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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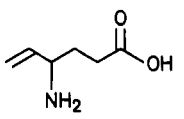
Inhibitors of 4-aminobutyrate–2-oxoglutarate aminotransferase (E.C. 2.6.1.19, GABA-T) are of interest as anticonvulsant agents.[1] γ-Vinyl-GABA (**1**)[2] and γ-fluoromethyl-GABA (**2**)[3] have been demonstrated to be enzyme-activated irreversible inhibitors of GABA-T. The mechanism of inactivation 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



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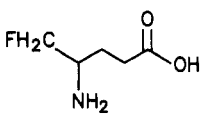

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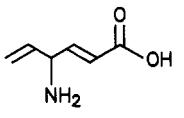

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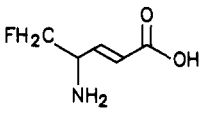

4

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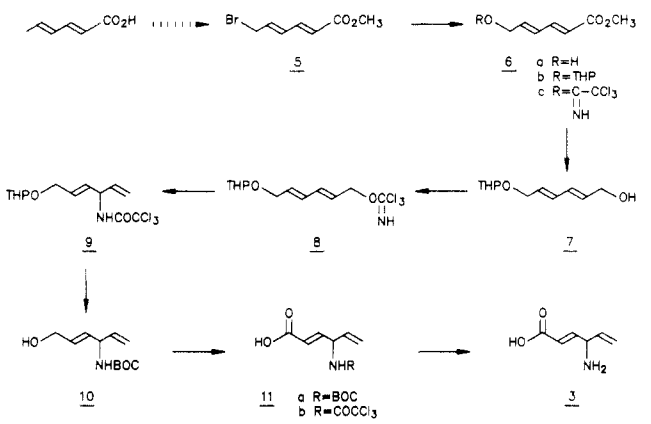
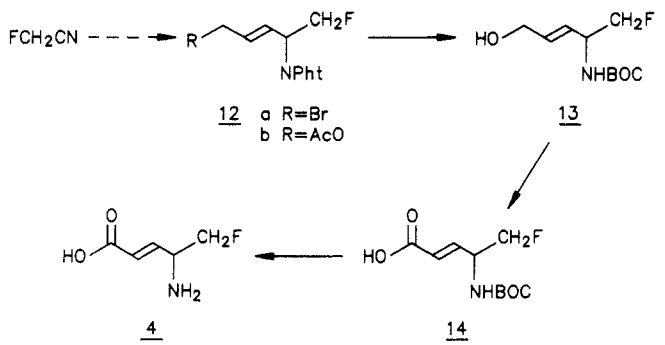
0022-3263/86/1951-2835$01.50/0

Scheme I



Scheme II



displacement of the allylic bromide with acetate; (b) removal of the phthaloyl group with hydrazine; (c) protection of the freed amine as its *tert*-butyloxycarbonyl derivative; and (d) hydrolytic cleavage of the acetate with lithium hydroxide.

Difficulties were encountered at the stage of the transformation of the key allylic alcohols **10** and **13** to the corresponding conjugated carboxylic acids **11a** and **14**. Oxidation of **10** with Jones' reagent stopped at the level of the conjugated aldehyde. Further oxidation to the conjugated acid with silver(I) oxide in presence of sodium cyanide and methanol as described by Corey et al.[10] failed whereas silver(II) oxide led essentially to the β,γ-unsaturated acid as judged by the ^{1}H NMR spectrum of the crude reaction mixture. The conjugated acids **11a** and **14** were eventually obtained via a sequential oxidation of **10** and **13** with first Jones' reagent and then sodium chlorite in presence of an excess of 2-methyl-2-butene as reported by Bal et al.[11] for the oxidation of sensitive α,β-unsaturated aldehydes. Cleavage of the BOC group of **11a** and **14** in a mixture of dilute hydrochloric acid and methanol followed by neutralization of the hydrochloride salt afforded γ-vinyldehydro-GABA (**3**) and γ-(fluoromethyl)dehydro-GABA (**4**) in good yield. Under these mild aqueous acidic conditions, protonation of the double bond did not occur. Indeed, no incorporation of deuterium in **3** could be detected during ^{1}H NMR monitoring of the hydrolysis of **11a** in a mixture of CD_3OD, D_2O, and DCl. In contrast, when an excess of anhydrous hydrochloric acid in ether was used, the removal of the BOC group of **11a** was extremely slow and a concomitant migration of the double bond took place. This propensity of the double bond to migrate into the β,γ position under strong acidic or basic conditions prompted the exchange of the trichloroacetyl group for a BOC group as a protection for the amine function. Indeed hydrolytic cleavage of the trichloroacetamido group of **8b** could not be achieved without a concomitant isomerization of the conjugated double bond.

The assignment of the *E* configuration to the double bond of the side chain in the fluoromethyl and vinyl series was made from the analysis of the ^{1}H NMR spectra at 200 MHz. A vicinal coupling constant of 15.7 to 16 Hz was consistently measured for the olefinic protons of the side chain in the intermediates and final products in both series. This value is in agreement with an *E* configuration of the double bond.[12]

The inhibitory activity of **3** and **4** toward GABA-T was evaluated in vitro as previously described for the saturated analogues **1** and **2**.[2,3] In both cases, an enzyme-activated irreversible inhibition pattern was observed. As expected, the introduction of an *E* double bond in the chain greatly increased the inhibitory potency of **2**. The apparent dissociation constant (K_I) of the dehydro analogue **4** (0.12 mM) for GABA-T was 17 times lower than that of the saturated analogue, while the rate constants for the inactivation of GABA-T by **2** and **4** were within the same range. In the case of γ-vinyl-GABA (**1**) on the contrary, the double bond in the chain decreased significantly the inhibitory activity. At all concentrations, **3** proved to inhibit GABA-T at about 1/6th the rate of **1**.

Experimental Section

Melting points were determined on a Mettler FP 5 or a Kofler hot bank melting point apparatus and are uncorrected. Microanalyses were conducted on a Perkin-Elmer 240 CHN analyzer. The IR, NMR, and UV data were consistent with the assigned structure. Unless otherwise stated, the ^{1}H NMR spectra were recorded at 60 MHz on a Varian Associates Model T60 spectrometer. The 200-MHz ^{1}H NMR spectra were recorded on a Brucker WP 200 spectrometer. The NMR spectra are reported in parts per million from internal tetramethylsilane or 2,2-dimethyl-2-silapentane-5-sulfonate in the δ scale. Data are presented as follows: solvent, chemical shift, integration, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet), interpretation, and coupling constants.

6-(2-Tetrahydropyranyloxy)-3,4-hexadien-1-ol (7). A mixture of methyl 6-hydroxy-2,4-hexadienoate (10.44 g or 0.0733 mol),[5] dihydropyran (10.03 mL or 0.11 mol), pyridinium tosylate (1.93 g or 0.0073 mol), and CH_2Cl_2 (200 mL) was stirred at room temperature for 4 $^1/_2$ h and then washed with water and brine and dried over $MgSO_4$. Concentration in vacuo afforded crude methyl 6-(2-tetrahydropyranyloxy)-2,4-hexadienoate (15.53 g) as an oil which was dissolved in anhydrous ether (300 mL). To the ethereal solution cooled to 0 °C was added slowly at 30-min intervals, 2 portions of 60 mL of a suspension prepared from $LiAlH_4$ (4.4 g), anhydrous ether (200 mL), and ethanol (0.53 g). After cautious quenching with water, the aluminum salts were filtered and washed extensively with diethyl ether. The filtrate was dried over $MgSO_4$ and concentrated in vacuo. The oily residue was purified by flash chromatography on silica gel. Elution with 30% diethyl ether in petroleum ether afforded pure **7** (10.4 g) in 71% yield as an oil: ^{1}H NMR ($CDCl_3$) δ 1.33–1.86 [6 H, m, $(CH_2)_3$], 2.07 (1 H, s, OH), 3.33–4.4 (6 H, m, OCH_2), 4.67 (1 H, m, OCHO), 5.5–6.53 (4 H, m, olefinic H). No analysis.

1-(2-Tetrahydropyranyloxy)-3-(trichloroacetamido)-2,5-hexadiene (9). To a suspension of NaH (0.171 g of a 55% oil suspension or 0.0039 mol washed 3 times in pentane) in anhydrous ether (50 mL) was added under N_2 a solution of **7** (7.74 g or 0.039 mol) in anhydrous ether (60 mL). The reaction mixture was stirred for 10 min at room temperature and then cooled to 0 °C whereupon a solution of trichloroacetonitrile (3.91 mL or 0.039

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mol) in ether (20 mL) was added slowly. Stirring was continued for 40 min at room temperature. Concentration in vacuo left a residue which was triturated with a mixture of methanol (0.5 mL) and pentane (50 mL). Evaporation in vacuo gave the imidic ester **8** as an oil which was dissolved in xylene (150 mL). The solution was heated at reflux temperature for 20 h and then concentrated in vacuo. The residue was purified by flash chromatography on silica gel. Elution with 25% diethyl eter in petroleum ether afforded first the unreacted imidic ester **8** (0.95 g) and then pure **9** (10.4 g) as an oil (77% yield): ^{1}H NMR ($CDCl_3$) δ 1.26–1.86 [6 H, m, $(CH_2)_3$], 3.33–4.33 [4 H, m, (OCH_2)], 4.66 (1 H, m, OCHO), 4.9–6.16 (6 H, m, olefinic H and CHN), 6.66 (1 H, br s, NH). Anal. Calcd for $C_{13}H_{18}Cl_3NO_3$: C, 45.57; H, 5.29; N, 4.09. Found: C, 44.98; H, 5.35; N, 4.14.

4-(Trichloroacetamido)-2,5-hexadien-1-ol. A mixture of **9** (9.85 g or 0.0287 mol), methanol (250 mL), and *p*-TsOH (0.12 g) was stirred at room temperature overnight and then concentrated in vacuo. The residue was dissolved in diethyl ether (100 mL). The organic layer was extracted with water and brine and dried over $MgSO_4$. Concentration in vacuo afforded pure 4-trichloroacetamido-2,5-hexadien-1-ol (7.1 g) (96% yield) as an oil: ^{1}H NMR ($CDCl_3$) δ 2.36 (1 H, m, OH), 4.03–4.3 (2 H, m, OCH_2), 4.77–6.06 (6 H, m, olefinic H and CHN), 6.9 (1 H, br s, NH). Anal. Calcd for $C_8H_{10}Cl_3NO_2$: C, 37.77; H, 3.90; N, 5.42. Found: C, 37.74; H, 4.11; N, 5.72.

4-((*tert*-Butyloxycarbonyl)amino)-2,5-hexadien-1-ol (10). A solution of 4-trichloroacetamido-2,5-hexadien-1-ol (3.84 g or 0.0148 mol), methanol (10 mL), and 5 N aqueous sodium hydroxide (15 mL or 0.075 mol) was stirred for 1 h at room temperature, then concentrated in vacuo, saturated with NaCl, and extracted with diethyl ether (4 × 20 mL). The ethereal layers were pooled, dried over $MgSO_4$, and evaporated under vacuum to afford crude 6-hydroxy-1,4-hexadien-3-amine (1.11 g) as an oil which was treated with di-*tert*-butyl dicarbonate (2.14 g or 0.0098 mol) in tetrahydrofuran (80 mL) at reflux temperature for 5 h. Concentration in vacuo left a residue which was purified by flash chromatography on silica gel. Elution with 50% diethyl ether in petroluem ether afforded **10** (1.49 g) as an oil (47% yield): ^{1}H NMR ($CDCl_3$) δ 1.40 [9 H, s, $C(CH_3)_3$], 4.10 (2 H, d, CH_2O, J = 4 Hz), 4.95–5.90 (5 H, m, olefinic H). Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 61.89; H, 8.72; N, 6.30.

(*E*)-4-((*tert*-Butyloxycarbonyl)amino)-2,5-hexadienoic Acid (11a). To a solution of **10** (1.675 g or 0.0079 mmol) in acetone (30 mL distilled over $KMnO_4$) cooled to 0 °C was added slowly over 40 min a solution of 2.5 M Jones' reagent (4.72 mL or 0.01185 mol). The excess oxidizing reagent was destroyed by addition of isopropyl alcohol (1 mL). Evaporation in vacuo left a residue which was extracted with diethyl ether. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo to give crude 4-(*tert*-butyloxycarbonyl)-amino)-2,5-hexadien-1-al as an oil (1.48 g) which was dissolved in *tert*-butyl alcohol (146 mL) and 2-methyl-2-butene (35 mL). A solution of sodium chlorite (5.83 g or 0.064 mol) and NaH_2PO_4, H_2O (6.68 g) in H_2O (58 mL) was then added dropwise. The reaction mixture was stirred at room temperature overnight and then concentrated in vacuo to a volume of about 50 mL. The aqueous residue was extracted with hexane (3 × 20 mL), then cooled to 0 °C, and cautiously acidified with 1 N HCl to pH 4–5, saturated with NaCl and finally extracted with diethyl ether (3 × 50 mL). Evaporation in vacuo of the dried ($MgSO_4$) ethereal layers afforded a solid residue which was recrystallized from diethyl ether–pentane to give analytically pure **11a** (1.3 g) (72% yield). mp: 105 °C; 200-MHz ^{1}H NMR ($CDCl_3$) δ 1.45 [9 H, s, $C(CH_3)_3$], 4.74 (1 H, m, NH), 4.91 (1 H, m, CH_DNH Boc), 5.25 (2 H, m, CH_AH_B=C, $J_{H_AH_B}$ = 3.5 Hz), 5.83 [1 H, d of d of d, CH_AH_B=CH_C-, $J_{H_CH_D}$ = 5.8 Hz, $J_{H_CH_A}$(trans) = 17.4 Hz, $J_{H_CH_B}$(cis) = 10.5 Hz], 5.97 (1 H, d of d, C=CH_FCO_2H, $J_{H_FH_E}$ = 15.7 Hz, $J_{H_FH_D}$ = 1.6 Hz), 7.00 (1 H, d of d, -CH_E=C, $J_{H_EH_F}$ = 15.7 Hz, $J_{H_EH_D}$ = 4.3 Hz). Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 58.08; H, 7.54; n, 6.50.

(*E*)-4-Amino-2,5-hexadienoic Acid (3). A suspension of **11a** (0.85 g or 0.00375 mol) in a mixture of methanol (4 mL) and 1 N aqueous HCl (15 mL) was stirred at room temperature for 30 h. The solution was concentrated in vacuo to give an oil residue which was dissolved in water (10 mL) and treated with charcoal. The colorless filtrate was neutralized with triethylamine (0.51 mL or 0.0037 mol) and concentrated in vacuo. The solid residue was washed with hot chloroform (4 × 25 mL). The insoluble residue was recrystallized from water–ethanol to afford analytically pure **3** (0.35 g) (74% yield): mp 134 °C; TLC (AcOH/BuOH/H_2O, 2/6/2) R_f 0.4; 200-MHz ^{1}H NMR (D_2O) δ 4.57 (1 H, t, >CH_DNH$_2$, $J_{H_DH_C}$ = $J_{H_DH_E}$ = 6.6 Hz), 5.45 (2 H, m, CH_AH_B=C), 5.90 [1 H, m, H_BH_AC=CH_C-, $J_{H_CH_A}$(cis) = 10.5 Hz, $J_{H_CH_B}$(trans) = 17 Hz, $J_{H_CH_D}$ = 6.6 Hz], 6.11 (1 H, d, C=CH_FCO_2H, $J_{H_FH_E}$ = 15.8 Hz), 6.52 (1 H, q, -CH_E=CH_F-, $J_{H_EH_F}$ = 15.8 Hz, $J_{H_EH_D}$ = 6.6 Hz). Anal. Calcd for $C_6H_9NO_2$: C, 56.68; H, 7.14; N, 11.20. Found: C, 56.51; H, 7.00; N, 11.12.

1-Fluoro-2-phthalimido-5-acetoxy-3-pentene (12b). A mixture of **12a**[9] (3.12 g or 0.01 mol), silver acetate (1.84 g or 0.011 mol), and acetic acid was heated at 80–100 °C for 25 min. The insoluble material was filtered and the filtrate was concentrated in vacuo. The residue was dissolved in diethyl ether (75 mL). The organic layer was washed with 10% aqueous $NaHCO_3$, water, and brine and then dried over $MgSO_4$. Concentration in vacuo left a solid residue which was recrystallized from CH_2Cl_2/pentane to give **12b** (2.14 g) (70% yield): mp 70 °C; ^{1}H NMR ($CDCl_3$) δ 2.05 (3 H, s, CH_3OCO-) 4.13–5.5 (5 H, m, CH_2F, CH_2OAc and CHNPht), 7.8 (4 H, m, aromatic H). No analysis.

(*E*)-5-Fluoro-4-((*tert*-butyloxycarbonyl)amino)-2-penten-1-ol (13). A mixture of **12b** (4.15 g or 0.0143 mol) and hydrazine hydrate (0.716 g or 0.0143 mol) in ethanol (50 mL) was heated at reflux temperature for 3 h. The solid which separated upon cooling was filtered and washed with ethanol (2 × 5 mL). The filtrate was concentrated in vacuo to give an oily residue which was triturated with 1 N aqueous HCl (15 mL). The solid which separated upon cooling to 4 °C was discarded. The filtrate was concentrated in vacuo to afford crude 1-fluoro-5-acetoxy-3-pentene-2-amine hydrochloride which was dissolved in water (20 mL). To this solution was added $NaHCO_3$ (1.2 g or 0.0143 mol) and di-*tert*-butyl dicarbonate (3.24 g or 0.0143 mol) in tetrahydrofuran (50 mL). The reaction mixture was heated at reflux temperature for 3 h, then concentrated in vacuo. The residue was taken up with diethyl ether (100 mL). After washing with water, brine and drying over $MgSO_4$, the ethereal layer was concentrated to yield an oily residue which was dissolved in water (30 mL) and dimethoxyethane (90 mL). Lithium hydroxide hydrate (2.77 g or 0.0286 mol) was added. The reaction mixture was stirred overnight at room temperature and then extracted twice with diethyl ether (75 mL). The ethereal layers were pooled, washed with water and brine, and dried over $MgSO_4$. Concentration in vacuo yielded a solid residue which was recrystallized from diethyl ether/pentane to give **13** (2.3 g) (76% yield): mp 65 °C; TLC (diethyl ether) R_f 0.7; 200-MHz ^{1}H NMR ($CDCl_3$) δ 1.45 [9 H, s, $C(CH_3)_3$], 1.64 (1 H, m, OH) 4.17 (2 H, br t, d after exchange with D_2O, CH_AH_BOH, $J_{H_AH_C}$ = $J_{H_BH_C}$ = 5.0 Hz), 4.37 (1 H, m, CH_EN, J_{H_FF} = 23 Hz), 4.43 (1 H, d of d of d, CH_FF, $J_{H_FH_G}$ = 8.8 Hz, J_{H_FF} = 47 Hz, $J_{H_FH_E}$ = 3.5 Hz), 4.47 (1 H, d of d of d, CH_GF, $J_{H_GH_F}$ = 8.8 Hz, J_{H_GF} = 47 Hz, $J_{H_GH_E}$ = 4.5 Hz), 4.77 (1 H, m, NH), 5.75 (1 H, t of d of d, NCCH_D=C, $J_{H_DH_E}$ = 5.0 Hz, $J_{H_DH_A}$ ≤ 1 Hz, $J_{H_DH_C}$ = 15.8 Hz), 5.89 (1 H, t of d of d, CH_D=$CH_CCH_AH_B$-, $J_{H_CH_E}$ ≤ 1 Hz, $J_{H_CH_A}$ = 5.0 Hz, $J_{H_CH_D}$ = 15.8 Hz). Anal. Calcd for $C_{10}H_{18}NO_3F$: C, 54.90; H, 7.95; N, 6.35. Found: C, 54.85; H, 7.96; N, 6.37.

(*E*)-5-Fluoro-4-((*tert*-butyloxycarbonyl)amino)-2-pentenoic acid (14) was prepared from **13** (in 70% yield) in a manner similar to that described for the synthesis of **11a** from **10**: mp 120 °C (CH_2Cl_2/pentane); 200-MHz ^{1}H NMR ($CDCl_3$) δ 1.47 [9 H, s, $C(CH_3)_3$], 4.53 (2 H, d of d, CH_AH_BF, $J_{H_AH_C}$ = 3.2 Hz, J_{H_AF} = 49 HZ), 4.57 (1 H, br m, -CH_CN, J_{H_CF} ≈ 20 Hz), 4.96 (1 H, m, NH), 5.70 (1 H, br peak, COOH), 6.06 (1 H, d of d, C=CH_ECO_2H, $J_{H_EH_D}$ = 15.7 Hz, $J_{H_EH_C}$ = 1.6 Hz), 7.02 (1 H, d of d, -CH_D=C-, $J_{H_DH_E}$ = 15.7 Hz, $J_{H_DH_C}$ = 4.6 Hz). Anal. Calcd for $C_{10}H_{16}NO_4F$: C, 51.50; H, 6.91; N, 6.00. Found: C, 51.20; H, 6.88; N, 5.78.

(*E*)-5-Fluoro-4-amino-2-pentenoic acid (4) was prepared from **14** (in 82% yield) in a manner similar to that described for the synthesis of **3** from **11a**: mp 168 °C; 200-MHz ^{1}H NMR (D_2O + DCl pH 1.0) δ 4.46 (1 H, d of m, CH_AN, J_{H_AF} = 21 Hz), 4.71 (1 H, d of d of d, CH_BF, $J_{H_BH_C}$ = 10.8 Hz, $J_{H_BH_A}$ = 5.5 Hz, J_{H_BF} = 46.5 Hz), 4.82 (1 H, d of d of d, CH_CF, $J_{H_CH_B}$ = 10.8 Hz, $J_{H_CH_A}$ = 3.4 Hz, J_{H_CF} = 46.5 Hz), 6.26 (1 H, d of d, C=CH_DCO_2H, $J_{H_DH_E}$ = 16 Hz, $J_{H_DH_A}$ = 1.0 Hz), 6.92 (1 H, d of d, CH_E=C, $J_{H_EH_D}$ = 16 Hz, $J_{H_EH_A}$ = 6.5 Hz). Anal. Calcd for $C_5H_8NO_2F$: C, 45.11; H,

6.06; N, 10.52. Found: C, 45.08; H, 6.05; N, 10.43.

Registry No. **3**, 102420-40-6; **3** (alcohol), 102420-37-1; **4**, 102491-83-8; **4** (acetate), 102420-43-9; **6a**, 689-89-4; GABA-T, 9037-67-6; **7**, 102420-31-5; **8**, 102420-34-8; **9**, 102420-33-7; **9** (alcohol), 102420-35-9; **10**, 102420-36-0; **11a**, 102420-38-2; **11a** (aldehyde), 102420-39-3; **12a**, 82006-54-0; **12b**, 102420-41-7; **13**, 102420-42-8; **14**, 102420-44-0; **6b**, 102420-32-6; $NCCOCCl_3$, 545-06-2.

A Convenient Synthesis of a "Gable"-Type Porphyrin

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A dimeric porphyrin with a "gable" orientation, 1,3-bis[5-(10,15,20-triphenylporphinyl)]benzene, has recently been prepared by Tabushi and co-workers.[1] Metal complexes of this gable porphyrin were demonstrated to bind various ligands in a cooperative fashion.[1,2] The gable porphyrin thus serves as an interesting example of an *artificial allosteric system*.[3,4] Moreover, the orientation of the two porphyrin rings in the gable dimer resembles that found in cytochrome c_3[5] and in the cytochrome associated with the active site of a structurally characterized photosynthetic bacterium.[6] Gable-type porphyrins may thus emerge as interesting models in electron and energy transfer studies.

Unfortunately, the synthesis reported for Tabushi's gable porphyrin is long and tedious: It involves six chemical steps, including two Rothemund condensations, and requires multiple chromatographic separations. It proceeds in an overall yield of ca. 1% from *m*-xylene.[1] We wish to report that gable-type dimeric porphyrins may be conveniently prepared from dipyrromethane intermediates by the MacDonald–Chang porphyrin synthesis.[7-10] We describe here the synthesis of a new gable-type dimeric porphyrin **1**. It is obtained in four steps from isophthalaldehyde in ca. 8% overall yield.[11]

The synthesis of **1** is outlined in Scheme I, part A. Condensation of ethyl 3-ethyl-4-methylpyrrole-2-carboxylate (**2**)[12] with isophthalaldehyde (**3**) in EtOH–HCl gave the bis(dipyrrylmethane) **4** in nearly quantitative yield. Saponification and decarboxylation by the procedure of Chang[8-10] gave the α-unsubstituted bis(dipyrrylmethane) **6**. The synthesis of the 5,5′-diformyldipyrrylmethane **11** is shown in part B of Scheme I. Ethyl 3,5-dimethyl-4-propylpyrrole-2-carboxylate (**7**), prepared by the method of Johnson,[13,14] was oxidized to the acetoxymethyl derivative **8** by using lead tetraacetate[14] and converted to the dipyrrylmethane **9** under acidic conditions.[15] Saponification and decarboxylation (to **10**) followed by Vilsmeier formylation, using the procedure of Clezy,[16] gave **11** in good yield. Various acidic catalysts and reaction conditions were employed in an effort to optimize the MacDonald[7] condensation between **6** and **11** (Scheme I, part C). These have included the use of MeOH, THF, HOAc, or mixtures thereof as solvents and HI, *p*-TsOH, or $HClO_4$ as acids. In general, our yields have been in the range of 10% (following oxidation and workup) and have proved to be rather insensitive to the reaction conditions. In fact, in our hands, the recently introduced Chang modification (0.4% $HClO_4$ in MeOH)[8-10] appears to be only slightly better than the original MacDonald procedure (HI in HOAc).[7] When the latter method is employed, it is possible to use the tetraacid **5** directly in the porphyrin synthesis; it is presumably decarboxylated to give **6** in situ.

The dimeric gable-type porphyrin **1** was characterized by ^1H NMR, ^{13}C NMR, electronic spectroscopy, mass spectrometry, and elemental analysis. The ^1H NMR spectrum of **1** was notable for two sharp low-field singlets (in 2:1 ratio) ascribable to the meso protons. This and the clean nature of the alkyl peaks suggest that the porphyrin condensation conditions do not cause scrambling of the substituents. Evidence for the gable orientation was obtained from electronic spectroscopy. As was observed in the case of the Zn_2·gable porphyrin of Tabushi,[1] the biszinc complex Zn_2·**1** shows a split Soret band. In contrast to the Tabushi system,[1] however, the free base **1** does not show such splitting. It presents instead a broad Soret band centered at 410 nm, which is considerably red shifted compared to etioporphyrin II (2,8,13,17-tetraethyl-3,7,12,18-tetramethylporphyrin) (λ_{max} 397 nm)[17] or the monophenyloctaalkylporphyrin, 5-phenyl-2,8,13,17-tetraethyl-3,7,12,18-tetramethylporphine, recently prepared by Chang (λ_{max} 402 nm).[18]

Experimental Section

NMR spectra were obtained in $CDCl_3$ with Me_4Si as an internal standard and recorded on either a Varian EM-390 or Nicolet FT-360 spectrometer. Routine mass spectra were measured with either a Finnigan MAT 4023 or a Bell and Howell 21-110B instrument. The mass spectrum of **1** was recorded by using fast atom bombardment on a Kratos MS-50 instrument at the University of Texas Health Science Center, Houston. Electronic spectra were measured in CH_2Cl_2 on a Beckman Instruments DU-7. Elementary analyses were performed by Galbraith Laboratories. Isophthalaldehyde was obtained from Aldrich Chemical

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