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TOTAL SYNTHESIS OF (±)-TRIPTOQUINONE A

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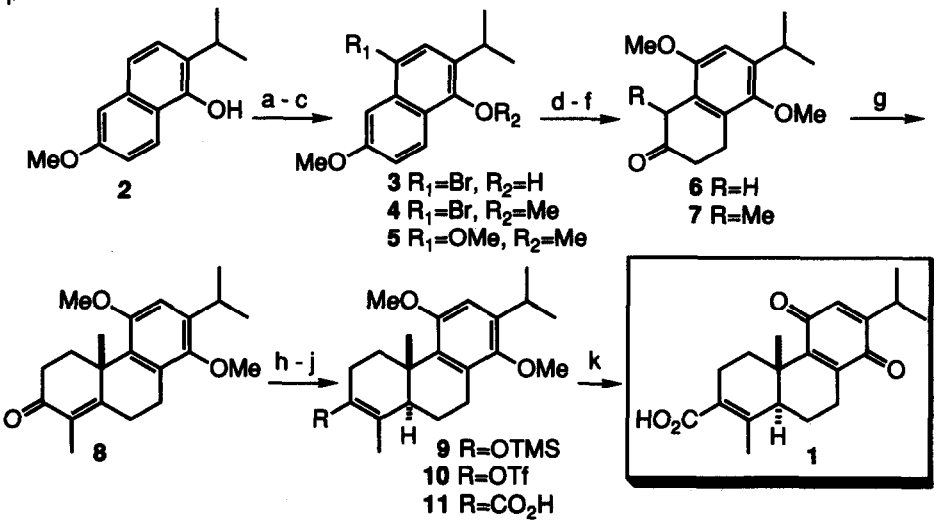
Abstract: A concise and practical total synthesis of (±)-triptoquinone A (**1**), a novel interleukin-1 inhibitor isolated from *Tripterygium wilfordii* var. *regelii*, has been achieved in 11 steps from the known naphthol **2**.

Triptoquinone A (**1**) is a novel diterpenoid quinone recently isolated from the extracts of the *Tripterygium wilfordii* var. *regelii* together with several related diterpenoids by us.[1] The structure including the absolute configurations was determined by spectroscopic techniques and X-ray crystallographic analysis. Its extremely potent inhibitory activity against interleukin(IL)-1α and IL-1β releases for human peripheral mononuclear cells has prompted synthetic studies in order to supply this compound for further biological tests. In this communication, we report the first and practical total synthesis of (±)-triptoquinone A.

Bromination of 2-isopropyl-6-methoxy-1-naphthol **2**[2] with N-bromosuccinimide followed by methylation of the resulting bromide **3**[3] and subsequent displacement of a bromine in **4** with methoxide in the presence of cuprous iodide provided 2-isopropyl-1,4,6-trimethoxynaphthalene **5** in high overall yield. Treatment of **5** with sodium in ethanol led to a mixture of 3,4- and 1,4-dihydro-2,5,8-trimethoxy-6-isopropylnaphthalene (ca. 3.4:1) which was immediately exposed to the conditions of an acid hydrolysis to afford the tetralone **6**. Methylation of the C-1 position in **6** utilizing enamine procedure provided the homologue **7** which was then treated with ethyl vinyl ketone and potassium hydroxide to give the annulated tricyclic enone **8** in 54 % overall yield from **6**. According to the protocol of Stork,[4] the enone **8** was smoothly converted to the silyl enol ether **9** by sequential Birch reduction and enolate trapping with chlorotrimethylsilane. Introduction of the requisite carboxyl functionality into the C-3 position was successfully achieved via the triflate **10** by a palladium catalyzed carboxylation reported by Murai.[5] Thus, the lithium enolate generated in situ by treatment of **9** with methyllithium[4] was reacted with N-phenyltrifluoromethanesulfonimide[6] to yield the triflate **10** which was treated with a catalytic amount of palladium acetate, 1,1'-bis(diphenylphosphino)ferrocene, and tributylamine, in

aqueous dimethylformamide under an atmosphere of carbon monoxide to produce the carboxylic acid **11** in 50 % yield from **9**. Finally, **11** was oxidized with cerium ammonium nitrate to provide (±)-triptoquinone A (**1**) in 82 % yield. Comparison (^{1}H-NMR, IR and mass spectra) of the material prepared in this way with natural triptoquinone A indicated that the total synthesis was completed.



Reagents : a, NBS, DMF, 85 %; b, Me_2SO_4, KOH, H_2O, 96 %; c, CuI, NaOMe, MeOH, DMF, 92 %; d, Na, EtOH; e, $(CO_2H)_2$, MeOH, H_2O, 95 % for 2 steps; f, pyrrolidine, 3A MS, benzene then MeI, dioxane, 81 %; g, ethyl vinyl ketone, KOH, MeOH, H_2O, 66 %; h, Li, liq.NH_3, ^{t}BuOH then TMSCl, Et_3N, THF, 94 %; i, MeLi, THF then $PhN(Tf)_2$, 94 %; j, $Pd(OAc)_2$, DPPF, $^n Bu_3N$, CO, H_2O, DMF, 53 %; k, CAN, MeCN, H_2O, 82 %.

References and Notes

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