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Enantioselective Synthesis of Goniobutenolides A and B

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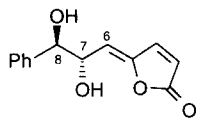
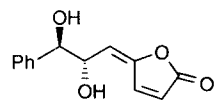
Abstract: Goniobutenolides A and B were synthesized in the enantiopure forms, employing the asymmetric dihydroxylation and cyclic sulfate rearrangement-opening reactions as the key stereocenter-forming steps.

Goniobutenolides A and B were isolated, together with other related styryllactones, from the ethanolic extracts of the stem bark of *Goniothalamus giganteus* Hook. f. & Thomas (Annonaceae).[1] These compounds were found to be marginally cytotoxic against human tumor cell lines, and have been the targets of synthetic efforts by several groups.[2] The structures of goniobutenolides A and B were originally determined by spectroscopy; in particular, a *threo* relationship was proposed for the diol moiety, largely based on the ^{1}H NMR data.[1a] While the original structural assignments seemed quite reasonable, independent confirmations were needed since both *threo* and *erythro* diol moieties had been found in the other styryllactones isolated from the same natural source. Indeed, two recent syntheses revealed that the natural goniobutenolides A and B contained *erythro*-7,8-dihydroxyl groups, with 7*S*, 8*R* absolute configurations.[3]



Goniobutenolide A

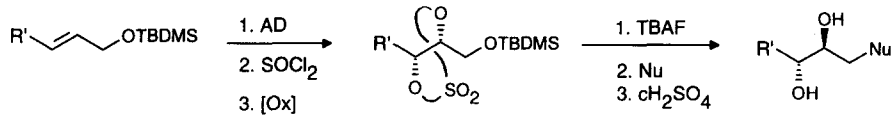


Goniobutenolide B

Sharpless' synthesis[3a] employed the asymmetric dihydroxylation (AD) as the key step.[4] The required *erythro*-diol group dictated the use of a (*Z*)-olefin as the substrate for the AD reaction, and even using the indolinylcarbamoyl ligand,[5] the enantioselectivity was predictably low (63-78% ee).

We have earlier developed a very efficient procedure accessing *erythro*-diols in high enantiomeric purities via AD reactions of *O*-silyl protected (*E*)-allylic alcohols (Scheme I).[6] Employing this method, the (7*S*, 8*R*)-*erythro* diol moiety of goniobutenolides would be prepared from (*E*)-cinnamyl alcohol. The choice of the nucleophile is determined by the subsequent transformations. In the present synthesis, the C-1 of cinnamyl alcohol (i.e., Nu-CH_2-) would later need to be oxidized to the level of C-6 of the final products. It was envisaged that this oxidation would be most conveniently achieved first by using benzenethiolate as the nucleophile in the rearrangement-opening process (Scheme I), then by performing Pummerer rearrangement with the corresponding sulfoxide.[7]

Scheme I

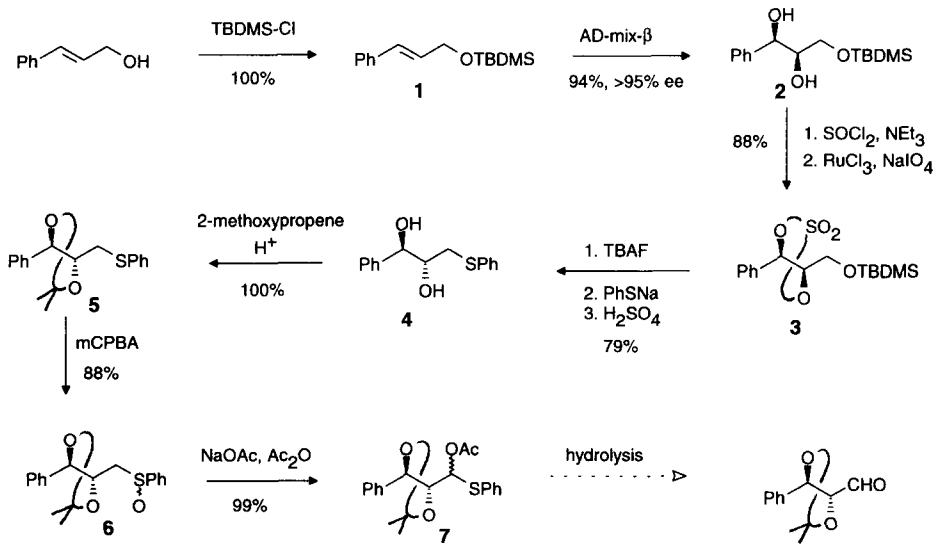


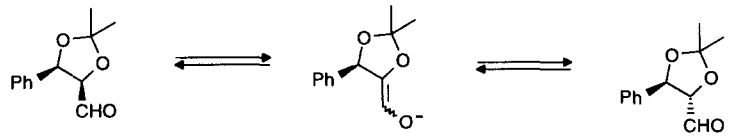
Nu = RS^-, N_3^-, RCO_2^-, NC^-, halides,
H^-, R^-(cuprates), $R-C\equiv C^-$

Thus, (*E*)-cinnamyl alcohol was TBDMS-protected (100%) and the product dihydroxylated using AD-mix-β (94%, >95% ee,[8] Scheme II). The resulting *threo*-diol **2** was converted to the cyclic sulfate **3** (88%).[9] The rearrangement-opening reaction was performed first by treating **3** with TBAF followed by PhSNa. After acidic hydrolysis, the desired phenylthio *erythro*-diol **4** was isolated in 79% yield. The dihydroxyl group was protected (100%) and the sulfide **5** oxidized to the sulfoxide **6** (88%, mixture of diastereomers). Pummerer rearrangement of **6** (NaOAc, Ac_2O, reflux) yielded **7** (99%, mixture of diastereomers), where the oxidation state of C-1 has now been brought to the desired level. Hydrolysis of the acetoxysulfide group would unmask the aldehyde functionality, which would then be coupled with 2-trimethylsiloxyfuran **8**.

Hydrolysis of Pummerer products are usually performed under alkaline conditions, under which the newly formed aldehydes could undergo enolization, resulting in the the loss of stereochemical integrity at the C-α center. In the present case, this enolization would lead to a complete epimerization at the C-2 stereocenter, to produce the thermodynamically more stable *threo*-aldehyde compound (Eq. 1).[10] While procedures are known for the hydrolysis of Pummerer products under neutral conditions,[10b] it was thought to be desirable to avoid the aldehyde intermediate, if possible.

Scheme II



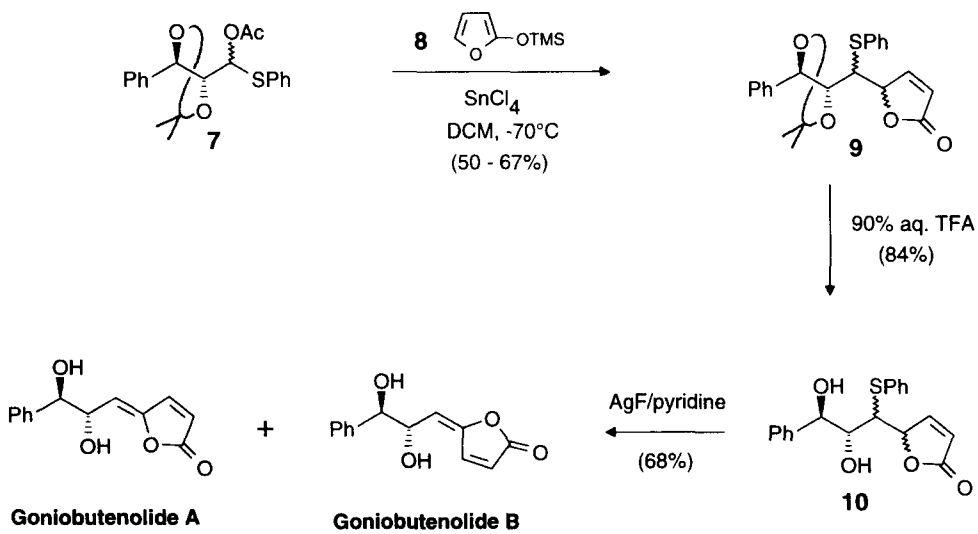


Eq. 1

Mukaiyama couplings of 2-trimethylsiloxyfuran **8** have been reported with acetals as well as acylals.[11] Therefore, it was hoped that the Pummerer product **7** would directly undergo the coupling reaction with **8** under Lewis acidic conditions. Thus, **7** was treated with **8** (2 equiv) in the presence of $SnCl_4$ (2 equiv) to yield a complex mixture of products (Scheme III). Careful chromatographic purification revealed the composition of the products: **9** (39-52%, mixture of diastereomers); **10** (7-15%, mixture of diastereomers); and a small amount (ca. 4%) of goniobutenolides A and B. Note that all these compounds are *desired products* for the synthesis, the total yield ranging 50-67%. The ketal protecting group of **9** was removed (84%). The elimination of benzenethiol was best accomplished with AgF/pyridine.[12] DBU generally resulted in lower yields, while Et_3N was not effective in this reaction. Chromatographic purification (hexane-EtOAc 1:2) afforded a 1.6:1 mixture of goniobutenolides A and B (68% combined yield), which were further separated from each other by flash chromatography using cyclohexane-*t*BuOMe (1:7). Goniobutenolide B, eluting first , was obtained as a white solid (mp 143-146°C), while goniobutenolide A was an oil.[13, 14]

Thus, an enantioselective synthesis of goniobutenolides A and B was accomplished with a full control of stereochemistry. Throughout the synthesis, no undesired stereoisomer -enantiomer or diastereomer- was observed as a byproduct. This synthesis demonstrates the synthetic utility of the cyclic sulfate rearrangement-opening process for the enantioselective preparaion of *erythro*-dihydroxy compounds.

Scheme III



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13. (a) The spectroscopic data of the synthetic goniobutenolides are consistent with the reported values. (b) All the synthetic intermediates exhibit satisfactory spectroscopic data.
14. There has been some discrepancy in the reported optical rotations of goniobutenolides. The optical rotations of our synthetic goniobutenolides ($[\alpha]_D$ +192 (c 0.25, $CHCl_3$) for A; $[\alpha]_D$ -106.8 (c 0.25, $CHCl_3$) for B) are in agreement with the data reported by Shing et al. (reference 3b), but not with the values observed from the natural products or Sharpless' synthetic compounds (reference 3a).

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