(8%) of the major isomer of 14: mp 126–127 °C; $R_f$ 0.63 (in ethyl acetate–acetone, 6:4); $^1$H NMR ($CDCl_3$) δ 2.01 (s, 3 H, $SCH_3$), 2.20 and 2.27 (2 s, 6 H, *N*-acetyls), 3.13 (m, 2 H, $CH_2S$), 3.83 and 3.93 (2 s, 6 H, methyl esters), 4.87 (m, 1 H, α-H), 6.67 (br, 1 H, NH), 8.87 (br, 1 H, NH). Anal. ($C_{13}H_{20}N_2O_6S_2$) C, H, N.

In a subsequent fraction eluted from the column, 20 mg (2%) of an oil was obtained that appeared to be an isomer of the above compound: $R_f$ 0.57 (in ethyl acetate–acetone, 6:4); $^1$H NMR ($CDCl_3$) δ 2.03 (s, 3 H, $SCH_3$), 2.17 and 2.33 (2 s, 6 H, *N*-acetyls), 3.40 (br s, 2 H, $CH_2S$), 3.83 and 3.97 (2 s, 6 H, methyl esters), 4.97 (m, 1 H, α-H), 7.63 (br, 1 H, NH), 7.97 (br, 1 H, NH).

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**Registry No.** **3**, 60084-47-1; **4**, 73972-24-4; *E*-**5**, 73972-25-5; *Z*-**5**, 73972-26-6; **6**, 35356-70-8; **7**, 73972-27-7; **8**, 73972-28-8; **9**, 73972-29-9; **10**, 73972-30-2; **11**, 73972-31-3; **12**, 60389-02-8; *E*-**13**, 73972-32-4; *Z*-**13**, 73972-33-5; *E*-**14**, 73972-34-6; *Z*-**14**, 73972-35-7; thioacetic acid, 507-09-5; benzyl mercaptan, 100-53-8; 2-tetrahydropyranthiol, 40446-64-8; *N*-acetyl-L-cysteine, 616-91-1; *N*-acetyl-L-cysteine methyl ester, 7652-46-2; methyl mercaptan, 74-93-1.

# Stereospecific Alkylation of the Schiff Base Ester of Alanine with 2-Substituted-(*E*)- and -(*Z*)-vinyl Bromides. An Efficient Synthesis of 2-Methyl-(*E*)-3,4-didehydroglutamic Acid, a Potent Substrate-Induced Irreversible Inhibitor of L-Glutamate-1-decarboxylase

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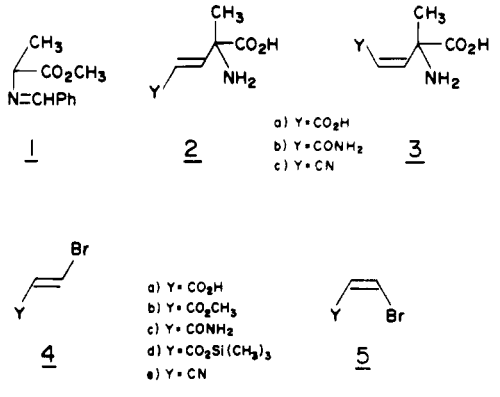
The nucleophilic vinylic substitution by the enolate of methyl *N*-benzylidenealanate (**1**) of (*E*)- and (*Z*)-vinyl bromides **4** and **5** has been examined as an approach to the synthesis of the *E* and *Z* isomers of 2-methyl-3,4-didehydroglutamic acid. Under aprotic conditions, the nucleophilic displacement has been found to proceed stereospecifically with retention of configuration of the double bond to afford in good yield the corresponding (*E*)- and (*Z*)-substituted products. The configuration of the substitution products has been assigned from the analysis of their $^1$H NMR spectra on the basis of the value of the coupling constant of the vicinal vinylic protons. Subsequent removal of the protecting groups from the substitution products **6** in the *E* series gives the corresponding 2-methyl-(*E*)-3,4-didehydroglutamic acid derivatives **2** in good yield. The *Z* isomers **3** prove to be very unstable and have not been isolated.

Enzyme-activated irreversible inhibitors are highly specific enzyme inactivators.[1] Their specificity results from their binding affinity and also from their effectiveness to serve as substrates for the target enzymes. The availability of such inhibitors for enzymes involved in metabolic pathways of bioactive molecules such as neurotransmitters has proven extremely useful to elucidate the physiological role of these molecules.[2] We recently demonstrated that 2-(*R*,*S*)-2-methyl-(*E*)-3,4-didehydroglutamic acid (**2a**) is a potent enzyme-activated irreversible inhibitor of chick-embryo brain L-glutamate-1-decarboxylase (E.C.4.1.1.15),[3] the enzyme catalyzing the formation of the inhibitory neurotransmitter γ-aminobutyric acid.[4] We report now an efficient and stereoselective synthesis of (*E*)-3,4-didehydro-2-methylglutamate derivatives **2**, as well as the attempted preparation of the corresponding *Z* isomers **3**.

The major synthetic challenge in the structural features of **2** and **3** lies in the presence of a 1,2-disubstituted double bond in a β,γ position relative to an α-amino acid functionality. Of the few methods available for the preparation of β,γ-unsaturated-α-amino acids,[5] none are suitable for the stereoselective formation of the double bond. Earlier studies from this laboratory demonstrated the utility of the enolates derived from Schiff base alkyl esters of α-amino acids as general synthons for the preparation of α-substituted-α-amino acids.[6] Of particular interest is the fact that these enolates add quantitatively in a Michael

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(2) (a) "Enzyme-Activated Irreversible Inhibitors", N. Seiler, M. J. Jung, and J. Koch-Weser, Eds., Elsevier, Amsterdam, 1978; (b) "Drug Action and Design: Mechanism-based Enzyme Inhibitors", T. I. Kalman, Ed., Elsevier, Amsterdam, 1979.

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Table I. Chemical Shifts and Vicinal Coupling Constants of Vinylic Protons

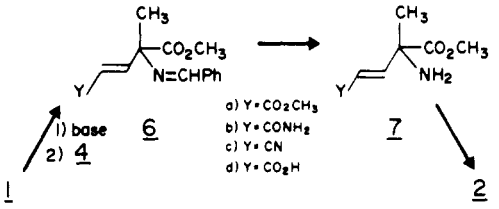
| compd | solvent | $\delta$[a] | $J_{AB}$, Hz | $\nu_{AB}$, Hz[b] |
|---|---|---|---|---|
| 4a | $CDCl_3$ | 7.06 | 14 | 72 |
| 5a | $CDCl_3$ | 6.86 | 8 | 29 |
| 4b | $CDCl_3$ | 7.0 | 14 | 63 |
| 5b | $CDCl_3$ | 6.71 | 9 | 22 |
| 4c | $CDCl_3$ | 7.10 | 14 | 76 |
| 5c | $CDCl_3$ | 6.83 | 8 | 9 |
| 4d | $D_2O$ | 6.83 | 14 | 62 |
| 5d | $D_2O$ | 6.80 | 8 | 22 |
| 4e | $CDCl_3$ | 6.70 | 14 | 63 |
| 6a | $CDCl_3$ | 6.56 | 15 | 61 |
| 8a | $CDCl_3$ | 6.25 | 12 | 43 |
| 6b | $CDCl_3$ | 6.58 | 15.5 | 54 |
| 12 | $CDCl_3$ | 6.47 | 10 | 40 |
| 6c | $CDCl_3$ | 6.38 | 16 | 67 |
| 7a | $D_2O$ | 6.46 | 16 | 46 |
| 9a | $D_2O$ | 6.23[c] | | |
| 7b | $D_2O$ | 6.13 | 15 | 27 |
| 14 | $D_2O$ | 6.66 | 10 | 40 |
| 7c | | 6.45 | 16 | 59 |
| 7d | $D_2O$ | 6.33 | 16 | 28 |
| 9d | $D_2O$ | 6.03[c] | | |
| 10 | $D_2O$ | 6.65 | 6 | 71 |
| 11 | $D_2O$ | 6.58 | 5.5 | 69 |
| 2a | $D_2O$ | 6.5 | 16 | 55 |
| 3a | NaOD | 5.8[c] | | |
| 2b | $D_2O$ | 6.55 | 16 | 38 |
| 2c | $D_2O$ | 6.39 | 16 | 68 |

[a] $\delta$ corresponds to the chemical shift of the center of the AB quartet. [b] $\nu_{AB}$ represents the difference between the chemical shifts of the 2 vinylic protons. [c] $A_2$ spectrum.

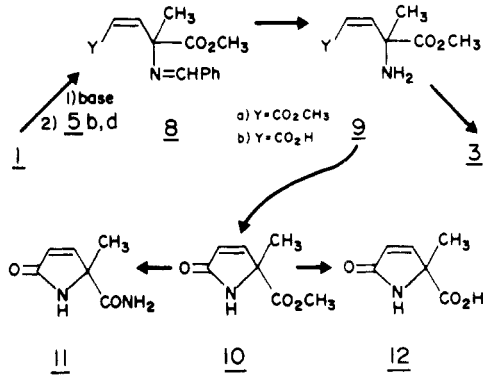
fashion to acrylonitrile and methyl acrylate, thus providing an easy entry into the $\alpha$-substituted glutamate series. In addition, displacement of vinyl halide by anionic nucleophiles is a well-documented reaction.[7] Electron-withdrawing groups bonded to the second vinylic carbon atom are known to facilitate the substitution which is then believed to proceed via an addition–elimination mechanism.[8] Interestingly, for the few carbanionic nucleophiles which have been reported to displace halides from vinyl halides substituted by electron-withdrawing groups to form new carbon–carbon bonds,[9] the displacement seems to usually occur with retention of configuration of the double bond. In view of these precedents, nucleophilic substitution of the functionalized (*E*)- and (*Z*)-vinyl bromides **4** and **5** by the anion derived from the Schiff base methyl ester of alanine (**1**) was investigated as a potential approach to the stereospecific synthesis of **2** and **3**.

## Results and Discussion

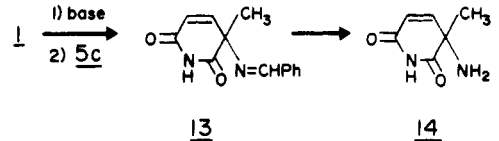
Reaction of the Schiff base methyl ester of alanine (**1**) with 1 equiv of methyl (*E*)-$\beta$-bromoacrylate (**4b**)[10] under conditions similar to those described previously[6] for the addition of **1** to methyl acrylate (catalytic amount of base in anhydrous methanol, room temperature) gave the *E* diester **6a** in low yield (<30 %), accompanied, as judged from the NMR spectrum of the crude reaction mixture, by products arising from addition of methanol to the unsaturated ester **4b**. The formation of these side products is in accordance with the observation of House et al.[11] who




reported under similar conditions a rapid addition of *tert*-butyl alcohol to methyl (*E*)-chloroacrylate to yield a complex mixture of ether esters. A convenient solution to this problem was found in a modification of the reaction conditions as suggested by the work of Herrmann et al.,[9a] and Kraus and Roth.[9b] Addition at −70 °C of 1 equiv of **4b** to a solution of the lithio derivative of **1** in THF (generated in situ from **1** with 1 equiv of lithium diisopropylamide) gave the *E* diester **6a** in almost quantitative yield. Methyl (*Z*)-$\beta$-bromoacrylate (**5b**)[12] under the same conditions led to the *Z* diester **8a**. Similar retention of




configuration was observed in the nucleophilic displacement of bromine by the lithium or sodium salt of **1** from (*E*)- and (*Z*)-$\beta$-bromoethylenic derivatives **4c–e** and **5c,d**. Owing to the rapid hydrolysis of the trimethylsilyl ester function in the presence of water and the instability of Schiff bases to acid, the products obtained from the substitution reaction of **4d** and **5d** were in fact the amino acids **7d** and **9b**, respectively. It is also noteworthy that protection of the primary amide function in **4c** and **5c** is not required in the vinylic substitution. With the *Z* isomer **5c**, however, the cyclic unsaturated imide **13** was obtained. Optimization of the yield of this reaction necessitated the use of 2 equiv of lithium diisopropylamide and a reverse addition of the carbanion solution to **5c**.




The configuration of the substitution products **6**, **7d**, **8**, and **9b** can be assigned unambigously from the analysis of their $^1H$ NMR spectra on the basis that, for any isomeric pair of 1,2-disubstituted ethylenes, the coupling constant of the vicinal vinylic protons is always larger for the *E* isomer.[13] The signals of the two ethylenic protons in the $^1H$ NMR spectra of **6**, **7d**, **8**, and **9b** are easily identifiable

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and usually appear as a characteristic AB quartet from which the vicinal interproton coupling constant can easily be measured (see Table I). Provided care was taken to maintain the temperature below 50 °C during workup of the reaction mixture, no contamination with the other geometric isomer could be detected from the NMR spectra of the crude substitution products, thus demonstrating the stereospecificity of the vinylic substitution by the enolate generated from 1. Above 50 °C, the unsaturated diester **8a** derived from methyl (*Z*)-β-bromoacrylate is slowly transformed into the diester **6a**, obtained from the substitution of methyl (*E*)-β-bromoacrylate, as indicated by the appearance in the $^1$H NMR spectrum of the signal of the vinylic protons of the *E* isomer. The cyclization reaction of **9a,b** subsequently described and the direct formation of the imide **13** from **5c** provide additional circumstantial evidence for the assignment of the *Z* configuration to the substitution products derived from (*Z*)-β-bromovinyl derivatives. Owing to its instability to distillation (isomerization above 50 °C) and chromatography (partial hydrolysis of the Schiff base), the *Z* adduct **8a** was not purified.

Removal of the protecting groups from the (*E*)-substitution products **6** under carefully controlled conditions proceeded in good yield to afford the corresponding (*E*)-β,γ-didehydro-α-methyl-α-amino acids **2**. The benzylidene and methyl ester functions of **6a** were cleaved simultaneously upon treatment with 3 M HCl at 60 °C for 24 h in a water–diethyl ether two-phase system. Higher temperatures or more acidic media resulted in extensive decomposition of **2a**. Catalytic hydrogenation of **2a** proceeded smoothly to yield the expected α-methylglutamic acid. Selective hydrolysis of the benzylidene and methyl ester groups in the presence of the primary amide and nitrile functions of **6b** and **6c** could be achieved by a sequential treatment with an excess of 0.5 M HCl at room temperature for 1 h to give the ester amine hydrochloride intermediates, which with 2 equiv of triethylamine in water at room temperature for 24 h afforded the (*E*)-β,γ-didehydro-α-methyl-α-amino acids **2b** and **2c**, respectively.

As was to be predicted from the observed formation in high yield of the cyclic imide **13**, access to the (*Z*)-β,γ-didehydro-α-methyl-α-amino acids (**3**) was complicated by the propensity displayed by derivatives of the *Z* series to cyclize. Indeed, the *Z* diester amine hydrochloride **9a**, obtained after removal of the benzylidene group from **8a** in aqueous HCl (0.2 M, room temperature, 1 h), was found to cyclize to the lactam **10** in a few hours upon standing in an aqueous solution at room temperature or instantaneously upon neutralization of the hydrochloride with a dilute solution of ammonia. Cleavage of the benzylidene group of **13** could be achieved without difficulty to give the corresponding amine hydrochloride **14**. Confirmation of the structure of **14** was obtained by catalytic hydrogenation to give the saturated imide amine. The latter compound was indistinguishable from a sample prepared by alkylation with methyl iodide of the dianion derived from 2-(benzylideneamino)glutarimide, followed by selective hydrolysis of the Schiff base of the methylated product. All attempts to hydrolyze **8**, **9**, **10**, and **14** to (*Z*)-β,γ-didehydro-α-methylglutamic acid (**3a**) under acidic conditions failed. In aqueous HCl (0.5 to 3 M) **9** and **10** were rapidly transformed into compounds lacking a disubstituted double bond. In fact, the $^1$H NMR spectrum and chromatographic properties of these compounds proved to be identical with those of methyl levulinate and levulinic acid, respectively. The formation of these ketone derivatives can easily be explained by the decarboxylation of the carboxylic acid resulting from the hydrolysis of the ester function of **9** and **10**. Similarly, treatment of the *Z* derivatives **9** in aqueous ammonia or sodium hydroxide (1 to 3 M) led to a rapid cleavage of the ester functions accompanied by a slower formation of levulinic acid, as judged by $^1$H NMR monitoring of the reaction. In concentrated (>6 M) ammonia solution, the lactam **10**, however, underwent a clean amidation to give the lactam amide **11** in excellent yield. Suitable conditions for hydrolysis of the ester functions of **9b** and **10** without concomitant decomposition of the resulting acids **3a** and **12**, respectively, were eventually provided by treatment with concentrated (>8 M) sodium hydroxide for a few minutes at 0 °C. Indeed, the $^1$H NMR spectrum of the crude product obtained from **10** after careful neutralization of the solution to pH 7 with concentrated hydrochloric acid lacked the signal corresponding to the methoxy group and displayed an AB quartet for the vinylic protons and a singlet for the methyl group. Similarly, $^1$H NMR monitoring of the hydrolysis of **9b** with 3 equiv of 40% NaOD in $D_2O$ indicated a rapid disappearance of the signal corresponding to the methoxy group, with concomitant apparition of a new singlet attributable to $CH_3OD$; the two singlets assignable to the vinylic protons ($A_2$ spectrum) and the α-methyl group were not modified during the reaction. These resonances are in accordance with structures **12** and **3a**, respectively. The acids **3a** and **12** proved to be extremely labile and all attempts to obtain **12** free of salt or to isolate **3a** resulted in total decomposition of the material.

## Conclusion

In summary, nucleophilic vinylic displacement of (*E*)- and (*Z*)-β-vinyl bromides substituted by electron-withdrawing functionalities by the enolate of the Schiff base methyl ester of alanine (**1**) proceeds stereospecifically with retention of configuration of the double bond. Cleavage of the protective groups from these products can easily be achieved in the *E* series to afford in high yield the corresponding (*E*)-β,γ-didehydro-α-methyl-α-amino acid derivatives **2**. In the *Z* series, the facility with which the substitution products form cyclic derivatives, in addition to general stability problems, impeded the isolation of pure (*Z*)-β,γ-didehydro-α-methyl-α-amino acid derivatives.

## Experimental Section

Melting points were determined on a Büchi SMP-20 or a Kofler hot-bank apparatus and are uncorrected, as are boiling points. Elemental analysis were carried out under the supervision of Dr. J. Wagner on a Perkin-Elmer Model 240 analyzer. Infrared spectra were recorded on a Perkin-Elmer Model 577 spectrophotometer. Proton nuclear magnetic resonance spectra (60 MHz) were taken on a Varian Associates T-60 spectrometer and are reported in parts per million from internal tetramethylsilane or 2,2-dimethyl-2-silapentane-5-sulfonate on the δ scale. Data are presented as follows: solvent, chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), integration, coupling constants, and interpretation.

Solvents and reagents were dried prior to use when deemed necessary. Tetrahydrofuran and diethyl ether were distilled from lithium aluminum hydride and diisopropylamine from solid KOH.

Lithium diisopropylamide (LDA) was always prepared in the following manner: a solution of diisopropylamine (1 M) in THF was cooled to −70 °C followed by addition of a hexane solution of *n*-BuLi (2 M, 1 equiv) via syringe. The cooling bath was removed and the temperature of the reaction mixture was allowed to rise to −20 °C, where it was maintained for a few minutes. The resulting solution was then cooled to the temperature desired for subsequent operations. Sodium hydride was always washed three times with pentane before use.

Bulb-to-bulb distillations were accomplished in a Büchi GKR-50 kugelrohrapparat at the oven temperature and pressure indicated.

**Preparation of (*E*)- and (*Z*)-β-Bromovinyl Derivatives 4 and 5.** (*E*)-3-Bromoacrylic acid (**4a**), (*E*)-3-bromoacrylamide (**4c**), and (*E*)-3-bromoacrylonitrile (**4e**) were obtained according to the method of Gryszkiewicz-Trochimosky et al.;[12a] methyl (*E*)- and (*Z*)-3-bromoacrylate (**4b** and **5b**) were prepared as described by Bowden;[10] (*Z*)-3-bromoacrylamide (**5c**) was synthesized according to the procedure of McGreer et al.[12b]

**(*Z*)-3-Bromoacrylic Acid (5a).** A solution of 17.5 g (0.25 mol) of propiolic acid and 180 g of 47% aqueous HBr in 600 mL of water was stirred at 55 °C for 5 days. The reaction mixture was then saturated with sodium chloride and extracted with chloroform (6 × 100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated at reduced pressure to give (*Z*)-3-bromoacrylic acid (35 g, 93 % yield) which could be used without further purification. Recrystallization from $CHCl_3$ at 0 °C afforded analytically pure material in 45% yield.

**Trimethylsilyl (*E*)-3-Bromoacrylate (4d).** To a solution of 7.55 g (0.05 mol) of **4a** in 50 mL of anhydrous ether maintained at 25 °C was added slowly 6.25 mL (0.025 mol) of bis(trimethylsilyl)acetamide. The reaction mixture was stirred at 25 °C for 48 h. The precipitated acetamide was filtered and the filtrate concentrated under reduced pressure. The residue was bulb-to-bulb distilled at room temperature (0.5 mm) to give 7.58 g of trimethylsilyl (*E*)-3-bromoacrylate (68%) contaminated with traces of *N*-(trimethylsilyl)acetamide. This material was sensitive to storage and was prepared immediately before use.

**Trimethylsilyl (*Z*)-3-bromoacrylate (5d)** was prepared from **5a** in a manner similar to that of **4d** from **4a** (58% after distillation).

**Dimethyl (*E*)-2-(Benzylideneamino)-2-methylpent-3-ene-2,5-dioate (6a).** To a solution of lithium diisopropylamide (0.060 mol) in THF cooled to −70 °C was added dropwise under nitrogen a solution of 10.5 g (0.055 mol) of methyl *N*-benzylidenealanate in 30 mL of THF. The reaction mixture was stirred at −70 °C for 30 min and then a solution of 9.07 g (0.055 mol) of methyl (*E*)-3-bromoacrylate (**4b**) in 50 mL of THF was added. After the addition was completed, the cooling bath was removed, the temperature was allowed to rise to 20 °C and stirring was continued for 2 h. The reaction mixture was then quenched with water and extracted with ether. The organic extracts were combined, washed with water, and dried over $MgSO_4$. Concentration at reduced pressure afforded an oily residue which on bulb-to-bulb distillation gave 14.2 g (86 %) of the diester **6a**: bp 150–155 °C (0.04 mm); $^1H$ NMR ($CDCl_3$) δ 1.60 (s, 3, $CH_3$), 3.67 (s, 6, $OCH_3$), 6.56 (AB, 2, $J_{AB}$ = 15 Hz, $\nu_{AB}$ = 61 Hz, HC=CH), 7.15–7.78 (m, 5, $C_6H_5$), 8.12 (s, 1, N=CH); IR (film) 1728 $cm^{-1}$. Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.43; H, 6.24; N, 5.09. Found: C, 65.47; H, 6.18; N, 5.01.

**Methyl (*E*)-2-(benzylideneamino)-2-methyl-4-cyanobut-3-enoate (6c)** was prepared in a manner similar to that of **6a** (75% after distillation): bp 170 °C (0.04 mm); $^1H$ NMR ($CDCl_3$) δ 1.58 (s, 3, $CH_3$), 3.72 (s, 3, $OCH_3$), 6.38 (AB, 2, $J_{AB}$ = 16 Hz, $\nu_{AB}$ = 67 Hz, HC=CH), 7.2–7.82 (m, 5, $C_6H_5$), 8.25 (s, 1, N=CH); IR (Nujol) 2224 (CN), 1730 $cm^{-1}$ (C=O). Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.39; H, 5.83; N, 11.56. Found: C, 69.04; H, 5.81; N, 11.77.

**Dimethyl (*Z*)-2-(benzylideneamino)-2-methylpent-3-ene-2,5-dioate (8a)** was prepared from **5b** in a manner similar to that of **6a** from **4b**. This diester was sensitive to heat and was not purified (100% crude): $^1H$ NMR ($CDCl_3$) δ 1.68 (s, 3, $CH_3$), 3.65 (s, 6, $OCH_3$), 6.25 (AB, 2, $J_{AB}$ = 12 Hz, $\nu_{AB}$ = 43 Hz, HC=CH), 7.20–7.80 (m, 5, $C_6H_5$), 8.20 (s, 1, N=CH).

**Methyl (*E*)-2-(benzylideneamino)-2-methyl-4-(aminocarbonyl)but-3-enoate (6b)** was prepared in a manner similar to that of **6a**, except that a reverse addition of **1** to **4c** was used (100% crude): $^1H$ NMR ($CDCl_3$) δ 1.60 (s, 3, $CH_3$), 3.70 (s, 3, $OCH_3$), 6.10 (br s, 2, $NH_2$), 6.58 (AB, 2, $J_{AB}$ = 15.5 Hz, $\nu_{AB}$ = 54 Hz, HC=CH), 7.2–7.8 (m, 5, $C_6H_5$), 8.20 (s, 1, N=CH); no analysis.

**3-(Benzylideneamino)-3-methyl-4,5-dehydropiperidine-2,6-dione (13)** was prepared in a manner similar to that of **6b** except that 2.2 equiv of lithium diisopropylamide was used (83% after recrystallization from ether): mp 154 °C; $^1H$ NMR ($CDCl_3$) δ 1.70 (s, 3, $CH_3$), 6.47 (AB, 2, $J_{AB}$ = 10 Hz, $\nu_{AB}$ = 40 Hz, HC=CH), 7.20–7.80 (m, 5, $C_6H_5$), 8.17 (br s, 1, NH), 8.36 (s, 1, N=CH). Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.39; H, 5.31; N, 12.27. Found: C, 68.34; H, 5.45; N, 12.24.

**(*Z*)-4-Amino-4-(methoxycarbonyl)-2-propen-1-oic acid (9b).** A mixture of NaH (0.023 mol) and 4.45 g (0.023 mol) of methyl *N*-benzylidenealanate in 40 mL of THF was stirred at room temperature for 12 h. The anion solution was then cooled to −70 °C, and a solution of 5.17 g (0.023 mol) of trimethylsilyl (*Z*)-3-bromoacrylate in 20 mL of THF was added dropwise. The temperature of the reaction mixture was allowed to rise slowly to 20 °C over a period of 12 h. Concentration of the solvent under reduced pressure left a residue which was taken up in anhydrous ether. The insoluble NaBr was separated by filtration on a sintered-glass funnel. The filtrate was washed with water (3 × 30 mL). The aqueous extracts were combined and concentrated in vacuo at a temperature not exceeding 30 °C. The residue was washed many times with anhydrous ether to eliminate all traces of the lactam **10** formed during the workup and then treated with charcoal to give 3.3 g of crude acid ester **9b** (83%), from which the analytical sample was obtained after recrystallization from water: $^1H$ NMR ($D_2O$) δ 1.71 (s, 3, $CH_3$), 3.76 (s, 3, $OCH_3$), 6.03 (s, 2, HC=CH). Anal. Calcd for $C_7H_{11}NO_4 \cdot 0.45\ H_2O$: C, 46.37; H, 6.62; N, 7.72. Found: C, 46.33; H, 6.39; N, 7.61.

After the compound was dried for 8 days under high vacuum at 20 °C over $P_2O_5$, the water content was reduced to 0.17 mol, as measured by combustion analysis and Karl Fisher determination.

**(*E*)-4-Amino-4-(methoxycarbonyl)-2-propene-1-oic acid (7d)** was prepared from **4d** in a manner similar to that of **9b** from **5d** (36% after recrystallization from water): mp 240 °C (sublimed); $^1H$ NMR ($D_2O$) δ 1.75 (s, 3, $CH_3$), 3.85 (s, 3, $OCH_3$), 6.33 (AB, 2, $J_{AB}$ = 16 Hz, $\nu_{AB}$ = 28 Hz, HC=CH). Anal. Calcd for $C_7H_{11}NO_4$: C, 48.54; H, 6.41; N, 8.09. Found: C, 48.56; H, 6.38; N, 7.97.

**(*E*)-2-Methyldehydroglutamine (2b).** To a solution of 14.3 g (0.055 mol) of **6b** in 100 mL of ether was added 250 mL of aqueous HCl (0.5 M). The mixture was vigorously stirred for 1 h. The aqueous layer was decanted, washed with ether, and then concentrated under reduced pressure at 30 °C to yield 2.1 g (100%) of the corresponding amine hydrochloride **7b**: $^1H$ NMR ($D_2O$) δ 1.60 (s, 3, $CH_3$), 3.45 (s, 3, $OCH_3$), 6.13 (AB, 2, $J_{AB}$ = 15 Hz, $\nu_{AB}$ = 27 Hz, HC=CH).

A solution of the crude amine hydrochloride **7b** in 50 mL of water was treated with 11.11 g (0.11 mol) of triethylamine, and the reaction mixture was stirred at room temperature for 12 h. The solid obtained after concentration under reduced pressure was washed many times with small portions of $CHCl_3$ to yield 6.77 g (78%) of **2b**. Recrystallization from ethanol–water afforded 5.76 g of analytically pure material: mp 177 °C; $^1H$ NMR ($D_2O$) δ 1.65 (s, 3, $CH_3$), 6.55 (AB, 2, $J_{AB}$ = 16 Hz, $\nu_{AB}$ = 38 Hz, HC=CH). Anal. Calcd for $C_6H_{10}N_2O_3 \cdot 2H_2O$: C, 37.10; H, 7.28; N, 14.43. Found: C, 37.12; H, 6.98; N, 14.45.

**(*E*)-2-Amino-2-methyl-4-cyano-3-butenoic acid (2c)** was prepared in a manner similar to that of **2b** (50% after recrystallization from water): mp 138 °C dec; $^1H$ NMR ($D_2O$) δ 1.62 (s, 3, $CH_3$), 6.39 (AB, 2, $J_{AB}$ = 16 Hz, $\nu_{AB}$ = 68 Hz, HC=CH). Anal. Calcd for $C_6H_8N_2O_2 \cdot H_2O$: C, 45.55; H, 6.38; N, 17.71. Found: C, 45.54; H, 6.64; N, 17.88.

**(*E*)-2-Methyldehydroglutamic acid (2a).** To a solution of 5.5 g (0.020 mol) of **6a** in 50 mL of ether was added 200 mL of aqueous HCl (3 M). The mixture was stirred at 60 °C for 24 h. The aqueous layer was decanted, washed with chloroform (3 × 100 mL), and concentrated in vacuo. The solid residue (3.5 g) was dissolved in 30 mL of methanol and excess propylene oxide was added to this solution to precipitate 2.1 g (75%) of **2a**: mp 132 °C dec; $^1H$ NMR ($D_2O$) δ 1.62 (s, 3, $CH_3$), 6.50 (AB, 2, $J_{AB}$ = 16 Hz, $\nu_{AB}$ = 55 Hz, HC=CH); Karl Fisher determination of water content, 1.71% (0.15 mol). Anal. Calcd for $C_6H_9NO_4 \cdot 0.15\ H_2O$: C, 44.52; H, 5.80; N, 8.65. Found: C, 44.17; H, 5.79; N, 8.63.

**Dimethyl (*Z*)-2-methyl-3,4-dehydroglutamate monohydrochloride (9a)** was obtained from **8a** in a manner similar to that of **7b** from **6b** except that aqueous HCl 0.2 M was used: $^1H$ NMR ($D_2O$) δ 1.75 (s, 3, $CH_3$), 3.67 (s, 3, $OCH_3$), 3.72 (s, 3, $OCH_3$), 6.23 (s, 2, HC=CH); no analysis.

**3-Amino-3-methyl-4,5-dehydropiperidine-2,6-dione monohydrochloride (14)** was obtained from **12** in a manner similar to that of **7b** from **6b** (85% after recrystallization from water): mp >250 °C; $^1H$ NMR ($D_2O$) δ 1.75 (s, 3, $CH_3$), 6.62 (AB, 2, $J_{AB}$ = 10 Hz, $\nu_{AB}$ = 40 Hz, HC=CH); IR (Nujol) 1730, 1690 $cm^{-1}$. Anal.

Calcd for $C_6H_8N_2O_2$·HCl: C, 40.81; H, 5.14; N, 15.86. Found: C, 40.46; H, 5.12; N, 16.10.

**Methyl 2-Methyl-5-oxo-3,4-dehydropyrrolidine-2-carboxylate (10).** An aqueous solution of 2.72 g of the hydrochloride **9a** was treated with aqueous $NH_4OH$ until the pH of the solution reached 7. Evaporation of the solvent at reduced pressure at 30 °C afforded a solid residue which was extracted many times with $CHCl_3$. The organic extracts were combined and concentrated in vacuo. Bulb-to-bulb distillation of the residue gave 2.48 g (80%) of **10** which crystallized spontaneously: bp 105 °C (0.02 mm); mp 64 °C; $^1H$ NMR ($D_2O$) $\delta$ 166 (s, 3, $CH_3$), 3.56 (s, 3, $OCH_3$), 6.65 (AB, 2, $J_{AB}$ = 6 Hz, $\nu_{AB}$ = 71 Hz, HC=CH); IR (Nujol) 3300, 1741, 1670 $cm^{-1}$. Anal. Calcd for $C_7H_9NO_3$: C, 54.18; H, 5.86; N, 9.03. Found: C, 54.22; H, 5.99; N, 9.05.

**2-Methyl-5-oxo-3,4-dehydropyrrolidine-2-carboxamide (11).** To a solution of 200 mg of **10** in 2 mL of water was added at 0 °C 50 mL of aqueous $NH_4OH$ (6 M). After the mixture was stirred for 5 min, the solvent was evaporated at reduced pressure at 20 °C to give 170 mg (95%) of **11**. The analytical sample was prepared by recrystallization from water–ethanol: mp 195 °C; $^1H$ NMR ($D_2O$) $\delta$ 1.53 (s, 3, $CH_3$), 6.0 (d, 1, $J$ = 5 Hz, HC=C), 7.16 (d, 1, $J$ = 5 Hz, C=CH); IR (Nujol) 1690 $cm^{-1}$. Anal. Calcd for $C_6H_8N_2O_2$: C, 51.41; H, 5.76; N, 19.99. Found: C, 51.23; H, 5.75; N, 20.00.

**Hydrolysis of 9b under Basic Conditions.** To a solution of 17 mg (0.098 mmol) of **9b** in 0.3 mL of $D_2O$ was added at 0 °C 32 mg of a solution of 40% NaOD in $D_2O$ (about 3 equiv). The hydrolysis reaction was followed by NMR spectroscopy by monitoring the disappearance of the singlet at $\delta$ 3.66 corresponding to the methyl ester group and the apparition of a new singlet at $\delta$ 3.30 assignable to $CH_3OD$. The hydrolysis was complete within 5 min. At that time, the NMR spectrum displayed the following signals: $\delta$ 1.36 (s, 3, $CH_3$), 3.30 (s, 3, $CH_3OD$), 5.8 (s, 2, HC=CH).

**2-(Benzylideneamino)glutarimide (15).** A solution of 2.67 g (0.010 mol) of 2-(amino(carbobenzoxy))glutarimide in 80 mL of THF was stirred for 12 h under an atmosphere of $H_2$ in presence of 0.450 g of Pd/C (5%). The catalyst was separated by filtration. To the filtrate was added 1 g (0.0094 mol) of benzaldehyde and the resulting mixture was stirred at room temperature for 3 h. The residue obtained after evaporation of the solvent was dissolved in chloroform. The organic phase was washed with water and dried over $MgSO_4$. Concentration and recrystallization from dichloromethane–pentane afforded 1.2 g (59%) of **15**: mp 137 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 2.30 (m, 2, $CH_2$), 2.60–3.40 (m, 2, $CH_2C$=O), 4.13 (t, 1, $J$ = 5 Hz, OCCHN=), 7.85 (s, 1, NH), 7.18–7.84 (m, 5, $C_6H_5$), 8.40 (s, 1, N=CH); IR ($CHCl_3$) 3220, 1705, 1645 $cm^{-1}$. Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.64; H, 5.60; N, 12.95. Found: C, 66.30; H, 5.60; N, 13.11.

**2-Amino-2-methylglutarimide Hydrochloride Monohydrate (16).** To a solution of lithium diisopropylamide (4 mmol) in THF at −70 °C was added slowly 432 mg (2 mmol) of **15** in 5 mL of THF. The reaction mixture was stirred for 1 h and then 568 mg (4 mmol) of $CH_3I$ was added. The cooling bath was removed and after the mixture was stirred for 12 h at room temperature, the reaction was quenched with water. Isolation of the product by ether extraction and recrystallization from chloroform–pentane afforded 150 mg (33%) of 2-benzylideneamino-2-methylglutarimide [$^1H$ NMR ($CDCl_3$) $\delta$ 1.55 (s, 3, $CH_3$), 2.47 (m, 4, $CH_2$), 7.07–7.70 (m, 5, $C_6H_5$), 8.16 (s, 1, NH), 8.18 (s, 1, N=CH)]. A solution of the above Schiff base in ether was treated with aqueous HCl (1 M). After stirring for 1 h at room temperature, the aqueous phase was decanted and concentrated at reduced pressure. Recrystallization of the residue from water afforded 60 mg of **16**: mp 250 °C; $^1H$ NMR ($D_2O$) $\delta$ 1.67 (s, 3, $CH_3$), 2.18–3.10 (m, 4, $CH_2$); IR (Nujol) 1720 $cm^{-1}$. Anal. Calcd for $C_6H_{10}N_2O_2$·HCl·$H_2O$: C, 36.63; H, 6.67; N, 14.24. Found: C, 36.47; H, 6.77; N, 14.26.

**Catalytic Hydrogenation of 14.** A solution of 35 mg (0.2 mmol) of **14** in 3 mL of water was stirred under $H_2$ at atmospheric pressure in presence of 5 mg of Pd/C (5%) for 1 h. The catalyst was filtered. Recrystallization from water of the residue obtained after concentration of the filtrate afforded 30 mg of material whose chromatographic, spectroscopic, and physical properties were identical with those of **16**.

**Registry No.** 1, 40216-71-5; **2a**, 73838-85-4; **2b**, 73838-86-5; **2c**, 73838-87-6; **3a**, 73855-18-2; **4a**, 6213-89-4; **4b**, 6213-87-2; **4c**, 72330-65-5; **4d**, 73838-88-7; **4e**, 41866-26-6; **5a**, 1609-92-3; **5b**, 6214-22-8; **5c**, 41866-46-0; **5d**, 73838-89-8; **6a**, 73838-90-1; **6b**, 73838-91-2; **6c**, 73838-92-3; **7a**, 73838-93-4; **7b**, 73838-94-5; **7c**, 73838-95-6; **7d**, 73838-96-7; **8a**, 73838-97-8; **9a**, 73838-98-9; **9b**, 73838-99-0; **10**, 73839-00-6; **11**, 73839-01-7; **12**, 73839-02-8; **13**, 73839-03-9; **14**, 73839-04-0; **15**, 73839-05-1; **16**, 73839-06-2; propiolic acid, 471-25-0; bis(trimethylsilyl)acetamide, 10416-58-7; 2-(amino(carbobenzoxy))-glutarimide, 24666-55-5.

# Direct C(1) Hydroxylation of Vitamin $D_3$ and Related Compounds

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A direct synthesis of C(1) hydroxylated vitamin D analogues from the corresponding vitamin D precursors has been developed. Allylic oxidation of 3,5-cyclovitamin D derivatives, readily obtained from the buffered solvolysis of vitamin D tosylates, with selenium dioxide yields 1$\alpha$-hydroxylated 3,5-cyclovitamin D compounds which are smoothly converted to the desired 1$\alpha$-hydroxyvitamin D derivatives by acid-catalyzed cycloreversion. Application of this scheme to vitamin $D_3$ (**1a**), 25-hydroxyvitamin $D_3$ (**1b**), and vitamin $D_2$ (**1c**) affords the 1$\alpha$-hydroxy products in ~20% overall yield.

The recent markedly increased activity in vitamin D synthetic chemistry can be directly traced to the isolation and structural characterization of the metabolic components of the vitamin D endocrine system.[1] Because of their possible therapeutic value in treating disorders of calcium and phosphorus metabolism, vitamin D metabolites and in particular 1$\alpha$-hydroxylated analogues represent attractive synthetic targets which should be readily available for biomedical research. Classical synthetic routes to 1$\alpha$-hydroxylated vitamin D derivatives have involved preparation of a suitably substituted $\Delta^5$ steroidal precursor and conversion to the corresponding 5,7-diene provitamin followed by the well-known photochemical and thermal isomerizations to the vitamin analogue.[2] The disadvantages associated with an approach of this type, namely, complex reaction mixtures and difficult separations, have prompted us to explore a conceptually at-

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