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A SYNTHETIC APPROACH TO PORTULAL

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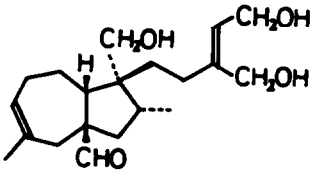
Portulal 1 is a diterpene which has been isolated from Portula grandiflora as an unique plant growth regulator[2]. Structurally it has the perhydroazulene skeleton with a clerodane type substitution. We report here the stereospecific synthesis of this structure starting from the Diels-Alder adduct 2[3] between 1-vinylcyclohexene and chloromethylmaleic anhydride.

2 was reduced with $LiAlH_4$ at room temperature to afford the diol 3 (92% yield)[4]. All attempts to effect the substitution reactions of the neopentyl type chlorides 2, 3 and 4 failed, presumably because of the steric hindrance strengthened by the presence of polar groups and the field effect. This difficulty was circumvented by conducting the reaction (NaCN-NaI-DMSO at 120-125°) on the cyclic ether 5 derived quantitatively from 2 by the treatment with tosyl chloride and pyridine. Thus the substitution product 6 was obtained in 94% yield. 6 was converted to the glycol 7 ($KMnO_4$-NaOH-t-BuOH-H_2O, -8°, 3 min, 70% yield) and then to the monotosylate 8, m.p.179-181°, which rearranges smoothly upon basic treatment (t-BuOH-t-BuOH)[5] to give perhydroazulenoid ketone 9. Regiospecific cleavage of the cyclic ether linkage and hydrolysis of the cyano group were achieved simultaneously by the treatment with 57% hydroiodic acid and red phosphorus in refluxing acetic acid to afford the iodide 10 (94.4% yield), which was deiodinated quantitatively to provide the keto-lactone 11, m.p.118-120° (Zn-AcOH, r.t.). Our concern was directed in this stage to the stereospecific introduction of the angular substituent in 1. The carbene addition to the enol ether or acetate[6] of 11 appeared to be an attractive measure but all attempts in this line were fruitless. The alkylation according to Ireland's procedure[7] also

failed. The extreme inactivity of 11 for these reactions is probably due to the steric hindrance on the convex side of the enolated molecules, caused by the carboxyl methylene of the γ-lactone group. Therefore intramolecular methods of the alkylation were sought next. 11 was transformed to the single tricyclic ketol 12 in 94% overall yield by the successive treatments: 1. NaOMe-HCO_2Et in DME-benzene(3:2), r.t., 2. acrolein-Et_3N-AcOEt and 3. 10% HCl-EtOH, reflux. The stereochemistry of the newly introduced carbon bridge is confirmed by the nmr spectra of 12 added with $Eu(dpm)_3$. The inspection of the model shows that the aldol cyclization would become difficult in α-alkylated intermediate 13 which is in equilibrium with β-isomer, since severe steric interaction between the aldehyde group and hydroxyl methylene of the lactone would exist in transition state. The deoxygenation of 12, which is very sensitive both to acid and base, was performed in 54% overall yield by the sequence of the reactions: 1. isopropenyl acetate-TsOH, 2. ethanedithiol-$BF_3 \cdot Et_2O$-AcOH, 3 days, 3. Raney Ni-EtOH and 4. 2N NaOH-MeOH. The product 14 was oxidized quantitatively to the tricyclic keto-lactone 15, m.p.148-149°. The cleavage of the extra ring in 15 was performed by the conversion to an enol acetate (isopropenyl acetate-TsOH) followed by RuO_4-$NaIO_4$ oxidation and, after methylation, the dimethyl ester 16 was obtained in 48% yield. 16 was partially hydrolyzed to 17 (69%) which was decarboxylated by Kochi's procedure[8] to give 18. Upon the treatment with 6N H_2SO_4-EtOH under refluxing 18 provided the nicely crystalline dilactone 19, m.p.250-250.5°. This product has been derived by the degradation of natural portulal in the following way. Portulol 20, derived from 1 by $LiAlH_4$ reduction[9], was transformed to the iodo-ether 21 (I_2-KI-$NaHCO_3$-THF, 100%), which reverted on treatment with Zn-Ag couple in ether (81%). The ozonization of 21, followed by the successive treatments: 1. Me_2S, 2. Zn-Ag and 3. HIO_4, furnished 22 in 50% overall yield. Degradation of the δ-lactone ring in 22 (1. HCO_2Et, NaH and 2. H_2O_2-KOH-MeOH) afforded the γ-lactone 23 (70% yield), which was subjected to Jones' oxidation and following acid treatment to give 19, m.p.278-282°. The identity of the synthetic product with the specimen derived from natural portulal is secured rigorously (ir, nmr, mixed TLC and melting point determination).

Thus our synthetic intermediate 18 is confirmed to possess the complete



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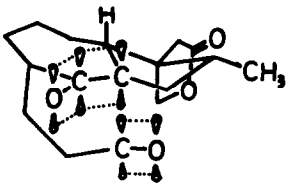

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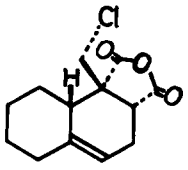

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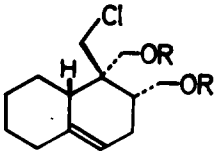
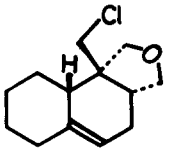


3 R=H
4 R=Ac



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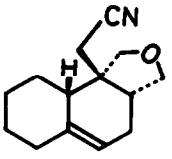

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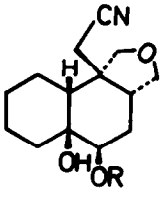
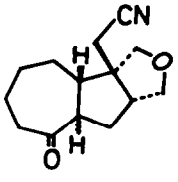


7 R=H
8 R=Ts



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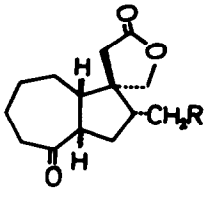
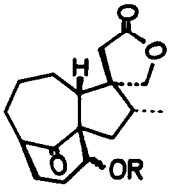
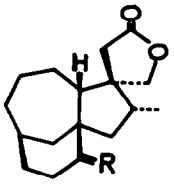


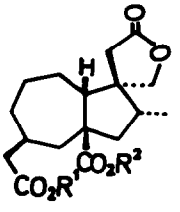
10 R=I
11 R=H



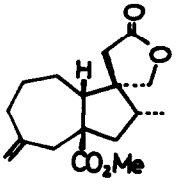
12 R=H



14 R=H, OH
15 R=O



16 $R^1=R^2=Me$
17 $R^1=H, R^2=Me$



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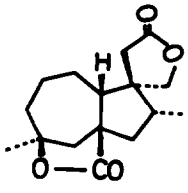

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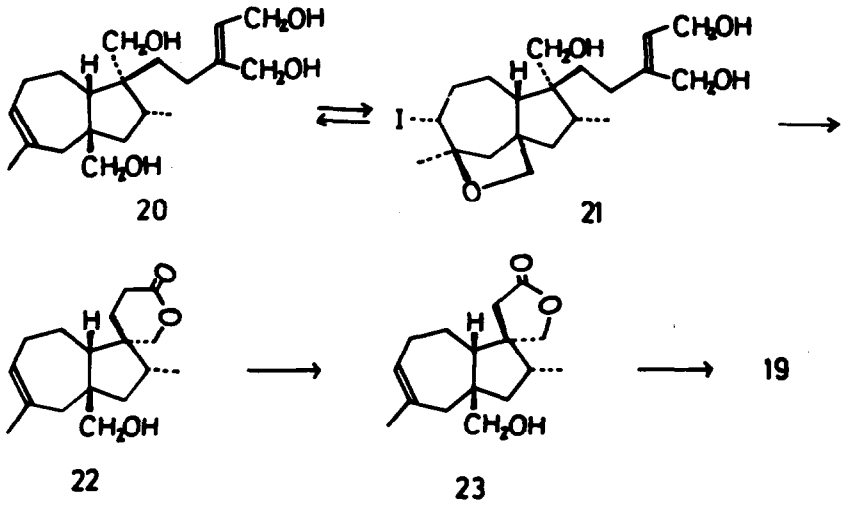
stereochemical feature of portulal 1. Works are under way to synthesize 1 from 18.



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