Articles

Cyclohexenone Construction by Intramolecular Alkylidene C−H Insertion: Synthesis of (+)-Cassiol

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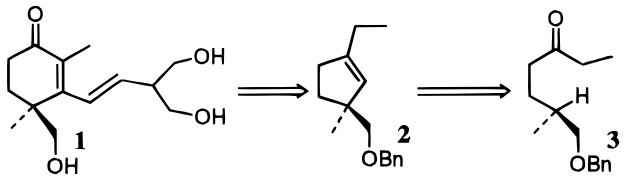
We report new procedures for stereoselective cyclopentene and cyclohexenone construction employing the alkylidene carbene C−H insertion reaction. Described are diastereoselective insertion into methylene and enantiospecific insertion into methine C−H bonds. The latter case leads directly to the enantioselective synthesis of (+)-cassiol (**1**).

Introduction

The stereospecific construction of functionalized five- and six-membered carbocycles continues to challenge practitioners of organic synthesis. The work of Gilbert[1a,b] and later of Ohira[1c,d] suggested that the intramolecular C−H insertion of an alkylidene carbene[1] could offer a general method for converting acyclic ternary stereogenic centers into cyclic quaternary centers of defined absolute configuration. We detail here our exploration of several procedures for generating alkylidene carbenes from ketones and our delineation of experimentally effective protocols for effecting these cyclizations. The utility of this approach is illustrated by an expeditious synthesis of (+)-cassiol (**1**), a potent antiulcerant isolated from *Cinnimomum cassia*, from the enantiomerically pure ketone **3** via the cyclopentene **2**.[2]



Background: The Transition State for C−H Insertion by Alkylidene Carbene

From a theoretical standpoint, the alkylidene carbene is an interesting species, bearing both similarities to alkyl carbenoids and significant differences. Ab initio calcuculations[3a,c] employing a 6-31G** basis set on **4** indicate that this is a singlet carbene, which is essentially sp hydridized: the HOMO extends linearly, as with an alkyne, and the p orbital is empty, making the LUMO. Experimental evidence for a singlet state may be found in earlier work by Gilbert and Ohira who have confirmed that C−H insertion into a stereochemically defined methine proceeded with retention of absolute configuration.[1]

4

A key issue that had not been resolved was one of diastereoselectivity. *Alkyl* carbenoids are known to effect C−H insertion to form cyclopentanes with significant diastereoselectivity.[4] We postulated that though more reactive the alkylidene carbene could show a similar diastereomeric preference. The transition state geometry for the C−H insertion may be represented as a half chair.

In this example, the phenyl substituent lies in a pseudoequatorial position. The methyl group adjacent to the phenyl group may either be pseudoequatorial or pseudoaxial. In each case only one of the two possible methylene C−H bond molecular orbitals is periplanar with and therefore can overlap with the empty orbital of the alkylidene carbene. The case where the methyl group is pseudoaxial leads to the syn diastereomer, and the case where the methyl group is pseudoequatorial leads to the

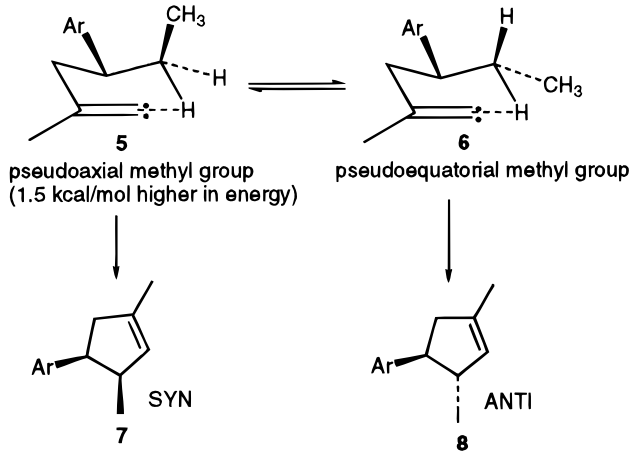
[⊗] Abstract published in *Advance ACS Abstracts,* August 1, 1996.

(1) For alkylidene carbene generation using dimethyl (diazomethyl)-phosphonate, see: (a) Gilbert, J. C.; Giamalva, D. H.; Weersooriya, U. *J. Org. Chem* **1983**, *48*, 5251. (b) Gilbert, J. C.; Giamalva, D. H.; Baze, M. E. *J. Org. Chem* **1985**, *50*, 2557. For alkylidene carbene generation and cyclization using (trimethylsilyl)diazomethane, see: (c) Ohira, S.; Okai, K.; Moritani, T. *J. Chem. Soc., Chem. Commun.* **1992**, 721. (d) Ohira, S.; Sawamoto, T.; Yamato, M. *Tetrahedron Lett.* **1995**, *36*, 1537. For our initial reports of the work described in full here, see: (e) Taber, D. F.; Meagley, R. P. *Tetrahedron Lett.* **1994**, *35*, 7909. (f) Taber, D. F.; Walter, R.; Meagley, R. P. *J. Org. Chem.* **1994**, *59*, 6014. (g) Taber, D. F.; Sahli, A.; Yu, H.; Meagley, R. P. *J. Org. Chem.* **1995**, *60*, 6571. For leading references to alternative strategies for the generation and subsequent C−H insertion reactions of alkylidene carbenes, see: (h) Karpf, M.; Dreiding, A. S. *Helv. Chim. Acta* **1979**, *62*, 852. (i) Ochiai, M.; Uemura, K.; Masaki, Y. *J. Am. Chem. Soc.* **1993**, *115*, 2528. (j) Williamson, B. L.; Tykwinski, R. R.; Stang, P. J. *J. Am. Chem. Soc.* **1994**, *116*, 93.

(2) For the three previous preparations of (+)-cassiol, see: (a) Corey, E. J.; Guzman-Perez, A.; Loh, T. *J. Am. Chem. Soc.* **1994**, *116*, 3611. (b) Uno, T.; Watanabe, H.; Mori, K. *Tetrahedron* **1990**, *46*, 5563. (c) Takemoto, T.; Fukaya, C.; Yokoyama, K. *Tetrahedron Lett.* **1989**, *30*, 723. Note added in proof: After this work was accepted for publication a fourth synthesis of (+)-cassiol appeared. Trost, B. M.; Li, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6625.

(3) (a) Geometries were optimized at the Hartree−Fock level (restricted for the singlet, unrestricted for the triplet) with the 6-31G** basis set. Single-point energies were calculated at the MP2 (frozen core) level. Hybridization was analyzed by the natural bond orbital method. (b) Molecular mechanics calculations were carried out using the program Mechanics, implemented on a Tektronix CAChe workstation interfaced with a Silicon Graphics Indigo workstation. This code is based on the MM2 molecular mechanics code of Allinger, with extensions provided by the CAChe group. (c) For a detailed analysis of the electronic structure of alkylidenes (vinylidenes) and of the rearrangement to the corresponding alkyne, see: Gallo, M. M.; Hamilton, T. P.; Schaefer, H. F., III. *J. Am. Chem. Soc.* **1990**, *112*, 8714.

S0022-3263(96)00973-5 CCC: $12.00



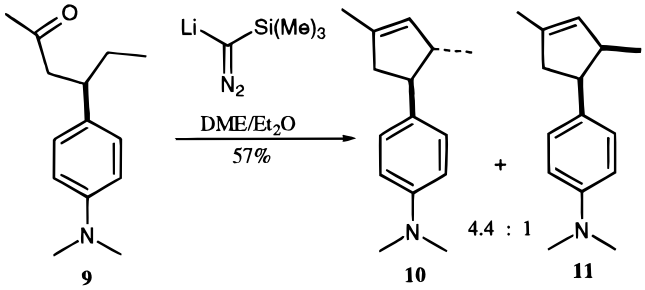
anti diastereomer. A molecular mechanics[3b] simulation of this system with an MM2 force field and a "weak bond" between the alkylidene carbon and the target H indicates that at the point of commitment the syn transition state lies 1.5 kcal/mol higher in energy than the anti transition state, largely due to 1,3 diaxial interactions with the methyl group. On the basis of this model, we predicted that the anti product would be the major diastereomer formed in the reaction.

Alkylidene Carbene Generation by Way of the Cumulated Diazoalkene

To test the above hypothesis, we prepared ketone **9** from 4-(4-(*N*,*N*-dimethylamino)phenyl)-3-buten-2-one,[5] by copper-mediated conjugate addition of ethylmagnesium bromide. We expected that this would be a challenging substrate to cyclize, as the inherently slower rate for methylene compared to methine insertion would be exacerbated by inductive electron withdrawal by the adjacent aromatic ring. Thus, alternative pathways could intervene.[1a]

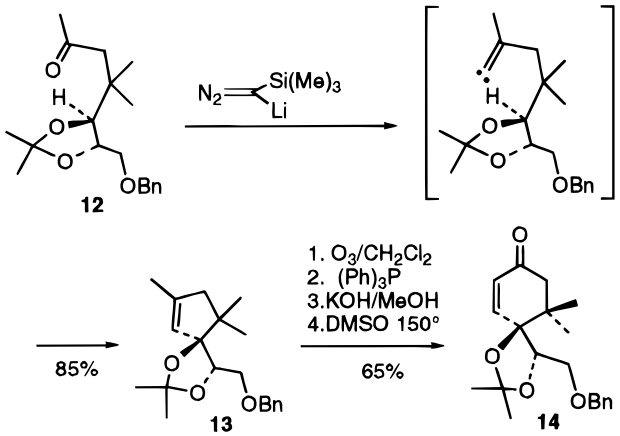
We first explored procedures that would convert ketones into alkylidene carbenes directly. The use of the anion of dimethyl (diazomethyl)phosphonate to effect this transformation was pioneered by Gilbert.[1a,b] This reagent is not commercially available but can be prepared from dimethyl (phthalimidomethyl)phosphonate in two steps. We have found Ohira's substitution of (trimethylsilyl)diazomethane in this reaction to be more convenient, since this reagent is commercially available.[1c−f]

We initially observed that the Ohira procedure, as published, was not effective for the C−H insertion into deactivated methine and methylene bonds. Selection of the solvent system proved to be critical to success.[6] It was crucial to employ DME for smooth insertion into the inherently less reactive methylene C−H bonds. Further, it was also determined that the system would not tolerate hexane, either as a solvent for the commercial (trimethylsilyl)diazomethane or as a solvent for the base (i.e., *n*-butyllithium). We therefore employed methyllithium, available as a salt free solution in diethyl ether, and carefully distilled the (trimethylsilyl)diazomethane away from the hexane solvent.[7] Treatment of the DME solution of (trimethylsilyl)diazomethane with methyllithium at −78 °C resulted in a slurry of [(trimethylsilyl)-diazomethyl] lithium that efficiently converted **4** to a 4.4:1 mixture of **5** and **6**.



Intramolecular Alkylidene Insertion: Methine Insertion

In support of our continuing studies toward the synthesis of taxol, we next investigated the preparation of enone **14**, a possible taxol A-ring synthon.[1f] Crucial to this effort is the conversion of ketone **12** to cyclopentene **13** via the kinetically favorable alkylidene carbene *methine* insertion reaction. Having accomplished the C−H insertion into the electronically deactivated methylene of **9**, we expected that application of our methodology to this system would pose little difficulty, for in addition to being a methine the target C−H bond is further activated for carbene insertion by α-oxygenation.[4b] Indeed, upon treatment with [(trimethylsilyl)diazomethyl]lithium, **12** was transformed efficiently into **13**.



Intramolecular Alkylidene Insertion: Chloromethylenation/Elimination

The efficiency of the cyclization of **12** to **13** suggested that this could be a good system with which to explore an alternative route[1g] to alkylidene carbenes, conversion

(4) For reviews of diastereoselectivity in Rh-mediated C−H insertion reactions, see: (a) Doyle, M. P.; Dyatkin, A. B.; Roos, G. H. P.; Canas, F.; Pierson, D. A.; van Basten, A.; Muler, P.; Polleux, P. *J. Am. Chem. Soc.* **1994**, *116*, 4507. (b) Wang, P.; Adams, J. *J. Am. Chem. Soc.* **1994**, *116*, 3296. (c) Doyle, M. In *Homogeneous Transition Metal Catalysis in Organic Synthesis*; Moser, W. R., Slocum, D. W., Eds.; ACS Advanced Chemistry Series 230; American Chemical Society: Washington, DC, 1992; Chapter 30. (d) Taber, D. F. *Comprehensive Organic Synthesis*, Vol. 3; Pattenden, G., Ed.; Pergamon Press: Oxford, 1991; p 1045. For more recent references, see: (e) Taber, D. F.; You, K. K. *J. Am. Chem. Soc.* **1995**, *117*, 5759. (f) Taber, D. F.; You, K. K., Rheingold, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 547.

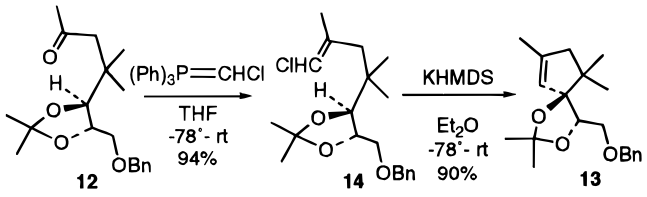
(5) Matsui, M.; Oji, A.; Hiramatsu, K.; Shibata, K.; Muramatsu, H. *J. Chem. Soc., Perkin Trans. 2* **1992**, 201.

(6) (a) Gilbert, J. C.; Blackburn, B. K. *J. Org. Chem.* **1986**, *51*, 3656. (b) Gilbert, J. C.; Giamalva, D. H. *J. Org. Chem.* **1992**, *557*, 4185.

(7) The commercial material also contains impurities that we were unable to remove by distillation.

(8) (a) Wittig, G.; Schlosser, M. *Chem. Ber.* **1961**, *94*, 1373. (b) Ketley, A. D.; Berlin, A. J.; Gorman, E.; Fisher, L. P. *J. Org. Chem.* **1966**, *31*, 305.

of **12** to the vinyl chloride **14** followed by α-elimination, and subsequent C−H insertion to give **13**.

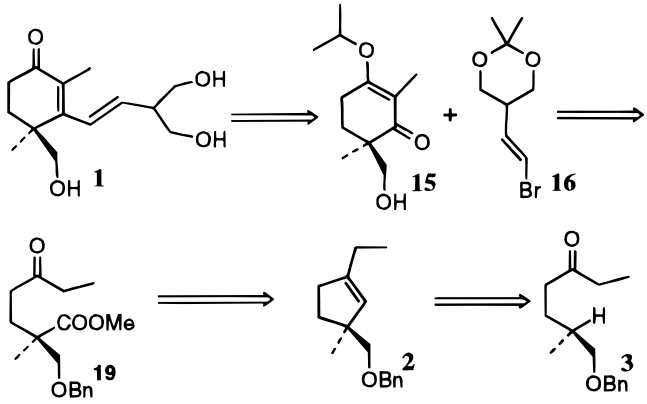


Treatment of the ketone **12** with (chloromethylene)-triphenylphosphorane (prepared by the action of sodium bis(trimethylsilylamide) upon (chloromethyl)triphenylphosphonium chloride in THF) gives **14** as 50/50 mixture of the *E* and *Z* vinyl chlorides. We found that the selection of an appropriate base was critical for eliciting α-elimination and subsequent C−H insertion by the alkylidene carbene. Both sodium hydride and potassium *tert*-butoxide proved to be ineffective. When LDA was used, cyclization was complicated by reduction of the alkylidene carbene to a simple alkene.[10] However, when either sodium or potassium bis(trimethylsilylamide) was used, the exclusive product was **13** in high yield. Thus, in systems for which C−H insertion is facile, chloromethylenation/α-elimination can take the place of treatment with (trimethylsilyl)diazomethane.[11]

Insertion in a Deactivated Methine: Total Synthesis of (+)-Cassiol

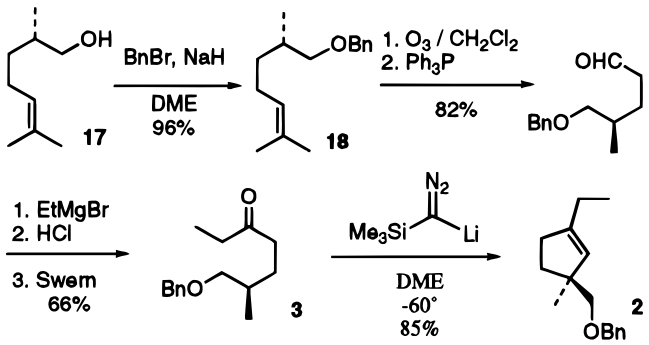
With the methodology proven successful in the two extreme cases, we turned our attention to C−H insertion into a *deactivated* methine, in the context of the total synthesis of the antiulcerant (+)-cassiol (**1**). Our approach to **1** used a convergent strategy (Scheme 1). The first task was to create a synthon for the 2,4-dimethyl-4-(hydroxymethyl)-2-cyclohexenone ring that forms the core of the molecule. A synthon that would become the 2-ethenyl-1,3-propanediol side chain was also required. For the enone synthon, we employed the vinylogous ester **15**. This was to be coupled with the lithio derivative of the side chain synthon 2,2-dimethyl-5-(2-bromoethenyl)-1,3-dioxane (**16**) to give (+)-cassiol after hydrolysis. The alcohol **15** was to be elaborated from the cyclopentene **2**, the expected product from the reaction of ketone **3** with [(trimethylsilyl)diazomethyl]lithium.

Scheme 1



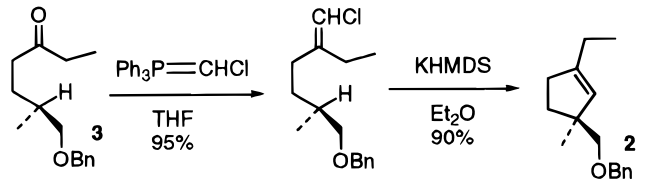
In the event, we prepared enantiomerically pure **3** from (−)-norcitronellol (**17**) (Scheme 2), available from geraniol following our published procedure.[4e] Benzyl protection of **17** gave an ether (**18**) which after selective ozonolysis gave the aldehyde. Homologation with ethylmagnesium bromide followed by hydrolysis gave a crude mixture of the diastereomeric secondary alcohols which was oxidized under Swern conditions to give the requisite ketone **3**.

Scheme 2



At this point we were ready to attempt cyclization. First we employed our modification of the Ohira cyclization, with the lithium derivative of (trimethylsilyl)-diazomethane.[1e,f] The cyclization was so efficient in this case that we could use *n*-butyllithium as the base, with the accompanying hexane solvent.

We then turned our attention to the alternative vinyl chloride cyclization procedure. Treatment of **3** with a THF solution of (chloromethylene)triphenylphosphorane gave an excellent yield of a 1:1 mixture of the *Z* and *E* vinyl chlorides. Treatment of this mixture with excess potassium bis(trimethylsilyl)amide in ether resulted in the formation of **2** in high yield, underscoring the utility of this procedure for generating alkylidene carbenes.



With cyclopentene in hand we carried on through ozonolysis, MacDonald oxidation[12] to the methyl ester **19**, and Claisen cyclization to the desired cyclohexanedione (Scheme 3). We found this vinylogous acid to be unstable, with a room temperature halflife in solution of only a few days, thus complicating its esterification. We solved this problem by effecting esterification with 2-diazopropane[13a] to generate a 4:1 mixture of regioisomers of the vinylogous ester **20**[13b] directly from the crude dione. The regioisomers were readily separable by column chromatography. It is noteworthy that (trimethylsilyl)diazomethane gave a 1:1 mixture of the two methyl ether regioisomers. Catalytic hydrogenation with 10% Pd−C at 20 °C cleanly gave the alcohol **15**.

(9) For earlier reports of 1,5 C−H insertion by alkylidene carbenes generated from vinyl halides, see: (a) Erickson, K. L.; Wolinsky, J. *J. Am. Chem. Soc.* **1965**, *87*, 1143. (b) Wolinsky, J.; Clark, G. W. *J. Org. Chem.* **1976**, *41*, 745. (c) Fisher, R. H.; Baumann, M.; Koebrich, G. *Tetrahedron Lett.* **1974**, 1207.

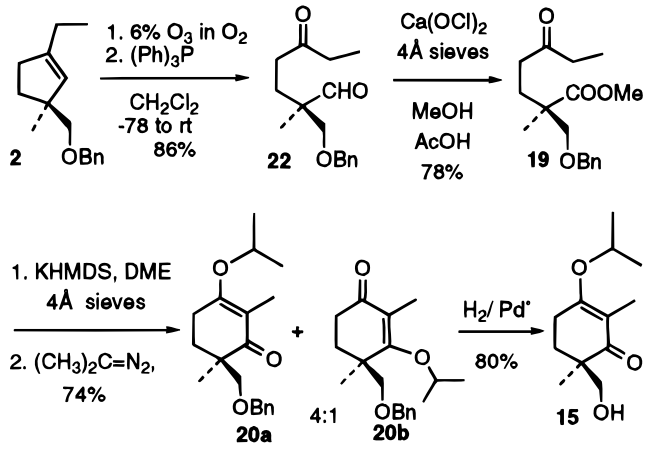
(10) Creary, X. *J. Am. Chem. Soc.* **1977**, *99*, 7632.

(11) Treatment of the chloromethylene derivative of **9** with KHMDS in diethyl ether resulted in a complex mixture of products, including small amounts of both **10** and **11**, and also the alkyne resulting from 1,2 methyl shift.

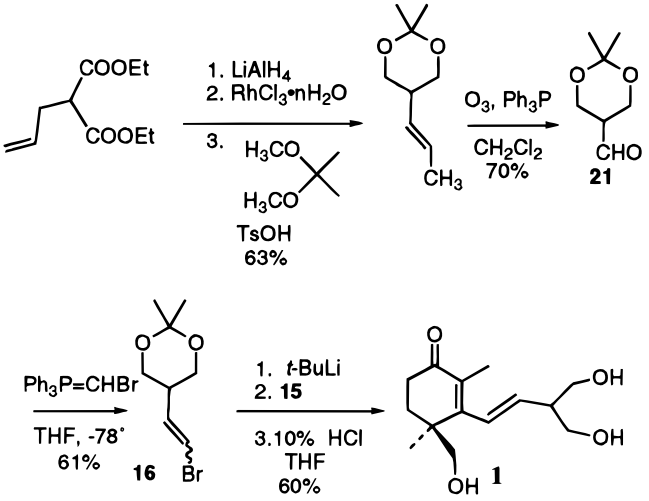
(12) MacDonald, C. E.; Nice, L. E.; Shaw, A. A.; Nestor, N. B. *Tetrahedron Lett.* **1993**, *34*, 2741.

(13) (a) For the preparation of 2-diazopropane, see: Andrews, S. D.; Day, A. C.; Raymond, P.; Whiting, M. C. *Org. Synth.* **1970**, *50*, 27. (b) For the use of 2-diazopropane to esterify vinylogous acids, see: Solas, D.; Wolinsky, J. *J. Org. Chem.*, **1983**, *48*, 670.

Scheme 3



Scheme 4



The side chain synthon we developed was 2,2-dimethyl-5-(2-bromoethenyl)-1,3-dioxane (**16**), readily prepared in five steps from commercial diethyl allylmalonate (Scheme 4). First the diester was reduced to the diol[14] with $LiAlH_4$; then the allyl group was isomerized with $RhCl_3 \cdot nH_2O$ and the diol was protected as the acetonide. Ozonolysis of the olefin gave an aldehyde[15] which was condensed with (bromomethylene)triphenylphosphorane to form **16** as an approximately equal *E*/*Z* mixture.

We lithiated **16** using *tert*-butyllithium and added the resulting anion to **15**. The intermediate alkoxide was unravelled with aqueous acid to give (+)-cassiol, identical (TLC, ^1H, ^{13}C NMR, and MS) with the natural product.

Conclusion

It is apparent that conversion of a ketone to the homologous cyclopentene via the intermediate alkylidene carbene can be achieved efficiently by employing [(trimethylsilyl)diazomethyl]lithium or by homologation to the chlorovinyl derivative followed by base treatment. We believe that the method outlined here represents a significant step[16] toward reducing to practicality the general cyclopentene synthesis originally adumbrated by Gilbert[1a,b] and Ohira.[1c,d].

Experimental Section

General. ^1H NMR and ^{13}C NMR spectra were obtained as solutions in deuteriochloroform ($CDCl_3$). ^{13}C multiplicities were determined with the aid of a JVERT pulse sequence, differentiating the signals for methyl and methine carbons as "d" from methylene and quaternary carbons as "u". The infrared (IR) spectra were determined as neat oils. Mass spectra (MS) were obtained at an ionizing potential of 15 eV. Substances for which C, H analyses are not reported were purified as specified and gave spectroscopic data consistent with being >95% the assigned structure. Optical rotations were determined as solutions in dichloromethane unless otherwise noted. R_f values indicated refer to thin layer chromatography (TLC) on 2.5 × 10 cm, 250 μm analytical plates coated with silica gel GF, unless otherwise noted, and developed in the solvent system indicated. Column chromatography was carried out following the procedure described by Taber.[17] The solvent mixtures used are volume/volume mixtures. All glassware was flame dried under a dry nitrogen stream immediately before use. Tetrahydrofuran (THF), diethyl ether, and 1,2-dimethoxyethane (DME) were distilled from sodium metal/benzophenone ketyl under dry nitrogen. Dichloromethane (CH_2Cl_2) and toluene were distilled from calcium hydride under dry nitrogen. All reaction mixtures were stirred magnetically, unless otherwise noted.

(*S*)-(−)-2,6-Dimethyl-7-(phenylmethoxy)-2-heptene (18). To a mixture of 28 mL of DME and 1.46 g of NaH (60% oil dispersion, 36.6 mmol, 1.3 equiv) was added a solution of **17** (4.00 g, 28.2 mmol) in DME (28 mL) dropwise over 2 min at rt. After the solution was stirred for 10 min, benzyl bromide (4.0 mL, 33.8 mmol, 1.2 equiv) was added at rt. The mixture was stirred for 75 min at rt while gas was evolved. After being heated to reflux for 3 min, the mixture was stirred for 15 h at rt. The reaction was quenched with 0.5 mL of 35% aqueous HCl followed by 5 g of Na_2SO_4 and then concentrated and chromatographed to give 6.21 g (27.8 mmol, 95% yield) of **18**: TLC R_f(10% ethyl acetate/petroleum ether) = 0.90, $bp_{0.25}$ (bath) = 100−105 °C. $[\alpha]_D$ = 3.1° (*c* = 79.2 CH_2Cl_2). ^1H NMR (δ): 7.30 (m, 5H), 5.10 (bt, *J* = 7.1 Hz, 1 H), 4.49 (s, 2H), 3.34 (m, 2H), 1.99 (t, *J* = 7.3 Hz, 2H), 1.83 (m, 1H), 1.68 (s, 3H), 1.59 (s, 3H), 1.49 (m, 1H), 1.14 (m, 1H), 0.94 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR (δ): u, 138.8, 131.2, 75.9, 73.0, 33.8, 25.4; d, 128.3, 127.5, 127.3, 127.0, 124.8, 33.1, 25.7, 17.6, 17.1. IR: 2913, 2854, 1496, 1453, 1376, 1098, 1028, 820, 734, 697. Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.84; H, 10.41. MS (*m*/*z*, %): 232 (15), 141 (14), 123 (55), 91 (100), 81 (29), 69 (28), 55 (12). HRMS: calcd for $C_{16}H_{24}O$ 232.182716, found 232.183394.

(*S*)-6-Methyl-7-(phenylmethoxy)-3-heptanone (3). A mixture of **18** (3.00 g, 12.9 mmol), Sudan III (1 mg as an indicator), and 30 mL of CH_2Cl_2 was chilled to −78 °C. A steady stream of 6% O_3 in O_2 (dried by passing through a −78 °C trap) was bubbled through the solution until the red color of the indicator faded to pale yellow. The solution was sparged with N_2 for 2 min to remove the residual O_3, then was treated with triphenylphosphine (3.72 g, 14.2 mmol, 1.1 equiv) and allowed to stir and come up to rt. The solution was concentrated to a thick yellow oil, presumably a mixture of (*S*)-1-(phenylmethoxy)-2-methylpentanal, TLC, R_f(10% ethyl acetate in petroleum ether) = 0.75, and triphenylphosphine oxide, TLC R_f(10% ethyl acetate in petroleum ether) = 0.00. This mixture was then redissolved in THF (30 mL) and chilled to 0 °C. To this mixture was added ethylmagnesium bromide (1.5 M in THF, 35 mL, 51 mmol, 4.0 equiv) over 5 min, resulting in a clear red solution. The ice bath was removed, and the mixture was allowed to warm to rt over 10 min. The mixture was

(14) Sells, T. B.; Nair, V. *Tetrahedron* **1994**, *50*, 117.
(15) Bates, H. A.; Farina, J.; Tong, M. *J. Org. Chem.* **1986**, *51*, 2637.
(16) Since the inception of our work, several alternative procedures for the generation and cyclization of alkylidene carbenes have been put forward. For leading references, see: (a) Tykwinski, R. R.; Stang, P. J.; Persky, N. E. *Tetrahedron Lett.* **1994**, *35*, 23. (b) Kunishima, M.; Hikoi, K.; Tani, S.; Kato, A. *Tetrahedron Lett.* **1994**, *35*, 7253. (c) Kim, S.; Cho, C. M. *Tetrahedron Lett.* **1994**, *35*, 8405. (d) Schildknegt, K.; Bohnstedt, A. C.; Feldman, K. S.; Sambandam, A. *J. Am. Chem. Soc.* **1995**, *117*, 7544. (e) Ohira, S.; Sawamoto, T.; Yamato, M. *Tetrahedron Lett.* **1995**, *36*, 1537.
(17) Taber, D. F. *J. Org. Chem* **1982**, *47*, 1351.

partitioned between 3% aqueous HCl and ethyl acetate. The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give the diasteromeric secondary alcohols, (6*S*,3*S*)- and (6*S*,3*R*)-6-methyl-7-(phenylmethoxy)-3-haptanol (2.57 g, 84% yield), TLC R_f(10% ethyl acetate/petroleum ether) = 0.25.

Dimethyl sulfoxide (5 M in CH_2Cl_2, 4.4 mL, 22 mmol, 2.2 equiv) was added over 5 min to a mixture of CH_2Cl_2 (11.5 mL) and oxalyl chloride (2 M in CH_2Cl_2, 5.5 mL, 11 mmol, 1.1 equiv) at −78 °C. After an additional 30 min, the secondary alcohol (2.36 g, 10 mmol, in 10 mL of CH_2Cl_2) was added over 12 min. After an additional 7.5 h, 6.4 mL of triethylamine (46 mmol, 4.6 equiv) was added and the mixture was allowed to warm to rt overnight. The mixture was partitioned between ethyl acetate and, sequentially, water, 5% aqueous HCl, and saturated aqueous $NaHCO_3$. The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give **3** (1.79 g, 65% yield from **18**): TLC R_f(10% ethyl acetate/petroleum ether) = 0.50, $bp_{0.25}$ (bath) = 105−110 °C. $[\alpha]_D$ = −2.15° (*c* = 52.2, CH_2Cl_2). ^{1}H NMR (δ): 7.30 (m, 5H) 4.49 (s, 2H), 3.29 (dd, *J* = 1.8, 6.0 Hz, 2H), 2.41 (m, 4H), 1.74 (m, 2H), 1.42 (m, 1H), 0.98 (t, *J* = 7.3 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (δ): u, 212.1, 138.5, 75.7, 72.8, 39.0, 36.1, 27.5; d, 129.2, 128.2, 127.5, 127.3, 127.2, 32.1, 15.5, 9.5. IR (cm^{-1}): 2931, 2872, 1713, 1455, 1414, 1367, 1102, 738, 697. MS (*m*/*z*, %): 234 (0.28), 143 (28), 128 (24), 127 (26), 107 (24), 99 (23), 97 (12), 91 (100), 85 (40), 73 (12), 65 (21), 57 (83). HRMS: calcd for $C_{15}H_{22}O_2$ 234.161980, found 234.16253.

(*S*)-1-Ethyl-3-methyl-3[(phenylmethoxy)methyl]cyclopentene (2) (via (Trimethylsilyl)diazomethane). A solution of *n*-butyllithium in hexane (2.16 M, 0.4 mL, 0.86 mmol, 1.8 equiv) was added to (trimethylsilyl)diazomethane (4.18 M in hexane, 0.2 mL, 0.88 mmol, 1.8 equiv) and DME (3.6 mL) at −68 °C. After 5 min, a solution of **3** (111 mg, 0.48 mmol) in DME (0.2 mL) was added. After 23 min between −53 and −68 °C, the mixture was partitioned between 10% aqueous HCl and 14% ethyl acetate/petroleum ether. The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give **2** (90 mg, 82% yield from **3**): TLC, R_f(7% ethyl acetate/petroleum ether) = 0.86, $bp_{0.25}$ (bath) = 100−110 °C. $[\alpha]_D$ = −38.7° (*c* = 1.6, EtOH). ^{1}H NMR (δ): 7.32 (m, 5H), 5.20 (bs, 1H), 4.57 (s, 2H), 3.27 (s, 2H), 2.31 (dt, *J* = 0.7, 7.2 Hz, 2H), 2.08 (dq, *J* = 1.0, 7.5 Hz, 2H), 1.92 (dt, *J* = 7.2, 12.7 Hz, 1H), 1.60 (m, 1H), 1.11 (s, 3H), 1.07 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (δ): u, 146.1, 139.0, 78.4, 75.5, 73.2, 73.0, 49.6, 34.7, 34.1, 24.2; d, 129.2, 128.2, 127.5, 127.3, 127.2, 24.1, 12.3. IR (cm^{-1}): 3030, 2964, 2845, 1496, 1454, 1367, 1205, 1098, 1029, 845. Anal. Calcd for $C_{16}H_{22}O$: C, 83.43; H, 9.63. Found: C, 83.62; H, 9.44. MS (*m*/*z*, %): 230 (2), 199 (9), 122 (7), 109 (100), 91 (79), 81 (35), 67 (53), 55 (25). HRMS: calcd for $C_{16}H_{22}O$ 230.167066, found 230.168383.

(*S*)-1-Ethyl-3-methyl-3-[(phenylmethoxy)methyl]cyclopentene (2) (via chloromethylenation). A solution of sodium bis(trimethylsilyl)amide in THF (1.0 M, 17.3 mL) was added to a suspension of (chloromethyl)triphenylphosphonium chloride (6.54 g, 17.9 mmol, 3 equiv) and THF (11 mL) at 0 °C. The mixture was then chilled to −78 °C, and a solution of **3** (1.40 g, 5.98 mmol, 1 equiv) in THF (6 mL) was added. After 12 h at rt the mixture was filtered through silica gel to give a 1:1 mixture of the *E* and *Z* vinyl chlorides (1.48 g, 5.75 mmol, 97% yield from **3**).

To the mixed vinyl chlorides (1.48 g, 5.75 mmol) and diethyl ether (225 mL) within a drybox was added potassium bis(trimethylsilyl)amide (4.49 g, 22.5 mmol, 4 equiv) as a dry powder over 15 min. After 12 h, the mixture was partitioned between saturated aqueous $NaHCO_3$ and 2% ethyl acetate in petroleum ether. The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give **2** (1.23 g, 89% from **3**) identical to the cyclopentene prepared with (trimethylsilyl)diazomethane.

Methyl (*S*)-2-Methyl-5-oxo-2-[(phenylmethoxy)methyl]-heptanoate (19). Following the procedure for converting **18** to **3**, **2** was ozonized to the crude keto aldehyde. The mixture was concentrated and chromatographed to give **22** (0.503 g, 1.92 mmol, 74% yield).

A mixture of **22** (398 mg, 1.52 mmol) in acetonitrile (7.6 mL), methanol (2.0 mL, 50 mmol, 33 equiv), and powdered 4 Å molecular sieves (1.3 g) was stirred 0.5 h at rt. Acetic acid (0.52 mL, 9.12 mmol, 6 equiv) and $Ca(OCl)_2$ (0.652 g, 4.56 mmol, 3 equiv) were added, and the mixture was stirred for 3.0 h with the exclusion of light. Powdered $Na_2S_2O_8$ (0.377 g, 5 equiv) was added, and the mixture was stirred 20 min at rt. The mixture was filtered through silica gel to give **16** (365 mg, 61% yield from **2**): $[\alpha]_D$ = 1.0° (*c* = 25.1, CH_2Cl_2). ^{1}H NMR (δ): 7.25 (m, 5H), 4.42 (s, 2H), 3.59 (s, 2H), 3.50 (d, *J* = 8.1 Hz, 1H), 3.41 (d, *J* = 8.1 Hz, 1H), 2.36 (m, 4H), 1.80 (m, 2H), 1.12 (s, 3H), 0.96 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (δ): u, 210.7, 175.9, 138.2, 75.2, 73.2, 46.5, 37.4, 35.8, 29.4; d, 128.2, 127.4, 110.2, 51.7, 20.0, 7.8. IR (cm^{-1}): 2978, 2359, 2338, 1735, 1715, 1454, 1376, 1102, 806, 741, 699. MS (*m*/*z*, %): 292 (2), 277 (87), 185 (14), 139 (7), 125 (12), 105 (100), 91 (62), 77 (22). HRMS: calcd for $C_{17}H_{24}O_4$ 292.167460, found 292.165948.

(*S*)-2,6-Dimethyl-3-(1-methylethoxy)-6[(phenylmethoxy)methyl]-2-cyclohexenone (20a) and (*S*)-2,4-Dimethyl-3-(1-methylethoxy)-4-[(phenylmethoxy)methyl]-2-cyclohexenone (20b). Under dry conditions, KHMDS (120 mg, 0.57 mmol, 1.5 equiv) was added as a dry powder to a mixture of **19** (111 mg, 0.38 mmol) and DME (1.5 mL). After 9.5 h at rt, TLC analysis showed conversion to the desired dione, TLC R_f = 0.19 (30% ethyl acetate/petroleum ether). The mixture was partitioned between ethyl acetate and saturated aqueous NH_4Cl (adjusted to pH = 7.0 by the addition of 10% aqueous HCl). The combined organic extract was dried (Na_2SO_4), chilled to 0°, and then treated with 2-diazopropane[1] (1.5 M in Et_2O, 8 mL, 12 mmol, 32 equiv). After 8 h at rt, the mixture was concentrated and chromatographed to give 69 mg of **20a** (59 % from **19**), TLC R_f = 0.55 (7% CH_2Cl_2/7% MTBE/petroleum ether) and 17 mg of **20b** (15 % from **19**), TLC R_f = 0.30 (7% CH_2Cl_2/7% MTBE/petroleum ether).

20a: $[\alpha]_D$ = 19.9° (*c* = 19.3, CH_2Cl_2). ^{1}H NMR (δ): 7.15 (m, 5H), 4.36 (m, 3H), 3.50 (d, *J* = 8.9 Hz, 1H), 3.16 (d, *J* = 8.9 Hz, 1H), 2.36 (m, 2H), 2.15 (m, 1H), 1.79 (m, 4H), 1.12 (d, *J* = 6.1 Hz, 3H), 1.08 (d, *J* = 6.1 Hz, 3H), 0.93 (s, 3H). ^{13}C NMR (δ): u, 201.2, 169.2, 138.3, 115.4, 75.4, 73.4, 44.2, 29.9, 22.5; d, 128.3, 127.3, 126.5, 69.8, 22.6, 20.1, 8.0. IR (cm^{-1}): 2977, 1724, 1615, 1380, 1358, 1239, 1155, 1057, 971, 865, 747, 700. MS (*m*/*z*, %): 302 (0.04), 196 (6), 211 (5), 168 (22), 139 (24), 126 (23), 113 (5), 111 (5), 98 (19), 91 (100), 83 (15), 57 (13). HRMS: calcd for $C_{19}H_{26}O_3$ 302.188195, found 302.189387.

20b. ^{1}H NMR (δ): 7.28 (m, 5H), 4.68 (m, 1H), 4.47 (s, 2H), 3.61 (d, *J* = 8.7 Hz, 1H), 3.25 (d, *J* = 8.7 Hz, 1H), 2.51 (m, 1H), 2.35 (m, 1H), 2.14 (m, 1H), 1.78 (s, 3H), 1.63 (m, 1H), 1.23 (d, *J* = 6.1 Hz, 3H), 1.20 (d, *J* = 6.0 Hz, 3H), 1.10 (s, 3H). ^{13}C NMR (δ): u, 200.2, 174.5, 138.3, 117.3, 75.9, 73.1, 41.7, 33.6, 30.6; d, 128.2, 127.4, 127.2, 73.8, 22.7, 21.4, 10.8. IR (cm^{-1}): 2978, 2872, 1726, 1658, 1602, 1453, 1376, 1300, 1178, 1102, 1029, 751, 699. MS (*m*/*z*, %): 302 (0.65), 274 (7), 230 (5), 196 (4), 181 (6), 139 (23), 125 (5), 105 (67), 91 (100), 83 (30), 77 (15), 57 (6). HRMS: calcd for $C_{19}H_{26}O_3$ 302.188195, found 302.189948.

(*S*)-4-(Hydroxymethyl)-2,4-dimethyl-3-(1-methylethoxy)-2-cyclohexenone (15). A 5 mL reactivial equipped with a gas inlet adapter was charged with **20a** (99 mg, 0.328 mmol) and ethanol (1.5 mL). To this was added 10% Pd−C (10 mg, 9 wt %), and the vial was purged with and stirred under H_2 for 78 min with monitoring by TLC. The mixture was then filtered through Florisil, concentrated, and chromaographed to give **15** (56 mg, 81% yield, TLC R_f = 0.55 (33% MTBE/33% CH_2Cl_2/33% petroleum ether). $[\alpha]_D$ = −45.0° (*c* = 4.8, CH_2Cl_2). ^{1}H NMR: 4.51 (m, *J* = 6.1 Hz, 1H), 3.48 (bs, 2H), 3.23 (bs, 1H), 2.55−2.54 (t, *J* = 1.9 Hz, 2H), 1.91 (m, 1H), 1.61 (s, 3H), 1.53 (m, 1H), 1.24 (d, *J* = 6.0 Hz, 6H), 1.07 (s, 3H). ^{13}C NMR (δ): u, 205.0, 170.0, 114.8, 69.6, 43.7, 29.6, 22.3; d, 70.3, 23.1, 23.0, 18.8, 7.7. IR (cm^{-1}): 3422, 2933, 1716, 1615, 1456, 1381, 1236, 1111, 1028, 943, 668. MS (*m*/*z*, %): 212 (18), 182 (10), 170 (18), 152 (30), 140 (31), 139 (24), 137 (11), 125 (15), 113 (4), 111 (8), 98 (100), 85 (22), 83 (62), 82 (40), 71 (33), 70 (35), 69 (43), 67 (11), 57 (57). HRMS: calcd for $C_{12}H_{20}O_3$ 212.141245, found 212.143461.

2,2-Dimethyl-1,3-dioxane-5-carboxaldehyde (21). 2-(2-Propenyl)-1,3-propanediol[14] (41.0 g, 353 mmol) and rhodum

trichloride hydrate (216.4 mg, 0.4 mol %) were stirred and heated to 120 °C for 108 h to give crude 2-(1-propenyl)-1,3-propanediol (41.2 g, 85% yield).

The crude 2-(1-propenyl)-1,3-propanediol (41.2 g, 353 mmol, 1 equiv) and 2,2-dimethoxypropane (110 mL, 1.06 mol, 3 equiv) were treated with camphorsulfonic acid (100 mg). A simple still equipped with vacuum takeoff was attached, and the mixture was distilled (21−90 °C, 760 mmHg) to remove acetone, methanol, and excess 2,2-dimethoxypropane; then the pressure was reduced and distillation was continued to give 2,2-dimethyl-5-(1-propenyl)-1,3-dioxane, bp_{18} (bath) = 90−145 °C (41.84 g, 76% yield).

Following the procedure for converting **18** to **3**, 2,2-dimethyl-5-(1-propenyl)-1,3-dioxane (29.6 g, 190 mmol) was ozonized to the crude aldehyde **21**. After 1 h at rt the solution was concentrated *(Caution: sufficient time must be given for this ozonide to be reduced before concentration to prevent rapid exothermic reaction and potential explosive decomposition)* and distilled to give **21**, bp_{19} (bath) = 104−108 °C (17.96 g, 125 mmol, 78% yield) which was identical to material produced by Bates.[15] ^{1}H NMR: 9.89 (s, 1H), 4.23 (m, 4H), 2.38 (m, 1H), 1.48 (s, 3H), 1.37 (s, 3H).

2,2-Dimethyl-5-(2-bromo-1-ethenyl)-1,3-dioxane (16). A solution of sodium bis(trimethylsilyl)amide (1.0 M in THF, 67 mL, 1.3 equiv) was added to a suspension of (bromomethyl)-triphenylphosphonium bromide (29.0 g, 66.5 mmol, 1.3 equiv) in THF (70 mL) at −78 °C. After 30 min, a solution of **21** (7.43 g, 51.6 mmol) in THF (20 mL) was added and the mixture was stirred and warmed to 0 °C. After 2 h the mixture was partitioned between saturated aqueous $NaHCO_3$ and diethyl ether. The combined extract was filtered through silica gel to give an oil which was distilled to give **16** ($bp_{3.0}$ (bath) = 80−100 °C, 6.7 g, 61% yield) as a 1:1 mixture of the *E* and *Z* vinyl bromides. ^{1}H NMR (δ): 6.33−6.05 (m, 2H), 4.07−3.83 (m, 2H), 3.76−3.68 (m, 2H), 3.01−2.94 (m, 0.5H), 2.78−2.54 (m, 0.5H), 1.45 (s, 6H). ^{13}C NMR (δ): u, 97.8, 97.7, 63.3, 62.6; d, 134.5, 131.9, 110.0, 107.6, 38.9, 36.4, 26.7, 25.1, 22.6, 20.9. IR (cm^{-1}): 2993, 2866, 1731, 1619, 1454, 1372, 1261, 1198, 1135, 1078, 937, 832, 792, 708, 518, 481, 456, 472. MS (*m*/*z*, %): 207 (43), 204 (44), 191 (14), 190 (13), 134 (93), 131 (100). HRMS: calcd for $C_7H_{10}O_2Br$ 206.984270, found 206.983579.

(+)-Cassiol (1). A solution of *tert*-butyllithium (1.34 mL, 1.73 M in hexane, 2.26 mmol, 8.0 equiv) was added to a mixture of **16** (250 mg, 1.15 mmol, 4 equiv) and ether (2.7 mL) at −78 °C. The mixture was allowed to warm to 0 °C; then a solution of **15** (60 mg, 0.28 mmol) in ether (0.3 mL) was added and rinsed in with ether (2 × 0.7 mL). After 48 h at rt the mixture was warmed to reflux for 2 min and then partitioned between ethyl acetate and saturated aqueous $NaHCO_3$ (buffered to pH = 8 with NH_4Cl). The combined organic extract was then dried (Na_2SO_4 and $NaHCO_3$) and concentrated.

The residue was redissolved in MTBE (5 mL) and treated with 5 mL of 10% aqueous HCl. After 2.5 h, solid $NaHCO_3$ (2.0 g) was added. The phases were separated, and the salts were washed with EtOAc. The combined organic extract was concentrated and chromatographed to give **1** (48 mg, 60% yield). $[\alpha]_D$ = 9.1° (*c* = 4.5, MeOH). ^{1}H NMR (400 MHz, D_2O, δ): 6.09 (d, *J* = 16.3 Hz, 1H), 5.48 (dd, *J* = 8.4, 16.3 Hz, 1H), 3.67−3.27 (m, 5H), 3.24 (d, *J* = 11.5 Hz, 1H), 2.49−2.34 (m, 2H), 2.02−1.95 (m, 1H), 1.66−1.53 (m, 4H), 0.93 (s, 3H); (400 MHz, $CDCl_3$, δ) 6.23 (d, *J* = 16.3, 1H), 5.61−5.55 (dd, *J* = 8.1, 16.3, 1H), 3.79−3.72 (m, 4H), 3.67 (d, *J* = 11.4, 1H), 3.37 (d, *J* = 11.4, 1H), 2.66−2.61 (m, 1H), 2.56−2.45 (m, 2H), 2.40−2.22 (m, 1H), 2.21−2.15 (m, 1H), 1.81 (s, 3H), 1.12 (s, 3H). ^{13}C NMR (101 MHz, D_2O, δ uncorrected): u, 204.9, 162.6, 132.1, 68.2, 62.3, 40.9, 33.6, 31.0; d, 136.9, 129.1, 48.1, 20.7, 13.4; (101 MHz, $CDCl_3$, δ) u, 199.5, 158.3, 131.8, 69.5, 63.8, 40.8, 33.8, 31.9; d, 135.1, 129.4, 47.5, 20.9, 13.5. IR (cm^{-1}): 3394, 2925, 1732, 1652, 1616, 1456, 1380, 1260, 1110, 1032, 802, 739. These data were identical (^{1}H and ^{13}C NMR in D_2O) with those reported[2a] for **1**.

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Supporting Information Available: ^{1}H and ^{13}C spectra for all new compounds (17 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 information.

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