First enantioselective total synthesis of neocarazostatin B, determination of its absolute configuration and transformation into carquinostatin A†‡

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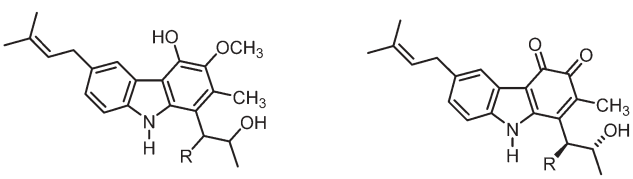
The first enantioselective total synthesis of neocarazostatin B, the determination of its absolute configuration and transformation into carquinostatin A are described.

It is known that oxygen-derived free radicals play a key role in the initiation of a variety of diseases like cerebral and myocardial ischemia,[1] arteriosclerosis, inflammation, rheumatism and cancer.[2] Antioxidants, acting as free radical scavengers, are substances that can protect cells from damage caused by free radicals. Therefore, free radical scavengers are extensively investigated as potential drugs for the treatment of such diseases.[1–3] In the course of a screening program directed towards the isolation of novel free radical scavenging substances from microorganisms, Kato *et al.* obtained in 1991 the neocarazostatins A, B and C (**1–3**) from the culture of *Streptomyces* sp. strain GP 38 (Scheme 1).[4] The neocarazostatins exhibited a strong inhibitory effect on the free radical induced lipid peroxidation in rat brain homogenate. Their IC_{50} values for inhibition of lipid peroxidation were much lower than those of the free radical scavenging brain protective agent flunarizine[5] and of the antioxidant butylhydroxytoluene (BHT).[4] The carquinostatins A (**4**) and B (**5**), isolated first by Seto *et al.* in 1993 from *Streptomyces exfoliatus* 2419-SVT2, contain an *ortho*-quinone moiety and were also shown to represent efficient antioxidants.[6–9] Similarly strong free radical scavenging activity was found for the carbazoquinocins A–F, structurally related carbazole-3,4-quinone alkaloids lacking the prenyl group in the 6-position.[10] Over the past decade, several research groups have developed diverse synthetic approaches to these natural products due to their pharmacological potential.[11–16]



1 Neocarazostatin A R = OH
2 Neocarazostatin B R = H
3 Neocarazostatin C R = OCH_3

4 Carquinostatin A R = H
5 Carquinostatin B R = OH

Scheme 1 Chiral 3,4-dioxygenated carbazole alkaloids.

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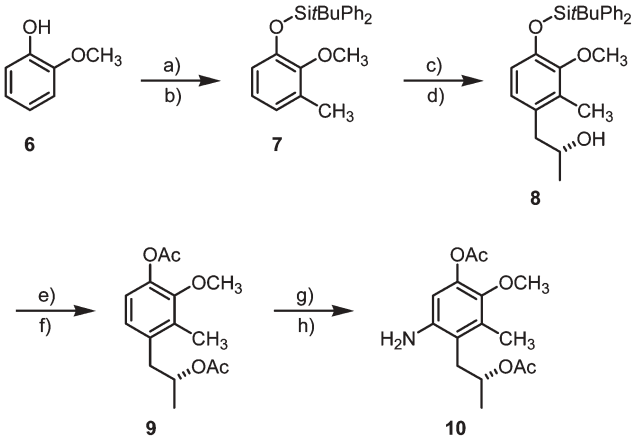
The structures of the carbazole alkaloids **1–5** have been assigned based on their spectroscopic data. For carquinostatin A (**4**), the absolute configuration has been determined by transformation into the corresponding Mosher ester.[6] However, the absolute configuration of the neocarazostatins has remained unknown.[4] In the present investigation we describe the first enantioselective total synthesis of neocarazostatin B, the determination of its absolute configuration and the transformation into carquinostatin A. By analogy with carquinostatin A (**4**) we assumed for neocarazostatin B (**2**) an *R* configuration of the stereogenic center. For a highly convergent approach by using our iron-mediated construction of the carbazole framework we prepared a fully functionalized chiral arylamine building block (Scheme 2).

Protection of guaiacol (**6**) as *tert*-butyldiphenylsilyl ether,[17] subsequent regioselective metalation and methylation afforded the 2,3-dioxygenated toluene **7**. For an *R* configuration of neocarazostatin B (**2**), the chiral side chain was planned to derive from (*R*)-propene oxide. Hydrolytic kinetic resolution of racemic propene oxide using the (*R*,*R*)-(salen)cobalt complex reported by Jacobsen provided (*R*)-propene oxide in 99% ee.[18] Regioselective bromination of **7** followed by halogen–metal exchange and ring opening of the (*R*)-propene oxide by the intermediate aryllithium provided the (2*R*)-2-hydroxypropylarene **8** ($[\alpha]_D^{20} = -13.6$ ($c = 1$, $CHCl_3$)). Removal of the silyl protecting group using tetra-*n*-butylammonium fluoride and subsequent acetylation led to the



Scheme 2 Synthesis of the (*R*)-arylamine **10**. *Reagents and conditions*: (a) *t*$BuPh_2SiCl$, Et_3N, reflux, 2 d, 98%; (b) 1. *n*BuLi, TMEDA, Et_2O, 25 °C; 2. MeI, −78 °C to 25 °C, 96%; (c) NBS, MeCN, 25 °C, 100%; (d) *t*BuLi, THF, (*R*)-(+)-propene oxide, −78 °C, 91%; (e) TBAF, THF/H_2O, 25 °C, 100%; (f) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 25 °C, 98%; (g) fuming HNO_3/HOAc, 25 °C, 77%; (h) H_2, Pd/C, MeOH, 25 °C, 100%.

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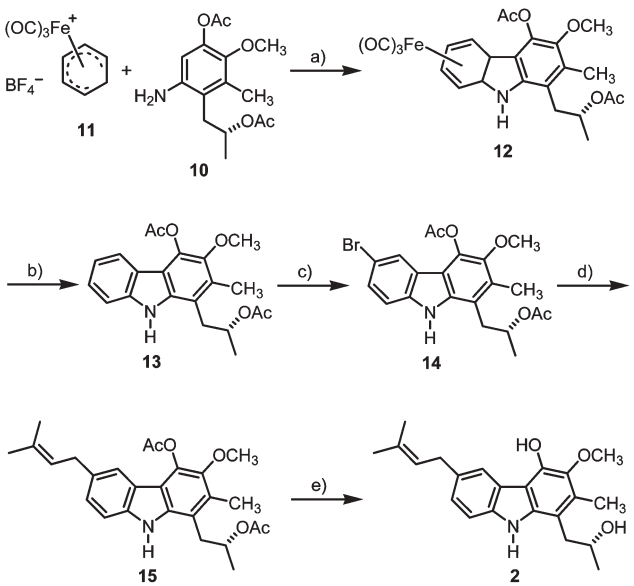
(*R*)-diacetate **9** ($[\alpha]_D^{20} = -35.3$ ($c = 1$, $CHCl_3$)). Regioselective nitration and catalytic hydrogenation provided the (*R*)-arylamine **10** ($[\alpha]_D^{20} = -5.2$ ($c = 0.5$, $CHCl_3$)) in eight steps and 65% overall yield.

A highly convergent construction of the carbazole framework has been achieved using our iron-mediated synthesis.[19] Stirring of an acetonitrile solution of the iron complex salt **11** and the arylamine **10** for 7 days in the air led to the tricarbonyl(η^4-4a,9a-dihydrocarbazole)iron complex **12** (Scheme 3).§ The reaction proceeds *via* an electrophilic aromatic substitution generating the C–C bond followed by an iron-mediated oxidative cyclization using air as an oxidizing agent under protic conditions.

The aromatization with concomitant demetalation of complex **12** to the carbazole **13** is readily effected using *N*-bromosuccinimide under basic reaction conditions.[20] Using the same reagent under acidic reaction conditions electrophilic bromination provided the 6-bromocarbazole **14**.§ At this stage of our synthesis we confirmed the structure of the 6-bromocarbazole **14** by an X-ray analysis (Fig. 1).¶ The absolute configuration of the stereogenic center in the chiral side chain at C-1 was unambiguously shown to be *R* using the anomalous dispersion (Flack parameter: $\chi = -0.002(9)$).[21] Regioselective introduction of the terpenoid side chain at C-6 by reaction of the 6-bromocarbazole **14** with the dimeric π-prenylnickel bromide complex, which is prepared *in situ* from prenyl bromide and tetracarbonylnickel(0),[22] led to di(*O*-acetyl)neocarazostatin B **15** in 64% yield along with some hydrodebromination product (carbazole **13**). Finally, cleavage of both acetyl groups by treatment with lithium aluminium hydride provided (*R*)-(−)-neocarazostatin B (**2**).§ A sample of compound **2** which was proven to be highly pure by elemental analysis exhibited a specific rotation of $[\alpha]_D^{25} = -16$ ($c = 0.1$, MeOH). The value reported for the natural product is: $[\alpha]_D^{25} = -24$ ($c = 0.1$, MeOH).[4] We found that the value observed



Scheme 3 Enantioselective synthesis of (*R*)-(−)-neocarazostatin B (**2**). *Reagents and conditions*: a) MeCN, air, 25 °C, 7 d, 68%; b) 2 equiv. NBS, 5 equiv. Na_2CO_3, MeCN, 25 °C, 100%; c) 1.02 equiv. NBS, cat. HBr, MeCN, 25 °C, 88%; d) 1. 2 equiv. prenyl bromide, 6 equiv. $Ni(CO)_4$, C_6H_6, 60 °C; 2. 1 equiv. **14**, DMF, 65 °C, 16 h, 66% **15** and 27% **13**; e) 3 equiv. $LiAlH_4$, Et_2O, 25 °C, 45 min, 92%.

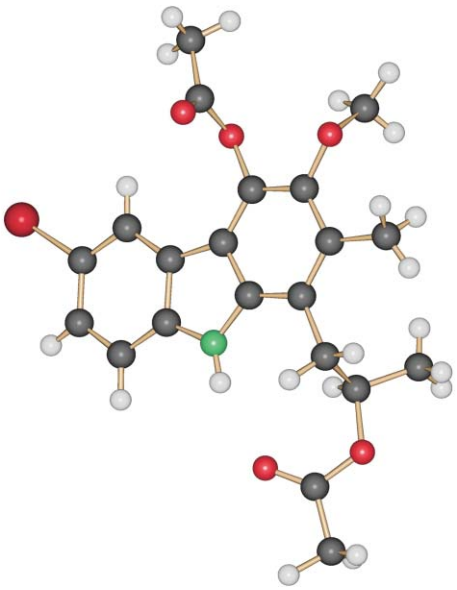
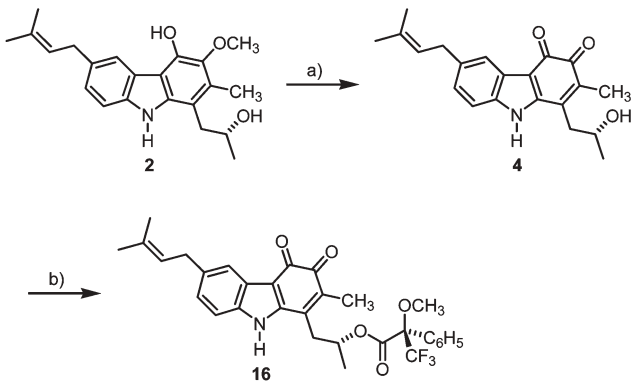


Fig. 1 Molecular structure of the 6-bromocarbazole **14** in the crystal.

for the specific rotation of a solution of (*R*)-(−)-neocarazostatin B (**2**) in methanol is increased by oxidation. After exposing the solution to air for 2 days the specific rotation was $[\alpha]_D^{25} = -22$ ($c = 0.1$, MeOH). Three days of air exposure prevented further measurement of optical rotation due to strong visual absorption. Carquinostatin A (**4**) could be detected in the mixture of products being formed. Although the reaction was very sluggish, this transformation may be of biomimetic relevance.

A clean and smooth conversion of (*R*)-(−)-neocarazostatin B (**2**) to carquinostatin A (**4**) was achieved by oxidation using cerium(IV) ammonium nitrate (Scheme 4).§ It was known from the isolation of carquinostatin A (**4**) that the optical rotation could not be determined due to the strong visual absorption.[6] Finally, in order to demonstrate the identical absolute configuration of (*R*)-(−)-neocarazostatin B (**2**) and carquinostatin A (**4**), a sample of compound **4**, obtained by CAN oxidation of **2**, was transformed to the (*R*,*R*)-Mosher ester **16** by reaction with (*S*)-(+)-MTPA chloride.[23] This product proved to be identical with the (*R*,*R*)-Mosher ester obtained by Seto from natural carquinostatin A (**4**).[6] Doping of the pure isomer **16** with 1% of the



Scheme 4 Transformation of (*R*)-(−)-neocarazostatin B (**2**) into carquinostatin A (**4**) and the (*R*,*R*)-Mosher ester **16**. *Reagents and conditions*: a) 3 equiv. CAN, $MeCN/H_2O$, 0 °C, 2 h, 92%; b) (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl (MTPA) chloride, pyridine, $CHCl_3$, 25 °C.

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diastereoisomeric (*R*)-Mosher esters obtained from racemic carquinostatin A[12b,d] and comparison of the corresponding 500 MHz ^{1}H NMR spectra confirmed an enantiomeric purity of > 99% ee for our synthetic carquinostatin A (**4**) and, hence, for (*R*)-(−)-neocarazostatin B (**2**).

In conclusion, using (*R*)-propene oxide as chiral building block, we have developed a highly efficient enantioselective route to (*R*)-(−)-neocarazostatin B (**2**) (five steps and 36% overall yield based on the iron complex salt **11**). The absolute configuration at the stereogenic center of **2** was unequivocally determined as *R* by an X-ray crystal structure determination of **14**, a comparison of the values for the specific rotation, and further transformation into carquinostatin A (**4**) and its known (*R*)-Mosher ester **16**.

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Notes and references

§ Selected physical data for the carbazole derivatives **12–15**, (*R*)-(−)-neocarazostatin B (**2**) and carquinostatin A (**4**): **12**: Yellow solid, m.p. 58–59 °C; $[\alpha]_D^{20} = -8.8$ (c = 0.25, $CHCl_3$); elemental analysis (%) calcd for $C_{24}H_{25}FeNO_8$: C 56.38, H 4.93, N 2.74; found: C 56.19, H 5.02, N 2.56. **13**: Viscous oil; $[\alpha]_D^{20} = -103.6$ (c = 0.5, $CHCl_3$); ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 12.91 (CH_3), 19.43 (CH_3), 20.88 (CH_3), 21.49 (CH_3), 35.14 (CH_2), 61.23 (CH_3), 71.82 (CH), 111.02 (CH), 114.25 (C), 116.09 (C), 119.24 (CH), 121.38 (CH, C), 125.66 (CH), 128.40 (C), 137.09 (C), 137.18 (C), 139.96 (C), 143.37 (C), 168.90 (C=O), 172.64 (C=O). **14**: Colorless crystals, m.p. 131.5–132.5 °C; $[\alpha]_D^{20} = -100.0$ (c = 0.5, $CHCl_3$); ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 12.97 (CH_3), 19.45 (CH_3), 20.89 (CH_3), 21.49 (CH_3), 35.13 (CH_2), 61.22 (CH_3), 71.82 (CH), 111.80 (C), 112.45 (CH), 113.45 (C), 116.37 (C), 123.11 (C), 124.02 (CH), 128.36 (CH), 129.38 (C), 137.12 (C), 137.55 (C), 138.55 (C), 143.63 (C), 168.84 (C=O), 172.81 (C=O); elemental analysis (%) calcd for $C_{21}H_{22}BrNO_5$: C 56.26, H 4.95, N 3.12; found: C 56.00, H 4.99, N 2.95. **15**: Viscous oil; $[\alpha]_D^{20} = -81.1$ (c = 0.45, $CHCl_3$); $[\alpha]_D^{20} = -15.0$ (c = 0.1, MeOH); ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 12.91 (CH_3), 17.86 (CH_3), 19.45 (CH_3), 20.80 (CH_3), 21.50 (CH_3), 25.84 (CH_3), 34.30 (CH_2), 35.16 (CH_2), 61.25 (CH_3), 71.81 (CH), 110.78 (CH), 114.20 (C), 116.02 (C), 120.45 (CH), 121.59 (C), 124.11 (CH), 126.46 (CH), 128.15 (C), 132.05 (C), 132.43 (C), 137.01 (C), 137.48 (C), 138.42 (C), 143.25 (C), 168.86 (C=O), 172.57 (C=O). (*R*)-(−)-Neocarazostatin B (**2**): Colorless crystals, m.p. 107–108 °C; $[\alpha]_D^{25} = -16.0$ (c = 0.1, MeOH); UV (MeOH): λ = 228, 248, 272 (sh), 291, 332, 344 nm; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.34 (d, J = 6.2 Hz, 3 H), 1.75 (s, 3 H), 1.78 (s, 3 H), 2.39 (s, 3 H), 2.92 (dd, J = 14.8, 8.4 Hz, 1 H), 3.01 (dd, J = 14.8, 3.5 Hz, 1 H), 3.50 (d, J = 7.3 Hz, 2 H), 3.81 (s, 3 H), 4.16 (m, 1 H), 5.43 (br t, J = 7.3 Hz, 1 H), 6.13 (br s, 1 H), 7.17 (dd, J = 8.2, 1.6 Hz, 1 H), 7.28 (d, J = 8.2 Hz, 1 H), 8.03 (br s, 1 H), 8.40 (br s, 1 H); ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 12.74 (CH_3), 17.90 (CH_3), 23.36 (CH_3), 25.81 (CH_3), 34.50 (CH_2), 37.68 (CH_2), 61.43 (CH_3), 69.00 (CH), 109.81 (C), 110.16 (CH), 110.88 (C), 121.86 (CH), 123.33 (C), 124.57 (CH), 125.49 (CH), 127.14 (C), 131.57 (C), 132.99 (C), 138.10 (C), 138.33 (C), 138.54 (C), 142.73 (C); MS (EI): m/z (%) = 353 (M^+, 100), 338 (19), 308 (84), 294 (12); elemental analysis (%) calcd for $C_{22}H_{27}NO_3$: C 74.76, H 7.70, N 3.96; found: C 74.88, H 7.83, N 3.75. Carquinostatin A (**4**): Black crystals, m.p. 179–180 °C; UV (MeOH): λ = 231, 268, 426 nm; ^{13}C NMR and DEPT (125 MHz, DMSO-d_6): δ = 12.18 (CH_3), 17.71 (CH_3), 23.75 (CH_3), 25.53 (CH_3), 33.87 (CH_2), 37.69 (CH_2), 65.88 (CH), 110.67 (C), 113.23 (CH), 119.25 (CH), 123.75 (CH), 124.92 (CH), 126.04 (C), 131.49 (C), 134.50 (C), 135.55 (C), 137.40 (C), 139.85 (C), 146.31 (C), 172.69 (C=O), 183.74 (C=O); MS (EI): m/z (%) = 339 (M^+ + 2, 100), 337 (M^+, 19), 335 (29), 320 (12), 319 (15), 294 (93).

¶ Crystal data for **14**: $C_{21}H_{22}BrNO_5$, crystal size: 1.2 × 1.2 × 1.0 mm^3, M_r = 448.31 g mol^{-1}, monoclinic, space group $P2_1$, λ = 0.71073 Å, a = 11.2163(8), b = 8.5454(8), c = 11.5523(12) Å, β = 112.480(6)°, V = 1023.1(2) Å^3, Z = 2, ρ_{calcd} = 1.455 g cm^{-3}, μ = 2.040 mm^{-1}, T = 293(2) K, θ range = 1.91–27.48°; reflections collected: 2513, independent: 2237 (R_{int} = 0.0169). The structure was solved by direct methods and refined by full-matrix least-squares on F^2; R_1 = 0.0279, wR_2 = 0.0710 [$I > 2\sigma(I)$]; absolute structure (Flack parameter)[21]: χ = −0.002(9), maximal residual electron density 0.406 e Å^{-3}. All hydrogen atoms were determined by Fourier difference calculation and refined isotropically. CCDC 289105. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b515674b

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