Total Synthesis of Enmein

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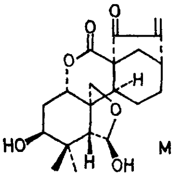
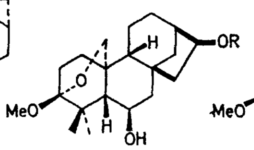
Summary A total synthesis of enmein (**1**) has been accomplished by a transformation of the previously synthesised relay compound (**2**).

ENMEIN (**1**) is a major bitter principle of the leaves of *Isodon trichocarpus* Kudo and *I. japonicus* Hara (Labiatae). Its complicated B-secokaurene-type structure and absolute configuration have been elucidated.[1] Here, we report the synthesis of enmein (**1**) from the optically active relay compound (**2**) derived from enmein.† Since the racemate of (**2**), m.p. 196—197°, has been synthesized by us,† the present conversion constitutes the total synthesis of enmein.

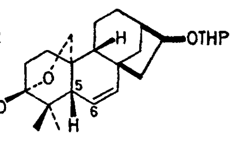
A partial tetrahydropyranylation of the optically active compound (**2**), m.p. 220—225°, $[\alpha]^{20}_{D}$ $-137°$, gave (**3**)‡ (58%), which was dehydrated ($SOCl_2$ in pyridine) to afford a mixture of the Δ^6-compound (**4**) and the Δ^5-isomer (**5**) (ratio *ca.* 2 : 1) (42%). The 6-mesylate of (**3**), on heating in pyridine, gave an inverse ratio of (**4**) and (**5**). Ethylene acetalization of (**4**) gave (**6**), m.p. 188—190° (>49%). Compound (**6**) was identical with the product (68%) from the Wolff–Kishner reduction of 7-hemiacetal (**7**) which was obtained in the foregoing conversion of enmein into (**2**).† Ozonolysis, oxidation, and successive methylation of (**6**) yielded a keto-lactone ester (**8**), m.p. 194—195° [13% overall from (**6**)]. Wittig reaction of (**8**) and treatment of the exo-methylene product with dilute HCl in acetone gave a tertiary alcohol (**9**), m.p. 171—172° (38%). Bromination at C-2 and dehydrobromination followed by dehydration (170° in DMSO)[2] of (**9**) gave dienone lactone ester (**10**), m.p. 120—121° [3·3% from (**8**)]. Hydrolysis of (**10**) (0·01N NaOH or 0·1N Na_2CO_3) gave (**11**), m.p. 235–240°. Hydrolysis (10% KOH) of (**12**) *i.e.* the ethylene acetal (88%) of (**10**), and successive acid treatment (BF_3–Et_2O in $CHCl_3$) yielded the desired dilactone (**13**), m.p. 192—195° (72%). The good yield of this cyclization can be attributed to the easy formation of a transition state which satisfies the stereo-electronic requirement for maximum overlap between the carboxylate anion, the π-electrons of the double bond, and the C–O bond of the acetal on the α-side of the molecule. None of the C-1 β epimer was detected. The structure of (**13**) was confirmed by a four step conversion (56%) from the known compound (**14**).[3] After deacetalization, it was transformed into 3β-ol (**15**), m.p. 270—275° (20%) by Meerwein–Ponndorf reduction. Selective $LiAlH_4$ reduction[4] of the γ-lactone gave hemiacetal (**16**), m.p. 228—232° (50%). Methylation and acetylation of (**16**) gave (**17**), m.p. 136—138° (86%), which was brominated at the allylic position, then epoxidation yielded (**18**), m.p. 199—201°. The subsequent reaction with Zn in ethanol gave alcohol (**19**). Oxidation to ketone, and hydrolyses of acetate and acetal by Na_2CO_3 and AcOH, respectively, yielded enmein (**1**), m.p. 290° [4·6% from (**17**) *via* six steps].



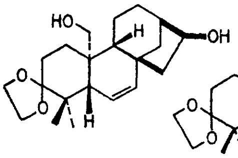
(1)



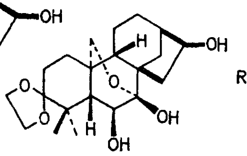
(2) R = H
(3) R = THP



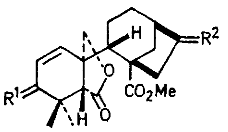
(4)
(5) Δ^5-isomer



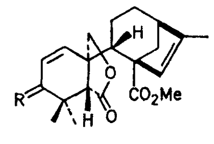
(6)



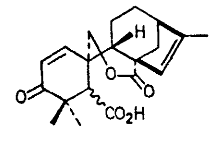
(7)



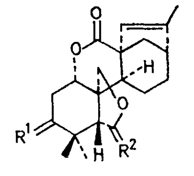
(8) R¹ = , R² = O
(9) R¹ = O , R² = Me,OH



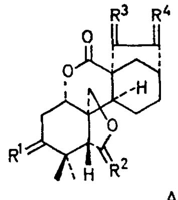
(10) R = O
(12) R =



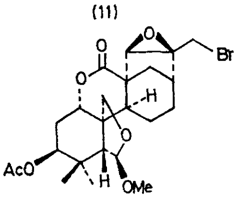
(11)



(13) R¹ = , R² = O
(15) R¹ = α-H, β-OH, R² = O
(16) R¹ = R² = α-H, β-OH
(17) R¹ = α-H, β-OAc,
R² = α-H, β-OMe



(14) R¹ = R² = R³ = O,
R⁴ = α-Me, β-H
(19) R¹ = α-H, β-OAc,
R² = α-H, β-OMe,
R³ = α-H, β-OH,
R⁴ = CH₂



(18)

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† These syntheses will be published elsewhere.

‡ All the intermediates showed reasonable spectroscopic data and those for which melting points were recorded gave satisfactory compositional analyses.

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[2] V. J. Traynelis, W. L. Hergenrother, H. T. Hanson, and J. A. Valicenti, *J. Org. Chem.*, 1964, **29**, 123.
[3] T. Kubota, T. Matsuura, T. Tsutsui, S. Uyeo, H. Irie, A. Numata, T. Fujita, and T. Suzuki, *Tetrahedron*, 1966, **22**, 1659.
[4] E. Fujita, T. Fujita, and H. Katayama, *J. Chem. Soc.* (*C*), 1970, 1681.