An aliquot, 3.0 g, of the oil was dissolved in 25 mL of ethyl ether, filtered, and concentrated to 12 mL. This solution was stirred while cooling at about -20 °C for crystallization. Filtration gave 1.86 g: mp 89-92 °C; ^{13}C NMR δ 149.18, 148.96, 145.75, 137.13, 134.50, 128.39 (2C), 127.09, 126.54 (2C), 123.67, 94.17, 69.03, 57.06, 55.07, 41.02, 22.18.

Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.18; H, 7.34; N, 9.19.

The hydrochloride was prepared by dissolving some of the oil in acetone and adding an equivalent of hydrochloric acid in acetone with stirring at room temperature and then cooling with stirring at about -20 °C. The crystals were filtered and dried: mp 196-199 °C; α^{25}_{365} -41.0° (c 1, H_2O). HPLC analysis confirmed this to be the pure *R,S* diastereomer.

Anal. Calcd for $C_{18}H_{23}N_2O_2Cl$: C, 64.57; H, 6.92; N, 8.37; Cl, 10.59. Found: C, 64.63; H, 7.00; N, 8.17; Cl, 10.58.

(*R*)-α-(1,3-Dioxan-5-yl)-3-pyridinemethanamine Dihydrochloride (5). To a round-bottomed flask was added 4.44 g (0.0149 mol) of **4**, 98 mL of ethanol, and 80 mL of cyclohexene. After cooling in an ice bath, 2.48 mL of hydrochloric acid and a slurry of 1.33 g of 10% Pd-C in 16.25 mL of water were added. With stirring, the mixture was heated at reflux for 20 h. The reaction mixture was filtered while hot and the catalyst was washed with hot ethanol. The filtrate was concentrated to about one-half volume and cooled to give 3.13 g of **5**; mp 232-236 °C dec. Further concentration gave an additional 0.35 g; mp 230-232 °C dec; ^1H NMR (H_2O) δ 9.01 (s, 1 H), 8.93 (d, 1 H), 8.78 (d, 1 H), 8.25 (m, 1 H), 5.12 (d, 1 H), 4.98 (d, 1 H), 4.88 (d, 1 H), 4.23 (m, 1 H), 4.17 (m, 1 H), 3.89 (m, 1 H), 3.62 (m, 1 H), 2.49 (m, 1 H). Anal. Calcd for $C_{10}H_{16}N_2O_2Cl_2$: C, 44.96; H, 6.04; N, 10.49; Cl, 26.54. Found: C, 44.72; H, 6.04; N, 10.76; Cl, 26.76.

(R)-(-)-α-(1,3-Dioxan-5-yl)-*N*,*N*-dimethyl-3-pyridinemethanamine Hydrochloride (1). In a round-bottomed flask was placed 3.55 g (0.0133 mol) of the dihydrochloride **5**, 25 mL of methanol, 5 mL of water, and 2.5 mL of ammonium hydroxide. Upon solution, the volatile solvents were removed under vacuum. To the residue was added 30 mL of formalin (37%) and 30 mL of formic acid. The solution was heated on a steambath for 18 h. Most of the volatile solvents were removed under vacuum and excess water and methylene chloride were added. Then 10% potassium carbonate solution was added with stirring until pH ~9. This mixture was extracted with 3 × 100 mL of methylene chloride. The combined organic layers were washed with brine, dried, and evaporated, giving 2.65 g of an oil. The NMR spectrum of this oil was identical with a previous sample.[1] The monohydrochloride was prepared by dissolving the oil in 100 mL of acetone, and with stirring a solution of 0.99 mL (0.12 mol) of hydrochloric acid in 20 mL of acetone was added dropwise. The crystals were filtered and washed with cold acetone to give 2.7 g, mp 229-232 °C dec. After recrystallization from ethanol there was obtained 2.3 g: mp 234-236 °C dec; α^{25}_{365} -16.7° (c 1, H_2O).

The free base was liberated from a sample and the NMR was run with a chiral shift reagent, $Eu(tfc)_3$, added. The six-proton *N*-dimethyl singlet showed no evidence of the *S* enantiomer. This assay was found to detect the other enantiomer at the 1% level.

Debenzylation-Dimethylation to 1. To a round-bottomed flask were added 13.4 g (0.045 mol) of **4**, 98 mL of formic acid (90%), and 42 mL of formalin. The solution was heated at reflux for 24 h. The solution was cooled to room temperature and 80 mL of water was added. This mixture was extracted with 3 × 25 mL of chloroform, and the wash was discarded. To the aqueous solution was added sufficient ammonium hydroxide with cooling to adjust the pH to 9. This solution was extracted with 3 × 60 mL of methylene chloride. The organic solution was washed with brine, dried, and evaporated, leaving 8.15 g of an oil. Both TLC and NMR showed good agreement with the free base of 1.

This oil was dissolved in 85 mL of acetone, and with stirring a solution of 3.1 mL of hydrochloric acid in 15 mL of acetone was added. This mixture was stirred at room temperature for 0.5 h and in an ice bath for 1 h. The mixture was filtered and the crystals were dried to give 8.5 g: mp 223-226.5 °C dec. Recrystallization from ethanol gave 6.6 g: mp 236-238 °C dec; α^{D}_{365} -16.6° (c, 1, H_2O).

Acknowledgment. We acknowledge the contributions of our colleagues in microanalysis and physical chemistry who obtained the data used in this paper. The assistance of Mr. J. W. Paschal in the generation and interpretation of some of the NMR data was especially valuable.

Registry No. 1·HCl, 69494-04-8; **1**, 62904-71-6; **2**, 85727-04-4; **3**, 94844-55-0; **4**, 94844-56-1; **4**·HCl, 94844-57-2; **4** *S,S* isomer, 94844-58-3; **5**, 94903-53-4; 3-acetylpyridine, 350-03-8; paraformaldehyde, 30525-89-4; *l*-(-)-α-methylbenzylamine, 2627-86-3.

A Simple and Convenient Method for the Preparation of Ketomethylene Peptide Analogues

John S. McMurray and Douglas F. Dyckes*

Department of Chemistry, University of Houston, Houston, Texas 77004

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Ketomethylene peptide analogues are peptide isosteres in which the -NH- group of a particular amide bond has been replaced by a methylene group. Unlike a peptide bond, the ketomethylene group is stable to enzyme-catalyzed hydrolysis, thus giving these molecules great potential as probes of protease enzyme mechanisms and active-site interactions. Ketomethylene analogues are finding increasing use both in this area[1-4] and in clinical applications.[5-8] In the course of our studies of ketomethylene compounds as serine protease inhibitors, to be reported elsewhere, we have synthesized a series of methyl 3-peptidylpropionates (ketomethyleneglycine analogues) and peptidylmethanes (peptide methyl ketones) (Table I). We describe here a simple, general procedure for the preparation of ketomethylene analogues in which protected peptides can be converted directly to carboxy terminal ketones.

Our new synthesis of ketomethylene analogues is based on a modification of the Dakin-West reaction[9] developed by Steglich and co-workers.[10-12] The precursor, a suitably protected N^{α}-acyl amino acid, dipeptide, or tripeptide (or presumably a larger peptide if desired) possessing a free terminal carboxyl function, is heated at 40-50 °C with triethylamine (Et_3N), 4-(dimethylamino)pyridine (DMAP), and the appropriate acid anhydride. Peptidylpropionates are prepared by using the symmetric anhydride of monomethyl succinate (MMS) (**10a**) whereas the corresponding methyl ketones are prepared by using acetic anhydride (**10b**). The benzyloxycarbonyl (Z) side-chain protection of lysine and the α-*tert*-butyloxycarbonyl (Boc) protecting

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Table I. Yields of Ketomethylene and Methyl Ketone Peptide Derivatives

peptide ketone[a]	yield, %	mp, °C	procedure[b]
1. Bz-AlaCH$_2$CH$_2$CO$_2$CH$_3$	70	72.5–74.5	A
2. Bz-Lys(Z)CH$_2$CH$_2$CO$_2$CH$_3$	90	79.0–81.5	A
3. Boc-Ala-Lys(Z)CH$_3$	85	oil	B
4. Boc-Ala-Lys(Z)-CH$_2$CH$_2$CO$_2$CH$_3$	72	oil	B
5. Boc-Lys(Z)-Ala-Lys(Z)CH$_3$	76	110.0–113.0	C
6. Boc-Lys(Z)-Ala-Lys(Z)-CH$_2$CH$_2$CO$_2$CH$_3$	70	72 (dec)	C
7. Ac-PheCH$_2$CH$_2$CO$_2$CH$_3$	70	81.0–83.0	B

[a] The bond between the methylene or methyl group and the carbonyl group of the amino acid is nonhydrolyzable (13, Scheme I). Therefore it is not depicted with a hyphen. [b] See Experimental Section.

Table II. Elemental Analysis of the Peptide Ketones

peptide ketone	formula	anal., % (a) calcd, (b) found	C	H	N
1. Bz-AlaCH$_2$CH$_2$CO$_2$CH$_3$	$C_{14}H_{17}NO_4$	(a)	63.86	6.50	5.31
		(b)	64.14	6.55	5.32
2. Bz-Lys(Z)-CH$_2$CH$_2$CO$_2$CH$_3$	$C_{25}H_{30}N_2O_6$	(a)	66.06	6.65	6.16
		(b)	65.80	6.85	5.98
3. Boc-Ala-Lys(Z)CH$_3$	$C_{23}H_{35}N_3O_6$	(a)	61.45	7.84	9.34
		(b)	60.84	7.69	9.07
4. Boc-Ala-Lys(Z)-CH$_2$CH$_2$CO$_2$CH$_3$	$C_{26}H_{39}N_3O_8$	(a)	59.86	7.53	8.05
		(b)	59.49	7.39	7.81
5. Boc-Lys(Z)-Ala-Lys(Z)CH$_3$	$C_{37}H_{53}N_5O_9$	(a)	62.42	7.50	9.83
		(b)	62.75	7.54	9.62
6. Boc-Lys(Z)-Ala-Lys(Z)-CH$_2$CH$_2$CO$_2$CH$_3$	$C_{40}H_{57}N_5O_{11}$	(a)	61.28	7.32	8.93
		(b)	61.22	7.32	8.93
7. Ac-PheCH$_2$CH$_2$CO$_2$CH$_3$	$C_{15}H_{19}NO_4$	(a)	64.96	6.90	5.04
		(b)	65.05	7.01	5.03

group for di- and tripeptides are stable to the conditions reported here as is the methyl ester moeity of MMS, so this procedure should be applicable to a wide variety of protected peptides. One notable exception is any peptide protected with a base-labile protecting group.

Natarajan et al.[6] and Meyer et al.[7] have each synthesized methyl 3-(N^{α}-benzoylphenylalaninyl)propionate (Bz-PheCH$_2$CH$_2$CO$_2$CH$_3$), an angiotensin converting enzyme inhibitor precursor, by a different modification of the Dakin–West procecure.[10,11] These syntheses both utilize the isolated 2-phenyl-4-benzyl-5(4*H*)-oxazolone (**11a**), prepared from benzoylphenylalanine, which is acylated with 3-carbomethoxypropionyl chloride and then decarboxylated. Our procedure (Scheme I) is capable of converting N^{α}-benzoyl amino acids directly to their ketopropionates in good yields in a single preparative step. The elaboration of larger peptides from the ketomethylenes of α-benzoylated amino acids is impractical as a general scheme, however. Removal of the benzoyl group requires extreme conditions which normally also remove side-chain protection and can also cause side-chain modification. Amino acids with N^{α}-urethane type protecting groups have been demonstrated to form isolable 2-alkoxy-5(4*H*)-oxazolones (11: R^1 = O-*t*-Bu or OCH$_2$Ph, R^2 = amino acid side chain)[13] and in principle might be used in a similar procedure. We have found, however, that these urethane

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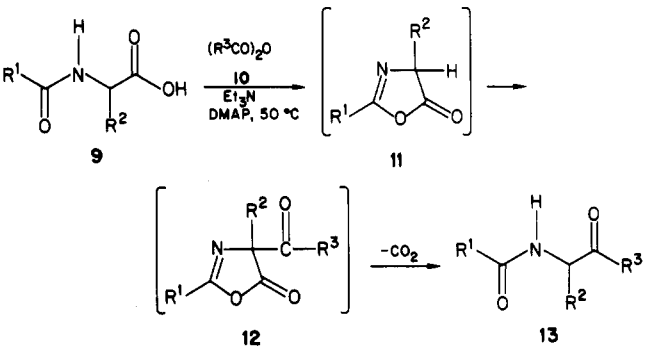
Scheme I



9 11 12 13

9,11a, R^1 = Ph; R^2 = benzyl
b, R^1 = Ph; R^2 = amino acid side chain
c, R^1 = 1-(acylamino)alkyl; R^2 = amino acid side chain
10a, R^3 = CH$_2$CH$_2$CO$_2$CH$_3$
b, R^3 = CH$_3$
12,13a, R^1 = Ph; R^2 = benzyl; R^3 = CH$_2$CH$_2$CO$_2$CH$_3$
b, R^1 = Ph; R^2 = amino acid side chain; R^3 = CH$_2$CH$_2$CO$_2$CH$_3$ or CH$_3$
c, R^1 = 1-(acylamino)alkyl; R^2 = amino acid side chain, R^3 = CH$_2$CH$_2$CO$_2$CH$_3$ or CH$_3$

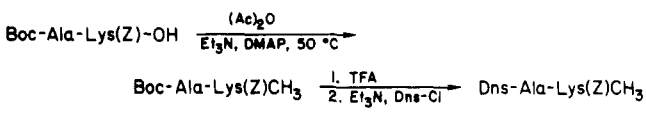
derivatives decompose to a large extent under Dakin–West conditions and give extremely poor yields. Thus a more logical route would seem to be to avoid protection problems by using peptides themselves as Dakin–West substrates when longer chain ketomethylene compounds are required.

Dipeptides will react to form C-terminal ketones under the conditions reported here, but not as readily as do α-benzoyl amino acids. The benzene ring of an N^{α}-benzoyl amino acid activates the intermediate 2-phenyl-5(4*H*)-oxazolone (**11b**) so that it can be acylated and decarboxylated readily at room temperature. With a 2-alkyl-5-(4*H*)-oxazolone (the intermediate which results from C-terminal cyclization of a peptide) (**11c**), heat is required to complete the acylation and decarboxylation (Scheme I). With gentle heating the reaction proceeds smoothly and yields are satisfactory.

N-Terminal deprotection of the dipeptidyl ketones Boc-Ala-Lys(Z)CH$_3$ (**3**) and Boc-Ala-Lys(Z)-CH$_2$CH$_2$CO$_2$CH$_3$ (**4**), whether with cold trifluoroacetic acid or 4 N HCl in methanol was unsatisfactory, however. The many side products generated during deprotection prevented the efficient conversion of these precursors to corresponding tripeptide derivatives (overall yields were less than 20%). For this reason the application of the modified Dakin–West procedure directly to larger peptides was explored. We have found that tripeptides will also form the requisite ketones in satisfactory yields but that extra amounts of the acid anhydride and triethylamine are required. A small amount of pyridine is also necessary to effect solution of the larger tripeptide. The N-terminal Boc protecting groups of these larger ketones can be removed cleanly and in good yield with cold trifluoroacetic acid. The products are also stable to the hydrogenolytic conditions (H_2 in CH$_3$OH using palladium/carbon as the catalyst) employed for the removal of the Z protecting group.

Although the products in Table I are chromatographically pure in the systems employed, it is assumed that the amino acid ketones are fully racemic mixtures of enantiomers and the peptide ketones are mixtures of diastereomers in which the C-terminal lysines are fully racemic. Examination of the mechanism of the Dakin–West reaction[14] and model building suggest no reason why either the

Scheme II



substitution of the acyl group for the C-4 proton of oxazolone **11** to give **12** or the final decarboxylation step should be stereoselective. Thus, racemization at the terminal α-carbon is expected. Separation of the resulting diastereomers in the case of di- and tripeptide ketones, however, has not been observed in any of our chromatography experiments. Further evidence that racemization does indeed occur was obtained by comparison of the proton NMR spectra of Boc-Ala-Lys(Z)CH_3, **3**, and [dansylalaninyl-ϵ-(benzyloxycarbonyl)lysinyl]methane[15] (Dns-Ala-Lys(Z)CH_3, **8**), which was synthesized as shown in Scheme II.[16] The ketomethyl peak of **3** appears as a singlet at δ 2.20, integrating for three protons. The corresponding methyl resonance of **8** is split into a doublet at δ 2.05 and 1.95, with each peak of equal intensity and the pair of peaks integrating for a total of three protons. This is interpreted as arising from the two different configurations about the lysine C^α in **8**. The ketomethyl groups of the two diastereomers experience two different degrees of magnetic anisotropy from the naphthyl rings of the dansyl group. Our protease inhibitor work (to be reported elsewhere) is done using diastereomeric mixtures of peptide ketones.

Experimental Section

All amino acid derivatives and peptides, with the exception of Boc-Lys(Z)-OH which was purchased from Peninsula Laboratories, Inc., were prepared by using classical coupling techniques. MMS, DMAP, and 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDC) were purchased from Aldrich Chemical Co. The MMS and DMAP were recrystallized before use and the EDC was used as purchased. Et_3N and pyridine were distilled prior to use. Reagent grade solvents were used without further purification. Melting points were taken on a Thomas-Hoover Uni-Melt apparatus and are uncorrected. NMR spectra were taken on Varian T60, Varian FT-80A, and Nicolet NT300WB spectrometers. TLC was performed on pre-coated silica gel plates (EM Reagents 5761) using the following solvent systems: A, chloroform/methanol (9:1); B, chloroform/methanol/acetic acid (17:2:1); and C, chloroform/acetone (7:1). The chromatograms were evaluated by using a sequence of three visualization techniques on the same plate: (1) irradiation at 254 nm; (2) spraying with ninhydrin (1% in acetone) and heating at 100 °C for 5 min; and (3) exposing the plate to chlorine vapor for 3–10 s and after 5 min spraying with 1% starch–1% potassium iodide solution. All final products showed one spot on TLC.

The compounds listed in Table I were prepared by three variations of the same basic procedure. One example of each variation, for N^α-benzoyl amino acids, for dipeptides, and for tripeptides, is given below. For the synthesis of amino acid or peptidyl propionates the freshly prepared symmetric anhydride of MMS was used. The corresponding methyl ketones are prepared by using acetic anhydride.

Preparation of the Symmetric Anhydride of Monomethyl Succinate (10a). MMS (1.16 g, 8.8 mmol) was dissolved in 20 mL of CH_2Cl_2 and 0.843 g of EDC (4.4 mmol) was added. The reaction was stirred for 20 min and then extracted with 2 × 5 mL of ice-cold water, 5 mL of ice-cold 5% $NaHCO_3$, and 5 mL of ice-cold water. The CH_2Cl_2 solution was dried over $MgSO_4$ and filtered into the reaction flask for the subsequent Dakin–West reaction, and the solvent was evaporated in vacuo.

Procedure A. For N^α-Benzoyl Amino Acids.[12] Preparation of Methyl 3-[N^α-Benzoyl-N^ϵ-(benzyloxycarbonyl)-lysinyl]propionate (2). Bz-Lys(Z)-OH (0.769 g, 2.00 mmol) was added to 2.2 mmol of the freshly prepared **10a**. DMAP (0.010 g, 0.084 mmol) and Et_3N (0.42 mL, 3.00 mmol) were added, and the reaction was stirred. After 1 min, the reaction warmed slightly and vigorous evolution of gas was observed. The reaction was stirred for 1 h at room temperature at which time 1.5 mL of glacial acetic acid was added. After an additional 30 min of stirring, the Et_3N and acetic acid were removed in vacuo. The oily residue was stirred with 20 mL of 5% $NaHCO_3$ for 30 min to hydrolyze any remaining anhydride, extracted into ethyl acetate, and washed with 0.1 N acetic acid. The ethyl acetate solution was dried over $MgSO_4$, filtered, and evaporated, leaving behind 0.867 g of an oily residue (1.91 mmol, 95% crude yield). The residue was purified by chromatography (40 g of silica gel, chloroform/acetone 7:1), yielding 0.82 g of a white solid, **2** (1.80 mmol, 90%): mp 79.0–81.5 °C; NMR δ ($CDCl_3$) 7.00–8.00 (m, 11 H, BzC_6H_5, ZC_6H_5, LysαNH), 4.60–5.40 (m, 4 H, ZCH_2 LysαCH, LysϵNH), 3.65 (s, 3 H, OCH_3), 3.00–3.37 (m, 2 H, LysϵCH_2), 2.40–3.00 (m, 4 H, $COCH_2CH_2CO$), 1.10–2.10 (m, 6 H, LysβCH_2, γCH_2, δCH_2); TLC R_f 0.66 (B), 0.34 (C).

Procedure B. For Dipeptides. Preparation of Methyl 3-[N^α-(*tert*-Butyloxycarbonyl)alaninyl-N^ϵ-(benzyloxycarbonyl)lysinyl]propionate (4). Boc-Ala-Lys(Z)-OH (0.786 g, 1.74 mmol) was added to 3.8 mmol of **10a**. Et_3N (0.35 mL, 2.61 mmol) was added followed by 9 mg of DMAP (0.073 mmol). The mixture was stirred in a water bath at 50 °C for 1 h. Gas evolution was not as prolific in the case of peptides as it was for N^α-benzoyl amio acids. The Et_3N was evaporated in vacuo, and the residue was stirred with 10 mL of 5% $NaHCO_3$ for 30 min. The product was extracted into ethyl acetate and washed with 0.1 N acetic acid and brine. The ethyl acetate solution was dried over $MgSO_4$, filtered, and evaporated, leaving 0.809 g (88% crude yield) of an oily residue. This was chromatographed as described in method A to give 0.654 g of **4** as a clear oil (1.25 mmol, 72% yield): NMR δ ($CDCl_3$) 7.32 (s, 5 H, Z C_6H_5), 6.90 (d, J = 7.2 Hz, 1 H, LysαNH), 4.95–5.30 (m, 4 H, ZCH_2, AlaαNH, LysϵNH), 4.55 (m, 1 H, LysαCH), 4.14 (m, J = 7.2 Hz, 1 H, AlaαCH), 3.62 (s, 3 H, OCH_3), 3.15 (m, 2 H, LysϵCH_2), 2.40–2.85 (m, 4 H, $COCH_2CH_2CO$), 1.15–1.90 (m, 18 H, $BocCH_3$, AlaβCH_3, LysβCH_2, γCH_2, δCH_2); TLC R_f 0.56 (A), 0.64 (B).

Procedure C. For Tripeptides. Preparation of Methyl 3-[N^α-(*tert*-Butyloxycarbonyl)-N^ϵ-(benzyloxycarbonyl)-lysinylalaninyl-N^ϵ-(benzyloxycarbonyl)lysinyl]propionate (5). Boc-Lys(Z)-Ala-Lys(Z)-OH (0.117 g, 0.164 mmol) was added to 0.986 mmol of **10a**. Et_3N (0.046 mL, 0.329 mmol), 2.0 mg of DMAP (0.016 mmol) and 0.13 mL of pyridine were added, the reaction flask as fitted with a reflux condenser, and the reaction was placed in a 45–50 °C water bath. Some gas evolution was apparent. After being stirred for an hour, 5 mL of $NaHCO_3$ was added and the reaction was stirred for an additional 30 min. The product was extracted into ethyl acetate and washed with 0.1 N acetic acid and brine. The ethyl acetate solution was dried over $MgSO_4$, filtered, and evaporated in vacuo to give a light brown oily residue which was chromatographed on 50 g of silica gel with 2% CH_3OH in $CHCl_3$. The CH_3OH concentration was raised to 4% after the first peak was eluted. The product was evaporated from toluene to give 0.090 g of **5** as a white powder (0.115 mmol, 70%): mp 72 °C dec; NMR δ ($CDCl_3$) 7.33 (s, 10 H, $2ZC_6H_5$), 7.14 (m, 1H, Lys$^3\alpha$NH), 6.78(m, 1 H, Ala$^2\alpha$NH), 5.14–5.70 (m, 3 H, Lys$^1\alpha$NH, Lys$^1\epsilon$NH, Lys$^3\epsilon$NH), 5.01 (m, 4 H, $2ZCH_2$), 4.51 (m, 1 H, Lys$^3\alpha$CH), 4.43 (m, 1 H, Ala$^2\alpha$CH), 4.05 (m, 1 H, Lys$^1\alpha$CH), 3.61 (s, 3 H, OCH_3), 3.16 (m, 4 H, Lys$^1\epsilon CH_2$, Lys$^3\epsilon CH_2$), 2.46–2.85 (m, 4 H, $COCH_2CH_2CO$), 1.25–1.95 (m, 25 H, $BocCH_3$, Lys$^1\beta CH_2$, γCH_2, δCH_2, Lys$^3\beta CH_2$, γCH_2, δCH_2, Ala$^2\beta CH_3$); TLC R_f 0.54 (A), 0.57 (B).

Acknowledgment. We are grateful to the Robert A. Welch Foundation for the financial support of this work

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(15) Dansyl = [(dimethylamino)naphthyl]sulfonyl and is abbreviated Dns.
(16) Dns-Ala-Lys(Z)CH_3 (**8**): mp 121.0–124.5 °C. Anal. Calcd for $C_{30}H_{38}N_4O_6S$: C, 61.84; H, 6.57; N, 9.61; S, 5.50. Found: C, 61.35; H, 6.41; N, 9.54; S, 5.68. NMR δ ($CDCl_3$) 8.20–8.60 (m, 3 H, Dns-naphthyl), 7.10–7.65 (m, 8 H, Dns-naphthyl, ZC_6H_5), 6.84 (d, 1 H, J = 8 Hz, LysαNH), 5.88 (d, 1 H, J = 8 Hz, AlaαNH), 5.10–5.25 (m, 3 H, LysϵNH, ZCH_2), 4.35 (m, 1 H, LysαCH), 3.80 (m, 3 H, J = 8 Hz, AlaαCH), 3.08 (m, 2 H, LysϵCH_2), 2.91 (s, 6 H, $DnsN(CH_3)_2$, 2.05, 1.91 (d, 3 H, $COCH_3$), 1.05–1.65 (m, 9 H, AlaβCH_3, LysβCH_2, LysγCH_2, LysδCH_2); TLC R_f 0.54 (A), 0.14 (C).

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Registry No. 1, 94942-26-4; 2, 94859-79-7; 3, 94859-80-0; 4, 94859-81-1; 5, 94859-82-2; 6, 94859-83-3; 7, 94942-27-5; 8, 94859-84-4; **10a**, 52944-79-3; **10b**, 108-24-7; Bz-Ala-OH, 2198-64-3; Bz-Lys(Z)-OH, 1946-80-1; Boc-Ala-Lys(Z)-OH, 92073-01-3; Boc-Lys(Z)-Ala-Lys(Z)-OH, 94904-24-2; MMS, 3878-55-5.

Stereoselective Synthesis of Octahydro-3-oxospiro[benzofuran-2(3*H*),2′-[2*H*]-pyran] Systems

Mark J. Kurth,* Edward G. Brown, Estelita Hendra, and Hakon Hope

Department of Chemistry, University of California, Davis, Davis, California 95616

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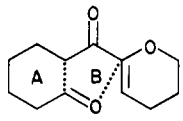
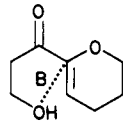
The dioxaspiro functional group is found in numerous structurally and biologically interesting natural products.[1] Phyllanthoside[2,3] and breynolide[4] are two prominent examples which have a common spiro[benzofuran-2-(3*H*),2′-[2*H*]pyran] skeleton. We now report a synthesis of this unique ring system which proceeds in three stereocontrolled steps (see Scheme I) from dihydropyran. In addition, a series of diastereomer interconversions is presented which demonstrate ketal equilibration and unambiguously establish stereochemistry in these dioxaspiro systems.

Two approaches to the target skeleton **3** were investigated. We first envisioned a one-pot acid-catalyzed aldol condensation/spiroketalization procedure for the construction of rings A and B. Unfortunately, all attempts to form this ring system from substrate **1**[5] under a variety of acidic conditions ($TiCl_4$, $SnCl_4$, $BF_3{\cdot}Et_2O$, PTSA) produced complicated reaction mixtures from which neither the starting material or desired spiroketal could be isolated. Similarly, treatment of **2**[6] with a variety of Lewis acids gave none of the desired 1,6-dioxaspiro[4.5]decan-4-one.

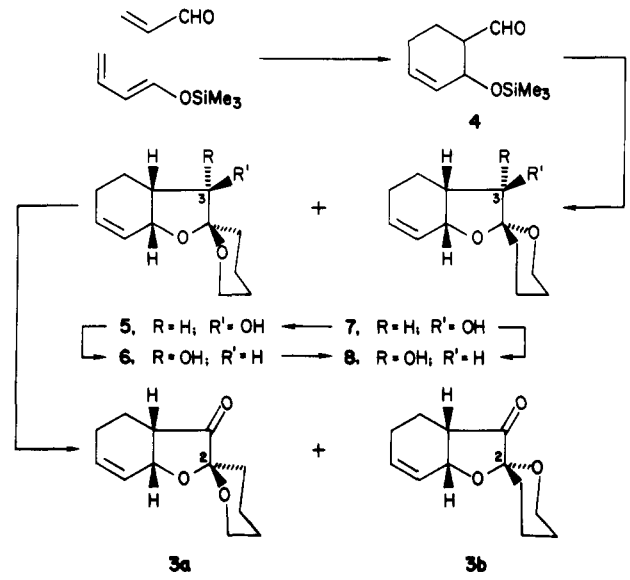


1



2

Scheme I



In light of these results, a stepwise approach to **3** was developed which is delineated in Scheme I. Diels–Alder condensation of acrolein and 1-[(trimethylsilyl)oxy]-1,3-butadiene[7] gave cyclohexenecarboxaldehyde **4** in 88% yield as a 11:1 mixture of cis and trans isomers. In a one-pot operation, this aldehyde mixture was added to a THF solution of 2-lithiodihydropyran,[8] and the resulting solution was treated with 48% hydrofluoric acid to effect concomitant desilylation and spiroketalization. Workup gave four spiro alcohols which were readily separable by MPLC on silica gel (**5**:**6**:**7**:**8** = 2.8:4.6:1.0:1.4; 50% combined yield). Parikh-modified[9] Moffatt oxidation of the carbinol mixture produced a 3:1 mixture of **3a** and **3b** in 76% yield. These spiro ketones proved inseparable by silica gel chromatography. The major diastereomer **3a** could be isolated by fractional crystallization of this mixture, while pure **3b** was available only by oxidation of previously isolated spiro alcohols **7** and **8**.

While dioxaspiro compounds **3a**, **3b**, and **5**–**8** were all readily differentiable by high-field ^1H NMR, complete structure assignments based on these differences in the proton spectra proved untenable. Therefore, the structure of **3a** was determined by single-crystal X-ray diffraction analysis and structural assignments for **3b** and **5**–**8** were then deduced by chemical correlation with **3a** as follows. Steric considerations suggested that reduction of the carbonyl in **3a** would occur via hydride addition from the β face. Indeed, lithium triethylborohydride reduction[10] of **3a** produced a single spiro alcohol which was assigned structure **6**. Likewise, reduction of **3b** produced a single spiro alcohol which was assigned structure **8**, again based on steric approach considerations.[10] Parikh-modified Moffat oxidation of either **6** or its C(3) epimer **5** produced the major spiro ketone **3a** as the sole product while similar oxidation of either **8** or its C(3) epimer **7** produced only the minor spiro ketone **3b**. In analogy with the equilibrations observed by Kozluk[11] for the diastereomers of 4-hydroxy-1,6-dioxaspiro[4.5]decane, we found that alu-

(1) The following are representative examples of dioxaspiro-containing natural products which have attracted recent synthetic investigation. (a) Olive fruit fly sex pheromone: Kocienski, P.; Yeates, C. *Tetrahedron Lett.* **1983**, *24*, 3905–6. (b) Antiparasitic agent avermectin Bla: Hanessian, S.; Ugolini, A.; Therien, M. *J. Org. Chem.* **1983**, *48*, 4427–30. (c) Antibiotic ionophore A-23187: Evans, D. A.; Sacks, C. E.; Kleschick, W. A.; Taber, T. R. *J. Am. Chem. Soc.* **1979**, *101*, 6789–91. (d) Steroidal sapogenins: Blunden, G.; Jaffer, J. A.; Jewers, K.; Griffin, W. J. *Tetrahedron* **1981**, *37*, 2911–15.

(2) Isolation of phyllanthoside: Kupchan, S. M.; LaVoie, E. J.; Branfman, A. R.; Fei, B. Y.; Bright, W. M.; Bryan, R. F. *J. Am. Chem. Soc.* **1977**, *99*, 3199–201. (d) Steroidal sapogenins: Blunden, G.; Jaffer, J. A.; Jewers, K.; Griffin, W. J. *Tetrahedron* **1981**, *37*, 2911–5.

(3) Phyllanthocin, the aglycon of **1** (R = CH_3) has been synthesized: (a) Collum, D. B.; McGuirk, P. R. *J. Org. Chem.* **1984**, *49*, 843–52. (b) Williams, D. R.; Sit, S. Y. *J. Am. Chem. Chem. Soc.* **1984**, *106*, 2949–54. (c) Smith, A. B., III; Fukui, M. "Abstracts of Papers", 187th National Meeting of the American Chemical Society, St. Louis, MO, April 1984; American Chemical Society: Washington, DC, 1984; ORGN 6.

(4) Isolation of breynolide: Sasaki, K.; Hirata, Y. *Tetrahedron Lett.* **1973**, 1439–42.

(5) Prepared in four steps from 2-lithiodihydropyran[8] and 7-[(methylthio)methoxy]heptanal.

(6) Prepared in low yield by the direct acylation of 2-lithiodihydropyran[8] with β-propiolactone.

(7) Makin, S. M.; Nguyen, P. T.; Shavrygina, O. A.; Arshava, B. M.; Romanova, I. A. *Zh. Org. Khim.* **1983**, *19*, 727–32; *Chem. Abstr.* **1983**, *99*, 88261p.

(8) Boeckman, R. K.; Bruza, K. J. *Tetrahedron* **1981**, *37*, 3997–4006.

(9) Parikh, J. R.; Doering, W. *J. Am. Chem. Soc.* **1967**, *89*, 5505–7.

(10) Wunderly, S. W.; Borchmann-Hanssen, E. *J. Org. Chem.* **1977**, *42*, 4277–8.

(11) Kozluk, T.; Cottier, L.; Descotes, G. *Tetrahedron* **1981**, *37*, 1875–80.

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