JOC The Journal of Organic Chemistry

Article

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Asymmetric Synthesis of Cyclobutanones: Synthesis of Cyclobut-G

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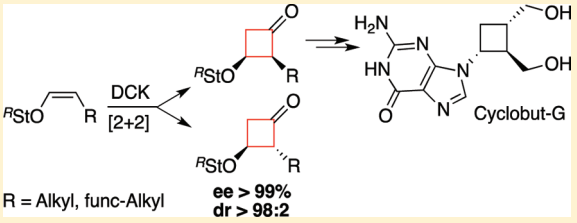
Supporting Information

ABSTRACT: A simple, efficient, and stereoselective approach has been developed for obtaining chiral cis- and trans-disubstituted cyclobutanones from readily available alkyl- and functionalized alkyl-substituted enol ethers. The usefulness of these cyclobutanones is illustrated by an enantioselective synthesis of cyclobut-G (Lobucavir).



INTRODUCTION

The cyclobutane ring is found within numerous natural products,[1] some of which possess significant biological activity (for example, (−)-biyouyanagin A,[2] (+)-kelsoene,[3] and (−)-bielschowskysin[4] (Figure 1)). Four-membered carbocycles

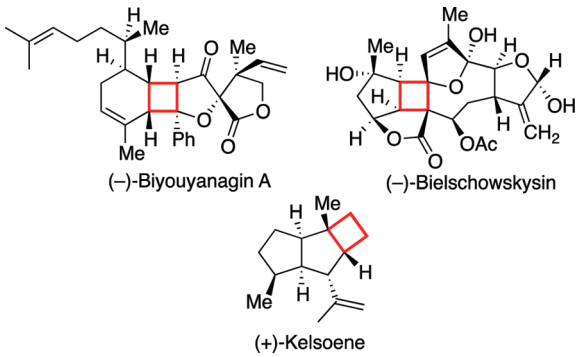


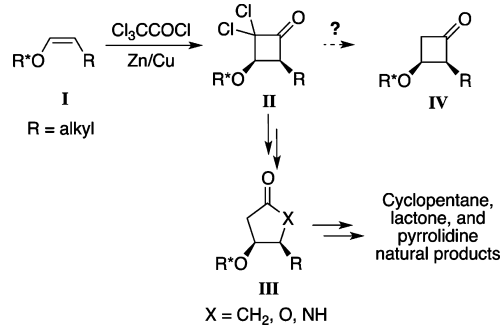
Figure 1. Examples of cyclobutane-containing natural products.

are also valuable building blocks for synthesis, a consequence of their substantial strain energy (26.3 kcal/mol), essentially that of cyclopropanes (27.5 kcal/mol).[5] For example, piperidines,[6] tetrahydropyrans,[7] cyclohexanones,[8] and oxazepines[9] can be efficiently accessed through an approach that uses donor−acceptor cyclobutane derivatives as 1,4-dipole precursors.[10] Cyclobutanes have also been used in transition-metal-catalyzed ring-opening reactions for the construction of larger rings and functionalized noncyclic products.[11]

The interest in cyclobutane derivatives has, of course, fostered efficient methods for their preparation. The most useful procedures involve [2 + 2] cycloaddition, intramolecular nucleophilic substitution, and ring contraction/expansion reactions.[5b,12] However, effective routes described to date are still scarce, compared with those available for accessing five- and six-membered carbocycles. Moreover, it should be noted that the reported approaches to 4-membered carbocycles are generally limited in scope, and few are able to provide enantioselection.

In recent years, our laboratory has exploited the diastereoselective [2 + 2] thermal cycloaddition of dichloroketene (DCK) with chiral enol ethers **I** for the enantioselective synthesis of a variety of 5-membered ring-containing natural products (Scheme 1). The instability of the intermediate *α,α*-

Scheme 1. Transformations of *α,α*-Dichlorocyclobutanones



dichlorocyclobutanones **II** in general thwarts their purification, but fortunately, the crude intermediates can nevertheless be used to obtain the corresponding cyclopentanones,[13] *γ*-lactones,[14] and *γ*-lactams[15] **III**. Given the interest in cyclobutane derivatives, the possibility of obtaining the chiral 3-alkoxycyclobutanones **IV** through direct dechlorination of these sensitive dichlorocyclobutanone intermediates seemed worth examining. Herein, we present our results toward this end.[16,17]

DISCUSSION

To study the [2 + 2] cycloaddition/dechlorination sequence, the model *Z* enol ether **3a** was prepared from Stericol[18] through a straightforward procedure developed by our group (Scheme 2).[19]

Received: November 2, 2011
Published: December 27, 2011

   dx.doi.org/10.1021/jo202261z | J. Org. Chem. 2012, 77, 1710–1721

Scheme 2. Synthesis of Model Enol Ether 3a

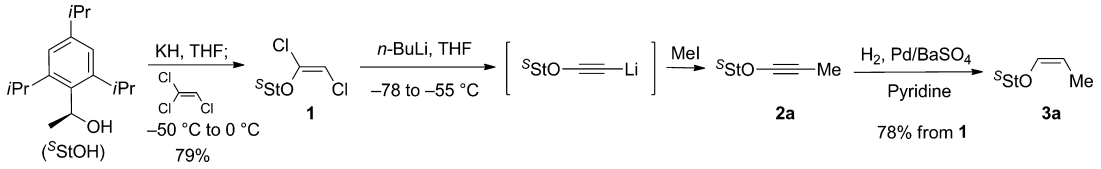
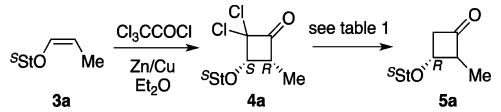


Table 1. Optimization of Dechlorination Conditions with Dichlorocyclobutanone 4a



entry	dechlorination conditions	yield[a,b] (%)
1	Bu_3SnH, ACCN, toluene, 90 °C, 1 h	68 (62:38)
2	Zn/Cu, AcOH, 50 °C, 1 h	37 (100:0)
3	Zn/Cu, MeOH/NH_4Cl, reflux,12 h	59 (45:55)
4	Zn/Cu, MeOH/NH_4Cl, reflux, 10 min	63 (100:0)
5	**Zn/Cu, MeOH/NH_4Cl, reflux, 10 min (one pot)**	**91 (100:0)[c]**

[a]Overall yield from **3a** after chromatography (without separation of diastereomers). [b]Cis/trans cyclobutanone ratio in parentheses. [c]dr = 92:8. [S]StOH = (*S*)-(−)-1-(2,4,6-triisopropylphenyl)ethanol ((*S*)-(−)-Stericol). ACCN = 1,1′-azobis(cyclohexanecarbonitrile).

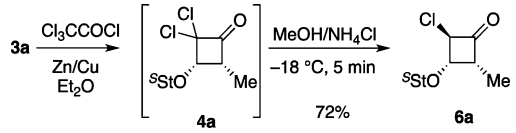
In the first step of the sequence, Stericol was treated sequentially with potassium hydride and trichloroethylene, which yielded the corresponding dichloroenol ether (79%). The latter was treated at −78 °C with 2 equiv of *n*-butyllithium and then warmed to −55 °C to generate the lithiated ynol ether. This intermediate was trapped with methyl iodide to form the methylated ynol ether **2a**, which was directly hydrogenated to afford the *Z* enol ether **3a** (78% from the dichloroenol ether).

This reactive ketenophile was then subjected to [2 + 2] cycloaddition by exposure to in situ generated dichloroketene.[20] The reaction occurred rapidly at room temperature to provide the rather unstable crude dichlorocyclobutanone **4a** as a 92:8 mixture (^{1}H NMR) of diastereomers (Table 1).

While dechlorination of simple dichlorocyclobutanones can be achieved with a variety of reducing agents (Bu_3SnH, Zn/AcOH, Zn/NH_4Cl/MeOH, Al/Hg, etc.),[21] the presence of an acid-sensitive and elimination-prone alkoxyl group at C-3 in the α,α-dichlorocyclobutanone was cause for concern. Radical conditions were therefore first examined to try to avoid potential side reactions involving this C-3 group. Although complete dechlorination of the cycloadduct **4a** could be effected in acceptable yield with a large excess of Bu_3SnH in hot toluene, partial isomerization in the product was observed (Table 1, entry 1). In any event, use of this toxic reagent, especially in large excess, was of course to be avoided if possible. Among the other frequently used methods for dechlorination of dichlorocyclobutanones, the zinc-based procedures seemed much more appropriate in this regard. Encouragingly, zinc−copper couple, also used for the generation of dichloroketene, in warm acetic acid produced the cis-disubstituted cyclobutanone **5a** in moderate yield, along with some Stericol-containing degradation products (Table 1, entry 2). Since the relatively strong acidity of acetic acid could have been detrimental, a less acidic proton source was next examined. On replacing the acetic acid with a methanolic ammonium chloride solution, an improved yield of the dechlorinated cyclobutanone could be obtained after 12 h at reflux, however, now as a 45:55 cis−trans mixture (entry 3). Gratifyingly, by employing the same reaction conditions, but refluxing the reaction mixture for only 10 min, the desired cis cyclobutanone **5a** was uniquely produced in a respectable 63% overall yield (entry 4). Since excess zinc−copper couple was used in both this reduction and the preceding cycloaddition, it was hoped that a one-pot sequence might be developed, which would obviate the need to handle the sensitive dichlorocyclobutanone. A highly effective, one-pot procedure was indeed found: after cycloaddition, a methanolic solution of NH_4Cl was added to the reaction mixture (containing residual zinc−copper couple), which was then refluxed for 10 min to give exclusively the cis cyclobutanone **5a** (92:8 diasteromeric ratio) in 91% overall yield (entry 5).

Interestingly, during the course of this model study, it was found that brief exposure of dichlorocyclobutanone **4a** to the dechlorination conditions for 5 min at −18 °C cleanly afforded the unstable monochlorocyclobutanone **6a** as a unique product (72% overall yield, Scheme 3).

Scheme 3. Synthesis of Monochlorocyclobutanone 6a



This monochlorocyclobutanone was shown to possess the trans relationship between the chlorine atom and the alkoxyl group by NOE experiments (Figure 2). The considerably more facile removal of a chlorine from the dichloride **4a** than from the monochloride **6a** can be attributed to a combination of

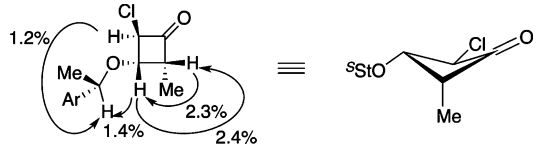


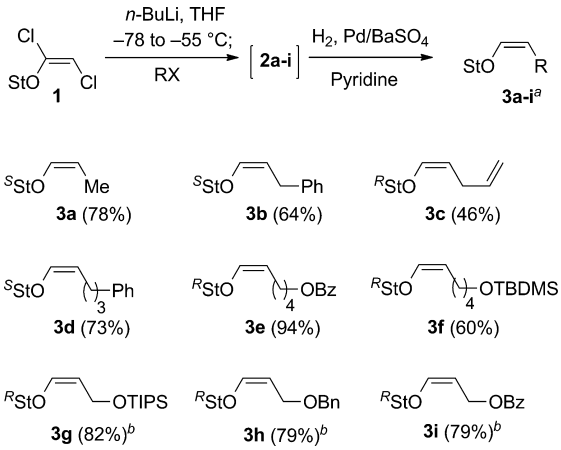
Figure 2. NOE results for monochlorocyclobutanone **6a**.

dx.doi.org/10.1021/jo202261z | J. Org. Chem. 2012, 77, 1710−1721

electronic (withdrawing) and stereoelectronic (axial chlorine) factors that favor reduction of the former.

Following this development of reaction conditions for a one-pot cycloaddition−dechlorination, the scope of the transformation was examined. *Z*-Enol ethers (**3b−i**) were prepared from the Stericol-derived dichloroenol ether **1** in the same manner as was enol ether **3a** (Scheme 4).

Scheme 4. Synthesis of *Z*-Enol Ethers 3a−i

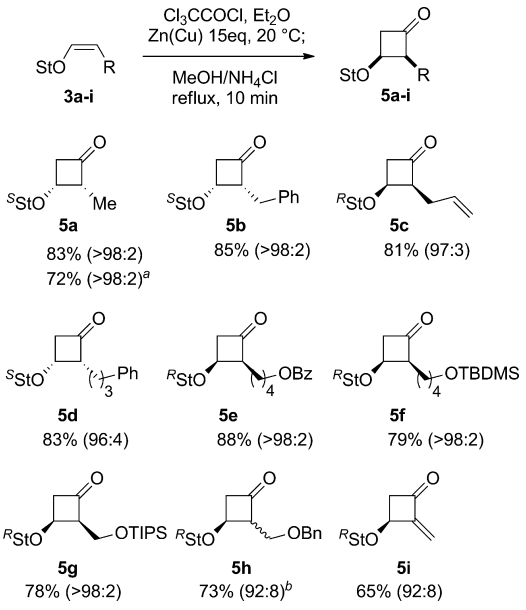


[a]In the case of **2c**, partial reduction of the triple bond was effected with Dibal-H in THF.

[b]Yield takes into account the protection of the corresponding alcohol (**3j**, not shown, formed with CH_2O in place of RX).

The enol ethers were then subjected to one-pot cycloaddition−reduction to give the corresponding cyclobutanones in good to excellent overall yields and, in most cases, in stereopure form after simple flash chromatography (Scheme 5).[22] From (*S*)- and (*R*)-Stericol, the 3*R* and 3*S* configurations,

Scheme 5. Synthesis of Cyclobutanones 5a−i



[a]10 mmol scale.

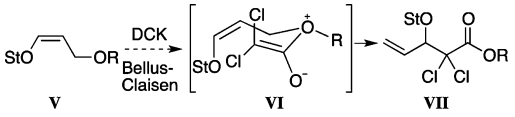
[b]Isolated as a 33:67 mixture (epimerization occurs during purification over silica, alumina, or Florisil).

respectively, were assigned in **5a−i** based on considerable antecedent.[13−15]

Pleasingly, benzyl, allyl, and 3-phenylpropyl substituents (products **5b−d**, Scheme 5), as well as hydrolysis-susceptible benzoyl- and TBDMS-protected 4-hydroxybutyl groups (products **5e**,**f**), were compatible with the cycloaddition−reduction sequence. The outcomes with the TIPS-, benzyl-, and benzoyl-protected hydroxymethyl substituents (products **5g−i**) proved particularly interesting in several respects.

Chiral acyclic enol ethers bearing a protected hydroxyl function at the allylic position have not, to the best of our knowledge, previously been subjected to dichloroketene cycloaddition. These molecules in the presence of dichloroketene can potentially undergo, in competition with the cycloaddition pathway, a [3,3]-sigmatropic (Bellus−Claisen) rearrangement.[23] This reaction, well precedented with allylic alcohol, thiol, and amine derivatives, would result from attack by the nucleophilic heteroatom in **V** on the electrophilic center of the ketene, followed by a [3,3]-sigmatropic rearrangement of the zwitterionic intermediate **VI** to give **VII** (Scheme 6). The higher reactivity of the enol ethers, compared with simple

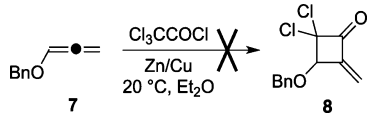
Scheme 6. Potential Bellus−Claisen Rearrangement



alkenes, toward [2 + 2] cycloaddition might be expected, however, to override this eventuality and lead to cycloaddition rather than Bellus-Claisen rearrangement. Fortunately, the TIPS-, benzyl-, and benzoyl-protected γ-hydroxy enol ethers **3g−i** in the presence of dichloroketene indeed produced predominantly, if not exclusively, cycloaddition, as only the dechlorinated cyclobutanones could be detected in the crude reaction mixtures.

While purification of the TIPS-protected crude product cleanly gave stereochemically pure **5g** (78% overall yield), unexpectedly, the crude benzyloxymethyl cyclobutanone suffered epimerization under several different chromatographic purification conditions to produce a mixture of the cis and trans isomers **5h**. Less surprisingly, perhaps, the crude benzoyloxymethyl derivative, upon simple silica gel filtration, underwent facile elimination to afford the novel methylenecyclobutanone **5i** (65% overall yield). This synthetically attractive intermediate is the formal product of a Stericol-derived allenyl ether−ketene cycloaddition. It should be noted that such a reaction is, in fact, unprecedented, and indeed failed in our hands with allenyl ether **7**[24] and dichloroketene (Scheme 7). The ready cycloaddition of these hydroxy-substituted enol ether derivatives is significant in that it allows useful functionality to be easily introduced into the cyclobutanones in a key position (see below).

Scheme 7. Attempt at Allenyl Ether 7 Cycloaddition



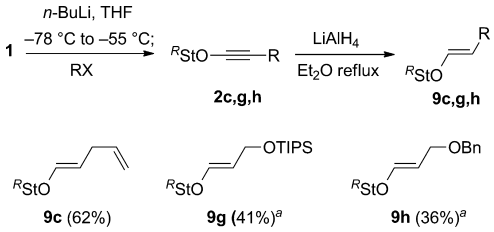
Preparation of trans-disubstituted cyclobutanones was also examined starting from the *E* enol ethers **9c**,**g**,**h**. The latter

dx.doi.org/10.1021/jo202261z | J. Org. Chem. 2012, 77, 1710−1721

could be prepared by modification of the previous procedure at the reduction stage, namely, by using $LiAlH_4$ in lieu of H_2/Pd (Scheme 8).[14c]

These *E* enol ethers **9** also participated, albeit less satisfactorily, in the [2 + 2] cycloaddition−dechlorination

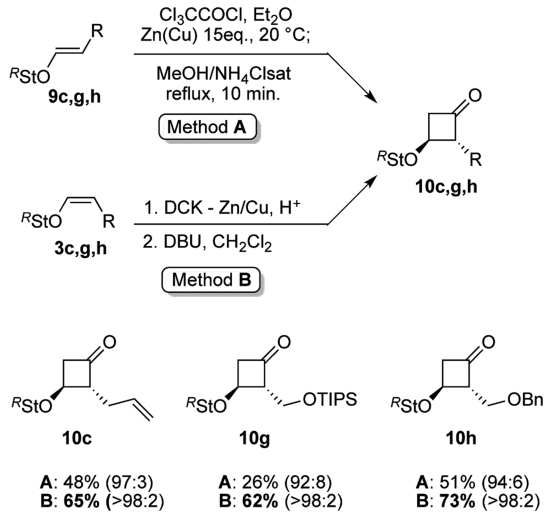
Scheme 8. Synthesis of *E*-Enol Ethers 9c,g,h



[a]Yield takes into account the protection of the corresponding alcohol (**9j**, not shown, formed with CH_2O in place of RX).

sequence to afford the expected trans cyclobutanones (method A, Scheme 9). The lower yields do not seem to come from less efficient cycloaddition, but rather less efficient dechlorination of the intermediate dichlorocyclobutanones (longer reaction

Scheme 9. Synthesis of trans Cyclobutanones 10c,g,h

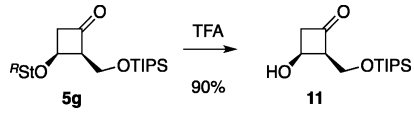


times). Fortunately, it was found, based on the aforementioned behavior of the benzyloxy derivative, that the cis-disubstituted cyclobutanones were generally prone to epimerization. Among the different bases examined (EtONa, EtN-*i*-Pr_2, DBU, etc.), DBU (cat.) in dichloromethane proved most effective and delivered the thermodynamically more stable trans isomers in good yields and excellent stereopurity (method B). Overall, this approach affords the trans cyclobutanones in considerably better yields than those obtained through the alternative *E* enol ether route.

Finally, it is important to point out that the chiral auxiliary, which in part plays the role of an effective protecting group for the C-3 hydroxyl, can be cleaved in a straightforward and selective manner, as demonstrated by the clean conversion of **5g** into the surprisingly stable 3-hydroxy cyclobutanone **11** (Scheme 10).[25]

To demonstrate some of the potential of this asymmetric approach to cyclobutane derivatives, a synthesis of cyclobut-G (Lobucavir)[26] was undertaken. This cyclobutyl guanine nucleo-

Scheme 10. Stericol Cleavage



side analogue, a derivative of the highly potent anti-HIV natural product, oxetanocin A,[27] was developed by Bristol Myers Squibb some 20 years ago (Figure 3).[26a−d] Since then, others groups have achieved the synthesis of this compound.[28]

The TIPS-protected hydroxymethyl cyclobutanone **5g** appeared to be an attractive starting material for the preparation of cyclobut-G. The synthesis began by Wittig methoxy

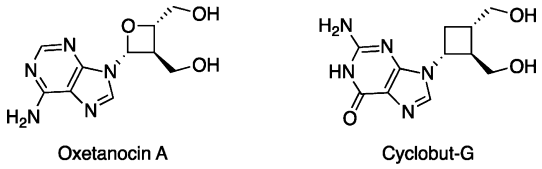


Figure 3. Oxetanocin A and cyclobut-G.

olefination of **5g**, which was followed by hydrolysis of the enol ether and isomerization of the resulting formyl group (13:1 trans/cis) to afford aldehyde **12** in 64% yield for the three steps (Scheme 11). Sodium borohydride reduction of **12** cleanly furnished the corresponding hydroxymethyl derivative **13** (93%), which was protected prior to selective cleavage of the chiral auxiliary to give cyclobutanol **14** (75% yield, two steps). In preparation for the introduction of a latent guaninyl group through the procedure developed by Bisacchi, Singh, and co-workers,[26a−d] triflation of alcohol **14** was next attempted. Surprisingly, this resulted in only decomposition of the starting material, whereas use of the readily prepared, but less reactive, nosyl derivative proved to be completely unproductive.

With the objective of preparing a more robust substrate for the triflation reaction, the TIPS group in **13** was cleaved and the resulting diol **16** was dibenzoylated to provide, after Stericol cleavage, alcohol **17**[26b−d,29] in 78% overall yield (Scheme 12). As expected,[26c,d] triflation of this alcohol now proceeded uneventfully, as did the subsequent displacement reaction, to produce the purine derivative **18** in 78% yield. This derivative could be readily transformed, as previously described, into cyclobut-G (**19**), which provided spectral data identical to those reported in the literature ($[\alpha]^{20}_D$ −24.7; lit.[26d] $[\alpha]^{22}_D$ −24.4).[26c,d] This stereocontrolled approach to cyclobut-G could permit novel structural modifications at several points.

■ CONCLUSION

A simple, efficient, and stereoselective approach has been developed for obtaining chiral, functionalized, cis- and trans-disubstituted cyclobutanones from readily available enol ethers. Given the dearth of generally useful routes to chiral cyclobutane derivatives and the ever-increasing demand for these versatile building blocks, this effective approach should soon find additional application.

■ EXPERIMENTAL SECTION

General Information. Reactions were carried out under argon in oven-dried glassware. Standard inert atmosphere techniques were used in handling all air- and moisture-sensitive reagents. Dry THF and diethyl ether were obtained by filtration over activated molecular

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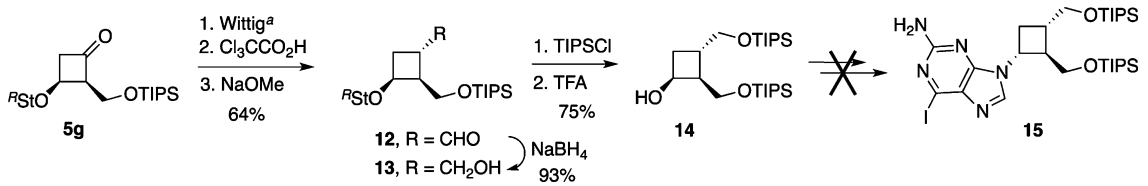
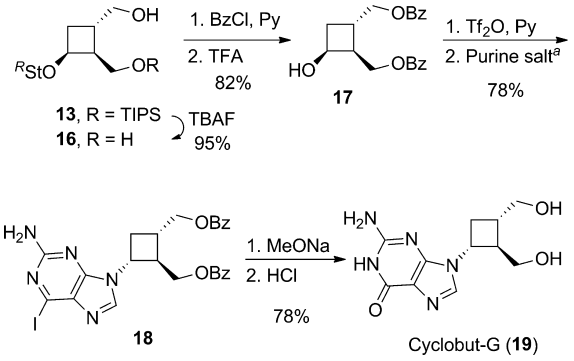
Scheme 11. First Approach to Cyclobut-G



[a](Ph_3PCH_2OMe,Cl), KHMDS.

Scheme 12. Synthesis of Cyclobut-G (19)



[a]2-Amino-6-iodopurine tetrabutylammonium salt.

sieves and dry CH_2Cl_2 by filtration through activated aluminum oxide. The zinc−copper couple used in all experiments was prepared according to a procedure reported by our group[30] and stored under argon. Thin-layer chromatography was performed on silica sheets (0.2 mm), which were visualized with ultraviolet light and by heating the plate after treatment, generally with phosphomolybdic acid in ethanol. Silica gel (0.040−0.063 mm) was employed for flash column chromatography. A Fourier transform infrared spectrometer was used to record IR spectra. ^{1}H NMR and ^{13}C NMR spectra were recorded on either a 300 or 400 MHz apparatus. All shifts for ^{1}H spectra were referenced to the residual solvent peak and are reported in ppm. When ambiguous, proton and carbon assignments were established through COSY, HMQC, and/or DEPT experiments. Mass spectra were recorded by using either DCI (ammonia/isobutane 63/37), EI, or ESI techniques. HRMS were recorded on an Orbitrap apparatus (ESI). Microanalyses were performed in-house.

(*S*,*E*)-2-(1-(1,2-Dichlorovinyloxy)ethyl)-1,3,5-triisopropylbenzene (1). An argon-flushed flask was charged with potassium hydride (30% suspension in mineral oil, 14.3 g, 107 mmol). The mineral oil was removed by washing with pentane (3 × 10 mL), and anhydrous THF (60 mL) was then added. A solution of (*S*)-1-(2,4,6-triisopropylphenyl)ethanol[18] (12.0 g, 48.3 mmol) in anhydrous THF (40 mL) was added dropwise at 0 °C. The mixture was stirred at room temperature for 2 h, cooled to −50 °C, and treated dropwise with a solution of trichloroethylene (4.8 mL, 53 mmol) in anhydrous THF (20 mL). The reaction mixture was allowed to warm to 0 °C and stirred until TLC (eluent pentane) showed complete disappearance of starting material. The mixture was then carefully treated with methanol (6 mL) and water (12 mL). The crude product was extracted with pentane in the usual way, and the combined extracts were washed with water, dried over Na_2SO_4, and concentrated under vacuum at 0 °C. The residue was purified by flash chromatography on silica gel (pretreated with 2.5% of triethylamine, v/v) (eluent pentane) to afford 13.0 g (79%) of dichloroenol ether **1** as a white solid: mp 38−41 °C; $[\alpha]^{20}_D$ −16.2 (*c* 1.0, $CHCl_3$); IR (film) 3086, 1623, 1609, 1078, 1040 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (s, 2H), 6.00 (q, *J* = 6.9 Hz, 1H), 5.60 (s, 1H), 3.75−3.15 (br s, 2H), 2.90 (sept, *J* = 6.9 Hz, 1H), 1.70 (d, *J* = 6.9 Hz, 3H), 1.35−1.20 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.5 (C_q), 142.9 (C_q), 131.2 (C_q), 122.1 (CH), 98.3 (CH), 76.4 (CH), 34.1 (CH), 29.4 (CH), 24.7 (CH_3), 24.5 (CH_3), 23.9 (CH_3), 20.3 (CH_3); MS (EI$^+$) *m*/*z* 343 and 341 (M^+), 248, 231 (100). Anal. Calcd for $C_{19}H_{28}Cl_2O$: C, 66.47; H, 8.22. Found: C, 66.63; H, 8.36.

(*S*,*Z*)-1,3,5-Triisopropyl-2-(1-(prop-1-enyloxy)ethyl)benzene (^{S}3a). To a solution of the dichloroenol ether ^{S}**1** (2.40 g, 6.99 mmol) in anhydrous THF (30 mL) at −78 °C was added dropwise *n*-BuLi (2.5 M in hexanes, 6.2 mL, 15.5 mmol). The solution was allowed to warm to −55 °C and stirred for 10 min, and then MeI (2.6 mL, 41.8 mmol) (prefiltered through a pad of basic alumina) and distilled HMPA (10 mL) were added. The solution was allowed to warm to 0 °C over 45 min and was then stirred at 0 °C for an 45 additional min. MeOH (3 mL) was added, and the crude mixture was poured into a cold saturated aqueous solution of NH_4Cl. The product was extracted with cold pentane, and the combined organic layers were washed with cold brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure at 0 °C. The crude ynol ether was used immediately without purification. The crude ynol ether in 15 mL of pyridine was hydrogenated over palladium (5% w/w on $BaSO_4$, 480 mg) at room temperature until IR showed no starting material remained (triple bond ≈ 2260 cm^{-1}, 1.5 h). The reaction mixture was filtered through Celite, and water was added. The mixture was extracted with Et_2O, the combined organic layers were successively washed with saturated aqueous $CuSO_4$, water, and brine, dried over anhydrous Na_2SO_4, and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pretreated with 2.5% of Et_3N, v/v) (eluent pentane) to afford 1.57 g (78%) of enol ether ^{S}**3a** as a colorless oil: $[\alpha]^{20}_D$ +25.6 (*c* 1.0, $CHCl_3$); IR (neat) 2955, 2927, 2861, 1665, 1452, 1090 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (s, 2H), 5.97−5.93 (m, 1H), 5.33 (q, *J* = 6.8 Hz, 1H), 4.29 (quint., *J* = 6.7 Hz, 1H), 3.93−3.05 (m, 2H), 2.86 (sept, *J* = 6.9 Hz, 1H), 1.63−1.57 (m, 6H), 1.29−1.18 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 144.7, 133.2, 121.9, 100.1, 75.2, 34.0, 29.0, 24.6, 23.93, 23.90, 22.5, 9.4; MS (ESI) *m*/*z* 295.2 $(M + Li)^+$; HRMS (ESI) calcd for $C_{20}H_{32}O_1Na$ $(M + Na)^+$ 311.2345, found 311.2551.

(*S*,*Z*)-1,3,5-Triisopropyl-2-(1-(3-phenylprop-1-enyloxy)-ethyl)benzene (^{S}3b). To a solution of the dichloroenol ether ^{S}**1** (1.16 g, 3.38 mmol) in anhydrous THF (16 mL) at −78 °C was added dropwise *n*-BuLi (2.5 M in hexanes, 3.0 mL, 7.5 mmol). The solution was allowed to warm to −55 °C and stirred 15 min, and then BnBr (1.62 mL, 13.5 mmol), distilled HMPA (3.5 mL), and a catalytic quantity of tetrabutylammonium iodide were added. The solution was allowed to warm to room temperature over 1 h and was then stirred at this temperature until TLC showed disappearance of the terminal alkyne. The crude mixture was poured into a cold saturated aqueous solution of NH_4Cl, and the product was extracted with cold Et_2O. The combined organic layers were washed with cold brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum at 0 °C to yield the crude ynol ether, which was used immediately without purification. The crude ynol ether in pyridine (6 mL) and Et_2O (10 mL) was hydrogenated over palladium (5% w/w on $BaSO_4$, 460 mg) at room temperature until IR showed no starting material remained (≈2260 cm^{-1}, 5 h). The reaction mixture was filtered through Celite, and saturated aqueous $CuSO_4$ was added. The mixture was extracted with Et_2O, and the combined organic layers were successively washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pretreated with 2.5% of Et_3N, v/v) (eluent pentane) to afford 793 mg (64%) of the enol ether ^{S}**3b** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.13 (m, 5H), 7.01

dx.doi.org/10.1021/jo202261z | J. Org. Chem. 2012, 77, 1710−1721

(s, 2H), 6.08 (dt, J = 6.2, 1.4 Hz, 1H), 5.38 (q, J = 6.8 Hz, 1H), 4.49 (dt, J = 7.0, 6.8 Hz, 1H), 3.80−3.20 (m, 4H), 2.86 (sept, J = 6.9 Hz, 1H), 1.63 (d, J = 6.8 Hz, 3H), 1.30−1.18 (m, 18H); ^{13}C NMR (75 MHz) δ 147.7, 144.4, 141.9, 132.9, 128.3, 128.2, 125.5, 121.9, 104.9, 75.4, 34.1, 30.5, 29.2, 24.7, 24.0, 22.6. Data are consistent with published results from our group.[15b]

(*R*,*Z*)-1,3,5-Triisopropyl-2-(1-(penta-1,4-dienyloxy)ethyl)-benzene (*R*3c). To a solution of the dichloroenol ether *R*1 (290 mg, 0.845 mmol) in anhydrous THF (3 mL) at −78 °C was added dropwise *n*-BuLi (2.5 M in hexanes, 0.743 mL, 1.86 mmol). The solution was allowed to warm to −55 °C and stirred 15 min, and then allyl iodide (0.155 mL, 1.69 mmol) (prefiltered through a pad of basic alumina) and distilled HMPA (0.3 mL) were added. The solution was allowed to warm to −5 °C over 1.5 h, at which time IR showed no remaining terminal alkyne (≈ 2140 cm^{-1}). Cold water was added, and the mixture was extracted with cold pentane. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure at 0 °C. The crude ynol ether was used immediately without purification. A cold solution of the ynol ether in THF (1.5 mL) was added dropwise to a solution of Dibal-H (1 M in toluene, 1.27 mL, 1.27 mmol) at 50 °C, and the reaction mixture was stirred at this temperature until IR showed no starting material remained (≈2260 cm^{-1}, 1 h). The solution was poured into cold saturated aqueous NH_4Cl, and the mixture was extracted with cold pentane. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pretreated with 2.5% of Et_3N, v/v) (eluent pentane) to afford 122 mg (46%) of the enol ether *R*3c as a slightly yellow oil: $[\alpha]^{20}_D$ −24.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (s, 2H), 6.00 (dt, J = 6.3, 1.5 Hz, 1H), 5.83 (ddt, J = 17.1, 10.1, 6.3 Hz, 1H), 5.34 (q, J = 6.8 Hz, 1H), 5.03 (ddt, J = 17.1, 1.9, 1.8 Hz, 1H), 4.93 (ddt, J = 10.1, 2.0, 1.5 Hz, 1H), 4.29 (dt, J = 7.2, 6.3 Hz, 1H), 3.76−3.20 (m, 2H), 3.00−2.76 (m, 2H), 1.60 (d, J = 6.9 Hz, 3H), 1.31−1.16 (m, 18H). This spectrum matched that published by our group.[15j]

(*S*,*Z*)-1,3,5-Triisopropyl-2-(1-(5-phenylpent-1-enyloxy)ethyl)-benzene (*S*3d). To a solution of the dichloroenol ether *S*1 (524 mg, 1.53 mmol) in anhydrous THF (6 mL) at −78 °C was added dropwise *n*-BuLi (2.5 M in hexanes, 1.34 mL, 3.35 mmol). The solution was allowed to warm to −55 °C and stirred 15 min, and then $Ph(CH_2)_3OTf$[31] (573 mg, 2.14 mmol) was added. The solution was allowed to warm to −30 °C over 40 min at which time IR showed no remaining terminal alkyne (≈2140 cm^{-1}). Pyridine (6 mL) and palladium (5% w/w on $BaSO_4$, 105 mg) were added, and the mixture was hydrogenated at room temperature until IR showed no starting material remained (≈2260 cm^{-1}, 1 h). The mixture was then filtered through Celite, and water was added. The mixture was extracted with Et_2O, the combined organic layers were successively washed with saturated aqueous $CuSO_4$, water, and brine, dried over anhydrous Na_2SO_4, and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pretreated with 2.5% of Et_3N, v/v) (eluent pentane/Et_2O, 100/0 to 98/2) to afford 440 mg (73%) of enol ether *S*3d as a colorless oil: $[\alpha]^{20}_D$ +28.6 (*c* 1.0, $CHCl_3$); IR (neat) 3028, 2963, 2930, 2865, 1658, 1459, 1080 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.11 (m, 5H), 7.00 (s, 2H), 5.97 (dt, J = 6.3, 1.4 Hz, 1H), 5.32 (q, J = 6.8 Hz, 1H), 4.34−4.23 (m, 1H), 3.80−3.14 (m, 2H), 2.86 (sept, J = 6.9 Hz, 1H), 2.68−2.58 (m, 2H), 2.28−2.02 (m, 2H), 1.67 (quint, J = 7.6 Hz, 2H), 1.60 (d, J = 6.8 Hz, 3H), 1.30−1.15 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.7, 144.2, 142.8, 133.1, 128.5, 128.2, 125.5, 122.0, 105.8, 75.3, 35.6, 34.0, 31.6, 29.1, 24.6, 23.94, 23.90, 22.5; MS (ESI) m/z 399.1 (M + Li)$^+$. Anal. Calcd for $C_{28}H_{40}O$: C, 85.66; H, 10.27. Found: C, 85.44; H, 10.49.

***(R,Z)*-6-(1-(2,4,6-Triisopropylphenyl)ethoxy)hex-5-enyl Benzoate (*R*3e).** To a solution of the dichloroenol ether *R*1 (950 mg, 2.77 mmol) in anhydrous THF (10 mL) at −78 °C was added dropwise *n*-BuLi (2.5 M in hexanes, 2.43 mL, 6.08 mmol). The solution was allowed to warm to −55 °C and stirred 15 min, and then $BzO(CH_2)_4OTf$ (1.36 g, 4.15 mmol) was added. The solution was allowed to warm to −30 °C over 40 min, at which time IR showed no remaining terminal alkyne (≈2140 cm^{-1}). Pyridine (10 mL) and palladium (5% w/w on $BaSO_4$, 190 mg) were added, and the mixture was hydrogenated (−30 °C to room temperature) until IR showed no starting material remained (≈2260 cm^{-1}, 1.75 h). The mixture was then filtered through Celite, and water was added. The mixture was extracted with Et_2O, and the combined organic layers were successively washed with saturated aqueous $CuSO_4$, water, and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pretreated with 2.5% of Et_3N, v/v) (eluent pentane/Et_2O, 98/2 to 97/3) to afford 1.18 g (94%) of enol ether *R*3e as a slightly yellow oil: $[\alpha]^{20}_D$ −21.1 (*c* 1.0, $CHCl_3$); IR (neat) 2955, 2930, 2865, 1723, 1665, 1275, 1080 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07−8.02 (m, 2H), 7.58−7.51 (m, 1H), 7.46−7.39 (m, 2H), 6.99 (s, 2H), 5.96 (dt, J = 6.3, 1.4 Hz, 1H), 5.32 (q, J = 6.8 Hz, 1H), 4.33 (t, J = 6.6 Hz, 1H), 4.26 (dd, J = 7.3, 6.4 Hz, 1H), 3.76−3.21 (m, 2H), 2.86 (sept, J = 6.9 Hz, 1H), 2.30−2.07 (m, 2H), 1.86−1.74 (m, 2H), 1.59 (d, J = 6.8 Hz, 3H), 1.56−1.43 (m, 3H), 1.28−1.16 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 147.6, 144.3, 133.0, 132.6, 130.5, 129.4, 128.2, 121.9, 105.4, 75.2, 64.9, 33.9, 29.0, 28.3, 26.1, 24.5, 23.85, 23.83, 23.7, 22.4; MS (ESI) m/z 457.2 (M + Li)$^+$. Anal. Calcd for $C_{30}H_{42}O_3$: C, 79.96; H, 9.40. Found: C, 79.66; H, 9.46.

***(R,Z)*-*tert*-Butyldimethyl(6-(1-(2,4,6-triisopropylphenyl)-ethoxy)hex-5-enyloxy)silane (*R*3f).** To a solution of the dichloroenol ether *R*1 (2.00 g, 5.83 mmol) in anhydrous THF (15 mL) at −78 °C was added dropwise *n*-BuLi (2.5 M in hexanes, 5.1 mL, 12.8 mmol). The solution was allowed to warm to −55 °C and stirred for 15 min, and then $TBDMSO(CH_2)_4I$ (4.5 mL, 17.5 mmol) and HMPA (5 mL) were added. The solution was allowed to warm to −5 °C over 1 h and was stirred at this temperature for 2 h (until IR showed no remaining terminal alkyne, ≈2140 cm^{-1}). The crude mixture was poured into cold saturated aqueous NH_4Cl, and the product was extracted with cold pentane. The combined organic layers were washed with cold brine, dried over anhydrous Na_2SO_4, and filtered, and the filtrate was concentrated under vacuum at 0 °C. The crude ynol ether was used immediately without purification. The crude ynol ether in pyridine (20 mL) was hydrogenated over palladium (5% w/w on $BaSO_4$, 400 mg) at room temperature (until IR showed no remaining triple bond, ≈2260 cm^{-1}, 4.5 h). The reaction mixture was filtered through Celite and water was added. The mixture was extracted with pentane, and the combined organic layers were successively washed with saturated aqueous $CuSO_4$, water, and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The excess iodoalkane was destroyed by stirring the crude product with Zn(Cu) (1.6 g, 25 mmol) and $NaHCO_3$ (2 g) in EtOH (20 mL). After 20 h, pentane was added, and the mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pretreated with 2.5% of Et_3N, v/v) (eluent pentane) to afford 1.60 g (60%) of enol ether *R*3f as a colorless oil: IR (neat) 2959, 2927, 2851, 1661, 1463, 1257, 1101 cm^{-1} ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (s, 2H), 5.94 (dt, J = 6.4, 1.4 Hz, 1H), 5.31 (q, J = 6.8 Hz, 1H), 4.25 (dd, J = 7.1, 6.6 Hz, 1H), 3.61 (t, J = 6.6 Hz, 2H), 3.59−3.23 (m, 2H), 2.86 (sept, J = 6.9 Hz, 1H), 2.22−2.02 (m, 1H), 1.86−1.74 (m, 1H), 1.59 (d, J = 6.8 Hz, 3H), 1.58−1.48 (m, 2H), 1.44−1.31 (m, 2H), 1.28−1.19 (m, 18H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6, 144.0, 133.1, 122.1, 106.2, 75.2, 63.3, 34.0, 32.6, 29.4, 29.0, 26.03, 26.00, 24.6, 23.93, 23.91, 22.5, 18.4; HRMS (ESI) calcd for $C_{29}H_{52}O_2SiNa$ (M + Na)$^+$ 483.3629, found 483.3619.

***(R,Z)*-3-(1-(2,4,6-Triisopropylphenyl)ethoxy)prop-2-en-1-ol (*R*3j).** To a solution of dichloroenol ether *R*1 (2.12 g, 6.19 mmol) in anhydrous THF (30 mL) at −78 °C was added dropwise *n*-BuLi (2.5 M in hexanes, 5.45 mL, 13.6 mmol). The solution was allowed to warm to −55 °C and stirred for 15 min, and then formaldehyde was added (generated by thermal depolymerization of paraformaldehyde (929 mg, 30.9 mmol)). When IR showed no remaining terminal alkyne (≈2140 cm^{-1}, 15 min), MeOH (1 mL) was added, and the mixture was allowed to warm to −40 °C. Pyridine (16 mL) and palladium (5% w/w on $BaSO_4$, 212 mg) were then added, and the

dx.doi.org/10.1021/jo202261z | J. Org. Chem. 2012, 77, 1710−1721

mixture was hydrogenated (−40 to 0 °C) until IR showed no remaining triple bond (≈2260 cm^{-1}, 4.5 h). The mixture was filtered through Celite, and water was added. The crude mixture was extracted with Et_2O, and then the combined organic layers were washed with saturated aqueous $CuSO_4$ and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pretreated with 2.5% of Et_3N, v/v) (eluent pentane/Et_2O, 8/2 to 6/4) to afford 1.65 g (87%) of enol ether ^{R}**3j** as a pasty white solid: $[\alpha]^{20}_{D}$ −7.4 (*c* 1.0, $CHCl_3$); IR (neat) 3362, 2958, 2925, 2866, 1661, 1458, 1076 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (s, 2H), 6.07 (dt, *J* = 6.4, 1.1 Hz, 1H), 5.38 (q, *J* = 6.8 Hz, 1H), 4.58 (q, *J* = 6.7 Hz, 1H), 4.37−4.25 (m, 1H), 4.25−4.13 (m, 1H), 3.60−3.30 (m, 2H), 2.85 (sept, *J* = 7.0 Hz, 1H), 1.62 (d, *J* = 6.9 Hz, 3H), 1.30−1.15 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 146.8, 146.1, 132.3, 121.9, 105.1, 76.0, 65.7, 56.6, 33.9, 29.0, 24.5, 23.81, 23.79, 22.4, 15.1; MS (ESI) *m*/*z* 311.3 (M + Li)$^+$; HRMS (ESI) calcd for $C_{20}H_{32}O_2Na$ (M + Na)$^+$ 327.2294, found 327.2289.

(*R*,*Z*)-Triisopropyl(3-(1-(2,4,6-triisopropylphenyl)ethoxy)-allyloxy)silane (^{R}3g). To a solution of the enol ether ^{R}**3j** (6.46 g, 21.2 mmol) in DMF (90 mL) at 0 °C were added imidazole (1.88 g, 27.6 mmol) and a catalytic quantity of DMAP. TIPSCl (5.9 mL, 27.6 mmol) was then added, and after 5 min, the mixture was allowed to warm to room temperature. When TLC showed complete disappearance of the starting material, the reaction was quenched with water, and the mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pretreated with 2.5% of Et_3N, v/v) (eluent pentane/Et_2O, 99/1 to 98/2) to afford 9.23 g (94%) of enol ether ^{R}**3g** as a colorless oil: $[\alpha]^{20}_{D}$ −32.3 (*c* 1.0, $CHCl_3$); IR (neat) 2953, 2866, 1660, 1463, 1067 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (s, 2H), 5.98−5.94 (m, 1H), 5.32 (q, *J* = 6.8 Hz, 1H), 4.57−4.48 (m, 2H), 4.31−4.21 (m, 1H), 3.63−3.28 (m, 2H), 2.85 (sept, *J* = 6.9 Hz, 1H), 1.59 (d, *J* = 6.8 Hz, 3H), 1.28−1.18 (m, 18H), 1.11−1.04 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8, 144.1, 132.8, 121.9, 106.7, 75.9, 57.5, 34.0, 29.1, 24.6, 23.92, 23.89, 22.5, 18.0, 12.0; MS (ESI) *m*/*z* 467.4 (M + Li)$^+$. Anal. Calcd for $C_{29}H_{52}O_2Si$: C, 75.59; H, 11.38. Found: C, 75.44; H, 11.14.

(*R*,*Z*)-2-(1-(3-(Benzyloxy)prop-1-enyloxy)ethyl)-1,3,5-triisopropylbenzene (^{R}3h). To a suspension of NaH (60 wt % in oil, 197 mg, 4.93 mmol) (washed with 2 mL of pentane) in anhydrous THF (2 mL) at 0 °C was added dropwise a solution of the enol ether ^{R}**3j** (500 mg, 1.64 mmol) in anhydrous THF (5 mL). After 5 min, benzyl bromide (0.391 mL, 3.28 mmol) and a catalytic quantity of tetrabutylammonium iodide were added. After an additional 5 min, the mixture was allowed to warm to room temperature. After TLC showed complete disappearance of the starting material, the reaction was quenched at 0 °C with water and the mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pretreated with 2.5% of Et_3N, v/v) (eluent pentane/Et_2O, 99/1 to 96/4) to afford 588 mg (91%) of enol ether ^{R}**3h** as a colorless oil: IR (neat) 2960, 2929, 2867, 1660, 1450, 1070 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.22 (m, 5H), 7.00 (s, 2H), 6.13 (dt, *J* = 6.4, 1.2 Hz, 1H), 5.37 (q, *J* = 6.8 Hz, 1H), 4.58−4.49 (m, 3H), 4.28 (ddd, *J* = 11.6, 7.6, 1.2 Hz, 1H), 4.08 (ddd, *J* = 11.6, 6.3, 1.2 Hz, 1H), 3.63−3.26 (m, 2H), 2.85 (sept, *J* = 6.9 Hz, 1H), 1.61 (d, *J* = 6.8 Hz, 3H), 1.29−1.13 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 146.9, 138.7, 132.5, 128.2, 127.8, 127.3, 122.0, 102.4, 76.0, 71.8, 63.5, 34.0, 29.1, 24.6, 23.9, 22.4; MS (ESI) *m*/*z* 401.2 (M + Li)$^+$. Anal. Calcd for $C_{27}H_{38}O_2$: C, 82.19; H, 9.71. Found: C, 81.83; H, 9.50.

(*R*,*Z*)-3-(1-(2,4,6-Triisopropylphenyl)ethoxy)allyl Benzoate (^{R}3i). To a solution of the enol ether ^{R}**3j** (336 mg, 1.10 mmol) in distilled pyridine (2 mL) at 0 °C was added benzoyl chloride (0.166 mL, 1.43 mmol). After 10 min, the mixture was allowed to warm to room temperature. After TLC showed complete disappearance of the starting material, the reaction was quenched with water, and the mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pretreated with 2.5% of Et_3N, v/v) (eluent pentane/Et_2O, 97/3) to afford 411 mg (91%) of the benzoyl-protected enol ether ^{R}**3i** as a low-melting solid: $[\alpha]^{20}_{D}$ +52.7 (*c* 1.0, $CHCl_3$); IR (neat) 2961, 2928, 2870, 1613, 1462, 1105 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09−8.02 (m, 2H), 7.58−7.50 (m, 1H), 7.47−7.38 (m, 2H), 7.02, (s, 2H), 6.21 (dt, *J* = 6.3, 1.0 Hz, 1H), 5.44 (q, *J* = 6.8 Hz, 1H), 5.03 (ddd, *J* = 12.2, 7.5, 1.1 Hz, 1H), 4.92 (ddd, *J* = 12.1, 7.0, 1.1 Hz, 1H), 4.69−4.61 (m, 1H), 3.71−3.26 (m, 2H), 2.87 (sept, *J* = 6.9 Hz, 1H), 1.66 (d, *J* = 6.8 Hz, 3H), 1.31−1.19 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 151.7, 147.9, 132.6, 132.2, 130.6, 129.4, 128.2, 122.1, 99.7, 75.3, 63.2, 34.0, 29.0, 24.6, 24.5, 23.9, 23.8, 22.4; MS (ESI) *m*/*z* 415.1 (M + Li)$^+$. Anal. Calcd for $C_{27}H_{36}O_3$: C, 79.38; H, 8.89. Found: C, 79.39; H, 8.75.

General Procedure for the Synthesis of Cyclobutanones 5a−i by Cycloaddition−Dechlorination. To the enol ether **3** (1 mmol) in degassed Et_2O (20 mL) at 20 °C was added Zn(Cu) (15 mmol), followed by trichloroacetyl chloride (2.0 mmol) dropwise over 30 min. A saturated solution of ammonium chloride in methanol (40 mL) was then added, and the resulting mixture was refluxed for 10 min. The crude product was isolated in the usual way and purified by flash chromatography on silica gel to afford the dechlorinated cyclobutanone.

(2*R*,3*R*)-2-Methyl-3-((*S*)-1-(2,4,6-triisopropylphenyl)ethoxy)-cyclobutanone (^{S}5a). According to the general procedure, enol ether ^{S}**3a** (141 mg, 0.489 mmol) afforded 134 mg (83%) of cyclobutanone ^{S}**5a** as white crystals: mp 50−51 °C; $[\alpha]^{20}_{D}$ −103 (*c* 1.0, $CHCl_3$); IR (neat) 2963, 2927, 2869, 1788, 1607, 1455, 1383, 1177, 1076 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (s, 1H), 6.96 (s, 1H), 5.05 (q, *J* = 6.8 Hz, 1H), 4.18−4.11 (m, 1H), 3.95 (sept, *J* = 6.8 Hz, 1H), 3.34−3.23 (m, 1H), 3.14 (sept, *J* = 6.8 Hz, 1H), 3.11 (ddd, *J* = 17.3, 5.7, 4.7 Hz, 1H), 2.97 (ddd, *J* = 17.3, 3.1, 1.7 Hz, 1H), 2.86 (sept, *J* = 7.0 Hz, 1H), 1.55 (d, *J* = 6.8 Hz, 3H), 1.28−1.14 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.6, 148.8, 147.6, 146.0, 132.3, 123.3, 120.5, 70.8, 63.9, 58.1, 52.0, 34.0, 29.1, 28.1, 25.1, 24.9, 24.5, 24.3, 23.9, 23.9, 23.1, 7.3; MS (ESI) *m*/*z* 337.1 (M + Li)$^+$. Anal. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 79.65; H, 10.43.

(2*R*,3*R*)-2-Benzyl-3-((*S*)-1-(2,4,6-triisopropylphenyl)ethoxy)-cyclobutanone (^{S}5b). According to the general procedure, enol ether ^{S}**3b** (111 mg, 0.304 mmol) afforded 101 mg (85%) of cyclobutanone ^{S}**5b** as white crystals: mp 146−146.5 °C; $[\alpha]^{20}_{D}$ −68.1 (*c* 1.0, $CHCl_3$); IR (neat) 2955, 2927, 2865, 1784, 1455, 1080 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.13 (m, 5H), 7.04 (s, 1H), 6.95 (s, 1H), 5.12 (q, *J* = 6.8 Hz, 1H), 4.27−4.19 (m, 1H), 3.86 (sept, *J* = 6.7 Hz, 1H), 3.54−3.42 (m, 1H), 3.21−3.00 (m, 5H), 2.85 (sept, *J* = 6.9 Hz, 1H), 1.59 (d, *J* = 6.8 Hz, 3H), 1.30−1.15 (m, 15H), 1.06−0.99 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.4, 148.8, 147.7, 146.0, 142.1, 132.2, 128.3, 128.2, 125.6, 123.3, 120.6, 71.0, 64.0, 63.2, 52.3, 35.9, 34.0, 29.5, 29.1, 28.1, 24.9, 24.8, 24.5, 24.4, 23.9, 23.9, 23.1; MS (ESI) *m*/*z* 413.1 (M + Li)$^+$. Anal. Calcd for $C_{28}H_{38}O_2$: C, 82.72; H, 9.42. Found: C, 82.65; H, 9.39.

(2*S*,3*S*)-2-Allyl-3-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)-cyclobutanone (^{R}5c). According to the general procedure, enol ether ^{R}**3c** (316 mg, 1.00 mmol) afforded 288 mg (81%) of cyclobutanone ^{R}**5c** as a colorless oil: $[\alpha]^{20}_{D}$ +75.4 (*c* 1.0, $CHCl_3$); IR (neat) 3075, 2959, 2927, 2865, 1784, 1604, 1173, 1105, 1076 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (s, 1H), 6.95 (s, 1H), 5.92 (ddt, *J* = 17.0, 10.1, 6.9 Hz, 1H), 5.10−5.00 (m, 3H), 4.22−4.17 (m, 1H), 3.93 (sept, *J* = 6.8 Hz, 1H), 3.29−3.22 (m, 1H), 3.10−3.00 (m, 3H), 2.86 (sept, *J* = 6.9 Hz, 1H), 2.55−2.40 (m, 2H), 1.55 (d, *J* = 6.7 Hz, 3H), 1.26−1.16 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.9, 148.8, 147.6, 146.0, 136.0, 132.1, 123.3, 120.6, 115.9, 71.0, 63.8, 62.7, 52.3, 34.0, 29.0, 28.3, 28.1, 25.2, 25.0, 24.5, 24.4, 23.90, 23.88, 23.1; MS (ESI) *m*/*z* 363.1 (M + Li)$^+$; HRMS (ESI) calcd for $C_{24}H_{36}O_2Na$ (M + Na)$^+$ 379.2607, found 379.2615.

(2*R*,3*R*)-2-(3-Phenylpropyl)-3-((*S*)-1-(2,4,6-triisopropylphenyl)ethoxy)cyclobutanone (^{S}5d). According to the general procedure, enol ether ^{S}**3d** (98 mg, 0.25 mmol) afforded 90 mg (83%) of cyclobutanone ^{S}**5d** (white solid), as a mixture of diastereoisomers (dr = 96:4). Data for the major diastereoisomer: IR

dx.doi.org/10.1021/jo202261z | J. Org. Chem. 2012, 77, 1710−1721

(neat) 3024, 2959, 2927, 2865, 1781, 1457, 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30−7.11 (m, 5H), 7.05 (s, 1H), 6.95 (s, 1H), 5.05 (q, J = 6.8 Hz, 1H), 4.20−4.11 (m, 1H), 3.89 (sept, J = 6.8 Hz, 1H), 3.22−2.94 (m, 4H), 2.86 (sept, J = 6.9 Hz, 1H), 2.69−2.52 (m, 2H), 1.90−1.64 (m, 4H), 1.53 (d, J = 6.8 Hz, 3H), 1.28−1.06 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.8, 148.8, 147.6, 146.0, 142.2, 132.2, 128.4, 128.2, 125.6, 123.2, 120.5, 71.0, 64.0, 63.2, 52.3, 35.9, 34.0, 29.5, 29.1, 28.1, 25.1, 24.9, 24.5, 24.4, 23.91, 23.89, 23.6, 23.1; MS (ESI) m/z 441.1 $(M + Li)^+$. Anal. Calcd for $C_{30}H_{42}O_2$: C, 82.90; H, 9.74. Found: C, 83.24; H, 9.85.

4-((1*S*,4*S*)-2-Oxo-4-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)-cyclobutyl)butyl Benzoate (^{R}5e). According to the general procedure, enol ether ^{R}**3e** (116 mg, 0.257 mmol) afforded 112 mg (88%) of cyclobutanone ^{R}**5e** as a colorless oil: $[\alpha]^{20}_D$ +57.5 (c 1.0, $CHCl_3$); IR 2959, 2927, 2865, 1784, 1719, 1451, 1116, 1069 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.08−8.00 (m, 2H), 7.58−7.50 (m, 1H), 7.47−7.38 (m, 2H), 7.05 (s, 1H), 6.95 (s, 1H), 5.06 (q, J = 6.8 Hz, 1H), 4.39−4.22 (m, 2H), 4.21−4.13 (m, 1H), 3.89 (sept, J = 6.7 Hz, 1H), 3.26−2.97 (m, 4H), 2.86 (sept, J = 6.9 Hz, 1H), 1.91−1.60 (m, 6H), 1.54 (d, J = 6.8 Hz, 3H), 1.28−1.14 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.6, 166.6, 148.7, 147.6, 146.0, 132.7, 132.1, 129.5, 128.3, 123.2, 120.6, 70.9, 64.8, 63.9, 63.1, 52.2, 33.9, 29.0, 28.8, 28.1, 25.1, 24.9, 24.8, 24.5, 24.4, 23.9, 23.6, 23.1; MS (ESI) m/z 499.1 $(M + Li)^+$. Anal. Calcd for $C_{32}H_{44}O_4$: C, 78.01; H, 9.01. Found: C, 78.01; H, 8.96.

(2*S*,3*S*)-2-(4-(*tert*-Butyldimethylsilyloxy)butyl)-3-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)cyclobutanone (^{R}5f). According to the general procedure, enol ether ^{R}**3f** (74 mg, 0.161 mmol) afforded 64 mg (79%) of cyclobutanone ^{R}**5f** as a colorless oil: $[\alpha]^{20}_D$ +56.3 (c 1.0, $CHCl_3$); IR (neat) 2955, 2923, 2858, 1788, 1607, 1463, 1257, 1101 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.06 (s, 1H), 6.95 (s, 1H), 5.05 (q, J = 6.8 Hz, 1H), 4.19−4.12 (m, 1H), 3.93 (sept, J = 6.8 Hz, 1H), 3.59 (t, J = 6.3 Hz, 2H), 3.19−3.08 (m, 2H), 3.08−2.97 (m, 2H), 2.86 (sept, J = 6.9 Hz, 1H), 1.82−1.62 (m, 2H), 1.61−1.46 (m, 6H), 1.46−1.33 (m, 1H), 1.30−1.14 (m, 18H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.0, 148.8, 147.6, 146.0, 132.2, 123.3, 120.6, 70.9, 63.9, 63.4, 63.0, 52.2, 34.0, 32.9, 29.0, 28.1, 26.0, 25.1, 25.0, 24.5, 24.4, 24.2, 23.92, 23.90, 23.8, 23.1, 18.3, −5.3; MS (ESI) m/z 509.3 $(M + Li)^+$; HRMS (ESI) calcd for $C_{31}H_{54}O_3SiNa$ $(M + Na)^+$ 525.37344, found 525.37412.

(2*S*,3*S*)-3-((*R*)-1-(2,4,6-Triisopropylphenyl)ethoxy)-2-((triisopropylsilyloxy)methyl)cyclobutanone (^{R}5g). According to the general procedure, enol ether ^{R}**3g** (2.50 g, 5.43 mmol) afforded 2.12 g (78%) of cyclobutanone ^{R}**5g** as a colorless oil: $[\alpha]^{20}_D$ +57.2 (c 1.0, $CHCl_3$); IR (neat) 2962, 2890, 2869, 1789, 1462, 1383, 1122, 1098, 1076, 880 cm^{-1};^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (s, 1H), 7.05 (s, 1H), 5,07 (q, J = 6.8 Hz, 1H), 4.24−4.15 (m, 1H), 4.14−4.03 (m, 2H), 3.96 (sept, J = 6.7 Hz, 1H), 3.35−3.25 (m, 1H), 3.22−2.99 (m, 3H), 2.86 (sept, J = 6.9 Hz, 1H), 1.55 (d, J = 6.8 Hz, 3H), 1.29−1.00 (m, 39H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.0, 148.7, 147.6, 146.0, 132.4, 123.3, 120.5, 71.2, 65.8, 63.4, 57.8, 54.2, 34.0, 29.0, 28.2, 25.1, 24.7, 24.5, 23.91, 23.89, 23.1, 18.0, 11.9; MS (ESI) m/z 509.5 $(M + Li)^+$. Anal. Calcd for $C_{31}H_{54}O_3Si$: C, 74.05; H, 10.83. Found: C, 73.98; H, 10.97.

(*S*)-2-Methylene-3-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)-cyclobutanone (^{R}5i). According to the general procedure, enol ether ^{R}**3i** (149 mg, 0.365 mmol) afforded 78 mg (65%) of enone ^{R}**5i** as a mixture of diastereoisomers (dr = 92:8) and colorless oil. Data for the major diastereoisomer: IR (neat) 2955, 2927, 2865, 1766, 1080 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.14−6.90 (m, 2H), 5.83 (d, J = 2.2 Hz, 1H), 5.20 (d, J = 1.0 Hz, 1H), 5.12 (q, J = 6.9 Hz, 1H), 4.61−4.56 (m, 1H), 4.06−3.85 (m, 1H), 3.16 (m, 1H), 3.10 (dd, J = 17.4, 6.5 Hz, 1H), 3.00 (dd, J = 17.4, 4.8 Hz, 1H), 2.87 (sept, J = 6.9 Hz, 1H), 1.60 (d, J = 6.8 Hz, 3H), 1.30−1.12 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.4, 156.2, 148.8, 147.9, 146.1, 132.0, 123.3, 120.7, 115.5, 72.1, 68.2, 52.9, 34.0, 29.0, 28.3, 24.7, 24.6, 23.91, 23.88, 23.1; MS (ESI) m/z 335.1 $(M + Li)^+$; HRMS (ESI) calcd for $C_{22}H_{32}O_2Na$ $(M + Na)^+$ 351.2294, found 351.2303.

(2*R*,3*S*,4*R*)-2-Chloro-4-methyl-3-((*S*)-1-(2,4,6-triisopropylphenyl)ethoxy)cyclobutanone (^{S}6a). To enol ether ^{S}**3a** (70 mg, 0.243 mmol) in degassed Et_2O (5 mL) at 20 °C was added Zn(Cu) (71 mg, 1.1 mmol), followed by trichloroacetyl chloride (0.053 mL, 0.48 mmol) dropwise over 30 min. The mixture was stirred at 0 °C until TLC showed complete disappearance of the starting material, and then pentane was added, the mixture was filtered through sand, and the filtrate was concentrated under reduced pressure. The residue was dissolved in EtOH (0.2 mL) and a saturated solution of ammonium chloride in methanol (5 mL) and Zn(Cu) (142 mg, 2.2 mmol) were added. After being stirred for 5 min at −18 °C, the mixture was filtered through Celite. Water was added, and the crude product was isolated in the usual way and purified by flash chromatography on silica gel (eluent pentane/Et_2O, 98/2) to afford 64 mg (72%) of monochlorocyclobutanone ^{S}**6a** as a colorless oil: IR (neat) 2958, 2931, 2868, 1793, 1607, 1456, 1382, 1100, 1066, 879; ^1H NMR (300 MHz, $CDCl_3$) δ 7.05 (s, 1H), 6.98 (s, 1H), 5.29 (q, J = 6.8 Hz, 1H), 4.80 (dd, J = 4.3, 2.8 Hz, 1H), 4.10 (dd, J = 8.9, 4.3 Hz, 1H), 3.94−3.74 (m, 1H), 3.48−3.34 (m, 1H), 3.34−3.18 (m, 1H), 2.87 (sept, J = 6.9 Hz, 1H), 1.61 (d, J = 6.8 Hz, 3H), 1.37−1.08 (m, 21H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.2, 148.6, 147.9, 146.5, 131.6, 123.3, 120.7, 72.9, 72.3, 66.5, 54.8, 34.0, 29.0, 28.4, 25.2, 24.7, 23.9, 23.2, 8.4; MS (APCI) m/z 363 $(M - H)^-$; HRMS (ESI) calcd for $C_{22}H_{33}ClNaO_2$ $(M + Na)^+$ 387.20668, found 387.20628.

(*R*,*E*)-1,3,5-Triisopropyl-2-(1-(penta-1,4-dienyloxy)ethyl)-benzene (^{R}9c). To a solution of the dichloroenol ether ^{R}**1** (550 mg, 1.60 mmol) in anhydrous THF (5 mL) at −78 °C was added dropwise *n*-BuLi (2.5 M in hexanes, 1.41 mL, 3.52 mmol). The solution was allowed to warm to −55 °C and stirred for 20 min, and then allyl iodide (0.293 mL, 3.2 mmol) (prefiltered through a pad of basic alumina) and distilled HMPA (0.5 mL) were added. The solution was allowed to warm to −5 °C and was stirred for 20 min, at which time TLC showed no remaining terminal alkyne. The reaction mixture was then added to a solution of $LiAlH_4$ (1.0 M in THF, 4.8 mL, 4.8 mmol) in anhydrous Et_2O (5 mL) at reflux, and after 25 min, an additional portion of $LiAlH_4$ in THF (1.0 M, 3.2 mL, 3.2 mmol) was added. After an additional 50 min (no triple bond by IR), the reaction was quenched with aqueous NaOH (3 N, 4 mL), Na_2SO_4 added, the resulting mixture filtered, and the filtrate concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pretreated with 2.5% of Et_3N, v/v) (eluent pentane) to afford 315 mg (62%) of enol ether ^{R}**9c** as a colorless oil: $[\alpha]^{20}_D$ +53.3 (c 1.0, $CHCl_3$); IR (neat) 2958, 2926, 2866, 1669, 1460, 1150, 1061, 912 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.00 (s, 2H), 6.04 (td, J = 12.4, 1.3 Hz, 1H), 5.75 (ddt, J = 17.1, 10.1, 5.9 Hz, 1H), 5.36 (q, J = 6.8 Hz, 1H), 4.97−4.81 (m, 3H), 3.75−3.21 (m, 2H), 2.85 (sept, J = 6.9 Hz, 1H), 2.61−2.54 (m, 2H), 1.60 (d, J = 6.8 Hz, 3H), 1.28−1.18 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.7, 146.1, 138.0, 132.9, 121.9, 114.3, 103.5, 83.0, 74.4, 34.0, 31.7, 29.0, 24.6, 24.5, 23.92, 23.90, 22.5; MS (ESI) m/z 321.2 $(M + Li)^+$. Anal. Calcd for $C_{22}H_{36}O_2$ $(M + H_2O)$ C, 79.46; H, 10.91. Found: C, 79.43; H, 10.63.

(*R*,*E*)-3-(1-(2,4,6-Triisopropylphenyl)ethoxy)prop-2-en-1-ol (^{R}9j). To a solution of dichloroenol ether ^{R}**1** (4.17 g, 12.1 mmol) in anhydrous THF (30 mL) at −78 °C was added dropwise *n*-BuLi (1.6 M in hexanes, 16.7 mL, 26.7 mmol). The solution was allowed to warm to −55 °C and stirred for 10 min, and then formaldehyde was added (generated by thermal decomposition of paraformaldehyde (1.82 g, 60.7 mmol)). When IR showed no remaining terminal alkyne (≈2140 cm^{-1}, 15 min), MeOH (5 mL) was added, and the mixture was poured onto ice. The crude mixture was extracted with cold Et_2O, and the combined organic layers were washed with cold brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure at 0 °C. The crude ynol ether was used immediately without purification. A solution of the crude product in anhydrous Et_2O (20 mL) was added to a suspension of $LiAlH_4$ (3.69 g, 97.1 mmol) in anhydrous Et_2O (20 mL) at reflux, and the resulting mixture was refluxed until IR showed no remaining triple bond (≈ 2260 cm^{-1}, 10 min). The reaction mixture was then treated slowly with water (3.7 mL), a solution of NaOH (15%, 3.7 mL), and finally water (11 mL). Na_2SO_4 was added, the resulting mixture filtered, and the filtrate concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pretreated with 2.5% of Et_3N, v/v)

dx.doi.org/10.1021/jo202261z | J. Org. Chem. 2012, 77, 1710−1721

(eluent pentane/Et_2O, 7/3) to afford 1.73 g (47%) of enol ether ^{R}**9j** as a colorless, low-melting solid: $[\alpha]^{20}_D$ +38.2 (*c* 1.0, $CHCl_3$); IR (neat) 3360, 2964, 2929, 2866, 1674, 1453, 1165 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7,00 (s, 2H), 6.33 (dt, *J* = 12.3, 0.9 Hz, 1H), 5.42 (q, *J* = 6.8 Hz, 1H), 5.12 (dt, *J* = 12.3, 7.6 Hz, 1H), 3.95 (ddd, *J* = 7.6, 5.7, 0.9 Hz, 2H), 3.45 (s, 2H), 2.86 (sept, *J* = 6.9 Hz, 1H), 1.62 (d, *J* = 6.8 Hz, 3H), 1.28−1.18 (18H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.9, 147.7, 132.4, 121.7, 104.6, 74.8, 60.1, 33.9, 28.9, 24.5, 24.4, 23.8, 23.7, 22.3; MS (ESI) *m*/*z* 311.3 $(M + Li)^+$; HRMS (ESI) calcd for $C_{20}H_{32}O_2Na$ $(M + Na)^+$ 327.2294, found 327.2292.

(*R*,*E*)-Triisopropyl(3-(1-(2,4,6-triisopropylphenyl)ethoxy)-allyloxy)silane (^{R}9g). The procedure for the formation of enol ether **3g** was applied to enol ether ^{R}**9j** (500 mg, 1.64 mmol) affording 669 mg (88%) of enol ether ^{R}**9g** as a yellowish oil: $[\alpha]^{20}_D$ +39.6 (*c* 1.0, $CHCl_3$); IR (neat) 2959, 2861, 1676, 1466, 1061 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.99 (s, 2H), 6.26 (dt, *J* = 12.3, 1.1 Hz, 1H), 5.40 (q, *J* = 6.8 Hz, 1H), 5.04 (dt, *J* = 12.9, 6.5 Hz, 1H), 4.08 (dd, *J* = 6.6, 1.2 Hz, 2H), 3.61−3.33 (m, 2H), 2.85 (sept, *J* = 6.9 Hz, 1H), 1.61 (d, *J* = 6.8 Hz, 3H), 1.30−1.17 (18H, m), 1.04−0.94 (21H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8, 147.5, 132.7, 122.0, 105.3, 74.7, 61.2, 34.0, 29.0, 24.5, 24.5, 23.95, 23.90, 22.5, 18.0, 12.0; MS (ESI) *m*/*z* 467.4 $(M + Li)^+$; HRMS (ESI) calcd for $C_{29}H_{52}O_2SiNa$ $(M + Na)^+$ 483.3629, found 483.3619.

(*R*,*E*)-2-(1-(3-(Benzyloxy)prop-1-enyloxy)ethyl)-1,3,5-triisopropylbenzene (^{R}9h). The procedure for the formation of enol ether **3h** was applied to enol ether ^{R}**9j** (254 mg, 0.834 mmol) affording 255 mg (77%) of enol ether ^{R}**9h** as a colorless oil: $[\alpha]^{20}_D$ +50.0 (*c* 1.0, $CHCl_3$); IR (neat) 2960, 2929, 2866, 1667, 1453, 1064 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39−7.19 (m, 5H), 7.00 (s, 2H), 6.29 (d, *J* = 12.5 Hz, 1H), 5.43 (q, *J* = 6.8 Hz, 1H), 5.04 (dt, *J* = 12.4, 7.5 Hz, 1H), 4.37 (s, 2H), 3.87−3.82 (m, 2H), 3.62−3.32 (m, 2H), 2.85 (sept, *J* = 6.9 Hz, 1H), 1.62 (d, *J* = 6.8 Hz, 3H), 1.30−1.17 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9, 147.9, 138.5, 132.5, 128.3, 127.8, 127.4, 121.9, 101.7, 74.9, 70.6, 67.3, 34.0, 29.1, 24.6, 24.5, 23.90, 23.88, 22.4; MS (ESI) *m*/*z* 401.2 $(M + Li)^+$; HRMS (ESI) calcd for $C_{27}H_{38}NaO_2$ $(M + Na)^+$ 417.27695, found 417.27712.

General Procedure for the Synthesis of trans Cyclobutanones 10c,g,h by Epimerization of cis Cyclobutanones. A solution of the cyclobutanone **5** (1 mmol) in anhydrous CH_2Cl_2 (10 mL) was treated with DBU (0.3 mmol) and then stirred for 3.5 h. Water was added, and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent pentane/Et_2O, 99/1 to 98/2) to afford the trans cyclobutanone.

(2*R*,3*S*)-2-Allyl-3-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)-cyclobutanone (^{R}10c). According to the general procedure for the synthesis of trans cyclobutanones, cis cyclobutanone ^{R}**5c** (37 mg, 0.104 mmol) afforded 30 mg (81%) of cyclobutanone ^{R}**10c** as white crystals: mp 47−48 °C; $[\alpha]^{20}_D$ +126 (*c* 1.0, $CHCl_3$); IR (neat) 3078, 2955, 2923, 2865, 1784, 1607, 1188, 1101, 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.02 (s, 2H), 5.77−5.66 (m, 1H), 5.07 (q, *J* = 6.8 Hz, 1H), 5.03−4.95 (m, 2H), 3.94 (q, *J* = 5.6 Hz, 1H), 3.92−3.55 (m, 1H), 3.77−3.29 (m, 1H), 3.29−2.97 (m, 3H), 2.86 (sept, *J* = 6.8 Hz, 1H), 2.30−2.16 (m, 2H), 1.58 (d, *J* = 6.8 Hz, 3H), 1.30−1.15 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.3, 148.8, 147.7, 145.5, 134.4, 132.7, 123.1, 120.6, 117.0, 77.2, 72.2, 67.0, 65.9, 51.8, 34.0, 31.4, 28.8, 24.8, 23.9, 22; MS (ESI) *m*/*z* 363.1 $(M + Li)^+$. Anal. Calcd for $C_{24}H_{36}O_2$: C, 80.85; H, 10.18. Found: C, 80.60; H, 10.39.

(2*R*,3*S*)-3-((*R*)-1-(2,4,6-Triisopropylphenyl)ethoxy)-2-((triisopropylsilyloxy)methyl)cyclobutanone (^{R}10g). According to the general procedure for the synthesis of trans cyclobutanones, the cis cyclobutanone ^{R}**5g** (99 mg, 0.197 mmol) afforded 79 mg (80%) of cyclobutanone ^{R}**10g** as white crystals: mp 50−51 °C; $[\alpha]^{20}_D$ +100 (*c* 1.0, $CHCl_3$); IR (neat) 2959, 2865, 1792, 1604, 1459, 1383, 1192, 1112, 1080 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.11−6.87 (m, 2H), 5.05 (q, *J* = 6.8 Hz, 1H), 4.34 (dt, *J* = 6.3, 4.4 Hz, 1H), 3.97 (dd, *J* = 10.3, 2.6 Hz, 1H), 3.94−3.73 (m, 1H), 3.70 (dd, *J* = 10.3, 3.4 Hz, 1H), 3.27−3.22 (m, 1H), 3.22−3.11 (m, 1H), 3.07 (ddd, *J* = 17.6, 6.4, 1.7 Hz, 1H), 2.98 (dt, J_1 = 17.6, 4.4 Hz, 1H), 2.85 (sept, *J* = 6.9 Hz, 1H), 1.60 (d, *J* = 6.8 Hz, 3H), 1.27−1.17 (m, 18H), 0.96−0.83 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.0, 148.6, 147.6, 145.8, 132.6, 123.3, 120.5, 71.8, 68.7, 64.4, 59.2, 53.2, 34.0, 28.8, 24.7, 24.0, 23.9, 22.8, 17.8, 11.7; MS (ESI) *m*/*z* 509.2 $(M + Li)^+$. Anal. Calcd for $C_{31}H_{54}O_3Si$: C, 74.05; H, 10.83. Found: C, 73.73; H, 10.76.

(2*R*,3*S*)-2-(Benzyloxymethyl)-3-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)cyclobutanone (^{R}10h). According to the general procedure for the synthesis of cis cyclobutanones, enol ether ^{R}**3h** (203 mg, 0.514 mmol) was transformed into cis cyclobutanone ^{R}**5h**, which was epimerized, without purification, according to the general procedure for the synthesis of trans cyclobutanones, to afford 165 mg (73%, two steps) of cyclobutanone ^{R}**10h** as white crystals: mp 89−90 °C; $[\alpha]^{20}_D$ +103 (*c* 1.0, $CHCl_3$); IR (neat) 2959, 2922, 2865, 1781, 1603, 1451, 1361, 1192, 1108, 1076 cm^{-1};^1H NMR (400 MHz, $CDCl_3$) δ 7.40−7.14 (m, 5H), 7.12−6.89 (m, 2H), 5.10 (q, *J* = 6.8 Hz, 1H), 4.39 (s, 2H), 4.34−4.27 (m, 1H), 4.01−3.71 (m, 1H), 3.60 (dd, *J* = 9.8, 4.2 Hz, 1H), 3.46−3.35 (m, 2H), 3.24−2.98 (m, 3H), 2.87 (sept, *J* = 6.9 Hz, 1H), 1.57 (d, *J* = 6.8 Hz, 3H), 1.30−1.12 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.3, 147.6, 137.8, 132.8, 128.3, 127.54, 127.49, 123.3, 120.5, 73.1, 72.1, 67.2, 65.4, 65.1, 52.6, 34.0, 24.6, 23.9, 22.6; MS (ESI) *m*/*z* 443.1 $(M + Li)^+$. Anal. Calcd for $C_{29}H_{40}O_3$: C, 79.78; H, 9.24. Found: C, 79.88; H, 9.32.

(2*S*,3*S*)-3-Hydroxy-2-((triisopropylsilyloxy)methyl)-cyclobutanone (11). To a solution of cyclobutanone ^{R}**5g** (81.0 mg, 0.161 mg) in CH_2Cl_2 (1.6 mL) at 0 °C was added TFA (0.124 mL, 1.61 mmol). The mixture was stirred at 0 °C until TLC showed complete disappearance of the starting material (7 min). The reaction mixture was then quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent pentane/Et_2O, 95/5 to 1/1) to afford 39.5 mg (90%) of cyclobutanol **11** as a colorless oil: $[\alpha]^{20}_D$ +40.8 (*c* 1.0, $CHCl_3$); IR (neat) 3498, 2945, 2890, 2869, 1781, 1462, 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.75 (ddt, *J* = 9.4, 7.5, 4.9 Hz, 1H), 4.27 (dd, *J* = 10.6, 3.9 Hz, 1H), 4.10 (dd, *J* = 10.5, 3.1 Hz, 1H), 3.87 (d, *J* = 9.4 Hz, 1H), 3.43−3.33 (m, 2H), 3.05−2.95 (m, 1H), 1.15−1.03 (m, 21H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.5, 65.0, 61.8, 59.8, 58.2, 17.9, 17.8, 11.7; MS (ESI) *m*/*z* 279.0 $(M + Li)^+$; HRMS (ESI) calcd for $C_{14}H_{28}O_3SiNa$ $(M + Na)^+$ 295.1700. Found: 295.1706.

(1*S*,2*S*,3*S*)-3-((*R*)-1-(2,4,6-Triisopropylphenyl)ethoxy)-2-((triisopropylsilyloxy)methyl)cyclobutanecarbaldehyde (12). To a suspension of Ph_3PCH_2OMe,Cl (3.61 g, 10.5 mmol) in anhydrous THF (35 mL) at −35 °C was added dropwise a solution of KHMDS (0.5 M in toluene, 18.4 mL, 9.2 mmol). After 10 min, the reaction mixture was allowed to warm to room temperature and stirred for 1.25 h, whereupon it was cooled again to −35 °C. A solution of the cyclobutanone ^{R}**5g** (1.32 g, 2.63 mmol) in anhydrous THF (20 mL) was added, and the mixture was allowed to warm to room temperature over 1.5 h and then refluxed for 2 h. The cooled reaction mixture was quenched with aqueous NH_4Cl and then water. The reaction mixture was extracted with Et_2O, and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pretreated with 2.5% of Et_3N, v/v) (eluent pentane/Et_2O, 99/1 to 98/2) to afford 1.03 g (74%) of a *Z*/*E* mixture of the corresponding enol ethers. To a solution of the mixture of enol ethers (318 mg, 0.599 mmol) in CH_2Cl_2 (40 mL) was added few drops of water and then trichloroacetic acid (980 mg, 5.99 mmol). After 1 h, the reaction mixture was quenched with aqueous $NaHCO_3$, and extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture of aldehydes was used without purification. A solution of the mixture of aldehydes (0.60 mmol based on a 100% yield for the previous reaction) in MeOH (10 mL) was stirred at room temperature with NaOMe (50 mg, 0.93 mmol) for 25 h. Water was added, and the mixture was extracted with Et_2O. The combined organic layers were washed with

dx.doi.org/10.1021/jo202261z | *J. Org. Chem.* 2012, 77, 1710−1721

brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent pentane/Et_2O, 98/2 to 96/4) to afford 266 mg (86%) of aldehyde **12** as a colorless oil: $[\alpha]^{20}_D$ +68.4 (*c* 1.0, $CHCl_3$); IR (neat) 2954, 2892, 2862, 1719, 1466, 1116, 1073 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.77 (d, *J* = 1.5 Hz, 1H), 7.01 (s, 1H), 6.92 (s, 1H), 4.91 (q, *J* = 6.8 Hz, 1H), 4.05−3.74 (m, 4H), 3.24−3.15 (m, 1H), 3.15−3.00 (m, 1H), 2.84 (sept, *J* = 6.9 Hz, 1H), 2.79−2.69 (m, 1H), 2.58−2.47 (m, 1H), 2.27−2.15 (m, 1H), 1.48 (d, *J* = 6.8 Hz, 3H), 1.28−1.00 (m, 39H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.2, 148.5, 147.3, 145.6, 133.1, 123.1, 120.4, 70.4, 69.3, 67.6, 61.4, 59.2, 48.5, 44.4, 44.1, 40.2, 33.9, 29.0, 28.34, 28.25, 24.5, 23.90, 23.87, 23.2, 18.04, 18.00, 17.97, 12.0; MS (ESI) *m*/*z* 523.3 $(M + Li)^+$. Anal. Calcd for $C_{32}H_{56}O_3Si$: C, 74.37; H, 10.92. Found: C, 74.28; H, 11.03.

((1*S*,2*S*,3*S*)-3-(1-(2,4,6-Triisopropylphenyl)ethoxy)-2-((triisopropylsilyloxy)methyl)cyclobutyl)methanol (13). To a solution of the aldehyde **12** (400 mg, 0.774 mmol) in EtOH (4 mL) at 0 °C was added $NaBH_4$ (59 mg, 1.55 mmol). The mixture was stirred at 0 °C until TLC showed complete disappearance of the starting material. The reaction was then quenched with water and a 30% solution of H_3PO_4. The mixture was extracted with AcOEt, the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and filtered, and the filtrate was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (eluent pentane/Et_2O, 9/1 to 8/2) to afford 375 mg (93%) of alcohol **13** as a colorless oil: $[\alpha]^{20}_D$ +37.6 (*c* 1.0, $CHCl_3$); IR (neat) 3411, 2959, 2894, 2865, 1459, 1101, 1072 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.02 (s, 1H), 6.91 (s, 1H), 4.96 (q, *J* = 6.8 Hz, 1H), 3.97−3.77 (m, 4H), 3.70−3.60 (m, 1H), 3.36 (dt, *J* = 10.2, 1.4 Hz, 1H), 3.16−3.02 (m, 1H), 2.97 (dd, *J* = 9.0, 1.5 Hz, 1H), 2.84 (sept, *J* = 6.9 Hz, 1H), 2.75−2.60 (m, 1H), 2.30−2.19 (m, 1H), 2.15−2.05 (m, 1H), 1.75−1.64 (m, 1H), 1.50 (d, *J* = 6.8 Hz, 3H), 1.27−1.00 (m, 39H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.5, 147.1, 145.7, 133.3, 123.0, 120.2, 70.6, 69.5, 66.7, 62.4, 47.1, 39.9, 33.9, 28.9, 28.4, 28.0, 25.1, 24.8, 24.4, 24.2, 23.9, 23.8, 23.3, 17.9, 11.9; MS (ESI) *m*/*z* 525.3 $(M + Li)^+$; HRMS (ESI) calcd for $C_{32}H_{58}O_3SiNa$ $(M + Na)^+$ 541.4047, found 541.4044. Anal. Calcd for $C_{32}H_{58}O_3Si$: C, 74.08; H, 11.27. Found: C, 74.23; H, 11.53.

((1*S*,2*S*,3*S*)-3-(1-(2,4,6-Triisopropylphenyl)ethoxy)-cyclobutane-1,2-diyl)dimethanol (16). A solution of tetrabutylammonium fluoride (1.0 M in THF, 6 mL) was added to neat **13** (357 mg, 0.69 mmol) at room temperature, and the solution was stirred for 20 min. Water was added, and the reaction mixture was extracted with AcOEt. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent pentane/Et_2O, 25/75 to 15/85) to afford 238 mg (95%) of the diol **16** as a white solid: $[\alpha]^{20}_D$ +107 (*c* 1.0, $CHCl_3$); IR (neat) 3364, 2959, 2930, 2869, 1611, 1463, 1383, 1112, 1080, 1029 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.03 (s, 1H), 6.93 (s, 1H), 5.01 (q, *J* = 6.8 Hz, 1H), 4.04 (dt, *J* = 6.9, 5.0 Hz, 1H), 3.90−3.74 (m, 3H), 3.60 (dd, *J* = 10.6, 6.3 Hz, 1H), 3.50 (dd, *J* = 10.6, 7.4 Hz, 1H), 3.10 (sept, *J* = 6.7 Hz, 1H), 2.85 (sept, *J* = 6.9 Hz, 1H), 2.51−2.31 (m, 2H), 2.24−2.13 (m, 1H), 1.98−1.87 (m, 1H), 1.53 (d, *J* = 6.8 Hz, 3H), 1.28−1.13 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.5, 147.3, 145.9, 132.3, 123.0, 120.3, 70.9, 69.6, 65.7, 62.2, 44.1, 34.7, 33.8, 29.7, 28.9, 28.3, 24.9, 24.6, 24.4, 24.3, 23.80, 23.77, 23.2; MS (ESI) *m*/*z* 369.1 $(M + Li)^+$; HRMS (ESI) calcd for $C_{23}H_{38}O_3Na$ $(M + Na)^+$ 285.2713, found 285.2716.

((1*S*,2*S*,3*S*)-3-Hydroxycyclobutane-1,2-diyl)bis(methylene) Dibenzoate (17). To a solution of the diol **16** (219 mg, 0.604 mmol) and a catalytic quantity of tetrabutylammonium iodide in distilled pyridine (2 mL) at 0 °C was added BzCl (0.154 mL, 1.33 mmol), and the solution was stirred for 30 min. Water was added, and the crude mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent pentane/Et_2O, 93/7) to afford 306 mg (89%) of the diester as a white solid: mp 100−101 °C; $[\alpha]^{20}_D$ +51.0 (*c* 1.0, $CHCl_3$); IR (neat) 3060, 2963, 2930, 2865, 1792, 1719, 1604, 1455, 1275, 1119 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07−7.88 (m, 4H), 7.58−7.46 (m, 2H), 7.42−7.27 (m, 4H), 7.03 (s, 1H), 6.93 (s, 1H), 5.00 (q, *J* = 6.8 Hz, 1H), 4.71−4.61 (m, 2H), 4.36 (dd, *J* = 11.1, 5.9 Hz, 1H), 4.28 (dd, *J* = 11.1, 7.2 Hz, 1H), 4.20−4.11 (m, 1H), 4.00−3.81 (m, 1H), 3.23−3.02 (m, 1H), 2.95−2.64 (m, 3H), 2.48−2.33 (m, 1H), 2.19−2.04 (m, 1H), 1.51 (d, *J* = 6.8 Hz, 3H), 1.32−1.11 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 166.5, 148.7, 147.3, 145.8, 134.5, 132.7, 130.5, 130.4, 130.0, 129.50, 129.47, 128.8, 128.3, 128.2, 123.2, 120.4, 69.7, 68.9, 67.5, 64.1, 41.3, 33.9, 32.3, 30.5, 29.0, 28.2, 25.0, 24.6, 24.3, 23.90, 23.89, 23.3; MS (ESI) *m*/*z* 577.1 $(M + Li)^+$; HRMS (ESI) calcd for $C_{37}H_{46}O_5Na$ $(M + Na)^+$ 593.3237, found 593.3231. To a solution the above diester (269 mg, 0.471 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added TFA (0.500 mL, 6.53 mmol), and the resulting solution was stirred for 8 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent pentane/AcOEt, 65/35) to afford 147 mg (92%) of cyclobutanol **17** as white crystals: mp 73−74 °C; $[\alpha]^{20}_D$ −12.1 (*c* 1.0, $CHCl_3$); IR (neat) 3461, 2937, 1714, 1275, 1112 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07−7.99 (m, 4H), 7.60−7.53 (m, 2H), 7.47−7.39 (m, 4H), 4.84 (dd, *J* = 11.5, 8.9 Hz, 1H), 4.48 (m, 1H), 4.41 (dd, *J* = 11.2, 5.5 Hz, 1H), 4.34 (dd, *J* = 11.2, 6.7 Hz, 1H), 4.27 (dd, *J* = 11.5, 4.5 Hz, 1H), 3.13 (d, *J* = 3.0 Hz, 1H), 2.82−2.72 (m, 1H), 2.71−2.62 (m, 1H), 2.25−2.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 166.6, 133.2, 133.1, 130.1, 129.8, 129.7, 129.6, 128.4, 67.2, 66.0, 63.1, 43.3, 33.0, 31.4; MS (ESI) *m*/*z* 347.0 $(M + Li)^+$; HRMS (ESI) calcd for $C_{20}H_{20}O_5Na$ $(M + Na)^+$ 363.1203, found 363.1210.

((1*S*,2*R*,3*R*)-3-(2-Amino-6-iodo-9*H*-purin-9-yl)cyclobutane-1,2-diyl)bis(methylene) Dibenzoate (18).[26c,d] To a solution of cyclobutanol **17** (67.8 mg, 0.199 mmol) in anhydrous CH_2Cl_2 (0.7 mL) was added distilled pyridine (0.024 mL, 0.299 mmol) and then Tf_2O (0.0503 mL, 0.299 mmol) dropwise over 5 min. After an additional 5 min, the mixture was allowed to warm to room temperature and was stirred for 5 min. The reaction mixture was quenched with ice-cold water and then extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude triflate was used without purification. To a solution of the above triflate (0.199 mmol based on a 100% yield for the previous reaction) in anhydrous CH_2Cl_2 (0.7 mmol) was added the 2-amino-6-iodopurine tetrabutylammonium salt[26c] (100 mg, 0.199 mmol). The mixture was stirred at room temperature for 19 h, and then the volatiles were removed under reduced pressure. The residue was dissolved in AcOEt (1 mL) and toluene (1 mL), and the solution was washed with aqueous H_3PO_4 (30%) and then with water (until TLC showed complete disappearance of the ammonium salt). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent pentane/AcOEt, 4/6) to afford 91.1 mg (78%) of compound **18**: $[\alpha]^{20}_D$ −16.3 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.10−8.03 (m, 2H), 7.91−7.79 (m, 3H), 7.62−7.50 (m, 2H), 7.50−7.34 (m, 4H), 5.05 (s, 2H), 4.68 (q, *J* = 8.8 Hz, 1H), 4.62−4.48 (m, 4H), 3.45−3.33 (m, 1H), 2.75−2.53 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 166.2, 158.5, 149.8, 140.2, 133.20, 133.17, 132.7, 129.7, 129.5, 129.3, 128.5, 128.4, 122.8, 65.9, 64.6, 48.9, 45.2, 31.1, 28.7; MS (ESI) *m*/*z* 589.9 $(M + Li)^+$.

9-((1*R*,2*R*,3*S*)-2,3-Bis(hydroxymethyl)cyclobutyl)-2-amino-1*H*-purin-6(9*H*)-one (Cyclobut-G, 19). To a solution of **18** (58.0 mg, 0.0994 mmol) in freshly distilled MeOH (0.5 mL) was added a solution of NaOMe (4 M in MeOH, 0.037 mL, 0.148 mmol). The mixture was stirred at reflux for 1.5 h. After the pH was adjusted to 0.5−1.0 with a solution of 1 N HCl, the reaction mixture was extracted with CH_2Cl_2, and the aqueous layer was stirred at 90 °C for 3 h. The reaction mixture was then neutralized with 3 N aqueous NaOH to give a white precipitate. This mixture was centrifuged, and the solid was washed several times with ice-cold distilled water. The solid was dried over P_2O_5 under vacuum to afford 20.5 mg (78%) of Cyclobut-G

dx.doi.org/10.1021/jo202261z | *J. Org. Chem.* 2012, 77, 1710−1721

(**19**): mp 275−280 °C dec (lit.[26c] mp ∼290 dec); $[\alpha]_D^{20}$ −24.7 (*c* 1.0 DMSO) [lit.[26d] $[\alpha]_D^{22}$ −24.4 (*c* 1.0 DMSO)]; ^{1}H NMR (400 MHz, DMSO) δ 10.52 (s, 1H), 7.82 (s, 1H), 6.37 (s, 1H), 4.62 (t, J = 4.9 Hz, 1H), 4.58 (t, J = 5.1 Hz, 1H), 4.42 (dd, J = 16.6, 8.4 Hz, 1H), 3.54−3.42 (m, 4H), 2.72−2.63 (m, 1H), 2.40−2.29 (m, 1H), 2.09−1.97 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8, 153.2 150.9, 135.8, 116.8, 63.5, 61.4, 47.7, 46.5, 33.1, 29.6; MS (ESI) m/z 265.9 $(M + H)^+$.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENTS

We thank Dr. J. Einhorn (UJF) for his interest in our work, the CNRS and the French Ministry of Research for financial support (UMR 5250), and the French Ministry of Research for a fellowship (to B.D.).

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