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SYNTHETIC APPLICATIONS OF MASKED O-BENZOQUINONES. A NOVEL TOTAL SYNTHESIS OF (±)FORSYTHIDE AGLUCONE DIMETHYL ESTER[1]

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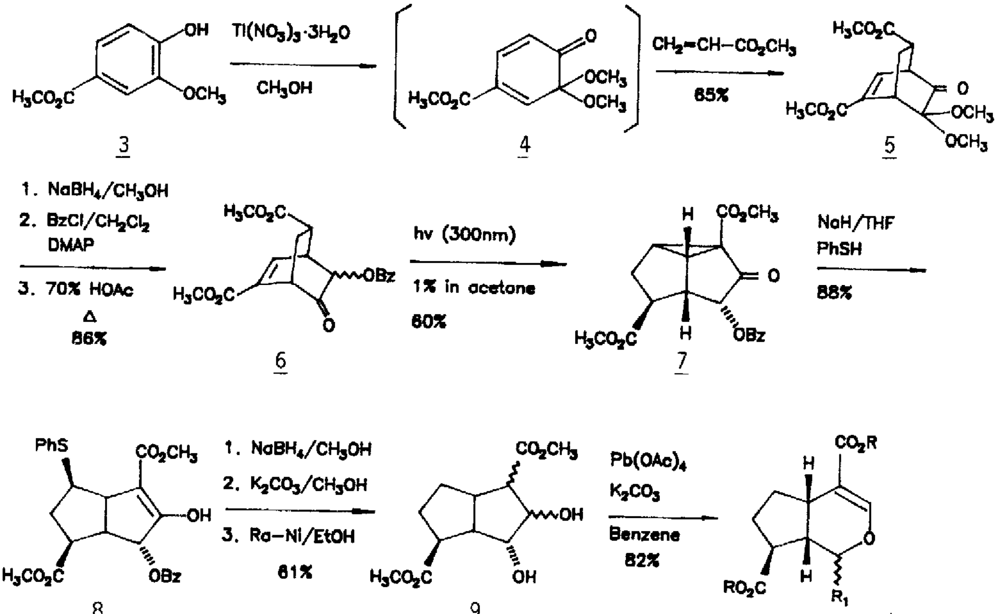
Abstract: The title compound has been synthesized from methyl vanillate in 10 steps and in a 15% overall yield; the Diels-Alder reaction of a masked o-benzoquinone and the oxa-di-π methane rearrangement are the key reactions.

Forsythide 1 is a naturally occurring iridoid glucoside isolated from fresh leaves of Forsythia viridissima Lindl.[2] The total synthesis of its aglucone dimethyl ester 2 has been accomplished by Miwa[3] and Isoe[4]. Recently, we have reported that the cycloadditions of masked o-benzoquinones with substituted alkenes afford bicyclo[2.2.2]octenone derivatives in good to excellent yields.[5,6] The cycloadditions are of high regioselectivity and stereoselectivity with monosubstituted alkenes having electron-withdrawing ($-CO_2CH_3$), electron-donating ($-OC_2H_5$) and conjugative ($-C_6H_5$) substitutents. Bicyclo[2.2.2]oct-5-en-2-ones are known to undergo the oxa-di-π-methane rearrangement upon photosensitization to give tricyclo-[3.3.0.0^{2,8}]octan-3-ones[7]. This type of rearrangement has been used by Schaffner and Demuth[8] as key steps in many examples of the total syntheses of natural products. In this report, we describe a short and efficient synthesis of 2 from methyl vanillate 3 by utilizing the Diels-Alder reaction of a masked o-benzoquinones and the oxa-di-π-methane rearrangement as the key steps.

Oxidation of methyl vanillate 3 with thallium(III) nitrate[9] in methanol afforded masked o-benzoquinone 4, which was not stable enough to be isolated; however, it could be trapped with methyl acrylate to yield 5. The transposition of the carbonyl group in 5 was accomplished by the reduction of 5 with sodium borohydride, followed by benzoylation of the thus generated alcohol and the subsequent hydrolysis of the dimethoxy ketal moiety to furnish 6. Irradiation of a solution of 6 (1%) in acetone with a Rayonet reactor (λ=300 nm) afforded 7; its stereochemistry was unambiguously established by the X-ray diffraction method.[10] Treatment of 7 with thiophenol and sodium hydride in tetrahydrofuran resulted in the ring-opening of the cyclopropane moiety[11] to give 8 whose nmr ($CDCl_3$) and ir (KBr) spectra indicated that it was in an enol form. The stereochemistry of the phenylsulfide group was tentatively assigned in the β position assuming that the displacement reaction was an S_N2-like reaction. Sequential operations, including reduction, trans-esterification and desulfurisation, furnished a diastereomeric mixture 9. The nmr spectrum of 9 revealed that it contained two diastereomers although, in principle, four isomers are possible. At the present stage, no effort was made to isolate the isomers in the pure form and to determine their stereochemistry. Oxidation of 9 afforded 2 which contained a mixture of epimers in the ratio of about 2:1, and showed identical ^1H nmr and ir spectra with those of the authentic samples.



1 R=H, R_1=OGlu(β isomer)
2 R=CH_3, R_1=OH(α&β isomers)

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