Formation of Two 4-Imidazolylmethylphosphonium Salts and their Synthetic Studies Toward Histamine H_3-Ligands

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Abstract: A simple and convenient preparation of {[1*H*-imidazol-4(5)-yl]methyl}triphenylphosphonium chloride (**5**) is described. The phosphonium salt **5** could be applied to the synthesis of 1-[1*H*-imidazol-4(5)-yl]-5-arylpentan- or 6-arylhexan-3-ones **4a**–**d** exhibiting histamine H_3-antagonistic activities via a 1,3-diazafulvene intermediate **6** generated from **5**. Further, two-methylene-enlongated homolog **3** of imifuramine was efficiently synthesized, starting from Wittig olefination of aldehyde **24** using [(1-tritylimidazol-4-yl)methyl]triphenylphosphonium chloride **7**.

Key words: imidazole, histamine H_3-ligand, phosphonium salts, diazafulvene, Wittig olefination

Introduction

The C-4 substituted imidazoles are biologically important heterocyclic compounds[1] and they are a common and essential structural feature of the ligands for the histamine H_3-receptor.[2] The H_3-agonists are regarded as a target for new therapeutics of bronchial asthma, and H_3-antagonists are now expected to be potential drugs for memory degenerative disorders like Alzheimer's disease.[2] Most H_3-ligands are active as well at the novel H_4- receptor, which was identified by cloning and pharmacological characterization in the year 2000, but no specific ligands for the H_4-receptor are available.[3]

4(5)-[(2*R*,5*R*)-5-Aminomethyltetrahydrofuran-2-yl]imidazole (**1**, imifuramine) exhibited a clear H_3-agonistic activity from the results of an in vivo brain microdialysis (Figure 1).[4] Further, it has been very recently found that a methylcyanoguanidine derivative (**2**, OUP-**16**) of imifuramine showed full agonistic activities for the H_4-receptor with 40- to 45-fold selectivity over the H_3-receptor.[5] The findings of imifuramine and OUP-**16** encouraged us to synthesize 4(5)-{2-[(2*R*,5*R*)-5-aminomethyltetrahydrofuran-2-yl]ethyl}imidazole (**3**), which has the two-carbon-elongated structure between the imidazole and tetrahydrofuran of **1**, because it is known that elongation of the alkyl spacer of histamine or H_3-agonists influences the potency and high affinity for the H_3-receptor.[6] Further, many biologically active molecules and drugs have two-methylene groups between functional groups.

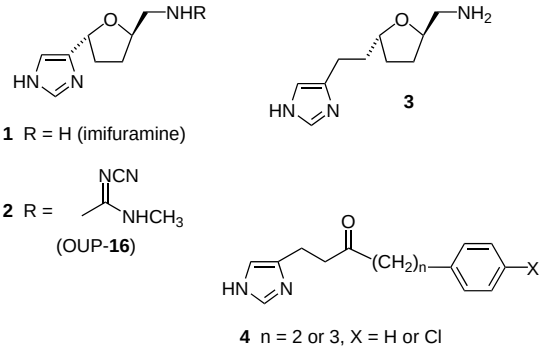

Figure 1

As limited synthetic methods for the synthesis of the C-4 substituted imidazoles have been employed, reliable and effective procedures are still required.[1,2] We recently reported a Horner–Wardsworth–Emmons (HWE) type reagent **9** as a useful reagent for functionalizing the 4(5)-methyl group of imidazole (Scheme 1).[7] While Lassalle and co-workers used [(1-tritylimidazole-4(5)-yl)methyl]triphenylphoshphonium chloride (**7**) in the patent applications,[8] only a little work has been done concerning Wittig reagents or phosphonium salts incorporating an imidazole group. In our preparation of the phoshphonium chloride **7**, we found the coexistence of a novel {[1*H*-imidzole-4(5)-yl]methyl}triphenylphosphonium chloride (**5**). We herein report a simple and convenient preparation of triphenylphosphonium salt **5** which generates a 1,3-diazafulvene **6**[9] in the presence of a base (Scheme 1). Thus, the phosphonium salt **5** could be applied to the synthesis of 1-(1*H*-imidazol-4-yl)-5-arylpentan- or 6-arylhexan-3-ones **4a**–**d** exhibiting H_3-antagonistic activities. Alternatively, two-metylene-enlongated homolog **3** of imifuramine **1** was synthesized via five steps, starting from Wittig olefination of aldehyde **24** using phosphonium salt **7**.

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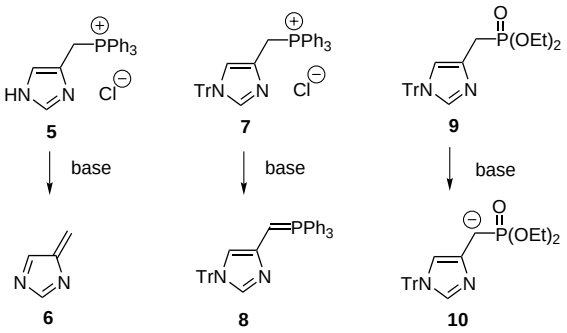
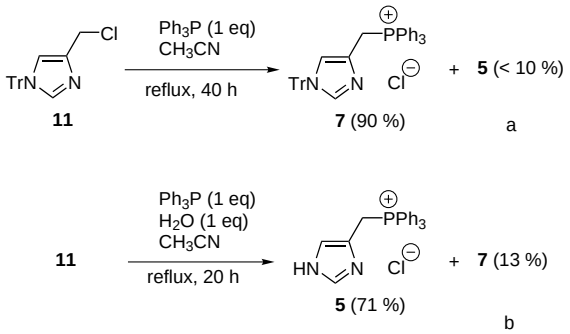


Scheme 1

Preparations of 4-Imidazolmethylphosphonium Salts 5 and 7

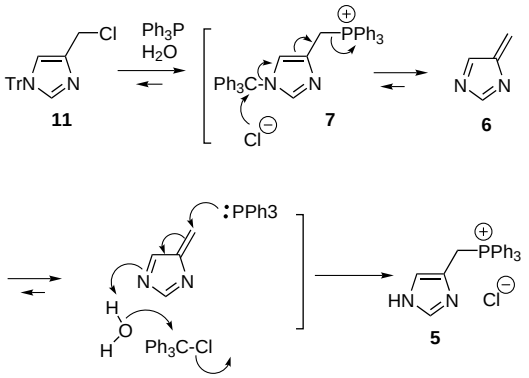
When we first refluxed a mixture of 1-trityl-4-chloromethylimidazole (**11**)[10] and Ph_3P in CH_3CN for 40 hours, a small amount of white precipitate (< 10%) was observed at the bottom of the flask. After filtration and careful purification, the precipitate was confirmed as a novel 4-imidazoylmethylphosphonium chloride **5** [mp 276–286 °C (dec.)] lacking the trityl group of **7**, confirmed from spectroscopic data and elemental analysis (Scheme 2, a). Phosphonium chloride **7** was obtained in 90% yield from the filtrate. On the other hand, in the presence of one equivalent of water, the reaction liberated **5** in 71% yield (Scheme 2, b). Although this reaction was accompanied by the formation of **7** (13%), simple filtration gave almost pure **5**, which could be used without further purification for the reactions described below.

The formation of **5** is presumed as shown in Scheme 3. A chloro-counterpart of the formed phosphonium salt **7** attacks the trityl group to form an active diazafulvene **6** by Hofmann-type elimination with liberation of Ph_3P and tritylchloride. Subsequent addition of Ph_3P to **6** followed by protonation regenerates the imidazole system to provide **5**.



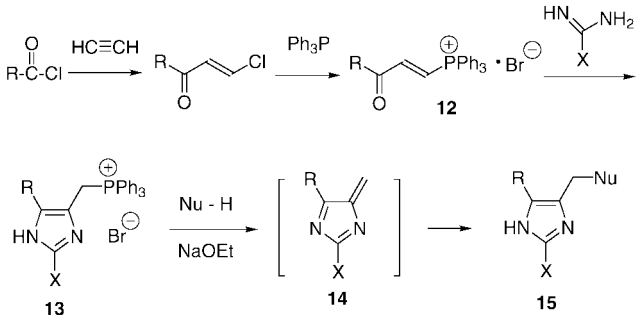
Scheme 2

A synthetic method of polysubstituted imidazolylmethylphosphonium salts **13** has been developed by Zbiral and co-workers using reaction of triphenyl-β-acylvinylphosphonium bromides **12** with amidines (Scheme 4).[11] These phosphonium salts **13** provided polysubstituted imidazoles **15** by addition of nucleophiles to diazafulvene **14**



Scheme 3

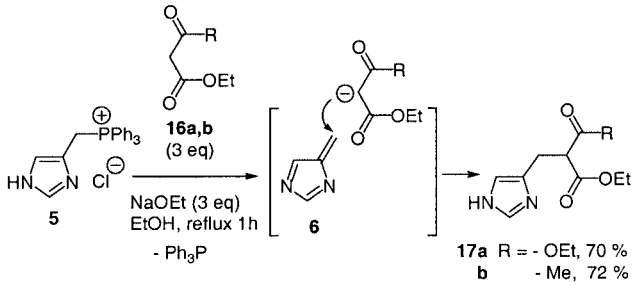
generated in the presence of alkali. However, the Zbiral method would be difficult for the synthesis of **5**, which has unsubstituted imidazole, because this synthetic process needs unstable formyl chloride (R = H) as the starting material (Scheme 4), which exists only for 1 hour at –60 °C and easily decomposes to CO and HCl.[12]



Scheme 4

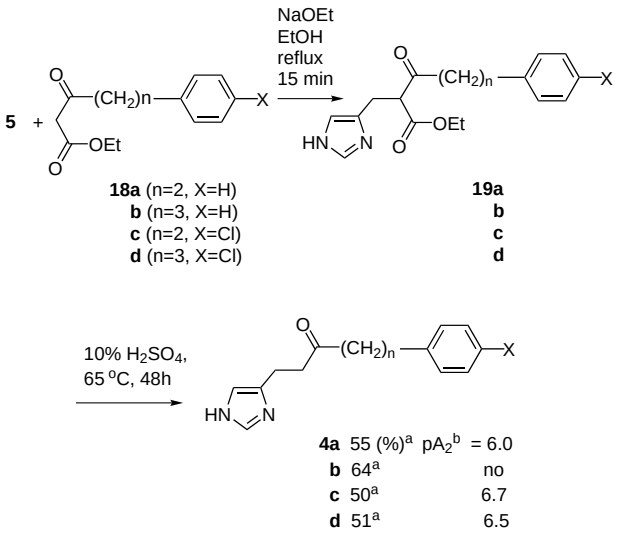
Synthesis of 1-(1*H*-Imidazol-4-yl)-ω-arylalkan-3-ones Using Phosphonium Salt 5

As the phosphonium salt **5** may represent a masked 1.3-diazafulvene, the C–C bond formation at 4(5)-methyl group of imidazole was first examined by the reaction of **5** with diethyl malonate or ethyl acetoacetate (**16a** or **16b**) using the Zbiral procedure (Scheme 5).[11] Refluxing of **5** with **16a** or **16b** in the presence of NaOEt proceeded as expected to afford **17a**[13] (70%) or **17b** (72%), together with Ph_3P which could be re-used.



Scheme 5

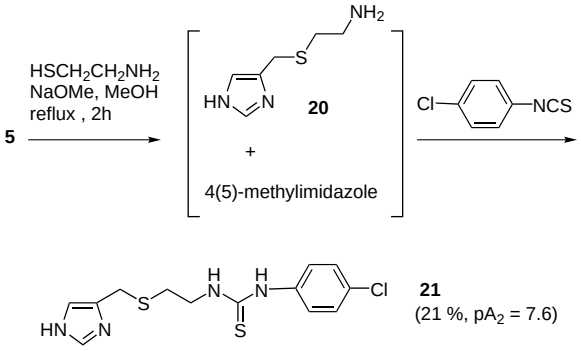
We next directed our efforts to synthesize imidazolyl-arylalkan-3-ones **4**, since many H_3-antagonists exhibit common structural features as indicated by Schunack et al.,[2] i.e. 4(5)-substituted-1*H*-imidazole head group, alkyl spacer containing a polar group, and a hydrophobic tail group. Reaction of **5** with ethyl 3-oxo-5-phenylpentanoates **18a**[14] similarly afforded β-ketoester **19a**, which was subsequently treated with diluted H_2SO_4 to afford imidazolylphenylpentanone **4a** in 55% yield from **5** (Scheme 6). Synthesis of **4b**–**d** was similarly carried out from **5** in 50–64% yields.



Scheme 6 a) Two steps yields from **5**. b) H_3-Antagonistic activities of **4a**–**d** on the in vitro test system on the guinea pig ileum.

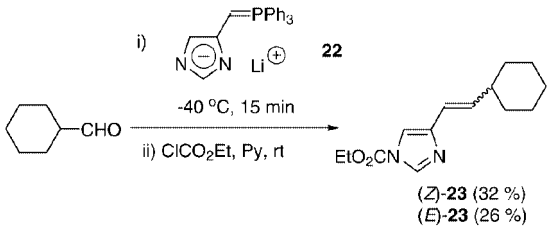
The diazafulvene method was also applied to the C–S bond formation.[11c] Reaction of phosphonium salt **5** with sodium salt of cystenamine afforded thioamine **20** together with 4(5)-methylimidazole as by-product, although the mechanism of production of this material is unclear (Scheme 7). The crude thioamine **20** was treated with *p*-chlorophenyl isothiocyanate to synthesize thiourea derivative **21** (21% yield from **5**), which has an interesting structural feature. The distance between the imidazole and the hydrophobic moiety in **21** is ca. 16 Å (estimated from a molecular-model examination), and it is approximately equal to that of a potent H_3-antagonist, clobenpropit.[2]

H_3-Antagonistic properties of the synthesized five compounds **4a**–**d** and **21** were examined by a preliminary in vitro assay using guinea pig ileum preparation.[15] The results indicated that: 1) phenylpentanone **4a** is a weak H_3-antagonist (pA_2 = 6.0), but one carbon homolog **4b** is inactive; 2) substitution of the phenyl group by a 4-chlorophenyl group enhances H_3-antagonistic activities [pA_2; **4c** (6.7), **4d** (6.5)], and 3) thiourea **21** exhibits relatively more potent antagonistic activitiy (pA_2 = 7.6).



Scheme 7

As another extension of the phosphonium salt **5**, its use in a Wittig reaction was examined (Scheme 8). When we attempted olefination of cyclohexenecarboxaldehyde using a phosphorus ylide **22**, which was generated by treatment of **5** with 2 equivalents of LiHMDS in DMF, (*Z*)-vinylimidazole, (*Z*)-**23** (32%) and (*E*)-vinylimidazole, (*E*)-**23** (26%) could be obtained, after ethoxycarbonylation owing to easy chromatographic isolation.



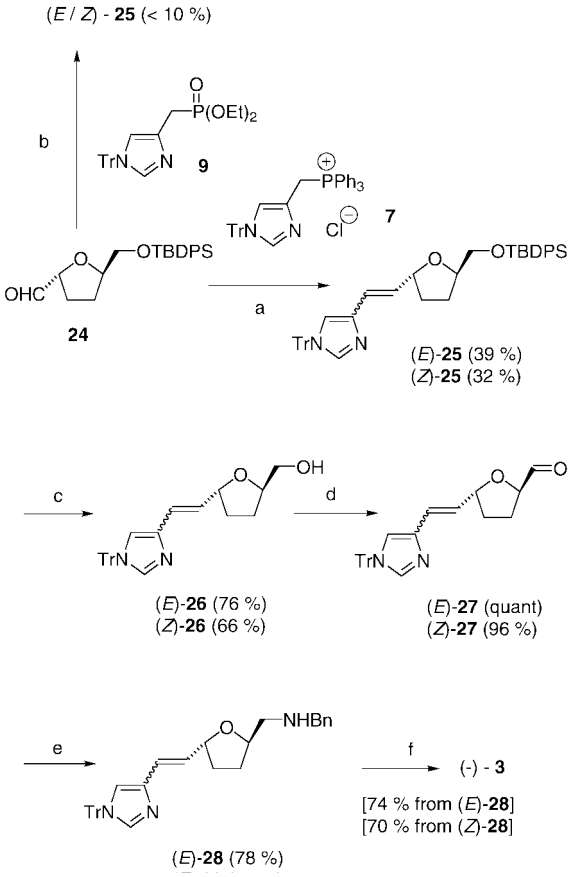
Scheme 8

Synthesis of Imifuramine Homolog 3 Incorporating Ethyl Spacer

The two-carbon-elongated homolog (–)-**3** of imifuramine was synthesized from (2*R*,5*R*)-5-[(*tert*-butyldiphenylsiloxy)methyl]tetrahydrofuran-2-carbaldehyde (**24**) prepared by Koert and co-workers[16] (Scheme 9). We first attempted conversion of **24** into vinylimidazole **25** using HWE olefination of phosphonate **9**[7] in the presence of *t*-BuOK, but the yield was only <10% yield with recovery of **9**. The result may be ascribed to the strong basicity of the HWE reagent and the nature of aldehyde **24**, which may lead to enolization by proton abstraction at C2. On the other hand, **24** could be converted into (*E*)-and (*Z*)-vinylimidazoles [(*E*)-**25** (39%) and (*Z*)-**25** (32%)] in better yields by Wittig olefination using ylide **8** generated from the phosphonium salt **7**. After removal of the TBDPS group of (*E*)-**25** thus obtained with Bu_4NF, oxidation of the resulting primary alcohol (*E*)-**26** into aldehyde (*E*)-**27** was carried out. In the case of Dess–Martin periodinane oxidation, the isolated yields of (*E*)-**27** were variable (0–70%) and varied with each batch of Dess–Martin periodinane bought.[17] Swern oxidation of (*E*)-**26** gave (*E*)-**27** in 70% yield, and the use of freshly prepared *o*-iodoxybenzoic acid (IBX)[18] afforded a quantitative yield of (*E*)-**27**.

The reductive amination[19] of (*E*)-**27** proceeded to give benzylamine (*E*)-**28** (78%). Finally, hydrogenation of (*E*)-**28**·2HCl attained the synthesis of (–)-**3** in 74% yield, causing simultaneous removal of the trityl and benzyl groups as well as saturation of the double bond.[7] Similarly, (*Z*)-vinylimidazole [(*Z*)-**25**] was also converted into (–)-**3** through the respective intermediates (*Z*)-**26**, **27**, and **28** by the same reaction sequence described herein.

Phosphonium salt **7** may be more efficient than phosphonate **9** for olefination of the aldehydes, which are susceptible to enolization. As the preparation of C-4 substituted imidazoles using phosphonium salts **5** is experimentally straightforward, they would become useful tools in the synthesis of bioactive imidazole compounds.



Scheme 9 (a) (i) **7** (1.2 equiv), BuLi (1.2 equiv), THF, –70 °C; (ii) **24**, –70 °C, then r.t.; (b) **9** (1.2 equiv), *t*-BuOK (1.2 equiv), reflux, 17 h; (c) Bu_4NF, THF, 0 °C; (d) IBX, THF, reflux; (e) (i) $BnNH_2$, MS 3 Å, EtOH; (ii) $NaBH_4$; (f) (i) 1 N HCl; (ii) H_2/Pd-C.

The melting points were determined on a hot stage apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR 435 pectrometer. ^1H and ^{13}C NMR were taken with tetramethylsilane as an internal reference on a Varian Gemini-200, Varian Mercury-300 and Varian UNITY INOVA-500 spectromters. Reactions with air- and moisture-sensitive compounds were carried out under Ar. Unless otherwise noted, all extracts were dried over Na_2SO_4 or $MgSO_4$, and the solvents were removed in a rotary evaporator under reduced pressure. Chromatography was performed on silica gel. THF was distilled from Na-benzophenone.

Reaction of 11 and Ph_3P in CH_3CN

A mixture of 1-trityl-4-chloromethylimidazole[10] (**11**, 750 mg, 2.09 mmol) and Ph_3P (548 mg, 2.09 mmol) in CH_3CN (10 mL) was refluxed for 40 h under Ar. The resulting white precipitate was separated by filtration and dried over P_2O_5 at 100 °C under reduced pressure to give white powder **5** (69 mg, 10%). The filtrate was evaporated to give an amorphous residue, which was subsequently dissolved in water. The aq layer was washed twice with hexane–EtOAc (1:1) and evaporated to give an amorphous product, which was then dried over P_2O_5 at 100 °C under reduced pressure to give pale yellow powder **7** (1170 mg, 90%).

Although further purification of **5** and **7** was not required for the following experiments, they were purified owing to their elemental analyses by chromatography using $CHCl_3$–MeOH (65:25 and 6:1, respectively) as eluent.

5

R_f 0.32 ($CHCl_3$–MeOH, 65:25); white powder; mp 276–286 °C (dec.).

^1H NMR (DMSO): δ = 5.08 (d, *J* = 14.4 Hz, 2 H), 6.73 (s, 1 H), 7.51–7.93 (m, 16 H).

^{31}P NMR (CD_3OD): δ = 23.06 (s), 23.13 (s) (tautomer).

MS (SIMS): *m*/*z* = 343 [M^+ – Cl].

HRMS: *m*/*z* [M^+ – Cl] calcd for $C_{22}H_{20}N_2P$: 343.1366; found: 343.1357.

Anal. Calcd for $C_{22}H_{20}ClN_2P·0.8MeOH$: C, 67.70; H, 5.78; N, 6.93. Found: C, 67.88; H, 5.50; N, 7.11.

7

R_f 0.65 ($CHCl_3$–MeOH, 65:25); white powder; mp 214–246 °C (dec.).

^1H NMR ($CDCl_3$): δ = 5.31 (d, *J* = 13.6 Hz, 2 H), 6.90–7.01 (m, 5 H), 7.18–7.40 (m, 9 H), 7.58–7.98 (m, 18 H).

MS (SIMS): *m*/*z* = 585 [M^+ – Cl].

HRMS: *m*/*z* [M^+ – Cl] calcd for $C_{41}H_{34}N_2P$: 585.2457; found: 585.2450.

Anal. Calcd for $C_{41}H_{34}ClN_2P·0.5MeOH$: C, 78.23; H, 5.70; N, 4.40. Found: C, 78.24; H, 5.67; N, 4.00.

Preparation of {[1*H*-imidzole-4(5)-yl]methyl}triphenylphosphonium Chloride (5)

Water (54 mg, 3.0 mmol) was added to a solution of 1-trityl-4-chloromethylimidazole (1077 mg, 3.0 mmol) and Ph_3P (786 mg, 3.0 mmol) in CH_3CN (10 mL). The mixture was refluxed for 20 h to yield a white precipitate which was subsequently filtered and dried over to give **5** (806 mg, 71%). **7** (248 mg, 13%) was also obtained as an amorphous product from the filtrate by the same method as described above.

Ethyl 2-Carboethoxy-3-[1*H*-imidazol-4(5)-yl]propionate (17a)

Phosphonium salt **5** (189 mg, 0.5 mmol) was added to a mixture of diethyl malonate (400 mg, 2.5 mmol) and 1 M solution of NaOEt (2.5 mL, 2.5 mmol). The whole mixture was refluxed for 1 h to give a white suspension. The resulting mixture was then acidified to pH 3 with 1 N HCl and evaporated. The residue was dissolved in water (10 mL) and washed with cold benzene (20 mL). The aq layer was neutralized by addition of $NaHCO_3$, and then extracted with $CHCl_3$ (4 × 15 mL) by salting-out techniques. The combined organic layer was dried and concentrated to give **17a**[13] (84 mg, 70%) as a viscous oil.

IR (film): 1660–1780 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.21 (t, *J* = 7.2 Hz, 6 H), 3.12 (d, *J* = 8.0 Hz, 2 H), 3.76 (t, *J* = 8.0 Hz, 1 H), 4.15 (q, *J* = 7.2 Hz, 4 H), 6.80 (s, 1 H), 7.58 (s, 1 H).

MS (SIMS): *m*/*z* = 241 [M^+ + 1].

HRMS: *m*/*z* [M^+ +1] calcd for $C_{11}H_{17}N_2O_4$: 241.1187; found: 241.1190.

Ethyl 2-[1*H*-Imidazol-4(5)-ylmethyl]-3-oxo-butyrate (17b)

A mixture of **5** (189 mg, 0.5 mmol), ethyl acetoacetate (195 mg, 1.5 mmol), and 1 M solution of NaOEt (1.5 mL, 1.5 mmol) was refluxed for 1 h to give a viscous oil **17b** (76 mg, 72%) using the same procedure as for the preparation of **17a**.

IR (film): 1710, 1735 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.24 (t, *J* = 7.2 Hz, 3 H), 2.24 (s, 3 H), 3.15 (d, *J* = 8.0 Hz, 2 H), 3.95 (t, *J* = 8.0 Hz, 1 H), 4.18 (q, *J* = 7.2 Hz, 2 H), 6.80 (s, 1 H), 7.56 (s, 1 H).

MS (SIMS): *m*/*z* = 211 [M^+ + 1].

HRMS: *m*/*z* [M^+ + 1] calcd for $C_{10}H_{15}N_2O_3$: 211.1082; found: 211.1078.

1-[1*H*-imidazol-4(5)-yl]-5-arylpentan-3-ones (4a) or 1-[1*H*-imidazol-4(5)-yl]-6-arylhexan-3-ones (4b); General Procedure

A mixture of 1 M EtOH solution of NaOEt (1.0 mL, 1.0 mmol) and **18** (1.5 mmol) was stirred at r.t. for 10 min under Ar. Phosphonium salt **5** (189 mg, 0.5 mmol) was added to the mixture, and the whole mixture was refluxed for 15 min. The resulting mixture was then acidified to pH 3 with 1 N HCl and evaporated to give a residue, which was dissolved in water (10 mL). The aq solution was washed with benzene (20 × 2 mL). The aq solution was neutralized by addition of $NaHCO_3$, and extracted with $CHCl_3$ (3 × 15 mL) by salting-out techniques. The combined organic layer was dried ($MgSO_4$) and evaporated to give crude **19**. It was dissolved in 3.6 N aq H_2SO_4 (2 mL) and heated at 65 °C for 48 h. The reaction mixture was then diluted with water (10 mL), neutralized with $NaHCO_3$, and extracted with $CHCl_3$ (3 × 15 mL) by salting-out techniques. The combined organic layer was dried ($MgSO_4$) and concentrated to give a residue, which was subsequently purified by column chromatography.

4a

Yield: 55%; viscous oil.

IR (film): 1705 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.64–2.96 (m, 8 H), 6.76 (s, 1 H), 7.12–7.36 (m, 5 H), 7.57 (s, 1 H).

MS (SIMS): *m*/*z* = 229 [M^+ + 1].

HRMS: *m*/*z* [M^+ + 1] calcd for $C_{14}H_{17}N_2O$: 229.1339; found: 229.1341.

4b

Yield: 64%; viscous oil.

IR (film): 1705 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.94 (quint, *J* = 8.0, 8.0 Hz, 2 H), 2.41 (t, *J* = 8.0 Hz, 2 H), 2.60 (t, *J* = 8.0 Hz, 2 H), 2.70–2.94 (m, 4 H), 6.78 (s, 1 H), 7.02–7.38 (m, 5 H), 7.53 (s, 1 H).

MS (SIMS): *m*/*z* = 243 [M^+ + 1].

HRMS: *m*/*z* [M^+ + 1] calcd for $C_{15}H_{19}N_2O$, 243.1496; found, 243.1495.

4c

Yield: 57%; prisms; mp 103–106 °C (EtOAc–hexane).

IR (nujol): 1695 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.62–2.94 (m, 8 H), 6.75 (s, 1 H), 7.04 (d, *J* = 8.0 Hz, 2 H), 7.20 (d, *J* = 8.0 Hz, 2 H), 7.51 (s, 1 H).

MS (EI, 70 eV): *m*/*z* = 262 [M^+].

HRMS: *m*/*z* [M^+] calcd for $C_{14}H_{15}ClN_2O$: 262.0872; found: 262.0864.

Anal. Calcd for $C_{14}H_{15}ClN_2O$: C, 64.00; H, 5.75; N, 10.66. Found: C, 64.13; H, 5.97; N, 10.70.

4d

Yield: 51%; needles; mp 85–86 °C (EtOAc–hexane).

IR (nujol): 1705 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.91 (quint, *J* = 7.2 Hz, 2 H), 2.42 (t, *J* = 7.2 Hz, 2 H), 2.56 (t, *J* = 7.2 Hz, 2 H), 2.62–2.95 (m, 4 H), 6.73 (s, 1 H), 7.03 (d, *J* = 8.8 Hz, 2 H), 7.21 (d, *J* = 8.8 Hz, 2 H), 7.55 (s, 1 H).

MS (EI, 70 eV): *m*/*z* = 276 [M^+].

HRMS: *m*/*z* [M^+] calcd for $C_{15}H_{17}ClN_2O$: 276.1028; found: 276.1025.

Anal. Calcd for $C_{15}H_{17}ClN_2O$: C, 65.10; H, 6.19; N, 10.12. Found: C, 64.99; H, 6.19; N, 10.03.

1-(4-Chlorophenyl)-3-{2-[1*H*-imidazol-4(5)-ylmethylsulfanyl]-ethyl}thiourea (21)

A mixture of 0.5 M MeOH solution of NaOMe (4.0 mL, 2.0 mmol) and cysteamine (1.0 mmol) was stirred at r.t. for 10 min under Ar. After **5** (378 mg, 1.0 mmol) was added, the whole mixture was refluxed for 2 h and then evaporated. The residue was dissolved in cold water (12 mL) and washed with benzene (20 × 2 mL). After the aq layer was diluted with cold MeOH (12 mL), the resulting solution was extracted with $CHCl_3$ (5 × 15 mL) by salting-out techniques. The combined organic layer was dried ($MgSO_4$) and concentrated to give crude **20**, which was subsequently dissolved in THF (4 mL). 4-Chlorophenyl isothiocyanate (254 mg, 1.5 mmol) was added to the THF solution and the mixture was stirred at r.t. for 3 h under Ar and then evaporated. The residue was purified by column chromatography to give **21** (68 mg, 21%) as a white amorphous product.

^{1}H NMR ($CDCl_3$): δ = 2.72 (t, *J* = 7.2 Hz, 2 H), 3.67–3.79 (m, 4 H), 7.02 (s, 1 H), 7.34 (s, 4 H), 7.62 (s, 1 H).

MS (SIMS): *m*/*z* = 327 [M^+ + 1].

HRMS: *m*/*z* [M^+ +1] calcd for $C_{13}H_{16}ClN_4S_2$: 327.0504; found: 327.0503.

Wittig Reaction of Phosphorus Ylide 22 with Cyclohexanecarbaldehyde

1 M THF solution of LiHMDS (1.5 mL, 1.5 mmol) was added dropwise to a suspension of **5** (284 mg, 0.75 mmol) in DMF (10 mL) at –40 °C, and the resulting deep red solution was stirred for 0.5 h at the same temperature. A solution of cyclohexancarbaldehyde (56 mg, 0.5 mmol) in DMF (2 mL) was added dropwise to the solution. After 15 min, it was allowed to reach r.t. (26 °C) and stirred for 1.5 h. Then, pyridine (0.12 mL, 1.5 mmol), ethyl chloroformate (0.14 mL, 1.5 mmol), and a cat. amount of 4-DMAP were added, and the whole mixture was stirred for 0.5 h. Water was added to the resulting mixture which was subsequently extracted with EtOAc (20 × 3 mL). The organic layer was dried and evaporated to give a crude oil. Chromatography on silica gel using 7% EtOAc in hexane as eluent gave (*Z*)-ethyl 4-(2-cyclohexylvinyl)imidazole-1-carboxylate [(*Z*)-**23**] (40 mg, 32%) and (*E*)-**23** (32 mg, 26%) in that order.

(*Z*)-23

Viscous oil.

^{1}H NMR ($CDCl_3$): δ = 1.10–1.38 (m, 5 H), 1.46 (t, *J* = 8.0 Hz, 3 H), 1.56–1.89 (m, 5 H), 2.70–2.90 (br, 1 H), 4.51 (q, *J* = 8.0 Hz, 2 H),

5.54 (dd, *J* = 11.6, 10.0 Hz, 1 H), 6.15 (d, *J* = 11.6 Hz, 1 H), 7.29 (s, 1 H), 8.09 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 14.2, 25.7, 32.6, 37.6, 64.4, 114.0, 118.2, 136.4, 139.7, 140.9, 148.6.

MS (EI, 70 eV): *m*/*z* = 248 [M^+].

HRMS: *m*/*z* [M^+] calcd for $C_{14}H_{20}N_2O_2$: 248.1524; found: 248.1527.

(*E*)-23
Viscous oil.

^{1}H NMR ($CDCl_3$): δ = 1.10–1.38 (m, 5 H), 1.44 (t, *J* = 8.0 Hz, 3 H), 1.55–1.95 (m, 5 H), 2.00–2.20 (br, 1 H), 4.48 (q, *J* = 8.0 Hz, 2 H), 6.29 (d, *J* = 16.0 Hz, 1 H), 6.42 (dd, *J* = 16.0, 6.6 Hz, 1 H), 7.20 (s, 1 H), 8.08 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 14.2, 26.0, 32.7, 40.9, 64.3, 112.3, 117.7, 137.0, 138.4, 142.1, 148.6.

MS (EI, 70 eV): *m*/*z* = 248 [M^+].

HRMS: *m*/*z* [M^+] calcd for $C_{14}H_{20}N_2O_2$: 248.1524; found: 248.1525.

4-{(*E*)-2-[(2*R*,5*R*)-5-*tert*-Butyldiphenylsiloxymethyl-tetrahydrofuran-2-yl]vinyl}-1-tritylimidazole [(*E*)-25] and (*Z*)-25
A 1.6 M hexane solution of BuLi (7.05 mL, 11.28 mmol) was added dropwise over 50 min to a suspension of **7** (6.99 g, 11.28 mmol) in THF (100 mL) at –70 °C, and the resulting red brown suspension was stirred for 15 min at the same temperature. A solution of aldehyde **24**[16] (3.46 g, 9.40 mmol) in THF (20 mL) was added dropwise over 40 min to the suspension. After stirring for 0.5 h, it was allowed to reach r.t. After evaporation of the solvent, water (100 mL) was added to the residue, which was subsequently extracted with $CHCl_3$ (3 × 100 mL). The organic layer was dried ($MgSO_4$) and evaporated to give a crude oil. Chromatography on silica gel using EtOAc–hexane (1:3) as eluent gave (*Z*)-**25** (1.99 g, 32%) and (*E*)-**25** (2.49 g, 39%) in that order.

(*E*)-25
Viscous oil.

^{1}H NMR ($CDCl_3$): δ = 1.03 (s, 9 H), 1.65–2.20 (m, 4 H), 3.64 (dd, *J* = 10.6, 5.3 Hz, 1 H), 3.68 (dd, *J* = 10.6, 4.4 Hz, 1 H), 4.15–4.24 (m, 1 H), 4.55 (q, *J* = 6.2 Hz, 1 H), 6.27 (dd, *J* = 15.5, 6.2 Hz, 1 H), 6.42 (d, *J* = 15.5 Hz, 1 H), 6.74 (s, 1 H), 7.10–7.70 (m, 26 H).

MS (EI, 70 eV): *m*/*z* = 675 [M^+ + 1].

HRMS: *m*/*z* [M^+ + 1] calcd for $C_{45}H_{47}N_2O_2Si$: 675.3404; found: 675.3410.

(*Z*)-25
Viscous oil.

^{1}H NMR ($CDCl_3$): δ = 1.03 (s, 9 H), 1.60–2.20 (m, 4 H), 3.48 (dd, *J* = 10.0, 6.4 Hz, 1 H), 3.66 (dd, *J* = 10.0, 4.8 Hz, 1 H), 4.10–4.22 (m, 1 H), 5.20 (q, *J* = 8.0 Hz, 1 H), 5.58 (dd, *J* = 12.0, 8.0 Hz, 1 H), 6.28 (d, *J* = 12.0 Hz, 1 H), 6.77 (s, 1 H), 7.05–7.75 (m, 26 H).

MS (EI, 70 eV): *m*/*z* = 675 [M^+ + 1].

HRMS: *m*/*z* calcd for $C_{45}H_{47}N_2O_2Si$: 675.3404; found: 675.3415.

4-{(*E*)-2-[(2*R*,5*R*)-5-Hydroxymethyltetrahydrofuran-2-yl]vinyl}-1-tritylimidazole [(*E*)-26]
A 1 M THF solution of TBAF (4.1 mL, 4.1 mmol) was added to a solution of (*E*)-**25** (2.49 g, 3.69 mmol) in THF (80 mL) at 0 °C. After the reaction mixture was stirred at r.t. for 3 h, the solvent was removed by evaporation to give a residue. It was then purified by column chromatography using EtOAc to give (*E*)-**26** (1.22 g, 76%) as white powder; mp 201–207 °C.

^{1}H NMR ($CDCl_3$): δ = 1.60–2.20 (m, 4 H), 3.42–3.70 (m, 2 H), 4.14–4.23 (m, 1 H), 4.57 (q, *J* = 7.2 Hz, 1 H), 6.30 (dd, *J* = 15.6, 7.2 Hz, 1 H), 6.45 (d, *J* = 15.6 Hz, 1 H), 6.77 (s, 1 H), 7.08–7.40 (m, 16 H).

MS (SIMS): *m*/*z* = 437 [M^+ + 1].

HRMS: *m*/*z* [M^+ + 1] calcd for $C_{29}H_{29}N_2O_2$: 437.2227; found: 437.2224.

(*Z*)-26

Yield: 66%; white powder.

^{1}H NMR ($CDCl_3$): δ = 1.60–2.25 (m, 4 H), 3.40–3.72 (m, 2 H), 4.13–4.22 (m, 1 H), 5.38 (q, *J* = 8.4 Hz, 1 H), 5.59 (dd, *J* = 12.0, 8.4 Hz, 1 H), 6.33 (d, *J* = 12.0 Hz, 1 H), 6.80 (s, 1 H), 7.08–7.43 (m, 16 H).

MS (EI, 70 eV): *m*/*z*: 436 [M^+].

HRMS: *m*/*z* [M^+] calcd for $C_{29}H_{28}N_2O_2$: 436.2149; found: 436.2149.

(2*R*,5*R*)-5-[(*E*)-2-(1-Tritylimidazol-4-yl)vinyl]-tetrahydrofuran-2-carbaldehyde [(*E*)-27]
Freshly prepared IBX (96 mg, 0.35 mmol) was added to a solution of (*E*)-**26** (100 mg, 0.23 mmol) in THF (4 mL), and the resulting suspension was refluxed for 2 h. The solvent was evaporated to give a residue, which was subsequently dissolved in CH_2Cl_2 (10 mL). Sat. aq solution of $NaHCO_3$ (10 mL) containing $Na_2S_2O_3{\cdot}5H_2O$ (595 mg) was added to the CH_2Cl_2 solution, and the resulting mixture was stirred for 10 min. The CH_2Cl_2 layer was separated and the aq layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined CH_2Cl_2 layer was dried (Mg SO_4) and evaporated to give (*E*)-**27** (100 mg, quant.) as a white amorphous product.

IR ($CHCl_3$): 1724 (CHO) cm^{-1}.

^{1}H NMR ($CDCl_3$) δ = 1.70–2.30 (m, 4 H), 4.40 (t, *J* = 8.0 Hz, 1 H), 4.68 (q, *J* = 5.3 Hz, 1 H), 6.30 (dd, *J* = 14.7, 5.3 Hz, 1 H), 6.48 (d, *J* = 14.7 Hz, 1 H), 6.77 (s, 1 H), 7.06–7.40 (m, 16 H), 9.68 (s, 1 H).

MS (EI, 70 eV): *m*/*z* = 434 [M^+].

HRMS: *m*/*z* [M^+] calcd for $C_{29}H_{26}N_2O_2$: 434.1992; found: 434.1990.

(*Z*)-27
Yield: 96%; white amorphous product.

^{1}H NMR ($CDCl_3$): δ = 1.60–2.30 (m, 4 H), 4.34 (t, *J* = 8.0 Hz, 1 H), 5.40–5.50 (m, 1 H), 5.58 (dd, *J* = 12.0, 8.4 Hz, 1 H), 6.33 (d, *J* = 12.0 Hz, 1 H), 6.85 (s, 1 H), 7.06–7.43 (m, 16 H), 9.55 (s, 1 H).

MS (EI, 70 eV): *m*/*z* = 434 [M^+].

HRMS: *m*/*z* [M^+] calcd for $C_{29}H_{26}N_2O_2$: 434.1992; found: 434.1982.

4-{(*E*)-2-[(2*R*,5*R*)-5-Benzylaminomethyltetrahydro-furan-2-yl]vinyl}-1-tritylimidazole [(*E*)-28]
To a solution of (*E*)-**27** (78 mg, 0.18 mmol) and benzylamine (547 mg, 5.12 mmol) in EtOH (4 mL) was added powdered 3A molecular sieves (200 mg). After stirring of the mixture at r.t. for 3 h, $NaBH_4$ (195 mg, 5.12 mmol) was added and the mixture was stirred for 17 h at r.t. The reaction mixture was filtered through Celite pad and EtOH was evaporated to give a residual oil, which was subsequently purified by chromatography to give (*E*)-**28** (73 mg, 78%) as an oil.

^{1}H NMR ($CDCl_3$) δ = 1.60–2.20 (m, 4 H), 2.60–2.80 (m, 2 H), 3.00–3.35 (br s, 1 H), 3.86 (d, *J* = 5.2 Hz, 2 H), 4.20–4.32 (m, 1 H), 4.52 (q, *J* = 6.5 Hz, 1 H), 6.28 (dd, *J* = 15.6, 6.5 Hz, 1 H), 6.42 (d, *J* = 15.6 Hz, 1 H), 6.75 (s, 1 H), 7.05–7.40 (m, 21 H).

MS (SIMS): *m*/*z* = 526 [M^+ + 1].

HRMS: *m*/*z* [M^+ + 1] calcd for $C_{36}H_{36}N_3O$: 526.2856; found: 526.2843.

(*Z*)-28
Yield: 68%; oil.

^{1}H NMR ($CDCl_3$) δ = 1.50–2.20 (m, 4 H), 2.30–2.80 (br s, 1 H), 2.65 (d, *J* = 8.0 Hz, 2 H), 3.80 (s, 2 H), 4.27 (quint, *J* = 6.4 Hz, 1 H), 5.30 (q, *J* = 8.0 Hz, 1 H), 5.58 (dd, *J* = 12.0, 8.0 Hz, 1 H), 6.30 (d, *J* = 12.0 Hz, 1 H), 7.79 (s, 1 H), 7.00–7.60 (m, 21 H).

MS (SIMS): *m*/*z* = 526 [M^+ + 1].

HRMS: *m*/*z* [M^+ + 1] calcd for $C_{36}H_{36}N_3O_1$: 526.2856; found: 526.2850.

(–)-4(5)-{2-[(2*S*,5*R*)-5-Aminomethyltetrahydrofuran-2-yl]ethyl}imidazole [(–)-3]
A solution of (*E*)-**28** (73 mg, 0.14 mmol) in aq 1 N HCl (0.7 mL)–EtOH (5 mL) was stirred at r.t. for 10 min, and evaporated to give a white residue (**28**·2HCl). A solution of the dihydrochloride in MeOH (5 mL) was subsequently hydrogenated with 10% Pd-C (100 mg) as catalyst at initial pressure of 3.2 kg/cm^2 for 48 h. The catalyst was removed by filtration and the filtrate was concentrated to give a residue, which was subsequently placed on a column. Chromatography using $CHCl_3$–MeOH–28% NH_4OH (30:2:1) as the eluent gave **3** (20 mg, 74%) as a colorless oil; $[\alpha]_D$ –19.2 (*c* 2.00, MeOH).

^{1}H NMR (CD_3OD): δ = 1.45–2.12 (m, 6 H), 2.50–2.76 (m, 4 H), 3.88–4.05 (m, 2 H), 6.77 (s, 1 H), 7.47 (s, 1 H).

SIMS: *m*/*z* = 196 [M^+ + 1].

HRMS: *m*/*z* [M^+ + 1] calcd for $C_{10}H_{18}N_3O$: 196.1449; found: 196.1431.

References

(1) Grimmett, M. R. In *Comprehensive Heterocyclic Chemistry II: Imidazoles*, Vol. 3; Katritzky, A. R.; Rees, C. W.; Scriven, E. F., Eds.; Pergamon: Oxford, **1996**, 77–220.

(2) For reviews, see: (a) Stark, H.; Schlicker, E.; Schunack, W. *Drugs Future* **1996**, *21*, 507. (b) Leurs, R.; Blandian, P.; Tedford, C.; Timmerman, H. *TIPS* **1998**, *19*, 177. (c) Watanabe, T.; Timmerman, H.; Yanai, K. *Histamine Reseach in the New Millennium*; Elsevier: Amsterdom, **2001**.

(3) For a review, see: Hough, L. B. *Mol. Pharmacol.* **2001**, *59*, 415.

(4) (a) Harusawa, S.; Imazu, T.; Takashima, S.; Araki, L.; Ohishi, H.; Kurihara, T.; Yamamoto, Y.; Yamatodani, A. *Tetrahedron Lett.* **1999**, *40*, 2561. (b) Harusawa, S.; Imazu, T.; Takashima, S.; Araki, L.; Ohishi, H.; Kurihara, T.; Sakamoto, Y.; Yamamoto, Y.; Yamatodani, A. *J. Org. Chem.* **1999**, *64*, 8608.

(5) Hashimoto, T.; Harusawa, S.; Araki, L.; Zuiderveld, O. P.; Smit, M. J.; Imazu, T.; Takashima, S.; Yamamoto, Y.; Sakamoto, Y.; Kurihara, T.; Leurs, R.; Bakker, R.; Yamatodani, A. *J. Med. Chem.* **2003**, *46*, 3162.

(6) (a) Vollinga, R. C.; Menge, W. M. P. B.; Leurs, R.; Timmerman, H. *J. Med. Chem.* **1995**, *38*, 266. (b) Vollinga, R. C.; Menge, W. M. P. B.; Leurs, R.; Timmerman, H. *J. Med. Chem.* **1995**, *38*, 2244. (c) De Esch, I. J. P.; Gaffar, A.; Menge, W. M. P. B.; Timmerman, H. *Bioorg. Med. Chem.* **1999**, *7*, 3003. (d) Kazuta, Y.; Hirano, K.; Natsume, K.; Yamada, S.; Kimura, R.; Matsumoto, S.; Furuichi, K.; Matsuda, A.; Shuto, S. *J. Med. Chem.* **2003**, *46*, 1980.

(7) Harusawa, S.; Koyabu, S.; Inoue, Y.; Sakamoto, Y.; Araki, L.; Kurihara, T. *Synthesis* **2002**, 1072.

(8) (a) Lassalle, G.; Purcell, T.; Galtier, D.; Williams, P. H.; Galli, F. Eur. Pat. Appl., EP 565396, **1993**. (b) Perard, S.; Zard, L.; Rossey, G. Eur. Pat. Appl., EP 614986, **1994**. (c) Lassalle, G.; Galtier, D.; Galli, F. Eur. Pat. Appl., EP 643047, **1995**. (d) Galtier, D.; Lassalle, G. Eur. Pat. Appl., EP 643046, **1995**. (e) Lassalle, G.; Galtier, D.; Galli, F. Fr Demande., FR 2710067, **1995**. (f) Lassalle, G.; Purcell, T.; Galtier, D.; Williams, P. H.; Galli, F. US Pat., US 5453430, **1996**. (g) Yokohama, S.; Takeda, Y.; Kawakoshi, K.; Yamamoto, K. Jpn. Kokai Tokkyo Koho, JP 11279156, **1999**.

(9) (a) Bruice, T. C.; Herz, J. L. *J. Am. Chem. Soc.* **1964**, *86*, 4109. (b) Harusawa, S.; Murai, Y.; Moriyama, H.; Imazu, T.; Ohishi, H.; Yoneda, R.; Kurihara, T. *J. Org. Chem.* **1996**, *61*, 4405.

(10) (a) Coates, I. H.; Charles, N. P.; William, O. A. Eur. Pat. Appl., EP 306323, **1989**. (b) Cordi, A. A.; Snyers, M. P.; Giraud-Mangin, D.; Van der Maesen, C.; Van Hoeck, J. P.; Beuze, S.; Ellens, E.; Napora, F.; Gillet, C. L.; Gorissen, H.; Calderon, P.; Remacle, M. D.; Janssens de Varebeke, P.; Van Dorsser, W.; Roba, J. *Eur. J. Med. Chem.* **1990**, *25*, 557.

(11) (a) Zbiral, E.; Hugl, E. *Phosphorus* **1972**, *2*, 29. (b) Zbiral, E. *Synthesis* **1974**, 775. (c) Webb, R. L.; Lewis, J. J. *J. Heterocycl. Chem.* **1981**, *18*, 1301.

(12) (a) Staab, H. A.; Datta, A. P. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 132. (b) Devos, A.; Remion, J.; Frisque-Hesbain, A. M.; Colens, A.; Ghosez, L. *J. Chem. Soc., Chem. Commun.* **1979**, 1180. (c) Villeneuve, G. B.; Chan, T. H. *Tetrahedron Lett.* **1997**, *38*, 6489.

(13) Chaturvedi, N.; Goodman, M.; Bowers, C. *Int. J. Peptide Protein Res.* **1981**, *17*, 72.

(14) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.

(15) (a) Vollinger, R. C.; Zuiderveld, O. P.; Scheerens, H.; Bast, A.; Timmerman, H. *Methods Find Exp. Clin. Pharmacol.* **1992**, *14*, 747. (b) Hashimoto, T.; Hidaka, R.; Yamamoto, Y.; Harusawa, S.; Araki, L.; Kurihara, T.; Sakamoto, Y.; Yamatodani, A. *Inflamm. Res.* **2003**, in press.

(16) Koert, U.; Stein, M.; Wagner, H. *Liebings Ann.* **1995**, 1415.

(17) Dess–Martin periodinane was purchased from Lancaster or Aldrich.

(18) (a) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272. (b) Frigerio, M.; Santagostino, M. *Tetrahedron. Lett.* **1994**, *35*, 8019. (c) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

(19) Bonnet, B.; Soullez, D.; Girault, S.; Maes, L.; Landry, V.; Davioud-Charvet, E.; Sergheraert, C. *Bioorg. Med. Chem.* **2000**, *8*, 95.