Total synthesis and absolute configuration of FR65814

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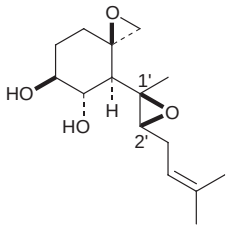
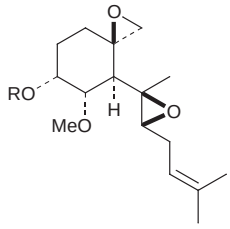
The chiral and highly stereoselective synthesis of FR65814 1, a novel immunosuppressant, starting from D-glucose is described; this first total synthesis fully confirms the proposed structure of 1.

FR65814 **1** is a sesquiterpene isolated from the culture broth of *Penicillium* and is reported to show potent immunosuppressive



FR65814 **1**

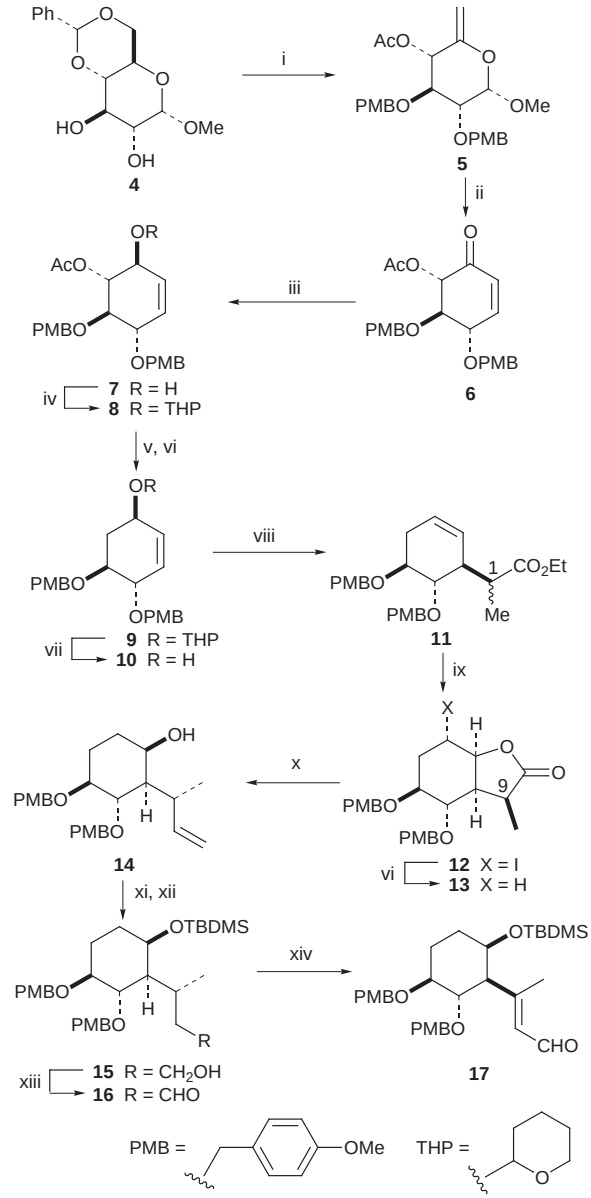


fumagillin **2** R = CO(CH=CH)$_4$CO$_2$H (*E*)

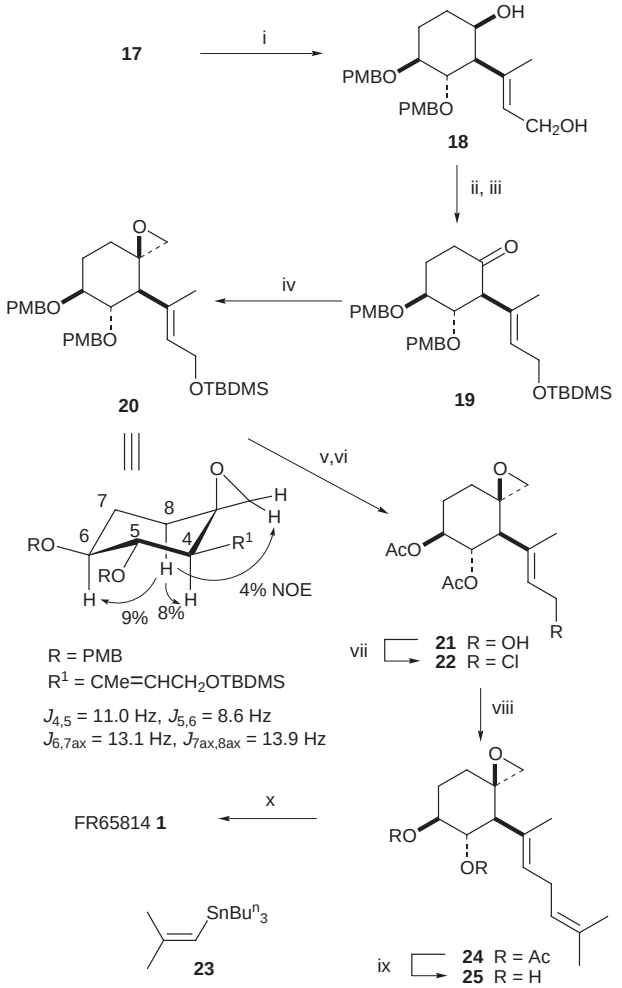
fumagillol **3** R = H

activity.[1] The structure of **1** was tentatively assigned[1] on the basis of the spectral similarity to fumagillol **2**, a hydrolysis product of fumagillin **3**, which showed antiparasitic and carcinolytic activity.[2] The recent discovery of the inhibitory activity of fumagillin against endothelial cell proliferation and tumor-induced angiogenesis has attracted much biological attention,[3] and compounds related to fumagillin are expected to be anti-cancer drug candidates.[3] Such interesting biological activity as well as their challenging structures have stimulated synthetic efforts and the total syntheses of racemic fumagillin[4a] and optically active fumagillol[4b] have been reported. However, no report on the synthesis of **1** has appeared. Here, as a part of our continuous studies on the synthesis of biologically important compounds containing the cyclohexane unit, starting from aldohexoses and utilizing Ferrier's carbocyclization,[5,6] we report the first total synthesis of **1** from D-glucose.

Commercially available methyl 4,6-*O*-benzylidene-α-D-glucopyranoside **4** was transformed into 2,3-di-*O*-(4-methoxybenzyl)-6-deoxyhex-5-enopyranoside derivative **5** (Scheme 1) by essentially the same procedure as that reported for the preparation of the corresponding di-*O*-benzyl derivative[6a] (4-methoxybenzyl chloride was employed instead of benzyl bromide). Catalytic Ferrier's carbocyclization of **5** with Hg(OCOCF$_3$)$_2$ in aqueous acetone,[7] followed by β-elimination afforded cyclohexenone **6** in 84% yield. Reduction of the carbonyl group using Luche's conditions gave allyl alcohol **7** as the sole product in 90% yield. After protection of the alcohol function as a tetrahydropyranyl (THP) ether (99% yield), the acetoxy function in **8** was removed *via* a xanthate to provide **9** in 63% yield. Deprotection of the *O*-THP group afforded **10** in 96% yield. Claisen rearrangement of **10** with triethyl orthopropionate at 140 °C successfully introduced a carbon-side chain with the correct stereochemistry to provide **11** (74% yield).‡ Saponification of the ester group in **11** with Bu^{t}OK in DMSO[8] followed by iodolactonization gave **12** as the sole product,‡ whose iodo function was cleanly removed with Bu$^n_3$SnH to give **13** in 80% yield from **11**. DIBAL-H reduction of **13** afforded the corresponding lactol, whose Wittig reaction with Ph$_3$P=CH$_2$ gave **14** in 90% yield. After protection of the hydroxy group in **14**, the alkene portion was converted into primary alcohol by



Scheme 1 *Reagents and conditions*: i, see ref. 6(*a*); ii, Hg(OCOCF$_3$)$_2$ (5 mol%), acetone–H$_2$O, then MsCl, Et$_3$N, CH$_2$Cl$_2$; iii, NaBH$_4$, CeCl$_3$·7H$_2$O, MeOH, 0 °C; iv, 3,4-dihydro-2*H*-pyran, PPTS, CH$_2$Cl$_2$; v, MeONa, MeOH, then NaH, imidazole, CS$_2$, MeI, THF; vi, AIBN, Bu$^n_3$SnH, toluene, reflux; vii, PPTS, EtOH, 50 °C; viii, EtC(OEt)$_3$, EtCO$_2$H, 140 °C; ix, Bu^{t}OK, DMSO, then I$_2$, KI, aq. NaHCO$_3$–THF; x, DIBAL-H, toluene, −78 °C, then Ph$_3$PMe$_3$Br, BuLi, THF; xi, TBDMSOTf, 2,6-lutidine, CH$_2$Cl$_2$, 0 °C; xii, BH$_3$·THF, THF, 0 °C, then H$_2$O$_2$, NaOH; xiii, Pr$^n_4$NRuO$_4$, NMO, CH$_2$Cl$_2$; xiv, KN(SiMe$_3$)$_2$, TMSCl–Et$_3$N, THF, 0 °C, then Pd(OAc)$_2$, MeCN, 0 °C



Scheme 2 *Reagents and conditions*: i, DIBAL-H, toluene, −78 °C, then Bu^n_4NF, THF; ii, TBDMSCl, imidazole, DMF; iii, DMSO, Ac_2O; iv, $Me_3S(O)I$, NaH, DMSO, room temp.; v, DDQ, CH_2Cl_2–H_2O; vi, Ac_2O, pyridine, then Bu^n_4NF, THF; vii, LiCl, $MeSO_2Cl$, collidine, DMF; viii, **23**, $Pd(PPh_3)_4$ (10 mol%), THF, 50 °C; ix, MeONa, MeOH; x, vanadyl acetylacetonate (5 mol%), Bu^tOOH, CH_2Cl_2, −18 °C

hydroboration-oxidation to provide **15** (85% yield). Perruthenate oxidation[9] of **15** gave aldehyde **16** in 81% yield, which was converted into α,β-unsaturated aldehyde with *E*-geometry§ **17** in 45% yield by silyl enol ether formation followed by treatment with stoichiometric amount of $Pd(OAc)_2$.[10] The *Z*-isomer of **17** was isolated as the minor product (4% yield).

Having finished the preparation of highly oxygenated cyclohexane ring with carbon side-chain, elongation of the carbon chain and introduction of the bis-epoxide functionality were explored. DIBAL-H reduction of **17** and subsequent deprotection of the *O*-silyl group afforded diol **18** (Scheme 2). Protection of the primary alcohol function followed by oxidation of the secondary alcohol with Ac_2O–DMSO generated ketone **19** in 82% yield from **17**. Reaction of **19** with stabilized sulfur ylide[11] proceeded stereoselectively and afforded spiro epoxide **20** as the sole product in 57% yield. The observed coupling constants and NOE of **20** supported the assigned structure. Treatment of **20** with DDQ followed by conventional acetylation afforded diacetate, whose *O*-silyl protecting group was removed to provide **21** in 90% yield. The allyl alcohol **21** was transformed into allylic chloride **22** quantitatively. Stille coupling[12] of **22** with isobutenyltributyltin[13] **23** in the presence of $Pd(PPh_3)_4$ successfully provided the coupling product, *E*-diene§ **24**, in 72% yield. Removal of the *O*-acetyl group gave diol **25** in 95% yield. The final transformation, introduction of the second epoxide functionality, was stereoselectively achieved by vanadium-catalyzed epoxidation[14] to give FR65814 **1** in 70% yield.¶ The spectroscopic (^1H and ^{13}C NMR) data for synthetic **1** were identical with those of natural FR65814, and the physical properties of **1** {mp 39–40 °C (from Et_2O–hexanes); $[\alpha]_D^{21}$ − 41 (*c* 0.25, MeOH)} showed good accord with those of the natural product {mp 39–40 °C (from Et_2O–hexanes); mixed mp, 39–40 °C; $[\alpha]_D^{23}$ − 38.4[1] (*c* 2.4, MeOH)}. This successful first total synthesis of **1** confirmed the assigned structure of FR65814, and provided a novel synthetic pathway from carbohydrates to highly oxygenated terpenes possessing a cyclohexane unit.

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Notes and References

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‡ Compound **11** was obtained as an inseparable diastereomeric mixture at C-1 (1 : 1). Interestingly, epimerization at C-1 occurred during the saponification step and compound **12** was obtained as the single product. The stereochemistry at C-9 in **12** was confirmed by NOE experiments.

§ The NOE experiments clearly showed that the geometry of the double bond in both **17** and **24** should be *E*. No isomerization of the double bond was observed during the coupling reaction between **22** and **23**.

¶ A small amount (less than 5%) of diastereomeric epoxide (1′,2′-diepi-FR65814) was isolated. The chemical shifts and appearance of the hydrogen attached to the carbon bearing epoxide ring (H-2′) of **1** and its diastereomer in the ^1H NMR spectra ($CDCl_3$) are found to be characteristic: FR65814, fumagillol, δ 2.61 (dd, *J* 5.9, 7.1); 1′,2′-diepi-FR65814, δ 3.14 (br m); *cf.* δ 2.56 (dd, *J* 5.9, 7.1).

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