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A MECHANISTIC AND SYNTHETIC STUDY OF ORGANOCOPPER SUBSTITUTION REACTIONS WITH SOME HOMOALLYLIC AND CYCLOPROPYLCARBINYL SUBSTRATES

APPLICATION TO ISOPRENOID SYNTHESIS

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Abstract—The double bond of cholesteryl and 5-norbornen-2-yl tosylates and the cyclopropane ring of cyclopropylmethylcarbinyl tosylate participate in organocuprate substitution reactions; retention of configuration at the nucleofugal sp^3-C atom and skeletal reorganizations are observed. A plausible mechanism for these reactions is discussed. Coupling of homogeranyl iodide with a four-carbon, functionalized, vinylic cuprate reagent is applied to stereospecific synthesis of *trans, trans*-farnesol.

Organocuprate (I) reagents are now widely used for preparation of many different types of synthetic intermediates and for construction of complex and structurally diverse natural products.[1] The widespread use of these nucleophilic reagents is due in large part to the stereospecificity of their reactions; substitution at sp^2-hybridized carbon proceeds with complete retention,[1,2] whereas displacement at sp^3-hybridized carbon usually proceeds with complete inversion of stereochemistry.[3,4] Furthermore, even such a substrate as neopentyl *p*-toluenesulfonate, which undergoes skeletal rearrangement at the slightest provocation, is converted into neopentylbenzene in high yield by the bulky lithium diphenylcuprate reagent.[5] In contrast, we have reported recently that the double bond of cholesteryl and 5-norbornen-2-yl tosylates and the cyclopropane ring of cyclopropylmethylcarbinyl tosylate *participate* in organocuprate substitution reactions; retention of configuration at the nucleofugal sp^3-C atom and skeletal reorganization have been observed in these systems.[6] We report now the details of this study which has led to a new isoprenoid synthesis based on coupling of a homoallylic substrate with a novel, 4-carbon, functionalized, vinylic cuprate(I) reagent.

$$R_2Cu\smile\!\!\!\rightarrow R'\!-\!\overset{\frown}{X} \longrightarrow \underset{\text{III}}{R\!-\!\overset{R'}{\overset{|}{Cu}}\!-\!R} \longrightarrow R\!-\!R' + R\!-\!Cu \qquad (1)$$

A mechanistic rationale has been developed to account for these results.[1,3-5] The rationale invokes oxidative addition of a halide or tosylate (R'–X) to the organocuprate(I), thus generating a transient copper(III) intermediate which then rapidly undergoes reductive elimination of the coupled product (eqn 1). Oxidative addition and reductive elimination must proceed stereospecifically, and the lifetime of the proposed copper(III) intermediate must be sufficiently short (or its stability sufficiently high) to preclude racemization or skeletal rearrangement of R'.

The cholesteryl—cyclocholestanyl system. Cholesteryl tosylate **1** reacts with excess lithium dimethylcuprate(I) in diethyl ether at 25° to form 3-β-methyl-5-cholestene **2** and 6-β-methyl-3α,5α-cyclocholestane **3** in approximately equal amounts (80% yield).‡ The stereochemistry of 3β-methylcholestene **2** prepared in this way was established by the identity of its spectral and physical properties with those of **2** prepared via a different, stereochemically unambiguous route starting with 3β-carboxy-5-cholestene.[7] The stereochemistry of 6β-methylcyclocholestane **3** was assigned on the basis of its spectral and physical properties which differed from those of the known 6α-methyl-3α, 5α-cyclocholestane.[8] Formation of 3-β-methyl-5-cholestene stereospecifically with retention of configuration at the C atom undergoing substitution and formation of the rearranged cyclocholestane stereospecifically with axial Me attachment at C-6 strongly suggest participation by the 5,6-double bond of cholesteryl tosylate.[9] Although rigorous kinetic data could not be obtained for this reaction, preliminary indications are that the reaction is of third order, which would be consistent with a recent report from Normant[10] and with the apparent behavior of the organocuprate as an electrophile which acts as a Lewis acid on the substrate; accepting electrons from the tosylate substrate, the organocuprate can increase from 14 to 16 the number of valence electrons associated with copper. In this connection, it is interesting to note that cholesteryl tosylate reacts more rapidly with lithium dimethylcuprate than with lithium di-n-butylcuprate or with lithium t-butoxy(t-butyl) cuprate both of which are probably stronger nucleophiles (weaker Lewis acids) than lithium dimethylcuprate.§

Finally, under identical conditions the relative rate of reaction with lithium dimethylcuprate(I) of cholesteryl tosylate and of *trans*-4-t-butylcyclohexyl tosylate is approximately 3 to 1, which result is also consistent with an increased driving force for reaction of the cholesteryl tosylate.[11]

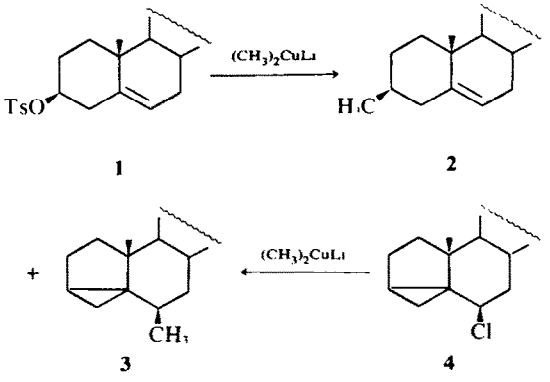
6β-Chloro-3,5-cyclocholestane reacts with lithium dimethylcuprate(I) much more rapidly than any other alkyl

†This paper is taken in part from the Ph.D. thesis of J-S. Ting, The Johns Hopkins University, Baltimore, Maryland (1975).

‡Also 3,5-cholestadiene is formed in 10–15% yield.

§The stronger Lewis acidity of lithium dimethylcuprate over lithium di-n-butylcuprate may account for the heretofore puzzling difference in reaction products from these two cuprate reagents and $CH_3O_2C(CH_2)_2COCl$ see G. H. Posner, C. E. Whitten and P. E. McFarland, *J. Am. Chem. Soc.* **94**, 5106 (1972).

chloride[1] and forms an equal mixture of 3β-methylcholestene and 6β-methyl-3,5-cyclocholestane, which suggests that the same intermediate is formed from this cyclopropylcarbinyl chloride **4** as from homoallylic tosylate **1**. Although our experiments do not permit unambiguous characterization of this intermediate, it would appear to possess carbocationic rather than radical character.[12-14] Control experiments were performed to study whether homoallylic tosylate **1** rearranged to 6β-iodo-3,5-cyclocholestane prior to reaction with the organocuprate; exposing cholesteryl tosylate(**1**) to anhydrous lithium iodide or to tri-n-butylphosphinecopper iodide in diethyl ether gave no cyclocholestane derivatives. Thus cholesteryl tosylate(**1**) rearrangement to the cyclocholestanyl system occurs *during and not prior* to reaction with the organocuprate reagent.



Halide and carboxylate leaving groups were tried as well. Cholesteryl bromide is stable to lithium dimethylcuprate(I) in refluxing diethyl ether for longer than 24 hr! 6β-Acetoxy-3,5-cyclocholestane is cleanly cleaved by lithium dimethylcuprate into 6β-hydroxy-3,5-cyclocholestane,[15] but cholesteryl pivalate (trimethylacetate) is stable toward Me_2CuLi for longer than 32 hr.

The 5-norbornen-2-yl–nortricyclyl system. *exo*-5-Norbornen-2-yl tosylate (**5**) reacts with excess organocuprate reagents to form 2-alkylnortricyclanes in high yields (Table 1). The identity of the products as substituted nortricyclanes was confirmed by matching their physical and spectral properties with those of authentic samples.[16] It is noteworthy that, unlike the cholesteryl system, the cyclopropyl partner in this 7-carbon system is thermodynamically more stable than the olefinic unit;[9] no alkylated norbornenes were detected. Thus this organocuprate synthesis of 2-alkylnortricyclanes may be an improvement over Wittig's approach to these compounds using norbornadiene and organolithium reagents,[16] and preparation of regiospecifically deuterated nortricyclanes might be possible using a copper deuteride reagent.[17] Control reactions using norbornenyl tosylate **5** and lithium alkyls themselves (in the absence of copper) causes sulfur oxygen cleavage with formation of *exo*-5-norbornen-2-ol (Table 1).[18]

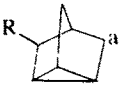
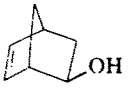
Evidence for participation of the double bond of *exo*-norbornenyl tosylate **5** in reaction with organocuprates rests not only on formation of tricyclic products but also on the kinetics of this reaction.[9] The *endo* and *exo* isomers of 5-norbornen-2-yl tosylates were compared; whereas the *exo* epimer is consumed completely by lithium dimethylcuprate within 6 hr at 25°, the *endo* epimer is recovered in 57% yield even after 24 hr at 25°, and no alkylated products are formed from the *endo* isomer.† Although the exact nature of the intermediate formed from the *exo* isomer is uncertain, it is probably cationic rather than radical in nature because formation of 5-norbornenyl-2-yl radicals is not assisted by participation of the double bond.[19]

Bromide and acetate leaving groups were also tried in this system. Somewhat surprisingly 2-nortricyclyl bromide was recovered in 50% yield when exposed to excess lithium dimethylcuprate for 48 hr at 25°. *Exo*-5-Norbornen-2-yl acetate was cleaved into *exo*-5-norbornen-2-ol in 82–85% yields by lithium dimethylcuprate and di-n-butylcuprate reagents.[15]

The acyclic homoallylic–cyclopropylcarbinyl–cyclobutyl system. Scheme I represents some possibilities for reaction of organocuprates with cyclopropylcarbinyl tosylate **6**, with homoallylic tosylate **9**, and with the corresponding cyclobutyl tosylate. We have investigated two (**6** and **9**) of these three types of substrates; the results are summarized in eqns (2)–(7). Cyclopropylcarbinyl tosylate **6** reacts with lithium di-n-butylcuprate probably via an intermediate represented simply and in absence of any definitive evidence about its structure as copper(III)

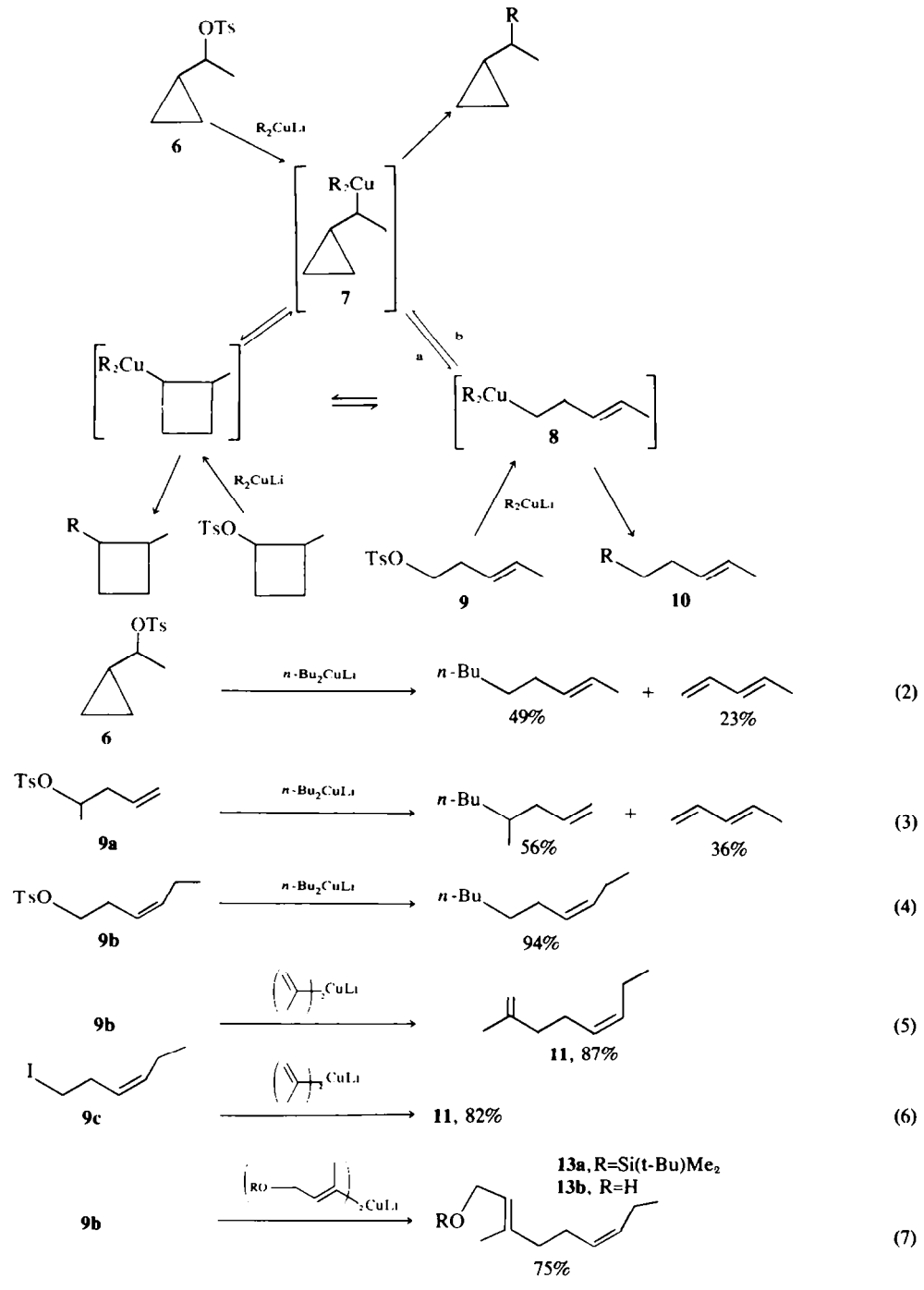
†A relevant observation has been reported in the lithium dimethylcuprate reaction with *exo*- and *endo*-norbornyl tosylates; the *endo* isomer gives only *exo*-2-methylnorbornane (inversion), but the *exo* isomer gives about 14% *endo*-2-methylnorbornane (inversion) and 44% *exo*-2-methylnorbornane (*retention*): see Ref. 4.

Table 1. Reaction of *exo*-5-norbornen-2-yl tosylate (**5**) with organometallic reagents in diethyl ether

Organometallic reagents (5 eq)	Reaction time (hr)	Reaction temperature			
			R	a	OH
Me_2CuLi	6	25°	R=Me	62%[b]	13%
n-Bu_2CuLi	3	0°	R=n-Bu	84%	—
t-BuO(*t*-Bu)CuLi	3.5	−53°[c]	R=*t*Bu	87%	—
PhS(*t*-Bu)CuLi	72	0°	R=*t*Bu	91%	—
MeLi	6	25°		—	67%[a]
n-BuLi	5	0°		—	86%[a]

[a] % yield of distilled product based on starting tosylate.
[b] Glpc yield using a calibrated internal standard.
[c] Tetrahydrofuran was used as solvent.

Scheme 1.



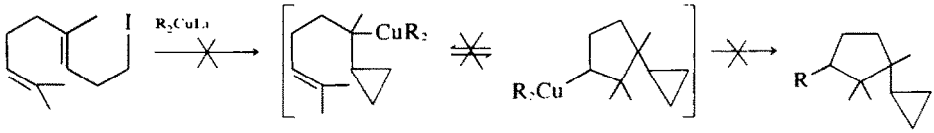
species 7;[1,†] whether intermediate 7 is indeed a copper (II)-radical complex[20] or *more likely a cuprate*(I)-*cation complex*[12] remains to be determined. Also for simplicity, cyclopropylcarbinyl intermediate 7 is depicted as distinct from homoallylic intermediate 8, whereas in reality 7 and 8 may be just extreme canonical forms of a truly delocalized intermediate.[9] That cyclopropylcarbinyl tosylate 6 gives only rearranged (open chain) products[21] in an irreversible process *argues against* a cationic intermediate,[22] but sterospecific formation of *trans*-olefin 10 from tosylate 6 *supports* the intermediacy of a cation in analogy with the cationic intermediates in the Julia method for acid catalyzed conversion of cyclopropylcarbinols into *trans*-olefins.[23]

Homoallylic intermediate 8 could in principle be formed also from homoallylic tosylate 9; indeed, homoallylic tosylate 9a is converted into the corresponding butylated

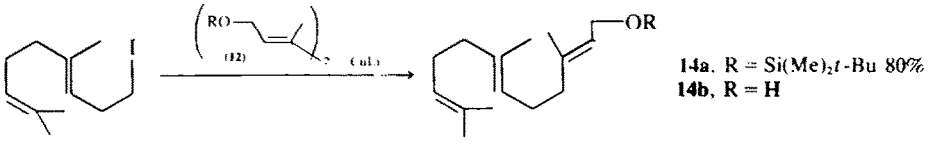
†A relatively stable copper(III)–allene has recently been reported: P. Vermeer, J. Meijer and L. Brandsma, *Recl. Trans Chim.* **94**, 112 (1975); J. L. Luche, E. Barreiro, J. M. Dollat, and P. Crabbé, *Tetrahedron Letters* 4615 (1975), for recent examples of Cu(III) in biological systems see D. W. Margerum, K. L. Chellappa, F. P. Bossu, and G. L. Burce, *J. Am. Chem. Soc.* **97**, 6894 (1975); G. R. Dyrkacz, R. D. Libby and G. A. Hamilton, *Ibid.* **98**, 626 (1976).

product as in eqn (3). If an equilibrium linking intermediates **7** and **8** were to exist, then the stereochemistry about the double bond in **8** might be lost; in particular, if intermediate **8** possessed a *cis*-double bond, its conversion to cyclopropylcarbinyl intermediate **7** and then back to **8** might cause isomerization of the *cis*-double bond to the thermodynamically more stable *trans*-isomer. That such an isomerization does *not* occur is amply demonstrated in eqns (4)–(7) in which *cis*-3-hexenyl tosylate and iodide are butylated, isopropenylated, and butenylated (eqn 7) with retention of the *cis*-configuration about the double bond. Apparently pathway b in Scheme 1 is not operative.

These results led us to explore the possibilities of coupling homogeranyl tosylate or iodide with 4-carbon vinylic cuprate reagent **12** so as to produce a 1,5-diene having the characteristic substitution pattern of an isoprenoid.[24] The requisite vinylic cuprate reagent **12** was prepared from E-3-iodo-2-butenol which itself was prepared from 2-butynoic acid using a literature procedure.[25]† An undesirable reaction between organocuprate reagent **12** and homogeranyl iodide might have occured as shown in (eqn 8), but in fact no cycloalkyl products were formed. To our gratification, homogeranyl iodide reacted with the 4-carbon vinylic cuprate **12** to form *trans, trans*-farnesol silyl ether **14a** stereospecifically in 80% isolated yield (eqn 9). This convergent 1-carbon plus 4-carbon sterospecific elaboration of the isoprenoid 1,5-diene unit is clearly applicable to construction of other interesting isoprenoids.‡§



(8)



14a, R = Si(Me)$_2$*t*-Bu 80%
14b, R = H (9)

EXPERIMENTAL

M.ps and b.ps are uncorrected. IR spectra were recorded with a Perkin Elmer 457 Spectrophotomer, and NMR spectra were recorded on a Varian A-60 or JEOL MH-100 spectrometer. Mass spectra were measured on a Hitachi-Perkin Elmer RMU-6 spectrometer, and microanalyses were performed by Galbraith Laboratories Inc. and by Chemalytics, Inc. Analytical gas liquid phase chromatography was done using a Varian Aerograph Model 1200 Chromatograph with the following columns:

Column A: 10′ × 1/4″, 10% FFAP on Chrom w (60/80)
Column E: 10′ × 1/8″, 20% Reoplex 400 on Anachrom AS (80/90)

Glpc yields were determined by comparing peak areas of products with those of an internal standard whose response factors relative to the authentic product had been previously calibrated.

Preparative glpc was carried out on a Varian Aerograph Model 90-p Chromatograph using the following columns:

Column G: 20′ × 3/8″, 20% Carbowax on Chrom W (60/80)
Column H: 20′ × 3/8″, 20% QF-1 on Chrom W (45/60)

The following materials were purchased from Aldrich Chemical Co: 4-penten-2-ol, cyclopropylmethyl carbinol, *cis*-3-hexenol, and cholesteryl bromide and iodide. Cuprous iodide (Fischer Scientific Co.) was washed with THF in a Soxhlet extractor for 24 hr, and it was dried *in vacuo* at 25°, or it was purified by precipitation from aqueous potassium iodide.[26]

Alkyl-lithium reagents were purchased from Foote Mineral Co. and Ventron Co. and were used directly from the bottle via hypodermic syringes. Analyses of the organolithium reagents were performed using the Gilman double titration procedure.[27] All reactions involving organocuprate reagents were carried out in an inert atmosphere of prepurified nitrogen, and these reagents were prepared as previously described.[1]

Usual product work-up involved quenching the reaction with aqueous ammonium chloride and extraction with diethyl ether.

Cholesteryl tosylate (**1**) *reaction with lithium dimethylcuprate*

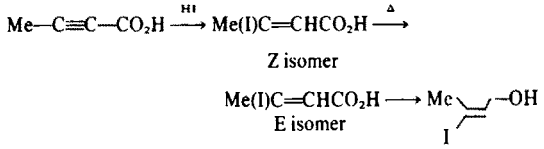
To 5 mmol of lithium dimethylcuprate at 25° under N_2 was added 540 mg (1 mmol) of cholesteryl tosylate in 2 ml of THF. The mixture was stirred for 6 hr. After aqueous ammonium chloride-diethyl ether work-up, the crude product (377 mg 97.6%, NMR spectrum showed an equal mixture of **2** and **3** was poured onto a column packed with neutral activity I alumina and eluted with methylene chloride, and then subjected to preparative TLC separation (SiO_2 PF 254 containing $CaSO_4$ with 3% $AgNO_3$ in $CHCl_3$). A small amount (13 mg) of **2** was obtained from the origin of the TLC plate. NMR ($CDCl_3$): δ 5.2 (m, 1H, vinyl), its NMR and IR spectra were the same as those of authentic 3β-methyl-5-cholestene,[7] m.p. 82–84°, mixed m.p. with an authentic sample was undepressed (CD curve[28] 200 nm ($\Delta\epsilon$ + 3.3), 183 ($\Delta\epsilon$ − 11.5). The material collected from R_f = 0.7 which was a mixture of **2** and **3** was then subjected to two more preparative TLC separations. After being recrystallized from EtOH, pure **3** was obtained: M.p. 62–64°, NMR ($CDCl_3$) δ 0.7 (d), 0.4 (m, 3H, Δ), 2.0–0.9 (m); IR (CCl_4) 3050 cm^{-1} (Δ–H), 2950 (CH). (Found: C, 87.82; H, 12.61. Calc. for $C_{28}H_{48}$: C, 87.50; H, 12.50%).

The third product, 3,5-cholestadiene, was purified by SiO_2 column chromatography with n-hexane as eluent and was identified by its UV spectrum,[29] λ_{max}^{EtOH} 227 mμ, 235 and 243; m.p. 77–78.5° (lit.[29] m.p. 78–79°). Its yield was 86.5 mg (12%).

Preparation of 3,5-cyclocholestan-6β-ol

A mixture of 19.71 g (36.43 mmol) of cholesteryl tosylate, 95.68 g (160 mmol) of KOAc, 300 ml acetone and 75 ml water were refluxed for 15 hr. The acetone was evaporated on a rotary evaporator. The residue was extracted with pentane and the

†The following transformations were performed according to a modified method used by LeNoble, W. J. LeNoble, *J. Am. Chem. Soc.* **83**, 3897 (1961); see also M. Schlosser and E. Hammer, *Helv. Chim. Acta* **57**, 2547 (1974).



‡For syntheses of sex pheromones using homoallylic electrophiles and organocuprates, see J. A. Labovitz, C. A. Henrick and V. L. Corbin, *Tetrahedron Letters*, 4209 (1975) and R. J. Anderson and C. A. Henrick, *J. Am. Chem. Soc.* **97**, 4327 (1975).

§We have successfully performed a conjugate addition reaction of our 4-carbon functionalized vinylic cuprate reagent to cyclohexenone; cf. E. J. Corey and R. H. Wollenberg, *J. Org. Chem.* **40**, 2265 (1975).

pentane soln was poured onto a column of activated alumina. The elution order was hexane (500 ml), hexane–benzene (2:1) (200 ml) and ether (600 ml). The hexane–benzene eluent gave, after evaporation and crystallization, 5.720 g (40%) of 3,5-cyclocholestan-6β-ol: m.p. 69–71° (lit.[30] m.p. 66.7–67.9°); NMR (CCl_4) δ 4.65 (m, 1H, OH), 3.15 (m, 1H, methine).

Preparation of 6β-chloro-3,5-cyclocholestane (4)

Redistilled thionyl chloride 0.952 g (8 mmol) was added to an ice-cooled soln of 2.760 g (7.16 mmol) of 3,5-cyclocholestan-6β-ol in 25 ml of anhyd ether. The ether was then evaporated on a rotary evaporator without heating. Pentane (25 ml) was added to the white solid. The pentane soln was filtered through $CaCO_3$ (5 g) and then it was evaporated to dryness at room temp. After being recrystallized from acetone, 6β-chloro 3,5-cyclocholestane was obtained in 77% yield (2.520 g); m.p. 74–75° (lit.[14] 73–78°); NMR (CCl_4) δ 3.7 (m, 1H, methine), 0.4 (m, 3H, Δ).

Reaction of 6β-chloro-3,5-cyclocholestane (4) *with lithium dimethylcuprate*

To 5 mmol of lithium dimethylcuprate soln at room temp. was added 0.404 g (1 mmol) of 6β-chloro-3,5-cyclocholestane in 1 ml of anhyd ether and the mixture was stirred for 24 hr. After isolation as usual, the NMR spectrum of the crude product 0.354 g (92%) showed a mixture of **2** and **3** in equal amounts. The crude product was seperated on preparative silver nitrate TLC. Extraction with CCl_4 from the base line gave 17 mg of **2**, m.p. 84–86°. The extract from $R_f \sim 0.6$ contained 0.265 g of products which again were a mixture of **2** and **3**. After a few more preparative TLC separations and recrystallizations from abs. EtOH, pure **3** was obtained, having m.p. and NMR spectrum identical with those of the previously prepared sample.

Reaction of cholesteryl tosylate with lithium iodide

To LiI 2.676 g (20 mmol) suspended in 30 ml anhyd ether under N_2 was added 0.540 g (1 mmol) of cholesteryl tosylate in 2 ml anhyd THF stirring was continued at room temp. for 10 hr. The mixture was then quenched with water, washed with 5% $Na_2S_2O_3$aq, extracted with ether, dried over $MgSO_4$ and concentrated. The crude product (0.473 g) was shown by NMR to contain about 25% of the starting material. Recrystallization from abs EtOH gave 0.280 g (56%) of 3α-iodo-5-cholestene: m.p. 99.5–101.5°, NMR ($CDCl_3$) δ 5.2 (m, 1H, vinyl), 3.90 (m, 1H, ). The stereochemistry of the 3-iodo atom was assigned α due to the chemical shift of  (δ 3.90) different from that of the authentic 3β-isomer (Aldrich, δ 3.80 for ); IR (CCl_4) 1600 cm^{-1} (C=C).† (Found: C, 65.48; H, 9.18; I, 25.34. Calc. for $C_{27}H_{45}I$: C, 65.32 H, 9.07; I, 25.61%).

6β-Acetoxy-3,5-cyclocholestane

A. Preparation.[30] A soln of 5.50 g (14.25 mmol) of 3,5-cyclocholestan-6β-ol and 2.907 g (28.5 mmol) Ac_2O in 15 ml dry pyridine were stirred at room temp. for 24 hr. The mixture was diluted with distilled water, extracted with ether, washed with water, 6N HCl, water, 5% $NaHCO_3$ and water and dried over $MgSO_4$. After recrystallization from MeOH, 0.664 g (86%) of 6β-acetoxy 3,5-cyclocholestane was obtained, m.p. 67–68°; NMR (CCl_4) δ 4.6 (m, 1H, ), 1.95 (s, 3H, $\underline{CH_3}$), 0.45 (m, 3H, Δ-H).

B. Reaction with lithium dimethylcuprate. To 10 mmol of lithium dimethylcuprate soln at room temp. was added 0.856 g (2 mmol) of 6β-acetoxy-3,5-cyclocholestane in 2 ml anhyd ether. The mixture was stirred for 2 days and was isolated as usual. After recrystallization from acetone, 3,5-cyclocholestan-6-ol (0.664 g, 86%) was obtained, m.p. 69–70°; NMR is identical with that of the previously prepared sample.

Preparation of exo-5-*norbornen-2-yl acetate*

To 3.85 ml (4.04 g, 0.0672 mol) of AcOH in a pyrex glass tube (22 × 175 mm, which had been flamed down to a narrow neck) was added 12.5 ml (11.224 g, 0.122 mol) of norbornadiene. The contents of the test tube were then frozen in dry ice-acetone, treated briefly with a N_2 stream and sealed by an oxygen-acetylene torch. The tube was heated for 22 hr at 188 ± 5° in a mineral oil bath. The resulting mixture was poured into a flask and treated with $CaCO_3$ powder (10 g) and then extracted with pentane. The pentane soln was filtered and the pentane was evaporated along with excess norbornadiene on a rotary evaporator. After vacuum distillation (15 mm) at 74–75° (lit.[31] b.p.$_{12}$ 72–74°), *exo*-5-norbornen-2-yl acetate (8.066 g, 79%) was obtained: NMR (CCl_4) δ 6.1 (m, 2H, vinyl), 4.6 (m, 1H, ), 2.83 (m, 2H, methyne), 1.98 (s, 3H, $\underline{CH_3}$), 1.16–1.8 (m, 4H).

Preparation of exo-5-*norbornen-2-ol*

KOH (3.900 g) was dissolved in 3.9 ml distilled water in a round bottomed bottle and MeOH (12 ml) was added to produce a homogeneous soln. *exo*-5-Norbornen-2-yl acetate 3.800 g (25 mmol) was added slowly with stirring, and the mixture was refluxed for 4 hr. MeOH was distilled off, and the mixture was acidified by dil H_2SO_4, extracted with ether, dried over $MgSO_4$ and evaporated on a rotary evaporator. After being recrystallized from pentane, 2.038 g (74%) of *exo*-5-norbornen-2-ol was obtained: m.p. 98–99° (lit.[32] 97.5–99.2°); NMR ($CDCl_3$) δ 6.0 (m, 2H, vinyl), 4.3 (s, 1H, O–H), 3.75 (m, 1H, ), 2.7 (m, 2H methine), 1.0–1.75 (m, 4H); IR (CCl_4) 3630 and 3350 cm^{-1} (O–H), 3070 (C=C–H), 2980 (C–H), 1060 (C–O).

exo-5-*Norbornen-2-yl tosylate* (5)

A. Reaction with lithium dimethylcuprate. To 10 mmol of lithium dimethylcuprate soln at room temp. was added 0.528 g (2 mmol) of *exo*-5-norbornen-2-yl tosylate (its NMR spectrum identical with that in the lit.)[33] in 5 ml of anhyd ether, and the mixture was stirred for 6 hr. After the usual work-up, the products were shown on analytical glpc (column A, 105°) with 1-tetradecene as internal standard to be 133.4 mg (62%) of 3-methylnortricyclane and 29.2 mg (13%) of *exo*-5-norbornen-2-ol. 3-Methylnortricyclane was purified by preparative GLC (column H, 110°): NMR (CCl_4) δ 1.0–1.7 (m, 6H), 0.95 (d, 3H, $-CH_3$), 0.88 (d, 3H, Δ–H); IR (CCl_4) 3050 cm^{-1} (Δ–H), 2930 (C–H); mass spectral molecular weight: 108, Calc. for C_8H_{12}: 108; n_D^{20} 1.4548 (lit.[34] n_D^{20} 1.4559). *exo*-5-Norbornen-2-ol was identified by comparing its retention time and NMR spectrum to those of an authentic sample.

B. *Reaction with lithium di-n-butylcuprate.* To 10 mmol of lithium di-n-butylcuprate solution at 0° was added 0.528 g (2 mmol) of **5** in 5 ml anhyd ether, and the mixture was stirred for 3 hr. Isolation and purification by preparative glpc (column H, 110°) gave 3-n-butylnortricyclane: NMR (CCl_4) δ 1.0–1.7 (m, 12H), 0.9 (t, 3H, $-\underline{CH_3}$), 0.86 (d, 3H, Δ–H); IR (CCl_4) 3055 cm^{-1} (Δ–H), 2950 (C–H); mass spectral mol wt: 150, Calc. for $C_{11}H_{18}$: 150; n_D^{20} 1.4649 (lit.[35]) n_D^{20} 1.4640). Its yield was 251.3 mg (84%) by analytical glpc (column A, 110°) with 1-tetradecene as internal standard.

C. *Reaction with lithium* t-*butoxy*(t-*butyl*)*cuprate.* To 5 mmol of lithium t-butoxy(t-butyl)cuprate[36] soln at −78° was added 0.174 g (0.66 mmol) of *exo*-5-norbornen-2-yl tosylate in 2 ml of dry THF. The mixture was stirred at −78° for 1 hr then −55 ~ −53° for 3.5 hr, and finally was warmed up to room temp. Isolation as usual and distillation at 77 ~ 79° (20 mm) gave 87.1 mg (87%) of 3-t-butyl-nortricylane: NMR (CCl_4) δ 0.9–1.9 (m, 9H), 0.9 (m, 9H), 0.9

†For conversion of cholesteryl tosylate directly into 3α-chlorocholest-5-ene by lithium chloride, see D. N. Kevill, C. R. Degenhardt and R. L. Anderson, *J. Org. Chem.* **41**, 381 (1976).

(s, 9H, t-Bu); IR (CCl_4) 3060 cm^{-1} (Δ–H), 2950 (C–H), 1397 and 1365 (Me bending vibration). The NMR and IR spectra were identical with those of an authentic sample.[16]

D. *Reaction with lithium thiophenoxy(t-butyl)cuprate.* To 10 mmol of lithium thiophenoxy(t-Bu)cuprate[36] soln at 0° was added 0.528 g (2 mmol) of *exo*-5-norbornen-2-yl tosylate in 5 ml of anhyd ether, and the mixture was stirred for 3 days. Usual work-up and distillation under vacuum gave 0.271 g (91%) of 3-t-butylnortricyclane, $b.p._{.20}$ 78–79°. The NMR and IR spectrum were the same as those of authentic sample.[16]

Cyclopropylmethylcarbinyl tosylate (**6**)

A. *Preparation.*[37] To 1.14 g (0.05 mol) of Na with 50 ml anhyd ether under N_2 was added 4.300 g (0.05 mol) of cyclopropylmethylcarbinol in 100 ml anhyd ether and the mixture was stirred at room temp. overnight. To the alchoholate formed was added 9.532 g (0.05 mol) of recrystallized *p*-toluenesulfonyl chloride in 100 ml anhyd ether and the mixture was stirred at room temp for another 2 days. The mixture was centrifuged and the ether phase decanted. Cyclopropylmethylcarbinyl tosylate (18.402 g, 70%) was obtained: NMR (CCl_4) δ 7.7 (q, 4H, aromatic), 4.2 (m, 1H, C(OTs)H), 2.45 (s, 3H, φ–CH_2), 1.2 (m, 4H, CH_2 and CH–OTs), 0.9–0.4 (m, 4H, Δ–H); IR (CCl_4) 3050 cm^{-1} (Δ–H), 2950 (C–H), 1380 and 1190 (sulfonate).

B. *Reaction with lithium di-n-butyl-cuprate.* To 10 mmol of lithium di-n-butylcuprate at 0° was added 0.481 g (2 mmol) of cyclopropylmethylcarbinyl tosylate in 2 ml anhyd ether. The mixture was stirred for 2.5 days and was isolated as usual. Quantitative glpc analysis (column A, 70°) with *trans*-2-octene as internal standard showed 103 mg (49%) of *trans*-2-nonene and 31 mg (23%) of *trans*-1,3-pentadiene. *trans*-2-Nonene was isolated by preparative glpc (column G, 80°): NMR (CCl_4) δ 5.4 (m, 2H vinyl), 0.95 (t, 3H, $-CH_2CH_3$); IR (CCl_4) 3020 cm^{-1} (C=C–H), 2940 (CH), 1650 (C=C), 961 (*trans* C=C–H out-of-plane bending vibration); n_D^{20} = 1.4187 (lit.[38] n_D^{20} = 1.4172); mass spectral molecular weight: 126, calcd for C_9H_{18}: 126. *trans*-1,3-Pentadiene was identified by comparing its retention times with the retention times of an authentic sample on two different glpc columns.

Reaction of 4-penten-2-yl tosylate with lithium di-n-butylcuprate

To 10 mmol of lithium di-n-butylcuprate at 0° was added 0.481 g (2 mmol) of **4a** in 5 ml ether and the mixture was stirred for 24 hr. After usual work-up, 4-methyl-1-octene (1.42 mg, 56%) and *trans*-1,3-pentadiene (49 mg, 36%) were obtained (qualitative glpc analysis using column A, 65° with 1-tetradecene and *trans*-2-octene as internal standards). 4-Methyl-1-octene was isolated using preparative glpc (column H, 80°); NMR (CCl_4) δ 4.7–6.0 (m, 3H, vinyl), 2.0 (m, 2H, C=C–CH_2), 1.3 (m, 7H), 0.9 (m, 6H, 2–CH_3); IR (CCl_4) 3080 cm^{-1} (C=C–H), 2960 (C–H), 1640 (C=CC), 1470 (–CH_3 bending vibration), 990, 910 (C=C–H out-of-plane). (Found: C, 85.30; H, 13.93. Calc. for C_9H_{18}: C, 85.71; H, 14.29%).

trans-1,3-Pentadiene was identified by comparing its retention time with that of an authentic sample on two different glpc columns.

cis-3-*Hexen*-1-*yl tosylate* (**9b**)

A. *Preparation.*[39] To a stirred soln of 6.303 g (33 mmol) of *p*-toluenesulfonyl chloride in 20 ml dry pyridine at 0° was added 3.000 g (30 mmol) of *cis*-3-hexen-1-ol dropwise and the mixture was stirred for 3 days. After isolation and purification on a SiO_2 column with $CHCl_3$ as eluent *cis*- **9b** (3.031 g; 42.3%) was obtained: NMR (CCl_4) δ 7.5 (q, 4H, aromatic), 4.8–5.7 (m, 2H, vinyl) 3.9 (t, 2H, CH—OTs), 2.4 (s, 3H, φ–CH_3), 1.66–2.7 (m, 4H, C=C–(CH_2)$_2$), d 0.1 (t, 3H, $-CH_3$); IR (CCl_4) 3020 cm^{-1} (C=C–H), 2970 (C–H), 1600 (C=C), 1340 and 1187 (sulfonate).

B. *Reaction with lithium di-n-butylcuprate.* To 5 mmol of lithium di-n-butylcuprate soln at 0° was added 0.254 g (1 mmol) of *cis*- **9b** in 2 ml anhyd ether and the mixture was stirred for 10 hr. After isolation, *cis*-3-decene (132 mg, 94.2% by quantitative glpc analysis using 1-tetradecene as internal standard on column A, 80°) was obtained and was purified by preparative glpc (column H 80°). NMR (CCl_4) δ 5.23 (m, 2H, vinyl), 2.0 (m, 4H, 2 C=C–CH_2), 1.28 (m, 8H), 0.9 (double triplets, 6H, 2–CH_3); IR (CCl_4) 3010 cm^{-1} (C=C–H), 2960 and 2930 (C–H); b.p. 172–173° (lit.[40] b.p. 173.3°).

cis-3-*Hexen*-1-*yl iodide* (**9c**)

A. *Preparation.* To 0.825 g (5.5 mmol) of NaI in 20 ml acetone was added 1.390 g (5.47 mmol) of *cis*-3-hexen-1-yl tosylate, and the mixture was refluxed for 4 hr. Most of the acetone was evaporated, and the residue was extracted with ether, washed with distilled water and 5% $Na_2S_2O_3$, dried over $MgSO_4$, and concentrated. Distillation under reduced pressure gave 0.890 g (78%) of *cis* **9c**: $b.p._{.20}$ 67–68° (lit.[39] $b.p._{.15}$ 65°); NMR (CCl_4) δ 5.3 (m, 2H, vinyl), 3.1 (t, 2H, CH_2–I), 2.6 (9, 2H, C=C–CH_2–CH_2I), 2.0 (m, 2H, C=C–CH_2–CH_3, 0.95 (t, 3H, CH_3).

B. *Reaction with lithium di-n-butylcuprate.* To 5 mmol of lithium di-n-butylcuprate soln at 0° was added 0.210 g (1 mmol) of *cis*-3-hexen-1-yl iodide in 2 ml anhyd ether, and the mixture was stirred for 24 hr. Quantitative glpc analysis (column A, 80°) with 1-tetradecene as internal standard gave 82 mg (87%) of *cis*-3-decene. It was purified by preparative glpc (column H, 80°), and was identified by comparing its retention time and NMR spectrum with those of a previously prepared sample.

C. *Reaction with lithium diisopropenylcuprate.* To 5 mmol of lithium diisopropenylcuprate soln at −45° was added 0.420 g (2 mmol) of *cis*-3-hexen-1-yl iodide in 2 ml anhyd ether, and the mixture was stirred for 4 hr. Isolation and distillation under vacuum gave 202 mg (82%) of 2-methyl-*cis*-1,5-octadiene: n_D^{20} 1.4294; NMR ($CDCl_3$) δ 5.5 (m, 2H, vinyl), 4.85 (m, 2H, C=CH_2), 2.2–1.6 (m, 6H, methylene), 1.70 (s, 3H, C=C–CH_3), 1.0 (t, 3H, CH_3); IR (CCl_4) 3060 cm^{-1} (C=C–H), 2140 (C–H), 1640 (C=C), 890 (C=C–H out-of-plane). Its stereochemistry was assigned as *cis* due to the lack of a characteristic *trans* C=C–H absorption at 960–970 cm^{-1}.[41] (Found: C, 87.26; H, 12.65. Calc. for C_9H_{16}: C, 87.09; H, 12.90%).

Preparation of cuprate **12**

E-3-Iodo-2-butenol (**12a**) was converted into its *t*-butyldimethylsilyl ether **12b** according to the procedure of Corey.[42] Conversion of this vinylic iodide (**12b**) into the corresponding vinylic lithium species and then vinylic cuprate (**12**) was performed as follows.[42]

To a 50 ml round bottom flask which was flame dryed while purging with argon and which contained 15 ml anhyd ether was added **12b**. After cooling to −78°, t-BuLi (1.23M, 1.6 ml, 2.02 mmol) was added dropwise and stirring was continued for 2 hr at −78°. To this was added 0.095 g (0.50 mmol) CuI and stirring was continued for 30 min at −78° to yield the desired cuprate (**12**).

Reaction of cis-3-*hexenyl tosylate with cuprate* (**12**)

To the cuprate **12** was added 0.188 g (0.75 mmol) of *cis*-3-hexenyl tosylate in 1 ml diethyl ether and stirring was continued at −78° for 6 hr. After this time the mixture was allowed to warm to room temp. and stirred at this temp. for 15 min. The mixture was then poured into sat. NH_4Claq and diluted with ether. The organic phase was separated and the aqueous phase extracted with 50 ml ether. The organic phases were combined and dried over Na_2SO_4 and concentrated *in vacuo* to give a light yellow oil. The crude product was chromatographed on 75 g of silica gel, eluted with a gradient of cyclohexane/ether, affording 0.107 g (75%) of **13a**: NMR (CCl_4) δ 5.52–4.85 (m, 3H), 4.10 (d, j = 7 Hz 2H), 1.28 (s, 3H), 0.83 (s, 12H), 0.30 (s, 6H); IR (CCl_4) 1645 cm^{-1}, mass spectra (70 eV), *m/e* 268 (70) 133 (100) (relative intensities). The ether **13a** was quantitatively converted to alcohol **13b** by treatment with 20% HCl for 3 hr at room temp. Alcohol **13b** was purified by distillation at 83° (15 mm). (Found 77.83; H, 11.93. Calc. for $C_{10}H_{8}O$: C, 77.88; H, 11.76%).

Reaction of homogeranyl iodide with cuprate **12**

Homogeranyl iodide (0.140 g, 0.49 mmol, $b.p._{.01}$ 90°, prepared according to Ref. 43) in 1 ml dry diethyl ether was added at −78° to 1.0 mmol of **12**. The reaction was allowed to stir at −78° for 3 hr after which time the resulting mixture was warmed to room temp and quenched by pouring into sat NH_4Claq. The phases were

separated and the aqueous phase extracted with three 30 ml portions diethyl ether. The ether extracts were combined and dried over $MgSO_4$ and concentrated *in vacuo* to yield 0.220 g of a slightly yellow oil. The crude product was purified by column chromatography to afford 0.138 mg of a colorless oil which was identical by TLC, glpc, IR and NMR to ether **14a** which had been prepared from authentic *trans, trans*-farnesol.

Note added in proof. To rule out *unambiguously* any effect of LiI on these coupling reactions, we prepared PhS(*t*-Bu)CuLi from pure PhSCu and *t*-BuLi *in the absence of LiI* (G. H. Posner, D. J. Brunelle and L. Sinoway, *Synthesis* **1974**, 662); reaction with *exo*-5-norbornen-2-yl tosylate (**5**) still gave 2-*t*-butylnortricyclone in good yield!

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