Total Synthesis of (±)-Plumbazeylanone

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The first total synthesis of plumbazeylanone (1), which is a trimer of naphthoquinone, was carried out successfully utilizing the unsymmetrical methylene-bridged dimer with the naphthoquinone unit and the naphthol unit, 11b as a key intermediate in 11 steps. This synthesis features a regioselective nucleophilic 1,2-addition reaction and dienone-phenol-type rearrangement.

Key words trimeric naphthoquinone; plumbazeylanone; total synthesis; 1,2-addition; rearrangement

The roots of *Plumbago zeylanica* (Plumbaginaceae), which is a perennial herb, have long been used in a variety of medicinal applications in many Asian countries.[1] Since 1971, several naphthoquinones[1,2] have been isolated from the plant including plumbazeylanone (**1**) and plumbagin (**2a**), the latter of which demonstrates *in vitro* immunosuppressive or cytotoxic activity against primary cell cultures of granulocytes.[3] However, the essential active ingredient that provides the biological activity in the medicinal applications of this plant has not yet been established. One suggestion for exploration of the active ingredient has been the absence of constituents such as alkaloids, saponins, and glycosides in the roots of this plant. Plumbazeylanone (**1**) was selected as the synthetic target due not only to its unique structure, but also in order to determine the active constituent in the medicinal applications of this plant.

Herein, we report the first total synthesis of (±)-plumbazeylanone (**1**) utilizing the unsymmetrical methylene-bridged dimer **11b** as a key intermediate. We investigated the total synthesis of plumbazeylanone using the retrosynthetic plan as shown in Chart 1, in which (i) the condensation reaction between the naphthol **3a** and paraformaldehyde followed by transformation to **11b** as a key intermediate is performed, (ii) nucleophilic 1,2-addition reaction of the naphthyllithium reagent **4** to C-1 position on **11b** followed by a dienone-phenol-type rearrangement of the naphthyl group on **12b** to construct the trimer **13** is carried out, and (iii) finally demethylation of six methoxyls on **13**, followed by air oxidation to lead to the target compound **1** is achieved.

Compounds **3a** and **3b**[4] were first synthesized from the corresponding naphthoquinones **2a** and **2c** through the reaction sequence shown in Chart 2, respectively. Subsequently, the treatment of **3a** with ethylmagnesium bromide (EtMgBr) and then paraformaldehyde gave the symmetrical methylene-bridged dimer **8a**. The formation of **8a** by this reaction can be postulated as shown in Chart 3. Next, selective monomethylation of naphtholic hydroxyl group of **8a** using Me_2SO_4 in the presence of $Bu_4N^+HSO_4^-$ gave the corresponding compound **8b** in 71% yield. Moreover, the oxidation of the naphthol moiety on **8b** using 10% $FeCl_3$ in MeCN gave the corresponding naphthoquinone **9** in 95% yield. Magnesium bromide hexahydrate ($MgBr_2 \cdot 6H_2O$) effected selective demethylation of the methoxyl group at the C-5 position on **9** to afford the corresponding naphthol **11a** in excellent yield. The mechanism for this demethylation can be postulated as follows. The selective nucleophilic attack of H_2O on the methyl group of the methoxyl group at the C-5 position on **10** derived from **9** with $MgBr_2 \cdot 6H_2O$, in which the oxygen atom of the methoxyl group is chelated to the Mg atom with the carbonyl group at the C-4 position, may take place to form the demethylated compound **11a**. The naphtholic hydroxyl group of **11a** was protected by the bulky functional group using *tert*-butyldiphenylsilyl chloride (TBDPSCl) in the presence of 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) to afford the corresponding *O*-silylated compound **11b** in 88% yield. The selective nucleophilic addition of **4** to the C-1 position on **11b** in THF proceeded at −78 °C under a nitrogen atmosphere to give the expected 1,2-adduct

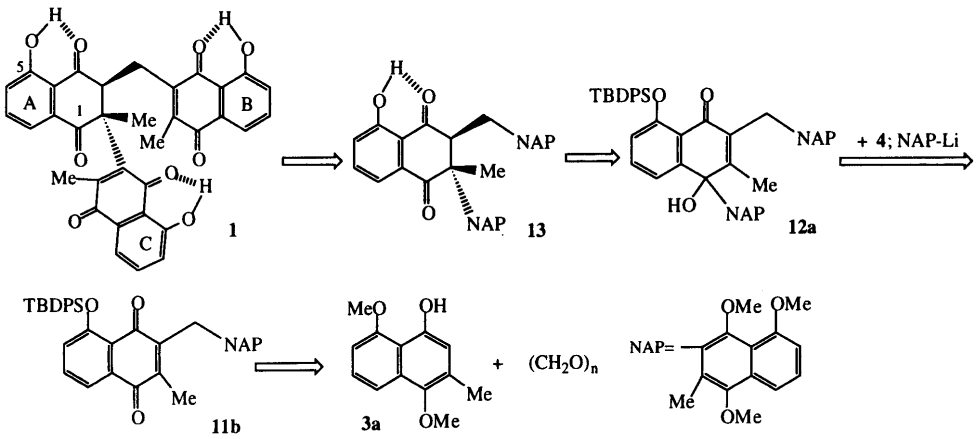

Chart 1

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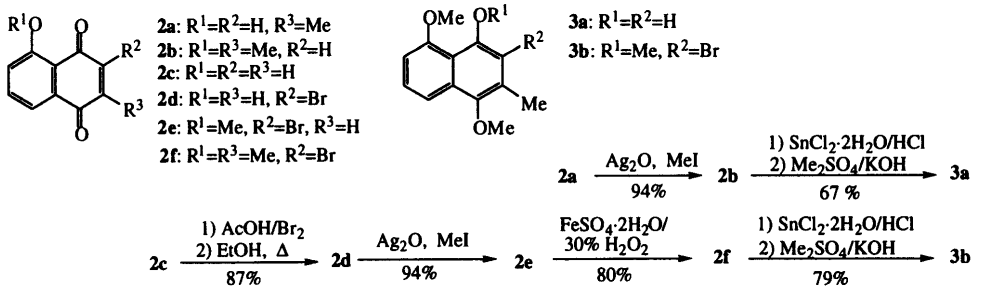

Chart 2

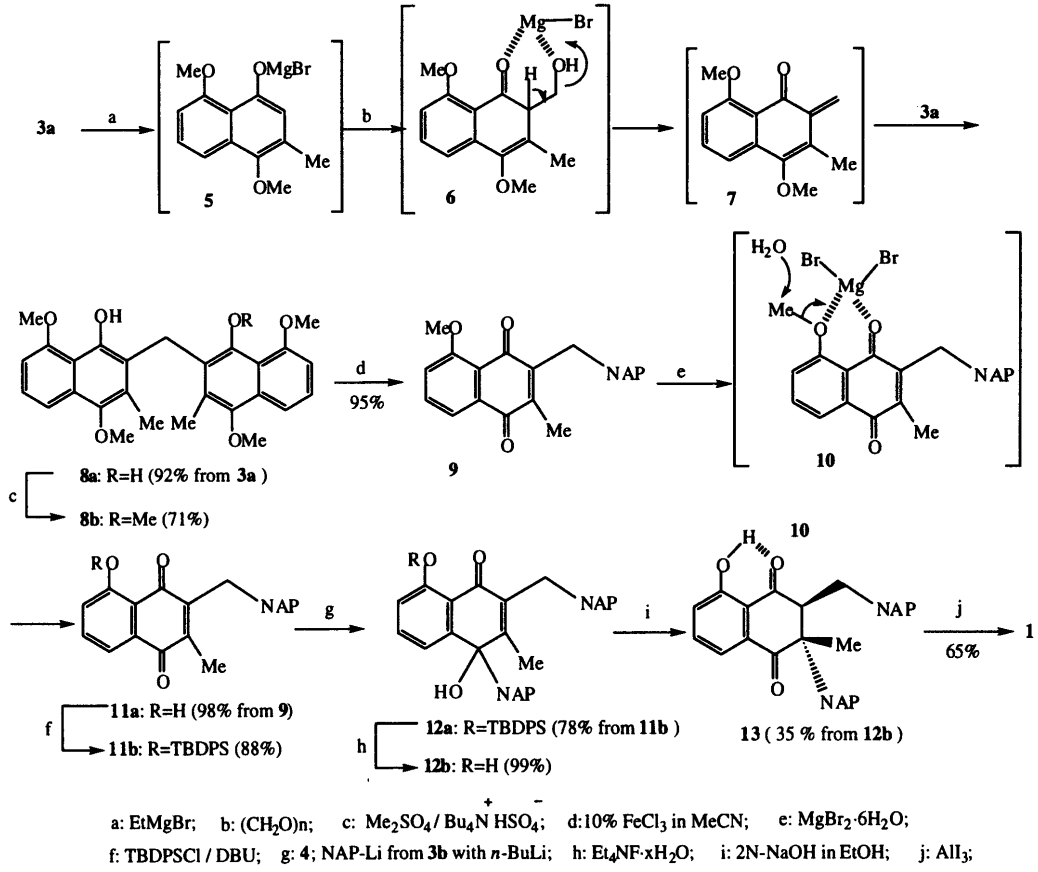

Chart 3

12a in 78% yield. The deprotection of the TBDPS group of **12a** with $Et_4N^+F^- \cdot xH_2O$ gave the corresponding naphthol **12b** in quantitative yield. The dienone-phenol-type rearrangement of **12b** with 2 N-NaOH in EtOH[5] stereoselectively gave a trimer **13** in 35% yield. The stereochemistry of **13** was established based on its NOESY experiments. The observation of correlation cross-peaks between the proton signal of C_2-Me (δ 2.03) and the methylenic proton signals of C_3-CH_2 (δ 2.85 and 3.25) indicated that C_2-Me and C_3-H in **13** have a *trans*-relative configuration. Finally, demethylation of **13** with AlI_3 in benzene followed by air oxidation afforded (±)-plumbazeylanone (**1**) in 65% yield, mp 245—248 °C. All physical data for the synthetic compound **1** was identical with those of the natural products.[2a,b] Thist first synthesis of (±)-1 consists of 11 steps from plumbagin (**2a**) and an overall yield of 5.9% is achieved.

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