Free-Radical Macrocyclization–Transannular Cyclization[1]

Ned A. Porter,* Vincent H.-T. Chang, David R. Magnin, and Bruce T. Wright

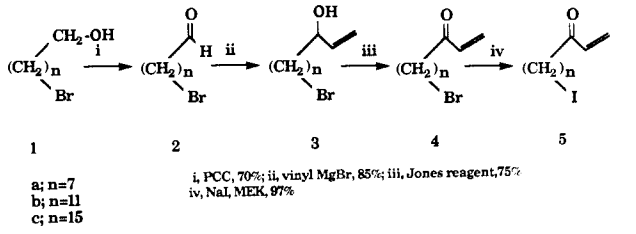
Contribution from the Department of Chemistry, Paul M. Gross Chemical Laboratories, Duke University, Durham, North Carolina 27706. *Received December 7, 1987*

Abstract: Intramolecular free-radical addition to olefins substituted with electron-withdrawing groups has been studied. The free radicals are generated from the corresponding iodides by reaction with tributyltin hydride or tributyltin chloride/sodium cyanoborohydride. Macrocyclic compounds of 12–20 members are generated by this procedure in good yield, while endocyclization is favored, exocyclization can be forced if 1,1-dicyano-substituted olefins are used. Macrocyclization–transannular cyclization sequences are possible if the transannular cyclization is 5-exo. Fused bicyclic [9.3.0] systems have been prepared, and other [*n*.3.0] systems should be available by this approach. Two-step cyclization sequences have also been investigated. The macrocycle is generated in one free-radical-mediated step, and the transannular cyclization is then achieved in a second free-radical reaction. Rates of transannular 5-exocyclizations in 14-membered rings are $\sim 10^4$ s^{-1}.

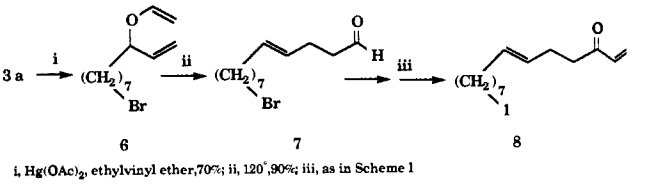
The construction of five- and six-membered rings by free-radical methods has received much attention. Methods utilized for free-radical generation are usually tin hydride mediated, and halides, selenides, and sulfur-containing compounds have been used as radical precursors in most studies.[2] Five-membered rings are readily prepared by this approach and the 5-exocyclization mode is generally favored,[3] with even carbon radical cyclization to aldehydes and ketone groups possible.[4] Six-membered rings have been prepared by this method, but the rate for 6-exo-cyclization to alkenes is significantly less than that for 5-exo-cyclization (≈80 °C, $k_{5\text{-exo}} = 1.4 \times 10^6$ s^{-1}, $k_{6\text{-exo}} = 4.4 \times 10^4$ s^{-1}).[3b] In addition, sequential radical cyclizations have been used to construct multiple rings in one step,[5] and guidelines for understanding the stereochemical influence of ring substituents have been published.[3c] Also, intermolecular radical additions have been used in recent synthetic efforts, and a number of natural products have been prepared by radical addition to electron-deficient olefins.[6]

We have questioned the dogma that only five- and six-membered rings can be readily prepared by free-radical cyclization. Rings larger than six members had not been previously constructed by radical cyclization, but activation of the alkene as an acrylate ester allowed preparation of larger rings (e.g., 12–20 members) in yields as high as 80%.[7] These larger rings could also be prepared by intramolecular carbon radical addition to α,β-unsaturated ketones.[1] We report here macrocyclization studies using several new substrates designed to define the scope of radical

Scheme I



Scheme II



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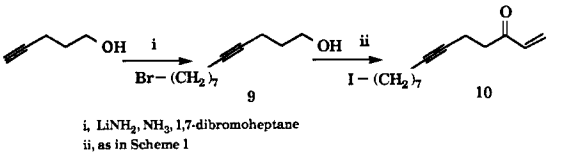
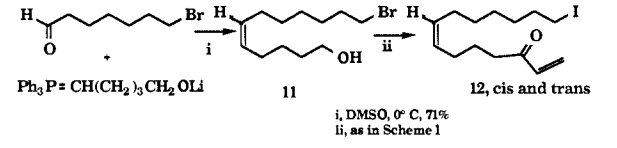
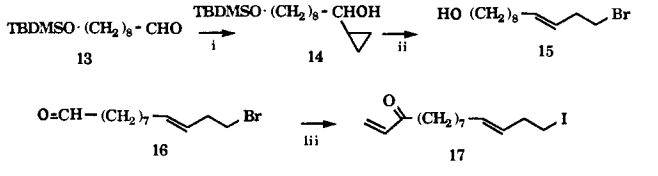


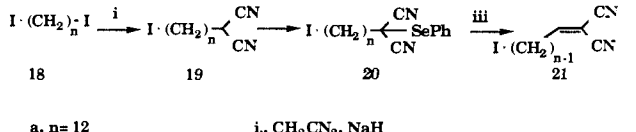
Scheme IV



Scheme V



Scheme VI



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(2) (a) Stork, G.; Mook, R., Jr. *Tetrahedron Lett.* **1986**, *27*, 4529. (b) Hart, D. J. *Science (Washington, D.C.)* **1984**, *223*, 883. (c) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901. (d) Barton, D. H. R.; Crich, D. *Tetrahedron Lett.* **1985**, *26*, 757. (e) Barton, D. H. R.; Crich, D.; Kretzschmar, G. *J. Chem. Soc., Perkin Trans 1* **1986**, 39. (f) Curran, D. P.; Rakeiwicz, D. M. *Tetrahedron* **1985**, *41*, 3943. (g) Newcomb, M.; Park, S. U. *J. Am. Chem. Soc.* **1986**, *108*, 4132. (h) Bhandal, H.; Pattenden, G.; Russell, J. J. *Tetrahedron Lett.* **1986**, *27*, 2299. (i) Giese, B.; Bartmann, D.; Habkerl, T. *Liebigs Ann. Chem.* **1987**, 427.

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(5) (a) Curran, D. P.; Kuo, S.-C. *J. Am. Chem. Soc.* **1986**, *108*, 1106. (b) Beckwith, A. L. J.; Roberts, D. H.; Schiesser, C. H.; Wallner, A. *Tetrahedron Lett.* **1985**, *26*, 3349. (c) Beckwith, A. L. J.; Roberts, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 5893.

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(7) Porter, N. A.; Chang, V. H.-T. *J. Am. Chem. Soc.* **1987**, *109*, 4976.

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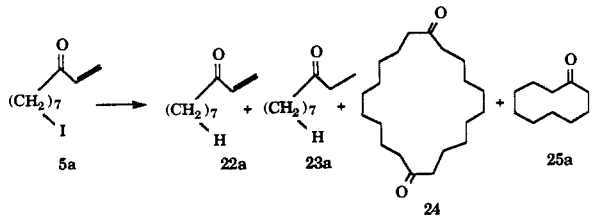
Scheme VII



macrocyclization and macrocyclization–serial cyclization sequences.

Results

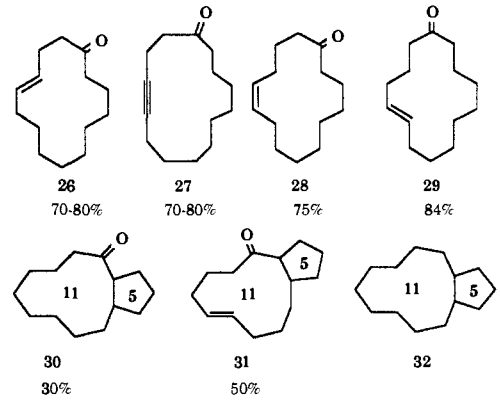
A. Iodoalkene Preparation. The method outlined in Scheme I was used to prepare the requisite iodoalkene precursors for macrocyclization to give simple cyclic ketones. Yields for most conversions in the scheme were high, and gram quantities of the iodoalkenes **5a–c** were readily obtained. The synthesis of eight unsaturated iodo compounds used in these macrocyclization studies is outlined in Schemes II–VI. The preparation strategy for substrates **8**, **10**, **12**, and **15** involves construction of the appropriate α,ω-bromo alcohol and conversion of that compound to the corresponding iodo α,β-unsaturated target by procedures analogous to those shown in Scheme I. For construction of the skeleton **8**, the key step is the Claisen rearrangement of vinyl ether **6**. For synthesis of the alkyne **10**, acetylenic coupling of 4-pentynol with 1,7-dibromoheptane gives the basic carbon framework, while Wittig coupling of 7-bromoheptanal gives the bromo alcohol **11** as a mixture of cis and trans isomers, with the cis compound predominating.

Synthesis of the homoallyl iodide **17** involves a cyclopropylcarbinyl–homoallyl rearrangement, providing **15** from **14**. This bromo alcohol is then converted to the target by standard conversions. Yields for most of the conversions outlined in Schemes II–VI are good to excellent, a notable exception being the acetylenic coupling leading to the alkyne **9**, which proceeds in 30–35% yield. The malonitriles **21a–c** were prepared by alkylation of malonitrile with the corresponding diiodide, followed by α-selenation with phenylselenyl chloride,[9] and finally elimination of the selenide by peroxide.[10] Yields of the alkylation products **19** were moderate (40–50%) due to bisalkylation of the diiodide.

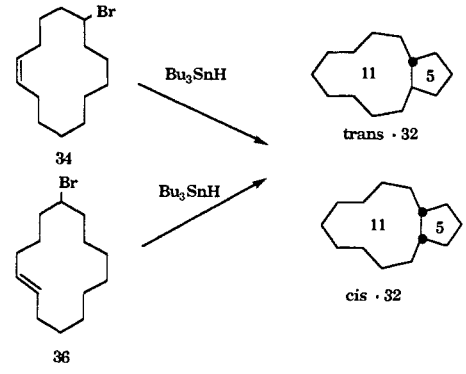
B. Macrocyclization and Product Identification. Two procedures proved useful for macrocyclization. The first is the standard tin hydride procedure utilizing 1.1 equiv of Bu_3SnH and 0.1 equiv of the free-radical initiator azobis(isobutyronitrile) (AIBN) in refluxing dry benzene for 3 h. Most of the macrocyclizations were carried out at concentrations of 2–10 mM. The second procedure utilizes Bu_3SnCl, $NaBH_3CN$, and AIBN in *tert*-butyl alcohol at reflux,[11,12] also for 3 h. We found the best concentrations for macrocyclization using the second procedure to be ~5 mM iodoalkene, 0.5 mM tin chloride, and 10 mM cyanoborohydride with 0.1 equiv of AIBN.

The simple iodoalkenes **5a–c** gave cyclic ketones in yields ranging from 15% (**5a**) to 55–65% (**5b,c**). Purification of the macrocyclic product generally was best achieved by medium-pressure chromatography on a Rainin Dynamax column. Products formed in the tin hydride reaction include the macrocyclic ketone **25**, the acyclic reduction product $CH_3(CH_2)_nCOCH{=}CH_2$ **22**, and occasionally the ethyl ketone $CH_3(CH_2)_nCOCH_2CH_3$ **23**. For reactions of the 10-carbon substrate **5a**, a compound with spectroscopic and analytical data expected from **24** was isolated by medium-pressure liquid chromatography. This material (Scheme VII), apparently resulting from intermolecular addition followed by macrocyclization, was isolated in ~5% yield. We have not isolated analogous dimers in any other systems investigated.

Chart I



Scheme VIII



The reaction utilizing Bu_3SnCl and cyanoborohydride proceeds at a lower yield than the tin hydride conversions (35–45% for **5b**), but this procedure has the advantage that byproducts **22** and **23** are formed to a lesser extent and purification of the macrocycle to >95% can be achieved by flash chromatography.

Macrocyclization products of iodides **8**, **10**, **12**, and **17** are shown in Chart I. They include **26** (from **8**), **27** (from **10**), **28** (from *cis*-12), and **29** (from *trans*-**12**). Compound **17** serves as a precursor to **30**, and an unsaturated compound analogous to **17**, but with a trans double bond at the $\delta_{7,8}$-position from the iodide gives **31**. The bicyclic compounds **30** and **31** are formed as mixtures of cis and trans ring-fused diastereomers. The less stable cis ring fusion is favored kinetically for both substrates by a factor of 2–2.5/1 cis/trans. The thermodynamically more stable trans-fused compounds are obtained by base-catalyzed epimerization of the mixture.[13] Both **30** and **31** give equilibrium mixtures favoring the trans compound by >98/2.[14]

The structures of cycles **26–31** are supported by carbon and hydrogen analysis, ^1H and ^{13}C NMR, and in some cases mass spectrometry. Simple macrocycles, **25a–c**, were compared to authentic materials chromatographically and spectroscopically. The bicyclic compound **30** was converted to **32** by reduction of the ketone to the alcohol, conversion of the alcohol to the methylxanthate, and reaction with Bu_3SnH.[15] Both *cis*- and *trans*-**30** could be converted to the corresponding cis or trans hydrocarbon by this procedure, while Wolff–Kishner reduction of either the cis or trans ketone **30** gave only the trans ring-fused compound **32**. Both *cis*- and *trans*-**32** gave eight ^{13}C signals in the NMR, consistent with molecular symmetry. For the trans isomer **32**, the NMR was acquired at 60 °C. At lower temperatures, splitting

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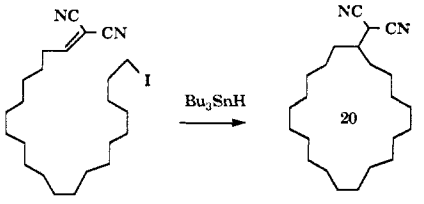
(14) A molecular mechanics calculation on over 400 conformations of *cis*- and *trans*-**30** generated by Still's Ringmaker program indicated that the trans isomer was more stable than the cis.
(15) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

Table I. Product Distribution from Reaction of Bromoalkenes **34** and **36** with Bu_3SnH in Benzene at 80 °C

bromide	concn,[a] M	*cis*-**32**/*trans*-**32**[b]	yield of **32**[b] (cis + trans), %
34	0.025	1.9	49
	0.015	2.4	55
	0.010	1.6	67
36	0.025	0.66	78
	0.014	0.63	81

[a] Concentration of bromide, in hydride = 1.1 equiv. [b] GC analysis of product mixture.

Scheme IX



21c 37c

of some ^{13}C signals was observed, indicating slow conformational interconversions at or near room temperature for this geometric isomer.

C. Two-Step Bicyclization. Substrate **28** proved to be a useful precursor to the bromide **34**. Thus, reduction of **28** with $NaBH_4$ gave the corresponding alcohol **33** in 91% yield, and **33** was converted to the bromide **34** in 83% yield with 2-chloro-3-ethylbenzoxazolium tetrafluoroborate and tetraethylammonium bromide at −78 °C.[16] Similarly, the *trans*-alkene macrocyclic ketone **29** could be converted to the *trans*-bromoalkene **36**. The bromides **34** and **36** then were reacted under standard tin hydride conditions, giving the bicyclo[9.3.0]tetradecanes *cis*- and *trans*-**32** (Scheme VIII). Product accountability in the tin hydride reduction was 85–90%. In addition to *cis*- and *trans*-**32**, *cis*-cyclotetradecene is a product in the reduction of **34**, and *trans*-cyclotetradecene is formed in the reduction of **36**. The data from the reactions of **34** and **36** with Bu_3SnH are presented in Table I.

D. Exocyclization. Several substrates with structures I-$(CH_2)_nCH{=}CXY$ were prepared to explore the potential for exomacrocyclization. The synthesis of **21**, where X = Y = CN, is outlined in Scheme VI. Other substrates prepared were X = H, Y = COOEt; X = COOEt, Y = CN; X = Y = COOEt; X = H, Y = NO_2; X = COOEt, Y = SO_2Ph; and CXY = methylene Meldrum's ester. Of these, only **21** gave significant amounts of macrocyclic product on reaction with Bu_3SnH. This is illustrated by the conversion of **21c** (Scheme IX). The isolated yield of macrocycle **37c** is 50%, **37b** is 35%, and **37a** is <5%. The major products isolated from reaction of substrates with X = H, Y = COOEt; X = COOMe, Y = SO_2Ph; and X = Y = COOEt were $H(CH_2)_nCH{=}CXY$, the simple acyclic reduction products. The major products isolated from reaction of substrates with X = H, Y = NO_2 and CXY = methylene Meldrum's ester were uncharacterized products in which Bu_3Sn apparently reacted with the olefinic site, the primary iodide remaining intact.

Discussion

The mechanism of Bu_3SnH-mediated reactions of alkyl halides has been thoroughly studied, and this sequence is currently a popular and successful method for generating carbon radicals. We have previously discussed mechanistic details of radical macrocyclization with iodoacrylate substrates,[7] and these discussions can serve as a mechanistic framework for the experiments reported here. Tin and carbon radicals carry the chain, and the intramolecular addition proceeds with minimal intermolecular competition at concentrations up to 10 mM. Iodides are preferred to bromides, and secondary and tertiary iodides appear to propagate more efficiently than primary substrates. There is no indication that any of the macrocyclizations occur by an atom-transfer sequence.[17]

Carbon radicals are nucleophilic, and electron-accepting groups on the alkene undergoing radical addition promote the addition by polar effects:[3e,18] carbon radicals (e.g., cyclohexyl) add to acrylate esters over 10^3 times faster than addition to propene ($k_{rel_{styrene}}$ = 1.0, $k_{rel_{ethyl\ acrylate}}$ = 6.7, $k_{rel_{propene}}$ = 0.004). Other olefin substituents promoting the addition of carbon radicals are ketone (k_{rel} = 13), aldehyde (k_{rel} = 34), amide, nitrile (k_{rel} = 24), and sulfonyl groups. Steric effects are also critical in determining the ease of carbon radical addition to alkenes, and substitution at the olefin site of radical attack reduces the rate of addition.[3e,18] Thus, substitution of a methyl group on the β-position of an acrylate ester reduces the rate of addition by nearly 100-fold.

Much of the free-radical chemistry described here for iodides **5**, **8**, **10**, **12**, **17**, and **21** can be understood by polar and steric effect criteria for intermolecular radical addition (vide supra). Intramolecular radical addition to unactivated alkenes does not occur for rings larger than six members, while substitution of electron-withdrawing groups on the terminal alkene in the compounds reported here makes the reaction synthetically useful for saturated rings greater than ~10 members. Thus, polar effects activate the terminal alkene for radical addition and promote macrocyclization. Yields of macrocyclic ketones formed by endocyclization are good to excellent, and introduction of unsaturation in the tether between the radical and target olefin appears to facilitate cyclization. This is true for other macrocyclization methods,[19] and it seems likely that the formation of 7- to 10-membered rings will be possible if unsaturation is built into the tether joining radical and alkene.

The rate of radical macrocyclization giving products **26–29** has been reported to be (1–5) × 10^4 s^{-1} at 80 °C.[7] Reaction rates of this magnitude suggest that macrocyclization should be competitive with 6-exocyclization, and we have confirmed this by studying compound **38**. Reaction of **38** under standard cyclization conditions gives a mixture of products, including the monocycles **39** and **40**. The ratio of **39**/**40** is ~2.4/1.0. Some acyclic reduction product is also observed at concentrations from 5 to 30 mM. Product accountability generally is no more than 55% for this substrate, even though repeated attempts were made. For reference, the rate of 6-exocyclization was measured for the model iodide **41** at 80 °C in benzene by standard competition methods (Chart II). For the radical derived from **41**, the rate of cyclization was 3.4 × 10^4 s^{-1}. This, coupled with the internal competition observed between formation of **39** and **40**, allows an independent estimate of the rate of macrocyclization for the radical derived from **38** (8.2 × 10^4 s^{-1}).

Polar and steric effects also provide a basis for understanding the regiochemistry of cyclization for iodides **5**, **8**, **10**, **12**, **17**, and **21** as well as the difficulties encountered in forcing exocyclizations in other substrates, like **21**. Radical addition to alkenes occurs preferentially at the less substituted end, and each terminal alkene studied underwent exclusive endocyclization. Both ends of alkenes for iodides **21a–c** are substituted, and exocyclization must be forced by double activation with two cyano groups, thus overcoming the fact that radical addition must occur on a substituted alkene. Interestingly, there is apparently an increase in ease of cyclization in the series **21a** → **21b** → **21c**. The endocyclization substrates **5b** (14-membered rings) and **5c** (18-membered rings) cyclize with comparable efficiencies, while in the exocyclization series enlarging the rings from 16 to 20 members improves the efficacy of cyclization. This suggests that exocyclization is sterically more demanding than endocyclization and larger rings are required for

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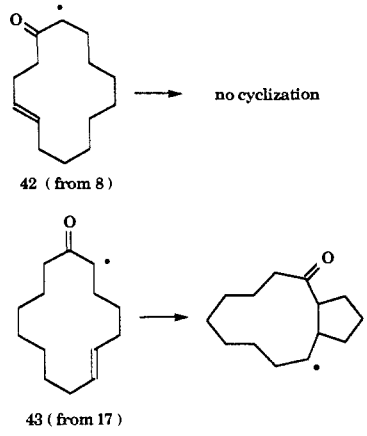
Scheme X



access to the correct exocyclic transition-state geometry. This is supported by our earlier report that competition of endo- and exocyclization is comparable for fumarate esters with rings of more than ~20 members.[7] The need to activate an alkene for successful cyclization is sensitive to the tin hydride methodology. Alkene activation is undoubtedly required to allow reaction, but some activating groups (e.g., NO_2 and Meldrum's ester) promote tin radical addition to the alkene, thus diverting the desired chain sequence. A survey of other propagation sequences might provide strategies that would allow use of other activating groups to facilitate exocyclization.

The bicyclic products **30** and **31** formed from homoallylic iodides, such as **17**, present an interesting contrast to the reaction of iodides **8**, **10**, and **12**, which give only monocyclic products.

The isomeric radicals **42** and **43** (Scheme X) are formed from macrocyclization of iodides **8** and **17**. Both radicals are constructed so that a transannular 5-exocyclization may follow the macrocyclization, but only **43** gives a bicyclic product. These results suggest a stereoelectronic effect, with a transannullar cyclization giving a cyclopentanone–cycloundecane fused product being disfavored, while a cyclization giving the cycloundecanone–cyclopentane system is favored. The latter can be understood if one assumes that the α-keto radical is delocalized into the carbonyl[20] and that this delocalization prevents **42** from assuming the favored transition state for the 5-exo pathway. This seems reasonable, since the •C–CO bond has partial double-bond character that is incorporated into the five-membered ring on cyclization. On the other hand, the correct transition-state geometry for radical **43** can be attained, since the partial double bond of the •C–CO bond is incorporated into the more flexible 11-membered ring. While this explanation provides a *qualitative* framework for understanding the reactions of **42** and **43**, more *quantitative* information about reactivity and stereochemical preferences in transannular cyclization requires further molecular mechanics analysis.[21] We note, without additional comment, that cis ring fusion is preferred in the formation of both **30** and **31**.

The rate of simple 5-exocyclization is reduced for transannular reaction in 14-membered rings compared to acyclic systems. Thus, while the rate of 5-exocyclization at 80 °C in an acyclic model is 1.4×10^6 s^{-1}, the rates of cyclization for radicals derived from **34** and **36** are 5×10^4 and 1.5×10^5 s^{-1}, respectively. This decrease appears reasonable, based on the fact that cyclization in these substrates contracts a 14-membered ring to a more strained 11-membered ring.[22] Apparently, this transannular strain is expressed in the transition state for cyclization.

Experimental Section

General Procedures. All reactions involving moisture-sensitive reagents were performed under a dry argon atmosphere. Benzene and THF were distilled from sodium/benzophenone. Methylene chloride was distilled from CaH_2.

Unless otherwise indicated, NMR data were obtained in $CDCl_3$ solution. The chemical shifts are reported relative to solvent $CDCl_3$ as δ 7.24 for ^{1}H and δ 77.0 for ^{13}C, respectively. ^{1}H NMR data (200 or 300 MHz) are reported as follows: chemical shift on the δ scale (multiplicity, number of hydrogens, coupling constant(s) in hertz).

The ^{1}H and ^{13}C spectra were obtained by Varian 200 or 300 series. Elemental analysis were performed by Galbraith Laboratories, Inc. (Knoxville, TN) or Atlantic Microlab, Inc. (Atlanta, GA). Mass spectra were obtained by Oreida Research Services (New York, NY).

In general, reaction workups culminated in drying the organic phase over $MgSO_4$, filtering, and removing the solvent on a rotory evaporator under reduced pressure.

Gas chromatography was performed by an HP5830 using capillary column SP2330 and SPB-1 silica. All columns are 30 ft long. The temperature conditions were as indicated in the Experimental Section. The medium-pressure liquid chromatograph was performed by Waters pump (Model 6000A) with silica column (Dynamax, Rainin). All chemicals were purchased from commercial sources without purification, except as indicated.

The following procedure for the synthesis of cyclotetradecanone is typical of the procedures used for the C10, C14, and C18 saturated cyclic ketones. Details for synthesis of other intermediates are presented in the supplementary material.

12-Bromododecanal (2b). To a stirred suspension of PCC (1.6 g, 7.4 mmol) and dry Celite (1.6 g) in 100 mL of methylene chloride was added at room temperature a solution of 12-bromododecanol (1.2 g, 4.5 mmol) in 10 mL of methylene chloride. The resulting dark suspension was stirred at room temperature for 3 h. The reaction mixture was filtered through a pad of Florisil and the filtrate concentrated. The crude residue was purified by elution through silica gel (1/1 ethyl acetate–hexane) to provide 12-bromododecanal: 0.9 g, 75%; TLC, R_f 0.50 (1/5 ethyl acetate–hexane); IR 2950, 2860, 2730, 1730, 1465, 1260, 730 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.70 (t, 1 H, J = 1.8 Hz), 3.35 (t, 2 H, J = 6.6 Hz), 2.36 (t[d], 2 H, J = 7.0, J = 1.8 Hz), 1.80 (q, 2 H, J = 6.75 Hz), 1.55 (m, 2 H), 1.40–1.10 (m, 14 H); ^{13}C NMR ($CDCl_3$) δ 202.7, 43.8, 33.9, 32.8, 29.3, 29.2, 29.1, 28.7, 28.1, 22.0. Anal. Calcd for $C_{13}H_{27}BrN_3O$ (semicarbazone): C, 48.60; H, 8.46. Found: C, 48.86; H, 8.36.

14-Bromo-1-tetradecen-3-ol (3b). A solution of 0.9 g (3.42 mmol) of 12-bromododecanal in 35 mL of THF at −78 °C was treated with vinylmagnesium bromide (4.4 mL, 4.4 mmol) in THF added dropwise over 5 min. The solution was stirred at −78 °C for 0.5 h and quenched with saturated aqueous NH_4Cl solution. The biphasic mixture was diluted with ethyl acetate and equilibrated. The organics were dried ($MgSO_4$) and concentrated. The resulting residue was purified by elution through silica gel (1/9 ethyl acetate–hexane) to provide 0.726 g (76%) of 14-bromo-1-tetradecen-3-ol (**3b**): TLC, R_f 0.30 (1/5 ethyl acetate–hexane); IR 3350, 3075, 2925, 2850, 1420, 1250, 990, 920 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.84 (m, 1 H), 5.20 (dd, 1 H, J = 17.2, 1.4 Hz), 5.09 (dd, 1 H, J = 10.3, 1.2 Hz), 4.10 (m, 1 H), 3.38 (t, 2 H, J = 6.8 Hz), 1.8 (m, 2 H), 1.60–1.10 (m, 18 H); ^{13}C NMR δ 141.3, 114.4, 73.2, 36.9, 34.0, 32.8, 29.5, 29.4, 28.7, 28.1, 25.3. Anal. Calcd for $C_{21}H_{32}NO_2Br$ (phenyl isocyanate): C, 61.46; H, 7.85. Found: C, 61.35; H, 7.99.

14-Bromo-1-tetradecen-3-one (4b). To a stirred solution of 0.481 g (1.70 mmol) of 14-bromo-1-tetradecen-3-ol (**3b**) in 20 mL of acetone was added dropwise Jones reagent (0.80 mL, 1.3 equiv, 2.67 M). After 5 min, the oxidation was quenched with 2-propanol added dropwise until a green color persisted. The reaction mixture was diluted with H_2O (50 mL) and ether (50 mL) and the biphasic mixture equilibrated. The aqueous fraction was drawn off, and the organics were dried ($MgSO_4$) and concentrated. The residue was purified by elution through silica gel (1/9 ethyl acetate–hexane) to provide 0.44 g (93%) of 14-bromo-1-tetradecen-3-one (**4b**): TLC, R_f 0.40 (1/9 ethyl acetate–hexane); IR 3100, 2925, 2850, 1680, 1615, 1455, 1400, 1260, 1200, 1080, 990, 960 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.35 (dd, 1 H, J = 17.5, 10.2 Hz), 6.20 (d, 1 H, J = 17.5 Hz), 5.80 (d, 1 H, J = 10.2 Hz), 3.40 (t, 2 H, J = 6.9

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Hz), 2.55 (t, 2 H, J = 6.3 Hz), 1.84 (m, 2 H), 1.63 (m, 2 H), 1.45–1.17 (m, 14 H); ^{13}C NMR ($CDCl_3$) δ 200.7, 136.5, 127.5, 39.6, 33.8, 32.7, 29.3, 29.1, 28.6, 28.0, 23.9. Anal. Calcd for $C_{14}H_{25}OBr$: C, 58.13; H, 8.71. Found: C, 58.07; H, 8.61.

14-Iodo-1-tetradecen-3-one (5b). A solution of 50 mg (0.17 mmol) of 14-bromo-1-tetradecen-3-one in 5 mL of methyl ethyl ketone was treated with sodium iodide (78 mg, 0.51 mmol) and refluxed for 3 h. The reaction mixture was cooled and concentrated. The residue was purified by elution through silica gel (1/11 ethyl acetate–hexane) to provide 55 mg (96%) of 14-iodo-1-tetradecen-3-one (**5b**): TLC, R_f 0.40 (1/9 ethyl acetate–hexane); IR 3100, 2940, 2850, 1680, 1620, 1460, 1400, 1200, 1080, 990, 960 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.30 (dd, 1 H, J = 17.6, 10.2 Hz), 6.15 (d, 1 H, J = 17.6 Hz), 5.77 (d, 1 H, J = 10.2 Hz), 3.14 (t, 2 H, J = 7.0 Hz), 2.53 (t, 2 H, J = 7.2 Hz), 1.80 (m, 2 H), 1.60 (m, 2 H), 1.4–1.10 (m, 14 H); ^{13}C NMR ($CDCl_3$) δ 200.8, 136.5, 127.7, 39.5, 33.4, 30.3, 29.2, 29.1, 28.4, 23.8, 7.2.

(*E*)-12-Bromo-4-dodecenal (7). To a solution of 2.35 g (10.04 mmol) of 10-bromo-1-decen-3-ol in 200 mL of ethyl vinyl ether was added 300 mg (0.94 mmol) of mercuric acetate. The reaction mixture was stirred overnight; to ensure complete vinyl ether formation, an additional 30 mg of mercuric trifluoroacetate was added and stirring continued for 4 h. The ethyl vinyl ether was removed under reduced pressure and the residue purified by elution through silica gel with 95/5/0.5 hexane–ethyl acetate–triethylamine to provide 1.9 g (73%) of the corresponding allyl vinyl ether: TLC, R_f 0.8 (1/5 ethyl acetate–hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.30 (q, 1 H, J = 7.0 Hz), 5.72 (m, 1 H), 5.20 (d, 1 H, J = 9.8 Hz), 5.16 (s, 1 H), 4.27 (d, 1 H, J = 13.7 Hz), 4.10 (q, 1 H, J = 7.2 Hz), 3.97 (d, 1 H, J = 6.3 Hz), 3.38 (t, 2 H, J = 6.9 Hz), 1.90–1.10 (m, 12 H); ^{13}C NMR δ 150.7, 137.9, 116.5, 88.5, 80.7, 34.8, 33.8, 32.7, 29.2, 28.6, 27.9, 24.9.

Into a sealable tube were placed 1.90 g (7.27 mmol) of the vinyl ether and 50 mL of benzene. After sealing, the tube was heated to 120 °C for 24 h. The tube was cooled and opened, and the contents were reduced in volume. The crude product was eluted through a column of silica gel with 5% ethyl acetate in hexane to yield 1.70 g (89%) of the Claisen rearrangement product **7** as a colorless oil. TLC, R_f 0.35 (1/8 ethyl acetate–hexane); IR 2950, 2850, 2725, 1720, 1440, 1250, 970, 730, 640 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74 (t, 1 H, J = 1.2 Hz), 5.40 (m, 2 H), 3.40 (t, 2 H, J = 7.0 Hz), 2.45 (t, 2 H, J = 7.8 Hz), 2.30 (q, 2 H, J = 6.4 Hz), 2.0–1.60 (m, 4 H), 1.45–1.10 (m, 8 H); ^{13}C NMR δ 201.9, 131.5, 127.6, 43.2, 33.7, 32.5, 32.1, 29.0, 28.6, 28.3, 27.8, 24.9.

(*E*)-14-Bromo-1,6-tetradecadien-3-ol. A solution of 1.7 g (6.7 mmol) of (*E*)-12-bromo-4-dodecanal (**7**) in 50 mL of THF at 0 °C was treated with vinylmagnesium bromide (10 mL, 10 mmol) in THF added dropwise over 7 min. The solution was stirred at 0 °C for 0.5 h and quenched with saturated aqueous NH_4Cl solution. The biphasic mixture was diluted with ethyl acetate and equilibrated. The aqueous portion was drawn off, and the organics were dried ($MgSO_4$) and concentrated. The resulting residue was purified by elution through silica gel with 15% ethyl acetate in hexane: TLC, R_f 0.25 (1/8 ethyl acetate–hexane); IR 3350, 3075, 3000, 2925, 2850, 1640, 1430, 1250, 1030, 990, 970, 920, 720 cm^{-1}; ^{1}H NMR δ 5.85 (m, 1 H), 5.40 (m, 2 H), 5.20 (d, 1 H, J = 17.0 Hz), 5.08 (d, 1 H, J = 10.1 Hz), 4.10 (m, 1 H), 3.38 (t, 2 H, J = 6.8 Hz), 2.20–1.70 (m, 6 H), 1.60–1.10 (m, 10 H); ^{13}C NMR δ 141.0, 130.9, 129.5, 114.5, 72.6, 36.6, 33.9, 32.7, 32.4, 29.3, 28.8, 28.5, 28.4, 28.0. Anal. Calcd for $C_{14}H_{25}OBr$: C, 58.13; H, 8.71. Found: C, 57.93; H, 8.64.

(*E*)-14-Iodo-1,6-tetradecadien-3-one (8). A solution of 0.90 g (3.10 mmol) of (*E*)-14-bromo-1,6-tetradecadien-3-one in 50 mL of methyl ethyl ketone was treated with 1.41 g (9.4 mmol) of sodium iodide and refluxed for 3 h. The reaction mixture was cooled and concentrated. The resulting residue was purified by elution through silica gel with 7% ethyl acetate in hexane to provide 0.90 g (87%) of (*E*)-14-iodo-1,6-tetradecadien-3-one. TLC, R_f 0.71 (1/5 ethyl acetate–hexane; IR 3100, 3050, 2930, 2850, 1680, 1620, 1440, 1400, 1180, 1100, 970 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.30 (dd, 1 H, J = 17.5, 10.4 Hz), 6.17 (d, 1 H, J = 17.5 Hz), 5.77 (d, 1 H, J = 10.2 Hz), 5.37 (m, 2 H), 3.13 (t, 2 H, J = 7.1 Hz), 2.60 (t, 2 H, J = 7.7 Hz), 2.25 (m, 2 H), 1.90–1.70 (m, 4 H), 1.40–1.10 (m, 8 H); ^{13}C NMR δ 200.1, 136.5, 131.3, 128.3, 127.9, 39.4, 33.4, 32.0, 30.3, 29.2, 28.7, 28.2, 26.7, 7.2. Anal. Calcd for $C_{14}H_{23}OI$: C, 50.30; H, 6.93. Found: C, 50.46; H, 6.79.

12-Bromo-4-dodecynol (9). A suspension of lithium amide in ammonia was prepared by adding 200 mg (0.28 mmol) of lithium wire to a solution of ferric nitrate (small crystal) in 65 mL of ammonia. The resulting gray suspension was treated with 1.0 g (11.9 mmol) of 4-pentynol dropwise at −78 °C. After 70 min, the dianion was treated with 2.5 g (9.7 mmol) of 1,7-dibromoheptane in 8 mL of THF with the aid of a cannula. This mixture was stirred at −78 °C for 1 h and warmed to −33 °C for 0.5 h, at which time the contents were diluted with 60 mL of ether and the ammonia was allowed to boil off. The reaction mixture was slowly quenched with aqueous ammonium chloride solution and adjusted to pH 5 with acetic acid. The biphasic mixture was separated, and the organics were dried ($MgSO_4$) and concentrated. The residue was then purified by elution through silica gel with 20% ethyl acetate in hexane to yield 0.80 g (31%) of 12-bromo-4-dodecyn-1-ol: TLC, R_f 0.50 (1/3 ethyl acetate–hexane); IR 3350, 3950, 2850, 1440, 1060, 940 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.75 (q, 2 H, J = 5.8 Hz), 3.40 (t, 2 H, J = 6.7 Hz), 2.40–2.00 (m, 4 H), 1.90–1.60 (m, 4 H), 1.50–1.10 (m, 8 H); ^{13}C NMR δ 80.6, 79.3, 61.6, 33.8, 32.6, 31.5, 28.7, 28.4, 28.0, 27.8, 18.5, 15.2.

14-Iodo-1-tetradecen-6-yn-3-one (10). A solution of 0.50 g (1.71 mmol) of 14-bromo-1-tetradecen-6-yn-3-one in 15 mL of methyl ethyl ketone was treated with sodium iodide (0.77 g, 5.13 mmol) and refluxed for 3 h. The reaction mixture was cooled and concentrated. The residue was purified by elution through silica gel (1/11 ethyl acetate–hexane) to provide 0.56 g (1.67 mmol, 98%) of 14-iodo-1-tetradecen-6-yn-3-one (**10**): TLC, R_f 0.50 (1/5 ethyl acetate–hexane); IR 3100, 3050, 2940, 2860, 1680, 1620, 1400, 1360, 1190, 1100, 990, 960, 790 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.33 (dd, 1 H, J = 17.4, 10.4 Hz), 6.21 (d, 1 H, J = 17.4 Hz), 5.85 (d, 1 H, J = 10.4 Hz), 3.15 (t, 2 H, J = 7.0 Hz), 2.78 (t, 2 H, J = 7.3 Hz), 2.43 (m, 2 H), 2.08 (m, 2 H), 1.78 (m, 2 H), 1.50–1.10 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 198.7, 136.2, 128.4, 80.6, 78.6, 38.8, 33.3, 30.3, 28.7, 28.4, 27.9, 18.5, 13.3, 7.2. Anal. Calcd for $C_{14}H_{21}OI$: C, 50.61; H, 6.37. Found: C, 50.81; H, 6.14.

(*E*)-12-Bromo-5-dodecenol and (*Z*)-12-Bromo-5-dodecenol 11. A dry two-neck flask was charged with 5 mL of anhydrous THF and 0.32 g (1.65 mmol) of 7-bromo-1-heptanal. The mixture was cooled to 0 °C and treated with a solution of 2.05 mmol of (triphenylphosphonio)-5-(lithiooxo)pentylide in 10 mL of THF at 0 °C via cannula over 1 min. The reaction mixture was stirred for 2 min and quenched with aqueous ammonium chloride solution. The biphasic mixture was diluted with ethyl ether and equilibrated. The aqueous portion was drawn off, and the organics were dried ($MgSO_4$) and concentrated. The resulting residue was purified by elution through silica gel (1/4 ethyl acetate–hexane) to provide 0.31 g (1.20 mmol, 71%) of (*E*)- and (*Z*-12-bromo-5-dodecen-1-ol: TLC, R_f 0.23 (1/4 ethyl acetate–hexane); IR 3350, 3050, 2950, 2860, 1440, 1260, 1050 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.35 (m, 2 H), 3.62 (t, 2 H, J = 7.2 Hz), 3.39 (t, 2 H, J = 6.8 Hz), 2.00 (m, 4 H), 1.83 (m, 2 H), 1.58–1.10 (m, 11 H); ^{13}C NMR δ 130.5, 130.0, 129.9, 129.5, 62.7, 33.9, 33.7, 32.3, 32.2, 32.1, 29.4, 29.2, 28.3, 28.1, 27.9, 26.9, 26.8, 25.8, 25.6. Anal. Calcd for $C_{12}H_{23}OBr$: C, 54.76; H, 8.90. Found: C, 54.63; H, 8.90.

(*E*)-14-Iodo-1,7-tetradecadien-3-one and (*Z*)-14-Iodo-1,7-tetradecadien-3-one 12. A solution of 4.60 g (16.0 mmol) of 14-bromo-1,7-tetradecadien-3-one in 85 mL of methyl ethyl ketone was treated with sodium iodide (7.2 g, 48.0 mmol) and refluxed for 3 h. The reaction mixture was cooled and concentrated. The residue was purified by elution through silica gel (1/11 ethyl acetate–hexane) to provide 4.8 g (14.4 mmol, 90%) of 14-iodo-1,7-tetradecadien-3-one.

Separation of the isomers was carried out by HPLC on a reversed-phase max column (Rainin) with 80/20 acetonitrile–water as a mobile phase. ^{1}H decoupling experiments revealed the faster eluting component contained an olefin coupling constant of 11.5 Hz (cis isomer) and the slower eluting fraction contained an olefin coupling constant of 15.2 Hz (trans isomer).

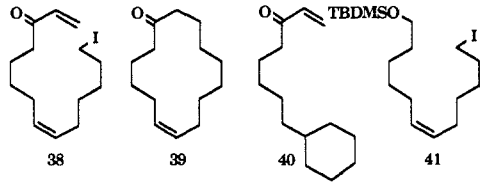
Trans isomer: TLC, R_f 0.50 (1/5 ethyl acetate–hexane); IR 3100, 3000, 2940, 2850, 1680, 1610, 1430, 1400, 1200, 1100, 990, 960 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.31 (dd, 1 H, J = 17.6, 10.3 Hz), 6.19 (d, 1 H, J = 17.6 Hz), 5.78 (d, 1 H, J = 10.3 Hz), 5.37 (m, 2 H), 3.15 (t, 2 H, J = 6.7 Hz), 2.57 (t, 2 H, J = 7.4 Hz), 1.95 (m, 4 H), 1.80 (m, 2 H), 1.67 (m, 2 H), 1.40–1.10 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 200.6, 136.5, 131.0, 129.3, 127.7, 38.9, 33.5, 32.4, 31.9, 30.3, 29.3, 28.0, 23.7, 7.3.

Cis isomer: TLC, R_f 0.50 (1/5 ethyl acetate–hexane; IR 3100, 3000, 2940, 2850, 1680, 1610, 1430, 1400, 1200, 1100, 990, 960 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.33 (dd, 1 H, J = 17.6, 10.3 Hz), 6.17 (d, 1 H, J = 17.6 Hz), 5.89 (d, 1 H, J = 10.2 Hz), 5.34 (m, 2 H), 3.16 (t, 2 H, J = 6.7 Hz), 2.57 (t, 2 H, J = 7.3 Hz), 2.00 (m, 4 H), 1.79 (m, 2 H), 1.66 (m, 2 H), 1.40–1.10 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 200.7, 136.6, 130.7, 128.9, 127.8, 38.8, 33.4, 30.3, 29.4, 28.0, 27.0, 26.5, 23.8, 7.2.

Anal. Calcd for $C_{14}H_{23}OI$ (mixture of both cis and trans): C, 50.30; H, 6.94. Found: C, 50.19; H, 7.08.

9-Cyclopropyl-1-[(*tert*-butyldimethylsilyl)oxy]-9-nonanol (14). The Grignard reagent was formed by reacting 4.5 mL (6.8 g, 56.2 mmol, 2.0 equiv) of cyclopropyl bromide with 1.3 g (54 mmol, 2.0 equiv) of magnesium metal in 100 mL of dry THF at 0 °C. A 0.5-mL portion of cyclopropyl bromide was added to the magnesium and THF at 0 °C and the resultant mixture stirred while warming to room temperature until initiation of Grignard formation; the ice bath was then replaced to slow

Chart II



38 39 40 41

the formation. The cyclopropyl bromide was added successively in small portions to retard violent frothing and heat evolution. Once the Grignard was formed and cooled with the ice bath for 10 min, a gray suspension resulted to which 7.5 g (28 mmol, 1 equiv) of 1-[(*tert*-butyldimethylsilyl)oxy]-9-nonanal in 20 mL of THF was added by syringe over 2 min. The solution was stirred for 30 min while being warmed to room temperature and then quenched with saturated NH_4Cl solution, diluted with hexane, washed twice with saturated NaCl solution, and dried with Na_2SO_4. The solution was filtered, concentrated, and purified by elution through silica gel with 10% EtOAc–hexane to give 7.6 g (24 mmol, 88%) of the cyclopropylcarbinol **14**: TLC, R_f 0.33 (25% EtOAc–hexane; IR 3375, 3090, 3000, 2950, 2850, 1710, 1460, 1440, 1390, 1360, 1260, 1100, 1045, 1020, 1005, 940, 920, 840, 780, 720, 66 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.55 (t, 2 H, J = 6.6 Hz), 2.81 (dt, 1 H, J = 8.2 Hz), 1.58–1.26 (m, 14 H), 0.85 (s, 9 H), 0.49–0.44 (m, 2 H), 0.25–0.16 (m, 2 H), 0 (s, 6 H); ^{13}C NMR δ 76.82, 63.22, 37.18, 32.77, 29.66, 29.55, 29.32, 25.91, 25.64, 18.28, 17.86, 2.67, 2.40, −5.34. Anal. Calcd for $C_{18}H_{37}O_2Si$: C, 68.95; H, 11.89. Found: C, 68.69; H, 11.69.

(*E*)-12-Bromo-9-dodecen-1-ol (15). Ring opening of the cyclopropylcarbinol **14** gave the trans homoallylic bromide and deprotection of the silyl-protected alcohol.

To 6.2 g (20 mmol) of neat 9-cyclopropyl-1-[(*tert*-butyldimethylsilyl)oxy]-9-nonanol at 0 °C was added 15.5 mL (4.0 equiv) of stock HBr–$ZnBr_2$ solution. The acid solution consisted of 15.2 g of $ZnBr_2$ (68 mmol) and 11.3 mL of HBr(aq). The acid solution worked better if made up several days prior to use. After addition of the HBr–$ZnBr_2$ to the cyclopropylcarbinol, the solution was stirred for 3 h, diluted with hexane, washed three times with water, and dried ($MgSO_4$). The solution was filtered, concentrated, and purified by elution through silica gel with 15% EtOAc–hexane to give 3.5 g (13 mmol, 67%) of (*E*)-12-bromo-9-dodecen-1-ol (**15**): TLC, R_f 0.21 (25% EtOAc–hexane); IR 3350, 2950, 2850, 1470, 1440, 1270, 1210, 1060, 975, 915, 740, 645 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.50 (dt, 1 H, J = 15.2 Hz, J = 6.4 Hz), 5.35 (dt, 1 H, J = 15.4 Hz, J = 6.4 Hz), 3.61 (t, 2 H, J = 6.6 Hz), 3.34 (t, 2 H, J = 7.1 Hz), 1.97 (q, 2 H, J = 6.5 Hz), 1.57–1.49 (m, 2 H), 1.40–1.18 (m, 10 H); ^{13}C NMR δ 133.76, 126.23, 62.58, 35.88, 32.79, 32.54, 32.33, 29.22, 29.11, 28.89, 25.60. Anal. Calcd for $C_{12}H_{23}OBr$: C, 54.76; H, 8.81. Found: C, 54.45; H, 8.88.

(*E*)-12-Bromo-9-dodecen-1-al (16). To a solution of 1.5 g (5.7 mmol) of (*E*)-12-bromo-9-dodecen-ol (**15**) and 15 mL of CH_2Cl_2 was added 1.84 g (8.6 mmol, 15 equiv) of PCC. The solution was stirred for 3 h, then concentrated, and purified by elution through Florisil with 10% EtOAc–hexane to give 1.39 g (4.85 mmol, 85%) of (*E*)-12-bromo-9-dodecen-1-al (**16**): TLC, R_f 0.45 (25% EtOAc–hexane); IR 2950, 2850, 2720, 1725, 1460, 1450, 1390, 1360, 1270, 1210, 970, 720, 640 cm^{-1}.

1,1-Dicyano-21-iodoheneicosane (19c). To the solution of 1.1 g (10 equiv) of dicyanomalonate in 40 mL of THF was added sodium hydride (60%) (67 mg, 1 equiv) portionwise. After the mixture was stirred for 5 min, 896 mg (1 equiv) of α,ω-diiodoeicosane in 30 mL of THF was added dropwise. The reaction was stirred overnight at room temperature under argon.

Saturated NH_4Cl solution in 3 mL was added dropwise to the reaction. The mixture was extracted with ethyl acetate–saturated NH_4Cl. The organic layer was separated, dried, and concentrated. The desired product, 288 mg (64%), 110 disubstituted products, and 390 mg of recovered starting material were obtained under silica gel column chromatography (1/1 = CH_2Cl_2/hexane): ^1H NMR δ 1.21–1.43 (m, 32 H), 1.60 (m, 2 H), 1.80 (m, 2 H), 2.02 (m, 2 H), 3.17 (t, 2 H, J = 7.2 Hz), 3.69 (t, 1 H, J = 6.9 Hz); ^{13}C NMR δ 7.43, 22.61, 24.03, 26.53, 28.32, 28.51, 29.05, 29.62, 29.49, 30.78, 33.53, 112.50.

1,1-Dicyano-1-(phenylseleno)-21-iodoheneicosane (20c). To the solution of 288 mg (1 equiv) of 1,1-dicyano-21-iodoheneicosane (**19c**) in 60 mL of THF, which was precooled in isopropyl alcohol/dry ice bath, was added 1.9 mL (2 equiv) of $KN(TMS)_2$ (0.65 M in toluene) dropwise. After the mixture was stirred for 10 min, PhSeBr 430 mg (3 equiv) was added all at once. The reaction was stirred for an additional 1.5 h, while the temperature was allowed to rise to ~0 °C. Saturated NH_4Cl solution (3 mL) was added to the reaction and the mixture extracted with ethyl acetate–saturated NH_4Cl. The desired product (239 mg, 63%) was obtained after workup and chromatography (1/1 = CH_2Cl_2/hexane): ^1H NMR δ 1.22–1.48 (m, 32 H), 1.70–1.90 (m, 4 H), 2.15 (m, 2 H), 3.19 (t, 2 H, J = 6.9 Hz), 7.46–7.58 (m, 3 H), 7.89 (m, 2 H); ^{13}C NMR δ 7.49, 26.74, 26.83, 28.61, 28.72, 29.16, 29.40, 29.48, 29.60, 29.73, 30.56, 33.62, 37.28, 114.32, 124.70, 129.87, 131.61, 137.74.

1,1-Dicyano-21-iodo-1-heneicosene (21c). The mixture of 239 mg of (phenylseleno)heneicosane **20c** and MCPBA (90 mg, 1.1 equiv) in 20 mL of dichloromethane was stirred at 0 °C for 0.5 h. TLC (hexane/CH_2Cl_2 = 1/1) indicated the reaction was complete. Excess peracid was destroyed by addition of 10% sodium sulfite until a test with starch–iodide paper was negative. The organic layer was separated, washed with $NaHCO_3$, and dried over $MgSO_4$. After concentration and purification (silica gel chromatography, 3/1 = hexane/CH_2Cl_2), 70 mg (40%) of the desired product was obtained. ^1H NMR δ 1.20–1.43 (m, 30 H), 1.58 (m, 2 H), 1.81 (m, 2 H), 2.58 (m, 2 H), 3.19 (t, 2 H, J = 6.6 Hz), 7.33 (t, 1 H, J = 8.1 Hz); ^{13}C NMR δ 7.59, 27.74, 28.69, 29.24, 29.28, 29.50, 29.57, 29.69, 29.82, 30.66, 33.02, 33.70, 89.91, 110.54, 112.13, 169.76. Anal. Calcd for $C_{23}H_{39}N_2I$: C, 58.72; H, 8.30; N, 5.69. Found: C, 58.91; H, 8.48; N, 5.81.

Cyclotetradecanone (25b). Method A. A solution of *tert*-butyl alcohol (750 mL) and 14-iodo-1-tetradecen-3-one (1.36 g, 3.75 mmol) was degassed under reduced pressure. The mixture was treated sequentially with Bu_3SnCl (101 μL, 0.37 mmol), $NaBH_3CN$ (0.47 g, 7.5 mmol), and AIBN (60 mg). The resulting mixture was refluxed for 3 h and reduced to a 30-mL volume under aspirator pressure. The residue was then treated with basic hydrogen peroxide for 30 min to cleave borate esters and diluted with ethyl acetate. The ethyl acetate fraction was separated, partitioned between 5% HCl and brine, dried, and reduced in volume. The crude residue was then oxidized with Jones reagent in acetone and worked up in the usual way. The residue following workup was purified by elution through silica gel (5% ethyl acetate–hexane) to provide 350 mg of cyclotetradecanone (**25b**).

Method B. A refluxing solution of 14-iodo-1-tetradecen-3-one (40 mg, 0.12 mmol) in 30 mL of dry benzene was treated sequentially with tributyltin hydride (38.4 mg, 1.1 equiv, 0.132 mmol) and AIBN (1 mg). The reaction mixture was refluxed for 3 h and concentrated under reduced pressure. The residue was purified by elution through silica gel (3/97 ethyl acetate–hexane) to provide cyclotetradecanone (16.8 mg, 67%), as analyzed by GC. Further purification of the reaction mixture by HPLC with 4% ethyl acetate–hexane on a Dynamax column (Rainin) provided spectroscopically pure cyclotetradecanone (**25b**): TLC, R_f 0.75 (2/8 ethyl acetate in hexane); IR 2940, 2860, 1705, 1430, 1380 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.42 (t, 4 H, J = 6.4 Hz), 1.65 (m, 4 H), 1.27 (s[br], 18 H); ^{13}C NMR ($CDCl_3$) δ 212.2, 40.7, 25.9, 25.7, 25.2, 25.1, 24.3, 22.8. MS (EI) M = 210 (10.4), 152 (7.5), 125 (17.1), 111 (17.5), 96 (26.5), 82 (26.1), 71 (87.5), 55 (100).

(*E*)-4-Cyclotetradecen-1-one (26): TLC R_f 0.45 (1/9 ethyl acetate–hexane); IR 3145, 2940, 2860, 1715, 1440, 1360, 1220, 980, 900 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.35 (m, 2 H), 2.45–2.20 (m, 6 H), 2.00 (m, 2 H), 1.60 (m, 2 H), 1.40–1.10 (m, 12 H); ^{13}C NMR δ 211.1, 131.6, 129.8, 42.0, 41.7, 30.5, 27.0, 26.6, 26.5, 25.6, 24.6, 24.1, 24.0. Anal. Calcd for $C_{14}H_{24}O$: C, 80.70; H, 11.61. Found: C, 80.60; H, 11.64.

4-Cyclotetradecyn-1-one (27): TLC, R_f 0.50 (1/5 ethyl acetate–hexane); IR 2940, 2850, 1710, 1420, 1350, 1160, 1210, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.60–2.30 (m, 6 H), 2.10 (s[br], 2 H), 1.60 (m, 2 H), 1.40–1.10 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ 209.5, 79.9, 79.5, 41.5, 41.0, 27.0, 26.3, 25.8, 25.5, 24.9, 24.6, 23.4, 17.5, 13.2. Anal. Calcd for $C_{14}H_{22}O$: C, 81.49; H, 10.74. Found: C, 81.51; H, 10.49.

(*Z*)-5-Cyclotetradecenone (28): TLC, R_f 0.75 (2/8 ethyl acetate–hexane); IR 3000, 2940, 2850, 1710, 1460, 1400, 1360, 1250, 1150, 1100, 1010 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.37 (m, 1 H), 5.18 (m, 1 H), 2.35 (t, 4 H, J = 6.35 Hz), 2.00 (q, 2 H, J = 6.5 Hz), 1.85 (q, 2 H, J = 7.1 Hz), 1.60 (m, 4 H), 1.20 (s[br], 10 H); ^{13}C NMR ($CDCl_3$) δ 211.1, 131.0, 129.0, 41.2, 39.6, 27.6, 26.2, 26.0, 25.6, 25.5, 24.7, 23.7, 21.6. Anal. Calcd for $C_{14}H_{24}O$: C, 80.70; H, 11.61. Found: C, 80.60; H, 11.61.

(*E*)-5-Cyclotetradecenone (29): TLC, R_f 0.75 (2/8 ethyl acetate–hexane); IR 2925, 2850, 1710, 1440, 1370, 1220, 970 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.40 (m, 2 H), 2.49 (t, 2 H, J = 7.4 Hz), 2.36 (t, 2 H, J = 6.7 Hz), 2.15–1.90 (m, 4 H), 1.65 (m, 4 H), 1.40–1.17 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 212.5, 132.7, 130.5, 43.0, 38.7, 31.7, 31.2, 27.5, 26.3, 25.6, 25.5, 24.6, 23.7, 21.8. Anal. Calcd for $C_{14}H_{24}O$: C, 80.70; H, 11.61. Found: C, 80.88; H, 11.53.

(Dicyanomethyl)cycloeicosane (37c): The solution of 65 mg of dicyano olefin (1 equiv) **21c**, 45 μL of Bu_3SnH (1.1 equiv), and AIBN (0.3 mg, 0.1 equiv) in 30 mL of benzene was stirred under reflux for 3 h. The reaction was evaporated and the residue purified by flash chromatography (hexane/CH_2Cl_2 = 3/1) to give 25 mg (53%) of cyclized product with no detection of reduced product by ^1H NMR: ^1H NMR δ 1.20–1.45 (m, 34 H), 1.69 (m, 4 H), 2.02 (m, 1 H), 3.71 (d, 1 H, J = 4.8 Hz); ^{13}C NMR δ 25.59, 27.63, 27.78, 28.01, 28.16, 28.24, 28.33, 28.37, 29.85,

30.49, 39.59, 112.30. Anal. Calcd for $C_{23}H_{40}N_2$: C, 80.23; H, 11.63; N, 8.14. Found: C, 80.08; H, 11.72; N, 8.07.

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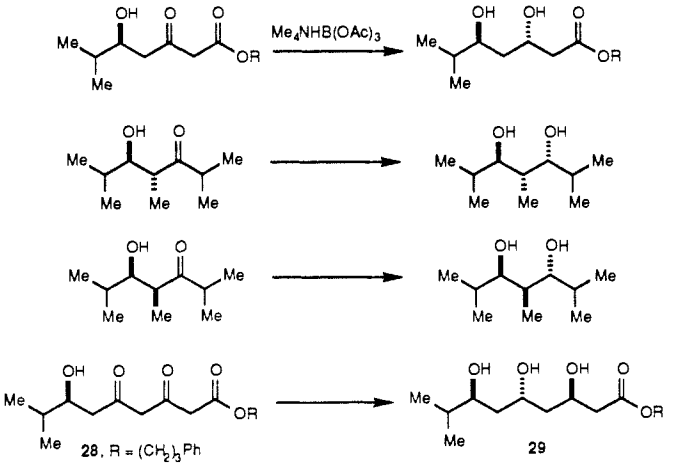
Supplementary Material Available: Details of the synthesis of intermediates not described in the Experimental Section (6 pages). Ordering information is given on any current masthead page.

Directed Reduction of β-Hydroxy Ketones Employing Tetramethylammonium Triacetoxyborohydride

D. A. Evans,* K. T. Chapman, and E. M. Carreira

Contribution from the Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138. *Received July 10, 1987*

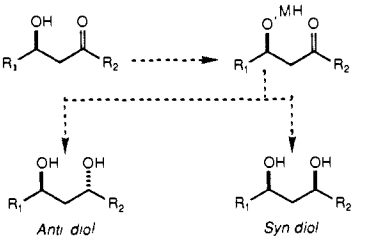
Abstract: The mild reducing agent tetramethylammonium triacetoxyborohydride reduces acyclic β-hydroxy ketones to their corresponding anti diols with high diastereoselectivity. α-Alkyl substitution does not significantly affect the stereoselectivity of these reductions. In all cases examined, good to excellent yields of diastereomerically homogeneous diols were obtained. The mechanism of these reductions involves an acid-promoted ligand exchange of acetate for substrate alcohol by the triacetoxyborohydride anion. The resultant hydride intermediate, presumably an alkoxydiacetoxyborohydride, reduces proximal



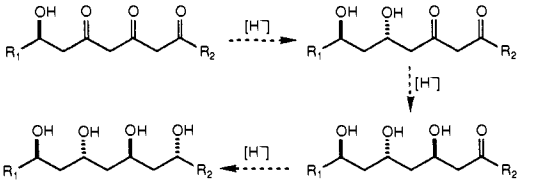
ketones by intramolecular hydride delivery. Ketones, β-ketoesters, and β-diketones are not reduced by tetramethylammonium triacetoxyborohydride in the absence of a suitably disposed hydroxyl group. Indeed both cyclic and acyclic β-hydroxy ketones may be conveniently reduced in a solvent of 1:1 acetone–acetic acid. Hydroxy diketo ester **28** undergoes sequential diastereoselective reductions with tetramethylammonium triacetoxyborohydride to afford a 50% isolated yield of anti–anti triol ester **29** in a unique stereopropagating reaction.

Over the last several years we have been concerned with the development of new stereoselective reactions relevant to the synthesis of polyketide-derived natural products in the polyether,[1] macrolide,[2] and polyene[3] families. Our recent focus on the development of hydroxyl-directed hydrogenation reactions, utilizing cationic rhodium catalysts, is an example of such a method that is genuinely useful in the predictable, stereoselective hydrogenation of hydroxy olefins in acyclic systems.[4,5] As a natural extension of this study we have initiated a complementary investigation aimed at the development of a family of hydride reagents which might participate in a strictly controlled, hydroxyl-directed reduction of hydroxy ketones and related substrates.[6] The sequence

Scheme I



Scheme II



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