filtered. The filter cake was washed with *ca.* 2 l. of water and air-dried to give **5** as an off-white solid, 82 g (89%), mp 153–159°. This solid was recrystallized in four batches from 50:50 v/v acetone–absolute ethanol to give **5**, 65.4 g (71%), mp 163–166, 164–167, 163–165, 162–165° (lit.[4] mp 163.5–165.5°). The infrared spectrum of the product exhibited absorption due to a nonconjugated cyano group at 2275 cm^{-1} (lit.[4] 2280 cm^{-1}).

Diethyl 2,6-Naphthalene-$\alpha,\alpha,\alpha',\alpha'$-tetracyanodiacetate (7). To sodium ethoxide [freshly prepared from sodium metal (22.6 g, 0.548 g-atom) and absolute ethanol (240 ml), followed by removal of excess alcohol at reduced pressure] was added diethyl carbonate (292 g, 2.48 mol), toluene (100 ml), and **5** (52.5 g, 0.25 mol). This mixture was stirred mechanically and distilled until the boiling point reached 111°. Toluene (100 ml) was added, and the mixture was cooled to 0°. Cyanogen chloride (36.9 g, 0.60 mol) was distilled into the reaction mixture kept at 0–5°. After the completion of the cyanogen chloride addition (*ca.* 6 hr), the mixture was heated at 55–60° for 2 hr and then cooled to room temperature and filtered. The filter cake was washed with ice-water and recrystallized from benzene to give **7** as an off-white solid, 60 g (60%), mp 141.5–143.5°. Recrystallization from benzene gave mp 142–143.5°. This compound showed infrared absorption at 2270 (nonconjugated CN), 1750 (ester carbonyl), and 1240 cm^{-1} (ester C–O). The nmr spectrum of **7** exhibited absorption at δ 1.20–1.45 (triplet, J = 7.5 Hz, 6 H, $-CH_2CH_3$), 4.25–4.65 (quartet, J = 7.5 Hz, 4 H, $-CH_2CH_3$) and 7.75–8.35 (multiplet, 6 aromatic protons).

Anal. Calcd for $C_{22}H_{16}N_4O_4$: C, 66.00; H, 4.03; N, 13.99. Found: C, 65.68; H, 3.83; N, 14.12.

2,6-Naphthalenedimalononitrile (6).[14] To a magnetically stirred 10% potassium hydroxide solution was added **7** (4.00 g, 10 mmol), and this mixture was stirred at room temperature until homogeneous. Hydrochloric acid (6 *N*, 11.2 ml) was added carefully, and a quantitative yield of **6**, mp 233–240° dec, precipitated.[15] The precipitate was recrystallized from acetonitrile[4] to give **6**, 1.86 g (72%), mp 251–253° dec (lit.[4] mp 241–243° dec). The infrared spectrum of this material (Nujol and Fluorolube) is in accord with that previously reported.[4]

Anal. Calcd for $C_{16}H_8N_4$: C, 74.99; H, 3.15; N, 21.86. Found: C, 74.98; H, 3.18; N, 21.80.

11,11,12,12-Tetracyano-2,6-naphthoquinodimethan (TNAP, 1). General Method of Preparation from 7.[14] As described above, **7** (10.0 g, 25 mmol) and 10% potassium hydroxide (75 ml) were stirred until homogeneous. Hydrochloric acid (6 *N*, 28 ml) was added; a precipitate of **6** formed. To this suspension of **6** was added bromine (5.0 g, 31.2 mmol) in ice-water (250 ml), and a purple precipitate formed immediately. This precipitate was filtered and washed with ice-water, acetonitrile, and ether to give 6 g (100%) of crude **1**. This material was purified in batches as follows. Crude **1** (*ca.* 500 mg) was suspended in boiling acetonitrile (2000 ml), the suspension was filtered, and a precipitate (300–400 mg) of **1** and its oligomer[4] formed. This precipitate was dissolved in acetonitrile and chromatographed on Florisil (60–100 mesh) and eluted with acetonitrile until no more **1** was eluted, as judged by the color of the column effluent. As much as 1 g of **1** and its oligomer could be chromatographed on 350–400 g of Florisil. The column effluent was concentrated by evaporation under reduced pressure, and the precipitated **1** was recrystallized from acetonitrile to give **1** as metallic purple plates, mp >365° (lit.[4] mp >420°). The recovery of **1** from the chromatographic experiment is *ca.* 50%. The infrared and uv-visible spectra of **1** are in accord with those previously reported.[4]

Anal. Calcd for $C_{16}H_6N_4$: C, 75.58; H, 2.38; N, 22.04. Found: C, 75.57; H, 2.57; N, 21.98.

Tetrathiafulvalinium 11,11,12,12-Tetracyanonaphtho-2,6-quinodimethanide (TTF-TNAP). To a hot solution of **1** (16 mg, 0.063 mmol) in acetonitrile (65 ml) was added a hot solution of **3** (14.2 mg, 0.069 mmol) in acetonitrile (5 ml). The mixture slowly cooled to room temperature, was filtered, and vacuum dried, 240–245° dec.

Anal. Calcd for $C_{22}H_{10}N_4S_4$: C, 57.62; H, 2.20; N, 12.22; S, 27.96. Found: C, 57.75; H, 2.35; N, 12.51; S, 27.97.

Diethyl 1,12-Biphenylene-$\alpha,\alpha,\alpha',\alpha'$-tetracyanodiacetate. A mechanically stirred mixture of diethyl carbonate (146.1 g, 1.24 mol), sodium ethoxide (18.0 g, 0.265 mol), *p,p'*-bis(cyanomethyl)-biphenyl (29.0 g, 0.125 mol), and toluene (100 ml) was distilled until a boiling point of 111° was reached. The mixture was cooled to 0°, and cyanogen chloride (18.45 g, 0.30 mol) was distilled into the mixture, which was kept at 0–5°. After cyanogen chloride addition was completed, the mixture was heated at 50°55° for 2 hr. Addition of hexane to the mixture formed a precipitate which was washed with ice-water to give a gummy solid. The gummy solid was heated in benzene and filtered. Evaporation of the benzene solution gave an oil which slowly crystallized. Absolute ethanol was found to be a satisfactory recrystallization solvent, and three crystallizations from it gave 7.0 g (13%) of the desired compound, mp 125–127.5°. This compound showed infrared absorption at 2270 (nonconjugated CN), 1760 (ester carbonyl), and 1230 cm^{-1} (ester C–O). The nmr spectrum exhibited resonances at δ 1.20–1.50 (triplet, J = 7.5 Hz, 6 H, $-CH_2CH_3$), 4.20–4.65 (quartet, J = 7.5 Hz, 4 H, $-CH_2CH_3$), and 7.65–8.00 (complex, 8 H, aromatic protons).

Anal. Calcd for $C_{24}H_{18}N_4O_4$: C, 67.60; H, 4.25; N, 13.14. Found: C, 67.59; H, 4.22; N, 13.15.

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Registry No.—**1**, 6251-01-0; **3**, 31366-25-3; **5**, 4949-02-4; **6**, 4948-93-0; **7**, 50764-74-4; TTF-TNAP, 50764-75-5; 2,6-bis(bromomethyl)naphthalene, 4542-77-2; *p,p'*-bis(cyanomethyl)biphenyl, 7255-83-6; diethyl 1,12-biphenylene-$\alpha,\alpha,\alpha',\alpha'$-tetracyanodiacetate, 50764-76-6.

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(1) (a) This work was supported by the National Science Foundation through the Laboratory for Research on the Structure of Matter and Grant No. GP-29583 and by the Advanced Research Projects Agency through DAHC-15-72C-0174. (b) Portions of this paper were presented at the 166th National Meeting of the American Chemical Society, Chicago, Ill., Aug. 26–31, 1973, Abstracts of Papers, ORGN 145. (c) Correspondence should be directed to this author at Xerox Corporation, Webster Research Center, W-114, Webster, New York 14580.
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(13) Melting points are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., or Midwest Microlab, Ltd., Indianapolis, Ind. Infrared spectra were recorded as Nujol mulls on a Perkin-Elmer 700 spectrophotometer. Proton magnetic resonance spectra were recorded on a Varian A-60 spectrometer in *ca.* 10% $CDCl_3$ solution. Chemical shifts are reported in parts per million downfield from internal tetramethylsilane.
(14) This experiment is best carried out in a glove box under an inert atmosphere.
(15) Material of this quality may be used for the preparation of **1**; indeed, **7** may be converted to **1** in one flask.[6]

Antimetabolites Produced by Microorganisms. IX. Chemical Synthesis of N^5-Hydroxyornithine and N^5-Hydroxyarginine[1]

Hubert Maehr* and Michael Leach

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

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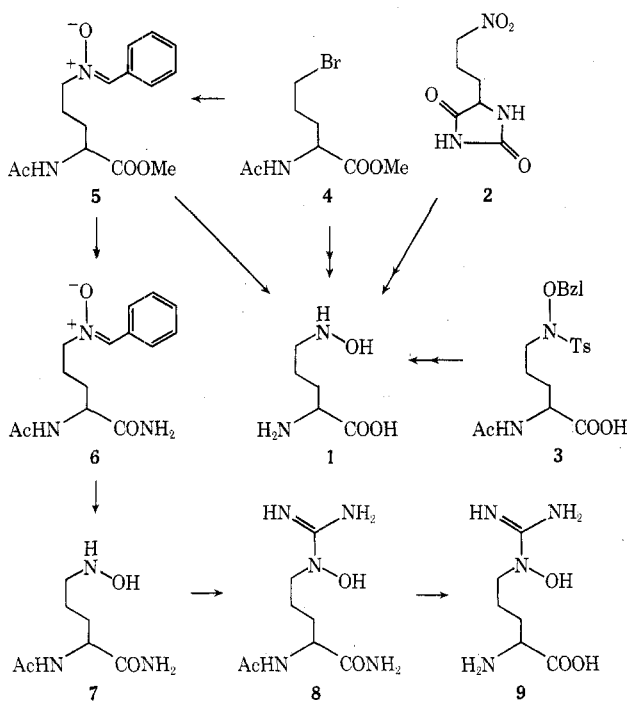
N^5-Hydroxyornithine (**1**), isolated as a degradation product of a host of naturally occurring hydroxamic

acids,[2,3] has not as yet been observed free in nature. In view of its antimicrobial activity,[4] an efficient chemical synthesis of 1 has again become of interest. The first previous approach,[5] based on partial reduction of 2 followed by hydrolysis, gave racemic 1 in very low overall yield. Alternatively, alkylation of *O*-benzyl-*N*-tosylhydroxylamine with 1,3-dibromopropane, subsequent condensation with diethyl acetamidomalonate, hydrolysis, decarboxylation, and acetylation furnished racemic 3 which served as substrate for enzymatic resolution, eventually affording both enantiomers of 1 in unspecified yield.[6] N^5-Hydroxyornithine was also prepared,[7] analogous to the methods employed in the synthesis of ferrichrome,[8] by partial reduction of methyl 2-acetamido-5-nitrovalerate[9] followed by hydrolysis.

We synthesized racemic 1 by hydrolysis of nitrone 5, prepared by N-alkylation[10,11] of *anti*-benzaldoxime[12] with methyl 2-acetamido-5-iodovalerate[9] derived from 4.[13] In a modification of Buehler's procedure[10] crystalline thallium(I) *anti*-benzaldoximate was reacted with methyl 2-acetamido-5-iodovalerate in dimethylformamide, but the yield of nitrone 5 was essentially the same as that attained with lithium and sodium salts of *anti*-benzaldoxime in methanol. Hydrolysis of the purified nitrone 5 afforded 1 in crystalline form for the first time.



N^5-Hydroxy-L-arginine (9), recently isolated as a metabolite of *Nannizzia gypsea*, a mold belonging to the class of *Ascomycetes*,[14] and as a metabolite of a *Bacillus* species,[1] exhibits antibiotic properties reversible by L-arginine and L-citrulline.[15] To further evaluate the biological properties of this new amino acid, a chemical synthesis of 9 was desirable.

Racemic 9 was prepared starting with nitrone 5, which, after conversion to amide 6 and short treatment with hydrochloric acid, afforded 7 containing the proper protective groups. The carboxamide function in 7 was desirable in view of the facile ring closure of 1 to give 3-amino-1-hydroxy-2-piperidone.[16] Amide 7 was treated with *S*-methylisothiourea and the reaction mixture was hydrolyzed to afford 9, which was isolated as the crystalline hydrochloride. As expected, synthetic 9 exhibited 50% of the antibiotic activity of the naturally occurring L form.[1]

Experimental Section

Melting points were observed on a Reichert Thermopan hot stage and are uncorrected; pmr spectra were recorded on a Varian H-100 spectrometer with TMS as either internal ($CDCl_3$) or external (D_2O) standard depending upon the solvent. Precoated silica gel F-254 layers (E. Merck, Darmstadt) were employed for tlc in connection with systems 1 (chloroform–ether, 1:5, v/v), 2 (chloroform–methanol–concentrated ammonium hydroxide–water, 1:4:2:1, v/v), and 3 (chloroform–ethyl acetate–methanol, 5:5:1, v/v). Adsorption chromatography was performed with silicic acid, 100 mesh (Mallinckrodt), or with silica gel, 0.05–0.20 mm (M. Woelm).

***anti*-Benzaldoxime Thallium(I) Salt.** To a solution of 2.65 g (21.9 mmol) of *anti*-benzaldoxime[12] in 25 ml of anhydrous ethanol was added 100 ml of 0.219 *N* thallous ethoxide solution, whereupon the product immediately deposited as light-yellow prisms. The suspension was concentrated to near dryness after addition of 100 ml of anhydrous benzene, resuspended in hexane, and filtered to yield 6.85 g of the thallium(I) salt (96.5% yield), mp >175° dec.

Anal. Calcd for C_7H_6NOTl: C, 25.91; H, 1.86; N, 4.32. Found: C, 25.57; H, 1.77; N, 4.32.

Methyl 2-Acetamidovalerate 5-(α-Phenylnitrone) (5). Procedure A. To a solution of 2.416 g (8.08 mmol) of methyl 2-acetamido-5-iodovalerate[9] in 20 ml of methanol and 10 ml of dimethylformamide was added 2.621 g (8.08 mmol) of *anti*-benzaldoxime thallium(I) salt. After stirring for 22 hr the pH value had dropped to *ca.* 8.5 (wet indicator paper) and solid ammonium chloride was added to reach neutrality. The mixture was filtered, the thallium salts were washed with methanol, and filtrate and washings were concentrated to a syrup. This syrup was extracted repeatedly with boiling chloroform; the extracts were filtered, concentrated, and charged to a column containing 100 ml of a chloroform slurry of silicic acid. The column was developed with 250 ml of chloroform eluting benzaldoxime, O-alkylated benzaldoxime emerged from the column after continued development with 250 ml of chloroform containing 2.5% 2-propanol; 5 was eluted as a sharp band with chloroform–2-propanol, 3:1, v/v, and obtained as crystalline residue after evaporation of the solvent. Recrystallization from ethyl acetate gave 0.970 g of colorless needles (41% yield): mp 127°; R_f 0.35 (system 3); δ_{TMS} ($CDCl_3$) 1.98 [m, $(CH_2)_2$], 2.00 (s, CH_3CO), 3.72 (s, CH_3O), 3.98 (t, H-5, $J_{4,5}$ = 6 Hz), 4.62 (dt, H-2, $J_{2,3a}$ = 5 and $J_{2,3b}$ = $J_{2,NH}$ = 7.5 Hz), 6.59 (d, NH, $J_{2,NH}$ = 7.5 Hz), 7.41 (s, -CH=, superimposed H-3′, H-4′, and H-5′), and 8.22 (m, H-2′ and H-6′).

Anal. Calcd for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.90; N, 9.58. Found: C, 61.89; H, 6.92; N, 9.56.

Procedure B. To a solution of 8.08 g (66.7 mmol) of *anti*-benzaldoxime and 19.95 g (66.7 mmol) of methyl 2-acetamido-5-iodovalerate in 48 ml of dimethylformamide was added 47.6 ml of 1.4 *M* lithium methoxide solution in methanol. The reaction mixture was concentrated to a syrup under reduced pressure after 20 hr, redissolved in chloroform, chromatographed, and purified as described in procedure A to yield 9.33 g of recrystallized 5 (48% yield).[17]

The yield of the N-alkylation step depends to a certain extent upon the purity of the *anti*-benzaldoxime employed, whose analysis is particularly desirable if older preparations are to be used. The ratio of syn/anti in a given preparation of benzaldoxime can be ascertained by nmr spectroscopy[18] but is more conveniently estimated by tlc (system 1), which permits differentiation between syn (R_f 0.82) and anti (R_f 0.72) isomers of benzaldoxime and its salts.

N^5-Hydroxy-DL-ornithine (1). A solution of 1.5 g (5.13 mmol) of nitrone 5 in 30 ml of 6 *N* hydrochloric acid was heated on the steam bath for 4 hr, and the solution was concentrated to dryness under reduced pressure and redissolved in 6 ml of solvent system 2. After 2 hr 374 mg (2.52 mmol) of crystalline 1 base (49%) was deposited: mp 197° dec; R_f 0.72 (system 2); δ_{TMS} (D_2O) 2.30 [m, broad, $(CH_2)_2$], 3.50 (t, H-5, $J_{4,5}$ = 7 Hz), 4.30 (t, H-2, $J_{2,3}$ = 6 Hz).

N^5-Hydroxyornithine (1) gave positive tests with ninhydrin and triphenyltetrazolium[19] and a negative test with $FeCl_3$, and could be degraded to ornithine (R_f = 0.55, system 2) upon treatment with 47% hydriodic acid at 100° for 10 hr.

Anal. Calcd for $C_5H_{12}N_2O_3$: C, 40.53; H, 8.16; N, 18.91. Found: C, 40.30; H, 8.19; N, 18.94.

The mother liquor was purified by chromatography on a column of Dowex 50[5] and the resulting 1 dihydrochloride was converted to the crystalline 2-nitro-1,3-indandione salt of 1[5] (415 mg, 1.22 mmol), exhibiting ir and nmr spectra identical with those of authentic N^5-hydroxy-L-ornithine 2-nitro-1,3-indandione salt ob-

tained from a hydrochloric acid hydrolysate of iron-free albomycin,[20,21] δ_{TMS} (DMSO-d_6) 1.77 [m, broad, $(CH_2)_2$], 3.04 (m, broad H-5), 3.62 (m, broad, H-2), and 7.20 (broad envelope representing 6 protons) overlapping with 7.51 (m, H-5′–H-8′).

Anal. Calcd for $C_5H_{12}N_2O_3 \cdot C_9H_5NO_4$: C, 49.56; H, 5.05; N, 12.38. Found: C, 49.41; H, 5.00; N, 12.42.

2-Acetamidovaleramide 5-(α-Phenylnitrone) (6). A suspension of 4.00 g (13.68 mmol) of **5** in *ca.* 40 ml of liquid ammonia was kept in a sealed tube at 50° for 4.5 days. The residue obtained after evaporation of ammonia was recrystallized from methanol–ether to afford colorless needles (3.19 g, 84% yield) of **6**, mp 170°, R_f 0.06 (system 3).

Anal. Calcd for $C_{14}H_{19}N_3O_3$: C, 60.64; H, 6.91; N, 15.15. Found: C, 60.43; H, 6.92; N, 15.21.

N^5-Hydroxy-DL-arginine (9). A solution of 3.19 g (11.5 mmol) of **6** in 70 ml of concentrated hydrochloric acid (*d* 1.188) was heated on the steam bath for 15 min. The solution was concentrated to dryness under reduced pressure and the resulting crude **7** was dried over sodium hydroxide *in vacuo* overnight. The entire residue was dissolved in 8 ml of water, 3.19 g (22.9 mmol) of *S*-methylisothiourea sulfate was added, and the pH of the solution was adjusted to 7 with dilute sodium hydroxide solution. The mixture was kept at room temperature for 5 days. During this period the pH of the solution was occasionally readjusted to 7. The solution of crude **8** was evaporated to dryness under reduced pressure, and the residue was redissolved in 100 ml of 6 *N* hydrochloric acid and heated on the steam bath for 10 hr, evaporated, and dried over sodium hydroxide. The resulting residue was dissolved in 50 ml of water and the solution, after pH adjustment to 3, was charged to a column (25 × 680 mm) of Dowex 50W X-8, 200–400 mesh (Na^+), previously rinsed with 3.4 l of a pH 6.1 buffer, prepared by adding 0.1 *M* citric acid to 0.2 *M* dibasic sodium phosphate solution until pH 6.1 was reached (approximate ratio of solutions was 15:8).

The column was subsequently developed with the pH 6.1 buffer to which 0.1 mol of sodium chloride per liter had been added. After 800 ml of effluent had been collected the column was eluted with the pH 6.1 buffer containing 0.3 mol of sodium chloride per liter. The effluent was now collected in 20-ml fractions, the antibiotic activity of the fractions was monitored bioautographically,[1] and fractions 50–120 were pooled and desalted by charging to a column (50 × 400 mm) of Dowex 50W X-4, 50–100 mesh (H^+). This column was rinsed with water until the effluent was neutral and then developed with 1 *N* ammonium hydroxide solution. Fractions of 500 ml each were collected as soon as ammoniacal development had started; fractions 7–11, containing the bioactive material, were pooled and concentrated to yield 1.1 g of viscous **9**. This material was redissolved in water, and the solution was adjusted to pH 5 with hydrochloric acid, concentrated, and diluted with ethanol to afford 1.04 g of **9** hydrochloride as needles (40% yield based on the conversion of **6** to **9** hydrochloride) with identical R_f values and pmr spectrum as reported for the L form.[1]

Anal. Calcd for $C_6H_{14}N_4O_3 \cdot HCl$: C, 31.79; H, 6.67; N, 24.72. Found: C, 31.75; H, 6.91; N, 24.86.

Registry No.—**1**, 40162-08-1; 1 dihydrochloride, 50678-85-8; 1 2-nitro-1,3-indandione salt, 50678-86-9; **5**, 50585-17-6; **6**, 50585-18-7; **9** hydrochloride, 50585-19-8; *anti*-benzaldoxime thallium(I) salt, 50585-20-1; *anti*-benzaldoxime, 622-32-2; methyl 2-acetamido-5-iodovalerate, 21753-88-8.

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Coupling Reactions between Resonance Stabilized Organolithium Reagents and Cycloalkyl Halides[1]

W. D. Korte,* K. Cripe, and R. Cooke

Department of Chemistry, California State University at Chico, Chico, California 95926

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Both lithium dialkylcuprates and organolithium reagents have recently been shown to be extremely useful reagents for the synthesis of unsymmetrical hydrocarbons *via* a Wurtz-type coupling process between the organometallic reagents and alkyl halides.[2] Lithium dialkylcuprates couple readily with a wide variety of alkyl, aryl, and vinyl halides[2a,b] and organolithium reagents condense with primary and secondary halides.[2c-g] The products from the coupling reaction can frequently serve as key intermediates for the synthesis of carbonyl compounds.[2c,g] One of the limitations of these versatile reagents appeared to be the low yields associated with the reaction when performed with cycloalkyl halides. Although lithium dimethylcuprate and cyclohexyl iodide did condense to give a 75% yield of methylcyclohexane,[2a] the reaction between cyclohexyl bromide and lithium di-*n*-butyl-(tri-*n*-butylphosphine)cuprate only gave a 25% yield of the coupled product, *n*-butylcyclohexane.[2b]

Resonance stabilized organolithium reagents, such as benzyllithium and allyllithium, are both strong nucleophiles and relatively weak bases compared to alkyllithium reagents such as *n*-butyllithium.[3] This combination of properties has proved to be compatible with the displacement of both bromide and iodide ions from cyclohexyl and cyclopentyl systems so that high yields of substituted cycloalkanes can be obtained by a direct Wurtz-type coupling procedure

$$RLi + R'X \longrightarrow RR' + LiX$$

Tables I and II summarize the results of this study with five different organolithium reagents and two cycloalkyl systems.

Four trends in reactivity are indicated from the data in Table I. (1) The use of cyclohexyl bromide and cyclohexyl iodide led to much higher yields of coupled products than the corresponding reactions with cyclohexyl chloride or cyclohexyl tosylate. (2) The yields from reactions with cyclohexyl bromide were greater than yields from reactions with cyclopentyl bromide. (3) Benzylic reagents, benzyl- and benzhydryllithium, were slightly superior to the allylic reagent in the displacement reaction. (4) Diethyl ether appeared to be slightly superior to tetrahydrofuran as a solvent for these reactions.[4] It should also be noted that displacement of the tosylate group was accomplished