Transition Metals in Organic Synthesis, Part 96.[1] First Total Synthesis of Streptoverticillin: Unambiguous Confirmation of the Absolute Configuration

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Abstract: Using an iron-mediated construction of the carbazole framework, the first synthesis of streptoverticillin is described and the absolute configuration of the natural product is confirmed. The synthesis exploits a novel oxygen-mediated aromatization of tricarbonyliron-coordinated dihydrocarbazoles. Moreover, non-natural (*R*)-streptoverticillin is prepared for comparison.

Key words: alkaloids, carbonyl complexes, cyclization, iron, total synthesis

A range of structurally diverse carbazole alkaloids has been isolated from different natural sources over the past decades.[2] The useful biological properties of carbazole natural products have inspired the development of several novel methods for their synthesis.[3,4] The iron-mediated route provides easy access to 1-oxygenated, 3-oxygenated, and 3,4-dioxygenated carbazoles.[5,6] The 1-(2-hydroxypropyl)-substituted 3,4-dioxygenated carbazole alkaloids **1**–**4** have been obtained from microorganisms (Figure 1). A recent report described the isolation of the antifungal streptoverticillin (**1**) from the ethanol extract of *Streptoverticillium morookaense* strain SC1169.[7] It is noteworthy that an *S* configuration has been assigned to the stereogenic center of the side chain at C-1, whereas neocarazostatin B (**2**),[8] carquinostatin A (**3**),[9] and lavanduquinocin (**4**)[10] all have *R* configuration at the stereogenic center of the 2-hydroxypropyl side chain. The assignment of the absolute configuration of streptoverticillin (**1**) was based solely on comparison of the value for its optical rotation ($[\alpha]_D^{20} = +18.4$) with the value we had reported for neocarazostatin B (**2**; $[\alpha]_D^{25} = -16$) from our enantioselective synthesis.[7,8c]

Access to larger amounts of streptoverticillin (**1**) would enable a more detailed study of the biological activities and provide confirmation of its absolute configuration. Therefore, we embarked on the total synthesis of this novel natural product. Our retrosynthetic analysis of **1** led us to the iron complex salt **5** and the (*S*)-arylamine **6** (Scheme 1).

Almost quantitative access to the iron complex salt **5** was provided by the 1-azadiene-catalyzed complexation of cyclohexa-1,3-diene (**7**) with pentacarbonyliron followed by hydride abstraction of the tricarbonyliron complex **8** (Scheme 2).[11,12]

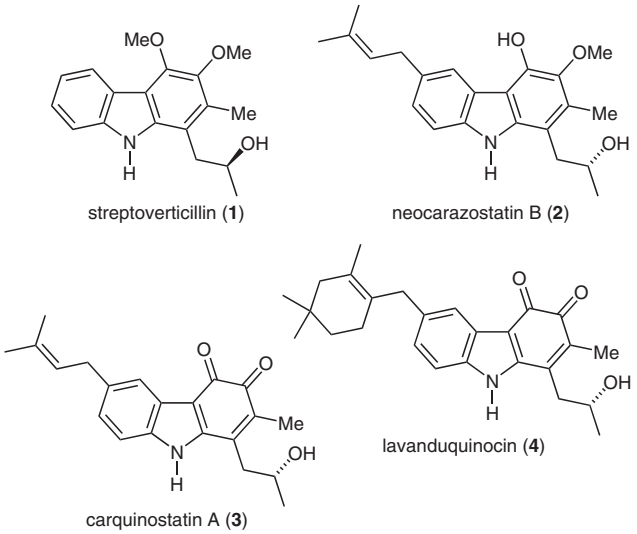
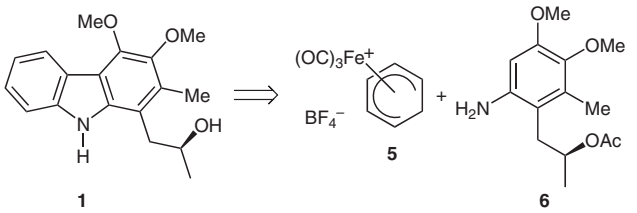
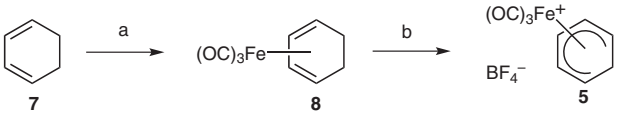


Figure 1 Naturally occurring 1-(2-hydroxypropyl)-substituted 3,4-dioxygenated carbazole alkaloids



Scheme 1 Retrosynthetic analysis of streptoverticillin (**1**)



Scheme 2 Synthesis of the complex salt **5**. *Reagents and conditions*: (a) $Fe(CO)_5$, cat. 1-(4-methoxyphenyl)-4-phenyl-1-azabutadiene, dioxane, 101 °C, 45 h, 99%; (b) Ph_3CBF_4, CH_2Cl_2, r.t., 40 min, 98%.

The synthesis of the (*S*)-arylamine **6** started from 3-methylveratrole (**9**) following the route described for the corresponding *R* enantiomer (Scheme 3).[9d,10c] Bromination of **9** to the bromoarene **10** followed by halogen–metal exchange using butyllithium and reaction with (*S*)-propene oxide (>99% ee) provided the (*S*)-carbinol **11**.

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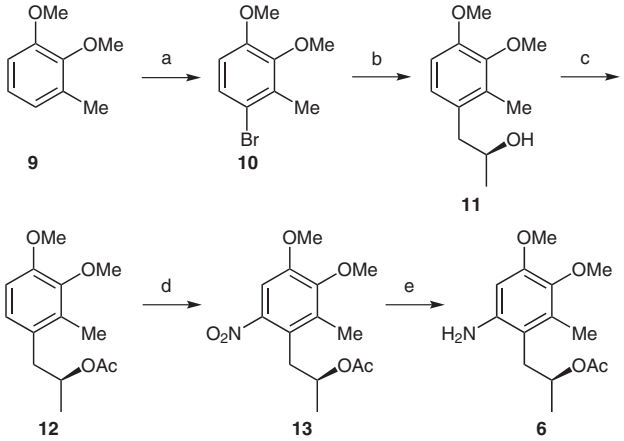
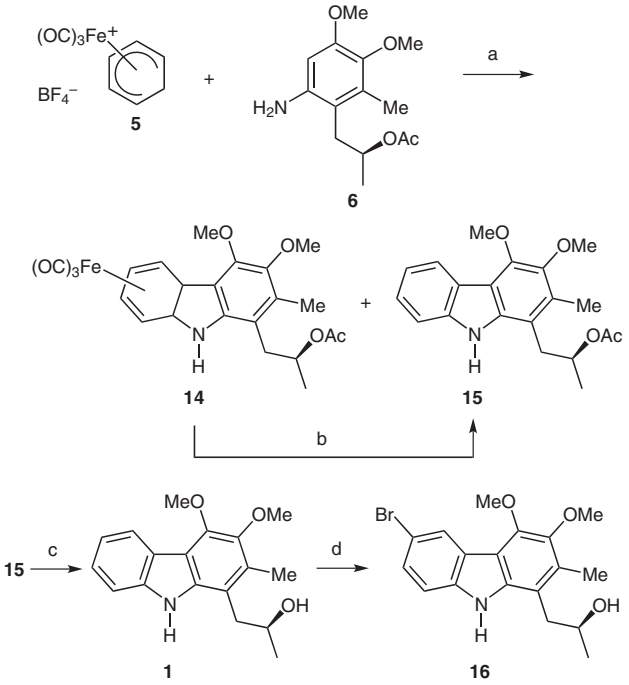
Acetylation of **11** led to the (*S*)-acetate **12**, and subsequent regioselective nitration using claycop (clay-supported copper(II) nitrate)[13] afforded (*S*)-nitroarene **13**. Catalytic hydrogenation of **13** provided (*S*)-arylamine **6** in five steps and 59% overall yield.

Construction of the carbazole framework was achieved by oxidative coupling of the complex salt **5** with (*S*)-arylamine **6**. The conditions previously applied to the synthesis of neocarazostatin B (**2**), carquinostatin A (**3**), and lavanduquinocin (**4**) (2 equiv of arylamine, MeCN, air, r.t., 7 d, exclusion of light)[8c,9c] provided 64% of the tricarbonyliron-coordinated dihydrocarbazole **14** along with 18% of the aromatized carbazole **15** (Scheme 4).



Scheme 3 Synthesis of (*S*)-arylamine **6**. *Reagents and conditions*: (a) NBS (1.05 equiv), MeCN, r.t., 27 h, 98%; (b) (1) BuLi (1.5 equiv), THF, –78 °C, 30 min; (2) (*S*)-propene oxide (3.0 equiv), –78 °C, 18 h, 79%; (c) Ac_2O (1.1 equiv), Et_3N (1.2 equiv), cat. DMAP, CH_2Cl_2, r.t., 2 h, 97%; (d) claycop, CCl_4, Ac_2O, 0 °C, 1.5 h, 84%; (e) 10% Pd/C, H_2, MeOH, r.t., 5 h, 93%.

Subsequent to the electrophilic substitution of (*S*)-arylamine **6** by reaction with the complex salt **5** and air-mediated oxidative cyclization to the tricarbonyliron-coordinated dihydrocarbazole **14**, a further air-mediated oxidation leading to the final aromatized carbazole **15** occurred. This observation indicated, for the first time, that the overall transformation of an arylamine and complex salt **5** into an aromatized carbazole may be achieved in a one-pot transformation under appropriate reaction conditions. Thus, further modification of the protocol led us to perform the coupling of complex salt **5** and (*S*)-arylamine **6** by exclusion of light, first under air and then under pure oxygen. These conditions led to almost complete aromatization of the cyclized product and gave 71% *O*-acetylstreptoverticillin (**15**) along with 12% of the dihydrocarbazole **14**. Compound **14** could be additionally converted into the aromatized carbazole **15** by using the established sequence of demetalation and dehydrogenation.[9b–d] Removal of the acetyl protecting group by treatment with lithium aluminum hydride provided streptoverticillin (**1**). The spectroscopic data for synthetic **1** are in full agreement with those reported for the natural product.[7,14] The value found for the optical rotation of



Scheme 4 Synthesis of streptoverticillin (**1**) and 6-bromostreptoverticillin (**16**). *Reagents and conditions*: (a) (1) **5** (1.0 equiv), **6** (2.0 equiv), MeCN, air, r.t., 7 d; (2) oxygen, r.t., 18 h, 12% of **14**, 71% of **15**; (b) (1) $(CH_3)_3CNO$ (8.0 equiv), acetone, 56 °C, 4 h; (2) 10% Pd/C, *o*-xylene, 145 °C, 4 h, 86%; (c) $LiAlH_4$ (1.5 equiv), Et_2O, 35 °C, 4 h, 87%; (d) NBS (1.03 equiv), CCl_4, 77 °C, 30 min, 89%.

synthetic **1** was $[\alpha]_D^{20}$ = +24.0 (*c* = 0.1, MeOH). In order to confirm the absolute configuration, 6-bromostreptoverticillin (**16**) was prepared by electrophilic bromination of **1**. An X-ray crystal structure determination of compound **16** unequivocally confirmed the *S* configuration of the stereogenic center of the side chain at C-1 by anomalous dispersion [Flack parameter: χ = –0.006(6); Figure 2].[15,16]

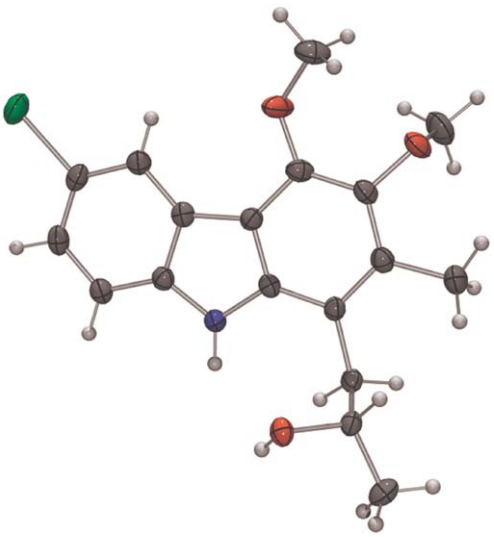
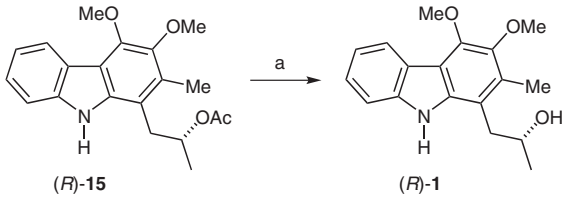


Figure 2 Molecular structure of 6-bromostreptoverticillin (**16**) in the crystal

Finally, streptoverticillin (**1**) was compared with its non-natural enantiomer (*R*)-streptoverticillin [(*R*)-**1**], which

corresponds to the natural products **2**–**4** regarding the configuration at the stereogenic center of the side chain. (*R*)-*O*-Acetylstreptoverticillin [(*R*)-**15**] has been a central intermediate in our enantioselective total syntheses of carquinostatin A (**3**) and lavanduquinocin (**4**).[9d,10c] Treatment of (*R*)-**15** with lithium aluminum hydride afforded (*R*)-streptoverticillin {(*R*)-**1**; $[\alpha]_D^{20} = -23.0$, $c = 0.1$, MeOH; Scheme 5}. The enantiomeric purity of (*R*)-**15** was >99% ee.[9d,10c] Thus, the same enantiomeric purity can be concluded for (*R*)-streptoverticillin [(*R*)-**1**] and also for our synthetic streptoverticillin (**1**).



Scheme 5 Synthesis of (*R*)-streptoverticillin [(*R*)-**1**]. *Reagents and conditions*: (a) $LiAlH_4$ (1.5 equiv), Et_2O, 35 °C, 4 h, 88%.

Comparison of the CD spectra for streptoverticillin (**1**) and (*R*)-streptoverticillin [(*R*)-**1**] confirmed that both compounds are enantiomeric by their opposite Cotton effects (Figure 3).

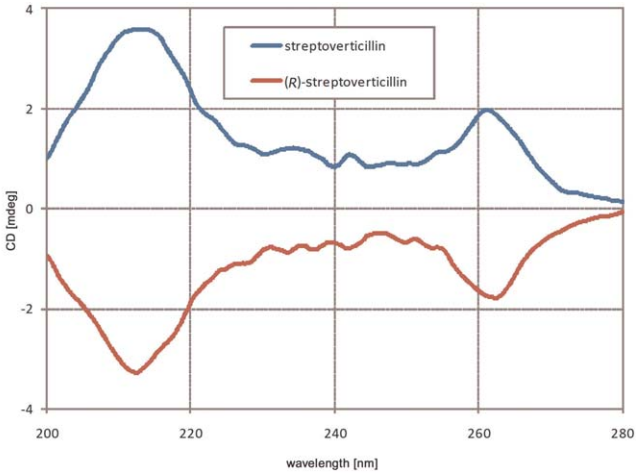


Figure 3 CD spectra of streptoverticillin (**1**) and (*R*)-streptoverticillin [(*R*)-**1**]

In conclusion, by using our iron-mediated approach, we have achieved the first synthesis of streptoverticillin (**1**) in three steps and 71% overall yield based on the complex salt **5**. The absolute configuration of the natural product, which was reported to be the *S* enantiomer, has been unambiguously confirmed by X-ray analysis of 6-bromostreptoverticillin (**16**) and comparison of the values for the optical rotation and of the CD spectra of streptoverticillin (**1**) with non-natural (*R*)-streptoverticillin [(*R*)-**1**].

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(14) Spectroscopic data for synthetic streptoverticillin (**1**): Light-yellow solid; mp 156–157 °C; $[\alpha]_D^{20}$ +24.0 (*c* = 0.1, MeOH) (Lit.[6] $[\alpha]_D^{20}$ +18.4, *c* = 0.179, MeOH); UV (MeOH): λ = 220, 242, 251, 262, 283, 293, 328, 340 nm; IR (ATR): 3475, 3293, 3055, 2955, 2926, 2850, 2823, 1608, 1500, 1451, 1398, 1348, 1318, 1304, 1271, 1225, 1194, 1166, 1148, 1086, 1060, 1001, 965, 934, 888, 872, 839, 787, 743, 702, 642 cm^{-1}; ^1H NMR (500 MHz, methanol-d_4): δ = 1.27 (d, *J* = 6.2 Hz, 3 H), 2.45 (s, 3 H), 3.04 (dd, *J* = 14.1, 6.6 Hz, 1 H), 3.13 (dd, *J* = 14.1, 6.9 Hz, 1 H), 3.90 (s, 3 H), 4.10 (s, 3 H), 4.15 (sext, *J* = 6.4 Hz, 1 H), 7.14 (t, *J* = 7.8 Hz, 1 H), 7.35 (t, *J* = 8.1 Hz, 1 H), 7.47 (d, *J* = 8.1 Hz, 1 H), 8.16 (d, *J* = 7.8 Hz, 1 H), 10.30 (br s, 1 H); ^{13}C NMR and DEPT (75 MHz, methanol-d_4): δ = 13.32 (CH_3), 23.42 (CH_3), 39.19 (CH_2), 61.07 (CH_3), 61.57 (CH_3), 69.17 (CH), 111.79 (CH), 115.90 (C), 117.36 (C), 119.93 (CH), 123.39 (CH), 123.76 (C), 126.16 (CH), 130.30 (C), 139.14 (C), 141.84 (C), 145.50 (C), 147.80 (C); MS (EI): *m*/*z* (%) = 299 (71) [M^+], 284 (25), 254 (100), 240 (7), 224 (8), 210 (10); HRMS: *m*/*z* calcd for $C_{18}H_{21}NO_3$: 299.1521; found: 299.1518.

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(16) Crystal data for 6-bromostreptoverticillin (**16**): $C_{18}H_{20}BrNO_3$; crystal size: 0.49 × 0.11 × 0.11 mm^3; M = 378.26 g mol^{-1}; monoclinic; space group: $P2_1$; λ = 0.71073 Å; *a* = 12.8825 (10), *b* = 4.8516 (4), *c* = 13.7636 (11) Å, β = 108.909 (4)°; V = 813.81 (11) $Å^3$; Z = 2; ρ_c = 1.544 g cm^{-3}; μ = 2.540 mm^{-1}; T = 198 (2) K; *c* range = 1.56–30.00°; reflections collected: 16453, independent: 4653 (R_{int} = 0.0532). The structure was solved by direct methods and refined by full-matrix least squares on F^2; R_1 = 0.0290, wR_2 = 0.0586 [$I > 2\sigma(I)$]; maximal residual electron density: 0.395 e $Å^{-3}$; absolute structure (Flack parameter): χ = –0.006 (6). CCDC-835819.