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TOTAL SYNTHESIS OF FRAXINELLONE

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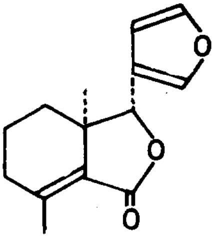
Fraxinellone(1) is a β-substituted furanoid lactone[1], isolated from several trees belonging to the Rutaceae and the Meliaceae[2,3]. Its biogenetic relationship with limonoid has been assumed on the basis of the common absolute configuration[3,4] and has received further support from the recent isolation of a closely related degraded limonoid, calodendrolide(2)[5]. We report here a total synthesis of fraxinellone.



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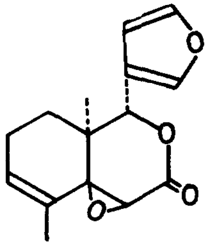
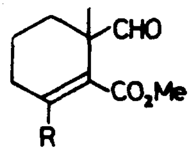
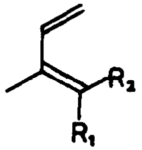


2

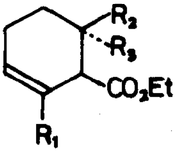
Our tactics of the synthesis was the preparation of the aldehyde ester 3 which would afford fraxinellone(1) with its diastereomer upon the reaction with 3-furyllithium. Methyl vinyl ketone was condensed with ethoxyethynyl magnesium bromide to give ethyl 3-methylpenta-2,4-dienoate(4) as a mixture of trans(4a) and cis(4b) forms (5:4) in 65% yield. The Diels-Alder reaction between the diene 4 and acrolein produced cis-6-carbethoxy-5-formyl-1-methylcyclohexene-1(5a) with small amount of trans adduct 5b and an unidentified product which is probably the 6-carbethoxy-4-formyl isomer. In addition cis-diene 4b was recovered unchanged and could be used for the reaction after irradiation at the presence of iodine which gave rise to the equilibrium mixture of a trans/cis ratio = 4:1. The treatment of the reaction mixture above with basic alumina afforded a product in which the trans aldehyde ester 5b predominated. The methylation of 5 using methyl iodide and conventional basic catalysts led to unsatisfactory results partly because of ready lactol formation. To overcome this difficulty the application of Wenkert procedure[6] *was examined using 3-carbethoxy-4-formylcyclohexene-1(6)*[7] *as a model compound. 6 was* firstly converted to the enol ether 7, ν_{max}1730, 1685, 1650 cm^{-1}, via the diethylacetal by the treatment with triethylorthoformate and anhydrous p-toluenesulfonic acid, and following pyrolysis. Selective carbene addition to 7 by means of Simmons-Smith reagent led to the formation of the cyclopropane derivative 8 in 88% yield as a mixture of stereoisomers, which were cleaved by refluxing with conc. HCl-EtOH(4:5). The product consisting of the normal ester 9 and the pseudo ester 10 were refluxed with 10% aq. KOH and then methylated with diazomethane to yield the conjugated ester 11, λ_{max}^{EtOH}213 nm(ε, 7100); ν_{max}2660, 1730, 1705, 1640 cm^{-1}; δ 1.24(3H, s), 3.64 (3H, s), 7.08(1H, t, J=4 Hz), 9.28(1H, s) by concomitant migration of trisubstituted double bond. The aldehyde ester 11 was tested for the second phase of fraxinellone synthesis -- namely the condensation reaction with 3-furyllithium. We have found this compound can be conveniently prepared from the reaction of more readily available 3-bromofurane with n-butyl lithium at -70° instead of using 3-iodofurane[8,9]. The reaction of 11 with 3-furyllithium proceeded smoothly to yield demethylfraxinellone(12) and its diastereomer 13 in a ratio of 3:4. The assignment of the configuration in both products was made on the basis of their n.m.r. spectra in which the signals of the angular methyl groups were observed at δ 0.84 and 1.32 respectively. The indirect methylation method thus proved to be effective in the model compound was applied to the aldehyde ester 5. However the acid cleavage of the cyclopropane derivative 15 obtained via the enol ether 14 were found to proceed in quite unanticipated manner. The main product of the reaction was the bicyclo(2·2·1)heptene derivative 16, M$^+$ = 238; λ_{max}^{EtOH} 232 nm(ε, 7200); ν_{max}1715, 1620 cm^{-1}; δ 1.12 (3H, t, J=7 Hz), 1.22(3H, s), 1.23(3H, t, J =7 Hz), 1.98(3H, s), 2.48(1H, dd, J=2,4 Hz), 2.76 (1H, br. s), 3.36(2H, m)[10], 4.16(2H, m)[10], presumably formed through intramolecular aldol-like condensation[11] of the intermediate carbonium ion 17. Unusual shielding(δ 2.76) of the proton attached to the bridging carbon(C-7) in the n.m.r. spectrum of 16 is partly explainable by the anisotropic effect of the double bond, since this signal was shifted to δ 3.12 in the dihydro derivative(16, $\Delta^{2,3}$ is saturated), obtained by catalytic hydrogenation. The desired products 3, 18 and 19 were detected only in minor quantities by preparative gas chromatography and the measurement of i.r. spectra. Eventually this discouraging situation was surmounted by the finding of a more direct method for the preparation of the methylated aldehyde ester 18. The reaction of ethyl 3-methylpenta-2,4-dienoate(4) with methacrolein at 110-120° for 20 hr did afford 18, ν_{max} 2700, 1740, 1730 cm^{-1}; δ o.96(3H, s), 1.28(3H, t, J=7 Hz), 1.72(3H, br.s), 2.80(1H, s), 4.04



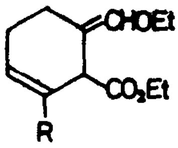
3 R=Me
11 R=H



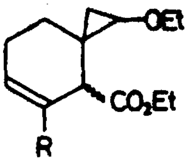
4a R_1=CO_2Et, R_2=H
4b R_1=H, R_2=CO_2Et



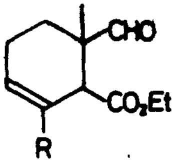
5a R_1=Me, R_2=CHO, R_3=H
5b R_1=Me, R_2=H, R_3=CHO
6 R_1=H, R_2,R_3=H,CHO



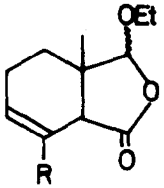
7 R=H
14 R=Me



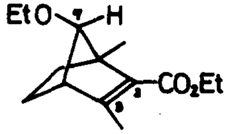
8 R=H
15 R=Me



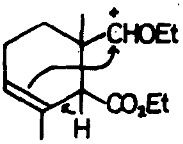
9 R=H
18 R=Me



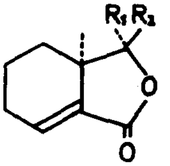
10 R=H
19 R=Me

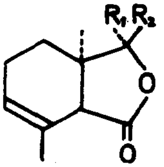


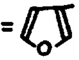
16

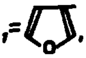


17





12 R_1=  , R_2=H
13 R_1=H, R_2= 

20 R_1=  , R_2=H
21 R_1=H, R_2= 

(2H, q, J=7 Hz), 5.48(1H,m), 9.48(1H, s) in 77.8% yield based on the *trans* compound *4a* in the diene mixture. When *18* was condesed with 3-furyllithium, a mixture of the diastereomers *20* and *21* was obtained in a ratio of 7:5. The both compounds were separated by the chromatography on neutral alumina and characterized by the measurement of i.r. and n.m.r. spectra. The treatment of above mixture with 5% MeOH-KOH under refluxing temperature afforded, after chromatography on neutral alumina, *dl*-fraxinellone as prisms, m.p.84-86°(*l*-form[1], m.p.116°), which was indistinguishable with natural specimen[3] in i.r., n.m.r. and mass spectra. Mixed m.p. determination of both samples did not show depression.

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REFERENCES AND NOTES

1. M. Pailer, G. Schaden, G. Spiteller and W. Fenzl, *Monatsh*. **96**, 1324(1965).
2. *Terpenoid and Steroids* -Vol. 1, Specialist Periodical Report, p.180, The Chemical Society, London(1971).
3. K. Nakanishi and T. Kurokawa, unpublished result. We had been informed from Prof. Nakanishi at March, 1969 the isolation of fraxinellone from *Dictamnus dasycarpus* and the assignment of its absolute configuration by means of ORD study.
4. P. Coggon, A. T. McPhail, R. Storer and D. W. Young, *Chem. Comm*. 828(1969).
5. J. M. Cassady and C.-S. Liu, *Chem. Comm*. 86(1972).
6. E. Wenkert, R. A. Mueller, E. J. Reardon,Jr., S. S. Sathe, D. J. Scharf and G. Tosi, *J. Am. Chem. Soc*. **92**, 7428(1970).
7. W. Cocker, T. B. H. McMurry and D. M. Sainsbury, *J. Chem. Soc*. 1153(1966).
8. S. Gronowitz and G. Sörlin, *Arkiv för Kimi* **19**, 515(1962).
9. L. Mangoni, M. Adinofi, G. Laonigro and R. Caputo, *Tetrahedron* **28**, 611(1972).
10. The multiplicity of these signals indicated nonequivalence of the methylene protons both in carbethoxy and ethoxy groups. cf. for examples: W. L. Meyer, D. L. Davis, L. Foster, A. S. Levinson, V. L. Swain, D. C. Shew and R. F. Weddleton, *J. Am. Chem. Soc*. **87**, 1573(1965), G. M. Whitesides, D. Holz and J. D. Roberts, *ibid*. **86**, 2628(1964) and references cited therein.
11. We have in mind the investigation on *16* directing the scope of its formation reaction and the n.m.r. peculiarities as well as further structure proof.