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TOTAL SYNTHESIS OF (+)-ALTHOLACTONE

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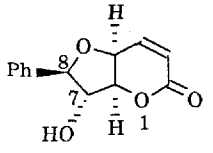
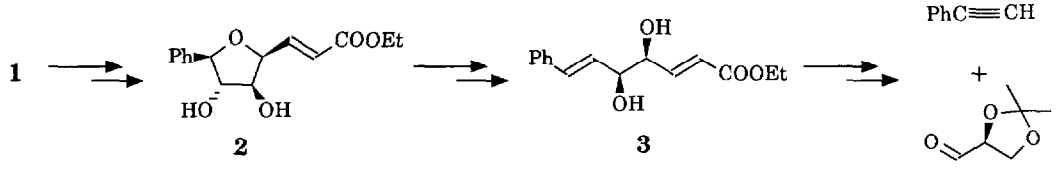
Summary : (+)-Altholactone **1**, an antitumor agent isolated from *Goniothalamus* species, has been synthesized starting from L-glyceraldehyde acetonide.

(+)-Altholactone **1** from an unknown *Polyathea* species has a novel phenyltetrahydrofurano-2-pyrone structure rare for natural compounds.[1] It turned out to be identical with goniothalenol from the stem bark of *Goniothalamus giganteus* Annonaceae, which displays cytotoxicity *in vitro* (BS, 9KB) and inhibitory activity *in vivo* against P 388 leukemia.[2] Several bioactive 2-pyrones from other *Goniothalamus* species retain the 6R configuration of (+)-altholactone (dihydrokawain-5-ol,[3] asperlin,[4] olguine[5] etc [6]) or the opposite 6S configuration (goniothalamine,[7] goniodiol and goniotriol [8]). Due to the unusual structure-biological activity relationship and the novel heterocyclic skeleton, we herein describe an enantiocomplementary total synthesis of (+)-altholactone **1** from L-glyceraldehyde acetonide, of which the identical sequence is also applicable to constructing (-)-altholactone from D-glyceraldehyde acetonide.[9]



1

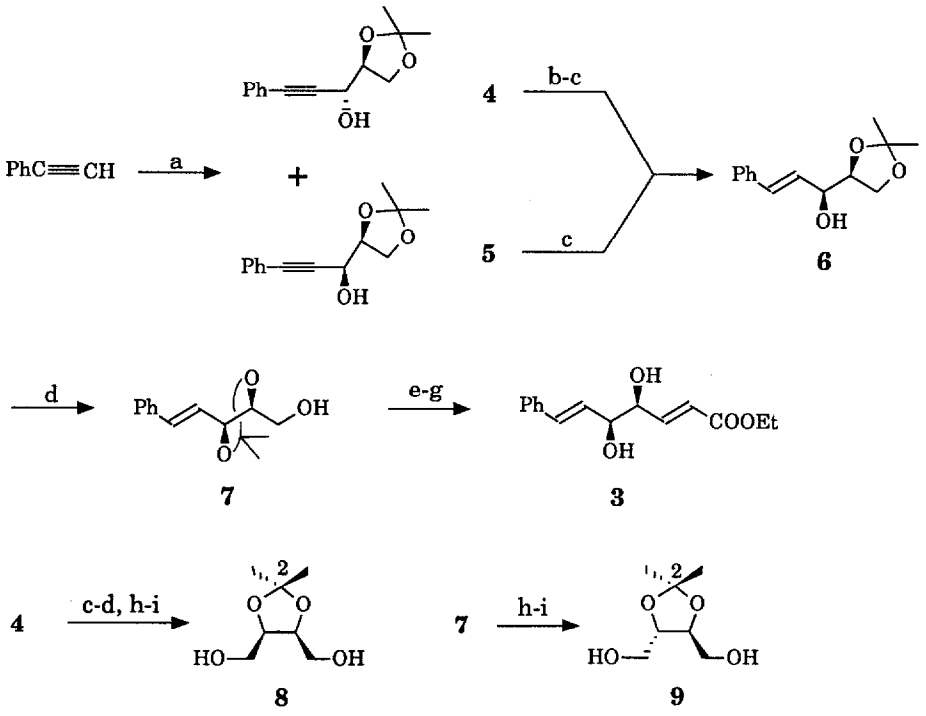
Based on the retrosynthetic analysis aimed at a synthesis of (+)-altholactone **1**, trans-allylic diol **3** comprising two stereogenic centers was decided as a crucial intermediate. Although the usual epoxidation of the olefinic double bond at C_6 of **3** was anticipated to suffer from low stereoselectivity,[10] the desired stereochemical outcome of the epoxidation followed by cyclization would provide the demanding four chiral centers on the tetrahydrofuranyl ring of **1** without any further adjustment of the functional groups.



2 **3**

The addition reaction of L-glyceraldehyde acetonide[11] to lithium phenylacetylide furnished a 1 : 1.15 diastereomeric mixture of propargylic alcohols **4** and **5** in 91% combined yield, of which the stereochemistry could be settled later (Scheme 1). Various reaction conditions attempted to improve the poor stereoselectivity[12] was useless in contrast to the results from dibenzyl-L-glyceraldehyde with zinc phenylacetylide.[13] After chromatographic separation of **4** and **5**, **4** was treated

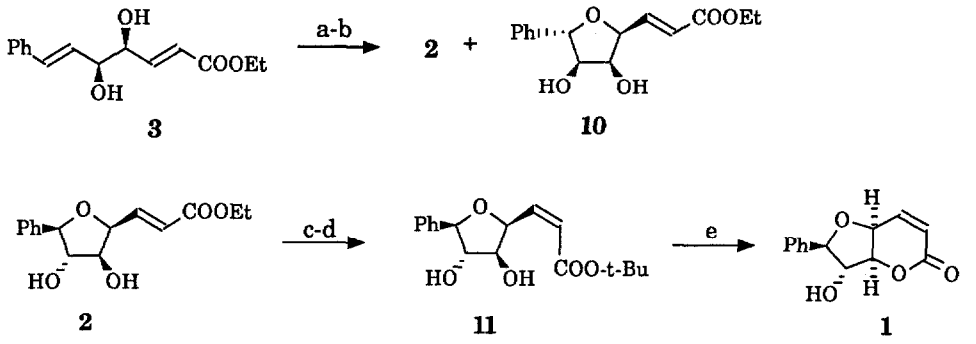
Scheme 1



Reagents : a. n-BuLi / THF / 0°C; L-Glyceraldehyde acetonide / -78°C ⟶ RT. b. Ph_3P / PhCOOH / diethyl azodicarboxylate / THF / RT. c. LAH / THF / 0°C. d. (±)-Camphorsulfonic acid(cat.) / acetone / RT. e. $(COCl)_2$ / DMSO / CH_2Cl_2 / -78°C ; Et_3N / -78°C ⟶ 0°C. f. $(EtO)_2P(O)CH_2COOEt$ / t-BuOK / THF / -78°C ⟶ RT. g. Acetic acid-H_2O (4 : 1) / 55°C. h. O_3 / MeOH / -78°C ; Me_2S / -78°C ⟶ RT. i. $NaBH_4$ / MeOH / 0°C.

with Mitsunobu conditions[14] and lithium aluminum hydride (LAH) reduction[15] in sequence, and **5** was reduced with LAH to afford the expected trans-allylic alcohol **6** in 92% and 97% yield, respectively. In the next event **6** should be transformed into a derivative decorated with two protected secondary hydroxyl groups and a free primary hydroxyl group. In this regard the most perspicacious route was conceived to rearrange the outer acetonide group of **6** to the inner one. Indeed acid-mediated equilibration of **6** in acetone successfully produced a 5 : 1 mixture of the desired rearranged acetonide **7**, $[\alpha]_D$= - 12.9° ($CHCl_3$, c=0.05) and the starting acetonide **6** in 92% yield. Now it is appropriate to mention how the stereochemistry of **4** and **5** were assigned. While the minor of the addition products was sequentially subjected to LAH reduction, acid-mediated equilibration, ozonolysis and sodium borohydride reduction to give diol **8**, treatment of **7** from the major with ozonolysis followed by sodium borohydride reduction yielded diol **9**. The ^{1}HNMR spectrum of **8** shows that the two methyl groups at 2-position are not identical [δ 1.37 (3H,s) and 1.46 ppm (3H,s)] ; whereas, **9** has the two identical methyl groups at 2-position [δ 1.43 (6H,s)]. The results conclude that the minor alcohol is **4** and the major is **5**. Swern oxidation[16] of **7**

Scheme 2



Reagents : a. MMPP / acetone / RT. b. (±)-Camphorsulfonic acid (cat.) / CH_2Cl_2 / RT. c. O_3 / MeOH / -78°C ; Me_2S / -78°C ⟶ RT. d. Ph_3P=CHCOO-t-Bu / MeOH / 0°C. e. CF_3COOH-CH_2Cl_2 (1 : 20) / RT.

followed by Wittig reaction using triethyl phosphonoacetate and potassium t-butoxide gave the expected trans-ester contaminated with less than 3% of the corresponding cis-ester, which were deprotected together in hot aqueous acetic acid to provide the trans-allylic diol **3**, $[\alpha]_D$= - 82.8° ($CHCl_3$, c=0.05) in 88% overall yield.[17]

To secure the required stereochemistry at 7- and 8- position, it is necessary to epoxidize **3** from β-face. Although the attempted hydroxyl-directing epoxidation with m-chloroperbenzoic acid (MCPBA) was disappointing as expected, employing magnesium monoperoxyphthalate (MMPP)[18] improved the stereoselectivity better. As a consequence, epoxidation of **3** with MMPP followed by acid-catalyzed cyclization furnished a 3.5 : 1 mixture of tetrahydrofuranyl derivatives **2**, $[\alpha]_D$= - 4.4° ($CHCl_3$, c=0.02) and **10** in 77% combined overall yield (Scheme 2).[19] To complete the requisite carbon moiety for 2-pyrone ring, the conjugated carboethoxy group of **2** was removed by ozonolysis and the resulting aldehyde was olefinated with t-butyl (triphenylphosphoranylidene)-acetate in methanol[20] to afford the desired cis-ester **11**, $[\alpha]_D$= + 111.4° ($CHCl_3$, c=0.03) and the corresponding trans-ester in a ratio of 5.6 to 1 in 86% combined overall yield. Finally **11** was converted in to (+)-altholactone **1**, m.p. 73~74°C, $[\alpha]_D$= + 186.8° (EtOH, c=0.04) with trifluoroacetic acid quantitatively.[21]

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17. Cis-ester was converted into lactone under the reaction conditions. It was not determined whether it is 5-membered or 6-membered.
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19. The same sequential treatment of **3** using MCPBA instead of MMPP produced **2** and **10** in a ratio of 1.7 to 1 in 80% combined overall yield. The relative stereochemistry of their two hydroxyl groups were unambiguously differentiated by the oxidative cleavage reactions using sodium periodate in methanol.
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21. All new compounds and the final product, (+)-altholactone **1** showed satisfactory spectral data.

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