Noncascade Tandem Transformations Involving Allylic Silanes. 1. Pericyclic and Ionic Reactions Combined into "One-Pot" Sequences

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Received October 29, 1996

Tandem reaction methodology is a powerful approach to rapid buildup of molecular complexity from potentially simple starting materials. Noncascade tandem reactions are those operations that involve sequential addition of reagents to some starting material, and these reagents become incorporated into the final product.[1] The development of sequences that combine transformations of differing fundamental mechanism broadens the scope of such procedures in synthetic chemistry. We have focused on silicon moieties as central functionalities in this chemistry because silicon can support a range of reactions including those of anionic,[2,3] cationic,[2,4] and radical reaction mechanism.[2,5]

Both 1- and 2-[(trialkylsilyl)methyl)] 1,3-dienes are known to undergo Diels−Alder cycloaddition with a range of electron-deficient olefins.[6] The same electrophiles react with the corresponding stannane to give the products of electrophilic substitution.[7] This has been attributed to the increased ionic character and, therefore, heightened reactivity of the tin−carbon bond relative to the silane.[7,8] Therefore, 2-[(trialkylsilyl)methyl)] 1,3-dienes can be used in multireaction sequences that maintain the silicon moiety in earlier steps because the metal component is stable and can tolerate a range of reaction conditions before it is activated *selectively*.[8] We have combined pericyclic and electrophilic substitution reactions involving allylsilanes that can be promoted with one catalyst in one reaction flask.

Reaction of dienes **1a** and **1b** (Scheme 1) with a variety of dienophile partners and Lewis acids has been investigated to probe aspects of regioselectivity, catalyst reactivity, and silane stability during cycloaddition. The data are summarized in Table 1.[9]

Electrophilic substitutions have been conducted on the resultant intermediate allylsilane cycloaddition products **3** (see Scheme 2 and Table 2).[10] Unless stated otherwise, 1.1 equiv of **5** was used relative to **3** for comparison sake between runs.

The reactions were then combined tandemly (Scheme 3), and the data are summarized in Table 3. Like the independent runs, the ratios of **1**, **2**, and **5** are 1:1:1.1 unless stated otherwise. When the Diels−Alder reaction was judged complete by TLC analysis, the electrophile was added followed by the catalyst solution.

A series of ^{1}H NMR spectroscopic experiments on reaction mixtures has provided insight into the different yields seen in these reactions. Protodesilylation of **3** is the principal cause for reduced yields in both reactions. Purified adducts **3** were protodesilylated to provide **4** in the presence of 20% $TiCl_4$ in CD_2Cl_2 over a 4−5 day period. Diels−Alder experiments with stoichiometric or catalytic $TiCl_4$ reveal that very little protodesilylation occurs on the time scale (10 min to 1 h) during which **3** is formed. However, quenching of these NMR study reactions with saturated NH_4Cl resulted in over 50% conversion of **3** to **4**. These results suggest that even a trace amount of acid in the presence of $TiCl_4$ is very detrimental to product recovery. Experiments using Me_2AlCl (Table 1, entries 2 and 6−8), which can only be a Lewis acid and never a Brønsted acid,[11] provided high yields of cycloadduct with no protodesilylation.

More useful information regarding yield came from ^{1}H NMR spectroscopic analysis of the reactions in Schemes 2 and 3. Diels−Alder runs using Me_2AlCl catalysis are almost quantitative (see Table 1, entries 6−8), but the electrophilic substitutions on the resultant cycloadducts using $TiCl_4$ catalysis, i.e., method A, were of moderate yield (see Table 2). Inspection of entries 7, 11, and 6 in Tables 1−3, respectively, reveals that the overall yield of the reactions performed independently is 53%, whereas the tandem yield is 75%. This same trend is seen in tandem runs with other diene, dienophile, and electrophile reaction partners. The only difference should be the presence of Me_2AlCl, which is in the tandem run, but not in the independent electrophilic substitution. Substitution reactions containing Me_2AlCl, i.e., method B,

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(9) All compounds in this study have been fully characterized by ^{1}H NMR, ^{13}C NMR, infrared, and mass spectroscopy. Each compound has been checked for accurate mass and/or elemental analysis.

(10) The structure of the *cis* and *trans* isomers from the electrophilic substitution reaction, i.e., **6** and **7**, has been determined by a combination of X-ray structural data and chemical derivatization. The details of structural determination will be revealed in due course.

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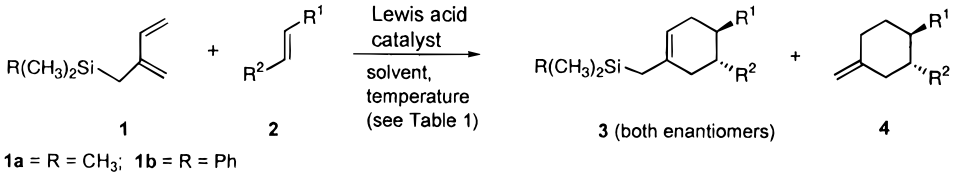
S0022-3263(96)02025-7 CCC: $14.00

Table 1. Diels–Alder Cycloaddition between 1 and Various Dienophiles

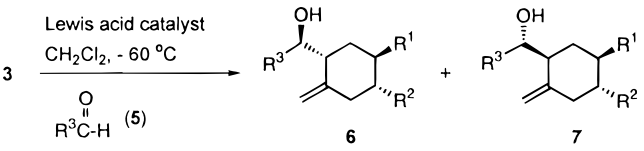
entry	product	R	R^1	R^2	catalyst[a]	T (°C)	solvent	yield[b] (%)
1	3a	$-CH_3$	$-CO_2CH_3$	H	$AlCl_3$	40	CH_2Cl_2	38[c]
2	3a	$-CH_3$	$-CO_2CH_3$	H	Me_2AlCl	40	CH_2Cl_2	88
3	3a	$-CH_3$	$-CO_2CH_3$	H	$EtAlCl_2$	40	CH_2Cl_2	52
4	3a	$-CH_3$	$-CO_2CH_3$	H	$BF_3{\cdot}OEt_2$	40	CH_2Cl_2	15
5	3a	$-CH_3$	$-CO_2CH_3$	H	$TiCl_4$	40	CH_2Cl_2	38[d]
6	3b	$-Ph$	$-CO_2CH_3$	H	Me_2AlCl	40	CH_2Cl_2	84
7	3c	$-Ph$	$-COCH_3$	H	Me_2AlCl	rt	CH_2Cl_2	97
8	3d	$-Ph$	$-COCH_2CH_3$	$-CH_3$	Me_2AlCl	rt	CH_2Cl_2	95

[a] 20% catalyst was used relative to **1**. [b] All reported yields are based on purified material following silica gel chromatography. [c] 35% of **4** was also formed. [d] 36% of **4** was also formed.

Scheme 1



Scheme 2



are significantly higher yielding. This can be seen in entries 6 vs 7, 9 vs 10, 12 vs 13, and 14 vs 15 in Table 2. This is seen again in the tandem run without Me_2AlCl (Table 3, entry 4) where the yield is 59%, compared to 66% (Table 3, entry 5) with the cocatalyst. $TiCl_4$ is extremely difficult to obtain "proton free", but it can be cleaned *in situ*, and we believe that Me_2AlCl is serving as a proton sponge in these reactions.[11] Therefore, our reactions do not require the second catalyst per se, only a proton-free catalyst source. We are continuing to pursue other means of purifying $TiCl_4$ to alleviate the acid problem.

In each parallel study, the tandem reaction provided a higher yield of the final product than the nontandem sequence. These results demonstrate that reaction workups and purifications can substantially reduce yield and lower synthetic efficiency. In one net process, three new bonds have been formed, leading to the formation of one ring with good diastereoselectivity, providing useful, well-functionalized synthetic intermediates. We have reason to believe that **6**, the products of axial addition,[12] are formed almost exclusively during the electrophilic substitution reaction. $TiCl_4$-catalyzed isomerization at the position on the ring adjacent to the carbonyl group following substitution results in formation of the diequatorial isomer **7**.[10] This has been confirmed by electrophilic substitution studies on cycloadducts possessing a group at the same position as **3c**, but lacking the carbonyl moiety. In these cases, only the axial substitution product (i.e., *trans*) is isolated. We are continuing to examine the cause of this epimerization and how to prevent it from occurring. Further, this sequence has allowed for the regiospecific formation of a 1,2,4-tri- and 1,2,4,5-tetrasubstituted cyclohexane structures. Were the diene 2,3-disubstituted to begin, the regioselectivity in the cycloaddition would not have been as controllable. When the substitution step was performed with excess aldehyde relative to the control experiments (see Table 2, entries 7 vs 8, and Table 3, entries 2 vs 3), substantial improvement in yield was observed, indicating that these sequences are synthetically useful.

An "ideal" mechanistically-diverse tandem sequence would be one where all reagents can simply be combined and all reactions take place in the desired order with no side products being formed. Such selectivity would be based on the kinetic reactivities of the transformations themselves. To this end we attempted such a sequence by adding together propionaldehyde, a highly reactive electrophile, methyl vinyl ketone, **1b**, and Me_2AlCl. This diene possesses an allylsilane moiety and has itself been used in allylic substitution reactions under nearly the same reaction conditions.[6] The desired Diels–Alder reaction proceeded uneventfully, and when it was judged complete by TLC analysis, $TiCl_4$ was added and the desired electrophilic substitution with **3c** took place, providing **6d** and **7d** in 40% combined yield. Although this result is not optimized, it further demonstrates the reliability of allylsilanes as partners in such tandem reactions.

In summary, there is an improvement in overall yield for tandem sequences involving allylsilanes in Diels–Alder cycloaddition and allylic substitution reactions compared to performing these transformations separately. There is no loss in regio- or stereoselectivity in these tandem sequences. Product handling and time have been reduced significantly and waste generated from the overall sequence of reactions has been cut in half by combining the steps tandemly. Thus, the methodology represents an efficient route to the production of polysubstituted cyclohexane derivatives. The use of chiral auxiliaries or chiral catalysts during the Diels–Alder reaction offers the ability to produce optically enhanced products from the overall sequence.[13] Further, we are currently developing this methodology toward the synthesis of pyran-, pyridine-, and piperidine-based heterocycles. This methodology may have direct ap-

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Table 2. Electrophilic Substitution Reactions with 3

entry	products	R	R^1	R^2	R^3	catalyst[a]	yield[d] (%)/**6**:**7**
1	**6a** and **7a**	$-CH_3$	$-CO_2CH_3$	H	$-CH_2CH_3$	$AlCl_3$	40[c]/4:1
2	**6a** and **7a**	$-CH_3$	$-CO_2CH_3$	H	$-CH_2CH_3$	Me_2AlCl	no reaction
3	**6a** and **7a**	$-CH_3$	$-CO_2CH_3$	H	$-CH_2CH_3$	$BF_3{\cdot}OEt_2$	trace
4	**6a** and **7a**	$-CH_3$	$-CO_2CH_3$	H	$-CH_2CH_3$	$TiCl_4$[b]	60[e]/4.4:1
5	**6a** and **7a**	−Ph	$-CO_2CH_3$	H	$-CH_2CH_3$	$TiCl_4$[b]	61[e]/4.3:1
6	**6b** and **7b**	−Ph	$-CO_2CH_3$	H	$-CH(CH_3)_2$	$TiCl_4$[b]	60[e]/1.1:1
7	**6b** and **7b**	−Ph	$-CO_2CH_3$	H	$-CH(CH_3)_2$	$Me_2AlCl/TiCl_4$[c]	70/1.3:1
8	**6b** and **7b**	−Ph	$-CO_2CH_3$	H	$-CH(CH_3)_2$	$Me_2AlCl/TiCl_4$[c]	82[f]/2:1
9	**6c** and **7c**	−Ph	$-CO_2CH_3$	H	$-CH_2CH_2Ph$	$TiCl_4$[b]	54[e]/5.8:1
10	**6c** and **7c**	−Ph	$-CO_2CH_3$	H	$-CH_2CH_2Ph$	$Me_2AlCl/TiCl_4$[c]	76/7.4:1
11	**6d** and **7d**	−Ph	$-COCH_3$	H	$-CH_2CH_3$	$TiCl_4$[b]	55[e]/3:1
12	**6e** and **7e**	−Ph	$-COCH_3$	H	$-CH_2CH_2Ph$	$TiCl_4$[b]	53[e]/4.4:1
13	**6e** and **7e**	−Ph	$-COCH_3$	H	$-CH_2CH_2Ph$	$Me_2AlCl/TiCl_4$[c]	62/4.4:1
14	**6f** and **7f**	−Ph	$-COCH_3$	H	$-CH(CH_3)_2$	$TiCl_4$[b]	54/2.3:1
15	**6f** and **7f**	−Ph	$-COCH_3$	H	$-CH(CH_3)_2$	$Me_2AlCl/TiCl_4$[c]	69/1.8:1
16	**6g** and **7g**	−Ph	$-COCH_2CH_3$	$-CH_3$	$-CH_2CH_3$	$Me_2AlCl/TiCl_4$[c]	65/4.6:1
17	**6h** and **7h**	−Ph	$-COCH_2CH_3$	$-CH_3$	$-CH(CH_3)_2$	$Me_2AlCl/TiCl_4$[c]	53/*trans* only

[a] One full equivalent of active catalyst is used in these reactions. [b] Method A: solution of aldehyde and **3** in CH_2Cl_2 is cooled to −60 °C and $TiCl_4$ is added dropwise. [c] Method B: A solution of dimethylaluminum chloride (0.2 equiv) and $TiCl_4$ (1.0 equiv) in CH_2Cl_2 is cooled to −60 °C and then added to a second flask containing **3**, the aldehyde, and 0.2 equiv of Me_2AlCl, also at −60 °C. [d] All reported yields are based on purified material following silica gel chromatography. [e] Up to 20% of the desilylated compound **4** is obtained in addition to the substitution products **6** and **7**. [f] Two equivalents of the aldehyde was used.

Scheme 3

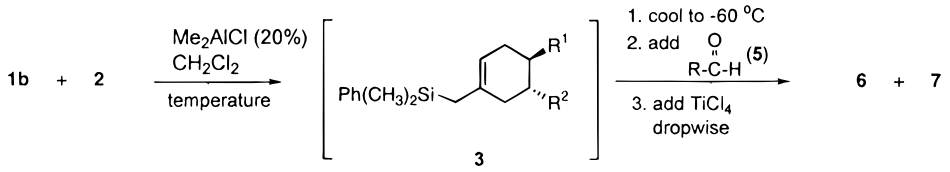

Table 3. Tandem Diels−Alder Cycloaddition/Electrophilic Substitution Sequence

entry	product	R^1	R^2	Diels−Alder temp (°C)	R	yield[a] (%)/**6**:**7**
1	**6a** and **7a**	$-CO_2CH_3$	H	40	$-CH_2CH_3$	73/4.3:1
2	**6b** and **7b**	$-CO_2CH_3$	H	40	$-CH(CH_3)_2$	41/2:1
3	**6b** and **7b**	$-CO_2CH_3$	H	40	$-CH(CH_3)_2$	66[b]/2:1
4	**6c** and **7c**	$-CO_2CH_3$	H	40	$-(CH_2)_2Ph$	59[c]/7:1
5	**6c** and **7c**	$-CO_2CH_3$	H	40	$-(CH_2)_2Ph$	66/7:1
6	**6d** and **7d**	$-COCH_3$	H	rt	$-CH_2CH_3$	75/3:1
7	**6e** and **7e**	$-COCH_3$	H	rt	$-(CH_2)_2Ph$	56/4.2:1
8	**6f** and **7f**	$-COCH_3$	H	rt	$-CH(CH_3)_2$	51/2.1:1
9	**6f** and **7f**	$-COCH_3$	H	rt	$-CH(CH_3)_2$	57[b]/3.1:1
10	**6g** and **7g**	$-COCH_2CH_3$	$-CH_3$	rt	$-CH_2CH_3$	64/2.8:1
11	**6h** and **7h**	$-COCH_2CH_3$	$-CH_3$	rt	$-CH(CH_3)_2$	40/*trans* only

[a] All reported yields are based on purified material following silica gel chromatography. [b] Two equiv of the aldehyde was used in the second step of the sequence. [c] One equiv of $TiCl_4$ was used in the first step with no Me_2AlCl followed by addition of the aldehyde upon complete formation of **3b**.

plicability to combinatorial synthesis of medicinally important molecules.

Experimental Section

General Procedure. All reactions were carried out under a positive atmosphere of dry argon. Solvents were distilled prior to use: Et_2O was distilled from sodium benzophenone ketyl; CH_2Cl_2 was distilled from CaH_2. Melting points are uncorrected. ^1H NMR spectra were recorded in $CDCl_3$ at 300 MHz. ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$. Chemical shifts are listed relative to $CHCl_3$ (δ 7.24) for ^1H NMR and (δ 77.00) for ^{13}C NMR. Diene **1a** was prepared using literature procedures.[6] Spectral data for allylsilane **3a** correspond to that previously published.[6]

2-[(Dimethylphenylsilyl)methyl]-1,3-butadiene (1b). To a flask was added 1.45 g of magnesium turnings (59.5 mmol) and a stir bar. The flask was flame dried under vacuum and purged with argon. Five mL of dry ether was added along with dropwise addition of 10.0 g of (chloromethyl)dimethylphenylsilane (54.1 mmol). Upon initiation of the reaction, the flask was cooled in an ice bath, and additional ether was added (40 mL total). Following complete addition of the (chloromethyl)-dimethylphenylsilane, the solution was heated to reflux for 4 h. In a separate flame-dried flask equipped with a stir bar was added 7.2 g of 2-chloro-1,3-butadiene (81.2 mmol), 1.1 g of [1,3-bis(diphenylphosphino)propane]dichloronickel (2.0 mmol), and 40 mL of dry ether. This orange solution was then cooled to 0 °C. The Grignard solution was cooled to 0 °C, added dropwise by cannula to the 2-chloro-1,3-butadiene solution, and refluxed for 5 h. The yellow slurry was cooled to rt, quenched slowly with saturated $NaHCO_3$, extracted with ether, and washed with water, and the organic layer was dried with $MgSO_4$. Following solvent removal *in vacuo*, the product was purified by flash chromatography (hexanes), providing 10.6 g of diene **1b** as a clear, colorless liquid (97%): IR (thin film) 3089, 3070 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.54−7.49 (m, 2 H), 7.38−7.31 (m, 3 H), 6.35 (dd, J = 17.6, 11.0 Hz, 1 H), 5.07 (d, J = 17.7 Hz, 1 H), 5.00 (d, J = 11.0 Hz, 1 H), 4.90 (s, 1 H), 4.75 (s, 1 H), 1.93 (s, 2 H), 0.26 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz, APT pulse sequence—evens up (+), odds down (−)) δ 143.5 (+), 139.8 (−), 139.1 (+), 133.6 (−), 128.9 (−), 127.7 (−), 114.9 (+), 113.8 (+), 20.3 (+), −2.8(−); HRMS calcd for $C_{13}H_{18}Si$ ($M^+ + H$) 203.1257, found 203.1251.

Methyl 4-[(Dimethylphenylsilyl)methyl]-3-cyclohexenecarboxylate (3b). To a flame-dried flask equipped with a stir bar was added 7 mL of dry CH_2Cl_2, 197 mg of **1b** (0.97 mmol), and 168 mg of methyl acrylate (1.95 mmol), and this was

followed by dropwise addition of dimethylaluminum chloride (195 μL of a 1 M solution, 0.20 mmol). The mixture was heated to reflux for 4.5 h, cooled to rt, and quenched with saturated $NaHCO_3$. The mixture was extracted with ether and washed with water, and the organic layer was dried over $MgSO_4$. Following solvent removal *in vacuo*, the product was purified by flash chromatography (5% ether in hexanes), providing 235 mg of allylsilane **3b** as a clear colorless liquid (84%). IR (thin film): 3070, 3001, 1737 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.54−7.47 (m, 2 H), 7.38−7.32 (m, 3 H), 5.21 (br s, 1 H), 3.67 (s, 3 H), 2.51−2.40 (m, 1 H), 2.27−2.20 (m, 2 H), 1.94−1.78 (m, 3 H), 1.66 (s, 2 H), 1.71−1.57 (m, 1 H), 0.30 (s, 3 H), 0.29 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz, APT pulse sequence—evens up (+), odds down (−)) δ 176.5 (+), 139.2 (+), 134.6 (+), 133.5 (−), 128.9 (−), 127.7 (−), 117.6 (−), 51.6 (−), 39.2 (−), 30.2 (+), 27.8 (+), 26.7 (+), 25.6 (+), −2.8 (−); HRMS calcd for $C_{17}H_{24}O_2Si$ 288.1546, found 288.1553.

1-Acetyl-4-[(dimethylphenylsilyl)methyl]-3-cyclohexene (3c). To a flame-dried flask equipped with a stir bar was added 5 mL of dry CH_2Cl_2, 100 mg of **1b** (0.49 mmol), 35 mg of methyl vinyl ketone (0.49 mmol), and dimethylaluminum chloride (100 μL of a 1 M solution, 0.10 mmol, added dropwise). The mixture was stirred at rt for 3 h, quenched with saturated $NaHCO_3$, extracted with ether, and washed with water, and the organic layer was dried over $MgSO_4$. Following solvent removal *in vacuo*, the product was purified by flash chromatography (7% ether in hexanes), providing 131 mg of allylsilane **3c** as a clear colorless liquid (97%): IR (thin film) 3069, 3001, 1713 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.51−7.45 (m, 2 H), 7.36−7.30 (m, 3 H), 5.20 (br s, 1 H), 2.50−2.39 (m, 1 H), 2.17−2.10 (m, 2 H), 2.13 (s, 3 H), 1.90−1.78 (m, 3 H), 1.64 (s, 2 H), 1.56−1.41 (m, 1 H), 0.28 (s, 3 H), 0.27 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz, APT pulse sequence—evens up (+), odds down (−)) δ 211.5 (+), 138.9 (+), 134.5 (+), 133.4 (−), 128.8 (−), 127.5 (−), 117.5 (−), 47.0 (−), 30.3 (+), 27.8 (−), 27.1 (+), 26.5 (+), 24.8 (+), −2.9 (−) (2 coincident); HRMS calcd for $C_{17}H_{24}OSi$ 272.1597, found 272.1595.

***trans*-4-[(Dimethylphenylsilyl)methyl]-2-methyl-1-(1-oxopropyl)-4-cyclohexene (3d).** To a flame-dried flask equipped with a stir bar was added 4 mL of dry CH_2Cl_2, 100 mg of **1b** (0.49 mmol), and 48 mg of 4-hexen-3-one (0.49 mmol), followed by dropwise addition of dimethylaluminum chloride (100 μL of a 1 M solution, 0.10 mmol). The mixture was stirred at rt for 3 h, and neutral alumina was added directly and the solvent removed *in vacuo*. The alumina was loaded to a prepacked silica gel column, and following flash chromatography (1.5% ether in hexanes), 140 mg of allylsilane **3d** was obtained as a clear colorless oil (95%). Quenching with NH_4Cl caused substantial epimerization to the *cis* product: IR (thin film) 3070, 3049, 1713 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.52−7.45 (m, 2 H), 7.36−7.30 (m, 3 H), 5.16 (br s, 1 H), 2.53−2.34 (m, 2 H), 2.32−2.21 (m, 1 H), 2.13−2.05 (m, 2 H), 1.93−1.74 (m, 2 H), 1.67−1.46 (m, 1 H), 1.62 (s, 2 H), 1.03 (t, J = 7.4 Hz, 3 H), 0.78 (d, J = 5.9 Hz, 3 H), 0.28 (s, 3 H), 0.27 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz, APT pulse sequence—evens up (+), odds down (−)) δ 215.6 (+), 139.1 (+), 134.3 (+), 128.9 (−), 127.6 (−), 117.3 (−), 53.2 (−), 39.3 (+), 36.0 (+), 30.8 (−), 28.9 (+), 26.4 (+), 19.7 (−), 7.6 (−), −2.9 (−), −2.8 (−); HRMS calcd for $C_{19}H_{28}OSi$ 300.1910, found 300.1925.

General Procedure for Addition of Aldehyde to Diels−Alder adduct. Method A. Methyl 3-(1-Hydroxypropyl)-4-methylenecyclohexanecarboxylate (6a and 7a). To a flame-dried flask equipped with a stir bar was added 3.0 mL of dry CH_2Cl_2, 100 mg of **3a** (0.35 mmol), and 24 mg of propionaldehyde (0.39 mmol). After the solution was cooled to −60 °C, 66 mg of $TiCl_4$ (0.35 mmol) was added dropwise, producing an orange solution. The mixture was stirred cold for 1 h and then allowed to warm gradually to −10 °C, quenched with saturated $NaHCO_3$, and extracted with ether, and the organic layer was dried over $MgSO_4$. Following solvent removal *in vacuo*, the product was purified by flash chromatography (45% ether in hexanes), providing 45 mg of product (4.3:1 **6a**:**7a**, 61%).

7a: white solid, recrystallized from hexanes; mp 54.9−58.0 °C; IR (thin film) 3455, 3082, 1736 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.84 (s, 1 H), 4.74 (s, 1 H), 3.86−3.77 (m, 1 H), 3.66 (s, 3 H), 2.51 (tt, J = 11.0, 3.7 Hz, 1 H), 2.35 (dt, J = 13.2, 4.4 Hz, 1 H), 2.11−1.91 (m, 4 H), 1.75−1.47 (m, 5 H), 0.96 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz, APT pulse sequence—evens up (+), odds down (−)) δ 176.0 (+), 148.7 (+), 107.4 (+), 72.3 (−), 51.7 (−), 46.3 (−), 42.2 (−), 35.0 (+), 30.0 (+), 28.7 (+), 27.6 (+), 10.6 (−). Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.83; H, 9.30.

6a: clear colorless oil; IR (thin film) 3447, 3071, 1733 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.73 (s, 1 H), 4.71 (s, 1 H), 3.70−3.63 (m, 1 H), 3.65 (s, 3 H), 2.68 (tt, J = 11.7, 3.5 Hz, 1 H), 2.36−1.95 (m, 5 H), 1.80 (br s, 1 H), 1.67−1.54 (m, 3 H), 1.30−1.20 (m, 1 H), 0.94 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.2, 148.0, 110.3, 71.2, 51.6, 48.5, 38.1, 31.4, 30.22, 30.15, 28.0, 9.9; HRMS calcd for $C_{12}H_{20}O_3$ (M^+ + H) 213.1491, found 213.1492.

Method B. Methyl 3-(1-Hydroxy-2-methylpropyl)-4-methylenecyclohexane carboxylate (6b and 7b). To a flame-dried flask equipped with a stir bar was added 0.75 mL of dry CH_2Cl_2, 50 mg of **3a** (0.17 mmol), and 14 mg of isobutyraldehyde (0.19 mmol). After the mixture was cooled to −60 °C, dimethylaluminum chloride (35 μL of a 1.0 M solution, 0.035 mmol) was added dropwise. In a separate flame-dried flask equipped with a stir bar was added 0.5 mL of dry CH_2Cl_2, dimethylaluminum chloride (35 μL of a 1 M solution, 0.35 mmol), and 36 mg of $TiCl_4$ (0.19 mmol). This yellow solution was stirred for 20 min at rt, cooled to −60 °C, and added by cannula to the allylsilane, generating an orange solution. The resultant orange mixture was stirred cold for 1 h and then allowed to warm gradually to −10 °C, quenched with saturated $NaHCO_3$, and extracted with ether, and the organic layer was dried over $MgSO_4$. Following solvent removal *in vacuo*, the product was purified by flash chromatography (35% ether in hexanes), providing 27 mg of product (1.3:1 **6b**:**7b**, 70%).

7b: clear colorless oil; IR (thin film) 3515, 3080, 1733 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.85 (br s, 1 H), 4.75 (br s, 1 H), 3.66 (s, 3 H), 3.55 (dd, J = 7.4, 3.7 Hz, 1 H), 2.50 (tt, J = 11.0, 3.7 Hz, 1 H), 2.37 (dt, J = 13.2, 4.4 Hz, 1 H), 2.28−2.19 (m, 1 H), 2.13−1.51 (m, 7 H), 0.98 (d, J = 6.6 Hz, 3 H), 0.87 (d, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz, APT pulse sequence—evens up (+), odds down (−)) δ 175.9 (+), 148.8 (+), 107.3 (+), 75.9 (−), 51.7 (−), 43.5 (−), 42.3 (−), 35.1 (+), 30.1 (−), 30.0 (+), 28.5 (+), 19.5 (−), 18.5 (−); HRMS calcd for $C_{13}H_{22}O_3$ (M^+ + H) 227.1648, found 227.1648.

6b: clear colorless oil; IR (thin film) 3460, 3070, 1738 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.77−4.72 (m, 2 H), 3.67−3.60 (m, 1 H), 3.65 (s, 3 H), 2.71 (tt, J = 11.8, 3.7, Hz, 1 H), 2.46−2.38 (m, 1 H), 2.34−1.92 (m, 4 H), 1.80−1.37 (m, 4 H), 0.95 (d, J = 6.6 Hz, 3 H), 0.84 (d, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz, APT pulse sequence—evens up (+), odds down (−)) δ 176.0 (+), 148.4 (+), 110.0 (+), 74.3 (−), 51.5 (−), 45.7 (−), 38.2 (−), 31.6 (+), 30.4 (+), 30.3 (+), 29.6 (−), 20.6 (−), 14.2 (−); HRMS calcd for $C_{13}H_{22}O_3$ (M^+ + H) 227.1648, found 227.1646.

General Procedure for Tandem Reaction Using an Aldehyde in the Second Step. Methyl 3-(1-Hydroxy-3-phenylpropyl)-4-methylenecyclohexane carboxylate (6c and 7c). To a flame-dried flask equipped with a stir bar was added 3.0 mL of dry CH_2Cl_2, 100 mg of **1b** (0.49 mmol), and 43 mg of methyl acrylate (0.49 mmol), and this was followed by dropwise addition of dimethylaluminum chloride (100 μL of a 1 M solution, 0.10 mmol). The mixture was heated to reflux for 4 h, at which time the cycloaddition was judged complete and the solution was cooled to −60 °C. Seventy-two mg of hydrocinnamaldehyde (0.54 mmol) was added, followed by 102 mg of $TiCl_4$ (0.54 mmol), producing a red mixture. After being stirred for 1 h, the mixture was allowed to warm to −10 °C, quenched with saturated $NaHCO_3$, extracted with ether, and washed with water, and the organic layer was dried over $MgSO_4$. Following solvent removal *in vacuo*, the product was purified by flash chromatography (35% ether in hexanes), providing 93 mg of product (6.8:1 **6c**:**7c**, 66%).

7c: clear colorless oil; IR (thin film) 3503, 3026, 1733 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.30−7.23 (m, 2 H), 7.21−7.13 (m, 3 H), 4.81 (s, 1H), 4.67 (s, 1 H), 3.84 (q, J = 6.6 Hz, 1 H), 3.65 (s, 3 H), 2.91−2.79 (m, 1 H), 2.72−2.60 (m, 1 H), 2.55−2.44 (m, 1 H), 2.26 (dt, J = 13.2, 4.4 Hz, 1 H), 2.10−1.52 (m, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz, APT pulse sequence—evens up (+), odds down (−)) δ 176.0 (+), 148.5 (+), 142.1 (+), 128.4 (−), 128.3 (−), 125.8 (−), 107.8 (+), 69.9 (−), 51.8 (−), 47.3 (−), 41.7 (−), 36.6 (+), 34.4 (+), 32.5 (+), 29.9 (+), 28.9 (+); HRMS calcd for $C_{18}H_{24}O_3$ (M^+ + H) 289.1805, found 289.1814.

6c: clear colorless oil; IR (thin film) 3450, 3065, 3026, 1717 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.30−7.23 (m, 2 H), 7.21−

7.13 (m, 3 H), 4.75 (s, 1 H), 4.73 (s, 1 H), 3.75 (td, J = 9.8, 2.9 Hz, 1 H), 3.65 (s, 3 H), 2.92−2.80 (m, 1 H), 2.71−2.57 (m, 2 H), 2.40-2.26 (m, 2 H), 2.24−1.83 (m, 5 H), 1.71−1.48 (m, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz, APT pulse sequence—evens up (+), odds down (−)) δ 176.1 (+), 147.7 (+), 142.0 (+), 128.3 (−) (2 coincident), 125.7 (−), 110.7 (+), 69.0 (−), 51.6 (−), 49.0 (−), 38.0 (−), 36.9 (+), 31.9 (+), 31.3 (+), 30.22 (+), 30.16 (+); HRMS calcd for $C_{18}H_{24}O_3$ (M^+ + H) 289.1805, found 289.1801.

1-Acetyl-3-(1-hydroxypropyl)-4-methylenecyclohexane (6d and 7d). Following the protocol for the preparation of **6c** and **7c**, 80 mg of **1b** (0.40 mmol), 28 mg of methyl vinyl ketone (0.40 mmol), dimethylaluminum chloride (80 μL of a 1 M solution, 0.08 mmol), 26 mg of propionaldehyde (0.44 mmol), and 83 mg of $TiCl_4$ (0.44 mmol) in 4 mL of dry CH_2Cl_2 gave, after flash chromatography (50% ether in hexanes), 59 mg of product (3.2:1 **6d**:**7d**, 75%).

7d: white needles, recrystallized from pentane; mp 67.0−67.7 °C; IR (CCl_4): 3535, 3078, 1713 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.84 (s, 1 H), 4.74 (s, 1 H), 3.87−3.79 (m, 1 H), 2.51 (tt, J = 11.0, 3.7 Hz, 1 H), 2.37 (dt, J = 13.2, 3.7 Hz, 1 H), 2.15 (s, 3 H), 2.18−1.90 (m, 4 H), 1.69−1.42 (m, 5 H), 0.96 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz, APT pulse sequence—evens up (+), odds down (−)) δ 211.6 (+), 148.7 (+), 107.4 (+), 72.4 (−), 50.7 (−), 46.3 (−), 35.3 (+), 29.7 (+), 28.1 (+), 27.8 (−), 27.6 (+), 10.7 (−). Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.40; H, 10.25.

6d: clear colorless oil; IR (thin film) 3413, 3070, 1702 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.71 (s, 1 H), 4.68 (s, 1 H), 3.64 (td, J = 8.8, 2.9 Hz, 1 H), 2.69 (tt, J = 11.8, 3.7 Hz, 1 H), 2.12 (s, 3 H), 2.36−1.87 (m, 5 H), 1.67−1.53 (m, 2 H), 1.51−1.35 (m, 2 H), 1.22 (m, 1 H), 0.93 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz, APT pulse sequence—evens up (+), odds down (−)) δ 212.1 (+), 148.0 (+), 110.5 (+), 71.2 (−), 48.9 (−), 46.0 (−), 31.3 (+), 29.8 (+), 29.6 (+), 28.1 (+), 28.0 (−), 9.9 (−); HRMS calcd for $C_{12}H_{20}O_2$ (M^+ + H) 197.1542, found 197.1542.

1-Acetyl-3-(1-hydroxy-3-phenylpropyl)-4-methylenecyclohexane (6e and 7e). Following the protocol for the preparation of **6c** and **7c**, 100 mg of **1b** (0.49 mmol), 35 mg of methyl vinyl ketone (0.49 mmol), dimethylaluminum chloride (100 μL of a 1 M solution, 0.10 mmol), 72 mg of hydrocinnamaldehyde (0.54 mmol), and 102 mg of $TiCl_4$ (0.54 mmol) in 4 mL of dry CH_2Cl_2 gave, after flash chromatography (45:55 ether:hexanes), 75 mg of product (4.2:1 **6e**:**7e**, 56%).

7e: white needles, recrystallized from hexanes; mp 83.5−84.4 °C; IR (thin film) 3465, 3062, 3026, 1705 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30−7.13 (m, 5 H), 4.82 (s, 1 H), 4.66 (s, 1 H), 3.93−3.86 (m, 1 H), 2.92−2.60 (m, 2 H), 2.49 (tt, J = 11.0, 3.7 Hz, 1 H), 2.31 (dt, J = 13.2, 4.4 Hz, 1 H), 2.23−1.45 (m, 9 H), 2.15 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz, APT pulse sequence—evens up (+), odds down (−)) δ 211.6 (+), 148.5 (+), 142.1 (+), 128.5 (−), 128.4 (−), 125.8 (−), 107.6 (+), 70.3 (−), 50.4 (−), 47.1 (−), 36.8 (+), 35.0 (+), 32.6 (+), 29.7 (+), 28.3 (+), 27.9 (−); HRMS calcd for $C_{18}H_{25}O_2$ (M^+ + H) 273.1856, found 273.1848.

6e: clear colorless oil; IR (thin film) 3424, 3065, 3026, 1698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30−7.23 (m, 2 H), 7.21−7.13 (m, 3 H), 4.74 (s, 1 H), 4.72 (s, 1 H), 3.75 (td, J = 9.6, 2.2 Hz, 1 H), 2.92−2.80 (m, 1 H), 2.72−2.58 (m, 2 H), 2.39−1.85 (m, 10 H), 1.64−1.35 (m, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz, APT pulse sequence—evens up (+), odds down (−)) δ 211.7 (+), 147.8 (+), 141.9 (+), 128.43 (−), 128.38 (−), 125.9 (−), 110.9 (+), 69.4 (−), 49.3 (−), 45.9 (−), 37.1 (+), 31.9 (+), 31.3 (+), 29.7 (+), 29.6 (+), 28.0 (−); HRMS calcd for $C_{18}H_{25}O_2$ (M^+ + H) 273.1856, found 273.1853.

1-Acetyl-3-(1-hydroxy-2-methylpropyl)-4-methylenecyclohexane (6f and 7f). Following the protocol for the preparation of **6c** and **7c**, 100 mg of **1b** (0.49 mmol), 35 mg of methyl vinyl ketone (0.49 mmol), dimethylaluminum chloride (100 μL of a 1 M solution, 0.10 mmol), 39 mg of isobutyraldehyde (0.54 mmol), and 102 mg of $TiCl_4$ (0.54 mmol) in 4 mL of dry CH_2Cl_2 gave, after flash chromatography (45% ether:hexanes), 53 mg of product (1.1:1 **6f**:**7f**, 51%).

7f: clear colorless oil; IR (thin film) 3489, 3081, 1702 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.84 (s, 1 H), 4.73 (s, 1 H), 3.55 (dd, J = 7.4, 3.7 Hz, 1 H), 2.50 (tt, J = 11.0, 3.7 Hz, 1 H), 2.38 (dt, J = 13.2, 3.7 Hz, 1 H), 2.14 (s, 3 H), 2.26−1.89 (m, 4 H), 1.81 (m, 1 H), 1.71 (br s, 1 H), 1.55−1.39 (m, 2 H), 0.97 (d, J = 6.6 Hz, 3 H), 0.86 (d, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 211.49, 148.84, 107.29, 75.97, 50.78, 43.51, 35.44, 30.14, 29.66, 29.91, 27.77, 19.52, 18.43; HRMS calcd for $C_{13}H_{22}O_2$ (M^+ + H) 211.1699, found 211.1690.

6f: white crystals, recrystallized from pentane; mp 75.1−75.6 °C; IR (CCl_4) 3460, 3073, 1713 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.73−4.70 (m, 2 H), 3.63 (dd, J = 9.6, 2.2 Hz, 1 H), 2.73 (tt, J = 11.8, 3.7 Hz, 1 H), 2.46−2.39 (m, 1 H), 2.34−2.26 (m, 1 H), 2.19 (dt, J = 14.0, 3.7 Hz, 1 H), 2.12 (s, 3 H), 2.05 (dd, J = 13.2, 4.4 Hz, 1 H), 2.01−1.88 (m, 1 H), 1.74 (m, 1 H), 1.56 (br s, 1 H), 1.52-1.40 (m, 2 H), 0.95 (d, J = 6.6 Hz, 3 H), 0.81 (d, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz, APT pulse sequence—evens up (+), odds down (−)) δ 211.6 (+), 148.2 (+), 110.2 (+), 74.0 (−), 46.0 (−), 45.9 (−), 31.4 (+), 30.0 (+), 29.8 (+), 29.4 (−), 28.0 (−), 20.7 (−), 13.6 (−); HRMS calcd for $C_{13}H_{23}O_2$ (M^+ + H) 211.1699, found 211.1700.

3-(1-Hydroxypropyl)-5-methyl-4-methylene-1-(1-oxopropyl)cyclohexane (6g and 7g). Following the protocol for the preparation of **6c** and **7c**, 100 mg of **1b** (0.49 mmol), 48 mg of 4-hexen-3-one (0.49 mmol), dimethylaluminum chloride (100 μL of a 1 M solution, 0.10 mmol), 31 mg of propionaldehyde (0.54 mmol), and 102 mg of $TiCl_4$ (0.54 mmol) in 4 mL of dry CH_2Cl_2 gave, after flash chromatography (30% ether in hexanes), 71 mg of product (2.8:1 **6g**:**7g**, 64%).

7g: white crystals, recrystallized from pentane; mp 106.2−106.9 °C; IR (KBr pellet) 3340, 3082, 1701 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.84 (s, 1 H), 4.72 (s, 1 H), 3.87 (td, J = 6.6, 3.7 Hz, 1 H), 2.59−2.21 (m, 4 H), 2.05−1.71 (m, 4 H), 1.60−1.31 (m, 4 H), 1.02 (t, J = 6.6 Hz, 3 H), 0.96 (t, J = 7.4 Hz, 3 H), 0.83 (d, J = 5.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz, APT pulse sequence—evens up (+), odds down (−)) δ 214.3 (+), 148.5 (+), 106.9 (+), 72.5 (−), 57.6 (−), 46.2 (−), 44.4 (+), 35.5 (−), 35.1 (−), 29.3 (+), 27.9 (+), 20.1 (−), 10.6 (−), 7.6 (−). Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.53; H, 10.53.

6g: clear colorless oil; IR (thin film) 3422, 3070, 1702 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.74−4.68 (m, 2 H), 3.63 (td, J = 8.8, 2.9 Hz, 1 H), 2.62−2.11 (m, 6 H), 1.90−1.13 (m, 6 H), 1.03 (t, J = 6.6 Hz, 3 H), 0.95 (t, J = 7.4 Hz, 3 H), 0.83 (d, J = 5.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz, APT pulse sequence—evens up (+), odds down (−)) δ 215.0 (+), 147.7 (+), 110.6 (+), 71.1 (−), 52.4 (−), 49.1 (−), 39.8 (+), 35.6 (+), 35.5 (−), 30.9 (+), 28.2 (+), 20.4 (−), 9.8 (−), 7,6 (−); HRMS calcd for $C_{14}H_{24}O_2$ (M^+ + H) 225.1856, found 225.1867.

3-(1-Hydroxy-2-methylpropyl)-5-methyl-4-methylene-1-(1-oxopropyl)cyclohexane (6h). Following the protocol for the preparation of **6c** and **7c**, 100 mg of **1b** (0.49 mmol), 48 mg of 4-hexen-3-one (0.49 mmol), dimethylaluminum chloride (100 μL of a 1 M solution, 0.10 mmol), 39 mg of isobutyraldehyde (0.54 mmol), and 102 mg of $TiCl_4$ (0.54 mmol) in 4 mL of dry CH_2Cl_2 gave, after flash chromatography (25% ether in hexanes), 47 mg of a single diastereomer **6h** (40%): clear colorless oil; IR (thin film) 3479, 3070, 1702 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.71 (br s, 2 H), 3.61 (d, J = 10.3 Hz, 1 H), 2.61−2.06 (m, 6 H), 1.88−1.48 (m, 4 H), 1.40 (td, J = 13.2, 4.4 Hz, 1 H), 1.01 (t, J = 7.4 Hz, 3 H), 0.95 (d, J = 6.6 Hz, 3 H), 0.81 (t, J = 6.6 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz, APT pulse sequence—evens up (+), odds down (−)) δ 214.9 (+), 147.9 (+), 110.3 (+), 73.7 (−), 53.3 (−), 46.3 (−), 39.8 (+), 35.7 (−), 35.6 (+), 31.1 (+), 29.3 (−), 20.8 (−), 20.4 (−), 13.3 (−), 7.6 (−); HRMS calcd for $C_{15}H_{26}O_2$ (M^+ + H) 239.2012, found 239.2008.

Acknowledgment. Support for this work has been provided by Eli Lilly and Company in the form of a research grant. D.D.W. acknowledges the School of Science at IUPUI for financial support in the form of a R.I.F. Fellowship. The authors are indebted to Dr. Ian Fleming for useful insight regarding the potential role of Me_2AlCl in these studies.

Supporting Information Available: ^{1}H or ^{13}C NMR spectra for **1b**, **3b**−**d**, **6a**−**h**, and **7b**,**c**,**e**,**f** (16 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO962025F