Pergamon

Tetrahedron Letters, Vol. 38, No. 30, pp. 5245-5248, 1997

0040-4039/97 $17.00 + 0.00

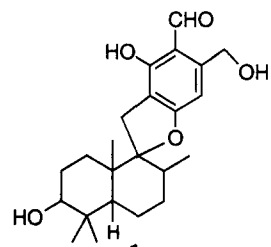
PII: S0040-4039(97)01146-5

Synthesis and Structure Revision of the *myo*-Inositol Monophosphatase Inhibitor L-671,776

J. R. Falck,* K. Kishta Reddy, and S. Chandrasekhar
Departments of Biochemistry and Pharmacology
University of Texas Southwestern Medical Center
Dallas, Texas 75235-9038

Abstract: Concomitant deprotection/spiro-heteroannulation of **6** utilizing $(EtO)_3SiI$ was exploited for the asymmetric total synthesis of the title tetracyclic terpenoid whose structure was revised to **13**. © 1997 Elsevier Science Ltd.

Microbial terpenoid L-671,776 is a potent and selective inhibitor of *myo*-inositol monophosphatase, a key regulator of brain inositol levels,[1] and, is consequently of interest for the management of manic/depressive disorders.[2] It was initially assigned structure **1** by Lam *et al.*[3] without designation of relative or absolute configuration. Synthetic studies[4] in these laboratories, however, led us to consider an alternative aromatic substitution pattern.[5] To unambiguously establish the complete structure of L-671,776 and to expedite SAR studies,[6] we describe herein a convergent, asymmetric total synthesis of **10** and its regioisomer **13** as well as their comparisons with natural material.[7]



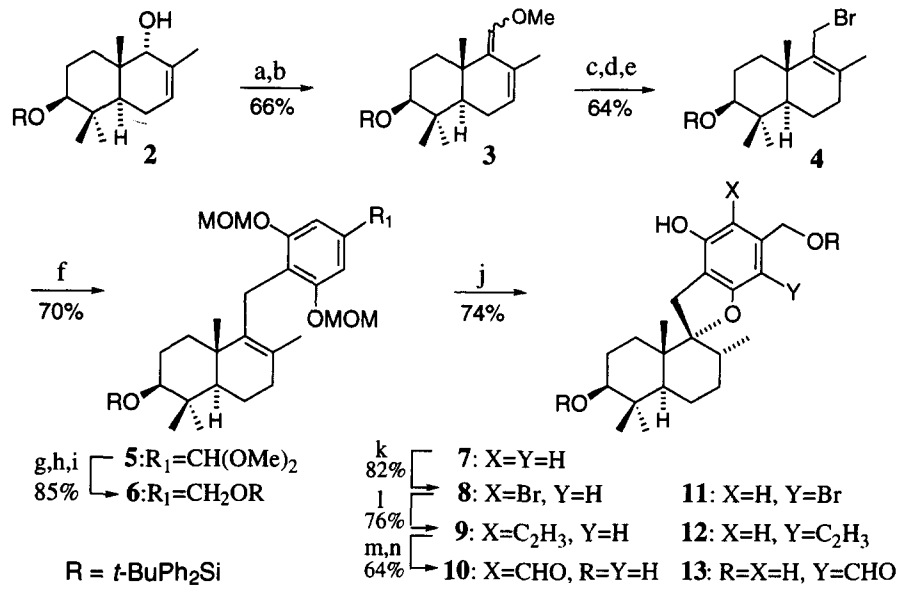
1

Our approach (Scheme 1) commenced with octalin **2**, a chiral AB-ring fragment readily available[8] from commercial 18β-glycyrrhetinic acid, which was homologated to enol ether **3** by Swern oxidation and condensation with diphenylmethoxymethylphosphine oxide.[9] Sequential cleavage of **3** using trimethylsilyl iodide, borohydride reduction of the derived α,β-unsaturated aldehyde, and conventional alcohol-to-halide interchange gave rise to allylic bromide **4** which was used to alkylate the higher order cuprate generated from aryl unit **16** via *ortho*-metalation in the presence of tetramethylethylenediamine (TMEDA). The resultant bis-MOM ether **5** was subjected to selective acidic hydrolysis of the dimethyl acetal, hydride reduction, and silyl protection to furnish **6**. Cleavage of both MOM-groups from **6** with concomitant spiro-heteroannulation[10] smoothly evolved tetracycle **7**[11] in a remarkable, one-pot process induced by *in situ* generated $(EtO)_3SiI$ in CH_3CN.[12] Trimethylsilyl iodide was unsatisfactory under similar conditions, resulting in low yields of **7** and extensive cleavage of the benzyl ether. Interestingly, only minor amounts (<5%) of the alternative six-membered tetrahydropyran annulation product or epi-**7** were observed using $(EtO)_3SiI$.

As anticipated, Reimer-Tiemann formylation[13] and desilylation led exclusively, albeit in low yield (>10%), to the product of *ortho*-substitution, **10**. Alternatively, aromatic bromination using NBS in $CHCl_3$ provided **8** as the sole product whereas *n*-Bu_4NBr_3[14] afforded a chromatographically separable mixture (~2:1) of **8** and **11**; TLC, EtOAc/hexane (1:9), R_f ~ 0.31 and 0.19, respectively.[15] This could be shifted to an ~1:4 ratio with prior derivatization of the phenol with *t*-$BuPh_2SiCl$. Stille vinylation of **8** mediated by $Pd(Ph_3P)_4$ evolved **9** whose structure was confirmed by extensive NMR analysis including ^1H NOe. Oxidative olefin

degradation and desilylation uneventfully provided **10**. An identical sequence transformed bromide **11** into regioisomer **13**. Spectral and chromatographic comparisons with natural material revealed L-671,776 is correctly represented by **13**.

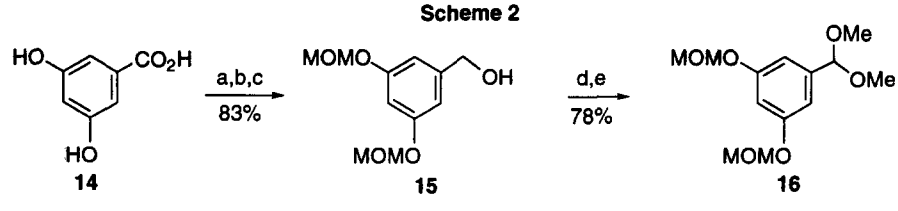
Scheme 1



Reagents and conditions: (a) $(COCl)_2$/DMSO, Et_3N, CH_2Cl_2, -60° to 23°C, 1h. (b) $Ph_2P(O)CH_2OCH_3$, *n*-BuLi, -78° to 23°C, 10h. (c) Me_3SiCl/NaI, CH_3CN, 0° to 23°C, 0.5h. (d) $NaBH_4$, MeOH, -78° to 0°C, 1h. (e) MsCl, Et_3N, CH_2Cl_2, -78°C, 15 min; LiBr, THF, 0°C, 1h. (f) **16**, *n*-BuLi, TMEDA (2 equiv), THF, -20°C, 40 min; CuCN, -20°C, 40 min; add to **4** and stir -78°C, 2h. (g) 1 N HCl/THF (1:3), 23°C, 1h. (h) $NaBH_4$, MeOH/THF (10:1), 0°C, 15 min. (i) *t*-$BuPh_2SiCl$, DMAP, py, 23°C, 4h. (j) $(EtO)_3SiCl$/NaI, CH_3CN/CH_2Cl_2 (4:1), -5°C, 0.5h. (k) *n*-Bu_4NBr_3 (1 equiv), MeOH/CH_2Cl_2 (2:3), 0°C, 1h. (l) *n*-$Bu_3Sn(CH{=}CH_2)$, $Pd(PPh_3)_4$, $PhCH_3$, 110°C, 3h. (m) $OsO_4/NaIO_4$, THF/H_2O (9:1), 23°C, 1h. (n) *n*-Bu_4NF, THF, 60°C, 13h.

Access to the arene moiety was achieved (Scheme 2) from commercial 3,5-dihydroxybenzoic acid[16] via esterification, protection of the phenols as MOM ethers, and reduction to the corresponding benzyl alcohol **15**. Pyridinium chlorochromate (PCC) oxidation and acetalization with MeOH yielded **16.**

Scheme 2



Reagents and conditions: (a) MeOH, HCl, 24°C, 12h. (b) MOM-Cl, NaH, DMF, 24°C, 4h. (c) $LiAlH_4$, THF, 24°C, 0.5h. (d) PCC/NaOAc, CH_2Cl_2, 24°C, 3h. (e) MeOH (anhydr.), TsOH, 24°C, 4h.

Acknowledgment: Supported financially by the Robert A. Welch Foundation and the USPHS NIH (GM31278). Dr. Y.K. Tony Lam (Merck & Co) is thanked for helpful discussions and a sample of natural L-671,776.

References and Notes

1. Piettre, S.R.; Ganzhorn, A.; Hoflack, J.; Islam, K.; Hornsperger, J.-M. *J. Am. Chem. Soc.* **1997**, *119*, 3201-3204 and cited references.
2. Barchas, J.D.; Hamblin, M.W.; Malenka, R.C. *Biochemical Hypotheses of Mood and Anxiety Disorders* . In *Basic Neurochemistry: Molecular, Cellular, and Medical Aspects* 5th ed.; Siegel, G.J., et al., eds.; Raven Press: New York, 1994, pp.979-1002.
3. Lam, Y.K.T.; Wichmann, C.F.; Meinz, M.S.; Guariglia, L.; Giacobbe, R.A.; Mochales, S.; Kong, L.; Honeycutt, S.S.; Zink, D.; Bills, G.F.; Huang, L.; Burg, R.W.; Monaghan, R.L.; Jackson, R.; Reid, G.; Maguire, J.J.; McKnight, .T.; Ragan, C.I. *J. Antibiot.* **1992**, *45*, 1397-1403.
4. Falck, J.R.; Reddy, K.K.; Chandrasekhar, S. *ACS 206th National Meeting*, Chicago, Il, Aug. 22-27, 1993; Div. Med. Chem. Abst. 222.
5. A similar conclusion was reached independently based on extensive NMR analysis: Ferrari, P.; Stefanelli, S.; Islam, K. *J. Chem. Res. (S)* **1995**, 110-111.
6. The structurally related K-76 also displays non-competitive inhibition of inositol monophosphatase: Pachter, J.A. *Molecular Pharmacology* **1991**, *40*, 107-111.
7. The same and several closely related, bioactive metabolites have been isolated: Kaneto, R.; Dobashi, K.; Kojima, I.; Sakai, K.; Shibamoto, N.; Okamoto, R.; Akagawa, H.; Mizuno, S. *J. Antibiot.* **1994**, *47*, 727-730. Stefanelli, S.; Sponga, F.; Ferrari, P.; Sottani, C.; Corti, E.; Brunati, C.; Islam, K. *ibid.* **1996**, *49*, 611-615. Chu, M.; Mierzwa, R.; Truumees, I.; King, A.; Patel, M.; Pichardo, J.; Hart, A.; Dasmahapatra, B.; Das, P.R.; Puar, M.S. *Tetrahedron Lett.* **1996**, *37*, 3943-3946. Ayer, W.A.; Miao, S. *Can. J. Chem.* **1993**, *71*, 487-493.
8. Falck, J.R.; Manna, S.; Chandrasekhar, S.; Alcaraz, L.; Mioskowski, C. *Tetrahedron Lett.* **1994**, *35*, 2013-2016.
9. Earnshaw, C.; Wallis, C.J.; Warren, S. *J.C.S. Perkin Transactions 1* **1979**, 3099-3106.
10. Compare with related spiro-heteroannulations: Morrison, G.A.; Sammes, P.G.; Simmonds, J.P. *Heterocycles* **1989**, *28*, 1037-1050. Corey, E.J.; Das, J. *J. Am. Chem. Soc.* **1982**, *104*, 5551-5553.
11. The stereochemistry of **7** was assigned using extensive ^{1}H NMR analysis with analogy to the structurally similar examples described in ref. 10.
12. In addition to ether cleavage, recent evaluations of $(EtO)_3SiI$ show it is a milder and more selective reagent than Me_3SiI for other types of reactions. Details will be reported elsewhere.
13. Wynberg, H.; Meijer, E.W. *Org. React.* **1982**, *28*, 2.
14. Kajigaeshi, S.; Kakinami, T.; Okamoto, T.; Nakamura, H.; Fuijawa, M. *Bull. Chem. Soc. Jap.* **1987**, *60*, 4187-4189.
15. Spectral data for **8**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.70 (d, J = 6.4 Hz, 3 H), 0.94 (s, 3 H), 0.96 (s, 3 H), 1.04 (s, 12 H), 1.12 (s, 9 H), 1.26-1.84 (m, 10 H), 2.75 (d, J = 16.4 Hz, 1 H), 3.10 (d, J = 16.4 Hz, 1 H), 3.38 (dd, J = 4.3, 11.5 Hz, 1 H), 4.62 (s, 2 H), 5.50 (s, 1 H, D_2O exchangeable), 6.65 (s, 1 H), 7.30-7.49 (m, 12 H), 7.63-7.72 (m, 8 H). **11**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.67 (d, J = 6.4 Hz, 3 H), 0.92 (s, 3 H), 0.94 (s, 3 H), 0.96 (s, 3 H), 1.04 (s, 9 H), 1.09 (s, 9 H), 1.19-1.69 (m, 10 H), 2.79 (d, J = 16.1 Hz, 1 H), 3.11 (d, J = 16.1 Hz, 1 H), 3.32 (dd, J = 4.1, 11.4 Hz, 1 H), 4.68 (s, 2 H), 5.12 (s, 1 H, D_2O

exchangeable), 6.63 (s, 1 H), 7.28-7.46 (m, 12 H), 7.63-7.71 (m, 4 H). **13**: $^{1}H/^{13}C$ NMR identical with natural material and published values. **16**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.09 (s, 1 H), 3.48 (s, 6 H), 4.73 (s, 2 H), 5.14 (s, 4 H), 6.63 (t, J = 2.1 Hz, 1 H), 6.73 (d, J = 2.1 Hz, 2 H), 7.31-7.47 (m, 6 H), 7.64-7.75 (m, 2 H),

16. Townsend, C.A.; Davis, S.G.; Christensen, S.B.; Link, J.C.; Lewis, C.P. *J. Am. Chem. Soc.* **1981**, *103*, 6885-6888.

(*Received in USA* 15 *May* 1997; *revised* 4 *June* 1997; *accepted* 5 *June* 1997)