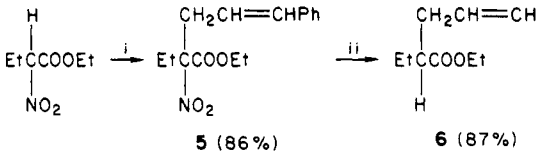

5 (86%) 6 (87%)

(i) $PhCH{=}CHCH_2OCO_2Et$, $Pd(PPh_3)_4$ (5 mol %), rt, 20 h; (ii) Bu_3SnH (1.2 equiv), AIBN (0.2 equiv), benzene, 80 °C, 2 h

mixture was stirred at room temperature for 20 h, and the mixture was filtered. The filtrate was evaporated under reduced pressure and the residue was purified by column chromatography (silica gel/benzene–hexane) to give **3**.

3a: IR (neat) 1380, 1545, 1720 cm^{-1}; NMR ($CDCl_3$) δ 0.78–0.92 (m, 6 H), 1.05–1.70 (m, 4 H), 2.05–2.30 (m, 2 H), 2.42 (t, 2 H, J = 7 Hz), 2.98 (d, 2 H, J = 7 Hz), 5.70–6.02 (m, 1 H), 6.44 (d, 1 H, J = 17 Hz), 7.3 (m, 5 H). Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.84; H, 8.11; N, 4.84.

3b: IR (neat) 1380, 1540, 1720 cm^{-1}; NMR ($CDCl_3$) δ 0.80–1.00 (m, 6 H), 1.10–1.70 (m, 4 H), 2.02–2.30 (m, 2 H), 2.41 (t, 2 H, J = 8 Hz), 2.84 (d, 2 H, J = 8 Hz), 4.98–5.20 (m, 2 H), 5.30–5.70 (m, 1 H). Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 61.88; H, 9.12; N, 6.38.

3c: IR (neat) 1370, 1538, 1720 cm^{-1}; NMR ($CDCl_3$) δ 0.80–1.01 (m, 6 H), 1.10–1.80 (m, 4 H), 2.02–2.28 (m, 2 H), 2.40 (t, 2 H, J = 7 Hz), 2.98 (d, 2 H, J = 7 Hz), 5.65–6.00 (m, 1 H), 6.42 (d, 1 H, J = 17 Hz), 7.5 (m, 5 H). Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.10; N, 4.84. Found: C, 70.56; B, 8.14; N, 4.74.

3d: IR (neat) 1380, 1545, 1720 cm^{-1}; NMR ($CDCl_3$) δ 0.80–1.05 (m, 6 H), 1.10–1.80 (m, 4 H), 1.96–2.20 (m, 2 H), 2.40 (t, 2 H, J = 7 Hz), 2.80 (d, 2 H, J = 7 Hz), 5.00–5.22 (m, 2 H), 5.30–5.70 (m, 1 H). Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; 6.57. Found: C, 62.25; H, 8.97; N, 6.47.

3e: IR (neat) 1370, 1545, 1720 cm^{-1}; NMR ($CDCl_3$) δ 0.78–0.92 (m, 3 H), 1.05–1.70 (m, 8 H), 1.60 (s, 3 H), 2.42 (t, 2 H, J = 7 Hz), 2.80–3.02 (m, 2 H), 5.80–6.05 (m, 1 H), 6.42 (d, 1 H, J = 17 Hz), 7.3 (m, 5 H). Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.25; H, 8.31; N, 4.62. Found: C, 70.96; H, 8.13; N, 4.93.

3f: IR (neat) 1380, 1545, 1720 cm^{-1}; NMR ($CDCl_3$) δ 0.78–1.00 (m, 3 H), 1.10–1.78 (m, 8 H), 1.66 (s, 3 H), 2.44 (t, 2 H, J = 7 Hz), 2.74–3.00 (m, 2 H), 5.0–5.22 (m, 2 H), 5.40–5.80 (m, 1 H). Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.41; H, 9.31; N, 6.12.

Allylation of ethyl α-nitrobutyrate[7] was carried out in the same way as allylation of **1**. Allylated product **5**[3] was obtained in 86% yield.

5: IR (neat) 1350, 1540, 1740 cm^{-1}; NMR ($CDCl_3$) δ 0.94 (t, 3 H, J = 7 Hz), 1.22 (t, 3 H, J = 7 Hz), 2.26 (t, 2 H, J = 7 Hz), 3.06 (d, 2 H, J = 8 Hz); 4.24 (q, 2 H, J = 7 Hz), 5.80–6.08 (m, 1 H), 6.50 (d, 1 H, J = 17 Hz), 7.3 (m, 5 H). Anal. Calcd for $C_16H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05. Found: C, 65.13; H, 6.97; N, 5.13.

Denitration of 3 and 5. A mixture of **3** or **5** (0.01 mol), Bu_3SnH (0.012 mol), and AIBN (0.002 mol) in benzene (5 mL) was heated at 80 °C for 2 h. The mixture was then subjected to column chromatography (silica gel/benzene–hexane) to give the denitrated product, **4** or **6**, respectively. Compounds **4a**, **4c**, **4e**, and **6** consisted of a single isomer and rearrangement product was not detected by NMR and GLC. When cinnamyl acetate was used, a small amount of allylic rearrangement product was formed (ca. 3%).[3]

4a: IR (neat) 1710 cm^{-1}; NMR ($CDCl_3$) δ 0.80–1.10 (m, 6 H), 1.10–1.80 (m, 6 H), 2.10–2.50 (m, 5 H), 5.90–6.18 (m, 1 H, 6.30 (d, 1 H, J = 17 Hz), 7.2 (m, 5 H); MS, m/e (M^+) calcd for $C_{17}H_{24}O$ 244.1828, found 244.1828.

4b: IR (neat) 1710 cm^{-1}; NMR ($CDCl_3$) δ 0.80–1.10 (m, 6 H), 1.10–1.80 (m, 6 H), 2.10–2.55 (m, 5 H), 5.0–5.36 (m, 2 H), 5.40–5.80 (m, 1 H); MS, m/e (M^+) calcd for $C_{11}H_{20}O$ 168.1513, found 168.1517.

4c: IR (neat) 1710 cm^{-1}; NMR ($CDCl_3$) δ 0.80–1.10 (m, 6 H), 1.10–1.80 (m, 6 H), 2.20–2.70 (m, 5 H), 5.90–6.22 (m, 1 H), 6.35 (d, 1 H, J = 17 Hz), 7.2 (m, 5 H); MS, m/e (M^+) calcd for $C_{17}H_{24}O$ 244.1828, found 244.1823.

(7) Kornblum, N.; Blackwood, R. K.; Poweres, Y. M. *J. Am. Chem. Soc.* **1957**, *79*, 2507.

4d: IR (neat) 1710 cm^{-1}; NMR ($CDCl_3$) δ 0.80–1.10 (m, 6 H), 1.10–1.80 (m, 6 H), 2.10–2.66 (m, 5 H), 5.0–5.30 (m, 2 H), 5.35–5.60 (m, 1 H); MS, m/e (M^+) calcd for $C_{11}H_{20}O$ 168.1513, found 168.1520.

4e: IR (neat) 1710 cm^{-1}; NMR ($CDCl_3$) δ 0.86 (t, 3 H, J = 7 Hz), 1.10–1.90 (m, 8 H), 2.20–2.75 (m, 8 H), 5.90–6.20 (m, 1 H), 6.30 (d, 1 H, J = 17 Hz), 7.3 (m, 5 H); MS, m/e (M^+) calcd for $C_{18}H_{26}O$ 270.1974, found 270.1982.

4f: IR (neat) 1710 cm^{-1}; NMR ($CDCl_3$) δ 0.85 (t, 3 H, J = 7 Hz), 1.10–1.90 (m, 8 H), 2.14–2.70 (m, 8 H), 5.02–5.30 (m, 2 H), 5.35–5.65 (m, 1 H); MS, m/e (M^+) calcd for $C_{12}H_{22}O$ 194.1669, found 194.1668.

6: IR (neat) 1730 cm^{-1}; NMR ($CDCl_3$) δ 0.80–1.02 (t, 3 H, J = 7 Hz), 1.08–1.32 (m, 3 H), 1.42–1.80 (m, 2 H), 2.20–2.62 (m, 3 H), 4.10 (q, 2 H, J = 7 Hz), 5.98–6.48 (m, 2 H), 7.2 (m, 5 H); MS, m/e (M^+) calcd for $C_{15}H_{20}O_2$ 232.1464, found 232.1475.

Registry No. 1 (R^1 = OEt, R^2 = Et) 2531-81-9; **19**, 83483-16-3; **1c**, 55601-75-7; **1e**, 85199-51-5; **2a**, 86537-61-3; **2b**, 1469-70-1; **3a**, 102492-82-0; **3b**, 102492-83-1; **3c**, 102492-84-2; **3d**, 102492-85-3; **3e**, 102492-86-4; **3f**, 102492-87-5; **4a**, 102492-88-6; **4b**, 102492-89-7; **4c**, 102492-90-0; **4d**, 102492-91-1; **4e**, 102492-92-2; **4f**, 102492-93-3; **5**, 79918-53-9; **6**, 102492-94-4.

Directed Ortho-Lithiation of Alkyl Arenesulfonates

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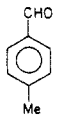
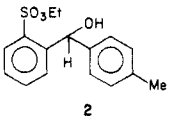
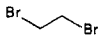
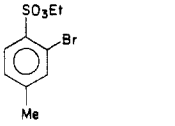
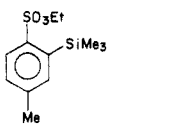
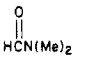
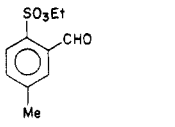
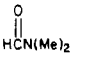
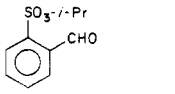
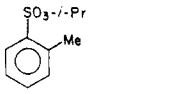
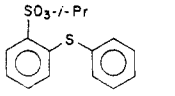
The well-documented, directed ortho-lithiation reaction has been utilized to prepare a wide variety of substituted aromatics. This reaction involves deprotonation ortho to heteroatom functions such as amides, sulfones, amines, sulfonamides, and many others.[1] The reactive anion thus formed can then be trapped by electrophiles. Recently Figuly and Martin reported the ortho-metalation of lithium arenesulfonates (**1a**).[2] The anion generated in this sequence could be reacted with a variety of electrophiles to furnish ortho-substituted arenesulfonic acids. The sulfonic acid functionality could be removed to afford substituted aromatic derivatives. The products of this procedure are lithium salts of sulfonic acids. The authors found these products difficult to separate from the starting material using standard manipulations such as chromatography. Some products were inseparable without prior chemical modification to remove the sulfonic acid group. In addition, Russian workers reported the polylithiation of both lithium arenesulfonates and alkyl arenesulfonates.[3] These lithiations were done in diethyl ether with up to a tenfold excess of *n*-butyllithium. Under these conditions the sequence is heterogeneous and products arising from polylithiation–alkylation predominate.

In this note, the ortho-metalation of alkyl arenesulfonates **1b–d** is reported as summarized in Table I. These examples demonstrate (1) that metalation is facile and (2) that the organolithium reagent can be trapped by

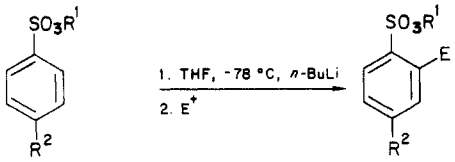
(1) For reviews, see: Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306. Snieckus, V. *Lect. Heterocycl. Chem.* **1984**, *7*, 95. For an updated list of references, see: Beak, P.; Brown, R. A. *J. Org. Chem.* **1982**, *47*, 34.
(2) Figuly, G. D.; Martin, J. C. *J. Org. Chem.* **1980**, *45* 3729.
(3) (a) Stoyanovich, F. M.; Goldfarb, Ya. L.; Marakatkina, M. A.; Karpenko, R. G. *I. Zvest. Akad.* Nank SSR, *Ser. Khem.* **1980**, 145. *Chem. Abstr.* **1980**, *93*, 26043m (b) For an example of the lithiation and alkylation of an alkyl sulfonate, see: Truce, W. E.; Vrencur, D. J. *J. Org. Chem.* **1970**, *35*, 1226.

0022-3263/86/1951-2833$01.50/0

Table I

reactant	electrophile	product (yield, %)
1c		 (63)
		2
1b		 (83)
		3
1b	$ClSiMe_3$	 (80)
		4
1b		 (74)
		5
1d		 (75)
		6
1d	MeI	 (75)
		7
1d	PhSSPh	 (65)
		8

a wide variety of electrophiles to give high yields of the expected products. Furthermore, the products from this easily executed reaction can be isolated and purified by standard techniques (i.e., chromatography, distillation, and crystallization). The reaction is homogeneous in tetrahydrofuran (THF).[4]



1a, R^1 = Li; R^2 = H or Me
1b, R^1 = Et; R^2 = Me
1c, R^1 = Et; R^2 = H
1d, R^1 = isopropyl; R^2 = H

Kinetic ortho-metalation and electrophilic trapping can be executed with ethyl *p*-toluensulfonate (**1b**). Competing benzylic lithiation was observed in one instance (R^2 = Me) when *N,N,N',N'*-tetramethylethylenediamine (TMEDA) was used in THF.[5] This observation was not pursued.

The choice of ester alkyl group was briefly examined. In general, the use of methyl esters led to lower isolated yields of product presumably due to competing displacement of the labile methyl group. Both ethyl and isopropyl esters are stable to the reaction conditions. The products derived from the ethyl esters can be readily distilled without decomposition which is not always true for the isopropyl esters. The bulkier isopropyl esters may be useful for products that are susceptible to lactonization or oxidation (i.e., **2** and **6**).

Thus, the ortho-metalation and electrophilic trapping of ethyl or isopropyl arenesulfonates can be accomplished in good yield with *n*-butyllithium. A wide range of electrophiles can be used in this reaction sequence. The expected products, which can be readily purified, are formed in high yield.

Experimental Section[6]

General Procedure. A 100-mL, round-bottomed flask equipped with a stir bar and a serum cap was flame-dried and cooled under Ar to room temperature. The flask was then charged with 25 mL of dry THF and 2.5 mmol of the desired alkyl arenesulfonate (**1b–d**). This solution, cooled to −78 °C, was then treated with 1.1 equiv of *n*-butyllithium over a 10-min period. Usually a color change accompanied the addition of the alkyllithium. The ethyl esters turned red while the isopropyl esters were straw yellow. After the addition of the alkyllithium, the reaction was stirred at −78 °C for 5 h. The reaction was quenched with 1.1 equiv of the desired electrophile and stirred at −78 °C for 1 h. The reaction was warmed to 0 °C and stirred for 0.5 h before quenching with 10 mL of cold saturated NH_4Cl solution. Most of the THF was removed under aspirator pressure. The residue was partioned between 50 mL of ether and 25 mL of saturated brine. The organic layer was removed and the aqueous layer extracted with ether (2 × 25 mL). The combined organic layers were washed with 5% Na_2CO_3 (1 × 50 mL) and brine (1 × 50 mL). The organic layer was dried with $MgSO_4$ and filtered and the solvent removed in vacuo. The crude product was purified according to the procedures given below.

Ethyl 2-(*p*-Tolylhydroxymethyl)benzenesulfonate (2). The crude oil crystallized upon standing. Recrystallization from ethyl acetate/hexane gave colorless crystals: mp 106–107 °C; IR ($CDCl_3$) 3600 (s br), 3150, 1450, 1355, 1180, and 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.05 (d, *J* = 7.2 Hz, 1 H), 7.62 (m, 2 H), 7.41 (m, 1 H), 7.25 (d, *J* = 7.7 Hz, 2 H), 7.18 (d, *J* = 7.7 Hz, 2 H), 6.71 (s, 1 H), 4.15 (m, 1 H), 3.97 (m, 1 H), 2.50 (s, br), 2.18 (s, 3 H), and 1.15 (t, *J* = 7.1 Hz, 3 H).

Anal. Calcd for $C_{16}H_{18}SO_4$: C, 62.74; H, 5.88; S, 10.46. Found: C, 62.75; H, 5.88; S, 10.84.

Ethyl 2-Bromo-*p*-toluenesulfonate (3). The crude product crystallized from the isolated oil after standing 3 days at room temperature. Recrystallization from pentane (with 0.1% CH_2Cl_2) gave colorless needles: mp 58–59 °C; IR ($CDCl_3$) 2950, 1350, 1175, and 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.95 (d, *J* = 7.4 Hz, 1 H), 7.60 (s, 1 H), 7.35 (m, 1 H), 4.10 (q, *J* = 7.4 Hz, 2 H), 2.18 (s, 3 H), and 1.35 (t, *J* = 7.4 Hz, 3 H); exact mass calcd for $C_9H_{11}SO_3Br$ *m/z* 279.9589, found, 279.9621.

(4) The reaction is heterogeneous in ether. Complete metalation required −78 °C overnight. Bonfiglio, J. N.; Pine, S.; Labinger, J.; Miller, J. S., unpublished observations.

(5) Figuly and Martin (ref 2) reported side-chain lithiation when an excess of base was utilized.

(6) Nuclear magnetic resonance (NMR) spectra were recorded on a Varian EM360A, Varian FT-80, or Varian XL300. Chemical shifts are expressed in parts per million downfield from internal Me_4Si and coupling constants are recorded in hertz. Infrared spectra were recorded on a Beckman IR4240 spectrometer. High resolution mass spectra were recorded by the University of Nebraska mass spectrum facility. Elemental microanalyses were performed by Galbraith Laboratories, Knoxville, TN. Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected. THF was freshly distilled from Na/benzophenone ketyl. All reactions were run under an atmosphere of dry Ar. The term flash chromatography refers to the method described by Still.[7] Ethyl *p*-toluenesulfonate was purchased from Aldrich, distilled and stored over 4A molecular sieves. Ethyl benzenesulfonate (1c) was prepared according to standard procedures, distilled, and stored over 4A molecular sieves.[8] Isopropyl benzenesulfonate was prepared from benzenesulfonyl chloride and isopropyl alcohol[9] and purified by flash chromatography on silica gel (10% ethyl acetate/hexane). It was evacuated to 10^{-4} torr overnight and stored over 4A molecular sieves. Alkyllithiums were purchased from Aldrich and used as received.

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

(8) Roose, A. T.; Gilman, H.; Beaber, N. J. *Organic Syntheses*; Wiley: New York, 1941; Collect. Vol. 1, pp 145–147.

(9) Tipson, R. S.; Clapp, M. A.; Cretcher, L. H. *J. Org. Chem.* **1947**, *12*, 133.

Ethyl 2-(Trimethylsilyl)-*p*-toluenesulfonate (4). The crude product was distilled under reduced pressure to give a colorless oil: bp 103–105 °C (0.1 mm); IR (film) 2950, 1350, 1175, and 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.80 (d, J = 8.0 Hz, 1 H) 7.49 (s, 1 H), 7.21 (m, 1 H), 3.95 (q, J = 7.8 Hz, 2 H), 2.30 (s, 3 H), 1.20 (t, J = 7.8 Hz, 3 H), and 0.31 (s, 9 H); exact mass calcd for $C_{12}H_{20}SO_3Si$ m/z 272.0897, found 272.0915.

Ethyl 2-Formyl-*p*-toluenesulfonate (5). The compound was purified by flash chromatography on silica gel (15% ethyl acetate/hexanes) to give an oil: IR (film) 2970, 1690, 1350, 1180, and 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.65 (s, 1 H), 7.61 (m, 2 H), 7.25 (m, 1 H), 4.1 (q, J = 7.6 Hz, 2 H), 2.45 (s, 3 H), and 1.25 (t, J = 7.6 Hz, 3 H); exact mass calcd for $C_{10}H_{12}SO_4$ m/z 228.0453, found 228.0811.

Isopropyl 2-Formylbenzenesulfonate (6). The crude product was purified by flash chromatography on silica gel (15% ethyl acetate/hexanes) to give a colorless oil: IR (film) 2910, 1650, 1340, 1165, and 980 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.86 (s, 1 H), 8.21 (m, 2 H) 7.85 (m, 2 H), 4.91 (heptet, J = 6.1 Hz, 1 H), and 1.31 (d, J = 6.1 Hz, 6 H); exact mass calcd for $C_{10}H_{12}SO_4$ m/z 228.0453, found 228.0661.

Isopropyl 2-Methyl-*p*-toluenesulfonate (7). The crude product was purified by flash chromatography on silica gel (10% ethyl acetate/hexanes) to give a colorless oil: IR (film) 2950, 1347, 1175, and 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.10 (m, 1 H), 7.4 (m, 3 H), 4.75 (heptet, J = 6.1 Hz, 1 H), 2.65 (s, 3 H), and 1.31 (d, J = 6.1 Hz, 6 H); exact mass calcd for $C_{10}H_{19}SO_3$ m/z 214.0663, found 214.0669.

Isopropyl 2-(Phenylthio)benzenesulfonate (8). The crude product was purified by flash chromatography on silica gel (40% ethyl acetate/hexanes) followed by recrystallization from ether/hexane to give colorless needles: mp 69–71 °C; IR ($CDCl_3$) 2950, 1450, 1350, 1180, and 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.05 (d, J = 7.1 Hz, 1 H), 7.5–7.2 (m, aromatic 7 H), 6.95 (d, J = 7.5 Hz, 1 H), 4.91 (heptet, J = 6.4 Hz, 1 H), and 1.40 (d, J = 6.4 Hz, 6 H).

Anal. Calcd for $C_{15}H_{16}S_2O_3$: C, 58.44; H, 5.19; S, 20.77. Found: C, 58.46; H, 5.19; S, 21.03.

Registry No. 1, 80-40-0; **1c**, 515-46-8; **1d**, 6214-18-2; **2**, 102537-92-8; **3**, 102537-93-9; **4**, 102537-94-0; **5**, 102537-95-1; **6**, 102537-96-2; **7**, 102537-97-3; **8**, 102537-98-4; CH_3C6H_4-*p*-CHO, 104-87-0; $BrCH_2CH_2Br$, 106-93-4; $ClSi(CH_3)_3$, 75-77-4; $OCN(CH_3)_2$, 68-12-2; CH_3I, 74-88-4; PhSSPh, 882-33-7.

Synthesis of (*E*)-4-Amino-2,5-hexadienoic Acid and (*E*)-4-Amino-5-fluoro-2-pentenoic Acid. Irreversible Inhibitors of 4-Aminobutyrate-2-Oxoglutarate Aminotransferase

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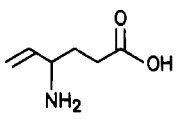
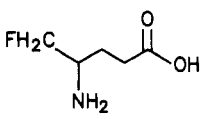
Inhibitors of 4-aminobutyrate–2-oxoglutarate aminotransferase (E.C. 2.6.1.19, GABA-T) are of interest as anticonvulsant agents.[1] γ-Vinyl-GABA (**1**)[2] and γ-fluoromethyl-GABA (**2**)[3] have been demonstrated to be enzyme-activated irreversible inhibitors of GABA-T. The mechanism of inactivation demands that **1** and **2** be substrates of GABA-T. Beart and Johnston[4] found that (*E*)-4-aminocrotonic acid, the α,β-unsaturated derivative of GABA was transaminated by GABA-T at 1.8 times the rate of GABA. On the basis of the result, the inhibitory activities of **1** and **2** could be expected to be increased by



1



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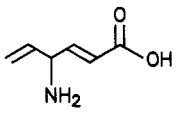

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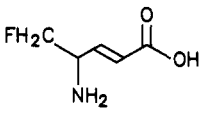

4

incorporation of an *E* double bond in the propionic acid side chain. In this note, we report the synthesis of (*E*)-4-amino-2,5-hexadienoic acid (**3**) (γ-vinyldehydro-GABA) and (*E*)-4-amino-5-fluoro-2-pentenoic acid (**4**) (γ-(fluoromethyl)dehydro-GABA) as well as their inhibitory properties toward GABA-T in vitro.

The actual sequences used to synthesize the dehydro analogues **3** and **4** are outlined in Schemes I and II, respectively. Both syntheses rely on a late construction of the chemically reactive α,β-unsaturated carboxylic acid functionality which was eventually achieved through oxidation of a primary allylic alcohol moiety. The key allylic alcohol intermediates **10** and **13** were prepared from sorbic acid and fluoroacetonitrile, respectively.

Allylic bromination of sorbic acid methyl ester as described by Schmid and Karrer[5] afforded the bromo ester **5** in 16% yield. Displacement of bromine with acetate (AcONa/AcOH, reflux temperature, 4 h), followed by transesterification of the acetate (CH_3ONa/CH_3OH) and tetrahydropyranylation of the resulting allylic alcohol using the conditions of Miyashita et al.[6] ($C_5H_5NH^+$, p-TsO^-, dihydropyran, CH_2Cl_2), gave **6b** in 67% overall yield. Reduction of the conjugated ester **6b** following the method of Davidson et al. ($LiAlH_4$, Et_2O, EtOH)[7] led cleanly to the dienic alcohol **7** which was smoothly transformed to the nonconjugated trichloroacetamide **9** via an Overman-type rearrangment[8] of the imidic ester **8** (reflux temperature of xylene). Disappointingly, the trichloroacetimidic ester **6c**, under similar conditions, failed to undergo the 3,3-sigmatropic rearrangement that would have had given a direct entry to a protected derivative of γ-vinyldehydro-GABA. Solvolysis of the tetrahydropyranyl group (MeOH, p-TsOH) followed by cleavage of the trichloroacetamide under basic conditions (NaOH, H_2O, THF) and introduction of the acid labile *tert*-butyloxycarbonyl group on the freed amine function [$(CO_2$-t-$Bu)_2O$, THF] afforded the desired allyl alcohol intermediate **10**.

The bromo derivative **12a**, prepared according to the general methodology we reported previously[9] for the synthesis of α-fluoromethylamines from fluoroacetonitrile, was converted to the key allylic alcohol **13** in 53% overall yield via a straightforward four-step sequence involving: (a)

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(1) Hammond, E. J.; Wilder, B. J. *Gen. Pharmacol.* **1985**, *16*, 441.
(2) Lippert, B.; Metcalf, B. W.; Jung, M. J.; Casara, P. *Eur. J. Biochem.* **1977**, *74*, 441.
(3) (a) Silverman, R. B.; Levy, M. A. *Biochem. Biophys. Res. Commun.* **1980**, *95*, 250. (b) Bey, P.; Jung, M. J.; Gerhart, F.; Schirlin, D.; Van Dorsselaer, V.; Casara, P. *J. Neurochem.* **1981**, *37*, 1341.
(4) Beart, P. M.; Johnston, G. A. R. *Brain Res.* **1973**, *49*, 459.
(5) Schmid, H.; Karrer, P. *Helv. Chim. Acta* **1946**, *29*, 573.
(6) Miyashita, N.; Yoshikoshi, A.; Grieco, P. *J. Org. Chem.* **1974**, *42*, 3772.
(7) Davidson, R. S.; Gunther, W. H. H.; Waddington-Feather, S. M.; Lythgoe, B. *J. Chem. Soc.* **1964**, 4907.
(8) Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218.
(9) Bey, P.; Gerhart, F.; Van Dorsselaer, V.; Danzin, C. *J. Med. Chem.* **1983**, *26*, 1551.

0022-3263/86/1951-2835$01.50/0