Addition of *n*-Butylcuprates to α-Methylenecycloalkylidene Epoxides

James A. Marshall* and Vicki H. Audia

Department of Chemistry, University of South Carolina, Columbia, South Carolina 29208

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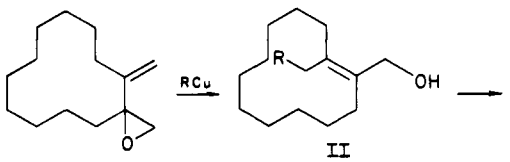
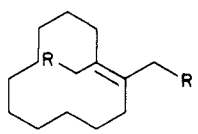
The addition of *n*-butylmagnesium bromide–copper(I) iodide in THF–dimethyl sulfide has been carried out with the 10-, 12-, 13-, 14-, 15-, and 16-membered α-methylenecycloalkylidene epoxides **2a–f**. In each case the S_N2' substitution products **4** and **5** were formed with the trans isomer predominating by 85:15 or greater. The findings are consistent with a reactant-like transition state involving the *s*-trans conformer of the epoxide–cuprate complex. The starting alkylidene epoxides **2a–d** and **2f** were prepared by addition of dimethylsulfonium methylide to the α-methylene ketones **1a–d** and **1f**. Epoxide **2e** was obtained via Wittig methylenation of epoxy ketone **3**.

Recently we found that the mono epoxide of 1,2-bis(methylene)cyclododecene (I) reacts cleanly with organocuprates via S_N2' substitution to give the tetrasubstituted *trans*-cyclododecenylcarbinols II.[1a] In the several cases examined, the trans product predominated over the cis by 95:5, or better. The process is especially noteworthy in



I II



III

view of the paucity of synthetic routes to such cycloalkenes.[1b] Presumably, the predominance of trans products reflects certain conformational preferences of the cyclododecylidene epoxide I as manifested in the reaction transition state.[2] This type of stereocontrol is of special interest in connection with macrocyclic natural product synthesis.[3]

In the case of I the preference for the trans product II offered an attractive solution to a difficult synthetic problem, but it remained to be seen whether the phenomenon was applicable to other ring sizes. In order to clarify this point, we undertook studies on the addition of butylcuprates to the medium- and large-ring cycloalkylidene epoxides **2a–f**.

Our synthesis of these epoxides utilized the α-methylenecycloalkanones **1a–f** prepared through condensation of the corresponding ketones with paraformaldehyde by the method of Gras[4] as modified.[5] Cyclodecanone reacted quite readily to give a separable mixture of enone **1a** and the α,α′-bis-methylenated ketone. This byproduct was not appreciably suppressed even by using short reaction times and limited paraformaldehyde. Cyclododecanone, cyclotridecanone, and cyclotetradecanone reacted more slowly requiring prolonged heating for completion. Again, the α,α′-bis-methylenated ketones were unavoidably formed. Cyclopentadecanone and cyclohexadecanone were the least reactive of the series. In these cases the condensations could not be brought to completion. Even so, the bis-methylenated ketones were still formed as significant, but separable, byproducts.

Epoxides **2a–d** and **2f** could be prepared directly from the related enones **1a–d** and **1f** through addition of dimethylsulfonium methylide[6] in THF–HMPA. The 15-membered α-methylene ketone **1e**, however, gave a complex mixture with this reagent. An alternative route involving epoxidation with *tert*-butyl hydroperoxide and Wittig methylenation of the resulting epoxy ketone **3** proceeded satisfactorily. This sequence was also examined with several of the other enones but was found to be less efficient than the sulfonium ylide method.

The epoxides **2a–f** were somewhat sensitive, particularly to acid. Silica gel chromatography led to low material recoveries and appeared to promote pinacol rearrangement to the ring expanded ketone **6** and a minor isomeric product of unknown structure. The 15- and 16-membered systems **2e** and **2f** were particularly troublesome. In our initial trials we used basic alumina or alumina–Celite combinations for purification of epoxides **2a–f**. Later we discovered that flash chromatography[7] on silica gel pretreated with triethylamine gave excellent results with the highly sensitive epoxides **2e** and **2f**. Yields of epoxides **2a–d** would also likely improve with this method of purification.

We previously found that cuprates prepared from Grignard reagents and cuprous iodide in THF–dimethyl sulfide gave clean S_N2' additions with the cyclododecylidene epoxide **2b**.[1] The analogous reagent was therefore used in the current studies. Our findings are summarized in Table I. In all cases the trans S_N2' product **4** was formed as the major product. Although physical separation of the trans and cis alcohols **4** and **5** could not be achieved, product ratios were easily determined through analysis of the ^1H NMR spectra. The trans alcohols **4**

(1) (a) Marshall, J. A.; Flynn, K. E. *J. Am. Chem. Soc.* **1984**, *106*, 723–730. Marshall, J. A.; Peterson, J. C.; Lebioda, L. *J. Am. Chem. Soc.* **1983**, *105*, 6515–6516. (b) Background material can be found in the excellent review on the stereochemistry of many membered rings. Sicher, J. *Prog. Stereochem.* **1962**, *3*, 210–213. For a more recent survey, see: Marshall, J. A. *Acc. Chem. Res.* **1980**, *13*, 213–218.

(2) A conceptually related reaction is the addition of bromine to 1,2-bis(methylene)cyclododecane to give *trans*-1,2-bis(bromomethyl)cyclododecene. Marshall, J. A.; Chung, K.-H. *J. Org. Chem.* **1979**, *44*, 1566–1567.

(3) Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981–3996 and references cited therein. Vedejs, E.; Dolphin, J. M.; Mastalerz, H. *J. Am. Chem. Soc.* **1983**, *105*, 127–130. Still, W. C.; Novack, V. J. *J. Am. Chem. Soc.* **1984**, *106*, 1148–1149. Schreiber, S. L.; Santini, C. *J. Am. Chem. Soc.* **1984**, *106*, 4038–4039.

(4) Gras, J.-L. *Tetrahedron Lett.* **1978**, 2111–2114, 2955–2958.

(5) Kruizinga, W. H.; Kellogg, R. M. *J. Am. Chem. Soc.* **1981**, *103*, 5183–5189. It should be noted that the ^1H NMR spectrum of the bis-α-methylenated byproduct is sufficiently similar to that of **1b** to be overlooked in the spectrum of a mixture of the two. Careful purification is therefore necessary at this stage of the sequence.

(6) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353–1364.

(7) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

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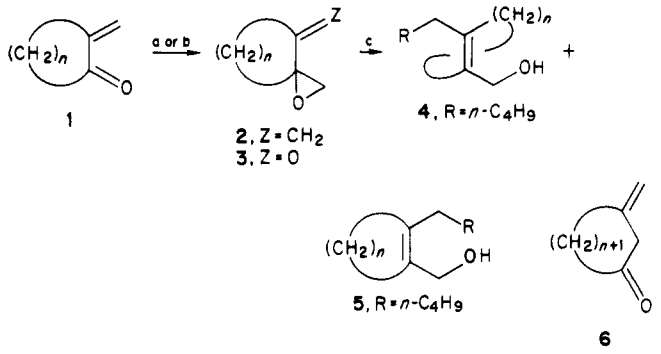


a series, $n = 8$; b series, $n = 10$; c series, $n = 11$; d series, $n = 12$; e series, $n = 13$; f series, $n = 14$.

(a) $(CH_3)_3S^+I^-$, *n*-BuLi, THF, HMPA; (b) *tert*-BuOOH, $PhCH_2N(CH_3)_3^+OH^-$, THF; $Ph_3PCH_3^+Br^-$, *n*-BuLi, THF; (c) *n*-BuMgBr, CuI, $(CH_3)_2S$, THF, −78 to −20 °C.

exhibited characteristic AB quartets for the carbinyl CH_2 resonance whereas the cis alcohols **5** gave rise to singlets at practically the same chemical shift. Lithium di-*n*-butylcuprate[8] and lithium *n*-butylcyanocuprate[9] also showed marked preferences for the formation of the trans product **4b** in their reaction with epoxide **2b**. The addition thus appears to be relatively insensitive to the nature of the cuprate species.[10a]

Recent work on additions of organocuprates to allylic alcohol esters supports a pathway involving initial π-complexation of the cuprate on the less hindered face of the double bond followed by rate determining S_N2' oxidative addition leading to a σ-copper complex which undergoes reductive elimination to product with retention of stereochemistry.[10b] The intermediate σ-allyl copper species may also equilibrate to an allylic isomer which could collapse to the S_N2 product. In the present case, S_N2' oxidative addition of the initial π-complex can occur via either a cisoid IVc or a transoid IVt transition state to give the cis or trans σ-allyl intermediate V or VII and thence the substitution product **5** or **4**. Allylic isomerization of V or VII could afford the exocyclic olefin **7** via the tertiary allylcopper intermediate VI. MM2 calculations using the Still RINGMAKER/BAKMOD program indicate that the *s*-trans conformation of epoxides **1a–d** is favored over the *s*-cis conformation by 2–3 kcal.[11] Related calculations show that *cis*-1,2-dimethylcycloalkenes are more stable than the trans isomers in the 10- and 12-membered rings while the trans isomer is preferred in the 14-membered ring.[12] The calculation is in good agreement with experimental findings for 1,2-dimethylcyclododecene.[13] Accordingly, the preference for trans products **4a–f** in the S_N2' additions of organocuprates to epoxides **2a–f** could stem from a favored reactant-like transition state involving the π-complex IVt of the lower energy *s*-trans conformer.

None of the systems examined to date gave detectable amounts of the α-substitution products **7** according to

(8) Posner, G. H. *Org. React. (N.Y.)* **1975**, *22*, 253–400.

(9) Acker, R. D. *Tetrahedron Lett.* **1978**, 2399–2402; **1977**, 3407–3410.

(10) (a) Levisalles, J.; Rudler-Chanvin, M.; Rudler, H. *J. Organomet. Chem.* **1977**, *136*, 103–110. (b) Goering, H. L.; Kantner, S. S. *J. Org. Chem.* **1984**, *49*, 422–426.

(11) We are indebted to Professor Still for performing calculations on the 10- and 12-membered epoxides and for sending a copy of his RINGMAKER and related programs.

(12) Our initial MM2 calculations of cycloalkenes were carried out by Professor Wayne Guida using the Allinger program. Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127–8134. The MM2 program is available from the Indiana University Quantum Chemistry Program Exchange. These calculations were in good agreement with more recent results obtained via the RINGMAKER/BAKMOD protocol.

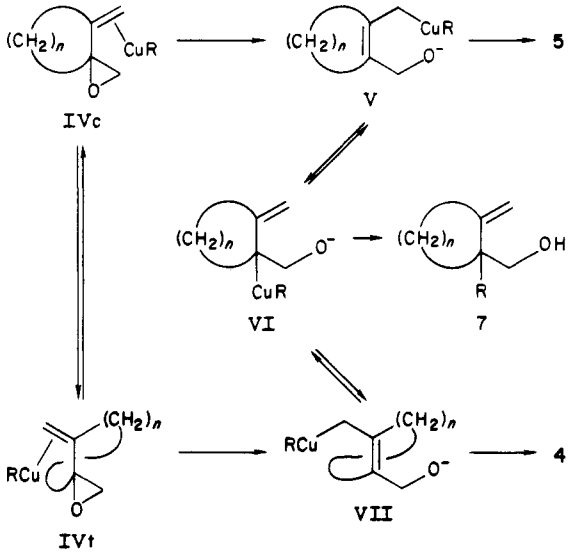
(13) Marshall, J. A.; Karas, L. J. *J. Am. Chem. Soc.* **1978**, *100*, 3615–3616. Marshall, J. A.; Karas, L. J.; Royce, R. D., Jr. *J. Org. Chem.* **1979**, *44*, 2994–2999.

Table I. Additions of Butylcuprates to Epoxides 2a–f

entry	epoxide	cuprate[a]	yield,[b] %	4[c]	5[c]
1	**2a**	*n*-BuMgBr, CuI, $(CH_3)_2S$	87	85	15
2	**2b**[1]	*n*-BuMgBr, CuI, $(CH_3)_2S$	76	98	2
3	**2c**	*n*-BuMgBr, CuI, $(CH_3)_2S$	52	95	5
4	**2d**	*n*-BuMgBr, CuI, $(CH_3)_2S$	82	90	10
5	**2e**	*n*-BuMgBr, CuI, $(CH_3)_2S$	71	93	7
6	**2f**	*n*-BuMgBr, CuI, $(CH_3)_2S$	87	94	6
7	**2b**	Li(*n*-Bu)CuCN	61	95	5
8	**2b**	$Li(n\text{-}Bu)_2Cu$	77	98	2

[a] Reactions conducted in THF at −78 to −20 °C for 8–12 h. [b] Isolated product after chromatography on silica gel. [c] Determined by ^1H NMR integration.

NMR analysis of crude reaction mixtures. Such products are formed as minor and often significant byproducts of cuprate couplings of halides and allylic phosphates related to II.[1] Possibly electrostatic repulsion disfavors the formation of complex VI in the epoxide substrates **2**.



The findings described in this paper indicate that a considerable variety of trans tetrasubstituted cycloalkenes can now be prepared via S_N2' coupling of organocuprates with α-methylenecycloalkylidene epoxides. We are currently examining other uses for such epoxides in stereodirected cycloalkene synthesis.

Experimental Section[14]

2-Methylenecyclohexadecanone (1f). The procedure of

(14) (a) The apparatus and methods described by G. W. Kramer, M. M. Midland, and A. B. Levy [Brown, H. C. "Organic Syntheses via Boranes"; Wiley: New York, 1975; pp 191–202] were used to maintain an argon or nitrogen atmosphere in the reaction flask. (b) Anhydrous solvents were obtained by distillation from sodium benzophenone ketyl (diethyl ether, tetrahydrofuran, 1,2-dimethoxyethane, and dioxane), calcium hydride (dichloromethane and hexamethylphosphoramide), or sodium (benzene and toluene). (c) Infrared absorption maxima are reported in wavenumbers (cm^{-1}) and are standardized by reference to the 1601-cm^{-1} peak of polystyrene. (d) Proton magnetic resonance spectra were recorded on Varian EM-390 and Bruker 400-MHz spectrometers. Carbon-13 spectra were recorded at 20 MHz on an IBM NR-80 Fourier transform spectrometer. All samples were prepared as dilute solutions in deuterochloroform ($CDCl_3$). Chemical shifts (δ) are reported downfield from tetramethylsilane (Me_4Si), in parts per million (ppm) of the applied field. Peak multiplicities are abbreviated: singlets, s; doublet, d; triplet, t; quartet, q; envelope, env; multiplet, m. Coupling constants (J) are reported in hertz (Hz). (e) Gas chromatography–mass spectral analysis (GC/MS) was performed on a Finnigan 4021 instrument. We are indebted to Dr. Michael D. Walla for his valued assistance in these analyses. (f) Combustion microanalyses were performed by Atlantic Laboratories, Atlanta, GA. (g) Analytical thin-layer chromatography (TLC) was routinely used to monitor reactions. Plates precoated with E. Merck silica gel 60 F254 of 0.25-mm thickness, supplied by Brinkmann Instruments, were used. (h) Column chromatography was performed by using E. Merck silica gel 60 (230–400 ASTM mesh).

Gras[4] was modified.[5] To 10.00 g (0.042 mol) of cyclohexadecanone[15] in 84 mL of dioxane was added 7.432 g (0.034 mol) of *N*-methylanilinium trifluoroacetate and 2.772 g (0.092 mol) of paraformaldehyde under argon. The mixture was brought to reflux for 45 min, and an additional 3.716 g (0.017 mol) of *N*-methylanilinium trifluoroacetate and 1.38 g (0.046 mol) of paraformaldehyde was added. After 1 h, 3.716 g (0.017 mol) of *N*-methylanilinium trifluoroacetate and 1.385 g (0.046 mol) of paraformaldehyde was again added, and the mixture was heated at reflux for 4 h, cooled, and decanted from the polymeric residue into ether and diluted with water. The residue was rinsed with ether, and the combined ether layers were washed with 10% sodium hydroxide, water, and brine and dried over magnesium sulfate. Removal of solvent and filtration through a short silica gel column followed by flash chromatography on silica gel (50:1 hexane/ethyl acetate) gave 5.277 g (50%) of the enone **1f** as a clear oil: IR (film) ν 2900, 2840, 1680, 1620 (w), 1460, 1370, 930 cm^{-1}; ^1H NMR (90 MHz) δ 1.25–1.4 (env, ring CH_2), 1.43–1.73 (m), 2.33 (t, $CH_2C{=}O$, J = 6.3 Hz), 2.65 (t, allylic CH_2, J = 6.3 Hz), 5.66, 5.88 ($C{=}CH_2$). Anal. Calcd for $C_{17}H_{30}O$: C, 81.54; H, 12.08. Found: C, 81.56; H, 12.10.

2-Methylenecyclodecanone (1a). The above procedure was followed by using 10.130 g (0.066 mol) of cyclodecanone[16] in 130 mL of dioxane to which a total of 16.415 g (0.074 mol) of *N*-methylanilinium trifluoroacetate and 4.950 g (0.165 mol) of paraformaldehyde was added in two appropriate portions over 2.5 h at reflux. Following workup and flash chromatography, 4.940 g (45%) of the enone **1a** was obtained as a light oil: IR (film) ν 2900, 2850, 1675, 1620, 1470, 1445, 1430, 1310, 1170, 918 cm^{-1}; ^1H NMR (90 MHz) δ 1.25–1.76 (env, ring CH_2), 1.76–2.06 (m), 2.1–2.26 (m), 2.45 (t, $CH_2C{=}O$, J = 4.5 Hz), 2.65 (t, allylic CH_2, J = 5.4 Hz), 5.53, 5.58 ($C{=}CH_2$). Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.33; H, 10.93.

2-Methylenecyclododecanone (1b). The above procedure was followed by using 6.00 g (0.033 mol) of cyclododecanone[16] in 25 mL of dioxane to which a total of 11.640 g (0.053 mol) of *N*-methylanilinium trifluoroacetate and 4.34 g (0.145 mol) of paraformaldehyde was added in three appropriate increments over 4.5 h at reflux. Following workup and flash chromatography, 2.30 g (48%) of the enone **1b** was obtained as a solid: mp 32.5–34.5 °C; IR (film) ν 2900, 2840, 1680, 1630, 1480, 1440, 1430, 1340, 1290, 930 cm^{-1}; ^1H NMR (90 MHz) δ 1.06–1.46 (env, ring CH_2), 1.53–1.85 (m), 2.26–2.46 (m), 2.67 (t, allylic CH_2, J = 6.0 Hz), 5.53, 5.83 ($C{=}CH_2$). The properties were identical with those reported by Flynn.[1]

2-Methylenecyclotridecanone (1c). The above procedure was followed by using 29.64 g (0.151 mol) of cyclotridecanone[16] in 45 mL of dioxane to which a total quantity of 33.62 g (0.152 mol) of *N*-methylanilinium trifluoroacetate and 17.89 g (0.596 mol) of paraformaldehyde was added in three appropriate increments over 3.5 h at reflux. Following workup and flash chromatography, 5.448 g (20%) of the enone was obtained as an oil: IR (film) ν 2900, 2850, 1675, 1620, 1460, 1445, 1360, 1080, 920 cm^{-1}; ^1H NMR (90 MHz) δ 1.03–1.43 (env, ring CH_2), 1.43–1.90 (m), 2.36 (t, $CH_2C{=}O$, J = 6.0 Hz), 2.66 (t, allylic CH_2, J = 6.0 Hz), 5.66, 5.93 ($C{=}CH_2$). Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.65; H, 11.61.

2-Methylenecyclotetradecanone (1d). The above procedure was followed by using 25.50 g (0.121 mol) of cyclotetradecanone[17] in 100 mL of dioxane to which a total quantity of 42.90 (0.194 mol) of *N*-methylanilinium trifluoroacetate and 15.97 g (0.532 mol) of paraformaldehyde was added in three appropriate increments over 3.5 h at reflux. Following workup and flash chromatography, 11.11 g (41%) of the enone **1d** was obtained as a light oil: IR (film) ν 2930, 2850, 1684, 1630, 1470, 1450, 1370, 1290, 940 cm^{-1}; ^1H NMR (90 MHz) δ 1.10–1.42 (env, ring CH_2), 1.6–1.86 (m), 2.38 (t, $CH_2C{=}O$, J = 4.5 Hz), 2.73 (t, allylic CH_2, J = 5.2 Hz), 5.67, 5.95 ($C{=}CH_2$). Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.94; H, 11.86.

(15) Stoll, M.; Commarmont, A. *Helv. Chim. Acta* **1948**, *31*, 1077–1081.
(16) Aldrich Chemical Co., Milwaukee, WI.
(17) Brannock, K. C.; Burpitt, R. D.; Goodlett, V. W.; Thweatt, J. G. *J. Org. Chem.* **1964**, *29*, 818–823.

2-Methylenecyclopentadecanone (1e). The above procedure was followed by using 25.00 g (0.11 mol) of cyclopentadecanone[18] in 250 mL of dioxane to which a total quantity of 39.43 g (0.178 mol) of *N*-methylanilinium trifluoroacetate and 14.52 g (0.48 mol) of paraformaldehyde was added in three appropriate increments over 2.8 h at reflux with an additional time of 5.5 h at reflux. Following workup and flash chromatography, 14.456 g (55%) of the enone **1e** was obtained as an oil: IR (film) ν 2900, 2845, 1675, 1625, 1460, 1415, 1370, 1300, 1110, 920 cm^{-1}; ^1H NMR (60 MHz) δ 1.16–1.40 (env, ring CH_2), 1.43–1.86 (m), 2.26–2.53 (m), 2.72 (t, allylic CH_2, J = 5.0 Hz), 5.56, 5.92 ($C{=}CH_2$). Anal. Calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94. Found: C, 81.17; H, 12.02.

1-Oxa-4-methylenespiro[2.13]hexadecane (2d). The procedure of Flynn was followed.[1] To a solution of 1.047 g (5.13 mmol) of trimethylsulfonium iodide in 10.0 mL of tetrahydrofuran was added 5.95 mL (34.2 mmol) of hexamethylphosphoric triamide under argon. To the cooled mixture at −20 °C was slowly added dropwise 3.37 mL (5.13 mmol) of 1.5 M low halide methyllithium in diethyl ether under argon. The pale cream mixture was stirred for 10 min at −20 °C, and then 0.760 g (3.42 mmol) of the enone **1d** in 3.0 mL of tetrahydrofuran was added. The mixture was stirred for 3 h at −20 °C under argon and then poured into water and extracted with ether. The combined ether layers were washed with water, saturated sodium thiosulfate, and brine and dried over potassium carbonate. Removal of solvent at reduced pressure followed by flash chromatography of the crude oil on basic alumina (activity III) with hexane eluant gave 0.606 g (84%) of the epoxide **2d** as a clear oil: IR (film) ν 2900, 2825, 1675, 1620, 1460, 1440, 1350, 920 cm^{-1}; ^1H NMR (90 MHz) δ 1.37 (env, ring CH_2), 1.87–2.13 (m, CH_2), 2.58 (ABq; J = 6.3, $\Delta\nu$ = 6.4 Hz, epoxide CH_2), 4.85, 5.05 ($C{=}CH_2$); GC/MS, m/e (M^+) 236, calcd (M^+) 236.2.

1-Oxa-4-methylenespiro[2.9]dodecane (2a). The procedure described above for **2d** was followed. Addition of 2.720 g (16.4 mmol) of the enone **1a** to the sulfonium ylide at −20 °C and stirring for 2.5 h followed by workup and flash chromatography of the crude product on basic alumina (activity II) (10:1 hexane–ether) gave 1.242 g (42%) of the epoxide **2a** as a clear oil: IR (film) ν 2900, 2860, 1640, 1485, 1450, 920 cm^{-1}; ^1H NMR (90 MHz) δ 1.28 (s), 1.36–1.8 (env, ring CH_2), 2.1–2.33 (m), 2.68 (s, epoxide CH_2), 5.12, 5.23 ($C{=}CH_2$); GC/MS, m/e (M^+) 180, calcd (M^+) 180.2.

1-Oxa-4-methylenespiro[2.12]pentadecane (2c). The procedure described above for **2d** was followed. Addition of 1.500 g (7.20 mmol) of the enone **1c** to the sulfonium ylide at −20 °C and stirring for 3.5 h followed by workup and flash chromatography on 2:1 alumina–Celite (hexane) afforded 0.933 g (60%) of the epoxide **2c** as a clear oil: IR (film) ν 2900, 2845, 1705 (w), 1675, 1640, 1460, 1445, 1350, 1010 cm^{-1}; ^1H NMR (90 MHz) δ 1.13–1.66 (env, ring CH_2), 1.76–2.20 (m), 2.62 (ABq; J = 5.4, $\Delta\nu$ = 6.0 Hz, epoxide CH_2), 4.93, 5.10 ($C{=}CH_2$); GC/MS, m/e (M^+) 222, calcd (M^+) 222.2.

1-Oxa-4-methylenespiro[2.14]heptadecane (2e). To 4.644 g (0.013 mol) of methyltriphenylphosphonium bromide in 30 mL of tetrahydrofuran was added 10.83 mL (0.013 mol) of 1.2 M *n*-butyllithium in hexane at 0 °C under argon. The orange solution was stirred at 0 °C for 1 h, and then 2.856 g (0.011 mol) of the epoxy ketone **3e** in 15 mL of tetrahydrofuran was added. The mixture was allowed to warm slowly to room temperature, stirred for 27 h, then poured into water, and extracted with ether. The combined ether layers were washed with water and dried over potassium carbonate. Filtration and removal of solvent gave an oily brown residue that was diluted with hexane and cooled to −40 °C. The solid triphenylphosphine oxide was removed via filtration, and the filtrate was concentrated in vacuum to give 2.334 g of crude product. Flash chromatography on deactivated silica gel (5% triethylamine–hexane) with hexane eluant gave 1.060 g (39%) of a yellow oil: IR (film) ν 2905, 2845, 1640, 1470, 1360, 1290, 910 cm^{-1}; ^1H NMR (90 MHz) δ 1.06–1.50 (env, CH_2), 1.66–2.10 (m), 2.60 (ABq; J = 6.3 Hz, $\Delta\nu$ = 6.4 Hz, epoxide CH_2), 4.85, 5.02 ($C{=}CH_2$); GC/MS, m/e (M^+) 250, calcd (M^+) 250.2.

(18) Fairfield Chemical Co., Blythewood, SC.

1-Oxa-4-methylenespiro[2.15]octadecane (2f). The procedure described above for **2d** was followed. Addition of 3.500 g (0.014 mol) of the enone **1f** to the sulfonium ylide at −20 °C and stirring for 3.1 h followed by workup afforded 3.688 g of a crude oil. Flash chromatography on deactivated silica gel (4% triethylamine–hexane) with hexane eluent gave 2.690 g (70%) of a light yellow oil: IR (film) ν 2900, 2825, 1640, 1440, 1350, 1070, 910 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.26–1.47 (env, ring CH_2), 1.48–1.56 (m), 1.60 (s), 1.88–1.95 (m), 1.98–2.12 (m), 2.65 (ABq; J = 4.0, $\Delta\nu$ = 43.8 Hz, epoxide CH_2), 4.93, 5.08 (C=CH_2); GC/MS, m/e (M^+) 264; calcd (M^+) 264.2.

1-Oxaspiro[2.14]heptadecan-4-one (3e). The procedure of Greico[19] was modified. To a solution of 7.559 g (0.032 mol) of the enone **1e** in 280 mL of tetrahydrofuran was added slowly 32.50 mL (0.339 mol) of *tert*-butyl hydroperoxide under argon. The mixture was stirred for 10 min, and then 32.50 mL of 40% benzyltrimethylammonium hydroxide in methanol was added slowly. The mixture was stirred at room temperature for 12 h, then concentrated, taken up in ether, and poured into water. The aqueous layer was extracted with ether, and the combined ether layers were washed with water and brine and dried over potassium carbonate. Filtration, removal of solvent, and flash chromatography of the crude product on silica gel (10:1 hexane–ethyl acetate) gave 4.57 g (57%) of the epoxy ketone **3e** as a clear oily liquid: IR (film) ν 2980, 2930, 2850, 1705, 1460, 1380, 1210 cm^{-1}; ^{1}H NMR (60 MHz) δ 1.23–1.9 (env, ring CH_2), 2.72 (s, epoxide CH_2); GC/MS, m/e (M^+) 252, calcd (M^+) 252.2.

2-Pentyl-1-cyclotetradecenylmethanol (4d). The procedure of Flynn was followed.[1] To a slurry of 0.060 g (0.315 mmol) of copper iodide in 3.0 mL of tetrahydrofuran was added 0.139 mL (1.90 mmol) of dimethyl sulfide at room temperature under argon. The solution was cooled to −78 °C, and 0.49 mL (0.315 mmol) of 0.64 M *n*-butylmagnesium bromide in tetrahydrofuran was slowly added dropwise over 10 min. The orange mixture was stirred at −78 °C for 20 min and then 0.037 g (0.16 mmol) of the epoxide **2d** in 1.5 mL of tetrahydrofuran was added slowly dropwise. The solution was allowed to warm slowly with stirring from −78 to −20 °C overnight. It was then diluted with saturated ammonium chloride and 3% ammonium hydroxide, allowed to reach room temperature, poured into saturated ammonium chloride, and extracted with ether. The combined ether layers were washed with 3% ammonium hydroxide, water, and brine and dried over potassium carbonate. Filtration and removal of solvent gave the crude product. Purification on silica gel (10:1 hexane–ethyl acetate) afforded 36.6 mg (82%) of the alcohol as a 90:10 mixture of trans and cis isomers **4d** and **5d**: IR (film) ν 3300, 2900, 2845, 1460, 1260, 1010 cm^{-1}; ^{1}H NMR (90 MHz) δ 0.8–1.0 (m, CH_3CH_2), 1.0–1.7 (env, ring CH_2), 1.8–2.7 (m), 4.2 (ABq; J = 10.8, $\Delta\nu$ = 43.7 Hz, trans CH_2O), 4.1 (s, cis CH_2O). Anal. Calcd for $C_{20}H_{38}O$: C, 81.56; H, 13.01. Found: C, 81.64; H, 13.04.

2-Pentyl-1-cyclodecenylmethanol (4a). The procedure described above for **4d** was followed. Addition of 0.155 g (0.860 mmol) of the epoxide **2a** to the cuprate complex at −78 °C and stirring for 24 h at −78 to −20 °C followed by workup and chromatography on basic alumina (activity III) (8:1 hexane–ether) afforded 0.176 g (87%) of the alcohol as an 85:15 mixture of trans and cis isomers **4a** and **5a**: IR (film) ν 3300, 2900, 2845, 1640 (w), 1485, 1380, 1000 cm^{-1}; ^{1}H NMR (90 MHz) δ 0.80–0.97 (m, CH_3CH_2), 1.0–1.6 (env, ring CH_2), 1.73–2.63 (m), 4.20 (ABq; J = 12.1, $\Delta\nu$ = 55.8 Hz, trans CH_2O), 4.13 (s, cis CH_2O). Anal. Calcd for $C_{16}H_{30}O$: C, 80.61; H, 12.68. Found: C, 80.49; H, 12.75.

2-Pentyl-1-cyclododecenylmethanol (4b). A. Using *n*-BuMgBr, CuI, and Me_2S. The procedure described above for **4d** was followed. Addition of 0.300 g (1.4 mmol) of the epoxide **2b** to the cuprate complex at −78 °C and stirring for 15 h at −78 to −23 °C followed by workup and flash chromatography on silica gel (10:1 hexane–ethyl acetate) afforded 0.290 g (76%) of a solid alcohol as a 98:2 mixture of trans and cis isomers **4b** and **5b**: mp 59.5–61.5 °C; IR (film) ν 3400, 2900, 2845, 1645, 1470, 1390, 1000, 980, 920 cm^{-1}; ^{1}H NMR (90 MHz) δ 0.77–0.98 (m, CH_3CH_2), 1.0–1.6 (env, ring CH_2), 1.76–2.3 (m), 2.1–2.6 (m), 4.15 (ABq; J = 10.5, $\Delta\nu$ = 49.3 Hz, trans CH_2O), 4.08 (s, cis CH_2O). Anal. Calcd for $C_{18}H_{34}O$: C, 81.13; H, 12.86. Found: C, 81.39; H, 12.97.

B. Using Li-*n*-BuCuCN. The procedure of Acker was followed.[9] To a slurry of 0.430 g (4.80 mmol) of copper cyanide in 95.0 mL of diethyl ether was added slowly dropwise 2.00 mL (4.80 mmol) of 2.40 M *n*-butyllithium in hexane at −78 °C under argon. The solution and bath were allowed to warm slowly until the solution became light yellow. The epoxide **2b** was added dropwise at −54 °C, and the now bright yellow mixture was warmed to −20 °C overnight. The mixture was diluted at 0 °C with 3% ammonium hydroxide and stirred at room temperature for 15 min. The mixture was poured into saturated ammonium chloride and extracted with ether. The combined ether layers were washed with 3% ammonium hydroxide, saturated ammonium chloride, water, and brine and dried over potassium carbonate. Filtration and removal of solvent gave a crude oil. Purification on silica gel (10:1 hexane–ethyl acetate) afforded 0.389 g (61%) of a solid alcohol as a 95:5 mixture of trans and cis isomers **4b** and **5b**, mp 58.5–60.0 °C, whose spectral properties were identical with those reported in part A.

C. Using Li(n-Bu)$_2$Cu. The procedure of House[20] was followed. To a slurry of 0.914 g (4.80 mmol) of copper iodide in 10.0 mL of diethyl ether was added 4.0 mL (9.60 mmol) of 2.40 M *n*-butyllithium in hexane at −50 °C under argon. The dark brown homocuprate solution was stirred for 15 min, and then 0.50 g (2.40 mmol) of the epoxide **2b** in 2.0 mL of ether was added. After 1 h the mixture was diluted with 3% ammonium hydroxide and stirred for 20 min. The mixture was poured into saturated aqueous ammonium chloride and extracted with ether. The combined ether layers were washed with aqueous 3% ammonium hydroxide, aqueous ammonium chloride, water, and brine and dried over potassium carbonate. Filtration and removal of solvent gave a clear oil. Purification by flash chromatography on silica gel (10:1 hexane–ethyl acetate) afforded 0.491 g (77%) of a solid alcohol as a 98:2 mixture of trans and cis isomers **4b** and **5b**, mp 59.5–61.5 °C, whose spectral properties were identical with those reported in part A.

2-Pentyl-1-cyclotridecenylmethanol (4c). The procedure described above for **4d** was followed. Addition of 0.249 g (1.1 mmol) of the epoxide **2c** to the cuprate complex at −78 °C and stirring for 15.5 h at −78 to −23 °C followed by workup and flash chromatography on silica gel (10:1 hexane–ethyl acetate) afforded 0.163 g (52%) of the alcohol as a 95:5 mixture of trans and cis isomers **4c** and **5c**: IR (film) ν 3400, 2900, 2845, 1640, 1470, 1390, 990, 900 cm^{-1}; ^{1}H NMR (90 MHz) δ 0.8–1.0 (m, CH_3CH_2), 1.13–1.5 (env, ring CH_2), 1.76–2.1 (m), 2.17–2.63 (m), 4.17 (ABq; J = 11.7, $\Delta\nu$ = 46.7 Hz, trans CH_2O), 4.07 (s, cis CH_2O). Anal. Calcd for $C_{19}H_{36}O$: C, 81.36; H, 12.94. Found: C, 81.49; H, 12.87.

2-Pentyl-1-cyclopentadecenylmethanol (4e). The procedure described above for **4d** was followed. Addition of 0.577 g (2.30 mmol) of the epoxide **2e** to the cuprate complex at −78 °C and stirring for 15 h at −78 to −23 °C followed by workup and flash chromatography on silica gel (6:1 hexane–ether) afforded 0.501 g (71%) of the alcohol as a 93:7 mixture of trans and cis isomers **4e** and **5e**: IR (film) ν 3300, 2905, 2845, 1470, 1010 cm^{-1}; ^{1}H NMR (90 MHz) δ 0.76–1.0 (m, CH_3CH_2), 1.03–1.63 (env, ring CH_2), 1.66–2.13 (m), 2.14–2.60 (m), 4.15 (ABq; J = 11.7, $\Delta\nu$ = 43.5 Hz, trans CH_2O), 4.08 (s, cis CH_2O). Anal. Calcd for $C_{21}H_{40}O$: C, 81.75; H, 13.07. Found: C, 81.61; H, 13.12.

2-Pentyl-1-cyclohexadecenylmethanol (4f). The procedure described above for **4d** was followed. Addition of 0.400 g (1.5 mmol) of the epoxide **2f** to the cuprate complex at −78 °C and stirring for 23 h at −78 to −23 °C followed by workup and flash chromatography on silica gel (4:1 hexane–ether) afforded 0.423 g (87%) of the alcohol as a 94:6 mixture of trans and cis isomers **4f** and **5f**: IR (film) ν 3300, 2900, 2840, 1460, 1380, 1120, 1000 cm^{-1}; ^{1}H NMR (90 MHz) δ 0.78–1.0 (m, CH_3CH_2), 1.08–1.55 (env, ring CH_2), 1.8–2.63 (m), 4.12 (ABq, J = 10.8, $\Delta\nu$ = 39.0 Hz, trans CH_2O), 4.10 (s, cis CH_2O). Anal. Calcd for $C_{22}H_{42}O$: C, 81.92; H, 13.12. Found: C, 82.01; H, 13.18.

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Registry No. **1a**, 3045-74-7; **1b**, 3045-76-9; **1c**, 24899-36-3; **1d**, 95784-87-5; **1e**, 95784-88-6; **1f**, 1027-10-7; **2a**, 95784-89-7; **2b**, 87336-89-8; **2c**, 95784-90-0; **2d**, 95784-91-1; **2e**, 95784-92-2; **2f**, 95784-93-3; **3e**, 95784-94-4; **4a**, 95784-95-5; **4b**, 95840-54-3; **4c**, 95784-97-7; **4d**, 95784-99-9; **4e**, 95785-01-6; **4f**, 95797-89-0; **5a**, 95784-96-6; **5b**, 95840-55-4; **5c**, 95784-98-8; **5d**, 95785-00-5; **5e**, 95785-02-7; **5f**, 95785-03-8; cyclodecanone, 1502-06-3; cyclododecanone, 830-13-7; cyclotridecanone, 832-10-0; cyclotetradecanone, 3603-99-4; cyclopentadecanone, 502-72-7.

Synthesis and Deamination of 7,12-Dihydrobenz[*a*]anthracen-7,12-imines. A New Benz[*a*]anthracene Synthesis

Gordon W. Gribble,* Craig S. LeHoullier, Mukund P. Sibi, and Robert W. Allen

Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755

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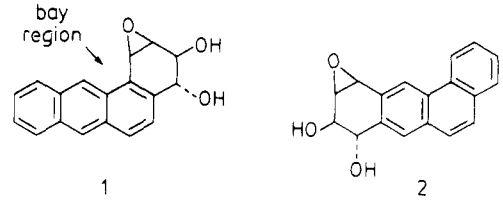
The Diels–Alder reaction between isoindoles (**7**) and 1-naphthalyne, as generated from 1-bromo-2-fluoronaphthalene (**11a**), 1-bromo-2-iodonaphthalene (**11b**), or 1-bromo-2-naphthyl *p*-toluenesulfonate (**11c**), affords the corresponding 7,12-dihydrobenz[*a*]anthracen-7,12-imine (**17**). Oxidative deamination of **17** with *m*-chloroperbenzoic acid gives the polyhalogenated benz[*a*]anthracenes (**3**, **19a–d**) in fair to good overall yields. A similar sequence with **7** and 5,6,7,8-tetrafluoro-1-naphthalyne, as generated from 1,2,3,4-tetrafluoro-5-chloronaphthalene (**14a**), 1,2,3,4-tetrafluoro-5-bromonaphthalene (**14b**), or 6-bromo-1,2,3,4-tetrafluoro-5-naphthyl *p*-toluenesulfonate (**16**), gives, after deamination of the intermediate benzanthracenimine **18**, benz[*a*]anthracenes **5** and **19e** in low overall yield.

During their pioneering study of 4-(dimethylamino)-azobenzene carcinogenesis, Miller and Miller[1] first proposed and utilized fluorine substitution as a probe to determine metabolic sites of carcinogenesis vis-à-vis detoxification in this and related carcinogens. The rationale was that fluorine would block metabolism at that site without affecting the ability of the molecule as a whole to be metabolized. Miller and Miller,[2] in collaboration with Newman,[3] extended this concept to the study of carcinogenic benz[*a*]anthracenes. Subsequent years have seen this "fluorine probe" tool used in many studies of several carcinogenic polynuclear aromatic hydrocarbons (PAH): methyl-substituted benz[*a*]anthracenes,[2,4] 5-methylchrysene,[5] benzo[*a*]pyrene,[6] benzo[*c*]phenanthrene,[7] dibenz[*a*,*h*]anthracene,[8] dibenzo[*a*,*i*]pyrene,[9] and 3-methylcholanthrene.[10] Depending on the position of fluorine substitution, the carcinogenicity of the PAH[11] may be suppressed, elevated, or unaffected.

These studies have invariably[12] focused on monofluorine substitution to answer questions about metabolism at a single carbon atom or arene double bond. Because current theories of PAH carcinogenesis[11,13,14] involve diol epoxides (e.g., "bay-region" **1**[13] diol epoxide and "non-bay-region"



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