Synthesis of Phorbol C-Ring Analogs: A Biomimetic Model Study on the Phorbol to 12-Hydroxydaphnetoxin Conversion

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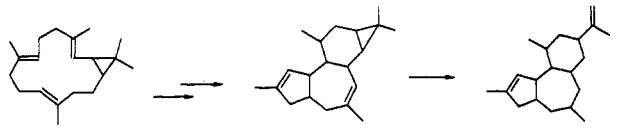
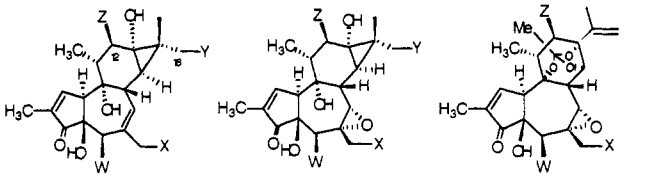
An eight-step synthesis of phorbol C-ring analogs is described. The results of a model study on the phorbol to 12-hydroxy daphnetoxin biomimetic conversion using a C-9 ester-assisted cyclopropyl carbinyl rearrangement are presented. Under the basic conditions used, the dominant reaction pathway is the participation of the C-13 hydroxyl group leading to cleavage of the wrong cyclopropane bond to generate an enone, rather than the desired orthoester. The key step in these synthetic studies is the use of the allyldimethylsilyl functionality as a latent form of hydroxyl group, which facilitates the introduction of the hydroxyl group at cyclic tertiary centers.

As part of a general scheme for the biosynthesis of cembrane-based diterpenes, Adolf and Hecker have suggested the possibility that synthesis of the daphnane skeleton occurs via the intermediacy of tigliane derivatives.[1]



1 (casbene) 2 (tigliane) 3 (daphnane)

Although these authors do not postulate a specific mechanism for conversion of the tigliane (phorbol) skeleton to the daphnane skeleton, several biogenetic clues are apparent from the literature. A vast number of tigliane and daphnane diterpenes have been isolated from many Euphorbiaceae and Thymelaeaceae species.[1] Table I lists names of the parent alcohol structures for the full oxidation range found with these diterpenes.

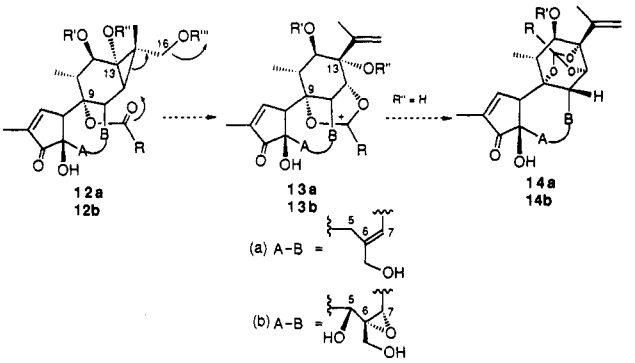


4 (W = X = Y = Z = H)
5 (W = Y = Z = H; X = OH)
6 (W = Y = H; X = Z = OH)
7 (W = Z = H; X = Y = OH)
8 (W = H; X = Y = Z = OH)

9 (W = X = OH; Y = Z = H)

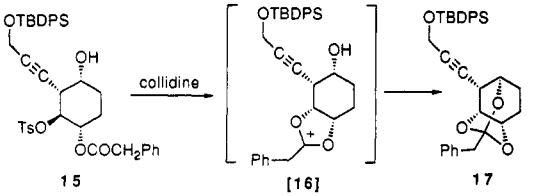
10 (W = X = OH; Z = H)
11 (W = X = Z = OH)

The most compelling evidence for the biogenetic conversion of the tigliane (phorbol) skeleton to the daphnane skeleton is found in the work of Hecker,[2h] where both of the structural types **5** and **10** *along with an intermediate oxidation state* **9** have been isolated from a single plant species. Further structures **7** and **8** have been isolated which bear a C-16 hydroxymethyl moiety.[2d,e] These facts, taken together, suggest that biosynthetic oxidation of the C-16 methyl group provides the activation necessary to trigger a C-9 ester-assisted cyclopropyl carbinyl rearrangement (**12** to **14**). Although consistent with the available data, it would be premature to conclude that the in vivo cyclization only occurs with C-5, -6, and -7 in the higher "b" series oxidation state (**12b** to **14b**).



12a **12b** **13a** **13b** **14a** **14b**

While neighboring-group participation involving esters is a well-established phenomenon,[3] it was only recently demonstrated that intramolecular capture of a bicyclic dioxolenium ion [**16**] could provide 1,2,4-ortho ester **17** similar to the daphnetoxin substructure.[4]



15 [**16**] **17**

While the intimate biogenetic details of the tigliane to daphnane conversion are of mechanistic interest, the ultimate practical question still remains: "can a similar transformation be effected in the laboratory?" The only chemical transformations recorded which bear on this question are very worrisome. Treatment of 16-(hydroxymethyl) cyclopropane derivatives **7** or **8** with acid or base effects cyclopropyl carbinyl cleavage of the *wrong* cyclopropane *bond* to produce ketone **18** (12-deoxybis-dehydrophorbol) and **19** (bis-dehydrophorbol), respec-

(1) Adolf, A.; Hecker, E. *Isr. J. Chem.* **1977**, *16*, 75. See also: West, C. A. *Biosynthesis of Isoprenoid Compounds*; John Wiley: New York, 1981; Vol. I, pp 403–405.

(2) (a) Hecker, E.; Schmidt, R. *Fortsch Chem. Org. Naturst* **1974**, *31*, 377. Evans, F. J.; Soper, C. J. *Lloydia* **1978**, *41*, 193. (b) Hergenhahn, M.; Adolf, W.; Hecker, E. *Tetrahedron Lett.* **1975**, 1595. (c) Cashmore, A. R.; Seelye, B. E.; Cain, B. E.; Mack, H.; Schmidt, R.; Hecker, E. *Tetrahedron Lett.* **1976**, 1737. McCormick, I. R. N.; Nixon, P. E.; Waters, T. N. *Tetrahedron Lett.* **1976**, 1735. Adolf, A.; Hecker, E. *Tetrahedron Lett.* **1980**, 2887. (d) Gschwendt, M.; Hecker, E. *Tetrahedron Lett.* **1970**, 567. Schmidt, R. J.; Evans, F. J. *Experientia* **1977**, *33*, 1197. (e) Okuda, T.; Koike, S.; Toh, N. *Phytochemistry* **1975**, *14*, 509. Weber, J.; Hecker, E. *Experientia* **1978**, *34*, 679. (f) Adolf, A.; Hecker, E. *Tetrahedron Lett.* **1975**, 1587. (g) Stout, G. H.; Balkenhol, W. G.; Poling, M.; Hickernell, G. H. *J. Am. Chem. Soc.* **1970**, *92*, 1070. Sakata, K.; Mitsui, T.; Masaki, N. *Tetrahedron Lett.* **1971**, 1141. Freeman, P. W. *Aust. J. Chem.* **1979**, *32*, 2495. (h) Zayed, S.; Hafez, A.; Adolf, W.; Hecker, E. *Experientia* **1977**, *33*, 1554. (i) *Naturally Occuring Phorbol Esters*, Evans, F. J. Ed.; CRC Press: Boca Raton, 1986. (j) Ronlan, A.; Wickberg, B. *Tetrahedron Lett.* **1970**, 4261. Kupchan, S. M.; Baxter, R. L. *Science* **1975**, 652. Kupchan, S. M.; Sweeny, J. G.; Baxter, R. L.; Murae, T.; Zimmerly, V. A.; Sickles, B. R. *J. Am. Chem. Soc.* **1975**, *97*, 672. Kupchan, S. M.; Shizuri, Y.; Summer, W. C., Jr.; Haynes, H. R.; Leighton, A. P.; Sickles, B. R. *J. Org. Chem.* **1976**, *41*, 3850. Kasai, R.; Lee, K. H.; Huang, H. C. *Phytochemistry* **1981**, *20*, 2592.

(3) (a) Winstein, S.; Buckles, R. E. *J. Am. Chem. Soc.* **1943**, *65*, 613. (b) Corey, E. J.; Carpino, P. *J. Am. Chem. Soc.* **1989**, *111*, 5472.

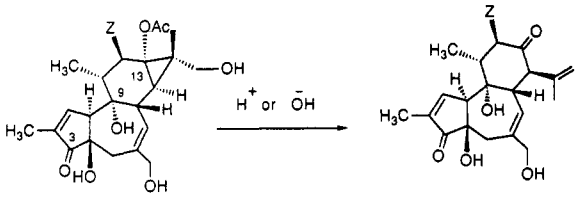
(4) Bloomfield, G. C.; Wrigglesworth, R.; Ritchie, T. J. *J. Chem. Soc., Chem. Commun.* **1991**, 215.

0022-3263/92/1957-5360$03.00/0

Table I. Relative Oxidation Levels of Related Diterpenes

0	1	2	3	4	5
		6 (phorbol)	**8** (16-hydroxyphorbol)		**11** (12-hydroxydaphnetoxin)
4 (Resinifera factor)	**5** (prostratin)	refs 1, 2a	ref 2e	**10** (daphnetoxin)	
		7 (12-deoxy-16-hydroxyphorbol)	**9** (Mancinellin)		
ref 2b	ref 2c	ref 2d	refs 2f,g	refs 2f–2h	ref 2j

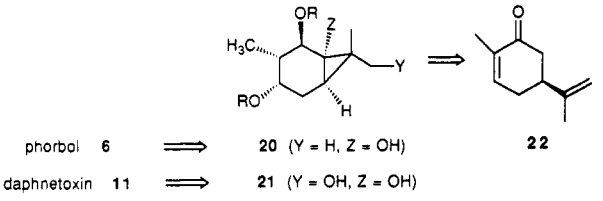
tively.[2e,f] It is possible that these latter two transformations might occur via migration of the acyl group from the C-13 hydroxyl moiety to the C-16 alcohol thereby providing both an activated cyclopropanol at C-13 simultaneously with the generation of a better leaving group at C-16. These latter experiments were not undertaken as a test of any biogenetic postulate but were conducted as an adjunct to the structure proof; therefore, the requisite acyl residue at C-9 was not in place. These results clearly demonstrate the viability of a reaction pathway which is potentially highly competitive to the one desired. This unpleasant possibility underscores the need to evaluate the chemistry required for the **12** to **14** transformation prior to conducting any extensive study on the total synthesis of 12-hydroxydaphnetoxin **11** which relies upon the success of this rearrangement.



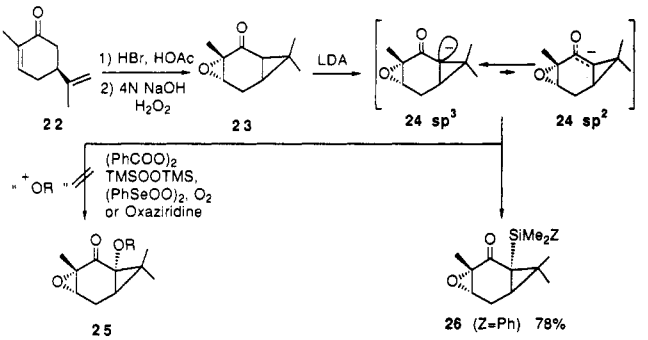
7 (Z = H)
8 (Z = OH)

18 (Z = H)
19 (Z = OH)

The goal of our synthetic studies was to provide a model for testing the cyclopropyl carbinyl rearrangement of phorbol **6** to 12-hydroxydaphnetoxin **11**, as well as to prepare a C-ring synthon which ultimately could be incorporated into the a total synthesis by application of an appropriate C → ABC annulation strategy.[5] It was specifically proposed to initially synthesize the highly functionalized C-ring fragments **20** and **21** from (+)-carvone (**22**) which bears the appropriate absolute configuration as well as all 10 carbon atoms of the C-ring required for the target molecules.



Our initial approach to synthesis of **20** utilized the known[6] conversion of (+)-carvone (**22**) to 3,4-epoxycaranone (**23**). In concept, treatment of enolate **24** with one of the known electrophilic hydroxylation reagents could produce **25**, a logical precursor of model **20**. In



practice, reaction of **24** with different oxygen electrophiles, viz. TMS peroxide,[7] MoOPh,[8] molecular oxygen,[9] bis(diphenyl)phosphinic peroxide,[10] benzoyl peroxide,[11] benzeneseleninic anhydride,[12] and 2-(phenylsulfonyl)-3-phenyloxaziridine[13] failed to provide any evidence of oxygen incorporation.[14] These results suggest that the failure of the ketone enolate to undergo reaction with the oxidizing agents (peroxides) may be due, at least in part, to the presence of amines derived from the base (LDA) used to generate the enolate.[15] In order to assay the stability of enolate **24**, this material was treated with phenyldimethylchlorosilane to afford the carbon-silylated derivative **26**. While carbon silylation of ketone enolates is extremely rare,[16] it is clear that this is another case where the alternative mode of oxygen silylation would lead to a prohibitively strained product.

The Kumada–Fleming–Tamao oxidation of silanes to alcohols has become an important weapon in the arsenal of the organic chemist.[17,18] Treatment of the α-phenyldimethylsilyl (PDMS) ketone **26** with either $HBF_4 \cdot Et_2O$ or $BF_3 \cdot 2AcOH$ complex failed to give substantial formation of the desired fluorosilane **27**, the latter method yielding only 29% of product contaminated with the starting ma-

(5) For the first reported total synthesis of phorbol and phorboid skeleton see: (a) Wender, P. A.; Kogen, H.; Lee, H. Y.; Munger, J. D.; Wilhelm, R. S.; Williams, P. D. *J. Am. Chem. Soc.* **1989**, *111*, 8957. (b) Wender, Lee, H. Y.; Wilhelm, R. S.; Williams, P. D. *J. Am. Chem. Soc.* **1989**, *111*, 8954 and references cited therein. (c) Wender, P. A.; McDonald, F. E. *J. Am. Chem. Soc.* **1990**, *112*, 4956.

(6) (a) Mass, D. D.; Blagg, M.; Wiemer, D. F. *J. Org. Chem.* **1984**, *49*, 853. (b) Burns, W. P. D.; Carson, M. S.; Cocker, W.; Shannon, W. D. P. *J. Chem. Soc. C* **1968**, 3073.

(7) Neumann, H.; Seebach, D. *Chem. Ber.* **1978**, *111*, 2785.

(8) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188.

(9) (a) Adam, W.; Cueto, O. *J. Org. Chem.* **1977**, *42*, 38. (b) Takano, S.; Morimoto, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun*, **1984**, 82.

(10) Dannley, R. L. *J. Am. Chem. Soc.* **1965**, *87*, 4806.

(11) Greene, A. E.; Muller, J. C.; Ourisson, G. *Tetrahedron Lett.* **1972**, 3375.

(12) Barton, D. H. R.; Morzycki, J. W.; Motherwell, W. B.; Ley, S. V. *J. Chem. Soc., Chem. Commun.* **1981**, 1044 and references cited therein.

(13) Davis, F. A.; Vishwakarma, L. C.; Billmers, J. M.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241.

(14) Desai, R. C.; Fuchs, P. L. Unpublished results.

(15) Vederas, J. C.; Gore, M. O. *J. Org. Chem.* **1986**, *51*, 3700.

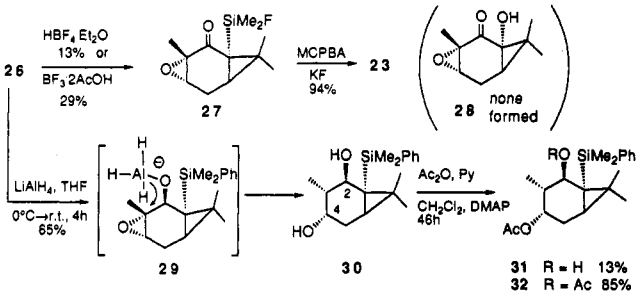
(16) Winkler, J. D.; Lee, C.-S.; Rubo, L.; Muller, C. L. *J. Org. Chem.* **1989**, *54*, 4491.

(17) (a) Fleming, I.; Henning, R.; Plaut, H. *J. Chem. Soc., Chem. Commun.* **1984**, 29. (b) Fleming, I.; Sanderson, P. E. J. *Tetrahedron Lett.* **1987**, *28*, 4229. (c) Bernhard, W.; Fleming, I. *J. Chem. Soc., Chem. Commun.* **1984**, 28.

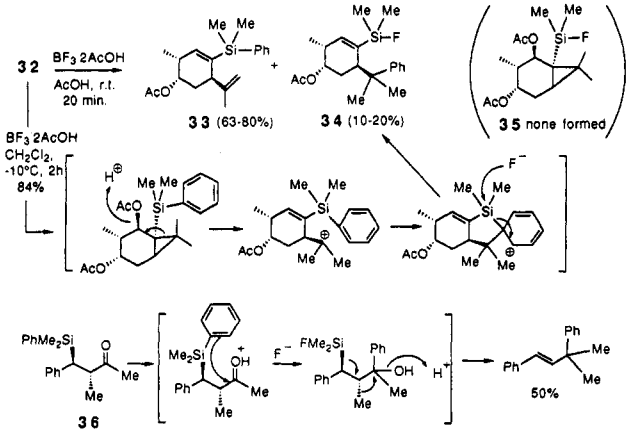
(18) (a) Tamao, K.; Akita, M.; Iwahara, T.; Kanatani, R.; Yoshida, J.; Kumada, M. *Tetrahedron* **1983**, *39*, 983. (b) Tamao, K. *J. Synth. Org. Chem. Jpn.* **1988**, *46*, 861.

terial.[19] Oxidation of the fluorosilane **27** with *m*-CPBA/KF simply returned desilylated epoxycaranone **23** presumably due to the presence of electron-withdrawing carbonyl group, which facilitates silyl cleavage. The mechanism of this cleavage may well involve direct protonation of sp^3-hybridization carbon, since those factors which destabilize **24** sp^2 presumably mitigate against formation of an enol during the cleavage process.

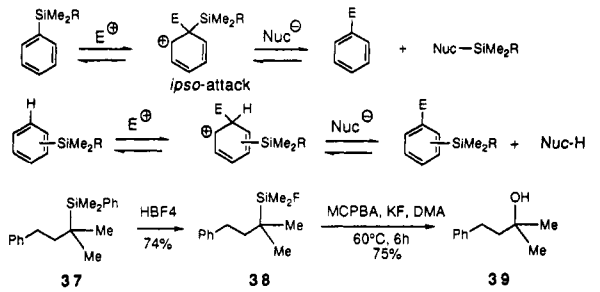
To overcome this problem, α-silyl ketone **26** was treated with LAH to afford 1,3-diol **30** in 65% yield. *It is worthy of note that this reaction creates three new stereocenters in a single step.* This reaction presumably proceeds through the mixed alkoxy alanate intermediate **29**[24] (α-face coordination of the epoxide moiety with an additional Lewis acid likely facilitates the intramolecular hydride delivery). Treatment of **30** with acetic anhydride in the presence of (dimethylamino)pyridine for 48 h provides diacetate **31** in 85% yield along with a small amount (13%) of the α-4-monoacetate **32** (the 2-hydroxy group undergoes slower reaction because of shielding from the β-face dimethylcyclopropyl group).



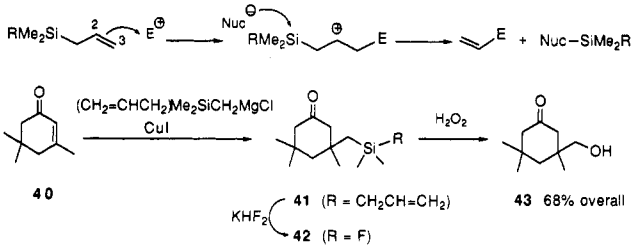
Treatment of the diacetate **32** under the protodesilylation conditions (0.5 equiv of BF_3·2AcOH complex, acetic acid solvent) did not give the desired fluorosilane **35**, but instead resulted in the formation of elimination product **33** (63–80%) along with minor amounts (10–20%) of rearrangement product **34**. Repetition of this reaction at lower temperature using dichloromethane as solvent afforded **34** as the exclusive product in 84% yield. The formation of **34** can be accounted for by a cyclopropyl carbinyl rearrangement followed by electrophilic ipso attack on the phenyl group which then undergoes fluoride-mediated aryl–silicon cleavage. A similar rearrangement was observed by Fleming during protodesilylation of β-silyloxy ketone **36**.[17c]



Phenylsilanes react with electrophiles mainly by ipso attack via an electrophilic aromatic substitution mechanism. In such reactions there is always the potential of a competing electrophilic substitution of hydrogen (in which case aryl–silicon bond cleavage does not occur), although the former pathway is much faster.[20] In the molecules containing the phenyldimethylsilyl group (PDMS) attached to a tertiary center (i.e., where R = a fragment containing tertiary C–Si bond), the ipso addition pathway may be sterically quite demanding. A survey of the vast literature on the use of PDMS as a latent form of hydroxyl group revealed only a single (acyclic) example leading to a *tertiary alcohol* (**37** → **38** → **39**).[17a]



The failure of the PDMS group in the case of phorbol C-ring was probably a result of the steric hindrance posed by the dimethylcyclopropane moiety toward electrophilic ipso attack on the phenyl ring, exacerbated by the ease of acid-catalyzed elimination of the vicinal oxygen moiety.[21] In view of these difficulties, an alternate functional group was sought which would be more reactive and less sterically hindered than the phenylsilyl moiety. Allylsilanes meet this criteria since they are very reactive toward addition of electrophiles via an S_E2' type pathway.[22]



Tamao et al. have used the (allyldimethylsilyl)methyl Grignard reagent as a hydroxymethyl anion synthon for conjugate addition to α,β-unsaturated ketones, via fluorodeallylation and H_2O_2 oxidation.[23] The above example clearly shows that the allyldimethylsilyl group is synthetically equivalent to the –OH group. Use of this functionality in our case required the preparation of α-allyldimethylsilyl (ADMS) ketone **44** which was easily achieved via silylation of the ketone enolate of **24** in 65–78% yield. Reduction with LAH[24] again stereospecifically yields the 1,3-diol **45** (63%). Subsequent protection afforded the diacetate **46** in 93% yield. Treatment of this diacetate, first with bromine (in CH_2Cl_2) as the electrophile followed by poly(hydrogen fluoride)·pyridine[25] as the fluoride source provided 96% yield of the fluorosilane **47**, which can be smoothly oxidized with basic hydrogen peroxide to the corresponding alcohol **48** in 85%

(19) This reaction also furnished trace amounts of the desilylated epoxycaranone **23**.

(20) (a) Fleming, I.; Chan, T. H. *Synthesis* **1979**, 762. (b) Eaborn, C.; Webster, D. E. *J. Chem. Soc.* **1959**, 4449. (c) Benkeser, R. A.; Hoke, D. I.; Hickner, R. A. *J. Am. Chem. Soc.* **1958**, *80*, 5294.

(21) Subsequent reaction of the ADMS diol **45** with either BF_3·2AcOH or tetrafluoroboric acid also resulted in the elimination of the hydroxyl group via cyclopropyl cleavage.

(22) Fleming, I.; Langley, J. A. *J. Chem. Soc., Perkin Trans. 1*, **1981**, 1421.

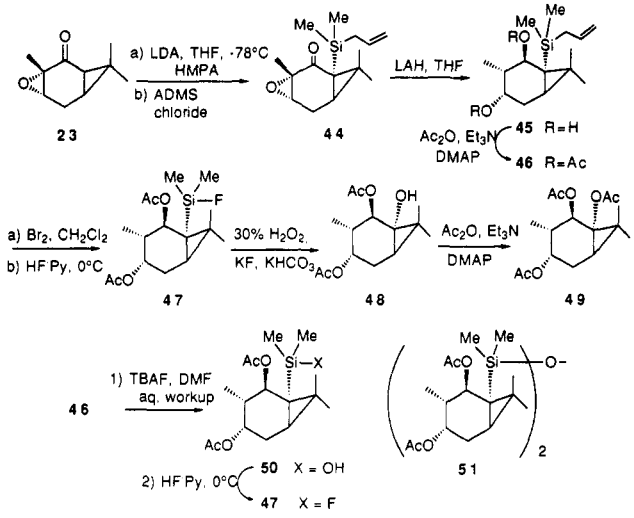
(23) Tamao, K.; Ishida, N. *Tetrahedron Lett.* **1984**, 4249.

(24) Finan, J. M.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2719;

(25) Pyridinium poly(hydrogen fluoride) is a convenient form of anhydrous HF, stable up to 50 °C. For conversion of secondary and tertiary alcohols to alkyl halides see: Olah, G. A.; Welch, J. *Synthesis* **1974**, 653.

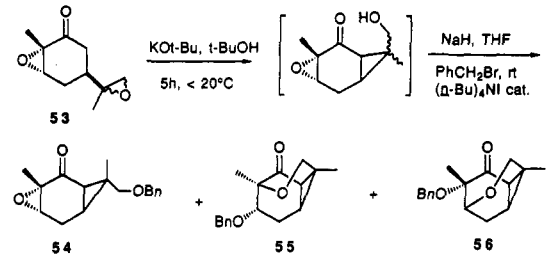
yield.[26] Alcohol **48** was further characterized as its triacetate **49** (92% yield).

In many trials, the alcohol **48** was isolated as a mixture along with minor amounts (5–15%) of silanol **50** (having the same R_f as **48**), which arises via hydrolysis of the fluorosilane **47**. Using an alternate method, treatment of allylsilane diacetate **46** with 2 equiv of TBAF in DMF (undistilled) at room temperature for 1 h gave silanol **50** as a single product, which on further treatment with pyridinium poly(hydrogen fluoride) afforded the desired fluorosilane **47** in 90% overall yield. Interestingly, when allylsilane **46** was treated with TBAF using *freshly distilled* DMF as solvent, the reaction gave the silanol **50** along with a new product, the siloxane **51** in 53 and 42% yield, respectively.[27]

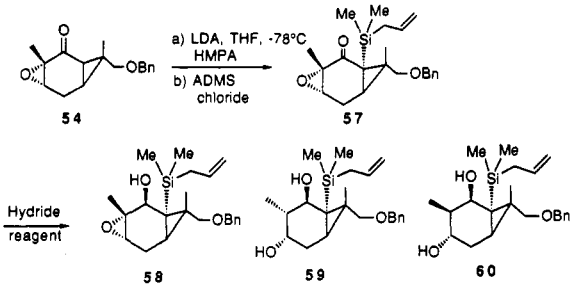


Having established a method of synthesis for the bridgehead tertiary alcohol moiety, attention was next turned to providing the requisite hydroxymethyl-substituted derivative for testing the biomimetic postulate. Since it is known that intramolecular carbon alkylation of enolates can be accomplished at tertiary centers[28] to form bicyclo [4.1.0] systems (including synthesis of **23**), diepoxycarvone (**53**)[29] was chosen as substrate for the cyclization reaction.

(+)-Carvone (**22**) was subjected to oxidation using alkaline hydrogen peroxide to give α,β-epoxy carvone (**52**)[30] as a single isomer in 94% yield. This material was then treated with *m*-CPBA in dichloromethane to furnish a 1:1 diastereomeric mixture of carvone diepoxide (**53**) in 81% yield. When the diepoxide **53** was subjected to enolate-induced intramolecular epoxide opening using potassium *tert*-butoxide as base, a mixture of diastereomers resulted. Chromatographic separation of this mixture could be achieved only after conversion to the corresponding benzyl ether derivatives under standard benzylation conditions (NaH, BnBr, THF, tetra-*n*-butylammonium iodide catalyst). Three compounds whose structures were assigned as **54**, **55**, and **56**, respectively, were obtained by chromatography in yields of 42%, 22%, and 10%. Compounds **55** and **56** apparently arose via intramolecular opening of the epoxide by the *endo*-hydroxymethyl diastereomer at the tertiary and secondary carbons, respectively. Presumably, each of the diepoxide diastereomers undergoes stereospecific annulation, although no attempt to optimize the selectivity of the peracid reaction was undertaken.



To incorporate the allylsilane functionality, the benzyl ether **54** was converted into its enolate with LDA/HMPA, followed by addition of allyldimethyl (ADMS) chloride to provide the α-ADMS ketone **57** in variable yields of 70–91%. In contrast to the excellent LAH reactions of **26** and **44**, the hydride reduction of the silylated epoxy ketone **57** was quite cumbersome, the reaction being either incomplete or nonstereoselective. The results obtained with a variety of reagents and conditions are summarized below.



LAH, Et_2O, 0→25°C	72-77%	-	-
AlH_3, Et_2O, 0→25°C	-	49-70%	trace-38%
AlH_3, THF, 0→25°C	-	26%	19%
AlH_3, Et_2O:toluene(3:2)	-	52%	33%

The reduction with $LiAlH_4$ was extremely slow even after 1–2 days, resulting in partial reduction to the epoxy alcohol **58**. Efforts to reduce this epoxy alcohol further with fresh $LiAlH_4$ afforded mainly the undesired 1,3-diol **60** along with recovered starting material. Better results were obtained with the electrophilic hydride source AlH_3 (made from $LiAlH_4$ and $AlCl_3$ in a 3:1 mole ratio).[31] The reaction rate increased substantially, although the stereoselectivity with regard to the formation of two diastereomeric 1,3-diols **59** or **60** was not reproducible. In general, the decrease in polarity of the solvent resulted in increased selectivity, although solubility problems limited the choice of the solvent. A solvent system comprised of ether–toluene (3:2) gave more reproducible results than using ether alone.

The desired 1,3-diol **59** was easily converted to its acetate diester **61** in 95% yield. Introduction of the hindered bridgehead alcohol moiety was next attempted using the new AMDS cleavage procedure. Treatment with bromine and pyridinium poly(hydrogen fluoride)[25] was expected to give the corresponding fluorosilane, but to our surprise, a cyclic siloxane **62** was obtained instead, in 80–85% isolated yield. The formation of **62** is believed to take place via anchimeric assistance at the stage of the bromonium ion intermediate. Control studies using bromine with pyridine alone (instead of the HF·Py complex) also fur-

(26) For additional examples involving ADMS as a latent alcohol synthon see: Magar, S. S.; Fuchs, P. L. *Tetrahedron Lett.* **1992**, *33*, 745.

(27) Our results suggest that, unlike the silanol, treatment of the siloxane with HF·Py fails to convert it to the corresponding fluorosilane.

(28) (a) Hartman, A. G.; Ong, A. Q. *J. Org. Chem.* **1970**, *35*, 4290. (b) Gaoni, Y. *Isr. J. Chem.* **1971**, *9*, 63. (c) Saddler, J. C.; Fuchs, P. L. *J. Am. Chem. Soc.* **1981**, *103*, 2112.

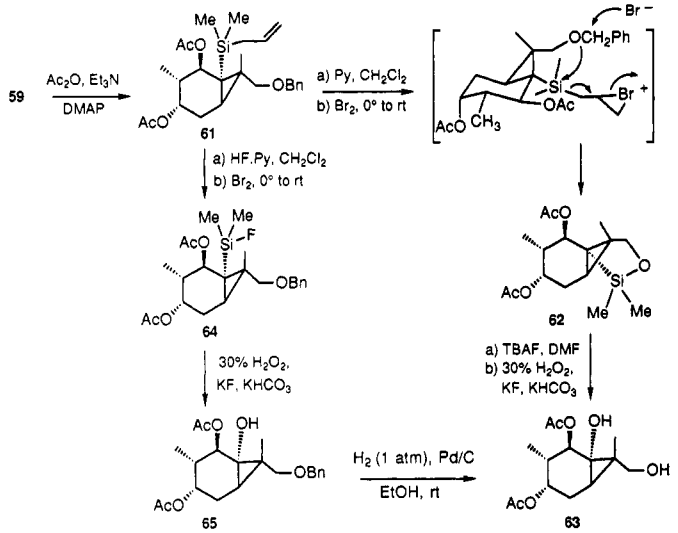
(29) Clemo, G. R.; MaQuillin, F. J. *J. Chem. Soc.* **1952**, 3839.

(30) (a) Baggiolini, E. G.; Henneessy, B. M.; Iacobelli, J. A.; Uskokovic, M. R. *Tetrahedron Lett.* **1987**, *28*, 2095. (b) Castedo, L.; Mascarenas, J. L.; Mourino, A. *Tetrahedron Lett.* **1987**, *28*, 2099.

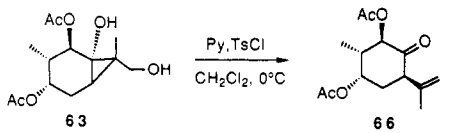
(31) (a) Murphy, D. K., Alunbaugh, R. L.; Rickborn, B. *J. Am. Chem. Soc.* **1969**, *91*, 2649. (b) Rickborn, B.; Lemke, W. E., II. *J. Org. Chem.* **1967**, *32*, 537.

nished the cyclic silyl ether **62**, albeit in a somewhat lower yield of 66%. Cyclic silyl ether **62** was easily converted into the desired target diol **63** in 68% yield, by literature oxidation methods[32] employing basic hydrogen peroxide. The reaction appeared to be much cleaner when using a pretreatment step ivolving TBAF rather than simply using KF alone.

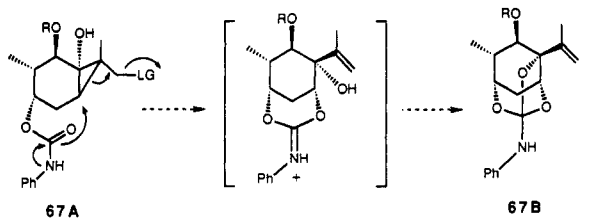
Subsequent work on the reaction of ADMS diacetate **61** with HF·Py/Br_2 has revealed that the unusual formation of cyclic silyl ether **62** possibly occurred as a result of using an older batch of HF·Py (wherein there may be insufficient fluoride concentration to influence the course of the reaction, the reagent being highly hygroscopic and volatile). Thus, when the experimental procedure was repeated using a freshly opened bottle of pyridinium poly(hydrogen fluoride), the fluorosilane **64** was obtained exclusively in 79% yield. Oxidation of the fluorosilane to the desired alcohol **65** in 82% yield was easily accomplished using basic peroxide with potassium fluoride catalyst. Finally, deprotection of the primary benzyl ether in **65** was conveniently carried out by hydrogenolysis over 10% Pd/C to afford diol **63** in quantitative yield.



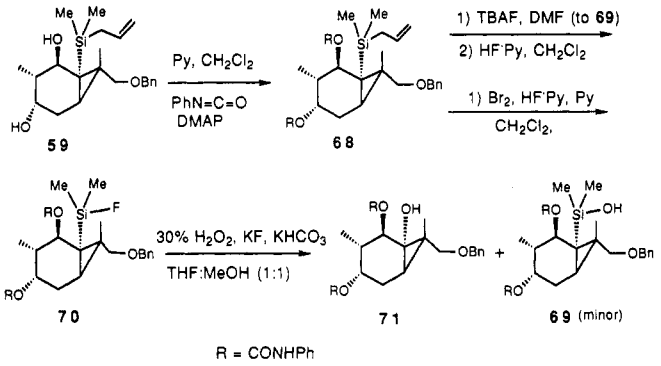
The stage was now set for testing the ester-assisted cyclopropyl carbinyl rearrangement on the diol **63**. Unfortunately, when the diol was subjected to conditions of cyclopropyl cleavage using 1 equiv of tosyl chloride with pyridine as base, no ester participation was observed; instead the reaction led to formation of the β,γ-unsaturated ketone **66**. That the wrong cyclopropane bond had undergone cleavage was not in doubt, likely a consequence of lone pair assistance by the tertiary alcohol which is undergoing transformation to the π system of the incipient ketone.



At this juncture, the supply of diol diacetate **63** needed to conduct further testing on the biomimetic hypothesis had been completely consumed. In preference to repeating the synthesis of diacetate **63**, we opted for the preparation of the corresponding dicarbamate (e.g., **67A**) which was felt to offer better anchimeric assistance in the desired cyclopropyl cleavage (**67A** → **67B**).

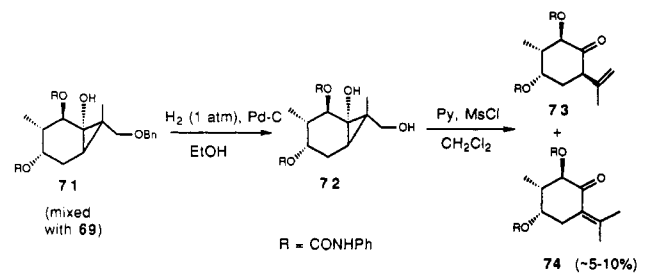


Diol **59** was converted to the dicarbamate **68** in 85% yield. Bromodesilylation with bromine and pyridinium poly(hydrogen fluoride) (HF·Py) afforded fluorosilane **70** in 85–90% yield. Similarly, the fluorosilane could also be prepared in 88% yield via silanol **69**, which was obtained by treatment of **68** with TBAF in DMF followed by reaction with HF·Py. This fluorosilane was oxidized under basic peroxide/KF conditions to afford an inseparable mixture of the alcohol **71** along with minor amounts of silanol **69** (as evident from NMR). The formation of silanol **69** must result from competitive hydrolysis of the fluorosilane **70** by the water present in the oxidation reaction (from the 30% H_2O_2). Addition of molecular sieves to the reaction did not have any beneficial effect; on the contrary, the reaction rate decreased considerably.



Separation of the alcohol **71** from the silanol side product **69** was quite easily achieved after reductive debenzylation. Hydrogenolysis over 10% Pd on C in ethanol at 1 atm afforded pure diol **72** (50% overall yield in three steps from **68**).

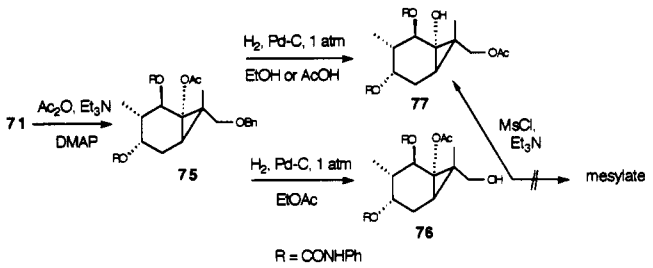
When the diol **72** was subjected to conditions for cyclopropyl cleavage (this time via primary mesylate using mesyl chloride and pyridine), the reaction again exclusively led to formation of the β,γ-unsaturated ketone **73** in 75% isolated yield along with minor amounts of isomerized product **74** which could only be obtained as a mixture with **73**.



In an attempt to overcome this undesired reaction mode, the tertiary hydroxyl group of benzyl ether **71** was converted to acetate **75** (Et_3N, Ac_2O, DMAP, CH_2Cl_2, 2 days;

(32) (a) Journet, M.; Magnol, E.; Agnel, G.; Malacria, M. *Tetrahedron Lett.* **1990**, *31*, 4445. (b) Koreeda, M.; George, I. A. *J. Am. Chem. Soc.* **1986**, *108*, 8098. (c) Nishiyama, H.; Kitajima, T.; Matsumoto, M.; Itoh, K. *J. Org. Chem.* **1984**, *49*, 2298. (d) Tamao, K.; Yamaguchi, T.; Ito, Y. *Chem. Lett.* **1987**, 171. (e) Tamao, K.; Maeda, K.; Tanaka, T.; Ito, Y. *Tetrahedron Lett.* **1988**, *29*, 6955. (f) Tamao, K.; Maeda, K.; Yamaguchi, T.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4984. (g) Tamao, K.; Nakagawa, Y.; Arai, H.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 3712. (h) Stork, G.; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500.

quantitative). Hydrogenolysis of **75** in polar–protic solvents like EtOH gave 61% yield of the product **77** resulting from acyl transfer. Carrying out the same sequence in ethyl acetate afforded up to 33% of the desired product **76** along with an equal amount of the primary acetate **77**.



The tertiary acetate **76** was subjected to standard conditions (1.1 equiv each of the Et_3N and MsCl) in an attempt to generate the primary mesylate. To our surprise, the sulfene-forming reaction conditions (probably via triethylamine catalysis) resulted in the migration of the acetyl group from the tertiary to the primary center to again give **77**.[33] At the present juncture, the biomimetic hypothesis remains unproven; however, the reasonable availability of substrates like **59** provides the potential for future research.

Experimental Section[34]

α-1-(Allyldimethylsilyl)-α-3,4-epoxycarvan-2-one (44). A solution of epoxycarvanone (**23**)[6] (8.22 g, 49.5 mmol) in THF (60 mL) was added dropwise to the solution of LDA (64.4 mmol) in 120 mL of THF, over a period of 0.5 h. This was followed by 17 mL (99 mmol) of HMPA and 10.8 mL (74.2 mmol) of ADMS chloride. The mixture was stirred for 12 h with gradual rise in temperature (color change: orange to deep red). Saturated NH_4Cl was added to the reaction mixture, and it was extracted with ether. All the organic extracts were combined and washed with water and brine and dried over Na_2SO_4. Concentration in vacuo afforded 15.3 g of crude red oil, which was purified by chromatography over SiO_2 using 0–5% EtOAc in hexanes to furnish 10.2 g (78%) of the pure ADMS ketone **44**: colorless oil; R_f = 0.2 (10% EtOAc in hexanes); ^1H NMR (470 MHz, $CDCl_3$) δ 5.65–5.75 (m, 1, H_1), 4.75–4.82 (m, 2, H_2), 3.10 (br s, 1, H_3), 2.40–2.50 (ddd, J = 16, 8, 2 Hz, 1, H_4), 1.84–1.90 (d, J = 16 Hz, 1, H_4), 1.5–1.7 (m, 2, H_5), 1.26 (s, 3, H_6), 1.12 and 0.8 (2s, 6, H_7), 1.03 (dd, J = 9, 2 Hz, 1, H_8), 0.2–0.4 (2s, 6, $SiMe_2$); MS (EI) m/e 224 (M – C_3H_4); MS (CI isobutane): 265 (M + H); $[\alpha]^{25}_D$ –87.4° (c = 3.1, $CDCl_3$).

1-(Allyldimethylsilyl)-β-2,α-4-dihydroxy-α-3,7,7-trimethylbicyclo[4.1.0]heptane (45). To a solution of ADMS epoxy ketone **44** (6.10g, 23.1 mmol) in 55 mL of THF at 0 °C was added 2.77 g (69.3 mmol) of LAH. After being stirred for 4.5 h, an equal amount of additional LAH was added to reduce the leftover **44**. After a total of 13 h at rt, the reaction was carefully quenched with saturated Na_2SO_4, the resulting solid was filtered out, and the filtrate was evaporated to furnish 5.80 g of solid. Chromatographic separation over SiO_2 using EtOAc–Et_2O–hexanes (15:5:80) afforded 3.90 g (63%) of **45** as a white solid: mp 90 °C; R_f = 0.32 (25% EtOAc in hexanes); ^1H NMR (470 MHz, $CDCl_3$) δ 5.88–5.98 (m, 1, H_1), 4.90–4.98 (m, 2, H_2), 3.98–4.04 (dd, J = 9, 5 Hz, 1, H_3), 3.70 (br s, 1, H_4), 2.08–2.14 (m, 1, H_5), 1.68–1.75 (m, 2, H_6), 1.50–1.56 (dt, J = 15, 3 Hz, 1), 1.34–1.36 (d, J = 5 Hz, 1), 1.22 and 1.21 (2s, 6, 2 Me), 1.11–1.13 (d, J = 6.5 Hz, 3, H7), 1.02–1.04 (dd, J = 9, 4 Hz, 1 H); IR (CCl_4) 3460 cm^{-1}; MS (EI) m/e 253 (M – CH_3), 75 ($SiMe_2OH$); CIMS 269 (M + H), 251 (M + H – H_2O), 209 (M + H – H_2O – C_3H_6); HRMS for $C_{15}H_{26}OSi$ calcd 251.1831, found 251.1826; $[\alpha]^{25}_D$ +43.6° (c = 1.0, $CHCl_3$).

Anal. Calcd for $C_{15}H_{28}O_2Si$: C, 67.13; H, 10.52. Found: C, 67.07; H, 10.83.

1-(Allyldimethylsilyl)-β-2,α-4-diacetoxy-α-3,7,7-trimethylbicyclo[4.1.0]heptane (46). To a solution of 343 mg (1.28 mmol) of diol **45** in CH_2Cl_2 (5 mL) at 0 °C were successively added 1.07 mL (7.68 mmol) of Et_3N and 0.60 mL (6.4 mmol) of Ac_2O, followed by 30 mg of DMAP as catalyst. The resulting mixture was stirred at rt for 4 h and then taken in a separatory funnel with 20 mL of CH_2Cl_2 and washed with 5% HCl (5 mL), saturated $NaHCO_3$, and brine. Drying over Na_2SO_4 and concentration in vacuo furnished 0.52 g of an oily residue which chromatographed using 10% EtOAc in hexanes to afford 420 mg (93%) of pure diacetate **46**: colorless oil; R_f = 0.62 (25% EtOAc in hexanes); ^1H NMR (470 MHz, $CDCl_3$) δ 5.74–5.80 (m, 1, H_1), 5.42–5.44 (d, J = 10 Hz, 1, H_2), 4.80–4.86 (m, 3, H_3), 2.19–2.25 (m, 1, H_4), 2.04 and 2.06 (2s, 6, OCOMe), 1.69–1.74 (m, 1, H_5), 1.57–1.61 (m, 1, H_5), 1.42–1.48 (m, 2, H_6 and H_4), 1.18 (2s, 6, H_7), 1.02–1.05 (dd, J = 10, 4 Hz, 1, H_8), 0.88–0.89 (d, J = 7 Hz, 3, Hg), 0.08, and 0.13 (2s, 6, $SiMe_2$); IR (neat) 1737, 1630, 1232 cm^{-1}; MS (EI) m/e 251 (M – HOAc – C_3H6); MS (CI, isobutane) 293 (M + H – HOAc); HRMS for $C_{17}H_{29}O_2Si$ calcd 293.1937, found 293.1931; $[\alpha]^{25}_D$ +94.5° (c = 7.2, $CHCl_3$).

Anal. Calcd for $C_{19}H_{32}O_4Si$: C, 64.74; H, 9.15. Found: C, 64.86; H, 9.44.

β-2,α-4-Diacetoxy-α-3,7,7-trimethyl-1-(fluorodimethylsilyl)bicyclo[4.1.0]heptane (47). Method 1. To a solution of 56.0 mg (0.16 mmol) of diacetate **46** in 10 mL of CH_2Cl_2 in a plastic reaction vessel at 0 °C were added 0.10 mL of Br_2 followed by 0.50 mL of HF·Py complex. The resulting mixture was stirred at 0 °C for 1 h. Excess HF was destroyed by pouring the mixture over alumina. Dilution with CH_2Cl_2, filtration, and concentration in vacuo furnished 50.2 mg (96%) of the fluorosilane **47**.

Method 2. To a solution of 53 mg (0.15 mmol) of diacetate **46** in 4 mL of DMF at rt was added 0.16 mL (0.16 mmol) of n-Bu_4NF (1.0 M solution in THF). TLC indicated complete disappearance of the starting material in 15 min. The reaction mixture was placed in a separatory funnel, diluted with 10 mL of water, and extracted several times with small portions of 1:1 Et_2O–hexanes. The combined organic extracts were dried (Na_2SO4) and concentrated to furnish silanol **50** which was used as such for the next step. The silanol was dissolved in 5 mL of CH_2Cl_2 and cooled to 0 °C in a plastic reaction vessel under argon. To this was added 0.45 mL of pyridine (as buffer) and an equal amount of hydrogen fluoride–pyridine complex (~70% HF:30% Py). This was stirred in an ice bath for 2 h. Excess HF was destroyed by pouring the mixture over alumina. Filtration, concentration in vacuo, and chromatographic separation of the residue over SiO_2 (eluent 20% EtOAc in hexanes) afforded 45 mg (90%) of pure fluorosilane **47**: oil; R_f = 0.52 (25% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.20–5.23 (d, J = 9 Hz, 1, H_1), 4.91 (br s, 1, H_2), 2.24–2.28 (m, 1, H_3), 2.04 and 2.06 (2s, 6, OCOMe), 1.42–1.53 (m, 2, H_3 and H_4), 1.27–1.31 (dd, J = 10, 4 Hz, 1, H_5), 1.18 and 1.20 (2s, 6, H_6), 0.89–0.91 (d, J = 7 Hz, 3, H_7), 0.46–0.49 (d, J = 8 Hz, 3, $SiCH_3F$), 0.22–0.24 (d, J = 8 Hz, 3, $SiCH_3F$); MS (CI, isobutane) m/e 331 (M + H), 311 (M + H – HF), 271 (M + H – AcOH).

β-2,α-4-Diacetoxy-3,7,7-trimethylbicyclo[4.1.0]heptan-1α-ol (48). To a solution of 40 mg (0.12 mmol) of the fluorosilane **47** in THF–MeOH (2 mL each) at rt were successively added 14 mg (0.24 mmol) of KF, 24 mg (0.24 mmol) of $KHCO_3$, and 0.30 mL (2.4 mmol) of 30% H_2O_2. The resulting mixture was stirred at rt for 16 h and then diluted with 20 mL of Et_2O, and 2 g of powdered $Na_2S_2O_3·5H_2O$ were added to the mixture to destroy excess peroxide. The resulting slurry was stirred vigorously for 0.5 h and then filtered through Celite, dried (Na_2SO4), and concentrated in vacuo. Column chromatography using SiO_2 (eluent: 20% EtOAc in hexanes) afforded 28 mg (85%) of the tertiary alcohol **48** (NMR indicated presence of ~5% w/w of the silanol side product **50**).

48: oil; ^1H NMR (300 MHz, $CDCl_3$) δ 4.96–4.99 (d, J = 9 Hz, 1, H_1), 4.90–4.92 (m, 1, H_2), 4.38 (br s, 1, OH), 2.23–2.28 (m, 1, H_3), 2.09–2.12 (2s, 6, OCOMe), 1.58–1.61 (m, 1, H_3), 1.23–1.35 (m, 1, H_4), 1.16 and 1.02 (2s, 6, H_6), 1.03–1.05 (d, J = 7 Hz, 3, H_7), 0.90–0.98 (m, 1, H_5).

α-3,7,7-Trimethyl-α-1,β-2,α-4-triacetoxybicyclo[4.1.0]heptane (49). The tertiary alcohol **48** (25 mg, 0.09 mmol) was dis-

(33) Similar migratory aptitude has been reported in the literature. See: Dodd, G. H.; Golding, B. T.; Ioannou, P. V. *J. Chem. Soc., Chem. Commun.* **1975**, 249.

(34) General experimental procedures may be found in: Govindan, S. V.; Fuchs, P. L. *J. Org. Chem.* **1988**, *53*, 2593. Compounds characterized by exact mass were shown to be greater than 95% pure by TLC and NMR.

solved in 5 mL of CH_2Cl_2 and cooled to 0 °C. To it were successively added 0.13 mL (0.92 mmol) of Et_3N, 0.09 mL (0.92 mmol) of Ac_2O, and 50 mg of DMAP. After being stirred for 17 h at rt, the mixture was diluted with 15 mL of CH_2Cl_2 and washed with 5% HCl, saturated $NaHCO_3$, and brine. Drying (Na_2SO4) and evaporation under reduced pressure gave an oily residue which was chromatographed over SiO_2 using 5% EtOAc in hexanes to afford 26.5 mg (92%) of the triacetate **49**: colorless oil; R_f = 0.37 (25% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.58–5.61 (d, J = 8 Hz, 1, H_1), 4.90 (br s, 1, H_2), 2.28–2.40 (m, 1, H_3), 2.00, 2.10, and 2.14 (3s, 3 each, OCOCH_3), 1.06–1.63 (m, 3, H_3 and H_4), 1.13 and 1.22 (2s, 6, H_5), 0.92–0.94 (d, J = 5 Hz, 3, H_6); MS (CI, NH_4) m/e 330 (M + NH_4), 270 (M + NH_4 – HOAc), 253 (M + H – HOAc), 193 (M + H – 2HOAc); $[\alpha]^{25}_D$ +86.2° (c = 0.60, $CDCl_3$).

β-2,α-4-Diacetoxy-α-3,7,7-trimethyl-1-(hydroxydimethylsilyl)bicyclo[4.1.0]heptane (50) and 1-Dimethylsiloxane of β-2,α-4-diacetoxy-α-3,7,7-trimethylbicyclo[4.1.0]heptane (51). To a solution of 95 mg (0.27 mmol) of diacetate **46** in 2 mL of distilled DMF containing powdered molecular sieves (4 Å) was added 0.27 mL (0.27 mmol) of n-Bu_4NF in THF. The resulting mixture was stirred for 1.5 h at rt. Water (10 mL) was added to the reaction mixture, and it was extracted with small portions of 1:1 Et_2O–hexanes. The combined organic extracts were dried (Na_2SO_4) and concentrated. Purification on SiO_2 column eluted with 20% EtOAc in hexanes furnished 36 mg (42%) of the siloxane **51** (fraction 1) and 47 mg (53%) of silanol **50** (fraction 2).

50: white solid; mp 74 °C; R_f = 0.24 (25% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.37–5.40 (d, J = 7 Hz, 1, H_1), 4.90 (br s, 1, H_2), 2.67 (br s, 1, OH), 2.32–2.34 (t, J = 6 Hz, 1), 2.23–2.29 (m, 1, H_3), 2.08–2.09 (2s, 6, OCOCH_3), 1.44–1.57 (m, 3, H_3 and H_4), 1.19–1.23 (2s, 6, H_5), 0.92–0.94 (d, J = 6 Hz, 3, H_6), 0.22–0.26 (2s, 6, SiMe_2); IR (neat) 3690 (–SiOH), 3554 (OH), 1735 (C=O), 1372 cm^{-1}; MS (EI) m/e 311 (M – OH); MS (CI, isobutane) 311 (M + H – H_2O), 269 (M + H – AcOH), 209 (M + H – 2AcOH); HRMS for $C_{14}H_{25}O_3Si$ calcd 269.1573, found 269.1565.

Anal. Calcd for $C_{16}H_{28}O_5Si$: C, 58.52; H, 8.59. Found: C, 58.31; H, 8.83.

51: colorless oil; R_f = 0.57 (25% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.37–5.40 (d, J = 9 Hz, 1, H_1), 4.90 (br s, 1, H_2), 2.17–2.26 (m, 1, H_3), 2.03 (2s, 6, OCOMe), 1.44–1.51 (m, 3, H_3 and H_4), 1.17–1.20 (2s, 6, H_5), 0.86–0.88 (d, J = 7 Hz, 3, H_6), 0.40 (s, 3, SiCH_3), 0.10 (s, 3, SiCH_3); IR (neat) 1736 (C=O), 1370 (CO) cm^{-1}.

Benzyl Ether of 7-*exo*-(Hydroxymethyl)-α-3,4-epoxy-3,7-dimethylbicyclo[4.1.0]heptan-2-one (54) and Tricyclic Isomers 55 and 56. The carvone epoxide **52**[28] (21g, 126 mmol) was dissolved in dichloromethane (400 mL), and the solution was cooled to 0 °C. To this was added m-chloroperbenzoic acid (31.8 g, 184 mmol) in small portions over a period of 10 min. The resulting slurry was stirred for 6 h while the temperature was allowed to rise gradually. The reaction mixture was then transferred to a separatory funnel and washed successively with cold saturated sodium bisulfite, saturated sodium carbonate, water, and brine. The organic layer was dried over sodium sulfate and concentrated in vacuo to afford the diastereomeric mixture of carvone diepoxide (**53**) as a brown oil (18.6 g, 81% yield), which was used as such for the next reaction.

53: 97% pure by GC (mixture of two diasteromers in the ratio 48.9:47.9); ^1H NMR (200 MHz, $CDCl_3$) δ 3.40–3.41 (d, J = 2.7 Hz, 1, H1), 1.38–2.64 (m, 6, $H_{2,3,4,5}$), 1.36 (s, 3, H_6), 1.23 (d, J = 7 Hz, 3, H_7); ^{13}C NMR (50 MHz, $CDCl_3$) showed two sets of carbons: δ 204.30 and 204.48 (e), 60.56 and 60.62 (o), 58.56 and 58.62 (e), 57.29 and 57.37 (e), 51.95 and 52.46 (e); 38.06 and 38.60 (e), 33.32 and 33.42 (o), 25.14 and 25.32 (e), 18.22 and 18.50 (o), 14.88 (o); IR (neat): 1708 (C=O) cm^{-1}; MS (Cl, isobutane) m/e (M + H), 165 (M + H – H_2O).

To a solution of diepoxycarvone (**53**) (18.0 g, 99 mmol) in 2-methyl-2-propanol (350 mL) was added potassium *tert*-butoxide (22.0g, 158 mmol), and the resulting mixture was stirred with a mechanical stirrer for 5 h while the temperature was maintained at or below 20 °C. Excess base was then neutralized by slow addition of saturated ammonium chloride solution, and the reaction mixture was extracted repeatedly with ether (3 × 100 mL). All the ethereal extracts were combined, washed with brine (2 × 100 mL), and dried with magnesium sulfate. The solvent was evaporated in vacuo to leave 17.5 g of crude cyclopropylcarbinol as an inseparable mixture of three isomers. Column chromatography over silica gel gave a small amount of the desired *exo*-(hydroxymethyl)cyclopropylcarbinol, which was used for analysis: ^1H NMR (470 MHz, $CDCl_3$) δ 3.39 (ABq, J = 11 Hz, 2, H_1), 3.18 (br s, 1, H_2), 2.58 (dd, J = 16, 8 Hz, H_3), 2.09 (d, J = 16 Hz, 1, H_4), 1.54 (d, J = 8 Hz, 1, H_6), 1.36 (s, 3, CH_3), 1.27 (t, 1, H_5), 1.04 (s, 3, CH_3); IR (neat) 1692 (C=O) cm^{-1}; MS for $C_{10}H_{14}O_3$ (CI, isobutane) m/e 183 (M + H), 165 (M + H – H_2O).

Part of the mixture (10 g, 55 mmol) of isomers obtained in the above case was dissolved in 30 mL of THF, and this was added dropwise by cannulation to a slurry of NaH (2.42 g of 60% NaH, 60 mmol) in 20 mL of THF. Tetra-n-butylammonium iodide (10.1 g, 27.5 mmol) was then added as catalyst followed by dropwise addition of benzyl bromide (6.54 mL, 55 mmol). TLC monitoring showed complete disappearance of the starting material after 3 h, at which point the reaction was quenched with saturated ammonium chloride (60 mL). The resulting mixture was extracted with ether (5 × 100 mL); all organic extracts were washed with brine and were dried over magnesium sulfate. Solvent evaporation in vacuo gave 18.2 g of a crude mixture consisting of three components. Column chromatography over silica gel (gradient elution with 5–15% EtOAc in hexanes) gave **54** (6.31 g, 42.2%) as the major product and two other fractions **55** (3.34 g, 22.3%) and **56** (1.52 g, 10.2%).

54: white crystalline solid, mp 85 °C; R_f = 0.32 (25% EtOAc in hexanes); ^1H NMR (470 MHz, $CDCl_3$) δ 7.28–7.35 (br s, 5, ArH), 4.44–4.51 (ABq, J = 10 Hz), 2, benzylic), 3.14–3.40 (ABq, J = 10 Hz, 2, H_2), 3.22 (s, 1, H_3), 2.53–2.59 (dd, J = 16, 8 Hz, 1, H_4), 2.05–2.08 (d, J = 16 Hz, 1, H_5), 1.53 (d, J = 8 Hz, 1, H_6), 1.25–1.28 (t, 1, H_7), 1.36 (s, 3, $-CH_3$), 1.04 (s, 3, $-CH_3$); ^{13}C NMR ($CDCl_3$, 50 MHz) ppm 202.63 (e), 138.08 (e), 128.4 (o), 128.3 (o), 127.84 (o), 127.76 (o), 77.58 (e), 72.59 (e), 60.67 (o), 57.54 (e), 26.51 (o), 25.79 (e), 18.74 (e), 17.09 (o), 14.55 (o), 11.35 (o); IR: 1690 (C=O) cm^{-1}; MS (EI) m/e 181 (M – C_7H_7), 91 ($C_7H_7^+$); MS (CI, isobutane) 273 (M + H); HRMS for $C_{17}H_{20}O_3$ calcd 272.1412, found 272.1407; $[\alpha]^{25}_D$ –14.1° (c = 3.15, $CHCl_3$).

Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.58; H, 7.49.

55: colorless oil; R_f = 0.28 (25% EtOAc in hexanes); ^1H NMR (470 MHz, $CDCl_3$) 7.27–7.37 (m, 5, ArH), 4.38–4.62 (ABq, J = 12 Hz, 2, benzylic), 3.92–4.06 (ABq, J = 11 Hz, 2, H_2), 3.65–3.66 (d, J = 4.7 Hz, 1, H_3), 2.29–2.33 (dd, J = 15, 5 Hz, 1, H_4), 2.14–2.19 (dd, J = 15, 7.5 Hz, 1, H_5), 2.00 (d, J = 8 Hz, 1, H_7), 1.77 (t, 1, H_6), 1.18 (s, 3, $-CH_3$), 1.15 (s, 3, $-CH_3$); ^{13}C NMR ppm 203 (e), 137.8 (e), 128.4 (o), 128.3 (o), 127.5 (o), 127.4 (o), 126.9 (o), 87.7 (o), 77.8 (e), 71.1 (e), 65.3 (e), 36.5 (e), 35.1 (o), 32.2 (o), 21.4 (e), 21.1 (o), 18.8 (o); IR carbonyl absorption at 1710 cm^{-1}; MS m/e 181 (m-C_7H_7), 91 ($C_7H_7^+$); CIMS 273 (M + 1); HRMS for $C_{17}H_{20}O_3$ calcd 272.1412, found 272.1404.

56: white crystalline solid; mp 69–70 °C; R_f = 0.24 (25% EtOAc in hexanes); ^1H NMR (470 MHz, $CDCl_3$) 7.27–7.34 (m, 5, ArH), 4.48–4.61 (ABq, J = 12 Hz, 2, benzylic), 3.89–4.16 (ABq, J = 11 Hz, 2, H_2), 3.23–3.27 (t, 1, H_3), 2.41–2.47 (m, 1, H_4), 2.08–2.13 (dd, J = 14, 8 Hz, 1, H_5), 1.85 (d, J = 8 Hz, 1, H_7), 1.68–1.71 (t, 1, H_6), 1.22 (s, 3, $-CH_3$), 1.12 (s, 3, $-CH_3$); ^{13}C NMR ($CDCl_3$, 50 MHz) ppm 204.5 (e), 137.8 (e), 128.4 (o), 128.3 (o), 127.84 (o), 127.76 (o), 82.0 (o), 80.5 (e), 72.1 (e), 64.9 (e), 35.2 (e), 34.0 (o), 30.1 (o), 23.7 (e), 21.1 (o), 17.4 (o); IR carbonyl absorption at 1702 cm^{-1}; MS m/e 181 (m-C_7H_7), 91 ($C_7H_7^+$); CIMS 273 (M + 1); HRMS for $C_{17}H_{20}O_3$ calcd 272.1412, found 272.1407.

Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.69; H, 7.41.

α-1-(Allyldimethylsilyl)-7-*exo*-[(benzyloxy)methyl]-β-3,7-dimethyl-α-3,4-epoxybicyclo[4.1.0]heptan-2-one (57). LDA (6.87 mmol) was made by adding 11.4 mL (25.5 mmol) of 2.22 M n-BuLi dropwise at –78 °C to a solution of diisopropylamine (3.68 mL, 26.3 mmol) in 10 mL of THF and then warming to 0 °C for 10 min and cooling back to –78 °C. After 20 min, 0.35 mL (2.01 mmol) of HMPA was added followed by addition of a mixture of benzyl ether **54** (5.50 g, 20.2 mmol) and ADMS chloride (9.00 mL, 61.9 mmol) in 20 mL of THF at –78 °C. The reaction was allowed to come to rt over a period of 14 h and then quenched with saturated NH_4Cl. Dilution with ether and washing the organic layer with saturated $NaHCO_3$ and brine followed by drying and evaporation in vacuo afforded a yellow oil which was chro-

matographed on SiO_2 using 20% EtOAc in hexanes to furnish 2.40 g of unreacted **54** (43.6% recovery) and 3.84 g (91%, based on the recovered starting material) α-ADMS ketone **57**: colorless oil; R_f = 0.46 (20% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.27–7.34 (m, 5, ArH), 5.63–5.78 (m, 1, H_1), 4.78–4.83 (m, 2, H_2), 4.42–4.53 (ABq, J = 12 Hz, 2, H_3), 3.47–3.50 and 3.04–3.07 (ABq, J = 9.5 Hz, 2, H_4), 3.17 (s, 1, H_5), 2.49–2.58 (dd, J = 16, 9 Hz, 1, H_6), 1.91–1.97 (d, J = 17 Hz, 1, H_6), 1.50–1.59 (m, 2, H_7), 1.32 (s, 3, CH_3), 1.17–1.21 (dd, J = 9, 2 Hz, H_7), 0.93 (s, 3, CH_3), 0.00 and −0.02 (2s, 6, $SiMe_2$); ^{13}C NMR (50 MHz, $CDCl_3$) ppm 208.37 (e), 137.99 (e), 128.4 (o), 128.3 (o), 127.84 (o), 127.76 (o), 134.44 (o, vinyl), 113.62 (e, vinyl), 76.12 (e), 72.9 (e), 62.43 (o), 58.92 (e), 28.2 (e, allylic), 27.15 (e), 23.53 (e), 21.93 (o), 19.40 (e), 14.70 (o), 14.54 (o), −2.59 (o), −4.03 (o); IR (neat) 1684 (C=O) cm^{-1} MS (CI, isobutane) m/e 371 (M + H), 329 (M + H − C_3H_6), 91 ($C_7H_7^+$); HRMS for $C_{14}H_{16}O_3$ calcd 329.1572, found 329.1566; $[\alpha]^{25}_D$ −56.7° (c = 2.9, $CHCl_3$).

Anal. Calcd for $C_{17}H_{20}O_3$: C, 71.32; H, 8.16. Found: C, 71.48; H, 8.43.

7-*exo*-[(Benzyloxy)methyl]-α-1-(allyldimethylsilyl)-α-3,4-epoxy-β-3,7-dimethyl-β-2-hydroxybicyclo[4.1.0]heptane (58). The ADMS epoxy ketone **57** (53 mg, 0.14 mmol) was dissolved in 5 mL of Et_2O, and to this was added 28 mg (0.73 mmol) of $LiAlH_4$ at rt. The resulting mixture was stirred at rt for 3 h, after which TLC still showed the presence of the starting material. An equal amount of LAH was then added, and the reaction mixture was stirred for another 21 h. Quenching with ice–water, 10% NaOH, and water and extracting with Et_2O–THF (1:1) followed by concentration in vacuo gave the epoxy alcohol. This was further purified on SiO_2 eluted with 10% EtOAc in hexanes to afford 41 mg (77% yield) of **58**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.25–7.38 (m, 5, ArH), 5.77–5.86 (m, 1, H_1), 4.82–4.88 (m, 2, H_2), 4.40–4.54 (ABq, J = 12 Hz, 2, H_3), 4.24–4.26 (d, J = 5 Hz, 1, H_4), 3.88–3.91 (d, J = 9 Hz, 1) 3.18–3.34 (ABq, J = 9 Hz, 2, H_5), 3.00–3.04 (br s, 1, H_6), 2.22–2.30 (dd, J = 18, 8 Hz, 1, H_7), 1.98–2.06 (m, 1, H_7), 1.61–1.75 (m, 2, H_8), 1.21 and 1.40 (2s, 6, 2 CH_3), 0.85–0.89 (m, 1, H_9), 0.04 and 0.05 (2s, 6, $SiMe_2$).

α-1-(Allyldimethylsilyl)-7-*exo*-[(benzyloxy)methyl]-7-methyl-β-2,α-4-dihydroxy-α-3,7-dimethylbicyclo[4.1.0]heptane (59) and α-1-(Allyldimethylsilyl)-7-*exo*-[(benzyloxy)-methyl]-α-3,7-dimethyl-β-2,α-4-dihydroxybicyclo[4.1.0]heptane (60). To a solution of 72 mg (0.54 mmol) of $AlCl_3$ in 5 mL of Et_2O at 0 °C was added dropwise a solution of 1.62 mL of $LiAlH_4$ (1.62 mmol, 1.0 M solution in THF). After the mixture was stirred for 1.5 h at rt, the clear supernant liquid from this mixture was carefully cannulated into a warm (35 °C) solution of the ADMS epoxy ketone **57** (100 mg, 0.27 mmol) in 10 mL of Et_2O. Excess hydride was quenched after 6 h by addition of saturated Na_2SO_4 solution to the ice-cooled reaction mixture. After being stirred vigorously for 0.5 h, the mixture was filtered through Celite, concentrated, and chromatographed on SiO_2 (eluent: 25% EtOAc in hexanes) to furnish 55.6 mg (55%) of the desired diol **59** and 38.4 mg (38%) of the undesired isomer **60**.

59: oil; R_f = 0.21 (25% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.27–7.35 (m, 5, ArH), 5.77–5.92 (m, 1, H_1), 4.84–4.89 (m, 2, H_2), 4.23–4.56 (ABq, J = 12 Hz, 2, H_3), 3.97–4.01 (m, 1, H_4), 3.71 (br s, 1, H_5), 3.24–3.34 (ABq, J = 10 Hz, 2, H_6), 2.06–2.15 (m, 1, H_7), 1.64–1.67 (d, J = 8 Hz, 2, H_8), 1.52–1.58 (m, 1, H_9), 1.36–1.43 (m, 1, H_8), 1.32 (s, 3, H_{10}), 1.13 (d, J = 6 Hz, 3, H_{11}), 0.03 and 0.08 (2s, 6, $SiMe_2$); ^{13}C NMR (50 MHz, $CDCl_3$) ppm 138.11 (e), 128.4 (o), 128.3 (o), 127.84 (o), 127.76 (o), 138.97 (o, vinyl), 113.0 (e, vinyl), 78.2 (e), 72.97 (o), 72.52 (e), 71.34 (o), 41.11 (o), 29.76 (e, allylic), 27.58 (e), 24.13 (e), 23.64 (o), 19.39 (e), 16.63 (o), 15.53 (o), −1.13 (o), −1.48 (o); MS (EI) m/e 357 (M − OH), 333 (M − C_3H_5); MS (CI, isobutane) 357 (M + H − H_2O); HRMS for $C_{22}H_{33}O_2Si$ calcd 357.2250, found 357.2243.

60: oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.4 (br s, 5, Ar-H), 5.82–5.96 (m, 1, H_1), 4.85–4.98 (m, 2, H_2), 4.85–4.92 (br s, 1, H_3), 4.44–4.60 (ABq, J = 12 Hz, 2, H_4), 3.64–3.78 (m, 1, H_5), 3.18–3.39 (ABq, J = 10 Hz, 2, H_6), 2.37–2.46 (dd, J = 16, 9 Hz, 1, H_7), 1.7 (m, 2, H_8), 1.53 (s, 3, H_9), 1.33 (m, 1, H_7), 1.12 (d, J = 7 Hz, 3, H_{10}), 0.99–1.01 (d, J = 7 Hz, 1, H_{11}), −0.02 and 0.02 (2s, 6, $SiMe_2$).

7-*exo*-[(Benzyloxy)methyl]-α-1-(allyldimethylsilyl)-β-2,α-4-diacetoxy-α-3,7-dimethylbicyclo[4.1.0]heptane (61). To a solution of 120 mg (0.32 mmol) of diol **59** in 5 mL of CH_2Cl_2 at 0 °C were successively added 0.22 mL (1.60 mmol) of Et_3N, 0.15 mL (1.60 mmol) of Ac_2O, and 40 mg of DMAP catalyst. The resulting mixture was stirred at rt for 21 h. When all the starting material was gone, 15 mL of CH_2Cl_2 was added to the reaction mixture, and the separated organic layers were washed with 5% HCl, saturated $NaHCO_3$, and brine. Drying (Na_2SO_4), concentration in vacuo, and chromatographic separation on SiO_2 using 10% EtOAc in hexanes afforded 140 mg (95%) of the 1,3-diacetate **61**: colorless oil; R_f = 0.45 (25% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$), δ 7.27–7.37 (m, 5, Ar-H), 5.65–5.74 (m, 1, H_1), 5.41–5.44 (d, J = 9 Hz, 1, H_2), 4.88–4.90 (m, 1, H_3), 4.75–4.80 (m, 2, H_4), 4.41–4.56 (ABq, J = 12 Hz, 2, H_5), 3.14–3.44 (ABq, J = 10 Hz, 2, H_6), 2.21–2.30 (m, 1, H_7), 2.05 and 2.06 (2s, 6, OCOMe), 1.45–1.66 (m, 4, H_7 and H_8), 1.32 (s, 3, H_9), 1.13–1.17 (dd, J = 10, 3.5 Hz, 1, H_{10}), 0.88–0.90 (d, J = 7 Hz, 3, H_{11}), 0.02 and 0.06 (2s, 6, $SiMe_2$); ^{13}C NMR (50 MHz, $CDCl_3$) ppm 170.89 (e), 170.68 (e), 138.38 (e), 128.5 (o), 128.4 (o), 127.94 (o), 127.78 (o), 135.19 (o, vinyl), 113.15 (e, vinyl), 77.73 (e), 75.78 (o), 74.42 (o), 72.64 (e), 38.82 (o), 30.77 (e), 24.72 (e, allylic), 24.72 (o), 24.13 (e), 21.38 (o), 21.23 (o), 17.28 (e), 16.42 (o), 15.33 (o), −1.68 (o), −1.69 (o); IR (neat) 1738 cm^{-1} (ester C=O), 1628 (aryl C=C); MS (CI NH_4) m/e 476 (M + NH_4), 416 (M + NH_4 − HOAc); $[\alpha]^{25}_D$ +41.2° (c = 2.5, $CHCl_3$).

Anal. Calcd for $C_{26}H_{38}O_5Si$: C, 68.24; H, 8.15. Found: C, 67.97; H, 8.49.

Cyclic Silyl Ether of β-2,α-4-Diacetoxy-7-*exo*-(hydroxymethyl)-α-3,7-dimethylbicyclo[4.1.0]heptane (62). To a solution of 80.0 mg (0.175 mmol) of the ADMS diacetate **61** in 5 mL of CH_2Cl_2 at 0 °C were added 0.5 mL of pyridine, followed by 0.10 mL (two drops) of bromine solution (reaction mixture turned yellowish-brown). After being stirred for 0.5 h, the mixture was diluted with 10 mL of CH_2Cl_2, washed with saturated $Na_2S_2O_3$ and brine, and dried over Na_2SO_4. Evaporation of the solvent in vacuo afforded an oily product which was chromatographed over silica gel (eluent: 15–20% EtOAc in hexanes) to furnish 37.5 mg (66% yield) of silyl ether **62**: colorless oil; R_f = 0.39 (25% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.54–5.60 (d, J = 10 Hz, 1, H_1), 4.88–4.94 (br s, 1, H_2), 3.79–3.84 (ABq, J = 10 Hz, 2, H_3), 2.18–2.29 (m, 1, H_4), 2.05 (s, 6, OCOMe), 1.45–1.62 (m, 2, H_4 and H_5), 1.26 (s, 3, H_6), 1.08–1.14 (dd, J = 10, 4 Hz, 1, H_7); 0.92–0.95 (d, J = 7 Hz, 3, H_8), 0.17 and 0.20 (2s, 6, $SiMe_2$); MS (EI) m/e 266 (M − HOAc), 191 (M − HOAc − $HOSiMe_2$); MS (CI, isobutane) 267 (M + H − HOAc), 207 (M + H − 2HOAc, base peak); HRMS for $C_{14}H_{23}O_3Si$ calcd 267.1416, found 267.1408; $[\alpha]^{25}_D$ +79.9° (c = 0.5, $CDCl_3$).

β-2,α-4-Diacetoxy-7-*exo*-(hydroxymethyl)-α-3,7-dimethylbicyclo[4.1.0]heptan-1α-ol (63). Method 1. A mixture of 12.0 mg (0.032 mmol) of benzyl ether **65** and 10 mg of 10% Pd/C in a flask was diluted with 3 mL of ethanol under an atmosphere of hydrogen (H_2 balloon). After being stirred for 12 h at rt, the reaction mixture was diluted with ethanol, filtered through Celite, evaporated in vacuo, and chromatographed over silica gel using 40% EtOAc in hexanes to afford 9 mg (99%) of the diol **63**.

Method 2. To a solution of 15.0 mg (0.05 mmol) of the silyl ether **62** in 3 mL of DMF was added 0.40 mL (0.40 mmol) of 1.0 M TBAF in THF at rt. After 3 h, the reaction showed complete disappearance of the starting material with emergence of a low R_f spot. At this juncture, 0.05 mL of 30% H_2O_2 (0.50 mmol) and 9 mg (0.09 mmol) of $KHCO_3$ were added to the reaction and the stirring was continued overnight. After 16 h, the mixture was diluted with 25 mL of water and extracted several times with small portions of 1:1 EtOAc–hexanes. The combined organic extracts were dried (Na_2SO_4), concentrated, and chromatographed over SiO_2 (eluent: 35% EtOAc in hexanes) to afford 7.8 mg (68% yield) of the diol **63** containing a slight impurity of the silanol.

63: colorless oil; R_f = 0.20 (80% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.05–5.11 (dd, J = 10, 8 Hz, 1, H_1), 4.91–4.92 (br s, 1, H_2), 3.15–3.37 (ABq, J = 11 Hz, 2, H_3), 2.18–2.28 (m, 1, H_4), 2.07 (s, 6, OCOMe), 1.01–1.60 (m, 3, H_4 and H_5), 1.20 (s, 3, H_6), 0.95–0.97 (d, J = 7 Hz, 3, H_7); MS (EI) m/e 227 (M − OAc), 208 (M − HOAc − H_2O); MS (CI, isobutane) 287 (M + H), 285 (M − H), 269 (M + H − H_2O), 227 (M + H − HOAc); HRMS for $C_{14}H_{21}O_6$ calcd 285.1338, found 285.1334.

7-*exo*-[(Benzyloxy)methyl]-α-1-(fluorodimethylsilyl)-β-2,α-4-diacetoxy-α-3,7-dimethylbicyclo[4.1.0]heptane (64). To 50 mg (0.11 mmol) of ADMS diacetate **61** in 5 mL of CH_2Cl_2 at

0 °C were successively added pyridine (0.5 mL), HF·Py complex (0.5 mL), and bromine (0.2 mL). The reaction mixture was stirred at rt for 2 h, at the end of which excess HF was destroyed by pouring the mixture over alumina. The resulting slurry was diluted with CH_2Cl_2 and filtered, and the filtrate was washed with 1 M $CuSO_4$ to remove excess pyridine, followed by washing with water and brine. Drying over Na_2SO_4 and concentration in vacuo afforded 70 mg of crude oil which was chromatographed over silica gel (eluent: 15% EtOAc in hexanes) to furnish 38 mg (79%) of the fluorosilane **64**: colorless oil; R_f = 0.34 (15% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26–7.33 (m, 5, ArH), 5.20–5.24 (d, J = 10 Hz, 1, H_1), 4.92–4.93 (br s, 1, H_2), 4.41–4.51 (ABq, J = 12 Hz, 2, H_3), 3.31–3.39 (ABq, J = 8 Hz, 2, H_4), 2.24–2.34 (m, 1, H_5), 2.05 and 2.08 (2s, 6, OCOMe), 1.38–1.61 (m, 3, H_5 and H_6), 1.30 (s, 3, H_7), 0.90–0.91 (d, J = 7 Hz, 3, H_8), 0.46–0.49 (d, J = 8 Hz, 3, SiMeF), 0.20–0.22 (d, J = 8 Hz, 3, SiMeF); ^{13}C NMR (50 MHz, $CDCl_3$) ppm 169.1 (e), 168.4 (e), 138.57 (e), 128.4 (o), 128.3 (o), 127.84 (o), 127.76 (o), 75.23 (o), 74.1 (o), 72.56 (e), 65.86 (e), 38.02 (o), 31.0 (e), 23.3 (o), 21.38 (o), 21.13 (o), 21.10 (e), 21.10 (e), 16.36 (o), 14.84 (o), –0.11 (o), –1.13 (o); MS (EI) m/e 376 (M – HOAc); MS (CI, isobutane) 417 (M + H – HF); HRMS for $C_{23}H_{33}O_5Si$ calcd 285.1338, found 285.1334.

7-*exo*-[(Benzyloxy)methyl]-β-2,α-4-diacetoxy-α-3,7-dimethylbicyclo[4.1.0]heptan-1α-ol (65). The fluorosilane **64** (25.3 mg, 0.06 mmol) was dissolved in a mixture of THF–MeOH (2 mL each) at rt. To this were successively added 16 mg (0.16 mmol) of $KHCO_3$, 10 mg (0.16 mmol) of KF, and 0.12 mL (1.16 mmol) of 30% H_2O_2. The resulting mixture was stirred for 8 h, by which time TLC monitoring showed formation of a single low R_f spot (R_f = 0.18; 25% EtOAc). Powdered solid $Na_2S_2O_3·5H_2O$ and 20 mL of Et_2O were added to the reaction mixture, which was then stirred vigorously for 0.5 h. Filtration through Celite, drying (Na_2SO_4), and concentration under reduced pressure gave a milky solution which was chromatographed on SiO_2 using 35% EtOAc in hexanes to afford 18 mg (82%) of the tertiary alcohol **65**: colorless oil; R_f = 0.18 (25% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26–7.38 (m, 5, ArH), 5.15–5.22 (d, J = 10 Hz, 1, H_1), 4.92–4.97 (br s, 1, H_2), 4.41–4.51 (ABq, J = 10 Hz, 2, H_3), 3.44–3.59 (ABq, J = 12 Hz, 2, H_4), 2.22–2.34 (m, 1, H_5), 2.11 (s, 6, OCOMe), 1.22–1.69 (m, 3, H_5 and H_6), 1.16 (s, 3, H_7), 1.03 (d, J = 7 Hz, 3, H_8); MS (CI, isobutane) m/e 377 (M + H, weak), 317 (M + H – HOAc); HRMS for $C_{21}H_{29}O_6$ calcd 377.1964, found 377.1957.

β-2,α-4-Diacetate of β-4-Isopropenyl-α-3-methylcyclohexanone (66). To 15.0 mg (0.04 mmol) of **63** in 2 mL of CH_2Cl_2 at 0 °C were successively added 0.11 mL (1.00 mmol) of pyridine and 10.0 mg (0.05 mmol) of tosyl chloride. TLC after 10 min, showed disappearance of most of the starting material with emergence of a new spot. After being stirred for 1 h, the reaction mixture was diluted with CH_2Cl_2 and washed with 1 M $CuSO_4$ solution to remove excess pyridine. Washing with water and brine, drying over Na_2SO_4, and evaporation gave an oily residue which after chromatography over silica gel using 15% EtOAc in hexanes furnished 8.4 mg (79%) of the β,γ-unsaturated ketone **66**: colorless oil; R_f = 0.30 (20% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.30–5.33 (dt, J = 5, 2.5 Hz, 1, H_1), 5.21–5.25 (d, J = 12 Hz, 1, H_2), 4.98–4.99 (br s, 1, H_3), 4.73 (s, 1, H_3), 3.40–3.46 (dd, J = 14, 5 Hz, 1, H_4), 2.21–2.33 (m, 2, H_5 and H_6), 2.18 (2s, 6, $OCOCH_3$), 1.94–2.10 (m, 1, H_7), 1.76 (s, 3, H_8), 1.07–1.09 (d, J = 6.5 Hz, 3, H_9); MS (EI) m/e 208 (M – HOAc); MS (CI, isobutane) 269 (M + H), 209 (M + H – HOAc, base peak); HRMS for $C_{14}H_{21}O_5$ calcd 269.1389, found 269.1383.

α-1-(Allyldimethylsilyl)-7-*exo*-[(benzyloxy)methyl]-β-2,α-4-(dicarbamoyloxy)-α-3,7-dimethylbicyclo[4.1.0]heptane (68). To a solution of 506 mg (1.35 mmol) of diol **59** in 6 mL of CH_2Cl_2 at rt were added 2 mL of pyridine and 0.59 mL (5.4 mmol) of phenyl isocyanate, followed by DMAP (0.10g). The reaction mixture was stirred at rt for 9 h and then taken in a separatory funnel and washed with 1 M $CuSO_4$, water, and brine. Drying of the organic layer (Na_2SO_4) and evaporation in vacuo afforded 1.2 g of a yellow solid. Chromatographic separation over SiO_2 using 20–30% EtOAc in hexanes as eluent gave 507 mg (85%) of dicarbamate **68**: white solid; mp 81 °C, R_f = 0.39 (25% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22–7.44 (m, 13, ArH), 7.05–7.12 (m, 2, ArH), 6.52 and 6.64 (2s, 2, NH), 5.77–5.86 (m, 1, H_1), 4.47–5.50 (d, J = 9 Hz, 1, H_2), 4.89 (br s, 1, H_3), 4.83, 4.89 (m, 2, H_4), 4.43–4.57 (ABq, J = 12 Hz, 2, H_5), 3.29–3.42 (ABq, J = 10 Hz, 2, H_6), 2.36–2.43 (m, 1, H_7), 1.55–1.75 (m, 4, H_7 and H_8), 1.36 (s, 3, H_9), 1.19–1.24 (dd, J = 9, 3 Hz, 1, H_{10}), 1.06–1.08 (d, J = 7 Hz, 3, H_{11}), 0.09 and 0.13 (2s, 6, $SiMe_2$); IR (neat) 3444, 1740, 1605, 1520 cm^{-1}; MS (EI) m/e 571 (M – C_3H_5), 474 (M – C_3H_5 – HCO_2NHPh); MS (CI, isobutane) 571 (M + H – C_3H_6); MS (DCI probe) 613 (M + H), 571 (M + H – C_3H_5, base peak).

Anal. Calcd for $C_{36}H_{44}N_2O_5Si$: C, 70.55; H, 7.23; N, 4.57. Found: C, 70.22; H, 7.51; N, 4.96.

β-2,α-4-Dicarbamate of 7-*exo*-[(Benzyloxy)methyl]-α-1-(hydroxydimethylsilyl)-α-3,7-dimethylbicyclo[4.1.0]heptane (69). To 760 mg (1.24 mmol) of ADMS dicarbamate **68** dissolved in THF–DMF (1 mL + 2 mL) was added a solution of 1.61 mL of TBAF (1.61 mmol, 1.0 M solution in THF) at rt, and the resulting mixture was stirred for 6 h. Workup of the mixture by first diluting with water and then extracting several times with small portions of ether followed by drying the organic layer with Na_2SO_4 and evaporation furnished 0.73g (~100%) of the silanol **69**, which was used as such in the next step: white solid; mp 78 °C, R_f = 0.22 (25% EtOAc in hexanes); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.97–7.50 (m, 15, ArH), 6.64 and 6.70 (2s, 2, NH), 5.50–5.58 (d, J = 10 Hz, 1, H_1), 4.85 (br s, 1, H_2), 4.37–4.52 (ABq, J = 12 Hz, 2, H_3), 3.18–3.42 (ABq, J = 10 Hz, 2, H_4), 2.35–2.62 (m, 1, H_5), 1.30–1.65 (m, 3, H_5 and H_6), 1.30 (s, 3, H_7), 1.00–1.08 (d, J = 7 Hz, 3, H_8), 1.10 and 0.22 (2s, 6, $SiMe_2$); IR (neat) 3446, 1740, 1686, 1600 cm^{-1}; MS (EI, 15 eV) m/e 296 (M – 2 $PhNHCO_2H$), 205 (296 – $PhCH_2$).

Anal. Calcd for $C_{33}H_{38}N_2O_6Si$: C, 67.43; H, 6.69; N, 4.77. Found C, 67.14; H, 6.94; N, 4.58.

7-*exo*-[(Benzyloxy)methyl]-α-1-(fluorodimethylsilyl)-β-2,α-4-(dicarbamoyloxy)-α-3,7-dimethylbicyclo[4.1.0]heptane (70). Method 1. Part of the silanol **69** (0.71 g, 1.21 mmol) obtained in the previous step was dissolved in 5 mL of CH_2Cl_2 in a plastic reaction vessel under argon and cooled to 0 °C, and to this were added 1 mL of pyridine and 1 mL of pyridinium poly(hydrogen fluoride) solution. The resulting solution was stirred at rt for 2 h. Excess HF was then destroyed by pouring over alumina. Filtration, evaporation in vacuo, and chromatography over SiO_2 (eluent: 25% EtOAc in hexanes) gave 628 mg of fluorosilane **70** (88% yield from **68** in two steps; lower yields were obtained when aqueous workup was used, i.e., when the mixture was washed with 1 M $CuSO_4$ solution to remove excess pyridine).

Method 2. To 680 mg (1.11 mmol) of ADMS dicarbamate **68** in 15 mL of CH_2Cl_2 in a plastic reaction vessel at 0 °C were added 0.4 mL of bromine, 0.9 mL of pyridine, and 0.9 mL of HF·Py. The resulting mixture was stirred between 0 °C and rt for 5 h. Excess HF was destroyed by pouring the reaction mixture over alumina. Filtration and evaporation of the filtrate in vacuo and then chromatographic separation over SiO_2 using 20% EtOAc in hexanes afforded 588 mg (90%) of the fluorosilane **70**: viscous oil; R_f = 0.35 (25% EtOAc in hexanes); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25–7.46 (m, 13, ArH), 7.06–7.14 (m, 2, ArH), 6.90 (s, 1, NH), 5.40–5.44 (d, J = 9 Hz, 1, H_1), 4.94 (br s, 1, H_2), 4.42–4.56 (ABq, J = 12 Hz, 2, H_3), 3.34–3.48 (ABq, J = 9 Hz, 2, H_4), 2.41–2.47 (m, 1, H_5), 1.30–1.62 (m, 3, H_5 and H_6), 1.37 (s, 3, H_7), 1.09–1.12 (d, J = 6.5 Hz, 3, H_8), 0.55–0.59 (d, J = 8 Hz, 3, SiMeF), 0.31–0.35 (d, J = 8 Hz, 3, SiMeF); MS (EI, 15 eV) m/e 316 (M – 2 $PhNHCO_2H$), 225 (316 – $PhCH_2$), 206 (225 – F).

β-2,α-4-Dicarbamate of 7-*exo*-[(Benzyloxy)methyl]-α-3,7-dimethylbicyclo[4.1.0]heptan-1α-ol (71). To a solution of 78 mg (0.13 mmol) of fluorosilane **70** in THF–MeOH (2 mL each) at rt were successively added 15 mg (0.26 mmol) of KF, 26 mg (0.26 mmol) of $KHCO_3$, and 0.13 mL (1.3 mmol) of 30% H_2O_2 solution. The mixture was stirred at rt for 9 h. At the end of the reaction, 2 g of powdered $Na_2S_2O_3$ and 20 mL of Et_2O were added, and the resulting mixture was stirred vigorously for 0.5 h. Filtration through Celite, drying with Na_2SO_4, and concentration under vacuo afforded 98 mg of an oily residue which contained the desired alcohol **71** along with a side product **69**, resulting from hydrolysis of the fluorosilane (**71**:**69** ratio from NMR integration is 3:1). This could only be partially separated by silica gel column chromatography (eluent: 35% EtOAc in hexanes). For practical purposes, the whole mixture was used as such in the hydrogenolysis step. **71**: viscous oil; R_f = 0.20 (25% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02–7.43 (m,

s, ArH), 6.99 (S, 1, NH) 5.18–5.25 (d, J = 10, 1, H_1), 5.20 (br s, 1, OH), 5.00 (br s, 1, H_2), 4.38–4.48 (ABq, J = 12 Hz, 2, H_3), 3.50–3.62 (ABq, J = 12 Hz, 2, H_4), 2.30–2.47 (m, 1, H_5), 1.64–1.68 (m, 1, H_6), 1.42–1.44 (br s, 1, H_5), 1.25–1.36 (dd, J = 15, 4 Hz, 1, H_7), 1.23 (s, 3, H_8), 1.14–1.17 (d, J = 7 Hz, 3, H_9); ^{13}C NMR (50 MHz, $CDCl_3$) 156.1 (e), 153.9 (e), 139.3 (e), 138.6 (e), 138.0 (e), 129.6 (o), 129.5 (o), 128.9 (o), 128.7 (o), 127.8 (o), 124.4 (o), 123.8 (o), 119.0 (o), 85.4 (o), 75.8 (e), 75.2 (o), 72.8 (e), 61.7 (e), 38.3 (o), 31.4 (e), 26.3 (o), 24.6 (e), 16.5 (o), 12.3 (o); IR (neat) 3440 (sharp, NH), 3346 (br, OH), 3065, 1731, 1602, 1522 cm^{-1}; MS (DCI probe) m/e 531 (M + H), 487 (M + H – CO_2).

β-2,α-4-Dicarbamate of 7-*exo*-(Hydroxymethyl)-α-3,7-dimethylbicyclo[4.1.0]heptan-1α-ol (72). The mixture (98 mg) of tertiary hydroxy benzyl ether **71** and silanol **69** obtained in the previous step was dissolved in 5 mL of EtOH and subjected to hydrogenolysis using 10% Pd/C under an atmosphere of hydrogen (using H_2 balloon). After being stirred for 14 h at rt, the reaction mixture was diluted with EtOH, filtered through Celite, evaporated in vacuo, and chromatographed over SiO_2 using 40% EtOAc in hexanes to afford 32.0 mg (.073 mmol) of the pure diol **72** (based on 0.13 mmol of fluorosilane used, the yield of diol **72** in two steps was 56%; overall yield 50% in three steps from ADMS dicarbamate **68**). **72**: R_f = 0.23 (80% EtOAc in hexanes); ^1H NMR (200 MHz, THF-d_8) δ 7.40–7.54 (m, 4, ArH), 7.10–7.23 (m, 4, ArH), 6.82–6.95 (m, 2, ArH), 5.14–5.22 (d, J = 12 Hz, 1, H_1), 4.84–4.91 (br s, 2, H_2 and OH), 3.45–3.52 (m, 2, H_3), 3.10–3.23 (br s, 1, OH), 2.20–2.45 (m, 1, H_4), 1.60–1.75 (m, 2, H_4 and H_5), 1.30–1.44 (dt, J = 16, 2 Hz, 1, H_6), 1.13 (s, 3, H_7), 1.02–1.06 (d, J = 6 Hz, 3, H_8); IR (neat) 3440 (sharp, NH), 3300–3400 (br, OH), 1736, 1604 cm^{-1}; MS (DCI probe) m/e 441 (M + H), 7), 397 (M + H – CO_2, base peak), 423 (M + H – H_2O), 413 (M + H – CO).

β-2,α-4-Dicarbamate of β-4-Isopropenyl-α-3-methylcyclohexanone (73) and Its Conjugated Enone Isomer (74). To 0.006 g (0.014 mmol) of **72** in 2 mL of CH_2Cl_2 and 0.2 mL of pyridine at rt was added 77 μL (0.018 mmol) of methanesulfonyl chloride. After being stirred for 9 h, the reaction mixture was diluted with CH_2Cl_2 and washed with 1 M $CuSO_4$ solution to remove excess pyridine. Washing with water and brine, drying over Na_2SO_4, and evaporation gave an oil which after column chromatography using 15% EtOAc in hexanes furnished 4.3 mg (75%) of the ketone **73** and 0.5 mg (~9%) of the isomerized enone **74**.

73: colorless oil; R_f = 0.27 (25% EtOAc in hexanes); ^1H NMR (200 MHz, $CDCl_3$) δ 7.25–7.50 (m, 8, ArH), 7.05–7.16 (m, 2, ArH), 6.87 (br s, 2, NH), 5.30–5.39 (d, J = 12 Hz, 1, H_1), 5.33–5.37 (d, J = 2 Hz, 1, H_2), 5.00 (br s, 1, H_3), 4.77 (s, 1, H_3), 3.46–3.58 (dd, J = 15, 5 Hz, 1, H_4), 2.24–2.52 (m, 2, H_5 and H_6), 2.00–2.17 (dt, J = 14, 2 Hz, 1, H_7), 1.78 (s, 3, H_8), 1.20–1.23 (d, J = 6 Hz, 3, H_9); IR (neat) 3442, 1740, 1602 cm^{-1}; MS (EI) m/e 422 (M^+), 286 (M – OCONHPh), 93 ($PhNH_2^+$); MS (CI, isobutane) 423 (M + H), 286 (M + H – HOCONHPh, base peak).

74: (this could only be isolated as a mixture with **73**) ^1H NMR (300 MHz, $CDCl_3$) δ 7.30–7.48 (m, 10, ArH), 5.26–5.30 (d, J = 12 Hz, 1, H_1), 5.24 (br s, 1, H_2), 3.23–3.29 (dd, J = 16, 3 Hz, 1, H_3), 2.25–2.52 (m, 2, H_4 and H_5), 1.98 (s, 3, H_6), 1.78 (s, 3, H_7), 1.22–1.24 (d, J = H_7, 3, H_8).

β-2,α-4-Dicarbamate of 7-*exo*-[(Benzyloxy)methyl]-α-1-acetoxy-α-3,7-dimethylbicyclo[4.1.0]heptane (75). To a solution of 100 mg (0.20 mmol) of tertiary alcohol **71** in CH_2Cl_2 (5 mL) at 0 °C were added 0.28 mL (2.0 mmol) of Et_3N, 0.19 mL (2.0 mmol) of Ac_2O, and about 50 mg of DMAP catalyst. The resulting mixture was stirred at rt for 46 h, at the end of which it was diluted with EtOAc (20 mL) and washed with saturated $NaHCO_3$, water, and brine. Drying with Na_2SO_4 and concentration in vacuo afforded 110 mg (~100%) of tertiary acetate **75** as a yellowish white solid: mp 81 °C; R_f = 0.25 (25% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (br s, 1, NH), 7.22–7.53 (m, 13, ArH), 7.02–7.13 (m, 2, ArH), 6.96 (br s, 1, NH), 5.66–5.75 (d, J = 12 Hz, 1, H_1), 4.84–4.91 (br s, 1, H_2), 4.46–4.59 (br s, 2, H_3), 3.40–3.50 (br s, 2, H_4), 2.43, 2.55 (m, 1, H_5), 2.01 (s, 3, OCOMe), 1.72–1.84 (m, 1, H_6), 1.45–1.56 (br d, J = 16 Hz, 1, H_7), 1.34–1.44 (dd, J = 13, 3 Hz, 1, H_8), 1.39 (s, 3, H_9), 1.12–1.16 (d, J = 6 Hz, 3, H_{10}); MS (EI) m/e 572 (M^+); MS (CI, isobutane) 572 (M^+), 436 (M + H – HOCONHPh); HRMS for $C_{33}H_{36}N_2O_7$ calcd 572.2523, found 572.2506.

Anal. Calcd for $C_{33}H_{36}N_2O_7$: C, 69.21; H, 6.34; N, 4.89. Found: C, 69.04; H, 6.62; N, 4.75.

β-2,α-4-Dicarbamate of 7-*exo*-(Hydroxymethyl)-α-1-acetoxy-α-3,7-dimethylbicyclo[4.1.0]heptane (76) and β-2,α-4-Dicarbamate of 7-*exo*-(Acetoxymethyl)-α-1-hydroxy-α-3,7-dimethylbicyclo[4.1.0]heptane (77). A flask containing 50 mg (0.09 mmol) of benzyl ether **75** and 20 mg of 10% Pd–C was evacuated under vacuum and then purged with H_2 gas (using a H_2 containing balloon). The reaction mixture was diluted with 5 mL of EtOAc and stirred at rt for 20 h. Filtration of the catalyst and evaporation of the filtrate under reduced pressure gave an oily residue which on column chromatography over SiO_2 eluted with 25–50% EtOAc in hexanes (gradient elution) afforded 14 mg (33%) of the tertiary acetate **76** along with an equal amount of the rearranged primary acetate **77**.

76: ^1H NMR (300 MHz, $CDCl_3$) δ 7.30–7.47 (m, 8, ArH), 7.04–7.19 (m, 2, ArH), 6.64 (s, 1, NH), 5.63–5.66 (d, J = 11 Hz, 1, H_1), 4.91 (s, 1, H_2), 3.26–3.29 and 3.65–3.70 (ABq, J = 12 Hz, 2, H_3), 2.42–2.51 (ddd, J = 16, 10, 2 Hz, 1, H_4), 2.10 (s, 3, OCOMe), 1.73–1.78 (m, 1, H_5), 1.42–1.56 (td, J = 14, 3 Hz, 1, H_6), 1.39 (s, 3, H_7), 1.29–1.38 (dd, J = 10, 2 Hz, 1, H_8), 1.08–1.10 (d, J = 6, 3, H_9).

77: R_f = 0.3 (30% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.26–7.44 (m, 8, ArH), 7.03–7.14 (m, 2, ArH), 6.73 (s, 1, NH), 5.27 (br s, 1, OH or NH), 5.06–5.10 (d, J = 10 Hz, 1, H_1), 5.02 (s, 1, H_2), 4.05–4.25 (ABq, J = 11 Hz, 2, H_3), 2.35–2.48 (m, 1, H_4), 1.86 (s, 3, OCOMe), 1.60–1.75 (m, 1, H_5), 1.26–1.45 (m, 2, H_6), 1.16–1.19 (d, J = 6, 3, H_7), 1.16 (s, 3, H_8); MS (EI) m/e 406 (M – OH – HOAc); MS (CI, isobutane) 439 (M + H – CO_2), 346 (M + H – HOCONHPh).

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Supplementary Material Available: ^1H NMR spectra of **44**, **49**, **51**, **55**, **59**, **60**, **62–65**, **70–72**, **76**, and **77** (21 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.