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STEREOSELECTIVE TOTAL SYNTHESIS OF (±)-EREMOFORTIN B, A SESQUITERPENOID MYCOTOXIN OF *Penicillium roqueforti* [1]

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The stereoselective total synthesis of (±)-eremofortin B (1), a sesquiterpenoid mycotoxin of *Penicillium roqueforti*, from 5β,6β-dimethyl-2,7-dioxo-$\Delta^{1(10)}$-octalin (2) is described. Stereochemistry of eremofortin B was confirmed as shown in 1.

Eremofortin B, a sesquiterpenoid mycotoxin of *Penicillium roqueforti*, was found by Moreau *et al.*[2] The structure of eremofortin B was proposed to be an eremophilane type sesquiterpenoid as shown in 1', however the stereochemistry was not clear.[3]

We previously reported the total synthesis of (±)-isopetasol,[4a] (±)-warburgiadione,[4a] (±)-petasitol,[4a] and (±)-phomenone[4b] from 5β,6β-dimethyl-2,7-dioxo-$\Delta^{1(10)}$-octalin (2). In this communication, we wish to report the first total synthesis of (±)-eremofortin B (1) from the key intermediate (2), the synthesis confirming the stereochemistry of 1.

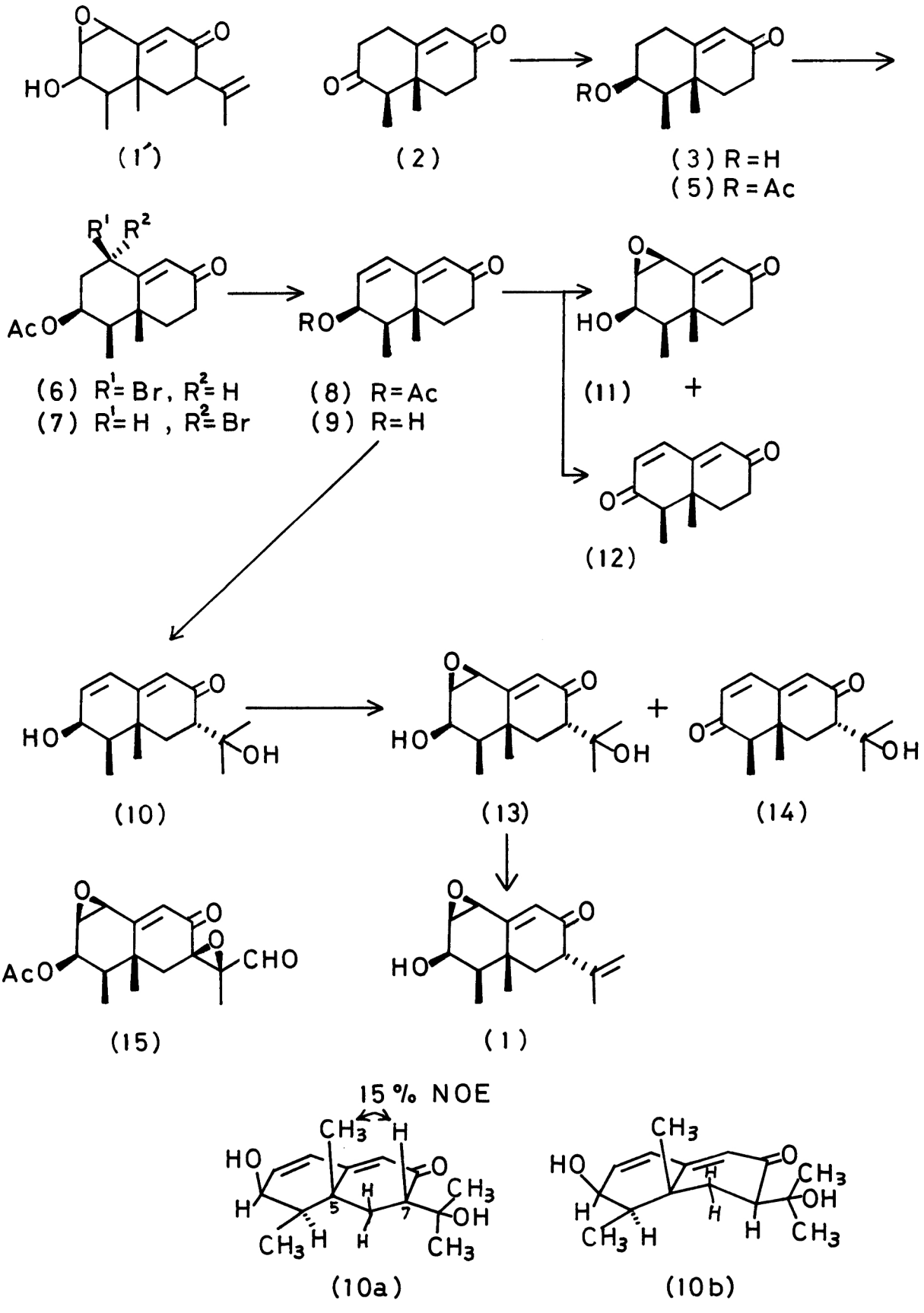
Reduction of the enone (2) with $NaBH_4$ in MeOH at 0°C for 30 min gave 3β-OH (3) (90%) together with a small amount of 3α-epimer (4) (10%). The configuration of C-3 hydroxyl group of 3 and 4 were determined by their NMR spectra [3: δ 3.94, $W_{1/2}$=7.5 Hz, 3α-H and 4: δ 3.55, $W_{1/2}$=25 Hz, 3β-H]. Acetylation of 3 with Ac_2O-pyridine-DMAP gave the 3β-acetate (5), mp 71-2°C [NMR δ: 5.08 ($W_{1/2}$=7.5 Hz, 3α-H)]. Bromination of 5 with NBS in refluxing CCl_4 for 1.5 hr afforded bromides (70-80%), which were separated by preparative TLC to give 6, mp 96-8°C(28.5%), and 7, mp 102-104°C(44.5%), while the reaction under 30 min reflux gave 6 (44%) and 7 (21%). The bromide (6) was initially formed and then epimerized to the bromide (7) on prolonged heating. The stereochemistry of the bromides (6) and (7) were confirmed to be 1β(axial)- and 1α(equatorial)-bromide, respectively, by their physical

properties [6: MS m/z: 314, 316, M^+; UV λ_{max}^{EtOH} 243.5 nm (ε 14000); NMR δ: 4.89 (m, $W_{1/2}$=9 Hz, 1-H), 5.95 (s, 9-H); 7: MS m/z: 314, 316, M^+; UV λ_{max}^{EtOH} 233.5 nm(ε14000); NMR δ: 4.98 (m, $W_{1/2}$=21 Hz, 1-H), 6.41 (d, J=2 Hz, 9-H)]. Dehydrobromination of the bromides (6) and (7) with LiBr, Li_2CO_3-DMF gave the same dienone (8), mp 99-100°C [MS m/z: 234, M^+; UV λ_{max}^{EtOH} 274 nm (ε 22000); IR cm^{-1}: 1728, 1655, 1628] in an 81% and 67% yield, respectively. Hydrolysis of 8 with methanolic K_2CO_3 gave the dienone (9), mp 129-130°C, in a 50% overall yield from 5. An alternative preparation of 9 was carried out as follows: bromination of 3 with NBS gave a bromide, mp 112-3°C, and then dehydrobromination under the same conditions as described above gave 9, however the overall yield from 3 was unfavorable (30%).

The dienone (9) was treated with LDA and condensed with acetone in the presence of $ZnCl_2$[4a] afforded 10, mp 181-2°C (66%) [IR cm^{-1}: 3360; UV λ_{max}^{EtOH} 281.5 nm (ε 16000)]. Dreiding models revealed that two isomers 10a and 10b were possible to be assigned to 10. In ^{1}H-NMR of 10, the 7-H was observed as a double doublet at δ 2.61, J=15 and 4.5 Hz, and the coupling constants were attributed to trans. When 5-CH_3 protons (δ 1.29) was irradiated, the integration of 7-H showed a 15% NOE enhancement. This fact indicated a 1,3-diaxial relationship between 5-CH_3 and 7-H, and consequently demonstrated that 10 should be shown as the 7α-side chain isomer (10a).

Stereoselective epoxidation of allyl alcohols have been reported,[5] whereas stereoselective epoxidation of linear dienone allyl alcohols has not yet been reported. Epoxidation of 9 with *tert*-butyl hydroperoxide in the presence of $VO(acac)_2$ in CH_2Cl_2, according to the Sharpless' procedure,[5a] gave 1β,2β-epoxide (11)(17%), mp 117-8°C, together with dienone (12)(54%), mp 103-4.5°C. Treatment of 10 under similar conditions (room temperature, 2 days) gave 1β,2β-epoxide (13) (20%), mp 180.5-2°C, and dienone (14)(54%), mp 125.5-8°C. The epoxidation in benzene containing a small amount of THF gave 13 (24%), 14 (9%), and unchanged 10 (28% recovery), but α-epoxy compound was not detected. Attempted preparation of the β-epoxide (13) from 10 with *m*-CPBA or basic H_2O_2 was unsuccessful.

For the purpose of conversion of 13 into eremofortin B (1), mild cis-elimination conditions were applied to the compound 13 without dehydration of the C-3 hydroxyl group by the trans-elimination. A solution of 13 in benzene containing a small amount of THF with (methylcarboxysulfamoyl)triethylammonium hydroxide inner salt[6] was warmed at 50°C for 3 hr. The product was separated by prepara-


(1′)
(2)
(3) R=H
(5) R=Ac
(6) R¹=Br, R²=H
(7) R¹=H, R²=Br
(8) R=Ac
(9) R=H
(11) +
(12)
(10)
(13)
(14)
(15)
(1)
15% NOE
(10a)
(10b)

tive TLC to give (±)-1, mp 114-7°C (from hexane-EtOAc), as colorless plates (20%) and unchanged 13 (27%). Compound (±)-1: MS m/z: 248, M^+; UV λ_{max}^{EtOH} 241 nm (ε15600); IR cm^{-1}: 3460, 1660, 1610; NMR δ: 1.09 (3H, d, J=7.5 Hz, 4-CH_3), 1.35 (3H, s, 5-CH_3), 1.73 (3H, bs, 11-CH_3), 3.26 (1H, dd, J=13.5, 6.0 Hz, 7-H), 3.67 (1H, d, J= 3.5 Hz, 1-H), 3.84 (1H, dd, J=4.5, 3.5 Hz, 2-H), 4.09 (1H, m, $W_{1/2}$=15 Hz, 3-H, changed to a triplet with J=4.5 Hz on addition of D_2O), 4.82 and 4.97 (each 1H, bs, $=\!\!<^{H}_{H}$), 6.17 (1H, s, 9-H). The IR and NMR spectra of (±)-1 were identical with those of (+)-eremofortin B.[2,3]

The total synthesis of (+)-PR-toxin (15) isolated from *P. roqueforti* by Wei *et al.*[7] and the other eremofortins is now in progress.

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