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Scope and Facial Selectivity of the Prins-Pinacol Synthesis of Attached Rings

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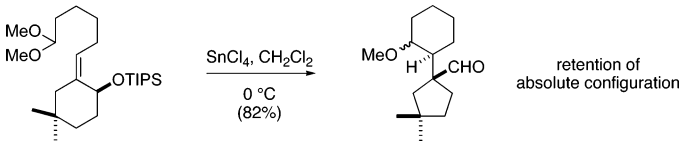

Using a *B*-alkyl Suzuki cross-coupling as a key step, a concise and stereocontrolled synthesis of five- to eight-membered triisopropylsiloxy ethers having (2*Z*)-(6,6-dimethoxyhexylidene) or (2*Z*)-(5,5-dimethoxypentylidene) side chains was developed. Prins-pinacol reactions of these precursors promoted by $SnCl_4$ provide bicyclic products in which 5-, 6-, or 7-membered rings are joined by a C−C single bond. Synthetically challenging attached ring systems in which both rings are chiral can be prepared in this fashion with high stereo- and enantioselectivity. Stabilizing through-space electrostatic interactions between the α-alkoxycarbenium ion and an axially positioned oxygen substituent are believed to play a significant role in organizing the transition structure of the Prins cyclization.

Introduction

A central objective in synthetic organic chemistry is to discover new methods for constructing complex molecules from relatively simple starting materials. One powerful method for accomplishing this feat is to combine two distinct reactions into a single transformation, often referred to as a cascade or tandem reaction.[1] For a number of years, we have been developing cascade reactions that combine a Prins cyclization with a pinacol rearrangement.[2,3] Using this strategy, a variety of architecturally complex fused or bridged oxacyclic and carbocyclic ring systems can be assembled in good yield and high stereoselectivity.[3]

Several years ago we described the first use of a Prins-pinacol reaction to assemble rings joined by a C−C σ-bond, hereafter referred to as attached rings.[4] Such rings are prominent structural features of several classes of natural products, with representative examples being depicted in Figure 1.[5] When the attached carbons are stereogenic, this motif of rings poses a formidable challenge for stereocontrolled total synthesis.[6,7]

In our earlier study, we found that reaction of $SnCl_4$ with (*Z*)-alkylidene cyclohexane **5a** promoted Prins cyclization and subsequent pinacolic ring-contraction to form 1-(cyclohexyl)-cyclopentanecarbaldehyde **6**, as a mixture of methoxy epimers, in useful yield (Scheme 1).[4] In contrast, similar treatment of the corresponding *E* stereoisomer **5b** produced a mixture of

(1) For recent reviews, see: (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136. (b) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137−165. (c) Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167−176. (d) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177−194. (e) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195−206. (f) Wang, K. K. *Chem. Rev.* **1996**, *96*, 207−222. (g) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223−269. (h) Malacria, M. *Chem. Rev.* **1996**, *96*, 289−306. (i) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307−338. (j) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131−163. (k) Ho, T.-L. *Tandem Organic Reactions*; Wiley & Sons: New York, 1992.

(2) (a) Martinet, P.; Mousset, G.; Michel, M. *C. R. Acad. Sci. Paris, Ser. C* **1969**, *268*, 1303−1306. (b) Martinet, P.; Mousset, G. *Bull. Soc. Chim. Fr.* **1970**, 1071−1076.

(3) For a recent review, see: Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143−7157.

(4) Overman, L. E.; Pennington, L. D. *Can. J. Chem.* **2000**, *78*, 732−738.

(5) (a) Nozoe, S.; Machida, Y. *Tetrahedron Lett.* **1970**, *31*, 2671−2674. (b) Desilva, E. D.; Morris, S. A.; Miao, S.; Dumdei, E.; Andersen, R. J. *J. Nat. Prod.* **1991**, *54*, 993−997. (c) Iliopoulou, D.; Mihopoulos, N.; Vagias, C.; Papazafiri, P.; Roussis, V. *J. Org. Chem.* **2003**, *68*, 7667−7674. (d) Butterworth, J. H.; Morgan, E. D. *J. Chem. Soc., Chem. Commun.* **1968**, 23−25.

(6) For a review of methods to make carbocyclic attached ring systems, see: Wills, M. In *Second Supplements to the 2nd Edition of Rodd's Chemistry of Carbon Compounds*; Sainsbury, M. Ed.; Elsevier: New York, 1994; Vol. II B (Partial), C, D, and E, pp 181−204.

(7) For representative examples of how this architectural motif has been addressed, see: (a) Lange, G. L.; Furlan, L.; MacKinnon, M. C. *Tetrahedron Lett.* **1998**, *39*, 5489−5492. (b) Lemieux, R. M.; Meyers, A. I. *J. Am. Chem. Soc.* **1998**, *120*, 5453−5457. (c) Gilbert, J. C.; Selliah, R. D. *J. Org. Chem.* **1993**, *58*, 6255−6265. (d) Sakai, K.; Tanaka, M. *Tetrahedron Lett.* **1991**, *32*, 5581−5584. (e) Ley, S. V.; Gutteridge, C. E.; Pape, A. R.; Spilling, C. D.; Zumbrunn, C. *Synlett* **1999**, 1295−1297. (f) Lebsack, A. D.; Overman, L. E.; Valentekovich, R. J. *J. Am. Chem. Soc.* **2001**, *123*, 4851−4852. (g) Kishi, Y.; Wang, W. *Org. Lett.* **1999**, *7*, 1129−1132.

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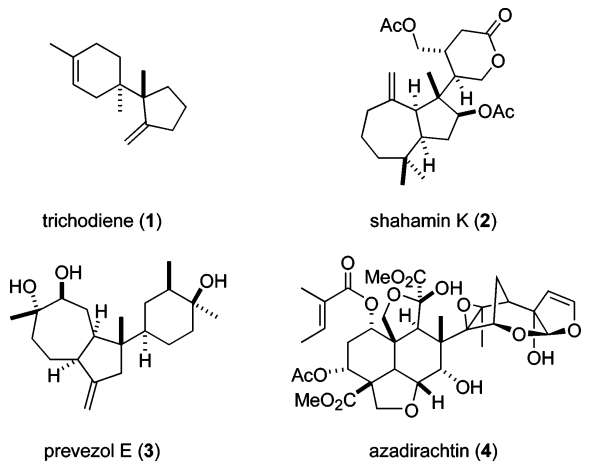
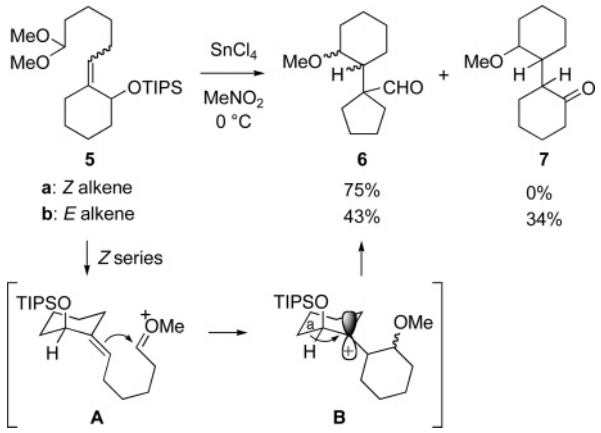


FIGURE 1. Representative natural products containing attached rings.

SCHEME 1

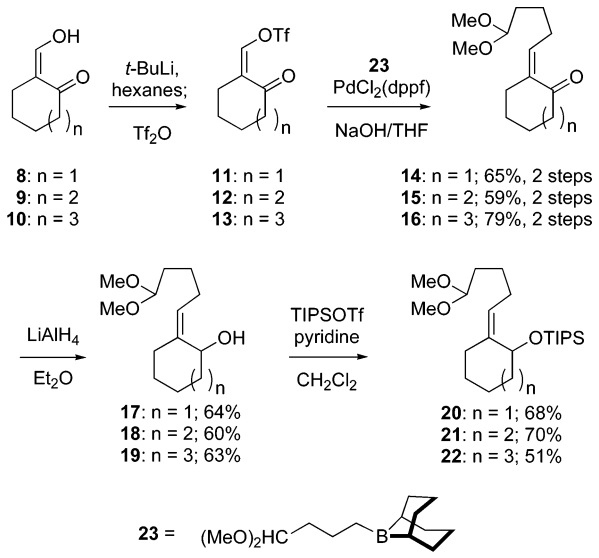


products resulting from a competition between ring-contraction and hydride migration in the pinacolic-rearrangement step. The clean formation of 1-(cyclohexyl)cyclopentanecarbaldehydes **6** in the former case was attributed to Prins cyclization occurring by chair conformer **A** in which $A^{1,3}$ interactions[8] are minimized by placing the siloxy group axial. If pinacol rearrangement occurred more rapidly than conformational equilibration, only ring bond a in the resulting cyclohexyl cation **B** would have sufficient overlap with the vacant p-orbital to undergo a pinacol rearrangement. Face selectivity in the Prins cyclization of the oxocarbenium ion derived from **5a** cannot be ascertained from the relative configuration of 1-(cyclohexyl)cyclopentanecarboxaldeyde **6** because C1 is not stereogenic.

Although our previous study pointed to the potential of Prins-pinacol reactions to construct attached rings,[4] several aspects of this strategy required further study. This paper addresses three issues: (1) development of a stereoselective synthesis of (*Z*)-2-alkylidene-1-siloxycycloalkanes; (2) investigation of the scope of the Prins-pinacol approach for assembling attached rings of varying sizes and ring substitution; and (3) exploration of facial stereoselection in the Prins cyclization, which, if high, would allow for the stereocontrolled construction of attached stereogenic rings by Prins-pinacol cyclizations.

(8) Eliel, E. L.; Wilen, S. H. In *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994, 738.

SCHEME 2



Results

Stereoselective Synthesis of 2(*Z*)-Alkylidenecycloalkanols. In our previous study, 2-(*Z*)-alkylidene-1-siloxycyclohexane **5a** was prepared by a nonstereoselective Wittig reaction, with tedious chromatography being required to obtain isomerically pure material. As a result, an improved synthesis of 2(*Z*)-alkylidenecycloalkanols that utilizes a *B*-alkyl Suzuki cross-coupling as the pivotal step was developed (Scheme 2).[9] This sequence was refined initially in the cyclohexyl series. The (*Z*)-vinyl triflate **11** was generated by rapid addition of *t*-BuLi to a hexanes solution of 2-(hydroxymethylene)cyclohexanone (**8**) at −78 °C, followed by quenching at −78 °C with Tf_2O.[10] Because of the instability of triflate **11**, it was used immediately without purification. Suzuki cross-coupling of crude **11** with alkyl borane **23**, generated by hydroboration of 4,4-dimethoxybut-1-ene with 9-BBN, provided (*Z*)-alkylidenecyclohexanone **14** in 65% overall yield from ketone **8**. Reduction of this product with $LiAlH_4$ yielded alcohol **17**, which upon silylation with triisopropylsilyl trifluoromethanesulfonate provided Prins-pinacol precursor **20**.[11] The *Z* configuration of **20** was confirmed by observing ^{1}H NMR NOE enhancements between the C1 siloxy hydrogen and the allylic hydrogens of the side chain. The cycloheptyl and cyclooctyl congeners of **20**, **21**, and **22** were prepared by identical sequences (Scheme 2).

Cyclization precursors having four methylene units between the alkene and acetal functional groups were prepared in similar fashion from the corresponding 2-(hydroxymethylene)cycloalkanones and alkyl borane **34**, derived from 5,5-dimethoxypent-1-ene (Scheme 3). As with the substrates reported in Scheme 2, the alkene configuration of **47**, **48**, and **49** was confirmed by ^{1}H NMR NOE experiments.

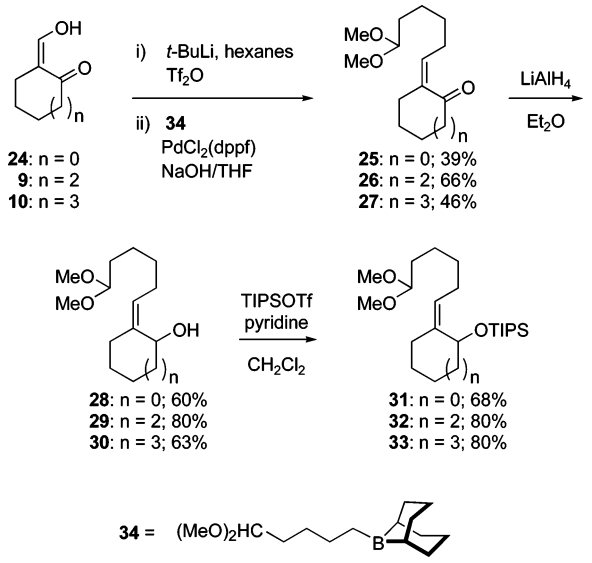
To explore the effect of ring substitution upon the Prins-pinacol synthesis of attached rings, three geminally disubstituted ring precursors were investigated. Starting from 2,2-dimethyl-

(9) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314−321.

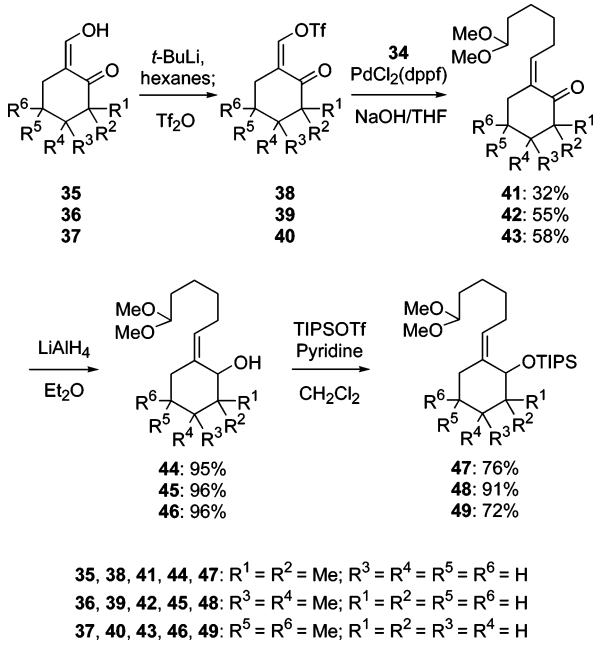
(10) Brückner, R.; Scheuplein, S. W.; Suffert, J. *Tetrahedron Lett.* **1991**, *32*, 1449−1452.

(11) Unless preceded by a stereochemical descriptor, all compounds are racemic.

SCHEME 3



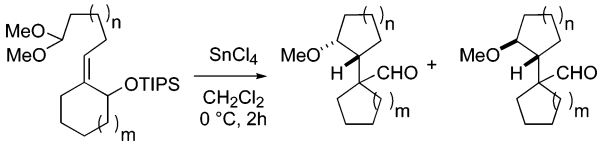
SCHEME 4



(**35**),[12] 3,3-dimethyl- (**36**),[13] and 4,4-dimethyl-6-(hydroxymethylene)cyclohexanone (**37**),[14] the corresponding Prins-pinacol precursors were synthesized by similar sequences (Scheme 4).

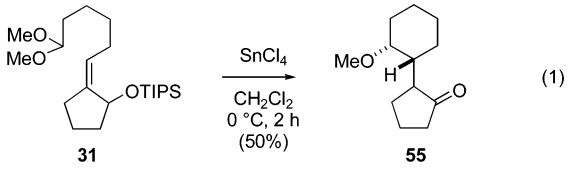
Prins-Pinacol Reactions. Although nitromethane was used as solvent in our earlier study,[4] in early phases of this investigation (vide infra) we found that these Prins-pinacol reactions were equally efficient in CH_2Cl_2. As CH_2Cl_2 is easier to obtain anhydrous, this solvent is preferred. Exposure of a CH_2Cl_2 solution of the alkylidenecyclohexyl Prins-pinacol substrates **20**, **21**, and **22** to 0.5 equiv of $SnCl_4$ for 2 h at 0 °C afforded 1-(cyclopentyl)cycloalkanecarbaldehydes **50**−**52** in 69−75% yield (Table 1, entries 1−3). Identical reaction of Prins-pinacol substrates **32** and **33** provided the 1-(cyclohexyl)-

TABLE 1. Prins-Pinacol Reactions To Form Various Attached Ring Systems



entry	substrate	*n*	*m*	yield, %	*cis*/*trans* (product)
1	**20**	1	1	69	1.0:3.4 (**50a** + **50b**)
2	**21**	1	2	75	1.0:1.0 (**51a** + **51b**)
3	**22**	1	3	71	1.2:1.0 (**52a** + **52b**)
4	**32**	2	2	82	1.5:1.0 (**53a** + **53b**)
5	**33**	2	3	68	2.4:1.0 (**54a** + **54b**)

cycloalkanecarbaldehydes **53** and **54** in 82% and 68% yield, respectively (Table 1, entries 4 and 5). In contrast, attempted construction of a 1-(2-methoxycyclohexyl)cyclobutanecarbaldehyde by Prins-pinacol conversion of the alkylidenecyclopentyl precursor **31** gave cyclopentanone **55** as the sole isolated product (eq 1). Only in this latter case wherein ring contraction would have generated a four-membered ring was Prins cyclization followed by hydride migration.

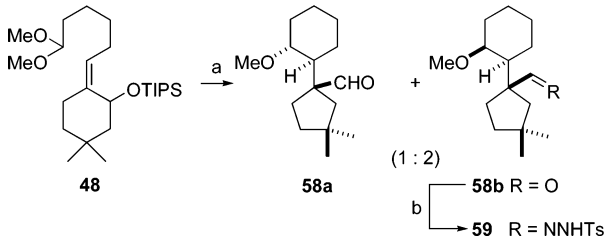


In the reactions summarized in Table 1, the methoxy epimers of the products were separable by flash column chromatography; epimer ratios were ascertained by ^{1}H NMR experiments. For the Prins-pinacol products reported in entries 1−3 of Table 1, the relative configuration of these epimers was determined by ^{1}H NMR NOE enhancements. A cis relationship of the methoxy methine hydrogen and the vicinal methine hydrogen was indicated by a positive NOE correlation, whereas in the epimeric series this enhancement was absent. For the products of Prins-pinacol rearrangements reported in entries 4 and 5 of Table 1, relative configuration followed directly from ^{1}H NMR spectra. A diagnostic triplet of doublets for the downfield methine hydrogen [**53b**: δ 2.84 ppm (J = 10.3, 4.2 Hz), **54b**: δ 2.78 ppm (J = 10.5, 4.4 Hz)] established an equatorial disposition of the methoxy substituent; whereas the trans isomers showed a broad singlet for this hydrogen (**53a**: δ 3.58 ppm, **54a**: δ 3.53 ppm).

The effect of substitution in the starting siloxy alkylidene ring was explored in the cyclohexyl series. Exposure of substrate **47**, which contains *gem*-dimethyl substitution adjacent to the siloxy substituent, to 0.5 equiv of $SnCl_4$ at 0 °C for 2 h in $MeNO_2$ provided a mixture of products. Similar results were obtained when CH_2Cl_2 was employed as the solvent. From this complex reaction mixture, the 1-(cyclohexyl)cyclopentanecarbaldehyde **56** was isolated in 8% yield (eq 2). Additionally, bicyclohexyl-2-one **57**, which arises from hydride migration following Prins cyclization, was isolated in 21% yield. The equatorial disposition of the methoxy group in both **56** and **57** followed from the diagnostic apparent triplet of doublets observed for the ether methine hydrogen: **56**: δ 2.98 ppm (J = 10.3, 4.2 Hz), **57**: δ 3.38 ppm (J = 9.5, 3.9 Hz). Because of

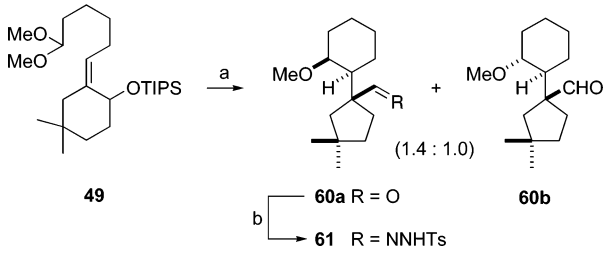
(12) Johnson, W. S.; Posvic, H. *J. Am. Chem. Soc.* **1947**, *69*, 1361−1366.
(13) Seifert, S. *Helv. Chim. Acta* **1951**, *34*, 728−735.
(14) Tietze, L. F.; Peterson, S. *Eur. J. Org. Chem.* **2001**, *9*, 1619−1624.

SCHEME 5 [a]



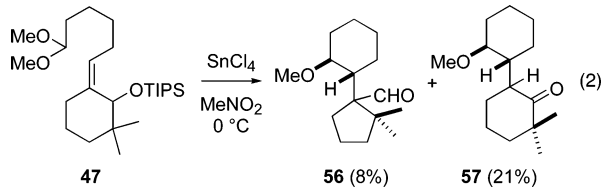
[a] Reagents and conditions: (a) $SnCl_4$, $MeNO_2$, 0 °C (48%); (b) NH_2NHTs, AcOH (50%).

SCHEME 6 [a]



[a] Reagents and conditions: (a) $SnCl_4$, $MeNO_2$, 0 °C (84%); (b) NH_2NHTs, AcOH (84%).

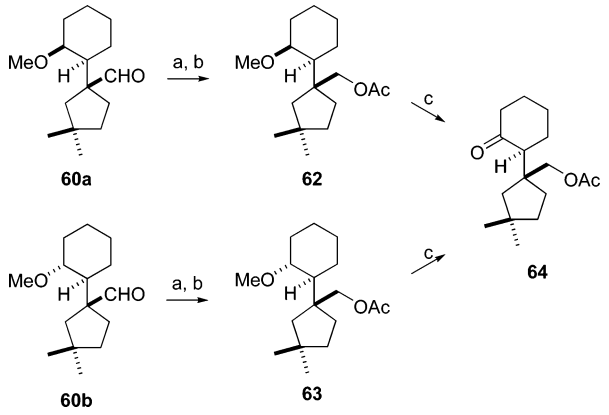
the low yield of these products, the relative configuration at the carbon adjacent to the carbonyl group was not determined.



The desired Prins-pinacol conversion was more efficient when the *gem*-dimethyl group was present at C3 or C4 of the cyclohexyl ether precursor. For example, exposure of substrate **48** to 0.5 equiv of $SnCl_4$ at 0 °C for 2 h in $MeNO_2$ gave a 1:2 mixture of 1-(2-methoxycyclohexyl)-3,3-dimethylcyclopentanecarbaldehydes **58a** and **58b** in 48% yield (Scheme 5). Several other unidentified products were apparent in the ^{1}H NMR spectrum of the crude reaction product. Similar results were realized using CH_2Cl_2 as the solvent. The relative configuration of the two methoxy epimers of **58** was apparent from their ^{1}H NMR spectra [**58a**: triplet of doublets at δ 2.60 ppm (J = 10.4, 4.3 Hz), **58b**: broad singlet at δ 3.43 ppm]. Additionally, the constitution and relative configuration of aldehyde **58b** was confirmed by single-crystal X-ray analysis of tosylhydrazone derivative **59**.[15]

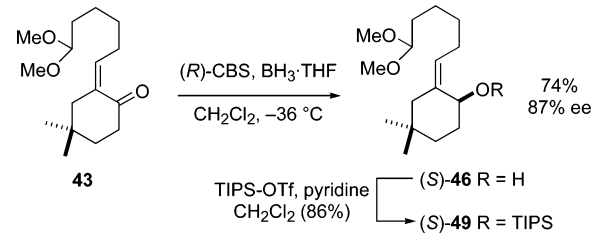
The most efficient Prins-pinacol conversion was realized with the 4,4-dimethyl-substituted substrate **49** (Scheme 6). When this precursor was exposed to 0.5 equiv of $SnCl_4$ for 2 h at 0 °C in $MeNO_2$, a 1.4:1 mixture of 1-(2-methoxycyclohexyl)-4,4-dimethylcyclopentanecarbaldehydes **60a** and **60b** was isolated in 84% yield. The equatorial disposition of the methoxy group in **60b** was apparent from the diagnostic triplet of doublets observed for the ether methine hydrogen: δ 2.70 ppm (J = 10.5, 4.3 Hz). Conversely, this hydrogen of **60a** appeared in the ^{1}H NMR spectrum as a broad singlet at δ 3.46 ppm. The constitution and relative configuration of aldehyde **60a** was confirmed by single-crystal X-ray analysis of tosylhydrazone derivative **61**.[15]

SCHEME 7 [a]



[a] Reaction conditions: (a) $NaBH_4$, MeOH; (b) Ac_2O, pyridine (67% over 2 steps for **62**, 85% for **63**); (c) $RuCl_3 \cdot xH_2O$, $NaIO_4$, CCl_4, MeCN, pH 7 buffer (50% for both **62** and 71% for **63**).

SCHEME 8



To establish that Prins-pinacol products **60a** and **60b** were indeed methoxy epimers, **60a** and **60b** were chemically correlated as summarized in Scheme 7. After transforming the formyl group of these two products to acetoxymethyl substituents, derivatives **62** and **63** were both converted to cyclohexanone **64** upon oxidation with RuO_4.

To survey the potential of Prins-pinacol cyclizations for the stereo- and enantioselective construction of attached rings in which the attached carbons are both stereogenic, cyclization substrate **49** was prepared in enantiomerically enriched form. By design, the route we employed for the synthesis of racemic cyclization substrates was easily adapted to this task (Scheme 8). Thus, using the (*R*)-CBS catalyst, oxazaborolidine-mediated reduction of enone **43** provided allylic alcohol (*S*)-**46** in 74% yield and 87% ee.[16,17] This product was assigned the *S* absolute configuration on the basis of strong precedent[17] and the established facial selectivity of the CBS reagents.[16] Silylation of alcohol (*S*)-**46** provided rearrangement substrate (*S*)-**49**.

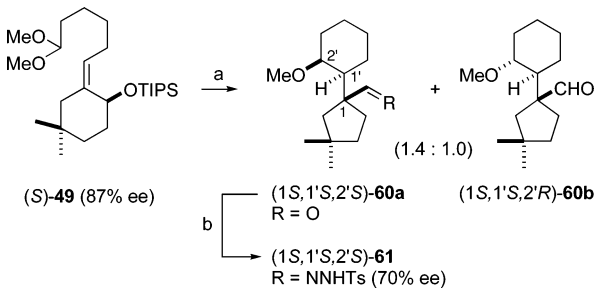
Exposure of siloxy acetal (*S*)-**49** to 0.5 equiv of $SnCl_4$ for 2 h at 0 °C in $MeNO_2$ provided 1-(2-methoxycyclohexyl)-4,4-dimethylcyclopentanecarbaldehydes (1*S*,1′*S*,2′*S*)-**60a** and (1*S*,1′*S*,2′*R*)-**60b** in high yields (Scheme 9). The epimers were separated, and (1*S*,1′*S*,2′*S*)-**60a** was allowed to react with acetic acid and tosylhydrazine to provide tosylhydrazone (1*S*,1′*S*,2′*S*)-**61**. The

(15) Crystallographic data for this compound was deposited at the Cambridge Crystallographic Data Centre: **59**, CCDC 287233; **61**, CCDC 287232. (1*S*,1′*S*,2′*S*)-**61**, 287234.

(16) For a review of oxazaborolidine mediated reductions with the CBS reagents, see: Corey, E. J.; Helal, C. J. *Angew. Chem.*, Int. Ed. **1998**, *37*, 1986−2012.

(17) Simpson, A. F.; Szeto, P.; Lathbury. D. C.; Gallagher, T. *Tetrahedron: Asymmetry* **1997**, *8*, 673−676.

SCHEME 9 [a]



[a] Reagents and conditions: (a) $SnCl_4$, $MeNO_2$, 0 °C (82%); (b) NH_2NHTs, AcOH (81%).

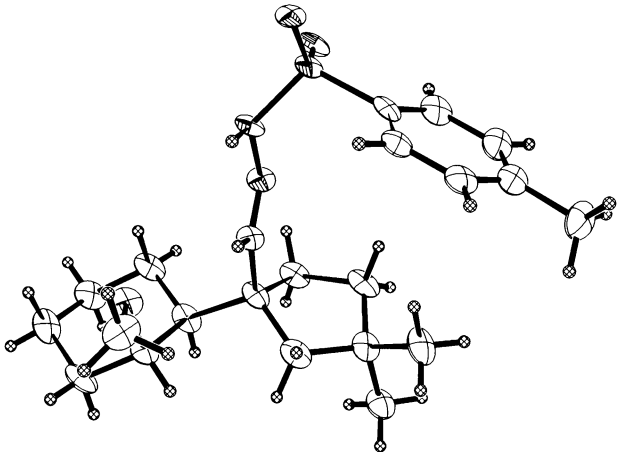


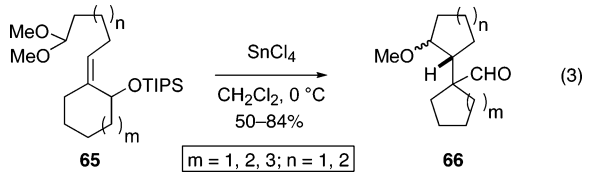
FIGURE 2. ORTEP representation of the X-ray model of (1*S*,1′*S*,2′*S*)-**61**.

enantiomeric excess of this product was determined to be 70% by HPLC analysis using a chiral phase, establishing that the Prins-pinacol reaction occurs with 80% transfer of chirality in this example.[18]

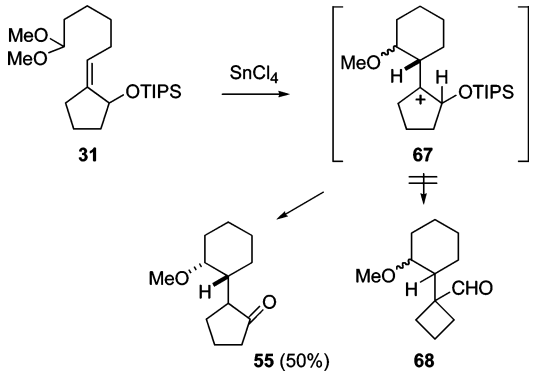
The absolute configuration of (1*S*,1′*S*,2′*S*)-**61** was determined by single-crystal X-ray analysis (Figure 2). A value of −0.25 for the Flack parameter established the absolute configuration of this sample to be 1*S*,1′*S*,2′*S* as depicted in Scheme 9.[15,19] Similar circular dichroism (CD) spectra were obtained for the single-crystal employed in the X-ray analysis and the bulk sample of (1*S*,1′*S*,2′*S*)-**61**.

Discussion

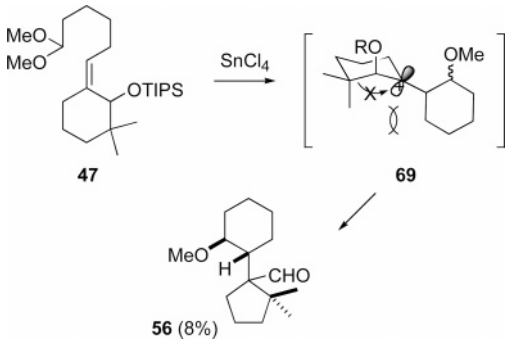
Scope and Limitations. Using a *B*-alkyl Suzuki cross coupling as a key step, a concise and stereocontrolled synthesis of 5- to 8-membered triisopropylsiloxy ethers having (2*Z*)-(6,6-dimethoxyhexylidene) or (2*Z*)-(6,6-dimethoxyhexylidene) side chains was developed. As the results reported in Table 1 and Schemes 5 and 6 show, $SnCl_4$-promoted Prins-pinacol reactions of these precursors can be employed to assemble a range of bicyclic products **66** in which 5-, 6-, or 7-membered rings are joined by a C−C single bond (eq 3). Two limitations have been



SCHEME 10



SCHEME 11



identified. First, if the starting ring is five-membered, the cation **67** produced upon Prins cyclization of acetal **31** does not undergo pinacol ring-contraction, but rather hydride migration to produce 2-cyclohexylcyclopentanone **55** (Scheme 10). Ring strain associated with the formation of the cyclobutane ring of 1-(2-methoxycyclohexyl)cyclobutanecarbaldehyde (**68**) is undoubtedly responsible for this outcome. Second, attached ring systems containing contiguous quaternary carbons apparently cannot be assembled efficiently by Prins-pinacol reactions. Thus, 1-(2-methoxycyclohexyl)-2,2-dimethylcyclopentanecarbaldehyde (**56**) was produced in low yield from Prins-pinacol reaction of precursor **47** (eq 2). Pinacol ring contraction of carbocation **69** is apparently disfavored by developing steric interactions between the axial methyl and pseudoaxial cyclohexyl substituents (Scheme 11).

A primary objective of the present study was to ascertain whether attached rings in which both rings are chiral could be prepared stereoselectively by Prins-pinacol reactions. Such an outcome would require that the initial Prins cyclization takes place with high facial selectivity and that pinacol ring contraction occurs from a single chair conformation of the resulting cyclohexyl carbenium ion.[4] The results summarized in Schemes 5 and 6 demonstrate that such ring systems can be assembled with high stereocontrol as mixtures of methoxy epimers.[20]

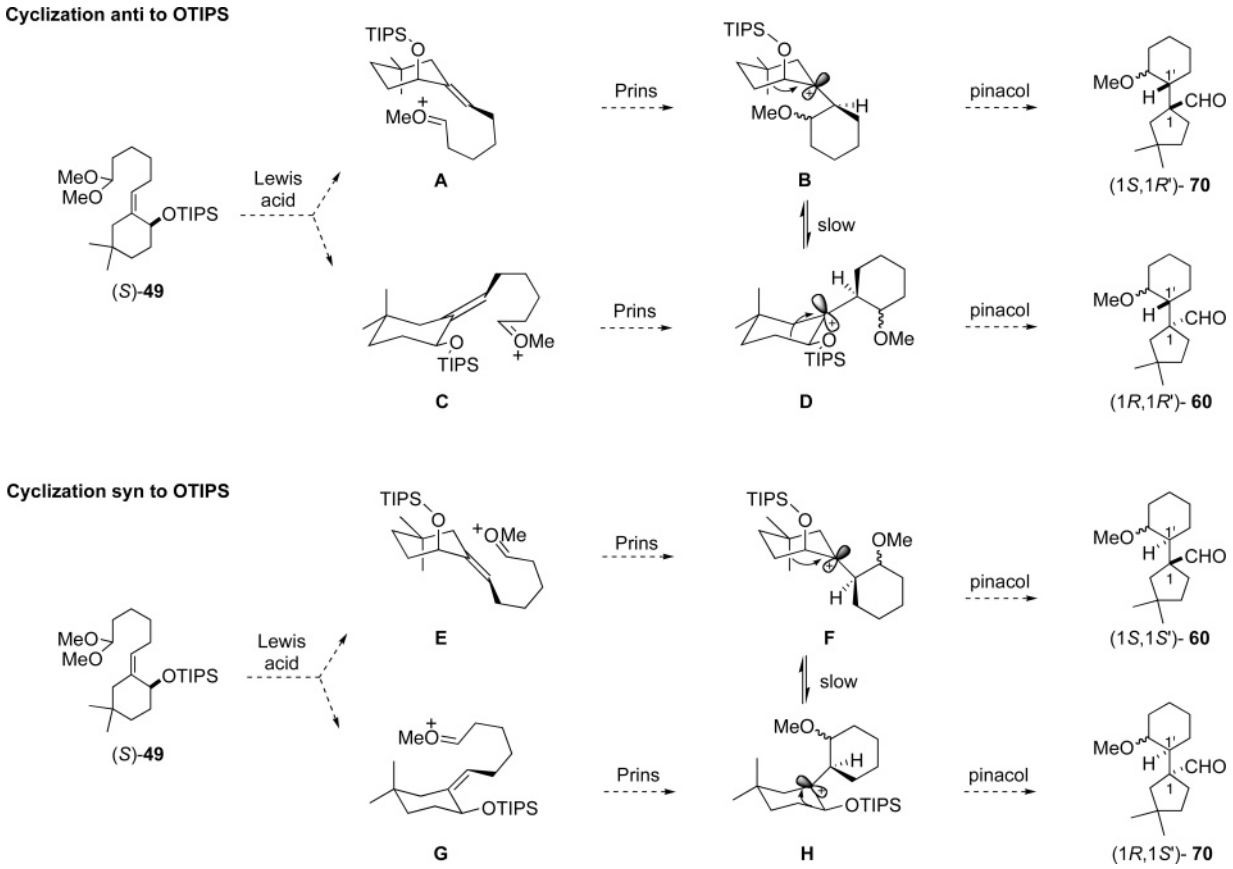
An analysis of the potential stereochemical outcome of the Prins-pinacol reaction of precursor **49** is presented in Scheme 12. Prins cyclization of the derived α-alkoxycarbenium ion could take place either syn or anti to the siloxy group in two possible

(18) The HPLC analysis employed the *p*-nitrobenzoyl derivative of the corresponding alcohol.

(19) Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876−881.

(20) The observed stereochemical outcome of the Prins-pinacol transformation is similar in the formation of the attached ring systems **58** (Scheme 5) and **60** (Scheme 6).

SCHEME 12



chair conformations of the alkylidenecyclohexane ring. If one assumes that pinacol rearrangements occur more rapidly than interconversion of chair cyclohexyl cations **B**/**D** and **F**/**H**,[21−23] the exclusive formation of *rel*-1*R*,1′*R* methoxy epimers **60a** and **60b** from precursor **49** is consistent with Prins cyclization taking place either anti to the siloxy substituent if this group were equatorial (**C** → **D**), or syn to the siloxy group (**E** → **F**) if this substituent were axial. Carrying out the Prins-pinacol reaction with an enantiomerically enriched precursor can differentiate these two scenarios. Thus, the transformation of (*S*)-**49** to the 1*S*,1′*S* enantiomer of (1-cyclohexyl)cyclopentanecarbaldehyde **60**, which proceeded with only slight erosion in enantiomeric purity, establishes that this reaction takes place largely by the **49** → **E** → **F** → **60** pathway. The small loss of absolute chirality observed in this reaction likely originates from a minor amount of Prins cyclization taking place by the **C** → **D** pathway.[24]

Several factors potentially contribute to the preference for Prins cyclization to occur syn to the siloxy group in the chair conformation depicted in **E**. As noted earlier,[4] the chair conformation of allylic siloxy ether **49** having the siloxy group equatorial suffers from a severe allylic ($A^{1,3}$) interaction between the alkylidene and siloxy substituents.[8] One factor disfavoring cyclization from the face opposite the axial siloxy group (**A** → **B**) would be a steric interaction between the C5 axial methyl and the methoxy substituents. However, this interaction does not appear to be decisive as the related Prins-pinacol conversion of the C3-dimethyl congener **48**, in which this steric interaction would be absent, proceeds by a pathway similar to that followed by precursor **49** to provide attached-ring products **58a** and **58b**.[25] A stabilizing through-space electrostatic interaction between the α-alkoxycarbenium ion and the axial oxygen substituent are most likely responsible for Prins cyclization occurring preferentially syn to the axial siloxy group.[26] The importance of such interactions in organizing transition structures for the reaction of nucleophiles with oxocarbenium ions has been demonstrated by recent incisive studies by Woerpel and co-workers.[27]

In conclusion, we demonstrated that Prins-pinacol reactions of cyclohexyl- and cyclopentyl triisopropylsiloxy ethers having (2*Z*)-(6,6-dimethoxyhexylidene) or (2*Z*)-(6,6-dimethoxyhexylidene) side chains can be employed to construct a variety of attached ring systems. Moreover, attached rings in which both rings are chiral can be prepared in this fashion with high stereoselectivity and moderate enantiospecificity. Stabilizing

(21) This assumption has considerable experimental justification.[3]

(22) Minor, K. P.; Overman, L. E. *Tetrahedron* **1997**, *53*, 8927−8940.

(23) In the absence of stereoelectronic constraints, pinacol rearrangements have extremely low activation barriers; see: (a) Bartok, M.; Molnar, A. In *Chemistry of Ethers, Crown Ethers, Hydroxyl Compounds and Their Sulfur Analogues*; Patai, S., Ed.; Wiley: New York, 1980; Part 2, pp 722−732. (b) Rickborn, B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, pp 721−732.

(24) To determine if siloxy acetal (*S*)-**49** partially racemizes during the course of this reaction sequence, the reaction was stopped prematurely and the entaniomeric excess of recovered acetal (*S*)-**49** was measured. HPLC analysis employing the *p*-nitrobenzoyl derivative of the corresponding alcohol indicated an 87% ee for this material, indicating that no loss of absolute chirality had occurred.

(25) These products would be produced if this cyclization proceeded by the **E** → **F** pathway.

(26) (a) Kahn, S. D.; Pau, C. F.; Chamberlin, A. R.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 650−663. (b) Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 666−671.

(27) Chamberland, S.; Ziller, J. W.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 5322−5323.

through-space electrostatic interactions between the α-alkoxycarbenium ion and an axially positioned oxygen substituent are believed to play a significant role in organizing the transition structure of the Prins cyclization (e.g., **E** → **F**, Scheme 12).

Experimental Section[28]

General Procedure for Enol Triflate Formation, Suzuki Coupling, and $LiAlH_4$ Reduction. Preparation of (*Z*)-[2-(5,5-Dimethoxypentylidene)cyclohexanol] (17). A pentane solution of *t*-BuLi (4.8 mL, 8.7 mmol, 1.8 M) was added in a rapid dropwise manner to a solution of 2-(hydroxymethylene)cyclohexanone **8**[29] (1.0 g, 7.9 mmol) in hexanes (70 mL) at −78 °C.[10] The reaction was maintained at −78 °C for 10 min, and freshly prepared trifluoromethanesulfonic anhydride (1.5 mL, 8.7 mmol) was added.[30] After being stirred for 10 min, the reaction mixture was partitioned between Et_2O (50 mL) and a mixture of saturated aqueous $NaHCO_3$ (125 mL) and brine (125 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated in the presence of 2,4,6-collidine (0.5 mL). Diagnostic characterization data: LRMS (ESI) *m*/*z* 281 (M + Na, 281 calcd for $C_8H_9F_3O_4S$). The crude triflate **11** was used immediately without further purification.

A solution of 9-borabicyclo[3.3.1]nonane (9-BBN, 13 mL, 6.5 mmol, 0.5 M in THF) was added to a solution of 4,4-dimethoxybut-1-ene[31] (0.9 g, 7.5 mmol) and THF (10 mL) at 0 °C. After 6 h, aqueous NaOH (2.3 mL, 7.0 mmol, 3.0 M) was added, and the mixture was stirred vigorously for 15 min. The crude organoborane **23** was cannulated into a solution of crude triflate **11** (1.3 g, 5.0 mmol), 2,4,6-collidine (0.3 mL, 2.5 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (0.4 g, 0.5 mmol), and degassed THF (18 mL). After being stirred for 3 h at room temperature, the reaction mixture was partitioned between Et_2O (50 mL) and H_2O (50 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 15 mL), and the combined organic layers were washed sequentially with saturated aqueous $CuSO_4$ (2 × 50 mL), saturated aqueous $NaHCO_3$ (25 mL), and brine (25 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was absorbed onto silica gel and purified by flash column chromatography on silica gel (10% ethyl acetate−hexanes) to yield 1.2 g (65% from **8**) of enone **14** as a pale yellow oil. Diagnostic characterization data: ^1H NMR (500 MHz, $CDCl_3$) δ 5.55 (ddd, *J* = 9.0, 7.5, 1.5 Hz, 1 H), 4.34 (t, *J* = 5.7 Hz, 1H), 3.29 (s, 6H); IR (neat) 1687 cm^{-1}.

A 1.1 g portion of sample **14** (4.8 mmol) was immediately dissolved in THF (25 mL) and cooled to 0 °C. Lithium aluminum hydride (2.4 mL, 2.4 mmol, 1.0 M in THF) was added dropwise, and the stirred reaction mixture was maintained for 1 h at 0 °C. The reaction then was quenched by the dropwise addition of saturated aqueous sodium/potassium tartrate (20 mL). The mixture was partitioned between Et_2O (50 mL) and H_2O (25 mL), and the organic layer was separated. The aqueous layer was extracted with Et_2O (2 × 25 mL), and the combined organic layers were washed with brine (40 mL), dried ($MgSO_4$), and concentrated. This residue was absorbed onto silica gel and purified by flash column chromatography on silica gel (30% ethyl acetate−hexanes) to yield 0.70 g of **17** (64%) as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 5.17 (ddd, *J* = 9.2, 7.5, 0.7 Hz, 1 H), 4.69 (bs, 1 H), 4.36 (t, *J* = 5.7 Hz, 1 H), 3.30 (s, 6 H), 2.42−2.39 (m, 1 H), 2.10−2.08 (m, 2 H), 1.98−1.91 (m, 2 H), 1.79−1.74 (m, 2 H), 1.61−1.57 (m, 4 H), 1.44−1.39 (m, 3 H), 1.28−1.25 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.5, 124.8, 104.7, 65.5, 52.9, 52.8, 34.1, 32.4, 32.1, 28.2, 26.6, 25.3, 20.6; IR (neat) 3420, 1444 cm^{-1}; HRMS (CI) *m*/*z* 211.1698 (M − OH, 211.1692 calcd for $C_{13}H_{24}O_3$). Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 67.91; H, 10.81.

General Procedure for Silylation. Preparation of (*Z*)-[[2-(5,5-Dimethoxypentylidene)cyclohexyloxy]triisopropylsilane] (20). Pyridine (0.60 mL, 7.4 mmol), triisopropylsilyl trifluoromethanesulfonate (0.86 mL, 3.2 mmol), and 2,6-(dimethylamino)pyridine (30 mg, 0.25 mmol) were added sequentially to a solution of alcohol **49** (0.56 g, 2.5 mmol) and CH_2Cl_2 (3 mL). After being stirred for 18 h at room temperature, the reaction mixture was partitioned between pentane (20 mL) and saturated aqueous $NaHCO_3$ (20 mL). The aqueous layer was extracted with pentane (2 × 10 mL), and the combined organic layers were washed with brine (40 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography on silica gel (1% ethyl acetate−hexanes) to yield **20** (0.64 g, 68%) as a pale yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 5.02 (t, *J* = 6.7 Hz, 1 H), 4.72 (bs, 1 H), 4.36 (t, *J* = 5.7 Hz, 1 H), 3.32 (s, 6 H), 2.56−2.45 (m, 1 H), 2.11−1.83 (m, 5 H), 1.79−1.73 (m, 1 H), 1.66−1.54 (m, 2 H), 1.48−1.32 (m, 3 H), 1.30−1.22 (m, 1 H), 1.09−1.02 (m, 22 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.4, 121.5, 104.7, 66.3, 52.8, 36.3, 32.7, 32.3, 29.1, 27.1, 25.3, 20.8, 18.3, 18.2, 12.6; IR(neat) 2936, 2862 cm^{-1}; HRMS (ESI) *m*/*z* 384.3059 (M, 384.3059 calcd for $C_{22}H_{44}O_3Si$). Anal. Calcd for $C_{22}H_{44}O_3Si$: C, 68.69; H, 11.53. Found: C, 68.84; H, 11.68.

General Procedure for Prins-Pinacol Reactions. Preparation of 50a and 50b. Stannic chloride[32] (60 μL, 0.33 mmol) was added dropwise to a stirring solution of unsaturated siloxy acetal **20** (0.25 g, 0.65 mmol) and CH_2Cl_2 (7 mL, 0.1 M) at 0 °C. After the reaction was maintained at 0 °C for 2 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$ (5 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified on silica gel (2% ethyl acetate−hexanes) to give the following fractions. **50a** (38 mg, 30%) as a clear pale yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 9.66 (s, 1 H), 3.62−3.61 (m, 1 H), 3.16 (s, 3 H), 2.24−2.18 (m, 1 H), 1.97−1.91 (m, 2 H), 1.78−1.68 (m, 4 H), 1.63−1.48 (m, 8 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.2, 83.3, 57.9, 56.1, 55.0, 33.6, 33.2, 30.3, 25.6, 25.1, 22.6, 17.9; IR(neat) 1722 cm^{-1}; HRMS (CI) *m*/*z* 165.1273 (M−OCH_3, 165.1279 calcd for $C_{12}H_{20}O_2$−OCH_3). **50b** (50 mg, 39%) as a clear pale yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 9.48 (s, 1 H), 3.47−3.45 (m, 1 H), 3.23 (s, 3 H), 2.21−2.19 (m, 1 H), 2.05−1.95 (m, 1 H), 1.94−1.93 (m, 1 H), 1.83−1.76 (m, 1 H), 1.68−1.49 (m, 7 H), 1.48−1.27 (m, 3 H), 1.25−1.06 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.9, 84.8, 60.2, 57.1, 50.6, 31.6, 31.0, 28.8, 27.0, 25.9, 25.6, 23.5; IR(neat) 1699 cm^{-1}; HRMS (CI) *m*/*z* 196.1470 (M^+, 196.1463 calcd for $C_{12}H_{20}O_2$).

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Supporting Information Available: Experimental procedures and tabulated characterization data for new compounds not reported in the Experimental Section, copies of ^1H and ^{13}C NMR spectra for all new compounds, and X-ray crystallographic files (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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