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TOTAL SYNTHESIS OF ANTIOXIDANT ALKALOID CARAZOSTATIN *VIA* ELECTROCYCLIC RING CLOSURE OF 3-BUTADIENYL-2-METHOXYINDOLE

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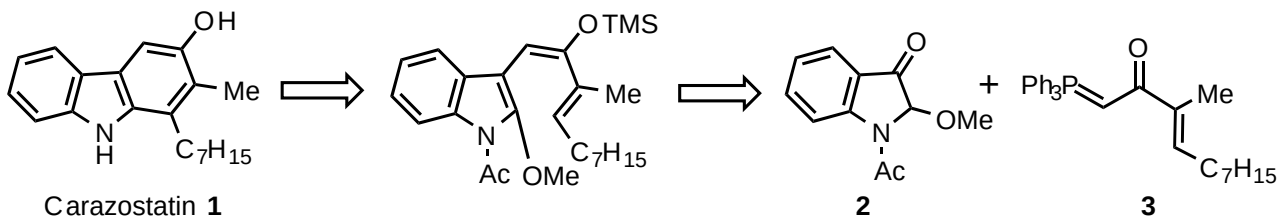
Abstract – Total synthesis of the naturally occurring antioxidant carazostatin was accomplished by an efficient method, Wittig reaction of 2-methoxyindol-3-one followed by electrocyclic reaction of 3-(1,3-butadienyl)indole.

Antioxidants are served as possible protective agents against a variety of diseases induced by oxygen-derived free radicals, like myocardial and cerebral ischemia, arteriosclerosis, inflammation, rheumatism, senility, autoimmune diseases, and cancer. [1] Recently, as a novel class of antioxidant active compounds, several poly-substituted 3-hydroxycarbazole alkaloids were isolated from *Streptomyces*. [2] Because of their potent antioxidative activities and unique structures, the interest of many synthetic chemists was attracted in developing novel synthetic methodologies for these alkaloids and their related compounds.[3] The representative 3-hydroxycarbazole, carazostatin (**1**) exhibits an antioxidant activity more effective than α-tocopherol.[2a] The total syntheses of carazostatin (**1**) were accomplished by some methodologies using the Diels-Alder reaction,[4a] iron-mediated oxidative cyclization,[4b] unique

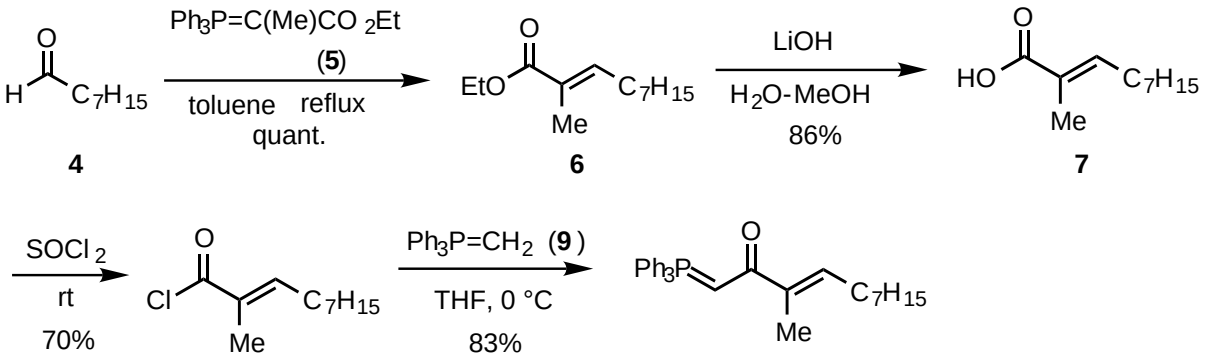


Carazostatin **1** **2** **3**

Scheme 1

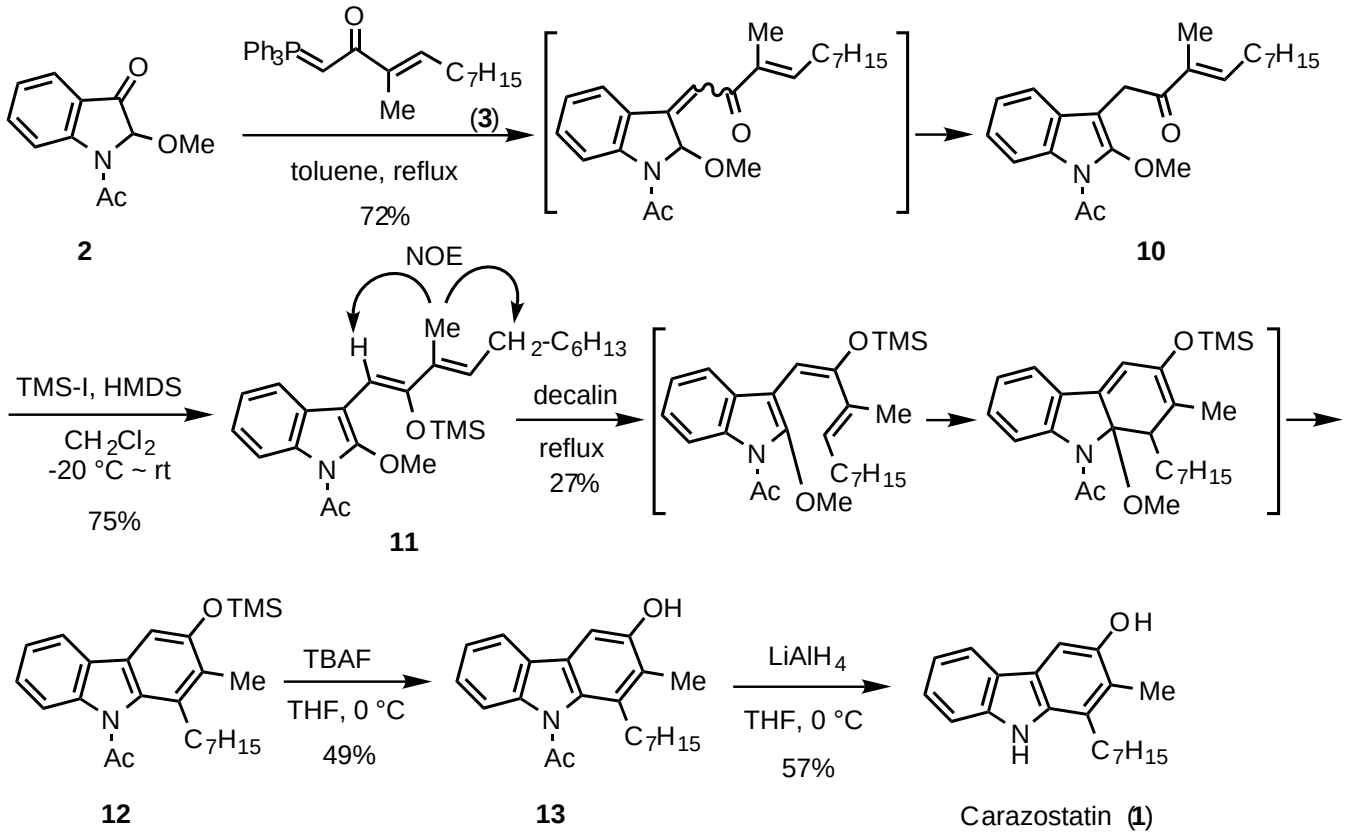
aromatic annulation,[4c] and electrocyclization of the allene intermediate.[4d] We earlier reported a synthetic method for poly-substituted 3-methoxycarbazole alkaloids, hyellazole and 4-deoxycarbazomycin B.[5] In this communication, we describe a novel synthesis of carazostatin (**1**) utilizing the thermal electrocyclic ring closure of 1-(2-methoxyindol-3-yl)-2-oxybutadiene as shown in Scheme 1.

The starting material 2-methoxyindol-3-one (**2**) was readily available by our previously described method.[6] The phosphonium ylide (**3**) was prepared as follows: Wittig reaction of octyl aldehyde (**4**) with the ylide (**5**) gave (*E*)-α,β-unsaturated ester (**6**) in quantitative yield with high stereoselectivity. After hydrolysis of the α,β-unsaturated ester (**6**) with LiOH, the carboxylic acid (**7**) was converted to α,β-unsaturated acid chloride (**8**) by treatment with thionyl chloride. The resulting acid chloride (**8**) was allowed to react with 2 equiv.of methylidene phosphorane (**9**) at 0 °C affording the desired ylide (**3**) in good yield.



Scheme 2

The reaction of 2-methoxyindol-3-one (**2**) with the ylide (**3**) in refluxing toluene took place smoothly with Wittig reaction followed by isomerization to afford the 3-substituted indole (**10**) in 72% yield. The resulting indole (**10**) was treated with trimethylsilyl iodide (TMSI) in the presence of 1,1,1,3,3,3-hexamethyldisilazane (HMDS) to give stereoselectively (*Z*)-enolate (**11**) in 75% yield. The stereochemistry of TMS-enolate (**11**) was confirmed by nuclear Overhauser effect (NOE) experiments; irradiation of methyl proton enhanced the signals of the olefinic and methylene protons as shown in Scheme 3. When the enolate (**11**) was heated in boiling decalin, isomerization, cyclization, and elimination of methanol occurred to give the desired 3-siloxycarbazole (**12**) in moderate yield. The desilylation of **12** was performed by treatment with tetrabutylammonium fluoride (TBAF) to afford 3-hydroxycarbazole (**13**) in 49% yield. The deacetylation of 3-hydroxycarbazole (**13**) by the usual hydrolysis method was unsuccessful, however, the reductive deacetylation of **13** with lithium aluminum hydride at 0 °C provided



Scheme 3

carazostatine (**1**) in 57% yield. The spectroscopic data of the synthetic material were virtually identical with those reported for the natural[2a] and synthetic product.[4, 7]

In conclusion, we accomplished the total synthesis of the naturally occurring antioxidant carazostatin (**1**) using an efficient method which was based on Wittig olefination of 2-methoxy-indol-3-one (**2**) followed by the electrocyclic reaction of 3-(2-trimethylsiloxybutadieny)indole (**11**) .

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7. Carazostatin (**1**): mp 157.5-159 °C (from ether-hexane), (lit., mp 149-152 °C[2a]; 159-160 °C[4d]). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.89 (3H, t, *J* = 7 Hz), 1.20-1.50 (8H, m), 1.60-1.70 (2H, m), 2.37 (3H, s), 2.88 (2H, t, *J* = 8 Hz), 4.58 (1H, br s), 7.16 (1H, t, *J* = 8 Hz), 7.32-7.46 (3H, m), 7.75 (1H, br s), 7.93 (1H, d, *J* = 8 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 12.2, 14.4, 22.9, 29.1, 29.6, 29.8, 30.3, 32.2, 103.2, 110.9, 119.2, 120.3, 121.1, 121.6, 123.9, 124.4, 125.5, 134.2, 140.0, 148.4.