

## Total Synthesis of (+)-Asperlin Starting with (S,S)-Tartaric Acid

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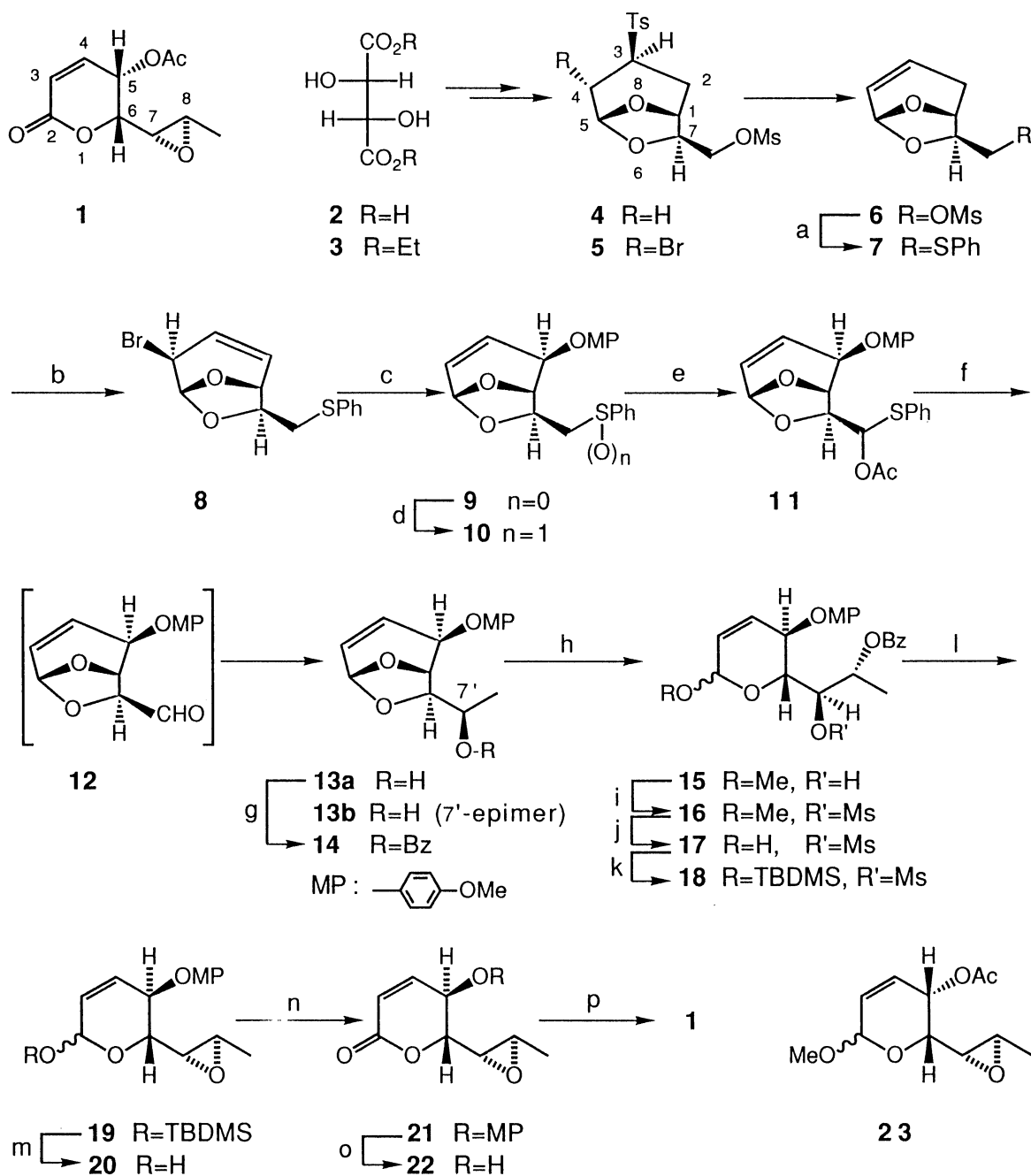
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Natural (+)-asperlin was synthesized stereoselectively starting with (S,S)-tartaric acid by way of the 6,8-dioxabicyclo[3.2.1]octane skeleton.

(+)-Asperlin (U-13,933) (**1**) with antibiotic and antitumor activities has been isolated as a crystalline metabolite from *Aspergillus nidulans* <sup>1a)</sup> and structurally determined including the absolute configuration of the chiral centers (5*S*,6*S*,7*S*,8*R*) <sup>1b)</sup> by NMR-spectroscopy, <sup>2)</sup> X-ray crystallography, <sup>3)</sup> and, very recently, an unambiguous total synthesis. <sup>4)</sup> Asperlin (**1**) is recognized structurally as the most fundamental and smallest representative of the family of biologically active 5-oxygenated 5,6-dihydro-2-pyrones with the oxygen-functionalized sidechain at the 6-position. <sup>5)</sup> We report here a stereoselective total synthesis of natural (+)-asperlin (**1**) starting with (S,S)-tartaric acid (**2**). The synthesis is featured by stereoselective introduction of the chiral oxygen function at the 2- and 7'-position (the latent 5- and 8-position of **1**, respectively) of the 6,8-dioxabicyclo[3.2.1]octane skeleton followed by partial ring opening to furnish a pyranoid and potential for wide applicability to synthesis of a series of 5-oxygenated and 6-substituted 5,6-dihydro-2-pyrones such as olguin, <sup>6a)</sup> goniotriol, <sup>6b)</sup> goniopyrone, <sup>6c)</sup> and anti-leukemic PD-113271. <sup>6d)</sup>

(+)-(1*R*,3*S*,5*R*,7*R*)-7-Mesyloxymethyl-3-tosyl-6,8-dioxabicyclo[3.2.1]octane (**4**) prepared in 54% overall yield by 4-steps sequence of reactions from diethyl (S,S)-tartrate (**3**) was transformed via the 4-bromo-derivative (**5**) to the 3,4-dehydrobicyclic compound (**6**) in 75% overall yield by consecutive treatments with bromine and then with zinc-copper couple. <sup>7)</sup> Radical bromination of the 7'-sulfenylated olefin (**7**), easily prepared from the 7'-O-mesylate (**6**), afforded highly regio- and stereo-selectively crystalline 4-bromo-olefin (**8**), <sup>8)</sup> which was treated with sodium 4-methoxyphenolate in THF to lead stereospecifically in 85% yield to crystalline (2*R*)-2-p-methoxyphenyl ether (**9**) (mp 64.5-65.0 °C; [ $\alpha$ ]<sub>D</sub> - 235.6° (c 1.36, CHCl<sub>3</sub>)).

Stereoselective introduction of the 7'-oxygen function (latent epoxide oxygen of asperlin (**1**)) was realized by methylation of 7-carboxyaldehyde (**12**) <sup>9)</sup> formed *in situ* from the  $\alpha$ -acetoxysulfide (**11**) which was obtained by the Pummerer reaction of the sulfoxide (**10**). Thus, oxidation of the sulfide (**9**) with MCPBA providing the sulfoxide (**10**) followed by heating **10** in Ac<sub>2</sub>O with 0.25 equiv of AcONa gave the  $\alpha$ -acetoxysulfide (**11**) in 88% overall yield. Reaction of **11** with 5 equiv of MeLi in THF at -90 °C provided the (7'*R*)-alcohol (**13a**) and the (7'*S*)-alcohol (**13b**) in 71 and 15% yield, respectively, after separation by column chromatography. The hydroxyl group of the major product (**13a**) was protected to give the key intermediate, crystalline benzoate (**14**) (mp 115.5-116.5 °C; [ $\alpha$ ]<sub>D</sub> -111.1° (c 1.13, CHCl<sub>3</sub>)), absolute structure of which was determined by the X-ray crystallography <sup>10)</sup> of the antipodal one ((+)-**14**) prepared from diethyl (R,R)-tartrate ((+)-**3**) in the preliminary experiments through the same route as described above and is shown as the



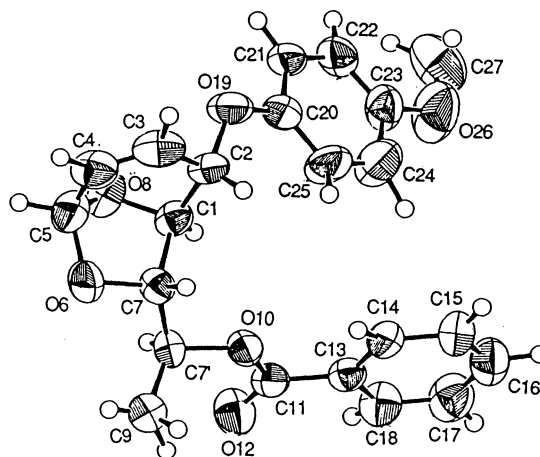
## ORTEP view.

The oxygen functionalized bicyclic compound (**14**) was treated with Amberlyst 15 in MeOH at r.t afforded the pyranoid acetal (**15**) in 89% yield. Its mesylate (**16**) was converted into the tert-butyldimethylsilyl (TBDMS) acetal (**18**) in 79% overall yield via the hemiacetal (**17**). Treatment of the mesylate (**18**) with  $K_2CO_3$  in MeOH afforded the epoxide (**19**) in 87% yield. After cleavage of TBDMS group with  $n\text{-Bu}_4NF$ , the hemiacetal (**20**) was oxidized with activated  $MnO_2$  to give unsaturated lactone (**21**) in 75% overall yield. The p-methoxyphenyl protecting group was cleaved with ceric ammonium nitrate (CAN)<sup>11</sup> in aqueous  $CH_3CN$  to lead to the alcohol (**22**) (63%). The configuration of the C-5 hydroxyl group of **22** was inverted by the Mitsunobu reaction in the presence of  $AcOH$ <sup>4c</sup> to lead in 70% yield to crystalline (+)-asperlin(**1**) (mp 74-76 °C;  $[\alpha]_D^{25} + 341.1^\circ$  (c 0.56, EtOH)), which was identified with the authentic sample of **1** by spectral comparisons ( $^1H$  NMR,  $^{13}C$  NMR, and IR).<sup>1a,4</sup> It should be worth noting that the formation of the epoxy-lactone system in **21** via oxidation of unsaturated epoxy-hemiacetal system of **20** with  $MnO_2$  appeared to be a method of choice, because in spite of extensive trials, direct Jones oxidation of the epoxy-acetal (**23**)<sup>12</sup> prepared from the mesylate (**16**) afforded only a little amount (7-9% yield) of desired (+)-asperlin (**1**) with variant recovery of **23** (35-75%).

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ORTEP view of (+)-**14** (Antipode of **14**).

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  - 8) Structures of all new compounds were characterized by  $^1\text{H}$  NMR (270 MHz), IR, and/or MS spectra and by microelemental analysis particularly for crystalline compounds.
  - 9) Pure aldehyde (**12**) could be obtained from **11** on treatment with  $\text{K}_2\text{CO}_3$  in MeOH, but was unstable and easily turned to the corresponding hydrate through column chromatography on silica gel.
  - 10) Crystal data for (+)-**14** (antipode of **14**):  $\text{C}_{22}\text{H}_{22}\text{O}_6$ ,  $M=382.41$ , space group  $P2_1$  (#4) with  $a=9.161$  (1),  $b=6.007$  (1),  $c=18.560$  (2) Å,  $\beta=102.99$  (1)°,  $D_c=1.276$  g cm $^{-3}$  for  $Z=2$ ,  $V=995.2$  (3) Å $^3$ , and  $R=0.048$  for 1672 reflections.
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  - 12) The epoxy-acetal (**23**) was obtained from **16** in 73% overall yield by a three step sequence including epoxidation, deprotection of p-methoxyphenyl ether, and the Mitsunobu inversion of 5-OH group. Jones oxidation of this type of epoxy-acetal proceeded sluggishly also in the other case (Ref. 4d), and gave intractable products when the reaction was carried out until all of **23** was consumed.

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