Synthesis of (−)-Probetaenone I: Structural Confirmation of Biosynthetic Precursor of Betaenone B

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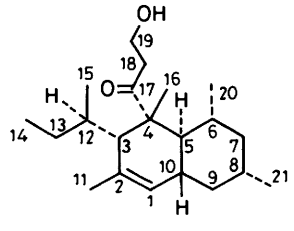
(−)-Probetaenone I (**1**) has been synthesized by an intramolecular Diels–Alder reaction and, thereby, its structure has been clearly confirmed; in the biosynthesis of betaenone B (**2**) the stereochemistry of the C-8 hydroxylation of (**1**) was proved to involve retention of configuration.

Oikawa and co-workers[1] isolated probetaenone I (**1**) as a biosynthetic precursor of betaenone B (**2**), which is one of the phytotoxic metabolites of *Phoma betae* Fr.,[2] causal fungus of leaf spot disease on sugar beet. That is, by addition of ancymidol, a potent inhibitor of cytochrome P-450, to the fungal culture medium, the production of (**2**) was suppressed and a corresponding accumulation of (**1**) was observed. Furthermore, by an incorporation experiment, ^{14}C labelled (**1**) was converted into (**2**) efficiently.[3] The structure of (**1**) has been elucidated on the basis of spectroscopic data, the stereochemistry being deduced from a comparison of the ^1H NMR spectrum of (**1**) with the spectra of (**2**) and diplodiatoxin (**3**).[4] However, the stereochemistry of C-8 has remained ambiguous because of the large amount of overlap in the ^1H NMR signals in the aliphatic region. Further, we are very interested in the biosynthetic route to (**1**), which could be biosynthesized by an enzymatic Diels–Alder reaction.[1] To obtain structural proof of (**1**) and to study its biosynthesis we synthesized (**1**) through the intramolecular Diels–Alder reaction as follows.

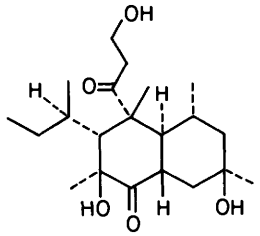
The starting chiral compound (**5**), (2*S*,4*R*)-2,4-dimethylpentan-5-olide, was easily prepared by a newly developed optical resolution method. That is, treatment of the racemic lactone (**5**) with D-α-phenylethylamine (in Et_2O, room temp., 4 days) afforded a diastereoisomeric mixture of amides in 91% yield. After TBDMS etherification of this mixture (TBDMSCl, imidazole in DMF, room temp., 4 h), the resultant diastereoisomers were easily separated chromatographically (silica gel, hexane–ether, 4:1). Hydrolysis of the less polar isomer (**4**) (1M HCl, reflux, 2 h) gave the dextrorotatory lactone (**5**) ($[\alpha]_D^{24}$ + 38.5°, *c* 1.3, $CHCl_3$, 98% e.e., lit.,[6] +39.1°)‡ in 96% yield.

On the other hand, (4*R*,*E*)-2,4-dimethylhex-2-en-1-ol (*ca.* 80% e.e.), prepared by following the procedure in the synthesis of (−)-betaenone C,[5] was converted into the phosphonium salt (**8**) in two steps in 82% yield: i, CCl_4, Ph_3P in CH_2Cl_2, room temp., 12 h; ii, Ph_3P in MeCN, 60–70 °C, 48 h.

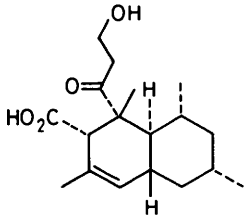
Reduction of the lactone (**5**) (1 equiv. of $LiAlH_4$, −20 °C, 30 min) and subsequent Wittig–Horner reaction [$Ph_2P(O)$-CH_2OMe, BuLi in THF, room temp., overnight, then NaH in THF, room temp. 24 h] yielded the enol ether (**6**) in 61% yield.† Benzoylation of (**6**) (Bz_2O, DMAP in pyridine, room temp. overnight, 84% yield) was followed by selective hydrolysis of the enol ether to give the aldehyde (**7**) cleanly (0.6M HCl–dioxane, 1:1, 0–4 °C, 72 h, 84% yield).‡ The Wittig reaction of (**7**) with (**8**) (BuLi in benzene, −40 °C, 3 h) afforded the dienes (**9**) in 78% yield. The *E*:*Z* ratio of the newly formed double bond was *ca.* 7:3.§ The dienes (**9**) (*E*, *Z* mixture) were converted into the dienals (**10**) by reductive cleavage of the ester ($LiAlH_4$ in ether, −40 °C, 1 h, 87% yield) and Swern oxidation[7] (81% yield). The Wittig–Horner reaction of (**10**) with the phosphonate (**11**) (BuLi in DMF, −10 to −6 °C, 26 h)



(**1**)



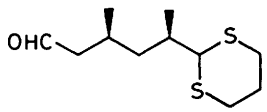
(**2**)



(**3**)

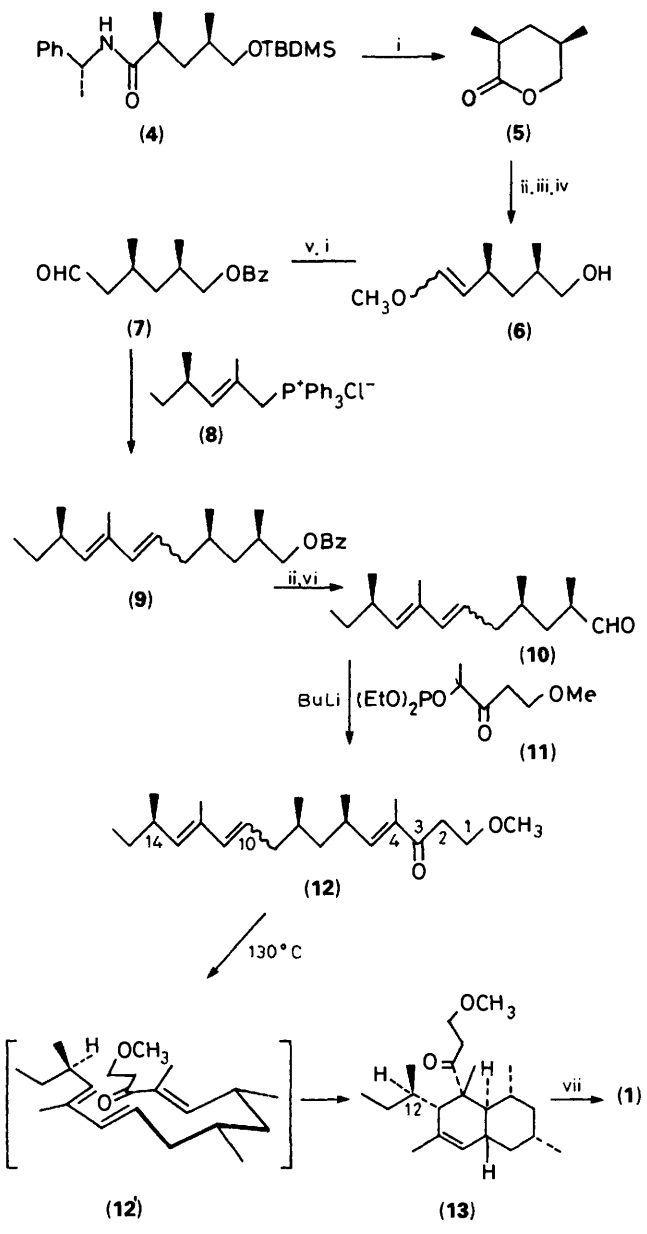
† All new compounds gave spectroscopic data in agreement with the assigned structures.

‡ Levorotatory lactone (−)-(**5**) ($[\alpha]_D^{24}$ −38.1 °C, *c* 1.17, $CHCl_3$) obtained from the diastereoisomer of (**4**) was also converted into the aldehyde (**14**), which is synthetically equivalent to (**7**), in 43% yield through five steps: i, 1 equiv. $LiAlH_4$, −20 °C, 30 min; ii, propane-1,3-dithiol, BF_3·OEt_2 in $CHCl_3$, room temp. 2 h; iii, CCl_4, PPh_3, reflux, 4 h; iv, NaCN in DMSO, 100 °C, 2 h; v, DIBAH in toluene, −70 °C ⟶ room temp., 3 h.



(**14**)

§ Syntheses of dienes by Kocienski–Lythgoe–Julia method (*J. Chem. Soc., Perkin Trans. 1*, 1978, 829) were also undertaken, but the chemical yields were below 41%.



Scheme. *Reagents and conditions:* i, H^+; ii, $LiAlH_4$; iii, $Ph_2P(O)CH_2OMe$, BuLi; iv, NaH; v, Bz_2O; vi, $(COCl)_2$, Me_2SO; vii, $AlCl_3$, EtSH.

afforded the 4*E* trienones (**12**) in 44% yield together with the 4*Z*-isomers in 14% yield. The intramolecular Diels–Alder reaction of the trienones (**12**) (benzene solution in a sealed tube, 130 °C, 4 days) proceeded slowly through an assumed transition state (**12'**) to give the cycloadduct (**13**) along with *ca.* 10% of the 12*S*-isomer in 44% yield. The 10*Z*-isomer of the trienones (**12**) was recovered unchanged from the cyclization,[4,5] whilst the desirable (10*E*,14*R*)-trienone reacted at a slightly higher rate in the Diels–Alder reaction than the corresponding 14*S*-isomer.¶ Separation of (**13**) and its 12*S*-isomer‖ was attained by low pressure LC on silica gel (hexane–ether, 93:7), to give the major isomer (**13**), $[\alpha]_D^{23}$ −16° (*c* 1.0, MeOH), identical in every respect (mass, IR, ^1H NMR, TLC) with the methyl ether of natural probetaenone I ($[\alpha]_D^{23}$ −17 °C, *c* 1.0, MeOH). Demethylation of (**13**) ($AlCl_3$, EtSH in CH_2Cl_2, −10 °C, 4 h, 23% yield) gave probetaenone I, which was identical in every respect (mass, IR, ^1H NMR, TLC) with the natural compound.

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¶ We lowered the reaction temperature to *ca.* 100 °C, but the difference of the Diels–Alder reaction rates of 14*R*- and 14*S*-trienones was too small to realize the kinetic resolution of these isomers.

‖ Although the yield of the 12*S*-isomer of (**13**) was too low for it to be isolated, satisfactory spectroscopic data (LR and HR-MS, IR, ^1H NMR) were obtained for the racemic substance synthesized from the racemic segments (**7**) and (**8**).

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