes.[2] The possibility of exploiting this biological activity for human health maintenance, most notably in the cancer,[3] AIDS,[4] and diabetes areas,[5] has prompted considerable interest in the preparation of more lipid soluble derivatives.[6] Particular attention has been paid to esters derived by controlled O-acylation at C-1,[7] C-6[8,9] and C-7[8] (e.g., **2**, **3**, and **4**, respectively).

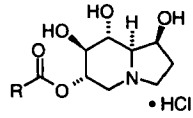
*To whom correspondence should be addressed.



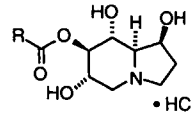
1



2

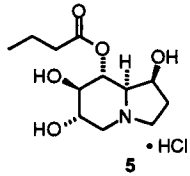


3

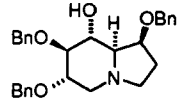


4

Since castanospermine is constituted of four quite similar secondary hydroxyl groups, direct *mono*acylation at a specific site is not universally possible. While **2** is available by regioselective enzyme-catalyzed acylation of **1**,[7] arrival at **3** and **4** is possible only by the implementation of selective protection/deprotection protocols. To the present time, no viable route to 8-acylated castanospermines has yet been uncovered.



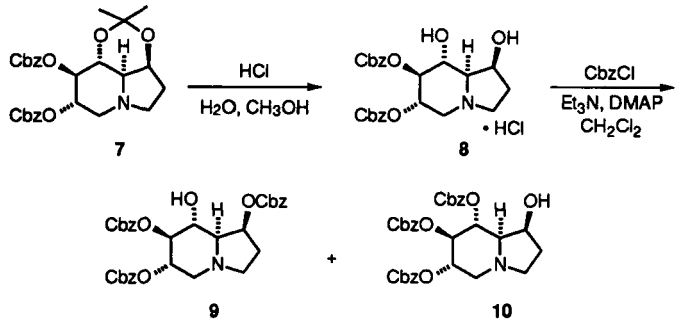
5



6

Although **5** is a simple positional isomer of the 6-butyryl derivative, an isomerization approach has not evolved into a viable synthesis of **5**.[10] A single literature report describes the preparation of a 1,6,7-protected castanospermine (the tribenzyl derivative **6**),[11] a potentially serviceable precursor to **5**. When repetition of this work could not be accomplished successfully, this strategy was abandoned.

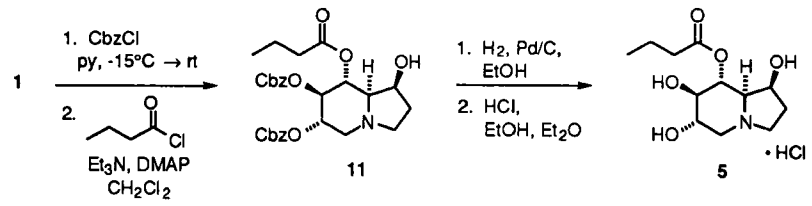
An alternative approach based upon differentially protected hydroxylated regions within **1** was next considered. Upon acid hydrolysis, compound **7**[12] underwent chemoselective loss of its isopropylidene group to deliver **8** (56%, Scheme 1). This diol was caused to react with slightly more than one molar



Scheme 1

equivalent of Cbz chloride in the presence of triethylamine and DMAP. Subsequent flash chromatography on silica gel gave only relatively minor amounts of the 1,6,7-tri-Cbz derivative **9** (4%) and its 6,7,8-tri-Cbz isomer **10** (13%). The dominant product was the tetraester, which was accompanied by unreacted **8**. While this route did not provide a useful means for securing **5**, the **9/10** ratio was construed to be an indicator of the relative nucleophilic reactivity of the 1-OH and 8-OH substituents in a 6,7-diprotected castanospermine.

Armed with this information, we proceeded to prepare 6,7-di-Cbz castanospermine by direct derivatization of **1** and to acylate this amine with butyryl chloride in conventional fashion. A complex mixture of products resulted in the first step, leading to a 19% isolated yield of **8** as the free amine. Direct chromatography after esterification then furnished **11** in 76% yield (Scheme 2). On a 75 g scale, the purification of **11** was simply accomplished by plug filtration. Removal of the Cbz protecting groups by catalytic hydrogenation provided the amino triol which was converted into the hydrochloride salt **5**. Although early attempts to effect hydrochloride formation proved problematic and resulted in the production of oils, it was subsequently determined that dropwise addition of an



Scheme 2

ethanolic solution of the hydrochloride to ether with rapid stirring gave rise to a white flocculent solid. This hygroscopic material was dissolved in water and isolated by freeze-drying.

With a feasible route to **5** now in hand, numerous other 8-substituted derivatives emerge as possible options for synthesis. The protocol outlined here should serve reliably in most of these contexts.

Experimental Section

General. NMR spectra were recorded on a Varian XL 300 and/or Varian GEMINI-300 spectrometers at 300 MHz, and at 75 MHz for ^{13}C, or UNITY 400 spectrometer at 400 MHz for ^{1}H, and at 100 MHz for ^{13}C. All chemical shifts are reported in parts per million (ppm, δ) relative to TMS standard. Mass spectra were obtained on a Finnigan MAT TSQ 700 spectrometer at 120 eV. Elemental analyses were performed by the Analytical and Structural Sciences Department, Marion Merrell Dow Research Institute, Cincinnati Center. Thin layer chromatography (TLC) was performed on silica gel 60 precoated plates (0.23 mm, Merck).

6,7-Di-*O*-carbobenzyloxycastanospermine Hydrochloride (8). Amine **7** (40.5 g, 0.0815 mmol) was dissolved in CH_3OH (150 mL) and treated with saturated HCl in ether (150 mL). The mixture was allowed to stir at rt overnight

and cooled to 0 °C. The white solid precipitate was collected by filtration, washed with Et_2O, allowed to air-dry, and dried *in vacuo* (25 Torr) to provide 22.5 g (56%) of **8**. A small amount of the salt was neutralized to the free amine for analysis. ^1H NMR ($CDCl_3$) δ 7.34 (m, 10 H), 5.13 (s, 2 H), 5.08 (dd, J = 7.5, 7.5 Hz, 2 H), 4.84 (m, 2 H), 4.34 (br s, 2 H), 4.20 (br s, 1 H), 3.90 (apparent t, J = 7 Hz, 1 H), 3.45 (br s, 1 H), 3.35 (dd, J = 11, 5 Hz, 2 H), 3.07 (apparent t, J = 7 Hz, 1 H), 2.28-2.12 (m, 1 H), 2.06 (m, 2 H), 1.98 (dd, J = 7.5, 7.5 Hz, 1 H), 1.78 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 155.3, 154.3, 135.1, 135.0, 128.6, 128.5, 128.4, 128.3, 128.2, 81.4, 74.1, 71.7, 70.2, 69.9, 69.8, 68.0, 52.9, 51.8, 33.8; MS (EI) *m/z* (rel. intensity) 456 (10%), 419 (21), 369 (47), 331 (42), 317 (54), 287 (33), 267 (100), 236 (68), 212 (90).

1,6,7-Tri-*O*-carbobenzyloxycastanospermine (9) and 6,7,8-Tri-*O*-carbobenzyloxycastanospermine (10). Diol **8** (2.47 g, 5.40 mmol) was dissolved in CH_2Cl_2 (60 mL) under N_2, treated with triethylamine (1.1 g, 11 mmol) and DMAP (20 mg), and cooled to 0 °C. CbzCl (0.94 g, 5.5 mmol) was added with stirring over 0.5 h and the reaction mixture was allowed to warm to rt overnight prior to being quenched with saturated $NaHCO_3$ solution (40 mL). The separated organic layer was washed with saturated $NaHCO_3$ solution (20 mL) and brine (30 mL), dried over Na_2SO_4, and filtered to remove inorganics. The solvent was removed *in vacuo* (42 °C/35 Torr) to leave an oil, flash chromatography of which on silica gel (10% EtOAc/90% hexane as eluent) provided 100 mg (4%) of **9** and 350 mg (13%) of **10**. ^1H NMR of **9** ($CDCl_3$) δ 7.34 (m, 15 H), 5.3-5.0 (m, 7 H), 4.84 (m, 2 H), 3.70 (apparent t, J = 7 Hz, 1 H), 3.42 (dd, J = 11, 5 Hz, 1 H), 3.18 (t, J = 8 Hz, 1 H), 3.13 (br s, 1 H), 2.4-1.9 (m, 5 H); ^{13}C NMR of **9** ($CDCl_3$) δ 155.7, 155.1, 154.1, 135.0, 134.9, 134.8, 128.7, 128.63, 128.58, 128.55, 128.51, 128.4, 128.3, 128.2, 80.6, 77.3, 77.2, 71.2, 70.2, 70.0, 69.8, 67.9, 52.7, 51.3, 30.9. ^1H NMR of **10** ($CDCl_3$) δ 7.34 (m, 15 H), 5.24-5.02 (m, 7 H), 4.99-4.85 (m, 2 H),

4.10 (br s, 1 H), 3.48 (br s, 1 H), 3.45 (dd, J = 11, 5 Hz, 1 H), 3.22 (t, J = 8 Hz, 1 H), 2.30-2.08 (m, 5 H), 1.90 (m, 1 H); ^{13}C NMR of **10** ($CDCl_3$) δ 155.6, 154.5, 154.0, 135.0, 134.9, 134.6, 128.8, 128.7, 128.6, 128.55, 128.5, 128.4, 128.3, 128.25, 128.2, 128.1, 78.3, 73.8, 73.7, 70.5, 70.3, 70.0, 69.9, 69.8, 52.4, 51.2, 32.1.

6,7-Di-*O*-carbobenzyloxy-8-*O*-butyrylcastanospermine (11). Castanospermine (55 g, 0.29 mol) in pyridine (350 mL) was stirred at -15 to -10 °C under N_2 while CbzCl (100 g, 0.59 mol) was slowly introduced. The mixture was allowed to warm to rt and stirred for 24 h. Water (150 mL) was added and the mixture was stirred at rt for 2 h. Solvents were removed *in vacuo* to leave a yellow oil. Ethyl acetate (200 mL) and water (100 mL) were added to this oil and the organic phase was separated. The aqueous layer was extracted with ethyl acetate (100 mL). Solvent evaporation from the combined organics gave a yellow oil, chromatography of which on silica gel (elution with 5:1 ethyl acetate-petroleum ether) afforded 25 g (19%) of 6,7-di-Cbz castanospermine. The spectral data of this material are identical to the data of the free amine of compound **8**.

The above amine (75.0 g, 164 mmol) was dissolved in CH_2Cl_2 (1.5 L) under N_2, treated with Et_3N (48.2 g, 477 mmol) and DMAP (900 mg), and cooled to 0 °C. Butyryl chloride (20.0 g, 188 mmol) was added with stirring over 0.5 h and the mixture was allowed to stir at 0 °C for 8 h, then allowed to warm to rt overnight before being quenched with saturated $NaHCO_3$ solution (300 mL). The separated organic layer was washed with saturated $NaHCO_3$ solution (250 mL) and brine (100 mL), then dried over Na_2SO_4, and filtered to remove inorganics. The solvent was removed in vacuo (42 °C/35 Torr) to give an oil (101 g) which was combined with the product from a smaller run (35 g) and purified by plug filtration in two equal batches. Flash chromatography on silica gel (10%

EtOAc/90% hexane as eluent) provided 66 g (76%) of **11**. ^{1}H NMR (DMSO) δ 7.34 (m, 10 H), 5.14 (m, 1 H), 5.13 (s, 2 H), 5.08 (dd, J = 7.5, 7.5 Hz, 2 H), 4.84 (dd, J = 10, 10 Hz, 1 H), 4.75 (m, 1 H), 4.65 (d, J = 7 Hz, 1 H), 4.02 (m, 1 H), 3.29 (dd, J = 11, 5 Hz, 2 H), 3.03 (apparent t, J = 7 Hz, 1 H), 2.21-2.00 (m, 6 H), 1.59 (m, 1 H), 1.42 (dt, J = 7, 7 Hz, 2 H), 0.81 (t, J = 7 Hz, 3 H); ^{13}C NMR (DMSO) δ 171.2, 154.1, 153.6, 135.2, 135.1, 128.5, 128.4, 128.3, 128.0, 127.8, 79.6, 73.6, 69.3, 69.1, 68.8, 68.6, 68.1, 51.8, 51.2, 35.3, 33.9, 17.8, 13.2; MS (CI/NH_3) *m/z* (rel. intensity) 528 ($M+H^+$, 100), 500 (4), 452 (12), 439 (5), 394 (36), 318 (3), 287 (4), 149 (4), 125 (2); Calcd for $C_{28}H_{33}NO_9$: C, 63.75; H, 6.30; N, 2.65. Found: C, 63.35; H, 6.11; N, 2.40.

8-*O*-Butyrylcastanospermine Hydrochloride (5). Butyrate **11** (5.0 g, 9.5 mmol) was dissolved in EtOH (100 mL) and placed in a Parr bottle, treated with 5% Pd/C catalyst, and hydrogenated on a Parr shaker (50 psi, rt) overnight. The mixture was filtered, ethanolic HCl (2.4 mL, 4 M) was introduced with stirring, the EtOH was removed *in vacuo* (30 °C/15 Torr), and the residue was dissolved in EtOH (10 mL). The ethanolic solution was added dropwise to rapidly stirring Et_2O to give a white solid, which was collected on a Büchner funnel, quickly transferred to a vacuum oven (RT, 30 Torr) and stored over the weekend. When the solid was removed from the vacuum oven, it turned into a gum. This gum was dissolved in H_2O (75 mL) and freeze-dried over the weekend to give 2.2 g (78%) of **5**. ^{1}H NMR (D_2O) δ 5.16 (dd, J = 10, 10 Hz, 1 H), 4.50 (m, 1 H), 3.92 (m, 1 H), 3.87-3.73 (m, 3 H), 3.50 (dd, J = 11, 3 Hz, 1 H), 3.26 (m, 1 H), 3.06 (t, J = 12 Hz, 1 H), 2.52 (m, 1 H), 2.47 (t, J = 7.5 Hz, 2 H), 2.08 (m, 1 H), 1.65 (dt, J = 7.5, 7.5 Hz, 2 H), 0.93 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (D_2O) δ 178.2, 77.4, 72.0, 70.0, 69.9, 55.2, 54.5, 38.4, 34.3, 20.7, 15.5; MS (CI/NH_3) *m/z* (rel. intensity) 260 ($M+H^+$, 100), 188 (1), 171 (24), 154 (8), 128 (4), 99 (1), 86

(1); K.F. = 7.3% H_2O; Calcd for $C_{12}H_{21}NO_5 \cdot HCl \cdot 1.3\ H_2O$: C, 45.17; H, 7.77; N, 4.39. Found: C, 44.76; H, 7.54; N, 4.39.

References and Notes

(1) (a) Hohenschutz, L. D.; Bell, E. A.; Jewess, P. J.; Leworthy, P. D.; Price, 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.

(2) Elbein, A. D. *CRC Critical Reviews in Biochemistry* **1984**, *16*, 21.

(3) Ostrander, G. K.; Scribner, N. K.; Rohrschneider, L. R. *Cancer Res.* **1988**, *48*, 1091 and relevant references cited therein.

(4) (a) Sunkara, P. S.; Bowlin, T. L.; Liu, P. S.; Sjoerdsma, A. *Biochem. Biophys. Res. Commun.* **1987**, *148*, 206. (b) Gruters, R. A.; Neefjes, J. J.; Tersmette, M.; de Goede, R. E. Y.; Tulp, A.; Huisman, H. G.; Miedema, F.; Ploegh, H. L. *Nature* **1987**, *330*, 74. (c) Tyms, A. S.; Berrie, E. M.; Ryder, T. A.; Nash, R. J.; Hegarty, M. P.; Taylor, D. L.; Mobberley, M. A.; Davis, J. M.; Bell, E. A.; Jeffries, D. J.; Taylor-Robinson, D.; Fellows, L. E. *Lancet* **1987**, *ii*, 1025.

(5) Rhinehart, B. L.; Robinson, K. M.; Payne, A. J.; Wheatley, M. E.; Fisher, J. L.; Liu, P. S.; Cheng, W. *Life Sci.* **1987**, *41*, 2325.

(6) Burgess, K.; Henderson, I. *Tetrahedron* **1992**, *48*, 4045 and relevant references cited therein.

(7) Margolin, A. L.; Delnick, D. L.; Whalon, M. R. *J. Am. Chem. Soc.* **1990**, *112*, 2849.

(8) Liu, P. S.; Hoekstra, W. J.; King, C.-H. R. *Tetrahedron Lett.* **1990**, *31*, 2829.

(9) Furneaux, R. H.; Gainsford, G. J.; Mason, J. M.; Tyler, P. C. *Tetrahedron* **1994**, *50*, 2131.

(10) King, C.-H. R.; Ashton, L. unpublished results.

(11) Tyler, P. C.; Furneaux, R. H.; Mason, J. M. *Tetrahedron Lett.* **1994**, *35*, 3143.

(12) Compound **7** was prepared from 1,8-*O*-isopropylidenylcastanospermine[8] by treatment with CbzCl/DMAP/Et_3N in CH_2Cl_2 at 25 °C. For **7**: ^1H NMR ($CDCl_3$) δ 7.32 (m, 10 H), 5.15 (d, J = 7.5 Hz, 2 H), 5.10 (d, J = 6.0 Hz, 2 H), 4.95 (m, 2 H), 4.51 (m, 1 H), 3.85 (t, J = 9.0 Hz, 1 H), 3.37 (m, 1 H), 3.06 (m, 1 H), 2.96 (m, 2 H), 2.83 (m, 1 H), 2.20 (m, 1 H), 1.91 (m, 1 H), 1.35 (s, 3 H), 1.16 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 154.4, 154.2, 135.2, 134.9, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 101.2, 78.5, 72.7, 71.1, 69.9, 69.6, 64.2, 62.8, 49.5, 49.3, 33.0, 27.5, 24.8; MS (Cl, NH_3) *m/z* (rel. intensity) 498 ($M + H^+$, 100%), 468 (9), 440 (5), 345 (8).

(Received in the USA 15 December 1995)