An Improved Synthesis of the Ethylene Acetal of 3-Iodopropanal and the Ethylene Ketal of 4-Iodo-2-butanone

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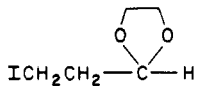
Recently a greatly improved preparation of the ethylene acetal of 3-iodopropanal (1) and the ethylene ketal of 4-iodo-2-butanone (2) on a reasonably large scale was reported.[2] This reaction employs aqueous HI, requires 18



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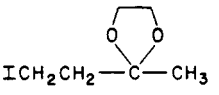

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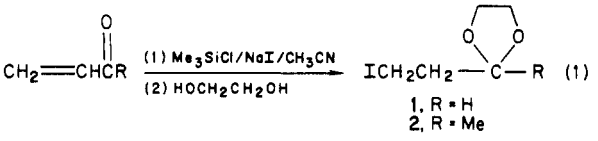
h, and provides 1 in 60% and 2 in 56% yields. We report herein a further improvement in the preparation of these important synthetic reagents.[3]

Our synthesis, which is similar in concept but simpler in practice to a recent preparation of β-halo acetals,[4] is based on three different reports in the literature: (1) the reported reaction of iodotrimethylsilane with α,β-unsaturated ketones to give 3-iodo enol silyl ethers,[5] (2) the ability to employ chlorotrimethylsilane and sodium iodide in acetonitrile in lieu of the more difficultly handled iodotrimethylsilane,[6] and (3) our report of some years ago that enol silyl ethers react rapidly and cleanly with diols to form the ketals.[7] It therefore seemed to us that the reaction sequence shown in eq 1 should provide a rapid, inexpensive and efficient preparation of 1 and 2. This is indeed the case.



(1)

Thus, the rapid, dropwise addition of chlorotrimethylsilane (12 mmol) to a rapidly stirred solution of acrolein (10 mmol) and sodium iodide (12 mmol) in acetonitrile (25 mL) produced an immediate precipitate and a yellow solution, which became dark orange with time.[8] The addition of ethylene glycol and workup gave 2.4 g (105%) of a light yellow liquid whose ^{1}H NMR spectrum was identical with that published[2] except for a small peak at 0.05 ppm for some hexamethyldisiloxane present. Material purified by alumina chromatography[2] with the concentrated material evacuated for 15 min at 1 mmHg gave 1.94 g (85%) of 1, which showed the expected ^{1}H NMR spectrum with the absence now of the hexamethyldisiloxane peak.

A similar procedure with 3-buten-2-one gave a 62% yield of 2 contaminated with a small amount of hexamethyldisiloxane.[9] This material turns dark within a few minutes at room temperature even when purified chromatographically.

Experimental Section

An oven-dried, standard apparatus under an atmosphere of nitrogen was employed. All reagents were normal commercial grade and were used as received.

2-(2-Iodoethyl)-1,3-dioxolane (1). To a solution of 18 g (120 mmol) of sodium iodide and 5.60 g (100 mmol) of acrolein in 250 mL of acetonitrile was rapidly added with vigorous stirring 15.3 mL (120 mmol) of chlorotrimethylsilane. The resulting suspension was stirred for 5 min and 6.69 mL (120 mmol) of ethylene glycol added rapidly followed by stirring for 5 min, after which time the reaction mixture was poured onto 100 mL of 5% $NaHCO_3$ overlaid with 300mL of pentane. This produced after thorough mixing three distinct liquid phases. The aqueous, undermost layer was removed, and the remaining organic phases were washed with 100 mL of 5% $Na_2S_2O_3$ and then with 100-mL portions of saturated NaCl until only a single organic phase was evident. This required from eight to ten washes. The pentane layer was dried over K_2CO_3. Solvent removal at reduced pressure (water aspirator) gave 21.9 g (96%) of 1 as a pale yellow liquid. Chromatography of this material over a 3 × 12 cm alumina column with hexane produced 19.4 g (85%) of 1 whose ^{1}H NMR spectrum was identical with that published as well as with that of the crude material prior to chromatography.

2-Methyl-2-(2-iodoethyl)-1,3-dioxolane (2). In a procedure exactly analogous to that described above 8.3 g (100 mmol) of 3-buten-2-one produced 18.9 g (78%) of crude 2 as a pink liquid containing hexamethyldisiloxane. Alumina chromatography with hexane gave 14.4 g (60%) of 2 as a light yellow liquid whose ^{1}H NMR spectrum corresponded with that published.[10]

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Registry No. 1, 83665-55-8; 2, 53750-51-9; $CH_3C(O)CH{=}CH_2$, 78-94-4; $ClSiMe_3$, 75-77-4; $HOCH_2CH_2OH$, 107-21-1; acrolein, 107-02-8.

(1) Visiting professor at Louisiana State University.
(2) Stowell, J. C.; King, B. T.; Hauck, H. F., Jr. *J. Org. Chem.* **1983**, *48*, 5381.
(3) Consult ref 2 and references therein.
(4) Gil, G. *Tetrahedron Lett.* **1984**, *25*, 3805.
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(6) Olah, G. A.; Narang, S. C.; Gupta, B. G. B.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247.
(7) Larson, G. L.; Hernandez, A. *J. Org. Chem.* **1973**, *38*, 3935.
(8) Experimentation revealed that in the acrolein reaction to form 1 the reaction can be quenched with ethylene glycol within 2 min or as long as 2 h of the addition of chlorotrimethylsilane with essentially the same results.
(9) This reaction mixture turns a dark orange within a few seconds after the addition of the chlorotrimethylsilane. Running the reaction at 0 °C gave comparable results.
(10) Trost, B. M.; Kunz, R. A. *J. Am. Chem. Soc.* **1975**, *97*, 7152. We thank Professor J. C. Stowell for a ^{1}H NMR spectrum of 2.

Syntheses of α-, β-, and γ-Substituted Carnitines via β-Keto Esters

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Carnitine (1) is extremely important in mammalian systems, where the highest concentrations are found in cardiac and skeletal muscle.[1] In these tissues carnitine

(1) Bremer, J. *Physiol. Rev.* **1983**, *63*, 1420–1480.

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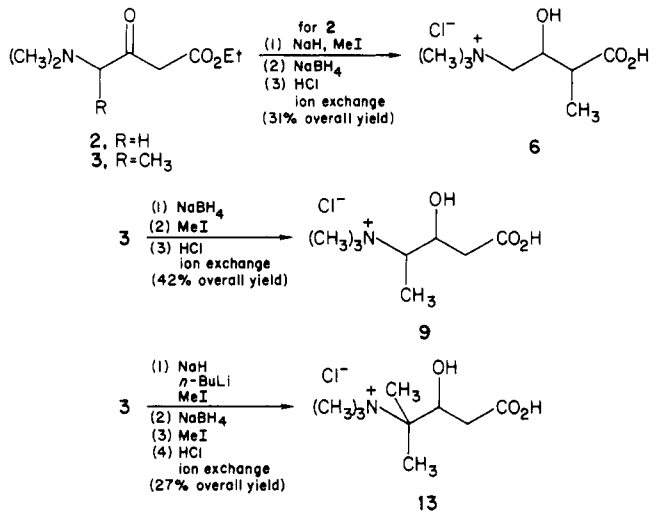
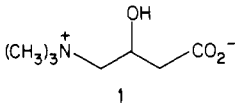
Scheme I



is intimately involved in fatty acid oxidation, a major energy pathway, in that it is required for the transport of



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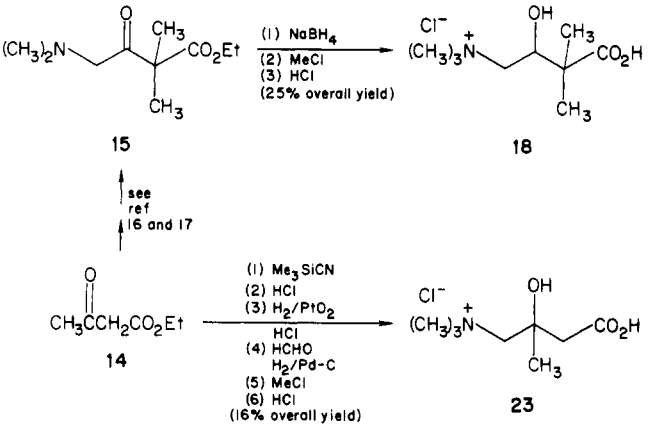
long-chain fatty acids into mitochondria. Recent evidence suggests that alterations in this transport pathway may be of benefit in diabetes and heart disease,[2] as well as in other conditions.

Although carnitine is of importance physiologically, very few syntheses of carnitine analogues have been reported, and none of these describe the preparation of α-, β-, or γ-substituted derivatives. Perhaps this is partly due to the practical difficulties involed in manipulating low molecular weight, hygroscopic quaternary ammonium compounds. In view of our interest in investigating carnitine analogues as possible modulators of fatty acid transport, we here describe the first syntheses of a number of α-, β-, and γ-methylated carnitines via the alkylation of appropriately substituted β-keto esters. The methodology employed offers the practical advantage of introducing the quaternary ammonium functionality at the penultimate step in the synthesis, allowing for the ready isolation and purification of intermediates. Furthermore, these methods should be useful for obtaining a variety of other C-substituted carnitines.

Results and Discussion

A number of carnitine syntheses have been reported,[3-10] although none of these appeared to be suitable for the efficient preparation of C-alkylated carnitines. We therefore recently developed a new synthesis[11] of carnitine

Scheme II



which incorporated the γ-(dimethylamino)-β-keto ester **2** (Scheme I) as intermediate. It was anticipated that intermediates such as **2** could be alkylated under basic conditions to provide 2- or 4-substituted derivatives.

As shown in Scheme I the synthesis of 2-methylcarnitine hydrochloride (**6**) was accomplished from keto ester **2**. It was proposed that **2** could be cleanly methylated at the 2-position under basic conditions; however, treatment of the sodium enolate of **2** with 1 equiv of methyl iodide produced only the quaternary ammonium derivative and no detectable amount of 2-methyl product. The sodium enolate of **2** was therefore reacted with a large excess of methyl iodide to produce ethyl 2-methyl-3-oxo-4-(trimethylammonio)butanoate iodide (**4**). Crude **4**, although clean by NMR, resisted purification (alumina or ion-exchange chromatography) and was therefore reduced directly with $NaBH_4$ to produce hydroxy ester **5** as a mixture of diastereomers. The inorganic salts were removed from this mixture on an alumina column (5% $EtOH/CHCl_3$ eluent), although resolution was insufficient for separation of the diastereomers. Compound **5** was then hydrolyzed in HCl and converted to the chloride form on an ion-exchange column to provide **6**. Compound **6**, like several other carnitine hydrochlorides that were subsequently prepared, was an oily hygroscopic material which was converted to the crystalline tetraphenylborate salt[12] in order to obtain a satisfactory elemental analysis.

The difficulties encountered in the isolation and purification of quaternary ammonium intermediates from the synthesis of **6** suggested that 2,2-dimethylcarnitine chloride (**18**) might be more efficiently prepared by an alternate route (see Scheme II). However, the approach given in Scheme I appeared suitable for the preparation of 4-methylcarnitines **9** and **13**. 3-(Dimethylamino)-2-butanone was thus prepared according to a literature procedure[13] and, as previously observed with (dimethylamino)acetone,[11] underwent a regioselective acylation with $(EtO)_2CO$ to give **3**. Keto ester **3** was then reduced with $NaBH_4$ to yield hydroxy ester **7** as a mixture of diastereomers. However, unlike the quaternary ammonium salt **5**, the diastereomers of **7** were neutral species and were readily separated on an alumina column. The major diastereomer of **7**, for which the absolute stereochemistry was not determined, was quaternized with CH_3I to produce crystalline **8**, which was then hydrolyzed and chromatographed on an ion-exchange column to give 4-methylcarnitine chloride (**9**).

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Keto ester **3** was also converted to 4,4-dimethylcarnitine chloride (**13**) as shown in Scheme I. In this procedure the dianion of **3**, generated in a manner analogous to that reported[14,15] for the dianion of methyl acetoacetate, was methylated at the 4-position to provide **10**. Note that, unlike the conversion of **2** to **6**, the quaternization of **3** was not a problem under these conditions due to the greater reactivity of the dianion of **3** as compared to the monoanion of **2**. Compound **10** was then readily converted to **13** by the methods previously discussed.

As shown in Scheme II the preparation of 2,2-dimethylcarnitine chloride (**18**) was accomplished from acetoacetic ester **14**. In this procedure, **14** was converted to ethyl 4-bromo-2,2-dimethyl-3-oxobutanoate according to the method of Cannon and Jones.[16] This was reacted with dimethylamine according to a literature method[17] to give **15**. Compound **15** was then reduced with $NaBH_4$ to yield hydroxy ester **16**, which was quaternized with CH_3Cl to produce **17**. Compound **17** was hydrolyzed directly to 2,2-dimethylcarnitine chloride (**18**), avoiding the need for ion-exchange chromatography.

In an approach analogous to the successful synthesis of **18**, the intermediate required for a more efficient synthesis of 2-methylcarnitine chloride (**6**), as compared to the procedure in Scheme I, was ethyl 4-bromo-2-methyl-3-oxobutanoate. Although the preparation of this keto ester from **14** has been reported,[18] we were unable to reproduce this procedure. In particular, upon bromination of ethyl 2-methyl-3-oxobutanoate in $CHCl_3$ at 0 °C followed by bubbling air through the mixture, the only product isolated was the 2-bromo ester, although these conditions are reported to provide the 4-bromo ester. Numerous additional attempts to rearrange the 2-bromo ester to the 4-bromo ester using air, light, and/or peroxides[18] also failed. This approach to **6** was therefore abandoned.

Finally, 3-methylcarnitine chloride (**23**) was prepared from acetoacetic ester **14** according to the procedure shown in Scheme II. In this procedure **14** was reacted with trimethylsilyl cyanide (Me_3SiCN)[19,20] to form the trimethylsilyl cyanohydrin ether, which was directly hydrolyzed with Et_2O/HCl to form cyanohydrin **19** in high yield. This was reduced on a Parr shaker to give the crude amine hydrochloride **20**, and **20** was carried on without further purification. A reductive amination of **20** provided the *N,N*-dimethyl derivative **21**, which was purified by chromatography on alumina. Compound **21** was then quaternized with CH_3Cl to give **22**, and this was hydrolyzed in HCl as before to directly provide **23**.

Experimental Section

Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. Preparative chromatographic separations were performed on Baker silica, 60–200 mesh, or Fisher alumina, 80–200 mesh. Elemental analyses were performed at Atlantic Microlab of Atlanta, GA.

Ethyl 4-(Dimethylamino)-3-oxopentanoate (3). To a suspension of 50% NaH/mineral oil (2.25 g, 47.0 mmol) and diethyl carbonate (5.54 g, 47.0 mmol) in 15 mL of DME under N_2 at 78 °C was added dropwise over 45 min a solution of 3-(dimethylamino)-2-butanone[13] (2.70 g, 23.5 mmol) in 5 mL of DME. The tan-colored mixture was maintained at this temperature for 3 h and cooled to 25 °C, acetic acid (5.0 g, 83 mmol) added dropwise with cooling, and the solvent removed in vacuo. The residue was dissolved in 15 mL of water, adjusted to pH 5 with additional HOAc, and mineral oil was removed by extraction with hexane (2 × 15 mL). The aqueous solution was adjusted to pH 7.8 with 50% NaOH and extracted with ethyl acetate (3 × 50 mL). The extracts were dried, the solvent removed, and the crude product was distilled to give **3** (82% yield) as a clear oil: bp 83 °C (0.95 mm); ^1H NMR ($CDCl_3$) δ 4.18 (q, 2 H, OCH_2CH_3), 3.58 (s, 2 H, CH_2CO_2Et), 3.28 (q, 1 H, $CHCH_3$), 2.25 (s, 6 H, $N(CH_3)_2$), 1.28 (t, 3 H, OCH_2CH_3), 1.12 (d, 3 H, $CHCH_3$); IR (liquid film) 1735, 1710 (C=O) cm^{-1}.

Anal. Calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.46; H, 9.11; N, 7.41.

Ethyl 2-Methyl-3-oxo-4-(trimethylammonio)butanoate, Iodide (4). A solution of **2**[11,21] (1.00 g, 5.87 mmol) in 2 mL of DME was added dropwise to a stirred solution of 50% NaH (0.277 g, 5.78 mmol) in 6 mL of DME at 25 °C. The resulting mixture was stirred for 2 h, CH_3I (3.28 g, 23.1 mmol) was added all at once, and stirring was continued overnight. To this mixture was slowly added 20 mL of H_2O, the solution was extracted with Et_2O (3 × 20 mL) followed by hexane (2 × 10 mL), and the extracts were discarded. The aqueous layer was concentrated on a rotary evaporator and the residue dried under vacuum (0.11 mm) to give 1.2 g (64%) of crude **4** as a yellow oil. Compound **4** was used in this form without further purification: ^1H NMR (D_2O) δ 4.4–4.05 (q, 2 H, OCH_2CH_3), 3.55 (s, 2 H, NCH_2), 3.35 (s, 9 H, $N(CH_3)_3$), 3.32 (q, 1 H, $CHCH_3$), 1.5–1.1 (m, 6 H, $CHCH_3$ and OCH_2CH_3); IR (liquid film) 1730 (sh), 1710 (C=O) cm^{-1}.

Ethyl 3-Hydroxy-2-methyl-4-(trimethylammonio)butanoate, Iodide (5). A solution of **4** (1.00 g, 4.95 mmol) in 12.4 mL of H_2O was cooled to 0 °C, $NaBH_4$ (0.140 g, 3.71 mmol) added all at once, the cooling bath removed, and the mixture stirred at room temperature for 4 h. This was cooled in an ice bath, adjusted to pH 3 with 10% HCl, and readjusted to pH 7 with 10% NaOH. The resulting solution was concentrated to dryness on a rotary evaporator (30 °C) and the residue applied to an alumina column (5 × 15 cm) as an ethanol solution. The column was eluted with 5% EtOH/$CHCl_3$, and the fractions containing material with R_f 0.33 were combined and concentrated in vacuo to provide 0.619 g (49.2%) of **5** as an oil: ^1H NMR (D_2O) δ 4.4–3.9 (m, 3 H, $CHOH$ and OCH_2CH_3), 3.6–3.3 (m, 2 H, NCH_2), 3.15 (s, 9 H, $N(CH_3)_3$), 2.9–2.5 (m, 1 H, $CHCH_3$), 1.35–1.05 (m, 6 H, $CHCH_3$ and OCH_2CH_3); IR (liquid film) 3360 (OH), 1700 (C=O) cm^{-1}.

The oily, hygroscopic product was converted to the tetraphenylborate salt:[12] mp 155–157 °C (CH_3OH/H_2O).

Anal. Calcd for $C_{34}H_{42}NO_3B$: C, 78.00; H, 8.09; N, 2.68. Found: C, 77.92; H, 8.15; N, 2.59.

Ethyl 4-Methyl-4-(dimethylamino)-3-oxopentanoate (10). To a suspension of 50% NaH (1.41 g, 29.4 mmol) in 70 mL of THF at 0 °C under N_2 was added dropwise keto ester **3** (5.0 g, 26.7 mmol). This was stirred for 15 min, and a 1.55 M solution of *n*-BuLi (18.1 mL, 28.1 mmol) was added dropwise. The resulting mixture was again stirred for 15 min, and CH_3I (4.17 g, 29.4 mmol) was added all at once. The ice bath was removed after 30 min and the mixture stirred for 20 h at 25 °C. Glacial acetic acid (1.60 g, 26.7 mmol) was added, the THF removed in vacuo, 25 mL of H_2O added, and the resulting solution adjusted to pH 5.5 with HOAc. This was extracted with hexane (3 × 20 mL) to remove mineral oil, and the aqueous solution was readjusted to pH 7.8 with 50% NaOH. This was extracted with EtOAc (4 × 50 mL), the extracts were dried (Na_2SO_4), and the solvent was removed in vacuo to give an oil. The oil was distilled to provide 3.31 g of **10**, bp 86–88 °C (0.70 mm). The residue from the distillation was chromatographed on silica (1% $CH_3OH/CHCl_3$), R_f 0.34, to provide an additional 0.6 g of **10**. The total yield of **10** was 3.9 g (73%). The distilled material contained slight impurities by TLC, and the analytical sample was therefore taken from the silica column: ^1H NMR ($CDCl_3$) δ 4.18 (q, 2 H, OCH_2CH_3), 3.73 (s, 2 H, CH_2CO_2Et), 2.18 (s, 6 H, $N(CH_3)_2$), 1.26 (t, 3 H, OCH_2CH_3),

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1.13 (s, 6 H, $C(CH_3)_2$); IR (liquid film) 1740, 1710 (C=O) cm^{-1}.

Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.67; H, 9.52; N, 6.96. Found: C, 59.70; H, 9.57; N, 6.84.

General Procedure for the Reduction of Keto Esters 3, 10, and 15. A 0.50 M solution of the appropriate keto ester in EtOH at 0 °C was treated with $NaBH_4$ (0.5 mol equiv). After being stirred for 6 h at 0 °C, the solution was adjusted to pH 4.5 with 2 N HCl (0 °C) and the solvent removed in vacuo at 30 °C. The residue was dissolved in 10 mL of water and treated with 1 equiv of 1 N NaOH. After removal of the water in vacuo (30 °C), the residue was triturated with EtOH and filtered to remove most of the salts. The filtrate was concentrated and the residue chromatographed on alumina. By this method were prepared the following.

Ethyl 4-(Dimethylamino)-3-hydroxypentanoate (7). Chromatography of the crude product on alumina ($CHCl_3$ eluent) yielded two close-running diastereomers. The major isomer (47% yield) eluted first, R_f 0.42, and was carried on for further reactions: bp 62 °C (0.2 mm); ^1H NMR ($CDCl_3$) δ 4.18 (q, 2 H, OCH_2CH_3), 4.4–3.5 (m, 2 H, CHOH and $CHCH_3$), 2.8–2.0 (m, 3 H, OH and CH_2CO_2Et), 2.25 (s, 6 H, $N(CH_3)_2$), 1.3 (t, 3 H, OCH_2CH_3), 0.9 (d, 3 H, $CHCH_3$); IR (KBr) 3300 (OH), 1740 (C=O) cm^{-1}.

Anal. Calcd for $C_9H_{19}NO_3$: C, 57.12; H, 10.12;, N, 7.40. Found: C, 56.97; H, 10.16; N, 7.39.

(The minor isomer, R_f 0.31, was produced in less than 10% yield and not further pursued).

Ethyl 4-Methyl-4-(dimethylamino)-3-hydroxypentanoate (11). Compound 11 was isolated from an alumina column ($CHCl_3$ eluent, R_f 0.41) in 48% yield as a clear oil: ^1H NMR ($CDCl_3$) δ 4.18 (q, 2 H, OCH_2CH_3), 4.07 (t, 1 H, $CHCH_2$), 4.1–3.8 (br s, 1 H, OH), 2.38 (d, 2 H, $CHCH_2$), 2.24 (s, 6 H, $N(CH_3)_2$), 1.28 (t, 3 H, OCH_2CH_3), 0.98 (s, 3 H, CCH_3), 0.88 (s, 3 H, CCH_3); IR (liquid film) 3440 (OH), 1730 (C=O) cm^{-1}.

Anal. Calcd for $C_{10}H_{21}NO_3$: C, 59.08; H, 10.41; N, 6.89. Found: C, 59.15; H, 10.42; N, 6.81.

Ethyl 2,2-Dimethyl-4-(dimethylamino)-3-hydroxybutanoate (16). Chromatography of the crude product on alumina (10% $Et_2O/CHCl_3$ eluent, R_f 0.54) provided 16 in 34% yield: ^1H NMR ($CDCl_3$) δ 4.35–3.55 (m, 4 H, OCH_2CH_3 and OH and CHOH), 2.65–1.9 (m, 8 H, $N(CH_3)_2$ and NCH_2), 1.45–1.1 (m, 9 H, $C(CH_3)_2$ and OCH_2CH_3); IR (liquid film) 3400 (OH), 1705 (C=O) cm^{-1}.

Anal. Calcd for $C_{10}H_{21}NO_3$: C, 59.08; H, 10.41; N, 6.89. Found: C, 59.24; H, 10.44; N, 6.83.

General Procedure for the Quaternization of Amines 7, 11, 16, and 21. The procedures utilized either CH_3Cl or CH_3I as shown in Schemes I and II. The iodides were prepared by stirring a 0.5 M solution of the appropriate amine in acetone with MeI (2 mol equiv) for 6 h. The chlorides were prepared by bubbling gaseous MeCl (5 molar excess) into a 0.5 M solution of the appropriate amine in acetone at −78 °C in a pear-shaped pressure bottle. The bottle was sealed and the mixture allowed to warm to 25 °C. In this manner the following were prepared.

Ethyl 3-Hydroxy-4-(trimethylammonio)pentanoate, Iodide (8). Compound 8, prepared from the major diastereomer of 7 at 25 °C, was isolated as an oily residue after removal of the solvent. This crystallized on standing to give 8 in 96% yield. Crude 8 was triturated with 1:1 $MeOH/Et_2O$, filtered, and dried under vacuum to provide the analytical sample: mp 121.5–122.5 °C (CH_3OH/Et_2O); ^1H NMR ($CDCl_3$) δ 4.8–3.9 (m, 5 H, NCH and CHOH and OCH_2CH_3), 3.5 (s, 9 H, $N(CH_3)_3$), 3.0–2.6 (m, 2 H, CH_2CO_2Et), 1.6–1.1 (m, 6 H, $CHCH_3$ and OCH_2CH_3); IR (KBr) 3300 (OH), 1735 (C=O) cm^{-1}.

Anal. Calcd for $C_{10}H_{22}NO_3I$: C, 36.27; H, 6.70; N, 4.23; I, 38.32. Found: C, 36.33; H, 6.74; N, 4.18; I, 38.40.

Ethyl 4-Methyl-3-hydroxy-4-(trimethylammonio)pentanoate, Iodide (12). The quaternization of 11 required heating in a pear-shaped pressure bottle at 55 °C for 6 h. Removal of the solvent produced a semisolid residue (100%), which resisted recrystallization but was shown to be pure by NMR, IR, and elemental analysis: ^1H NMR ($CDCl_3$) δ 4.87–4.43 (m, 2 H, CHOH), 4.14 (q, 2 H, OCH_2CH_3), 3.45 (s, 9 H, $N(CH_3)_3$), 2.8–2.43 (m, 2 H, CH_2CO_2Et), 1.57 (s, 3 H, CCH_3), 1.48 (s, 3 H, CCH_3), 1.3 (t, 3 H, OCH_2CH_3); IR (KBr) 3380 (OH), 1730 (C=O) cm^{-1}.

Anal. Calcd for $C_{11}H_{24}NO_3I$: C, 38.27; H, 7.01; N, 4.06; I, 36.76. Found: C, 38.40; H, 7.06; N, 3.99; I, 36.64.

Ethyl 2,2-Dimethyl-3-hydroxy-4-(trimethylammonio)butanoate, Chloride (17). Compound 17 crystallized from acetone solution at 25 °C in 74% yield: mp 150–151 °C; ^1H NMR (D_2O) δ 4.5–3.9 (m, 3 H, OCH_2CH_3 and CHOH), 3.5–3.3 (m, 2 H, NCH_2), 3.2 (s, 9 H, $N(CH_3)_3$), 1.4–1.1 (m, 9 H, $C(CH_3)_2$ and OCH_2CH_3); IR (liquid film) 3360 (OH), 1700 (C=O) cm^{-1}.

Anal. Calcd for $C_{11}H_{24}NO_3Cl$: C, 52.06; H, 9.53; N, 5.52; Cl, 13.97. Found: C, 52.13; H, 9.57; N, 5.51; Cl, 14.02.

Ethyl 3-Hydroxy-3-methyl-4-(trimethylammonio)butanoate, Chloride (22). After being stirred 48 h at 25 °C in acetone, the reaction mixture was cooled to −78 °C to form crystalline 22 in 55% yield: mp 111–112 °C; ^1H NMR (D_2O) δ 4.4–3.9 (q, 2 H, OCH_2CH_3), 3.6 (s, 2 H, NCH_2), 3.3 (s, 9 H, $N(CH_3)_3$), 2.7 (s, 2 H, CH_2CO_2Et), 1.6 (s, 3 H, CCH_3), 1.5–1.1 (t, 3 H, OCH_2CH_3); IR (liquid film) 3400 (OH), 1710 (C=O) cm^{-1}.

Anal. Calcd for $C_{10}H_{22}NO_3Cl$: C, 50.10; H, 9.25; N, 5.84; Cl, 14.79. Found: C, 49.92; H, 9.26; N, 5.79; Cl, 14.70.

General Procedure for the Hydrolysis of Quaternary Ammonium Esters 5, 17, and 22. A 0.1% solution of the appropriate ester in 20% HCl was heated at reflux for either 3 h (for 5 and 22) or 12 h (for 17). The solution was concentrated in vacuo to provide the acid as an oil in quantitative yield. By this method were prepared the following.

3-Hydroxy-2-methyl-4-(trimethylammonio)butanoic Acid, Chloride (6). Crude product 6 was chromatographed on a Baker Anga-542 (OH^- form) ion-exchange column (H_2O eluent). Acidification of the appropriate fractions (detected by spotting on alumina without elution and staining with I_2) with HCl and concentration in vacuo gave 10 as a mixture of diastereomers: ^1H NMR (D_2O) δ 4.5–4.0 (m, 1 H, CHOH), 3.4–3.2 (m, 2 H, NCH_2), 3.1 (s, 9 H, $N(CH_3)_3$), 2.6–2.2 (m, 1 H, $CHCH_3$), 1.2–1.0 (2 d, 3 H, $CHCH_3$); IR (liquid film) 3440 (OH), 1710 (C=O) cm^{-1}.

The oily, hygroscopic product was converted to the tetraphenylborate salt:[12] mp 121–125 °C (acetone/H_2O).

Anal. Calcd for $C_{32}H_{38}NO_3B$: C, 77.57; H, 7.73; N, 2.83. Found: C, 77.48; H, 7.75; N, 2.81.

2,2-Dimethyl-3-hydroxy-4-(trimethylammonio)butanoic acid, chloride (18): ^1H NMR (D_2O) δ 4.6–4.1 (m, 1 H, CHOH), 3.5–3.3 (m, 2 H, NCH_2), 3.1 (s, 9 H, $N(CH_3)_3$), 1.2–1.1 (2 s, 6 H, $C(CH_3)_2$); IR (liquid film) 3350 (OH), 1700 (C=O) cm^{-1}.

The oily hygroscopic product was converted to the tetraphenylborate salt:[12] mp 113–115 °C (CH_3OH/H_2O).

Anal. Calcd for $C_{33}H_{40}NO_3B$: C, 77.79; H, 7.91; N, 2.75. Found: C, 77.83; H, 7.94; N, 2.59.

3-Hydroxy-3-methyl-4-(trimethylammonio)butanoic acid, chloride (23): ^1H NMR (D_2O) δ 3.55 (s, 2 H, NCH_2), 3.25 (s, 9 H, $N(CH_3)_3$), 2.7 (s, 2 H, CH_2CO_2H), 1.5 (s, 3 H, CCH_3); IR (liquid film) 3300 (OH), 1720 (C=O) cm^{-1}.

The oily hygroscopic product was converted to the tetraphenylborate salt:[12] mp 140–142 °C (acetone/H_2O).

Anal. Calcd for $C_{32}H_{38}NO_3B$: C, 77.56; H, 7.73; N, 2.83. Found: C, 77.44; H, 7.76; N, 2.77.

General Procedure for the Hydrolysis of Quaternary Ammonium Esters 8 and 12. A 0.1 M solution of the appropriate ester in concentrated HCl was heated at 55 °C for 1.5 h. The mixture was concentrated to dryness and the residue chromatographed on a Dowex 50X8-200 column (H^+ form). The column was eluted with water until the eluent was no longer yellow (to remove I^-) followed by 2 N HCl. The fractions containing product were detected by spotting the eluent on silica (without elution) and staining with I_2. By this method were prepared the following.

3-Hydroxy-4-(trimethylammonio)pentanoic Acid, Chloride (9). Concentration of the appropriate fractions from ion-exchange chromatography produced a single diastereomer of 9 as a white crystalline solid in 94% yield: mp 176–178 °C (CH_3OH/Et_2O); ^1H NMR (D_2O) δ 4.77–4.13 (m, 1 H, CHOH), 3.97–3.27 (m, 1 H, $CHCH_3$), 3.17 (s, 9 H, $N(CH_3)_3$), 2.87–2.53 (m, 2 H, CH_2CO_2H), 1.37 (d, 3 H, $CHCH_3$); IR (KBr) 3360 (OH), 1735 (C=O) cm^{-1}.

Anal. Calcd for $C_8H_{18}NO_3Cl$: C, 45.39; H, 8.57; N, 6.62; Cl, 16.75. Found: C, 45.27; H, 8.57; H, 6.58; Cl, 16.84.

4-Methyl-3-hydroxy-4-(trimethylammonio)pentanoic Acid, Chloride (13). Concentration of the appropriate fractions following ion-exchange chromatography produced compound 13 as a white crystalline solid in 76% yield: mp 187–188 °C dec (CH_3OH/Et_2O); ^1H NMR (D_2O) δ 4.68–4.13 (m, 1 H, CHOH), 3.05 (s, 9 H, $N(CH_3)_3$), 2.75–2.42 (m, 2 H, CH_2CO_2H), 1.36 (s, 3 H,

CCH_3), 1.30 (s, 3 H, CCH_3); IR (KBr) 3300 (OH), 1735 (C=O) cm^{-1}.

Product **13** was converted to the tetraphenylborate salt:[12] mp 116–118 °C.

Anal. Calcd for $C_{33}H_{40}NO_3B$: C, 77.79; H, 7.91; N, 2.75. Found: C, 77.55; H, 7.94; N, 2.73.

Ethyl 3-Cyano-3-hydroxybutanoate (19). To a stirred solution of acetoacetic ester (10.0 g, 76.8 mmol) and trimethylsilyl cyanide (8.02 g, 76.8 mmol) was added approximately 5 mg each of KCN and 18-crown-6. The mixture became warm and was allowed to cool to room temperature. IR analysis at this point showed that the ketone carbonyl was completely gone. To the mixture was added 40 mL of ether, the solution was cooled in an ice bath, 40 mL of 15% HCl was added, and this was stirred vigorously for 15 min. The ether layer was separated, washed with 40 mL of water, dried ($MgSO_4$), and concentrated in vacuo to give 10.2 g (73.0%) of **19** as a pale orange oil. This was distilled to provide a colorless oil: bp 68–70 °C (0.2 mm) [lit.[19] bp 133 °C (23 mm)].

Ethyl 4-Amino-3-hydroxy-3-methylbutanoate, Hydrochloride (20). A mixture of cyanohydrin **19** (1.0 g, 0.64 mol), 50 mL of EtOH, 0.15 g of PtO_2, and 1.0 mL of concentrated HCl was hydrogenated on a Parr shaker at 50 psi overnight. The mixture was filtered and concentrated in vacuo to provide 1.1 g (86%) of crude **20** as an oil. The product was used in this form without further purification: ^1H NMR (D_2O) δ 4.35–3.95 (q, 2 H, OCH_2CH_3), 3.15 (s, 2 H, NCH_2), 2.7 (s, 2 H, CH_2CO_2Et), 1.4–0.8 (m, 6 H, CCH_3 and OCH_2CH_3); IR (liquid film) 3600–2600 (OH, $^+NH_3$), 1715 (C=O) cm^{-1}.

Ethyl 4-(Dimethylamino)-3-hydroxy-3-methylbutanoate (21). A solution of **20** (1.0 g, 5.1 mmol), 30 mL of water, 37% formaldehyde (0.82 g, 10 mmol), and 0.80 g of 10% Pd–C was hydrogenated on a Parr shaker at 50 psi overnight. The mixture was filtered, the filtrate was adjusted to pH 10.5 with granular Na_2CO_3, and the solution was extracted with $CHCl_3$ (4 × 25 mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo to provide 0.45 g (47%) of **21** as an oil. The analytical sample was obtained by chromatography of a portion of the crude product on alumina (80% $CHCl_3/Et_2O$, R_f 0.80): ^1H NMR ($CDCl_3$) δ 4.35–3.9 (q, 2 H, OCH_2CH_3), 3.8–3.5 (br s, 1 H, OH), 2.55–2.4 (m, 2 H, NCH_2), 2.3 (m, 8 H, $N(CH_3)_2$ and CH_2CO_2Et), 1.4–1.15 (t, 3 H, OCH_2CH_3), 1.2 (s, 3 H, CCH_3); IR (liquid film) 3400 (OH), 1690 (C=O) cm^{-1}.

Anal. Calcd for $C_9H_{19}NO_3$: C, 57.12; H, 10.12; N, 7.40. Found: C, 57.02; H, 10.17; N, 7.29.

Registry No. **2**, 96935-73-8; **3**, 97374-60-2; **4**, 97374-61-3; **5**, 97374-62-4; **5**·tetraphenylborate salt, 97374-64-6; **6**, 97374-65-7; **6**·tetraphenylborate salt, 97374-67-9; **7**, 97374-68-0; **8**, 97374-69-1; **9**, 97374-70-4; **10**, 97374-71-5; **11**, 97374-72-6; **12**, 97374-73-7; **13**, 97374-74-8; **13**·tetraphenylborate salt, 97374-76-0; **14**, 141-97-9; **15**, 97374-77-1; **16**, 97374-78-2; **17**, 97374-79-3; **18**, 97374-80-6; **18**·tetraphenylborate salt, 97374-82-8; **19**, 6330-37-6; **20**, 97374-83-9; **21**, 97374-84-0; **22**, 97374-85-1; **23**, 97374-86-2; **23**·teteraphenylborate salt, 97374-88-4; 3-(dimethylamino)-2-butanone, 10524-60-4; diethyl carbonate, 105-58-8; formaldehyde, 50-00-0.

Synthesis of γ-Lactam-Constrained Tryptophyllysine Derivatives

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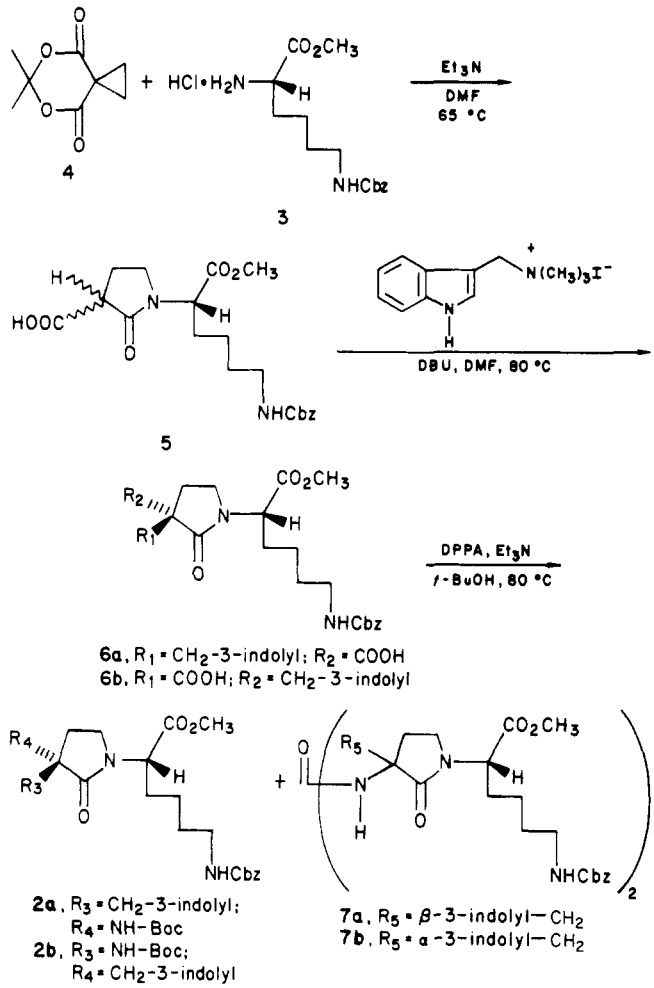
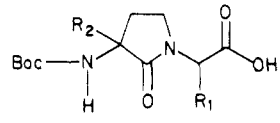
We previously reported the synthesis of γ-lactam-constrained dipeptides for use in conformation–activity studies of biologically active peptides.[1] Such lactams serve as analogues of glycyl dipeptides restricted to turn conformations. It is of general interest to similarly constrain dipeptide units not containing glycine. A specific example is the tryptophyllysine unit of somatostatin. The published synthesis utilized the cyclization of methylsulfonium salts of Boc-Met-X-OCH_3, where X was any of several α-amino acids, and provided ready access to lactam dipeptides such as **1a**. Extension of this synthetic route to prepare the Trp-Lys derivative **1b**, however, was not straightforward. We now describe the synthesis of the methyl ester of **1b** (**2**) by a novel approach that has potential generality for a variety of γ-lactam-constrained dipeptides.

Scheme I





The synthesis of **2** is outlined in Scheme I. ε-(Benzyloxycarbonyl)-L-lysine methyl ester hydrochloride **3** was warmed with electrophilic cyclopropane derivative **4**[2] in dimethylformamide (DMF) to produce the α-carboxy lactam **5** as a mixture of diastereomers. This reaction presumably occurs by initial attack of the lysine amino group at a cyclopropane methylene to open the three-membered ring. The intermediate then cyclizes on one of the lactone carbonyls to expel acetone and produce **5**.

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