First total synthesis of (+)-koninginin D

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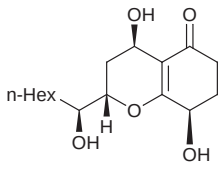
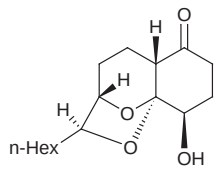
Received (in Cambridge, UK) 17th February 1999, Accepted 29th April 1999

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



(+)-koninginin D **1**

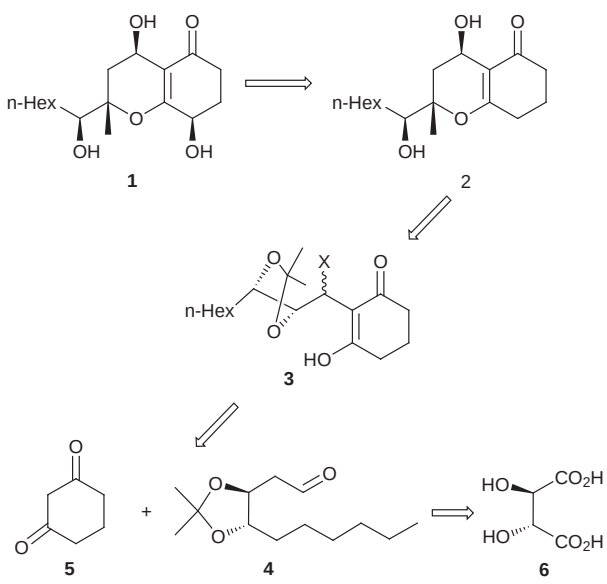


(–)-koninginin A

then four congeners of koninginin D have been isolated (koninginin A, B, C and E).[2] In 1995 Mori and Abe[3] and Xu and Zhu[4] published the total synthesis and absolute configuration of (−)-koninginin A independently. Here we report the total synthesis of (+)-koninginin D.

Mori constructed chiral centers C_9 and C_{10} 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 C_9 and C_{10} as that of (−)-koninginin A. Our retrosynthetic analysis of (+)-koninginin D is shown in Scheme 1.

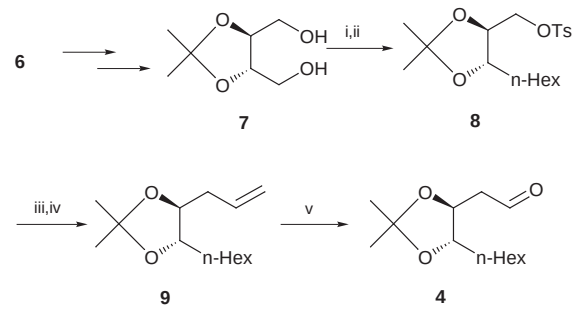
The synthesis of **4** is shown in Scheme 2. According to the known procedure[5] (+)-tartaric acid was transformed to diol **7**, which when treated with TsCl and $C_5H_{11}MgBr$ afforded monoalkylated acetonide **8** in 48.5% yield. Compound **8** was transformed to the iodo compound with NaI, which when reacted with CH_2=CHMgBr in the presence of CuI gave **9**.[6] Ozonolysis of **9** afforded **4**. The overall yield of **4** from **7** is 30% (5 steps).



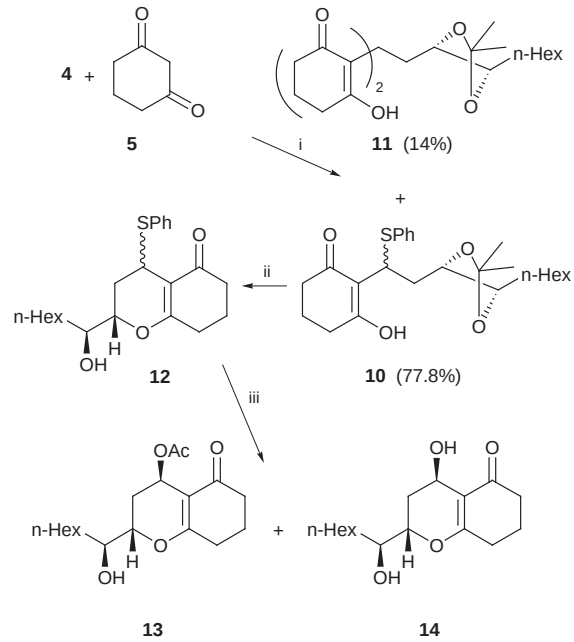
Scheme 1

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)

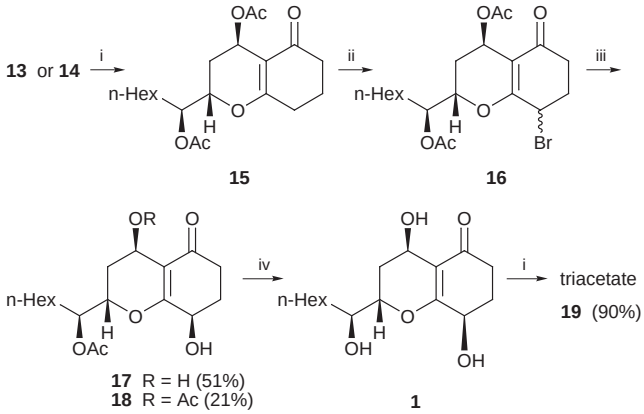
Treatment of **10** with dilute HCl in acetone resulted in deprotection and cyclization furnishing **12**. Under the reaction of $Hg(OAc)_2$ in AcOH the PhS group of **12** was replaced by an AcO group, affording **13** and a small amount of **14**. X-Ray diffraction analysis revealed that the C_7 acetoxy group of **13** is *trans* to the β-alkyl group.† Since the chiral centers C_9 and C_{10}



Scheme 2 *Reagents and conditions*: i, TsCl, CH_2Cl_2, Et_3N, rt, 6 h, 95%; ii, $C_5H_{11}MgBr$, THF, Li_2CuCl_4, −78 °C to rt, 5 h, 51%; iii, NaI, DMF, 80 °C, 2 h, 91%; iv, CH=CHMgBr, CuI, HMPA, THF, −30 to 10 °C, 20 h, 75%; v, O_3, CH_2Cl_2, MeOH, −78 °C, 91%.



Scheme 3 *Reagents and conditions*: i, PhSH, SiO_2, CH_2Cl_2, 30–35 °C; ii, 2 M HCl, acetone, rt, 24 h, 87%; iii, AcOH, $Hg(OAc)_2$, rt, 5 h, 84%.



Scheme 4 *Reagents and conditions*: i, Ac_2O, Et_3N, DMAP, rt, 2 h, 95%; ii, NBS, AlBN, CCl_4, reflux, 2 h, 69%; iii, NaI, dioxane, $CaCO_3$, H_2O, reflux, 48 h, 72%; iv, MeOH, Na_2CO_3, H_2O, rt, 1 h, 91%.

of **13** came from (+)-tartaric acid the absolute configuration of **13** can be assigned as 7*R*,9*S*,10*S*. Both of **13** and **14** treated with Ac_2O gave **15**. Attempts to introduce a hydroxy group at C_4 *via* allylic oxidation of **15** with reagents like SeO_2, $SeO_2{\cdot}SiO_2$, $Hg(OAc)_2$, $Pb(OAc)_4$ and $AcOBu^t$ failed.

Allylic bromination of **15** with NBS gave **16** in fairly good yield. Nucleophilic substitution of **16** *via* the method described by Wu [8] 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); $[\alpha]_D^{20}$ 171 (*c* 0.125, $CHCl_3$) [ref. mp 122–123 °C, $[\alpha]_D$ +166.9 (*c* 0.3, $CHCl_3$)] (Scheme 4). The H^1 NMR, C^{13} 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**: $C_{18}H_{28}O_5$, *M* = 324.42, orthorhombic, *a* = 13.690(4), *b* = 25.900(3), *c* = 5.179(3) Å, *V* = 1836(1) Å^3, *T* = 293 °C, *P*2,2,2 (#19), *Z* = 4, μ(Mo-Kα) = 0.84 cm^{-1}, 2487 reflections measured, 2487 unique (R_{int} = 0.000) which were used in all calculations. The final $wR(F^2)$ was 0.057 [for 1140 observed reflections with $I > 2.00\sigma(I)$]. CCDC 182/1244. See http://www.rsc.org/suppdata/cc/1999/1129/ for crystallographic files in .cif format.

‡ Selected data for **1**: δ_H(300 MHz, $CDCl_3$) 4.68 (dd, *J* 1, 2, 1H), 4.49 (q-like, *J* 4.8, 1H), 4.11 (ddd, *J* 2.2, 4.6, 12.1, 1H), 3.72 (q, *J* 6.4, 1H), 2.60 (ddd, *J* 4.74, 5.58, 17.00, 1H), 2.30 (m, 1H), 2.20 (m, 1H), 2.00 (m, 2H), 1.60 (m, 3H), 1.40–1.25 (m, 8H), 0.88 (t, *J* 6.80, 3H); δ_C(75 MHz, $CDCl_3$) 198.3, 171.4, 114.6, 77.0, 73.0, 66.7, 57.7, 34.0, 33.2, 31.8, 31.1, 29.3, 29.2, 25.4, 22.7, 14.1; *m/z* 298 (M^+, 1.3%), 281 (32.9), 262 (20.1), 242 (7.1), 209 (6.6), 191 (8.3), 166 (29.0), 165 (100), 155 (26.0), 139 (25.2), 109 (14.2) [$C_{16}H_{24}O_4$ (M − H_2O) requires 280.1675 found 280.1683]. For **19** $[\alpha]_D^{20}$ +127.4 (*c* 0.58, $CHCl_3$); δ_H(300 MHz, $CDCl_3$) 5.80 (m, 1H), 5.64 (t, *J* 4.90, 1H), 5.06 (td, *J* 3.82, 6.60, 1H), 4.14 (ddd, *J* 2.2, 3.7, 12.8, 1H), 2.63 (m, 1H), 2.39 (m, 1H), 2.20 (m, 1H), 2.13 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H), 1.99 (m, 1H), 1.75 (m, 1H), 1.65 (m, 2H), 1.25–1.30 (m, 9H), 0.87 (t, *J* 6.9, 3H); δ_C(75 MHz, $CDCl_3$) 194.8, 170.5, 169.8, 168.5(2), 112.2, 74.3, 73.0, 66.6, 59.7, 32.9, 31.7, 30.0, 29.3, 29.1, 26.5, 25.2, 22.6, 21.2, 20.9, 20.8, 14.1; *m/z* 380 (M^+ −44, 11.3%), 365 (17.7), 322 (14.7), 321 (25.0), 305 (67.4), 279 (7.9), 262 (14.4), 245 (44.4) 233 (14.0), 191 (15.8), 165 (15.3), 149 (17), 43 (100) ($C_{22}H_{32}O_8$: calc. C, 62.24; H, 7.60. Found: C, 61.93; H, 7.74%).

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Communication 9/01320B