Oxidation of Statine-Containing Peptides to Ketone Analogues via Novel Peptide Sulfonium Ylides

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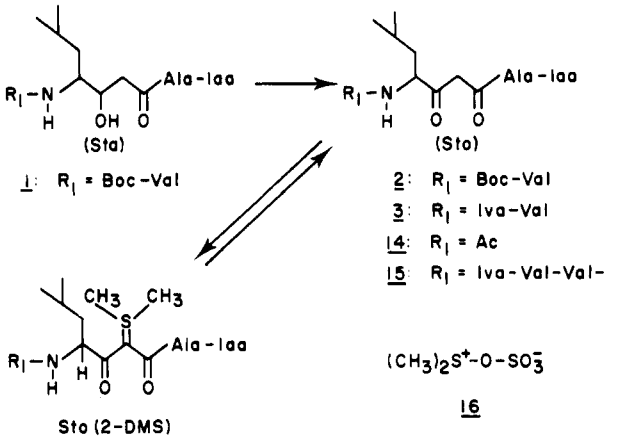
Reaction of peptides containing the amino acid statine, (3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid, with pyridine–sulfur trioxide and triethylamine in Me_2SO gave the corresponding peptides containing the 2-dimethylsulfonium ylide of statone, (*S*)-4-amino-6-methyl-3-oxoheptanoic acid, in high yield (83–97%). N-Protected amino acids containing the sulfonium ylide of statone can be deprotected and N-acylated. Desulfurization of the ylide using zinc in acetic acid gave the corresponding statone derivative in good yield (46–91%). The improved synthesis of statone peptides was applied to the synthesis of ^{13}C-labeled ketone derivatives of pepstatin.

Recently we reported[1] the synthesis and inhibition kinetics of a ketone analogue of pepstatin, a new type of inhibitor of aspartyl proteases.[2] Compound 1 (Scheme I) was oxidized to the ketone 2 (Me_2SO–oxalyl chloride in CH_2Cl_2).[3] After removal of the Boc group and neutralization of the amine salt, reaction with isovaleric acid anhydride gave the statone[4] derivative 3 in quantities suitable for evaluation as an inhibitor of pepsin but in only 11% overall yield. A variety of reaction conditions and oxidizing reagents subsequently were examined[5] in attempts to optimize the synthesis, but the reactions proved to be troublesome in all cases due to either poor solubility in the solvent or to the slow reaction with the oxidant leading to multiple products.

In order to prepare isotopically enriched keto pepstatin analogues, especially the 3-^{13}C-labeled analogue of 3, a more efficient synthesis of keto pepstatin analogues was required. When statine derivative 1 was oxidized in Me_2SO by using pyridine–sulfur trioxide and triethylamine as the oxidant,[6] a high yield of the dimethylsulfonium adduct of statone (4), Sto(2-DMS),[4] was obtained. Reaction of the enolate anion of the intermediate β-keto amide 2 with activated Me_2SO (16)[7] followed by proton abstraction gave this novel peptide product. We report here that the dimethylsulfonium ylides of statone are useful intermediates for the efficient synthesis of statone-containing peptides.

Table I lists other examples of novel peptides that were prepared from the statine-containing peptides 6–9.[8-10] Sulfonium ylides (4, 10, 11) can be deprotected and N-acylated in good yield under standard peptide synthesis conditions to give the N-substituted analogues (5, 12, 13, Table I). Subsequent reduction of the Sto(2-DMS) peptides with activated zinc in acetic acid at 70–75 °C affords

Scheme I



the desired statone derivatives 3, 14, and 15 in good yield. Statone peptide 3 was prepared in 40–50% overall yield from statine peptide 1, via 5, representing a 4–5-fold increase in yield with the new procedure. An alternate reduction procedure is available for desulfurization of Boc-protected peptides. Reduction of Boc-Val-Sto(2-DMS)-Ala-Iaa with sodium iodide in acetic acid at 25 °C gave the corresponding ketone in 83% yield.

Sulfonium ylides are easily distinguished from ketones spectroscopically. The ^{13}C NMR spectra of sulfonium ylides exhibit a peak for C-3 at 188 ppm (relative to Me_4Si in $CDCl_3$), while spectra of ketones exhibit a peak for the C-3 carbonyl at 205 ppm. In addition, sulfonium ylides exhibit a characteristic set of two barely resolvable singlets at 3.05 ppm (270 MHz, Me_4Si, $CDCl_3$) by ^1H NMR that are assignable to the diastereotopic *S*-methyl groups. The C-4 hydrogen of the 1,3-dicarbonyl-2-sulfonium moiety and alanine N–H (9.9 ppm, assigned by decoupling) are strongly deshielded compared to the corresponding hydrogens in the ketones. The ultraviolet spectra of sulfonium ylides are in excellent agreement with those reported for other sulfonium ylides derived from 1,3-dicarbonyl compounds.[7]

The reactions shown in Scheme I are relatively rapid, very clean, reproducible, and easy to perform on micro or preparative scale. The use of Me_2SO as solvent for the oxidation permits the synthesis of statone-containing

(1) Rich, D. H.; Boparai, A. S.; Bernatowicz, M. S. *Biochem. Biophys. Res. Commun.* **1982**, *104*, 1127–1133.

(2) Pepstatin has the sequence Iva-Val-Val-(3*S*,4*S*)-Sta-Ala-(3*S*,4*S*)-Sta. Morishima, H.; Takita, T.; Aoygi, T.; Takeuchi T.; Umezawa, H. *J. Antibiot.* **1970**, *23*, 263.

(3) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

(4) Abbreviations used follow IUPAC–IUB tentatiave rules as described in: *J. Biol. Chem.* **1972**, *247*, 977. Additional abbreviations used: Iva, isovaleryl; Sta, 4-amino-3-hydroxy-6-methylheptanoic acid (statine); Iaa, isoamylamide; Boc, *N-tert*-butyloxycarbonyl; Sto, (*S*)-4-amino-6-methyl-3-oxoheptanoic acid (statone); Sto(2-DMS), (*S*)-4-amino-6-methyl-2-(dimethylsulfonio)-3-oxoheptanoic acid ((dimethylsulfonio)-statone); DMAP, 4-(dimethylamino)pyridine; DMF, dimethylformamide.

(5) Alternate conditions conducted: pyridinium dichromate in DMF or CH_2Cl_2; pyridinium chlorochromate in DMF or CH_2Cl_2; $KMnO_4$ in pyridine; and activated MnO_2 in CH_2Cl_2.

(6) Parikh, J. R.; Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505–5506.

(7) Nozaki, H.; Tunemota, D.; Morita, Z.; Nakamura, K.; Watanabe, K.; Takaku, M.; Kondô, K. *Tetrahedron* **1967**, *23*, 4279–4290.

(8) Rich, D. H.; Sun, E. T.; Boparai, A. S. *J. Org. Chem.* **1978**, *43*, 3624–3626.

(9) Rich, D. H.; Sun, E. T. O.; Ulm, E. *J. Med. Chem.* **1980**, *23*, 27–33.

(10) Rich, D. H.; Bernatowicz, M. S. *J. Med. Chem.* **1982**, *25*, 791–795.

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Table I. Synthesis of Statone-Containing Peptides

starting peptide	Boc-Sto(2-DMS) peptide (yield,[a] %)	N-acyl-Sto(2-DMS) peptide (yield, %)	N-acyl-Sto peptide (yield, %)
Boc-Val-(3S,4S)-Sta-Ala-Iaa (1)	4 (83-88)	Iva-Val-Sto(2-DMS)-Ala-Iaa 5 (67)	Iva-Val-Sto-Ala-Iaa 3 (72-91)
Boc-(3S,4S)-Sta-Ala-Iaa (6)	10 (89)	N-Ac-Sto(2-DMS)-Ala-Iaa 12 (70)	N-Ac-Sto-Ala-Iaa 14 (46-52)
Boc-(3R,4S)-Sta-Ala-Iaa (7)	10 (97[b])		
Boc-Val-Val-(3R,4S)-Sta-Ala-Iaa (8)	11 (92)		
Boc-Val-Val-(3S,4S)-Sta-Ala-Iaa (9)	11 (92)	Iva-Val-Val-Sto(2-DMS)-Ala-Iaa 13 (88)	Iva-Val-Val-Sto-Ala-Iaa 15 (56-66)

[a] Yields of analytically pure compounds isolated after chromatography. [b] Yield of crude product.

peptides from starting peptides that are poorly soluble in methylene chloride. The Sto(2-DMS) peptides also are more soluble in organic solvents than the corresponding statine peptides. The 3-^{13}C-labeled Sto analogues of **3**, **14**, and **15** have been synthesized from [1-^{13}C]-L-leucine (99% C-13 enriched) for pepsin–inhibitor binding studies monitored by ^{13}C NMR.[11]

Experimental Section

Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Proton nuclear magnetic resonance spectra were recorded at 270 MHz on a Fourier transform quadrature phase detection spectrometer with a Bruker Instruments magnet and probe and a Nicolet 1180 computer. Chemical shifts were reported as δ units (ppm) relative to tetramethylsilane as internal standard.

TLC was performed on 0.25-mm thick silica gel plates (E. Merck, silica gel 60-F-254). TLC R_f's are reported for 1:9 CH_3OH–$CHCl_3$. For column chromatography, Brinkman silica gel 60 70–270 mesh was used. Compounds were visualized on the plates by reactions with: ninhydrin, chlorox–o-tolidine, 5% phosphomolybdic acid in ethanol, iodine, and ultraviolet light. All compounds appeared as a single spot on TLC. Microanalyses were performed by Galbraith Lab., Knoxville, TN.

General Procedures. A. Me_2SO Oxidations. Reactions were conducted on 0.1–0.8 mmol of peptide. The peptide was dissolved in a minimum amount of Me_2SO (0.25–3.0 mL), and 12 equiv of triethylamine were added. The stirred mixture was warmed to 35–40 °C and 5 equiv of solid sulfur trioxide pyridine complex (Aldrich, technical grade) were added. The yellow orange solution was stirred at 35–40 °C and monitored by TLC. (No reaction was observed at room temperature.) Reactions were generally complete within 1 h. The reaction mixture was partitioned between ethyl acetate and saturated aqueous $KHSO_4$. The organic phase was separated and washed two times with saturated $KHSO_4$, three times with saturated $NaHCO_3$, once with water, and finally once with saturated NaCl. The organic phase was dried ($MgSO_4$), filtered, concentrated in vacuo, and pumped to constant weight. Crude products were obtained in nearly quantitative yield (90–97%) and were pure enough to use synthetically without further purification. Analytically pure samples were obtained by chromatography on silica gel, eluting with CH_3OH in $CHCl_3$ systems.

B. Deprotection of Boc Sulfonium Ylides. To the Boc sulfonium ylide peptides was added a large excess of dry 4 N HCl in dioxane. The solution was allowed to stir for 45 min at room temperature. The solvent was removed in vacuo, and the residue was triturated with ether followed by concentration of the resulting mixture several times to remove residual dioxane. The resulting residue was pumped to constant weight over KOH and P_2O_5 to furnish the amine hydrochlorides, which were used without further purification.

C. N-Acylation of Sulfonium Ylide Peptides. The hydrochloride salts of deprotected peptides were dissolved in a minimum amount of CH_2Cl_2 (peptides **4**, **11**) or DMF (peptide **10**), and 1.1 equiv of triethylamine and 0.1 equiv of 4-(dimethylamino)pyridine were added. The solution was cooled in an ice bath, and 2.0 equiv of acetic anhydride (peptide **10**) or 5.0 equiv of isovaleric anhydride (peptides **4**, **11**) were added with stirring. The ice bath was removed, and the solutions were maintained at pH 8 by addition of small amounts of triethylamine. The reactions were monitored by TLC and were usually complete after approximately 1 h at room temperature. Normal workup furnished the N-acylated products in a nearly pure form. Analytical samples were obtained after column chromatography on silica gel, eluting with 2% CH_3OH in $CHCl_3$ (v/v).

D. Reduction of Sulfonium Ylides with Zinc in Acetic Acid. Zinc dust (Mallinckrodt, AR grade) was activated by washing several times in turn with 5% aqueous HCl, water, methanol, and ether and then dried. Reactions were generally conducted on 0.006–0.4 mmol of peptide. The peptide was dissolved in glacial HOAc (0.02 mmol/mL) and heated on an oil bath to 70–75 °C. Zinc dust (70 mmol/mmol peptide) was added, and the suspension was vigorously stirred at 70–75 °C for 1.5 h. The suspension was filtered and the solid was washed with small portions of acetic acid and ethyl acetate. Water was added to the filtrate, and the filtrate was neutralized by careful addition of solid potassium carbonate. The neutralized filtrate was extracted with portions of ethyl acetate, and the combined organic phase was washed several times each with saturated $NaHCO_3$ and saturated NaCl. The organic phase was dried ($MgSO_4$), filtered, concentrated in vacuo, and pumped to constant weight. Yields of crude products ranged from 93–100%. These products showed only traces of impurities by TLC. Analytical samples were obtained by silica gel chromatography, eluting with CH_3OH in $CHCl_3$. Column chromatography provided better product recovery than preparative-layer chromatography.

[*N*-(*tert*-Butyloxycarbonyl)-(*S*)-4-amino-6-methyl-2-(dimethylsulfonio)-3-oxoheptanoyl]-L-alanine Isoamylamide (10). The title compound was prepared from **6** or **7** by general procedure A: R_f 0.58; NMR ($CDCl_3$) δ 0.80–1.07 (m, 12 H), 1.23–1.75 (m, 18 H, includes 1.45 (s, 9 H), 3.05 (s, 6 H), 3.16 (quintet, 2 H, $J \simeq 6$ Hz), 4.39 (quintet, $J \simeq 7.5$ Hz), 4.97 (q, 1 H, $J \simeq 7.5$ Hz), 5.17 (d, 1 H, $J \simeq 8$ Hz) 6.53 (s, 1 H), 9.93 (d, 1 H, $J \simeq 7.5$ Hz). Anal. Calcd for $C_{23}H_{43}N_3O_5S$: C, 58.32; H, 9.15; N, 8.87. Found: C, 58.11; H, 9.06; N, 8.88.

***N*-(*tert*-Butyloxycarbonyl)-L-valyl-[(*S*)-4-amino-6-methyl-2-(dimethylsulfonio)-3-oxoheptanoyl]-L-alanine Isoamylamide (4).** The title compound was prepared from **1** by general procedure A: R_f 0.53; NMR ($CDCl_3$) δ 0.82–1.04 (m, 18 H), 1.30–1.66 (m, 18 H, includes 1.46 (s, 9 H)), 2.14 (m, 1 H), 3.05 (s, 6 H), 3.24 (m, 2 H), 3.92 (br, 1 H), 4.39 (quintet, 1 H, $J \simeq 7$ Hz), 4.96 (d, 1 H, $J \simeq 8$ Hz), 5.29 (q, 1 H, $J \simeq 7$ Hz), 6.56 (d, 2 H, $J \simeq 7$ Hz), 9.88 (d, 1 H, $J \simeq 7$ Hz). Anal. Calcd for $C_{28}H_{52}N_4O_6S$: C, 58.71; H, 9.15; N, 9.78. Found: C, 58.68; H, 9.38; N, 9.71.

***N*-(*tert*-Butyloxycarbonyl)-L-valyl-L-valyl-[(*S*)-4-amino-6-methyl-2-(dimethylsulfonio)-3-oxoheptanoyl]-L-alanine Isoamylamide (11).** The title compound was prepared from **8** or **9** by general procedure A: R_f 0.50; NMR ($CDCl_3$) δ 0.84–1.02 (m, 24 H), 1.22–1.75 (m, 18 H, includes 1.46 (s, 9 H)), 2.14, (m, 2 H), 3.04 (s, 3 H), 3.05 (s, 3 H), 3.24 (m, 2 H), 3.87 (m, 1 H), 4.24 (m, 1 H), 4.40 (quintet, 1 H, $J \simeq 7$ Hz), 5.03 (d, 1 H, $J \simeq 7$ Hz), 5.26 (q, 1 H, $J \simeq 7$ Hz), 6.46–6.64 (m, 3 H, includes 6.50 (d, 1 H, $J \simeq 7$ Hz)), 9.87 (d, 1 H, $J \simeq 7$ Hz).

(11) Rich, D. H.; Bernatowicz, M. S.; Schmidt, P. G. *J. Am. Chem. Soc.* **1982**, *104*, 3535–3536.

N-Acetyl-[(S)-4-amino-6-methyl-2-(dimethylsulfonio)-3-oxoheptanoyl]-L-alanine Isoamylamide (12). The title compound was prepared from the hydrochloride salt of deprotected **10** prepared by general procedure B. The hydrochloride was acylated by acetic anhydride as described in general procedure C: R_f 0.38; NMR ($CDCl_3$) δ 0.80–1.05 (m, 12 H), 1.24–1.70 (m, 9 H, includes 1.44 (d)), 2.00 (s, 3 H), 3.06 (s, 6 H), 3.25 (m, 2 H), 4.38 (t, 1 H, $J \simeq 7$ Hz), 5.29 (q, 1 H, $J \simeq 8$ Hz), 6.54 (s, 1 H), 9.90 (d, 1 H, $J \simeq 7$ Hz). Anal. Calcd for $C_{20}H_{37}N_3O_4S$: C, 57.80; H, 8.97; N, 10.11. Found: C, 57.67; H, 9.09; N, 9.91.

N-Isovaleryl-L-valyl-[(S)-4-amino-6-methyl-2-(dimethylsulfonio)-3-oxoheptanoyl]-L-alanine Isoamylamide (5). The title compound was prepared from the hydrochloride salt of deprotected **4**, prepared by general procedure B. The hydrochloride was acylated by isovaleric anhydride as described in general procedure C: R_f 0.44; NMR ($CDCl_3$) δ 0.82–1.04 (m, 24 H), 1.25–1.90 (m, 10 H, includes 1.42 (d, 3 H, $J \simeq 7$ Hz)), 2.00–2.20 (m, 3 H), 3.06 (s, 6 H), 3.18–3.30 (m, 2 H), 4.22–4.32 (m, 1 H), 4.41 (q, 1 H, $J \simeq 7$ Hz), 5.25 (q, 1 H, $J \simeq 7$ Hz), 5.96 d, 1 H, $J \simeq 8$ Hz), 6.56 (br, 1 H), 9.86 (d, 1 H, $J \simeq 7$ H). Anal. Calcd for $C_{28}H_{52}N_4O_5S$: C, 60.40; H, 9.41; N, 10.06. Found: C, 60.57; H, 9.21; N, 9.90.

N-Isovaleryl-L-valyl-L-valyl-[(S)-4-amino-6-methyl-2-(dimethylsulfonio)-3-oxoheptanoyl]-L-alanine Isoamylamide (13). The title compound was prepared from the hydrochloride salt of deprotected **11**, prepared by general procedure B. The hydrochloride was acylated by isovaleric anhydride as described in general procedure C: R_f 0.39; NMR ($CDCl_3$) δ 0.82–1.00 (m, 30 H), 1.22–1.62 (m, 10 H, includes 1.42 (d, 3 H, J $\simeq$ 7 Hz)), 2.02–2.19 (m, 4 H), 3.05 (s, 6 H), 3.25 (m, 2 H), 4.20 (m, 2 H), 4.40 (quintet, 1 H, $J \simeq 7$ Hz), 5.27 (m, 1 H), 6.14 (d, 1 H, $J \simeq 8$ Hz), 6.46–6.63 (m, 3 H), 9.88 (d, 1 H, $J \simeq 7$ Hz). Anal. Calcd for $C_{33}H_{61}N_5O_6S$: C, 60.43; H, 9.37; N, 10.68. Found: C, 60.19; H, 9.47; N, 10.52.

N-Acetyl-[(S)-4-amino-6-methyl-3-oxoheptanoyl]-L-alanine Isoamylamide (14). The title compound was prepared from **12** by general procedure D: R_f 0.29; NMR ($CDCl_3$) δ 0.84–0.99 (m, 12 H), 1.34–1.50 (m, 7 H, includes 1.40 (d, 3 H, $J \simeq 7$ Hz)), 1.52–1.74 (m, 2 H), 2.05 (s, 3 H), 3.20–3.32 (m, 2 H), 3.50 (dd, 2 H, $J_{AB} \simeq 15$ Hz), 4.41 (quintet, 1 H, $J \simeq 7$ Hz), 4.52 (m, 1 H), 6.07 (d, 1 H, $J \simeq 7$ Hz), 6.42 (s, 1 H), 6.90 (d, 1 H, $J \simeq 7$ Hz). Anal. Calcd for $C_{18}H_{33}N_3O_4$: C, 60.82; H, 9.36; N, 11.82. Found: C, 60.96; H, 9.45; N, 11.68.

N-Isovaleryl-L-valyl-[(S)-4-amino-6-methyl-3-oxoheptanoyl]-L-alanine Isoamylamide (3). The title compound was prepared from **5** by general procedure D. This material was identical by NMR, TLC, and melting point with the material prepared previously[1] by a different route.

N-Isovaleryl-L-valyl-L-valyl-[(S)-4-amino-6-methyl-3-oxoheptanoyl]-L-alanine Isoamylamide (15). The title compound was prepared from **13** by general procedure D. The product was isolated as a white crystalline solid: mp 213–214 °C (uncorrected); R_f 0.49; NMR (MeOH-d_4) δ 0.80–1.04 (m, 30 H), 1.27–1.46 (m, 9 H, includes 1.34 (d, 3 H, $J \simeq 8$ Hz), 1.52–1.73 (m, 3 H), 1.97–2.16 (m, 4 H), 3.23 (m, 2 H, partially obscured by solvent), 4.17 (d, 2 H, $J \simeq 7$ Hz), 4.31 (q, 1 H, $J \simeq 7$ Hz), 4.41 (m, 1 H). Anal. Calcd for $C_{31}H_{57}N_5O_6$: C, 62.49; H, 9.64; N, 11.75. Found: C, 62.17; H, 9.74; N, 11.56.

Acknowledgment. We are grateful to P. G. Schmidt (Oklahoma Medical Research Foundation) for running the 270-MHz ^1H NMR spectra of reported peptides. This work was supported by a grant from the National Institutes of Health (No. AM 20100).

Registry No. 1, 72155-63-6; 3, 81485-13-4; 4, 85702-25-6; 4 deprotected hydrochloride, 85702-33-6; 5, 81875-70-9; 6, 77658-87-8; 7, 77699-22-0; 8, 85719-05-7; 9, 81921-68-8; 10, 85702-27-8; 10 deprotected hydrochloride, 85702-34-7; 11, 85702-28-9; 11 deprotected hydrochloride, 85702-35-8; 12, 85702-29-0; 13, 85702-30-3; 14, 85702-31-4; 15, 85702-32-5; isovaleric anhydride, 1468-39-9; sulfur trioxide–pyridine complex, 26412-87-3.

Total Synthesis of Dioxane Analogues Related to Zoapatanol

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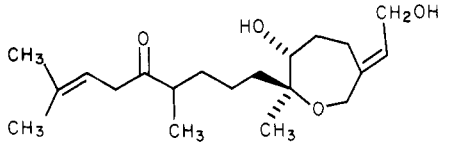
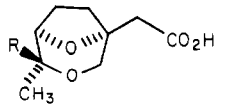
The zoapatanol-related dioxane analogues [(2*RS*,5*SR*)-5-(5-hydroxy-4,8-dimethyl-7-nonen-1-yl)-5-methyl-1,4-dioxan-2-yl]acetic acid (**3a**) and the corresponding 8-nonen-1-yl isomer (**3b**) have been synthesized. The dioxane ring is formed by a regioselective transacetalization and subsequent ring closure under basic conditions. The configurational assignments to the dioxane reaction products have been established by the separation and spectral investigation of a single epimer, **16a**.

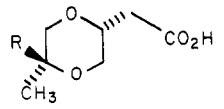
The isolation and structural elucidation of a novel oxepane diterpenoid, zoapatanol (**1**), from the Mexican plant



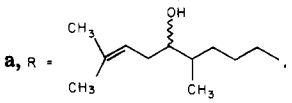
1

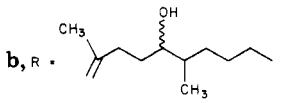


2a,b



3a,b





zoapatle has been reported.[1] During the course of a structure–activity relationship study, bicyclic compounds **2a** and **2b**[2] with similar pharmacological profiles[1-4] were obtained. As a continuation of our interest in this series, the structurally simplified 1,4-dioxane analogues **3a** and **3b** were synthesized. A recent publication by Wani et al.[3] describing the preparation of compounds within this series by a totally different synthetic route prompts this report of our results.

In light of the total synthesis of **2a** and **2b**,[4] a synthetic

(1) (a) Levine, S. D.; Adams, R. E.; Chen, R.; Cotter, M. L.; Hirsch, A. F.; Kane, V. V.; Kanojia, R. M.; Shaw, C.; Wachter, M. P.; Chin, E.; Huettemann, R.; Ostrowski, P.; Mateos, J. L.; Noriega, L.; Guzman, A.; Mijarez, A.; Tovar, L. *J. Am. Chem. Soc.* **1979**, *101*, 3404. (b) Kanojia, R. M.; Wachter, M. P.; Levine, S. D.; Adams, R. E.; Chen, R.; Chin, E.; Cotter, M. L.; Hirsch, A. F.; Huettemann, R.; Kane, V. V.; Ostrowski, P.; Shaw, C. J.; Mateos, J. L.; Noriega, L; Guzman, A.; Mijarez, A.; Tovar, L.; Shefter. E. *J. Org. Chem.* **1982**, *47*, 1310.

(2) Kanojia, R. M.; Wachter, M. P.; Chen, R. H. K. U.S. Patent 4 102 895, 1978.

(3) Wani, M. C.; Vishnuvajjala, B. R.; Swain, W. E.; Rector, D. H.; Cook, C. E.; Petrow, V.; Reel, J. R.; Allen, K. M.; Levine, S. G. *J. Med. Chem.* **1983**, *26*, 426.

(4) Hajos, Z. G. U.S. Patent 4 284 565, 1981.

0022-3263/83/1948-2001$01.50/0