Tetrahedron Letters,Vol.26,No.3,pp 397-400,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

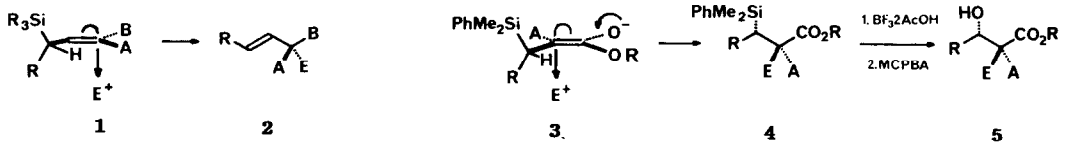
A SYNTHESIS OF THE PRELOG-DJERASSI LACTONE USING OPEN-CHAIN STEREOCONTROL BASED ON ALLYLSILANE CHEMISTRY[1]

Hak-Fun Chow and Ian Fleming*

University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England

Summary—A stereocontrolled synthesis of the Prelog-Djerassi lactone (**28**) is described; all the stereocontrol stems from the high diastereoselectivity of electrophilic attack on a double bond adjacent to a chiral centre carrying a silyl group.

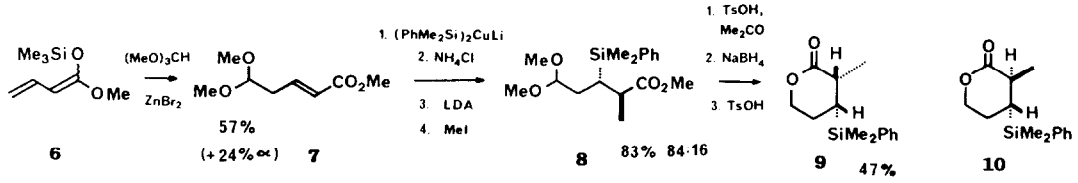
In this paper we show how three strands of our work on the control of stereochemistry in open-chain systems (**1** → **2** and **3** → **5**) can be put together in a synthesis of the Prelog-Djerassi lactone (**28**). In one strand of our work, a chiral centre carrying a silyl group is in an allylsilane (**1**), which reacts with electrophiles both stereoselectively and regioselectively,[2,3] in the sense (**1** → **2**). In the second strand, the chiral centre is still formally part of an allylsilane, but it is now β to an enolate (**3**). In this situation, electrophilic attack (alkylation or protonation) takes place in the same stereochemical sense, but with opposite regioselectivity (**3** → **4**).[4] The third strand is the two-step sequence which converts a phenyldimethylsilyl group



1 **2** **3** **4** **5**

into a hydroxyl group,[5] with retention of configuration (**4** → **5**). We carried out the present synthesis in order to demonstrate that the allylsilane reaction (**1** → **2**), coupled with our convergent synthesis of stereodefined allylsilanes,[2] is a versatile method for the control of relative stereochemistry at a site remote from any useful influence from other chiral centres. At the same time, we are able to demonstrate that the enolate reactions (**3** → **4** → **5**) are versatile in the control of relative stereochemistry at adjacent sites.

We began in a model series, in order to test whether extra functionality interfered with the stereoselectivity of the general reaction (**3** → **4**). The silyl dienol ether (**6**), derived

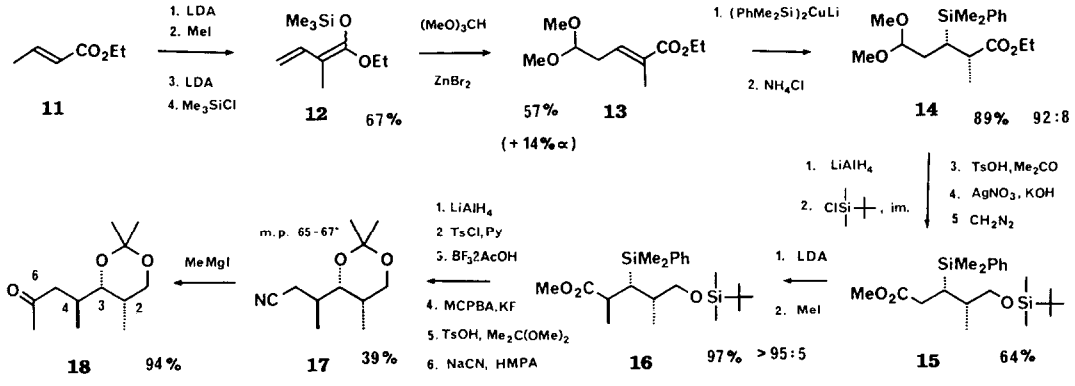


6 **7** **8** **9** 47% **10**

from methyl crotonate, reacted with methyl orthoformate largely (70:30)[6] in the γ-position, as expected from our earlier work on silyl dienol ethers.[7-9] Conjugate addition of our silyl cuprate reagent to the major product (**7**) and methylation gave the ester (**8**) in 70% yield, together with its diastereoisomer in 14% yield.[10] In order to confirm the assignment of stereochemistry

to these products, we converted the former to the lactone (**9**), which showed coupling from H-2 to H-3 of 6.8 Hz, typical of an equatorial-axial relationship. Methylation had therefore taken place in the sense (**3** → **4**). This was confirmed when we prepared (see below) the diastereoisomeric lactone (**10**), which showed coupling of 11 Hz, typical of an axial-axial relationship.

For the synthesis itself, we began with ethyl crotonate (**11**), and methylated it in the α-position using the lithium dienolate.[11] Then, again using a silyl dienol ether, we alkylated this product in the γ-position to give largely (80:20)[6] the αβ-unsaturated ester (**13**). The selectivity for γ-attack had increased slightly, as expected from our earlier work[9] on the effect of extra methyl groups on silyl dienol ether regioselectivity. Conjugate addition of our silyl-cuprate reagent followed by protonation gave the ester (**14**) with high stereoselectivity (92:8) and in good yield. We confirmed the stereochemistry of this intermediate by converting it into the lactone (**10**). The relative stereochemistry of C-2 and C-3 was now intact. Some simple functional group manipulations (**14** → **15**) set up suitable functionality for the introduction of the next chiral centre. Methylation of the enolate of **15** gave the ester (**16**); as far as we could tell from the ^{1}H- and ^{13}C-NMR spectra of this compound (and of compounds derived from it) this was a single diastereoisomer (>95:5). Thus we have been able to direct the stereochemical course of enolate reactions on both sides of the silyl group. A further series of

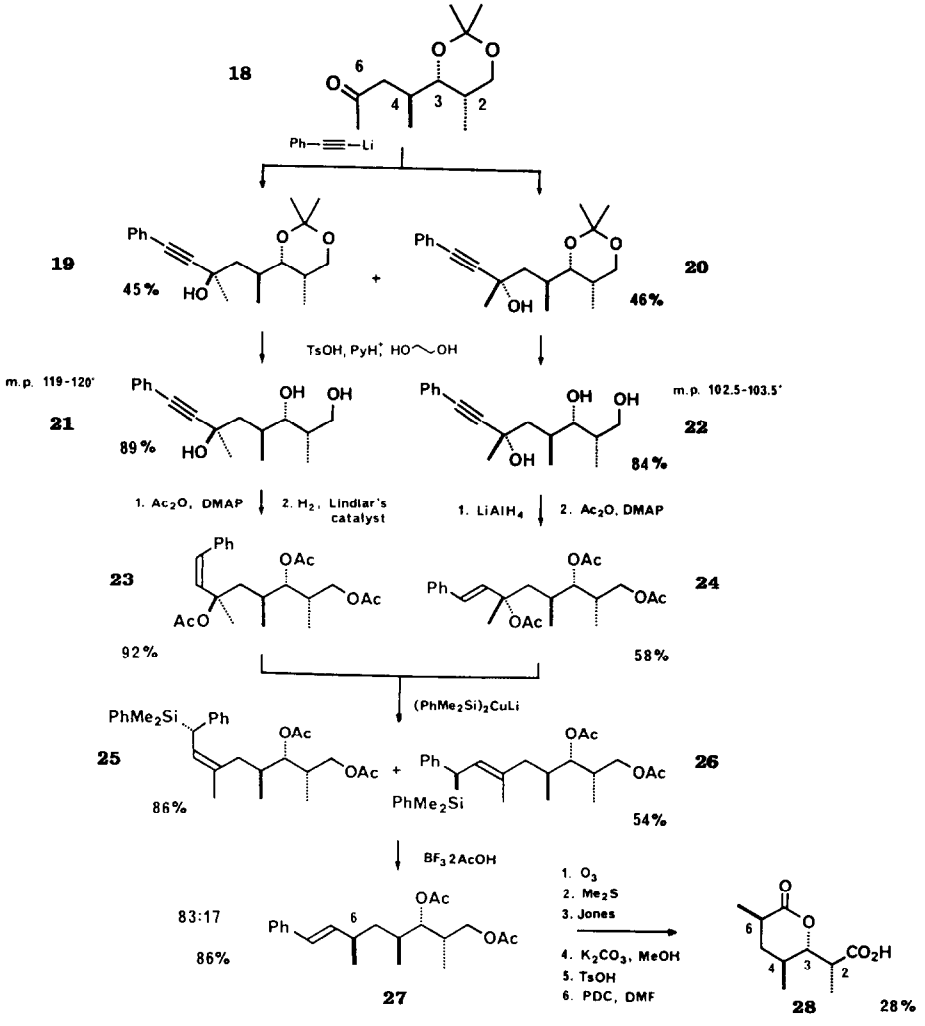


functional group manipulations (**16** → **18**), including the conversion[5,12] of the silyl into a hydroxyl group and the crystallisation of one intermediate (**17**), gave us the ketone (**18**). The future C-6 was present in this ketone as the carbonyl group, but we did not expect this centre to react with much stereoselectivity. This is a common problem in synthesis: how to develop a single stereoisomer, *when the steric constraints from the rest of the molecule make the two faces of a prochiral group negligibly different*. We now present a powerful solution to this problem.

The ketone reacted with phenylethynyl-lithium to give very nearly equal amounts of the diastereoisomeric alcohols (**19** and **20**), just as expected. We separated these products by column chromatography, and hydrolysed the acetal group in each to get the two crystalline acetylenic triols (**21** and **22**). We acetylated and hydrogenated one of these (subsequently revealed to be **21**) to get the *cis* allylic acetate (**23**), and we reduced the other (**22**) with lithium aluminium hydride and acetylated the product to get the *trans* allylic acetate (**24**). These two compounds differed in two respects—the geometry of the double bond and the relative stereochemistry of the tertiary allylic centre. They are therefore stereochemically equivalent, in the sense that the silyl-cuprate reagent, reacting stereospecifically *anti*,[2] gave the same pair of allylsilanes

(**25** and **26**) from each acetate (**23** and **24**). These allylsilanes are also stereochemically equivalent and do not need to be separated—if they react stereospecifically *anti* with electrophiles with the formation of a *trans* double bond, as usual,[2,3] they will give the same product. In practice, protodesilylation of the mixture of allylsilanes (**25** and **26**) took place in high yield and with moderately high diastereoselectivity (83:17)[13] in favour of the isomer (**27**). Some simple functional group manipulations converted this product into the racemic Prelog-Djerassi lactone (**28**), which had m.p. and spectra[14] identical with those reported.

This synthesis is inherently linear, and therefore low-yielding (0.72% overall). It cannot compete, as a practical synthesis, with any of the syntheses already published.[15] It has, however, some virtues. In the first place, it illustrates how allylsilane chemistry can be



applied to control stereochemistry at a formally remote site. As long as the mixture of propargyl alcohols (**19** and **20** in this case) can be separated, they can both be used to create either diastereoisomer. We did, in fact, take the same alcohols (**21** and **22**) through the complementary sequence to that illustrated above, and got another pair of allylsilanes, recognisably different from the previous pair of allylsilanes (**25** and **26**). When these were taken through the rest of the synthesis, they gave the 6-epi-lactone. Since protodesilylation is only one of many stereo-

specific reactions which allylsilanes can undergo, there are many secondary, tertiary and quaternary chiral centres which can be set up in this way. In the second place, and unlike most methods of stereocontrol, our methodology is, in principle, *equally amenable to the synthesis of any of the eight possible diastereoisomers*: an appropriate choice of alkylation or protonation can control C-2, C-3, and C-4 in any sense, and an appropriate choice of pathway in the allylsilane work controls C-6 in either sense, as we have in fact shown. Finally, our methods use *genuine open chain stereocontrol*: the three key steps in which the stereochemical relationships are set up do not even use cyclic transition states.[16]

NOTES and REFERENCES

1. No reprints available.
2. I. Fleming and N. K. Terrett, *J. Organomet. Chem.*, **264**, 99 (1984) and *Tetrahedron Lett.*, **25**, 5103 (1984).
3. T. Hayashi, M. Konishi, H. Ito, and M. Kumada, *J. Am. Chem. Soc.*, **104**, 4962 (1982); T. Hayashi, M. Konishi, and M. Kumada, *ibid.*, 4963; T. Hayashi, H. Ito, and M. Kumada, *Tetrahedron Lett.*, **23**, 4605 (1982); H. Wetter and P. Scherer, *Helv. Chim. Acta*, **66**, 118 (1983); G. Wickham and W. Kitching, *J. Org. Chem.*, **48**, 612 (1983).
4. W. Bernhard, I. Fleming, and D. Waterson, *J. Chem. Soc., Chem. Commun.*, 28 (1984).
5. I. Fleming, R. Henning, and H. Plaut, *J. Chem. Soc., Chem. Commun.*, 29 (1984).
6. We could undoubtedly have raised the selectivity by using the diisopropylmethyl ester[7] and the triphenylsilyl enol ether,[8] but in practice the separation of the products (**7** and **13**) from the products of α-attack was so easy (by fractional distillation) that it was more economical simply to use the cheaper starting materials.
7. I. Fleming, J. Goldhill, and I. Paterson, *Tetrahedron Lett.*, 3209 (1979).
8. I. Fleming and T. V. Lee, *Tetrahedron Lett.*, **22**, 705 (1981).
9. I. Fleming and J. Iqbal, *Tetrahedron Lett.*, **24**, 2913 (1983).
10. Direct methylation of the enolate (presumably[4] the *E*-isomer) produced by the conjugate addition gave a low yield (50%) and an unusually low selectivity (64:36). The more normal ratio (84:16) was the result of conjugate addition, protonation, and regeneration of the enolate, a procedure which gives the *Z*-enolate.[17]
11. J. L. Herrmann, G. R. Kieczykowski, and R. H. Schlessinger, *Tetrahedron Lett.*, 2433 (1973).
12. K. Tamao, T. Kakui, M. Akita, T. Iwahara, R. Kanatani, J. Yoshida, and M. Kumada, *Tetrahedron*, **39**, 983 (1983).
13. The loss of diastereoselectivity is probably a result of protonations taking place to some extent on the less-substituted end of the double bond[2,18] with consequent loss of stereochemical information. The choice of phenylethynyl may have been unfortunate in this respect, but it had helped in the separation of the diastereoisomers (**19** and **20**).
14. The m.p. was 112-112.5 °C. The literature quotes a range of m.p.'s, of which the highest[15a] is 119-120 °C and the lowest[15b] is 110-113 °C. The ^{1}H- and ^{13}C-NMR spectra are reported in several of the references 15, as also are the spectra of several distinguishably different diastereoisomers.
15. See, for example (a) S. Masamune, C. U. Kim, K. E. Wilson, G. O. Spessard, P. E. Georghiou, and G. S. Bates, *J. Am. Chem. Soc.*, **97**, 3512 (1975); (b) J. D. White and Y. Fukuyama, *ibid.*, **101**, 226 (1979); (c) G. Stork and V. Nair, *ibid.*, 1315; (d) P. A. Grieco, Y. Ohfune, Y. Yokoyama, and W. Owens, *ibid.*, 4749; (e) M. Hirama, D. S. Garvey, L. D.-L. Lu, and S. Masamune, *Tetrahedron Lett.*, 3937 (1979); (f) P. A. Bartlett and J. L. Adams, *J. Am. Chem. Soc.*, **102**, 337 (1980); (g) R. E. Ireland and J. P. Daub, *J. Org. Chem.*, **46**, 479 (1981); (h) S. Masamune, M. Hirama, S. Mori, S. A. Ali, and D. S. Garvey, *J. Am. Chem. Soc.*, **103**, 1568 (1981); (i) W. C. Still and K. R. Shaw, Tetrahedron Lett., **22**, 3725 (1981); (j) K. Maruyama, Y. Ishihara, and Y. Yamamoto, *ibid.*, 4235; (k) M. Isobe, Y. Ichikawa, and T. Goto, *ibid.*, 4287; (l) R. H. Schlessinger and M. A. Poss, *J. Am. Chem. Soc.*, **104**, 357 (1982); (m) S. Danishefsky, N. Kato, D. Askin, and J. F. Kerwin, *ibid.*, 360; (n) D. A. Evans and J. Bartroli, *Tetrahedron Lett.*, **23**, 807 (1982); (o) R. W. Hoffmann, H.-J. Zeiss , W. Ladner, and S. Tabche, *Chem. Ber.*, **115**, 2357 (1982).
16. The reduction of the propargylic alcohols did involve cyclic transition states, but these steps, although integral to the scheme, are not the ones in which the actual chiral centres are set up.
17. R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.*, **98**, 2868 (1976).
18. I. Fleming, D. Marchi, and S. K. Patel, *J. Chem. Soc., Perkin Trans. 1*, 2518 (1981).

(Received in UK 6 November 1984)