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Catalytic Diastereoselective Polycyclization of Homo(polyprenyl)arene Analogues Bearing Terminal Siloxyvinyl Groups

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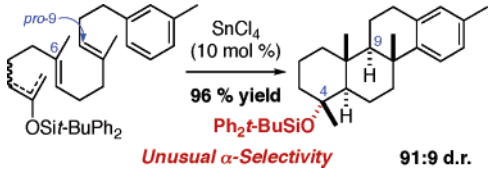
ABSTRACT



Highly diastereoselective polycyclization of homo(polyprenyl)arene analogues bearing terminal siloxyvinyl groups was catalyzed by tin(IV) chloride (10 mol %). The cyclizations of *tert*-butyldiphenylsilyl and triisopropylsilyl polyenol ethers gave 4α(equatorial)- and 4*β*(axial)-siloxypolycycles as major isomers, respectively. The strong nucleophilicity of *pro*-C(9), a (6*E*) geometry, and a bulky silyl group effectively favored the 4α-preference, whereas the weak nucleophilicity of *pro*-C(9), a (6*Z*)-geometry, and less steric hindrance of a silyl group favored the 4*β*-preference.

Biomimetic polyene cyclization is an important key step in the concise total synthesis of polycyclic natural products.[1,2] In particular, the Lewis acid promoted diastereoselective cyclization of polyenic aldehyde acetals to 4*β*(axial)-alkoxypolycycles[3] (4*β*/4α = ca. 2−17) has been established by Johnson et al.[1] However, excess $SnCl_4$ is often required as Lewis acid, and there are no methods available for the synthesis of 4α(equatorial)-alkoxypolycycles. We report here the $SnCl_4$ (10 mol %)-catalyzed polycyclization of homo(polyprenyl)arene analogues bearing terminal siloxyvinyl groups, which were much more reactive than other initiators such as acetals, aldehydes, and ketones.[4] The α(equatorial)/*β*(axial) selectivity of 4-siloxy group[3] at polycycles could be controlled by the nucleophilicity of *pro*-C(9)[3] and the steric effect of a silyl group.

Initially, we investigated the reactivity and diastereoselectivity of the cyclization of (*E*)-enone **1** in the presence of 10 mol % of $SnCl_4$ in CH_2Cl_2 at −78 °C (Scheme 1). The conversion to *trans*-tricycles **2** (4*β*-OH 68% ds) was 18% even after 24 h because of the relatively strong basicity of the carbonyl oxygen in **1**.[5] Interestingly, **2**α (4α-OH) was

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(1) For reviews, see: (a) Johnson, W. S. *Tetrahedron* **1991**, *47*, xi−1. (b) Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730−4756. To the best of our knowledge, there are no examples of polycyclization of ketals.

(2) For our recent contributions, see: (a) Kumazawa, K.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2004**, *6*, 2551−2554. (b) Ishibashi, H.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 11122−11123. (c) Uyanik, M.; Ishibashi, H.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2005**, *7*, 1601−1604. (d) Uyanik, M.; Ishihara, K.; Yamamoto, H. *Bioorg. Med. Chem.* **2005**, *13*, 5055−5065.

(3) Steroid numbering.

(4) For Pd(II)-catalyzed polyene cyclizations, see: (a) Koh, J. H.; Mascarenhas, C.; Gagné, M. R. *Tetrahedron* **2004**, *60*, 7405−7410. For Hg(II)-catalyzed polyene cyclizations, see: (b) Imagawa, H.; Iyenaga, T.; Nishizawa, M. *Org. Lett.* **2005**, *7*, 451−453.

(5) For an example of the successful cyclization of (*E*)-9-phenyl-1,1,1-trifluoronona-5-en-2-one with $MeAlCl_2$ (1.1 equiv) to 4-CF_3-*trans*-10-methylpodocarpatrienol (90% yield; 4*β*-OH 100% ds), see: Abouabdellah, A.; Bonnet-Delpon, D. *Tetrahedron* **1994**, *50*, 11921−11932.

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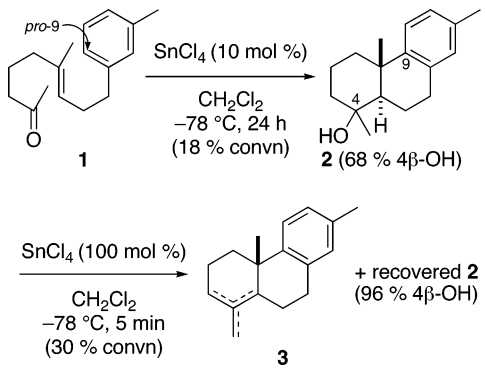
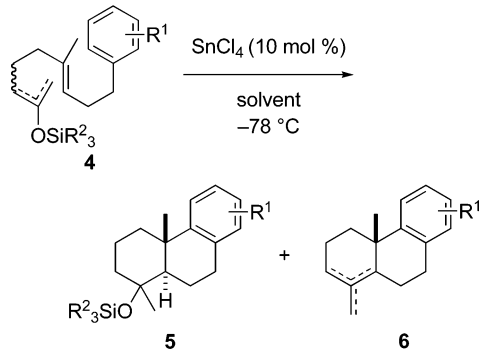
Scheme 1. Cyclization of (*E*)-Enone **1** to *trans*-Tricyclic Alcohols **2**



converted to dehydrated alkene **3** under more acidic conditions, but **2***β* (4*β*-OH) was stable under the same conditions.

Next, (2*E*,6*E*)-, (2*Z*,6*E*)-, and (1,6*E*)-isomeric mixtures of silyl (6*E*)-dienol ethers **4** derived from (*E*)-6-enones were examined in the presence of 10 mol % of $SnCl_4$ (Table 1).[6]

Table 1. Cyclization of Silyl (6*E*)-Dienol Ethers **4** to *trans*-Tricycles **5**



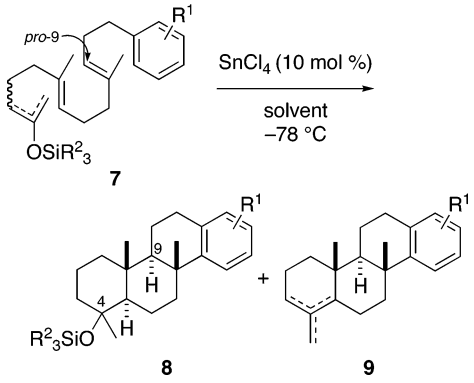
entry	**4** [R^1, SiR^2_3][a]	solvent, time (h)	**5**, yield (%)[b]	(**5**α:**6**):**5***β*
1[c]	**4a** [*p*-F, TIPS]	toluene, 24	**5a**, 90	(<1:<1):>99
2	**4b** [H, TIPS]	toluene, 2	**5b**, 99	(7:<1):93
3	**4c** [*p*-Me, TIPS][d]	CH_2Cl_2, 3	**5c**, 90	(1:10):89
4	**4c** [*p*-Me, TIPS][d]	toluene, 2	**5c**, 95	(11:5):84
5	**4c** [*p*-Me, TIPS][e]	CH_2Cl_2, 2.5	**5c**, 91	(9:8):83
6	**4c** [*p*-Me, TIPS][e]	toluene, 1.5	**5c**, 93	(13:2):85
7	**4d** [*m*-Me, TIPS]	toluene, 3	**5d**, 95	(36:4):60
8	**4e** [*p*-Me, TBDPS]	CH_2Cl_2, 3	**5e**, 93	(63:6):31
9	**4f** [*m*-Me, TBDPS]	CH_2Cl_2, 3	**5f**, 90	(85:9):6

[a] A (2*E*)-2-, (2*Z*)-2-, and 1-enyl mixture of **4**. [b] Isolated yield. See also ref 7. No detectable amount of *cis*-isomer **11** was obtained. [c] $SnCl_4$ (1 equiv) was used. [d] Isomeric ratio of (2*E*)-2-, (2*Z*)-2-, 1-enes **4c** = 14:71:15. [e] Isomeric ratio of (2*E*)-2-, (2*Z*)-2-, 1-enes **4c** = 2:29:69.

Fortunately, the 4α/4*β*-selective cyclization of **4** to 4-siloxytricycles **5** proceeded smoothly independent of the isomeric ratio of **4** (entries 3−6). These results suggested that the cyclization of **4** proceeded via siloxycarbenium ion intermediates. Although similar 4α/4*β*-selectivities were observed in CH_2Cl_2 and toluene (entries 3−6), not only cyclization but also the subsequent over-reaction from **5**α to alkene **6** proceeded more rapidly in CH_2Cl_2. 4*β*-Siloxy isomer **5***β* was produced as a major isomer from less bulky triisopropylsilyl-(TIPS) dienol ethers **4**, whereas 4α-siloxy isomer **5**α was produced as a major isomer from more bulky *tert*-butyldimethylsilyl(TBDPS) dienol ethers **4**. The substituents of the phenyl group of **4** also influenced the 4α/4*β*-selectivity: weaker nucleophilicity at the *ortho*-position (*pro*-C(9)[3]) of **4** increased 4*β*-selectivity, whereas stronger nucleophilicity increased 4α-selectivity. Thus, **5a***β* was produced from **4a** in 90% yield with >99:1 dr (entry 1). On the other hand, **5f**α was produced from **4f** in 90% yield with 14:1 dr (entry 9). The α-selectivity of **4f** was opposite that of the corresponding ketone **1** (see Scheme 1).

Next, (2*E*,6*E*)-, (2*Z*,6*E*)-, and (1,6*E*)-isomeric mixtures of silyl (6*E*,10*E*)-trienol ethers **7** derived from (*E*,*E*)-6,10-dienones were examined in the presence of 10 mol % of $SnCl_4$ (Table 2). Surprisingly, 4α-selective cyclization of **7** to 4-siloxytetracycles **8** proceeded catalytically independent of the nucleophilicity of the terminal aryl groups (entries 1 and 2). The cyclization of *tert*-butyldimethylsilyl trienol ether **7c** gave **8**α with 91:9 dr in 96% yield (entry 3). The α-preference for **8** could be understood by the relatively strong nucleophilicity of *pro*-C(9)[3] of **7**.[8]

Table 2. Cyclization of Silyl (6*E*,10*E*)-Trienol Ethers **7** to **8**



entry	**7** [R^1, SiR^2_3][a]	solvent, time (h)	**8** + **9**, yield (%)[b]	(**8**α:**9**):**8***β*
1	**7a** [*p*-Me, TIPS]	toluene, 4	**8a** + **9a**, 92	(58:5):37
2	**7b** [*m*-Me, TIPS]	toluene, 3	**8b** + **9b**, 91	(57:6):37
3	**7c** [*m*-Me, TBDPS]	CH_2Cl_2, 2	**8c**, 96	(91:<1):9

[a] A (2*E*)-2-, (2*Z*)-2-, and 1-enyl mixture of **7**. [b] **8** and **9** were inseparable. See also ref 7. No detectable amounts of *cis*-isomers **8** were obtained.

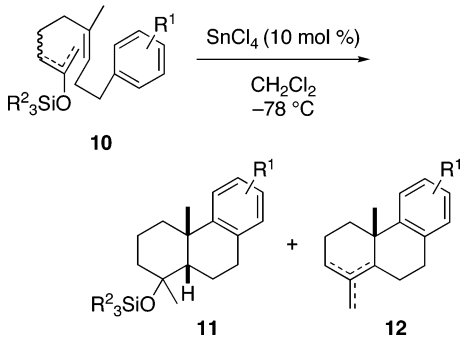
For comparison with silyl (6*E*)-dienol ethers **4**, cyclization of its (6*Z*)-isomers **10** was also performed under the same

(6) The cyclization of **1** with *i*-Pr_3SiOTf (1 equiv) at −78 °C for 24 h gave **2** (4*β*-OH 66% ds) and **3** in respective yields of 18% and 10%.

(7) 4α- and 4*β*-Hydroxy polycycles could be separated from each other by column chromatography.

(8) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66−77.

Table 3. Cyclization of Silyl (6*Z*)-Dienol Ethers **10** to *cis*-Tricycles **11**



entry	**10** [R^1, SiR^2_3][a]	time (h)	**11**, yield (%)[b]	(**11**α:**12**):**11**β
1	**10a** [*p*-Me, TIPS]	24	**11a**, 90	(<1:<1):>99
2	**10b** [*m*-Me, TIPS]	1	**11b**, 94	(6:7):87
3	**10c** [*m*-Me, TBDPS]	1	**11d**, 98	(62:<1):38

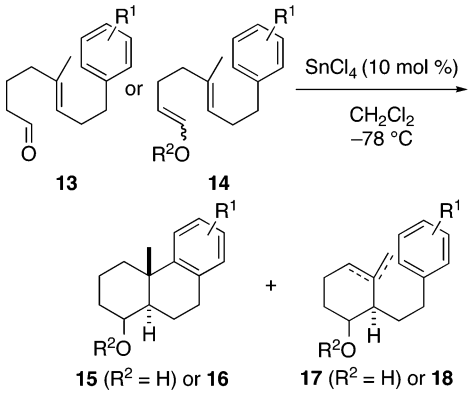
[a] A (2*E*)-2-, (2*Z*)-2-, and 1-enyl mixture of **10**. [b] Isolated yield. See also ref 7. No detectable amount of *cis*-isomer **11** was obtained.

conditions (Table 3). Surprisingly, *cis*-tricycles **11** were produced in high yield without any detectable **5**. Overall, the reactivity of **10** was much lower than that of **4** because the B-ring formation of **11** should occur through the thermodynamically unfavorable boat-like transition state. Interestingly, 4β-selectivity of **11** was increased in comparison with that of **5**. For example, the cyclization of **10a** gave **11a**β in 90% yield with >99:1 dr (entry 1), whereas the cyclization of **4c** gave **5c**β in 90% yield with 89:1 dr (entry 3, Table 1).

The cyclization of (*E*)-5-enals **13** and their silyl (5*E*)-dienol ethers **14** was also examined under the same conditions (Table 4). In the cyclization of **13**, A-ring formation occurred quantitatively with very low 4α/4β-selectivities,[9] but monocycles **17** were produced in ca. 10% yield together with bicycles **15** (entries 1 and 2). In contrast, in the cyclization of (1*Z*)-**14**, **16**β was produced in 97% yield with ≥99:1 dr regardless of the nucleophilicity of the aryl group of **14** (entries 3 and 4). Although (1*E*)-**14b** was much less reactive than (1*Z*)-**14b**, (1*E*)-**14b** also give **16b**β as a major isomer (entry 5). This result suggested that the *E*/*Z*-isomerization of silyl enol ethers derived from aldehydes was relatively slow and cyclization to **16**α was essentially disfavored.

The proposed mechanism is shown in Figure 1. The regioselective protonation of polyenic silyl enol ethers with $SnCl_4 \cdot (H_2O)_n$ would induce the subsequent polycyclization.[10]

Table 4. Cyclization of (*E*)-Enals **13** and Their Silyl Dienol Ethers **14**



entry	**13** or **14** [R^1, R^2]	time (h)	**15** or **16**, yield (%)[a]	**4**α:**4**β[b]
1[c]	**13a** [*p*-Me, −]	0.5	**15a**, 87	40:60
2[c]	**13b** [*m*-Me, −]	0.5	**15b**, 89	55:45
3	**14a** [*p*-Me, TIPS][d]	1	**16a**, 97	1:99
4	**14b** [*m*-Me, TIPS][d]	3	**16b**, 97	<1:>99
5[c,e]	**14b** [*m*-Me, TIPS][f]	12	**16b**, ca. 80	ca. 25:75

[a] Isolated yield. See also ref 7. No detectable amount of *cis*-isomer was obtained. [b] For **15** or **16**. [c] Yields of **17** or **18** were 11% (entry 1), 10% (entry 2), and ca. 20% (entry 5). [d] 1*E*/1*Z* ratio of **14** = <1:>99. [e] $SnCl_4$ (20 mol %) was used. [f] 1*E*/1*Z* ratio of **14** = 76:24.

The 4α-selective cyclization would proceed concertedly or stepwise through antiperiplanar (chair−chair-like) transition state (TS) **19**. On the other hand, the 4β-selective cyclization would proceed stepwise through synclinal TS-**20** or **21** stabilized by Coulomb attractive interaction (minimalization

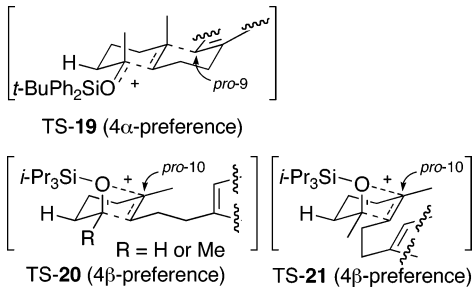


Figure 1. Proposed transition-state assemblies **19**−**21**.

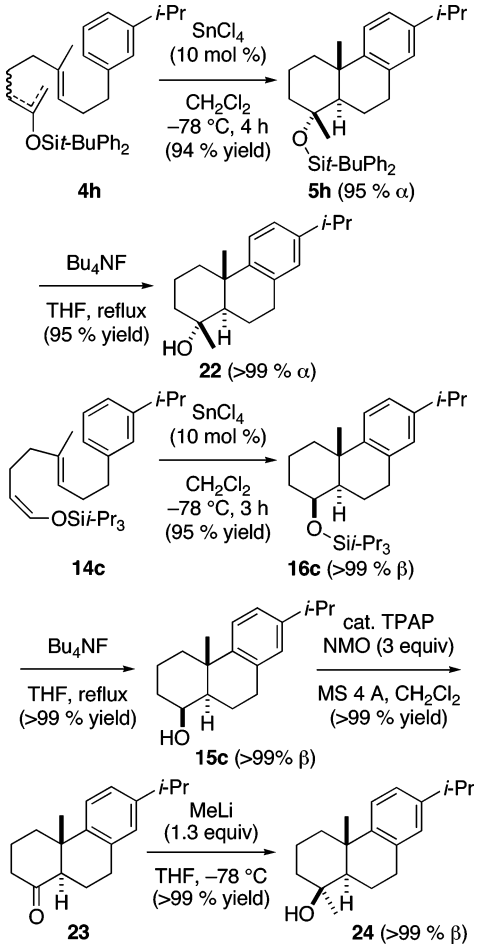
of charge separation) between O and *pro*-C(10).[3,11] The strong nucleophilicity of *pro*-C(9),[3] a (6*E*)-geometry, and a bulky silyl group would effectively favor TS-**19**, whereas the weak nucleophilicity of *pro*-C(9),[3] a (6*Z*)-geometry, and less steric hindrance of a silyl group would favor TS-**20** or **21**.

(9) For a previous example of the cyclization of a polyenal with $SnCl_4$ (3 equiv) to 4-hydroxypentacycles (49% yield; 4β-OH 84% ds), see: Fish, P. V.; Johnson, W. S. *J. Org. Chem.* **1994**, *59*, 2324−2335.

(10) Although the possibility of the stannylation with $SnCl_4$ cannot be completely exluded, the subsequent protiodestannation step would be difficult. In fact, the use of freshly distilled $SnCl_4$ was required to give polycycles in high yield. Nevertheless, the existence of a trace amount of water can not be denied. Therefore, $SnCl_4 \cdot (H_2O)_n$ may serve as a Lewis acid assisted Brønsted acid catalyst. Other Lewis acids such as $Sn(OTf)_2$, $Sc(OTf)_3$, and $Yb(OTf)_3$ were inert for the present cyclization under the same conditions as that for $SnCl_4$.

(11) For the synclinal preference by Coulomb attractive interaction, see: (a) Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413−1423. (b) Denmark, S. E.; Weber, E. J.; Wilson, T. M.; Wilson, T. M. *Tetrahedron* **1989**, *45*, 1053−1065. (c) Yamanaka, M.; Mikami, K. *Helv. Chim. Acta* ***2002***, *85*, 4264−4271.

Scheme 2. Total Syntheses of Epimers **22** and **24**



On the basis of the above experimental results, two natural diterpenoids, 18-norabieta-8,11,13-trien-4-ol (**22**),[12] which has antibacterial activity, and its epimer **24**[12] were synthesized from **4h** and **14c** with >99% 4α and >99% 4β, respectively (Scheme 2).[7] The anti-herpes active diterpenoid **15c**,[13] a synthetic intermediate of **24**, was also synthesized with >99:1 dr.

Although it was difficult to directly generate silyloxocarbenium ion intermediates from aldehydes and ketones with silyl Lewis acids,[6] we succeeded in their catalytic generation with $SnCl_4$ from silyl enol ethers instead of carbonyl compounds. The main advantage in the catalytic use of $SnCl_4$ is to avoid or to minimize secondary reactions of the polycyclic products, i.e., elimination of the siloxy groups (See Scheme 1). The present results demonstrate the synthetic advantages of using polyprenoid analogues bearing a terminal siloxyvinyl group as substrates of polyene cyclization with respect to both the reactivity and 4α/4β-diastereocontrol.[5]

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Supporting Information Available: Experimental procedures, full characterization of new compounds, and NMR spectra of polycyclic compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) (a) Rowe, J. W.; Nagasampagi, B. A.; Burgstahler, A. W.; Fitzsimmons, J. W. *Phytochemistry* **1971**, *10*, 1647−1651. (b) Lee, C.-K.; Fang, J.-M.; Cheng, Y.-S. *Phytochemistry* **1995**, *39*, 391−394. (c) Dakir, M.; El Hanbali, F.; Mellouki, F.; Akssira, A.; Benharref, A.; Quilez Del Moral, J. F.; Barrero, A. F. *Nat. Prod. Res.* **2005**, *19*, 719−722.

(13) (a) Akita, H.; Otsuka, Y. Japan Kokai Tokkyo Koho, JP51098258 and JP51098267, 1976. (b) Tagat, J. R.; Nazareno, D. V.; Puar, M. S.; McCombie, S. W.; Ganguly, A. K. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1101−1104.