THE USE OF SELECTIVE LACTONISATION TO ACHIEVE CHEMODIFFERENTIATION

OF TWO CARBOXYLIC ACID FUNCTIONS. A NOVEL ENTRY INTO THE

ELEMANOLIDE SESQUITERPENES 1.

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<u>Summary</u>: The synthesis of the lactone(2), a proposed intermediate for the preparation of the elemanolide lactones, is described. The key to the synthetic route is the use of a selective lactonisation to permit two carboxylic acid functions to be chemically differentiated.

The elemanolide lactones are a group of cytotoxic plant products, one member of which, vernolepin(1), has attracted considerable synthetic interest². However, existing routes to vernolepin are lengthy and only one would appear to be readily adaptable to the preparation of other elemanolides³. We now present a synthesis of an intermediate (2) which possesses all the structural features for conversion to vernolepin and the other elemanolides, e.g.

melitensin (3). Additionally the synthetic route employed demonstrates a means of differentiating between two carboxylic acid functions by incorporating an hydroxyl function into a molecule such that selective lactonisation can be achieved.

We have previously described a facile method for the regio- and stereospecific formation of the cis-fused keto-ester (5) from the phenylthioindanone (4) in 91% yield⁴. Subsequent ester hydrolysis and iodolactonisation afforded the iodolactone (6) which upon treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave the keto-lactone (7) in an overall yield of 70%. Exclusive formation of the 0-silylated enolate (8) in 95% yield was followed by ozonolysis in acetone to give, after oxidative work up (Jones reagent),

65% of the dicarboxylic acid (9). This product was fully characterized as the diester (10), formed by treatment of the diacid with diazomethane, and exhibiting two distinct singlets at 63.73 and 63.67 in the nmr⁵. Selective reduction of the lactone in (9) with lithium borohydride gave, after acidic work up, 60% of the spirolactone (11) exhibiting characteristic ir absorptions at 1780 and 1710 cm⁻¹. A consideration of the other lactones that could be formed in this sequence shows that their formation is disfavoured on steric grounds. By this selective lactonisation we have essentially 'internally activated' one of the two carboxylic acid functions to further reaction. Thus reduction with a five-fold excess of diisobutyl-aluminium hydride of the spiro lactone (11) gave, after acidic work up, the required 6-lactone (2) in 45% yield. In conclusion, this differentiation of two equivalent functions permits the facile preparation of a general intermediate for the synthesis of the elemanolide lactones. The route is enhanced by the avoidance of any formal protection-deprotection sequence which is unusual in the synthesis of such a highly oxygenated compound.

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$$\begin{array}{c} \text{PhS O} \\ \text{H} \\ \text{ii., } \text{BrCH}_2\text{CO}_2\text{Me} \\ \text{H} \\ \text{(4)} \end{array} \begin{array}{c} \text{NaOR, } \text{H}_2\text{O} \\ \text{XI, NaHCO}_3 \text{I} \\ \text{H} \\ \text{(6)} \end{array} \begin{array}{c} \text{DEU} \\ \text{H} \\ \text{(6)} \end{array} \begin{array}{c} \text{OS iMe}_3 \\ \text{H} \\ \text{(8)} \\ \text{(7)} \\ \text{(8)} \\ \text{(7)} \\ \text{(8)} \\ \text{(7)} \\ \text{(8)} \\ \text{(11)} \end{array} \begin{array}{c} \text{OS iMe}_3 \\ \text{H} \\ \text{(6)} \\ \text{(6)} \\ \text{(7)} \\ \text{(6)} \\ \text{(7)} \\ \text{(7)} \\ \text{(8)} \\ \text{(7)} \\ \text{(8)} \\ \text{(10)} \\ \text{(10)} \\ \text{(11)} \end{array}$$

REFERENCES AND NOTES

- 1. Some of this work was carried out at Brunel University, Uxbridge, England.
- For example, see: a) P.A. Grieco, M. Nishizawa, T. Oguri, S.D. Burke and N. Marinovic, J. Amer. Chem. Soc., (1977), 99, 5773. b) S. Danishefsky, P.F. Schuda, T. Kitahara and S.J. Etheredge, J. Amer. Chem. Soc., (1977), 99, 6066. c) R.M. Schlessinger and G.R. Kieczykowski, J. Amer. Chem. Soc., (1978), 100, 1938. d) M. Isobe, H. Iio, T. Kawai and T. Goto, J. Amer. Chem. Soc., (1978), 100, 1940.
- 3. M. Ando, K. Tajima and K. Takase, J. Org. Chem., (1983), 48, 1210 and references therein.
- 4. T.V. Lee and J. Toczek, J.C.S. Chem. Communs., (1982), 968.
- 5. All new compounds gave satisfactory spectral and analytical data.

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