

A New Synthesis of the Naturally Occurring Free Radical Scavenger Carazostatin

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A new synthesis of the naturally occurring free radical scavenger carazostatin has been developed by employing the two aromatic annulation reactions as key steps.

Carazostatin (**1**), exhibiting a strong inhibitory against free radical induced lipid peroxidation in rat brain homogenate, has been isolated from *Streptomyces chromofuscus* and determined by using a combination of spectroscopic techniques.¹ Its structure was soon verified unambiguously by the synthesis.² Because of its potential utility as a lead for the development of therapeutic agents, we attempted its synthesis by employing two aromatic annulation reactions, one discovered recently³ and the other some ten years ago,⁴ for the construction of the carbazole framework of carazostatin. We wish to report herewith our successful entry into the target molecule.

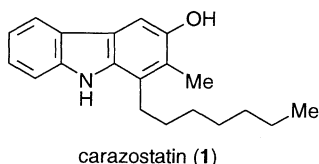


Figure 1.

The present synthesis of carazostatin (**1**) started by the palladium-mediated cross-coupling⁵ between *N*-carbethoxy-2-iodoaniline (**2**) and 1-decyne which afforded the arylacetylene **3** in 89% yield. The first aromatic annulation step was the base-induced indolization employing Yamanaka's conditions³ which allowed the transformation of **3** into 2-octylindole (**4**) in 98% yield on treatment with sodium ethoxide in refluxing ethanol. We found⁶ that the acetylene **3** could also be converted into the same indole **4** in 70% yield under neutral conditions on treating with lithium chloride in place of sodium ethoxide in refluxing *N,N*-dimethylformamide (DMF). Employing a standard four-step

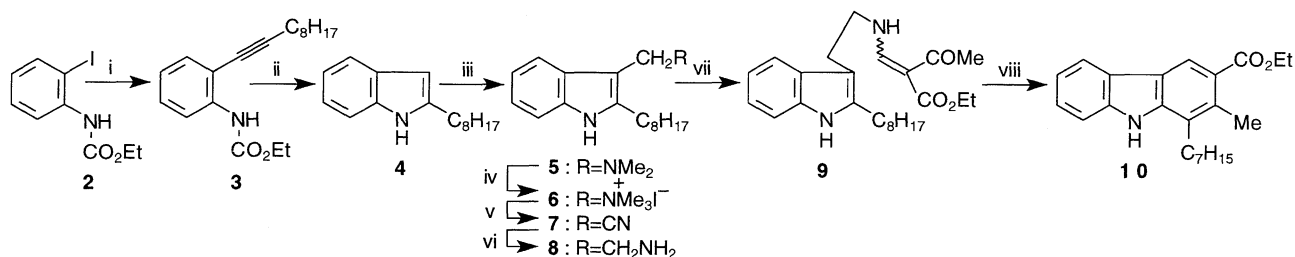
procedure,⁷ the indole **4** was transformed into 2-octyltryptamine (**8**), via the Mannich base **5**, the ammonium iodide **6**, and the cyanide **7**, which was condensed with ethyl ethoxymethyleneacetoacetate to furnish the conjugated enamine **9** serving as the substrate for the second aromatic annulation. The overall yield of **9** from **4** was 37% in five steps.

Having obtained the key intermediate **9**, this was refluxed with a 5:3 mixture of acetic anhydride and acetic acid⁴ to carry out the second annulation. The reaction occurred with concurrent removal of the ethenylamine scaffolding to furnish the carbazole **10** having functionalized aromatic ring in 53% yield in a single operation (**Scheme 1**).

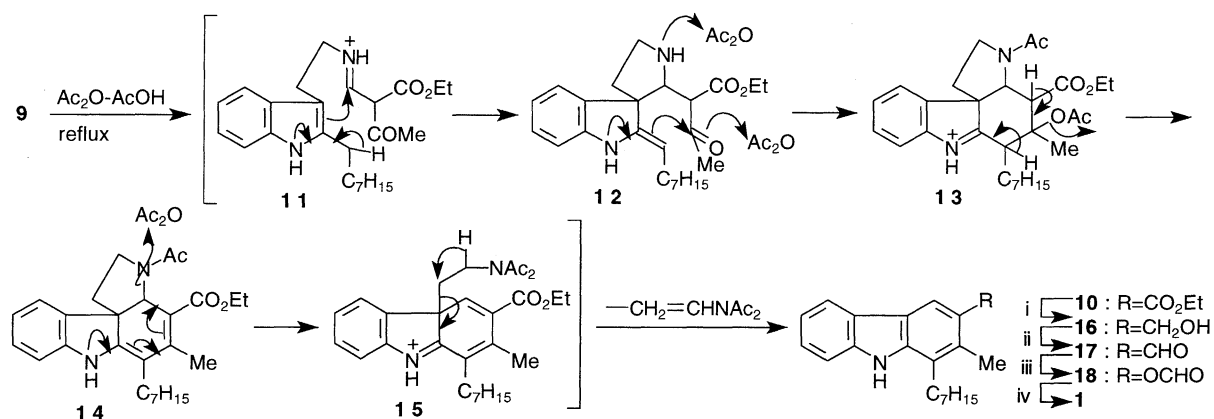
The observed cyclization may be explicable by a cascading process involving transient Mannich and Fischer⁸ base type intermediates as shown in **Scheme 2**. Thus, the reaction was initiated by protonation of the enamine **9** to give an iminium intermediate **11** to undergo Mannich cyclization to give rise to a Fischer base **12** which in turn underwent the second cyclization and elimination via transient intermediates, **13**, **14**, and **15**, to give rise to the carbazole **10** though it is difficult to reason the elimination of the ethenylamine moiety from the penultimate intermediate **15**.

To transform the carbazole **10** thus obtained into the target natural product carazostatin (**1**), we eventually chose a four-step sequence after several fruitless trials. Thus, **10** was first reduced with diisobutylaluminum hydride to the alcohol **16** which then was oxidized by the Dess-Martin reaction⁹ to give the aldehyde **17** in 79% overall yield. Finally, **17** was converted into carazostatin (**1**) by the Baeyer-Villiger reaction using *m*-chloroperbenzoic acid in the presence of potassium fluoride¹⁰ followed by reductive cleavage of the formate **18** generated. The reaction proceeded in 76% overall yield. The spectroscopic data of the synthetic material were virtually identical with those reported for the natural product.^{1,2,11}

In conclusion, we have developed a new entry into the naturally occurring free radical scavenger carazostatin (**1**). The procedure may be useful for the construction of a variety of the congeners for the pharmacological examination.



Scheme 1. Reagents and conditions: (i) 1-decyne (1.2 equiv.), PdCl₂(PPh₃)₂ (2 mol%), CuI (0.5 mol%), Et₃N, reflux, 1 h; 89%. (ii) Na (10 equiv.), EtOH, reflux, 2 h; 98% or LiCl (5 equiv.), DMF, reflux, 8 h; 70%. (iii) *N,N*-dimethylmethyleammonium chloride (2 equiv.), CH₂Cl₂, r.t., 45 min. (iv) MeI (excess), MeOH, r.t., 30 min. (v) NaCN (1.2 equiv.), DMF, 100 °C, 10 min; 64% from **4**. (vi) NaBH₄ (3 equiv.), CoCl₂·6H₂O (1.3 equiv.), MeOH, r.t., 30 min then NaBH₄ (10 equiv.), 0 °C, 50 min. (vii) ethyl ethoxymethyleneacetoacetate (1.5 equiv.), EtOH, r.t., 50 min; 57% from **7**. (viii) Ac₂O-AcOH, reflux, 17 h; 53%.



Scheme 2. Reagents and conditions: (i) DIBAL, CH_2Cl_2 , -78°C , 40 min; 95%. (ii) Dess-Martin reagent (1.5 equiv.), CH_2Cl_2 , r.t., 15 min; 94%. (iii) *m*-CPBA (1.5 equiv.), KF (1.5 equiv.), CH_2Cl_2 , 0°C , 50 min; 86%. (iv) LiAlH_4 (1.2 equiv.), THF, 0°C , 30 min; 87%.

References and Notes

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- 9 D. B. Dess and J. C. Martin, *J. Am. Chem. Soc.*, **113**, 7277 (1991).
- 10 F. Camps, J. Coll, A. Messegue, and M. A. Pericás, *Tetrahedron Lett.*, **22**, 3895 (1981).
- 11 Physical and spectral data: $\nu(\text{IR})$; $\delta(^1\text{H NMR}, 300 \text{ MHz})$: **3**: oil; $\nu(\text{film})=3396, 2220, 1741 \text{ cm}^{-1}$; $\delta=0.89$ (t, 3H, $J=6.6 \text{ Hz}$), 1.22-1.55 (m, 13H), 1.56-1.71 (m, 2H), 2.49 (t, 2H, $J=7.0 \text{ Hz}$), 4.24 (q, 2H, $J=7.1 \text{ Hz}$), 6.94 (td, 1H, $J=1.1, 7.7 \text{ Hz}$), 7.20-7.37 (m, 2H), 7.41 (br s, 1H), 8.12 (d, 1H, $J=8.4 \text{ Hz}$). **4**: oil; $\nu(\text{film})=3408 \text{ cm}^{-1}$; $\delta=1.06$ (t, 3H, $J=6.4 \text{ Hz}$), 1.20-1.63 (m, 10H), 1.78-1.98 (m, 2H),

2.89 (t, 2H, $J=7.7 \text{ Hz}$), 6.40 (d, 1H, $J=0.7 \text{ Hz}$), 7.15-7.35 (m, 2H), 7.43 (d, 1H, $J=7.7 \text{ Hz}$), 7.70 (d, 1H, $J=7.3 \text{ Hz}$), 7.93 (br s, 1H). **7**: mp $68-69^\circ\text{C}$; $\nu(\text{Nujol})=3364, 2248 \text{ cm}^{-1}$; $\delta=0.93$ (t, 3H, $J=6.8 \text{ Hz}$), 1.18-1.50 (m, 10H), 1.68-1.80 (m, 2H), 2.75 (t, 2H, $J=7.7 \text{ Hz}$), 3.77 (s, 2H), 7.14-7.38 (m, 3H), 7.55-7.66 (m, 1H), 8.10 (br s, 1H). **9**: oil; $\nu(\text{film})=3334, 1694, 1632 \text{ cm}^{-1}$; $\delta=0.87$ (t, 3H, $J=6.6 \text{ Hz}$), 2.10-2.40 (m, 13H), 2.43-2.65 (m, 2H), 2.40 (s, 0.3H), 2.45 (s, 2.7H), 2.60 (t, 2H, $J=7.7 \text{ Hz}$), 2.98 (t, 2H, $J=6.6 \text{ Hz}$), 3.56 (q, 2H, $J=6.6 \text{ Hz}$), 4.03-4.25 (m, 2H), 7.00-7.18 (m, 2H), 7.19-7.30 (m, 1H), 7.37-7.50 (m, 1H), 7.74 (d, 0.1H, $J=13.9 \text{ Hz}$), 8.05 (d, 0.9H, $J=14.7 \text{ Hz}$), 8.19 (br s, 0.1H), 8.23 (br s, 0.9H), 10.87-11.87 (m, 1H). **10**: mp $117-119^\circ\text{C}$; $\nu(\text{Nujol})=3364, 1688 \text{ cm}^{-1}$; $\delta=0.88$ (t, 3H, $J=6.8 \text{ Hz}$), 1.20-1.52 (m, 11H), 1.53-1.70 (m, 2H), 2.68 (s, 3H), 2.90 (t, 2H, $J=7.9 \text{ Hz}$), 4.42 (q, 2H, $J=7.1 \text{ Hz}$), 7.24 (td, 1H, $J=1.6, 7.3 \text{ Hz}$), 7.31-7.50 (m, 2H), 8.05 (d, 1H, $J=7.7 \text{ Hz}$), 8.11 (br s, 1H), 8.49 (s, 1H). **16**: mp $151-152^\circ\text{C}$; $\nu(\text{Nujol})=3500, 3214 \text{ cm}^{-1}$; $\delta=0.89$ (t, 3H, $J=6.8 \text{ Hz}$), 1.20-1.73 (m, 11H), 2.50 (s, 3H), 2.90 (t, 2H, $J=8.1 \text{ Hz}$), 4.86 (d, 2H, $J=1.5 \text{ Hz}$), 7.21 (td, 1H, $J=1.1, 8.1 \text{ Hz}$), 7.31-7.52 (m, 2H), 7.89 (s, 1H), 7.93 (br s, 1H), 8.01 (d, 1H, $J=7.7 \text{ Hz}$). **17**: mp $148-151^\circ\text{C}$; $\nu(\text{Nujol})=3260, 1658 \text{ cm}^{-1}$; $\delta=0.89$ (t, 3H, $J=6.8 \text{ Hz}$), 1.2-1.74 (m, 10H), 2.79 (s, 3H), 2.93 (t, 2H, $J=7.9 \text{ Hz}$), 7.29 (td, 1H, $J=1.5, 8.1 \text{ Hz}$), 7.38-7.58 (m, 2H), 8.08 (d, 1H, $J=7.7 \text{ Hz}$), 8.26 (br s, 1H), 8.42 (s, 1H), 10.36 (s, 1H). **18**: mp $96-97^\circ\text{C}$; $\nu(\text{Nujol})=3404, 1717 \text{ cm}^{-1}$; $\delta=0.89$ (t, 3H, $J=6.6 \text{ Hz}$), 1.22-1.75 (m, 10H), 2.31 (s, 3H), 2.89 (t, 2H, $J=7.9 \text{ Hz}$), 7.21 (td, 1H, $J=1.1, 7.7 \text{ Hz}$), 7.35-7.54 (m, 2H), 7.60 (s, 1H), 7.92 (br s, 1H), 7.96 (d, 1H, $J=7.7 \text{ Hz}$), 8.44 (s, 1H). Carazostatin (**1**): mp $159.5-160.5^\circ\text{C}$ (lit.: mp $149-152^\circ\text{C}$; $162-163^\circ\text{C}$); $\nu(\text{KBr})=3477, 3380 \text{ cm}^{-1}$; $\nu(\text{Nujol})=3498, 3416 \text{ cm}^{-1}$; $\delta=0.89$ (t, 3H, $J=6.6 \text{ Hz}$), 1.20-1.52 (m, 8H), 1.58-1.74 (m, 2H), 2.37 (s, 3H), 2.88 (t, 2H, $J=7.9 \text{ Hz}$), 4.55 (s, 1H), 7.16 (td, 1H, $J=1.5, 8.1 \text{ Hz}$), 7.32 (s, 1H), 7.34-7.46 (m, 2H), 7.74 (br s, 1H), 7.93 (d, 1H, $J=7.7 \text{ Hz}$).