254 (190) (sh), 251 (230), 247 (200); CD (CH_3OH, c 0.112) $[\theta]_{274}$ ±0, $[\theta]_{268}$ +370, $[\theta]_{265}$ +180, $[\theta]_{262}$ +430, $[\theta]_{259}$ +290, $[\theta]_{256}$ +340, $[\theta]_{253}$ +240.

Registry No. (*S*)-**2a**, 2627-86-3; (*S*)-**2b**, 17279-30-0; (*R*)-**2c**, 1517-69-7; (*S*)-**2d**, 2511-06-0; (*S*)-**2e**, 17279-33-3; (*S*)-**2f**, 3756-41-0; (*S*)-**2g**, 33877-11-1; (*S*)-**3b**, 38329-34-9; (*R*)-**7b**, 80988-38-1; (*R*)-**3d**, 3966-32-3; (*S*)-**3h**, 7782-24-3; (*S*)-**4b**, 2935-35-5; (*R*)-**4c**, 54385-47-6; (*R*)-**4d**, 130409-50-6; (*S*)-**4h**, 130409-51-7; (*S*)-**5a**, 82729-98-4; (*S*)-**5b**, 108082-57-1; (*R*)-**5c**, 23439-91-0; (*S*)-**5e**, 130409-52-8; (*S*)-**5h**, 36238-13-8; (*S*)-**3c**, 17199-29-0.

Hypervalent Iodine Oxidation of *N*-Acyltyramines: Synthesis of Quinol Ethers, Spirohexadienones, and Hexahydroindol-6-ones

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There is an increasing interest in the hypervalent iodine oxidation of phenols and related compounds. Although reaction of phenols themselves with phenyliodine(III) diacetate (PIDA) or phenyliodine(III) bis(trifluoroacetate) (PIFA) frequently leads to resinous products,[1,2] some para-substituted phenols (electron-withdrawing) yield *p*-benzoquinones.[2] Phenols bearing electron-withdrawing *o*-nitro and *o,p*-dinitro groups react with PIDA to give the corresponding iodonium salts[3] and some hindered phenols to give the corresponding quinol ethers.[4] Hypervalent iodine reagents have been also used for the oxidative cyclization of bisnaphthols to spiro compounds,[5] for intramolecular oxidative aryl–aryl coupling,[6] and for carbon–carbon bond cleavage of NH_2-tyrosine dipeptides.[7] As part of our continuing studies on hypervalent iodine chemistry,[8] we have reported the oxidation of para-substituted phenol derivatives leading to *p*-benzoquinone monoacetals,[9] spiro compounds,[9] *p*-benzoquinones,[10] and azacarbocyclic spiro dienones.[11] We have now examined the hypervalent iodine oxidation of *N*-acyltyramines **1a–d**, which have the amido group as the para substituent. Oxidation of **1** with PIFA leads to two modes of reaction, depending on the solvent used: (i) in a nucleophilic solvent such as alcohol or acetic acid, the solvent attacks the para position of **1** to give the corresponding quinol ether **2** and (ii) in a poorly nucleophilic polar solvent such as 2,2,2-trifluoroethanol,[12] cyclization occurs by the attack of the amido group to give the spirocyclohexadienone **3**.

A typical experimental procedure for the reaction of *N*-acetyltyramine (**1a**) with PIFA is as follows. To a solution of **1a** in anhydrous methanol was added 1.2 equiv of PIFA. The mixture was stirred at room temperature for 10 min to give **2a** in 76% yield. Oxidation of **1a** with PIFA in other nucleophilic solvents such as ethanol, 2-propanol, and acetic acid proceeded rapidly under similar conditions to give the corresponding quinol ethers **2b–d** as major products. Similarly, other phenols (**1b–d**) reacted with PIFA to give the corresponding quinol ethers **2e–j**. On the other hand, reaction of **1a–d** with PIFA in 2,2,2-trifluoroethanol or in methylene chloride in the presence of potassium carbonate gave mainly the spirocyclohexadienone derivatives **3a–d**, respectively.[13]

Next, we examined the PIFA oxidation of *N*-alkyl-*N*-benzoyltyramines. Treatment of *N*-methyl- and *N*-ethyl-*N*-benzoyltyramines **1e,f** with PIFA in 2,2,2-trifluoroethanol followed by aqueous workup gave the hexahydroindol-6-ones **4a,b** in fair yields. Similar results were observed in the thallium(III) trifluoroacetate (TTFA) oxidation of *N*-alkyl-*N*-benzoyltyramines.[14] An effort to convert the previously obtained spirocyclohexadienone **3c** to **4a,b** by alkylation followed by hydrolysis failed. The formation of **4a,b** by alkylation followed by hydrolysis failed. The formation of **4a,b** from **1e,f** can be explained by an intramolecular Michael-type addition of the amino group to the double bond of the dienone intermediate (**A**) (Scheme I). The reaction conditions, products, and yields are listed in Tables I and II.

The spiro dienone derivatives are not only useful synthetic intermediates but also a part of the structure of many pharmacologically important compounds,[15,16] and the hexahydroindolone is a useful intermediate in the synthesis of the lycorine alkaloids.[17]

Experimental Section

All melting points are uncorrected. IR absorption spectra were recorded in $CHCl_3$. ^1H NMR spectra were measured at 90 or 500 MHz with $CDCl_3$ as a solvent unless otherwise noted. Mass spectra were obtained with a direct inlet system. E. Merck silica gel 60 (70–230-mesh ASTM) for column chromatography and E. Merck precoated TLC plate, silica gel 60 F_{254}, for preparative thin-layer chromatography (preparative TLC) were used. The organic layers were dried with anhydrous $MgSO_4$. The known starting materials were prepared by reported methods: **1a**,[18] **1c**.[19] Other unknown *N*-acyltyramines **1b,d** were prepared by the

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(12) Other polar solvents such as acetonitrile, chloroform, and *N,N*-dimethylformamide did not give satisfactory result.

(13) Reaction of **1a** with PIFA in 2,2,2-trifluoroethanol under similar conditions probably produced the similar spirocyclohexadienone derivative, but isolation of it failed because of extreme instability against moisture.

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Scheme I. Hypervalent Iodine Oxidation of *N*-Acyltyramines (1a–f)

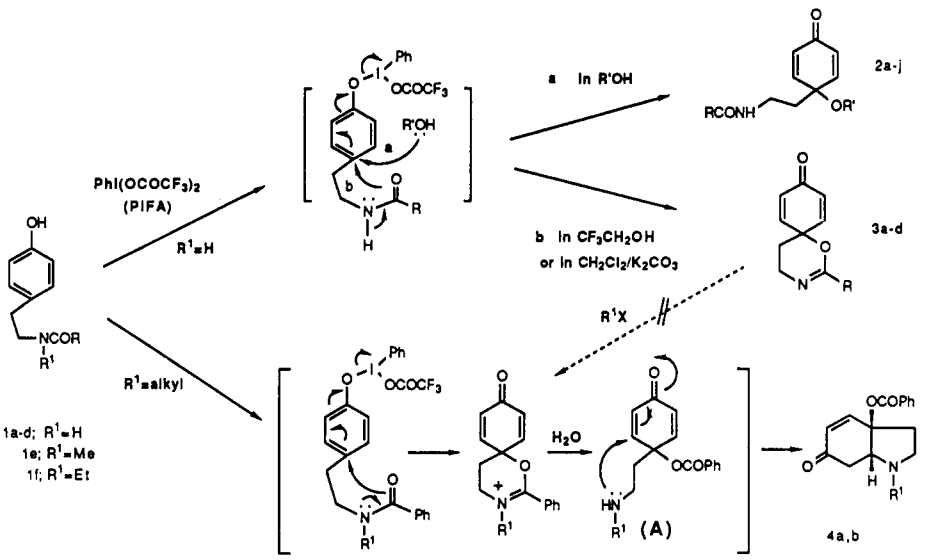
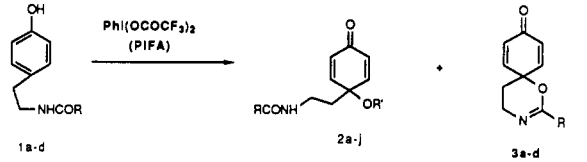


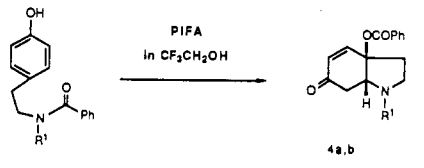
Table I



runs	starting *N*-acyltyramines R	1	reactn condtns	products (% Yields) 2, R′	3, R
1	Me	**1a**	in MeOH	**2a** (76) Me	
2			in EtOH	**2b** (47) Et	
3			in *i*-PrOH	**2c** (22) *i*-Pr	
4			in $MeCO_2H$	**2d** (20) COMe	
5			in CH_2Cl_2/K_2CO_3	*a*	**3a** (29) Me
6	*t*-Bu	**1b**	in MeOH	**2e** (64) Me	**3b** (18) *t*-Bu
7			in $MeCO_2H$	**2f** (44) COMe	**3b** (8)
8			in CF_3CH_2OH		**3b** (75)
9			in CH_2Cl_2/K_2CO_3		**3b** (24)
10	Ph	**1c**	in MeOH	**2g** (61) Me	**3c** (27) Ph
11			in $MeCO_2H$	**2h** (62) COMe	
12			in CF_3CH_2OH		**3c** (73)
13			in CH_2Cl_2/K_2CO_3		**3c** (38)
14	2,6-di-MeOPh	**1d**	in MeOH	**2i** (68) Me	
15			in $MeCO_2H$	**2j** (57) COMe	
16			in CF_3CH_2OH		**3d** (74) 2,6-di-MeOPh
17			in CH_2Cl_2/K_2CO_3		**3d** (17)

[a] The reaction in CF_3CH_2OH did not give **3a**.

Table II



runs	starting n-acyltyramines R^1	1	products (% yields) 4
1	Me	**1e**	**4a** (54)
2	Et	**1f**	**4b** (48)

standard method and are described below. PIFA is commercially available.

***N*-Pivaloyltyramine (1b)** was prepared by the standard method by the reaction of tyramine (2.0 g, 15 mmol), pivaloyl chloride (3.6 mL, 29 mmol), and triethylamine (2 mL) in $CHCl_3$ (50 mL) at room temperature for 12 h in 61% yield (1.97 g) as colorless crystals: mp 146–148 °C (from AcOEt); IR 3600, 3475, 1640, 1610 cm^{-1}; ^1H NMR δ 1.14 (s, 9 H), 2.72 (t, 2 H, J = 6 Hz), 3.42 (t, 2 H, J = 6 Hz), 5.65 (br, s, 1 H), 6.78 (d, 2 H, J = 9 Hz), 6.93 (d, 2 H, J = 9 Hz). Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.55: H, 8.65; N, 6.33. Found: C, 70.25; H, 8.75; N, 6.20.

***N*-(2,6-Dimethoxybenzoyl)tyramine (1d)** was prepared by the reaction of tyramine (412 mg, 3 mmol), 2,6-dimethoxybenzoyl chloride (602 mg, 3 mmol), and triethylamine (0.4 mL) in $CHCl_3$ (20 mL) at room temperature for 12 h in 54% yield (488 mg) as colorless crystals: mp 174–177 °C (from EtOH); IR 3600, 3445, 1650, 1610, 1595 cm^{-1}; ^1H NMR δ 2.77 (t, 2 H, J = 7 Hz), 3.59 (t, 2 H, J = 7 Hz), 3.68 (s, 6 H), 5.94 (br s, 1 H), 6.46 (d, 2 H, J = 8 Hz), 6.73 (d, 2 H, J = 8 Hz), 6.97 (d, 2 H, J = 8 Hz), 7.20 (t, 1 H, J = 8 Hz), 8.08 (br s, 1 H). Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.48; H, 6.33; N, 4.54.

***N*-Benzoyl-*N*-methyltyramine (1e).** Tyramine (274 mg, 2 mmol) was methylated as reported by Wawzonek[20] to give *N*-

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methyltyramine, which was benzoylated by the standard method to give **1e** in 16% overall yield as colorless plates: mp 143–144 °C (from EtOH); IR 3600, 1615, 1600, 1580 cm^{-1}; ^1H NMR δ 2.5–3.0 (m, 2 H, CH_2CH_2N), 2.83 (s, $3 \times {}^5/_9$ H, NMe), 3.13 (s, $3 \times {}^4/_9$ H, NMe), 3.44 (t, $2 \times {}^5/_9$ H, J = 7 H, CH_2N), 3.76 (t, $2 \times {}^4/_9$ H, CH_2N), 6.4–7.4 (m, 9 H, Ar H). Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 74.92; H, 6.59; N, 5.40.

***N*-Benzoyl-*N*-ethyltyramine (1f)** was prepared from tyramine (274 mg, 2 mmol) by a similar method as described for the preparation of **1e** in 23% overall yield as colorless plates: mp 154–155 °C (from AcOEt); IR 3600, 1610, 1600, 1575 cm^{-1}; ^1H NMR δ 1.0–1.1 (m, $3 \times {}^4/_7$ H, CH_2CH_3), 1.25–1.35 (m, $3 \times {}^3/_7$ H, CH_2CH_3), 2.6–2.7 (m, $2 \times {}^3/_7$ H, CH_2CH_2N), 2.85–2.95 (m, $2 \times {}^4/_7$ H, CH_2CH_2N), 3.15–3.25 (m, $2 \times {}^4/_7$ H, CH_2N), 3.35–3.45 (m, $2 \times {}^3/_7$ H, CH_2N), 3.55–3.65 (m, $2 \times {}^3/_7$ H, CH_2CH_3), 3.65–3.75 (m, $2 \times {}^4/_7$ H, CH_2CH_3), 6.13 (br s, $1 \times {}^4/_7$ H, OH), 6.28 (br s, $1 \times {}^3/_7$ H, OH), 6.6–7.5 (m, 9 H, Ar H). Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.72; H, 7.00; N, 5.23.

General Procedure for the Oxidation of *N*-Acyltyramines 1a–d to Quinol Ethers 2a–j and/or Spirocyclohexadienones 3a–d. Method i. To a stirred solution of *N*-acyltyramine **1** (1 mmol) in anhydrous nucleophilic solvent such as alcohol or acetic acid (4 mL) at room temperature under nitrogen was added PIFA (1.2 mmol). The mixture was stirred for 10 min under the same conditions and then neutralized by addition of powdered $NaHCO_3$. The mixture was concentrated in vacuo. The residue was dissolved in ethyl acetate and filtered. The filtrate was evaporated and the residue was purified by column chromatography on silica gel.

Method ii. To a solution of *N*-acyltyramine **1** (1 mmol) in CF_3CH_2OH (10 mL) was added PIFA (1.2 mmol). The mixture was stirred at room temperature for 30 min and concentrated in vacuo. The residue was worked up as described in method i.

Method iii. To a suspension of *N*-acyltyramine **1** (1 mmol) and powdered K_2CO_3 (2 mmol) in CH_2Cl_2 (5 mL) was added PIFA (1.2 mmol). The mixture was stirred at room temperature for 20 min and concentrated in vacuo. The residue was worked up as described in method i.

The reaction conditions and results for the oxidation reactions below are presented in the following abbreviated format: *N*-acyltyramine; oxidizing agent; solvent; yield; and physical state of the product.

4-(2′-(Acetylamino)ethyl)-4-methoxy-2,5-cyclohexadienone (2a) (method i): **1a** (36 mg, 0.2 mmol); PIFA (94.6 mg, 0.22 mmol); MeOH (1.2 mL); 31.8 mg (76%); colorless oil; IR 3460, 1670, 1630 cm^{-1}; ^1H NMR δ 1.92 (t, 2 H, J = 6 Hz, CH_2CH_2N), 1.94 (s, 3 H, COMe), 3.21 (s, 3 H, OMe), 3.36 (q, 2 H, J = 6 Hz, CH_2N), 5.7–6.1 (br s, 1 H, NH), 6.34 (d, 2 H, J = 10 Hz, CH=CHCO × 2), 6.77 (d, 2 H, J = 10 Hz, CH=CHCO × 2); HRMS calcd for $C_{11}H_{15}NO_3$ (M^+) 209.1051, found 209.1041.

4-(2′-(Acetylamino)ethyl)-4-ethoxy-2,5-cyclohexadienone (2b) (method i): **1a** (200 mg, 1.12 mmol); PIFA (578 mg, 1.34 mmol); EtOH (4.4 mL); 117 mg (47%); colorless plates; mp 75–77.5 °C (from acetone–*n*-hexane); IR 3450, 1665, 1630 cm^{-1}; ^1H NMR δ 1.18 (t, 3 H, J = 7 Hz, OCH_2CH_3), 1.92 (t, 2 H, J = 7 Hz, CH_2CH_2N), 1.95 (s, 3 H, COMe), 3.38 (q, 2 H, J = 7 Hz, OCH_2CH_3), 3.42 (t, 2 H, J = 7 Hz, CH_2N), 6.08 (br s, 1 H, NH), 6.34 (d, 2 H, J = 10 Hz, CH=CHCO × 2), 6.84 (d, 2 H, J = 10 Hz, CH=CHCO × 2); HRMS calcd for $C_{12}H_{17}NO_3$ (M^+) 223.1209, found 223.1209.

4-(2′-(Acetylamino)ethyl)-4-isopropoxy-2,5-cyclohexadienone (2c) (method i): **1a** (100 mg, 0.56 mmol); PIFA (289 mg, 0.67 mmol); *i*-PrOH (2.2 mL); 28.6 mg (22%); colorless plates; mp 97–99 °C (AcOEt); IR 3450, 1665, 1630 cm^{-1}; ^1H NMR δ 1.13 (d, 6 H, J = 6 Hz, $CH(CH_3)_2$), 1.88 (t, 2 H, J = 7 Hz, CH_2CH_2N), 1.95 (s, 3 H, COMe), 3.36 (q, 2 H, J = 7 Hz, CH_2N), 3.60 (q, 1 H, J = 6 Hz, $OCH(CH_3)_2$), 6.30 (d, 2 H, J = 10 Hz, CH=CHCO × 2), 6.91 (d, 2 H, J = 10 Hz, CH=CHCO × 2). Anal. Calcd. for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.81; H, 7.83; N, 5.85.

4-Acetoxy-4-(2′-(acetylamino)ethyl)-2,5-cyclohexadienone (2d) (method i): **1a** (30 mg, 0.17 mmol); PIFA (86.5 mg, 0.20 mmol); AcOH (0.8 mL); 8.0 mg (20%); yellow oil; IR 3450, 1750, 1670, 1630 cm^{-1}; ^1H NMR δ 1.94 (s, 3 H, COMe), 2.0–2.2 (m, 2 H, CH_2CH_2N), 2.05 (s, 3 H, OCOMe), 3.2–3.5 (m, 2 H, CH_2N), 5.54 (br s, 1 H, NH), 6.26 (d, 2 H, J = 10 Hz, CH=CHCO × 2), 6.84 (d, 2 H, J = 10 Hz, CH=CHCO × 2). Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.41; H, 6.62; N, 5.97.

2-Methyl-1,3-oxazaspiro[5.5]undeca-7,10-dien-9-one (3a) (method iii): **1a** (98.7 mg, 0.55 mmol); PIFA (285 mg, 0.66 mmol); K_2CO_3 (152 mg, 1.1 mmol); CH_2Cl_2 (2.2 mL); 28.5 mg (29%); colorless solid; IR 1675, 1635 cm^{-1}; ^1H NMR δ 1.87 (t, 2 H, J = 6 Hz, CH_2CH_2N), 1.98 (s, 3 H, Me), 3.48 (t, 2 H, J = 6 Hz, CH_2N), 6.25 (d, 2 H, J = 10 Hz, CH=CHCO × 2), 6.87 (d, 2 H, J = 10 Hz, CH=CHCO × 2); HRMS calcd for $C_{10}H_{11}NO_2$ (M^+) 177.0790, found 177.0790.

4-Methoxy-4-(2′-(pivaloylamino)ethyl)-2,5-cyclohexadienone (2e) and 2-*tert*-butyl-1,3-oxazaspiro[5.5]undeca-7,10-dien-9-one (3b) (method i): **1b** (20 mg, 0.09 mmol); PIFA (46.6 mg, 0.11 mmol); MeOH (0.4 mL); **2e** (14.5 mg, 64%) and **3b** (3.6 mg, 18%).

2e: colorless plates; mp 106–108 °C (from AcOEt); IR 3470, 1670, 1640 cm^{-1}; ^1H NMR δ 1.18 (s, 9 H, *t*-Bu), 1.93 (t, 2 H, J = 7 Hz, CH_2CH_2N), 3.22 (s, 3 H, OMe), 3.40 (t, 2 H, J = 7 Hz, CH_2N), 6.37 (d, 2 H, J = 10 Hz, CH=CHCO × 2), 6.82 (d, 2 H, J = 10 Hz, CH=CHCO × 2). Anal. Calcd. for $C_{14}H_{21}NO_3$: C, 66.90; H, 8.42; N, 5.57. Found: C, 66.57; H, 8.56; N, 5.55.

3b: colorless crystals; mp 69–71 °C (from AcOEt–*n*-hexane); IR 1670, 1635 cm^{-1}; ^1H NMR δ 1.16 (s, 9 H, *t*-Bu), 1.84 (t, 2 H, J = 6 Hz, CH_2CH_2N), 3.51 (t, 2 H, J = 6 Hz, CH_2N), 6.24 (d, 2 H, J = 10 Hz, CH=CHCO × 2), 6.84 (d, 2 H, J = 10 Hz, CH=CHCO × 2); HRMS calcd for $C_{13}H_{17}NO_2$ (M^+) 219.1259, found 219.1279.

4-Acetoxy-4-(2′-(pivaloylamino)ethyl)-2,5-cyclohexadienone (2f) and 3b (method i). **1b** (20 mg, 0.09 mmol); PIFA (46.6 mg, 0.11 mmol); AcOH (0.8 mL); **2f** (11.1 mg, 44%) and **3b** (1.5 mg, 8%).

2f: colorless oil; IR 3475, 1740, 1670, 1630 cm^{-1}; ^1H NMR δ 1.18 (s, 9 H, *t*-Bu), 2.05 (t, 2 H, J = 7 Hz, CH_2CH_2N), 2.08 (s, 3 H, COMe), 3.34 (q, 2 H, J = 7 Hz, CH_2N), 5.80 (br s, 1 H, NH), 6.29 (d, 2 H, J = 10 Hz, CH=CHCO × 2), 6.89 (d, 2 H, J = 10 Hz, CH=CHCO × 2); HRMS calcd for $C_{15}H_{21}NO_4$ (M^+) 279.1470, found 279.1490.

Oxidation of 1b by method ii: **1b** (30 mg, 0.14 mmol); PIFA (70 mg, 0.16 mmol); CF_3CH_2OH (1.3 mL); **3b** (22.5 mg, 75%).

Oxidation of 1b by method iii: **1b** (20 mg, 0.09 mmol); PIFA (51.6 mg, 0.12 mmol), K_2CO_3 (27.6 mg, 0.2 mmol); CH_2Cl_2 (1 mL); **3b** (4.8 mg, 24%).

4-(2′-(Benzoylamino)ethyl)-4-methoxy-2,5-cyclohexadienone (2g) and 2-phenyl-1,3-oxazaspiro[5.5]undeca-7,10-dien-9-one (3c) (method i): **1c** (30 mg, 0.12 mmol); PIFA (64.5 mg, 0.15 mmol); MeOH (0.6 mL); **2g** (20.5 mg, 61%) and **3c** (8.0 mg, 27%).

2g: colorless plates; mp 116–118 °C (from benzene); IR 1665, 1635, 1610 cm^{-1}; ^1H NMR δ 2.07 (t, 2 H, J = 7 Hz, CH_2CH_2N), 3.29 (s, 3 H, OMe), 3.63 (q, 2 H, J = 7 Hz, CH_2N), 6.39 (d, 2 H, J = 10 Hz, CH=CHCO × 2), 6.7–7.0 (br s, 1 H, NH), 6.85 (d, 2 H, J = 10 Hz, CH=CHCO × 2), 7.4–7.6 (m, 3 H, Ar H), 7.7–7.9 (m, 2 H, Ar H); HRMS calcd for $C_{16}H_{17}NO_3$ (M^+) 271.1206, found 271.1196.

3c: colorless plates; mp 126–127 °C (from benzene–*n*-hexane); IR 1675, 1655, 1630 cm^{-1}; ^1H NMR δ 1.98 (t, 2 H, J = 6 Hz, CH_2CH_2N), 3.74 (t, 2 H, J = 6 Hz, CH_2N), 6.26 (d, 2 H, J = 10 Hz, CH=CHCO × 2), 6.92 (d, 2 H, J = 10 Hz, CH=CHCO × 2), 7.3–7.5 (m, 3 H, Ar H), 7.8–8.0 (m, 2 H, Ar H). Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.08; H, 5.34; N, 5.59.

4-Acetoxy-4-(2′-(benzoylamino)ethyl)-2,5-cyclohexadienone (2h) (method i): **1c** (30 mg, 0.12 mmol); PIFA (64.5 mg, 0.15 mmol); AcOH (0.6 mL); 23.1 mg (62%); colorless oil; IR 3465, 1750, 1665, 1630 cm^{-1}; ^1H NMR δ 2.16 (t, 2 H, J = 7 Hz, CH_2CH_2N), 2.06 (s, 3 H, OCOMe), 3.55 (q, 2 H, J = 7 Hz, CH_2N), 6.30 (d, 2 H, J = 10 Hz, CH=CHCO × 2), 6.93 (d, 2 H, J = 10 Hz, CH=CHCO × 2), 7.3–7.5 (m, 3 H, Ar H), 7.6–7.8 (m, 2 H, Ar H); HRMS calcd for $C_{17}H_{17}NO_4$ (M^+) 299.1158, found 299.1158.

Oxidation of 1c by method ii: **1c** (100 mg, 0.41 mmol); PIFA (215 mg, 0.5 mmol); CF_3CH_2OH (4 mL); **3c** (71.9 mg, 73%).

Oxidation of 1c by method iii: **1c** (48.2 mg, 0.2 mmol); PIFA (103.2 mg, 0.24 mmol), K_2CO_3 (55.3 mg, 0.4 mmol); CH_2Cl_2 (1 mL); **3c** (17.9 mg, 38%).

4-[2′-((2,6-Dimethoxybenzoyl)amino)ethyl]-4-methoxy-2,5-cyclohexadienone (2i) (method i): **1d** (20 mg, 0.066 mmol); PIFA (34.2 mg, 0.08 mmol); MeOH (0.3 mL); 14.9 mg (68%): yellow oil; IR 3450, 1660, 1635, 1595 cm^{-1}; ^1H NMR δ 2.04 (t, 2 H, J = 7 Hz, CH_2CH_2N), 3.20 (s, 3 H, OMe), 3.56 (q, 2 H, J = 7 Hz, CH_2N), 3.80 (s, 6 H, OMe × 2), 6.05 (br s, 1 H, NH), 6.36 (d, 2 H, J = 10 Hz, CH=CHCO × 2), 6.54 (d, 2 H, J = 8 Hz, Ar H), 6.85 (d, 2 H, J = 10 Hz, CH=CHCO × 2), 7.27 (t, 1 H, J = 8 Hz, Ar H); HRMS calcd for $C_{18}H_{21}NO_5$ (M^+) 331.1420, found 331.1423.

4-Acetoxy-4-[2′-((2,6-dimethoxybenzoyl)amino)ethyl]-2,5-cyclohexadienone (2j) (method i): **1d** (30 mg, 0.12 mmol); PIFA (51.4 mg, 0.12 mmol); AcOH (0.9 mL); 20.4 mg (57%); colorless plates; mp 186–187 °C (from AcOEt); IR 3475, 1750, 1675, 1635, 1600 cm^{-1}; ^1H NMR δ 2.08 (s, 3 H, COMe), 2.16 (t, 2 H, J = 7 Hz, CH_2CH_2N), 3.55 (q, 2 H, J = 7 Hz, CH_2N), 3.80 (s, 6 H, OMe × 2), 5.79 (br s, 1 H, NH), 6.27 (d, 2 H, J = 10 Hz, CH=CHCO × 2), 6.54 (d, 2 H, J = 9 Hz, Ar H), 6.95 (d, 2 H, J = 10 Hz, CH=CHCO × 2), 7.20 (t, 1 H, J = 9 Hz, Ar H). Anal. Calcd for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.90. Found: C, 63.60; H, 5.90; N, 3.91.

2-(2′,6′-Dimethoxyphenyl)-1,3-oxazaspiro[5.5]undeca-7,10-dien-9-one (3d) (method ii): **1d** (50 mg, 0.17 mmol); PIFA (85.6 mg, 0.2 mmol); CF_3CH_2OH (1.6 mL); 36.8 mg (74%); colorless crystals; mp 116–118 °C (from AcOEt); IR 1670, 1630, 1600 cm^{-1}; ^1H NMR δ 2.04 (t, 2 H, J = 6 Hz, CH_2CH_2N), 3.73 (t, 2 H, J = 6 Hz, CH_2N), 3.81 (s, 6 H, OMe × 2), 6.26 (d, 2 H, J = 10 Hz, CH=CHCO × 2), 6.54 (d, 2 H, J = 8 Hz, Ar H), 7.06 (d, 2 H, J = 10 Hz, CH=CHCO × 2), 7.26 (t, 1 H, J = 8 Hz, Ar H); HRMS calcd for $C_{17}H_{17}NO_4$ 299.1158, found 299.1174.

Oxidation of 1d by method iii: **1d** (30 mg, 0.1 mmol); PIFA (51.1 mg, 0.12 mmol), K_2CO_3 (27.6 mg, 0.2 mmol); CH_2Cl_2 (0.8 mL); **3d** (5 mg, 17%).

General Procedure for the Oxidation of *N*-Alkyl-*N*-benzoyltyramines 1e,f to Hexahydroindol-6-ones 4a,b. To a solution of *N*-alkyl-*N*-benzoyltyramine 1 (1 mmol) in CF_3CH_2OH (10 mL) was added PIFA (1.2 mmol). The mixture was stirred at room temperature for 30 min and then neutralized by addition of powered $NaHCO_3$. The mixture was concentrated in vacuo to give the residue, which was worked up as described for method i in *N*-acyltyramines 1.

Oxidation of 1e by method ii: **1e** (21.1 mg, 0.08 mmol); PIFA (43 mg, 0.1 mmol); CF_3CH_2OH (1 mL); 1-(benzoyloxy)-7-methyl-*cis*-7-azabicyclo[4.3.0]non-2-en-4-one (**4a**) (12.1 mg, 54%); hydroscopic colorless oil; IR 1715, 1685, 1600 cm^{-1}; ^1H NMR δ 2.3–2.4 (m, 1 H), 2.4–2.55 (m, 2 H), 2.34 (s, 3 H, NMe), 2.71 (dd, 1 H, J = 2, 17 Hz, 5-CH), 2.95–2.99 (m, 1 H), 3.05 (dd, 1 H, J = 5, 17 Hz, 5-CH), 3.1–3.2 (m, 1 H, 6-CH), 6.03 (d, 1 H, J = 10 Hz, 3-CH), 7.06 (dd, 1 H, J = 2, 10 Hz, 2-CH), 7.46 (t, 2 H, J = 7 Hz, Ar H), 7.59 (t, 1 H, J = 7 Hz, Ar H), 8.01 (d, 2 H, J = 8 Hz, Ar H); HRMS calcd for $C_{16}H_{17}NO_3$ 271.1206, found 271.1204. Anal. Calcd for $C_{16}H_{17}NO_3 \cdot {}^1/_{10}H_2O$: C, 70.36; H, 6.35; N, 5.13. Found: C, 70.21; H, 6.39; N, 4.77.

Oxidation of 1f by method ii: **1f** (31.7 mg, 0.12 mmol); PIFA (60.8 mg, 0.14 mmol); CF_3CH_2OH (1.5 mL); 1-(benzoyloxy)-7-ethyl-*cis*-7-azabicyclo[4.3.0]non-2-en-4-one (**4b**) (16.1 mg, 48%); colorless oil; IR 1715, 1685, 1600 cm^{-1}; ^1H NMR δ 1.07 (t, 3 H, J = 7 Hz, CH_2CH_3), 2.20–2.27 (m, 1 H), 2.32–2.40 (m, 1 H), 2.44–2.52 (m, 2 H), 2.69 (dd, 1 H, J = 3, 17 Hz, 5-CH), 2.85–2.94 (m, 1 H, 6-CH), 3.01 (dd, 1 H, J = 5, 17 Hz, 5-CH), 3.22 (q, 2 H, J = 7 Hz, CH_2CH_3), 6.03 (d, 1 H, J = 10 Hz, 3-CH), 7.08 (dd, 1 H, J = 1, 10 Hz, 2-CH), 7.45 (t, 2 H, J = 7 Hz, Ar H), 7.59 (t, 1 H, J = 7 Hz, Ar H), 8.01 (d, 2 H, J = 7 Hz, Ar H); HRMS calcd for $C_{17}H_{19}NO_3$ 285.1365, found 285.1365. Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.24; H, 6.88; N, 4.52.

Registry No. **1a**, 1202-66-0; **1b**, 130699-26-2; **1c**, 41859-54-5; **1d**, 130699-27-3; **1e**, 130699-28-4; **1f**, 130699-29-5; **2a**, 130699-30-8; **2b**, 130699-31-9; **2c**, 130699-32-0; **2d**, 130699-33-1; **2e**, 130699-34-2; **2f**, 130699-35-3; **2g**, 130699-36-4; **2h**, 130699-37-5; **2i**, 130699-38-6; **2j**, 130699-39-7; **3a**, 130699-40-0; **3b**, 130699-41-1; **3c**, 130699-42-2; **3d**, 130699-43-3; **4a**, 130699-44-4; **4b**, 130699-45-5; PIFA, 2712-78-9.

Supplementary Material Available: ^1H NMR spectra for compounds **2a,b,f–i** and **3a,b,d** (10 pages). Ordering information is given on any current masthead page.

Stereoselective Syntheses of Hydroxyethylene Dipeptide Isosteres

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Hydroxyethylene dipeptide isosteres (1) play a prominent role as transition-state mimics in inhibitors of aspartic proteinases.[2] Considerable effort has been directed toward developing efficient syntheses for these molecules.[3] We desired a highly stereocontrolled and flexible method for the synthesis of hydroxyethylene dipeptide isosteres for studies in our renin inhibitors program. One avenue which has not been exploited is via deoxygenation of stereochemically defined aldol adducts.[4] In this paper, we report two methods which provide the Cha-Val hydroxyethylene dipeptide isostere **2** by this strategy.

Both of our routes make use of the versatile aldehyde **3**[5] as the P_1-containing partner in the aldol reaction. A similar aldol reaction has been reported by Thaisrivongs and co-workers for the synthesis of dihydroxyethylene isosteres.[6] In our initial route, outlined in Scheme II, the $P_{1'}$ fragment was provided by acyloxazolidinone **4**. Condensation of the boryl enolate of **4** with aldehyde **3** (8:1 mixture of 5*R*:5*S* diastereomers) led cleanly to aldol adduct **5** in good yield. With the exception of the adduct arising from the 5*S* diastereomer of **3**, no other aldol products were detected (^1H NMR, TLC). Barton–McCombie deoxygenation[7] proceeded by way of thionocarbamate **6**, which was reduced smoothly with tri-*n*-butyltin hydride to provide the diprotected isostere **7** in an overall yield of 48% for the three steps. The recently reported lithium hydroperoxide protocol for cleavage of hindered acyloxazolidinones[8] proved very efficacious for the hydrolysis of **7** to carboxylic acid **8**. The desired amide **9** then was cleanly synthesized without epimerization by first forming the *N*-hydroxybenzotriazole ester at 0 °C over 48 h, followed by addition of the amine component.[9] The free

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