Pergamon

Tetrahedron Letters 39 (1998) 5109–5112

TETRAHEDRON LETTERS

Stereocontrolled Polyol Synthesis *via* C-H Insertion Reactions of Silicon Tethered Diazoacetates

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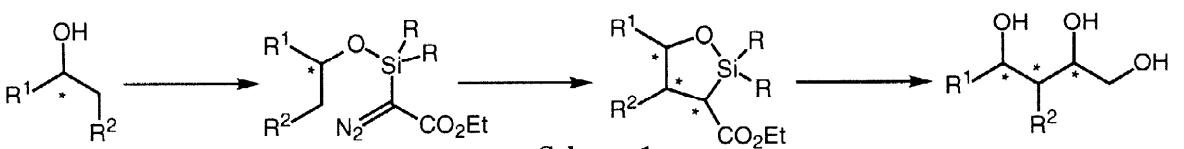
Received 3 April 1998; accepted 5 May 1998

Abstract: The preparation and rhodium catalysed C-H insertion reactions of (alkoxysilyl)diazoacetates are reported, leading to the diastereoselective synthesis of 3,4,5-trisubstituted 1-oxa-2-silacyclopentanes. Reduction of the pendant ester group followed by oxidative C-Si bond cleavage furnishes 1,2,4-triols.

Keywords: Carbenes and carbenoids; Diazo compounds; Silicon heterocycles; Triols

Many biologically significant molecules contain vicinal polyol motifs. Some of these compounds are in ready supply (*eg* pentose and hexose monosaccharides), but others (*eg* higher sugars such as N-acetylneuraminic acid) suffer from limited natural availability. We have been investigating a novel strategy for the synthesis of stereoregular polyols, based upon the C-H insertion reactions of silicon-tethered diazoacetates, and report herein our preliminary findings on the success of this approach.

Our strategy is outlined in Scheme 1. Previous work in our group has shown that simple trialkylsilyl substituted diazoacetates undergo rhodium (II) carboxylate catalysed C-H insertion reactions to the ester side chain, leading to α-silylated butyrolactones.[1] We reasoned that, given the known preference for five-ring formation in C-H insertion reactions,[2] it should be possible to prepare trisubstituted 1-oxa-2-silacyclopentanes by insertion of an ethyl diazoacetyl unit into a pendant alcohol linked through the intermediacy of a dialkylsilyl group. Such compounds should be readily prepared by condensation of the alcohol and ethyl diazoacetate with a silyl dichloride or ditriflate. Reduction of the 3-carboethoxy substituent followed by oxidative Si-C bond cleavage (Tamao oxidation)[3] would furnish the desired 1,2,4-triol. The silicon has thus acted both as a tethering group[4] and as a masked hydroxyl function. The overall transformation is equivalent to the intermolecular C-H insertion of a 'hydroxycarbene', leading to a two-carbon homologation and creating two new stereocentres.



Scheme 1

Our initial investigations focused on the use of menthol as the insertion substrate, since the reactions of menthyl diazoacetates and diazoacetoacetates are well documented.[5] A range of cyclisation precursors were prepared by one of two methods. The first follows the work of Maas,[6] and involves the stepwise addition of ethyl diazoacetate and the alcohol to a solution of a silyl ditriflate in the presence of an amine base. Thus, cyclisation precursors **1a**, **1b** and **1c** were prepared in 40, 78 and 37% yield respectively (Scheme 2). This method is limited by the expense and difficulty in preparation of the silyl ditriflates. We have therefore developed a more general method using cheap, readily available silyl dichlorides. The silyl dichloride is reacted with an equimolar amount of the alcohol in the presence of an amine base, to presumably generate a chloro(alkoxy)silane intermediate. Ethyl diazoacetate is then added, followed by two equivalents of a hindered lithium amide base such as lithium tetramethylpiperidide. In this manner, precursors **1d** and **1e** were prepared in 56 and 70% yield.

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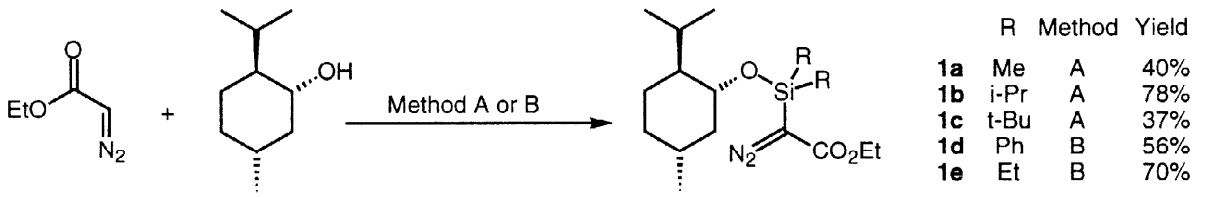
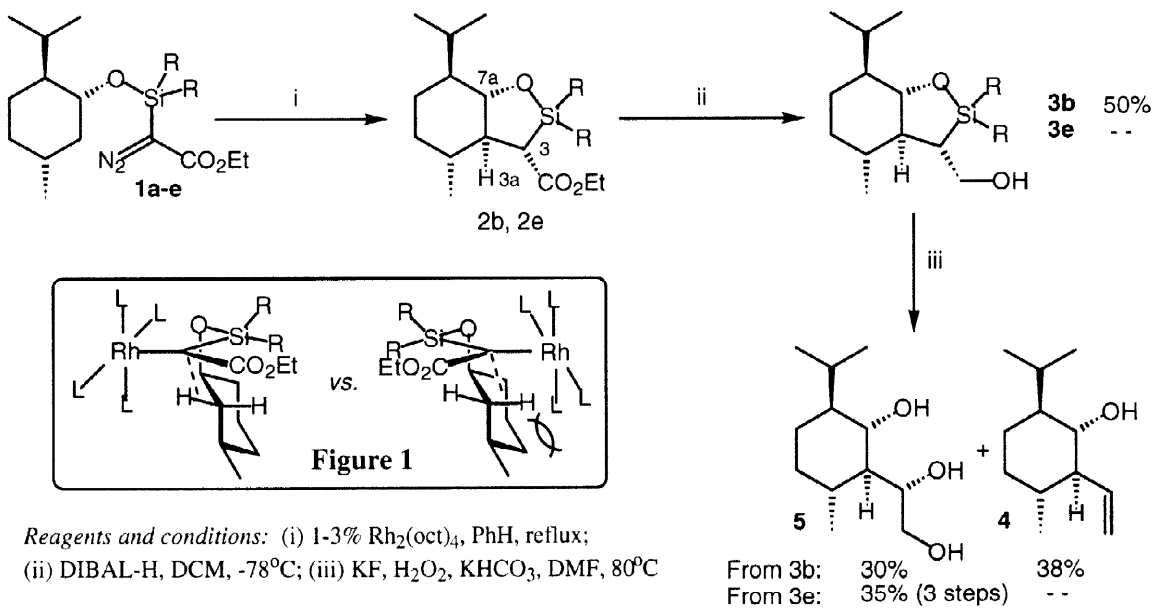


	R	Method	Yield
1a	Me	A	40%
1b	i-Pr	A	78%
1c	t-Bu	A	37%
1d	Ph	B	56%
1e	Et	B	70%

Reagents and conditions: Method A: EtO_2CHN_2, $R_2Si(OTf)_2$ (1 eq.), DIPEA, Et_2O, -78°C, then add alcohol (1 eq.) and DIPEA
Method B: Alcohol, R_2SiCl_2, Et_3N, DMAP, THF, 0°C, then add EtO_2CHN_2 followed by LiTMP (2 eq.) at -78°C

Scheme 2

The rhodium (II) octanoate catalysed decomposition of diazoacetates **1a-e** was then examined. We were delighted to find that compounds **1b** and **1e** cyclised rapidly to yield siloxanes **2b** and **2e** as single stereoisomers (Scheme 3). Owing to the sensitivity of these compounds to chromatography, neither material was purified at this stage but the purity of the crude materials was assessed from their ^1H nmr spectra (*ca.* 94% for **2b**, 62% for **2e**). By comparison, diazoacetates **1a** and **1d** suffered rapid and extensive decomposition on exposure to the reaction conditions, while only products apparently arising from insertion into the *tert*-butyl groups could be observed for diazoacetate **1c**. The stereochemistry of compounds **2b** and **2e** was assigned on the basis of the *J* values for the H3-H3a and H7a-H3a couplings, by comparison with related menthol derived 5,6-bicyclic systems.[7] This stereochemical outcome can be rationalised by considering the well known preference for diazocarbonyl compounds to undergo insertion to adjacent equatorial C-H bonds in cyclohexyl systems, to avoid unfavourable interactions between the ring and the sterically demanding rhodium catalyst (Figure 1).



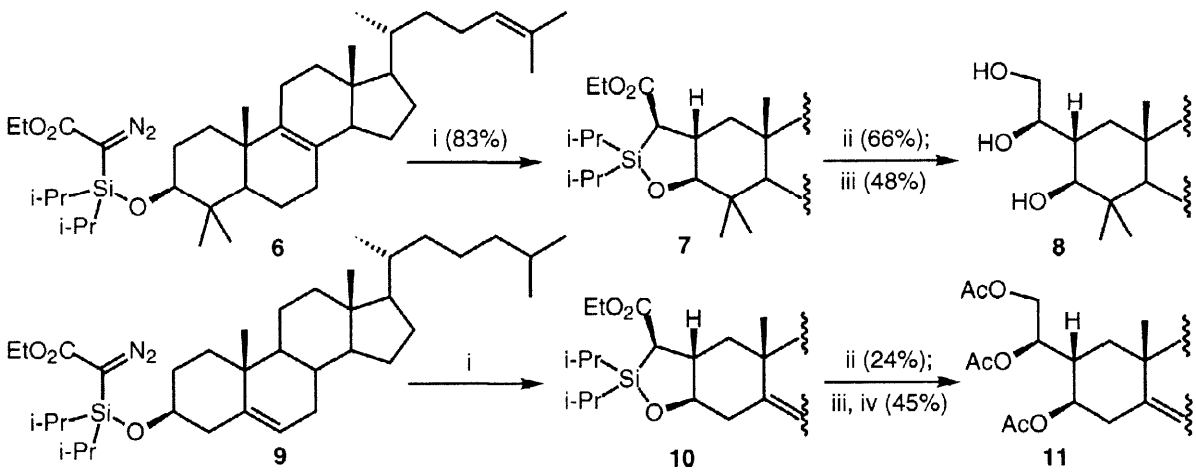
Reagents and conditions: (i) 1-3% $Rh_2(oct)_4$, PhH, reflux;
(ii) DIBAL-H, DCM, -78°C; (iii) KF, H_2O_2, $KHCO_3$, DMF, 80°C

Scheme 3

With the oxasilacyclopentanes in hand, it remained for us to demonstrate the viability of the oxidative C-Si bond cleavage to complete our projected 1,2,4-triol synthesis. Reduction of the ester functionality was most efficiently achieved using DIBAL-H at low temperature, giving alcohols **3b** (50% over 2 steps) and **3e**, which could not be separated from an unidentified impurity. Our first attempts at oxidative C-Si cleavage under standard conditions (H_2O_2, KF, $KHCO_3$, MeOH/THF) gave only recovered starting materials, while the use of alternative fluoride sources such as TBAF led exclusively to the product of Peterson-type olefination **4**. Finally, it was discovered that the use of hot DMF as solvent with alcohol **3e** gave the desired triol **5** in 35% yield over the three steps. Alcohol **3b** gave a 30% yield of **5**, along with 38% of the elimination product **4**.

Our next goal was the application of this protocol to alternative alcohols to examine the generality of the process. The lanosterol derived silyl diazoacetate **6** underwent a clean insertion reaction to give an excellent 83% isolated yield of siloxane **7** as a single stereoisomer (Scheme 4). The relative stereochemistry was again assigned

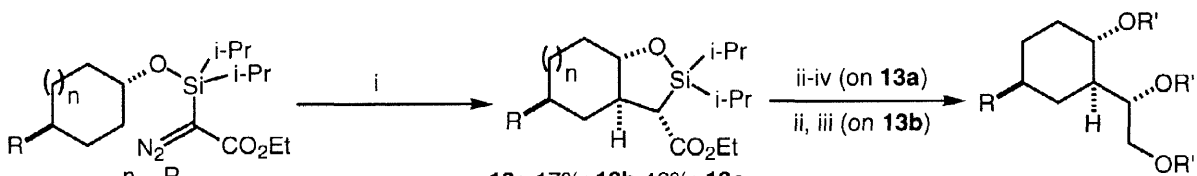
on the basis of *J* values. Reduction of the ester (66%) and Tamao oxidation under our newly developed conditions (48%) gave the α-C2-functionalised steroid **8**. We next investigated the behaviour of cholesterol derived diazoacetate **9**, since there exists here an issue of regioselectivity (C2 *vs.* C4) in the insertion reaction. In the event, insertion occurred exclusively at C2, giving the cyclic siloxane **10** as a single stereoisomer, which was isolated after reduction of the ester group (24% yield over two steps). Tamao oxidation gave the desired triol which was isolated as its triacetetate **11** for reasons of purification. The excellent regiocontrol may be explained by the known tendency for allylic positions to be deactivated towards C-H insertion,[8] or by the sp^2 centre adjacent to C4 preventing the favourable 'equatorial' disposition of the C-H bond for attack by the carbenoid.



Reagents and conditions: (i) 5 mol% $Rh_2(oct)_4$, PhH, reflux; (ii) DIBAL-H, DCM, -78°C; (iii) KF, H_2O_2, $KHCO_3$, DMF, 80°C; (iv) Ac_2O, pyridine

Scheme 4

Mindful of the advances in asymmetric C-H insertion reactions,[9] we next elected to examine insertions into prochiral alcohols. Somewhat disappointingly, the cyclohexanol derived silyl diazoacetate **12a** gave a complex mixture from which only a 17% yield of the desired siloxane **13a** could be isolated (Scheme 5). Although the insertion reaction had given rise to a single diastereomer, again demonstrating absolute selectivity for reaction with equatorial C-H bonds, we believed that the conformational freedom of the cyclohexyl ring may be retarding the insertion relative to non-productive decomposition pathways. We therefore investigated the reactions of the *trans*-4-*tert*-butylcyclohexanol derived substrate **12b**, in the hope that the ring would now be 'locked' into a reactive conformation, leading to a cleaner reaction. We were gratified to find that insertion proceeded to furnish **13b** in a respectable 46% yield, which could be converted to triol **14b** as shown.



	n	R
12a	1	H
12b	1	t-Bu
12c	0	H

13a 17%; **13b** 46%; **13c** - -

14a 40% (R' = Ac)
14b 22% (R' = H)

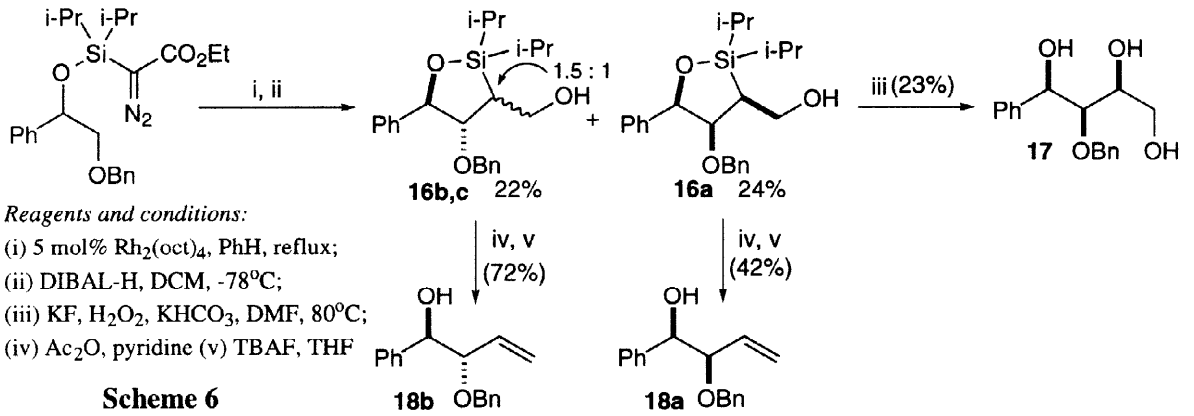
Reagents and conditions: (i) 5 mol% $Rh_2(oct)_4$, PhH, reflux; (ii) DIBAL-H, DCM, -78°C; (iii) KF, H_2O_2, $KHCO_3$, DMF, 80°C; (iv) Ac_2O, pyridine

Scheme 5

Attempts to extend the range of substrates to include cyclopentanol derivatives met with failure, substrate **12c** undergoing only destructive decomposition. It is possible that the increased ring strain associated with the formation of a 5,5-fused system may be a prohibitive factor. Initial attempts at asymmetric catalysis using Doyle's $Rh_2(MEPY)_4$ catalyst were also unsuccessful, with substrate **12b** being inert to the catalyst. Further attempts in this direction will focus on the use of chiral catalysts with more accessible co-ordination sites on rhodium.

Finally, we have begun investigations into the behaviour of acyclic alcohol derived systems in this chemistry. Styrene diol derived silyl diazoacetate **15** was subjected to the standard insertion conditions to yield a

mixture of three diastereomeric oxasilacyclopentanes, which were isolated as alcohols **16a-c** following reduction of the ester group (Scheme 6). The major diastereoisomer was obtained in 24% yield, and the minor diastereomers isolated as an inseparable 3:2 mixture in 22% yield (overall selectivity 52:29:19).



Reagents and conditions:
(i) 5 mol% $Rh_2(oct)_4$, PhH, reflux;
(ii) DIBAL-H, DCM, -78°C;
(iii) KF, H_2O_2, $KHCO_3$, DMF, 80°C;
(iv) Ac_2O, pyridine (v) TBAF, THF

Scheme 6

The major isomer was subjected to Tamao oxidation, and the relative stereochemistry of the resulting tetrol derivative **17** was determined by X-ray crystallographic analysis.[10] The exact identity of the two minor diastereomers is not known, but they were demonstrated to be C3-epimers as shown, since upon Peterson-type elimination they yielded *erythro*-3-benzyloxy-4-hydroxy-4-phenyl-1-butene **18b**, whereas the major isomer yielded the corresponding *threo*- compound **18a**. Efforts to understand and improve the selectivity of the insertion to substrates derived from acyclic alcohols are currently in hand.

In summary, we have developed a novel, stereoselective four-step synthesis of 1,2,4-triols from simple alcohol precursors, with the key step being the first example of a silicon tethered C-H insertion reaction. Further results of our studies into the scope and utility of this process will be published in due course.

ACKNOWLEDGEMENTS: We thank the EPSRC and Zeneca Agrochemicals for a CASE award (to S.N.K.). We gratefully acknowledge financial support from the Nuffield Foundation, Zeneca Strategic Research Fund, and Pfizer Central Research.

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