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Transition metal complexes in organic synthesis. Part 65: Iron-mediated synthesis of carazostatin, a free radical scavenger from *Streptomyces chromofuscus*, and *O*-methylcarazostatin☆

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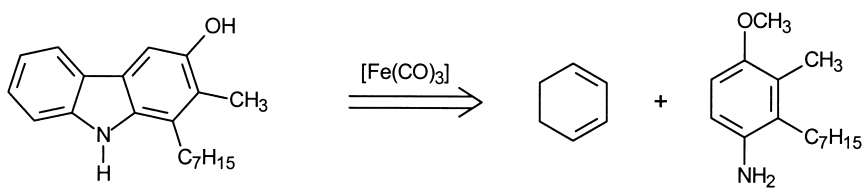
Abstract—Highly efficient syntheses of the free radical scavenger carazostatin and its *O*-methyl derivative are described using cyclohexa-1,3-diene and 2-heptyl-4-methoxy-3-methylaniline as starting materials and iron-mediated oxidative cyclizations as key-steps.

Many carbazole alkaloids with a broad range of useful biological activities were obtained from natural sources.[1] Kato isolated the free radical scavenger carazostatin from *Streptomyces chromofuscus* and assigned the structure as 1-heptyl-3-hydroxy-2-methyl-9*H*-carbazole.[2] Carazostatin shows a strong inhibition of the lipid peroxidation induced by free radicals and is more active than butylated hydroxytoluene (BHT), a well-known antioxidant. In liposomal membranes, carazostatin exhibits a stronger antioxidant activity than α-tocopherol.[3] It was found that oxygen-derived free radicals are responsible for a variety of diseases, e.g. myocardial and cerebral ischemia, arteriosclerosis, inflammation, and rheumatism.[4,5] Free radicals were also suggested to play a central role in senility and cancer initiation.[6] Thus, the isolation of free radical scavengers from natural sources may provide novel lead structures for the development of therapeutic agents against these diseases.

Due to its promising biological activities, carazostatin became an attractive target for organic synthesis.[7] In recent years, several new synthetic methodologies furnishing the carbazole framework were described.[1,8] We developed a convergent synthesis of carbazole alkaloids using an iron-mediated construction of the heterocyclic framework.[9] Our iron-mediated quinone imine cyclization was shown to be especially useful for the synthesis of 3-hydroxycarbazoles.[9,10] Therefore, we envisaged a total synthesis of the alkaloid carazostatin based on the approach depicted in the retrosynthesis (Scheme 1). The iron-mediated oxidative coupling of cyclohexa-1,3-diene **1** and the fully substituted arylamine **2** provided a direct route to carazostatin.[11] Herein, we describe full details of this synthesis.

The azadiene-catalyzed complexation of cyclohexa-1,3-diene **1** with pentacarbonyliron provides a simple and safe access to tricarbonyl(η^4-cyclohexa-1,3-diene)iron **3** even on



Carazostatin **1** **2**

Scheme 1.

☆ For Part 64, see Ref. 9d.

Keywords: carazostatin; Diels–Alder reaction; cyclization.

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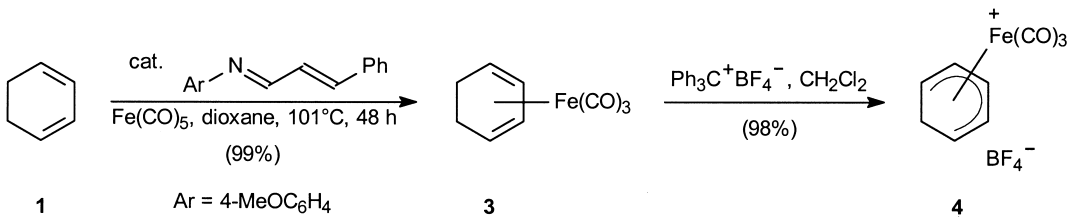
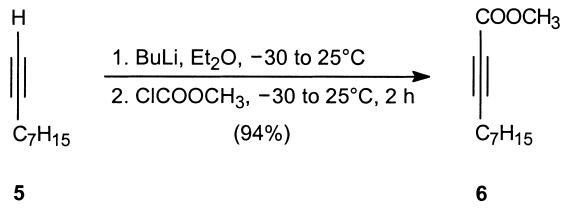
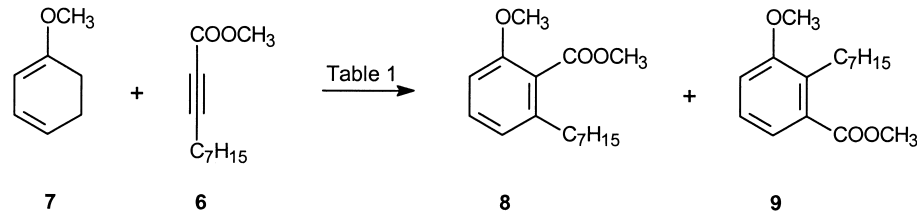


Scheme 2.



Scheme 3.



Scheme 4.

large scale (Scheme 2).[12] Complex **3** is converted to tricarbonyl(η^5-cyclohexadienylium)iron tetrafluoroborate **4** by hydride abstraction using triphenylcarbenium tetrafluoroborate as originally described by Fischer.[13] Thus, by this 2-step sequence the iron complex salt **4** is available almost quantitatively on large scale.

We projected to prepare the required arylamine **2** by Diels–Alder reaction with an appropriate alkyne building block analogous to our synthesis of hyellazole.[14] The synthesis of the alkyne was achieved by adaptation of literature procedures.[15] Deprotonation of 1-nonyne **5** with butyllithium and quenching with methyl chloroformate afforded methyl 2-decynoate **6** which could be used without further purification (Scheme 3).

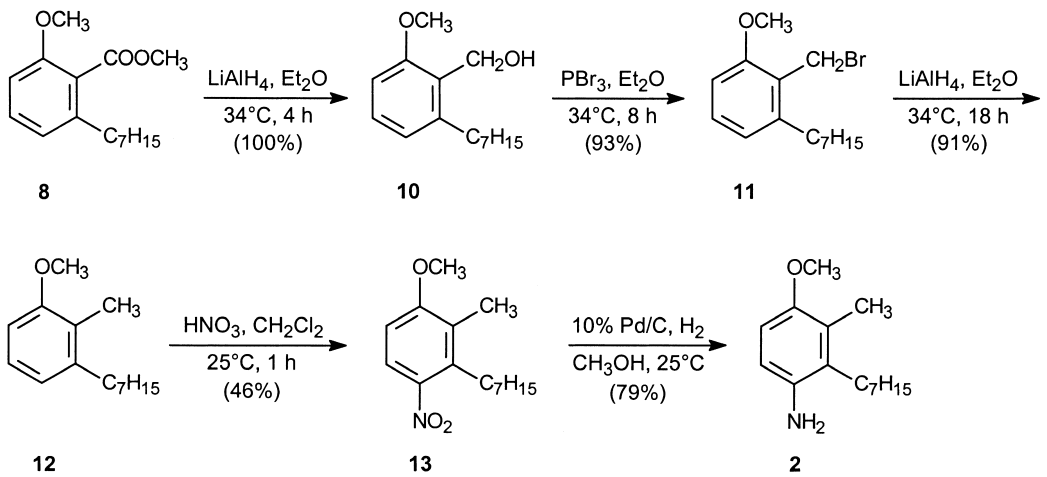
The Diels–Alder reaction of 1-methoxycyclohexa-1,3-diene **7** with methyl 2-decynoate **6** followed by retro-Diels–Alder reaction with extrusion of ethylene provided methyl 6-heptyl-2-methoxybenzoate **8** as the major product (Scheme 4). Subba Rao reported that this procedure leads to 6-alkyl-2-methoxybenzoates.[16] The regiochemistry in our case was confirmed by COLOC spectra of compound **12** and finally by conversion to the natural product (see below). An optimization of the reaction conditions was achieved by increasing the temperature to 200–210°C and extension of the reaction time to 14 d (Table 1). Using this set of reaction conditions, the desired product **8** was isolated in 84% yield and methyl 2-heptyl-3-methoxybenzoate **9** in 5% yield. Thus, in contrast to Subba Rao, we obtained the alternative regioisomer of the cycloaddition as a by-product but only under our optimized reaction conditions. In this context, it is interesting to note that, using ethyl phenylpropynoate as dienophile the regioselectivity of the Diels–Alder cycloaddition with 1-methoxycyclohexa-1,3-diene **7** reverses, as shown by us previously.[14]

The following 3 steps transform the methoxycarbonyl group of compound **8** to the methyl group present in the natural product. Reduction of the methyl ester **8** with lithium aluminum hydride afforded quantitatively the benzyl alcohol **10**, which was converted to the benzylic bromide **11** by treatment with phosphorous tribromide (Scheme 5). Reduction of the benzylic bromide **11** with lithium aluminum hydride afforded after purification by flash chromatography on silica gel, pure 3-heptyl-2-methylanisole **12**. Because of the clean course of the two former reactions, the crude product was taken to the next transformation in both cases. The benzylic bromide **11** turned out to be unstable and was submitted immediately to the reduction. Thus, an overall yield of 85% was achieved for the 3-step conversion of the Diels–Alder product **8** to 3-heptyl-2-methylanisole **12**.

Nitration of 3-heptyl-2-methylanisole **12** with concentrated nitric acid in dichloromethane at room temperature afforded the desired 3-heptyl-2-methyl-4-nitroanisole **13** in 46% yield along with 23% of 3-heptyl-2-methyl-6-nitroanisole. The regiochemistry for both products was confirmed by extensive NOE experiments (see Section 1). Catalytic hydrogenation of the nitro derivative **13** provided 2-heptyl-4-methoxy-3-methylaniline **2** (Scheme 5). Starting from 1-methoxycyclohexa-1,3-diene **7** the required arylamine **2** was obtained in 6 steps and 26% overall yield. The

Table 1. Reaction conditions and results of the Diels–Alder cycloaddition

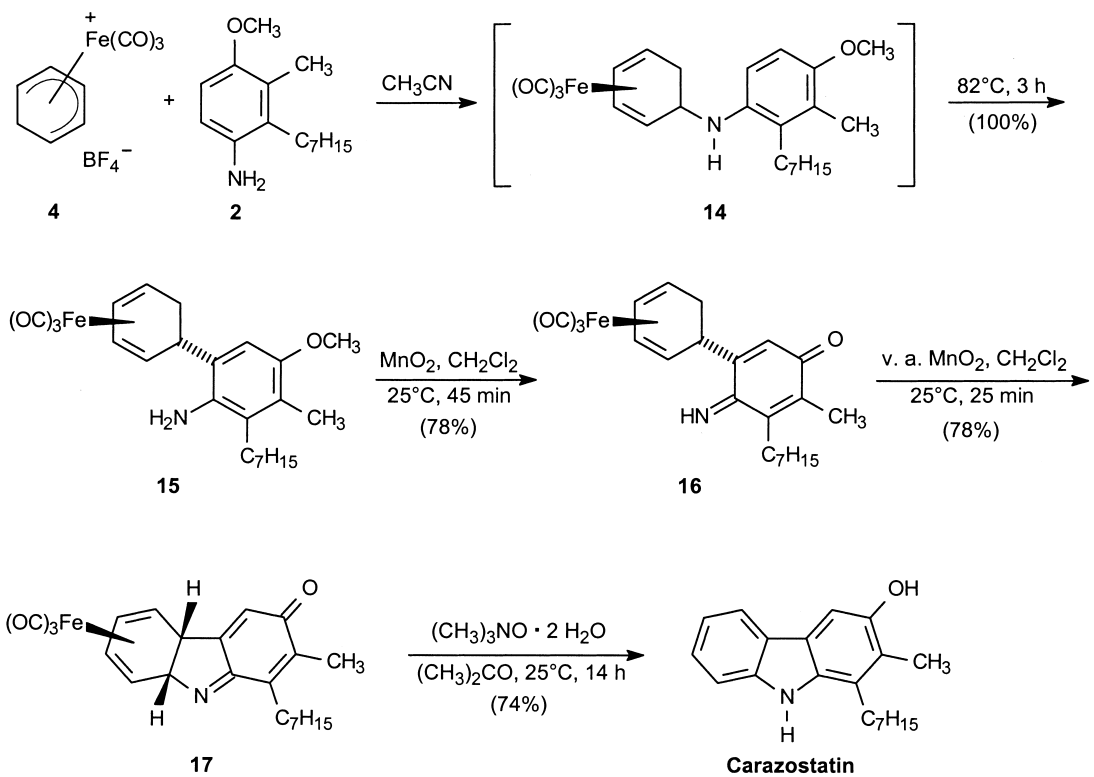
T (°C)	*t* (d)	**8**, Yield (%)	**9**, Yield (%)	**6**, Yield (%)
130	3	39	–	48
200	6	60	–	35
150	14	79	Trace	Trace
200–210	14	84	5	–



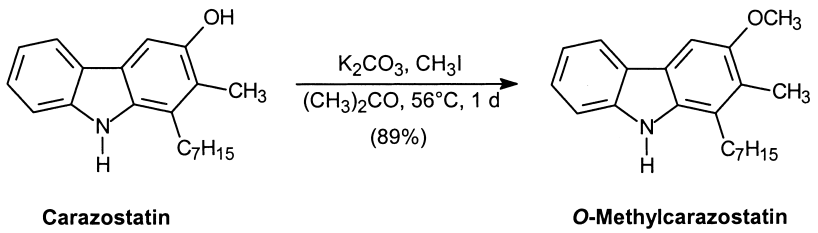
Scheme 5.

advantages of the present route are the cheap starting materials and the feasibility to perform all steps on a multigram scale.

The reaction of the arylamine **2** with the iron complex salt **4** afforded after 3 h in acetonitrile under reflux quantitatively the iron complex **15** (Scheme 6). This electrophilic aromatic substitution was monitored using thin-layer chromatography (TLC). After 1 min at room temperature a less polar product, presumably the N-alkylated arylamine **14**, was formed. At reflux temperature, this intermediate complex rearranged within 10 min to the final complex **15**. The TLC analysis shows that both complexes have the same R_f value but provide a different color on developing the TLC plate with the ceric(IV) sulfate/phosphomolybdic acid reagent.[17,18] Related examples for rearrangements of the N-alkylated arylamine (kinetic product) to the C-alkylated arylamine (thermodynamic product) have been described earlier.[18–20] In our iron-mediated quinone imine cyclization, sequential chemoselective oxidations of 5-aryl-substituted tricarbonyl(η^4-cyclohexa-1,3-diene)iron complexes are generally achieved using manganese dioxides of different activity.[10,14,21] Oxidation of complex **15** with commercial manganese dioxide[22] in dichloromethane at room temperature led to the quinone imine **16**. The oxidative cyclization of compound **16** using Fatiadi's very active manganese dioxide[23] provided the tricarbonyliron-complexed 4b,8a-dihydrocarbazol-3-one **17** as dark yellow crystals. The demetalation of complex **17** using trimethylamine *N*-oxide[24] proceeded at room temperature with instantaneous tautomerization to carazostatin. All spectral data (UV, IR, ^{1}H NMR, ^{13}C NMR, and MS) and the melting



Scheme 6.



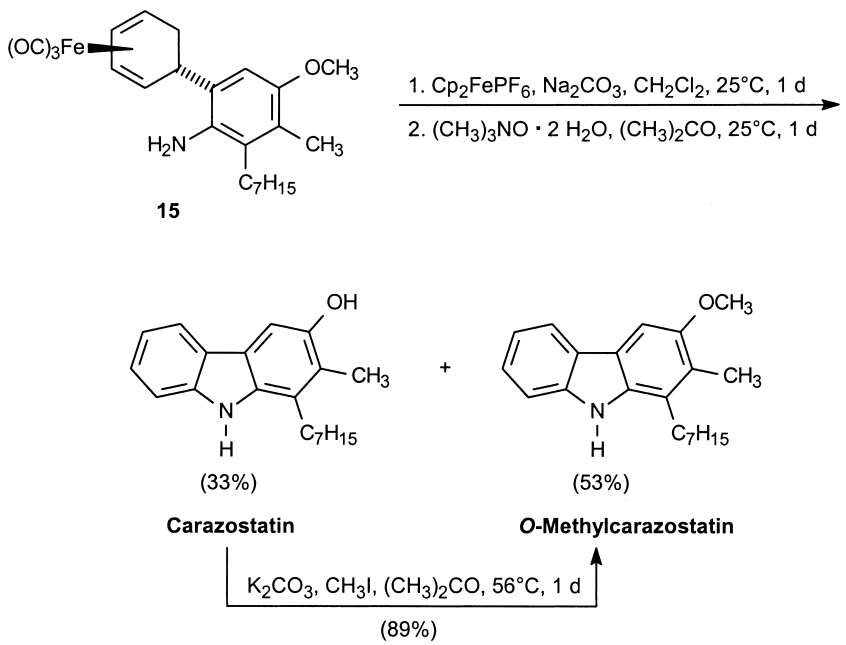
Scheme 7.

point of our synthetic carazostatin are in good agreement with those reported for the natural product.[2] The present synthesis provides carazostatin via the iron-mediated quinone imine cyclization in 4 steps and 45% overall yield based on the iron complex salt **4**.

O-Methylcarazostatin (1-heptyl-3-methoxy-2-methyl-9*H*-carbazole), a non-natural derivative of carazostatin, could be of pharmacological interest as well. Electrochemical studies have shown that it is also more active than BHT as antioxidant.[7b] We developed two different pathways to this compound. The first uses the iron-mediated quinone imine cyclization as described above and finally transforms carazostatin to *O*-methylcarazostatin by chemoselective *O*-methylation. The second utilizes the iron-mediated arylamine cyclization of the tricarbonyliron complex **15**.

The *O*-methylation of carazostatin with iodomethane and potassium carbonate, previously described by Moody,[7b] afforded after purification by flash chromatography on silica gel and subsequent recrystallization from dichloromethane/hexane pure *O*-methylcarazostatin in 89% yield (Scheme 7). The *N*-methylated product could not be detected. Thus, the route via the iron-mediated quinone imine cyclization provides *O*-methylcarazostatin in 5 steps and 40% overall yield based on the iron complex salt **4**.

An alternative method for the synthesis of 3-methoxycarbazoles is the iron-mediated arylamine cyclization of the arylamine-substituted tricarbonyl(η^4-cyclohexa-1,3-diene)-iron complexes. Using the appropriate oxidizing reagent, this oxidative cyclization can be performed as a one-pot reaction with concomitant aromatization and demetalation.[9,14] Thus, the iron-mediated arylamine cyclization could be used for a shorter access to *O*-methylcarazostatin. Oxidation of complex **15** with ferricenium hexafluorophosphate in the presence of sodium carbonate in dichloromethane at room temperature provided a mixture of *O*-methylcarazostatin and the 4b,8a-dihydrocarbazol-3-one complex **17**, which was not separable by chromatography. Therefore, the crude product was treated with trimethylamine *N*-oxide to demetalate complex **17** to carazostatin (Scheme 8). Separation of the two products by flash chromatography on silica gel provided *O*-methylcarazostatin in 53% yield and carazostatin in 33% yield. The *O*-methylation of carazostatin as described above afforded additional *O*-methylcarazostatin. In summary, the synthesis via the iron-mediated arylamine cyclization leads to *O*-methylcarazostatin in 3 steps and 82% overall yield based on the iron complex salt **4**. We noted already in our synthesis of hyellazole and isohyellazole,[14] that the iron-mediated arylamine cyclization is clearly superior to the iron-mediated quinone imine cyclization for the synthesis of 3-methoxycarbazoles, when using ferricenium hexafluorophosphate in the presence of sodium carbonate as the oxidizing agent.



Scheme 8.

1. Experimental

1.1. General

All reactions were carried out using anhydrous and degassed solvents under an inert gas atmosphere. Flash chromatography: Baker or Merck silica gel (0.03–0.06 mm). Melting points: Büchi 535. UV spectra: Perkin–Elmer Lambda 2 (UV/VIS spectrometer). IR spectra: Perkin–Elmer 882 and Bruker IFS-88. ^{1}H NMR and ^{13}C NMR spectra: Bruker WM-250 and AM-400; internal standard: the signal of the deuterated solvent; coupling constants J in Hz. Mass spectra: Finnigan MAT-90; ionization potential: 70 eV.

1.1.1. Methyl 2-decynoate (6). A 1.6 M solution of *n*-butyllithium in hexane (66.2 mmol, 41.4 mL) was added to a solution of 1-nonyne (**5**) (8.02 g, 64.6 mmol, 10.6 mL) in diethyl ether (80 mL) at −30°C. The mixture was warmed to room temperature over a period of 30 min and cooled again to −30°C. Methyl chloroformate (8.44 g, 89.3 mmol, 6.9 mL) was added, the reaction mixture was warmed to 25°C, and stirred for additional 2 h at this temperature. The mixture was poured into ice-water (150 mL) and the layers were separated. The aqueous layer was extracted with ether (4×50 mL) and the combined organic layers were dried over sodium sulfate. The solvent was removed in vacuo to provide methyl 2-decynoate (**6**) as a light yellow oil, yield: 11.1 g (94%). IR (film): $\tilde{\nu}$=2931, 2857, 2238, 1713, 1664, 1602, 1433, 1377, 1327, 1255, 1211, 1163, 1069, 815, 781, 751, 724 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.87 (t, J=6.8 Hz, 3H), 1.27 (m, 6H), 1.38 (m, 2H), 1.57 (quint, J=7.2 Hz, 2H), 2.32 (t, J=7.2 Hz, 2H), 3.75 (s, 3H); ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ=14.02 (CH_3), 18.62 (CH_2), 22.56 (CH_2), 27.49 (CH_2), 28.66 (CH_2), 28.76 (CH_2), 31.59 (CH_2), 52.52 (CH_3), 72.79 (C), 89.95 (C), 154.27 (C=O); MS (60°C): m/z (%)=181 (M^+-1, 1) 151 (81), 139 (35), 125 (26), 121 (34), 111 (29), 108 (35), 107 (28), 100 (80), 98 (21), 93 (47), 81 (67), 79 (100), 67 (47), 66 (33), 55 (53), 43 (55), 41 (52); HRMS: calcd for $C_{11}H_{17}O_2$ (M^+-1): 181.1228, found: 181.1216.

1.1.2. Methyl 6-heptyl-2-methoxybenzoate (8) and methyl 2-heptyl-3-methoxybenzoate (9). A mixture of 1-methoxycyclohexa-1,3-diene (**7**) (5.5 mL, content: 65%; 3.32 g, 30.1 mmol of 1,3-diene) and methyl 2-decynoate (**6**) (5.49 g, 30.1 mmol) was heated in a sealed glass tube for 14 d at 200–210°C. The resulting yellow oil was subjected to flash chromatography (hexane/EtOAc, 9:1) on silica gel to provide as the less polar fraction methyl 2-heptyl-3-methoxybenzoate (**9**) and as the more polar fraction methyl 6-heptyl-2-methoxybenzoate (**8**), both as colorless oils.

Compound **8**. Yield: 6.68 g (84%). IR (film): $\tilde{\nu}$=3071, 2929, 2857, 2021, 1931, 1734, 1583, 1468, 1431, 1376, 1269, 1187, 1107, 1074, 959, 826, 792, 748 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6): δ=0.88 (t, J=6.9 Hz, 3H), 1.29 (m, 8H), 1.57 (m, 2H), 2.52 (m, 2H), 3.79 (s, 3H), 3.82 (s, 3H), 6.86 (br d, J=8.0 Hz, 1H), 6.89 (br d, J=8.0 Hz, 1H), 7.30 (br t, J=8.0 Hz, 1H); ^{13}C NMR and DEPT (100 MHz, acetone-d_6): δ=15.00 (CH_3), 23.95 (CH_2), 30.75 (CH_2), 32.67 (CH_2), 33.15 (CH_2), 34.64 (CH_2), 52.70 (CH_3), 56.79 (CH_3), 110.12 (CH), 122.82 (CH), 125.55 (C), 131.67 (CH), 142.38 (C), 157.89 (C), 169.59 (C=O); the signal of one CH_2 group is missing due to overlapping with the signals of the solvent; MS (20°C): m/z (%)=264 (M^+, 65), 233 (41), 180 (30), 179 (16), 161 (100), 148 (10), 121 (15); HRMS: calcd for $C_{16}H_{24}O_3$ (M^+): 264.1725, found: 264.1697.

Compound **9**. Yield: 360 mg (5%). IR (CCl_4): $\tilde{\nu}$=2953, 2929, 2857, 1728, 1582, 1460, 1434, 1253, 1100, 1065, 816, 771, 728, 665 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.88 (t, J=6.9 Hz, 3H), 1.29–1.38 (m, 8H), 1.52 (m, 2H), 2.88 (m, 2H), 3.84 (s, 3H), 3.88 (s, 3H), 6.98 (br d, J=8.2 Hz, 1H), 7.19 (t, J=8.0 Hz, 1H), 7.35 (dd, J=8.0, 1.0 Hz, 1H); ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ=14.15 (CH_3), 22.70 (CH_2), 26.76 (CH_2), 29.15 (CH_2), 30.01 (CH_2), 30.26 (CH_2), 31.88 (CH_2), 51.95 (CH_3), 55.73 (CH_3), 113.37 (CH), 121.85 (CH), 126.14 (CH), 131.51 (C), 133.14 (C), 157.84 (C), 168.68 (C=O); MS (20°C): m/z (%)=264 (M^+, 64), 233 (25), 180 (29), 179 (100), 161 (26), 149 (17), 147 (12), 121 (11), 91 (19); HRMS: calcd for $C_{16}H_{24}O_3$ (M^+): 264.1725, found: 264.1721.

1.1.3. 6-Heptyl-2-methoxybenzyl alcohol (10). A suspension of lithium aluminum hydride (1.44 g, 37.9 mmol) in diethyl ether (20 mL) was cooled to −10°C and a solution of the benzoate **8** (6.67 g, 25.2 mmol) in diethyl ether (15 mL) was added over a period of 20 min. The reaction mixture was heated at reflux for 4 h, then quenched with ice-water, and the resulting precipitate was dissolved with a small amount of sulfuric acid (10%). The layers were separated and the aqueous layer was extracted with ether (4×35 mL). The combined organic layers were washed with a saturated solution of sodium bicarbonate and dried over sodium sulfate. The solvent was evaporated to afford the alcohol **10** as a colorless oil, yield: 5.96 g (100%). IR (film): $\tilde{\nu}$=3436, 2926, 2857, 1736, 1598, 1584, 1465, 1437, 1376, 1314, 1263, 1198, 1178, 1112, 1088, 1005, 782, 745, 724 cm^{-1}, ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.88 (t, J=6.9 Hz, 3H), 1.24–1.39 (m, 8H), 1.55 (m, 2H), 2.40 (br s, 1H), 2.67 (m, 2H), 3.86 (s, 3H), 4.73 (s, 2H), 6.76 (br d, J=8.0 Hz, 1H), 6.81 (br d, J=8.0 Hz, 1H), 7.19 (t, J=8.0 Hz, 1H); ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ=14.10 (CH_3), 22.65 (CH_2), 29.16 (CH_2), 29.61 (CH_2), 31.83 (CH_2), 32.16 (CH_2), 33.24 (CH_2), 55.42 (CH_3), 57.41 (CH_2), 108.03 (CH), 122.33 (CH), 126.82 (C), 128.51 (CH), 142.62 (C), 158.26 (C); MS (85°C): m/z (%)=236 (M^+, 100), 218 (83), 161 (39), 152 (32), 147 (33), 137 (29), 136 (14), 135 (28), 134 (19), 123 (13), 122 (44), 121 (44), 93 (21), 91 (32), 83 (16), 81 (29), 79 (22), 77 (13); HRMS: calcd for $C_{15}H_{24}O_2$ (M^+): 236.1776, found: 236.1793.

1.1.4. 6-Heptyl-2-methoxybenzyl bromide (11). Phosphorus tribromide (2.37 g, 8.74 mmol, 0.83 mL) was added to a solution of alcohol **10** (5.96 g, 25.2 mmol) in diethyl ether (30 mL) at −40°C over a period of 5 min and the mixture was heated at reflux for 3 h. Additional phosphorus tribromide (428 mg, 1.58 mmol, 0.15 mL) was added and the reaction mixture was heated at reflux for further 5 h. The cold mixture was poured on ice and the layers were separated. The aqueous layer was extracted with ether (5×30 mL) and the combined organic layers were dried over sodium sulfate. Evaporation of the solvent in vacuo at a temperature below 20°C afforded bromide **11** as a light yellow oil, yield: 7.06 g (93%). IR (film): $\tilde{\nu}$=2955,

2926, 2854, 1599, 1585, 1473, 1440, 1314, 1268, 1217, 1143, 1067, 791, 747, 603, 540 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=0.89 (t, J=6.8 Hz, 3H), 1.28–1.42 (m, 8H), 1.64 (m, 2H), 2.70 (m, 2H), 3.88 (s, 3H), 4.67 (s, 2H), 6.73 (br d, J=8.0 Hz, 1H), 6.80 (br d, J=8.0 Hz, 1H), 7.21 (t, J=8.0 Hz, 1H); ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ=14.13 (CH_3), 22.68 (CH_2), 25.80 (CH_2), 29.20 (CH_2), 29.71 (CH_2), 31.08 (CH_2), 31.82 (CH_2), 32.53 (CH_2), 55.80 (CH_3), 108.39 (CH), 121.84 (CH), 123.97 (C), 129.50 (CH), 143.57 (C), 157.85 (C); MS (45°C): m/z (%)=300 (M^+, 4.7), 298 (M^+, 4.8), 219 (44), 135 (100), 95 (26), 81 (20), 67 (12), 55 (16); HRMS: calcd for $C_{15}H_{23}OBr$ (M^+): 298.0932, found: 298.0921.

1.1.5. 3-Heptyl-2-methylanisole (12). A solution of the benzyl bromide **11** (7.06 g, 23.6 mmol) in diethyl ether (15 mL) was added to a suspension of lithium aluminum hydride (1.35 g, 35.6 mmol) in diethyl ether (20 mL) at −30°C over a period of 30 min. The reaction mixture was heated at reflux for 15 h, then additional lithium aluminum hydride (200 mg, 5.27 mmol) was added, and the mixture was heated at reflux for further 3 h. The cold solution was quenched with ice-water and the resulting precipitate was dissolved with a small amount of sulfuric acid (10%). The layers were separated and the aqueous layer was extracted with ether (5×25 mL). The combined organic layers were washed with a saturated solution of sodium bicarbonate and dried over magnesium sulfate. The solvent was removed in vacuo and the residue was subjected to flash chromatography (hexane/EtOAc, 5:1) on silica gel to provide the anisole **12** as a colorless oil, yield: 4.73 g (91%). IR (film): $\tilde{\nu}$=2927, 2857, 1584, 1464, 1437, 1376, 1310, 1256, 1191, 1167, 1119, 1096, 775, 719 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=0.88 (t, J=6.7 Hz, 3H), 1.28–1.43 (m, 8H), 1.48–1.57 (m, 2H), 2.17 (s, 3H), 2.59 (m, 2H), 3.82 (s, 3H), 6.71 (br d, J=7.9 Hz, 1H), 6.77 (br d, J=7.9 Hz, 1H), 7.09 (t, J=7.9 Hz, 1H); ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ=11.29 (CH_3), 14.22 (CH_3), 22.80 (CH_2), 29.36 (CH_2), 29.81 (CH_2), 30.72 (CH_2), 31.99 (CH_2), 33.83 (CH_2), 55.45 (CH_3), 107.69 (CH), 121.58 (CH), 124.45 (C), 125.90 (CH), 142.55 (C), 157.77 (C); MS (40°C): m/z (%)=220 (M^+, 52), 136 (100), 135 (29), 121 (13), 105 (14), 91 (5); HRMS: calcd for $C_{15}H_{24}O$ (M^+): 220.1827, found: 220.1839.

1.1.6. 3-Heptyl-2-methyl-4-nitroanisole (13) and 3-heptyl-2-methyl-6-nitroanisole. Over a period of 40 min, nitric acid (1.7 mL, content: 65%; 1.54 g, 24.4 mmol of acid) was added to a solution of the anisole **12** (1.06 g, 4.81 mmol) in dichloromethane (15 mL) at room temperature. During the addition, a light stream of argon was passed through the solution. After a reaction time of 1 h the mixture was poured onto ice (30 g) and then neutralized by addition of a sat. solution of sodium carbonate. The layers were separated and the aqueous solution was extracted three times with ether. The combined organic layers were dried over magnesium sulfate and the solvent was removed in vacuo. Flash chromatography (hexane/EtOAc, 7:1) of the residue on silica gel afforded as the less polar fraction 3-heptyl-2-methyl-6-nitroanisole and as the more polar fraction the 4-nitroanisole **13**.

Compound **13**. Orange oil, yield: 586 mg (46%). IR (film): $\tilde{\nu}$=2956, 2928, 2856, 1603, 1580, 1519, 1468, 1438, 1378, 1344, 1317, 1268, 1119, 1086, 816, 806, 763 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=0.87 (t, J=6.7 Hz, 3H), 1.28–1.43 (m, 8H), 1.57 (m, 2H), 2.21 (s, 3H), 2.78 (m, 2H), 3.87 (s, 3H), 6.72 (d, J=9.1 Hz, 1H), 7.74 (d, J=9.1 Hz, 1H); ^1H NMR NOE experiments (250 MHz, $CDCl_3$): (1) irradiation at 2.21, observed NOEs 1.57, 2.78; (2) irradiation at 2.78, observed NOE's 1.57, 2.21; (3) irradiation at 3.87, observed NOE 6.72; (4) irradiation at 6.72, observed NOEs 3.87, 7.74; (5) irradiation at 7.74, observed NOE 6.72; ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ=11.61 (CH_3), 14.09 (CH_3), 22.63 (CH_2), 28.95 (CH_2), 29.49 (CH_2), 29.58 (CH_2), 29.97 (CH_2), 31.81 (CH_2), 55.81 (CH_3), 107.19 (CH), 124.07 (CH), 126.73 (C), 137.71 (C), 143.89 (C), 160.73 (C); MS (30°C): m/z (%)=265 (M^+, 20), 248 (100), 164 (9), 135 (11); HRMS: calcd for $C_{15}H_{23}NO_3$ (M^+): 265.1678, found: 265.1667.

3-*Heptyl*-2-*methyl*-6-*nitroanisole*. Yellow oil, yield: 291 mg (23%). IR (film): $\tilde{\nu}$=2929, 2857, 1588, 1522, 1468, 1410, 1353, 1256, 1110, 1067, 1003, 808 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=0.88 (t, J=6.7 Hz, 3H), 1.28–1.42 (m, 8H), 1.55 (m, 2H), 2.27 (s, 3H), 2.62 (m, 2H), 3.86 (s, 3H), 6.98 (d, J=8.4 Hz, 1H), 7.60 (d, J=8.4 Hz, 1H); ^1H NMR NOE experiments (250 MHz, $CDCl_3$): (1) irradiation at 2.27, observed NOEs 1.55, 2.62, 3.86; (2) irradiation at 2.62, observed NOEs 1.55, 2.27, 6.98; (3) irradiation at 3.86, observed NOE 2.27; (4) irradiation at 6.98, observed NOE's 2.62, 7.60; (5) irradiation at 7.60, observed NOE 6.98; ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ=11.90 (CH_3), 14.07 (CH_3), 22.62 (CH_2), 29.11 (CH_2), 29.52 (CH_2), 29.84 (CH_2), 31.75 (CH_2), 33.98 (CH_2), 61.98 (CH_3), 122.34 (CH), 124.38 (CH), 132.33 (C), 141.99 (C), 149.11 (C), 151.83 (C); MS (25°C): m/z (%)=265 (M^+, 100), 235 (20), 220 (11), 203 (11), 201 (18), 198 (38), 181 (70), 153 (19), 151 (30), 147 (16), 136 (15), 135 (32), 131 (16), 105 (12), 103 (22), 101 (37), 87 (14), 85 (48); HRMS: calcd for $C_{15}H_{23}NO_3$ (M^+): 265.1678, found: 265.1652.

1.1.7. 2-Heptyl-4-methoxy-3-methylaniline (2). Palladium on carbon (10%, 85 mg) was added to a solution of the nitrobenzene **13** (564 mg, 2.13 mmol) in methanol (16 mL). This mixture was vigorously stirred under a hydrogen atmosphere (800–900 Torr) until no further hydrogen uptake was detected. The reaction mixture was filtered over a short path of Celite (which was subsequently washed with ethyl acetate) under an argon atmosphere and the solvent was evaporated. Flash chromatography (hexane/EtOAc, 5:1) of the residue on degassed silica gel afforded the arylamine **2** as a colorless oil, yield: 396 mg (79%). IR (film): $\tilde{\nu}$=3446, 3365, 2954, 2926, 2871, 2855, 1620, 1483, 1468, 1439, 1377, 1315, 1257, 1219, 1165, 1117, 1085, 1015, 800, 724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=0.89 (t, J=6.8 Hz, 3H), 1.28–1.52 (m, 10H), 2.18 (s, 3H), 2.53 (m, 2H), 3.36 (br s, 2H), 3.75 (s, 3H), 6.54 (d, J=8.6 Hz, 1H), 6.60 (d, J=8.6 Hz, 1H); ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ=11.69 (CH_3), 14.14 (CH_3), 22.69 (CH_2), 28.08 (CH_2), 28.55 (CH_2), 29.24 (CH_2), 30.15 (CH_2), 31.90 (CH_2), 56.19 (CH_3), 109.38 (CH), 113.39 (CH), 125.54 (C), 128.20 (C), 137.77 (C), 151.27 (C); MS (20°C): m/z (%)=235 (M^+, 100), 220 (26), 150 (45), 136 (15); HRMS: calcd for $C_{15}H_{25}NO$ (M^+): 235.1936, found: 235.1928.

1.1.8. (1-4-η)-5-(2-Amino-3-heptyl-5-methoxy-4-methylphenyl)cyclohexa-1,3-diene]tricarbonyliron (15). A solution of the arylamine **2** (145 mg, 0.616 mmol) and tricarbonyl(η^5-cyclohexadienylium)iron tetrafluoroborate (**4**) (86 mg, 0.281 mmol) in degassed acetonitrile (10 mL) was heated at reflux for 3 h. The solvent was evaporated in vacuo and the crude product was subjected to flash chromatography (hexane/EtOAc, 5:1) on silica gel to provide the iron complex **15** as a red–orange waxy solid, yield: 127 mg (100%). IR (film): $\tilde{\nu}$=3463, 3383, 2927, 2855, 2043, 1966, 1621, 1600, 1464, 1420, 1377, 1257, 1225, 1193, 622, 563 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.89 (t, J=6.8 Hz, 3H), 1.28–1.48 (m, 10H), 1.61 (br d, J=15.2 Hz, 1H), 2.15 (s, 3H), 2.41 (ddd, J=15.2, 11.1, 3.9 Hz, 1H), 2.52 (m, 2H), 3.18 (m, 2H), 3.33 (br s, 2H), 3.45 (dt, J=11.1, 3.7 Hz, 1H), 3.78 (s, 3H), 5.52 (m, 2H), 6.60 (s, 1H); ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ=11.58 (CH_3), 14.09 (CH_3), 22.64 (CH_2), 28.35 (2 CH_2), 29.16 (CH_2), 30.15 (CH_2), 31.45 (CH_2), 31.84 (CH_2), 39.32 (CH), 56.49 (CH_3), 60.24 (CH), 64.91 (CH), 84.84 (CH), 85.63 (CH), 107.99 (CH), 123.64 (C), 128.20 (C), 128.56 (C), 135.05 (C), 150.78 (C), 211.93 (3 CO); MS (80°C): m/z (%)=453 (M^+, 5), 425 (2), 397 (4), 369 (29), 367 (15), 313 (41), 312 (52), 311 (31), 289 (37), 235 (100), 220 (26), 151 (11), 150 (46), 136 (15), 85 (10); HRMS: calcd for $C_{24}H_{31}FeNO_4$ (M^+): 453.1602, found: 453.1610.

1.1.9. Tricarbonyl[(1-4-η)-5-(5-heptyl-6-imino-4-methylcyclohexa-1,4-dien-3-onyl)cyclohexa-1,3-diene]-iron (16). Commercial manganese dioxide[22] (600 mg) was added to a solution of the iron complex **15** (120 mg, 0.265 mmol) in dichloromethane (4 mL) and stirred for 30 min at room temperature. Additional manganese dioxide (240 mg) was added and the reaction mixture was stirred at room temperature for further 15 min. The mixture was filtered over a short path of silica gel/Celite, which was subsequently washed with ethyl acetate several times. The filtrate was evaporated in vacuo and the red crude product was subjected to flash chromatography (hexane/EtOAc, 5:1) on silica gel to provide the quinone imine complex **16** as a yellow–brown waxy solid, yield: 90 mg (78%). IR (film): $\tilde{\nu}$=3283, 2955, 2928, 2857, 2045, 1969, 1647, 1629, 1602, 1467, 1441, 1335, 1157, 1138, 1120, 878, 622, 618, 614 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.89 (t, J=6.8 Hz, 3H), 1.28–1.46 (m, 11H), 1.98 (s) and 2.00 (s, Σ3H), 2.31–2.51 (m) and 2.70 (m, Σ3H), 2.92 (m) and 3.04 (m, Σ1H), 3.14 (m, 1H), 3.31 (dt) and 3.89 (dt, J=11.3, 3.5 Hz, Σ1H), 5.42–5.59 (m, 2H), 6.41 (s) and 6.49 (s, Σ1H), 10.71 (br s) and 10.85 (br s, Σ1H); ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): (*anti*-imine stereoisomer) δ=11.99 (CH_3), 14.10 (CH_3), 22.63 (CH_2), 27.45 (CH_2), 29.03 (CH_2), 29.06 (CH_2), 29.86 (CH_2), 31.72 (CH_2), 32.77 (CH_2), 37.25 (CH), 60.46 (CH), 62.95 (CH), 84.86 (CH), 86.18 (CH), 127.09 (CH), 135.67 (C), 141.43 (C), 157.27 (C), 165.31 (C=N), 187.67 (C=O), 211.66 (3 CO); MS (105°C): m/z (%)=437 (M^+, 0.4), 409 (6), 407 (10), 381 (19), 353 (52), 351 (100), 349 (10), 295 (10), 267 (30), 191 (20), 182 (8), 56 (8); HRMS: calcd for $C_{23}H_{27}FeNO_4$ (M^+): 437.1289, found: 437.1304.

1.1.10. Tricarbonyl[(5-8-η)-4b,8a-dihydro-1-heptyl-2-methyl-3*H*-carbazol-3-one]iron (17). Very active manganese dioxide[23] (440 mg) was added to a solution of the quinone imine complex **16** (90 mg, 0.206 mmol) in dichloromethane (3 mL). The mixture was stirred at room temperature for 25 min and then filtered over a short path of silica gel/Celite, which was subsequently washed with ethyl acetate several times. Evaporation of the solvent and flash chromatography (hexane/EtOAc, 5:1) of the residue on silica gel afforded the iron complex **17** as dark yellow crystals, yield: 68 mg (78%), mp 95–98°C. IR (drift): $\tilde{\nu}$=2956, 2925, 2856, 2057, 1981, 1953, 1939, 1931, 1656, 1626, 1601, 1458, 1371, 1301, 1286, 1264, 1171, 1142, 1128, 923, 871, 695, 649, 627 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.88 (t, J=6.8 Hz, 3H), 1.25–1.36 (m, 8H), 1.47 (m, 2H), 1.99 (s, 3H), 2.63 (m, 2H), 3.10 (m, 1H), 3.47 (m, 2H), 4.92 (dd, J=6.1, 4.5 Hz, 1H), 5.39 (m, 2H), 6.18 (d, J=1.8 Hz, 1H); ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ=11.98 (CH_3), 14.07 (CH_3), 22.60 (CH_2), 27.83 (CH_2), 29.12 (CH_2), 29.16 (CH_2), 29.74 (CH_2), 31.78 (CH_2), 45.01 (CH), 57.24 (CH), 59.13 (CH), 78.08 (CH), 85.10 (CH), 86.26 (CH), 122.29 (CH), 138.30 (C), 142.69 (C), 155.44 (C), 163.36 (C=N), 187.65 (C=O), 210.41 (3 CO); MS (80°C): m/z (%)=435 (M^+, 6), 407 (39), 351 (100), 349 (25), 307 (11), 295 (6), 293 (8), 281 (11), 267 (18); HRMS: calcd for $C_{23}H_{25}FeNO_4$ (M^+): 435.1133, found: 435.1146.

1.1.11. Carazostatin (1-heptyl-3-hydroxy-2-methyl-9*H*-carbazole). Trimethylamine *N*-oxide dihydrate (134 mg, 1.21 mmol) was added to a solution of the iron complex **17** (64 mg, 0.147 mmol) in acetone (5 mL) and the reaction mixture was stirred for 14 h at room temperature. The suspension was filtered over a short path of silica gel/Celite, which was subsequently washed with ethyl acetate several times. The solvent was evaporated and the residue was subjected to flash chromatography (hexane/EtOAc, 6:1) on silica gel to provide carazostatin as colorless crystals, yield: 32 mg (74%), mp 153–155°C (CH_2Cl_2/hexane) (Ref. 2 149–152°C; Ref. 7a,b 162–163°C from CH_2Cl_2/light petroleum; Ref. 7c 159.5–160.5°C; Ref. 7d,e 159–160°C from CH_2Cl_2/light petroleum). UV (MeOH): λ=217, 233, 253, 264, 295 (sh), 302, 341, 350 nm; IR (drift): $\tilde{\nu}$=3474, 3416, 3379, 2956, 2924, 2855, 1593, 1500, 1463, 1437, 1379, 1356, 1311, 1259, 1231, 1157, 1147, 1063, 832, 771, 753, 741, 659 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.89 (t, J=6.8 Hz, 3H), 1.27–1.40 (m, 6H), 1.46 (m, 2H), 1.66 (m, 2H), 2.38 (s, 3H), 2.88 (t, J=7.9 Hz, 2H), 4.58 (br s, 1H), 7.17 (br t, J=7.8 Hz, 1H), 7.33 (s, 1H), 7.37 (br t, J=7.8 Hz, 1H), 7.42 (d, J=8.0 Hz, 1H), 7.75 (br s, 1H), 7.93 (d, J=7.8 Hz, 1H); ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ=11.98 (CH_3), 14.12 (CH_3), 22.68 (CH_2), 28.78 (CH_2), 29.32 (CH_2), 29.53 (CH_2), 30.00 (CH_2), 31.86 (CH_2), 102.96 (CH), 110.62 (CH), 118.89 (CH), 120.06 (CH), 120.79 (C), 121.37 (C), 123.66 (C), 124.12 (C), 125.24 (CH), 133.97 (C), 139.75 (C), 148.09 (C); MS (90°C): m/z (%)=295 (M^+, 100), 210 (55), 197 (4), 180 (5), 167 (6); HRMS: calcd for $C_{20}H_{25}NO$ (M^+): 295.1936, found: 295.1928.

1.2. *O*-Methylcarazostatin (1-heptyl-3-methoxy-2-methyl-9*H*-carbazole)

1.2.1. By *O*-methylation of carazostatin. A mixture of carazostatin (12.3 mg, 41.6 μmol), potassium carbonate (115 mg, 0.832 mmol), and iodomethane (2.37 g, 16.7 mmol, 1.04 mL) in acetone (5 mL) was heated under

reflux for 1 d. The solvent was removed in vacuo and the residue was dissolved in diethyl ether (10 mL). The suspension was filtered over a short path of silica gel/Celite, which was subsequently washed with diethyl ether. Evaporation of the solvent in vacuo and flash chromatography (hexane/EtOAc, 7:1) of the residue on silica gel afforded *O*-methylcarazostatin as a colorless solid, which was recrystallized from hexane/dichloromethane to obtain colorless needles, yield: 11.5 mg (89%), mp 98–101°C (hexane/CH_2Cl_2) (Ref. 7b 94–95°C). UV (MeOH): λ=217, 233, 252, 263, 293 (sh), 301, 335, 350 nm; IR (drift): $\tilde{\nu}$=3424, 2923, 2855, 1611, 1583, 1494, 1452, 1426, 1307, 1269, 1256, 1225, 1207, 1161, 1147, 1125, 1113, 1099, 830, 769, 750, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=0.88 (t, J=6.8 Hz, 3H), 1.26–1.39 (m, 6H), 1.45 (m, 2H), 1.65 (m, 2H), 2.35 (s, 3H), 2.87 (t, J=7.9 Hz, 2H), 3.94 (s, 3H), 7.18 (dt, J=0.9, 7.8 Hz, 1H), 7.35 (dt, J=1.1, 8.1 Hz, 1H), 7.37 (s, 1H), 7.42 (d, J=8.1 Hz, 1H), 7.77 (br s, 1H), 7.99 (d, J=7.8 Hz, 1H); ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ=12.04 (CH_3), 14.13 (CH_3), 22.69 (CH_2), 28.79 (CH_2), 29.33 (CH_2), 29.52 (CH_2), 30.03 (CH_2), 31.88 (CH_2), 56.14 (CH_3), 98.92 (CH), 110.65 (CH), 118.87 (CH), 119.83 (CH), 120.30 (C), 123.75 (C), 124.09 (C), 124.17 (C), 124.93 (CH), 133.68 (C), 139.52 (C), 152.68 (C); MS (60°C): *m/z* (%)=309 (M^+, 100), 294 (4), 224 (21), 210 (6), 180 (7); HRMS: calcd for $C_{21}H_{27}NO$ (M^+): 309.2093, found: 309.2080.

1.2.2. Via the iron-mediated arylamine cyclization of complex 15. Over a period of 30 min, four portions of ferricenium hexafluorophosphate (4×18 mg, 54.4 μmol) were added at room temperature to a solution of the iron complex **15** (99 mg, 0.218 mmol) in dichloromethane (60 mL). After a reaction time of 60 min, sodium carbonate (237 mg, 2.24 mmol) was added. Additional oxidizing reagent (6×72 mg, 0.218 mmol) was added after a reaction time of 65, 80, 100, 130, 170, and 200 min. After a total reaction time of 24 h the suspension was filtered over a short path of silica gel/Celite, which was subsequently washed with ethyl acetate. The solvent was evaporated and ferrocene was removed in vacuo by sublimation. The crude product (69 mg of a mixture of *O*-methylcarazostatin and the iron complex **17**) was dissolved in acetone (8 mL), trimethylamine *N*-oxide dihydrate (60 mg, 0.540 mmol) was added, and the reaction mixture was stirred at room temperature for 1 d. Filtration of the reaction mixture over a short path of silica gel/Celite with ethyl acetate, evaporation of the solvent in vacuo, and flash chromatography (hexane/EtOAc, 6:1) of the residue on silica gel afforded as the less polar fraction, *O*-methylcarazostatin (yield: 35.6 mg, 53%) and as more polar fraction carazostatin (yield: 21 mg, 33%), both as colorless solids. Carazostatin was transformed to *O*-methylcarazostatin (19.6 mg, 89% yield) in 1 step as described above. Total yield of *O*-methylcarazostatin: 55.2 mg (82% based on **15**). Spectral data, see above.

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