Tetrahedron Letters, Vol.31, No.20, pp 2829-2832, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

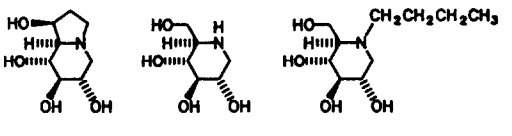
SYNTHESIS OF POTENT ANTI-HIV AGENTS: ESTERS OF CASTANOSPERMINE

Paul S. Liu*[a], William J. Hoekstra[b] and Chi-Hsin R. King[a]

[a]Merrell Dow Research Institute, 2110 East Galbraith Road, Cincinnati, Ohio 45215, U.S.A.
[b]Merrell Dow Research Institute, 9550 Zionsville Road, Indianapolis, Indiana 46268, U.S.A.

Abstract: The syntheses of 6-O- and 7-O-acyl derivatives of the indolizidine alkaloid castanospermine, are described. These compounds are potent inhibitors of the human immunodeficiency virus (HIV) and are potential anti-AIDS agents.

Castanospermine [(1S,6S,7R,8R,8aR)-1,6,7,8-tetrahydroxyindolizidine] (1), an indolizidine alkaloid isolated from Castanospermum australe[1] as well as Alexa leiopetala,[2] is a potent inhibitor of the glycoprotein trimming enzyme, glucosidase I.[3] Recent studies showed that 1 and deoxynojirimycin (2) reduced replication and infectivity of the human immunodeficiency virus (HIV)--the etiologic agent for Acquired Immune Deficiency Syndrome (AIDS) and AIDS-related complex (ARC).[4] The potential usefulness of 1 and 2 in the clinic is limited, primarily due to their low potencies in vitro[4] and in vivo.[5] The anti-HIV activity of these glucosidase I inhibitors can, however, be improved significantly by increasing the lipophilicity of the compounds. Thus, N-butyldeoxynojirimycin (3)[6]



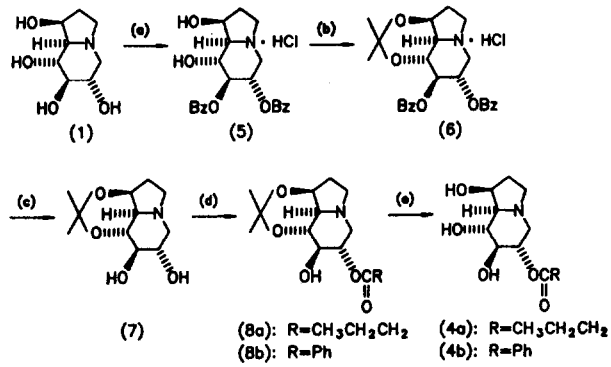
(1) (2) (3) (4a) R=$CH_3CH_2CH_2$-

and 6-O-butanoylcastanospermine (4a)[7] were reported independently to be more efficacious than the parent compounds. Herein, we report facile syntheses of 6-O- and 7-O-acyl derivatives[7] of castanospermine.

The parent alkaloid, castanospermine (1), was isolated in kg quantities from the seeds of Castanospermum australe.[8] Since 1 contains four relatively similar secondary alcohols, the direct mono-acylation procedure (1.2 eq RCOCl/pyridine) of 1 afforded a complex reaction mixture with poor yield.[9] However, we took advantage of our prior observation[9] that dibenzoylation of 1 in pyridine (2.2 eq PhCOCl/pyridine) provided 6,7-di-O-benzoylcastanospermine hydrochloride (5)[10] as the major product in 65-70% yield (Scheme I). Treatment of 5 with excess 2-methoxypropene and a catalytic amount of p-TsOH·H_2O in DME at 55°C gave 6,7-di-O-benzoyl-1,8-O-isopropylidenylcastanospermine hydrochloride (6)[10] in 82% yield. The benzoyl protecting groups in 6 were removed by reaction with sodium methoxide in methanol to provide 1,8-O-isopropylidenylcastanospermine (7)[10] in 92% yield. Acylation of (7) with 1.1

eq of the appropriate acid chloride in THF or CH_2Cl_2 regiospecifically gave the

Scheme I

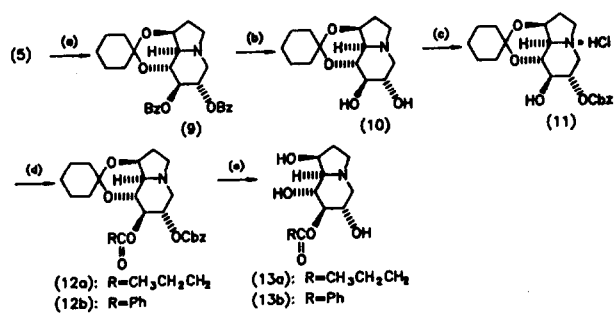


Conditions: (a) 2.2 eq PhCOCl, pyridine, 0°C→room temp, 3 days; (b) 2-methoxypropene, pTsOH·H_2O, DME, 55°C; (c) $NaOCH_3$, CH_3OH, room temp; (d) RCOCl, THF or CH_2Cl_2; (e) C_2H_5OH, HCl.

6-O-acyl derivative (**8a**,[10] R=$CH_3CH_2CH_2$: 94%; **8b**,[10] R=Ph: 78%) which was conveniently deprotected by treatment with ethanolic HCl to provide the final product (**4a**,[10] R=$CH_3CH_2CH_2$: 90%; **4b**,[10] R=Ph: 91%).

In a similar approach, reaction of **5** with 1-methoxycyclohexene resulted in a 79% yield of crystalline ketal-diester **9**[10] (Scheme II). Base (NaOH, aq THF) hydrolysis of **9** gave

Scheme II



Conditions: (a) 1-methoxycyclohexene, CH_3SO_3H, DME, reflux; (b) 1N NaOH, THF, room temp; (c) Cbz-Cl, DMAP (0.05 eq), CH_2Cl_2, room temp; (d) RCOCl, Et_3N, CH_2Cl_2; (e) 10% Pd/C, H_2, EtOH, 18 h, followed by C_2H_5OH, HCl.

1,8-O-cyclohexylidenylcastanospermine **10**[10] in 85% yield. The suitably protected **10** has also been acylated regiospecifically with butanoyl chloride to provide, after deprotection, compound **4a**. Treatment of **10**, however, with benzyl chloroformate and a catalytic amount of DMAP in CH_2Cl_2 gave 6-O-carbobenzyloxy-1,8-O-cyclohexylidenylcastanospermine hydrochloride (**11**)[10] in 92% yield. Acylation of **11** with butanoyl chloride or benzoyl chloride in CH_2Cl_2 containing Et_3N (3 eq) gave the 7-O-acyl derivatives (**12a**,[10] R=$CH_3CH_2CH_2$: 73%; **12b**,[10] R=Ph: 99%). Stepwise deprotection of **12** by catalytic hydrogenation (10% Pd/C, EtOH) and acid

hydrolysis (EtOH, HCl) gave 7-O-butanoyl- (**13a**)[10] and 7-O-benzoylcastanospermine (**13b**)[10] in 71% and 83% yields,[11] respectively.

The compounds described here are currently undergoing biological evaluation and the results will be reported in detail in a forthcoming paper.

Acknowledgments: We thank Roland S. Rogers and Nelsen L. Lentz for their assistance in the chemical synthesis. We are also indebted to Dr. Edward Huber, Dr. Michael Whalon and William Magner for recording and analyzing the NMR spectra.

REFERENCES AND NOTES

1. L.D. Hohenschutz, E.A. Bell, P.J. Jewess, D.P. Leworthy, R.J. Pryce, E. Arnold and J. Clardy, Phytochemistry, *1981*, **20**, 811.
2. R.J. Nash, L.E. Fellows, J.V. Dring, C.H. Stirton, D. Carter, M.P. Hegarty and E.A. Bell, Phytochemistry, *1988*, **27**, 1403.
3. R. Saul, J.P. Chambers, R.J. Molyneux and A.D. Elbein, Arch. Biochem. Biophys., *1983*, **221**, 593; Y.T. Pan, H. Hori, R. Saul, B.A. Sanford, R.J. Molyneux and A.D. Elbein, Biochemistry, *1983*, **22**, 3975.
4. A.S. Tyms, E.M. Berrie, T.A. Ryder, R.J. Nash, M.P. Hegarty, D.L. Taylor, M.A. Mobberley, J.M. Davis, E.A. Bell, D.J. Jeffries, D. Taylor-Robinson and L.E. Fellows, Lancet, *1987*, **ii**, 1025; R.A. Gruters, J.J. Neefjes, M. Tersmette, R.E.Y. de Goede, A. Tulp, H.G. Huisman, F. Miedema and H.L. Ploegh, Nature, *1987*, **330**, 74; B.D. Walker, M. Kowalski, W.C. Goh, K. Kozarsky, M. Krieger, C. Rosen, L. Rohrschneider, W.A. Haseltine and J. Sodroski, Proc. Natl. Acad. Sci. U.S.A., *1987*, **84**, 8120; P.S. Sunkara, T.L. Bowlin, P.S. Liu and A. Sjoerdsma, Biochem. Biophys. Res. Commun., *1987*, **148**, 206.
5. R.M. Ruprecht, S. Mullaney, J. Andersen and R. Bronson, J. Acquired Immune Defic. Synd., *1989*, **2**, 149.
6. A. Karpas, G.W.J. Fleet, R.A. Dwek, S. Petursson, S.K. Namgoong, N.G. Ramsden, G.S. Jacob and T.W. Rademacher, Proc. Natl. Acad. Sci. U.S.A., *1988*, **85**, 9229.
7. P.S. Sunkara, D.L. Taylor, M.S. Kang, T.L. Bowlin, P.S. Liu, A.S. Tyms and A. Sjoerdsma, Lancet, *1989*, **i**, 1206.
8. B.L. Rhinehart, K.M. Robinson, A.J. Payne, M.E. Wheatley, J.L. Fisher, P.S. Liu and W. Cheng, Life Sci., *1987*, **41**, 2325.
9. P.S. Liu, J.K. Daniel and B.L. Rhinehart, Eur. Patent Appl., *1989*, EP 297,534; Chem. Abstr., *1989*, **111**, 7659r.
10. All new compounds gave satisfactory spectral (IR, MS, 300 MHz-NMR) and elemental analysis.
5: m.p. 229-231°C. ^{1}H NMR (DMSO-d_6) δ 7.90 (m, 4H), 7.65 (m, 2H), 7.50 (t, 4H), 5.60 (m, 2H), 4.55 (m, 1H), 4.25 (m, 1H), 3.90 (m, 1H), 3.75 (br s, 1H, -OH), 3.55 (m, 2H), 3.20 (m, 1H), 2.50 (br s, 1H, -OH), 2.00 (m, 1H). MS (CI, CH_4) 398 (MH^+).
6: m.p. 235-236°C. ^{1}H NMR (DMSO-d_6) δ 8.26 (d, 2H), 8.08 (d, 2H), 7.75 (m, 2H), 7.60 (m, 4H), 5.48 (s, 1H), 5.30 (d, 1H), 4.70 (m, 1H), 4.60 (m, 1H), 3.6-4.2 (m, 4H), 2.1-2.6 (m, 3H), 1.37 (s, 3H), 1.34 (s, 3H). MS (CI, CH_4) 438 (MH^+).
7: foamy solid. ^{1}H NMR ($CDCl_3$) δ 4.52 (m, 1H, H_1), 3.75 (m, 1H, H_6), 3.64 (t, J=10.0 Hz, 1H, H_8), 3.48 (dd, J=8.3, 10.0 Hz, 1H, H_7), 3.20 (dd, 1H), 3.00 (m, 2H), 2.80 (m, 2H), 2.25 (m, 1H), 1.90 (m, 1H), 1.41 (s, 3H), 1.39 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 101.06, 76.52, 71.08, 68.48, 66.10, 62.76, 51.86, 48.96, 32.54, 27.69, 24.83. MS (CI, CH_4) 230 (MH^+).
8a: m.p. 103-105°C. ^{1}H NMR ($CDCl_3$) δ 4.98 (m, 1H, H_6), 4.54 (m, 1H, H_1), 3.70 (m, 2H, H_7 and H_8), 3.30 (dd, 1H), 3.05 (m, 2H), 2.7-2.9 (m, 3H), 2.35 (m, 2H), 2.22 (m, 1H), 1.90 (m, 1H), 1.66 (m, 2H), 1.42 (s, 3H), 1.39 (s, 3H), 0.96 (t, 3H). MS (CI, CH_4) 300 (MH^+).
8b: m.p. 183-184°C. ^{1}H NMR ($CDCl_3$) δ 8.05 (m, 2H), 7.55 (m, 1H), 7.43 (m, 2H), 5.22 (m, 1H, H_6), 4.55 (m, 1H, H_1), 3.85 (t, J=7.9 Hz, 1H, H_7), 3.80 (t, J=10.0 Hz, 1H, H_8), 3.40 (dd, 1H), 3.10 (m, 2H), 2.7-3.0 (m, 3H), 2.25 (m, 1H), 1.95 (m, 1H), 1.42 (s, 3H), 1.38 (s, 3H). MS (EI) 333 (M^+).
4a: m.p. 113-114°C; ·HCl: m.p. 227-228°C. ^{1}H NMR (CD_3OD) δ 5.00 (m, 1H, H_6), 4.58 (m, 1H, H_1), 3.85 (t, J=10.0 Hz, 1H, H_8), 3.7-3.8 (m, 2H), 3.65 (t, J=9.4 Hz, 1H, H_7), 3.0-3.3 (m, 3H), 2.3-2.5 (m, 3H), 2.06 (m, 1H), 1.65 (m, 2H), 0.95 (t, 3H). MS (CI, CH_4) 260 (MH^+).

4b: m.p. 233-236°C. ^{1}H NMR (DMSO-d_6/D_2O) δ 8.00 (d, 2H), 7.66 (t, 1H), 7.55 (t, 2H), 4.85 (m, 1H, H_6), 4.17 (m, 1H, H_1), 3.55 (t, J=9.2 Hz, 1H, H_8), 3.45 (t, J=9.1 Hz, 1H, H_7), 3.20 (q, 1H), 3.0 (m, 1H), 1.5-2.2 (m, 5H). MS (CI, CH_4) 294 (MH^+).
9: m.p. 157-160°C. ^{1}H NMR ($CDCl_3$) δ 7.97 (m, 4H), 7.49 (m, 2H), 7.35 (t, 4H), 5.55 (t, J=9.6 Hz, 1H, H_7), 5.44 (m, 1H, H_6), 4.59 (t, J=7.0 Hz, 1H, H_1), 4.08 (t, J=10.3 Hz, 1H, H_8), 3.53 (dd, 1H), 3.24 (m, 2H), 3.05 (m, 2H), 2.28 (m, 1H), 2.02 (m, 1H), 1.70 (m, 2H), 1.20-1.66 (m, 8H). MS (EI) 477 (M^+).
10: m.p. 135-136°C. ^{1}H NMR ($CDCl_3$) δ 4.49 (t, J=7.8 Hz, 1H, H_1), 3.82 (m, 1H, H_6), 3.66 (t, J=10.0 Hz, 1H, H_8), 3.51 (dd, J=8.2, 10.0 Hz, 1H, H_7), 3.22 (dd, 1H), 3.03 (m, 2H), 2.82 (m, 2H), 2.21 (m, 1H), 1.93 (dd, 1H), 1.25-1.82 (m, 10H). MS (EI) 269 (M^+).
11: m.p. 132-135°C. ^{1}H NMR ($CDCl_3$) δ 7.38 (m, 5H), 5.2 (s, 2H), 4.8 (m, 1H, H_6), 4.50 (m, 1H, H_1), 3.7 (m, 2H, H_7 and H_8), 3.36 (m, 1H), 3.0 (m, 2H), 2.80 (m, 2H), 2.10 (m, 2H), 1.27-1.79 (m, 10H). MS (EI) 403 (M^+).
12a: oil. ^{1}H NMR ($CDCl_3$) δ 7.33 (s, 5H), 5.10 (m, 3H, H_7 and $-CH_2$-Ph), 4.94 (m, 1H, H_6), 4.50 (t, J=6.8 Hz, 1H, H_1), 3.78 (t, J=10.4 Hz, 1H, H_8), 3.31 (dd, 1H), 2.95 (m, 4H), 2.20 (m, 3H), 1.91 (dd, 1H), 1.28-1.69 (m, 12H), 0.89 (t, J=7.8 Hz, 3H). MS (EI) 473 (M^+).
12b: oil. ^{1}H NMR ($CDCl_3$) δ 8.02 (d, 2H), 7.22-7.59 (m, 8H), 5.33 (dd, J=8.7, 10.4 Hz, 1H, H_7), 5.12 (m, 1H, H_6), 5.05 (s, 2H), 4.55 (m, 1H, H_1), 3.96 (t, J=10.4 Hz, 1H, H_8), 3.39 (dd, 1H), 3.19 (m, 1H), 3.05 (m, 2H), 2.88 (m, 1H), 2.25 (m, 1H), 1.98 (m, 1H), 1.19-1.86 (m, 10H). MS (EI) 507 (M^+).
13a: m.p. 193-194°C. ^{1}H NMR (DMSO-d_6) δ 4.90 (d, 1H, OH), 4.68 (d, 1H, OH), 4.60 (t, J=9.3 Hz, 1H, H_7), 4.30 (d, 1H, OH), 4.10 (m, 1H, H_1), 3.4-3.6 (m, 2H, H_6 and H_8), 2.95 (m, 2H), 2.30 (t, 2H), 1.5-2.2 (m, 7H), 0.90 (t, 3H). MS (CI, CH_4) 260 (MH^+).
13b: m.p. 200-202°C. ^{1}H NMR (CD_3OD) δ 8.1 (d, 2H), 7.50 (m, 3H), 5.05 (t, J=9.7 Hz, 1H, H_7), 4.35 (m, 1H, H_1), 3.8-4.0 (m, 2H, H_6 and H_8), 3.20 (m, 2H), 1.7-2.4 (m, 5H). MS (EI) 293 (M^+).

11. Both compounds were obtained as pure regioisomers after acid-catalyzed deprotection. The yield of **13a** was reduced substantially upon workup with aqueous $NaHCO_3$ solution since the compound is water soluble.

(Received in USA 12 December 1989; accepted 20 March 1990)