Tetrahedron Letters, Vol 32, No 42, pp 5953-5956 1991
Printed in Great Britain

0040-4039/91 $3 00 + 00
Pergamon Press plc

Towards the Total Synthesis of Clerodin. Part I.

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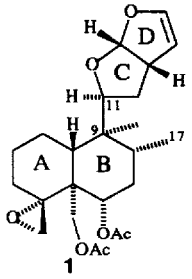
Key Words clerodin, antifeedant, stereospecific Claisen rearrangement, quaternary asymmetric carbon, terpene

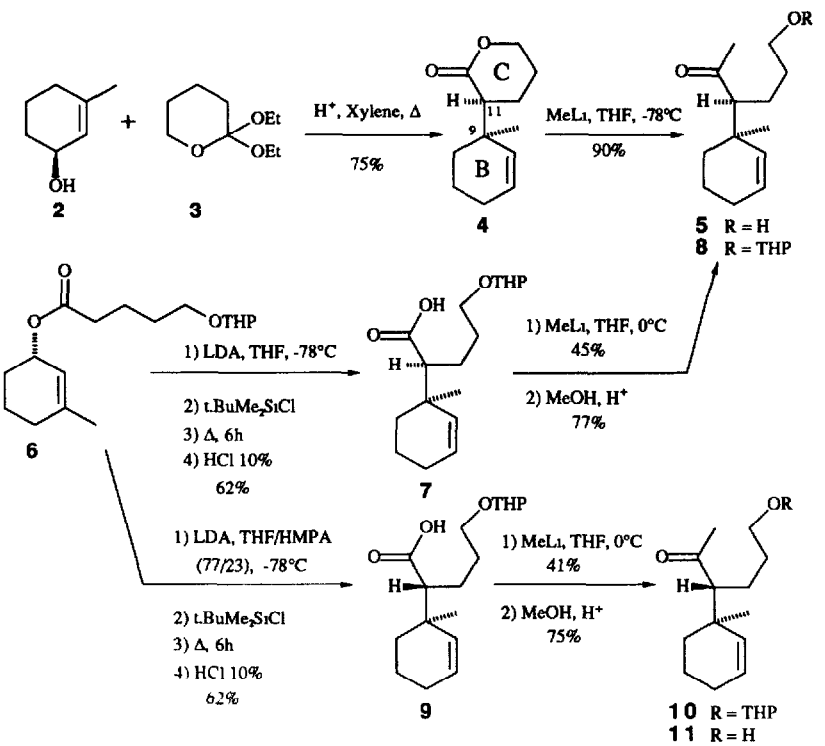
Abstract *A highly stereo- and enantioselective approach to clerodin* ***1****, an insect antifeedant, is described The key step involved the stereospecific formation of the* C_9-C_{11} *bond, at an early stage of the synthesis, using a Claisen rearrangement*

Clerodin type compounds have attracted a lot of interest over the last few years on account of their useful insect antifeedant activity [1] and challenging structures Some models of clerodin **1**, including either the A/B trans-decalin system [2] or the C/D furo-furan system [3] , have already been synthesised However, to the best of our knowledge, no one has yet succeeded in the totally stereospecific linkage of these two main systems For this purpose, we have devoted our efforts to the early stereospecific formation of the C-9/C-11 bond, in a general synthetic strategy that can be applied to other compounds of the clerodin family



1

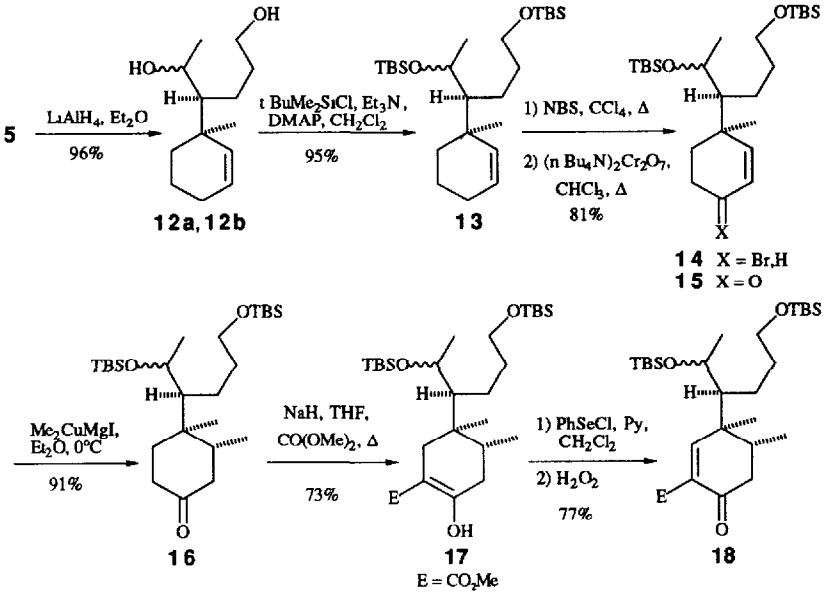
The key step of our approach relies on a stereospecific Claisen rearrangement of the reaction product between the cyclohexenol **2** and the cyclic orthoester **3**, which provides the lactone **4** as the sole product [4] This compound has been easily opened with methyllithium to afford the methyl ketone **5** It should be noted that the stereochemistry of the quaternary asymmetric carbon and the lactonic asymmetric centre are respectively induced by the stereochemistry of the starting alcohol and the nature of the transition state Starting from Lythgoe's results[5] , we first attributed to **4** the relative stereochemistry as shown below It is generally considered that this type of Claisen rearrangement goes through a tricyclic transition state which in our case has to be in a boat-like form [5] We have been able to correlate this attribution by studying the Ireland [6] type rearrangement in the open chain model **6**



The ester-enolate rearrangement [6] of the allylic ester **6** [7] was performed under two different reaction conditions Firstly, in THF, the Z-lithium-enolate [8] was preferentially formed and trapped as its silyl ether It was subsequently rearranged under THF reflux (bicyclic chair-like transition state), and finally hydrolysed This sequence gave the acid **7** [9], which, when treated with methyllithium afforded the methyl-ketone **8** Deprotection of the THP moiety afforded the same compoud **5** as before (pair of enantiomers) Secondly, in THF/HMPA (77/23), the E-enolate isomer [8] was formed, and the former sequence yielded acid **9** [10], methyl-ketone **10** and finally compound **11**, which appeared to be a diastereoisomer of **5**

Using optically pure (S)-(-)-3-methyl cyclohex-2-enol, obtained from the racemic acetate by resolution with pig liver esterase [11], as starting material, this strategy allows enantio- and stereocontrolled preparation of clerodin synthetic intermediates

We next turned to the correct functionalisation of the cyclohexene ring of compound **5** From our previous work on the trans-decalinic system [2a], it required the stereocontrolled introduction of the corresponding " 17-methyl " of clerodin **1**, and further transformation into an unsaturated keto-ester as depicted below



Methyl-ketone **5** was reduced with lithium aluminium hydride, providing an easily separable diastereoisomeric mixture of diols **12a** and **12b** In order to simplify the following sequence, we decided to work with only one of the two diols Protection of the diol **12a** as its disilyl derivative gave us compound **13** in quantitative yield Allylic oxidation of the cyclohexene ring was best accomplished using a two step sequence allylic bromination of **13** afforded **14** which was then efficiently oxidized into cyclohexenone **15** using bis(tetrabutylammonium)dichromate [12] (81% overall yield from **13**) Conjugate addition of dimethylcuprate to **15** occured from the less hindered face of the unsaturated system, leading to dimethylcyclohexanone **16** The stereochemistry of the methyl addition was unambiguously established from NMR data [13] , irradiation of the " 17-methyl " gave a doublet of doublets for the α-proton (J = 3 5 and 9 8 Hz) thus confirming that the added methyl is in the equatorial position

When treated with a mixture of sodium hydride and dimethyl carbonate in refluxing THF, cyclohexanone **16** underwent regiospecific functionalisation to afford the keto-ester **17** in its enol form Various other attempts at enolate formation and trapping gave only poor regioselectivity Introduction of a phenylselenyl group followed by an oxidation-elimination step completed the final conversion of the keto-ester **17** into the unsaturated system **18** [14] Further investigations on **18** are underway in order to achieve the total synthesis of clerodin Synthesis of the trans-decaline moiety has already been achieved on a model compound [2a] Construction of the furo-furanic moiety clerodin **1** from lactone **4** is reported in the following paper

Acknowledgements We thank Rhône-Poulenc Santé for financial support

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4 Since the starting alcohol **2** is racemic, the lactone **4** is also racemic

5 R J Cave, B Lythgoe, D A Metcalfe and I Waterhouse, *J Chem Soc Perkin I*, **1977**, 1218

6 R E Ireland, R H Mueller and A K Willard, *J Am Chem Soc* , **1976**, *98*, 2868

7 The ester **6** was prepared from THF using the following sequence 1) gaseous HCl, 50°C (21%), 2) DHP, H^+ (85%), 3) Mg, Et_2O then CO_2 (29%), 4) alcohol **2**, 2-chloro 1-methylpyridinium iodide, CH_2Cl_2 , Et_3N (94%)

8 E and Z isomers refers to the position of the allylic ether and the side chain For further informations, see
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9 Compound **7** ^{1}H NMR (200 MHz, $CDCl_3$, ppm) 1 08 (s, 3H), 1 15-2 05 (m, 16H), 2 32 (m, 1H), 3 44 and 3 74 (m, 4H), 4 59 (broad t, J = 3 Hz, 1H), 5 33 (broad d, J = 10 1 Hz, 1H), 5 68 (m, 1H), 10 45 (m, 1H), ^{13}C NMR (50 3 MHz, $CDCl_3$, ppm) 19 1, 19 6, 24 5, 24 8, 25 0, 25 5, 29 5, 30 7, 31 8, 37 0, 55 6, 62 3, 67 2, 98 8, 127 2, 134 8, 180 1

10 Compound **9** ^{1}H NMR (200 MHz, $CDCl_3$, ppm) 1 07 (s, 3H), 1 15-2 05 (m, 16H), 2 32 (m, 1H), 3 46 and 3 65 (m, 4H), 4 59 (broad t, J = 4 Hz, 1H), 5 34 (broad d, J = 10 1 Hz, 1H), 5 70 (m, 1H), 10 30 (m, 1H), ^{13}C NMR (50 3 MHz, $CDCl_3$, ppm) 19 2, 19 6, 24 5, 24 7, 25 0, 25 6, 26 6, 30 7, 31 7, 36 6, 56 6, 62 2, 68 0, 98 8, 126 6, 134 0, 180 9

11 K Mori and J I.J Ogoche, *Liebigs Ann Chem* , **1988**, 903 Optical purity obtained $[\alpha]_D$ (c=11, $CHCl_3$) = -93, ee $\geq$ 95 %

12 a) D Landini and F Rolla, *Chem and Industry*, **1979**, 213
b) E Santaniello and P Ferraboschi, *Synth Commun* , **1980**, 75

13 Compound **16** ^{1}H NMR (200 MHz, $CDCl_3$, ppm) 0 05 (s, 6H), 0 07 (s, 6H), 0 90 (m, 21H), 1 07 (s, 3H), 1 17 (d, J = 6 Hz, 3H), 1 05-2 16 (m, 8H), 2 25-2 32 (m, 4H), 3 59 (m, 2H), 4 14 (broad q, J = 6 Hz, 1H), ^{13}C NMR (50 3 MHz, $CDCl_3$, ppm) -5 1, -4 4, 16 2, 18 2, 20 4, 21 3, 25 8, 26 0, 32 9,33 6, 37 7, 37 9, 46 0, 50 6, 63 5, 69 0, 211 8

14 Compound **18** ^{1}H NMR (200 MHz, $CDCl_3$, ppm) 0 04 (s, 6H), 0 06 (s, 6H), 0 90 (broad s, 18H), 0 95 (d, J = 6 5 Hz, 3H), 1 07 (s, 3H), 1 21 (d, J = 6 3 Hz, 3H), 1 05-2 16 (m, 8H), 3 61 (m, 2H), 3 75 (s, 3H), 4 08 (broad q, J = 6 3 Hz, 1H), 7 39 (broad s, 1H)

(Received in France 21 June 1991)