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Stereoselective synthesis of carbocyclic ring systems by pinacol-terminated Prins cyclizations

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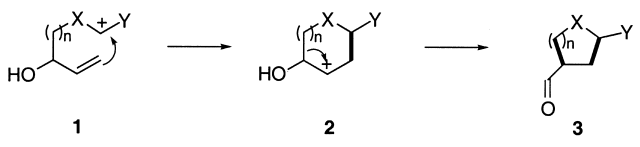
We are delighted to dedicate this paper to Yoshi Kishi on the occasion of his receipt of the 2002 Tetrahedron Prize

Abstract—Studies that expand the scope of the Prins-pinacol synthesis of carbocyclic ring systems are described. The construction of cyclopentacyclooctanones by ring-enlarging cyclopentane annulations of cycloheptanone precursors is broadly examined as is the synthesis of related bicyclic ketones containing larger rings. Prins-pinacol reactions of acyclic alkenyl acetals were examined to gain insight into intrinsic stereochemical control elements in ring-enlarging cyclopentane annulations. The outcome of the carbocyclic constructions described in this report are rationalized by the mechanistic analysis we developed recently to describe Prins-pinacol constructions of tetrahydrofurans.

1. Introduction

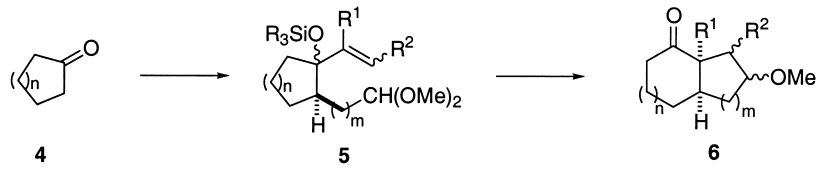
The efficient construction of natural products and increasingly complex pharmaceutical agents requires that new methods for stereocontrolled construction of complex ring systems be developed. Within this context, we have described a suite of ring-forming processes that employ pinacol rearrangements to terminate cationic cyclization reactions.[1] The general strategy is outlined in Scheme 1 wherein the two new C–C bonds formed in the process are emboldened. Using this reaction design paradigm, stereoselective syntheses of oxygen[2,3] and sulfur[4] heterocycles and several carbocyclic ring systems have been reported.



Scheme 1.

In the carbocyclic area, the most extensively developed reaction is an unusual annulation in which a starting ketone is ring-expanded by one carbon as it is fused in *cis* fashion to a new 5- or 6-membered carbocyclic ring: **4→5→6** (Scheme 2).[5a,c,d] This method is particularly useful for assembling angularly-fused ring systems, as in the stereoselective transformation of **7→8**, which was the central strategic step in our inaugural total syntheses of *Lycopodium* alkaloids of the magellanine family (Scheme 3).[5d]

We describe herein recent studies aimed at expanding the scope of the Prins-pinacol synthesis of carbocyclic ring systems. The construction of cyclopentacyclooctanones from cycloheptanone precursors is broadly examined, as is the synthesis of related bicyclic ketones containing larger rings (9- and 13-membered). We show for the first time that depending upon the size of the starting ring and the relative



Scheme 2.

Keywords: cyclization; Prins-pinacol reaction; dione; stereoelectronic effect.

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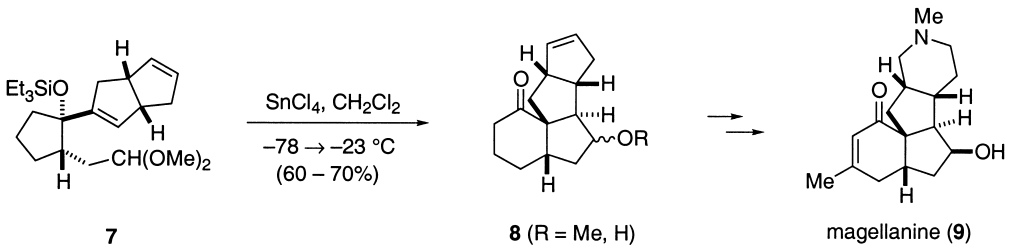


Scheme 3.

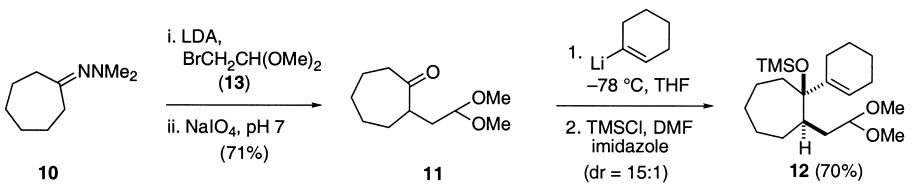
configuration of the alkene and acetal side chains, pinacol-terminated Prins cyclization reactions can give *trans*-fused and inside–outside bicyclic carbocycles, as well as *cis*-fused products of the type illustrated in Scheme 2.

2. Results

2.1. Ring-enlarging cyclopentane annulations

A representative series of 1-alkenyl-2-(2,2-dimethoxyethyl)cycloalkanol silyl ethers was prepared from cycloheptanone, cyclooctanone and cyclododecanone by the general sequence illustrated in Scheme 4 for the synthesis of cycloheptane derivative **12**. Following prescriptions of Stork,[6] and Corey and Enders,[7] dimethylhydrazone **10**[8] was deprotonated with LDA at low temperature and alkylated with bromoacetal **13** to provide cycloheptanone acetal **11** after cleavage[9] of the hydrazone. As a result of the poor reactivity of **13**, direct reaction of the lithium enolate of cycloheptanone with this electrophile was inefficient. Condensation of **11** with 1-lithiocyclohexene[10] at −78°C in THF proceeded with high diastereoselection to give a 15:1 mixture of epimeric alcohols. After silyl protection and removal of the minor stereoisomer by flash chromatography, alkenyl acetal **12** was isolated in 70% yield. We had shown earlier that alkenyl organometallic nucleophiles add to 2-alkylcycloheptanones with high selectivity from the face opposite the side chain,[11] precedent that formed the basis of the configuration assignment for **12** and other cycloheptane alkenyl acetals. The related synthesis of the other siloxy alkenyl acetals employed in this investigation is summarized in Table 1.

Ring-enlarging cyclopentane annulations of alkenyl acetals were best accomplished by adding 1.1 equiv. of $SnCl_4$ to CH_2Cl_2 solutions of the alkenyl acetals at −78°C, followed by allowing reactions to warm to ca. −23°C (typically over 10–15 min) prior to aqueous quenching. Results obtained from reactions of a representative set of cycloheptane alkenyl acetals under these conditions are summarized in Scheme 5. Consistent with our previous experience,[5] annulated products were produced as mixtures of methoxy epimers. To simplify product isolation, these keto ethers were not separated but directly oxidized with RuO_4[12] to give dione products. As was observed earlier with analogous cyclopentane and cyclohexane precursors,[5a,d] the *cis*-fused product of ring-enlarging cyclopentane annulation was formed with high selectivity.[13] Only in the reaction of **17** was >1% of a volatile byproduct (3% in this case) seen by capillary GLC analysis of crude reaction products. When the alkene was a weakly nucleophilic terminal vinyl group, it was necessary to protect the tertiary alcohol with a robust silyl substituent to prevent capture of the oxocarbenium ion

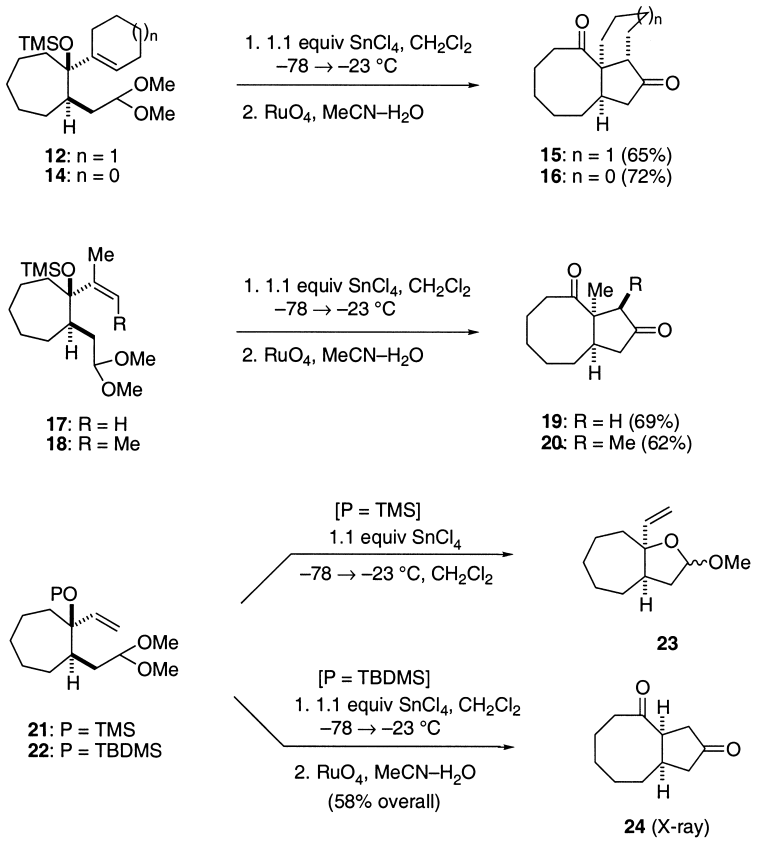


Scheme 4.

Table 1. Synthesis of alkenyl acetal cyclization precursors by the general sequence exemplified in Scheme 4

Starting ketone	α-(2,2-Dimethoxyethyl) derivative yield (%)[a]	Alkenyl organometallic addition			
		Reagent	ds[b]	Yield (%)[c]	Major product[c]
Cycloheptanone	**11**, 71	Cyclopentenyllithium	18:1	73	**14**
		2-propenyllithium	>20:1	74	**17**
		(*E*)-2-Butenyllithium and $CeCl_3$	20:1	64	**18**
		Vinylmagnesium bromide	15:1	71	**21**
			15:1	61	**22**
Cyclooctanone	52	2-Propenyllithium	20:1	67	**25**
Cyclododecanone	65	See Scheme 7			
3-Pentanone	67	2-Propenyllithium	5:3	28	**35**
				47	**38**

[a] Overall yield.
[b] By capillary GLC analysis.
[c] After silylation; overall yield for the two steps.

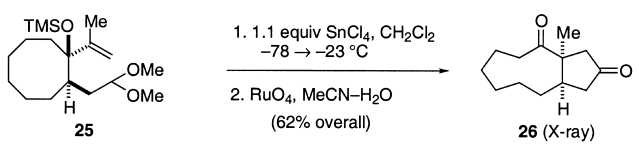


Scheme 5.

by the proximal siloxy group to produce oxabicyclodecane acetal **23**. If the hydroxyl protecting group was TBDMS, bicyclo[6.3.0]undecandione **24** was formed in 58% overall yield from **22**. The constitution and relative configuration of **24** was secured by single-crystal X-ray analysis, whereas stereochemical assignments for the other bicyclo[6.3.0]-undecandiones were made on the basis of ^{1}H nOe studies.[14]

Bicyclo[7.3.0]dodecanediones can be prepared in similar fashion. Thus, cyclooctane alkenyl acetal **25** was converted under identical conditions to *cis*-bicyclo[7.3.0]dodecane-dione **26** in 62% overall yield (Scheme 6). The *cis* configuration of this dione product was confirmed by single crystal X-ray diffraction analysis.

The capacity of this chemistry to prepare diones containing large rings was explored in the cyclododecane series (Scheme 7). Condensation of cyclododecanone acetal **27** with 2-propenyllithium at −78°C gave largely (dr=20:1) one crystalline alcohol **28**, whose configuration was established by single-crystal X-ray analysis. Silylation of this product provided **30**. Epimeric siloxy alkenyl acetal **31** could be obtained by carrying out this condensation reaction at 0°C. The minor alcohol product **29** of this less selective process was separated by flash chromatography and

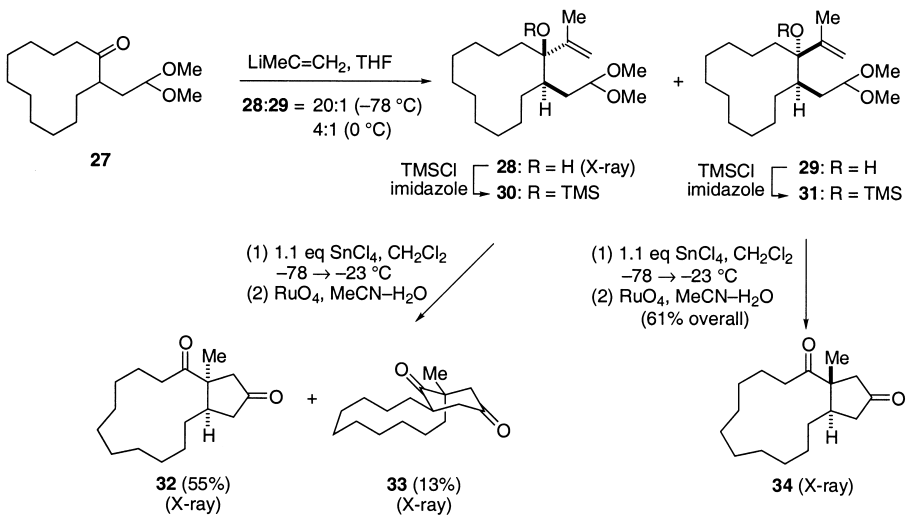


Scheme 6.

silylated to give **31**. Consistent with ring-enlarging annulations of smaller ring congeners having similar stereochemistry (Schemes 5 and 6), Prins-pinacol reaction of **30** gave *cis*-bicyclo[11.3.0]hexadecandione **32** as the major product (55% yield). In this case, a second crystalline product, the unusual inside–outside bicyclic dione **33** was also isolated in 13% yield. Identical treatment of epimeric alkenyl acetal **31** produced neither **32** nor **33**, but rather *trans*-bicyclo[11.3.0]hexadecandione **34** (61% yield). These results contrast markedly with the outcome of Prins-pinacol reactions in the cyclohexane series[5a] where both propenyl dimethyl acetal stereoisomers gave the same *cis*-fused product of ring-enlarging cyclopentane annulation. Single crystal X-ray analysis confirmed the structures of **32**–**34**.

2.2. Conversion of acyclic 5-alkenyl acetals to cyclopentanyl ketones

In order to gain insight into intrinsic stereochemical control elements in ring-enlarging cyclopentane annulations, we examined related Prins-pinacol reactions of acyclic alkenyl acetals (Scheme 8). Using chemistry identical to that described in Scheme 4, 3-pentanone was elaborated to the 5-hexenyl acetal stereoisomers **35** and **38**, which could be separated by preparative HPLC. To allow their relative configurations to be established by ^{1}H NMR nOe experiments, these epimers were converted to lactones **36** and **40** by the routine sequences summarized in Scheme 8. Lactone **36** showed diagnostic reciprocal ^{1}H NMR nOe enhancements between the C3-Me and the *i*-Pr methine hydrogen and between the C3-H and methylene hydrogens of the Et substituent, whereas lactone **40** showed diagnostic

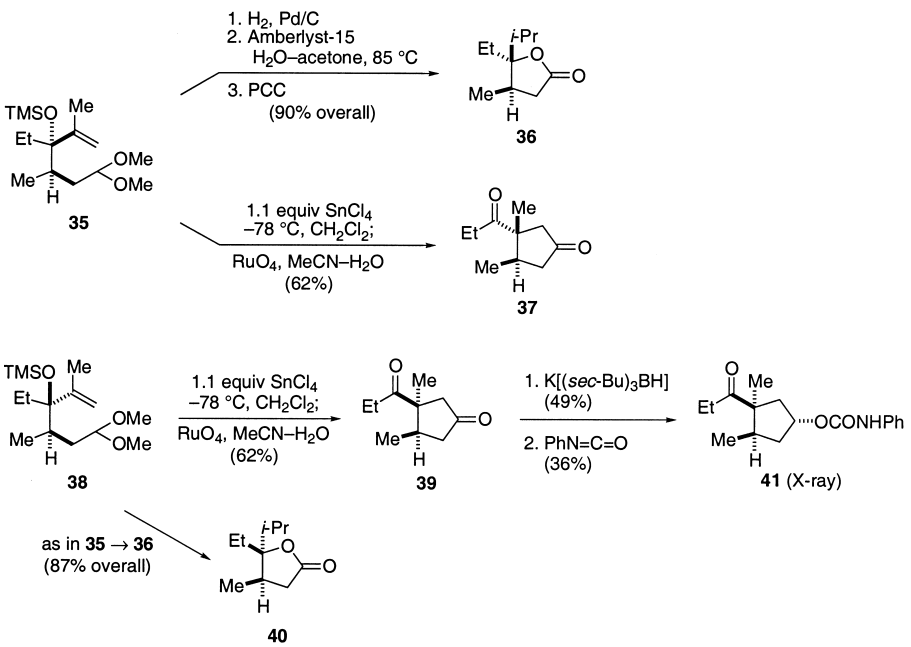


Scheme 7.

reciprocal ^{1}H nOe enhancements between the C3-Me and methylene hydrogens of the Et substituent. When exposed to 1.1 equiv. of $SnCl_4$ (−78→−23°C, CH_2Cl_2) followed by oxidative cleavage of the resulting mixture of methyl ethers, **35** and **38** were converted respectively to the stereoisomeric propanoyl cyclopentanones **37** and **39**. Crossover in these reactions was less than 1% as determined by capillary GLC analysis. The relative configuration of these epimeric diketone products was secured as follows. Reduction of dione **39** with 1 equiv. of K[(*sec*-Bu)$_3$BH] provided a 3:1 mixture of alcohol products, which could be resolved by preparative HPLC to provide the major isomer in 49% yield. Condensation of this alcohol epimer with phenyl isocyanate provided X-ray quality crystals of carbamate **41**.

3. Discussion

The outcome of the carbocyclic constructions described in this report can be rationalized by the mechanistic analysis we developed recently to describe Prins-pinacol constructions of tetrahydrofurans.[2g] As the alkene substituents of the cyclization substrates reported here, with but one exception, contained electron-releasing alkyl substituents on their internal vinylic carbons, the Prins cyclization step is expected to occur by an early transition state.[2g,15] Thus, in the absence of overriding steric effects, Prins cyclization should take place preferentially by way of conformers in which hyperconjugative interactions between $\pi^*_{C=C}$ and the allylic σ_{C-R} are maximized and interactions between the allylic σ^*_{C-O} and the alkene $\pi_{C=C}$ are minimized.[2g,16] This analysis predicts that acyclic 5-alkenyl acetal **35** would preferentially cyclize by the **A→C** pathway, whereas the **E→G** pathway would be favored for epimeric substrate **38** (Fig. 1). Our previous experience strongly suggests that pinacol rearrangement of **C** and **G** would take place more rapidly than conformational inversion of these cyclohexanyl carbenium ions.[5e,f] Thus, the stereoelectronic analysis



Scheme 8.

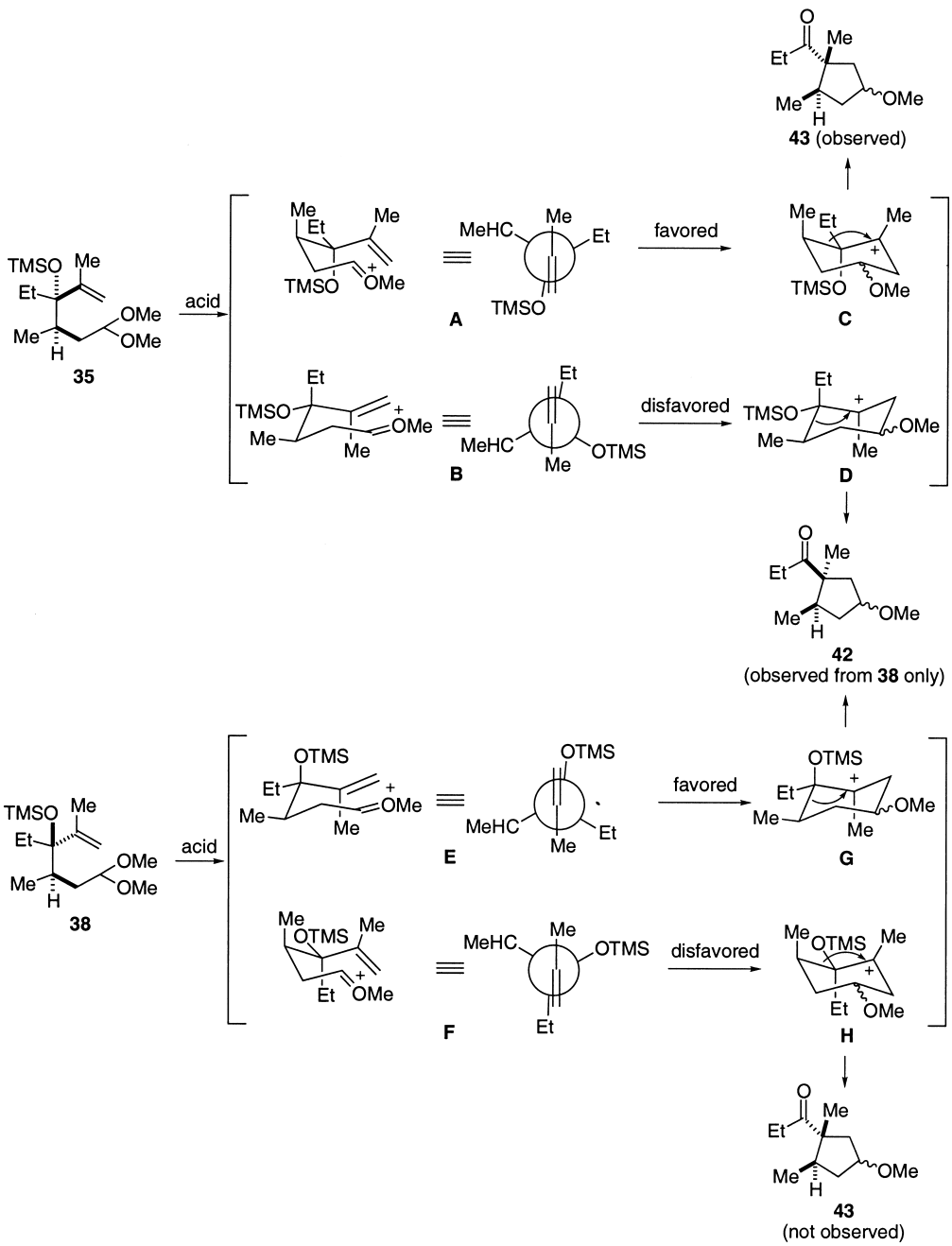


Figure 1. Stereoelectronic rationale for stereoselection in the Prins-pinacol synthesis of cyclopentanoids.

developed in Fig. 1 rationalizes the preferential formation of acylcyclopentanes **43** and **42** from **38** and **39**, respectively.[17] If steric effects alternatively were paramount, cyclization of alkenyl acetal stereoisomer **35** would have been expected to occur by the **B→D** pathway wherein the homoallylic methyl group adopts a favored quasi-equatorial orientation. The >99:1 stereoselection observed in the cyclization of **35** to generate **43** and ultimately dione **37** (Scheme 8) indicates that the stereoelectronic effects that regulate the stereochemical outcome in this reaction are significant in magnitude.[18]

This stereoelectronic analysis also rationalizes the stereochemical outcome of other reactions disclosed here.[19] Thus, the Prins cyclization step of ring-enlarging cyclopentane annulations of cyclic substrates having a *trans* orientation of alkene and acetal side chains should take place by the **I→J** pathway to deliver *cis*-fused products **45** (Fig. 2). For substrates containing rings of eight members or less, reaction by this pathway would be enforced by the inability of these rings to access the alternate chair cyclization topography. The formation of small amounts of the inside–outside bicyclic dione **33** from the cyclization of alkenyl acetal **30** (Scheme 7) signals that the alternate cyclization topography (**K→L**) is energetically accessible in the cyclododecane series. Certainly, the 12-membered ring is large enough to span adjacent *trans*-diaxial positions in this alternate chair transition structure. Why, however, is this stereoelectronically disfavored pathway observed in the cyclododecane and not in the acyclic series? Although we

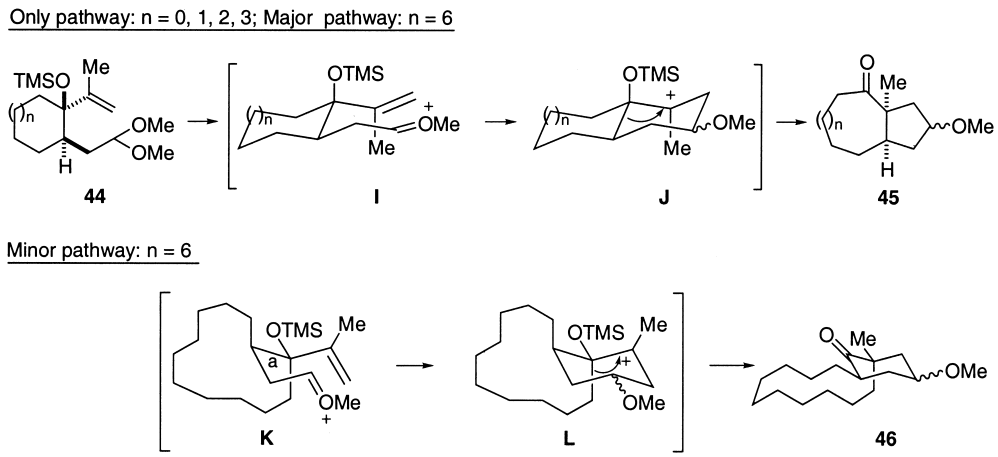


Figure 2. Stereoselection in Prins-pinacol reactions of cyclic sustrates having a *trans* relationship of acetal and alkene side chains.

have not examined this issue yet in sufficient depth to provide an authoritative answer, we speculate that the *anti* orientation about bond a in **K** is better accommodated in the 12-membered ring than the *gauche* orientation of this bond found in **I**.[20] Finally, the formation of the inside–outside bicyclic dione **33** from **30**, rather than the *trans*-fused product of ring-enlarging cyclopentane annulation, indicates that migration of the axial ring methylene carbon of carbenium ion intermediate **L** is favored over migration of the ring bond.

The situation is more complex with cyclic substrates having a *cis* orientation of the alkene and acetal side chains, because two chair cyclization topographies are possible irrespective of the size of the starting ring (Fig. 3). The exclusive formation in the cyclododecane series of the *trans*-fused product **48** (n=6) arising from the **M**→**O** pathway again reflects the importance of the stereoelectronic factors discussed earlier. However, this result stands in contrast to our earlier observation that in the cyclohexane series the epimer having a *cis* orientation of propenyl and acetal side chains, like its *trans* epimer, gives the *cis*-fused product of ring-enlarging cyclopentane annulation.[5a] As suggested in Fig. 3, this latter outcome would result if Prins cyclization took place by the stereoelectronically disfavored **N**→**P** pathway and the ring fusion bond of **P** migrated preferentially.[21] In the cyclohexane series, the stereoelectronically favored cyclization topography would suffer destabilizing steric interactions between the original vinylic methyl group and two carbons of the chair cyclohexane ring (the starred carbons of **M** and **O**, n=1). Apparently, this steric destabilization is sufficient to override the stereoelectronic advantage of this cyclization topography. In the cyclododecane series, the starting ring should be able to adopt a low energy conformation (illustrated schematically by **Q**) that avoids one of these

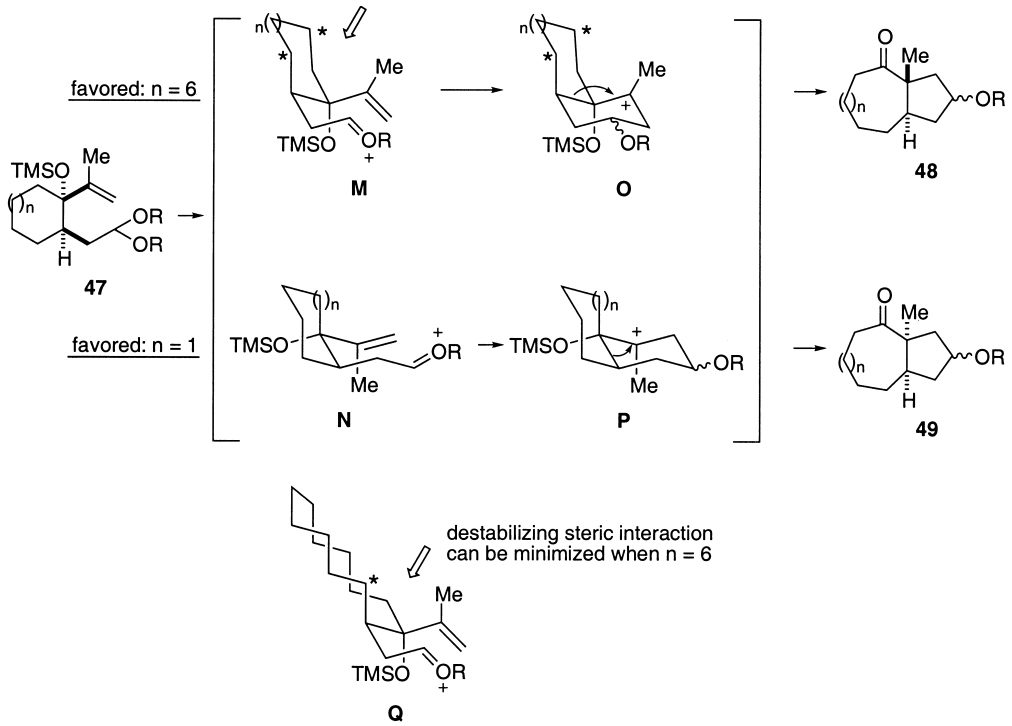


Figure 3. Stereoselection in Prins-pinacol reactions of cyclic substrates having a *cis* relationship of acetal and alkene side chains.

destabilizing non-bonded steric interactions. Evidently, this difference is sufficient to favor the **M→O** pathway in the case of the larger ring.

In summary, this study provides additional illustrations of the diversity of carbocyclic ring systems that can be prepared in useful yield in 4–5 steps from ketone precursors by pinacol-terminated Prins cyclizations. We show for the first time that depending upon the size of a starting ring and the relative configuration of the acetal and alkene side chains, Prins-pinacol reactions can give either *cis*- or *trans*-fused products of ring-enlarging cyclopentane annulation or inside–outside bicyclic products. Stereoselection in these reactions is determined by the interplay of steric and stereoelectronic effects.

4. Experimental[22]

4.1. General procedure for preparing α-(2,2-dimethoxyethyl) ketones

4.1.1. Synthesis of 2-(2,2-dimethoxyethyl)cyclododecanone (27). Following the general procedure of Corey,[7a] a hexane solution of *n*-BuLi (26.7 mL, 2.9 M, 77 mmol) was added slowly to a solution of diisopropylamine (10.8 mL, 77.0 mmol) and dry THF (50 mL) at −78°C. The reaction was maintained at −78°C for 45 min prior to adding a THF (30 mL) solution of cyclododecanone dimethylhydrazone (15.7 g, 70.0 mmol) over 30 min. Care was taken not to allow the internal temperature to exceed −65°C. After the addition was complete, the reaction was maintained at −78°C for 1 h then warmed to 0°C where it was maintained for 1 h. The reaction was then cooled to −78°C and bromoacetaldehyde dimethylacetal (16.5 mL, 140 mmol) was added dropwise. The resulting solution was allowed to warm slowly to 23°C. The reaction solution was then partitioned between EtOAc (160 mL) and water (80 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2×40 mL). The organic layers were combined and washed with brine (50 mL), dried ($MgSO_4$) and concentrated. The crude residue was filtered through a 60 g plug of basic, activity I, alumina, using 400 mL of EtOAc as the eluent to give a thick oil (22.2 g), which was dissolved in CH_2Cl_2 (500 mL). Following the general procedure of Walborsky,[9] this solution was cooled to −60°C, *m*-chloroperbenzoic acid (74%, 18 g, 77 mmol) was added slowly with vigorous stirring, and the reaction was maintained at −60°C for 25 min. The mixture was then poured into cold aqueous saturated $NaHCO_3$ (50 mL), the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2×100 mL). The combined organic layers were washed successively with cold aqueous saturated $NaHSO_3$ (100 mL), cold aqueous saturated $NaHCO_3$ (100 mL) and brine (100 mL), and then dried ($MgSO_4$) and concentrated. Purification of the residue by flash chromatography (10% EtOAc in hexanes) gave 13.6 g (72%) of ketone **27** as a thick colorless oil, which was a single spot by TLC analysis and showed no volatile impurities by GLC analysis: ^{1}H NMR (300 MHz) 4.27 (app t, *J*=5.8 Hz, 1H), 3.28 (s, 3H), 3.26 (s, 3H), 2.78–2.67 (m, 2H), 2.31 (ddd, *J*=17.3, 7.7, 3.5 Hz, 1H), 2.10–1.83 (m, 1H), 1.82–1.76 (m, 1H), 1.67–1.50 (m, 4H), 1.42–1.00 (m, 14H); ^{13}C NMR (75 MHz) 213.7, 103.4, 53.5, 52.9, 47.4, 37.4, 33.6, 29.8, 26.1, 25.9, 24.0, 23.4, 23.1, 22.2, 22.0, 21.7; IR (CCl_4), 810, 1066, 1127, 1249, 1446, 1470, 1550, 1710 cm^{-1}; MS (CI) *m/z* 239.2029 (239.2011 calcd for $C_{15}H_{27}O_2$, MH−MeOH). Anal. calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 70.97; H, 11.16.

4.2. General procedure for adding alkenyllithium reagents to α-(2,2-dimethoxyethyl) ketones to prepare rearrangement substrates

4.2.1. Synthesis of (1*R,2*R**)-2-(2,2-dimethoxyethyl)-1-(2-propenyl)-1-(trimethylsiloxy)cyclododecane (30) and (1*R**,2*S**)-2-(2,2-dimethoxyethyl)-1-(2-propenyl)-1-(trimethylsiloxy)cyclododecane (31).** To a THF (30 mL) solution of 2-bromopropene (0.8 mL, 9 mmol) at −78°C was added *t*-BuLi (12 mL, 18 mmol, 1.54 M in pentane) dropwise.[10] The reaction was maintained at −78°C for 0.5 h prior to the slow addition (over 30 min by syringe pump) of a THF (15 mL) solution of **27** (810 mg, 3.0 mmol). The resulting solution was maintained at −78°C for 4 h before being quenched with saturated aqueous NH_4Cl (10 mL). The organic layer was separated and the aqueous phase was extracted with EtOAc (2×25 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and concentrated to give 820 mg of a nearly colorless oil, which was a 15:1 mixture of epimers by GLC analysis. This mixture was silylated directly without purification. Diagnostic ^{1}H NMR data for the major epimer **28**: ^{1}H NMR (500 MHz) 4.90 (d, *J*=1 Hz, 1H), 4.89 (app s, 1H), 4.47 (app t, *J*=6.0 Hz, 1H), 3.31 (s, 3H), 3.29 (s, 3H), 2.36 (broad s), 1.74 (s, 3H), 1.1–1.9 (m, 23H).

Imidazole (820 mg, 12 mmol) and TMSCl (0.76 mL, 6.0 mmol) were added sequentially to a solution of this crude epimer mixture and DMF (15 mL) at 0°C.[23] The resulting solution was allowed to warm slowly to 23°C where it was maintained for 12 h before being partitioned between Et_2O (20 mL) and water (10 mL). The separated organic layer was washed with water (2×5 mL), brine (5 mL), dried ($MgSO_4$) and concentrated. Purification of the residue by flash chromatography (2% EtOAc in hexanes) gave 829 mg of **30** as a thick oil (72% over two steps, a 20:1 mixture of epimers by GLC analysis): ^{1}H NMR (500 MHz) δ 4.84 (app t, *J*=1.4 Hz, 1H), 4.82 (app s, 1H), 4.45 (dd, *J*=7.6, 4.5 Hz, 1H), 3.29 (s, 3H), 3.27 (s, 3H), 1.8–1.9 (m, 2H), 1.72 (s, 3H), 1.2–1.6 (m, 21H), 0.14 (s, 9H); ^{13}C NMR (125 MHz) 145.0, 110.6, 104.4, 85.7, 53.0, 52.4, 37.9, 37.8, 35.5, 27.7, 27.5, 27.0, 26.4, 26.3, 25.1, 23.4, 23.0, 22.0, 21.2, 3.1; IR (film) 2936, 2864, 1470, 1447, 1386, 1371, 1250, 1082, 898 cm^{-1}; MS (CI) *m/z* 385.3115 (385.3138 calcd for $C_{22}H_{45}O_3Si$, MH), 353.2859 (353.2876 calcd for $C_{21}H_{41}O_2Si$, MH−MeOH).

Separation of a 6.8 g sample of the 4:1 mixture of epimeric alcohols generated from the reaction of **27** with 2-lithiopropene at 0°C by MPLC (Lobar size C column packed with 63–125 μm Lichroprep Si 60 using 5% EtOAc–hexanes as eluent) provided a 330 mg sample of **29**, which was silylated to give **31**: ^{1}H NMR (500 MHz) 4.92 (d, *J*=0.9 Hz, 1H), 4.88 (app t, *J*=1.4 Hz, 1H), 4.59 (dd, *J*=6.9, 5.3 Hz 1H), 3.36 (s, 3H), 3.31 (s, 3H), 2.17 (app tt, *J*=14.2, 5.7 Hz, 1H), 0.8–2.0 (m, 25H), 1.76 (s, 3H), 0.10 (s, 9H);

^{13}C NMR (125 MHz) 149.4, 112.9, 105.6, 82.7, 54.1, 51.6, 36.5, 34.5, 33.7, 28.3, 26.5, 24.9, 23.0, 22.8, 22.5, 22.4, 22.2, 19.5, 2.4; IR (film) 2936, 2884, 1470, 1457, 1250 cm^{-1}; MS (CI) *m/z* 385.3123 (385.3138 calcd for $C_{22}H_{45}O_3Si$, MH), 353.2870 (353.2876 calcd for $C_{21}H_{41}O_2Si$, MH−MeOH).

4.2.2. (1*R,2*R**)-2-(2,2-Dimethoxyethyl)-1-(1-cyclohexenyl)-1-(trimethylsiloxy)cycloheptane (12).** ^{1}H NMR (500 MHz) 5.66 (app s, 1H), 4.42 (dd, *J*=8.2, 3.4 Hz, 1H), 3.32 (s, 3H), 3.21 (s, 3H), 1.2–2.1 (m, 21H), 0.09 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (125 MHz) 142.0, 120.7, 104.1, 83.9, 53.9, 50.4, 41.4, 41.3, 33.2, 30.4, 28.3, 27.6, 25.2, 25.1, 24.1, 23.3, 22.4, 2.8; IR (film) 2930, 2858, 1463, 1448, 1250 cm^{-1}; MS (CI) *m/z* 323.2349 (323.2327 calcd for $C_{19}H_{34}O_2Si$, MH−MeOH).

4.2.3. (1*R,2*R**)-2-(2,2-Dimethoxyethyl)-1-(1-cyclopentenyl)-1-(trimethylsiloxy)cycloheptane (14).** ^{1}H NMR (500 MHz) 5.53 (app s, 1H), 4.42 (dd, *J*=8.5, 3.5 Hz, 1H), 3.32 (s, 3H), 3.20 (s, 3H), 2.28–2.31 (m, 4H), 2.09 (dd, *J*=14.0, 8.6 Hz, 1H), 1.3–1.9 (m, 14H), 0.09 (s, 9H); ^{13}C NMR (125 MHz) 150.3, 124.4, 104.1, 81.9, 53.9, 50.5, 42.1, 41.2, 33.3, 32.4, 32.0, 30.4, 28.4, 27.3, 23.9, 23.3, 2.7; IR (film) 2948, 2863, 1463, 1446, 1250 cm^{-1}; MS (CI) *m/z* 341.2515 (341.2512 calcd for $C_{19}H_{37}O_3Si$, MH), 309.2267 (309.2250 calcd for $C_{18}H_{33}O_2Si$, MH−MeOH).

4.2.4. (1*R,2*R**)-2-(2,2-Dimethoxyethyl)-1-(2-propenyl)-1-(trimethylsiloxy)cycloheptane (17).** ^{1}H NMR (300 MHz) 4.95 (1H, d, *J*=2.1 Hz), 4.80 (1H, app t, *J*=1.5 Hz) 4.41 (1H, dd, *J*=3.3, 8.4 Hz), 3.31 (s, 3H), 3.24 (s, 3H), 1.74 (s, 3H), 2.11–1.20 (m, 13), 0.13 (s, 9H); ^{13}C NMR (75 MHz) 150.8, 111.6, 104.2, 84.2, 53.5, 51.2, 41.6, 41.5, 34.0, 30.8, 29.0, 28.1, 24.2, 20.7, 2.7; IR (film) 838, 887, 1010, 1055, 1091, 1021, 1364, 1390, 1457, 1639 cm^{-1}; MS (EI) *m/z* 314.2770 (314.2778 calcd for $C_{17}H_{34}O_3Si$, M).

4.2.5. (1*R,2*R**)-2-(2,2-Dimethoxyethyl)-1-[(*E*)-2-butenyl]-1-(trimethylsiloxy)cycloheptane (18).** ^{1}H NMR (500 MHz) 5.24 (q, *J*=7.3 Hz, 1H), 4.44 (dd, *J*=8.7, 3.0 Hz, 1H), 3.32 (s, 3H), 3.22 (s, 3H), 2.19 (dd, *J*=14.7, 9.1 Hz, 1H), 1.77 (d, *J*=7.5 Hz, 3H), 1.71 (s, 3H), 1.3–1.9 (m, 12H), 0.15 (s, 9H); ^{13}C NMR (125 MHz) 142.1, 120.9, 104.0, 85.6, 53.6, 50.6, 43.2, 42.3, 34.3, 30.3, 28.7, 27.4, 25.0, 24.1, 16.1, 2.8; IR (film) 2955, 2947, 2925, 1457, 1260, 1120, 838 cm^{-1}; MS (CI) *m/z* 296.2167 (296.2171 calcd for $C_{17}H_{32}O_2Si$, MH−MeOH).

4.2.6. (1*R,2*R**)-2-(2,2-Dimethoxyethyl)-1-(1-ethenyl)-1-(*tert*-butyldimethylsiloxy)cycloheptane (22).** ^{1}H NMR (500 MHz) 5.97 (dd, *J*=17.4, 11.0 Hz, 1H), 5.16 (d, *J*=17.4 Hz, 1H), 5.02 (d, *J*=11.2 Hz, 1H), 4.41 (dd, *J*=8.4, 3.2 Hz, 1H), 3.30 (s, 3H), 3.25 (s, 3H), 2.01 (dd, *J*=14.0, 9.2 Hz, 1H), 1.2–1.9 (m, 12H), 0.88 (s, 9H), 0.86 (s, 3H), 0.47 (s, 3H); ^{13}C NMR (125 MHz) 145.1, 111.8, 104.2, 80.7, 53.0, 51.7, 44.4, 41.2, 34.2, 30.4, 29.5, 27.7, 26.1, 26.0, 22.5, 18.7, −1.6, −2.0; IR (film) 2949, 3931, 2857, 1472, 1463, 1253, 1124, 1077 cm^{-1}; MS (EI) *m/z* 342.2573 (342.2590 calcd for $C_{19}H_{38}O_3Si$, M), 311.2392 (311.2406 calcd for $C_{18}H_{35}O_2Si$, M−OMe).

4.2.7. (1*R,2*R**)-2-(2,2-Dimethoxyethyl)-1-(2-propenyl)-1-(trimethylsiloxy)cyclooctane (25).** ^{1}H NMR (300 MHz) 4.89 (br s, 1H), 4.82 (br s, 1H), 4.39 (dd, 1H, *J*=8.6, 3.0 Hz), 3.31 (s, 3H), 3.30 (s, 3H), 1.94–1.24 (m, 15H), 1.74 (s, 3H), 0.14 (s, 9H); ^{13}C NMR (75 MHz) 149.8, 110.3, 104.5, 85.4, 53.0, 38.9, 36.6, 35.7, 29.7, 28.8, 26.6, 25.6, 23.6, 21.1, 3.1; IR (film) 838, 1076, 1122, 1250 cm^{-1}; MS (CI) *m/z* 297.2216 (297.2250 calculated for $C_{17}H_{33}O_2Si$, MH−MeOH).

4.3. General procedure for Prins-pinacol reaction and oxidation of the crude product

4.3.1. Synthesis of (1*R,13*S**)-1-methylbicyclo[11.3.0]-hexadecan-2,15-dione (32) and (1*R**,12*R**)-1-methylbicyclo[10.3.1]hexadecan-14,16-dione (33).** A solution of allylic silyl ether **30** (397 mg, 1.03 mmol) and CH_2Cl_2 (5 mL) was cooled to −78°C and $SnCl_4$ (1 M in CH_2Cl_2, 1.1 mL) was added dropwise. The resulting solution was maintained at −78°C for 5 min, was warmed to −23°C over 6 min and then maintained at −23°C for 5 min. The reaction was then quenched by the addition of saturated aqueous NaCl (3 mL), and the aqueous phase was separated and extracted with CH_2Cl_2 (2×5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated before being filtered through a 1 in. plug of silica gel using 25 mL of CH_2Cl_2 as eluent. Concentration gave 300 mg of an epimeric mixture of crude methoxy ketones as a colorless oil.

Following the general procedure of Sharpless,[12] a 135 mg sample of this crude residue was added to a mixture of CCl_4 (1 mL), MeCN (1 mL) and H_2O (1.5 mL) at 23°C; $NaIO_4$ (514 mg, 2.4 mmol) was then added. After stirring for 15 min, $RuCl_3{\cdot}3H_2O$ (1 mg) was added and the mixture was stirred overnight at 23°C. Additional $NaIO_4$ (514 mg, 2.4 mmol) was then added and the mixture was stirred for an additional 6 h, filtered through Celite (0.25 in. pad), dried ($MgSO_4$) and the eluent was concentrated. This residue was purified by flash chromatography (1→10% EtOAc in hexanes) to give 68 mg (55%) of the *cis* diketone **32** and 16 mg (13%) of the inside outside bridged bicyclic diketone **33**, each as crystalline solids. Both products were single spots by TLC analysis and showed no volatile impurities by capillary GLC analysis. Crystals suitable for single crystal X-ray analysis were obtained from **32** and **33** by slow evaporation of hexane solutions.

(1*R**,13*S**)-1-*Methylbicyclo*[11.3.0]*hexadecan*-2,15-*dione* (**32**). Mp 125–126°C; ^{1}H NMR (500 MHz) δ 2.88 (d, *J*=18.4 Hz, 1H), 2.82 (ddd, *J*=18.8, 10.0, 2.4 Hz, 1H), 2.37–2.44 (m, 2H), 2.14–2.25 (m, 2H), 2.01–2.05 (m, 1H), 1.87 (d, *J*=18.3 Hz, 1H), 1.40 (s, 3H), 1.0–1.5 (m, 17H); ^{13}C NMR (125 MHz) 216.7, 212.8, 55.4, 47.1, 45.7, 41.1, 36.6, 27.9, 26.3, 25.1, 24.8, 24.33, 24.28, 23.8, 23.3, 21.2; IR (CCl_4) 2924, 2863, 1751, 1709, 1550, 1460, 1407, 1012 cm^{-1}; MS (CI) *m/z* 265.2151 (265.2167 calcd for $C_{17}H_{29}O_2$, MH). Anal. calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.19; H, 10.72.

(1*R**,12*R**)-1-*Methylbicyclo*[10.3.1]*hexadecan*-14,16-*dione* (**33**). Mp 111–112°C; ^{1}H NMR (500 MHz) δ 3.16–3.22 (m, 1H), 2.96 (d, *J*=14.7 Hz, 1H), 2.64 (ddd, *J*=17.2, 6.3, 0.8 Hz, 1H), 2.38 (d, *J*=14.8 Hz, 1H), 2.23 (dd, *J*=17.1,

14.4 Hz, 1H), 2.01–2.07 (m, 1H), 1.60–1.68 (m, 1H), 1.52–1.58 (m, 2H), 1.1–1.4 (m, 16H), 1.1 (s, 3H); ^{13}C NMR (125 MHz) 216.7, 212.8, 55.4, 47.1, 45.7, 41.1, 36.6, 27.9, 26.3, 25.1, 24.8, 24.34, 24.27, 23.8, 23.3, 21.1; IR (CCl_4) 2932, 2857, 1719, 1549, 1254, 1007, 795 cm^{-1}; MS (CI) *m/z* 265.2148 (265.2167 calcd for $C_{17}H_{29}O_2$, MH). Anal. calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.26; H, 10.64.

4.3.2. (1*R,8*R**,11*S**)-Tricyclo[6.3.0.4^{1,11}]pentadecan-2,10-dione (15).** ^{1}H NMR (500 MHz) 2.91 (ddd, *J*=13.5, 8.8, 5.0 Hz, 1H), 2.85 (d, *J*=3.8 Hz, 1H), 2.76 (dd, *J*=19.5, 8.8 Hz, 1H), 2.47 (app t, 9.0 Hz, 1H), 2.30 (ddd, *J*=13.5, 8.0, 5.4 Hz, 1H), 2.20 (dd, *J*=13.7 Hz, 1H), 2.09 (dd, *J*=13.3 Hz, 1H), 1.99 (dd, *J*=19.5 Hz, 1H), 0.9–1.9 (m, 14H); ^{13}C NMR (125 MHz) 218.4, 215.4, 58.7, 47.9, 46.1, 42.5, 38.1, 33.7, 32.0, 26.7, 26.3, 24.4, 22.6, 22.4, 21.2; IR (film) 2956, 2869, 1740, 1718, 1457 cm^{-1}; MS (CI) *m/z* 221.1536 (221.1541 calcd for $C_{14}H_{21}O_2$, MH). Anal. calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 77.01; H, 9.49.

4.3.3. (1*R,8*R**,11*S**)-Tricyclo[6.3.0.3^{1,11}]tetradecan-2,10-dione (16).** ^{1}H NMR (500 MHz) 3.12 (app d, *J*=9.4 Hz, 1H), 2.87 (m, 1H), 2.57 (m, 2H), 2.46 (dd, *J*=17.7, 7.4 Hz, 1H), 2.34 (app dt, *J*=13.8, 5.8 Hz, 1H), 2.18 (ddd, *J*=17.7, 5.9, 1.7 Hz, 1H) 1.4–2.1 (m, 13H); ^{13}C NMR (125 MHz) 220.1, 215.3, 67.6, 52.9, 46.0, 43.2, 38.7, 36.1, 32.5, 29.4, 27.6, 25.2, 23.5; IR (film) 2956, 2869, 1740, 1718, 1457 cm^{-1}; MS (CI) *m/z* 221.1536 (221.1541 calcd for $C_{14}H_{21}O_2$, MH). Anal. calcd for $C_{14}H_{20}O_2$: C, 77.22; H, 10.67. Found: C, 77.16; H, 10.71.

4.3.4. (1*R,8*R**)-1-Methylbicyclo[6.3.0]undecan-2,10-dione (19).** ^{1}H NMR (500 MHz) 2.89 (ddd, *J*=13.9, 9.1, 4.6 Hz, 1H), 2.87 (d, *J*=17.9 Hz, 1H), 2.5–2.7 (m, 2H), 2.29 (ddd, *J*=13.5, 7.7, 4.7 Hz, 1H), 2.04 (app d, *J*=15.8 Hz, 1H), 1.95 (d, *J*=18.1 Hz, 1H), 1.8–2.0 (m, 2H), 1.4–1.7 (m, 6H), 1.37 (s, 3H); ^{13}C NMR (125 MHz) 216.7, 216.0, 55.2, 45.8, 45.4, 45.1, 37.8, 32.2, 27.2, 25.2, 24.1, 24.0; IR (film) 2931, 2863, 1744, 1705, 1694, 1457 cm^{-1}; MS (EI) *m/z* 195.1386 (195.1385 calcd for $C_{12}H_{19}O_2$, MH). Anal. calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.39; H, 9.42.

4.3.5. (1*R,8*R**,11*R**)-1,11-Dimethylbicyclo[6.3.0]undecan-2,10-dione (20).** ^{1}H NMR (500 MHz) 2.8–2.9 (m, 2H), 2.64 (dd, *J*=19.0, 8.6 Hz, 1H), 2.55 (app dt, *J*=16.1, 7.8 Hz, 1H), 3.31 (app dt, *J*=13.6, 6.9 Hz, 1H), 2.00 (d, *J*=19.0 Hz), 1.89 (app dt, *J*=12.5, 6.1 Hz, 2H), 1.4–1.7 (m, 6H), 1.17 (s, 3H), 0.99 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz) 218.9, 215.2, 57.6, 46.7, 45.6, 43.3, 38.0, 33.8, 26.5, 26.1, 24.9, 19.2, 9.1; IR (film) 2934, 2863, 1741, 1700, 1461, 1406, 1222 cm^{-1}; MS (EI) *m/z* 209.1541 (209.1541 calcd for $C_{13}H_{21}O_2$, MH). Anal. calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.03; H, 9.59.

4.3.6. (1*R,8*S**)-Bicyclo[6.3.0]undecan-2,10-dione (24).** ^{1}H NMR (500 MHz) 2.18 (ddd, *J*=13.5, 8.8, 5.0 Hz, 1H), 2.85 (d, *J*=3.8 Hz, 1H), 2.76 (dd, *J*=19.5, 8.8 Hz, 1H), 2.47 (app t, 9.0 Hz, 1H), 2.30 (ddd, *J*=13.5, 8.0, 5.4 Hz, 1H), 2.20 (dd, *J*=13.7 Hz, 1H), 2.09 (dd, *J*=13.3 Hz, 1H), 1.99 (dd, *J*=19.5 Hz, 1H), 0.9–1.9 (m, 14H); ^{13}C NMR (125 MHz) 216.6, 216.5, 47.2, 44.9, 43.0, 41.7, 41.5, 29.9, 28.7, 25.1, 24.3; IR (film) 2956, 2869, 1740, 1718, 1457 cm^{-1}; MS (EI) *m/z* 181.1231 (181.1309 calcd for $C_{11}H_{17}O_2$, MH).

4.3.7. (1*R,9*S**)-1-Methylbicyclo[7.3.0]dodecan-2,15-dione (26).** Crystals suitable for single crystal X-ray analysis were obtained by slow evaporation from hexane: mp 65.5–66.0°C; ^{1}H NMR (300 MHz) 3.07 (ddd, *J*=18.6, 11.7, 3.1 Hz, 1H), 2.88 (d, 18.6 Hz, 1H), 2.57 (dd, *J*=18.4, 7.8 Hz, 1H), 2.31–2.40 (m, 2H), 2.01–2.08 (m, 1H), 1.86 (d, 18.6 Hz, 1H), 1.38 (s, 3H), 1.0–1.5 (m, 10H); ^{13}C NMR (75 MHz) 214.7, 217.1, 65.8, 45.3, 43.4, 35.7, 29.6, 28.0, 25.7, 23.1, 23.0, 21.7, 15.2; IR (film) 2925, 2852, 1744, 1695, 1474, 1465, 1407, 1143 cm^{-1}; MS (CI) *m/z* 209.1447 (209.1541 calcd for $C_{13}H_{21}O_2$, MH). Anal. calcd for $C_{13}H_{20}O_2$: C, 74.76; H, 9.68. Found: C, 74.97; H, 9.66.

4.3.8. (1*R,13*R**)-1-Methylbicyclo[11.3.0]hexadecan-2,15-dione (34).** Crystals suitable for single crystal X-ray analysis were obtained by slow evaporation from hexane: mp 129–130°C; ^{1}H NMR (500 MHz) 3.03 (d, *J*=17.9 Hz, 1H), 2.82 (ddd, *J*=8.4, 18.7 Hz, 1H), 2.46 (ddd, *J*=18.4, 7.0, 3.1 Hz, 1H), 2.22–2.32 (m, 1H), 2.05 (d, *J*=17.8 Hz, 1H), 1.89–1.99 (m, 2H), 1.24 (s, 3H, CH_3), 1.2–1.4 (m, 17H); ^{13}C NMR (125 MHz) 216.3, 213.3, 54.7, 51.2, 43.9, 42.0, 37.3, 27.5, 26.35, 26.27, 25.12, 24.9, 24.61, 24.60, 23.2, 21.8, 16.0; IR (CCl_4) 2934, 2863, 1741, 1700, 1461, 1406, 1226 cm^{-1}; MS (CI) *m/z* 265.2158 (265.2167 calcd for $C_{17}H_{29}O_2$, MH). Anal. calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.04; H, 10.69.

4.3.9. (2*R,3*S**)-1,1-(Dimethoxy)-3,5-dimethyl-4-ethyl-4-(trimethylsiloxy)-5-hexene (35) and (2*R**,3*R**)-1,1-(dimethoxy)-3,5-dimethyl-4-ethyl-4-(trimethylsiloxy)-5-hexene (38).** The mixture of hexenyl siloxy acetals was separated by HPLC (5% EtOAc in hexanes, Supelco column packed with Supelcosil LC-Si semiprep silica gel) to give pure samples of both epimers as clear oils. Both compounds were single spots by TLC analysis and showed no volatile impurities by GLC analysis. Compound **35**. ^{1}H NMR (500 MHz) 4.95 (d, *J*=2.3 Hz, 1H), 4.89 (app t, *J*=1.0 Hz, 1H), 4.39 (dd, *J*=8.0, 3.6 Hz, 1H), 3.30 (s, 3H), 3.27 (s, 3H), 1.4–1.8 (m, 7H), 1.1–1.2 (m, 1H), 0.94 (d, *J*=6.7 Hz, 3H), 0.77 (t, *J*=7.4 Hz, 3H), 0.14 (s, 9H); ^{13}C NMR (125 MHz) 147.3, 112.4, 104.0, 85.4, 53.1, 52.1, 36.0, 34.4, 28.7, 20.1, 14.0, 8.7, 2.6; IR (film) 2966, 2830, 1456, 1382, 1251 cm^{-1}; MS (CI) *m/z* 289.2204 (289.2199 calcd for $C_{15}H_{33}O_3Si$, MH), 257.1935 (257.1937 calcd for $C_{14}H_{29}O_2Si$, MH−MeOH). Compound **38**. ^{1}H NMR (500 MHz) 4.91 (d, *J*=2.3 Hz, 1H), 4.87 (d, *J*=1.3 Hz, 1H), 4.45 (dd, *J*=8.2, 3.5 Hz, 1H), 3.33 (s, 3H), 3.31 (s, 3H), 1.9–2.0 (m, 1H), 1.60 (s, 3H), 1.1–1.8 (m, 4H), 0.76–0.81 (m, 6H), 0.14 (s, 9H); ^{13}C NMR (125 MHz) 147.5, 112.6, 104.3, 85.3, 52.9, 52.4, 36.5, 34.1, 26.9, 20.3, 14.7, 8.7, 2.7; IR (film) 2971, 2830, 1450, 1378, 1250 cm^{-1}; MS (CI) *m/z* 289.2200 (289.2199 calcd for $C_{15}H_{33}O_3Si$, MH), 257.1934 (257.1937 calcd for $C_{14}H_{29}O_2Si$, MH−MeOH).

4.3.10. Preparation of (4*R,5*S**)-dihydro-5-ethyl-4-methyl-5-(2-propyl)-2(3*H*)-furanone (40) from 38.** A solution of allylic silyl ether **38** (18 mg, 0.062 mmol) and EtOAc (2 mL) was stirred over palladium on carbon (5 mg, Pd content 1%) under an atmosphere of hydrogen for 18 h. The reaction mixture was then filtered through a 0.5 in. plug

of silica gel using 30 mL of EtOAc as eluent. Concentration afforded 16 mg of the crude hydrogenation product. This sample was dissolved in acetone (3 mL) and H_2O (3 mL), 250 mg of Amberlyst-15 acidic resin was added and the mixture was heated at reflux (ca. 85°C) for 1 h. After allowing the reaction to cool to 23°C, the mixture was filtered and the filtrate was extracted with EtOAc (3×15 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and concentrated to give 11.6 mg of a mixture of lactols. Pyridinium chlorochromate (PCC, 20 mg, 0.093 mmol) was added to a solution of these crude lactols and CH_2Cl_2 (3 mL). The resulting mixture was stirred for 1.5 h at 23°C before being diluted with Et_2O (20 mL). This mixture was filtered through Celite (0.25*in. pad) and the filtrate was concentrated. Purification of the residue by flash chromatography (20% EtOAc in hexanes) provided 10 mg (87%) of lactone **40** as a clear oil, which was a single spot by TLC analysis and showed no volatile impurities by GLC analysis: ^{1}H NMR (500 MHz) 2.5–2.7 (m, 2H), 2.1–2.3 (m, 2H), 1.6–1.8 (m, 2H), 1.11 (d, J=6.7 Hz, 3H), 0.98 (t, J=7.4 Hz, 3H), 0.93 (t, J=7.1 Hz, 6H); ^{13}C NMR (125 MHz) 176.2, 92.7, 38.0, 33.3, 32.7, 24.8, 17.4, 16.4, 16.2, 7.6; IR (film) 2971, 2926, 1771, 1283, 1239 cm^{-1}; MS (CI) *m/z* 171.1375 (171.1385 calcd for $C_{10}H_{19}O_2$, MH).

4.3.11. (4*R,5*R**)-Dihydro-5-ethyl-4-methyl-5-(2-propyl)-2(3*H*)-furanone (36).** ^{1}H NMR (500 MHz) 2.68 (dd, J=17.6, 9.2 Hz, 1H), 2.53 (m, 1H), 2.28 (dd, J=17.6, 9.5 Hz, 1H), 2.06 (m, 1H), 1.74 (m, 2H), 1.15 (d, J=7.1 Hz, 3H), 1.00 (d, J=6.8 Hz, 3H), 0.96 (d, J=6.8 Hz, 3H), 0.92 (t, J=7.6 Hz, 3H); ^{13}C NMR (125 MHz) 176.6, 92.2, 38.2, 37.3, 31.2, 29.0, 18.0, 15.5, 7.9; IR (film) 2971, 2886, 1772, 1468, 1251 cm^{-1}; MS (CI) *m/z* 171.1374 (171.1385 calcd for $C_{10}H_{19}O_2$, MH).

4.3.12. (3*R,4*R**)-3,4-Dimethyl-3-(1-oxopropyl)cyclopentanone (37).** ^{1}H NMR (500 MHz) 2.66 (d, J=18.1 Hz, 1H), 2.53 (m, 3H), 2.43 (dd, J=18.9, 8.2 Hz, 1H), 2.13 (d, J=17.8 Hz, 1H), 1.95 (ddd, J=18.8, 9.9, 1.2 Hz, 1H), 1.20 (s, 3H), 1.05 (t, J=7.2 Hz, 3H), 1.03 (d, J=6.9 Hz, 3H); ^{13}C NMR (125 MHz) 215.8, 213.4, 54.2, 50.0, 44.1, 36.2, 31.3, 16.9, 15.2, 8.1; IR (film) 2972, 2910, 1744, 1702, 1457, 1406, 1375, 1243 cm^{-1}; MS (CI) *m/z* 169.1235 (169.1228 calcd for $C_{10}H_{17}O_2$, MH). Anal. calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.23; H, 9.62.

4.3.13. (3*R,4*S**)-3,4-Dimethyl-3-(1-oxopropyl)cyclopentanone (39).** ^{1}H NMR (500 MHz) 2.81 (d, J=18.3 Hz, 1H), 2.4–2.6 (m, 3H), 2.32 (m, 1H) 2.07 (dd, J=19.0, 6.8 Hz, 1H), 1.92 (d, J=18.3 Hz, 1H), 1.41 (s, 3H), 1.05 (t, J=7.2 Hz, 3H), 0.94 (d, J=7.1 Hz, 3H); ^{13}C NMR (125 MHz) 216.4, 213.9, 54.8, 47.6, 44.4, 40.7, 32.7, 23.0, 16.4, 7.4; IR (film) 2988, 1744, 1702, 1460, 1407 cm^{-1}; MS (CI) *m/z* (169.1228 calcd for $C_{10}H_{17}O_2$, MH). Anal. calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.33; H, 9.69.

4.3.14. Preparation of (3*R,4*S**)-3,4-dimethyl-3-(1-oxopropyl)cyclopentanol phenylurethane (41).** A solution of dione **39** (69 mg, 0.37 mmol) and THF (2 mL) was cooled to −78°C and KS-selectride (370 μL, 0.37 mmol) was added. The resulting solution was allowed to warm to 23°C and after 4 h, MeOH (0.5 mL), 1N NaOH (0.5 mL) and 30% aqueous H_2O_2 (0.5 mL) were added. After stirring the resulting mixture for 15 min, the organic layer was separated and the aqueous layer extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated to afford 68 mg of a 3:1 mixture of alcohol epimers (by GLC analysis). The major epimer (34 mg, 49%) was isolated by HPLC (40% EtOAc in hexanes, Supelco column packed with Supelcosil LC-Si semiprep silica gel).

This alcohol (18 mg, 0.11 mmol), CH_2Cl_2 (1 mL) and phenylisocyanate (12 μL, 0.11 mmol) were combined and heated at reflux for 12 h. The solution was cooled and the crystalline product was collected by filtration. Recrystallization by slow evaporation of a $CHCl_3$ solution resulted in X-ray quality crystals of phenylurethane **41** (11 mg, 36%): mp 129–130°C; ^{1}H NMR (500 MHz) 7.0–7.5 (m, 5H, C_6H_5), 6.60 (brs, 1H), 5.39 (m, 1H), 2.8 (dd, J=14.2, 7.9 Hz, 1H), 2.4–2.6 (m, 2H), 2.1–2.2 (m, 1H), 1.9–2.0 (m, 2H), 1.55 (dd, J=14.2, 2.9 Hz, 1H), 1.42 (s, 3H), 1.05 (t, J=6.9 Hz, 3H), 0.91 (d, J=6.7 Hz, 3H); ^{13}C NMR (125 MHz) 215.0, 153.2, 138.0, 129.0, 123.3, 118.7, 76.5, 57.5, 44.1, 43.2, 40.5, 33.3, 24.2, 15.6, 7.6; IR (film) 3419, 2960, 2875, 1719, 1683, 1532, 1464, 1445, 1222 cm^{-1}; MS (CI) *m/z* 288.1482 (288.1600 calcd for $C_{10}H_{19}O_2$, MH).

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