Stereoselective Synthesis of Dihydropyrans *via* Vinylsilane-Terminated Cyclizations of Ester-Substituted Oxycarbenium Ion Intermediates

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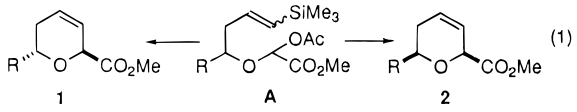
Received February 28, 1997

Six-membered ring saturated oxygen heterocycles are an integral part of many biologically active compounds.[1] Notable examples, apart from the regular carbohydrates, are the 2-carboxytetrahydropyrans KDO[2] and DAHP[3] and the neuraminic acids.[4] The 2,6-disubstituted dihydropyrans **1** and **2** (eq 1) are potential starting materials toward this compound class, as both the double bond and the ester group enable multiple structural variations.



(1)

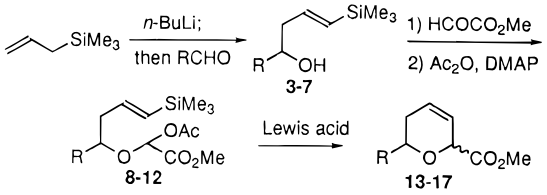
Cyclic oxycarbenium ions with a carboxyl substituent on the cationic carbon atom have been implicated as important intermediates in biological processes.[5] We have shown that acyclic ester-substituted oxycarbenium ions are useful, highly electrophilic intermediates in organic synthesis.[6] We now wish to report our results on cyclizations *via* such intermediates that are terminated by vinylsilane nucleophiles and lead to the dihydropyran building blocks **1** and **2**. We have discovered a remarkable influence of the double bond geometry of the vinylsilane **A** on the stereochemistry of the product, *viz.* (*E*)-**A** gives *trans* product **1**, whereas (*Z*)-**A** leads to *cis* product **2** (see eq 1). Although vinylsilane-terminated cyclizations *via* oxycarbenium[7] and iminium[8] ions have been widely studied, the above stereoselectivity is unprecedented.

By using the methodology delineated in Tables 1 and 2, a variety of homoallylic alcohols containing the vinylsilane moiety were constructed from easily available starting materials. The (*E*)-vinylsilanes **3**−**7** were prepared by reaction of lithiated allyltrimethylsilane[9] with the corresponding aldehydes (Table 1). Reaction of lithiated (trimethylsilyl)acetylene with substituted oxiranes[10] followed by selective *cis* reduction with P_2−Ni[11] afforded the (*Z*)-vinylsilanes **19**−**21** in reasonable overall yields (Table 2). Optically active alcohol **22** (entry 4, Table 2) was prepared in a similar manner from commercially available (*S*)-glycidol.

The homoallylic alcohols were transformed into the cyclization precursors **8**−**12** and **23**−**26** by a one-pot two-step procedure involving addition to methyl glyoxylate and subsequent *in situ* acetylation of the unstable hemiacetal (see Tables 1 and 2).[6]

In most cases, optimal conditions for the cyclization reactions required $BF_3{\cdot}OEt_2$ (2 equiv) as the Lewis acid

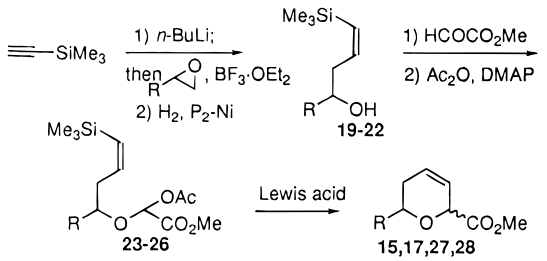
Table 1. Synthesis and Cyclization of (*E*)-Vinylsilanes



entry	R	alcohol (yield, %)[a]	acetal (yield, %)[b]	Lewis acid	product (yield, %; *cis*/*trans* ratio)
1	H	**3** (53)[c]	**8** (51)	$BF_3{\cdot}OEt_2$	**13** (62)
2	Me	**4** (37)	**9** (47)	$BF_3{\cdot}OEt_2$	**14** (73; 30:70)
3	*c*-C_6H_{11}	**5** (60)	**10** (65)	$BF_3{\cdot}OEt_2$	**15** (94; 11:89)
4	*t*-Bu	**6** (60)	**11** (76)	$SnCl_4$	**16** (87; 17:83)
5	Bn	**7** (60)	**12** (57)	$BF_3{\cdot}OEt_2$	**17** (66; 72:28) + **18** (13)[d]

[a] Overall yield from the aldehyde. [b] Ca. 1:1 mixture of diastereomers, except for **8**. [c] From paraformaldehyde. [d] For compound **18** see eq 2.

Table 2. Synthesis and Cyclization of (*Z*)-Vinylsilanes



entry	R	alcohol (yield, %)[a]	acetal (yield, %)[b]	Lewis acid	product (yield, %; *cis*/*trans* ratio)
1	Et	**19** (41)	**23** (71)	$BF_3{\cdot}OEt_2$	**27** (69; 93:7)
2	*c*-C_6H_{11}	**20** (50)	**24** (36)	$BF_3{\cdot}OEt_2$	**15** (86; 92:8)
3	Bn	**21** (36)	**25** (79)	$BF_3{\cdot}OEt_2$	**17** (76; 95:5) + **18** (21)[c]
4	CH_2OBn	**22** (90)[d]	**26** (62)	$SnCl_4$	**28** (64; >98:2)[e]

[a] Overall yield from the epoxide. [b] Ca. 1:1 mixture of diastereomers. [c] For compound **18** see eq 2. [d] 92% ee determined by HPLC for the benzyl ether of (*S*)-glycidol precursor of **22**. [e] 92% ee, determined by HPLC, $[\alpha]^{25}_D = -68.4$ ($c = 1.0$, toluene).

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(1) For some examples see: (a) Class, Y. J.; DeShong, P. *Chem. Rev.* **1995**, *95*, 1843. (b) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041. (c) Markó, I. E.; Bayston D. J. *Synthesis* **1996**, 297.

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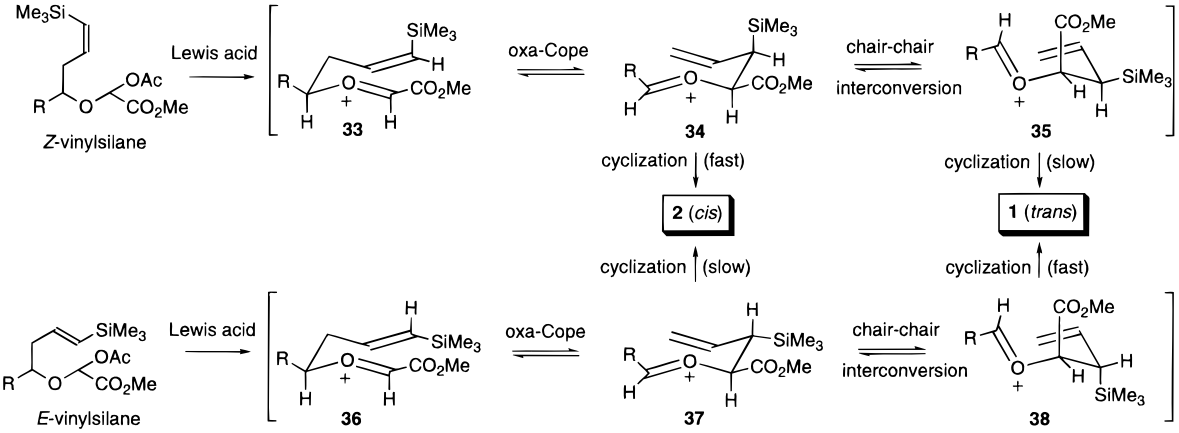
S0022-3263(97)00369-1 CCC: $14.00

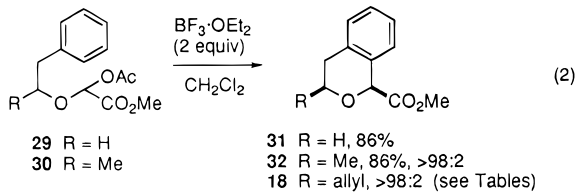
Scheme 1



in dichloromethane as the solvent. The Lewis acid was added to the reaction mixture at −78 °C, which was then allowed to slowly warm to room temperature. Interestingly, the *tert*-butyl-containing precursor **11** did not cyclize under the influence of $BF_3{\cdot}OEt_2$. In this case, the stronger Lewis acid $SnCl_4$ was successful. The latter Lewis acid was also used for the cyclization of the optically active precursor **26**. The stereochemistry of the separated *cis*- and *trans*-2,6-disubstituted dihydropyrans was proven by NOE-difference measurements.[12]

The parent (*E*)-vinylsilane precursor **8** cyclized in 62% yield to dihydropyran **13** (entry 1, Table 1). This result is similar to that reported earlier for a 1:6 *E*/*Z* mixture.[6] The alkyl-substituted precursors **9**−**12** cyclized in good to excellent yields to 2,6-disubstituted dihydropyrans **14**−**17** (entries 2−5, Table 1). In most cases, the *trans* isomer appeared to be the major product. The cyclization of precursor **12**, however, proceeded differently, giving the *cis* isomer of **17** as the major product. Moreover, the bicyclic byproduct **18** was obtained with high selectivity for the *cis* isomer. The latter product results from attack of the benzyl group on the oxycarbenium ion. To confirm the feasibility of this type of cyclization, acetals **29** and **30** were prepared from the corresponding commercially available alcohols (eq 2). The cyclizations of **29** and **30** proceeded in excellent yields to **31** and **32**, showing that the phenyl ring is a good nucleophile for the α-ester oxycarbenium ion. These reactions led to the *cis* products with high stereoselectivity.

The cyclization reactions of (*Z*)-vinylsilane precursors **23**−**26** were also successful and proceeded in similar



yields (Table 2). Interestingly, the *cis*-2,6-disubstituted products were obtained with high selectivity (>90:10) in all cases. Cyclization of the benzyl-substituted (*Z*)-vinylsilane **25** resulted in a similar amount of byproduct **18** as was obtained from the(*E*)-vinylsilane **12**. Comparison of the cyclizations of **12** and **25** furthermore shows that in the latter case the selectivity for the *cis* product is somewhat higher. The cyclization of **26** proceeded with complete retention of optical activity, which was proven by chiral HPLC analysis.[13]

These results show that the geometry of the vinylsilane double bond is important in determining the *cis*/*trans* ratio of the products. In the sequel to this paper, a probable mechanism is presented to explain this remarkable stereoselectivity (see Scheme 1). The oxa-Cope rearrangement of the cationic intermediate is believed to play an important role in this mechanism. A second relevant presumption is the relatively high rate of cyclization of an *allylsilane* from a chairlike conformation with an *axially disposed* silyl substituent.[8] In such an orientation the β-effect of silicon is most effective.[14]

The preferred formation of the *trans* product from the (*E*)-vinylsilanes can be understood as follows (Scheme 1). The incipient carbocation **36** (drawn in its most stable chairlike conformation) is in equilibrium with **37** *via* a cationic oxa-Cope equilibrium. The latter is probably somewhat more stable in view of the substitution pattern of the carbocation. However, the cyclization of **37**, which would lead to the *cis* product, will be slow because the silyl group is not well oriented to assist in the cyclization. When **37** undergoes chair−chair interconversion of the oxycarbenium ion, cation **38** is formed featuring an allylsilane with an axial silyl function. Cyclization of **38** is a fast process and leads to the *trans* product.

In the case of the (*Z*)-vinylsilane, the observed *cis* selectivity is the result of cyclization of conformation **34** (see Scheme 1) in which the oxycarbenium ion has the favorable axially oriented trimethylsilyl group due to the (*Z*)-double bond geometry of the precursor.

The above mechanistic picture may also serve to explain the somewhat higher selectivity observed with (*Z*)-vinylsilanes than with their (*E*)-isomers. If we make the reasonable assumption that the conformational equilibria are fast compared to the cyclization reactions, it means that the relative ease of cyclization of **38** versus **37** is less pronounced than the relative ease of cyclization of **34** versus **35**. This observation seems very sensible in view of the relative number of axial substituents destabilizing the transition state of cyclization. The explanation of the exceptional stereochemical outcome of the cyclization of **12** (Table 1) requires further study.

Supporting Information Available: Experimental details for the synthesis (including spectroscopic and analytical data) of alcohols **5**, **20**, and **22**, precursors **10**, **24**, and **26**, and all cyclization products (10 pages).

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(12) For example, in the case of product **15** irradiation of H2 of the *cis* product gave an enhancement of 7% on H6 while similar irradiation of the *trans* product showed no effect.

(13) Chiralpak AS column, eluent *n*-heptane/2-propanol 95:5, flow 0.5 mL/min, 250 × 4.5 mm.

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