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Synthesis of Polygodial[1]

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Polygodial[2], isolated from Polygonum hydropiper L., was elucidated to have the structure (X), to which the other names tadeon [3], tadeonal[4] and tadenal[5] were also proposed by independent research groups. From a synthetical point of view, polygodial is of special interest since it has two formyl groups in close positions on a driman skeleton. Polygodial is reported to be fairly unstable as in the case of helminthosporal[6,7] which has also two formyl groups in the molecule.

We have previously reported the syntheses of drimenin (IV) and cinnamolide (V) as shown in the chart[8,9,10] starting from monocyclofarnesic acid (I). This communication describes the conversion of (±) cinnamolide to the polygodial, which means the completion of the total synthesis of the latter compound in a dl-form.

Sodium salt (VIa) of cinnamolide, obtained by hydrolysis with methanolic sodium hydroxide, was converted to the corresponding methyl ester (VIb) by simultaneous addition of diazomethane in ether and diluted hydrochloric acid under vigorous stirring. The reaction products consist of a mixture of V and VIb, which, without separation owing to the labile nature of VIb in contact with silica gel, was oxidized with chromic trioxide-pyridine complex[11] to afford a mixture of formyl ester (VII) and V. Since these two compounds were closely located on a developed silica gel thin layer plate, the mixture was, without separation, treated with methyl orthoformate in the presence of *p*-toluenesulfonic acid to give a mixture of VIII and V, which were separated by silica gel chromatography to isolate white crystal VIII in ca 30% overall yield from the cinna-

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molide. No other products excepting VIII and V were separated by the chromatography indicating the sequence of the above reactions proceeded exclusively from VI. VIII; mp 71-73°; IR(CCl_4) 1719, 1120, and 1073 cm^{-1}; NMR(CCl_4)[12] 2.55(C_9-H, d, 6 Hz), 3.28(6H, s), 3.70(3H, s), 4.25(C_{11}-H, d, 6 Hz), and 6.82(C_7-H, m) ppm. Reduction of VIII with lithium aluminum hydride and subsequent treatment with active manganese dioxide yielded acetal aldehyde (IX) quantitatively. IX; mp 108-110°, IR(CCl_4) 1688, 1130, and 1077 cm^{-1}, NMR(CCl_4) 3.31 and 3.42(3H, each, two methoxyl groups), 4.79(C_{11}-H, d, 3 Hz), 6.82(C_7-H, m), and 9.59(C_{12} -H, s). Stirring of IX in aqueous acetone in the presence of oxalic acid afforded a hydrolyzed product (X), the IR spectrum of which in carbon tetrachloride was completely superimposable with that of natural polygodial.

Although the compound X, thus synthesized, formed two major condensation products on treatment with 2,4-dinitrophenylhydrazine as in the case of natural polygodial and the 2,4-dinitrophenylhydrazones could not be clarified exactly, the sequence of the synthetic route as well as the identity of IR spectrum confirm unequivocally the structure of polygodial proposed by Barnes and Loder.

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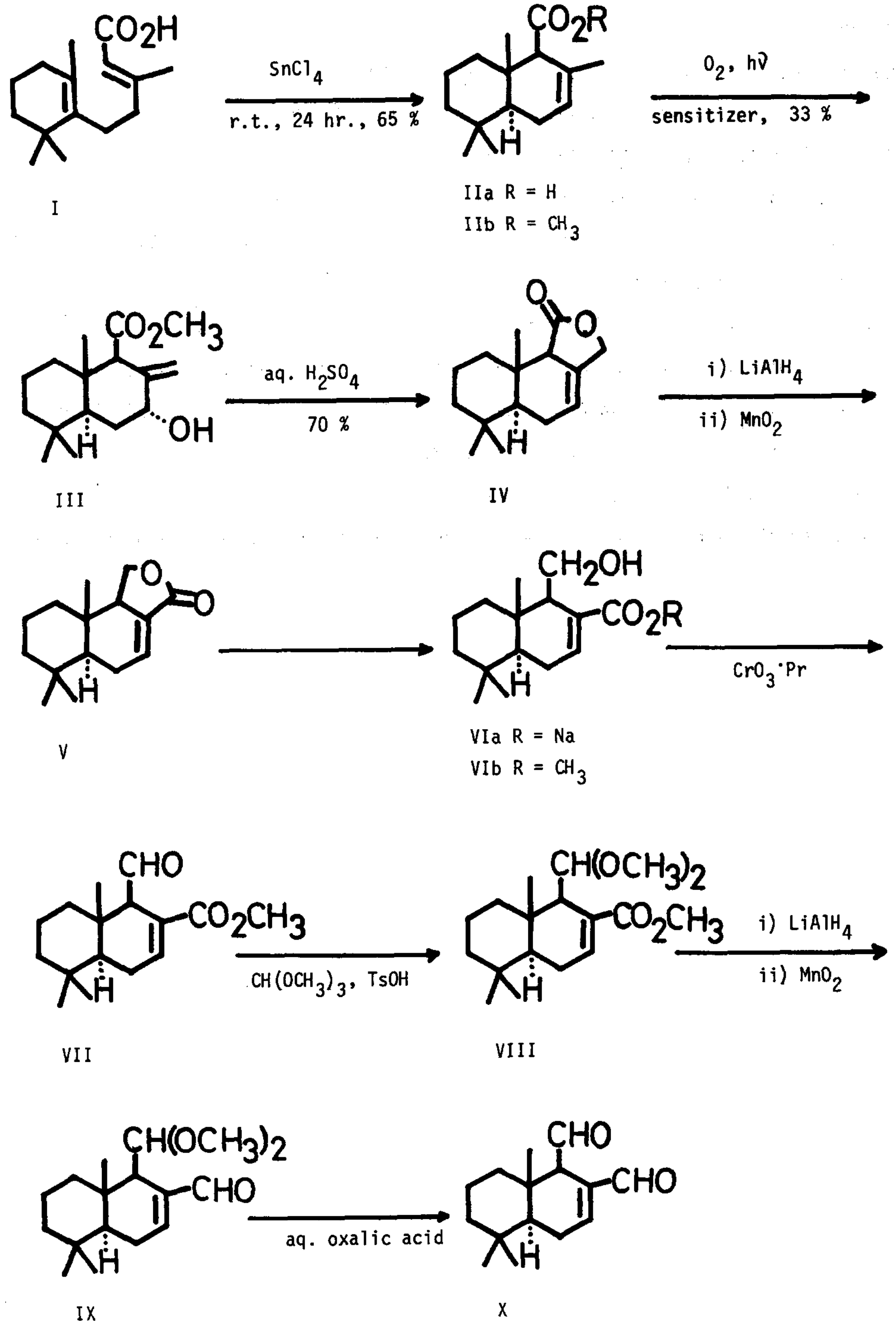
CO2H
SnCl4
r.t., 24 hr., 65 %
CO2R
H
O2, hν
sensitizer, 33 %
I
IIa R = H
IIb R = CH3
CO2CH3
OH
H
aq. H2SO4
70 %
O
O
H
i) LiAlH4
ii) MnO2
III
IV
O
O
H
CH2OH
CO2R
H
CrO3·Pr
V
VIa R = Na
VIb R = CH3
CHO
CO2CH3
H
CH(OCH3)3, TsOH
CH(OCH3)2
CO2CH3
H
i) LiAlH4
ii) MnO2
VII
VIII
CH(OCH3)2
CHO
H
aq. oxalic acid
CHO
CHO
H
IX
X

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12. NMR were measured with Varian T-60 with chemical shifts given in ppm down field from internal TMS