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First Total Synthesis of the Free Radical Scavenger (±)-Neocarazostatin B *via* Iron- and Nickel-Mediated Coupling Reactions

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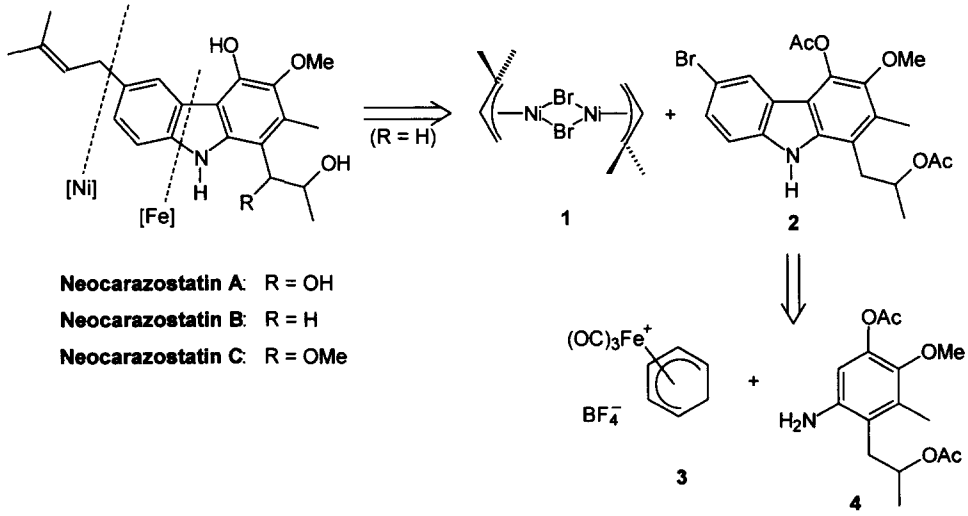
Abstract: The first total synthesis of the naturally occurring free radical scavenger (±)-neocarazostatin B is described by using a one-pot iron-mediated construction of the carbazole skeleton and a nickel-mediated prenylation as the key-steps.

A broad range of structurally diverse carbazole alkaloids with useful biological activities have been isolated from different natural sources over the past 20 years and prompted several groups to develop novel strategies for their synthesis.[2] Many of the alkaloids isolated from streptomyces exhibit antibiotic, antifungal, or antioxidant and neuronal cell protecting activities and contain a 3,4-dioxygenated carbazole framework. On their screening for free radical scavenging substances from microorganisms Kato *et al.* isolated in 1991 the neocarazostatins A, B, and C from the culture of *Streptomyces* sp. strain GP 38. The neocarazostatins were shown to exhibit strong inhibitory activities against lipid peroxidation induced by free radicals.[3] To our knowledge the relative and absolute stereochemistry of the neocarazostatins has not been determined yet. However, by analogy with carquinostatin A[4] and lavanduquinocin[5] an *R* configuration at the stereogenic center in the side chain of neocarazostatin B can be assumed. A total synthesis of a member of the neocarazostatin family has not been reported so far. We describe herein the first synthesis of (±)-neocarazostatin B.



Scheme 1

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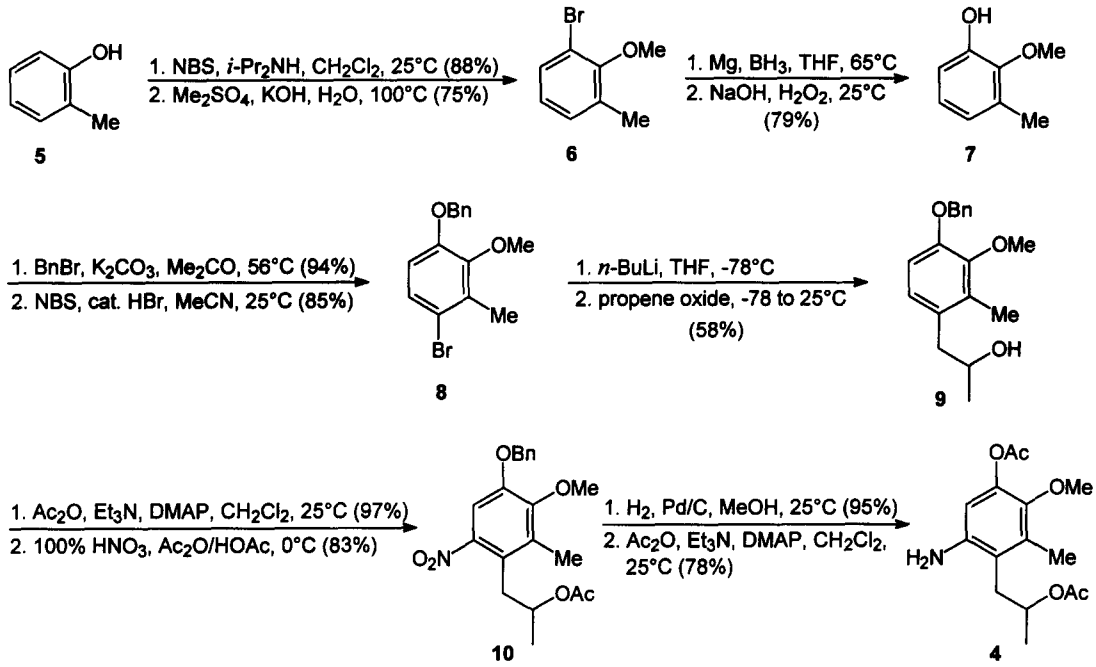
We devised a highly convergent synthesis of 3,4-dioxygenated carbazole alkaloids based on a consecutive iron-mediated C–C and C–N bond formation,[6] which has been applied to the total synthesis of the antibiotic carbazomycins A-E, G, and H.[7] The cyclization to the carbazole can alternatively be achieved by oxidation in the air.[8] This method was used for a one-pot construction of the carbazole framework and applied to the total syntheses of carbazoquinocin C,[9] (±)-carquinostatin A,[10] and (±)-lavanduquinocin.[1] The substituted allyl groups of the two latter alkaloids were introduced by a nickel-mediated coupling[11] with the corresponding bromocarbazole.[1,10] For the total synthesis of (±)-neocarazostatin B we envisaged a prenylation of the bromocarbazole **2** by reaction with the dimeric π-prenylnickel bromide complex **1**[11] as depicted in Scheme 1. The carbazole should be accessible by coupling of the iron complex salt **3** and the corresponding arylamine **4**. In contrast to the synthesis of the structurally related (±)-carquinostatin A, an arylamine differently protected at the two hydroxy groups was required for the synthesis of (±)-neocarazostatin B (Scheme 2).

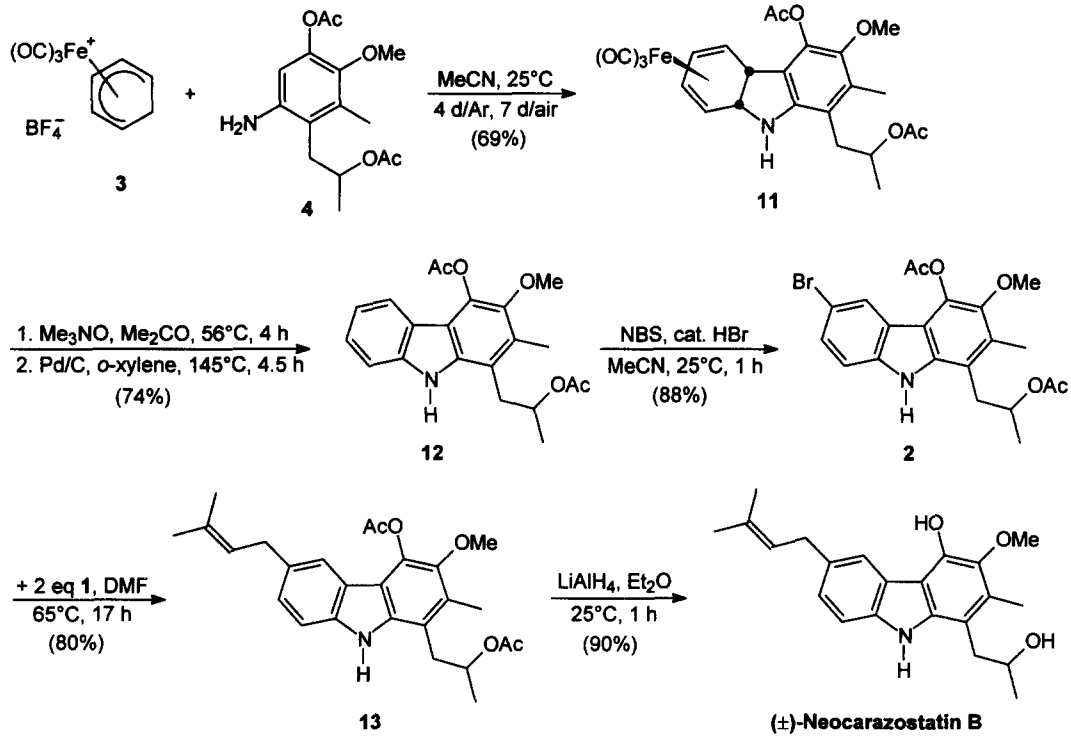


Scheme 2

The *ortho*-hydroxy selective diisopropylamine-catalyzed bromination[12] of *o*-cresol **5** with *N*-bromosuccinimide in dichloromethane and subsequent *O*-methylation with dimethyl sulfate provided the *o*-bromoanisole **6**. Treatment of **6** with magnesium in the presence of diborane followed by basic hydrogen peroxide[13] gave the *o*-hydroxyanisole **7**. Etherification of **7** with benzyl bromide and potassium carbonate in refluxing acetone followed by regioselective bromination with *N*-bromosuccinimide provided the bromo derivative **8**, which on halogen-metal exchange with *n*-butyllithium in THF and subsequent reaction of the intermediate aryl lithium compound with (±)-propene oxide afforded the carbinol **9**. The *O*-acetylation of **9** and subsequent regioselective nitration led to the nitro aryl derivative **10**. Catalytic hydrogenation of **10** with concomitant cleavage of the benzyl ether followed by a chemoselective *O*-acetylation of the aminophenol provided the arylamine **4**.

Using the route described in Scheme 2 the required fully functionalized building block **4** is available in 10 steps and 14% overall yield based on *o*-cresol **5**.

The one-pot C–C and C–N bond formation between the iron complex salt **3** and the arylamine **4** was realized by using the optimized conditions used for previous syntheses of carbazole alkaloids.[1,9,10] Reaction of **3** with two equivalents of **4** to the exclusion of light for 4 d under inert gas atmosphere and subsequently 7 d in the air afforded the tricarbonyl(η^4-4a,9a-dihydro-9*H*-carbazole)iron complex **11** in 69% yield as a 1:1 mixture of diastereoisomers. The ready transformation of these tricarbonyliron-complexed dihydrocarbazoles into the aromatized 9*H*-carbazoles was previously demonstrated.[14] Demetalation of complex **11** using trimethylamine *N*-oxide in acetone at reflux[15] and subsequent aromatization by catalytic dehydrogenation with 10% palladium on activated carbon in boiling *o*-xylene provided the carbazole **12** in 74% yield. Regioselective bromination by electrophilic substitution of **12** with *N*-bromosuccinimide in the presence of catalytic amounts of hydrogen bromide in acetonitrile at room temperature provided the 6-bromocarbazole **2** in 88% yield. The nickel-mediated prenylation of **2** by reaction with two equivalents of the dimeric π-prenylnickel bromide complex **1**[11] in dry and degassed *N*,*N*-dimethylformamide at elevated temperature led to the 6-prenylcarbazole **13** in 80% yield. Cleavage of the esters using lithium aluminum hydride provided in 90% yield (±)-neocarazostatin B.



Scheme 3

The present synthesis provides (±)-neocarazostatin B in 6 steps and 32% overall yield based on **3**. The spectral data (UV, IR, ^{1}H-NMR, ^{13}C-NMR, and MS)[16] of the synthetic (±)-neocarazostatin B are in good agreement with those reported for the natural product.[3] However, the melting point of our racemic synthetic product (m.p. 121-123°C)[16] is considerably higher than the one reported for the enantiopure natural product (m.p. 55-57°C).[3]

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16. **(±)-Neocarazostatin B**: colorless crystals, m.p. 121-123°C (*n*-hexane/EtOAc); UV (MeOH): $\lambda(\varepsilon)$ = 228 (35300), 248 (48100), 272 (sh) (11000), 291 (18100), 332 (4800), 344 (5400) nm; IR (KBr): $\tilde{\nu}$ = 3535, 3403, 3330 (br), 2967, 2916, 1617, 1503, 1458, 1409, 1309, 1107, 1006, 805 cm^{-1}; ^{1}H-NMR (500 MHz, CD_3OD): δ = 1.21 (d, J = 6.2, 3 H), 1.75 (d, J = 0.9, 3 H), 1.76 (s, 3 H), 2.38 (s, 3 H), 2.92 (dd, J = 14.2, 6.8, 1 H), 3.02 (dd, J = 14.2, 6.6, 1 H), 3.44 (d, J = 7.3, 2 H), 3.74 (s, 3 H), 4.08 (br sext., J = 6.4, 1 H), 5.40 (br t, J = 7.3, 1 H), 7.07 (dd, J = 8.2, 1.3, 1 H), 7.28 (d, J = 8.2, 1 H), 8.00 (d, J = 1.3, 1 H); ^{13}C-NMR and DEPT (125 MHz, CD_3OD): δ = 13.04 (CH_3), 17.91 (CH_3), 23.00 (CH_3), 25.97 (CH_3), 35.44 (CH_2), 38.60 (CH_2), 61.31 (CH_3), 69.03 (CH), 110.80 (CH), 111.45 (C), 111.99 (C), 122.67 (CH), 124.64 (C), 125.82 (CH), 126.04 (CH), 128.64 (C), 132.00 (C), 132.82 (C), 139.32 (C), 139.67 (2 C), 144.53 (C); MS (135°C): *m/z* (%) = 353 (M^+, 100), 338 (19), 308 (84), 294 (12), 278 (9), 240 (11); HRMS: calcd. for $C_{22}H_{27}NO_3$ (M^+): 353.1991, found: 353.1980; Anal. calcd. for $C_{22}H_{27}NO_3$: C 74.76, H 7.70, N 3.96; found: C 74.27, H 7.73, N 3.98.