First total synthesis of (+)-koninginin D

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A total synthesis of (+)-koninginin D (1) is described; the absolute configuration of the immediate antecedent of 1 is shown to have the configuration 7R,9S,10S by X-ray diffraction analysis.

(+)-Koninginin D, a biologically active natural product, was isolated from the culture of *Trichoderma koningii* Oudem by Ghisalberti *et al.* in 1989.1 The structure and relative stereochemistry were determined as shown in structure 1. Since then four congeners of koninginin D have been isolated (koninginin A, B, C and E).2 In 1995 Mori and Abe3 and Xu and Zhu4 published the total synthesis and absolute configuration of (−)-koninginin A independently. Here we report the total synthesis of (+)-koninginin D.

Mori constructed chiral centers C9 and C10 of (−)-koninginin A via the Sharpless asymmetric dihydroxylation, while Xu used tartaric acid as the starting material to establish the two chiral vicinal hydroxy groups. Because koninginins A–E were isolated from a culture of the same species of microorganism, we suggested that (+)-koninginin D has the same absolute configuration at C9 and C10 as that of (−)-koninginin A. Our retrosynthetic analysis of (+)-koninginin D is shown in Scheme 1.

The synthesis of 4 is shown in Scheme 2. According to the known procedure5 (+)-tartaric acid was transformed to diol 7, which when treated with TsCl and C5H11MgBr afforded monoalkylated acetonide 8 in 48.5% yield. Compound 8 was transformed to the iodo compound with NaI, which when reacted with CH2=C(CH3)2Br in the presence of CuI gave 9.6 Ozonolysis of 9 afforded 4. The overall yield of 4 from 7 is 30% (5 steps).

The condensation of 4 and cyclohexane-1,3-dione 5 was performed by the method described by Paquette *et al.*,7 giving 10 and a small amount of the Michael addition product 11 (Scheme 3)

Treatment of 10 with dilute HCl in acetone resulted in deprotection and cyclization furnishing 12. Under the reaction of Hg(OAc)2 in AcOH the PhS group of 12 was replaced by an AcO group, affording 13 and a small amount of 14. X-Ray diffraction analysis revealed that the C7 acetoxy group of 13 is trans to the β-alkyl group.† Since the chiral centers C9 and C10

Scheme 1

Scheme 2 Reagents and conditions: i, TsCl, CH2Cl2, Et3N, rt, 6 h, 95%; ii, C5H11MgBr, THF, Li2CuCl4, 78 °C to rt, 5 h, 51%; iii, NaI, DMF, 80 °C, 2 h, 91%; iv, CH2NCHMgBr, CuI, HMPA, THF, 30 to 10 °C, 20 h, 75%; v, O3, CH2Cl2, MeOH, −78 °C, 91%.

Scheme 3 Reagents and conditions: i, PhSH, SiO2, CH2Cl2, 30–35 °C; ii, 2 M HCl, acetone, rt, 24 h, 87%; iii, AcOH, Hg(OAc)2, rt, 5 h, 84%.
of 13 came from (+)-tartaric acid the absolute configuration of 13 can be assigned as 7R,9S,10S. Both of 13 and 14 treated with Ac₂O gave 15. Attempts to introduce a hydroxy group at C₄ with reagents like SeO₂, SeO₂·SiO₂, Hg(OAc)₂, Pb(OAc)₄ and AcOBu followed failed.

Allylic bromination of 15 with NBS gave 16 in fairly good yield. Nucleophilic substitution of 16 via the method described by Wu⁹ produced a mixture of 4β-hydroxy compounds 17 and 18, both of which upon hydrolysis gave (+)-koninginin D 1 as a white powder, mp 140–142 °C (hot plate); [α]D²⁰ 171 (c 0.125, CHCl₃) [ref. mp 122–123 °C, [α]D +166.9 (c 0.3, CHCl₃)] (Scheme 4). The H¹ NMR, C¹³ NMR and mass spectra of 1 and its triacetate 19 were identical with those of natural (+)-koninginin D and its triacetate, respectively. The overall yield of (+)-koninginin D from tartaric acid was 4.1% (15 steps).

Notes and references
† Crystal data for 13: C₁₅₂H₂₇₀₂₃O₁₇, M = 324.42, orthorhombic, a = 13.690(4), b = 25.900(3), c = 5.179(3) Å, V = 1836(1) Å³, T = 293 °C, P2₁2₁2₁ (no 19), Z = 4, μ(Mo-Kα) = 0.84 cm⁻¹, 2487 reflections measured, 2487 unique (Rint = 0.007) which were used in all calculations. The final wR2(F²) was 2.057 [for 1140 observed reflections with F > 2σ(F)]. CCDC 182/1244. See http://www.rsc.org/suppdata/cc/1999/1129/ for crystallographic files in cif format.
‡ Selected data for 12: δ(C) (60 MHz, CDCl₃, internal: TMS), δ(H) (300 MHz, CDCl₃); i, MeOH, Na₂CO₃, H₂O, reflux, 2 h, 68%; ii, CH₂Cl₂, reflux, 48 h, 57%; iii, MeOH, Na₂CO₃, H₂O, reflux, 2 h, 69%; iv, NBS, AlBN, CCl₄, reflux, 2 h, 67%; v, NaI, dioxane, CaCO₃, H₂O, reflux, 24 h, 57%. Attempts to introduce a hydroxy group at C₄ via allylic oxidation of 15, both of which upon hydrolysis gave (+)-koninginin D 1, 72%; iv, MeOH, Na₂CO₃, H₂O, reflux, 1 h, 91%.

Scheme 4 Reagents and conditions: i, Ac₂O, Et₃N, DMAP, rt, 2 h, 95%; ii, NBS, AlBN, CCl₄, reflux, 2 h, 69%; iii, NaI, dioxane, CaCO₃, H₂O, reflux, 48 h, 72%; iv, MeOH, Na₂CO₃, H₂O, reflux, 1 h, 91%.


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