A Total Synthesis of (+)-Perrottetianal A

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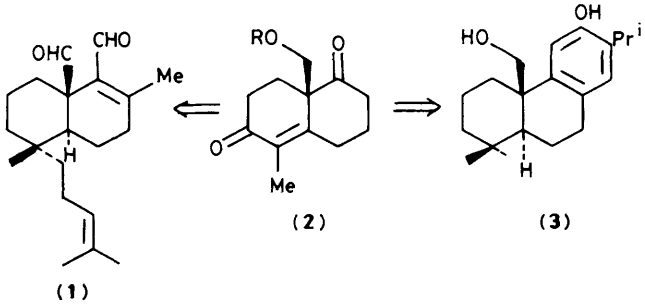
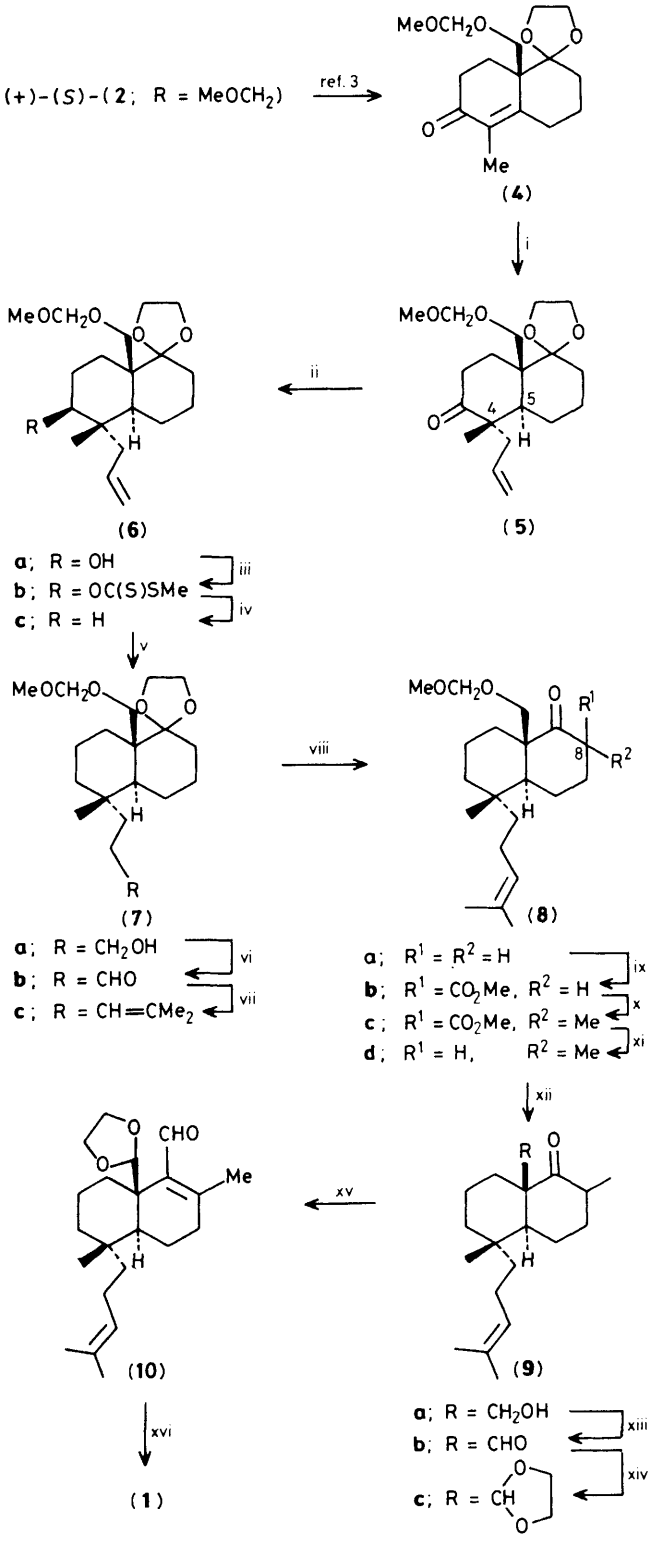
A total synthesis of (+)-perrottetianal A (**1**), one of the sacculatane diterpenes, has been achieved; the absolute stereochemistry of (**1**) is thus established as 4*S*,5*S*,10*R*.

Diterpenoids having an angular oxygenated-methyl-substituted hydronaphthalene skeleton often possess prominent biological activities, as exemplified by the insect antifeedant clerodanes.[1] As versatile starting materials for synthesis of such natural products in optically active form, we have reported the preparation of optically active Wieland–Miescher ketone analogues (**2**) bearing an angular protected hydroxymethyl group.[2] The potential of these compounds (**2**) in natural product synthesis has been demonstrated already by the total synthesis of (+)-pisiferol (**3**) from the protected methoxymethyl derivative (+)-(*S*)-(**2**; R = $MeOCH_2$).[3] We disclose here a total synthesis of (+)-perrottetianal A (**1**), a



(**1**) (**2**) (**3**)



Scheme 1. *Reagents:* i, Li, liq. NH_3, CH_2=$CHCH_2Br$, H_2O (1 equiv.); ii, LAH, Et_2O; iii, Bu^nLi, THF, CS_2, MeI, room temp., iv, Bu^n_3SnH, AIBN, toluene, reflux; v, BH_3, THF, then NaOH, H_2O_2; vi, PDC, 4Å molecular sieve, CH_2Cl_2; vii, Ph_3P=$C(Me)_2$, Et_2O; viii, PPTS, aq. acetone, reflux; ix, NaH, $(MeO)_2CO$, 15-crown-5, THF; x, NaH, MeI, HMPA: xi, LiCl, HMPA, 130 °C; xii, conc. H_2SO_4 (catalytic), aq. EtOH; xiii, $(COCl)_2$, Me_2SO, Et_3N, CH_2Cl_2; xiv, $(CH_2OSiMe_3)_2$, $Me_3SiO_3SCF_3$, CH_2Cl_2; xv, LDA, CH_2Cl_2 then $LiClO_4$, $CaCO_3$, HMPA, 130 °C; xvi, PPTS, aq. acetone, 80 °C.

sacculatane-type dialdehydic diterpene, isolated from the liverwort *Porella perrottetiana* or *Makinoa crispata*, the absolute stereochemistry of which has been tentatively assigned by comparison of the c.d. spectrum with that of a sesquiterpenoid, (−)-polygodial.[4] (+)-Perrottetianal A (**1**) has a weak inhibitory activity towards germination of rice in the husk.

The known enone (**4**)[3] {$[\alpha]_D$ +88.7° (*c* 0.11 in $CHCl_3$), 100% enantiomer excess} was subjected to reductive allylation by treatment with lithium–liquid ammonia in tetrahydrofuran (THF) and then allyl bromide, to provide the allylated *trans*-decalone (**5**)† in 92% yield as sole product. Attempted direct alkylation with 1-iodo-4-methyl-pent-3-ene gave only the reduction product. Assignment of stereochemistry at C-4 and C-5 in compound (**5**) followed from analogous examples of reductive alkylation of octalone derivatives,[3,5] and by conversion of (**5**) into the natural product (**1**). All attempts failed to eliminate directly the ketone function of (**5**), probably because of steric hindrance due to the substituents at C-4. The ketone function was therefore removed in a stepwise manner. Reduction with lithium aluminium hydride (LAH) gave the alcohol (**6a**) (97%), which was converted into the xanthate (**6b**) (quantitative) by successive treatment with n-butyl-lithium, carbon disulphide, and MeI. Reduction of (**6b**) with tributylstannane catalysed by 2,2′-azoisobutyronitrile (AIBN)[6] gave the decalin (**6c**) in 82% yield.

The allyl group of the decalin (**6c**) was transformed into the 4-methylpent-3-enyl group of the target molecule in a straightforward manner. Hydroboration to the alcohol (**7a**) (75%), followed by oxidation with pyridinium dichromate (PDC) to the aldehyde (**7c**) (88%) in the presence of 4 Å molecular sieves,[7] and finally a Wittig condensation of the aldehyde (**7b**) with isopropylidenetriphenylphosphorane afforded the desired intermediate (**7c**) in 68% yield. Selective deprotection of the ring acetal function in (**7c**) was achieved with pyridinium toluene-*p*-sulphonate (PPTS)[8] in refluxing aqueous acetone to give the decalone (**8a**) (quantitative). Since attempted direct methylation with lithium di-isopropylamide (LDA) or KH resulted only in the recovery of (**8a**), a methoxycarbonyl functionality was introduced by the reaction of (**8a**) with NaH, $(MeO)_2CO$, and 15-crown-5 giving the β-keto ester (**8b**) (95%). Methylation of compound (**8b**) with NaH and MeI in the presence of 4 equiv. of hexamethylphosphoric triamide (HMPA) (97%), followed by demethoxycarbonylation of the product (**8c**) with LiCl in HMPA, yielded compound (**8d**) in 92% yield.

Of the two aldehyde groups in the target molecule (**1**), the one at the ring junction was produced first. Removal of the methoxymethyl group of (**8d**) with a catalytic amount of conc. H_2SO_4 in refluxing aqueous ethanol (EtOH) [88% based on recovered (**8d**)] and Swern oxidation[9] of the resulting alcohol (**9a**) produced the aldehyde (**9b**) (91%), which was protected selectively by acetal formation with ethylene glycol bistrimethylsilyl ether (trimethylsilyl trifluoromethanesulphonate as catalyst)[10] to give (**9c**) (86%). The α,β-unsaturated aldehyde group was introduced according to the Nozaki-Yamamoto procedure,[11] giving (**10**) in 64% yield. Finally, deprotection of (**10**) completed the synthesis of (+)-perrottetianal A (**1**) (78%), $[\alpha]_D$+395° (*c* 0.05, $CHCl_3$) [lit.,[4] +282° (*c* 2.0, $CHCl_3$)], identical (^{1}H n.m.r., i.r., and mass spectral) with the natural material. Thus, the absolute stereochemistry of (**1**) was unambiguously established as 4*S*,5*S*,10*R*, as depicted.

† All yields refer to pure isolated products, which exhibited satisfactory ^{1}H n.m.r., i.r., and high resolution mass spectra and/or elemental analyses.

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