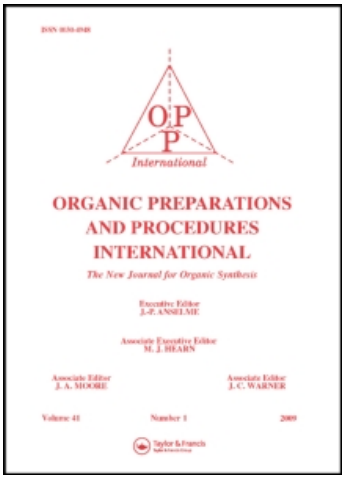


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# SYNTHESIS OF (±)-3-BROMOMETHYL-1,5-HEXADIENE AND (±)-3-BROMOMETHYL-3-METHYL-1,5-HEXADIENE

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# OPPI BRIEFS

## SYNTHESIS OF (±)-3-BROMOMETHYL-1,5-HEXADIENE AND (±)-3-BROMOMETHYL-3-METHYL-1,5-HEXADIENE

*Submitted by* (8/21/95)

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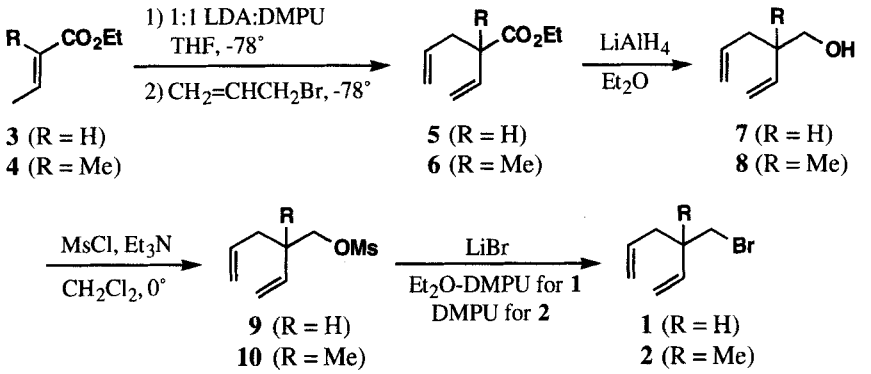
Current studies on tandem reaction processes in this laboratory required access to (±)-3-bromomethyl-1,5-hexadiene (**1**) and (±)-3-bromomethyl-3-methyl-1,5-hexadiene (**2**). A review of the literature revealed that neither **1** nor **2** has been reported previously. This Brief describes the successful synthesis of these bromides in four steps with overall yields of 42% and 31%, respectively.




**3** (R = H)
**4** (R = Me)

**5** (R = H)
**6** (R = Me)

**7** (R = H)
**8** (R = Me)

**9** (R = H)
**10** (R = Me)

**1** (R = H)
**2** (R = Me)

The synthesis began with ethyl crotonate (**3**) and ethyl tiglate (**4**). Deconjugative alkylation[1,2] of the unsaturated esters, by treatment with 1:1 LDA:DMPU[3,4] at -78° in THF followed by allyl bromide, provided diene esters **5** (67% yield) and **6** (87.5% yield). In the preparation of **5**, mild work-up with aqueous $NH_4Cl$ yielded the deconjugated ester containing less than 1% (by GC) of the conjugated isomer; 10-12% of dialkylated material in the crude product was readily removed by distillation. Ester reduction using lithium aluminum hydride afforded alcohols **7** (80.5% yield) and **8** (68% yield), which were converted to the mesylates **9** and **10** in nearly quantitative yields.[5] Finally, treatment of mesylate **9** with lithium bromide[6] in 4:1 ether:DMPU[3,7] effected $S_N2$ conversion to bromide **1** in 78% yield. The hindered mesylate **10** required treatment with lithium bromide under more forcing conditions (DMPU, 90°, 48 hrs) but furnished bromide **2** in a respectable 52% yield. The two-step alcohol-to-bromide conversion was found to be the most convenient procedure for large scale work.

## EXPERIMENTAL SECTION

Ethyl crotonate (**3**) and ethyl tiglate (**4**) were purchased from Lancaster Synthesis, Inc. THF was distilled from lithium aluminum hydride; diisopropylamine and triethylamine were distilled from calcium hydride and stored over 4Å molecular sieves; DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone) was stored over 4Å molecular sieves. All other reagents and solvents were used as received. All reactions were run under dry $N_2$ in oven-dried glassware. Reactions were monitored using capillary GC with FI detection (SE-30 column, 6 m x 0.25 mm i.d., 0.25 μm film thickness) programmed between 50-200°. The saturated $NH_4Cl$, saturated $NaHCO_3$, 10% HCl, and saturated NaCl used in workup procedures refer to aqueous solutions. IR spectra were referenced to polystyrene. $^1H$ and $^{13}C$ NMR spectra were measured in $CDCl_3$ at 400 MHz and 100 MHz, respectively, and are referenced to internal $Me_4Si$. High resolution mass spectra (HRMS, EI/DP) were obtained at 70 eV.

**(±)-Ethyl 2-Ethenyl-4-pentenoate** (**5**).- The general procedure of Schlessinger and co-workers[1] as modified by Kuwajima and Urabe[2] was used. To a magnetically stirred solution of 11.6 g (115 mmol) of diisopropylamine in 150 mL of THF at -78° was added 79.2 mL of 1.44 *M* *n*-butyllithium in hexanes (114 mmol) by syringe during 15 min. The mixture was stirred for 10 min and 14.6 g (13.7 mL, 114 mmol) of DMPU[3,4] was added by syringe during 10 min. The reaction was stirred for 30 min at -78° and a solution of 11.4 g (100 mmol) of ethyl crotonate (**3**) in 25 mL of THF was added dropwise during 20 min. The mixture was stirred for 10 min and a solution of 13.9 g (9.95 mL, 115 mmol) of allyl bromide in 25 mL of THF was added dropwise during 20 min. The reaction was stirred for 20 min, quenched at -78° with 50 mL of $NH_4Cl$, and warmed to 25°. The crude reaction mixture was transferred to a separatory funnel with 250 mL of ether and the layers were separated. The organic phase was washed with $NH_4Cl$ (3x), $H_2O$ (1x), and NaCl (1x), dried ($MgSO_4$), and concentrated under vacuum to afford a light yellow oil. GC analysis of the crude product indicated the presence of *ca.* 2% unreacted ethyl crotonate, 1% of the conjugated alkylation product, and 10% of the dialkylated product in addition to the monoalkylated ester. Fractional vacuum distillation through a 15-cm Vigreux column afforded 10.3 g (66.7 mmol, 67%) of pure **5** as a colorless oil, bp. 78-80° (28 mm Hg).

IR (thin film): 3082, 1736, 1644, 1374, 1004, 926 $cm^{-1}$; $^1H$ NMR: δ 5.88-5.69 (complex, 2 H), 5.17-5.02 (complex, 4 H), 4.14 (q, 2 H, J = 7.2 Hz), 3.09 (q, 1 H, J = 7.6 Hz), 2.51 (m, 1 H), 2.32 (m, 1 H), 1.25 (t, 3 H, J = 7.2 Hz); $^{13}C$ NMR: δ 173.3, 135.5, 134.9, 117.2, 116.9, 60.5, 49.9, 36.3, 14.1; HRMS *m/e* Calcd for $C_9H_{14}O_2$: 154.0994. Found: 154.0999.

*Anal.* Calcd for $C_9H_{14}O_2$: C, 70.13; H, 9.09. Found: C, 69.98; H, 9.05

**(±)-Ethyl 2-Ethenyl-2-methyl-4-pentenoate** (**6**).- This preparation was carried out on a 100 mmol scale from ethyl tiglate (**4**) by the same procedure used to prepare **5**. The yield of **6** was 14.7 g (87.5 mmol, 87.5%) as a colorless oil, bp. 32-34° (2 mm Hg).

IR (thin film): 3084, 1736, 1650, 1375, 1002, 922 $cm^{-1}$; $^1H$ NMR: δ 6.01 (dd, 1 H, J = 17.5, 10.8 Hz), 5.69 (ddt, 1 H, J = 17.5, 10.8, 7.3 Hz), 5.13-5.04 (complex, 4 H), 4.14 (q, 2 H, J = 7.1 Hz), 2.48 (dd, 1 H, J = 13.7, 7.4 Hz), 2.33 (dd, 1 H, 13.7, 7.4 Hz), 1.26 (t, 3 H, J = 7.1 Hz); $^{13}C$ NMR: δ 175.2, 141.3, 133.7, 118.1, 113.7, 60.6, 48.3, 43.2, 20.3, 14.1; HRMS *m/e* Calcd for $C_{10}H_{16}O_2$: 168.1151. Found: 168.1146.

*Anal.* Calcd for $C_{10}H_{16}O_2$: C, 71.42; H, 9.52. Found: C, 71.31; H, 9.47

**(±)-2-Ethenyl-4-penten-1-ol (7).**- To a suspension of 4.44 g (117 mmol) of lithium aluminum hydride in 150 mL of ether was added a solution of 18.0 g (117 mmol) of **5** in 50 mL of ether dropwise during 45 min. The mixture was stirred for 10 min at 25°, refluxed for 15 min, cooled and cautiously treated with 4 mL of $H_2O$, 4 mL of 15% NaOH, and enough water to form a granular precipitate. The mixture was filtered through a mixture of Celite® and $MgSO_4$ and the precipitate was washed with 150 mL of warm ether (3x). The filtrate was concentrated under vacuum and distilled at reduced pressure to afford 10.6 g (94.1 mmol, 80.5%) of **7** as a colorless oil, bp. 77-78° (28 mm Hg).

IR (thin film): 3352, 3082, 1644, 1004, 918 $cm^{-1}$; $^1H$ NMR: δ 5.83-5.61 (complex, 2 H), 5.17-5.00 (complex, 4 H), 3.58 (m, 1 H), 3.47 (dd, 1 H, J = 10.3, 7.6 Hz), 2.32 (m, 1 H), 2.19 (m, 1 H), 2.13 (m, 1 H), 1.94 (bs, 1 H); $^{13}C$ NMR: δ 139.2, 136.1, 116.9, 116.2, 65.0, 46.1, 35.2; HRMS *m/e* Calcd for $C_7H_{12}O$: 112.0889. Found: 112.0888.

*Anal.* Calcd for $C_7H_{12}O$: C, 75.00; H, 10.71. Found: C, 74.87; H, 10.70

**(±)-2-Ethenyl-2-methyl-4-penten-1-ol (8).**- This preparation was carried out on a 100 mmol scale from ester **6** by the same procedure used to prepare **7**. The yield of **8** was 8.58 g (68.1 mmol, 68%) as a colorless oil, bp. 37-38° (3 mm Hg).

IR (thin film): 3358, 3084,1642, 1375, 1002, 914 $cm^{-1}$; $^1H$ NMR: δ 5.82-5.71 (complex, 2 H), 5.17-5.03 (complex 4 H), 3.38 (dd, 2 H, J = 17.4, 10.7 Hz), 2.13 (m, 2 H), 1.86 (bs, 1 H), 1.00 (s, 3 H); $^{13}C$ NMR: δ 143.6, 134.4, 117.3, 114.3, 69.6, 41.9, 41.5, 20.0; HRMS *m/e* Calcd for $C_8H_{14}O$: 126.1045. Found: 126.1041.

*Anal.* Calcd for $C_8H_{14}O$: C, 76.19; H, 11.11. Found: C, 76.24; H, 11.13

**(±)-2-Ethenyl-1-methanesulfonyloxy-4-pentene (9).**- The general procedure of Crossland and Servis was used.[5] A solution of 9.00 g (80.4 mmol) of **7** and 12.2 g (16.77 mL, 120 mmol) of triethylamine in 200 mL of $CH_2Cl_2$ was stirred at 0° while a solution of 10.1 g (6.82 mL, 88.4 mmol) of methanesulfonyl chloride in 30 mL of $CH_2Cl_2$ was added dropwise during 20 min. The reaction was stirred for 15 min and transferred to a separatory funnel containing $H_2O$ and crushed ice. The layers were separated and the $CH_2Cl_2$ layer was washed with ice cold $H_2O$ (2x), 10% HCl (1x), $NaHCO_3$ (1x), NaCl (1x), dried ($Na_2SO_4$), and concentrated under vacuum at 30-35°C. The crude mesylate (15.2 g, 79.9 mmol, 99%) was used without further purification.

IR (thin film): 3082, 1643, 1360, 1176, 962 $cm^{-1}$; $^1H$ NMR: δ 5.78-5.64 (complex, 2 H), 5.18-5.06 (complex, 4 H), 4.15 (m, 2 H), 3.00 (s, 3 H), 2.55 (m, 1 H), 2.26 (m, 1 H), 2.20 (m, 1 H); $^{13}C$ NMR: δ 136.8, 134.7, 117.5, 117.3, 71.5, 42.4, 37.2, 34.9.

**(±)-2-Ethenyl-1-methanesulfonyloxy-2-methyl-4-pentene (10).**- This preparation was carried out on a 75.2 mmol scale from alcohol **8** by the same procedure used to prepare **9**. The crude mesylate (15.1 g, 74.2 mmol, 99%) was used without further purification.

IR (thin film): 3084, 1641, 1355, 1182, 964 $cm^{-1}$; $^1H$ NMR: δ 5.81-5.70 (complex, 2 H), 5.17-5.06 (complex, 4 H), 3.99 (s, 2 H), 2.99 (s, 3 H), 2.19 (m, 2 H), 1.08 (s, 3 H); $^{13}C$ NMR: δ 141.4, 133.1, 118.5, 114.6, 75.3, 41.3, 40.0, 37.0, 20.4.

**(±)-3-Bromomethyl-1,5-hexadiene (1).**- To a stirred suspension of 28.3 g (325 mmol) of LiBr in 100 mL of anhydrous ether[6] was slowly added 25 mL of DMPU followed by a solution of 12.4 g (65.0 mmol) of **9** in 25 mL of ether. The reaction was stirred at 25° for 1 h and at reflux for 18 h, then cooled, cautiously added to 100 mL of saturated $NH_4Cl$, and the layers separated. The aqueous layer was washed with ether and the combined ether layers were washed with $NH_4Cl$ (3x), $H_2O$ (1x), NaCl (1x), dried ($MgSO_4$), and concentrated under vacuum. The crude product was vacuum distilled through a 15-cm Vigreux column to afford 8.85 g (50.6 mmol, 78%) of **1** as a colorless oil, bp. 68-70° (28 mm Hg).

IR (thin film): 3082, 1648, 996, 922 $cm^{-1}$; $^1H$ NMR: δ 5.79-5.65 (complex, 2 H), 5.16-5.05 (complex, 4 H), 3.40 (ddd, 2 H, J = 15.8, 9.9, 5.9 Hz), 2.47 (m, 1 H), 2.31 (m, 1 H), 2.24 (m, 1 H); $^{13}C$ NMR: δ 138.9, 135.1, 117.2, 116.6, 44.7, 37.3, 37.1; HRMS *m/e* Calcd for $C_7H_{11}{}^{79}Br$: 174.0044. Found: 174.0040.

*Anal.* Calcd for $C_7H_{11}Br$: C, 48.00; H, 6.29. Found: C, 47.92; H, 6.30

**(±)-3-Bromomethyl-3-methyl-1,5-hexadiene (2).**- To a solution of 23.2 g (266 mmol) of LiBr in 125 mL of DMPU[4,7] was added 10.9 g (53.2 mmol) of **10**. The mixture was heated at 90° for 48 h, then cooled, added to a mixture of 100 mL of saturated $NH_4Cl$ and 150 mL of ether, and the layers separated. The aqueous layer was washed with ether and the combined ether layers were washed with $NH_4Cl$ (3x), $H_2O$ (1x), $NaHCO_3$ (1x), NaCl (1x), dried ($MgSO_4$), and concentrated under vacuum. The crude product was distilled at reduced pressure through a 15-cm Vigreux column to afford 5.24 g (27.7 mmol, 52%) of **2** as a light yellow oil, bp. 76-77° (28 mm Hg).

IR (thin film): 3084, 1642, 1376, 1008, 922 $cm^{-1}$; $^1H$ NMR: δ 5.83-5.67 (complex, 2 H), 5.14-5.02 (complex, 4 H), 3.32 (dd, 2 H, J = 12.2, 10.0 Hz), 2.22 (d, 2 H, J = 7.4 Hz), 1.12 (s, 3 H); $^{13}C$ NMR: δ 143.0, 133.7, 118.3, 114.1, 43.7, 42.9, 40.4, 22.4; HRMS *m/e* Calcd for $C_8H_{13}{}^{79}Br$: 188.0201. Found: 188.0204.

*Anal.* Calcd for $C_8H_{13}Br$: C, 50.79; H, 6.88. Found: C, 50.65; H, 6.86



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Collect. Vol. VIII, p. 486. This report describes a modification of the procedure reported in ref. 1 which uses 1:1 LDA:DMPU as the base for the deconjugative alkylation.

3. For safety reasons, DMPU was substituted for the HMPA used in the original procedure. When the deconjugative alkylations were run on the same scale in HMPA, products **5** and **6** were produced in 62% and 85% purified yields (unoptimized). Our lower yield of **5** in both solvents, compared with the earlier report of 90% by Schlessinger, likely results from mixing and localized heating problems associated with the larger scale used in the current reactions.

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7. This reaction also proceeded in HMPA but, for safety reasons, DMPU was used. The yield was essentially the same in both solvents.



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## A FACILE PREPARATION OF BUSPIRONE N-OXIDE USING DAVIS' REAGENT

*Submitted by* Bang-Chi Chen*† and Derron R. Stark
(08/16/95)

*Process Exploration Laboratory I, Bio/Chem Division*
*Bristol-Myers Squibb Company, Syracuse, NY 13221*

The heterocyclic compound 8-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-8-azaspiro[4,5]-decane-7,9-dione (*buspirone*, **1**) is a novel, effective antianxiety drug.[1] It is equipotent with benzodiazepines but does not cause habituation and side-effects such as sedation, muscle relaxation, motor impairment and anticonvulsion that are associated with benzodiazepine therapy.[2] In a project related to the metabolism of *buspirone* (**1**), we required efficient access to buspirone N-oxide (**3**). Conversion of trialkylamines to the corresponding amine N-oxides by oxidation with hydrogen peroxide and peracids is well documented.[3] However, these reagents are also known to oxidize pyrimidines to pyrimidine N-oxides.[4] Indeed, when *buspirone* (**1**) was treated with one equivalent of the commercially available *m*-chloroperbenzoic acid in methylene chloride at 0°, a mixture of products was obtained which consisted of the buspirone N-oxide (**3**) and the other pyrimidine N-oxide in a ratio of 90:10. Attempts to purify this crude product by recrystallization were unsuccessful. The formation of the pyrimidine N-oxide by-product was due, at least in part, to the protonation of the most basic piperazine nitrogen by the resulting *m*-chlorobenzoic acid which resulted in the turnover of the oxidation