Tetrahedron Letters,Vol.30,No.42,pp 5777-5780,1989
Printed in Great Britain

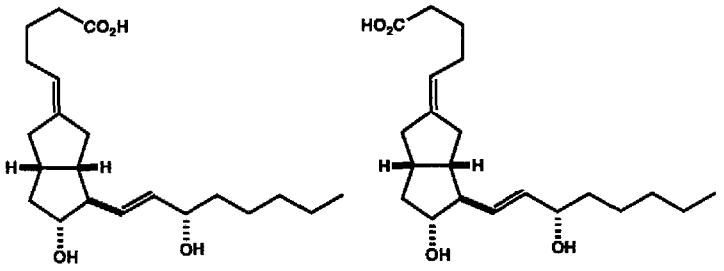
0040-4039/89 $3.00 + .00
Pergamon Press plc

THE STEREOSPECIFIC SYNTHESIS OF A CARBACYCLIN ANALOGUE USING THE PROTODESILYLATION OF AN ALLYLSILANE

Ian Fleming* and Dick Higgins
(University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England)

Summary—Protodesilylation of the allylsilane **15** gives the E-carbacyclin **16**, with excellent (>96:4) control of the geometry of the double bond exocyclic to the ring.

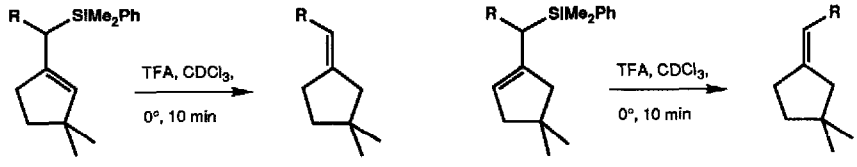
E-Carbacyclin **1**,[1] a prostacyclin analogue much more potent in inhibiting platelet aggregation than its Z isomer **2**,[2] poses a significant challenge in synthesis, because the control of



1 **2**

the geometry of an exocyclic double bond as remote from steric influence as this one does not have obvious solutions. Although a few stereoselective syntheses[3] have now appeared, the original Wittig routes gave, as one might expect, both isomers in essentially equal amounts.[4] We now report another solution, based on the protodesilylation of allylsilanes, to the problem of controlling the double bond geometry in a carbacyclin analogue.

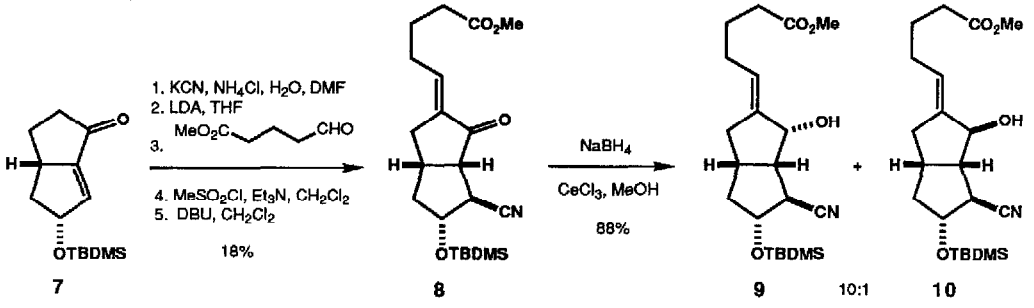
We first carried out a model study (**3** or **5** → **4** + **6**), already reported,[5] in which we found that the protodesilylation was stereospecific in the sense **3** → **4** and **5** → **6** only when



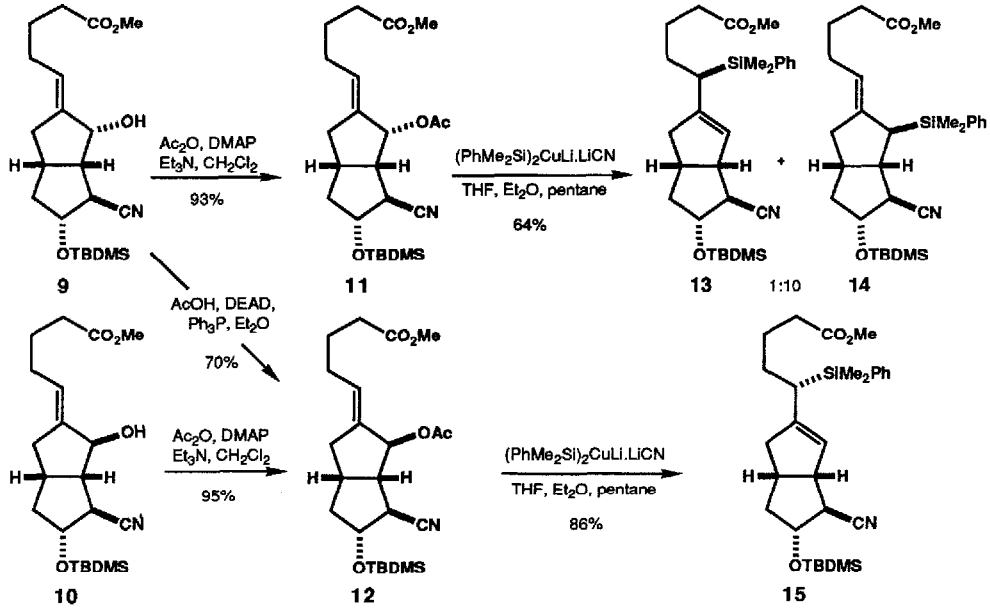
3 **4** **5** **6**

the group R was isopropyl: the ratio of isomers (**4**:**6** from **3** and **6**:**4** from **5**) was 90:10 in both cases. However, when the group R was phenyl, selectivity fell markedly, and when R was methyl, both stereoisomers (**4** and **6**) were produced in nearly equal amounts from either allylsilane **3** or **5**. At first sight, this approach did not look promising for the

synthesis of carbacyclins. The allylsilane we will be using will have, as the carbon group R on the exocyclic chiral centre, only a methylene chain, which is likely to be more like a methyl group than an isopropyl in its steric demand, and hence in its influence on the double bond geometry. However, the structure of this particular target molecule brings other factors into play, and we were hopeful that we would get good stereoselectivity in spite of this apparent limitation.



We chose not to deal with the problem of the lower side chain, which is, in any case, the main site of variation in the molecules being tested for clinical usefulness, and assembled instead a cyano analogue, starting from the known, racemic unsaturated ketone **7**,[6] which gave the ketone **8**, with the usual E geometry, in a conventional sequence.

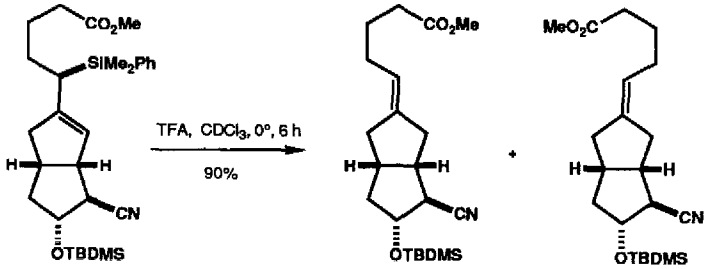


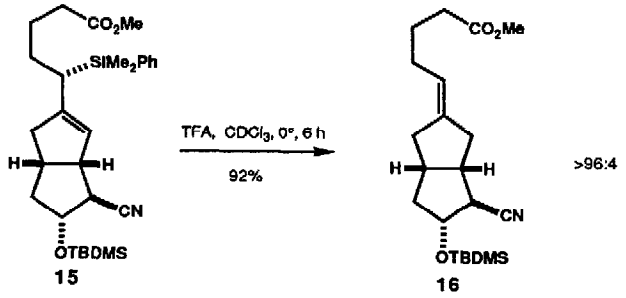
Reduction of this ketone gave a separable mixture of the alcohols **9** and **10** in a ratio of 10:1, and acetylation gave the acetates **11** and **12** respectively. The latter could also be made by Mitsunobu reaction from the major alcohol **9**.

The acetate **11** reacted with our silyl-cuprate reagent giving a mixture of the regioisomeric allylsilanes **13** and **14**, with the latter as the major product, just as we had

found earlier in the model series. In welcome contrast, the acetate **12** gave only the allylsilane **15**. By analogy with our earlier work,[7] these reactions can be relied upon to be stereospecifically anti, and, in confirmation, the allylsilanes **13** and **15** were discernibly different. Presumably an allylsilane analogous to **14** was not formed from the acetate **12**, because it would have involved endo attack on the bicyclo[3.3.0]octane system.

The protodesilylation of the two allylsilanes were not equally stereoselective with respect to double bond geometry. Protodesilylation of the diastereoisomer **13** gave a mixture of the E- and Z-isomers **16** and **17** in a ratio of about 2:1, which looked, on the face of it,



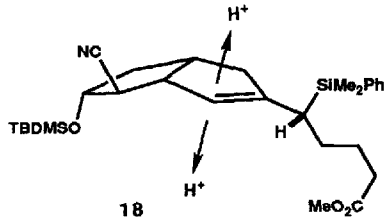


very much what one might have expected from our work in the model series. However, the more readily available allylsilane **15** gave very largely (>96:4, GC supported by ^{13}C NMR) the E-isomer **16**, exactly as we had hoped. The assignment of configuration to the alkenes **15** and **16** was easy by comparison of the ^{13}C-NMR spectra with those reported for the E and Z isomers of a close analogue of carbacyclin.[8] Although our work with the model compounds would suggest that the methylene chain will not be an effective group in controlling the double bond geometry, we have somehow achieved an extraordinarily high level of control with one of the diastereoisomers but not the other.

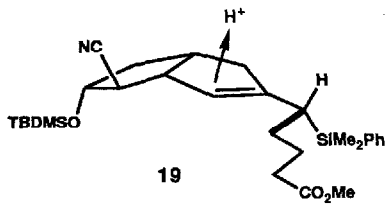
The allylsilane **13** that does not give good stereocontrol will probably adopt most readily a conformation close to that shown as **18**, with the hydrogen atom eclipsing, or partly eclipsing, the double bond. Protodesilylation in this conformation will lead to the E-isomer **16**, but it will involve attack by the proton either syn to the silyl group or endo on the bicyclic system. Since neither of these pathways is likely to be favourable, it is not surprising that this diastereoisomer does not lead cleanly to the E-carbacyclin **16**. The alternative conformation **19**, which will lead to the Z-isomer **17**, although probably not

present in as high a concentration, can be protonated in the stereoelectronically favourable sense, that is exo on the bicyclic system and anti to the silyl group.

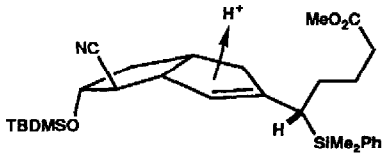
With the allylsilane **15** that does give good stereocontrol, everything is favourable for the formation of the E-isomer **16**: the probably more populated conformation **20** is protonated exo on the bicyclic system and anti to the silyl group. The higher-energy conformation **21**



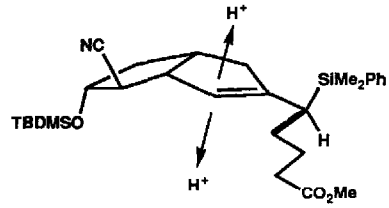
18



19



20



21

of this diastereoisomer, if it were to give any of the Z-isomer **17**, would have to be protonated either endo on the bicyclic system or syn to the silyl group, and the combination of unfavourable factors effectively suppresses this pathway. We note finally that the convergent synthesis of the acetate **12**, the highly regioselective synthesis of the allylsilane **15**, and the highly stereospecific protodesilylation conspire to make the four-step sequence from the enone **8** to the carbacyclin analogue **16** reasonably efficient (50%).

REFERENCES

1. R. C. Nickolson, M. H. Town, and H. Vorbrüggen, Med. Res. Rev., 1985, **5**, 1.
2. B. J. R. Whittle and S. Moncada, Prog. Med. Chem., 1984, **21**, 237 and ref. 4(b).
3. H. Rehwinkel, J. Skupsch, and H. Vorbrüggen, Tetrahedron Lett., 1988, **29**, 1775; H.-J. Gais, G. Schmiedl, W. A. Ball, J. Bund, G. Hellmann, and I. Erdelmeier, Tetrahedron Lett., 1988, **29**, 1773; D. K. Hutchinson and P. L. Fuchs, J. Am. Chem. Soc., 1987, **109**, 4755; M. Shibasaki, M. Sodeoka, and Y. Ogawa, J. Org. Chem., 1984, **49**, 4096; M Sodeoka, S. Satoh, and M. Shibasaki, J. Am. Chem. Soc., 1988, **110**, 4823; I Erdelmeier and H.-J. Gais, ibid. 1989, **111**, 1125.
4. K. C. Nicolaou, W. J. Sipio, R. L. Magolda, S. Seitz, and W. E. Barnette, J. Chem. Soc., Chem. Commun., 1978, 1067; K. Kojima and K. Sakai, Tetrahedron Lett., 1978, 3743; C. Gandolfi, Symposium on the Chemistry & Biochemistry of Prostanoids, Salford, July 1978; W. Skuballa, E. Schillinger, C.-St. Stürzebecher, and H. Vorbrüggen, J. Med. Chem., 1986, **29**, 313. (b) M. Shibasaki, J. Ueda, and S. Ikegami, Tetrahedron Lett., 1979, 433; D. R. Morton Jr and F. C. Brokaw, J. Org. Chem., 1979, **44**, 2880.
5. I. Fleming and D. R. Higgins, J. Chem. Soc., Perkin Trans. 1, 1989, 206.
6. M. F. Haslanger and S. Ahmed, J. Org. Chem., 1981, **46**, 4808.
7. I. Fleming and A. P. Thomas, J. Chem. Soc., Chem. Commun., 1985, 411 and 1986, 1456.
8. K. V. Schenker, W. von Philipsborn, C. A. Evans, W. Skuballa, and G.-A. Hoyer, Helv. Chim. Acta, 1986, **69**, 1718.

(Received in UK 4 September 1989)