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Total Synthesis of (+)-Goniothalenol [(+)-Altholactone], a Novel Bioactive Tetrahydrofurano-2-pyrone

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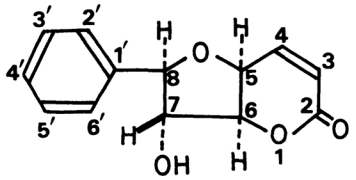
A novel plant-origin tetrahydrofurano-2-pyrone, (+)-goniothalenol has been synthesized from L-arabinose. The central feature of the present synthesis is a silica-gel catalyzed intramolecular epoxy ring opening by hydroxyl group for construction of the tetrahydrofuran in the title compound.

(+)-Goniothalenol (formerly named as altholactone) (1) was isolated from the bark of an unnamed *Polyalthia* species in 1977, and the structure was determined by chemical degradation and spectral analysis.[1] This unique tetrahydrofurano-2-pyrone 1 was also isolated from the stem bark of *Goniothalamus giganteus* (Annonaceae) in 1985, and the relative configuration of 1 was established by X-ray crystallographic analysis.[2] The remarkable bioactive features of 1 are a toxicity against P388 leukemia cell in mice and a lethality to brine shrimp.[2] As a structurally related compound, (+)-asperlin (2) which exhibits antimicrobial and antitumor activity was isolated from a fungus (*Aspergillus nidulans*).[3] Meanwhile, the establishment of the absolute configuration of 1 is required for solution to the biosynthetic correlation of 1 to 2. In this letter, we wish to disclose the total synthesis of (+)-1.[4]

As an enantiomerically pure starting material, we chose L-arabinose for introduction of (*R*)-configuration at C-6 in 1. The (*R*)-configuration at C-6 in 1, if it is established, is the same as that of C-6 on the 2-pyrone portion in (+)-2. L-Arabinose was transformed to 1,3-O-benzylidene-L-arabinitol (3) according to the reported procedure.[5] The glycol in 3 was cleaved by periodate and Wittig olefination of thus formed aldehyde with benzylidenetriphenylphosphorane ($PhCH_2P^+Ph_3Cl^-$, BuLi, THF, r.t.) gave 4-Z[6a,b,7] (20%) and 4-E[6a,b] (60%) which were separated by silica-gel chromatography. The hydroxyl group in 4-E was benzoylated to give 5[6a,b] in 93% yield. Oxidation of 5 by *m*-chloroperbenzoic



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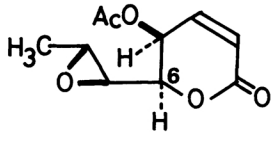

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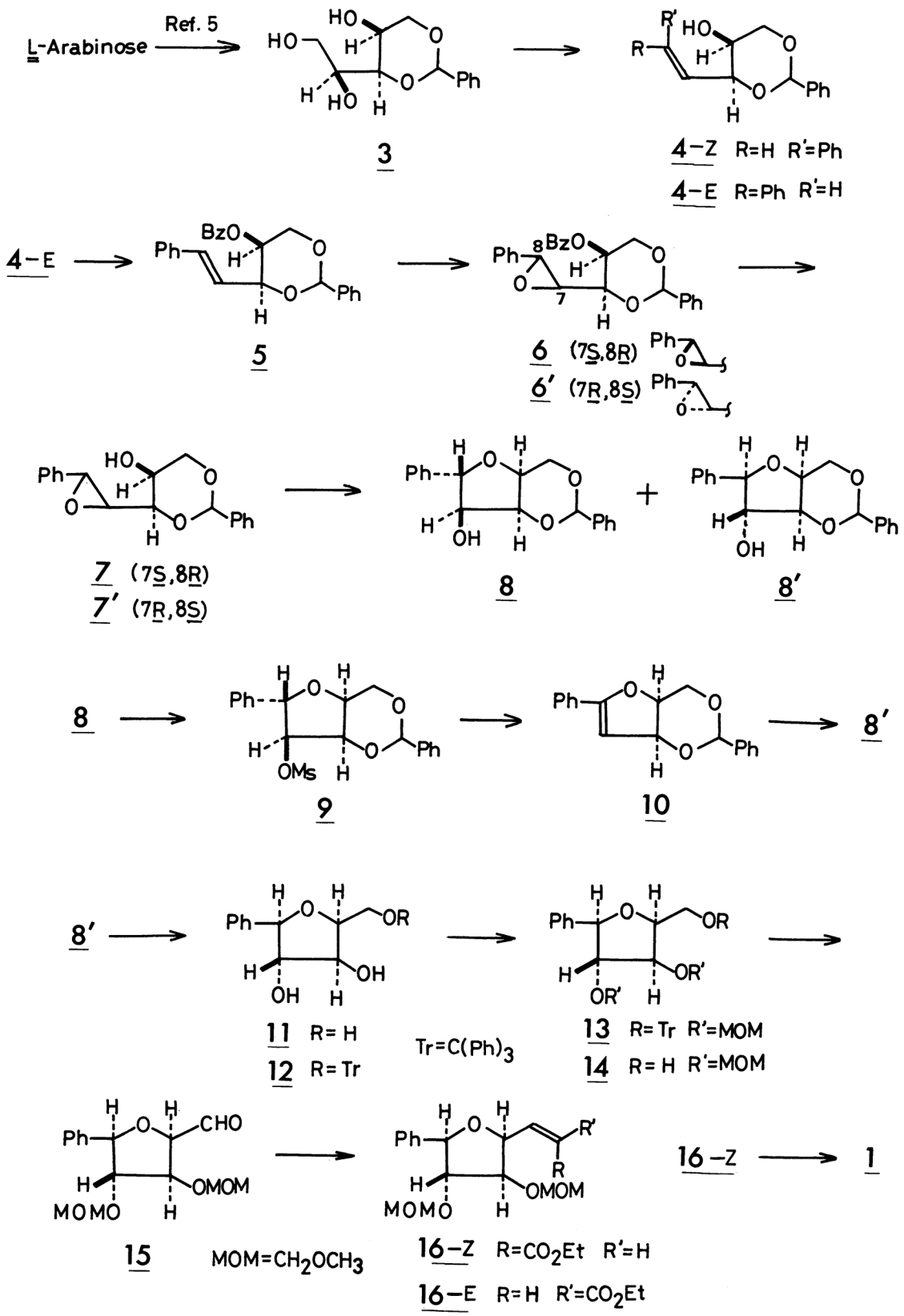
L-Arabinose
Ref. 5
3
4-Z R=H R'=Ph
4-E R=Ph R'=H
4-E
5
6 (7S,8R)
6' (7R,8S)
7 (7S,8R)
7' (7R,8S)
8
8'
9
10
11 R=H
12 R=Tr
Tr=C(Ph)3
13 R=Tr R'=MOM
14 R=H R'=MOM
15
MOM=CH2OCH3
16-Z R=CO2Et R'=H
16-E R=H R'=CO2Et
16-Z
1

acid in CH_2Cl_2 under reflux provided an inseparable mixture[6a] of (7*S*,8*R*)-epoxide 6 and (7*R*,8*S*)-epoxide 6'. This mixture was directly O-debenzoylated with sodium methoxide. After neutralization and work-up, the O-debenzoylated mixture (7+7') in CH_2Cl_2 was dealt with silica gel at r.t. for 32 h. Under these conditions, both epoxy rings in 7 and 7' opened to form bicyclic tetrahydrofurans 8 and 8' stereoselectively.[8] Compounds 8 and 8' were cleanly separated by recrystallization then by silica-gel chromatography of the mother liquor. As a main product, (7*S*,8*S*)-tetrahydrofuran 8[6a,b] was isolated in 52% yield from 5 along with 4% of (7*R*,8*R*)-diastereomer 8'.[6a,b] From these results, we estimated that the ratio of 6 and 6' was approximately 13:1. The desired 8' for (+)-1 synthesis was obtained in an unpractical yield.[9] Therefore, the transformation of 8 to 8' was pursued. O-Mesylation of 8 gave the mesylate 9[6a,b] in 96% yield. A brief treatment of 9 with *t*-BuOK (3.5 mol equiv.) in refluxing THF (20 min) followed by hydroboration of thus formed dihydrofuran 10[6a] with $(BH_3)_2$ and successive oxidative work-up (35% H_2O_2 in THF:1 mol dm^{-3} NaOH:H_2O=15:6:5) furnished 8' (64%). The hydroboration proceeded exclusively from the convex-face of 10, and none of 8 was detected. Compound 8' possesses all of the four chiral carbons in (+)-1, and the remaining subject was the construction of the 2-pyrone portion in 1. Hydrolysis of 8' with 1 mol dm^{-3} HCl in dioxane (reflux) provided the O-debenzylidene derivative 11[6a] (89%). The primary hydroxyl group in 11 was preferentially protected as a trityl ether giving 12[6a] in 75% yield (TrCl, 4-DMAP in pyridine). The secondary hydroxyl groups in 12 were then protected as methoxymethyl (MOM) ethers giving 13[6a,b] (MOMCl, *i*-Pr_2EtN in THF)(89%). The trityl ether in 13 was deblocked by acid hydrolysis to give 14[6a,b] (94%) ($TsOH \cdot H_2O$ in AcOEt and MeOH). Collins oxidation of 14 (CrO_3/pyridine in CH_2Cl_2) gave an aldehyde 15 which was subjected to Wittig carbon elongation. Treatment of 15 with (ethoxycarbonylmethylene)triphenylphosphorane in refluxing benzene provided the α,β-unsaturated esters 16-Z[6a,b] (39%) and 16-E[6a,b] (30%). In this Wittig olefination, the Z-isomer was obtained somewhat preferentially. By hydrolysis with $TsOH \cdot H_2O$ in refluxing MeOH for 3 h, 16-Z was converted into 1 as a result of deblocking of the MOM ethers followed by 2-pyrone formation in 47% yield. The melting point and $[\alpha]_D$ of the synthetic 1[10] [mp 113-114 °C, $[\alpha]_D^{33}$+181° (*c* 0.52, EtOH)] coincide well with the reported values for natural 1 [mp 110 °C,[2] mixed mp 112-113 °C, $[\alpha]_D^{20}$+188° (*c* 0.5, EtOH)[1] and $[\alpha]_D^{25}$+184.7° (EtOH)[2]]. The TLC behavior of 1 in several solvent-systems is identical with that of natural (+)-1. The ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) of the synthetic 1 were in complete accordance with those of natural (+)-1. The absolute configuration of (+)-1 was thus established to be (5*S*,6*R*,7*R*,8*R*).

We would like to express our thanks to Professor Jerry L. McLaughlin (Purdue University) for sending us a precious sample of natural (+)-1 and the spectra (^1H and ^{13}C NMR, IR, and MS) of it.

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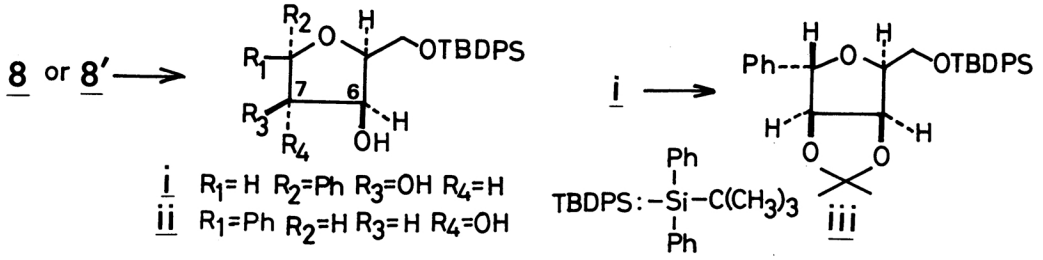
6) a) All new compounds were fully characterized by the spectral means (IR and ^{1}H NMR) and b) gave satisfactory elemental analyses and/or high-resolution mass spectra. The physical [[α]$_D$ in $CHCl_3$] and spectral (^{1}H NMR in $CDCl_3$) data of selected compounds are as follows. 4-Z : mp 106-107 °C; $[\alpha]_D^{23}$-340° (*c* 1.05). 4-E: mp 109.5-111 °C; $[\alpha]_D^{22}$+61° (*c* 1.15). 5: mp 164.5-165.5 °C; $[\alpha]_D^{22}$+161° (*c* 1.19). 8: mp 127-128 °C; $[\alpha]_D^{23}$-11° (*c* 1.00); ^{1}H NMR δ 5.01 (1H, d, *J*=9 Hz). 8': mp 131-132 °C; $[\alpha]_D^{25}$+28° (*c* 0.90); ^{1}H NMR δ 4.80 (1H, d, *J*=2 Hz). 9: mp 186-186.5 °C; $[\alpha]_D^{22}$-75° (*c* 1.24). 16-Z : $[\alpha]_D^{29}$+176° (*c* 1.13); ^{1}H NMR δ 5.92 (1H, dd, *J*=12 and 1.5 Hz), 6.53 (1H, dd, *J*=12 and 7.5 Hz). 16-E: $[\alpha]_D^{30}$+16° (*c* 0.96); ^{1}H NMR δ 6.23 (1H, dd, *J*=16.5 and 1.5 Hz), 7.08 (1H, dd, *J*=16.5 and 6 Hz).

7) Compound 4-Z was isomerized to 4-E by treatment with PhSH in the presence of AIBN in refluxing benzene for 30 min (87%).

8) The 7,8-epoxides (as a diastereomers mixture) prepared from 4-Z by *m*-chloroperbenzoic acid did not react under the conditions employed for the mixture 7 and 7'.

9) The structures of 8 and 8' were established as follows. O-Debenzylidenation of 8 and 8' followed by preferential O-silylation of each product gave i (70 %) and ii (70%). O-Isopropylidenation (2,2-dimethoxypropane, TsOH) of i gave iii (87%) smoothly. Under the same conditions, however, ii was recovered quantitatively. Therefore, the 6,7-cis-diol system in 8 and the trans-diol system in 8' were confirmed.



10) Anal. Found: C, 67.24; H, 5.18%. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21%. HRMS, calcd for $C_{13}H_{13}O_4$: *m/z* 233.0813, found: M+H, 233.0802.

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