Tetrahedron Letters,Vol.25,No.44,pp 5103-5104,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

STEREOSPECIFIC ALLYLSILANE REACTIONS: A TOTAL SYNTHESIS OF DIHYDRONEPETALACTONE[1]

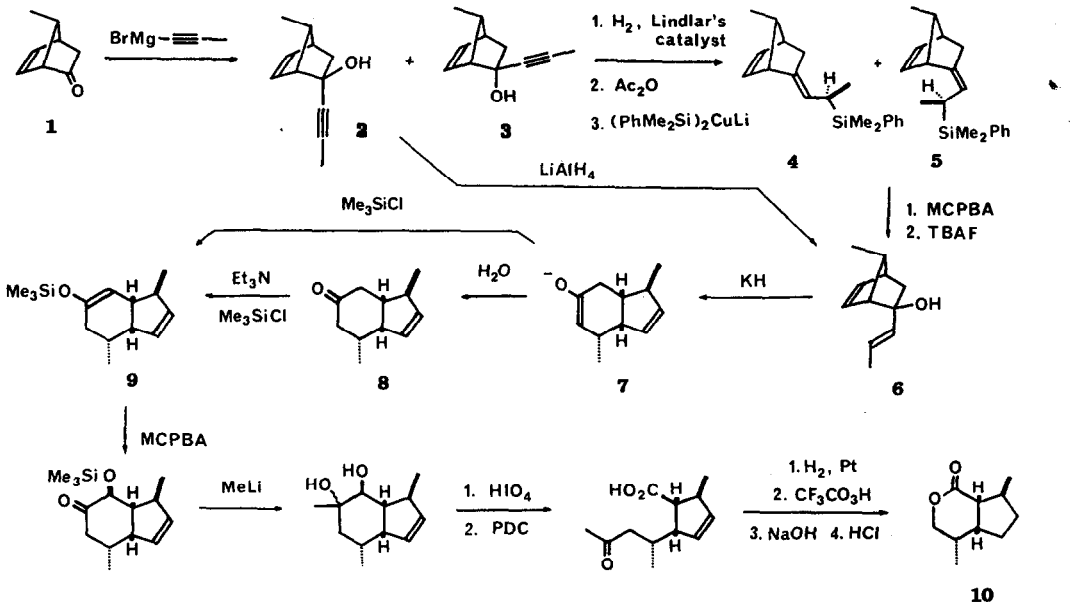
Ian Fleming* and Nicholas K. Terrett
University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England

Summary—A stereospecific synthesis of allylsilanes and their stereospecific reaction with peracid are used to prepare the *endo*-prop-1-enylnorbornenol (**6**), a substrate for an oxy-Cope rearrangement leading eventually to dihydronepetalactone (**10**) with complete stereocontrol.

We reported earlier[2] a stereospecific allylsilane synthesis, in which a tertiary allylic acetate combines regioselectively, and stereospecifically *anti* with our silyl-cuprate reagent. Several people have shown that allylsilanes react stereospecifically *anti* with electrophiles,[3] and we have shown that this is particularly clean when the electrophile is a bridging electrophile, and when the face of the double bond *anti* to the silyl group is also the more accessible face.[2] We now report a completely stereocontrolled total synthesis of racemic dihydronepetalactone (**10**), in which we use this allylsilane chemistry to set up an *endo-trans*-prop-1-enylnorbornene (**6**), a substrate for an oxy-Cope rearrangement (**6** → **7**). *Endo*-alkenylnorbornenols, suitable for oxy-Cope rearrangement, have been prepared before using 7,7-disubstituted norbornenones, in which the 7-substituents hinder the *exo* face to attack by alkenylmetal reagents.[4] However, for dihydronepetalactone, and similar targets such as iridomyrmecin, a single methyl substituent is needed on this atom; in consequence, alkenyl-metal reagents will attack *exo*, and the product will be useless for subsequent Cope rearrangement.

Our starting material was Grieco's norbornenone (**1**),[5] which we made by trapping 5-methylcyclopentadiene with chloroacrylonitrile, and hydrolysing the α-chloronitrile. The yield, based on sodium cyclopentadienide, was only 27%, but the route was short. The propynyl Grignard reagent attacked this ketone predominantly from the *exo* direction to give the propargylic alcohol (**3**) in 90% yield, with only 4% of the diastereoisomer (**2**). To correct the stereochemistry of the major product, we reduced the triple bond to a *cis* double bond, made the acetate (83%), and treated it with the silyl-cuprate reagent. As expected, by analogy with our earlier work,[2] we got a mixture (74%) of two allylsilanes (**4** and **5**), both of which are the result of an *anti* stereospecific reaction. These allylsilanes are stereochemically equivalent, and did not need to be separated. Epoxidation, followed by treatment with fluoride ion, cleanly converted the mixture into the *endo-trans*-propenylnorbornenol (**6**) in 90% yield. This was the key reaction, in which the *anti* selective reaction of the allylsilanes combines with the preference for *exo* attack by the electrophile, to give the high level of control in setting up the *trans*-propenyl group *endo* in the norbornene ring. This product was identical with a sample prepared directly by reduction of the *endo*-propynylnorbornenol (**2**). The latter reaction actually makes the synthesis of **6** convergent, although convergence was not practically important in this particular synthesis, since the amount of the *endo*-propynyl alcohol produced in the first

step was so small. The oxy-Cope rearrangement (**6** → **7**) could be relied upon stereochemically, since the only accessible conformation is the boat transition state. In the event, treatment with potassium hydride[6] followed by an aqueous work up gave a single ketone (**8**)(92%), in which all four chiral centres were correctly disposed. This ketone enolised very strongly in one direction, to give only the silyl enol ether (**9**).[7] The remaining eight steps were conventional functional group manipulations, and led (24%) to dihydronepetalactone (**10**) with IR and ^{1}H-NMR spectra identical with those of authentic material.[8] The overall yield was 12% based on **1**.



NOTES and REFERENCES

1. No reprints available.
2. I. Fleming and N. K. Terrett, *J. Organomet. Chem.*, **264**, 99 (1984).
3. H. Wetter and P. Scherer, *Helv. Chim. Acta*, **66**, 118 (1983); A. Eschenmoser, P. R. Jenkins, and V. Matassa, personal communication; G. Wickham and W. Kitching, *J. Org. Chem.*, **48**, 612 (1983); 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).
4. M. E. Jung and J. P. Hudspeth, *J. Am. Chem. Soc.*, **100**, 4309 (1978) and **102**, 2463 (1980).
5. This ketone is available in optically active form, by a longer route: P. A. Grieco, Y. Ohfune, Y. Yokoyama, and W. Owens, *J. Am. Chem. Soc.*, **101**, 4749 (1979). Clearly, we could have carried out our synthesis in the optically active series, if there had been any point in doing so.
6. D. A. Evans and A. M. Golob, *J. Am. Chem. Soc.*, **97**, 4765 (1975).
7. We were unable to trap the potassium enolate (**7**) as its silyl enol ether. Had we been able to, an exactly similar sequence of operations to those we actually used would have led to iridomyrmecin. All our attempts to silylate the enolate (**7**) led instead directly to the silyl enol ether (**9**) and the overall yield (97%) was higher when we made **9** in this way. Potassium enolates are known to isomerise rapidly in the presence of a proton source: C. A. Brown, *J. Org. Chem.*, **39**, 1324 (1974).
8. We thank Professor J. Wolinsky for the spectra of authentic material: T. Sakan, S. Isoe, S. B. Hyeon, R. Katsumura, T. Maeda, J. Wolinsky, D. Dickerson, M. Slabaugh, and D. Nelson, *Tetrahedron Lett.*, 4097 (1965). Several of the other stereoisomers have been reported, and they all have distinguishable spectroscopic features, different from those in our spectra. For an earlier synthesis, see J. Wolinsky and E. J. Eustace, *J. Org. Chem.*, **37**, 3376 (1972).

(Received in UK 13 August 1984)