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TOTAL SYNTHESIS OF PORTULAL

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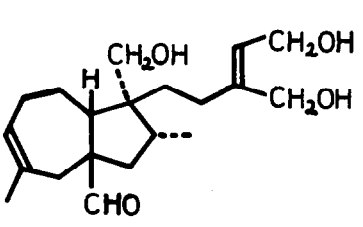
In the previous communication[1] we reported a stereospecific synthesis of the intermediate 2 which posseses the essential carbon skeleton with the correct stereochemistry and pertinent functionalities for the elaboration of portulal 1. The stereochemical validity of 2 has been confirmed by the correlation of 2 with the natural product via 3 and 4. We describe here the conversion of 2 to 1 using the degradation product 4 of natural 1 as a relay compound, which constitute, in conjunction with our previous result[1,2], a formal total synthesis of this unique diterpene.

The first objective of our synthesis was the conversion of 2 to 4. The obvious route would be the isomerisation of the terminal olefinic bond in 2 followed by the partial reduction of the angular carbomethoxy group to an alcohol group or vice versa. However our attempts to effect either of these processes on 2 all failed. Another route starting from the dicarboxylic acid 5, from which 2 is derived, was also fruitless. The half ester 6, obtained through the preferential esterification of 5, was convertible to the hydroxy ester 7, by thiol ester-Raney nickel reduction method[3], but the corresponding hydroxy acid could not be obtained owing to the extreme easiness of the lactone ring formation (seven membered!). Finally these difficulties has been circumvented as follows. 2 was smoothly reduced to the lactol 8 by Vitride solution [$NaAlH_2(OCH_2CH_2OCH_3)_2$] added with one equivalent of ethanol[4]. After tetrahydropyranylation, 8 was subjected to the treatment with $LiAlH_4$ and the resulted alcohol 10 was again protected. The bis-tetrahydropyranyl ether 11 was exposed to an olefin isomerising condition (t-BuOK-DMSO, 110°, 7 hr) and the product was successively



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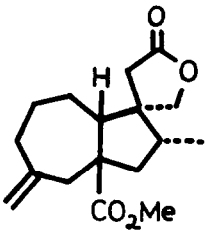

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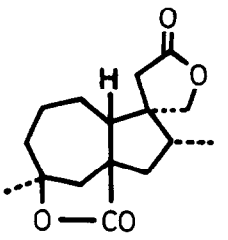

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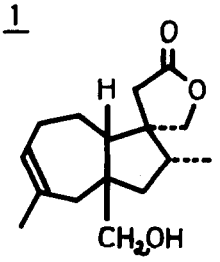

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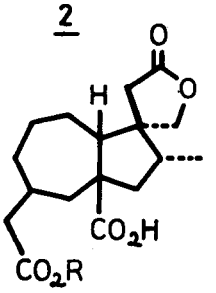
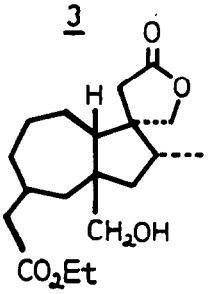


5 R = H, 6 R = Et



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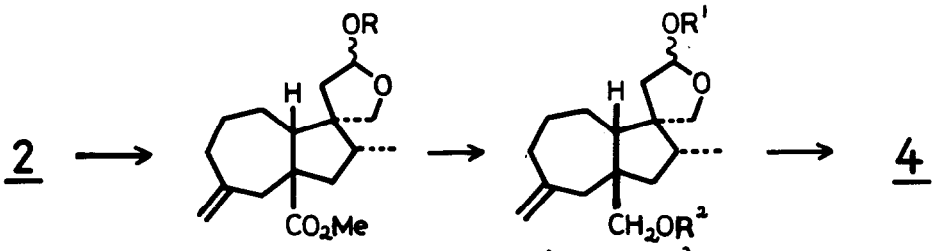
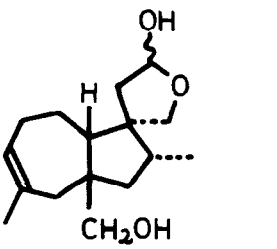
treated with dil. HCl-acetone and Ag_2O. The isomerisation occurs mostly in the desired direction and led to the formation of 4, contaminated with small amount of another product, possibly the double bond isomer, as revealed by the measurement of the nmr spectrum, although the ir spectrum is indistinguishable with that of 4 derived from natural 1. The identity of synthetic and natural 4 has been secured rigorously by the conversion of both samples to crystalline acetates (m.p. 117° and 145° respectively) and the comparison of spectral data. Thus 4 derivable from natural 1 served as a relay compound and our attention was directed to the introduction of four carbon unit for the completion of the side chain. For this aim β-furyl group seemed to be an



8 R = H
9 R = THP

10 R' = THP, R² = H
11 R' = R² = THP

attractive synthon. Firstly the reaction of β-furyl lithium[5] was carried out on the lactol 13, prepared from 4 by partial reduction with Vitride reagent but this merely resulted in the recovery of the starting material. Therefore the method of the side chain extention was explored on the model compound 14[2]. 14 was allowed to react with β-furyl lithium using an inverse addition procedure. The resultant hemiketal 15 was very liable to undergo dehydration and the product obtained after silica gel chromatography was the enol ether 16. However the reaction mixture above was added in situ with Vitride solution and the acetylation of the product yielded the diacetate 17. The allylic acetoxy group in 17 was removed by the hydrogenolysis with Li-liq.NH_3 without being accompanied by the reduction of furan ring to afford 18. This sequence of the reactions,



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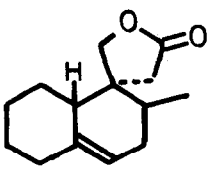

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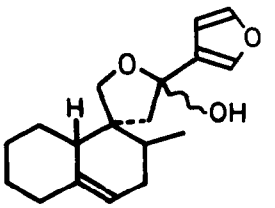

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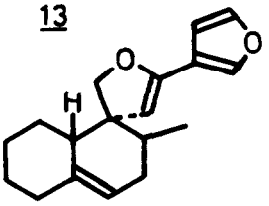

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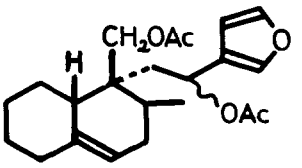

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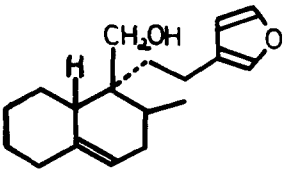

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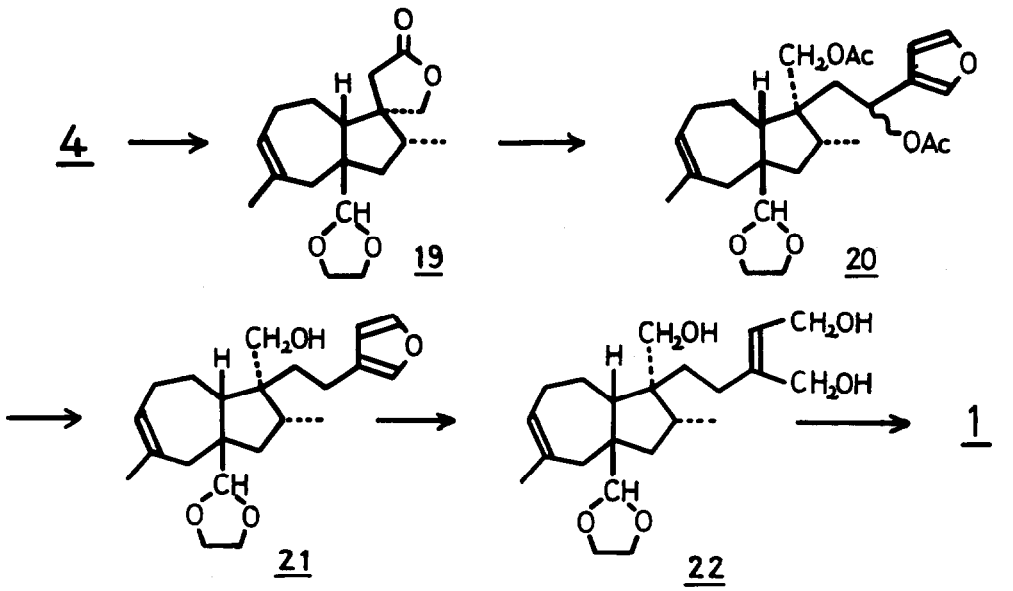
which had been secured on the model compound, was successfully applied to the aldehyde ethylene ketal 19, obtained from 4 by the oxidation with Collins reagent and following ketalisation. The series of the conversions gave rise to the β-furan compound 21 by way of 19 and 20. 21 was found to be identical with the compound derived from 1 by the treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone and ketalisation. The furan ring in 21 was modified by sensitized photooxygenation (Rose bengal) followed by reduction with Vitride to furnish 22. Since the 2-butene-1,4-diol system was found to be acid-sensitive[6] the



deketalisation of 22 (dil.HCl-acetone) was performed after the protection of this group as acetate and finally the product was hydrolyzed by methanolic NaOH to afford portulal 1.

REFERENCES AND NOTES

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3. E. Menárd, H. Wyler, A. Hiestand, D. Arigoni, O. Jeger and L. Ruzicka, Helv. Chim. Acta, 38, 1517(1955).
4. This procedure is found to be quite reproducible and can be used as an substitute of diisobutylalminum hydride. Details will be published elsewhere.
5. Y. Fukuyama, Y. Kawashima, T. Miwa and T. Tokoroyama, Synthesis, 443(1974).
6. cf. Y. Abe, E. Taniguchi, M. Eto and Y. Oshima, J. Agr. Soc., Japan, 45, 169 (1971).