A new strategy for synthesis of attached rings

Larry E. Overman and Lewis D. Pennington

Abstract: The first investigation of the use of pinacol-terminated Prins cyclizations to form attached rings is reported. Treatment of triisopropylsilyl ethers of (*Z*)- or (*E*)-[2-(6,6-dimethoxyhexylidene)cyclohexanol with $SnCl_4$ provides bicyclic products having attached rings. The approach is synthetically useful in the *Z* alkylidenecyclohexane series, proceeding selectively by a pathway involving carbon migration in the pinacol rearrangement step, to provide methoxy epimers of 1-(2-methoxycyclohexyl)cyclopentylcarboxaldehyde. Reaction of the corresponding *E* stereoisomer is more complex and yields a mixture of products resulting from both hydride and carbon migration in the pinacol rearrangement step.

Key words: Prins cyclization, pinacol rearrangement, attached rings.

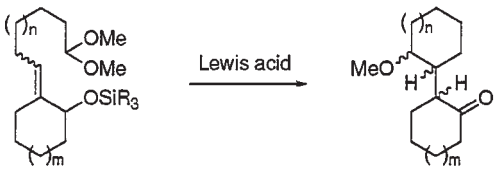
Résumé : On a réalisé la première étude de l'utilisation de cyclisations de Prins terminées par du pinacol dans le but de former produits auxquels des cycles sont attachés. Le traitement des éthers triisopropyliques des (*Z*)- et (*E*)-[2-(6,6-diméthoxyhexylidène)]-cyclohexanol avec du $SnCl_4$ conduit à la formation de produits bicycliques auxquels des cycles sont attachés. L'approche est utile en synthèse dans la série du *Z*-alkylidènecyclohexane puisque, par le biais d'une voie impliquant la migration d'un carbone dans l'étape du réarrangement pinacolique, elle conduit d'une façon sélective aux 1-(2-méthoxycyclohexyl)-cyclopentylcarboxaldéhydes épimères au niveau du méthoxy. La réaction du stéréoisomère *E* correspondant est plus complexe et elle conduit à un mélange de produits qui, dans l'étape du réarrangement pinacolique, résultent de migrations tant d'hydrure que de carbone.

Mots clés : cyclisation de Prins, réarrangement pinacolique, cycles attachés.

[Traduit par la Rédaction]

Introduction

Myriad opportunities in ring construction are realized by utilizing a pinacol rearrangement to terminate a Prins cyclization. One of the earliest examples is credited to Mousset and co-workers (1), who discovered serendipitously the synthesis of substituted tetrahydrofurans by acid-promoted reaction of allylic diols with aldehydes. Recent investigations in our laboratory (for brief reviews of our early work in this area, see ref. 2) (3), and elsewhere (for contributions from other laboratories, see ref. 4) have documented the utility of "Prins-pinacol" reactions for forming various oxacyclic and carbocyclic ring systems. We have highlighted the power of this ring construction method by employing it as the key strategic element in the synthesis of natural products having diverse architectures (5). Prins-pinacol reactions have been most widely employed to form fused polycyclic ring systems (2–5), while their use to form spirocyclic rings is less developed (3*i*). Herein we report the first use of a Prins-pinacol reaction to access attached rings, rings linked by a C—C σ-bond (eq. [1]). When the attachment centers are stereogenic,

[1] 

attached rings pose a notable challenge for stereocontrolled synthesis (the insect antifeedant azadirachtin is exemplary, see ref. 6).

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Dedicated to Professor Stephen Hanessian in recognition of his many contributions to the science of organic synthesis.

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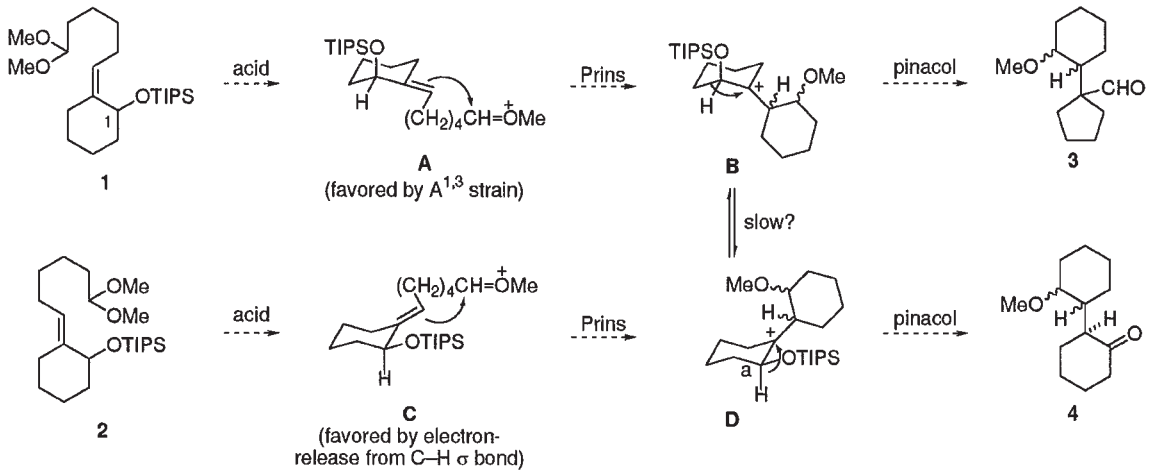
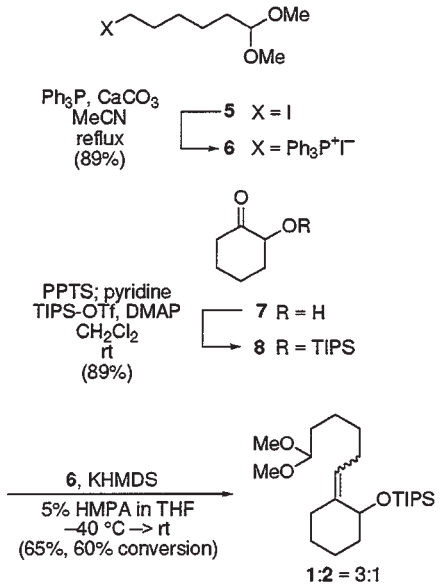
Results

The *Z* and *E* alkylidenecyclohexanes **1** and **2** were chosen for this exploratory investigation (Scheme 1). The stereochemical outcome of the Prins-pinacol reactions studied in our laboratory is accommodated by a sequence in which stereochemistry is dictated in the Prins cyclization step, that is pinacol rearrangement occurs more rapidly than conformational changes of the putative carbocation generated upon Prins cyclization (3*i*). Thus, our initial expectation was that **1** and **2** would cyclize to give aldehyde **3** and ketone **4**, respectively. This prediction follows from the presumption that allylic interactions between the siloxy group and the alkylidene side chain ($A^{1,3}$ strain) would favor cyclization topography **A** for the *Z* substrate (7), while an electronic preference for having an electronegative oxygen substituent in the plane of the nucleophilic alkene π-system would favor topography **C** for the *E* substrate (8).

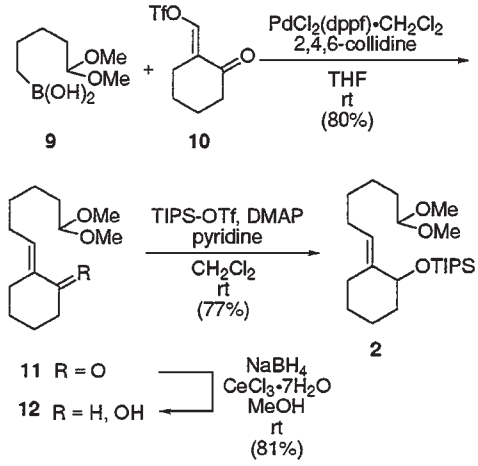
Scheme 1.



Scheme 2.



Scheme 3.



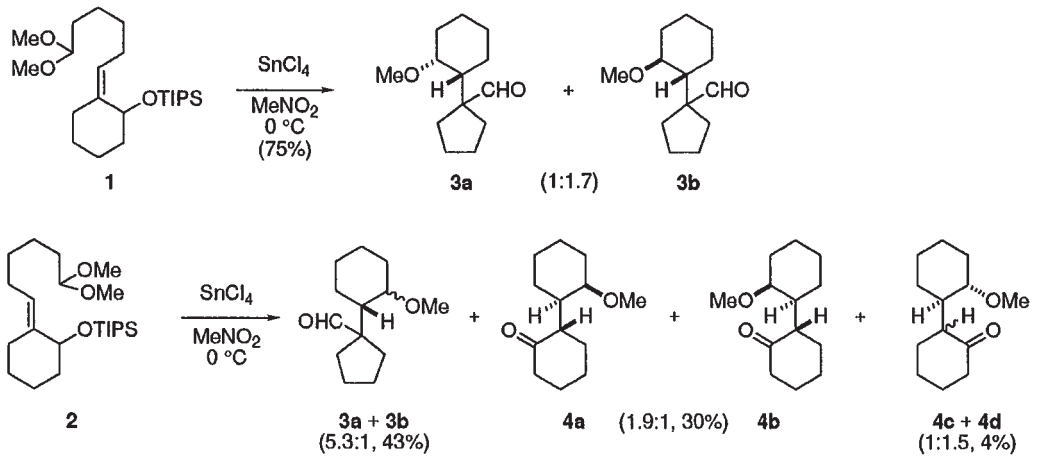
Pinacol rearrangement of carbocation **B** would occur by migration of a ring carbon to yield **3**, since the C_1—H σ-bond is orthogonal to the vacant *p*-orbital, preventing hydride migration. Pinacol rearrangement of carbenium ion **D** would produce **4** if hydride migration occurred in preference to migration of ring bond a (for reviews of the pinacol rearrangement, see ref. (9*a*)). The relative stereochemistry at the stereogenic attached carbons of **4** would be governed by which face of the alkene participated in the transformation of **C** → **D**. Additionally, the stereochemistry of the methoxy substituent in the products would be determined by the orientation of the alkene and the oxocarbenium ion during Prins cyclization. Although our exploratory investigations would be carried out with racemic substrates, one appeal of the route to **4** proposed in Scheme 1 was the expectation that **2** would also be readily available in enantioenriched form.

Alkylidenecyclohexyl ethers **1** and **2** were initially prepared by coupling phosphonium salt **6** (the known iodide **5** (10) was prepared in three steps and 72% yield from 6-bromohexan-1-ol: (*i*) PCC, CH_2Cl_2, rt; (*ii*) *p*-TsOH·H_2O, MeOH, rt; and (*iii*) NaI, acetone, rt) and α-siloxycyclohexanone **8**, utilizing "salt-free" Wittig conditions (11) (Scheme 2). The 3:1 mixture of **1** and **2** thus obtained could be separated by flash chromatography using $AgNO_3$-impregnated silica gel.

A route that would lend itself to obtaining enantioenriched **2** by enantioselective reduction of an enone precursor (12) was also developed (Scheme 3). The key step in this sequence was Suzuki coupling of boronic acid **9** generated in situ from the corresponding alkene (14) by a standard hydroboration–oxidation sequence (13), and enol triflate **10** (15) (although not mentioned in (15), triflate 10 decomposed rapidly at room temperature if 2,4,6-collidine was not present) to give enone **11**. Luche reduction (16) of **11** produced alcohol **12**, which was then silylated to furnish **2**.

^{1}H NMR nOe difference experiments readily confirmed stereochemical assignments for the alkylidene stereoisomers: **2** displayed reciprocal nOe enhancements between the vinylic and C1 hydrogens, while **1** did not. ^{1}H NMR spectra of **1** and **2** suggested somewhat different conformations for the two substrates. Diagnostic were signals for the C1

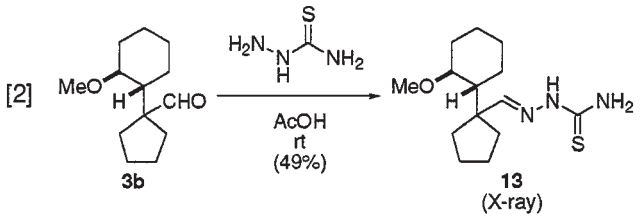
Scheme 4.



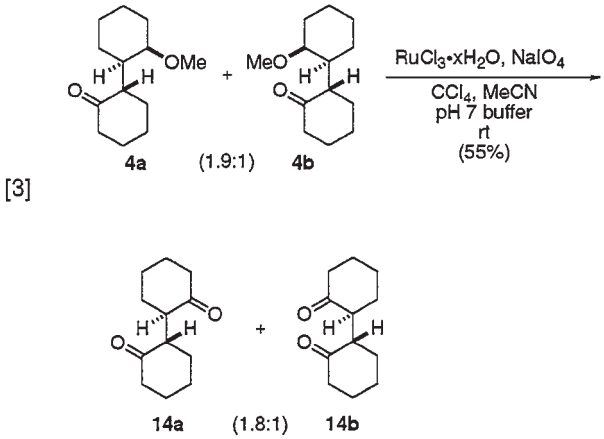
hydrogen, which for **1** appeared as a broad singlet ($w_{h/2}$ = 7.7 Hz) at δ 4.71, whereas the corresponding hydrogen of **2** appeared as a multiplet ($w_{h/2}$ = 15.4 Hz) at δ 4.10. These differences reflect the greater proportion of conformers having the siloxy substituent axial in **1**.

Exposure of **1** or **2** in $MeNO_2$ to 0.5 equiv. of $SnCl_4$ at 0°C for 2 h resulted in efficient Prins-pinacol reaction to give bicyclic products (Scheme 4). No reaction was observed under identical conditions at –23°C. The *Z* alkylidene substrate **1** provided exclusively aldehyde products **3a** and **3b** in a 1:1.7 ratio. In contrast, the *E* alkylidene substrate **2** delivered a complex mixture of six products, in which the ratio of cyclopentylcarboxyaldehyde to cyclohexanone products was 1.3:1. In this latter case, aldehyde stereoisomer **3a** was favored to the extent of 5.3:1, while two major ketone stereoisomers **4a** and **4b** were produced in a 1.9:1 ratio. With the exception of **4a** and **4b**, all products could be separated by medium pressure liquid chromatography (MPLC). The mixture of **4a** and **4b** was contaminated with triisopropylsiloxy residues, thus the yield and ratio of these products are estimates based on ^{1}H NMR analysis.

The stereochemistry of **3a** and **3b** were defined by single-crystal X-ray analysis of thiosemicarbazone derivative **13** prepared from **3b**[2] (eq. [2]). The relative stereochemistry of



the attached stereogenic carbons of **4a** and **4b** was determined by oxidizing (17) a 1.9:1 mixture of these stereoisomers with RuO_4 to yield a 1.8:1 mixture of the known diketones **14a** and **14b** (18) (eq. [3]). These diketones were readily separated by MPLC and characterized by their distinctive ^{1}H and ^{13}C NMR spectra (18). The



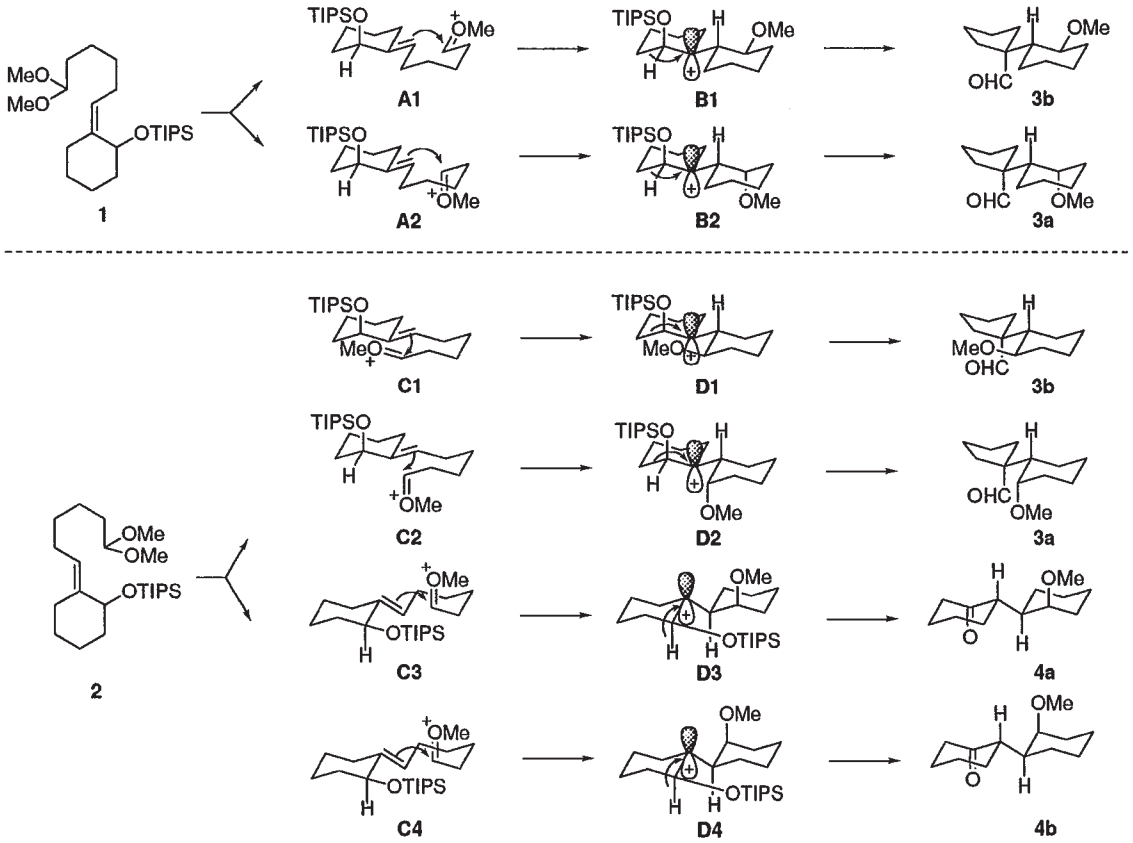
axial disposition of the methoxy substituent in **4a** and **4b** was readily apparent from ^{1}H NMR spectra: the ether methine hydrogens in the **4a**–**4b** mixture appear as partially overlapping broad singlets at δ 3.39 and δ 3.36, while the corresponding signals of **4c** and **4d** appear as diagnostic triplet of doublets at δ 3.30 (*J* = 10.3, 4.0 Hz) and δ 2.84 (*J* = 9.7, 4.0 Hz), respectively.

Discussion

The results summarized in Scheme 4 establish that Prins-pinacol reactions can be profitably employed to prepare attached ring systems. However, our initial expectations were realized to only a limited extent. As we had anticipated, the pinacol rearrangement step in the reaction of *Z* alkylidene stereoisomer **1** occurs exclusively by ring contraction (carbon migration) to form 1-(cyclohexyl)cyclopentylcarboxaldehyde products **3** (Scheme 5). Since hydride migration to form ketone products was not observed, conformational conversion of **B1** or **B2** to their pseudoequatorial siloxy counterparts apparently was not competitve with pinacol rearrangement. Attack of the alkene is depicted in Scheme 5

[2] The authors have deposited atomic coordinates for 13 with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2, 1EZ, U.K.

Scheme 5.



to occur opposite the siloxy group in **A1** and **A2**, although there is no experimental support for this supposition. The stereochemical information necessary to define face selectivity is lost since C1 in **3** is not stereogenic.

The generation of both cyclopentylcarboxaldehyde and cyclohexanone products from Prins-pinacol reaction of *E* stereoisomer **2** is consistent with cyclization–rearrangement occurring through pathways of similar energy having the siloxy substituent either pseudoequatorial or pseudoaxial in the starting cyclohexane ring (Scheme 5). If this group is axial, cyclopentylcarboxaldehydes **3a** and **3b** would be formed (**C1** → **D1** → **3b** and **C2** → **D2** → **3a**). Alternatively, Prins cyclization of oxocarbenium ion conformers **C3** and **C4** having the siloxy substituent equatorial, would initially generate cyclohexyl cations **D3** and **D4**. Migration of either the ring bond to generate **3a**, or methine hydrogen to generate **4a** from **D3** (and **4b** from **D4**), is stereoelectronically feasible (the dihedral angle between both of these groups and the vacant *p*-orbital would be ca. 60°C; this analysis assumes that pinacol rearrangement occurs faster than conformational interconversion of the cyclohexylcarbenium ion (3*i*)). The typical preference for hydride migration in stereoelectronically unbiased systems suggest that **4a** and **4b** would be the major products of these latter pathways (for pinacol rearrangements of cyclohexylcarbenium ions, see ref. (9*b*)).

The stereochemistry of the methoxy substituent in aldehydes **3** and ketones **4** reflects the orientation of the alkene and the oxocarbenium ion in the Prins cyclization (Fig. 1). If

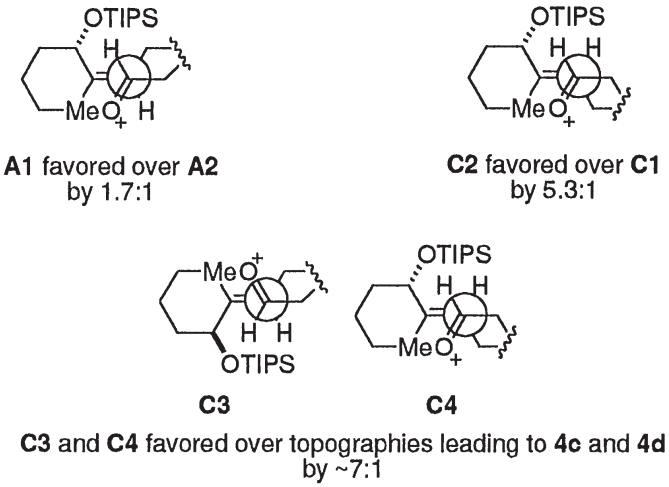


Fig. 1. Favored synclinal orientations in the Prins cyclization step of the exocyclic alkene and the α-alkoxycarbenium ion.

one assumes that the stereoisomeric products are generated by the sequences proposed in Scheme 5, a synclinal orientation (19) having the methoxy portion of the oxocarbenium ion oriented away from the siloxy group is favored in both reaction manifolds (Fig. 1).

Experimental section[3]

2-(Triisopropylsiloxy)cyclohexanone (8)

A mixture of pyridinium *p*-toluenesulfonate (PPTS, 0.22 g, 0.88 mmol), 2-hydroxycyclohexanone (1.0 g, 8.7 mmol), and CH_2Cl_2 (33 mL) was stirred at rt for 3 h. Pyridine (1.1 mL, 14 mmol), triisopropylsilyl triflate (TIPS-OTf, 3.3 mL, 12 mmol), and 4-(dimethylamino)pyridine (DMAP, 0.11 g, 0.92 mmol) were added sequentially and the resulting mixture was stirred at rt for 10 min. The mixture was partitioned between saturated aqueous $NaHCO_3$ (200 mL) and pentane (200 mL), the layers were separated and the organic layer was washed sequentially with H_2O (200 mL), and brine (200 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by column chromatography on silica gel (18:1 hexane–ethyl acetate) gave 2.1 g (89%) of **8** as a clear pale yellow oil. FT-IR (neat): 1727 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.21–4.16 (m, 1H), 2.68–2.59 (m, 1H), 2.26–2.17 (m, 1H), 2.08–1.58 (m, 6H), 1.15–0.96 (m, 21H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 210.4, 39.7, 37.3, 27.7, 22.2, 17.9, 17.7, 12.2. HRMS (FAB): *m*/*z* 271.2098 (MH, 271.2093 calcd. for $C_{15}H_{31}O_2Si$). Anal. calcd. for $C_{15}H_{30}O_2Si$: C 66.61, H 11.18; found: C 66.70, H 11.12.

***Z*-[2-(6,6-Dimethoxyhexylidene)cyclohexyloxy]triisopropylsilane (1)**

Calcium carbonate (0.81 g, 8.1 mmol), Ph_3P (5.1 g, 19 mmol), and CH_3CN (5.0 mL) were added sequentially to iodide **5** (10, 11, 24) (4.4 g, 16 mmol). After bubbling N_2 through the mixture for 5 min, the mixture was heated to reflux. After stirring for 2.5 h, the mixture was cooled to rt and concentrated. The crude product was purified by column chromatography on neutral alumina (sequential elution, 1:1 hexane–ethyl acetate, to isolate excess Ph_3P; 18:1 CH_2Cl2–MeOH, to isolate **6**) to give 7.7 g (89%) of slightly impure **6** as a hygroscopic and colorless waxy solid. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.75–7.61 (m, 15H), 4.21 (t, *J* = 5.5 Hz, 1H), 3.57–3.48 (m, 2H), 3.19 (s, 6H), 1.59–1.23 (m, 8H). HRMS (CI): *m*/*z* 407.2131 (M–I, 407.2140 calcd. for $C_{26}H_{32}O_2P$).

Using a modified version of the general procedure of Koreeda et al. (12), potassium bis(trimethylsilyl)amide (KHMDS, 30 mL, 15 mmol, 0.5 M solution in toluene) was added to a solution of phosphonium salt **6** (7.4 g, 14 mmol) in THF (83 mL) and hexamethylphosphoramide (HMPA, 9.2 mL) at –40°C. After stirring the resulting mixture for 10 min, a cooled (–40°C) solution of **8** (1.9 g, 9.9 mmol) and THF (7.7 mL) was added, and the cooling bath was removed. After 1 h, saturated aqueous $NaHCO_3$ (100 mL) and hexanes (200 mL) were added and the layers were separated. The organic layer was washed sequentially with saturated aqueous $NaHCO_3$ (200 mL), 10% aqueous $Na_2S_2O_3$ (200 mL), H_2O (100 mL), brine (100 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by column chromatography on $AgNO_3$-impregnated silica gel (9:1 CH_2Cl_2–benzene), yielding 0.92 g of a mixture of **1** and **8** and 0.13 g of a mixture of **1** and **2**.

Pure **1** was obtained from the mixture of **1** and **8** as follows. Sodium borohydride ($NaBH_4$, 41 mg, 1.1 mmol) was added to a solution of the **1**–**8** mixture (0.92 g) and MeOH (5.0 mL). After stirring for 20 min, saturated aqueous $NaHCO_3$ (5 mL) and hexanes (100 mL) were added, the organic layer was washed with saturated aqueous $NaHCO_3$ (3 × 50 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated. The silyl ether protecting group of the diols derived from **8** was then selectively removed (to facilitate isolation of pure **1**) by maintaining a solution of this residue, tetra-*n*-butylammonium fluoride (TBAF, 0.86 mL, 0.86 mmol, 1.0 M solution in THF), and THF (5.0 mL) at rt for 12 h. Saturated aqueous $NaHCO_3$ (10 mL) and hexanes (70 mL) were added, the organic layer was washed with saturated aqueous $NaHCO_3$ (5 × 50 mL), brine (50 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by column chromatography on silica gel (18:1 hexane–ethyl acetate) to give 0.70 g (42%, 3 steps, 60% conversion during Wittig coupling) of **1** as a clear yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 5.01 (t, *J* = 6.9 Hz, 1H), 4.71 (br s, 1H), 4.35 (t, *J* = 5.6 Hz, 1H), 3.31 (s, 6H), 2.50–2.45 (m, 1H), 2.03–1.22 (m, 15H), 1.04–0.93 (m, 21H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 141.8, 121.5, 104.4, 66.0, 52.6, 52.5, 36.1, 32.4, 30.0, 28.9, 27.0, 24.4, 20.5, 18.1, 18.0, 12.3. FT-IR (neat): 2938, 2864 cm^{-1}. HRMS (FAB): *m*/*z* 397.3148 (M–H, 397.3138 calcd. for $C_{23}H_{45}O_3Si$). Anal. calcd. for $C_{23}H_{46}O_3Si$: C 69.29, H 11.63; found: C 69.38, H 11.53.

***E*-[2-(6,6-Dimethoxyhexylidene)]cyclohexanone (11)**

A mixture of 9-borabicyclo[3.3.1]nonane (9-BBN, 2.5 g, 10 mmol) in THF (65 mL) was added to a solution of 1,1-dimethoxypent-4-ene (15) (2.4 mL, 16 mmol) and THF (21 mL) at 0°C, and the cooling bath was removed. After stirring for 6 h, 3 M aqueous NaOH (7.6 mL, 23 mmol) was added, and after stirring vigorously for an additional 15 min, the crude organoborane was added by cannula to a solution of triflate **10** (2.1 g, 8.3 mmol), 2,4,6-collidine (3.0 g, 25 mmol), $PdCl_2(dppf)\bullet CH_2Cl_2$ (0.93 g, 1.1 mmol), and THF (40 mL). After stirring for 30 min, the reaction mixture was partitioned between pentane (200 mL) and H_2O (200 mL) and the layers were separated. The organic layer was washed sequentially with saturated aqueous $CuSO_4$ (3 × 200 mL), saturated aqueous $NaHCO_3$ (200 mL), and brine (200 mL), dried ($MgSO_4$), and concentrated. The residue was triturated with pentane and the filtrate was concentrated. The crude product was purified by column chromatography on silica gel (5:1 hexane–ethyl acetate) to give 2.2 g (80%) of **11** as a clear pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 6.58 (t, *J* = 7.5 Hz, 1H), 4.32 (t, *J* = 5.7 Hz, 1H), 3.28 (s, 6H), 2.46–2.37 (m, 4H), 2.08 (q, *J* = 7.3 Hz, 2H), 1.86–1.30 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 201.1, 139.2, 136.2, 104.3, 52.6, 40.1, 32.2, 28.2, 27.6, 26.6, 24.3, 23.5, 23.3. FT-IR (neat): 1688, 1615 cm^{-1}. HRMS (FAB): *m*/*z* 263.1616 (M+Na, 263.1623 calcd. for $C_{14}H_{24}NaO_3$).

***E*-[2-(6,6-Dimethoxyhexylidene)]cyclohexanol (12)**

Cerium(III) chloride heptahydrate (3.4 g, 9.0 mmol) was added to a solution of **11** (2.2 g, 9.0 mmol) and MeOH

[3] Experimental details for preparation of **5** and correlation of the **4a**–**4b** mixture with diketones **14*a*** and **14*b*** are provided as Supplementary Material.

(49 mL). After stirring for 5 min, $NaBH_4$ (0.37 g, 9.7 mmol) was added portionwise, and after stirring for an additional 20 min, saturated aqueous $NaHCO_3$ (10 mL) and pentane (250 mL) were added. The organic layer was washed with saturated aqueous $NaHCO_3$ (2 × 150 mL), brine (2 × 150 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by column chromatography on silica gel (5:1 hexane–ethyl acetate) to give 1.7 g (78%) of **12** as a clear pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.32 (t, *J* = 6.8 Hz, 1H), 4.33 (t, *J* = 5.7 Hz, 1H), 4.04 (br s, 1H), 3.28 (s, 6H), 2.41–2.33 (m, 1H), 2.01–1.33 (m, 16H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 141.1, 120.8, 104.4, 73.6, 52.5, 36.1, 32.2, 29.7, 27.2, 26.6, 25.9, 24.2, 22.8. FT-IR (neat): 3440 cm^{-1}. HRMS (FAB): *m*/*z* 265.1773 (M+Na, 265.1779 calcd. for $C_{14}H_{26}NaO_3$). Anal. calcd. for $C_{14}H_{26}O_3$: C 69.38, H 10.81; found: C 69.17, H 10.65.

_E_-[2-(6,6-Dimethoxyhexylidene)cyclohexyloxy]triisopropylsilane (2)

Pyridine (0.77 mL, 9.5 mmol), TIPS-OTf (2.6 mL, 9.5 mmol), and DMAP (0.083 g, 0.68 mmol) were added sequentially to a solution of **12** (1.7 g, 6.8 mmol) and CH_2Cl_2 (68 mL). After stirring for 20 min, the reaction mixture was partitioned between pentane (125 mL) and saturated aqueous $NaHCO_3$ (100 mL). The organic layer was washed sequentially with saturated aqueous $NaHCO_3$ (100 mL), H_2O (75 mL), saturated aqueous $CuSO_4$ (75 mL), H_2O (75 mL), and brine (2 × 75 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by column chromatography on silica gel (18:1 hexane–ethyl acetate) to give 2.0 g (73%) of **2** as a clear pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.34 (t, *J* = 7.3 Hz, 1H), 4.35 (t, *J* = 5.7 Hz, 1H), 4.11–4.09 (m, 1H), 3.31 (s, 6H), 2.38–2.35 (m, 1H), 2.01–1.34 (m, 15H), 1.10–0.98 (m, 21H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 141.5, 120.4, 104.5, 74.5, 52.6, 37.5, 32.4, 29.8, 27.6, 26.6, 25.9, 24.3, 22.8, 18.1, 12.3. FT-IR (neat): 2939, 2863 cm^{-1}. HRMS (CI): *m*/*z* 398.3216 (M, 398.3216 calcd. for $C_{23}H_{46}O_3Si$). Anal. calcd. for $C_{23}H_{46}O_3Si$: C 69.29. H 11.63; found: C 69.39, H 11.69.

Prins-pinacol rearrangement of 2

Tin(IV) chloride ($SnCl_4$, 0.20 mL, 1.7 mmol) was added dropwise to a stirring suspension of **2** (1.4 g, 3.4 mmol) and $MeNO_2$ (34 mL) at 0°C. After stirring at 0°C for 2 h, Et_3N (15 mL) and MeOH (15 mL) were added sequentially, and the mixture was warmed to rt and was diluted with hexanes (250 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (3 × 200 mL) and brine (200 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by medium pressure liquid chromatography (MPLC) (Lobar prepacked column, LiChroprep™ Si 60 silica gel; gradient elution, hexane → 18:1 hexane–ethyl acetate) to give the following fractions.

3a

0.27 g (37%) as a clear, pale yellow oil. FT-IR (neat): 1715 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.56 (s, 1H), 3.39 (br s, 1H), 3.15 (s, 3H), 2.27–2.21 (m, 1H), 2.02–1.96 (m, 2H), 1.79–1.13 (m, 14H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 203.7, 60.4, 55.7, 53.0, 32.6, 31.4, 27.8, 26.7, 24.8, 24.1, 23.3, 19.9. HRMS (FAB): *m*/*z* 211.1703 (M+H, 211.1698 calcd. for $C_{13}H_{22}O_2$). This product was unstable and was converted immediately to the corresponding thiosemicarbazone **15** for additional characterization (vide infra).

3b

0.039 g (5%) as a clear colorless oil. FT-IR (neat): 1714 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.28 (s, 1H), 3.11 (s, 3H), 2.67 (td, *J* = 9.7, 3.7 Hz, 1H), 2.14–2.03 (m, 2H), 1.85–1.04 (m, 15H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 201.3, 82.1, 58.8, 55.6, 47.5, 31.3, 30.9, 26.9, 25.8, 25.2, 25.1, 24.9, 24.5. HRMS (FAB): *m*/*z* 211.1696 (M+H, 211.1698 calcd. for $C_{13}H_{22}O_2$). This product was unstable and was converted immediately to thiosemicarbazone **13** (vide infra).

4a* + *4b

0.25 g (30%, contaminated with what is estimated by ^{1}H NMR analysis to be 40 mg of hydroxytriisopropylsilane, TIPS-OH) as a clear, pale yellow oil. Characterization data for this mixture, FT-IR (neat): 1707 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.39 (br s, 1H), 3.36 (br s, 1H), 3.25 (s, 3H), 3.21 (s, 3H), 2.61–1.12 (m, 36H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 214.3, 77.6, 74.7, 56.2, 55.6, 53.5, 51.9, 42.8, 42.7, 39.5, 39.1, 31.2, 30.9, 29.1, 28.8, 27.8, 27.5, 26.5, 26.0, 25.9, 24.9, 24.8, 23.2, 19.9, 19.8. HRMS (CI): *m*/*z* 211.1696 (M+H, 211.1698 calcd. for $C_{13}H_{22}O_2$). This mixture was converted immediately to known diketones **14a** and **14b** (vide infra).

4c

10 mg (1.5%) as a clear, colorless oil. FT-IR (neat): 1707 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.30 (td, *J* = 10.3, 4.0 Hz, 1H), 3.26 (s, 3H), 2.61–2.56 (m, 1H), 2.39–1.02 (m, 17H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 212.6, 80.4, 55.9, 50.0, 45.2, 42.2, 30.8, 30.0, 26.8, 26.5, 26.1, 24.9. HRMS (CI): *m*/*z* 211.1695 (M+H, 211.1698 calcd. for $C_{13}H_{22}O_2$).

4d

17 mg (2.3%) as a clear, colorless oil. FT-IR (neat): 1707 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.24 (s, 3H), 2.84 (td, *J* = 9.7, 4.0 Hz, 1H), 2.62 (m, 1H), 2.46 (m, 1H), 2.29–1.61 (m, 12H), 1.29–0.87 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 212.9, 80.3, 55.7, 50.9, 41.7, 30.8, 27.7, 27.5, 27.1, 25.6, 24.7, 24.1. HRMS (FAB): *m*/*z* 211.1694 (M+H, 211.1698 calcd. for $C_{13}H_{22}O_2$).

Prins-pinacol rearrangement of 1

The procedure was identical to that described above for **2**; **1** gave 0.11 g (29%) of **3a** and 0.17 g (46%) of **3b** as clear, pale yellow oils.

(±)-*rel*-*R*,*S*-[1-(2-Methoxycyclohexyl)cyclopentylmethylene]thiosemicarbazone (15)

A solution of **3a** (0.049 g, 0.23 mmol), glacial acetic acid (2.3 mL), and thiosemicarbazide (0.043 g, 0.47 mmol) was maintained at rt for 4 h. The reaction mixture was diluted with toluene (5.0 mL), concentrated, and the residue was purified by column chromatography on silica gel (5:1 hexane–ethyl acetate) to give 66 mg (81%) of **15** as an off-white solid, mp 175–177°C. FT-IR (KBr): 3435, 3256, 3149, 3029,

1594, 1534 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.99 (br s, 1H), 7.33 (s, 1H), 7.03 (br s, 1H), 6.26 (br s, 1H), 3.47 (br s, 1H), 3.19 (s, 3H), 2.13–1.92 (m, 3H), 1.76–1.13 (m, 14H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 177.8, 154.8, 77.2, 55.5, 53.3, 52.9, 34.8, 34.7, 28.1, 26.5, 23.7, 23.4, 19.8. HRMS (CI): *m*/*z* 283.1712 (M, 283.1718 calcd. for $C_{14}H_{25}N_3OS$). Anal. calcd. for $C_{14}H_{25}N_3OS$: C 59.33, H 8.89, N 14.83; found: C 59.45, H 8.86, N 14.71.

(±)-*rel*-*S*,*S*-[1-(2-Methoxycyclohexyl)cyclopentylmethylene]thiosemicarbazone (13)

The procedure followed was identical to that described for **3a**; **3b** gave 0.088 g (49%) of **13** as a colorless solid, mp 168–170°C. FT-IR (KBr): 3430, 3269, 3142, 1589, 1522 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 10.03 (br s, 1H), 7.29 (s, 1H), 7.05 (d, *J* = 3.0 Hz, 1H), 6.68 (br s, 1H), 3.21 (s, 3H), 2.76 (td, *J* =10.0, 3.9 Hz, 1H), 2.13–1.93 (m, 3H), 1.84–0.91 (m, 14H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 177.4, 154.8, 82.1, 55.4, 52.7, 52.1, 36.4, 32.6, 31.2, 27.3, 25.8, 24.5, 24.2, 23.2. HRMS (CI): *m*/*z* 283.1719 (M, 283.1718 calcd. for $C_{14}H_{25}N_3OS$). Anal. calcd. for $C_{14}H_{25}N_3OS$: C 59.33, H 8.89, N 14.83; found: C 59.36, H 8.84, N 14.72.

Conclusions

This study constitutes the first investigation of the use of pinacol-terminated Prins cyclizations to form attached rings. In the *Z* alkylidenecyclohexane series, the approach is synthetically useful, proceeding selectively by a pathway involving carbon migration, to provide methoxy epimers of 1-(2-methoxycyclohexyl)cyclopentylcarboxaldehyde. Reaction of the corresponding *E* stereoisomer is more complex and yields a mixture of products resulting from both hydride and carbon migration. Future efforts to exploit this novel approach to the synthesis of attached rings should focus on *Z* alkylidene substrates.

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References

1. (*a*) P. Martinet, G. Mousset, and M.C.R. Colineau. Acad. Sci. Ser. C, **268**, 1303 (1969); (*b*) P. Martinet and G. Mousset. Bull. Soc. Chim. Fr. 1071 (1970); (*c*) P. Martinet and G. Mousset. Bull. Soc. Chim. Fr. 4093 (1971).
2. (*a*) L.E. Overman. Lect. Heterocycl. Chem. **8**, 59 (1985); (*b*) L.E. Overman. NATO ASI Ser. Ser. C, **289**, 1 (1989); (*c*) L.E. Overman. Acc. Chem. Res. **25**, 352 (1992); (*d*) L.E. Overman. Aldrichimica Acta, **28**, 107 (1995).
3. (*a*) P.M. Herrinton, M.H. Hopkins, P. Mishra, M.J. Brown, and L.E. Overman. J. Org. Chem. **52**, 3711 (1987); (*b*) M.H. Hopkins and L.E. Overman. J. Am. Chem. Soc. **109**, 4748 (1987); (*c*) G.C. Hirst, P.N. Howard, and L.E. Overman. J. Am. Chem. Soc. **111**, 1514 (1989); (*d*) T.O. Johnson, Jr. and L.E. Overman. Tetrahedron Lett. **32**, 7361 (1991); (*e*) M.H. Hopkins, L.E. Overman, and G.M. Rishton. J. Am. Chem. Soc. **113**, 5354 (1991); (*f*) M.J. Brown, T. Harrison, P.M. Herrinton, M.H. Hopkins, K.D. Hutchinson, P. Mishra, and L.E. Overman. J. Am. Chem. Soc. **113**, 5365 (1991); (*g*) L.E. Overman and G.M. Rishton. Org. Synth., **71**, 63 (1992); (*h*) S. Ando, K.P. Minor, and L.E. Overman. J. Org. Chem. **62**, 6379 (1997); (*i*) K.P. Minor and L.E. Overman. Tetrahedron, **53**, 8927 (1997); (*j*) M.J. Cloninger and L.E. Overman. J. Am. Chem. Soc. **121**, 1092 (1999).
4. (*a*) M. Sworin and W.L. Neumann. J. Org. Chem. **53**, 4894 (1988); (*b*) B.M. Trost and D.C. Lee. J. Am. Chem. Soc. **110**, 6556 (1988); (*c*) T. Nakamura, T. Matsui, K. Tanino, and I. Kuwajima. J. Org. Chem. **62**, 3032 (1997).
5. (*a*) M.J. Brown, T. Harrison, and L.E. Overman. J. Am. Chem. Soc. **113**, 5378 (1991); (*b*) G.C. Hirst, T.O. Johnson, and L.E. Overman. J. Am. Chem. Soc. **115**, 2992 (1993); (*c*) T.A. Grese, K.D. Hutchinson, and L.E. Overman. J. Org. Chem. **58**, 2468 (1993); (*d*) D.W.C. MacMillan and L.E. Overman. J. Am. Chem. Soc. **117**, 10391 (1995).
6. S.V. Ley, A.A. Denholm, and A. Wood. Nat. Prod. Rep. 109 (1993).
7. E.L. Eliel and S.H. Wilen. *In* Stereochemistry of organic compounds. John Wiley & Sons, New York. 1994, p. 738.
8. (*a*) K.N. Houk, S.R. Moses, W. Yun-Dong, R. Nelson, J. Volker, R. Schohe, and F.R. Fronczek. J. Am. Chem. Soc. **106**, 3880 (1984); (*b*) K.N. Houk, J. Haller, and T. Strassner. J. Am. Chem. Soc. **119**, 8031 (1997).
9. (*a*) M. Bartok and A. Molnar. *In* Chemistry of ethers, crown ethers, hydroxyl compounds and their sulfur analogs. Part 2. *Edited by* S. Patai. New York. 1980; and B. Rickborn. *In* Comprehensive organic synthesis. Vol. 3. *Edited by* B.M. Trost. Pergamon Press, Oxford, U.K. 1991; (*b*) P.L. Barili, G. Berti, B. Macchia, F. Macchia, and L. Monti. J. Chem. Soc. C, 1168 (1970).
10. B.G. Kovalev, R.N. Vaskan, and E.S. Lavrinenko. Zh. Org. Khim. **7**, 667 (1971).
11. M. Koreeda, P.D. Patel, and L. Brown. J. Org. Chem. **50**, 5910 (1985).
12. A.F. Simpson, D.C. Lathbury, and T. Gallagher. Tetrahedron: Asymmetry, **8**, 673 (1997).
13. N. Miyaura and A. Suzuki. Chem. Rev. **95**, 2457 (1995).
14. C.C. Price and R.B. Balsley. J. Org. Chem. **31**, 3406 (1966).
15. K. Brickmann, F. Hambloch, J. Suffert, and R. Bruckner. Liebigs Ann. Chem. 457 (1996).
16. A.L. Gemal and J.L. Luche. J. Am. Chem. Soc. **103**, 5454 (1981).
17. P.H.J. Carlsen, T. Katsuki, V.S. Martin, and K.B. Sharpless. J. Org. Chem. **46**, 3936 (1981).
18. S.E. Denmark, C.J. Cramer, and J.A. Sternberg. Tetrahedron Lett. **27**, 3693 (1986).
19. S.E. Denmark, E.J. Weber, T.M. Wilson, and T.M. Willson. Tetrahedron, **45**, 1053 (1989).