Diastereoselective Intramolecular Bis-Silylation of a Carbon−Carbon Double Bond. A Highly Stereocontrolled Synthesis of (−)-Avenaciolide

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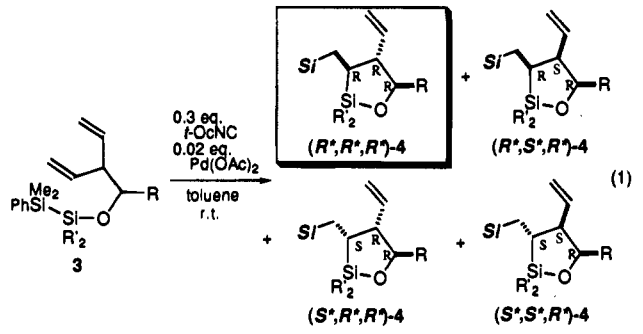
Synthetic reactions that involve the simultaneous selection of a diastereo- or enantiotopic C=C group and its π-face have provided useful methodologies for stereocontrol of multiple stereogenic centers.[1] Such stereoselective transformations have been exemplified in the reactions of cyclic dienes, whose rigid conformation makes diastereotopic group and/or face selection effective.[1c-g] However, little is known for acyclic dienes, e.g., the Sharpless epoxidation of 1,4-pentadien-3-ol, which proceeded with enantiotopic group selection as well as diastereotopic face selection in the presence of diisopropyl L- or D-tartrate with Ti(O-*i*-Pr)$_4$.[1a]

Recently, we reported that intramolecular bis-silylation of homoallylic alcohols having a substituent α or β to the double bond took place with high diastereoselectivity to give 5-exo ring closure products, whose oxidation with H_2O_2 afforded 1,2,4-triols stereoselectively.[2] In this communication, we describe that the intramolecular bis-silylation of dienols **1** proceeded with high diastereoselectivity to produce a five-membered cyclic product, in which three stereogenic chiral centers were highly controlled. A synthetic application of the bis-silylation reaction is demonstrated by total synthesis of (−)-avenaciolide (**2**) from optically pure dienol **1** (R = *n*-C_8H_{17}) prepared by enantioselective γ-pentadienylation of nonanal (Scheme 1).

Disilanyl ethers **3a−e** derived from 1-phenyl-2-vinyl-3-buten-1-ol (**1**, R = Ph) were subjected to intramolecular bis-silylation in the presence of 0.02 equiv of $Pd(OAc)_2$ and 0.3 equiv of 1,1,3,3-tetramethylbutyl isocyanide in toluene (eq 1; Table 1, entries 1−5). The 2-phenyltetramethyldisilanyl group, which



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has induced sufficiently high diastereoselectivity in the bis-silylation so far reported,[2] gave two of the four possible

Scheme 1

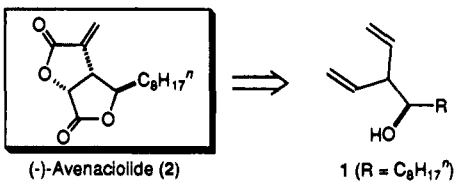

Table 1. Diastereotopic Group and Face Selective Intramolecular Bis-Silylation of Dienes

entry	3	disilanyl group R′	R	product 4 (yield/%)	ratio (%)[a] (*R**,*R**,*R**):(*R**,*S**,*R**)
1	**a**	Me	Ph	98	59:41
2	**b**	Et	Ph	82	75:25
3	**c**	*i*-Pr	Ph	27	92:8
4	**d**	Ph	Ph	87	83:17
5	**e**	*i*-Bu	Ph	90	88:12
6	**f**	*i*-Bu	Me	92	90:10

[a] Less than 1% of other isomers, (*S**,*R**,*R**) and (*S**,*S**,*R**), was found.

diastereomers, i.e., (*R**,*R**,*R**) and (*R**,*S**,*R**), in a 6:4 ratio (entry 1). This result indicated that the cyclization occurred with high diastereofacial selection but with low diastereotopic group selection (vide infra). Improved diastereotopic group selectivity was found in the cyclization of **3** having a disilanyl group with more bulky substituents on the silicon atom proximal to the ether oxygen. Thus, in the case of *i*-Pr-substituted **3c** (R′ = *i*-Pr), the selectivity reached a 92:8 ratio, though the reaction was too sluggish to obtain a reasonable yield of **4c** (entry 3). It was found that use of *i*-Bu-substituted disilanyl ether was preferable with respect to chemical yield as well as diastereoselectivity (entry 5). The disilanyl group was also effective for the bis-silylation of 3-vinyl-4-penten-2-ol to afford **4f** with high chemical yield and diastereoselectivity (entry 6).

As proposed, the intramolecular bis-silylation proceeds via a bis(silyl)palladium complex in a chair-like conformation, which is formed by oxidative addition of the Si−Si bond onto a palladium−isocyanide complex, followed by insertion of the C=C bond into the Pd−Si bond (Scheme 2). A strong tendency of R groups to occupy an equatorial position may render the conformers **eq-eq** and **eq-ax** more favorable. The rate-determining insertion step via the conformer **eq-eq** may be sterically less encumbered by the nonreacting vinyl group, resulting in high diastereotopic group selection.

Stereoselective bis-silylation could be applied to the total synthesis of the antifungal metabolite (−)-avenaciolide (**2**), which has the three contiguous chiral centers, (*R*,*R*,*R*), identical with those in the bis-silylation product **4** (Scheme 3).[3,4] The optically active (>98% ee) 3-vinyl-1-undecen-4-ol ((*R*)-**1**, R = *n*-C_8H_{17}) was prepared by enantioselective γ-pentadienylation

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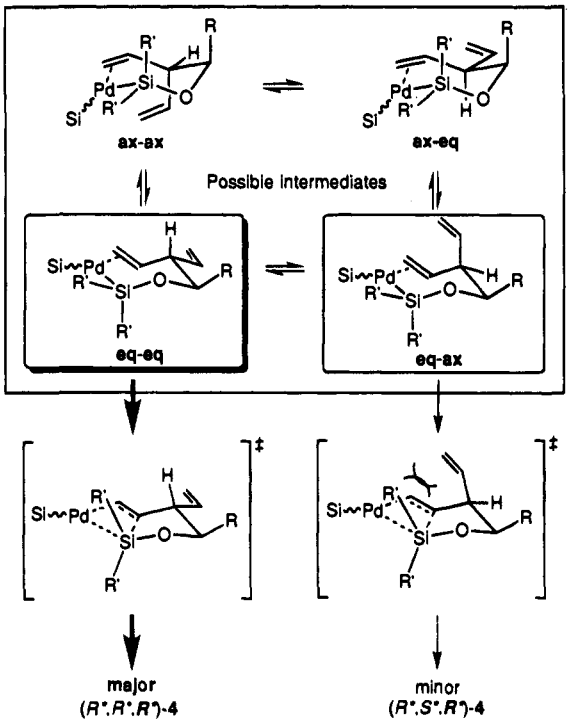
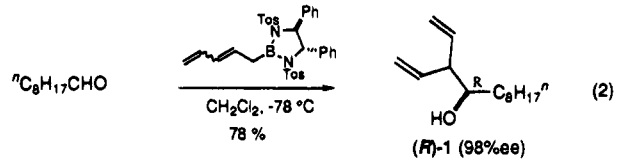
Scheme 2



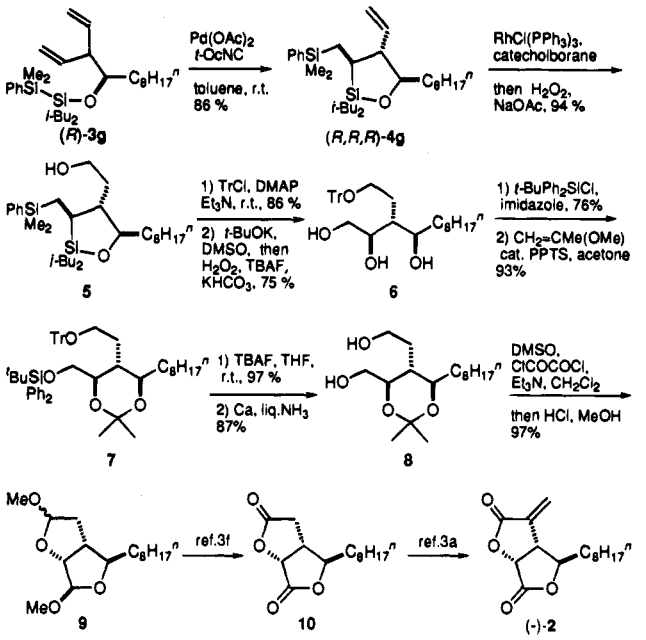
of nonanal, using a pentadienylborane reagent with Corey's chiral auxiliary which was used for enantioselective allylation (eq 2).[5-7] The diastereoselective intramolecular bis-silylation



(2)

of the optically active (*R*)-**3g** gave quantitatively a 9:1 mixture of (*R,R,R*)-**4g** and (*R,S,R*)-**4g**, from which the desired (*R,R,R*) isomer was isolated by column chromatography in nearly pure form. (*R,R,R*)-**4g** was transformed into alcohol **5** through a rhodium-catalyzed hydroboration–oxidation sequence in high yield.[8,9] The Si–C bonds were not affected by alkaline hydrogen peroxide oxidation. After trityl protection of the hydroxy group followed by cleavage of Si–Ph bonds, the Si–C bonds were subjected to hydrogen peroxide oxidation *in the presence of tetrabutylammonium fluoride* to afford triol **6** in good yield.[2b,10] Final elaboration for the total synthesis of (−)-avenaciolide (**2**) involved stepwise oxidation with appropriate protection and deprotection followed by exo-methylenation of the resultant bis-lactone **10** according to Scheme 3. The transformation of racemic bis-lactol **9** to **10** has been reported by Schreiber and Hoveyda.[3f] The structure of (−)-**2** was identified by comparison with spectroscopic data as well as the optical rotation reported.[4e] The successful total synthesis of (−)-avenaciolide demonstrates efficient construction of multiple chiral centers by diastereoselective bis-silylation.

Scheme 3



Supporting Information Available: Detailed experimental procedures and characterization of new compounds (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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