Total Synthesis of (+)-Dysideapalaunic Acid

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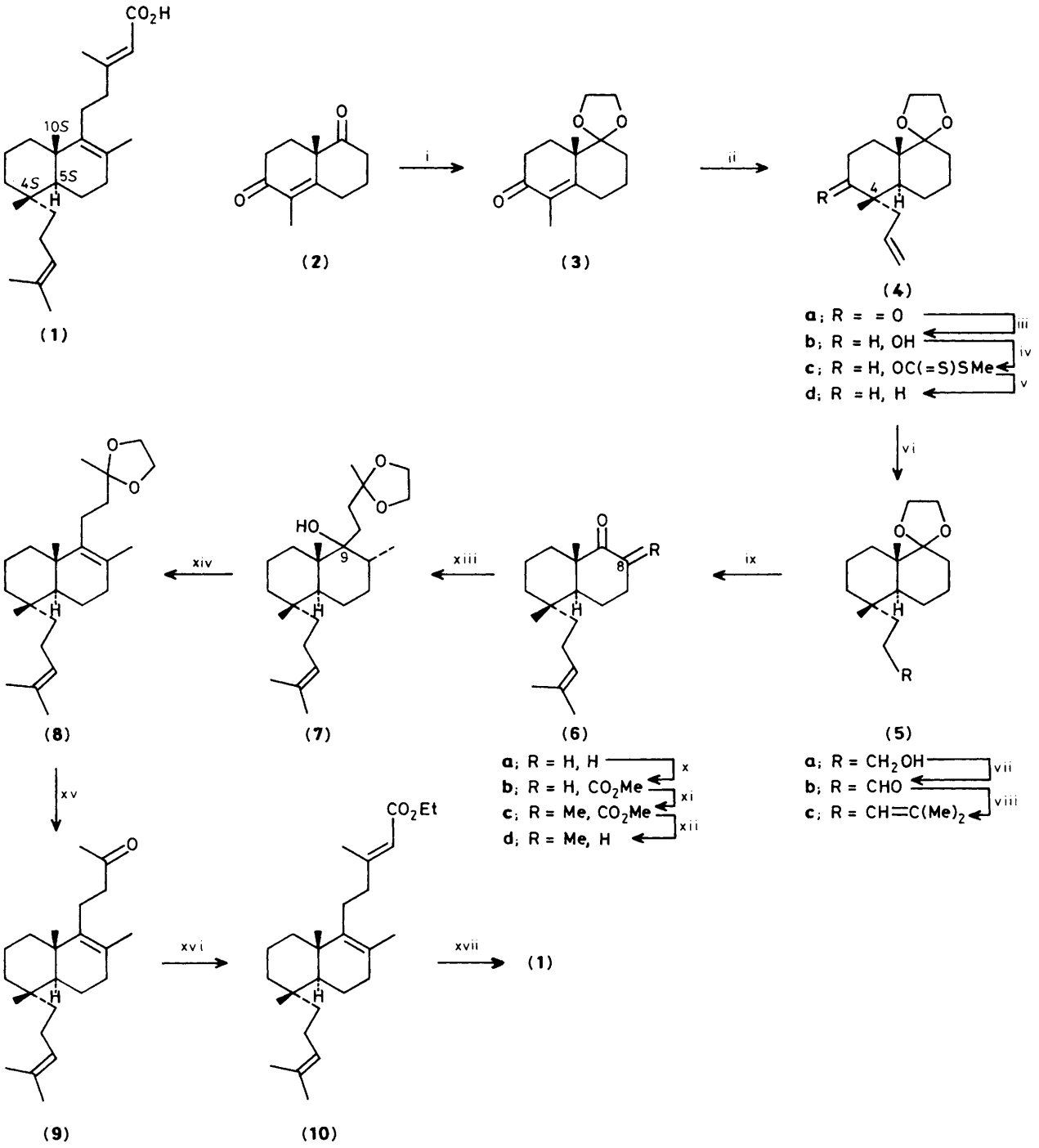
The total synthesis of (+)-dysideapalaunic acid (**1**), a sesterterpenic aldose reductase inhibitor, has been accomplished; the absolute stereochemistry of (**1**) is thus established as 4*S*,5*S*,10*S*.

An inhibitor of aldose reductase is expected to prevent neuropathy or cataract as a complication of diabetes: these diseases are caused by the accumulation of sorbitol in the peripheral nerve or the crystalline lens, as a result of enzymic reduction of glucose by the aldose reductase in the sorbitol cycle.[1] Owing to increasing therapeutic need, the inhibitors of aldose reductase are being actively investigated; recently Nakagawa *et al.* isolated some metabolites which inhibit aldose reductase from the marine sponge *Dysidea sp.* in Palauan sea.[2] Among the active principles isolated was dysideapalaunic acid (**1**), a new sesterterpenic acid having an uncommon structure with sacculatane and labdane units in the



Scheme 1. *Reagents and conditions*: i, $(CH_2OH)_2$, D-CSA, butan-2-one ethylene acetal, 45 °C; ii, Li, liq. NH_3, CH_2=$CHCH_2Br$, H_2O (1 equiv.); iii, LAH, Et_2O, −50 °C; iv, Bu^nLi, THF, CS_2, MeI, room temp.; v, Bu_3^nSnH, ABIBN, xylene, reflux; vi, BH_3·THF, THF, then NaOH, H_2O_2, ice-bath then room temp.; vii, $(COCl)_2$, Me_2SO, Et_3N, CH_2Cl_2, −65 to −20 °C; viii, Ph_3P=CMe_2, Et_2O, ice-bath then room temp.; ix, PPTS, aq. Me_2CO, reflux; x, NaH, $(MeO)_2CO$, THF, room temp.; xi, NaH, MeI, THF, room temp.; xii, LiCl, HMPA, 130 °C; xiii, 4-bromobutan-2-one ethylene acetal, Mg, THF, ultrasonic then reflux; xiv, $SOCl_2$, pyridine, ice-bath temp.; xv, PTSA H_2O, aq. Me_2CO, reflux; xvi, NaH, $(EtO)_2P(=O)CH_2CO_2Et$, THF, reflux; xvii, aq. 15% NaOH, EtOH, reflux.

molecule, the absolute stereochemistry of which has not yet been assigned.[2] In view of the current interest in bioactivity,[1] along with our recent observations on the synthesis of the diterpenoid sacculatane,[3] we now delineate our synthesis of natural (+)-dysideapalaunic acid (**1**) and determination of its absolute stereochemistry.

The known optically active ene-dione (**2**)[4] {$[\alpha]_D$ +112° (*c* 0.13 in MeOH); 80% enantiomeric excess} was selectively protected by acetal exchange with the ethylene acetal of butan-2-one to give the acetal (**3**) [89%† after a recycle of

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

recovered (**2**)]. Treatment of (**3**) with lithium–liquid ammonia in tetrahydrofuran (THF) and then allyl bromide provided the allylated *trans*-decalone (**4a**) in 70% yield as sole product. The relative stereochemistry at C-4 and C-5 of compound (**4a**) is assigned on the basis of analogous examples of reductive alkylation and the final conversion into the natural product (**1**). Since attempts to eliminate the ketone functionality of (**4a**) by Wolff–Kishner reduction failed, Barton's protocol[5] for free radical deoxygenation was employed. Reduction of (**4a**) with lithium aluminium hydride (LAH) gave the alcohol (**4b**) (quantitative), which was transformed into the dithiocarbonate (**4c**) by successive treatment with n-butyl-lithium, carbon disulphide, and MeI. Radical cleavage of the carbon–oxygen bond in (**4c**) with tributylstannane catalysed by 2,2′-azobisisobutyronitrile (ABIBN) afforded the decalin (**4d**) in 86% yield from (**4b**).

The requisite 4-methylpent-3-enyl chain of (**1**) was furnished by hydroboration of (**4d**) to give the alcohol (**5a**) (58%), followed by Swern oxidation[6] to the aldehyde (**5b**) (77%), and then a Wittig condensation with isopropylidenetriphenylphosphorane. Thus, the desired intermediate (**5c**) was obtained in 81% yield. Deprotection of (**5c**) was achieved with pyridinium toluene-*p*-sulphonate (PPTS) in refluxing acetone to give the key precursor (**6a**) (quantitative) for the synthesis of sacculatane diterpenoids.‡ To avoid overmethylation at C-8 (**6a**), a methoxycarbonyl group was introduced with NaH and dimethyl carbonate in THF to give (**6b**) (87%). Methylation of (**6b**) with NaH and MeI (77%) followed by demethoxycarbonylation of the product (**6c**) with LiCl in hot HMPA yielded compound (**6d**) (72%).

Elongation of the side chain at C-9 of (**6d**) was achieved by addition of the Grignard reagent ultrasonically generated from 4-bromobutan-2-one ethylene acetal[7] to give the adduct (**7**) (82%). Dehydration with $SOCl_2$ in pyridine produced the unsaturated acetal (**8**) (86%), which was deprotected with toluene-*p*-sulphonic acid monohydrate ($PTSA \cdot H_2O$) in refluxing aqueous acetone to afford the ketone (**9**) (quantitative). Condensation of (**9**) with the Horner–Emmons reagent in refluxing THF led to a single unsaturated ester (**10**) (quantitative). Finally, hydrolysis of (**10**) completed the synthesis of (+)-dysideapalaunic acid (**1**) (67%), $[\alpha]_D$ +58° (*c* 0.33 in $CHCl_3$) [lit.,[1] +61° ($CHCl_3$)], identical (^1H n.m.r., i.r., and mass spectra) with the natural material. Thus, the absolute stereochemistry of (**1**) was unambiguously established as 4*S*,5*S*,10*S*, as depicted.

We thank Drs. M. Nakagawa and M. Endo, Suntory Institute for Biomedical Research, for the spectral data of natural (+)-dysideapalaunic acid (**1**).

Received, 22nd February 1988; Com. 8/00662H

‡ A strong tumour promoter, sacculatal, has been synthesised from the intermediate (**6a**). The results will be reported in due course.

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