Tetrahedron Letters, Vol.31, No.25, pp 3645-3648, 1990
Printed in Great Britain

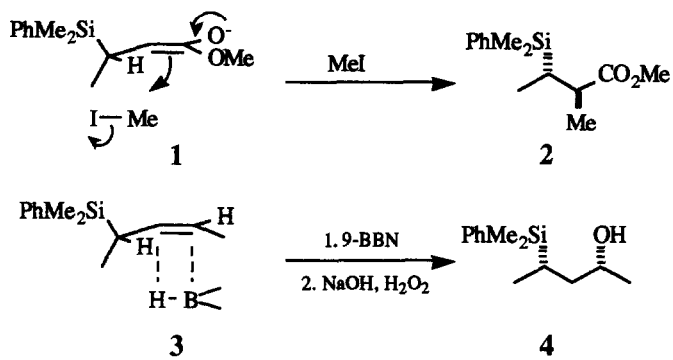
0040-4039/90 $3.00 + .00
Pergamon Press plc

A SYNTHESIS OF (-)-TETRAHYDROLIPSTATIN IN WHICH THE RELATIVE STEREOCHEMISTRY IS CONTROLLED BY A PHENYLDIMETHYLSILYL GROUP

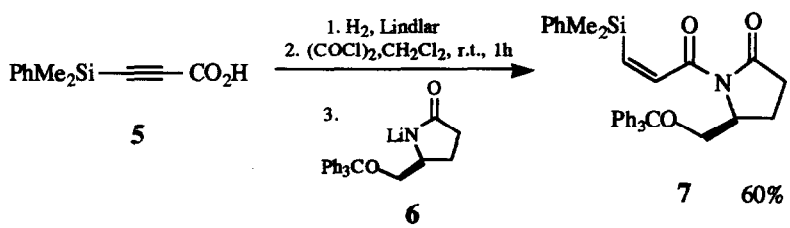
Ian Fleming* and Nicholas J. Lawrence
(University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England)

Summary—The alkylation of a β-silylenolate and the hydroboration of an allylsilane successively control the relative stereochemistry of the three stereogenic centres on the carbon backbone in a synthesis of the esterase inhibitor tetrahydrolipstatin (**21**).

In earlier papers, we reported that the alkylation of β-silylenolates (**1** → **2**)[1] gives high levels of stereocontrol in 1,2-related stereogenic centres, and that the hydroboration of allylsilanes (**3** → **4**)[2] takes place with a high level of regio- and stereocontrol in the creation of 1,3-related stereogenic centres, in the sense illustrated. We

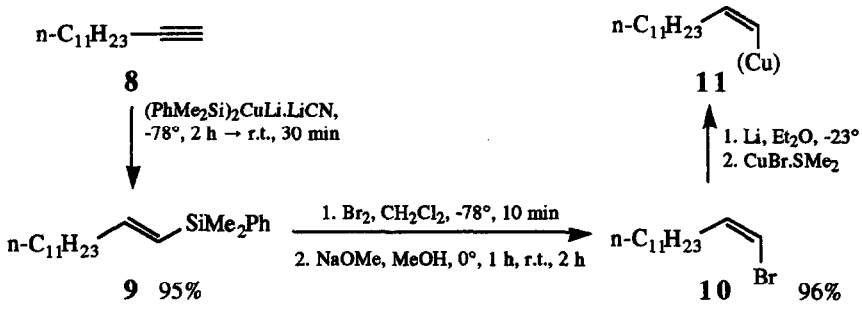


now report that these reactions can be used in succession to control efficiently the relative stereochemistry of the three stereogenic centres on the carbon backbone of the esterase inhibitor tetrahydrolipstatin (**21**),[3] and that the absolute stereochemistry can be controlled using Koga's chiral auxiliary (**6**), as we had already established with simple systems.[4]



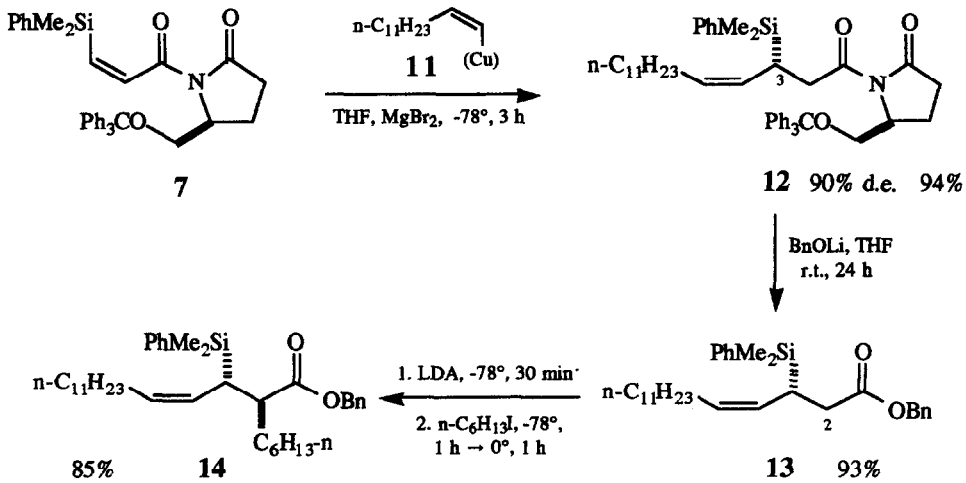
To set up C-3 with the correct absolute stereochemistry, we prepared the *Z*-silylacryloyl derivative (**7**) from Koga's chiral auxiliary (**6**) and the acetylenic acid (**5**). In order to have the allysilane with the correct geometry, we needed the *Z*-vinyl-cuprate (**11**), which we prepared by a method that also uses the

phenyldimethylsilyl group: the silyl-cupration[5] of the terminal acetylene (**8**) took place with high regioselectivity, placing the silyl group at the end of the carbon chain, and stereospecifically *syn*, giving the *trans*-vinylsilane (**9**). Bromodesilylation of the vinylsilane took place cleanly with inversion of configuration, as expected,[6] giving the *cis*-bromide (**10**), which was easily converted into the appropriate cuprate (**11**). Combining the cuprate (**11**) and



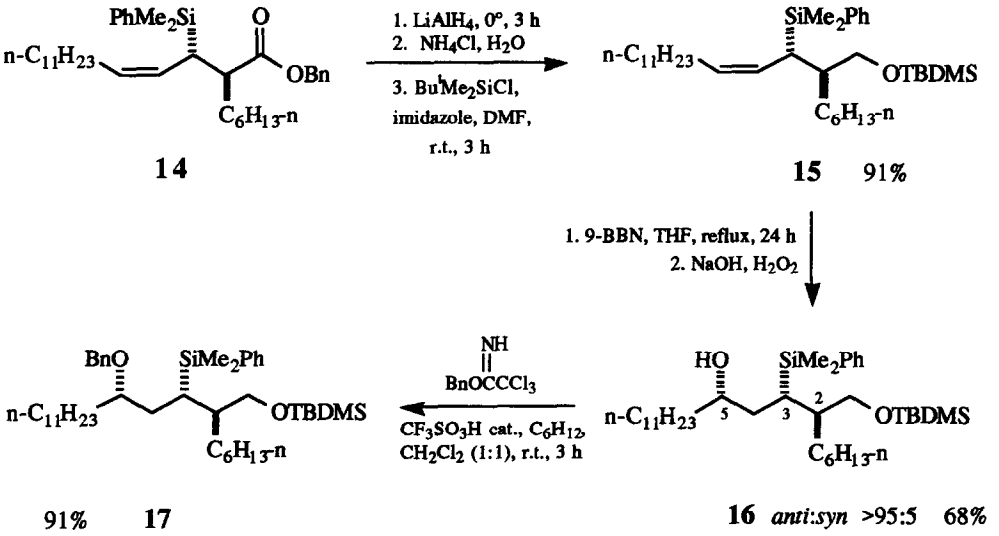
the acryloyl-lactam (**7**) in the presence of magnesium bromide to chelate the carbonyl oxygens, we prepared the allylsilane (**12**) with 90% d.e. (^{1}H-NMR), in favour of the desired isomer. This compound did not crystallise, and it was therefore carried forward as a mixture of epimers at C-3.

We removed the chiral auxiliary (and recovered it, 64%) to give the benzyl ester (**13**), which we alkylated at C-2 with n-hexyl iodide to give the ester (**14**), with, as far as we could tell (^{1}H-NMR), the production of only one diastereoisomer. We had established in our earlier work[1] that the stereochemistry of this reaction would be

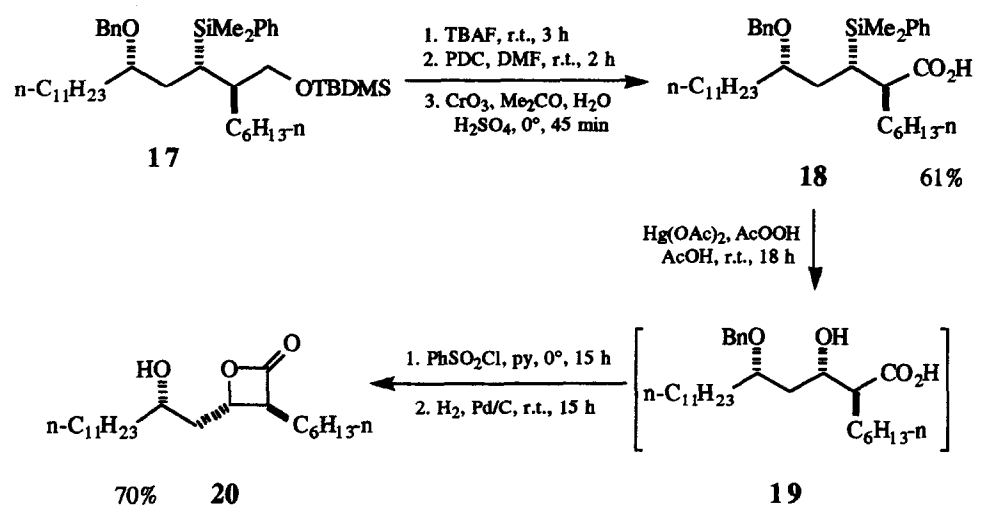


well controlled, and we were, therefore, confident of the assignment by analogy. The next step was the hydroboration of the allylsilane unit, but this proved to be impossible without the concomitant reduction of the ester group. We therefore chose to reduce the ester group completely first, and to protect the alcohol produced as its TBDMS ether (**15**). Hydroboration of this allylsilane was slow but stereochemically very clean, giving, after the usual oxidation, only (>95:5) the C-5 alcohol (**16**). By carrying out the same sequence, but using the *E*-double bond throughout, we prepared, as expected,[2] largely the C-5 diastereoisomer, which was measurably

different (^{1}H-NMR) from **16**, but not measurably present in the hydroboration-oxidation (**15** → **16**). We protected the new hydroxyl group as its benzyl ether (**17**) using the acid-catalysed method of Iversen and

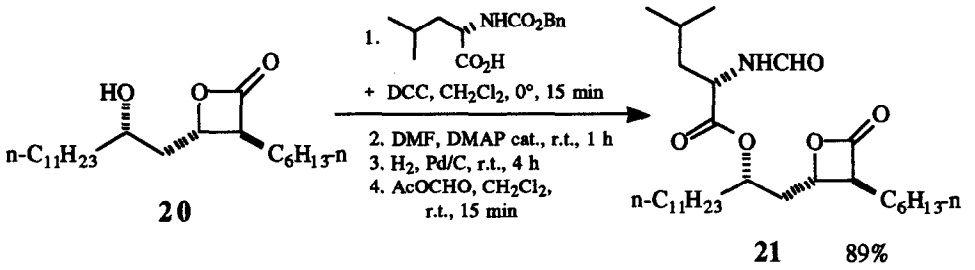


Bundle,[7] because the usual base-catalysed conditions (NaH, BnBr) gave only the cyclic silyl ether produced by intramolecular displacement of the phenyl group by the alkoxide ion. At this stage we restored the carboxylic acid function by deprotection and oxidation, and the stage was set for the conversion of the phenyldimethylsilyl group



into a hydroxyl (**18** → **19**).[8] Although our attempts to isolate the first-formed product (**19**) led only to low yields, carrying the crude product through two more steps gave the β-lactone (**20**), in as good an overall yield as this type of β-lactone-forming reaction usually goes in on its own,[9] indicating that the conversion of the silyl to the hydroxyl group must have been very efficient.

At this stage, the product (**20**) crystallised, and one recrystallisation was enough to give the pure diastereoisomer and enantiomer, as judged by its sharp and correct m.p. and rotation.[10] This confirms our ^{1}H-NMR evidence that the diastereoselectivity of both critical steps, the alkylation reaction (**13** → **14**) and the hydroboration-oxidation (**15** → **16**), must have been very high, since this recrystallisation was also removing the minor enantiomer present (5%) since the step (**7** + **11** → **12**). Finally, since it had not already been reported, we



used standard chemistry (**20** → **21**) to attach the leucine residue to complete the total synthesis of tetrahydrolipstatin, which was identical (m.p.,[11] mixed m.p., rotation,[11] ^{1}H-NMR, and mixed ^{1}H-NMR) with an authentic sample kindly sent to us by Dr. Barbier. Our synthesis joins four others.[12-15]

NOTES and REFERENCES

1. I. Fleming, J. H. M. Hill, D. Parker, and D. Waterson, *J. Chem. Soc., Chem. Commun.*, 1985, 318.
2. I. Fleming and N. J. Lawrence, *Tetrahedron Lett.*, 1988, **29**, 2077.
3. E. Hochuli, E. Kupfer, R. Maurer, W. Meister, Y. Mercadal, and K. Schmidt, *J. Antibiotics*, 1987, **40**, 1086.
4. I. Fleming and N. D. Kindon, *J. Chem. Soc., Chem. Commun.*, 1987, 1177.
5. I. Fleming, T. W. Newton, and F. Roessler, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2527.
6. A. W. P. Jarvie, A. Holt, and J. Thompson, *J. Chem. Soc. (B)*, 1969, 852; R. B. Miller and G. McGarvey, *J. Org. Chem.*, 1979, **44**, 4623.
7. T. Iversen and D. R. Bundle, *J. Chem. Soc., Chem. Commun.*, 1981, 1240.
8. I. Fleming and P. E. J. Sanderson, *Tetrahedron Lett.*, 1987, **28**, 4229.
9. W. Adam, J. Baeza, and J.-C. Liu, *J. Am. Chem. Soc.*, 1972, **94**, 2000; S. Mageswaran and M. U. S. Sultanbawa, *J. Chem. Soc., Perkin Trans. 1*, 1976, 884; J. Mulzer, A. Pointner, A. Chucholowski, and G. Brüntrup, *J. Chem. Soc., Chem. Commun.*, 1979, 52; I. Fleming and A. K. Sarkar, *J. Chem. Soc., Chem. Commun.*, 1986, 1199.
10. m.p. 64-65 °C (lit.,[16] m.p. 64.5-65.5 °C); $[\alpha]_D$ -15.3° (c.1 in CH_2Cl_2) [lit.,[16] $[\alpha]_D$ -15° (c.1 in $CHCl_3$)].
11. m.p. 40-41 °C (lit. 43 °C,[3] 41-42.5 °C,[12] 40-42 °C,[13] and 40-41 °C.[14] $[\alpha]_D$ -33.4° (c. 1.33 in $CHCl_3$) [lit., $[\alpha]_D$ -32° (c. 1 in $CHCl_3$),[3] -34.45° (c. 1 in $CHCl_3$),[12] -33° (c. 0.36 in $CHCl_3$),[13] and -31.2° (c. 1 in $CHCl_3$)[14]].
12. P. Barbier and F. Schneider, *Helv. Chim. Acta*, 1987, **70**, 196.
13. P. Barbier and F. Schneider, *J. Org. Chem.*, 1988, **53**, 1218.
14. J.-M. Pons and P. Kocienski, *Tetrahedron Lett.*, 1989, **30**, 1833.
15. P. Barbier, F. Schneider, and U. Widmer, *Helv. Chim. Acta*, 1987, **70**, 1412.
16. S. Kondo, K. Uotani, M. Miyamoto, T. Hazato, H. Naganawa, and T. Aoyagi, *J. Antiobiotics*, 1978, **31**, 797.

(Received in UK 30 April 1990)