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# Total Synthesis of Gymnorrhizol, an Unprecedented 15-Membered Macrocyclic Polydisulfide from the Chinese Mangrove *Bruguiera gymnorrhiza*

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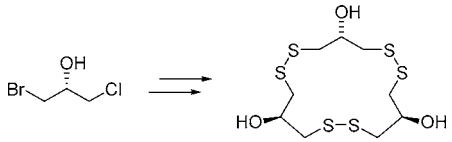
## ABSTRACT




**The total synthesis of gymnorrhizol, a naturally occurring macrocyclic polydisulfide with a new skeleton and a potent proteintyrosinephosphatase 1B inhibitor, was prepared in three steps, starting from (*R*)-1-bromo-3-chloroisopropanol and 1,3-dichloropropan-2-ol.**

Cyclic polysulfides are relatively uncommon in nature, and many of them show various interesting biological activities ranging from antifungal,[1] antibacterial,[1c,d] and cytotoxic effects[1a,c,2] to inhibition of protein kinase C.[3] Gymnorrhizol (**1**) is a macrocyclic polysulfide isolated by Sun and Guo from the Chinese mangrove *Bruguiera gymnorrhiza*.[4] Its unprecedented new skeleton was established by a combination of spectroscopic and X-ray crystallographic analysis.[5] The structure of gymnorrhizol (**1**) is characterized by a 15-membered macrocyclic polydisulfide with three symmetrically substituted hydroxyl groups. The achiral molecule has a plane of symmetry; two of the hydroxyl groups are *syn*, and the other one has an *anti* orientation.

Protein tyrosine phosphatase 1B (PTP1B) is a potential drug target for the treatment of Type II diabetes and obesity.[6] A large number of PTP1B inhibitors have been developed over the past decade in an effort to design potent and selective compounds as drug candidates. Unfortunately, most of them have been hampered owing to their poor cell

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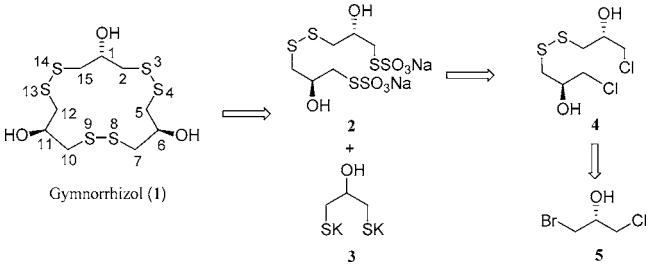
permeability and oral bioavailability. In our screening program to search for PTP1B inhibitors from the Chinese medicinal plants, a MeOH extract of stems and leaves of mangrove *B. gymnorrhiza* exhibited PTP1B inhibitory activity, which led us to investigate the PTP1B inhibitory compounds from this plant. Of the compounds, gymnorrhizol (**1**) exhibited the strongest inhibitory activity with an $IC_{50}$ value of 14.9 $\mu$M (unpublished data). The PTP1B inhibitory activity for this unique type of macrocyclic polydisulfide warrants further investigation and optimization. However, the scarcity of available sample from natural sources is a major problem for additional study of structure−activity relationship (SAR) and structural derivatization/modification. In addition, the new polydisulfide skeleton of gymnorrhizol represents a synthetic challenge. All of these facts inspired us to synthesize gymnorrhizol. In the following we report on the total synthesis of this compound.

The key to the synthesis of the gymnorrhizol skeleton was the construction of the sulfur−sulfur bonds. Many methods for the formation of disulfides have been reported, such as oxidative coupling of thiols or Bunte salts;[7] reductive formation from sulfenyl, sulfinyl, sulfonyl or thiocyanate derivatives;[8] or the reaction of an alkyl halide with sodium disulfide.[9] A general method for the synthesis of unsymmetrical disulfides is the reaction of an alkyl sulfenyl thiocarbonate or sulfenyl thiocyanate with another thiol.[10] Bunte salts, prepared from alkyl halides, are available not only for synthesis of symmetrical disulfides but also for unsymmetrical disulfides.[11] The formation of unsymmetrical disulfides using Bunte and thiol salts is mild and convenient. Therefore, we used the Bunte salts in the synthesis of gymnorrhizol (**1**). According to the retrosynthesis analysis (Scheme 1), condensation of the dithiolate anion **3** with the Bunte salt **2** may directly lead to gymnorrhizol (**1**). Intermediate **2** can be obtained from dichloride **4**, which in turn may be produced using (*R*)-1-bromo-3-chloroisopropanol (**5**) as the starting material.

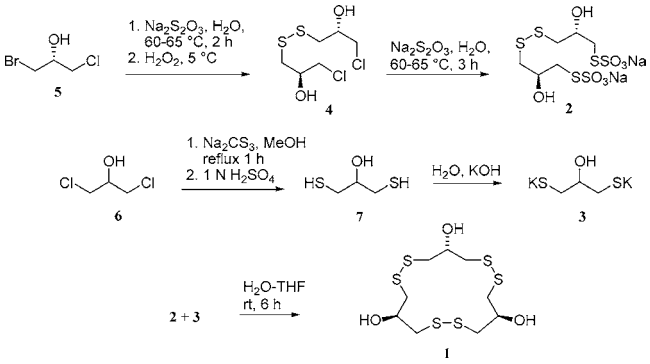
The synthetic routine started from (*R*)-1-bromo-3-chloroisopropanol (**5**) as shown in Scheme 2. (*R*)-1-Bromo-3-chloroisopropanol[12] was reacted with sodium thiosulfate in

**Scheme 1.** Retrosynthetic Analysis of Gymnorrhizol




water, followed by oxidation with 30% $H_2O_2$ to give the disulfide **4** in 74% yields. The intermediate Bunte salt **2** was then produced by reaction of **4** with sodium thiosulfate in aqueous ethanol. The dithiol **7** as the second building block was prepared in 65% yield by the condensation of 1,3-dichloro-2-propanol (**6**) with sodium trithiocarbonate in

**Scheme 2.** Synthesis of Gymnorrhizol




refluxing methanol, followed by acidification with 1 N $H_2SO_4$.[13] The dithiol **7** was then converted into its bispotassium salt **3** by treatment with KOH solution. Subsequent condensation of this salt with the Bunte salt **2** in aqueous THF at ambient temperature gave the target compound gymnorrhizol (**1**) in 34% yield. The spectral and analytical data of the synthetic material are in total agreement with the data reported for the natural product.[4]

In summary, the first total synthesis of gymnorrhizol (**1**) has been achieved in only three steps in 25% overall yield from **5**. The synthesis is amenable to large scale, and a similar strategy will allow the synthesis of related macrocyclic polydisulfides and analogs of **1** for further SAR study.

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**Supporting Information Available:** Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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