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Diastereoselective Prins-Type Reaction of Cycloalkenylcyclopropanol Silyl Ethers and α,β-Unsaturated Aldehyde Acetals

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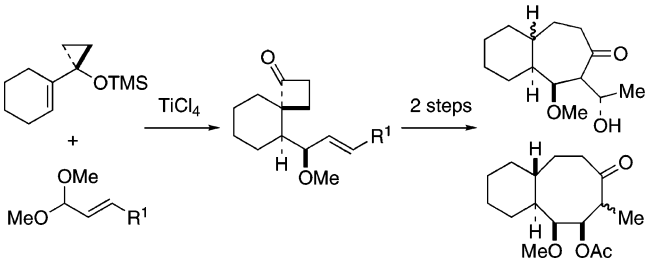

Electrophilic addition of 1-(1-cyclohexenyl)-1-cyclopropanol trimethylsilyl ether to α,β-unsaturated aldehyde acetals under Lewis acidic conditions proceeds with good to excellent diastereoselectivity to afford spirocyclobutanones containing three contiguous stereocenters. A convenient entry to enantioselective syntheses is available by use of a nonracemic C_2-symmetric acetal. Elaboration of the resulting adducts provides ready access to medium-sized carbocycles.

Introduction

The release of strain arising from cleavage of cyclopropanes has been frequently utilized in organic synthesis.[1] Heteroatom-substituted cyclopropanes display enhanced nucleophilicity and provide convenient methods for regio- and stereoselective ring-opening. For example, ring-opening reactions of cyclopropanols and siloxy derivatives have been extensively investigated and render them a "homoenol" or "homoenolate" equivalent.[2−4] The juxtaposition of a cyclopropanol and an olefin or an alkyne generates unique conjunctive functionalities suitable for different modes of C−C bond formation, and the Trost group documented facile addition of the trimethylsilyl ethers of 1-vinylcyclopropanols to oxocarbenium ions (generated in situ from acetals).[5,6] In the absence of overriding geometrical factors, electrophilic attack takes place preferentially at the double bond, leading to formation of the corresponding spirocyclobutanones bearing three contiguous stereocenters (eq 1). It is not surprising that diastereocontrol proved to be difficult,[5,7] and a handful of known diastereoselective examples reported have been limited primarily to intramolecular variants.[5,8] We report herein diastereoselective Prins-type reactions of 1-(1-cyclohexenyl)-1-cyclopropanol trimethylsilyl ether (**2**) and α,β-unsaturated aldehyde acetals.

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(3) Kuwajima, I.; Nakamura, E. *Top. Curr. Chem.* **1990**, *155*, 1.

(4) For represenative examples, see: (a) Carey, J. T.; Knors, C.; Helquist, P. *J. Am. Chem. Soc.* **1986**, *108*, 8313. (b) O'Neil, K. E.; Kingree, S. V.; Minbiole, K. P. C. *Org. Lett.* **2005**, *7*, 515. (c) Epstein, O. L.; Lee, S.; Cha. J. K. *Angew. Chem., Int. Ed.* **2006**, *45*, 4988. (d) Lee, H. G.; Lysenko, I. L.; Cha. J. K. *Angew. Chem., Int. Ed.* **2007**, *46*, 3326.

(5) For reviews, see: (a) Trost, B. M. *Top. Curr. Chem.* **1986**, *133*, 3. (b) Salaün, J. *Top. Curr. Chem.* **1988**, *144*, 1. (c) Trost, B. M.; Brandi, A. *J. Am. Chem. Soc.* **1984**, *106*, 5041. (d) Trost, B. M.; Lee, D. C. *J. Am. Chem. Soc.* **1988**, *110*, 6556. (e) Trost, B. M.; Chen, D. W. C. *J. Am. Chem. Soc.* **1996**, *118*, 12541.

(6) (a) Wasserman, H. H.; Cochoy, R. E.; Baird, M. S. *J. Am. Chem. Soc.* **1969**, *91*, 2375. (b) Wasserman, H. H.; Hearn, M. J.; Cochoy, R. E. *J. Org. Chem.* **1980**, *45*, 2874. (c) Gassman, P. G.; Riehle, R. J. *J. Am. Chem. Soc.* **1989**, *111*, 2319.

(7) (a) Oh, H.-S.; Lee, H. I.; Cha, J. K. *Org. Lett.* **2002**, *4*, 3707. (b) Oh, H.-S.; Cha, J. K. *Tetrahedron: Asymmetry* **2003**, *14*, 2911. (c) Manivannan, E.; Oh, H.-S.; Cha, J. K. *Org. Lett.* **2007**, *9*, 2693.

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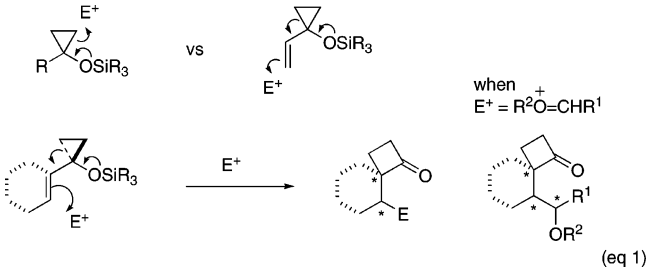


(eq 1)

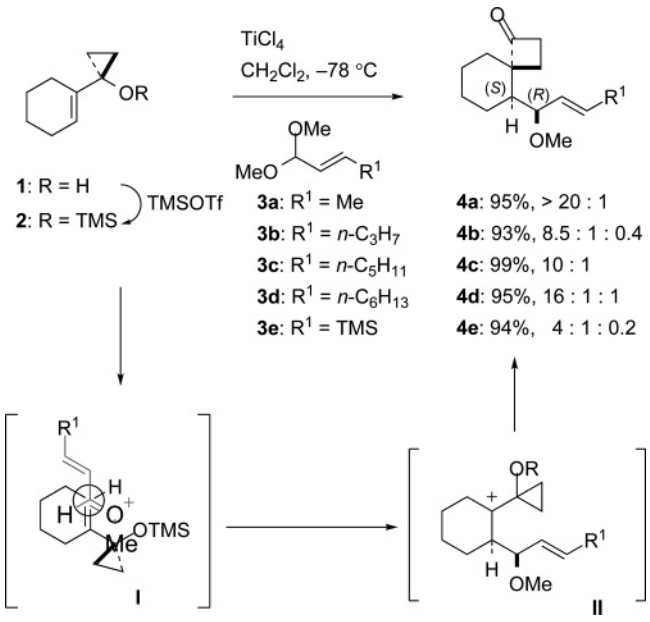
Results and Discussion

Cyclopropanol **1**, which was readily prepared by the Kulinkovich cyclopropanation of methyl 1-cyclohexene-1-carboxylate,[9,10] was selected for a vinylogous homo-Prins- or homo-Mukaiyama-type reaction[11] with acetals under Lewis acidic conditions (Scheme 1). Ring expansion induced by addition of an oxocarbenium ion to a trisubstituted olefin (e.g., 1-cyclohexenyl moiety) should provide ready access to a quaternary center.[12] This straightforward procedure was applicable to a full range of acetals derived from aliphatic, α,β-unsaturated, aromatic aldehydes and alkynals to give the corresponding spirocyclobutanones in excellent yields. Diastereoselectivity was found to be not only sensitive to the reaction parameters (e.g., reaction temperatures, Lewis acids, the presence of lutidine, etc.), but also modest (typically 3−4:1).

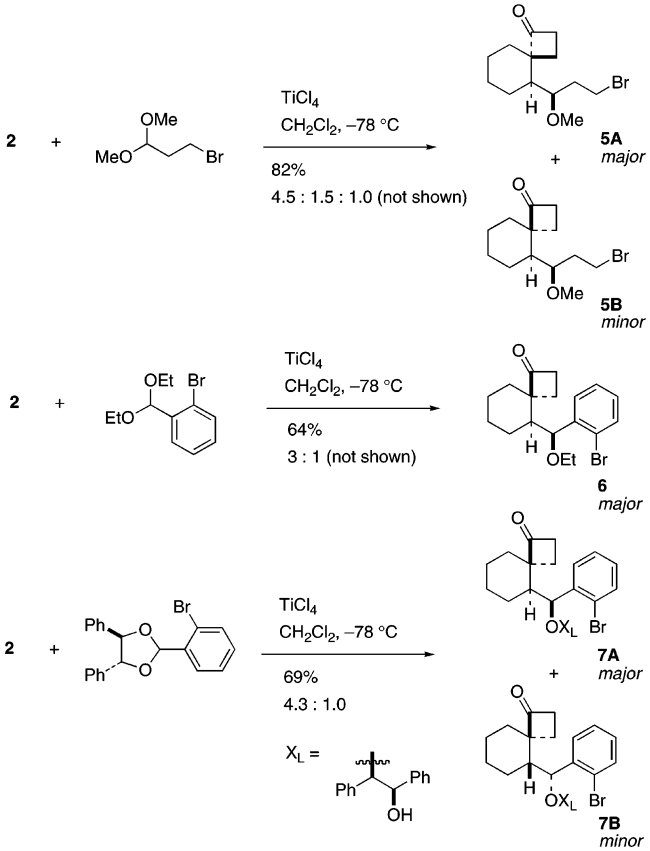
However, the use of α,β-unsaturated aldehyde acetals was shown to be an exception. Treatment of a mixture of trimethylsilyl ether **2** and dimethyl acetals **3a**−**e** with $TiCl_4$ at −78 °C afforded spirobutanones **4a**−**e** in 93−99% (combined) yield and with good diastereoselectivity. Only the stereochemistry of the major isomers is shown in Scheme 1, where the product ratios were determined by GC−MS and also analysis of ^{1}H NMR spectra. Formation of two (e.g., **4a** and **4c**) or three (e.g., **4b**, **4d**, and **4e**) isomers was usually observed out of four possible diastereomers. Fortuitously, the major isomers were easily separated by silica gel chromatography from the remaining isomers in all cases. Cyclopropanols could also be used directly without silylation, but the resulting diastereoselectivity was often different from that obtained for the corresponding trimethylsilyl ethers. For example, coupling of **1** and **3a** afforded a 1:3 mixture of two products epimeric at the quaternary carbon in 85% yield, and the minor isomer corresponded to **4a**.

The unequivocal stereochemical determination of **4e** was established by single-crystal X-ray analysis.[13] The stereochemical assignment of **4a**−**d** was then made by the correlation study

SCHEME 1. Coupling of 2 and Acetals 3a−e



SCHEME 2. Coupling Reactions of 2 with Aliphatic and Aryl Aldehyde Acetals[7]



involving oxidative cleavage of the double bond of **4e** (subsequent to desilylation) and **4a**−**d**, in addition to difference NOE measurements or comparison of key coupling constants. TLC behavior of these isomers was also informative because of regular patterns apparent among several related spirobutanones (Scheme 2), the stereochemistry of which had previously been secured by single-crystal X-ray analysis: R_f values of the indicated (*S*,*R*)-products (e.g., **4a**−**e**) were lower than those of

(9) (a) Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 4198. (b) Kim, S. H.; Sung, M. J.; Cha, J. K. *Org. Synth.* **2003**, *80*, 111.

(10) For reviews, see: (a) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789. (b) Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835. (c) Kulinkovich, O. G. *Eur. J. Org. Chem.* **2004**, 4517.

(11) (a) Mukaiyama, T. *Org. React.* **1982**, *28*, 203. (b) Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 3248. (c) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095. (d) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929.

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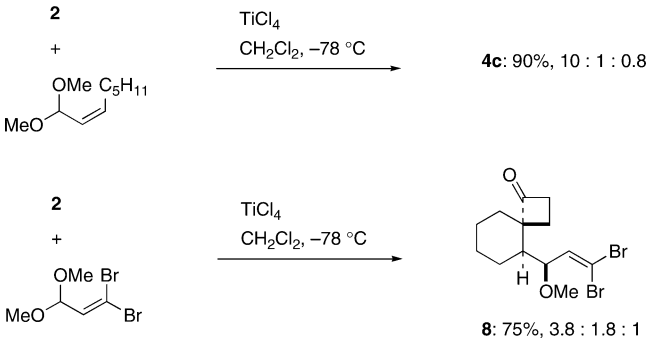
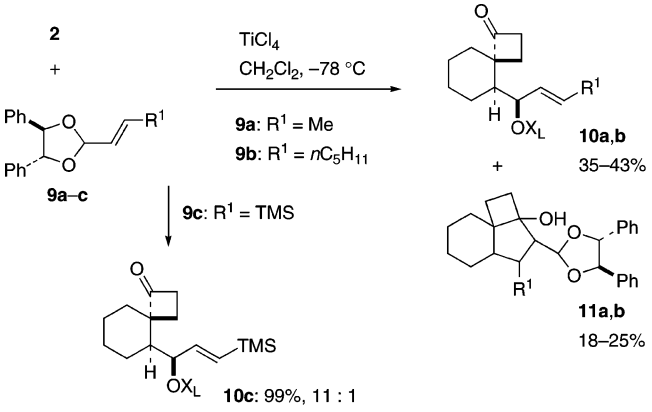
(13) We thank Dr. Mary Jane Heeg for single-crystal X-ray analysis. The X-ray data have been deposited with the Cambridge Structural Database: please refer to CSD nos. 265946 (**4e**), 256733 (**5A**), and 263915 (**10a**). X-ray structures are also secured for **6** (cf. 239454 and 239496), **7A** (cf. 232509), **7B** (232508), and **8** (232506).

SCHEME 3. Reactions of (*Z*)-α,*β*-Unsaturated Aldehyde Acetals



SCHEME 4. Use of Nonracemic C_2-Symmetric Acetals



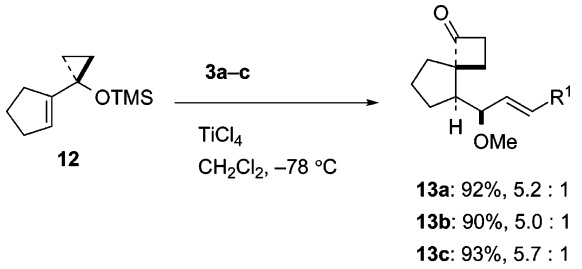
the respective (*R*,*R*)-isomers. The observed (*S*,*R*)-stereochemistry can be rationalized by synclinal approach of the vinylcyclopropanol to the oxocarbenium ion to avoid nonbonded interactions between the cyclopropane ring and the alkenyl substituent, as shown in the Newman projection **I** in Scheme 1.

Conspicuous is the *cis*-stereochemical relationship between the two newly formed C−C bonds of **4a**−**e**, which is indicative of the intermediacy of the stable tertiary cyclopropylcarbinyl cations **II**.[7,14] The diastereofacial bias of ring expansion appears to be steric in origin; depending on the substrates (e.g., **4a**−**e** and **5A** vs **6** and **7A**), both net "*cis*" and net "*trans*" additions are observed. The preferential formation of **4a**−**e** (*cis* addition) might be attributed in part to the minimization of torsional strain during ring expansion (1,2-alkyl shift): as 1,2-alkyl shift occurs, *trans* addition would have to go through a fully eclipsed arrangement between the newly introduced side chain and the C−C═O bond.[15]

When (*Z*)-α,*β*-unsaturated aldehyde acetals were employed, complete isomerization to the (*E*)-double bond was observed, and this result is in accord with generation and subsequent trapping of oxocarbenium ions (Scheme 3). Diminished diastereoselectivity was observed for formation of **8**.

As was the case with **7A**/**7B**,[7b,c] a straightforward entry to enantioselective synthesis was available by utilizing a nonracemic C_2-symmetric acetal (Scheme 4). Hydrobenzoin was chosen as a chiral auxiliary primarily because of its commercial availability and ease of removal. The coupling reaction of **2** and **9a**,**b** resulted in both 1,2- and 1,4-addition, and no attempt was made to assign the stereochemistry of **11a**,**b**. The placement of a bulky substituent at the *β*-position precluded 1,4-addition, as shown in the stereoselective (11:1) formation of **10c**. The stereochemistry of the major products **10b**,**c** was assigned by analogy to that of **10a**, which had been secured by X-ray analysis.[13] The observed 1,3-diastereofacial selectivity by the chiral C_2-symmetric acetal is consistent with literature precedents.[16]

SCHEME 5. Reactions of 12 and Acetals 3a−c



To probe the scope of the key coupling reaction, we next studied the reactions of **12** and **3a**−**c** (Scheme 5). The diastereoselectivity exerted by **12** was considerably lower than that by **2**, where the stereochemistry of **13a**−**c** was tentatively assigned by analogy to that of **4a**−**c**. The observed decrease in selectivity with the cyclopentene system **12** reflects a smaller difference in energy between the two transition states leading to *cis* and *trans* addition. As the final step involves rehybridization from the sp^2 carbon to the sp^3 quaternary carbon, both transition states involving cyclopentanes contain an increasing number of eclipsing interactions. On the other hand, cyclohexanes, in which a staggered arrangement is possible, presumably display a larger difference in energy between the two transition states corresponding to *cis* and *trans* addition. Acyclic di- and trisubstituted alkenylcyclopropanols gave only low diastereoselectivity.

These addition products possess useful functionalities and are well suited for subsequent elaboration such as annulation of various ring sizes. To demonstrate the synthetic versatility of these products, functionalized seven- and eight-membered carbocycles **19**−**21** were next prepared from **4a** by radical-induced fragmentation of the spirocyclobutanone moiety (Scheme 6).[7a,b,17,18] Treatment of **4a** with iodine in acetic acid provided a separable 2.5:1 mixture of **14** and **15** in 90% yield and with high diastereofacial selectivity. However, the low regiocontrol was surprising. The stereochemical assignment of **14** and **15** was supported by not only ample literature examples on electrophilic addition of allylic alcohol derivatives,[19] but also several correlation studies (including preparation and elaboration of **16** and **17**).[20] The free radical-mediated cyclization−fragmentation reaction of **15** was next achieved by slow addition

(14) In our initial studies (ref 7a) involving cognate reactions of alkanal acetals, antiperiplanar *trans* addition was mistakenly assumed in their tentative assignment of the ring junction stereochemistry by extrapolation of **6** and **7A**. Subsequent studies, as documented in this work, clearly indicate a stepwise reaction pathway.

(15) Cf. von R. Schleyer, P. *J. Am. Chem. Soc*. **1967**, *89*, 701.

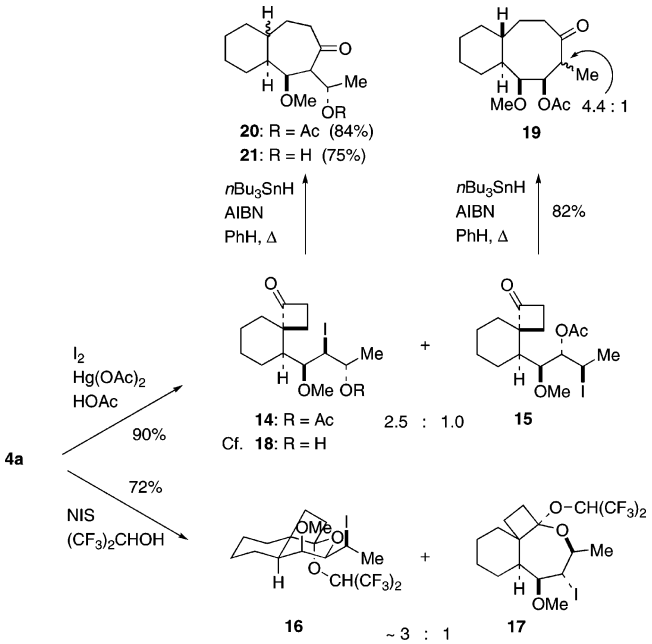
(16) See, inter alia: (a) Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477. (b) Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc*. **1991**, *113*, 8089. (c) Sammakia, T.; R. S. Smith, *J. Am. Chem. Soc*. **1992**, *114*, 10998.

(17) *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001.

(18) (a) Dowd, P.; Zhang, W. *J. Am. Chem. Soc*. **1991**, *113*, 9875. (b) Dowd, P.; Zhang, W. *Chem. Rev*. **1993**, *93*, 2091. (c) Zhang, W. *Curr. Org. Chem*. **2002**, *6*, 1015.

(19) Chamberlin, A. R.; Mulholland, R. L. *Tetrahedron* **1984**, *40*, 2297.

SCHEME 6. Free Radical-Mediated Annulation of Medium-Sized Rings



of *n*-tributyltin hydride in the presence of AIBN to give **19** as an easily separable mixture of two epimers (4.4:1, 82% yield), where the *trans*-ring junction stereochemistry resulted from 1,5-hydrogen transfer. Similarly, free radical-mediated cyclization−fragmentation of **14** and **18** proceeded smoothly to afford **20** and **21** in 84% and 75% yield, respectively. It is interesting to note that **20** was isolated as a mixture of all four diastereomers, whereas **21** was obtained as a ∼2:1 mixture of two isomers.

Conclusions

In summary, a family of coupling reactions between 1-(1-cyclohexenyl)-1-cyclopropanol trimethylsilyl ether (**2**) and α,β-unsaturated aldehyde acetals have been developed to quickly assemble spirocyclobutanones containing three contiguous stereocenters. Particularly noteworthy is high diastereoselectivity obtained by employing α,β-alkenal acetals in marked contrast to modest selectivity (3−4:1) observed for other acetals. The resulting products contain useful functionalities such as a cyclobutanone and an allylic ether, which are well suited for elaboration. Mechanistic studies to elucidate dominant factors for diastereocontrol and other methods for diastereoselective functionalization of the coupling products will be reported in due course.

Experimental Section

Representative Procedure for Vinylogous Mukaiyama- or Prins-Type Reactions of Cycloalkenylcyclopropanol Silyl Ethers. To a cooled (−78 °C) solution of silyl ether **2** (421 mg, 2 mmol) and acetal **3d** (559 mg, 3 mmol) in dichloromethane (20 mL) was added dropwise a solution of $TiCl_4$ (570 mg, 3 mmol) in dichloromethane (3 mL). The reaction mixture was stirred at −78 °C for 15 min and then quenched by sequential addition of saturated NaCl (20 mL) and ether (40 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl ether (2 × 10 mL). The combined organic extracts were passed through a short pad of Na_2SO_4−Al_2O_3, and the filtrate was concentrated under reduced pressure. Purification of the residue by column chromatography (30 g SiO_2, 15:1 to 10:1 hexanes−EtOAc) afforded **4d** (491 mg, 84%) as a colorless oil, in addition to two diastereomers (64 mg, 11%): IR (film) 1777 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.59 (dt, J = 15.5, 6.6 Hz, 1H), 5.18 (ddt, J = 15.5, 9.1, 1.6 Hz, 1H), 3.19 (t, J = 9.1 Hz, 1H), 3.15 (s, 3H), 2.95−2.84 (m, 2H), 2.04 (qd, J = 6.6, 1.4 Hz, 2H), 1.98 (tdd, J = 11.3, 7.6, 1.6 Hz, 1H), 1.78 (ddd, J = 13.5, 9.7, 3.7 Hz, 1H), 1.59 (m, 1H), 1.40−1.10 (m, 15H), 0.88 (t, J = 7.0 Hz, 3H), 0.82 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.4, 136.8, 129.1, 85.2, 66.9, 55.1, 45.5, 41.2, 33.8, 32.2, 31.6, 29.1, 28.8, 25.8, 25.1, 22.6, 22.0, 18.3, 14.0; HRMS m/z calcd for $C_{19}H_{32}O_2$ (M^+) 292.2402, found 292.2412.

Data for 4a: IR (film) 1778 cm^{-1}; ^1H NMR ^1H NMR (500 MHz, $CDCl_3$) δ 5.60 (dq, J = 15.2, 6.6 Hz, 1H), 5.19 (ddq, J = 15.2, 9.1, 1.5 Hz, 1H), 3.18 (t, J = 9.1 Hz, 1H), 3.12 (s, 3H), 2.96−2.84 (m, 2H), 1.95 (m, 1H), 1.80−1.66 (m, 2H), 1.72 (dd, J = 6.6, 1.5 Hz, 3H), 1.66−1.60 (m, 2H), 1.59−1.56 (m, 2H), 1.46 (m, 1H), 1.28−1.10 (m, 2H), 0.81 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.4, 131.1, 130.5, 85.1, 66.9, 55.1, 45.5, 41.2, 33.8, 25.7, 25.1, 22.0, 18.2, 17.7; HRMS m/z calcd for $C_{14}H_{42}O_2$ (M^+) 222.1620, found 222.1623.

Data for 4b: IR (film) 1778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.58 (dt, J = 15.4, 6.9 Hz, 1H), 5.19 (ddt, J = 15.4, 8.9, 1.4 Hz, 1H), 3.19 (t, J = 8.9 Hz, 1H), 3.13 (s, 3H), 2.97−2.83 (m, 2H), 2.04 (m, 2H), 1.96 (tdd, J = 11.4, 7.7, 1.6 Hz, 1H), 1.78 (ddd, J = 13.4, 9.7, 3.7 Hz, 1H), 1.74−1.35 (m, 8H), 1.31−1.10 (m, 2H), 0.89 (t, J = 7.7 Hz, 3H), 0.82 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.3, 136.5, 129.2, 85.2, 66.9, 55.1, 45.5, 41.2, 34.3, 33.8, 25.8, 25.1, 22.4, 22.1, 18.3, 13.7; HRMS m/z calcd for $C_{16}H_{26}O_2$ (M^+) 250.1933, found 250.1938.

Data for 4c: IR (film) 1777 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.58 (dt, J = 15.5, 6.5 Hz, 1H), 5.19 (ddt , J = 15.5, 9.0, 1.5 Hz, 1H), 3.18 (t, J = 9.0 Hz, 1H), 3.14 (s, 3H), 2.97−2.85 (m, 2H), 2.08−2.03 (m, 2H), 1.96 (m, 1H), 1.78 (ddd, J = 12.5, 10.0, 3.5 Hz, 1H), 1.70 (m, 1H), 1.67−1.61 (m, 2H), 1.60−1.55 (m, 2H), 1.47 (m, 1H), 1.42−1.11 (m, 7H), 0.93−0.78 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.4, 136.8, 129.1, 85.2, 66.9, 55.1, 45.5, 41.2, 33.8, 32.1, 31.3, 28.9, 25.8, 25.1, 22.4, 22.0, 18.3, 14.0; HRMS m/z calcd for $C_{18}H_{30}O_2$ (M^+) 278.2246, found 278.2247.

Data for 4e: IR (film) 1779 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.82 (d, J = 18.5 Hz, 1H), 5.74 (dd, J = 18.5, 7.5 Hz, 1H), 3.20 (dd, J = 9.5, 7.5 Hz, 1H), 3.15 (s, 3H), 2.97−2.86 (m, 2H), 1.97 (m, 1H), 1.80 (ddd, J = 13.0, 10.0, 3.5 Hz, 1H), 1.71 (ddd, J = 13.0, 5.0, 3.0 Hz, 2H), 1.67−1.56 (m, 2H), 1.56−1.43 (m, 2H), 1.30−1.12 (m, 2H), 0.85 (m, 1H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.3, 144.7, 136.4, 87.9, 66.8, 55.6, 45.0, 41.2, 33.8, 25.6, 25.1, 22.0, 18.3, −1.3; HRMS m/z calcd for $C_{16}H_{28}O_2$-Si (M^+) 280.1859, found 280.1863.

Data for 5A: IR (film) 1774 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 3.44 (dd, J = 8.1, 7.3 Hz, 2H), 3.28 (s, 3H), 3.18 (dt, J = 9.0, 4.0 Hz, 1H), 2.87−3.01 (m, 2H), 2.26 (m, 1H), 2.07 (m, 1H), 1.85−1.99 (m, 2H), 1.59−1.73 (m, 5H), 1.47 (m, 1H), 1.26 (m, 2H), 0.97 (m, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 215.0, 81.3, 67.1, 56.5, 44.3, 41.5, 34.3, 34.2, 28.8, 26.3, 25.4, 22.0, 18.6.

Data for 5B: IR (film) 1766 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 3.44−3.57 (m, 3H), 3.33 (s, 3H), 2.91 (t, J = 8.4 Hz, 2H), 2.25 (dt, J = 11.0, 8.4 Hz, 1H), 1.74−1.82 (m, 2 H), 1.48−1.68 (m, 9H), 1.22 (m, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 215.2, 80.2, 67.1, 58.2, 46.3, 41.6, 36.1, 35.8, 31.1, 25.9, 25.7, 23.3, 23.1.

Data for 5C (third isomer; structure not shown in Scheme 2): IR (film) 1770 cm^{-1}; ^1H NMR ^1H NMR (500 MHz, $CDCl_3$) δ 3.35−3.46 (m, 2H), 3.32 (s, 3H), 3.28 (td, J = 6.8, 3.2 Hz, 1H), 3.00 (ddd, J = 18.4, 10.0 Hz, 6.8 Hz, 1H), 2.90 (ddd, J = 18.4, 10.0, 6.4 Hz, 1H), 2.34 (m, 1H), 2.08 (m, 1H), 1.97 (m, 1H), 1.68−

(20) Treatment of **14** and **15** with guanidine furnished the identical *erythro*-(*E*)-epoxide, which was also secured by acidic hydrolysis of **17** and subsequent epoxide formation. On the other hand, the *threo*-(*E*)-epoxide was obtained from **16**. Additionally, iodohydrin formation gave **18** as the major product, along with a mixture of the two (*E*)-epoxides.

1.77 (m, 4H), 1.60−1.68 (m, 2H), 1.48 (m, 1H), 1.34 (m, 1H), 1.15−1.30 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.5, 80.8, 69.1, 57.8, 43.2, 42.2, 35.6, 34.6, 30.1, 25.6, 23.0, 22.0, 19.9.

Data for 10a: IR (film) 1778 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20−7.24 (m, 3H), 7.10−7.14 (m, 3H), 6.95−7.02 (m, 4H), 5.16−5.27 (m, 2H), 4.72 (d, J = 8.0 Hz, 1H), 4.70 (br s, 1H, -O*H*), 4.41 (d, J = 8.0 Hz, 1H), 3.38 (t, J = 9.5 Hz, 1H), 3.23 (ddd, J = 18.0, 10.0, 5.0 Hz, 1H), 3.15 (ddd, J = 18.0, 10.0, 7.5 Hz, 1H), 2.01 (m, 1H), 1.88 (ddd, J = 12.6, 9.5, 3.7 Hz, 1H), 1.77 (m, 1H), 1.58−1.70 (m, 3H), 1.68 (d, J = 5.2 Hz, 3H). 1.44−1.54 (m, 2H), 1.28 (m, 1H), 1.16 (m, 1H), 0.73 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 218.3, 139.5, 137.2, 132.5, 130.3, 128.2, 128.1, 127.9, 127.7, 127.3, 127.1, 83.3, 79.6, 77.9, 66.9, 45.4, 41.9, 33.9, 25.9, 25.0, 22.0, 18.1, 17.7.

Data for 10b: IR (film) 1769 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18−7.22 (m, 3H), 7.10−7.16 (m, 3H), 6.95−7.04 (m, 4H), 5.12−5.27 (m, 2H), 4.71 (d, J = 8.5 Hz, 1H), 4.45 (d, J = 8.5 Hz, 1H), 3.39 (dd, J = 9.3, 8.5 Hz, 1H), 3.24 (ddd, J = 18.0, 9.7, 4.9 Hz, 1H), 3.15 (ddd, J = 18.0, 9.7, 7.7 Hz, 1H), 1.98−2.03 (m, 2H), 1.89 (m, 1H), 1.76 (m, 1H), 1.58−1.72 (m, 3H), 1.42−1.57 (m, 2H), 1.10−1.40 (m, 10H), 0.88 (t, J = 7.3 Hz, 3H), 0.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.1, 139.5, 137.9, 137.1, 128.9, 128.2, 128.0, 127.8, 127.6, 127.2, 127.1, 83.2, 79.6, 77.9, 67.0, 45.5, 42.0, 33.9, 32.2, 31.4, 28.8, 25.7, 25.1, 22.5, 22.1, 18.2, 14.1.

Data for 10c: IR (film) 3565, 1778 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20−7.24 (m, 3H), 7.05−7.12 (m, 3H), 6.98−7.12 (m, 2H), 6.94−6.97 (m, 2H), 5.71 (dd, J = 18.7, 8.1 Hz, 1H), 5.50 (d, J = 18.7 Hz, 1H), 4.72 (d, J = 8.1 Hz, 1H), 4.38 (d, J = 8.1 Hz, 1H), 3.57 (dd, J = 9.6, 9.1 Hz, 1H), 3.22 (dd, J = 17.7, 9.6, 5.1 Hz, 1H), 3.15 (ddd, J = 17.7, 9.6, 7.1 Hz, 1H), 1.99 (m, 1H), 1.92 (ddd, J = 13.0, 9.6, 3.5 Hz, 1H), 1.78 (m, 1H), 1.55−1.70 (m, 4H), 1.51 (m, 1H), 1.42 (m, 1H), 1.29 (m, 1H), 1.17 (m, 1H), 0.75 (m, 1H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 218.3, 144.4, 139.7, 138.3, 137.0, 128.3, 128.1, 128.0, 127.8, 127.4, 127.0, 83.5, 82.3, 77.9, 66.9, 44.7, 42.0, 33.9, 25.4, 25.0, 22.0, 18.2, −1.4.

Data for 13a: IR (film) 1771 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63 (dq, J = 15.4, 6.5 Hz, 1H), 5.22 (ddq, J = 15.4, 8.5, 1.6 Hz, 1H), 3.32 (dd, J = 10.1, 8.5 Hz, 1H), 3.15 (s, 3H), 2.93 (t, J = 8.3 Hz, 2H), 2.14−2.30 (m, 2H), 1.98 (m, 1H), 1.55−1.84 (m, 5H), 1.71 (dd, J = 6.5, 1.6 Hz, 3H), 1.19 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.3, 130.5, 129.8, 84.3, 71.9, 55.2, 50.3, 42.9, 37.7, 28.1, 23.2, 21.1, 17.7; HRMS *m*/*z* calcd for $C_{12}H_{17}O_2$ (M^+−Me) 193.1229, found 193.1233.

Data for 13b: IR (film) 1778 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61 (dt, J = 15.4, 6.9 Hz, 1H), 5.20 (ddt, J = 15.4, 8.5, 1.6 Hz, 1H), 3.34 (dd, J = 10.1, 8.5 Hz, 1H), 3.17 (s, 3H), 2.95 (t, J = 8.3 Hz, 2H), 2.14−2.32 (m, 2H), 1.93−2.04 (m, 2H), 1.80 (m, 1H), 1.55−1.68 (m, 3H), 1.35−1.45 (m, 2H), 1.18 (m, 1H), 0.89 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.3, 135.2, 129.4, 84.4, 72.0, 55.3, 50.4, 42.9, 37.8, 34.3, 28.2, 23.2, 22.4, 21.2, 13.6; HRMS *m*/*z* calcd for $C_{15}H_{24}O_2$ (M^+) 236.1776, found 236.1779.

Data for 13c: IR (film) 1778 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61 (dt, J = 15.4, 6.9 Hz, 1H), 5.20 (ddt, J = 15.4, 8.5, 1.6 Hz, 1H), 3.33 (dd, J = 10.1, 8.5 Hz, 1H), 3.18 (s, 3H), 2.94 (t, J = 8.3 Hz, 2H), 2.06−2.32 (m, 2H), 1.94−2.04 (m, 3H), 1.81 (m, 1H), 1.56−1.68 (m, 4H), 1.05−1.23 (m, 7H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.3, 135.5, 129.2, 84.4, 72.0, 55.3, 50.4, 42.9, 37.8, 32.2, 31.3, 28.9, 28.2, 23.2, 25.5, 21.8, 14.1; HRMS *m*/*z* calcd for $C_{17}H_{28}O_2$ (M^+) 264.2089, found 264.2096.

Preparation of 14 and 15. A mixture of cyclobutanone **4a** (178 mg, 0.8 mmol), $Hg(OAc)_2$ (318.7 mg, 1.0 mmol), and iodine (254 mg, 1.0 mmol) in acetic acid (4.0 mL) was stirred at room temperature for 4 h. The solvent was evaporated under reduced pressure. The residue was dissolved in ether, washed with brine and an aqueous sodium bicarbonate solution, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by preparative TLC to afford **14** (209.3 mg, 64%) and **15** (84.1 mg, 26%).

Data for 14: IR (film) 1776, 1739 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.17 (dq, J = 9.7, 6.1 Hz, 1H), 4.13 (dd, J = 9.7, 1.2 Hz, 1H), 3.36 (s, 3H), 2.98 (ddd, J = 17.8, 9.7, 6.9 Hz, 1H), 2.85 (ddd, J = 17.8, 9.7, 4.9 Hz, 1H), 2.55 (dd, J = 9.3, 1.2 Hz, 1H), 2.10 (s, 3H), 1.99 (ddd, J = 12.2, 9.3, 3.4 Hz, 1H), 1.89 (dddd, J = 11.4, 9.7, 6.9, 1.6 Hz, 1H), 1.60−1.80 (m, 6H), 1.52 (d, J = 6.1 Hz, 3H), 1.20−1.40 (m, 2H), 1.12 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.2, 169.4, 80.5, 72.6, 66.5, 59.2, 46.8, 43.1, 41.1, 33.8, 27.6, 24.9, 22.0, 21.9, 21.3, 19.4.

Data for 15: IR (film) 1776, 1743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.37 (dd, J = 4.9, 1.8 Hz, 1H), 4.48 (qd, J = 6.9, 4.9 Hz, 1H), 3.38 (s, 3H), 3.34 (dd, J = 9.3, 1.8 Hz, 1H), 2.94 (ddd, J = 17.0, 9.7, 6.9 Hz, 1H), 2.81 (ddd, J = 17.0, 9.7, 5.3 Hz, 1H), 2.18 (s, 3H), 2.03 (m, 1H), 1.99 (d, J = 6.9 Hz, 3H), 1.85−1.58 (m, 7H), 1.08−1.36 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.6, 170.0, 84.8, 78.7, 66.6, 59.1, 43.6, 41.0, 33.9, 27.8, 25.1, 24.6, 23.5, 21.7, 21.0, 18.9.

Data for 16: IR (film) 2934, 2859 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.54 (hept, J = 6.1 Hz, 1H), 4.43 (dq, J = 10.1, 6.9 Hz, 1H), 3.80 (dd, J = 2.5, 0.8 Hz, 1H), 3.68 (dd, J = 10.1, 0.8 Hz, 1H), 3.59 (s, 3H), 2.14−2.28 (m, 2H), 2.04 (d, J = 6.9 Hz, 3H), 1.96 (m, 1H), 1.60−1.80 (m, 4H), 1.40−1.53 (m, 5H), 1.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 103.3, 78.9, 78.3, 68.9 (q, J = 32.8 Hz), 68.6 (q, J = 32.8 Hz), 62.0, 47.2, 43.6, 32.0, 31.0, 26.3, 26.2, 25.5, 24.4, 22.2, 21.3 (2C).

Data for 17: IR (film) 2934, 2859 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 (hept, J = 6.1 Hz, 1H), 4.26−4.34 (m, 2H), 3.80 (br s, 1H), 3.43 (s, 3H), 2.72 (m, 1H), 2.22 (m, 1H), 2.05 (dd, J = 12.6, 2.4 Hz, 1H), 1.95 (ddd, J = 13.0, 10.1, 3.7 Hz, 1H), 1.52−1.78 (m, 5H), 1.43 (d, J = 6.5 Hz, 3H), 1.34−1.48 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.3, 94.7, 94.5, 73.4, 69.7 (q, J = 33 Hz), 69.3 (q, J = 33 Hz), 59.3, 53.9, 39.5, 39.3, 34.3, 30.9, 29.3, 26.4, 21.6, 21.4, 19.5.

Data for 18: IR (film) 3434, 1764 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (dq, J = 9.3, 6.5 Hz, 1H), 4.01 (dd, J = 9.3, 1.8 Hz, 1H), 3.48 (s, 3H), 3.03 (dd, J = 9.3, 1.8 Hz, 1H), 2.84−3.00 (m, 2H), 2.06 (ddd, J = 11.8, 9.3, 3.2 Hz, 1H), 1.98 (m, 1H), 1.47−1.78 (m, 7H), 1.54 (d, J = 6.5 Hz, 3H), 1.18−1.38 (m, 2H), 1.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.0, 80.3, 70.0, 66.8, 58.8, 46.8, 46.5, 41.1, 33.9, 27.8, 25.0, 25.0, 21.9, 19.5.

Representative Procedure for Free Radical Cyclization. A solution of **15** (20 mg, 0.049 mmol) in benzene (5.0 mL) was heated at reflux under an argon atmosphere. A solution of *n*-Bu_3SnH (30 mg, 0.1 mmol) and AIBN (1.6 mg, 0.01 mmol) in benzene (1.0 mL) was added over 6 h. The solvent was evaporated under reduced pressure, and the residue was treated with Et_3N•3HF complex (0.5 mL) in ether (3.0 mL). The resulting mixture was stirred for 1 h at room temperature and passed through a pad of SiO_2. The filtrate was concentrated under reduced pressure. The crude product was purified by SiO_2 (1.0 g) column chromatography using 10:1 hexanes−ethyl acetate as the eluent to give **19** (11.3 mg, 82%) as a 4.4:1 mixture of diastereomers. Data for the major diastereomer: IR (film) 1740, 1702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.08 (dd, J = 5.0, 2.8 Hz, 1H), 3.41 (dq, J = 6.5, 5.0 Hz, 1H), 3.35 (s, 3H), 3.24 (d, J = 2.8 Hz, 1H), 2.72 (m, 1H), 2.30 (ddd, J = 19.1, 6.5, 3.2 Hz, 1H), 2.12 (s, 3H), 1.55−1.80 (m, 7H), 1.05−1.22 (m, 5H), 1.01 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.2, 170.5, 87.8, 79.6, 61.0, 44.7, 42.9, 38.5, 36.4, 36.0, 34.0, 26.6, 26.2, 21.1, 12.5 (there is an overlap corresponding to 2C); HRMS *m*/*z* calcd for $C_{16}H_{26}O_4$ (M^+) 282.1831, found 282.1838.

Data for 21 (higher R_f, *trans*-ring junction isomer): IR (film) 3435, 1693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97 (apparent quintet, J = 6.1 Hz, 1H), 3.64 (d, J = 6.1 Hz, 1H), 3.40 (s, 3H), 3.30 (d, J = 4.5 Hz, 1H), 2.79 (dd, J = 6.1, 4.5 Hz, 1H), 2.73 (ddd, J = 15.0, 10.1, 2.8 Hz, 1H), 2.39 (ddd, J = 15.0, 10.1, 2.8 Hz, 1H), 1.95 (m, 1H), 1.45−1.56 (m, 6H), 1.03−1.40 (m, 3H), 1.27 (d, J = 6.5 Hz, 3H), 0.96−1.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.5, 84.0, 67.7, 60.7, 59.1, 45.5, 41.8, 37.1, 34.5, 32.9, 30.9, 26.5, 26.1, 21.7.

Data for 21 (lower R_f, *cis*-ring junction isomer): IR (film) 3454, 1697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.22 (qd, J = 6.5, 2.4 Hz, 1H), 3.79 (dd, J = 10.9, 2.4 Hz, 1H), 3.42 (s, 3H), 2.57 (ddd, J = 12.2, 12.2, 2.8 Hz, 1H), 2.46 (dd, J = 10.9, 2.4 Hz, 1H), 2.40 (d, J = 6.5 Hz, 1H), 2.34 (ddd, J = 12.2, 6.5, 2.0 Hz, 1H), 2.12 (ddd, J = 12.6, 6.5, 2.8 Hz, 1H), 1.74−2.00 (m, 3H), 1.50−1.65 (m, 5H), 1.20−1.50 (m, 2H), 1.25 (d, J = 6.5 Hz, 3H), 1.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.3, 82.3, 68.2, 60.5, 57.4, 43.6, 42.6, 38.5, 33.6, 26.8, 26.6, 21.6, 21.2, 20.7.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of key intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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