The Stereochemistry of the Epoxypropyl Side-chain of Asperlin

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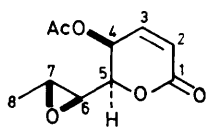
The absolute configuration of the oxirane moiety in asperlin is shown to be (6*S*,7*R*) by an unambiguous synthesis of its (6*R*,7*S*)-diastereoisomer from D-glucose involving a tandem epoxide formation and intramolecular Wadsworth–Emmons–Horner olefination.

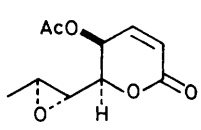
Asperlin, a 5-acetoxy-5,6-dihydro-6-(1,2-epoxypropyl)-2-pyrone isolated[1] from cultures of fungus *Aspergillus nidulans*, has been demonstrated to possess antibiotic and antitumour activity.[2] Earlier n.m.r. spectroscopic[3,4] and synthetic studies[4] of asperlin have shown that the 4,5-substituents† of the lactone ring had the L-*threo* configuration and the exocyclic epoxypropyl moiety was *trans*. These data have reduced the possible structures of asperlin to absolute configuration (**1**) or its 6,7-diastereoisomer (**2**); it has not proven feasible to determine the structure of asperlin by *X*-ray crystallography because the only form of the compound available consists of twinned crystals.[5] Recently, using spin relaxation rates and n.O.e. experiments, Perlin and Dais[5] have indicated that asperlin was the (6*R*,7*S*)-diastereoisomer, *i.e.* (**2**). We now report, starting from D-glucose, an unambiguous synthesis of (**2**) which is diastereoisomeric to asperlin, thereby establishing by exclusion that the natural material is the (6*S*,7*R*)-diastereoisomer (**1**).

The strategy for the enantiospecific construction of (**2**), shown in Scheme 1, involves a tandem epoxide formation and intramolecular Wadsworth–Emmons–Horner[6] olefination (this would guarantee the *Z*-geometry of the double bond) of the lactol (**3**) which is readily derived from D-glucose.

The acetonide (**4**),[7] obtained from D-glucose in two steps, was partially hydrolysed and then esterified to give the dimethanesulphonate (**5**) (m.p. 123—124 °C).[8] The primary methanesulphonate in (**5**) was displaced with lithium alu-



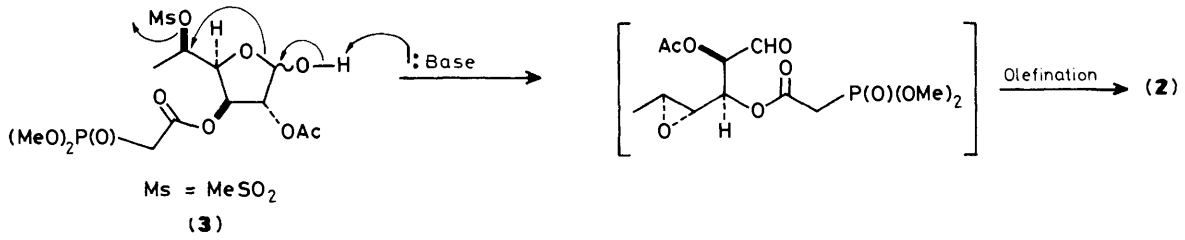
(**1**)



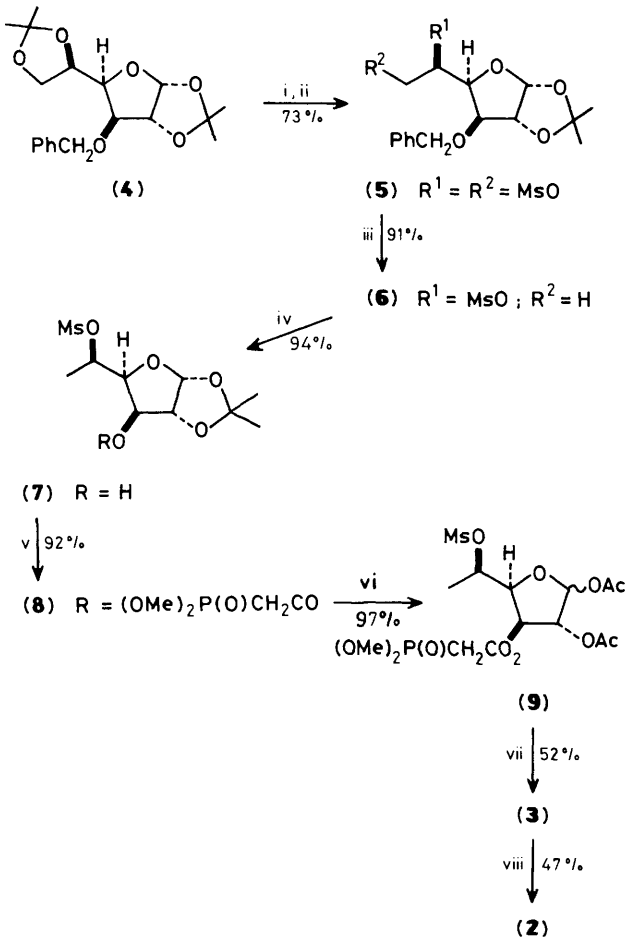
(**2**)

Ac = MeCO

† The numbering is indicated on structure (**1**).



Scheme 1



Scheme 2. *Reagents*: i, aq. MeOH, HCl; ii, $MeSO_2Cl$, Et_3N, CH_2Cl_2; iii, $LiAlH_4$, THF; iv, $Pd(OH)_2$, H_2, EtOH; v, $(MeO)_2P(O)CH_2CO_2H$, $(C_6H_{11}N)_2C$, CH_2Cl_2; vi, $(MeCO)_2O$, BF_3; vii, $SnCl_4$, MeCN, then aq. $HCONMe_2$; viii, LiCl, 1,8-diazabicyclo[5.4.0]undec-7-ene, MeCN.

minium hydride to form the deoxy-derivative (**6**),‡ {m.p. 82—84 °C; $[\alpha]_D$ −25.4° (*c* 4.4, acetone)} which was debenzylated to the alcohol (**7**), {m.p. 56—58 °C, $[\alpha]_D$ −22.0° (*c* 2.9, acetone)}. Esterification of (**7**) with dimethylphosphonoacetic acid gave the phosphonate (**8**), {$[\alpha]_D$ −8.4° (*c* 3.4, acetone)}, which was acetolysed to yield the diacetate (**9**), {$[\alpha]_D$ +17.4° (*c* 9.3, acetone)}. The anomeric acetoxy group in (**9**) was selectively[9] hydrolysed to the lactol (**3**) {$[\alpha]_D$ +13.3° (*c* 1.9, acetone)}, which on mild base treatment[10] was transformed into the target epoxy-lactone (**2**),§ {m.p. 55—57 °C, $[\alpha]_D$ +172° (*c* 1, EtOH), R_F 0.45 (silica gel t.l.c., diethyl ether)}, with spectroscopic data (mass, i.r., ^1H n.m.r.) similar to those of an authentic sample of asperlin.¶ Since asperlin had m.p. 71—73 °C, $[\alpha]_D$ +345° (*c* 0.5, EtOH),[1] and R_F 0.50 (diethyl ether), (**2**) must be its diastereoisomer. The absolute configuration (**1**) is therefore assigned to asperlin.

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‡ All new compounds gave satisfactory analytical and spectral data.

§ The biological activity of this new 2-pyrone will be reported later.

¶ *Selected spectroscopic data* for (**2**): ^1H n.m.r. ($CDCl_3$, 300 MHz) δ 1.34 (d, 3H, $J_{8,7}$ 5.1 Hz, 8-H), 2.15 (s, 3H, CH_3CO), 3.00 (dd, 1H, $J_{6,7}$ 2.2, $J_{6,5}$ 4.9 Hz, 6-H), 3.04 (dq, 1H, 7-H), 4.35 (dd, 1H, $J_{5,4}$ 3.6 Hz, 5-H), 5.50 (dd, 1H, $J_{4,3}$ 5.2 Hz, 4-H), 6.22 (d, 1H, $J_{2,3}$ 9.8 Hz, 2-H), 6.86 (dd, 1H, 3-H).

For authentic asperlin: ^1H n.m.r. ($CDCl_3$) δ 1.39 (d, 3H, $J_{8,7}$ 5.0 Hz, 8-H), 2.14 (s, 3H, CH_3CO), 3.04—3.10 (m, 2H, 7,6-H), 4.10 (dd, 1H, $J_{5,6}$ 6.9, $J_{5,4}$ 2.8 Hz, 5-H), 5.31 (dd, 1H, $J_{4,3}$ 5.7 Hz, 4-H), 6.22 (d, 1H, $J_{2,3}$ 9.7 Hz, 2-H), 7.07 (dd, 1H, 3-H).