Synthesis of 1-(1*H*-Imidazol-2-yl)ethane-1,2-diol Derivatives: a Novel Class of Protein Kinase C Inhibitors

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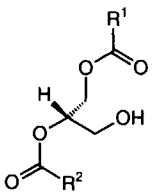
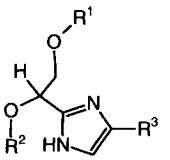
Compounds **6**–**13** were prepared starting from 1-(triphenylmethyl)-protected 1*H*-imidazoles **14** and **15** in several steps. Lithiation with BuLi in THF followed by reaction with (triphenylmethoxy)acetaldehyde (**16**) afforded **17** and **18**, respectively. *O*-Methylation of **17** and **18** gave diethers **19** and **20**, respectively. The *N*- and *O*-trityl protecting groups of **17**–**20** were cleaved by acid treatment to give deprotected compounds **21**–**24**. Acylation with equimolar amounts (for mono- or di-*O*-acylation) of the corresponding acyl chlorides yielded 1*H*-imidazoles **6**–**13**. Compounds **7**, **8**, **10**, and **11** exhibited moderate protein kinase C inhibition.

Introduction. – Protein kinase C (PKC), the major receptor for a number of tumor-promoting agents utilizes di-*O*-acylglycerol (DAG; **1a**) in combination with calcium to modulate various cellular functions, including cellular signal transduction, differentiation, and proliferation [1]. The acyl groups in the majority of di-*O*-acylglycerols produced in cells are stearoyl (= octadecanoyl) and arachidonoyl (= eicosa-5,8,11,14-tetraenoyl) in the 1- and 2-positions, respectively [2]. A series of synthetic di-*O*-acylglycerols with a variety of chain lengths and degrees of unsaturation are also able to bind to an activate PKC [3]. Phorbol esters have been found to substitute for di-*O*-acylglycerol as a potent enzyme stimulator [2][4]. Unlike di-*O*-acylglycerol, phorbol esters are not rapidly metabolized and thus can effect prolonged enzyme stimulation often leading to neoplastic events and intense inflammation [5]. Given the biological responses induced by activators of PKC, the development of inhibitors of this enzyme may lead to therapeutic agents useful in the treatment of chronic inflammatory and proliferative diseases.

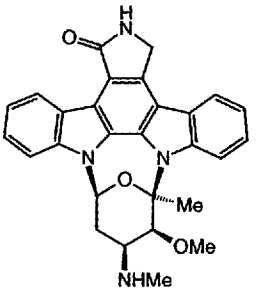


1a DAG



1b

Since the most potent PKC inhibitors have amphoteric characteristics (*e.g.*, staurosporine (**2**) [6], 2-(aminomethyl)piperidines **3** [7], balanol (**4**) [8] and analogues [9], and indolocarbazoles **5** [10]), we speculated that compounds of type **1b** having an imidazolyl group instead of a hydroxymethyl group in DAG (**1a**) could modify the activity of PKC.



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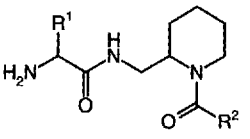

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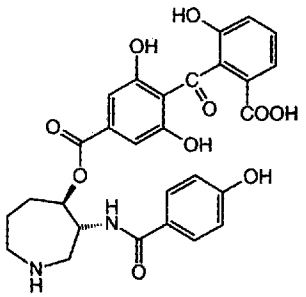

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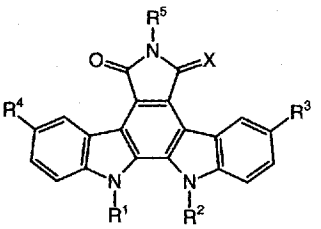

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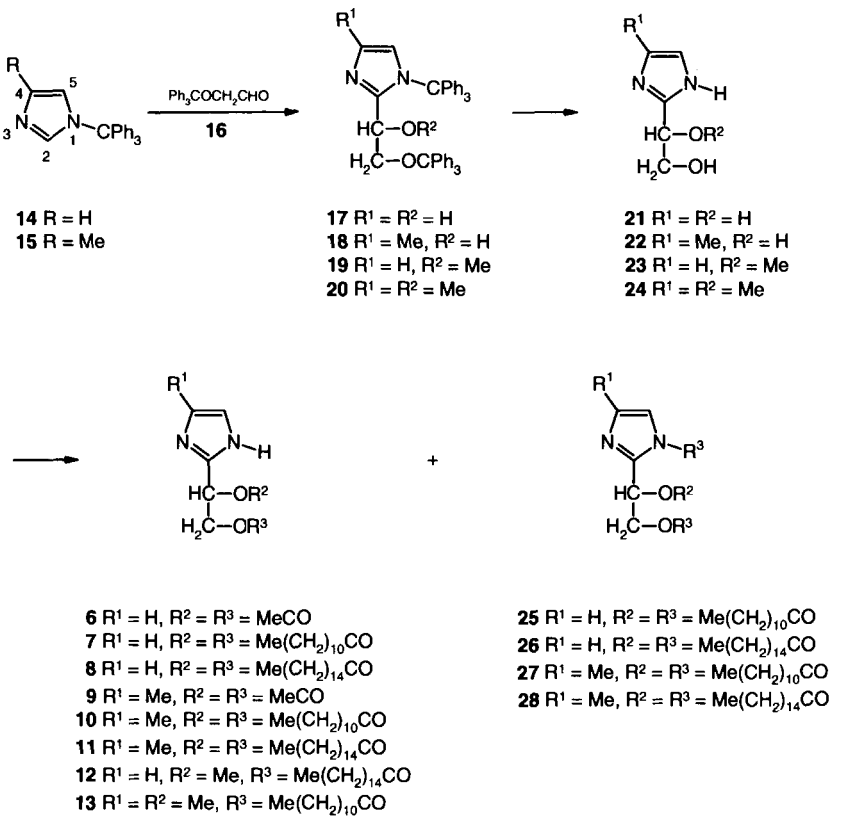
Thus, 1-(1*H*-imidazol-2-yl)ethane-1,2-diol-derived esters and ethers **6**–**13** were prepared.

Results and Discussion. – Compounds **6**–**13** were prepared starting from 1-(triphenylmethyl)-protected 1*H*-imidazoles **14** and **15** which are readily available from 1*H*-imidazole and 4(5)-methyl-1*H*-imidazole, respectively [11]. Lithiation with BuLi in THF [11][12] followed by reaction with (triphenylmethoxy)acetaldehyde (**16**) afforded **17** and **18**, respectively. The preparation of (triphenylmethoxy)acetaldehyde (**16**) from 1-*O*-(triphenylmethyl)glycerol by oxidation with $Pb(OAc)_4$ in benzene was described earlier [13], but the authors were not able to obtain **16** in pure form (a yellow foam was isolated). Using toluene instead of benzene furnished in our hands pure, crystalline **16** in high yield (see *Exper. Part*). *O*-Methylation of **17** and **18** with dimethyl sulfate in DMF using NaH as base afforded diethers **19** and **20**, respectively. The *N*- and *O*-trityl protecting groups of **17**–**20** were cleaved by acid treatment (MeOH/HCl) to give the deprotected alcohols **21**–**24**. Acylation of **21**–**24** with equimolar amounts (for mono- or di-*O*-acylation) of the corresponding acyl chlorides in CH_2Cl_2 using pyridine as base gave the products **6**, **9**, **12**, and **13** (yields 62–81%) without *N*-acylated by-products, while, besides the products **7**, **8**, **10**, and **11** (yields 61–77%), also *N*-acyl compounds **25**–**28** were observed in minor amounts (< 15%). The amount of *N*-acyl derivatives **25**–**28** could be

Scheme



increased (> 50%) by using 3 equiv. of acyl chloride at the expense of **7**, **8**, **10**, and **11** (23–44%). The N–acyl bond could be cleaved selectively by refluxing, *e.g.*, **26** in MeOH in the presence of catalytic amounts of AcOH (→ 1*H*-imidazole **8**).

Assignment of position 4 to the Me group in 1-trityl 1*H*-imidazole **15** by *Cohen* and coworkers [11] was based on the H,H-coupling constants $J(2,4)$ and $J(2,5)$. Since position 2 is substituted in the 1-acyl-1*H*-imidazoles **27** and **28**, an analogous assignment was not possible. Although NMR spectra suggest the existence of single position isomers, an unambiguous assignment was not feasible.

Compounds **7**–**13** were tested for PKC inhibition as described earlier [14]. Compounds **7**, **8**, **10**, and **11** exhibited moderate PKC inhibition with IC_{50} values in the μM range, while the IC_{50} value of staurosporine (**2**) is in the nM range [10][1]).

In grateful remembrance, we are mindful of the initiation of this work by the late Prof. Dr. *W. Klötzer*. We are greatly indebted to Dr. *C. Schächtele*, *Gödecke AG*, Freiburg, Germany, for evaluation of PKC inhibition. We wish to thank Prof. Dr. *K.-H. Ongania* for performing the mass spectra and Prof. Dr. *E. Ellmerer-Müller* and Mag. *W. Mühlecker* for recording the NMR spectra (Institute of Organic Chemistry, University of Innsbruck). We further thank the Analytical Department of *F. Hoffmann-La Roche Ltd.*, Basel, for elemental analyses.

[1]) The tests were carried out for us through the courtesy of Dr. *C. Schächtele*, *Gödecke AG*, Freiburg, Germany.

Experimental Part

General. M.p.: *Kofler* melting-point microscope; uncorrected. IR Spectra: in cm^{-1}; *Shimadzu IR-470* apparatus. ^1H- and ^{13}C-NMR Spectra: *Bruker-AM-300* spectrometer; δ in ppm rel. to $SiMe_4$ as internal reference, J in Hz. Mass spectra: in *m/z*; *Finnigan MAT-44/S*. Elemental analyses were performed at the Analytical Department of *F. Hoffmann-La Roche Ltd.*, Basel.

(Triphenylmethoxy)acetaldehyde (**16**) [13]. $Pb(OAc)_4$ (13.44 g, 25 mmol) was added in portions to a stirred soln. of 1-*O*-(triphenylmethyl)glycerol [15] (8.36 g, 25 mmol) in toluene (170 ml) under N_2 at r.t. The resulting mixture was stirred vigorously for 2 h, then poured on H_2O (250 ml), and filtered after addition of toluene (170 ml). The org. layer of the filtrate was washed with H_2O (2 × 80 ml) and sat. $NaHCO_3$ soln. (2 × 80 ml), dried (Na_2SO_4), and evaporated. 7.1 g (94%) of **16**. Colorless crystals. M.p. 58–85°. IR (KBr): 1731 (CO). ^1H-NMR ($CDCl_3$): 9.49 (*t*, J = 1.2, CHO); 7.47–7.21 (*m*, 15 arom. H); 3.84 (*d*, J = 1.2, CH_2). ^{13}C-NMR ($CDCl_3$): 200.53 (CHO); 143.17 (arom. C); 128.58, 128.08, 127.44 (arom. CH); 87.60 (Ph_3C); 70.42 (CH_2). CI-MS: 303 ($[M + 1]^+$).

Compounds **17** *and* **18**. BuLi (1.6M in hexane, 13.75 ml) was added dropwise 10 min to a soln. of the 1*H*-imidazole derivative **14** or **15** (20 mmol) in anh. THF (300 ml) at −40° under N_2 while stirring. The resulting mixture was stirred at −40° for 2 h and for another hour after removal of the cooling bath (the temp. raised to 5°). The now reddish mixture was cooled to −40° again, and a soln. of **16** (7.26 g, 24 mmol) in anh. THF (50 ml) was added dropwise within 10 min. The resulting mixture was stirred at −40° for 30 min and another 3.5 h while the temp. was gradually raised to 14°. The mixture was cooled to 0° and poured on ice-cold sat. NH_4Cl soln. (60 ml), the org. layer dried (Na_2SO_4) and evaporated, and the yellow foam crystallized from MeOH (60 ml; **17**) or i-PrOH (60 ml; **18**).

α-[(Triphenylmethoxy)methyl]-1-(triphenlymethyl)-1H-imidazole-2-methanol (**17**): 5.19 g (42%). M.p. 197–200°. IR (KBr): 3415 (OH). ^1H-NMR ($CDCl_3$): 7.28–7.08 (*m*, 30 arom. H); 6.94 (*d*, J = 1.4, 1 H (im)); 6.68 (*d*, J = 1.4, 1 H (im)); 4.27 (*m*, CHO); 3.28 (*dd*, J = 9.5, 8.7, 1 H, CH_2); 2.32 (*dd*, J = 9.5, 2.9, 1 H, CH_2); 2.07 (*d*, J = 6.2, OH). ^{13}C-NMR ($CDCl_3$): 149.22 (C(2)(im)); 143.80 (arom. C); 142.41 (arom. C); 129.69, 128.94, 128.01, 127.60, 126.79 (arom. CH); 126.30 (C(4) or C(5)(im)); 121.50 (C(4) or C(5)(im)); 86.43 (Ph_3CO); 75.11 (Ph_3CN); 66.91 (CHO); 66.21 (CH_2O). CI-MS: 613 ($[M + 1]^+$). Anal. calc. for $C_{43}H_{36}N_2O_2$ (612.77): C 84.29, H 5.92, N 4.57; found: C 84.44, H 5.89, N 4.49.

4-Methyl-α-[(triphenylmethoxy)methyl]-1-(triphenylmethyl)-1H-imidazole-2-methanol (**18**): 2.83 g (23%). M.p. 165–170°. IR (KBr): 3555, 3405 (OH). ^1H-NMR ($CDCl_3$): 7.30–7.09 (*m*, 30 arom. H); 6.36 (*q*, J = 0.9, 1 H (im)); 4.24 (*m*, CHO); 3.30 (*dd*, J = 9.5, 8.5, 1 H, CH_2); 2.35 (*dd*, J = 9.5, 2.9, 1 H, CH_2); 2.11 (*d*, J = 0.9, Me); 1.99 (*d*, J = 6.1, OH). ^{13}C-NMR ($CDCl_3$): 148.31 (C(2)(im)); 143.90 (arom. C); 142.66 (arom. C); 135.11 (C(4)(im)); 129.71, 129.01, 127.95, 127.91, 127.57, 126.76 (arom. C); 118.06 (C(5)(im)); 86.32 (Ph_3CO); 74.81 (Ph_3CN); 67.08 (CHO); 66.44 (CH_2O). CI-MS: 627 ($[M + 1]^+$). Anal. calc. for $C_{44}H_{38}N_2O_2$ (626.80): C 84.31, H 6.11, N 4.47; found: C 84.08, H 6.07, N 4.44.

Compounds **19** *and* **20**. NaH (96 mg, 4 mmol; obtained from 175 mg of 60% NaH dispersion in oil by washings with petroleum ether) was added to a suspension of **17** or **18** (1 mmol) in anh. DMF (10 ml) under N_2 at 5° (bath temp., in the case of **17**) or 90° (bath temp.; in the case of **18**) while stirring. After 30 min, the temp. was brought to 5°, dimethyl sulfate (0.12 ml, 1.2 mmol) added, and the resulting mixture stirred at 5° (bath temp.) for 90 min. Excess NaH was destroyed carefully by addition of small pieces of ice. Then the mixture was diluted with H_2O (50 ml) and extracted with CH_2Cl_2 (4 × 10 ml), the combined org. phase washed with H_2O (3 × 10 ml) and brine (10 ml), dried (Na_2SO_4), and evaporated and the crystalline residue treated with hot MeOH (15 ml).

2-[1-Methoxy-2-(triphenylmethoxy)ethyl]-1-(triphenylmethyl)-1H-imidazole (**19**): 480 mg (77%). M.p. 220–235° (dec.). ^1H-NMR ($CDCl_3$): 7.21–7.11 (*m*, 30 arom. H); 6.92 (*s*, 1 H (im)); 6.61 (*s*, 1 H (im)); 3.87 (*m*, CHO); 3.78 (*m*, 1 H, CH_2); 3.14 (*s*, MeO); 2.48 (*m*, 1 H, CH_2). ^{13}C-NMR ($CDCl_3$): 147.59 (C(2)(im)); 143.81 (arom. C); 142.54 (arom. C); 129.76, 129.02, 127.96, 127.58, 126.74 (arom. CH); 126.29 (C(4) or C(5)(im)); 121.53 (C(4) or C(5)(im)); 86.74 (Ph_3CO); 75.42 (CHO); 75.16 (Ph_3CN); 66.90 (CH_2O); 59.53 (MeO). CI-MS: 627 ($[M + 1]^+$). Anal. calc. for $C_{44}H_{38}N_2O_2$ (626.80): C 84.31, H 6.11, N 4.47; found: C 84.25, H 6.26, N 4.38.

2-[1-Methoxy-2-(triphenylmethoxy)ethyl]-4-methyl-1-(triphenylmethyl)-1H-imidazole (**20**): 510 mg (80%). M.p. (toluene) 195–205° (dec.). ^1H-NMR ($CDCl_3$): 7.29–7.10 (*m*, 30 arm. H); 6.29 (*s*, 1 H (im)); 3.83 (*m*, CHO); 3.75 (*dd*, J = 9.4, 8.5, 1 H, CH_2); 3.15 (*s*, MeO); 2.49 (*dd*, J = 9.4, 1.7, 1 H, CH_2); 2.09 (*s*, Me). ^{13}C-NMR ($CDCl_3$): 146.71 (C(2)(im)); 143.89 (arom. C); 142.78 (arom. C); 135.07 (C(4) (im)); 129.78, 129.08, 128.20, 127.86, 127.54, 126.71 (arom. CH); 118.04 (C(5)(im)); 86.64 (Ph_3CO); 75.68 (CHO); 74.86 (Ph_3CN); 67.10 (CH_2O); 59.71 (MeO); 13.64 (Me). CI-MS: 641 ($[M + 1]^+$). Anal. calc. for $C_{45}H_{40}N_2O_2 \cdot 0.5$ toluene (686.89): C 84.81, H 6.46, N 4.08; found: C 84.74, H 6.49, N 4.05.

Compounds **21**–**24**. A mixture of 1*H*-imidazole **17**, **18**, **19**, or **20** (5 mmol), MeOH (50 ml), and conc. HCl soln. (5 ml) was refluxed for 6 h and then cooled to 0–5°. Crystalline Ph_3COH precipitated and was removed by filtration. The filtrate was evaporated and the resulting residue dried in an exsiccator, first over P_2O_5, then over KOH. The dry residue was dissolved in little anh. EtOH (hot), anh. Et_2O (150 ml) was added, and the mixture kept refrigerated overnight. The colorless precipitation was isolated, washed with anh. Et_2O, and dried (products are hygroscopic).

1-(1H-Imidazol-2-yl)ethane-1,2-diol Hydrochloride (**21** · HCl): 750 mg (91%). M.p. 124–137°. ^{1}H-NMR ((D_6)DMSO): 14.33 (br. *s*, NH, NH^+); 7.55 (*s*, 2 H (im)); 6.51, 5.22 (2 br. *s*, 2 OH); 4.92 (*m*, CHO); 3.71 (*m*, CH_2O). ^{13}C-NMR ((D_6)DMSO): 148.37 (C(2)(im)); 118.74 (C(4), C(5)(im)); 66.37 (CHO); 63.72 (CH_2O). CI-MS: 129 ($[M + 1]^+$). Anal. calc. for $C_5H_8N_2O_2 \cdot HCl$ (164.59): C 36.49, H 5.51, N 17.02; found: C 36.19, H 5.53, N 16.98.

1-[4(5)-Methyl-1H-imidazol-2-yl]ethane-1,2-diol Hydrochloride (**22** · HCl): 848 mg (95%). M.p. 109–112°. ^{1}H-NMR ((D_6)DMSO): 14.11 (br. *s*, NH, NH^+); 7.23 (*s*, 1 H (im)); 6.46, 5.21 (2 br. *s*, 2 OH); 4.85 (*m*, CHO); 3.68 (*m* CH_2O); 2.23 (*s*, Me). ^{13}C-NMR ((D_6)DMSO): 147.51 (C(2)(im)); 128.49 (C(4) or C(5)(im)); 115.13 (C(4) or C(5)(im)); 66.37 (CHO); 63.79 (CH_2O); 9.50 (Me). CI-MS: 143 ($[M + 1]^+$). Anal. calc. for $C_6H_{10}N_2O_2 \cdot HCl$ (178.62): C 40.35, H 6.21, N 15.68; found: C 40.12, H 6.32, N 15.41.

β-Methoxy-1H-imidazole-2-ethanol Hydrochloride (**23** · HCl): 725 mg (81%). M.p. 113–123°. ^{1}H-NMR ((D_6)DMSO): 14.60 (br. *s*, NH, NH^+); 7.61 (*s*, 2 H (im)); 5.30 (br. *s*, OH); 4.70 (*t*, *J* = 5.3, CHO); 3.78 (*d*, *J* = 5.3, CH_2O); 3.32 (*s*, MeO). ^{13}C-NMR ((D_6)DMSO): 145.32 (C(2)(im)); 119.23 (C(4), C(5)(im)); 75.48 (CHO); 61.44 (CH_2O); 57.55 (MeO). CI-MS: 143 ($[M + 1]^+$). Anal. calc. for $C_6H_{10}N_2O_2 \cdot HCl \cdot 0.3\ H_2O$ (184.03): C 39.19, H 6.35, N 15.22; found: C 39.22, H 6.38, N 15.26.

β-Methoxy-4(5)-methyl-1H-imidazole-2-ethanol Hydrochloride (**24** · HCl): 665 mg (69%). M.p. 70–76°. ^{1}H-NMR ((D_6)DMSO): 14.30 (br. *s*, NH, NH^+); 7.30 (*s*, 1 H (im)); 5.27 (br. *s*, OH); 4.61 (*t*, *J* = 5.3, CHO); 3.76 (*d*, *J* = 5.3, CH_2O); 3.32 (*s*, MeO); 2.25 (*s*, Me). ^{13}C-NMR ((D_6)DMSO): 144.40 (C(2)(im)); 129.08 (C(4) or C(5)(im)); 115.73 (C(4) or C(5)(im)); 75.55 (CHO); 61.46 (CH_2O); 57.50 (MeO); 9.53 (Me). CI-MS: 157 ($[M + 1]^+$). Anal. calc. for $C_7H_{12}N_2O_2 \cdot HCl \cdot 0.1\ H_2O$ (194.45): C 43.24, H 6.84, N 14.41; found: C 43.05, H 7.08, N 14.15.

Diesters **6**–**11**. A soln. of the acyl chloride (2 mmol) in anh. CH_2Cl_2 (5 ml) was added dropwise to a mixture of 1 mmol of **21** · HCl or **22** · HCl, pyridine (3 mmol), and anh. CH_2Cl_2 (15 ml), while stirring. The resulting colorless soln. was refluxed for 16 h and then evaporated, the residue chromatographed (silica gel, CH_2Cl_2/MeOH 95:5), and the product fraction evaporated: diesters **6**–**11** as solid materials which were recrystallized if necessary.

1-(1H-Imidazol-2-yl)ethane-1,2-diol Diacetate (**6**): 145 mg (68%). Colorless crystals. M.p. 112–113° (CH_2Cl_2/petroleum ether). ^{1}H-NMR ($CDCl_3$): 10.50 (br. *s*, NH); 7.07 (s, 2 H (im)); 6.07 (*m*, CHO); 4.66 (*m*, CH_2O); 2.08, 2.06 (2*s*, 2 Me). ^{13}C-NMR ($CDCl_3$): 170.90, 170.52 (2 C=O); 142.73 (C(2)(im)); 67.22 (CHO); 63.56 (CH_2O); 20.76, 20.64 (Me). CI-MS: 213 ($[M + 1]^+$). Anal. calc. for $C_9H_{12}N_2O_4$ (212.20): C 50.94, H 5.70, N 13.20; found: C 50.69, H 5.79, N 13.09.

1-(1H-Imidazol-2-yl)ethane-1,2-diyl Didodecanoate (**7**): 345 mg (70%). Colorless crystals. M.p. 65–66°. ^{1}H-NMR ($CDCl_3$): 9.97 (br. *s*, NH); 7.01 (*s*, 2 H (im)); 6.00 (*m*, CHO); 4.67 (*m*, CH_2O); 2.30 (*m*, 2 CH_2CO); 1.57 (*m*, 2 CH_2); 1.23 (br. *s*, 2 $(CH_2)_8$); 0.85 (2 *t*, *J* = 6.6, 2 Me). ^{13}C-NMR ($CDCl_3$): 174.09, 173.25 (2C=O); 142.85 (C(2)(im)); 67.14 (CHO); 63.17 (CH_2O); 34.16, 34.09, 31.87, 29.57, 29.43, 29.29, 29.09, 29.01, 24.82, 22.63 ($(CH_2)_{10}$); 14.03 (Me). CI-MS: 493 ($[M + 1]^+$). Anal. calc. for $C_{29}H_{52}N_2O_4$ (492.74): C 70.69, H 10.64, N 5.69; found: C 70.55, H 10.68, N 5.71.

Didodecanoate **25** (50 mg, 7%) was isolated as a by-product (anal. data below).

1-(1H-Imidazol-2-yl)ethane-1,2-diyl Dihexadecanoate (**8**): 370 mg (70%). Colorless crystals. M.p. 72–74°. ^{1}H-NMR ($CDCl_3$): 10.02 (br. *s*, NH); 7.01 (*s*, 2 H (im)); 6.01 (*m*, CHO); 4.67 (*m*, CH_2O); 2.31 (*m*, 2 CH_2CO); 1.58 (*m*, 2 CH_2); 1.25 (br. *s*, 2 $(CH_2)_{12}$); 0.86 (2 *t*, *J* = 6.7, 2 Me). ^{13}C-NMR ($CDCl_3$): 174.07, 173.25 (2 C=O); 142.86 (C(2)(im)); 67.14 (CHO); 63.19 (CH_2O); 34.16, 34.09, 31.89, 29.66, 29.63, 29.45, 29.32, 29.26, 29.22, 29.10, 29.02, 24.86, 24.82, 22.64 ($(CH_2)_{14}$); 14.04 (Me). CI-MS: 605 ($[M + 1]^+$). Anal. calc. for $C_{37}H_{68}N_2O_4$ (604.93): C 73.46, H 11.33, N 4.63; found: C 73.39, H 11.46, N 4.59.

Dihexadecanoate **26** (100 mg, 12%) was isolated as by-product (anal. data below).

1-[4(5)-Methyl-1H-imidazol-2-yl]ethane-1,2-diol Diacetate (**9**): 140 mg (62%). Colorless crystals. M.p. 100–104° ($(i\text{-}Pr)_2O$). ^{1}H-NMR ($CDCl_3$): 9.71 (br. *s*, NH); 6.68 (*s*, 1 H (im)); 5.93 (*m*, CHO); 4.63 (*m*, CH_2O); 2.19 (*s*, Me (im)); 2.06, 2.03 (2*s*, 2 Me). ^{13}C-NMR ($CDCl_3$): 171.19, 170.51 (2 C=O); 141.76 (C(2)(im)); 67.38 (CHO); 63.48 (CH_2O); 20.88, 20.72 (Me). CI-MS: 227 ($[M + 1]^+$). Anal. calc. for $C_{10}N_{14}N_2O_4 \cdot 0.3\ H_2O$ (231.64): C 51.85, H 6.35, N 12.09; found: C 52.03, H 6.09, N 11.97.

*1-[4(5)-Methyl-1*H*-imidazol-2-yl]ethane-1,2-diyl Didodecanoate* (**10**): 390 mg (77%). Colorless crystals. M.p. 56–59°. ^{1}H-NMR ($CDCl_3$): 9.58 (br. *s*, NH); 6.68 (*s*, 1 H (im)); 5.93 (*m*, CHO); 4.64 (*m*, CH_2O); 2.29 (*m*, 2 CH_2CO); 2.19 (*s*, Me (im)); 1.57 (*m*, 2 CH_2); 1.22 (br. *s*, 2 $(CH_2)_8$); 0.85 (2*t*, *J* = 6.7, 2 Me). ^{13}C-NMR ($CDCl_3$): 174.12, 173.25 (2 C=O); 141.94 (C(2)(im)); 67.26 (CHO); 63.21 (CH_2O); 34.21, 34.12, 31.88, 29.58, 29.44, 29.29, 29.10, 29.03, 24.87, 22.64 ($(CH_2)_{10}$); 14.04 (Me). CI-MS: 507 ($[M+1]^+$). Anal. calc. for $C_{30}H_{54}N_2O_4$ (506.77): C 71.10, H 10.74, N 5.53; found: C 71.13, H 10.98, N 5.47.

Didodecanoate **27** (30 mg, 4%) was isolated as by-product (anal. data below).

*1-[4(5)-Methyl-1*H*-imidazol-2-yl]ethane-1,2-diyl Dihexadecanoate* (**11**): 446 mg (72%). Colorless crystals. M.p. 72–75°. ^{1}H-NMR ($CDCl_3$): 9.42 (br. *s*, NH); 6.68 (*s*, 1 H (im)); 5.92 (*m*, CHO); 4.65 (*m*, CH_2O); 2.30 (*m*, 2 CH_2CO); 2.20 (*s*, Me(im)); 1.57 (*m*, 2 CH_2); 1.23 (br. *s*, 2 $(CH_2)_{12}$); 0.85 (2 *t*, *J* = 6.7, 2 Me). ^{13}C-NMR ($CDCl_3$): 174.16, 173.24 (2 C=O); 141.97 (C(2)(im)); 67.29 (CHO); 63.18 (CH_2O); 34.22, 34.13, 31.91, 29.67, 29.63, 29.46, 29.33, 29.27, 29.23, 29.11, 29.04, 24.86, 24.89, 22.66 ($(CH_2)_{14}$); 14.05 (Me). Anal. calc. for $C_{38}H_{70}N_2O_4$ (618.99): C 73.74, H 11.40, N 4.53; found: C 73.65, H 11.55, N 4.44.

Dihexadecanoate **26** (10 mg, 2%) was isolated as by-product (anal. data below).

Monoesters **12** *and* **13**. A soln. of the acyl chloride (0.5 mmol) in anh. CH_2Cl_2 (5 ml) was added dropwise to a mixture of 0.5 mmol of **23** · HCl or **24** · HCl, pyridine (1 mmol), and anh. CH_2Cl_2 (10 ml) while stirring. The resulting colorless soln. was refluxed for 16 h and then evaporated. The residue was chromatographed (silica gel, CH_2Cl_2/MeOH 95:5) and the product fraction evaporated: monoesters **12** and **13**.

*2-(1*H*-Imidazol-2-yl)-2-methoxyethyl Hexadecanoate* (**12**): 154 mg (81%). Colorless crystals. M.p. 83–84°. ^{1}H-NMR ($CDCl_3$): 9.66 (br. *s*, NH); 7.03 (br. *s*, 2 H (im)); 4.66 (*m*, CHO); 4.39 (*m*, CH_2O); 3.38 (*s*, MeO); 2.29 (*t*, *J* = 7.5, CH_2CO); 1.57 (*m*, 2 CH_2); 1.23 (br. *s*, $(CH_2)_{12}$); 0.86 (*t*, *J* = 6.7, 2 Me). ^{13}C-NMR ($CDCl_3$): 173.37 (C=O); 145.27 (C(2)(im)); 76.08 (CHO); 65.05 (CH_2O); 57.79 (MeO); 34.16, 31.91, 29.66, 29.45, 29.34, 29.26, 29.07, 24.90, 22.67 ($(CH_2)_{14}$); 14.08 (Me). CI-MS: 381 ($[M+1]^+$). Anal. calc. for $C_{22}H_{40}N_2O_3$ (380.57): C 69.43, H 10.59, N 7.36; found: C 69.28, H 10.74, N 7.35.

*2-[4(5)-Methyl-1*H*-imidazol-2-yl]-2-methoxyethyl Dodecanoate* (**13**): 120 mg (71%). Colorless oil. ^{1}H-NMR ($CDCl_3$): 6.71 (br. *s*, 1 H (im)); 4.60 (*m*, CHO); 4.37 (*m*, CH_2O); 3.37 (*s*, MeO); 2.29 (*t*, *J* = 7.5, CH_2CO); 2.22 (*s*, Me(im)); 1.57 (*m*, 2 CH_2); 1.24 (br. *s*, 2 $(CH_2)_8$); 0.86 (*t*, *J* = 6.3, Me). ^{13}C-NMR ($CDCl_3$): 173.35 (C=O); 76.00 (CHO); 65.10 (CH_2O); 57.77 (MeO); 34.17, 31.89, 29.58, 29.44, 29.30, 29.07, 24.90, 22.65 ($(CH_2)_{10}$); 14.05 (Me); 12.10 (Me(im)). CI-MS: 339 ($[M+1]^+$). Anal. calc. for $C_{19}H_{34}N_2O_3$ (338.49): C 67.42, H 10.12, N 8.28; found: C 67.35, H 10.44, N 7.70.

*1-Acyl-1*H*-imidazolyl-Substituted Diesters* **25**–**28**. A soln. of the acyl chloride (1.5 mmol) in anh. CH_2Cl_2 (5 ml) was added dropwise to a mixture of 0.5 mmol of **21** · HCl or **22** · HCl, pyridine (2 mmol), and anh. CH_2Cl_2 (10 ml) while stirring. The resulting colorless soln. was refluxed for 16 h and then evaporated. The residue was chromatographed (silica gel, CH_2Cl_2/MeOH 95:5) and the product fraction evaporated: 1-acyl-1*H*-imidazoles **25**–**28** as solid materials which were recrystallized if necessary.

*1-(1-Dodecanoyl-1*H*-imidazol-2-yl)ethane-1,2-diyl Didodecanoate* (**25**): 176 mg (52%). Colorless crystals. M.p. 63–66°. ^{1}H-NMR ($CDCl_3$): 7.27, 7.00 (2*d*, *J* = 1.7, 2 H (im)); 6.53 (*m*, CHO); 4.56 (*m*, CH_2O); 2.82 (*t*, *J* = 7.4, CH_2CO); 2.37 (*t*, *J* = 7.5, CH_2CO); 2.29 (*t*, *J* = 7.5, 2 CH_2CO); 1.77 (*m*, CH_2); 1.60 (*m*, 2 CH_2); 1.26 (br. *s*, 3 $(CH_2)_8$); 0.88 (*t*, *J* = 6.6, 3 Me). ^{13}C-NMR ($CDCl_3$): 173.31, 172.80, 170.69 (3 C=O); 146.09 (C(2)(im)); 129.27 (C(4) or C(5)(im)); 117.79 (C(4) or C(5)(im)); 67.65 (CHO); 63.33 (CH_2O); 36.36, 34.04, 31.90, 29.61, 29.57, 29.48, 29.39, 29.28, 29.11, 29.08, 28.94, 24.85, 24.78, 24.00, 22.63 ($(CH_2)_{10}$); 14.06 (Me). CI-MS: 675 ($[M+1]^+$). Anal. calc. for $C_{41}H_{74}N_2O_5$ (675.05): C 72.95, H 11.05, N 4.15; found: C 72.81, H 11.02, N 4.12.

Compound **7** (108 mg, 44%), which was identical with authentic material, was also isolated.

*1-(1-Hexadecanoyl-1*H*-imidazol-2-yl)ethane-1,2-diyl Dihexadecanoate* (**26**): 245 mg (58%). Colorless crystals. M.p. 78–80°. ^{1}H-NMR ($CDCl_3$): 7.25, 6.98 (2 *d*, *J* = 1.7, 2 H (im)); 6.51 (*m*, CHO); 4.54 (*m*, CH_2O); 2.80 (*t*, *J* = 7.4, CH_2CO); 2.35 (*t*, *J* = 7.5, CH_2CO); 2.27 (*t*, *J* = 7.5, CH_2CO); 1.75 (*m*, CH_2); 1.58 (*m*, 2 CH_2); 1.24 (br. *s*, 3 $(CH_2)_{12}$); 0.86 (2*t*, *J* = 6.5, 3 Me). ^{13}C-NMR ($CDCl_3$): 173.25, 172.72, 170.62 (3 C=O); 146.01 (C(2)(im)); 129.21 (C(4) or C(5)(im)); 117.71 (C(4) or (C(5)(im)); 67.58 (CHO); 63.25 (CH_2O); 36.30, 33.98, 31.85, 29.61, 29.43, 29.28, 29.22, 29.04, 28.88, 24.78, 23.94, 22.60 ($(CH_2)_{14}$); 14.00 (Me). CI-MS: 843 ($[M+1]^+$). Anal. calc. for $C_{53}H_{98}N_2O_5$ (843.37): C 75.48, H 11.71, N 3.32; found: C 85.30, H 11.87, N 2.95.

Compound **8** (94 mg, 31%), which was identical with authentic material, was also isolated.

*1-[1-Dodecanoyl-4(5)-methyl-1*H*-imidazol-2-yl]ethane-1,2-diyl Didodecanoate* (**27**): 214 mg (62%). Colorless crystals. M.p. 57–60°. ^{1}H-NMR ($CDCl_3$): 6.94 (*q*, *J* = 1.1, 1 H (im)); 6.50 (*m*, CHO); 4.51 (*m*, CH_2O); 2.74 (*t*, *J* = 7.4, CH_2CO); 2.35 (*t*, *J* = 7.5, CH_2CO); 2.27 (*t*, *J* = 7.5, 2 CH_2CO); 2.16 (*d*, *J* = 1.1, Me(im)); 1.73 (*m*, CH_2); 1.57 (*m*, 2 CH_2); 1.24 (br. *s*, 3 $(CH_2)_8$); 0.86 (*t*, *J* = 6.6, 3 Me). ^{13}C-NMR ($CDCl_3$): 173.33, 172.90, 170.52 (3 C=O); 145.48 (C(2)(im)); 138.55 (C(4) or C(5)(im)); 113.91 (C(4) or C(5)(im)); 67.66 (CHO);

63.51 (CH_2O); 36.38, 34.08, 31.90, 29.62, 29.58, 29.50, 29.41, 29.30, 29.12, 29.08, 28.97, 24.88, 24.81, 24.03, 22.66 ($(CH_2)_{10}$); 14.06 (Me); 13.41 (Me(im)). Anal. calc. for $C_{42}H_{76}N_2O_5 \cdot 1.4\ H_2O$ (714.30): C 70.62, H 11.12, N 3.92; found: C 72.69, H 11.04, N 4.11.

Compound **10** (76 mg, 30%), which was identical with authentic material, was also isolated.

1-[1-Hexadecanoyl-4(5)-methyl-1H-imidazol-2-yl]ethane-1,2-diyl Dihexadecanoate (**28**): 322 mg (75%). Colorless crystals. M.p. 71–76°. ^{1}H-NMR ($CDCl_3$): 6.94 (*q*, *J* = 1.2, 1 H (im)); 6.49 (*m*, CHO); 4.51 (*m*, CH_2O); 2.74 (*t*, *J* = 7.4, CH_2CO); 2.35 (*t*, *J* = 7.5, CH_2CO); 2.27 (*t*, *J* = 7.5, CH_2CO); 2.15 (*d*, *J* = 1.2, Me(im)); 1.73 (*m*, CH_2); 1.59 (*m*, 2 CH_2); 1.24 (br. *s*, 3 $(CH_2)_{12}$); 0.86 (*t*, *J* = 6.5, 3 Me). ^{13}C-NMR ($CDCl_3$): 173.30, 172.88, 170.50 (3 C=O); 145.47 (C(2)(im)); 138.54 (C(4) or C(5)(im)); 113.89 (C(4) or C(5)(im)); 67.65 (CHO); 63.50 (CH_2O); 36.37, 34.07, 31.91, 29.67, 29.48, 29.41, 29.34, 29.29, 29.11, 29.07, 28.97, 24.88, 24.80, 24.02, 22.66 ($(CH_2)_{14}$); 14.06 (Me); 13.41 (Me(im)). Anal. calc. for $C_{54}H_{100}N_2O_5$ (857.39): C 75.65, H 11.76, N 3.27; found: C 75.70, H 12.12, N 2.96.

Compound **11** (70 mg, 23%), which was identical with authentic material, was also isolated.

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