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A ROUTE TO LARGE CARBOCYCLES USING AN ALICYCLIC CLAISEN REARRANGEMENT.

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Summary: A potentially general route to large carbocycles is described involving a Claisen rearrangement of silyl enolates derived from appropriate unsaturated macrolides.

The Claisen rearrangement of both allyl aryl and allyl vinyl ethers is an extremely valuable synthetic method.[1] A useful variant of this reaction is the rearrangement of silyl enolates of allyl esters, leading to γ, δ-unsaturated carboxylic acids, developed primarily by Ireland.[2] This method offers the twin advantages of readily available starting materials and milder rearrangement conditions. Our idea was to apply this method to the synthesis of large carbocycles (3) by rearrangement of the enolates (2) derived from appropriate unsaturated macrolides (1). Until recently, there were no efficient, general syntheses of such macrolides but due to the notable efforts of Corey, Masamune, Mukaiyama and Gerlach, among others, a number of methods are now available for their elaboration, usually from the corresponding ω-hydroxy-acids.[3] The transformation (1) → (3) has previously been shown by Danishefsky[4a] to be useful for the preparation of six- and seven-membered carbocycles from ω-vinyl-valerolactones and caprolactones and used in an elegant synthesis of the sesquiterpene widdrol.[4b] A recent report by Funk et.al.[5] which further extends this idea prompts us to report our own results in this area.

As starting materials, we used the readily available ω-oxo-esters (4a) and (4b). The former was obtained by ozonolysis of methyl 10-undecenoate while (4b) was prepared from cyclododecanone by sequential Baeyer-Villiger oxidation, methanolysis and oxidation using pyridinium chlorochromate. These were then converted into the hydroxy-acids (5a) and (5b) by reaction with vinyl magnesium bromide at -78°C followed by saponification and also into the hydroxy-acids (6a) and (6b) by Wittig reaction with formyltriphenylphosphorane followed by borohydride reduction and saponification. Good yields were obtained in all these steps. We next examined a number of procedures[3] for the lactonisation of the hydroxy-acids (5a,b) and (6a,b). While these were moderately successful, they were not amenable for the preparation of multigram quantities of the required macrolides as expensive reagents and high dilution conditions were required. These problems were overcome by converting the hydroxy-acids to the corresponding allylic chlorides (5c,d) and (6c,d), and using the lactonisation procedure of Galli and Mandolini[6] (see below). Initially, a major drawback with the approach was that both isomers of the allylic chloride were formed from a single hydroxy-acid; for example, treatment of hydroxy-acid (5b) with thionyl chloride gave a mixture of (6d) and (5d) in a ratio of 77:23. However, both (6a) and (6b) could be cleanly converted into the

corresponding chlorides (6c) and (6d) by using hexachloroacetone and triphenylphosphine at -78°C → 0°C in > 70% isolated yield.[7] The hydroxy-acids (5a) and (5b) were also converted into the chlorides (5c) and (5d) respectively by using the same reagent mixture but at room temperature. In these cases, the regioselectivity was > 90%. The macrolides (7a,b) and (8a,b) were prepared by adding a solution of the corresponding chlorides in DMSO *via* motor driven syringe to a hot suspension of potassium carbonate in DMSO.[6] A key factor with this method is that the macrolides can be isolated simply by continuous extraction of the reaction mixture with petrol (b.p. 40-60°), thus avoiding a tedious and wasteful aqueous work-up. (The residual DMSO may be distilled and re-used). In this way, the desired macrolides (7a,b) and (8a,b) were obtained in *ca.* 60% isolated yields, accompanied by 5-10% of the corresponding diolides.

After a number of trials, we found that the macrolides (7a,b) and (8a,b) could be efficiently converted into the corresponding silyl enolates (*c.f.* 2; R = $SiBu^tMe_2$) by reaction with two equivalents of hexane-free lithium diisopropylamide in THF-HMPA (3:1)[2] for 0.75h at -78°C, followed by quenching with t-butyldimethylsilyl chloride. After a simple aqueous work-up, the silyl enolates were refluxed in toluene for *ca.* 4h, and the products hydrolysed with HF in aceto-nitrile, then esterified (CH_2N_2) and chromatographed, to give the carbocycles (9a,b) and (10a,b)[2] in 60-70% overall, isolated, yields. This method therefore represents a relatively brief, efficient and potentially general route to medium-sized and large carbocycles. Unfortunately, the overall stereoselectivity in all the cases is rather low. The carbocycles (9a) and (9b) were isolated as 5:1 and 3:1 mixtures of the *cis* and *trans* isomers respectively while (10a) and (10b) were isolated as 1·2:1 and 1·5:1 mixtures respectively of the *trans*- and *cis*-isomers. Molecular models indicate that the rearrangements of the enolates derived from macrolides (7a,b) could proceed *via* a chair or boat-like transition state,[4a] if it is assumed that only (*Z*)-lithio- and hence the (*E*)-silyl enolates are formed[8], giving rise to the *trans*- or *cis*- carbocycles (9a,b) respectively. Similarly, reasonable chair and boat conformations can be constructed which account for the formation of both the *cis*- and *trans*- isomers of (10a,b) from the macrolides (8a,b)[5].

Finally, we have also examined the rearrangement of the 11-membered macrolide (11), readily prepared from 2-methyldimedone by the method of Mahajan[9]. Treatment of (11) with 3.5 eq. of LDA followed by trapping of both the ketone and lactone enolates with Bu^tMe_2SiCl and thermolysis in toluene resulted, after the usual work up, in the isolation of only two, separable, diastereoisomers in a ratio of 95:5. We have assigned structure (12) to the major isomer on the basis of spectral data and molecular models[5], assuming that the kinetic (*i.e.* the less substituted) enolate of the ketone and only the (*E*)-silyl enolate of the lactone function are formed[8]. The minor isomer is epimeric at the methyl group α- to the ketone group, and both are probably formed *via* a boatlike transition state.[5] Thus, in agreement with the findings of Danishefsky *et.al.*[4] and Funk *et. al.*[5], such rearrangements seem to have considerable potential for internal asymmetric induction.

Acknowledgements

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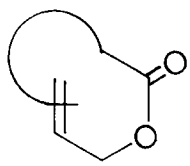
REFERENCES

1. S.J. Rhoads and N.R. Raulins, *Org.React.*, 1975, *22*, 1; G.B. Bennett, *Synthesis*, 1977, 589; F.E. Ziegler, *Acc.Chem.Res.*, 1977, *10*, 227.



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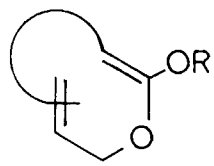

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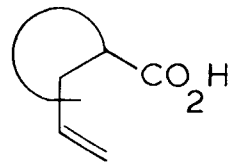

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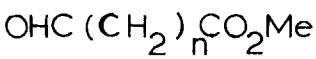

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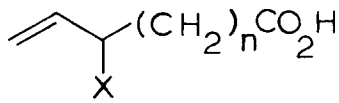
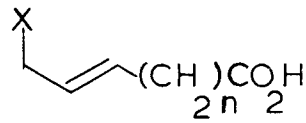
b; n=10



(5) a; n=8;X=OH
b; n=10;X=OH
c; n=8;X=Cl
d; n=10;X=Cl



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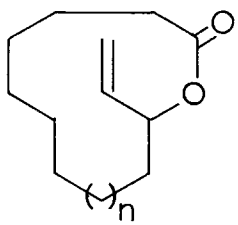

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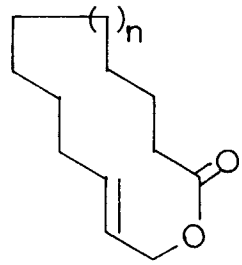

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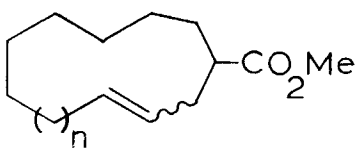

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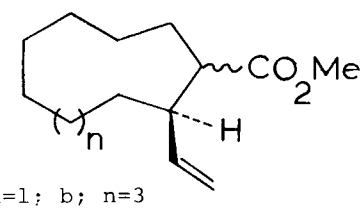

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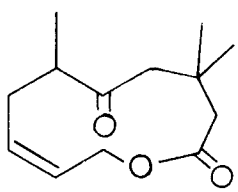

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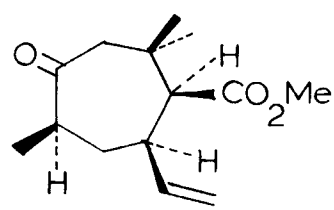

(12)

2. R.E. Ireland and R.H. Mueller, J.Am.Chem.Soc., 1972, 94, 5897; R.E. Ireland and A.K. Willard, Tetrahedron Lett., 1975, 3975; R.E. Ireland, A.K. Willard, and R.H. Mueller, J.Am.Chem.Soc., 1976, 98, 2868, J.Org.Chem., 1976, 41, 986; R.E. Ireland, S. Thaisrivongs, and C.S. Wilcox, J.Am.Chem.Soc., 1980, 102, 1155; R.E. Ireland, J.D. Godfrey, andS. Thaisrivongs, ibid., 1981, 103, 2446. See also, R.T. Arnold and C. Hoffmann, Synth. Commun., 1972, 2,27; J.E. Baldwin and J.A. Walker, J.Chem.Soc.,Chem.Commun., 1973, 117; J.A. Katzenellbogen and K.J. Christry, J.Org.Chem., 1974, 39, 3315; S.R. Wilson and R.S. Myers, ibid., 1975, 40, 3309; G.Fráter, Chimica, 1975, 29, 528.

3. For reviews, see K.C. Nicolaou, Tetrahedron, 1977, 33, 683; S. Masamune, G.S. Bates, and J.W. Corcoran, Angew. Chem. Int. Ed. Engl., 1977, 16, 585.

4. (a) S. Danishefsky, R.L. Funk, and J.F. Kerwin, Jr., J.Am.Chem. Soc., 1980, 102, 6889; (b) S. Danishefsky and K. Tsuzuki, ibid., p.6891.

5. M.M. Abelman, R.L. Funk, and J.D. Munger, Jr., J.Am.Chem.Soc., 1982, 104, 4030. These authors have introduced the term "alicyclic Claisen rearrangement" to describe transformations such as (1) → (3).

6. C. Galli and L. Mandolini, Org. Synth., 1978, 58, 98.

7. R.M. Magid, O.S. Fruchey, W.L. Johnson, and T.G. Allen, J.Org.Chem., 1979, 44, 359.

8. W.C. Still and I. Galynker, Tetrahedron, 1981, 37, 3981.

9. J.R. Mahajan, Synthesis, 1976, 110.

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