Synthesis of (±)-Gymnomitrol. $Mn(OAc)_3$-Initiated Free-Radical Cyclization of Alkynyl Ketones

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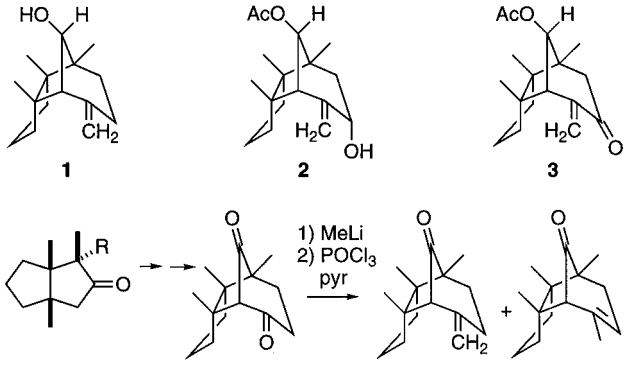
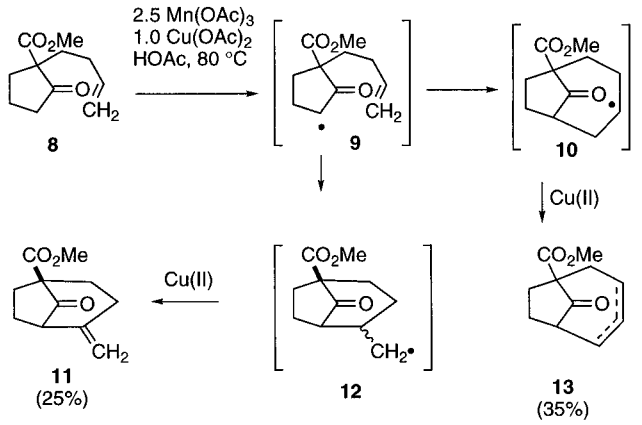
Received December 2, 1996[⊗]

$Mn(OAc)_3$-initiated cyclization of alkynyl ketones in 9−19:1 EtOH/HOAc at 90 °C is a useful cyclization procedure in favorable cases. Cyclization of (trimethylsilyl)alkynyl ketone **4e** provides 62% of silylalkenes **26** and **27** in the key reaction of a seven-step (16% overall yield) synthesis of gymnomitrol (**1**) from readily available ketone **23**. 9α-Hydroxygymnomitryl acetate (**2**) and 9-oxogymnomitryl acetate (**3**) have been prepared from gymnomitrol. Cyclization of propargyl cyclohexanones **39a**−**c** provides bicyclic compounds **40**−**42** in 40−60% yield.

Connolly reported the isolation of (+)-gymnomitrol (**1**) and seven related sesquiterpenoids with the novel perhydro-4,8-methanoazulene skeleton from the liverwort *Gymnomitrion obtusum* (Lindb) Pears (Hepaticae) in the early 1970s.[1] Asakawa isolated 9α-hydroxygymnomitryl acetate (**2**) and 9-oxogymnomitryl acetate (**3**) from the liverwort *Plagiochila Trabeculata* in 1988.[2] The unusual tricyclic gymnomitrane ring system attracted much interest, culminating in five different syntheses reported in 1979.[3−8] Coates[3] and Paquette[4] prepared dione **5** by an aldol reaction of keto aldehyde **4a** and oxidation of the resulting alcohol. Addition of methyllithium to **5** and dehydration gave a difficultly separable mixture of gymnomitrone (**6**) and isogymnomitrone (**7**). Welch[5] prepared dione **5** by a Dieckmann cyclization of **4b**.



We recently described Mn(III)-based oxidative cyclizations of unsaturated ketones that proceed in synthetically useful yield if the ketone enolizes to only one side and the product ketone does not enolize.[9,10] This procedure should convert 3-butenylbicyclooctanone **4c** to gymnomitrone (**6**) without the formation of isogymnomitrone (**7**). However, the regiochemistry of the radical cyclization may be a problem since 7-*endo*-cyclization can occur in addition to the desired 6-*exo*-cyclization that leads to **6**. For instance, oxidation of 2-(3-butenyl)cyclopentanone **8** with $Mn(OAc)_3$ and $Cu(OAc)_2$ in HOAc at 80 °C leads to radical **9**, which undergoes both 6-*exo*-cyclization to give radical **12**, which is oxidized by Cu(II) to provide 25% of methylenebicyclo[3.2.1]octane **11**, and 7-*endo*-cyclization to afford radical **10**, which is oxidized by Cu(II) to give 35% of bicyclo[4.2.1]nonene **13** as a mixture of double-bond isomers.[9] This suggests that oxidative cyclization of **4c** will give similar mixtures of 6-*exo*- and 7-*endo*-cyclization products.



We then considered whether oxidative cyclization of 3-butynylbicyclooctanone **4d** would provide **6**. Oxidation of β-keto ester **14** with $Mn(OAc)_3$ in EtOH at 25 °C leads to the α-keto radical, which cyclizes to give vinyl radical **15**.[11] The vinyl radical abstracts an α-hydrogen from ethanol to give 20% of methylenecyclopentanone **16** and the hydroxyethyl radical, which is oxidized to acetalde-

(1) Connolly, J. D.; Harding, A. E.; Thornton, I. M. S. *J. Chem. Soc., Chem. Commun.* **1972**, 1320; *J. Chem. Soc., Perkin Trans. 1* **1974**, 2587.
(2) Toyota, M.; Nagashima, F.; Asakawa, Y. *Phytochemistry* **1988**, *27*, 2161.
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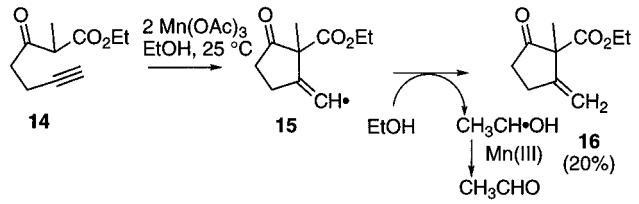
(10) For reviews on $Mn(OAc)_3$ cyclizations, see: (a) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339. (b) Melikyan, G. G. *Org. React.* **1996**, *49*, 427.
(11) Snider, B. B.; Merritt, J. E.; Dombroski, M. A.; Buckman, B. O. *J. Org. Chem.* **1991**, *56*, 5544.

S0022-3263(96)02233-5 CCC: $14.00

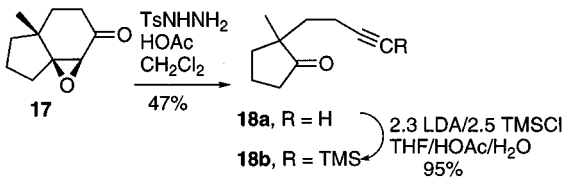
hyde by a second equivalent of $Mn(OAc)_3$. This cyclization is not regiospecific; the analogous 6-*endo*-cyclization leads to 12% of the corresponding cyclohexenone. This suggests that oxidative cyclization of **4d** will also lead to mixtures of **6** and the cycloheptenone.



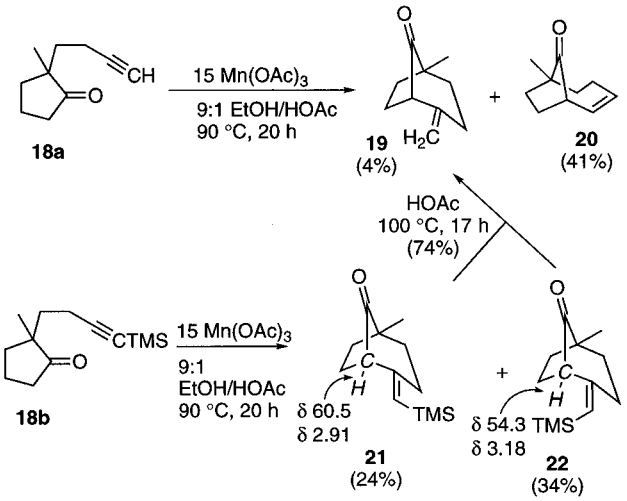
A trimethylsilyl group on the acetylene improves the yield slightly in radical cyclizations and strongly favors *exo*-cyclization.[12,13] We therefore anticipated that oxidative cyclization of [(trimethylsilyl)butynyl]bicyclooctanone **4e** with $Mn(OAc)_3$ would give the vinylsilane corresponding to **6**, which could be easily desilylated to give gymnomitrone (**6**). However, oxidative free-radical cyclizations to alkynes must be carried out in ethanol since acetic acid does not transfer a hydrogen atom efficiently to the vinyl radical. Oxidations of ketones by Mn(III) requires much higher temperatures (80 °C) than that of β-keto esters (25 °C) because ketones are much less acidic. We were concerned that EtOH would be oxidized more rapidly than a ketone by $Mn(OAc)_3$ at the elevated temperatures needed for enolization of the ketone.

Results and Discussion

Model studies were conducted with alkynylcyclopentanone **18a**, which was prepared in 47% yield by Eschenmoser fragmentation[14] of epoxy ketone **17**[15] with $TsNHNH_2$ and HOAc in CH_2Cl_2. Silylation of the terminal alkyne by treatment of **18a** with 2.3 equiv of LDA and 2.5 equiv of TMSCl and hydrolysis of the silyl enol ether gives **18b** in 95% yield. Mn(III)-induced cyclization of **18a** and **18b** was investigated with both $Mn(OAc)_3$ and $Mn(pic)_3$[10a,16] in a variety of solvents. No cyclic products are obtained in EtOH at reflux, while cyclization occurs in low yield in HOAc at 80−100 °C. Fortunately, the reaction occurs efficiently in EtOH containing 5−30% HOAc. A greater percentage of HOAc in the solvent mixture is required with $Mn(pic)_3$ to achieve a reasonable rate of oxidation. As a consequence, vinylsilanes **21** and **22** partially desilylate during oxidative cyclization with $Mn(pic)_3$.



Heating alkynylcyclopentanone **18a** at 90 °C with 15 equiv of $Mn(OAc)_3 \cdot 2H_2O$ in 9:1 EtOH/HOAc in a resealable tube for 20 h yields 41% of a 1:12 mixture of bicyclic ketones **19** and **20** resulting from 6-*exo*- and 7-*endo*-cyclization, respectively. As expected, 7-*endo*-cyclization is the major product with the terminal alkyne. A large excess of $Mn(OAc)_3$ is presumably required because of concomitant oxidation of EtOH to acetaldehyde or HOAc.



Fortunately, (trimethylsilyl)alkyne **18b** undergoes exclusively the desired 6-*exo*-cyclization under identical conditions, providing 58% of a 1:1.4 mixture of bicyclic ketones **21** and **22**. As expected,[12,13] the TMS group improves the yield of the cyclization and favors 6-*exo*-cyclization. Desilylation of the mixture of vinylsilanes **21** and **22** in HOAc at 100 °C gives 74% of **19**. The stereochemistry of **21** and **22** was assigned on the basis of the ^1H and ^{13}C NMR chemical shift of the allylic proton and the carbon at the ring fusion. Curran has shown that a TMS group deshields a cis proton and shields a cis carbon in similar systems.[17] Therefore structure **22** is assigned to the isomer with the methine proton and carbon at δ 3.18 and 54.3, respectively, and structure **21** is assigned to the isomer with the methine proton and carbon at δ 2.91 and 60.5, respectively.

There are several possible explanations for the improved yield obtained in the cyclization of (trimethylsilyl)-alkyne **18b**. The silicon may accelerate the radical cyclization by making the alkyne more electron rich so that it reacts faster with the electron deficient α-keto radical. The silicon could also stabilize the intermediate cyclic vinyl radical[18a] or facilitate H atom abstraction by the radical, making termination of the reaction a more efficient process.[18b,c] Lastly, the silicon may be stabilizing the product.

Synthesis of Gymnomitrol. The successful cyclization of [(trimethylsilyl)butynyl]cyclopentanone **18b** to vinylsilanes **21** and **22** suggested that oxidative cyclization of [(trimethylsilyl)butynyl]bicyclooctanone **4e** and desilylation of the product would provide a practical route to gymnomitrone (**6**). As part of an unsuccessful route to gymnomitrol based on the Conia ene reaction, Paquette prepared **4e** in 17% yield by the copper-catalyzed addition

(12) Choi, J.-K.; Hart, D. J.; Tsai, Y. M. *Tetrahedron Lett.* **1982**, *23*, 4765.
(13) Sha, C.-K.; Jean, T.-S.; Wang, D.-C. *Tetrahedron Lett.* **1990**, *31*, 3745.
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(15) O'Dell, D. E.; Loper, J. T.; Macdonald, T. L. *J. Org. Chem.* **1988**, *53*, 5225.
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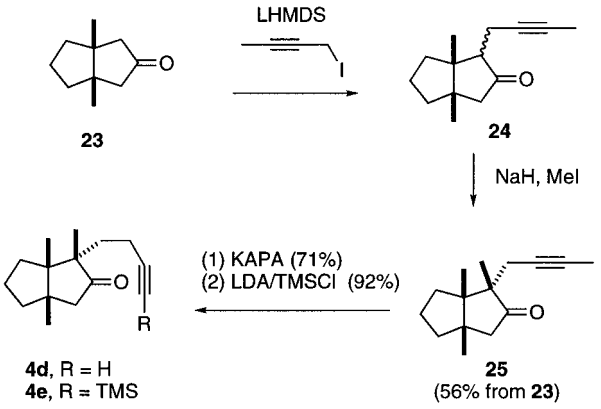
(18) (a) Wilt, J. W.; Belmonte, F. G.; Zieske, P. A. *J. Am. Chem. Soc.* **1983**, *105*, 5665. (b) Wilt, J. W.; Lusztyk, J.; Peeran, M.; Ingold, K. U. *J. Am. Chem. Soc.* **1988**, *110*, 281. (c) Wilt, J. W. *Tetrahedron* **1985**, *41*, 3979.

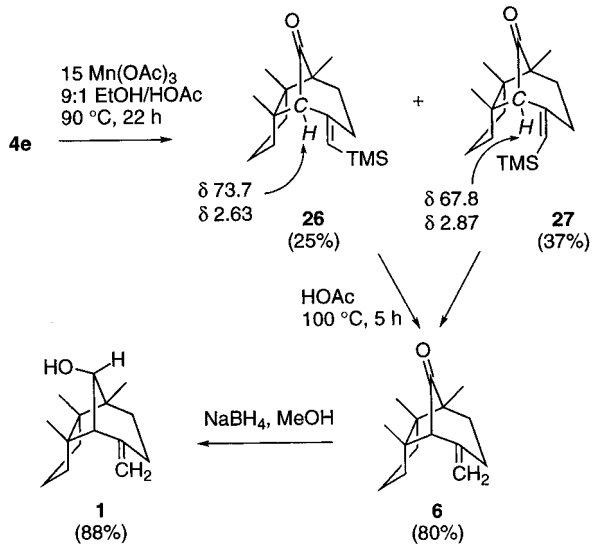
of [(trimethylsilyl)propargyl]magensium bromide to 1,5-dimethyl-2-methylenebicyclo[3.3.0]octanone followed by trapping of the enolate with methyl iodide.[4] Since this procedure proceeded in even lower yield in our hands, we developed an efficient synthesis of **4e**.

Alkylation of bicyclooctanone **23**[4] with LHMDS and 1-iodo-2-butyne affords 70% of a 3.6:6.7:1 mixture of the two stereoisomers of **24** and geminally dialkylated material and 24% of recovered **23**. Methylation of **24** with NaH and MeI gives **25** in 42% yield from **23** (56% based on recovered **23**). Methylation occurs from the convex face of the thermodynamically more stable enolate as reported by Welch for a similar system.[5] Treatment of **25** with KAPA[19] isomerizes the internal alkyne to give terminal alkyne **4d** in 71% yield. Silylation of **4d**, as described above for **18a**, gives **4e** in 92% yield. This four-step procedure reproducibly converts ketone **23** to (trimethylsilyl)alkyne **4e** in 37% overall yield.

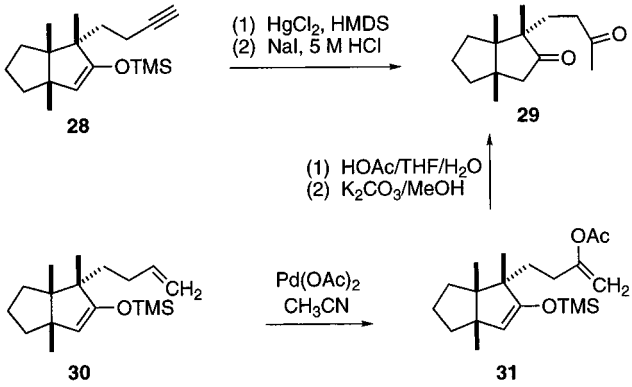


Oxidative cyclization of **4e** with 15 equiv of $Mn(OAc)_3$ in 9:1 EtOH/HOAc at 90 °C for 22 h gives 47% (62% based on recovered **4e**) of a 1:1.4 mixture of diastereomeric vinylsilanes **26** and **27**. The methine proton and carbon absorb at δ 2.63 and 73.7, respectively, in **26**, and at δ 2.87 and 67.8, respectively, in **27**, establishing the stereochemistry as discussed above for **21** and **22**. Desilylation of the mixture of **26** and **27** in HOAc at 100 °C for 5 h affords 80% of gymnomitrone (**6**), while desilylation with TFA at room temperature overnight provides isogymnomitrone (**7**). Reduction of gymnomitrone (**6**) with $NaBH_4$ completes the synthesis, giving gymnomitrol (**1**) in 88% yield.

Unsuccessful Approaches for the Cyclization of 4c and 4d. Oxidative cyclization of terminal alkyne **4d** under the conditions used successfully for the cyclization of **4e** gives mainly oligomeric material and a trace of gymnomitrone (**6**) as the only identifiable product. Hydrogenation of **4d** over 5% $Pd/BaSO_4$ in pyridine[20] affords 90% of alkene **4c**. Oxidative cyclization of alkene **4c** with 3 equiv of $Mn(OAc)_3$ and 1 equiv of $Cu(OAc)_2$ in HOAc at 80 °C for 18 h provides mainly oligomeric material with <5% of gymnomitrone (**6**). The low yield of **6** obtained in the oxidative cyclizations of **4c** and **4d** is consistent with the high degree of strain in the gymnomitrane ring system noted in previous syntheses.[3,4] If the α-keto radical does not cyclize rapidly enough, it will initiate oligomerization. The TMS group of **4e** apparently accelerates the cyclization of the 6-heptynyl radical in addition to directing the regioselectivity of the cyclization by its steric bulk.



Paquette reported that the thermal Conia ene reaction of **4d** does not give gymnomitrone (**6**).[4] Since that time Drouin and Conia developed a $HgCl_2$-catalyzed cyclization of alkynyl silyl enol ethers that proceeds at room temperature.[21] However, this procedure is also not suitable for the preparation of gymnomitrone (**6**). Alkyne **4d** was converted to alkynyl silyl enol ether **28**, which was treated with 1.2 equiv of $HgCl_2$ and 0.33 equiv of HMDS in CH_2Cl_2 for 1 h to afford diketone **29**,[4] resulting from hydration of the alkyne, in good yield. The reaction is very slow (104 h) when excess HMDS (20 equiv) is used to scavenge water, but still gives bicyclic ketone **29** as the only product. Apparently, the silyl enol ether cannot reach the alkyne−mercury complex.



Kende has developed $Pd(OAc)_2$-induced cyclizations of unsaturated silyl enol ethers as a versatile route to bicyclic enones.[22] This cyclization procedure also cannot be used to prepare gymnomitrone (**6**). Alkene **4c** was converted to alkenyl silyl enol ether **30**, which was treated with $Pd(OAc)_2$ in CH_3CN for 48 h to provide a mixture with enol acetate **31** being the major identifiable product. Hydrolysis of the silyl enol ether of **31** in HOAc/THF/H_2O and hydrolysis of the enol acetate with K_2CO_2

(19) (a) Brown, C. A.; Yamashita, A. *J. Am. Chem. Soc.* **1975**, *97*, 891. (b) Brown, C. A. *J. Chem. Soc., Chem. Commun.* **1975**, 222.

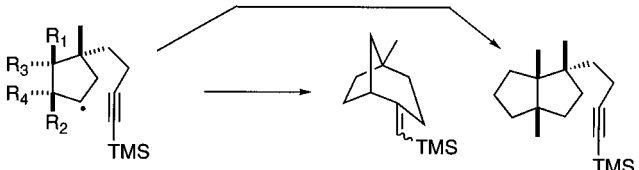
(20) (a) Smith, A. B.; Guaciaro, M. A.; Schow, S. R.; Wovkulich, P. M.; Toder, B. H.; Hall, T. W. *J. Am. Chem. Soc.* **1981**, *103*, 219. (b) Johnson, F.; Paul, K. G.; Favara, D. *J. Org. Chem.* **1982**, *47*, 4254.

(21) (a) Drouin, J.; Boanventura, M.-A.; Conia, J.-M. *J. Am. Chem. Soc.* **1985**, *107*, 1726. (b) Boaventura, M.-A.; Drouin, J. *Bull. Soc. Chim. Fr.* **1987**, 1015.

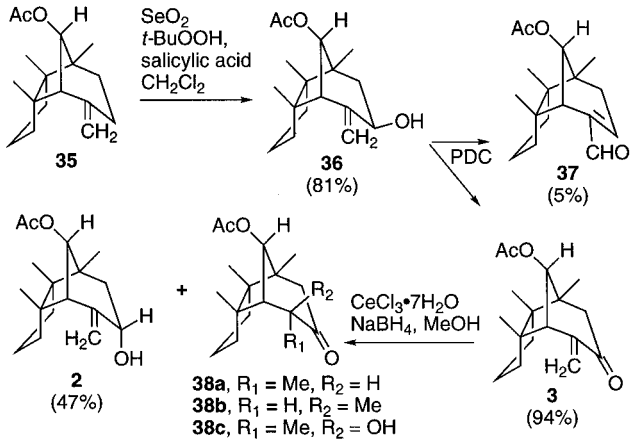
(22) Kende, A. S.; Roth, B.; Sanfilippo, P. J.; Blacklock, T. J. *J. Am. Chem. Soc.* **1982**, *104*, 5808.

in MeOH provides diketone **29**. Apparently the silyl enol ether cannot reach the alkene−palladium complex.

Koreeda found that 3-methyl-3-[4-(trimethylsilyl)-3-butynyl]cyclopentyl (**32a**), generated reductively with Bu_3SnH, cyclizes to give 65% of bicyclic vinylsilane **33** resulting from the desired 6-*exo*-cyclization but that radical **32b** abstracts a hydrogen from Bu_3SnH to afford mainly **34** resulting from reduction.[8b] The failure of **32b** to cyclize provides further evidence of the ring strain in the gymnomitrane ring system. Oxidative generation of the radical from **4e** with Mn(III) produces an electrophilic α-keto radical that adds more rapidly to the electron rich silylalkyne than does the nucleophilic radical of **32b**. Furthermore, ketone **4e** will be regenerated if the α-keto radical from **4e** abstracts a hydrogen atom from EtOH. Such a process would consume oxidant but not starting material. For these reasons, the oxidative cyclization of **4e** proceeds efficiently, while the reductive cyclization of **32b** fails.



Synthesis of 9-Oxogymnomitryl Acetate and 9α-Hydroxygymnomitryl Acetate. With gymnomitrol (**1**) in hand we turned our attention to the preparation of the recently isolated, more highly oxidized gymnomitranes **2** and **3**. Acetylation of gymnomitrol in 1:1 Ac_2O/pyridine at 90 °C for 12 h affords gymnomitryl acetate (**35**) in 70% yield.[1] Allylic oxidation of **35** with SeO_2 and *t*-BuOOH[23] affords 9*β*-hydroxygymnomitryl acetate (**36**) in 81% yield. As expected the alcohol is delivered from the less hindered *β*-face. Treatment of **36** with PCC[24] in CH_2Cl_2 provides a 5:1 mixture of 9-oxogymnomitryl acetate (**3**), possessing ^1H and ^{13}C NMR data identical to those reported for the natural compound[2] and enal **37**. Use of PDC[25] improved the ratio to 15:1. Reduction of **3** to 9α-hydroxygymnomitryl acetate (**2**) was problematic due to competing conjugate reduction.[26] Treatment of **3** with $CeCl_3$ and $NaBH_4$ in MeOH[27] gave a 4.6:2.5:1:1 mixture of **2**, **38a**, **38b**, and **38c**. Compound **2**, with ^1H and ^{13}C NMR spectral data identical to those reported for the natural compound,[2] was isolated in 47% yield. The stereochemistry of **38a** was established by the similarity of the ^1H NMR spectrum to that of the desacetoxy compound.[28] Hydroxy ketone **38c**[29] may be formed by addition of oxygen[30] to the least hindered *β*-face of the enolate formed by conjugate addition of hydride to **3**.



Oxidative Cyclization of 5-Hexynyl Radicals. We examined the $Mn(OAc)_3$-induced cyclizations of **39a−c** and **43a−c** to determine the scope of oxidative cyclization of alkynyl ketones. Alkylation of the sodium salt of the cycloalkanone carboxylate with the requisite propargyl halide in THF affords 65−85% of **39** and **43**. Reaction of **39a** with 7 equiv of $Mn(OAc)_3$ in 19:1 EtOH/HOAc at 90 °C for 4 d affords 2% of **40a**[9] and 38% of **42a**.[9] Oxidative cyclization of the analogous ethyl 1-allyl-2-oxocyclohexanecarboxylate[9] with $Mn(OAc)_3$ and $Cu(OAc)_2$ affords 4% of **40a**, 66% of **42a**, and 7% of a double-bond position isomer of **42a**, indicating that both the 5-hexenyl and 5-hexynyl radicals undergo 6-*endo*-cyclization 20 times faster than 5-*exo*-cyclization. Treatment of **39b** with 7 equiv of $Mn(OAc)_3$ in 19:1 EtOH/HOAc at 90 °C for 4 d affords 13% of **40b**, 16% of **41b**, and 29% of **42b**. The methine carbon of **41b** absorbs at δ 54.3 while the methine carbon of **40b** is shifted upfield to δ 50.6 by the cis methyl group. A 1:1 mixture of 6-*endo*- and 5-*exo*-cyclization products is obtained with a methyl group on the triple bond.

Oxidative cyclization of (trimethylsilyl)alkyne **39c** with 7 equiv of $Mn(OAc)_3$ in 9:1 EtOH/HOAc at 100 °C for 1 d provides 21% of **40c**, 19% of **41c**, and 5% of **42c**. The methine proton and carbon absorb at δ 3.09 and 53.7, respectively, in **40c** and at δ 2.88 and 57.7, respectively, in **41c**, establishing the stereochemistry as discussed above for **21** and **22**.[17] An 8:1 mixture of 5-*exo*- and 6-*endo*-cyclization products is obtained with a trimethylsilyl group on the triple bond indicating that a trimethylsilyl group is much more effective than a methyl group at promoting 5-*exo*-cyclization as noted previously by Hart.[12] Desilylation of **40c** and **41c** in TFA at 25 °C affords 80% of **40a**.[9] Desilylation is slow in HOAc at 100 °C or with *p*-toluenesulfinic acid in wet acetonitrile at reflux.[31]

Oxidative cyclization of **43a**, **43b**, and **43c** with 6−8 equiv of $Mn(OAc)_3$ in 9−19:1 EtOH/HOAc for 1−4 d at 90 °C affords only the 6-*exo*-cyclization products **44a** (7%),[9] **44b** (10%),[9] and **44c** (<2%) in very low yield. Oxidative cyclization of the analogous 1-allyl- and 1-crotyl-2-oxocyclopentanecarboxylates with $Mn(OAc)_3$ and $Cu(OAc)_2$ affords 6-*endo*-cyclization products in 83−90% yield and no 5-*exo*-cyclization products.[9] 2-Oxocyclopentyl radicals show a much stronger preference for 6-*endo*-cyclization than 2-oxocyclohexyl radicals. The low yields of **44a−c** indicate that 6-*endo*-cyclization of the 5-hexynyl radicals obtained from **43** is much less efficient than

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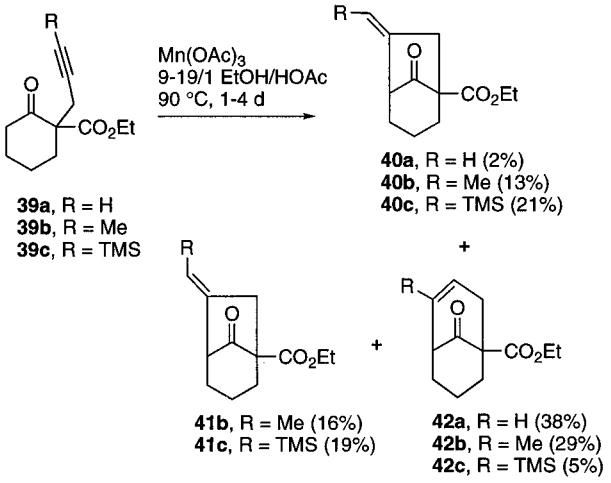
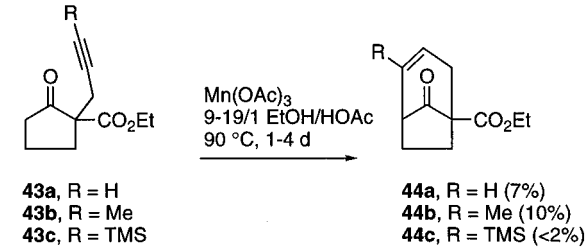


6-*endo*-cyclization of the analogous 5-hexenyl radicals or of the 5-hexynyl radicals obtained from **39**.



In conclusion, $Mn(OAc)_3$-initiated cyclization of alkynyl ketones in 9−19:1 EtOH/HOAc at 90 °C is a useful cyclization procedure in favorable cases. Cyclization of (trimethylsilyl)alkynyl ketone **4e** provides 62% of silylalkenes **26** and **27** in the key reaction of a seven-step (16% overall yield) synthesis of gymnomitrol (**1**) from readily available ketone **23**.

Experimental Section

General. All NMR spectra were recorded at 300 MHz in $CDCl_3$ unless otherwise indicated. Chemical shifts are reported in δ and coupling constants are reported in hertz.

(1α,3a*β*,6a*β*)- and (1*β*,3a*β*,6a*β*)-1-(2-Butynyl)-hexahydro-3a,6a-dimethyl-2(1*H*)-pentalenone (24). To a solution containing 11 mL of 1.0 M LHMDS in 10 mL of THF at −78 °C was added 1.1 g (7.24 mmol) of ketone **23**[4] in 10 mL of THF dropwise over 15 min. The solution was stirred at −78 °C for 15 min and at 0 °C for 1 h, and 2.0 g (11.1 mmol) of 1-iodo-2-butyne was added. The solution was slowly warmed to rt and stirred at rt for 1 h. The reaction was quenched by the addition of 10 mL of 1.0 M HCl, and the mixture was diluted with 150 mL of Et_2O, washed with H_2O and brine, and dried ($MgSO_4$). Removal of the solvent under reduced pressure followed by flash chromatography on silica gel (50:1 hexane/EtOAc) gave 1.03 g of an inseparable 3.6:6.7:1 mixture of the two stereoisomers of **24** and geminally dialkylated product, respectively, followed by 268 mg (24%) of recovered **23**.

Data for **24**: ^{1}H NMR (α-butynyl) 2.61 (ddd, 1, J = 17.0, 4.7, 2.7), 2.32 (ddd, 1, J = 8.5, 4.7, 1.3), 2.16 (dd, 1, J = 19.1, 1.2), 2.07 (d, 1, J = 19.1), 2.12−1.40 (series of m, 7), 1.76 (t, 3, J = 2.7), 1.18 (s, 3), 1.08 (s, 3); (*β*-butynyl) 2.58 (ddd, 1, J = 17.0, 4.7, 2.7), 2.37 (d, 1, J = 19.2), 2.28 (dd, 1, J = 6.6, 4.7), 1.97 (d, 1, J = 19.2), 2.12−1.40 (series of m, 7), 1.77 (t, 3, J = 2.7), 1.03 (s, 3), 0.91 (s, 3); ^{13}C NMR (α-butynyl) 217.8, 77.7, 77.4, 57.2, 51.9, 50.5, 46.9, 37.6, 34.5, 22.7, 21.2, 20.9, 15.6, 3.5; (*β*-butynyl) 77.7, 77.1, 55.6, 52.2, 48.9, 46.7, 40.1, 36.5, 22.6, 21.2, 16.4, 14.8, 3.5, carbonyl carbon not observed; IR (neat) 2955, 2871, 1739, 1451, 1381, 1251, 1166 cm^{-1}.

Data for geminally dialkylated product: mp 154.5−155.5 °C (crystallized from crude mixture in MeOH); ^{1}H NMR 2.81 (dq, 1, J = 17.5, 2.7), 2.73 (dq, 1, J = 16.5, 2.7), 2.48 (d, 1, J = 18.4), 2.40 (dq, 1, J = 16.5, 2.7), 2.13 (d, 1, J = 18.4), 2.12 (dq, 1, J = 17.5, 2.7), 1.79 (t, 3, J = 2.7), 1.77 (t, 3, J = 2.7), 1.80−1.45 (m, 6), 1.23 (s, 3), 1.16 (s, 3); ^{13}C NMR 79.0, 78.1, 75.8, 74.1, 56.7, 53.1, 51.8, 44.7, 43.9, 39.6, 26.7, 23.5, 22.4, 21.1, 17.7, 3.6, 3.6, carbonyl carbon not observed; IR (CCl_4) 2954, 2920, 2874, 1736, 1431, 1384, 1330, 1164 cm^{-1}.

(1α,3a*β*,6a*β*)-1-(2-Butynyl)-hexahydro-1,3a,6a-trimethyl-2(1*H*)-pentalenone (25). To a suspension of 235 mg (5.8 mmol) of 60% NaH in 30 mL of DME at rt was added 1.0 g of the above mixture containing **24** in 10 mL of DME over 15 min. The solution was stirred at rt for 3 h and cooled to −10 °C. To the solution was added 0.46 mL (7.4 mmol) of MeI, and the resulting solution was stirred at rt for 5 h, quenched with 10 mL of 1.0 M HCl, diluted with 150 mL of Et_2O, washed with H_2O and brine, and dried ($MgSO_4$). Removal of the solvent under reduced pressure followed by flash chromatography on silica gel (100:1 hexane/EtOAc) gave 650 mg (42% from **23**, 56% based on recovered **23**) of pure **25**: ^{1}H NMR 2.35 (d, 1, J = 19.3), 2.34 (dq, 1, J = 17.1, 2.6), 2.19 (br d, 1, J = 17.1), 2.18 (d, 1, J = 19.3), 1.79 (t, 3, J = 2.6), 1.80−1.59 (m, 6), 1.19 (s, 3), 1.18 (s, 3), 1.14 (s, 3); ^{13}C NMR 222.6, 77.6, 76.2, 53.9, 53.8, 51.6, 45.8, 41.1, 38.6, 25.6, 25.2, 21.4, 20.7, 17.1, 3.5; IR (neat) 2953, 2874, 1734, 1448, 1382, 1190, 1064 cm^{-1}.

(1α,3a*β*,6a*β*)-1-(3-Butynyl)-hexahydro-1,3a,6a-trimethyl-2(1*H*)-pentalenone (4d). To 3.6 g (31.5 mmol) of 35% KH (rinsed with hexane three times) was added 23 mL of diaminopropane. The KAPA solution was stirred at rt for 2.5 h, and 550 mg (2.52 mmol) of ketone **25** in 10 mL of diaminopropane was added dropwise over 15 min. After 30 min of stirring at rt, the solution was cooled to 0 °C and carefully quenched by the addition of dilute HCl. The resulting solution was extracted with Et_2O three times, and the combined organic layers were washed with 1 M HCl, H_2O, and brine, dried ($MgSO_4$), and concentrated under reduced pressure to yield 500 mg of a yellow oil. Flash chromatography of the crude residue on silica gel (100:1 hexane/EtOAc) yielded 393 mg (71%) of pure crystalline **4d** which was recrystallized from hexane: mp 70−71 °C (lit.[4] mp 70−71 °C); ^{1}H NMR 2.53 (dddd, 1, J = 16.5, 11.9, 4.8, 2.7), 2.36 (d, 1, J = 18.8), 2.23 (dddd, 1, J = 16.5, 12.0, 5.4, 2.7), 2.20 (d, 1, J = 18.8), 1.94 (t, 1, J = 2.7), 1.84 (ddd, 1, J = 14.2, 12.0, 4.9), 1.75−1.49 (m, 7), 1.18 (s, 3), 1.07 (s, 3), 0.97 (s, 3); ^{13}C NMR 222.8, 85.0, 68.1, 54.0, 53.8, 51.9, 45.8, 41.2, 38.4, 34.2, 25.7, 21.4, 19.3, 17.0, 13.8; IR (CCl_4) 3266, 2931, 2877, 2114, 1731, 1470, 1450, 1389, 1245 cm^{-1}.

(1α,3a*β*,6a*β*)-Hexahydro-1,3a,6a-trimethyl-1-[4-(trimethylsilyl)-3-butynyl]-2(1*H*)-pentalenone (4e). To 1.25 mmol of LDA in 10 mL of THF at −78 °C was added 109 mg (0.5 mmol) of **4d** in 10 mL of THF dropwise over 15 min. The solution was stirred at rt for 2.5 h, and 0.17 mL (1.34 mmol) of TMSCl was added. After being stirred for an additional 15 min at rt, the solution was quenched by addition of 5 mL of H_2O and 10 mL of HOAc. The quenched solution was stirred for 12 h, diluted with Et_2O, washed with H_2O, saturated $NaHCO_3$ solution (×3), and brine, dried ($MgSO_4$), and concentrated under reduced pressure to yield 150 mg of a clear oil. Flash chromatography of the crude residue on silica gel (50:1 hexane/EtOAc) gave 134 mg (92%) of pure **4e**: ^{1}H NMR 2.53 (ddd, 1, J = 16.5, 11.6, 4.8), 2.35 (d, 1, J = 19.0), 2.26 (ddd, 1, J = 16.5, 11.7, 4.8), 2.20 (d, 1, J = 19.0), 1.82 (ddd, J = 14.1, 11.7, 4.8), 1.75−1.51 (m, 7), 1.17 (s, 3), 1.06 (s, 3), 0.97 (s, 3), 0.14 (s, 9); ^{13}C NMR 222.8, 107.8, 84.2, 54.0, 53.9, 51.8, 45.8, 41.1, 38.4, 34.4, 25.7, 21.4, 19.4, 17.1, 15.2, 0.1 (3 C); IR (neat) 2956, 2875, 2175, 1732, 1248 cm^{-1}.

$Mn(OAc)_3$-Initiated Cyclization of 4e. A solution containing 45 mg (0.16 mmol) of ketone **4e** and 416 mg (1.6 mmol) of $Mn(OAc)_3 \cdot 2H_2O$ in 3.5 mL of degassed 9:1 EtOH/HOAc was heated at 90 °C in a resealable tube under N_2 for 10 h. An additional 208 mg (0.78 mmol) of $Mn(OAc)_3 \cdot 2H_2O$ was added, and heating was continued for another 12 h at 90 °C. Workup as described for the cyclization of **18a** gave 52 mg of crude material. Flash chromatography of the residue on silica gel (100:1 hexane/EtOAc) gave 21 mg (47%, 62% based on recovered **4e**) of a 1:1.4 mixture of diastereomeric vinylsilanes **26** and **27** followed by 11 mg (24%) of recovered **4e**. Early

fractions contained a ≈9:1 mixture of **27** and **26**. Late fractions contained a ≈9:1 mixture of **26** and **27**.

Data for **26**: ^{1}H NMR 5.27 (d, 1, J = 2.5), 2.63 (s, 1), 2.47−2.30 (m, 2), 2.15−1.33 (series of m, 8), 0.93 (s, 6), 0.82 (s, 3), 0.08 (s, 9); ^{13}C NMR 157.1, 127.6, 73.7, 52.3, 48.9, 47.7, 38.5, 36.7, 35.7, 27.6, 27.0, 24.0, 23.2, 17.7, 0.06 (3 C), carbonyl carbon not observed; IR (neat) 2955, 2175, 1745, 1605, 1456, 1388, 1248 cm^{-1}.

Data for **27**: ^{1}H NMR 5.32 (dd, 1, J = 2.4, 0.8), 2.87 (s, 1), 2.73−2.59 (m, 1), 2.19−1.33 (series of m, 9), 0.96 (s, 3), 0.92 (s, 3), 0.83 (s, 3), 0.12 (s, 9); ^{13}C NMR 217.2, 157.7, 127.3, 67.8, 51.9, 49.0, 47.5, 38.1, 36.8, 35.7, 32.2, 26.9, 24.0, 23.2, 17.7, 0.6 (3 C); IR (neat) 2955, 2174, 1743, 1607, 1456, 1249 cm^{-1}.

Gymnomitrone (6). A solution of 15 mg (0.052 mmol) of a mixture of vinylsilanes **26** and **27** in 2 mL of HOAc was heated at 100 °C for 5 h. The solution was diluted with 30 mL of ether, washed three times with saturated $NaHCO_3$ solution and once with brine, dried ($MgSO_4$), and concentrated under reduced pressure to yield 11 mg of crude material. Flash chromatography of the crude residue on silica gel (100:1 hexane/EtOAc) gave 9 mg (80%) of gymnomitrone (**6**): ^{1}H NMR 4.77 (br s, 1), 4.76 (br s, 1), 2.64 (s, 1), 2.55 (ddddd, 1, J = 16.3, 12.9, 8.1, 2.7, 2.7), 2.18 (br dd, 1, J = 16.3, 7.0), 2.09 (br dd, 1, J = 12.5, 7.0), 2.01−1.34 (series of m, 7), 0.95 (s, 3), 0.93 (s, 3), 0.83 (s, 3); ^{13}C NMR 148.9, 112.2, 68.9, 52.2, 48.9, 47.3, 38.6, 36.7, 35.7, 28.0, 26.8, 24.0, 23.2, 17.7, carbonyl carbon was not observed; IR (CCl_4) 3077, 2959, 2869, 1745, 1641, 1461, 1388, 1276 cm^{-1}. The ^{1}H NMR spectral data are identical to those previously reported.[1,3−5]

Gymnomitrol (1). To a solution of 8 mg (0.037 mmol) of gymnomitrone (**6**) in 1 mL of MeOH at 0 °C was added 8 mg of $NaBH_4$. The mixture was stirred at 0 °C for 1 h, and the reaction was quenched by the addition of 2 drops of 1 M HCl. The quenched reaction was diluted with ether, washed with 1 M HCl and brine, dried ($MgSO_4$), and concentrated under reduced pressure to yield 8 mg of crude gymnomitrol. Flash chromatography of the residue on silica gel (50:1 hexane/EtOAc) gave 7 mg (88%) of pure gymnomitrol (**1**): ^{1}H NMR 4.66 (s, 1), 4.65 (s, 1), 3.72 (s, 1), 2.51−2.33 (m, 1), 2.34 (s, 1), 2.14 (dd, 1, J = 16.8, 8.0), 2.00−1.10 (series of m, 7), 1.40 (ddd, 1, J = 14.0, 12.2, 8.2), 1.24 (s, 3), 1.09 (s, 3), 0.96 (s, 3); ^{13}C NMR 151.3, 108.9, 91.8, 62.7, 55.3, 54.3, 47.5, 38.5, 37.2, 37.0, 28.8, 28.3, 27.2, 24.7, 19.8; IR (CCl_4) 3625, 3416, 3071, 2933, 2868, 1644, 1464, 1372 cm^{-1}. The ^{1}H NMR spectral data are identical to those previously reported.[1,3−5]

Gymnomitryl Acetate (35). A mixture of 9 mg (0.041 mmol) of gymnomitrol (**1**), 1 mL Ac_2O, and 1 mL of pyridine was heated at 90 °C for 12 h. The crude mixture was diluted with 30 mL of ether, washed with H_2O (×3), $CuSO_4$ solution, saturated $NaHCO_3$ solution, and brine, and dried ($MgSO_4$). Removal of the solvent under reduced pressure and purification by flash chromatography on silica gel (100:1 hexane/EtOAc) gave 7.5 mg (70%) of pure **35**: ^{1}H NMR 4.77 (s, 1), 4.72 (d, 1, J = 2.6), 4.71 (d, 1, J = 2.6), 2.50−2.37 (m, 1), 2.38 (s, 1), 2.19 (dd, 1, J = 16.9, 8.0), 2.08 (s, 3), 2.00−1.10 (series of m, 8), 1.15 (s, 3), 1.07 (s, 3), 0.87 (s, 3); ^{13}C NMR 149.5, 110.4, 92.5, 60.3, 55.2, 54.9, 46.8, 38.3, 37.2, 36.8, 28.2, 28.0, 27.2, 24.1, 21.5, 20.0, acetate carbonyl carbon not observed; IR (CCl_4) 2958, 2869, 1741, 1644, 1464, 1362, 1233 cm^{-1}.

9β-Hydroxygymnomitryl Acetate (36). To a solution of 0.1 mg (0.9 μmol) of SeO_2, 1 mg (7.2 μmol) of salicylic acid, and 30 mg (0.3 mmol) of 90% *t*-BuOOH in 1 mL of CH_2Cl_2 was added 3.5 mg (13 μmol) of gymnomitryl acetate (**35**) in 1 mL of CH_2Cl_2. The solution was stirred at rt under N_2 for 8 h, diluted with 20 mL of ether, washed with 15% NaOH solution and brine, and dried ($MgSO_4$). Removal of the solvent under reduced pressure yielded 5 mg of crude material. Flash chromatography on silica gel (5:1 hexane/EtOAc) gave 3 mg (81%) of pure **36**: ^{1}H NMR 5.13 (dd, 1, J = 2.3, 1.4), 4.94 (br s, 1), 4.85 (s, 1), 4.54 (m, 1), 2.55 (s, 1), 2.33 (dd, 1, J = 13.8, 8.4), 2.08 (s, 3), 1.96−1.72 (m, 4), 1.37 (dd, 1, J = 13.8, 10.3), 1.25−1.18 (m, 2), 1.16 (s, 3), 1.08 (s, 3), 0.89 (s, 3); ^{13}C NMR 151.9, 109.9, 91.7, 67.6, 60.2, 55.4, 55.3, 48.5, 48.2, 38.7, 37.2, 28.4, 27.1, 23.9, 21.4, 18.7, acetate carbonyl carbon not observed; IR (CCl_4) 3418, 2958, 2870, 1741, 1649, 1465, 1375, 1240, 1046 cm^{-1}.

9-Oxogymnomitryl Acetate (3). A solution of 1 mg (3.6 μmol) of allylic alcohol **36** and 10 mg (26 μmol) of PDC in 0.5 mL of CH_2Cl_2 was stirred at rt under N_2 for 3 h. The crude mixture was filtered through a short silica gel plug and concentrated under reduced pressure to give a quantitative yield of a 15:1 mixture of enone **3** and enal **37**. Enone **3** was easily obtained pure by flash chromatography on silica gel (10:1 hexane/EtOAc): ^{1}H NMR 6.07 (d, 1, J = 1.7), 5.21 (d, 1, J = 1.2), 5.04 (s, 1), 2.81 (d, 1, J = 19.9), 2.73 (s, 3), 2.23 (d, 1, J = 19.9), 2.13 (s, 3), 1.85−1.10 (m, 6), 1.20 (s, 3), 1.11 (s, 3), 0.96 (s, 3); ^{13}C NMR 145.2, 123.1, 87.0, 58.2, 55.8, 55.0, 51.5, 48.4, 40.3, 38.8, 28.0, 25.5, 24.2, 21.3, 19.8, carbonyl carbon not observed. The spectral data are identical to those reported.[2]

Partial ^{1}H NMR data for **37** were determined from the mixture: 9.44 (s, 1), 6.56 (m, 1), 4.93 (s, 1), 2.10 (s, 3), 1.20 (s, 3), 1.07 (s, 3), 0.97 (s, 3).

9α-Hydroxygymnomitryl Acetate (2). To a solution of 1.5 mg (5.4 μmol) of enone **3** and 6 mg (16 μmol) of $CeCl_3 \cdot 7H_2O$ in 0.5 mL of MeOH at 0 °C was added a trace of $NaBH_4$. The solution was stirred at 0 °C for 5 min, diluted with ether, washed with 1 M HCl and brine, and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave 1.4 mg of a mixture of **2**, **38a**, **38b**, and **38c** in a 4.6:2.5:1.0:1.0 ratio, respectively. Flash chromatography of the crude residue on silica gel (200:1 CH_2Cl_2/MeOH) gave 0.7 mg (47%) of pure **2**: ^{1}H NMR 5.20 (d, 1, J = 2.4), 5.03 (s, 1), 4.91 (d, 1, J = 2.4), 4.47 (m, 1), 2.46 (s, 1), 2.08 (s, 3), 1.95 (dd, 1, J = 14.9, 9.7), 1.86 (m, 1), 1.83 (dd, 1, J = 14.9, 8.4), 1.5−0.9 (m, 5), 1.15 (s, 3), 1.03 (s, 3), 0.94 (s, 3); ^{13}C NMR 150.5, 111.7, 83.4, 65.1, 58.2, 54.9, 48.6, 42.5, 40.0, 39.4, 28.0, 24.7, 24.6, 21.7, 21.4, acetate carbonyl carbon and one quaternary carbon were not observed. Spectral data are identical to those reported except the carbon observed at 83.4 was reported to be 84.3.[2]

Acknowledgment. We thank the National Institutes of Health for financial support.

Supporting Information Available: Experimental procedures for all other compounds and ^{1}H and ^{13}C NMR spectra of new compounds (52 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9622338