Pergamon

Tetrahedron Letters 39 (1998) 669–672

TETRAHEDRON LETTERS

Oxasilacyclopentanes as Intermediates for Silicon Tethered Ene Cyclisations

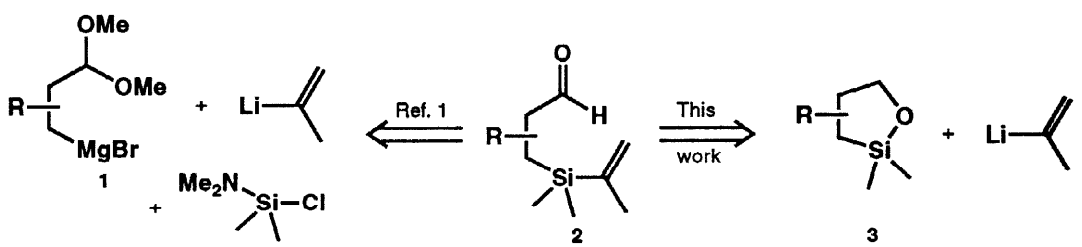
Jeremy Robertson,*[a] Donald S Middleton,[b] Garry O'Connor,[a] and Tsarina Sardharwala[a]

[a] Dyson Perrins Laboratory, South Parks Road, Oxford, OX1 3QY, U.K.
[b] Discovery Chemistry, Pfizer Central Research, Sandwich, Kent, CT13 9NJ, U.K.

Received 20 August 1997; accepted 29 August 1997

Abstract: Oxasilacyclopentanes **3**, generated by either free-radical cyclisation, intramolecular hydrosilylation, or silicon tethered Diels-Alder reaction, may be efficiently opened with 2-propenyllithium and the product alcohols oxidised to prepare precursors **2** for silicon tethered ene cyclisation. Efficient and highly stereoselective ene reactions have been achieved with these precursors.

In an earlier communication we disclosed preliminary results of a project concerned with investigating the viability, stereochemical features, and scope of the silicon tethered ene reaction[1] of which the Type II variant[2] still remains the most successful. The overriding aim of this project is to take advantage of the intramolecularity of these modified ene reactions by converting the products into polyhydroxylated synthetic intermediates with predictable control of stereochemistry. In attempting to build on our early results we found that the route to the precursors **2**, which involved sequential addition of organometallic nucleophiles to chlorodimethyl(dimethylamino)silane, was limited by the availability of the organometallic equivalent of substituted propionaldehyde homoenolates **1**.[3] For this reason we sought to identify a more flexible synthetic route to the ene precursors that would allow straightforward incorporation of varied substitution α- and/or β- to the silicon atom. In this *Letter* we describe our solution to this problem which relies on the ring opening of oxasilacyclopentanes **3** by alkenyl organometallic nucleophiles.



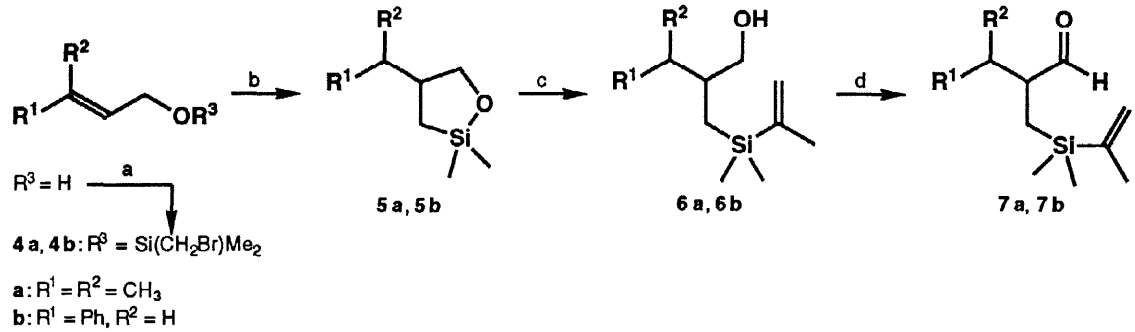
Oxasilacyclopentanes are extremely common synthetic intermediates that have been most usually opened with methyllithium,[4] or cleaved oxidatively[5] to generate diols. Few reports[6] describe the ring opening of such intermediates with more complex organometallic nucleophiles and the only systematic work that we are aware of is a study of the stereochemistry of substitution at silicon.[7] Given the wide variety of methods for generating oxasilacyclopentanes we set out to explore the possibility that they could be opened in a synthetically useful sense to generate ene precursors **2** after oxidation of the resulting hydroxyl group.

Initially we chose the Stork-Nishiyama free-radical cyclisation[8] to generate intermediates **3** and by starting with allylic alcohols substituted at the 3-position we hoped to identify a reasonably general route to β-

0040-4039/98/$19.00
PII: S0040-4039(97)01818-2

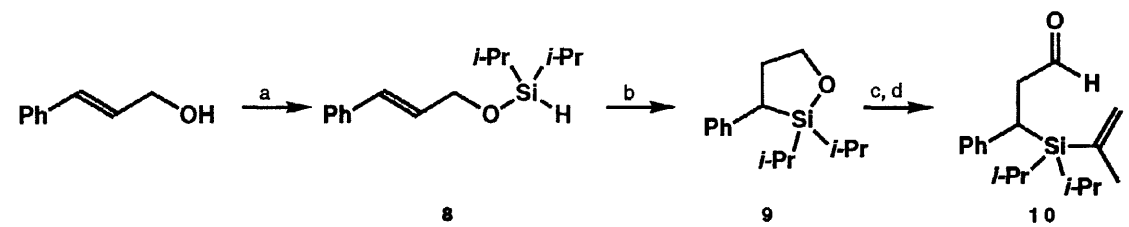
substituted (with respect to the silicon atom) ene precursors. Our first experiments were performed with 3-methylbutenol which was silylated with (bromomethyl)chlorodimethylsilane then subjected to free-radical cyclisation. As a result of its volatility oxasilacyclopentane **5a** was difficult to isolate when the cyclisation was performed in benzene but the problem was alleviated when ether was used instead although in this case competing formation of the direct reduction product (3-methyl-1-(trimethylsilyloxy)but-2-ene) could not be avoided (*ca.* 10–30% of the crude product). Addition of distilled intermediate **5a** to a THF solution of 2-propenyllithium produced alcohol **6a** which was oxidised to ene precursor **7a**.

An analogous sequence of reactions was achieved starting with cinnamyl alcohol but in this case the lower volatility of the derived oxasilacyclopentane **5b** allowed benzene to be used for the free-radical reaction and no direct-reduction product was observed. This time intermediate **5b** was not separated from the tin residues (by distillation), instead the crude residue from the radical reaction was added directly to a THF solution of 2-propenyllithium to give alcohol **6b** in comparable overall yield to that of analogue **6a**.



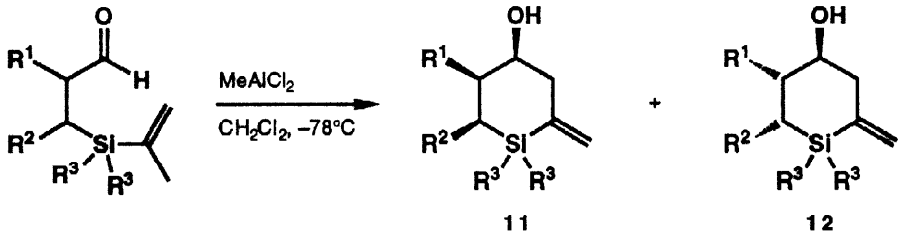
(a) $BrCH_2SiMe_2Cl$, Et_3N, DMAP (cat.), CH_2Cl_2; 80% (**4a**), 86% (**4b**); (b) *n*-Bu_3SnH, AIBN, Et_2O or PhH (see text); 61% (**5a**); (c) 2-propenyllithium, THF; 61% (**6a**), 39% (**6b** from **4b**); (d) PDC, MS4Å, CH_2Cl_2; 74% (**7a**), 72% (**7b**).

Unfortunately, this route is not easily applicable to the preparation of α-substituted (with respect to silicon) ene precursors since this would require the preparation and cyclisation of radical precursors in which the original $SiCH_2Br$ function was modified to SiCHRBr.[9] Instead, the α-substituted precursors were more effectively prepared by intramolecular hydrosilylation.[10] For example chromatographically stable silane **8**[11] was obtained in high yield from cinnamyl alcohol and induced to undergo hydrosilylation[12] in essentially quantitative yield giving moisture-sensitive oxasilacyclopentane **9**. Even this relatively sterically encumbered siloxane could be opened in 66% yield with 2-propenyllithium and the resulting alcohol oxidised as before to give α-substituted ene precursor **10**.



(a) *i*-$Pr_2Si(H)Cl$, Et_3N, DMAP (cat.), hexane; 88%; (b) $(Ph_3P)_3RhCl$, MS4Å, THF; quant.; (c) 2-propenyllithium, THF; 66%; (d) PDC, MS4Å, CH_2Cl_2; 64%.

As in our earlier work the Type II ene cyclisations were most readily effected with methylaluminium dichloride in dichloromethane (–78°C, 6–7 h) but with the new precursors, bearing bulkier substituents, the stereoselectivity was somewhat higher.[1] The table summarises the results of the ene reactions of precursors **7a**, **7b** and **10**, and of the previously reported methyl substituted analogues for comparison.

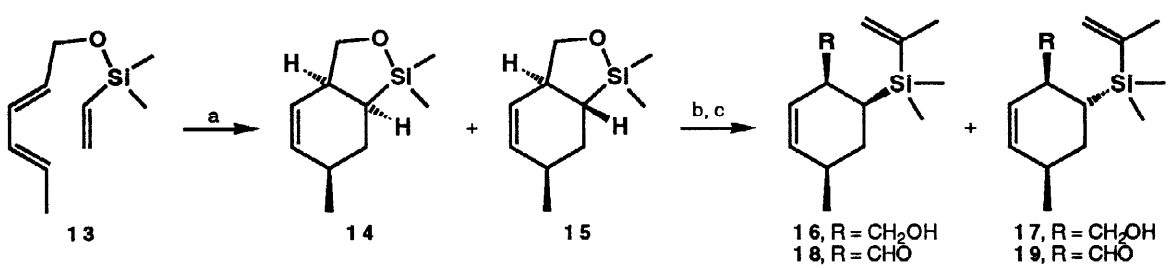


11 12

Entry	R^1	R^2	R^3	Yield (%)	Ratio[a] 11:12
1[1]	Me	H	Me	80	93:7
2 (**7a**)	*i*-Pr	H	Me	84	95.5:4.5
3 (**7b**)	Bn	H	Me	79	>98:<2[b]
4[1]	H	Me	Me	69	<2:>98[b]
5 (**10**)	H	Ph	*i*-Pr	76	<2:>98[b]

[a] Determined by examination of the CHOH integral ratio in the ^{1}H n.m.r. spectra (500 MHz) of crude products.
[b] Resonances corresponding to the minor diastereomer were not observed.

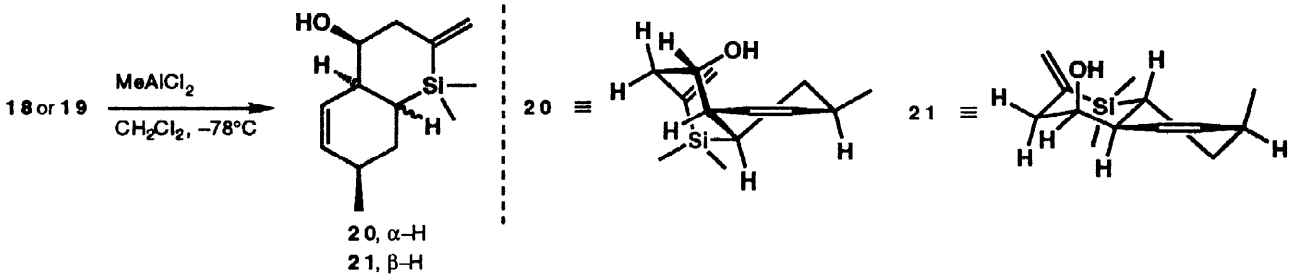
Free-radical cyclisation or intramolecular hydrosilylation, followed by ene reaction, may therefore be used to access α- or β-alkylated α'-methylenesilacyclohexanols reliably and efficiently but a more powerful demonstration of the potential in this area is an extension of the chemistry of silicon tethered Diels-Alder reactions[4,13] which exploits the oxasilacyclopentanes formed during the cycloaddition. For example, triene **13** underwent [4+2] cycloaddition to give a mixture of Si-*endo*- and Si-*exo*- adducts **14** and **15** repectively[13] (65:35 ratio) which was treated with 2-propenyllithium giving separable alcohols **16** and **17** in an isolated ratio of 60:40. PDC oxidation provided ene precursors **18** and **19** although the reaction was not as clean as might be expected and in the case of aldehyde **19** the product was contaminated with inseparable impurities.



13 14 15

(a) 170°C, PhH; (b) 2-propenyllithium, THF; 40% (**16**), 27% (**17**) from **13**; (c) PDC, MS4Å, CH_2Cl_2; 65% (**18**), 58% (**19**).

The ene reaction of precursor **18**, derived from the *endo*- adduct, was very clean, only a single cyclisation product **20** being isolated in 88% yield. The reaction of the diastereomer **19** was less high yielding (**21**, 48%) but examination of the ^{1}H n.m.r. spectra of crude and purified material indicated that the reduced yield was largely a reflection of the presence in the starting material of impurities that were unaffected by the ene reaction. The stereochemistry within the ene products was assigned, in the case of **20**, on the basis of the coupling constants for the CH_2C= protons (H_α: δ 2.64, d, *J* 14.2; H_β: δ 2.73, dd, *J* 14.2, 4.1) which showed the CHOH proton to be equatorial (no diaxial coupling). This suggested the conformation shown with the alternative *cis*-siladecalin conformer (not shown) suffering from severe diaxial interactions between the ring CH_3- and one of the silyl CH_3- substituents. A similar analysis in the case of the conformationally defined *trans*-siladecalin **21**, as well as a lack of discernible coupling constants for the CHOH proton (δ 4.03, *ca.* s), again indicated an axial hydroxyl substituent. Both of these stereochemical results are consistent with a concerted, asynchronous transition state in which the forming silacycle adopts a distorted chair conformation.[1]



In conclusion, we have developed versatile methods for preparing a range of Type II ene precursors and are actively pursuing the elaboration of this chemistry to molecules of wider interest.

ACKNOWLEDGMENTS

We thank the EPSRC for an Earmarked Studentship, Pfizer Central Research for a CASE Award (to GOC), and the EPSRC Mass Spectrometry Service Centre for exact mass measurements during the course of this work.

REFERENCES

1. Robertson, J.; O'Connor, G.; Middleton, D. S. *Tetrahedron Lett.*, **1996,** *37,* 3411–3414.
2. Nomenclature: Oppolzer, W.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.*, **1978,** *17,* 476–486.
3. Review: Kuwajima, I.; Nakamura, E. In *Comprehensive Organic Synthesis,* Vol. 2; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; pp 441–454.
4. Many examples are given in Bols, M.; Skrydstrup, T. *Chem. Rev.*, **1995,** *95,* 1253–1277.
5. Tamao, K.; Kakui, T.; Akita, M.; Iwahara, T.; Kanatani, R.; Yoshida, J.; Kumada, M. *Tetrahedron,* **1983,** *39,* 983–990; Fleming, I.; Henning, R.; Plaut, H. *J. Chem. Soc., Chem. Commun.*, **1984,** 29–31.
6. Examples of aryllithium additions to oxasilacyclopentanes: Yamamoto, Y.; Takeda, Y.; Akiba, K.-Y. *Tetrahedron Lett.*, **1989,** *30,* 725–728; Bergens, S. H.; Noheda, P.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.*, **1992,** *114,* 2121–2128; Murakami, M.; Oike, H.; Sugawara, M.; Suginome, M.; Ito, Y. *Tetrahedron,* **1993,** *49,* 3933–3946; Murakami, M.; Suginome, M.; Fujimoto, K.; Nakamura, H.; Andersson, P. G.; Ito, Y. *J. Am. Chem. Soc.*, **1993,** *115,* 6487–6498.
7. Corriu, R.; Guerin, C. *J. Organomet. Chem.*, **1980,** *195,* 261–274; Corriu, R. J. P.; Kpoton, A.; Barrau, J.; Satge, J. *J. Organomet. Chem.*, **1976,** *114,* 21–33.
8. Stork, G.; Kahn, M. *J. Am. Chem. Soc.*, **1985,** *107,* 500–501; Nishiyama, H.; Kitajima, T.; Matsumoto, M.; Itoh, K. *J. Org. Chem.*, **1984,** *49,* 2298–2300.
9. Conceptually such substrates could be prepared by deprotonation and alkylation of the $SiCH_2Br$ function, *cf.* Burford, C.; Cooke, F.; Ehlinger, E.; Magnus, P. *J. Am. Chem. Soc.*, **1977,** *99,* 4536–4537; Seyferth, D.; Hansen, E. M.; Armbrecht, F. M. *J. Organomet. Chem.*, **1970,** *23,* 361–371; Seyferth, D, Lambert, Jr., R. L.; Hansen, E. M. *J. Organomet. Chem.*, **1970,** *24,* 647–661.
10. Tamao, K.; Tanaka, T.; Nakajima, T.; Sumiya, R.; Arai, H.; Ito, Y. *Tetrahedron Lett.*, **1986,** *27,* 3377–3380; Tamao, K.; Nakajima, T.; Sumiya, R.; Arai, H.; Higuchi, N.; Ito, Y. *J. Am. Chem. Soc.*, **1986,** *108,* 6090–6093; and references therein.
11. Use of di*iso*propylsilanes for hydrosilylation: Anwar, S.; Davis, A. P.; *J. Chem. Soc., Chem. Commun.*, **1986,** 831–832; although compound **8** has been prepared (Bergens *et al.* in ref. 6) a different rhodium catalyst was used for its hydrosilylation.
12. Wilkinson's catalyst in related reactions: Anwar, S.; Davis, A. P.; *Proc. R. Ir. Acad.*, **1989,** *89B,* 71–78.
13. Diels-Alder reactions forming oxasilacyclopentanes: Stork, G.; Chan, T.-Y.; Breault, G. A. *J. Am. Chem. Soc.*, **1992,** *114,* 7578–7579; Sieburth, S. McN.; Fensterbank, L. *J. Org. Chem.*, **1992,** *57,* 5279–5281.