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 recently[3] 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.
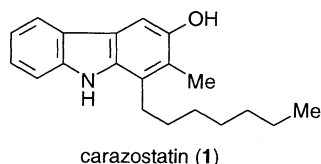

carazostatin (**1**)

Figure 1.

The present synthesis of carazostatin (**1**) started by the palladium-mediated cross-coupling[5] 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 conditions[3] which allowed the transformation of **3** into 2-octylindole (**4**) in 98% yield on treatment with sodium ethoxide in refluxing ethanol. We found[6] 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 acid[4] 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 Fischer[8] 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 reaction[9] 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 fluoride[10] 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.
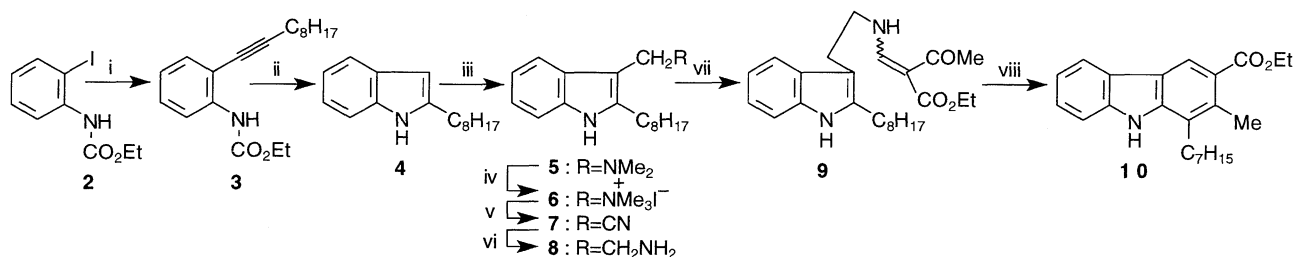
Scheme 1. *Reagents and conditions*: (i) 1-decyne (1.2 equiv.), $PdCl_2(PPh_3)_2$ (2 mol%), CuI (0.5 mol%), Et_3N, reflux, 1 h; 89%. (ii) Na (10 equiv.), EtOH, reflux, 2 h; 98% or LiCl (5 equiv.), DMF, reflux, 8 h; 70%. (iii) *N,N*-dimethylmethyleneammonium chloride (2 equiv.), CH_2Cl_2, r.t., 45 min. (iv) MeI (excess), MeOH, r.t., 30 min. (v) NaCN (1.2 equiv.), DMF, 100 °C, 10 min; 64% from **4**. (vi) $NaBH_4$ (3 equiv.), $CoCl_2 \cdot 6H_2O$ (1.3 equiv.), MeOH, r.t., 30 min then $NaBH_4$ (10 equiv.), 0 °C, 50 min. (vii) ethyl ethoxymethyleneacetoacetate (1.5 equiv.), EtOH, r.t., 50 min; 57% from **7**. (viii) Ac_2O-AcOH, reflux, 17 h; 53%.
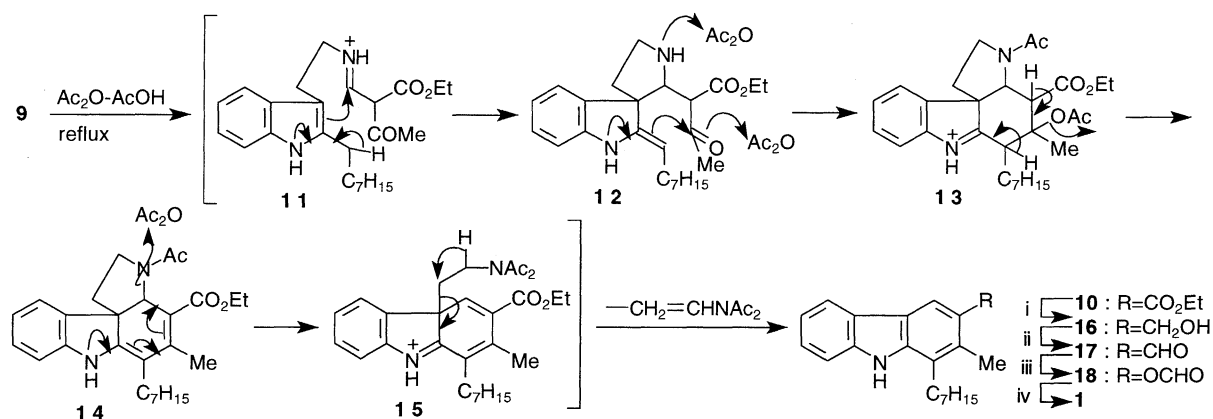
Scheme 2. *Reagents and conditions*: (i) DIBAL, CH₂Cl₂, -78 °C, 40 min; 95%. (ii) Dess-Martin reagent (1.5 equiv.), CH₂Cl₂, r.t., 15 min; 94%. (iii) *m*-CPBA (1.5 equiv.), KF (1.5 equiv.), CH₂Cl₂, 0 °C, 50 min; 86%. (iv) LiAlH₄ (1.2 equiv.), THF, 0 °C, 30 min; 87%.

References and Notes

1   S. Kato, H. Kawai, T. Kawasaki, Y. Toda, T. Urata, and Y. Hayakawa, *J. Antibiot.*, **42**, 1879 (1989).

2   Former synthesis, see: P. M. Jackson and C. J. Moody, *Synlett*, **1990**, 521; P. M. Jackson, C. J. Moody, and R. J. Mortimer, *J. Chem. Soc., Perkin Trans. 1*, **1991**, 2941.

3   T. Sakamoto, Y. Kondo, and H. Yamanaka, *Heterocycles*, **24**, 31 (1986).

4   (a) S. Takano, K. Shishido, M. Sato, K. Yuta, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, **1978**, 943. (b) S. Takano, K. Yuta, S. Hatakeyama, and K. Ogasawara, *Tetrahedron Lett.* **1979**, 369. (c) S. Takano, Y. Suzuki, and K. Ogasawara, *Heterocycles*, **16**, 1479 (1981).

5   K. Sonogashira, Y. Tohda, and N. Hagiwara, *Tetrahedron Lett.*, **1975**, 4467.

6   We also found that a similar aromatic annulation occurred with *o*-methoxyphenylacetylenes to give the benzofuran derivatives under these neutral conditions, see: K. Hiroya, K. Hashimura, and K. Ogasawara, *Heterocycles*, **38**, 2463 (1994).

7   cf. S. Takano, T. Sato, K. Inomata, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, **1991**, 462.

8   G. H. Alt, *J. Org. Chem.*, **33**, 2858 (1968).

9   D. B. Dess and J. C. Martin, *J. Am. Chem. Soc.*, **113**, 7277 (1991).

10   F. Camps, J. Coll, A. Messeguer, and M. A. Pericás, *Tetrahedron Lett.*, **22**, 3895 (1981).

11   Physical and spectral data: ν(IR); δ(¹H NMR, 300 MHz):
3: oil; ν(film)=3396, 2220, 1741 cm⁻¹; δ=0.89 (t, 3H, *J*=6.6 Hz), 1.22-1.55 (m, 13H), 1.56-1.71 (m, 2H), 2.49 (t, 2H, *J*=7.0 Hz), 4.24 (q, 2H, *J*=7.1 Hz), 6.94 (td, 1H, *J*=1.1, 7.7 Hz), 7.20-7.37 (m, 2H), 7.41 (br s, 1H), 8.12 (d, 1H, *J*=8.4 Hz). **4**: oil; ν(film)=3408 cm⁻¹; δ=1.06 (t, 3H, *J*=6.4 Hz), 1.20-1.63 (m, 10H), 1.78-1.98 (m, 2H),

2.89 (t, 2H, *J*=7.7 Hz), 6.40 (d, 1H, *J*=0.7 Hz), 7.15-7.35 (m, 2H), 7.43 (d, 1H, *J*=7.7 Hz), 7.70 (d, 1H, *J*=7.3 Hz), 7.93 (br s, 1H). **7**: mp 68-69 °C; ν(Nujol)=3364, 2248 cm⁻¹; δ=0.93 (t, 3H, *J*=6.8 Hz), 1.18-1.50 (m, 10H), 1.68-1.80 (m, 2H), 2.75 (t, 2H, *J*=7.7 Hz), 3.77 (s, 2H), 7.14-7.38 (m, 3H), 7.55-7.66 (m, 1H), 8.10 (br s, 1H). **9**: oil; ν(film)=3334, 1694, 1632 cm⁻¹; δ=0.87 (t, 3H, *J*=6.6 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 Hz), 2.98 (t, 2H, *J*=6.6 Hz), 3.56 (q, 2H, *J*=6.6 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 Hz), 8.05 (d, 0.9H, *J*=14.7 Hz), 8.19 (br s, 0.1H), 8.23 (br s, 0.9H), 10.87-11.87 (m, 1H). **10**: mp 117-119 °C; ν(Nujol)=3364, 1688 cm⁻¹; δ=0.88 (t, 3H, *J*=6.8 Hz), 1.20-1.52 (m, 11H), 1.53-1.70 (m, 2H), 2.68 (s, 3H), 2.90 (t, 2H, *J*=7.9 Hz), 4.42 (q, 2H, *J*=7.1 Hz), 7.24 (td, 1H, *J*=1.6, 7.3 Hz), 7.31-7.50 (m, 2H), 8.05 (d, 1H, *J*=7.7 Hz), 8.11 (br s, 1H), 8.49 (s, 1H). **16**: mp 151-152 °C; ν(Nujol)=3500, 3214 cm⁻¹; δ=0.89 (t, 3H, *J*=6.8 Hz), 1.20-1.73 (m, 11H), 2.50 (s, 3H), 2.90 (t, 2H, *J*=8.1 Hz), 4.86 (d, 2H, *J*=1.5 Hz), 7.21 (td, 1H, *J*=1.1, 8.1 Hz), 7.31-7.52 (m, 2H), 7.89 (s, 1H), 7.93 (br s, 1H), 8.01 (d, 1H, *J*=7.7 Hz). **17**: mp 148-151 °C; ν(Nujol)=3260, 1658 cm⁻¹; δ=0.89 (t, 3H, *J*=6.8 Hz), 1.2-1.74 (m, 10H), 2.79 (s, 3H), 2.93 (t, 2H, *J*=7.9 Hz), 7.29 (td, 1H, *J*=1.5, 8.1 Hz), 7.38-7.58 (m, 2H), 8.08 (d, 1H, *J*=7.7 Hz), 8.26 (br s, 1H), 8.42 (s, 1H), 10.36 (s, 1H). **18**: mp 96-97 °C; ν(Nujol)=3404, 1717 cm⁻¹; δ=0.89 (t, 3H, *J*=6.6 Hz), 1.22-1.75 (m, 10H), 2.31 (s, 3H), 2.89 (t, 2H, *J*=7.9 Hz), 7.21 (td, 1H, *J*=1.1, 7.7 Hz), 7.35-7.54 (m, 2H), 7.60 (s, 1H), 7.92 (br s, 1H), 7.96 (d, 1H, *J*=7.7 Hz), 8.44 (s, 1H). Carazostatin (**1**): mp 159.5-160.5 °C (lit.: mp 149-152 °C¹; 162-163 °C²); ν(KBr)=3477, 3380 cm⁻¹; ν(Nujol)=3498, 3416 cm⁻¹; δ=0.89 (t, 3H, *J*=6.6 Hz), 1.20-1.52 (m, 8H), 1.58-1.74 (m, 2H), 2.37 (s, 3H), 2.88 (t, 2H, *J*=7.9 Hz), 4.55 (s, 1H), 7.16 (td, 1H, *J*=1.5, 8.1 Hz), 7.32 (s, 1H), 7.34-7.46 (m, 2H), 7.74 (br s, 1H), 7.93 (d, 1H, *J*=7.7 Hz).