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Synthesis and Chemistry of Bridgehead Allylsilanes. Stereoselective Reactions with Aldehydes

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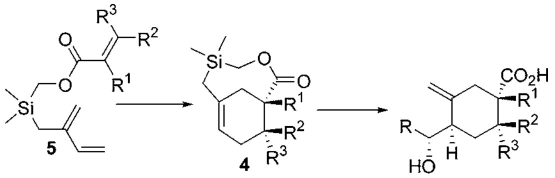
ABSTRACT



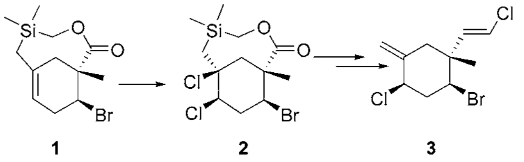
A type II intramolecular Diels–Alder reaction provides access to bicyclo[5.3.1] ring systems with an imbedded bridgehead allylsilane. The Lewis acid catalyzed reactions of these compounds with aldehydes proceed efficiently and with control of stereochemistry.

Allylsilanes are important intermediates for carbon–carbon bond-forming reactions.[1] They are stable to water and air, yet react readily with activated carbonyls and enones. A high degree of stereocontrol can be achieved in these reactions when either the allylsilane or electrophile possesses asymmetry.[2] Such stereocontrol and ease of reaction of allylsilanes has led to efficient syntheses of many medicinally useful natural products.[3]

Recently, we reported the synthesis of *Plocamium* marine natural product **3**. A bridgehead allylsilane (**1**) incorporated into a bicyclo[5.3.1] ring system was a key intermediate in the synthesis (Scheme 1).[4]

The stereoselective reaction of the bridgehead allylsilane with heteroatom electrophiles (**1** to **2**) was a key step in the synthesis. Encouraged by these results, we set out to extend this methodology to carbon atom electrophiles. In this paper, we detail the syntheses of bridgehead allylsilanes of varying substitution pattern and investigate their behavior in reactions with aldehydes.

Scheme 1. Bridghead Allylsilane Intermediate in the Synthesis of *Plocamium* Monoterpene **3**



Bridgehead allylsilanes **4** may be assembled by a type II intramolecular Diels–Alder reaction from simple acyclic triene precursors **5**.[5] The triene precursors in turn were envisioned to be assembled from a difunctional silyl containing tether **7** (Scheme 2).

In the synthetic direction, commercially available bis(chloromethyl)dimethylsilane **9** served as the starting mate-

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[1] (a) Langkopf, E.; Schinzer, D. *Chem. Rev.* **1995**, *95*, 1375. (b) Majetich, G. *Org. Synth.: Theor. Appl.* **1989**, *1*, 173. (c) Hosomi, A. *Acc. Chem. Res.* **1988**, *21*, 200.

[2] (a) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063. (b) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (c) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293.

[3] Some recent examples include: (a) Mulzer, J.; Hanbauer, M. *Tetrahedron Lett.* **2002**, *43*, 3381. (b) Su, Q. B.; Panek, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 2425. (c) Su, Q. B.; Panek, J. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 1223.

[4] Whitney, J. M.; Parnes, J. S.; Shea, K. J. *J. Org. Chem.* **1997**, *62*, 8962.

[5] Bear, B. R.; Sparks, S. M.; Shea, K. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 820.

10.1021/ol051363c CCC: $30.25

Scheme 2. Retrosynthetic Analysis of Bridghead Allylsilanes and Synthesis of the Tether

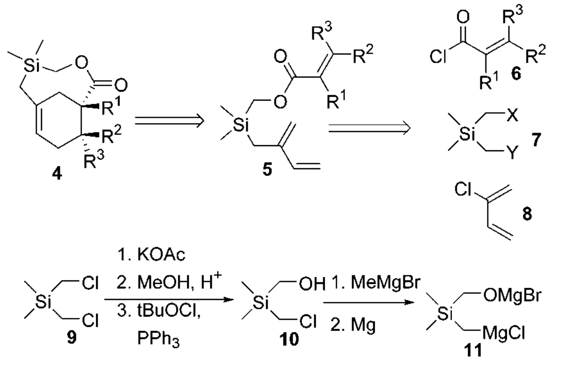
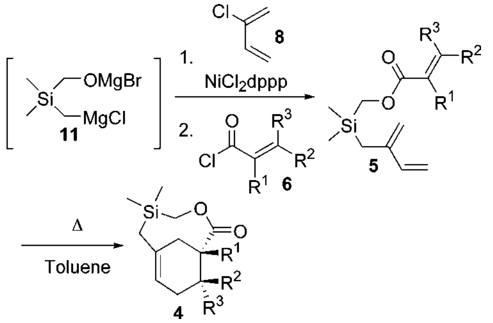
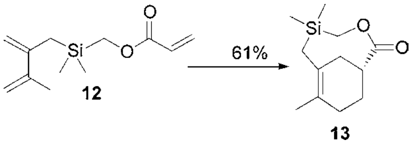


Table 1. Coupling of Trienes to Silicon Linker and Subsequent Regioselective Intramolecular Diels−Alder Reactions



entry	R1	R2	R3	yield (**5**) (%)	yield (**4**) (%)
a	H	H	H	92	80
b	CH_3	H	H	82	90
c	H	CH_3	H	95	94
d	CH_3	CH_3	H	90	77
e	H	CH_3	CH_3	71	0
f	H	Ph	H	89	96
g	CH_3	Br	H	85	74
h	$-CH_2OCH{=}CH-$		H	96	0
i	H	CO_2Me	H	71	75
j	CN	Ph	H	72	89



rial.[4] Desymmetrization was achieved in three steps to give chloromethylhydroxymethyldimethylsilane **10** in excellent yield on a 50 g scale. Coupling of this tether unit to the desired diene and dienophile commenced with protection of the free alcohol as the magnesium salt via depronation with methylmagnesium bromide. The salt was reacted with magnesium to give the Normant−Grignard reagent **11**,[6] which was coupled to chloroprene via Hosomi's nickel-mediated cross-coupling protocol.[7] The resulting diene alkoxide was reacted with an acid chloride in situ. In this manner, both the diene and dienophile were joined to the silyl linker in a one-pot procedure. This sequence gave good to excellent yields of triene Diels−Alder precursors **5** as shown in Table 1.

The intramolecular Diels−Alder cyclizations of the trienes **5** were conducted as 0.01 M solutions in toluene. The solutions were placed in sealed tubes and heated to 200 °C until reaction completion.[8] The reaction accommodated a variety of substituents at both the R1 and R2 positions of the dienophile to give exlusive formation of the meta-regioisomeric product. Exceptions include the sterically encumbered dienophile **5e** and furan derivative **5h**. It is of particular note that substitution at R1 (**5b**,**d**,**g**,**j**) results in the stereoselective formation of a quaternary carbon center. In addition to substitution at the dienophile, substitution at the 3-position of the diene was also investigated. Methyl substution was well tolerated in the cyclization of **12**, which generated the tetrasubstitued bridgehead allylsilane **13** in 61% yield.

The phenyl-substituted bridgehead allylsilane **4f** proved to be a solid and yielded a crystal amenable to X-ray structure determination (Figure 1). Bridgehead olefins are often twisted well out of plane,[9] but the longer bonds to Si in this case allow the double bond to adopt a nearly planar conformation. The torsional angle (τ = 5.5°) represents only a minor distortion. Importantly, the geometry of the bridgehead allylsilane moiety was found to have a dihedral angle (Si−C_2−C_1−C_{11}) of 77.7°. This is close to the ideal 90° angle for stabilization of carbocation intermediates formed during reactions with electrophiles.[10] This suggests that stereoelectronic factors will favor high reactivity of bridgehead allylsilanes.

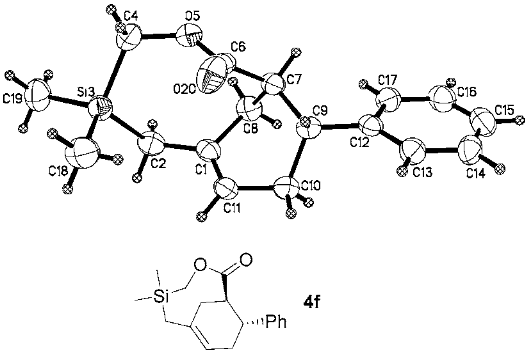


Figure 1. X-ray crystal structure of **4f**.

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(6) (a) Cahiez, G.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1978**, *19*, 3013. (b) Umio, S.; Ueda, I.; Nojima, H. *J. Med. Chem.* **1972**, *15*, 855.

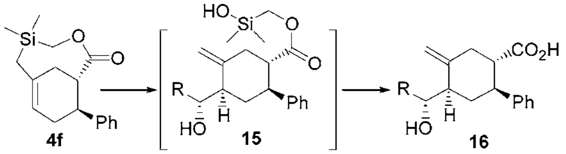
(7) (a) Hosomi, A.; Saito, M.; Sakurai, H. *Tetrahedron Lett.* **1979**, *20*, 429. (b) Hosomi, A.; Sakata, Y.; Sakurai, H. *Tetrahedron Lett.* **1985**, *26*, 5175.

(8) Lewis acid promoted reactions were also attempted but were unsuccessful, although intermolecular reactions of similar untethered dienes proceed readily. (a) Organ, M. G.; Winkle, D. D. *J. Org. Chem.* **1997**, *62*, 1881. (b) Organ, M. G.; Winkle, D. D.; Huffmann, J. *J. Org. Chem.* **1997**, *62*, 5254.

(9) (a) Warner, P. M. *Chem. Rev.* **1989**, *89*, 1067. (b) Lease, T. J.; Shea, K. J. *Adv. Theor. Interest. Mol.* **1992**, *2*, 79.

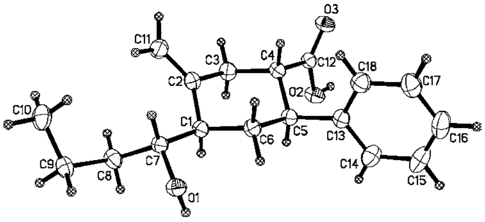
The reactivity of bridgehead allylsilane **4f** with electrophiles was tested using fluoride sources to enhance the nucleophilicity of the allylsilane and Lewis acids to activate electrophiles. Fluoride sources caused intramolecular attack of the allylsilane on the lactone, resulting in formation of the strained bicyclic enone **14**.

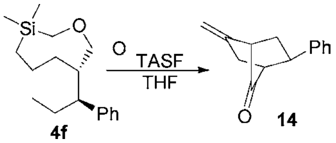
Table 2. Reaction of Bridgehead Allylsilane **4f** with Aldehydes[a]



entry	R	yield (%)
a	$(CH_3)_3C$	50
b	$(CH_3)_2CH$	74
c	$CH_3CH_2CH_2$	79
d	$3\text{-}NO_2Ph$	67

[a] The crystal structure of adduct **16c** is shown below.





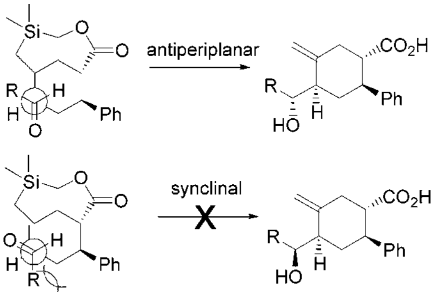
4f **14**

Lewis acid promoted reactions with aldehydes, on the other hand, proved successful. The initial protocol was to complex the Lewis acid and aldehyde in CH_2Cl_2 with a proton scavenger[11] at −78 °C, followed by adding a solution of bridgehead allylsilane **4f**. After 1 h at −78 °C, the reactions were quenched and the products isolated. At this stage of the reaction, addition to the aldehyde was generally complete, but the remnant of the tether chain remained attached as the ester. The silanol **15** complicated isolation by apparently binding to SiO_2 in flash column purification, and cleaving the ester with acid or base was not entirely successful. It was found that stirring the reaction mixture for 48 h at ambient temperature resulted in in situ cleavage of the tether to give the free acids **16** which were then isolated. Unfortunately, these conditions were incompatible with aromatic aldehydes lacking electron-withdrawing groups, as the benzyl alcohols formed underwent secondary reactions.

The aldehyde adducts **16** showed higher yields when the aldehyde was less sterically demanding. The yield with 1-butanal was highest at 79%, but with the hindered pivaldehyde the yield dropped to 50%. In all cases, aldehydes reacted to give a single diastereomer. A crystal structure of the 1-butanal adduct **16c** permits assignment of the stereochemistry indicated in Table 2.

The high diastereoselectiviy is analyzed within the context of two working models for allylsilane addition; the antiperiplanar and synclinal models (Scheme 3).

Scheme 3. Rationalization of Stereochemical Outcome[a]



[a]Complexation to $TiCl_4$ is omitted for clarity.

The synclinal model aligns the carbonyl oxygen gauche to the allysilane double bond, and the antiperiplanar model aligns the carbonyl oxygen 180° to the double bond. The bridgehead allylsilane adopts a distorted boat conformation in the six-membered ring. The steric environment permits only the aldehyde hydrogen access to the interior of this region. The other relevant interaction is that of the aldehyde R group. Since, in the synclinal model, the R group would be brought into close proximity to one of the cyclohexene methylenes, the aldehyde is limited to the antiperiplanar mode of attack. The crystal structure of the 1-butanal adduct **16c** confirms that it is the product of antiperiplanar addition.

The suggested transition state is similar to that proposed in the reaction of aldehydes with allylsilanes imbedded in cyclohexene rings.[8] Aliphatic aldehydes in that study also resulted in a single diastereomer at the aldehydic carbon, although mixtures of cis/trans isomers were obtained. In contrast, π-facial selectivity of bridgehead allylsilanes is dictated by exclusive convex face approach of the aldehyde, resulting in formation of a single product.[5]

To understand the role of the phenyl group in these studies, bridgehead allylsilane **4a** was reacted with isobutyraldehyde (Scheme 4). The product **17** was a single diastereomer isolated in 77% yield, showing that the observed selectivity is an inherent feature of the bridgehead allylsilane bicyclo[5.3.1] ring system.

A measure of the reactivity of bridgehead allylsilanes was established through a competition study.[12] A solution of 1 equiv each phenyl-substituted bridgehead allylsilane **4f** and allyltrimethylsilane was added to 1 equiv of isobutyraldehyde

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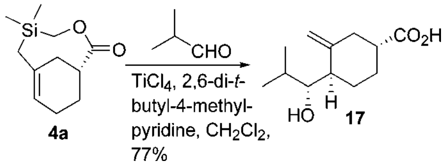
[10] Lambert, J. B.; Zhao, Y.; Emblidge, R. W.; Salvador, L. A.; Liu, X.; So, J.-H.; Chelius, E. C. *Acc. Chem. Res.* **1999**, *32*, 183.

[11] 2,6-Di-*tert*-butyl-4-methylpyridine was used as the proton scavenger.

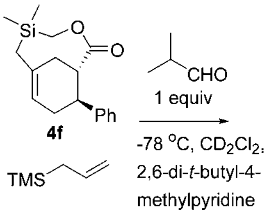
[12] Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66.

Scheme 4. Stereoselectivity with Parent Bridgehead Allylsilane



precomplexed with $TiCl_4$ at −78 °C in the presence of 2,6-di-*tert*-butyl-4-methylpyridine in CD_2Cl_2 (Scheme 5). After being stirred for 1.5 h, the reaction was warmed to ambient temperature and then analyzed by NMR for the remaining allylsilane resonances. Upon consumption of isobutyraldehyde, **4f** and allyltrimethylsilane were present in a 1:1.6 ratio. This result shows that the bridgehead allylsilane reacts roughly 1.6 times faster than allyltrimethylsilane with isobutyraldehyde.

Scheme 5. Competition Study to Determine Reactivity of Bridgehead Allylsilanes



In summary, we have developed an expedient synthesis of bicyclo[5.3.1] ring systems with imbedded bridgehead allylsilanes using the type II intramolecular Diels—Alder reaction which is highly regioselective. Reactions of these compounds reveal reactivity superior to that of allyltrimethylsilane in the presence of aldehyde electrophiles. Reactions with aldehydes are highly diastereoselective, and this selectivity can be explained by a discrimination between antiperipanar and synclinal modes of attack. The unique shape of these bridgehead allylsilanes results in exclusive attack on the convex face of the π-plane.

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Supporting Information Available: Experimental details for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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