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

Yoshinori Nonaka,*1 Tomomi Kawasaki,2 and Masanori Sakamoto*2

1 Kissei Pharmaceutical Co., LTD., 4365-1 Kashiwabara, Hotaka, Minamiazumi, Nagano 399-8304, Japan
2 Meiji Pharmaceutical University, 2-522-1 Noshio, Kiyose, Tokyo 204-8588, Japan

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

Scheme 1
aromatic annulation,\textsuperscript{4c} and electrocyclization of the allene intermediate.\textsuperscript{4d} We earlier reported a synthetic method for poly-substituted 3-methoxycarbazole alkaloids, hyellazole and 4-deoxycarbazomycin B.\textsuperscript{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.\textsuperscript{6} The phosphonium ylide (3) was prepared as follows: Wittig reaction of octyl aldehyde (4) with the ylide (5) gave (E)-\(\alpha,\beta\)-unsaturated ester (6) in quantitative yield with high stereoselectivity. After hydrolysis of the \(\alpha,\beta\)-unsaturated ester (6) with LiOH, the carboxylic acid (7) was converted to \(\alpha,\beta\)-unsaturated acid chloride (8) by treatment with thionyl chloride. The resulting acid chloride (8) was allowed to react with 2 equiv. of methyldiene phosphorane (9) at 0 °C affording the desired ylide (3) in good yield.

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
carazostatine (1) in 57% yield. The spectroscopic data of the synthetic material were virtually identical with those reported for the natural\textsuperscript{2a} and synthetic product.\textsuperscript{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-methoxyindol-3-one (2) followed by the electrocyclic reaction of 3-(2-trimethylsiloxybutadieny)indole (11).

**ACKNOWLEDGMENT**

We wish to thank Professor Satoshi Hibino (Fukuyama University, Japan) for providing the \textsuperscript{1}H-NMR spectrum of synthetic carazostatin.

**REFERENCES AND NOTES**


7. Carazostatin (1): mp 157.5-159 °C (from ether-hexane), (lit., mp 149-152 °C<sup>2a</sup>; 159-160 °C<sup>4d</sup>). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ: 0.89 (3H, t, <i>J</i> = 7 Hz), 1.20-1.50 (8H, m), 1.60-1.70 (2H, m), 2.37 (3H, s), 2.88 (2H, t, <i>J</i> = 8 Hz), 4.58 (1H, br s), 7.16 (1H, t, <i>J</i> = 8 Hz), 7.32-7.46 (3H, m), 7.75 (1H, br s), 7.93 (1H, d, <i>J</i> = 8 Hz). <sup>1</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) 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.