Synthesis of Terrein, a Metabolite of *Aspergillus terreus*

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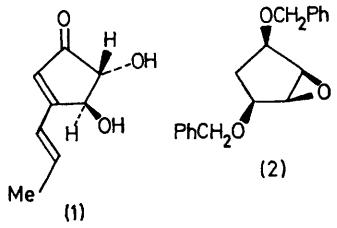
Summary Terrein, a metabolite of *Aspergillus terreus*, has been synthesized in racemic form from *cis*-1,4-bisbenzyloxy-2,3-epoxycyclopentane.

TERREIN, a metabolite of *Aspergillus terreus*, was first discovered and investigated nearly forty years ago.[1] Subsequent work by Grove[2] and by Barton[3] established the structure and absolute stereochemistry of terrein as shown in (**1**). More recently, Birch[4] has studied the biosynthesis of this metabolite, proving its acetate origin. Several chlorinated antifungal antibiotics have been isolated which are closely related to terrein in both structure and biogenesis.[5] We now report a total synthesis of racemic terrein.

The readily available epoxide (**2**),[6] was heated in refluxing dimethoxyethane–4% H_2SO_4 (3 : 1) for 22 h to give the oily *trans*-diol (**3**) in 86% yield after silica gel chromatography. Treatment of (**3**) with NaH and chloromethyl methyl ether in dimethylformamide at room temperature produced the diacetal (**4**) (85%), which was debenzylated with Na–liq. NH_3, affording the oily diol (**5**) (62%).

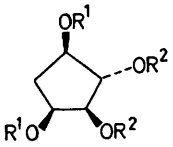
Oxidation of (**5**) with 1·1 equiv. of Jones reagent[7] in acetone (0°; 60 min) gave an unstable mixture of keto-alcohols (**6**) [i.r. (film) 3450 and 1750 cm^{-1}] which without purification was dehydrated with Ac_2O in pyridine (−20°; overnight), affording the cyclopentenone (**7**) [66% yield from (**5**)] by bulb to bulb distillation at 145° and 0·2 mm Hg; i.r. (film) 1710 cm^{-1}; δ ($CDCl_3$)[8] 7·50 (1H, dd, *J* 6, 2 Hz), 6·25 (1H, dd, *J* 6, < 1 Hz), 4·6—5·1 (5H, m), 4·24 (1H, d, *J* 2·8 Hz), 3·41 (3H, s), and 3·43 (3H, s).

Treatment of the cyclopentenone (**7**) with allylmagnesium bromide[9] in ether at −78° produced a mixture of alcohols (**8**) (58%) which without separation was treated with Jones reagent[7,10] in acetone (22°; 2 h) giving the substituted cyclopentenone (**9**) (30%): i.r. (film) 1710 and 1620 cm^{-1}; λ_{max} (MeOH) 226 nm. This compound is exceedingly sensitive to base and upon treatment with dilute NaOH in MeOH at room temperature is instantaneously converted into the fully conjugated cyclopentadienone (**10**) (50%): i.r. (film) 1700 and 1640 cm^{-1}; λ_{max} (MeOH) 276 nm; δ ($CDCl_3$) 1·92 (3H, d, *J* 7 Hz), 3·43 (6H, s),

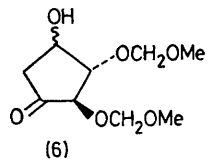


(1)

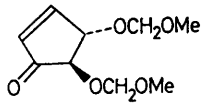
(2)



(3) $R^1 = CH_2Ph$, $R^2 = H$
(4) $R^1 = CH_2Ph$, $R^2 = CH_2OMe$
(5) $R^1 = H$, $R^2 = CH_2OMe$



(6)



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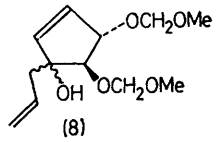

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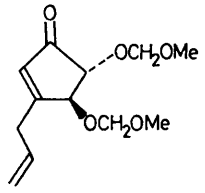

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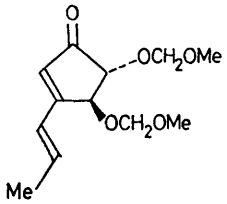

(10)

4·2 (2H, m, –CH–O–), 4·6—5·2 (4H, m), and 5·9—6·6 (3H, m).

The two alcohol protecting groups were then cleaved by treating (**10**) with a trace of concentrated HCl in MeOH at 62° for 15 min, giving racemic terrein, m.p. 87—89°, which was indistinguishable (solution i.r., n.m.r., u.v., mass spectrum, and t.l.c.) from natural material.

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