Pure & Appl. Chem., Vol. 66, Nos 10/11, pp. 2049–2052, 1994.
Printed in Great Britain.

Stereocontrol using silicon: A synthesis of methyl (+)-nonactate

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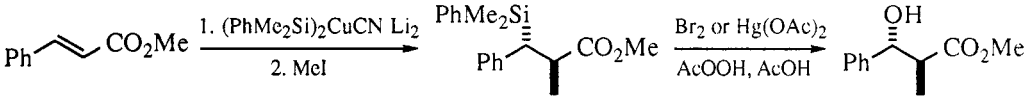
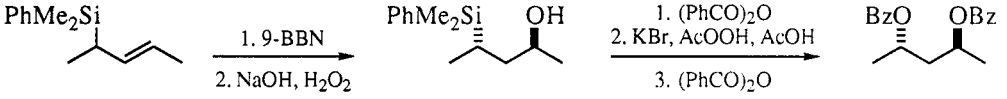
Abstract: The phenyldimethylsilyl group is separately introduced (**10** → **11** and **13** → **14**) onto a carbon chain with absolute stereocontrol, controlling the relative stereochemistry of 1,4-related centres; the silyl groups are independently used to control the relative stereochemistry of 1,3- and 1,2-related centres (**11** → **12** and **15** → **16**) in a synthesis of methyl (+)-nonactate **7**.

In earlier work (1) we developed silicon-based methods for 1,2- and 1,3-control of new stereocentres using the alkylation of β-silylenolates **1** → **2** and the hydroboration of allylsilanes **4** → **5**, and methods (2) for converting the phenyldimethylsilyl group into a hydroxyl with retention of configuration **2** → **3** and **5** → **6**. In none of this work had we found a method for controlling a 1,4-relationship like that between C-3 and

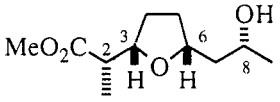


1 **2** 88% (97:3) **3** 84%



4 **5** 93% (>95:5) **6** 48%

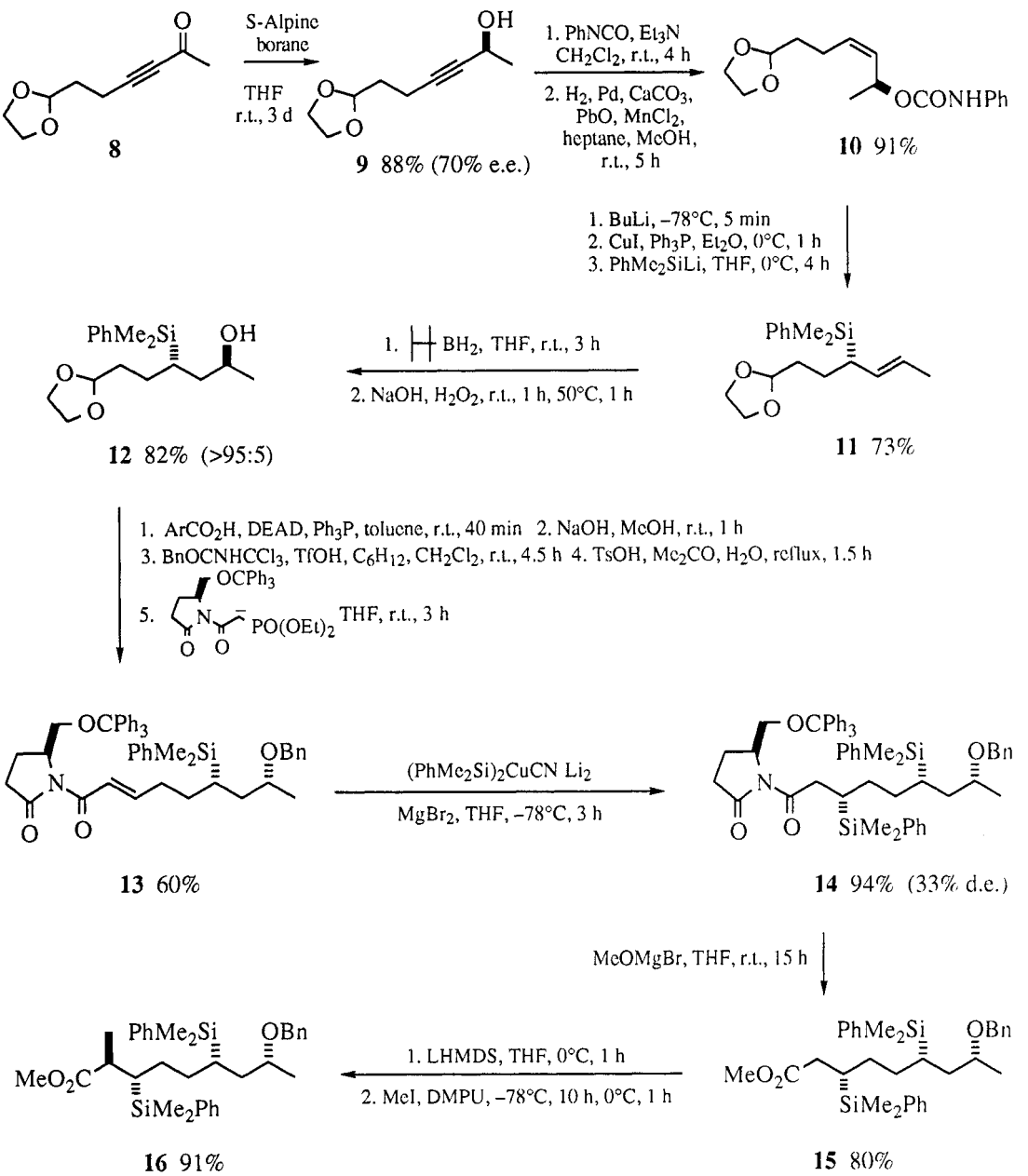
C-6 in methyl nonactate **7**, which has therefore been a standing challenge to us to extend our methods, especially since this molecule, much used as a testing ground for synthetic methodology (3,4), has a 1,2-relationship between C-2 and C-3 and a 1,3-relationship between C-6 and C-8 that we do know how to control. In this lecture, I should like to describe our first solution to this problem, in which we used successively each of the two methods we have developed for introducing the silicon with *absolute* stereocontrol, in order simultaneously to control the *relative* stereochemistry of the 1,4-relationship (5,6).



7

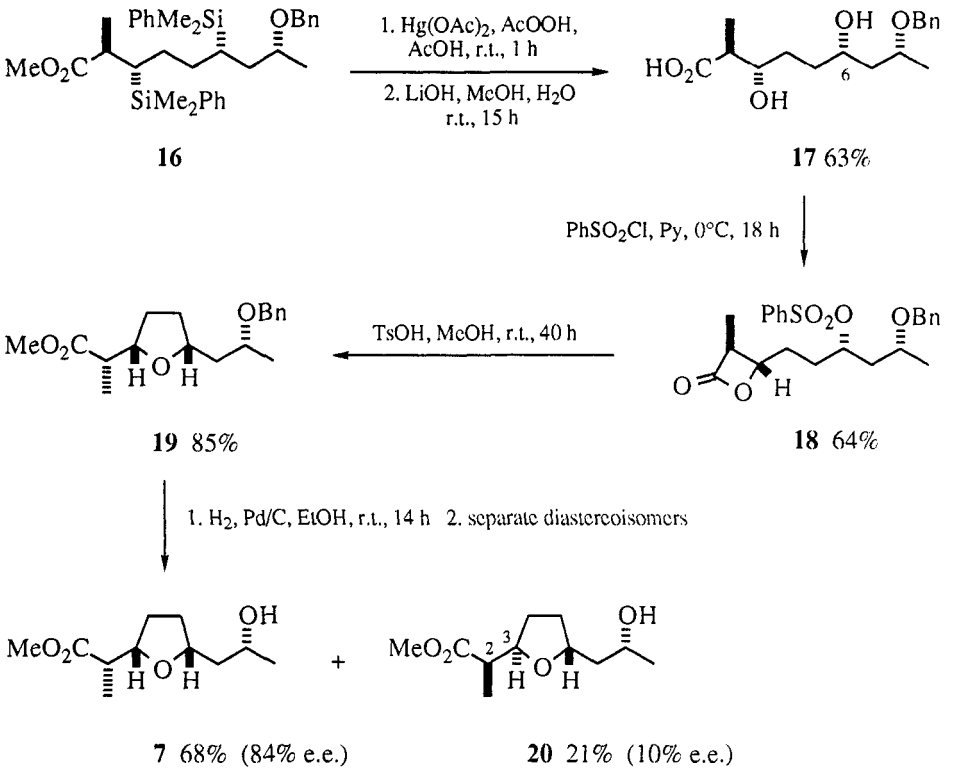
We prepared the alcohol **9**, in 70% enantiomeric excess (e.e.) using Midland's and Brown's alpine borane (7) and the ketone **8**. We then converted the corresponding (*Z*)-allylic carbamate **10** into the homochiral allylsilane **11**, using the method that we had already established was regioselective with allylic shift and stereospecifically suprafacial (5). Hydroboration of the allylsilane gave the alcohol **12** with regio- and stereoselectivity better than 95:5, as expected from our earlier work (8). In this reaction we used thexylborane, because 9-BBN was too slow, and borane itself, as expected, was unselective. Further elaboration, including a Mitsunobu inversion (9), an acid-catalysed benzylation (10), and a Wadsworth-Emmons-Horner reaction, gave the enone system of **13** attached to Koga's chiral auxiliary, which we have

found is usually effective in controlling the stereochemistry of conjugate additions of the silylcuprate reagent (6). It gave the product **14** in good yield but with unhappily low diastereoisomeric excess (33% d.e.), the lowest that we have experienced with this chiral auxiliary. We were neither inclined, for reasons given below, nor able to separate the diastereoisomers at this stage. We removed the chiral auxiliary using bromomagnesium methoxide, which we find is much superior to lithium methoxide, and methylated the ester **15** to introduce the fourth stereocentre in **16** with probably high (11) but unassessable selectivity, in view of the mixture of diastereoisomers present at this stage.



Conversion of the silyl groups to hydroxyls **16** → **17**, now left only the problem of differentiating the hydroxyls in such a way as to allow inversion of configuration specifically at C-6. We found that treatment with benzenesulphonyl chloride achieved both ends—a β-lactone was formed rather than the seven-membered ring lactone, and subsequently the free hydroxyl was converted into the benzenesulphonate **18**.

Acidic methanol then opened the lactone ring and the tetrahydrofuran ring **19** formed spontaneously. Deprotection and chromatographic separation gave methyl (+)-nonactate **7** (68%)(12), together with its C-2 and C-3 diastereoisomer **20** (21%), which is present as a consequence of the low d.e. of the conjugate addition step **13** → **14**. These two products were readily identifiable by their ^{1}H NMR spectra (4). The methyl nonactate **7** had an e.e. of 84%, and the diastereoisomer **20** an e.e of 10%, assessed in both cases by attaching (4*R*,5*R*)-2-chloro-4,5-dimethyl-1,2,3-dioxaphospholane 2-oxide (13).



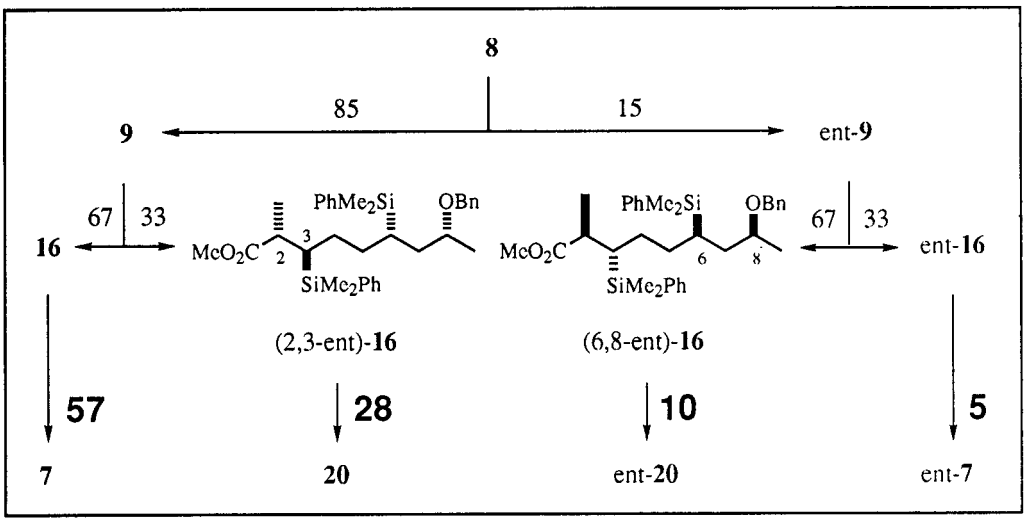
16 **17** 63%

19 85% **18** 64%

7 68% (84% e.e.) **20** 21% (10% e.e.)

With an indifferent 70% e.e. in the first enantiocontrolled step **8** → **9**, and a feeble 33% d.e. in the second **13** → **14**, it might at first seem surprising that the major product **7** is present with such a high e.e. (84%). The reason for the improvement in the e.e. of the desired product is summarised in the box, where the large bold numbers identify the calculated proportions, normalised to add up to 100%, of the four major diastereoisomers and enantiomers that ought to be present if the first step is 70% e.e. and the second 33% d.e. assuming no chiral recognition of the resident stereocentres on C-6 and C-8 in the step **13** → **14**. The minor amounts of other diastereoisomers stemming from incomplete 1,2- and 1,3-control are discounted—they were not detectable, although they must, of course, have been present to some extent. The effect of two successive enantiocontrolled reactions is to create a pair of diastereoisomers in which the major diastereoisomer **7** has an enhanced e.e. (57:5 = 92:8 = 84% e.e.) and the minor **20** a reduced e.e. (28:10 = 74:26 = 48% e.e.). Separation of the diastereoisomers, then gives the major product in a more or less acceptable state of enantiomeric purity, at the expense of some loss in yield. It was this arithmetic that had first attracted us to using two successive enantiocontrolled reactions as a solution to the 1,4 problem embedded in the structure of nonactic acid. In practice, the measured e.e. of the major product was exactly that calculated from the scheme in the box, but the minor product proved to be rather worse. We found subsequently that the 3,5-dinitrobenzoate of the propargylic alcohol **9** could be recrystallised efficiently with a rapid improvement in the e.e., two recrystallisations raising it to 98.8%. Had we used this material in the succeeding steps, the methyl nonactate would have been a very acceptable 99.4% e.e. We did not use it, because we turned instead to a second, better controlled synthesis of nonactic acid derivatives (14), having established that the approach described in this paper was not without its advantages.

We thank Rhône-Poulenc and the CNRS for financial support (CD and MA, respectively), and Dr. Usha Ghosh for help in preparing some of the early intermediates and for the recrystallisation of the 3,5-dinitrobenzoate of **9**.



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