step by reaction of lithium ethyl acetate with ethyl carbonate or ethyl chloroformate. Diethyl carbonate failed to react at the low temperature needed to prevent self-condensation of the ethyl lithioacetate. However reaction between ethyl chloroformate and the ethyl lithioacetate, generated from ethyl acetate by the use of 1 equiv of lithium bis(trimethylsilyl)amide, afforded a 48% yield of diethyl malonate. We reasoned that the poor yield was due to protonation of the ethyl lithioacetate by the product, diethyl malonate. This decomposition of the ethyl lithioacetate was avoided by the use of slightly more than 2 equiv of the lithium bis(trimethylsilyl)amide, and excellent yields (86–92%) of diethyl malonate were obtained. The yield was estimated by GLC of the crude product which was contaminated with some bis(trimethylsilyl) ether. This impurity was not deleterious in subsequent conversion of the diethyl malonate to diethyl 2-acetamidomalonate.[2] Poorer yields of diethyl malonate were obtained when the ethyl lithioacetate was generated with lithium diisopropylamide or lithium 2,2,6,6-tetramethylpiperidide.[7]

Experimental Section

Diethyl [2-^{13}C]Malonate. *n*-Butyllithium (15 mL of a 2.1 M solution in hexane, 31.5 mmol) was added slowly to a solution of bis(trimethylsilyl)amine (4.04 g, 40 mmol) in dry THF (30 mL), stirred magnetically, in a N_2 atmosphere, cooled to −65 °C (internal thermometer). The solution was warmed to 20 °C during 20 min and then cooled to −72 °C in a dry ice–methanol bath. Ethyl [2-^{13}C]acetate (1.353 g, 15.2 mmol, 92% ^{13}C) dissolved in THF (3.5 mL) was added to the reaction mixture during 7 min by means of a syringe. An additional quantity of THF (3.5 mL) was used to rinse out the syringe and flask which had contained the labeled ethyl acetate. The solution was stirred for 30 min at −72 to −75 °C and then freshly distilled ethyl chloroformate (1.65 g, 15.2 mmol) was added by means of a syringe, keeping the temperature below −55 °C. After the reaction mixture was stirred for another 2 h at −75 °C, 6 M HCl (4 mL) was added, followed by water (20 mL) and ether (100 mL). The ether layer was separated and the aqueous solution extracted with additional ether (50 mL). The combined ether extracts were washed successively with 3 M HCl (20 mL), water (50 mL), and 5% aqueous $NaHCO_3$ (50 mL). The HCl and water washes were combined and extracted with ether (2 × 20 mL). These ether extracts were washed with 5% aqueous $NaHCO_3$ and then combined with the original ether extract. Evaporation (50 °C, 12 mm) of the dried (Na_2SO_4) extract yielded crude diethyl [2-^{13}C]malonate (2.430 g). Analysis of this material by GLC[8] indicated a purity of 86.8%; thus the actual yield of diethyl malonate was 2.109 g (86%). Proton NMR indicated that the ^{13}C enrichment of the product was essentially the same as the starting ethyl [2-^{13}C]acetate: ^{1}H NMR (80 MHz, FT, $CDCl_3$) δ 4.18 (4 H, q, OCH_2CH_3, $^3J_{H,H}$ = 7.1 Hz), 3.32 (1.84 H, d, C(O)^{13}CH_2C(O), $^1J_{C,H}$ = 132 Hz), 3.32 (0.16 H, s, C(O)CH_2C(O), 1.27 (6 H, t, OCH_2CH_3, $^3J_{H,H}$ = 7.1 Hz); ^{13}C NMR (25.2 MHz, FT, ^{1}H decoupled, $CDCl_3$) δ 166.6 (d, C(O)CH_2, $^1J_{C,C}$ = 59.2 Hz, singlet from unenriched material not discernible from background), 61.5 (s, OCH_2CH_3), 41.7 (t, C(O)CH_2C(O), $^1J_{C,C}$ = 59.2 Hz), 14.1 (s, OCH_2CH_3).

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Registry No. Ethyl [2-^{13}C]acetate, 58735-82-3; ethyl chloroformate, 541-41-3; diethyl [2-^{13}C]malonate, 67035-94-3.

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Folate Analogues. 17. Synthesis of Pteroic Acid and 4-Amino-4-deoxypteroic Acid[1]

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In connection with our studies concerning the development of synthetic substrates[2] of the enzyme dihydrofolate reductase (EC 1.5.1.3) it occurred to us that the protected bromomethyl ketone **6** would be a useful intermediate for the construction of certain classical folate analogues such as 7,8-dihydro-8-oxafolic acid[3] and 7,8-dihydro-8-thiofolic acid.[4] In addition, the protected amino ketone **11** derived from **6** appeared to be of potential value for alternate syntheses[5,6] of the biologically relevant[7-9] pteroic acids **1**, **2**, and **3**, based on the well-known Boon–Leigh strategy.[10,11] In this paper we describe the preparation of these ketones and their conversions to **1** and **3** (Chart I).

Fusion of 1 equiv of bromoacetic acid with 1 equiv of ethyl *p*-aminobenzoate resulted in the formation of *N*-(*p*-carbethoxyphenyl)glycine (**4**) which, upon treatment with trifluoroacetic anhydride[12] and aqueous workup, gave the *N*-trifluoroacetyl derivative **5**. This compound was converted to the corresponding acid chloride with the use of thionyl chloride and was subsequently elaborated to the diazo ketone **5b** by treatment with diazomethane. Gaseous HBr or HCl converted an ethereal solution of **5b** to the corresponding bromomethyl ketone **6** or chloromethyl ketone **7** in good yield.[1]

Conversion of the bromomethyl ketone to the azidomethyl ketone **8** was accomplished by treating **6** with sodium azide under a carefully controlled set of conditions in anhydrous acetone.[1] The carbonyl group of the crystalline azide **8** was protected as the dimethyl ketal **9**, using methanol and H_2SO_4. Hydrolysis of **9** with NaOH also resulted in the removal of the protective group and gave an excellent yield of **10**. Hydrogenation of **10** in MeOH using 5% palladium on carbon gave the protectd α-amino

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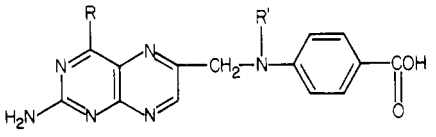
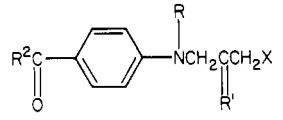
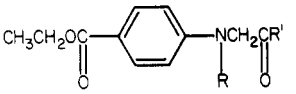
Chart I



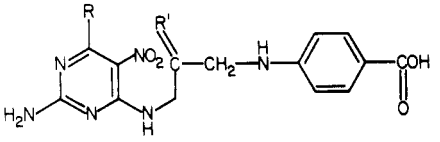
1, R = OH; R′ = H
2, R = NH_2; R′ = CH_3
3, R = NH_2; R′ = H



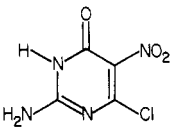
6, R = $C(O)CF_3$; R′ = O; R^2 = OEt; X = Br
7, R = $C(O)CF_3$; R′ = O; R^2 = OEt; X = Cl
8, R = $C(O)CF_3$; R′ = O; R^2 = OEt; X = N_3
9, R = $C(O)CF_3$; R′ = $(OMe)_2$; R^2 = OEt; X = N_3
10, R = H; R′ = $(OMe)_2$; R^2 = OH; X = N_3
11, R = H; R′ = $(OMe)_2$; R^2 = OH; X = NH_2



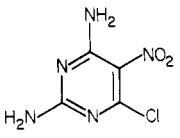
4, R = H; R′ = OH
5, R = $C(O)CF_3$; R′ = OH
5b, R = $C(O)CF_3$; R′ = CHN_2



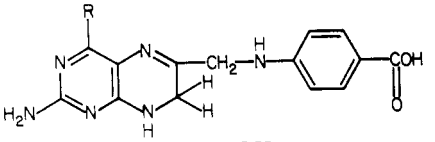
14, R = OH; R′ = $(OMe)_2$
15, R = OH; R′ = O
16, R = NH_2; R′ = $(OMe)_2$
17, R = NH_2; R′ = O



12



13



18, R = OH
19, R = NH_2

ketone 11 which was used as a common intermediate for the synthesis of both pteroic acids 1 and 3.

The desired 2-amino-6-chloro-4-hydroxy-5-nitropyrimidine (12)[13] and 6-chloro-2,4-diamino-5-nitropyrimidine (13)[14] were prepared according to published procedures. Reaction of 11 with the 4-hydroxypyrimidine 12 gave 14, which after isolation was treated with HCl and trifluoroacetic acid to remove the carbonyl protective group as described previously.[1] The carbonyl compound 15 thus obtained was reduced with sodium dithionite, cyclized to 7,8-dihydropteroic acid (18), and oxidized to pteroic acid (1) with the use of 5% $KMnO_4$ in dilute NaOH. In a similar manner, 11 was reacted with the 4-amino-6-chloropyrimidine 13 which gave 16 as the product. Deprotection of the carbonyl group of 16 was accomplished with TFA and HCL to 17, which, on reductive cyclization and oxidation as described previously,[2,15] gave 4-amino-4-deoxypteroic acid (3) in 35% yield based on 17. The yield of 1 from 15 was ~50%. Since most of these intermediates are crystalline compounds obtained in high yield from relatively cheap starting materials, and the cyclization, oxidation, and isolation of the final products starting with the dithionite reduction products of 15 and 17 could be carried out in the same reaction vessel without the isolation of intermediates 18 and 19, the series of reactions described here constitutes a convenient synthesis of these pteroic acids. Since radiolabeled bromoacetic acid and *p*-aminobenzoic acids are easily accessible, these synthetic procedures can also be applied for specific ^{14}C and ^{3}H labeling of the pteroic acids.

Experimental Section

Melting points were determined on a Fisher Model 355 digital melting-point analyzer. NMR spectra were run on a 90-MHz Perkin-Elmer R-32 spectrometer with Me_4Si as internal lock signal. Peak multiplicity is depicted as follows: s, singlet; d, doublet; t, triplet, etc.; br, broadened singlet or unresolved multiplet, the center of which is given. UV spectra were determined on a Beckman Model 25 spectrophotometer. Elemental analyses were done by Galbraith Laboratories, Inc., Knoxville, TN.

Preparation of *N*-(*p*-Carbethoxyphenyl)glycine (4). In a round-bottomed flask was placed a mixture of 24.75 g (150 mmol) of ethyl *p*-aminobenzoate and 20.8 g of bromoacetic acid (150 mmol), and it was slowly heated with stirring in a stream of N_2 with the use of an oil bath. When the outside bath temperature reached 80 °C the mixture melted to form a homogeneous solution which slowly began to solidify during a 20-min period at an outside bath temperature of 100 °C. The solid residue thus obtained was transferred to a beaker with the aid of a spatula and 400 mL of distilled water. After the lumps were broken up with a spatula, the mixture was stirred vigorously and the pH adjusted slowly to 9 with 2 N NaOH. At this point the mixture was filtered and the filtrate acidified to pH 3.0 by using 1 N HCl and chilled overnight in the refrigerator. Light yellow crystals of 4 were formed which were separated by filtration, washed with ice-cold water, and dried: yield 15.0 g (67.3 mmol, 44.8%); mp 163 °C; NMR (TFA) δ 7.75, 7.2 (d, d, 4 H, aromatic), 4.05 (s, 2 H, methylene), 4.0 (q, 2 H, ethoxy), 0.95 (t, 3 H, ethoxy). Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.2; H, 5.83; N, 6.23; O, 28.70. Found: C, 59.30; H, 5.91; N, 6.17; O, 28.95.

Preparation of *N*-(*p*-Carbethoxyphenyl)-*N*-(trifluoroacetyl)glycine (5). A solution of 10 g (44.843 mmol) of fusion product 4 in 200 mL of methylene chloride was chilled to 0 °C in a 500-mL round-bottomed flask with an ice bath, and during a period of 10 min 10 mL (70.8 mmol) of trifluoroacetic anhydride was added. The mixture was allowed to stir at this temperature for 2 h and then evaporated. The viscous product thus obtained was treated with 100 mL of ice-cold water and 150 mL of methanol, whereupon a clear solution was obtained. This solution was evaporated to dryness at reduced pressure at 40 °C and the residue partitioned between 200 mL each of ethyl acetate and water. The ethyl acetate layer was separated, washed with three 100-mL portions of water, dried, and evaporated. On addition of benzene (100 mL) crystals were formed, and crystallization was made complete by the addition of small portions of hexane. These crystals of 5 were filtered and dried: yield 10.84 g (33.98 mmol, 75.7%); mp 107.8–112.4 °C; NMR ($CDCl_3$) δ 8.10, 7.45 (d, d, 4 H, aromatic), 4.43 (s, 2 H, methylene), 4.38 (q, 2 H, ethoxy), 1.35 (t, 3 H, ethoxy). Anal. Calcd for $C_{13}H_{12}F_3NO_5$: C, 48.90; H, 3.76; N, 4.39. Found: C, 48.99; H, 3.91; N, 4.33.

Preparation of Ethyl *N*-(1-Bromo-2-oxopropyl)-*N*-(trifluoroacetyl)-*p*-aminobenzoate (6). In a 300-mL round-bottomed flask 9.57 g (30 mmol) of the trifluoroacetyl derivative 5 was refluxed with 50 mL of benzene and 12.5 mL of thionyl chloride for 1.5 h under strictly anhydrous conditions. Excess reagent and benzene were removed by evaporation and the acid chloride thus obtained as a viscous gum was dried in vacuo for

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3 h. A solution of 75 mmol of diazomethane was prepared in 500 mL of dry ether and treated with an ethereal solution of the acid chloride (100 mL) and the mixture stirred for 1 h. Examination of the reaction mixture by TLC at this stage revealed the presence of a single product, later identified as the diazo ketone **5b**. This solution was placed in an ice bath and gaseous HBr was bubbled in for about 10 min until the solution became acidic to litmus. Evaporation of the ether and HBr under reduced pressure was followed by treatment of the residue with 200 mL of ice-cold water, producing a semicrystalline product which was extracted into 300 mL of ethyl acetate. The ethyl acetate layer was washed successively three times with distilled water, evaporated, and dried. The brownish residue thus obtained was treated with 50 mL of dry ether and filtered. The white crystalline compound thus obtained was washed twice with 20-mL portions of ether and dried: yield 8.7 g (73.4%); mp 96–97 °C; NMR ($CDCl_3$) δ 8.1, 7.42 (d, d, 4 H, aromatic), 4.72 (s, 2 H, bromomethyl), 4.4 (q, 2 H, ethoxy), 3.94 (s, 2 H, methylene), 1.4 (t, 3 H, ethoxy).

This compound was stable for several months below 0 °C, but undergoes rapid degradation at room temperature. Although the compound was found to be pure by TLC and NMR, it failed to give a satisfactory elemental analysis. Since the corresponding chloromethyl ketone was analyzed, and both the chloromethyl ketone **7** and the bromomethyl ketone **6** could be converted to the same azidomethyl ketone **8** (vide infra), the structure of **6** was considered to be correct; low-resolution mass spectrum, m/e 395 and 397 (1:1 ratio), calcd 396.

The chloromethyl ketone **7** was prepared in an analogous manner, merely by substituting HCl for HBr in the previous reaction: yield 7.8 g (74%); mp 79 °C; NMR ($CDCl_3$) δ 8.1, 7.43 (d, d, 4 H, aromatic), 4.7 (s, 2 H, chloromethyl), 4.4 (q, 2 H, ethoxy), 4.12 (s, 2 H, methylene), 1.4 (t, 3 H, ethoxy). Anal. Calcd for $C_{14}H_{13}F_3ClNO_4$: C, 47.86; H, 3.70; N, 3.99. Found: C, 48.05; H, 3.81; N, 4.01.

Evaporation of the solution obtained after treating the acid chloride with diazomethane for 1 h gave a yellow crystalline product which was identified as the diazo ketone **5b**: mp 81 °C; NMR ($CDCl_3$) δ 8.1, 7.45 (d, d, 4 H, aromatic), 5.36 (s, 1 H, diazo ketone), 4.42 (s, 2 H, methylene), 4.41 (q, 2 H, ethoxy), 1.4 (t, 2 H, ethoxy). Anal. Calcd for $C_{14}H_{12}F_3N_3O_4$: C, 48.98; H, 3.5; N, 12.24. Found: C, 49.03; H, 3.68; N, 11.82.

Preparation of Ethyl *N*-(1-Azido-2-oxopropyl)-*N*-(trifluoroacetyl)-*p*-aminobenzoate (8). To 250 mL of dry acetone in a round-bottomed flask were added 362 mg (2.12 mmol) of finely powdered KI and 3.35 g (51.5 mmol) of sodium azide and the mixture was vigorously stirred under strictly anhydrous conditions. After 10 min a solution of 4 g (10.1 mmol) of bromomethyl ketone **6** in 10 mL of acetone was slowly added and the stirring continued for 2 h. The reaction mixture was evaporated to dryness, treated with 100 mL of ether, and filtered. The filtrate was reevaporated and the residue dissolved in 30 mL of benzene, and chromatographed on a column of silica gel CC_7 in benzene. The column was eluted with benzene and all the fractions corresponding to the new product were pooled and evaporated: yield 2.97 g (82%); mp 65 °C; NMR ($CDCl_3$) δ 8.05, 7.4 (d, d, 4 H, aromatic), 4.52 (s, 2 H, azidomethyl), 4.35 (q, 2 H, ethoxy), 4.05 (s, 2 H, methylene), 1.4 (t, 3 H, ethoxy); characteristic intense IR band at 2100 cm^{-1} due to the azide moiety (Nujol mull). Anal. Calcd for $C_{14}H_{13}F_3N_4O_4$: C, 46.92; H, 3.63; N, 15.64. Found: C, 47.15; H, 3.71; N, 15.69.

Preparation of *N*-(1-Azido-2,2-dimethoxypropyl)-*p*-aminobenzoic Acid (10). A. Ketalization of 8. To a solution of 3.58 g (10 mmol) of **8** in 300 mL of absolute methanol, was carefully added 0.75 mL of concentrated H_2SO_4 and the mixture was stirred at room temperature for 48 h under anhydrous conditions. After addition of 1.5 g (15 mmol) of potassium bicarbonate to this reaction mixture, it was evaporated to dryness in vacuo, followed by the addition of 200 mL of 10% $KHCO_3$ and extraction of the product in 100 mL of ethyl acetate. The ethyl acetate layer was washed twice with 50-mL portions of water, dried with Na_2SO_4, and evaporated. The viscous product thus obtained, although pure by TLC, failed to crystallize: NMR ($CDCl_3$) δ 7.8, 6.54 (d, d, 4 H, aromatic), 4.25 (q, 2 H, ethoxy), 3.3 (s, 2 H, azidomethyl), 3.2 (br, 8 H, dimethoxy, methylene), 1.3 (t, 3 H, ethoxy). This product, **9**, was hydrolyzed without further characterization to **10** as follows.

B. Hydrolysis of 9. A mixture of 2.02 g (~5 mmol) of the ketal **9** was stirred at room temperature with 200 mL of 1.0 N NaOH and 100 mL of tetrahydrofuran for 18 h. Most of the THF was evaporated off at reduced pressure in a rotary evaporator at 30 °C and the turbid solution thus obtained was filtered. The clear filtrate was acidified to pH 4.0 with glacial HOAc whereupon white crystals of **10** were formed. After being chilled for 2 h at 0 °C, the crystals were collected by filtrations, washed with acidified water, and dried: yield 1.175 g (84%); mp 137–138 °C; NMR ($CDCl_3$) δ 7.92, 6.5 (d, d, 4 H, aromatic), 3.41, 3.39 (s, s, 4 H, methylenes), 3.3 (s, 6 H, dimethoxy); IR (Nujol), intense absorption due to azide at 2100 cm^{-1}. Anal. Calcd for $C_{12}H_{16}N_4O_4$: C, 51.43; H, 5.71; N, 20.00; O, 22.86. Found: C, 51.52; H, 5.70; N, 20.08; O, 22.80.

Hydrogenation of 10. Preparation of *N*-(1-Amino-2,2-dimethoxypropyl)-*p*-aminobenzoic Acid (11). This hydrogenation was carried out as usual, using 5% palladium on carbon as a catalyst at 25 psig. In a typical experiment, 560 mg (2 mmol) of the azide was dissolved in 100 mL of methanol, 100 mg of the catalyst was added, and the mixture was hydrogenated for 18 h. During this period all the starting material was transformed to the more polar amine as judged by TLC. The mixture was filtered and the filtrate containing **11** was used for the reaction with either of the pyrimidines as follows.

Reaction of 11 with Pyrimidine 12. Preparation of 1-[(2-Amino-4-hydroxy-5-nitropyrimidin-6-yl)amino]-2,2-dimethoxy-3-[(*p*-carboxyphenyl)amino]propane (14). A solution of 378 mg (2 mmol) of **12** dissolved in 75 mL of methanol was mixed with the filtrate containing **11** from the previous hydrogenation and refluxed for 3 h, concentrated to ~50 mL, and chilled overnight. Light yellow crystals of **14** formed and were collected by filtration. After being washed with two 10-mL portions of methanol, the product was dried overnight under vacuum: yield 720 mg (80%); mp 210–214 °C; UV (0.1 N NaOH) λ_{max} 343, 300 nm; NMR (TFA) δ 7.5, 6.5 (d, d, 4 H, aromatic), 3.45 (br, 6 H, dimethoxy), 3.1, 3.05 (s, s, 4 H, methylenes). Anal. Calcd for $C_{16}H_{20}N_6O_7{\cdot}CH_3OH{\cdot}0.5H_2O$: C, 53.67; H, 3.84; N, 26.92; O, 15.40. Found: C, 53.40; H, 4.11; N, 27.07; O, 15.61.

Deprotection of 14. Preparation of 1-[(2-Amino-4-hydroxy-5-nitropyrimidin-6-yl)amino]-3-[(*p*-carboxyphenyl)amino]-2-propanone (15). To a solution of 1.8 g (4 mmol) of **14** in 25 mL of TFA, in a water bath maintained at 55 °C, was added 35 mL of 0.1 N HCl dropwise with stirring during a period of 30 min. Upon removal of most of the TFA under reduced pressure and dilution with ice-cold water to 300 mL, a creamy white solid was formed which was filtered, washed with water, and dried: yield 1.25 g (86%); mp >250 °C; NMR (TFA) δ 7.65, 6.7 (d, d, 4 H, aromatic), 3.25, 3.12 (s, s, 4 H, methylenes). Anal. Calcd for $C_{14}H_{14}N_6O_6$: C, 44.75; H, 3.87; N, 23.20; O, 26.52. Found: C, 44.45; H, 3.96; N, 23.50; O, 26.82.

Conversion of 15 to Pteroic Acid (1). Dithionite Reduction of 15. In a 250-mL Erlenmeyer flask, a solution of 1.08 g (3 mmol) of **15** in 15 mL of DMF was prepared and kept in a water bath maintained at 55 °C. While the mixture was stirred vigorously, 7.0 g of purified sodium dithionite was added, followed by the portionwise addition of ~20 mL of distilled water over a period of 20 min. At one point during the addition, a clear homogeneous solution was obtained. When the addition of water was complete, the mixture was added to ~300 g of crushed ice and stirred. The white precipitate of the reduction product thus obtained was filtered and washed three times with distilled water; UV (0.1 N NaOH) λ_{max} 280 with shoulder at 325 nm.

The wet reaction product was transferred to a beaker with the aid of 200 mL of 0.1 N NaOH and stirred for 1 h. The UV spectrum of this solution was identical with that of an authentic sample of 7,8-dihydropteroic acid (**18**). Oxidation of **18** to **1** was carried out by first adding 6 mL of methanol to the solution, followed by the dropwise addition of 3 mL of 5% $KMnO_4$ in water during a 5-min period. The solution was stirred for an additional 15 min, filtered, and acidified at pH 4.0 with glacial HOAc. A bright yellow precipitate of **1** was formed which was filtered, washed with water, and dried; yield 480 mg (51%). The UV and NMR spectra of this material were found to be identical with those of an authentic sample of pteroic acid. Anal. Calcd for $C_{14}H_{12}N_6O_3$: C, 53.67; H, 3.84; N, 26.92; O, 15.38. Found: C, 53.04; H, 4.11; N, 27.07; O, 15.61.

Reaction of 11 with Pyrimidine 13. Preparation of 1-[(2,4-Diamino-5-nitropyrimidin-6-yl)amino]-2,2-dimethoxy-3-[(*p*-carboxyphenyl)amino]propane (16). A solution of 700 mg (4 mmol) of 6-chloro-2,4-diamino-5-nitropyrimidine in 200 mL of methanol was refluxed with 4 mmol of 11 for 4 h and evaporated to dryness, and the residue was triturated with 150 g of crushed ice, filtered and dried: yield 650 mg (80%); mp 262 °C; UV (0.1 N NaOH) λ_{max} 340, 280, 215 nm; NMR (TFA) δ 7.7, 6.7 (d, d, 4 H, aromatic), 4.0 (d, 2 H, methylene), 3.9 (br, 2 H, methylene), 3.3 (s, 6 H, dimethoxy). Anal. Calcd for $C_{16}H_{21}N_7O_6$: C, 47.17; H, 5.16; O, 23.59. Found: C, 46.99; H, 5.40; O, 23.30.

Conversion of 16 to 4-Amino-4-deoxypteroic Acid (3). A. Deprotection of 16. This reaction was carried out by dissolving 407 mg (1 mmol) of 16 in 10 mL of TFA and treating with 10 mL of 0.1 N HCl at 55 °C, as described for the deprotection of 14. After the addition of HCl was complete, the reaction mixture was evaporated to dryness and the residue was triturated with 50 g of crushed ice, filtered, and dried: yield 310 mg (86%); mp 212 °C dec; UV (0.1 N NaOH) λ_{max} 335, 270 nm.

B. Dithionite Reduction of 17. A solution of 271 mg (0.75 mmol) of 17 in 5 mL of DMF was kept in a water bath maintained at 55 °C. To this solution was added 1.5 g of solid purified sodium dithionite and the mixture was stirred. During a period of 15 min 5 mL of distilled water was added to this stirred suspension which was then diluted to 100 mL with crushed ice, whereupon the creamy white reduction product was separated. This was filtered, washed with water, and stirred with 75 mL of 0.05 N NaOH for 1.5 h (UV λ_{max} 285 nm with shoulder at 325 nm). Oxidation of this dihydro derivative to 3 was carried out by adding 2 mL of ethanol to this solution, followed by 1.0 mL of 5% $KMnO_4$ over 5 min. The oxidation was allowed to proceed for 15 min more and then the mixture was filtered. The bright yellow filtrate showed λ_{max} (0.1 N NaOH) 372 and 262 nm, indicating complete oxidation. Upon acidification of this solution to pH 4.5 with glacial HOAc, a bright orange precipitate of 3 was formed. The product was filtered, washed and dried: UV (0.1 N NaOH) λ_{max} 372 nm (ϵ 5210), 252 (21747); UV (0.1 N HCl) λ_{max} 336 nm (ϵ 8143), 298 (16443), 244 (12855); NMR (TFA) δ 8.5 (s, 1 H, pteridine), 7.85, 7.28 (d, d, 4 H, aromatic), 4.79 (2 H, methylene); yield 36.5% based on 17. Anal. Calcd for $C_{14}H_{13}N_7O_2$: C, 54.02; H, 4.18; N, 31.51; O, 10.29. Found: C, 53.95; H, 4.26; N, 31.45; O, 10.41.

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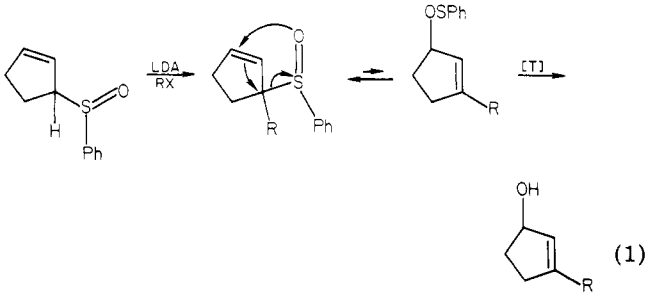
Registry No. 1, 119-24-4; 3, 36093-85-3; 4, 59081-60-6; 5, 574-02-7; 5 acid chloride, 77773-72-9; 5b, 77773-73-0; 6, 77773-74-1; 7, 77773-75-2; 8, 77773-76-3; 9, 77773-77-4; 10, 77773-78-5; 11, 77773-79-6; 12, 1007-99-4; 13, 6036-64-2; 14, 77773-80-9; 15, 62019-04-9; 16, 77773-81-0; 17, 77773-82-1; 18, 2134-76-1; 19, 77773-83-2; ethyl *p*-aminobenzoate, 94-09-7; bromoacetic acid, 79-08-3.

Communications

Synthesis of Allylic Sulfoxides from Alkenes by $EtAlCl_2$-Catalyzed Ene Reaction with *p*-Toluenesulfinyl Chloride

Summary: Ethylaluminum dichloride ($EtAlCl_2$) catalyzes the ene reaction of alkenes with arylsulfinyl chlorides to give allylic sulfoxides since $EtAlCl_2$ acts as a proton scavenger as well as a Lewis acid, reacting with the hydrogen chloride produced in the reation to give aluminum trichloride and ethane.

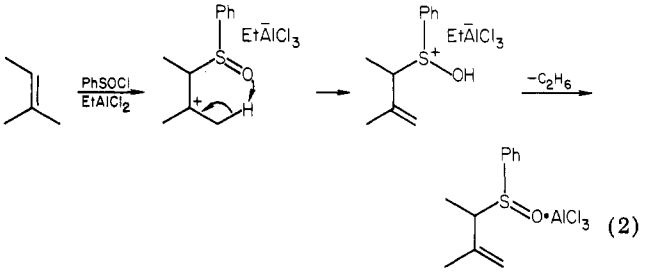
Sir: Allylic sulfoxides are versatile intermediates in organic synthesis, since they can be selectively alkylated in the α-position and converted to a rearranged allylic alcohol by trapping the allylic sulfenate, present in equilibrium with the sulfoxide, with a thiophile (eq 1).[2] These sulfoxides



(1)

have been synthesized by reaction of allylic alcohols with arylsulfenyl chlorides,[2] by oxidation of the sulfides formed from thiophenoxide and allylic halides,[2] and from carbonyl compounds via an aldol condensation or Wittig reaction to give a vinylic sulfoxide which can be isomerized to an allylic sulfoxide.[3] We report here a novel procedure which makes a wide variety of allylic sulfoxides available directly from an alkene.

Treatment of an alkene with 1 equiv of toluenesulfinyl chloride and 1 equiv of ethylaluminum dichloride ($EtAlCl_2$) in ether at 25 °C for 1–4 h gives an allylic sulfoxide via a formal ene reaction (see eq 2).[4] The reaction is quite versatile, proceeding in good yield with a wide variety of alkenes (see Table I).



(2)

The reaction sequence shown in eq 1 is analogous to the cyclization of unsaturated sulfinic acid derivatives obtained from penicillins to give the 3-methylenecepham sulfoxides developed by Kukolja (eq 3).[6,7] Due to the ease of six-membered-ring formation this cyclization can be carried out on the sulfinyl chloride (X = Cl) with a wide variety

(1) Fellow of the Alfred P. Sloan Foundation, 1979–1981.
(2) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147 and references cited therein.
(3) Hoffmann, R. W.; Goldmann, S.; Maak, N.; Gerlach, R.; Frickel, F.; Steinbach, G. *Chem. Ber.* **1980**, *113*, 819 and references cited therein.
(4) For a review of Lewis acid catalyzed ene reactions see: Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426.
(5) The instability of allylic and benzylic sulfoxides has been previously noted. See ref 2 and: Mizuno, H.; Matsuda, M.; Iino, M. *J. Org. Chem.* **1981**, *46*, 520 and references cited therein. Bond homolysis to give an allylic radical and sulfinyl radical occurs. Substitution in the α- and γ-positions stabilizes the allylic radical. Substitution in the α-position destabilizes the sulfoxide by steric hindrance.

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