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

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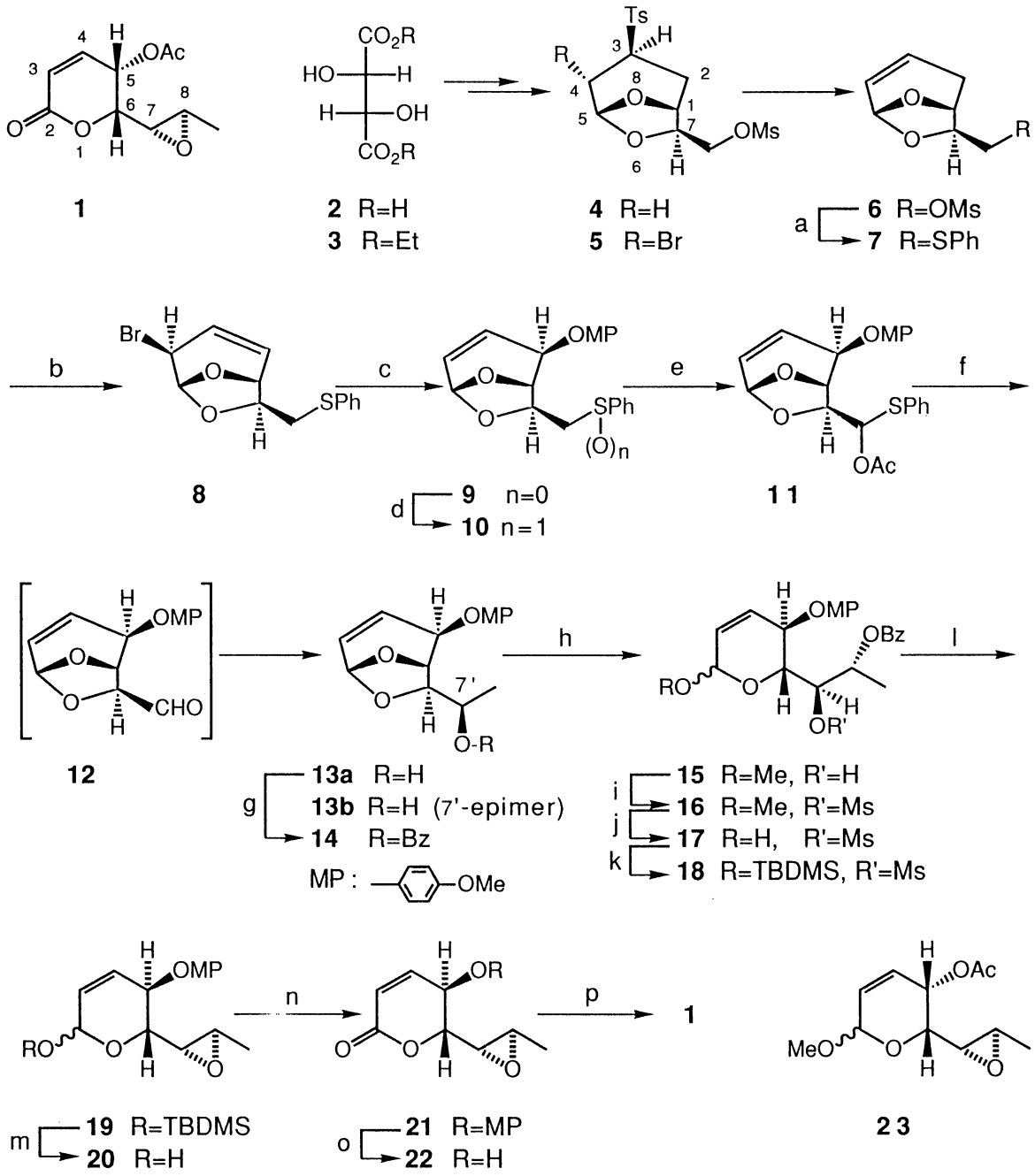
Natural (+)-asperlin was synthesized stereoselectively starting with (*S*,*S*)-tartaric acid by way of the 6,8-dioxabicyclo[3.2.1]octane skeleton.

(+)-Asperlin (U-13,933) (**1**) with anitibiotic and antitumor activities has been isolated as a crystalline metabolite from *Aspergillus nidulans* [1a] and structurally determined including the absolute configuration of the chiral centers (5*S*,6*S*,7*S*,8*R*)[1b] by NMR-spectroscopy,[2] X-ray crystallography,[3] and, very recently, an unambiguous total synthesis.[4] 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.[5] 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,[6a] goniotriol,[6b] goniopypyrone,[6c] and anti-leukemic PD-113271.[6d]

(+)-(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.[7] 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**),[8] 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; $[\alpha]_D$ - 235.6° (c 1.36, $CHCl_3$)).

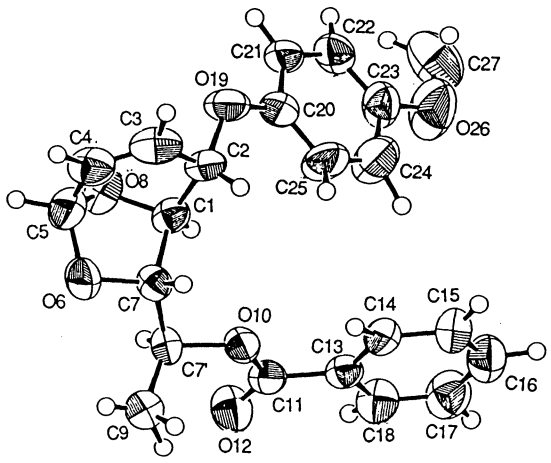
Stereoselective introduction of the 7'-oxygen function (latent epoxide oxygen of asperlin (**1**)) was realized by methylation of 7-carboxyaldehyde (**12**)[9] formed *in situ* from the α-acetoxysulfide (**11**) which was obtained by the Pummerer reaction of the sulfoxide (**10**). Thus, oxidation of the sulfide (**9**) with MCPBA providing the sulfoxide (**10**) followed by heating **10** in Ac_2O with 0.25 equiv of AcONa gave the α-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; $[\alpha]_D$ -111.1° (c 1.13, $CHCl_3$)), absolute structure of which was determined by the X-ray crystallography[10] 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



(a) PhSNa / DMF / 80 °C / 22 h (83%) ; (b) NBS / AIBN (cat.) / CCl_4 / reflux / 4 h (63%) ; (c) MPONa / THF / r.t. / 60 h (85%) ; (d) MCPBA (1 equiv.) / CH_2Cl_2 / 0 °C / 20 min (92%) ; (e) Ac_2O / AcONa (0.25 equiv.) / reflux / 7 h (97%) ; (f) MeLi (5 equiv.) / THF / -90 °C / 4 h (71%) ; (g) BzCl / pyridine / 0 °C / 1 h (98%) ; (h) Amberlyst 15 / MeOH / r.t. / 84 h (89%) ; (i) MsCl / Et_3N / CH_2Cl_2 / 0 °C / 1.5 h (98%) ; (j) AcOH-H_2O (3:1) / 60 °C / 13 h (88%) ; (k) TBDMSCl / imidazole / DMF / r.t. / 0.5 h (90%) ; (l) K_2CO_3 / MeOH / r.t. / 9 h (87%) ; (m) n-Bu_4NF-3H_2O / THF / 0 °C / 2.5 min (93%) ; (n) MnO_2 (excess) / CH_2Cl_2 / r.t. / 24 min (81%) ; (o) CAN (3 equiv.) / pyridine (3 equiv.) / CH_3CN-CH_2Cl_2-H_2O (4:1:1) / 0 °C /1 h (63%) ; (p) PPh_3 / AcOH / DEAD / THF / r.t. / 1 h (70%)

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-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)[11] 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 [4c] to lead in 70% yield to crystalline (+)-asperlin(**1**) (mp 74-76 °C; $[\alpha]_D$ + 341.1° (c 0.56, EtOH)), which was identified with the authentic sample of **1** by spectral comparisons (^1H NMR, ^{13}C NMR, and IR).[1a,4] 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**)[12] prepared from the mesylate (**16**) afforded only a little amount (7-9% yield) of desired (+)-asperlin (**1**) with variant recovery of **23** (35-75%).



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

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8) Structures of all new compounds were characterized by ^{1}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 K_2CO_3 in MeOH, but was unstable and easily turned to the corresponding hydrate through column chromatograpy on silica gel.

10) Crystal data for (+)-**14** (antipode of **14**): $C_{22}H_{22}O_6$, M=382.41, space group $P2_1$ (#4) with a=9.161 (1), b=6.007 (1), c=18.560 (2) Å, β=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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