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Transition metal complexes in organic synthesis. Part 58:[1] First enantioselective total synthesis of the potent neuronal cell protecting substance carquinostatin A from (*R*)-propene oxide

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Abstract

Starting from enantiopure (*R*)-propene oxide the first enantioselective total synthesis of the potent neuronal cell protecting alkaloid carquinostatin A has been accomplished by using iron- and nickel-mediated coupling reactions.
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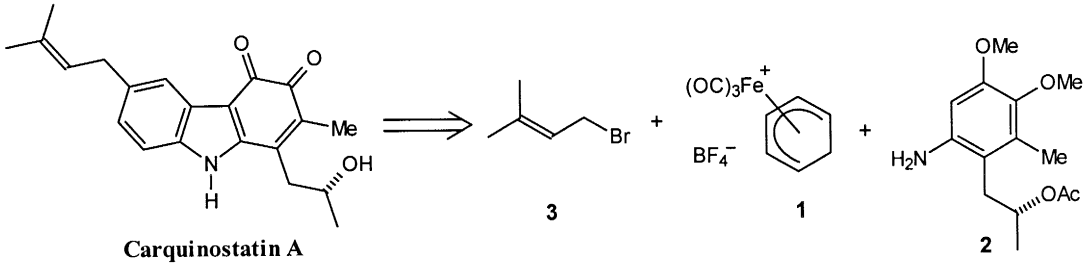
A broad range of biologically active carbazole alkaloids has been obtained from natural sources.[2] In 1993 Seto et al. isolated carquinostatin A, the first example of a carbazole-3,4-quinone alkaloid, from *Streptomyces exfoliatus* 2419-SVT2.[3] Carquinostatin A was shown to be a potent neuronal cell protecting substance which also exhibits a free radical scavenging activity. We have a continuous program directed towards the development of novel methodologies for the total synthesis of pharmacologically active carbazole alkaloids.[4] So far only two total syntheses for racemic carquinostatin A have been reported.[5] The first route used an iron-mediated oxidative coupling of cyclohexadiene with a fully substituted arylamine[5a] and the second approach proceeded via a palladium-mediated oxidative coupling of *p*-prenylaniline and an *ortho*-benzoquinone.[5b] In the present work we describe the first enantioselective total synthesis of carquinostatin A based on the iron-mediated synthesis (Scheme 1).



Scheme 1.

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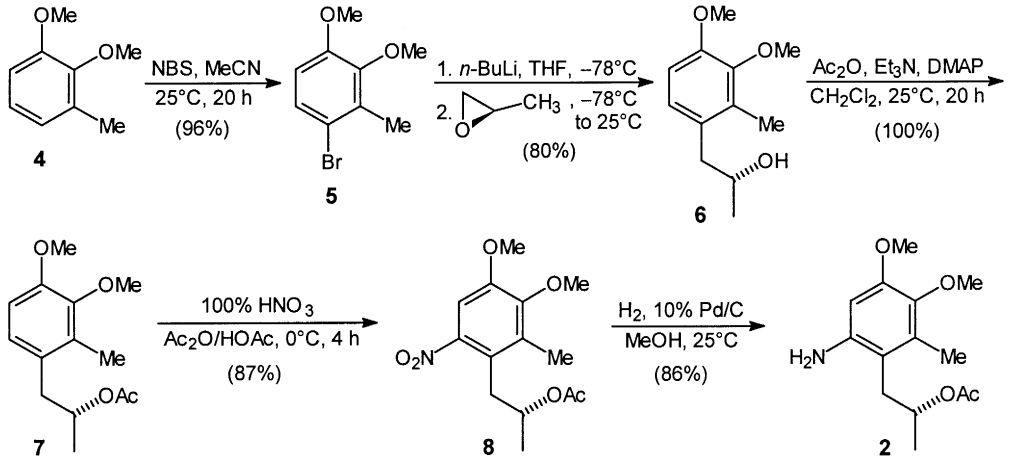
The precursors for the carbazole framework are the complex salt **1** and the enantiopure (*R*)-arylamine **2**. Introduction of the prenyl group was projected by a regioselective nickel-mediated coupling using prenyl bromide **3** at a later stage of the synthesis. The chiral side chain of the required (*R*)-arylamine **2** should derive from (*R*)-propene oxide.

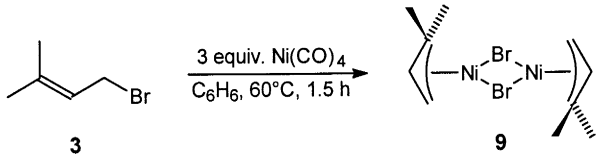
Hydrolytic kinetic resolution of racemic propene oxide using the (*R*,*R*)-(salen)cobalt(II) complex as described by Jacobsen[6] afforded the enantiopure (*R*)-propene oxide ($[\alpha]_D^{20}$=+11.96, neat). Because of contradictory assignments,[6] the absolute configuration at the stereogenic center was unambiguously confirmed by an X-ray crystal structure determination at the stage of the 6-bromocarbazole (see below).

By modification of the original procedure[7] for the regioselective bromination of 3-methylveratrole **4**, the bromo derivative **5** was prepared almost quantitatively (Scheme 2). Halogen–metal exchange using *n*-butyllithium followed by reaction with the (*R*)-propene oxide, obtained by Jacobsen's method[6] (see above), afforded the (*R*)-carbinol **6** ($[\alpha]_D^{20}$=−34.4, c=1, $CHCl_3$). Protection of **6** as the (*R*)-acetate **7** ($[\alpha]_D^{20}$=−16.5, c=1, $CHCl_3$) and subsequent regioselective nitration led to the (*R*)-nitro compound **8** ($[\alpha]_D^{20}$=+173.2, c=1, $CHCl_3$). Catalytic hydrogenation of **8** provided the (*R*)-arylamine **2** ($[\alpha]_D^{20}$=−1.7, c=1, $CHCl_3$). This route affords the (*R*)-arylamine **2** in five steps and 57% overall yield from commercial 3-methylveratrole **4**.



Scheme 2.

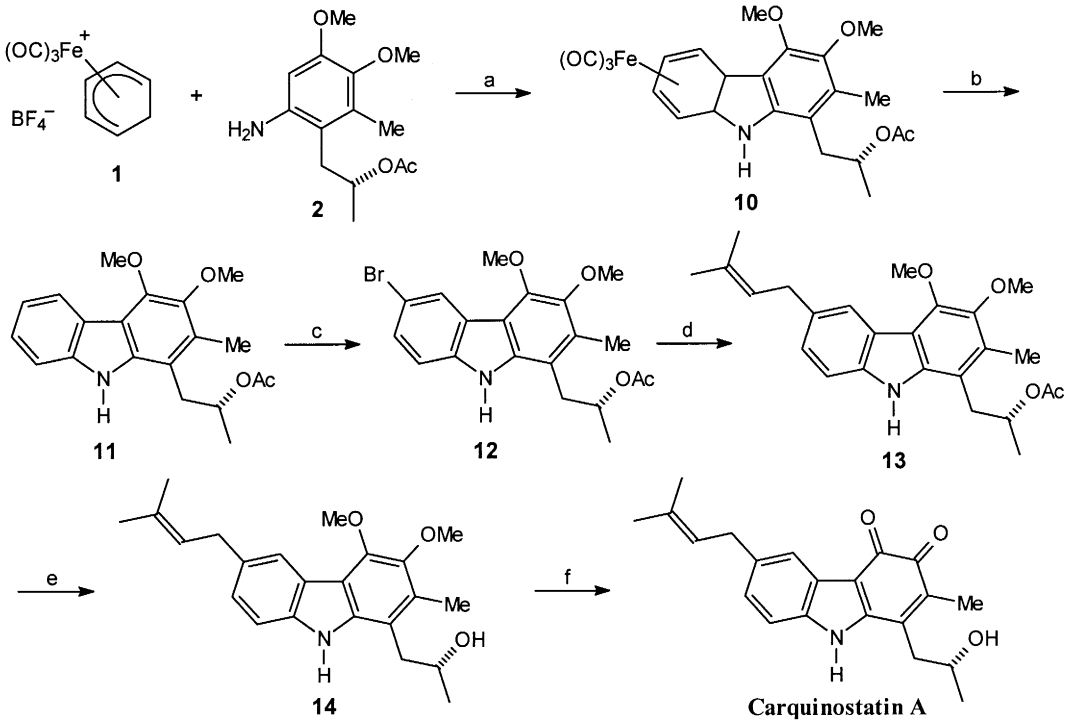
Treatment of a 6-bromocarbazole with bis[(μ-bromo)(η^3-prenyl)nickel] **9** was envisaged for the regioselective prenylation.[8] Complex **9** was prepared by reaction of prenyl bromide **3** with 3 equiv. of tetracarbonylnickel in benzene at 60°C (Scheme 3) and is used in situ.



Scheme 3.

Construction of the carbazole framework was achieved using the previously reported conditions for the oxidative coupling of the complex salt **1** with arylamines.[5a,9] Reaction of **1** with 2 equiv. of the (*R*)-arylamine **2** in acetonitrile at room temperature for 9 days in the air provided in 94% yield the tricarbonyl(η^4-4a,9a-dihydro-9*H*-carbazole)iron complex **10** ($[\alpha]_D^{20}$=−6.50, c=0.5, $CHCl_3$) (Scheme 4). Demetalation of the tricarbonyliron complex **10** with trimethylamine *N*-oxide in acetone at reflux[10] and subsequent aromatization[11] by dehydrogenation using 10% palladium on activated carbon in boiling *o*-xylene with 1-hexene for the trapping of hydrogen provided the carbazole **11** ($[\alpha]_D^{20}$=−95.3, c=1,

$CHCl_3$) in 87% yield over both steps. Regioselective bromination of the carbazole **11** by electrophilic substitution using *N*-bromosuccinimide in the presence of catalytic amounts of hydrogen bromide in acetonitrile at room temperature afforded quantitatively the 6-bromocarbazole **12** ($[\alpha]_D^{20}=-43.0$, c=0.5, $CHCl_3$). The X-ray analysis of the 6-bromocarbazole **12** (Fig. 1)[12] showed unequivocally that the absolute configuration is *R* by the anomal dispersion (Flack parameter: $\chi=-0.010(9)$).[13]



Scheme 4. Reagents and conditions: (a) MeCN, air, 25°C, 9 days (94%); (b) 1. $Me_3NO\cdot 2H_2O$ (8 equiv.), acetone, 56°C, 4 h, 2. 10% Pd/C, *o*-xylene/15 vol.-% 1-hexene, reflux, 4 h (87%, two steps); (c) NBS, HBr (cat.), MeCN, 25°C, 1 h (100%); (d) complex **9** (2 equiv.), DMF, 65°C, 15 h (94%); (e) $LiAlH_4$ (1.6 equiv.), Et_2O, 25°C, 45 min (98%); (f) CoF_3 (4 equiv.), dioxane (2 equiv.)/water (10 equiv.), 25°C, 1 h (70%)

Prenyl coupling of the 6-bromocarbazole **12** by reaction with 2 equivalents of the in situ-prepared dimeric nickel complex **9** in dry and degassed *N*,*N*-dimethylformamide at 65°C provided the 6-prenylcarbazole **13** ($[\alpha]_D^{20}=-47.2$, c=0.5, $CHCl_3$) in 94% yield (Scheme 4). Removal of the acetyl group by reduction with lithium aluminum hydride afforded almost quantitatively the carbinol **14** ($[\alpha]_D^{20}=-10.5$, c=0.5, $CHCl_3$). Recently, Nakata et al. reported the oxidative demethylation of 1,4-dimethoxybenzenes to *p*-benzoquinones using cobalt(III) fluoride.[14] We could now demonstrate that this method is also useful for the transformation of 1,2-dimethoxybenzenes to *o*-benzoquinones. Thus, oxidation of **14** with cobalt(III) fluoride provided enantiopure carquinostatin A (m.p. 179–180°C) which was in agreement with the natural product (m.p. 144–145°C)[3] in all spectral data. Conversion of the synthetic carquinostation A to the (*R*)-Mosher ester,[3,15] addition of 1% of the diastereoisomeric (*R*)-Mosher esters obtained from (±)-carquinostatin A,[5] and comparison of the corresponding ^1H NMR spectra at 500 MHz confirmed that the enantiomeric purity of our product is >99% ee.

The present synthesis provides enantiopure carquinostatin A in seven steps and 53% overall yield based on **1**.

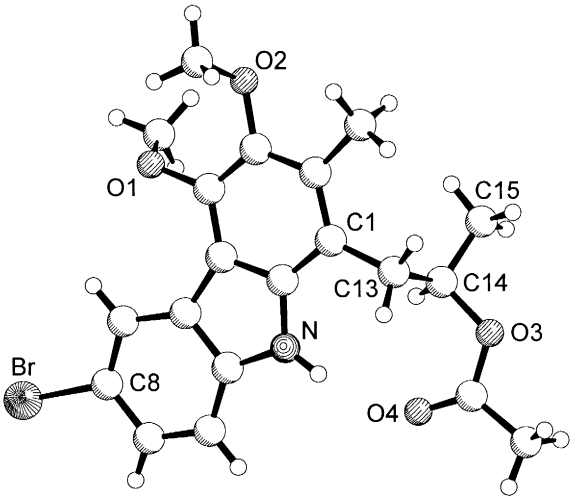


Fig. 1. Molecular structure of **12** in the crystal. Selected bond lengths (Å): C8–Br 1.906(3), C1–C13 1.501(4), C13–C14 1.523(5), C14–C15 1.500(5), C14–O3 1.470(4)

Acknowledgements

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12. Crystal data for **12**: $C_{20}H_{22}BrNO_4$; M=420.30 g/mol, crystal size: 0.8×0.7×0.3 mm, orthorhombic, space group $P2_12_12_1$, λ=0.71073 Å, a=9.4004(12) Å, b=10.1916(14) Å, c=20.098(3) Å, V=1925.5(5) Å^3, Z=4, μ=2.159 mm^{-1}, ρ_{calc}=1.450 g/cm^3, T=200(2) K, θ range: 2.03–26.12°, reflections collected: 11941, independent reflections: 3761 (R_{int}=0.0584), refinement method: full-matrix least-squares on F^2 (program: SHELXL-93), final R values [$I>2\sigma(I)$]: R_1=0.0358, wR_2=0.0891, absolute structure (Flack parameter)[13]: χ=−0.010(9), maximal residual electron density: 0.427 e/Å^3. Diffractometer: STOE IPDS area detector. Graphical representation: SCHAKAL-97. Crystallographic data (excluding structure factors) for this structure have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-137202, and may be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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