Pergamon

Tetrahedron Letters, Vol. 37, No. 3, pp. 371-374, 1996

0040-4039/96 $15.00 + 0.00

0040-4039(95)02125-6

Total Synthesis of (+)-Goniodiol

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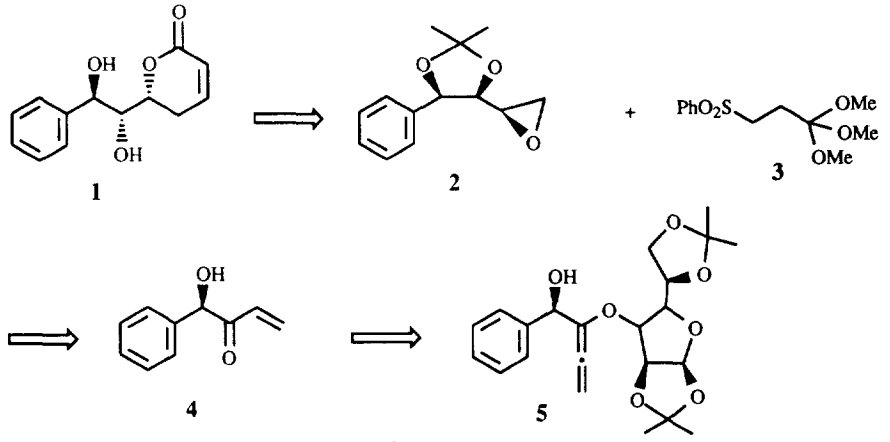
Abstract : Cytotoxic styryl lactone, (+)-goniodiol **1**, was prepared in enantioenriched form (ee 92%) in 15 steps from the α-(α'-alkoxyallenic) alcohol **5**.

Goniodiol **1**, one of the member of the styryl lactone family[1], was isolated from several *Goniothalamus* species (Annonaceae)[2] growing in Asia and India. This compound was found to be significantly and selectivity cytotoxic against several human tumor cell lines particularly human lung carcinoma (A-549) (ED_{50} $1.22x10^{-1}$ μg/ml)[2b]. The structure and relative configuration of **1** were established by NMR spectral studies[2a-b] and X-ray crystallography[2b]. Its absolute configuration was determined as being 6R,7R,8R by Honda *et al.*[3] by total synthesis starting from 2,3-O-isopropylidene-D-glyceraldehyde. We report herein the synthesis of (+)-goniodiol from 3-O-allenyl diacetone-D-glucose.

In our synthetic plan, depicted in Scheme 1, we envisioned that the α,β-unsaturated-δ-lactone unit could be easily obtained from the epoxide **2** by Ghosez' methodology which uses sulfonyl ester **3**[4] as a homoenolate reagent. The epoxy diol **2** in turn would arise from the unsaturated ketol **4** where the chiral information could be transferred into the α and β positions by well-documented stereoselective reactions.



Scheme 1

Compound **4** itself is readily accessible in enantioenriched form by our recently described procedure, which involves a highly diastereoselective addition of the 1'-lithated derivative of 3-O-allenyl diacetone glucose to benzaldehyde (diastereoselection 96:4) followed by acid hydrolysis of the resulting allenic alcohol **5**.

The choice of the OH-protecting group of **4** was crucial because it would have the dual role to induce a *syn*-diastereoselective reduction of the α-carbonyl function and to enhance the known $VO(acac)_2$-catalyzed *erythro*-selective epoxidation of the subsequently formed allylic alcohol. For this purpose, we chose the t-butyl diphenylsilylgroup (TBDPS), a very sterically demanding group, known to favour a *syn* reduction of α-hydroxy ketones through an open-chain model[6].

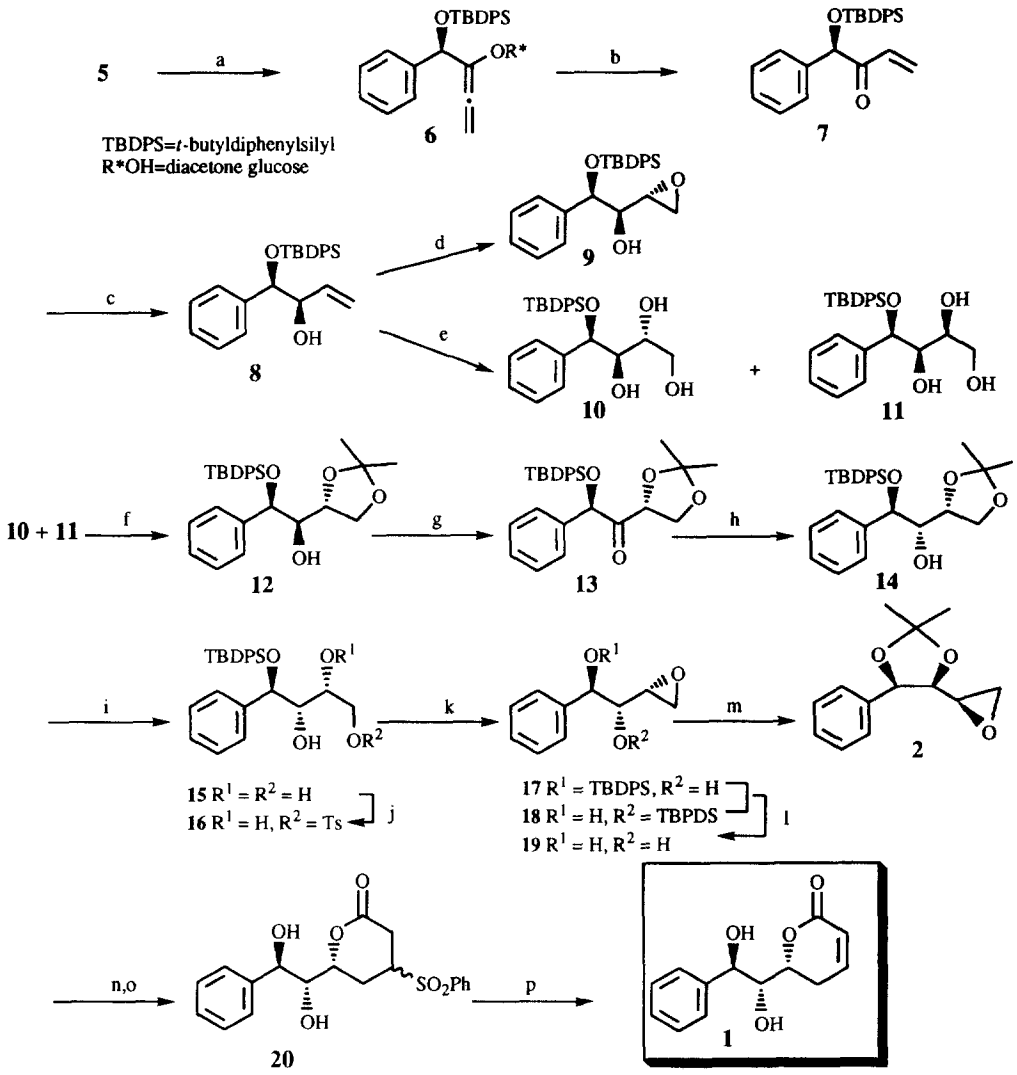
Protection of allenic alcohol **5** [5a] with *t*-butylchlorodiphenylsilane, in the presence of *p*-dimethylaminopyridine (DMAP), furnished silylether **6** (Scheme 2). After hydrolysis of the alkoxyallene function of crude **6** with 50% CF_3CO_2H in CH_2Cl_2 (81% yield for the two steps), we studied the reduction of α-ketol **7** with a variety of hydride reagents. The highest *syn*-diastereoselectivity (de ≥ 96%)[7a] was obtained by the Luche protocol[7b] ($NaBH_4$, $CeCl_3.7H_2O$, MeOH), at -78°C, leading to the anti-Cram product **8** in 98% yield. The relative configuration of **8** was assigned by comparison of the spectral data of the corresponding acetonide with the published values[8].

Unexpectedly, vanadium-catalyzed epoxidation[9] of allylic alcohol **8** was very slow, giving several by-products. On the other hand, the diastereoselectivity of this epoxidation reaction was high, favouring the *erythro* epoxy alcohol **9** (ratio = 95:5)[10]. Other epoxidizing agents gave either poor selectivity (MCPBA, 1:1) or reacted very slugghisly (H_2WO_4, H_2O_2[11] ; L-(+)-DIPT, $Ti(OiPr)_4$, t-BuOOH[12]).

Clearly, an alternative route to epoxide **9** was needed. To this goal, a stereoselective dihydroxylation of **8** was effected under Van Rheenen conditions[13], giving rise to an unseparable mixture of triols **10** and **11** (ratio = 8:1). The assignment of the relative configuration of the major product **10** was established by using the empiric rule of Kishi[14].

Regioselective acid catalyzed ketalization of the mixture of compounds **10** and **11** with excess of 2-methoxypropene afforded pure **12** in 83% yield after purification by flash chromatography. Next, we turned our attention to the inversion of the stereogenic center at C-2 of alcohol **12**. This was best achieved through an oxidation-reduction sequence. Accordingly, compound **12** was oxidized to **13** by Ley oxidation method[15] ($Pr_4N^+RuO_4^-$(TPAP), NMO, 4Å sieves, CH_2Cl_2). L-Selectride® reduction of **13**, at -100°C, yielded the desired alcohol **14** in 70% overall yield after chromatographic separation of the 92:8 mixture of the two diastereomers. Having set up the three stereogenic centers of Gonodiol **1**, we focussed our attention to the formation of epoxide **2**. Towards that end, compound **14** was subjected to aqueous acidic conditions in order to hydrolyze the ketal. Selective monotosylation[16] of the resulting triol **15** afforded compound **16** in 55% overall yield after flash chromatography purification. Treatment of **16** with 1 equiv of sodium hydride in THF containing a trace of DMSO[17] gave a mixture of the two regioisomers **17** and **18** in a 2:3 ratio and 57% yield. The 1,2-O-trialkylsilyl group migration is well precedented[18] and was not a major drawback since treatment of the mixture of compounds **17** and **18** with NBu_4F in THF provided diol **19** which, upon reaction with 2-methoxypropene in the presence of camphorsulfonic acid, gave acetonide **2** in 68% overall yield.

At this stage, our goal became the installation of the α,β-unsaturated-δ-lactone unit. For this purpose, epoxide **2** was treated with 2 equiv of the lithio derivative of methyl 3-phenylsulfonyl orthopropionate[4a] **3** and 2 equiv of $BF_3.Et_2O$ at -78°C. Addition of 3M H_2SO_4 solution to the reaction mixture and heating at 50°C for 3h effected deketalization, orthoester hydrolysis and lactone formation to give the β-sulfonyl lactone **20**. Finally, DBU-induced elimination of $PhSO_2H$ gave rise to (+)-goniodiol **1** in 60% overall yield from epoxide **2** :



Scheme 2

Reagents and conditions : (a) t-BuPh2SiCl, DMAP, CH_2Cl_2, 3 days ; (b) 50% CF_3CO_2H-CH_2Cl_2, 3 h (81% for the 2 steps) ; (c) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 1 h, -78°C (98%) ; (d) $VO(acac)_2$, TBHP, CH_2Cl_2, 0°C (30%) ; (e) cat. OsO_4, NMO, 5 h, RT, acetone (90%) ; (f) 2-methoxypropene, camphorsulfonic acid, CH_2Cl_2, RT, 10 min then separation by SiO_2 chromatography (83%) ; (g) cat. $Pr_4N^+RuO_4^-$, NMO, 4Å sieves, CH_2Cl_2, RT, 1 h ; (h) L-Selectride®, THF, -100°C, 1 h (70% for the two steps) ; (i) 80% AcOH, 60°C, 2 h (77%) ; (j) p.TsCl, Et_3N, DMAP, CH_2Cl_2, -20°C, overnight (72%) ; (k) NaH, THF-DMSO (50:1), 0°C, 1 h (57%) ; (l) NBu_4F, THF ; (n) 2-methoxypropene, camphorsulfonic acid, CH_2Cl_2, 10 min, RT (68% for the two steps) ; (n) methyl-3-phenylsulfonyl orthopropionate **3**, n-BuLi, $BF_3.Et_2O$, THF, -78°C, 30 min ; then epoxyde **2**, -78°C, RT, 2 h ; (o) 3M H_2SO_4, 50°C, 3 h ; (p) 3 equiv DBU, CH_2Cl_2, 1 h, 0°C (60% yield from the epoxide **2**).

Colourless oil, $[\alpha]_D^{20}$ + 70 (C 1.2, $CHCl_3$) [lit. $[\alpha]_D^{30}$ + 75.76($CHCl_3$)[2a] and $[\alpha]_D^{22}$ + 74.4 (C 0.3, $CHCl_3$)[2b]. Synthetic gonodiol **1** exhibited spectral data (^1H and ^{13}C NMR, IR) identical to those reported for the natural material[2b].

In conclusion, we have devised a diastereoselective approach to goniodiol **1** from enantioenriched α-hydroxy α'-vinyl ketone **4**, readily available by a method recently developed in our laboratory. Further extension of this work to the synthesis of other styryl lactones is in progress.

Acknowledgments : One of us (JPS) thanks the Ministère de l'Enseignement Supérieur et de la Recherche for a fellowship. We are grateful to Prof. L. Ghosez and Dr O. Miserque for helpful informations, prior to publication.

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(*Received in France* 23 *October* 1995; *accepted* 2 *November* 1995)