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Total Synthesis of (+)-Asperlin

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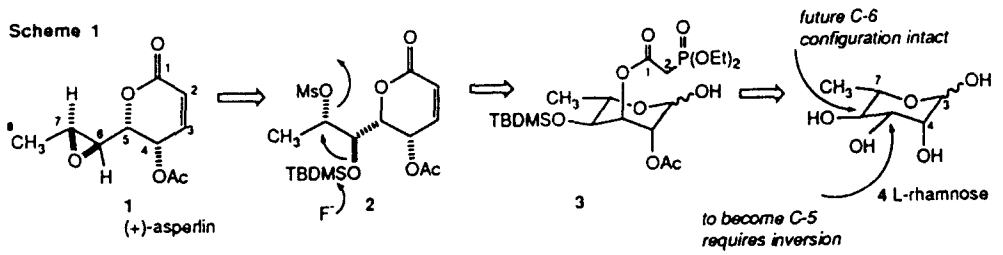
Abstract: A stereochemically unambiguous synthesis of (+)-asperlin from L-rhamnose establishes the configuration of the antibiotic as 4S, 5S, 6S, 7R.

Asperlin (1), a crystalline metabolite from *Aspergillus nidulans*, has been shown to exhibit antitumor and antibacterial activity. The gross structure of 1 was assigned by Argoudelis in 1966,[1] and early synthetic studies by Perlin demonstrated that the C-4 and C-5 substituents of the lactone ring had the L-threo configuration. Perlin also proved the *trans* stereochemistry of the epoxypropyl sidechain.[2] However the absolute stereochemistry of the sidechain of this deceptively simple molecule has eluded a definitive assignment. Thus, NMR studies[3a] were used to propose the absolute stereochemistry of the sidechain epoxide as 6R,7S, an assignment that contradicted the X-ray analysis which assigned the 6S,7R configuration.[3b] Rabanal[4a] and, very recently, Shing[4b] have synthesized unnatural diastereomers of asperlin and deduced the absolute stereochemistry by exclusion. In fact, there has been only one synthesis of (+)-asperlin reported in the literature[5]; and the method used to prepare the epoxide did not establish its absolute configuration. In this communication, we wish to report an enantiospecific synthesis of 1 which furnishes incontrovertible evidence for its absolute stereochemistry as 4S, 5S, 6S, 7R. We chose to use a sugar precursor that had the requisite stereochemistry at the future C-4 and C-6, that combined with unambiguous chemical transformations, leaves no doubt about C-5 and C-7. As illustrated in the retrosynthesis scheme 1, we envisioned the epoxide as arising from 2 and an intramolecular Horner-Wadsworth-Emmons reaction producing the lactone. The appropriate precursor for 3 was L-rhamnose, since it is readily available and needs an inversion only at C-3.

Scheme 1



L-Rhamnose was converted to methyl rhamnoside using Binkley's procedure.[6] The manuever that left the C-3 OH free and blocked the C-2 and C-4 OH's was performed as follows. The C-2 and C-3 OH's were protected as an orthoacetate and the C-4 OH was silylated with TBDMSOTf to afford 6 (Scheme 2). The crude silyl ether-orthoacetate was hydrolyzed with 90% aqueous CH_3COOH, following well-established precedents for the regioselective ring opening of axial-equatorial orthoesters.[7] We thus obtained 7 in 52% overall yield from methyl rhamnoside. With the C-3 0H unblocked, its inversion was the next problem to be solved. Although Mitsunobu conditions were unsuccessful in our hands, the transformation was accomplished cleanly in two steps: PCC-MS oxidation[8] of the alcohol 7 gave the ketone 8 which was stereoselectively reduced to the axial alcohol 9 in 94% overall yield.[9] The alcohol was esterified to give the phosphonate 10 in 95% yield.[10] Conventional methods (e.g. aqueous acid) when employed to hydrolyze the methyl glycoside led to deblocking of TBDMS and/or phosphonate groups. The hydrolysis was efficiently done in two steps:(i) the methyl glycoside was converted to the 1-chloro sugar 11 by reacting it with BCl_3 in CH_2Cl_2 at -78°C and (ii) the 1-chloro sugar was reacted with Ag_2CO_3 in aqueous acetone to give 3 in 73% overall yield. The stage was set for the intramolecular HWE reaction. Several bases and reaction conditions were tried[12] but NaH/THF at room temperature gave satisfactory results to produce the lactone 12 in 32% yield. The lactone was converted to (+)-asperlin as follows: the remaining free OH was converted to its mesylate; then reaction of the mesylate with n-$Bu_4NF.3H_2O$ in CH_2Cl_2 at room temperature[13] produced asperlin in 22% yield[14]. This material was identical to a sample of the natural product in all respects.[15] Synthetic (+)-Asperlin: mp = 68-70°, $[\alpha]_D25°$=+322° (c= 0.2, 95% EtOH); lit.mp 71-73°, $[\alpha]_D25°$=+345 (c= 0.9, 95% EtOH)[1]; ^1H NMR ($CDCl_3$, 300MHz) δ 7.11 (dd, 1H, J= 5.78, 9.77, H3), 6.26 (d, 1H, J= 9.74, H2), 5.35 (dd, 1H, J= 5.73, 2.82, H4), 4.14 (dd, 1H,J= 6.95, 2.81, H5), 3.14-3.09 (m, 2H, H6, H7), 2.18 (s, 3H,OAc), 1.43 (d, 3H, J= 5.04, CH_3); 13C NMR ($CDCl_3$, 75MHz) δ 169.8 ($COCH_3$); 161.5 (C1) ; 140.5 (C3); 124.9 (C2); 78.9 (C4); 62.1 (C5); 54.9 (C6); 54.6 (C7); 20.6 (CH_3CO); 17.0 (C8).Thus, we have achieved a total synthesis of (+)-asperlin which unambigously establishes the absolute stereochemistry of the epoxide as drawn in 1.

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References and Notes

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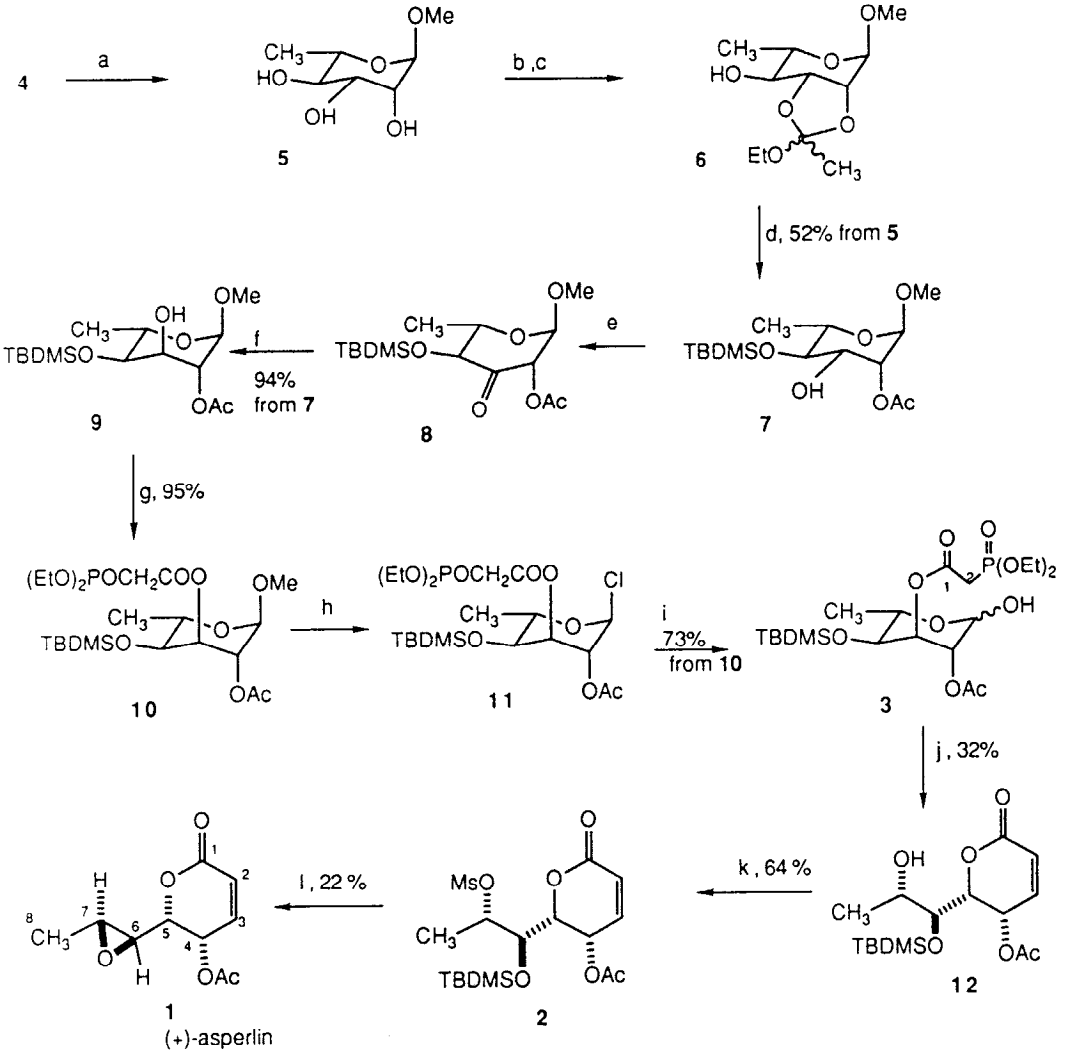
Scheme 2



(a) MeOH, Dowex-H^+, heat (b) $(EtO)_3CCH_3$, DMF, cat. p-TosH, heat
(c) TBDMSOTf , 2, 6-lutidine, CH_2Cl_2, 0°C(d) aq. acetic acid (90 %)
(e) PCC-MS, 3A° MS, NaOAc, CH_2Cl_2, RT (f) $NaBH_4$ / MeOH, -78 °C
(g) $(EtO)_2POCH_2CO_2H$, DCC, CH_2Cl_2, RT (h) BCl_3, CH_2Cl_2, -78°C
(i) Ag_2CO_3, aq. acetone, RT (j) NaH / THF , RT
(k) MsCl , Et_3N, 0° to RT (l) $Bu_4NF.3H_2O$, CH_2Cl_2, RT

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11. G. R. Perdomo and J.J. Krepinsky, *Tetrahedron Lett.*, **1987**, *28*, 5595. We have independently shown that BCl_3 in CH_2Cl_2 at -78°C converts methyl glycosides to 1-chloro sugars and that -OAc, -TBDMS and phosphonates are stable under these conditions.

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14.(+)-Asperlin is not particularly stable to Bu_4NF. Thus, no other characterizable epoxylactone could be detected in, or isolated from the reaction mixture.

15. All numbered compounds except for **6** and **11** were purified by chromatography to homogeneity and every compound gave ^1H and ^{13}C NMR consistent with the assigned structure. For **10**: $[\alpha]_D25°$=-51.9° (c= 2.72, CH_2Cl_2), ^1H NMR ($CDCl_3$, 300MHz) δ 4.97 (t, $J_{2,3}$ and $J_{3,4}$ = 3 Hz, H3); 4.80 (d,J = 3, H2); 4.42 (bs, H1); 4.1 (m, CH_2OP); 3.96 (m, H5); 3.58 (dd, $J_{4,5}$= 9, $J_{3,4}$ = 3, H4); 3.27 (s, OMe); 2.91 (ABq with added coupling to P, CH_2-P); 2.01 (s, CH_3CO);1.25 (t, CH_3); 1.15 (d, CH_3); 0.77 (s, t-Bu); 0.00 (s, MeSi); -0.2 (s, MeSi); ^{13}C NMR ($CDCl_3$, 75MHz) δ 169.1 ($COCH_3$); 165.0 ($COCH_2P$); 98.1 (C1); 70.8, 69.9, 69.6 (C2,C3,C5); 64.4 (C2); 62.5,62.6 (CH_2OP); 55.1 (OMe); 33.9 (d, J=135, CH_2P); 25.5 (Me of t-Bu); 20.8 (CH_3CO); 17.8 (qC of t-Bu); 17.7 (C6);16.3,16.2 (CH_3CH_2OP); -4.6,-4.9 (MeSi). M/e calcd. for $C_{21}H_{41}O_{10}PSi$: 512; Found (CI-methane) M+1 513. For **12**: $[\alpha]_D25°$=+112.8° (c= 1.95, CH_2Cl_2), ^1H NMR ($CDCl_3$, 300MHz) δ 7.27 (dd, J=9.6,6.0, H3); 6.19 (d, J=9.6, H2); 5.15 (dd, J= 6.0,1.9, H4); 4.41 (dd, J= 8.8,1.9, H5); 4.20 (m, H7); 4.18 (dd, J= 8.8, 2.2, H6); 2.12 (s, CH_3CO); 1.29 (d, CH_3CH); 0.93 (s, t-Bu); 0.21,0.09 (MeSi); ^{13}C NMR ($CDCl_3$, 75MHz) δ 169.9 ($COCH_3$); 162.2 (CO-lactone); 141.5, 124.6 (C=C); 78.1, 72.6, 68.2, 62.4 (C4-C7); 25.7 (Me of t-Bu); 20.8 (CH_3CO); 18.3 (qC of t-Bu); 16.8 (C8);-4.2,-5.1 (MeSi). M/e Calcd. for C16H28O6Si: 344; Found (CI-methane) M+1 345.