Synthesis of New Heterocyclic Fatty Compounds

Sandra Fürmeier[a] and Jürgen O. Metzger*[a]

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The terminal tetrazoles 1–5, the tetrazole analogues of the most important naturally occurring fatty acids, have been synthesized from fatty nitriles and completely characterized. The linear C_{12} bis(tetrazole) 6 was prepared and represents a valuable supplement to the previously known C_{2}–C_{4} alkyl- and alkenyl-linked bis(tetrazoles). The tetrazoles 1–6 were converted into the respective 1,3,4-oxadiazoles 13–17 by heating in acetic anhydride. Three bis(oxadiazoles) 18–20 were also obtained. A 1,5-disubstituted tetrazole 12 was synthesized from methyl 9(10)-oxooctadecanoate by means of an improved Schmidt reaction. From methyl cis-9,10-epoxyoctadecanoate (21), various heterocycles such as the 4,5-dihydrooxazoles 22, the oxazolidines 24, the imidazoles 26, the oxazoles 27, and the imidazolinethione 28 were prepared. Because of their structural relationship to the naturally occurring prostaglandins, compounds 12, 22, 24, 26, 27, and 28 should be of interest as homoprostanoids.

Introduction

Over the last three years, Sharpless et al. have introduced “click chemistry” as an important tool for drug discovery.[1] The major requirement for the synthetic methods involved is that “all searches must be restricted to molecules that are easy to make”, the goal being to develop an expanding set of powerful, selective, and modular blocks with which to combine small units together with heteroatom links (C–X–C), working reliably in both small- and large-scale applications. Sharpless defined stringent criteria for click reactions: “The reaction must be modular, wide in scope, give very high yields, generate onlyoinoffensive by-products that can be removed by non-chromatographic methods, and be stereospecific. The required process characteristics include simple reaction conditions, readily available starting materials and reagents, the use of no solvent or a solvent that is benign or easily removed, and simple product isolation.” Carbon–heteroatom bond-forming reactions represent the most common click reactions. Typical examples are cycloadditions, especially 1,3-dipolar cycloaddition reactions and nucleophilic substitutions, particularly ring-opening reactions of strained heterocyclic compounds such as epoxides, aziridines, aziridinium ions and episulfonium ions, and also carbonyl reactions of the “non-aldol”-type and oxidative additions to C–C multiple bonds such as epoxidations, dihydroxylations, and azidinations. Our work on the synthesis of heterocyclic fatty compounds is closely related to Sharpless’s click chemistry. Our idea was to achieve access to pharmacologically interesting compounds based on renewable raw materials that serve as important feedstocks for the chemical industry with regard to a sustainable development[2] through simple transformations starting from easily available fatty compounds. The different types of interesting heterocycles are presented below.

The discovery of the pharmacological and biochemical properties of tetrazoles initiated an enormous development in tetrazole chemistry over the last 40 years.[3] In N-unsubstituted tetrazoles the tetrazole moiety is isosteric with the carboxylic acid group, and a large number of amino acids and naturally occurring carboxylic acids have therefore been synthesized with a tetrazole ring in place of the carboxylic acid group. Tetrazole analogues of fatty acid ethers are known as substrates for N-myristoyl transferase and its respective coenzyme, and show fungicidal and antiviral (including HIV) activity.[4] In addition to their various biochemical properties, tetrazoles also serve as precursors for the synthesis of further interesting heterocycles, such as 1,3,4-oxadiazoles. These are used as biologically active compounds in medical science and agriculture, and also as dyes and UV absorbents. Various 2,5-diaryl-, 2,5-dialkyl-, and 2-alkyl-5-aryl-1,3,4-oxadiazoles show herbicidal effects, especially against broad leafed weeds and grasses in crops such as rice and corn.[5] 4,5-Dihydrooxazoles show antimicrobial activity and are used as tranquilizers. Derivatives with a fatty acid residue at the C-2 position of the dihydrooxazole ring show surface-active properties, and the respective salts are good cationic surfactants.[6] Many imidazoles have been prepared as potentially pharmacological agents, including 2-nitroimidazole (azomycine) as a naturally occurring antibiotic or the synthetic clotrimazole (cane-
stene) as an antimycotic. Ergothionine should be mentioned as a biologically active imidazolinethione acting as antihistamine.[7]

Vegetable oils are the most important renewable feedstocks in the chemical industry.[8] We were interested in the synthesis of tetrazoles, 1,3,4-oxadiazoles, and further N- and O/S-containing heterocyclic fatty acid derivatives in order to enlarge the variety of interesting fatty compounds and to open up a new potential for renewable raw materials as possible biologically active compounds.

Results and Discussion

The respective fatty nitriles of the most important fatty acids served as starting materials for gaining access to the tetrazole analogues. These nitriles are conveniently available as intermediates in the industrial synthesis of fatty amines. By the method of Koguro et al.[9] we converted various fatty nitriles into the corresponding 5-alkyl-1H-tetrazoles by use of 3 equiv. of sodium azide and triethylamine hydrochloride in dry toluene (Table 1). The reaction was performed in about 2 d at reflux temperature, after which the reaction mixture was dissolved in water and the layers were separated. Since the tetrazoles were formed as their ammonium salts, the aqueous layer was in each case acidified to release the tetrazole and extracted with diethyl ether. The detailed workup and the properties of the different tetrazoles are given in Table 1.

In this manner, treatment of dodecanenitrile yielded tetrazole 1, octadecanenitrile yielded 2, (Z)-9-octadecenitrile yielded 3, tetradecanenitrile yielded 4, 10-undecene-nitrile yielded 5, and dodecanedinitrile yielded 6. Compounds 1–7 represent the first examples of 5-alkyltetrazoles substituted with long-chain fatty acid derived residues. Pernice et al. reported on 5-undecyl-1H-tetrazole (1) in a study concerning the permeation properties of carboxylic acids and their tetrazole analogues without giving any data for the characterization of the compound.[10] Although tetrazole 2 is documented in CAS, a reference is missing, indicating that the compound is the subject of a patent. To provide the alkyl-branched tetrazole 7, methyl oleate (8) was treated with iodoacetanilide in the presence of copper powder in a free radical reaction[11] (Scheme 1). The resulting cyanomethyl-iodo derivative 9 (30% yield) was subsequently reduced under hydrogen in the presence of palladium on charcoal to afford the cyanomethyl derivative 10 (96% yield), which was converted into the tetrazole 7 as already described.

The applicability of an improved Schmidt synthesis with fatty acid derivatives for the preparation of 1,5-disubstituted tetrazoles from ketones, as reported by Suzuki et al.[12] was investigated. We thus heated a mixture of methyl 9(10)-oxooctadecanoate (11), sodium azide and titanium(IV) chloride under reflux, and obtained the tetrazole 12 as a yellow oil in 71% yield (Scheme 2).

Compound 12 was produced as a mixture of four isomers, as shown by NMR spectroscopy. Suzuki et al. reported on the reaction mechanism and the formation of two

Table 1. Preparation of 5-alkyl-1H-tetrazoles 1–7 from fatty nitriles (PE = petroleum ether; EE = ethyl acetate)

<table>
<thead>
<tr>
<th>R-CN</th>
<th>Na3N, NEt3·HCl</th>
<th>Work-up</th>
<th>Yield</th>
<th>Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃(CH₂)₆CN</td>
<td>CH₃(CH₂)₆-CN</td>
<td>Recrystallization from MeCN</td>
<td>89%</td>
<td>white solid mp. 86-72°C</td>
</tr>
<tr>
<td>CH₃(CH₂)₆CN</td>
<td>CH₂(CH₂)₆-CN</td>
<td>Recrystallization from MeCN/EOH 10:1</td>
<td>99%</td>
<td>white solid mp. 82-85°C</td>
</tr>
<tr>
<td>CH₃(CH₂)₇(CH₂)₂CN</td>
<td>CH₃(CH₂)₇-CN</td>
<td>Column Chromatography PE/EE/AcOH 10:3:1</td>
<td>94%</td>
<td>white wax</td>
</tr>
<tr>
<td>CH₃(CH₂)₇CN</td>
<td>CH₂(CH₂)₇-CN</td>
<td>Recrystallization from PE</td>
<td>91%</td>
<td>white solid mp. 74-77°C</td>
</tr>
<tr>
<td>CH₃(CH₂)₇CN</td>
<td>CH₂(CH₂)₇-CN</td>
<td>Recrystallization from PE/EOH 2:1</td>
<td>91%</td>
<td>orange solid mp. ~ rt</td>
</tr>
<tr>
<td>NC(CH₂)₇CN</td>
<td>NC(CH₂)₇-CN</td>
<td>Recrystallization from MeCN</td>
<td>72%</td>
<td>beige solid mp. 146-149°C</td>
</tr>
<tr>
<td>CH₃(CH₂)₈(CH₂)₃COOCH₃</td>
<td>CH₃(CH₂)₈-CN</td>
<td>Column Chromatography PE/EE/MeOH 7:3:1</td>
<td>32%</td>
<td>orange oil</td>
</tr>
</tbody>
</table>
Synthesis of New Heterocyclic Fatty Compounds

Scheme 1. Synthesis of the alkyl-branched tetrazole 7 from methyl oleate (8)

\[
\text{CH}_3(\text{CH}_2)_7(\text{CH}_2)_7\text{COOCH}_3 \xrightarrow{\text{ICH}_2\text{CN}, \text{Cu}} 10^\circ\text{C} \xrightarrow{\text{H}_2, \text{Pd/C}, \text{NaHCO}_3, \text{MeOH 2.9 bar, 50}^\circ\text{C}} \text{CH}_3(\text{CH}_2)_7(\text{CH}_2)_7\text{COOCH}_3 + \text{regioisomer}
\]

Scheme 2. Synthesis of the 1,5-dialkyl-substituted tetrazole 12 from methyl 9(10)-oxooctadecanoate (11), sodium azide, and titanium(IV) chloride

\[
\text{CH}_3(\text{CH}_2)_{\eta(7)}(\text{CH}_2)_{\eta(8)}\text{COOCH}_3 \xrightarrow{\text{Na}_3\text{N}, \text{Et}_3\text{N}, \text{HCl}} \text{toluene} \xrightarrow{\text{Na}_3\text{N}, \text{TiCl}_4} 12
\]

isomers.\(^{[12]}\) Since the ketone 11 was a ca. 1.2:1 regioisomeric mixture, the possible isomers of the tetrazole 12 were formed as their two regioisomers as well. The ratio of isomers could be determined from \(^{13}\text{C}\) NMR spectroscopic data, the intensities of the four signals for C-1 indicating a ratio of 1:1.6:1.6:1.2.

The 5-alkyl-1\(^H\)-tetrazoles 1–6 were also treated in a Huisgen reaction with acetic anhydride in 7 h under reflux to yield the 1,3,4-oxadiazoles 13–18 (Table 2).

Table 2. Preparation of 1,3,4-oxadiazoles 13–20 from the respective tetrazoles 1–10 (PE = petroleum ether; EE = ethyl acetate)

<table>
<thead>
<tr>
<th>R–N–N–R’</th>
<th>acid anhydride</th>
<th>Work-up</th>
<th>Yield</th>
<th>Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>reflux</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>CH$_3$(CH$_2$)$_9$</td>
<td>13</td>
<td>80%</td>
<td>pale yellow oil</td>
</tr>
<tr>
<td>2</td>
<td>CH$_3$(CH$_2$)$_6$</td>
<td>14</td>
<td>97%</td>
<td>beige solid mp. 43-46°C</td>
</tr>
<tr>
<td>3</td>
<td>CH$_3$(CH$_2$)$_7$</td>
<td>15</td>
<td>73%</td>
<td>pale yellow oil</td>
</tr>
<tr>
<td>4</td>
<td>CH$_3$(CH$_2$)$_7$</td>
<td>16</td>
<td>85%</td>
<td>beige solid mp. 32-33°C</td>
</tr>
<tr>
<td>5</td>
<td>CH$_3$(CH$_2$)$_6$</td>
<td>17</td>
<td>65%</td>
<td>colourless oil</td>
</tr>
<tr>
<td>6</td>
<td>CH$_3$(CH$_2$)$_7$</td>
<td>18</td>
<td>72%</td>
<td>pale pink solid mp. 45-50°C</td>
</tr>
<tr>
<td>1</td>
<td>CH$_3$(CH$_2$)$_9$</td>
<td>19</td>
<td>72%</td>
<td>beige solid mp. 96°C</td>
</tr>
<tr>
<td>1</td>
<td>CH$_3$(CH$_2$)$_9$</td>
<td>20</td>
<td>34%</td>
<td>beige solid mp. 80-82°C</td>
</tr>
</tbody>
</table>
Scheme 3. Reaction pathway to the long-chain bis(oxadiazoles) 19 and 20 by treatment of 5-undecyl-1H-tetrazole (1) with succinic and glutaric anhydriderespectively.

The bis(oxadiazoles) 19 and 20 were unexpectedly isolated from treatment of 5-undecyl-1H-tetrazole (1) with succinic and glutaric anhydrides, respectively, treatment of 1 with succinic anhydride (1, n = 2) in dry xylene yielding the bis(oxadiazole) 19 after 24 h of reflux, and bis(oxadiazole) 20 being obtained in the analogous conversion with glutaric anhydride (1, n = 3). The mechanism, based on investigations carried out by Huisgen et al.,[13] is shown in Scheme 3. In the first step of the reaction the cyclic anhydride is attacked by the tetrazole 1 with ring-opening and formation of an acyl tetrazole II with a short-chain carboxylic acid residue. 3-(5-Undecyl[1,3,4]oxadiazole-2-yl)propanoic acid IV (n = 2) and 3-(5-undecyl[1,3,4]oxadiazole-2-yl)butanoic acid IV (n = 3) should be formed, with loss of nitrogen and intramolecular cyclization of the dipolar intermediate III. However, the carboxylic acid group in compound IV seems to react with a second molecule of tetrazole 1, finally giving the isolated bis(oxadiazoles) 19 and 20.

Finally, methyl cis-9,10-epoxyoctadecanoate (21) was converted into a number of different N/O- and/or S-containing heterocycles. Treatment of 21 with acetonitrile in the presence of boron trifluoride diethyl ether yielded 60% of the 4,5-dihydrooxazole 22 as a mixture of two isomers (Scheme 4). The cis-epoxide was transformed into a trans-dihydrooxazole with inversion at the carbon atom attacked by acetonitrile.

An alternative reaction pathway to the same 4,5-dihydrooxazoles 22 was by treatment of the amino alcohols 23 with Cd(OAc)₂·2H₂O in acetonitrile, which turned out to be inferior with regard to the yield (27%).

The dihydrooxazole was sensitive towards hydrolysis and was completely converted into the ring-opened product after 7 d. The characteristic NMR spectroscopic data of the 4,5-dihydrooxazoles 22 and the ring-opened compound methyl 9(10)-acetylamino-10(9)-hydroxyoctanoate (I) are compared in Table 3.

Our observation corresponds to the findings of Ahmad and Ansari,[14] who treated 2,3-epoxy fatty esters with nitriles in the presence of equimolar amounts of boron trifluoride—diethyl ether and observed the formation of...
4,5-dihydrooxazoles. The isolation of the dihydrooxazoles failed because of the rapid hydrolysis to the open-chain hydroxy amides. These could in turn be transformed into the dihydrooxazoles by pyrolysis under nitrogen at 210–220 °C in 6–8 h in yields of about 70%. Ahmad and Ansari's NMR spectroscopic data correspond to ours, and therefore confirm our results.

In general, oxazolidines are formed by condensation of amino alcohols with carbonyl compounds. Treatment of the amino alcohols with an excess of paraformaldehyde in methanol yielded the oxazolidines as a pale yellow oil in 44% yield (Scheme 5). The threo-amino alcohol is converted with retention of the configuration into the trans-oxazolidine, as a mixture of two isomers.

Scheme 5. Condensation of the amino alcohols with paraformaldehyde to give the oxazolidines

Methyl 9(10)-hydroxy-10(9)-oxooctadecanoate (25) served as a precursor for the synthesis of further interesting heterocycles. The α-hydroxy ketone 25 was prepared analogously to the method described by Brousse and Lefort by oxidation of methyl cis-9,10-epoxyoctadecanoate (21) with dimethyl sulfoxide at 90–100 °C in the presence of boron trifluoride–diethyl ether.

In a Bredereck reaction the α-hydroxy ketone 25 was treated with formamide to afford the imidazoles and the oxazoles (Scheme 6). Treatment of 25 in formamide under nitrogen at 150 °C yielded 54% of the imidazoles 26 as an orange oil, together with 7% of the oxazoles 27. The oxazoles 27 could be isolated as major products in the analogous conversion carried out with a different temperature pattern in the presence of concentrated sulfuric acid, a 36% yield of the oxazoles 27 being obtained as an orange oil, together with a further 26% of the imidazoles 26.

Vandenberghe and Willems developed a method for the synthesis of 4,5-substituted oxazoline- and imidazoline-2-thiones based on the cyclization of α-hydroxy ketones with thiocyanic acid and its salts. In application of this procedure to fatty acids we therefore treated the α-hydroxy ketone (25) with a threefold excess of ammonium thiocyanate in dioxane under reflux. The corresponding imidazoline-thione 28 was isolated as a beige, waxy solid in 77% yield (Scheme 6). We are dealing with a condensation reaction, because above 70 °C ammonium thiocyanate is converted into thiourea, which reacts with the α-hydroxy ketone.

Compounds 12, 22, 24, 26, 27, and 28, each with a five-membered ring at the C-9/C-10 positions of the fatty acid chain, are related in structure to the naturally occurring prostaglandins PGE1 and PGE2. Bender et al. have prepared several prostaglandin-like heterocyclic fatty acid derivatives with promising interesting pharmacological effects. In particular, those compounds with a trans-configured ring corresponding to PGE1 and PGE2 showed distinctive effects.

Conclusion

In summary, we report on the synthesis of tetrazoles as analogues of fatty acids, as well as on the corresponding 1,3,4-oxadiazoles and bis(oxadiazoles). An alkyl-branched tetrazole 7 was prepared from methyl oleate, and a 1,5-dialkyl-substituted tetrazole 12 from methyl 9(10)-oxooctadecanoate. We have also synthesized 4,5-dihydroox-
azoles 22, oxazolines 24, imidazoles 26, oxazoles 27, and an imidazolinethione 28. Compounds 12, 22, 24, 26, 27, and 28 could be of interest as homoprostanoids.

Experimental Section

General: The fatty nitriles were obtained from Clariant GmbH as technical products. 10-Undecenoic acid was obtained from Elf Atochem. Methyl oleate and methyl cis-9,10-epoxyoctadecanoate were provided by Henkel KGaA and Cognis Deutschland GmbH, respectively. The compositions of the fatty compounds (by GC analysis) were as follows: dodecanenitrile (after distillation) 95%, octadecanenitrile 63%, (Z)-9-octadecenitrile 80%, tetradecanenitrile (after distillation) 87%, dodecanedinitrile 97%, 10-undecenoic acid 98%, methyl oleate (new sunflower) 84%, methyl 9,10-decanenitrile 63%, (CH2)4N(C6H4SO2)2 as solvent.

23.37, 27.66, 28.96, 29.02, 29.15, 30.52, 31.78 (CH2), 156.92 (m, 2 H, 11-H) 1.87 (quint, 3 H, 10-H) ppm. 13C NMR: δ = 13.98 (CH3), 22.64, 25.37, 27.72, 29.09, 29.12, 29.33, 29.43, 29.58, 29.64, 29.69, 31.92 (CH3), 157.11 (C-1) ppm. HR MS (EI, 70 eV): calcd. for C14H26N4 [M]+ 308.2940; found 308.2939.

5-Heptadecyl-1H-tetrazole (2): Octadecanenitrile (5.31 g, 20 mmol) was treated as described above. Recrystallization from a mixture of acetonitrile/ethanol (10:1) yielded the product (6.09 g, 99%) as a white solid, m.p. 85–87 °C. 1H NMR: δ = 0.88 (t, 3 H, CH3), 1.15–1.40 (m, 26 H, CH2), 1.42 (m, 2 H, 11-H), 1.87 (quint, J1H,11H = 7.7 Hz, 2 H, 3-H), 3.13 (t, J1H,2H = 7.7 Hz, 2 H, 2-H) ppm. 13C NMR: δ = 13.96 (CH3), 22.55, 23.27, 27.66, 28.96, 29.02, 29.21, 29.33, 29.48, 31.78 (CH3), 156.92 (C-1) ppm. HR MS (EI, 70 eV): calcd. for C12H24N4 [M]+ 224.2001; found 224.2000.

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Synthesis of New Heterocyclic Fatty Compounds

Methyl 9-(Cyanomethyl)octadecanoate and Methyl 10-(Cyanomethyl)octadecanoate (10): A solution of compound Methyl 9-(Cyanomethyl)octadecanoate and Methyl 10-(Cyanomethyl)octadecanoate (21.62, 22.59, 24.84, 26.45, 26.52, 28.98, 29.02, 29.05, 29.18, 29.22, 29.23, 29.26, 29.54, 31.64, 31.93, 33.34, 34.08 (CH2), 37.33, 38.54 (C-8, C-11), 41.57, 42.28 (CH(CH2)CN), 43.42, 43.93 (CH2), 51.27 (OCH3), 118.37, 118.55 (CH3), 173.95 (COOCH3) ppm.

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Methyl 9-(Cyanomethyl)octadecanoate and Methyl 10-(Cyanomethyl)octadecanoate (10): A solution of compound Methyl 9-(Cyanomethyl)octadecanoate and Methyl 10-(Cyanomethyl)octadecanoate (21.62, 22.59, 24.84, 26.45, 26.52, 28.98, 29.02, 29.05, 29.18, 29.22, 29.23, 29.26, 29.54, 31.64, 31.93, 33.34, 34.08 (CH2), 37.33, 38.54 (C-8, C-11), 41.57, 42.28 (CH(CH2)CN), 43.42, 43.93 (CH2), 51.27 (OCH3), 118.37, 118.55 (CH3), 173.95 (COOCH3) ppm.

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Methyl 9-(Cyanomethyl)octadecanoate and Methyl 10-(Cyanomethyl)octadecanoate (10): A solution of compound Methyl 9-(Cyanomethyl)octadecanoate and Methyl 10-(Cyanomethyl)octadecanoate (21.62, 22.59, 24.84, 26.45, 26.52, 28.98, 29.02, 29.05, 29.18, 29.22, 29.23, 29.26, 29.54, 31.64, 31.93, 33.34, 34.08 (CH2), 37.33, 38.54 (C-8, C-11), 41.57, 42.28 (CH(CH2)CN), 43.42, 43.93 (CH2), 51.27 (OCH3), 118.37, 118.55 (CH3), 173.95 (COOCH3) ppm.

Methyl 9-(Cyanomethyl)octadecanoate and Methyl 10-(Cyanomethyl)octadecanoate (10): A solution of compound Methyl 9-(Cyanomethyl)octadecanoate and Methyl 10-(Cyanomethyl)octadecanoate (21.62, 22.59, 24.84, 26.45, 26.52, 28.98, 29.02, 29.05, 29.18, 29.22, 29.23, 29.26, 29.54, 31.64, 31.93, 33.34, 34.08 (CH2), 37.33, 38.54 (C-8, C-11), 41.57, 42.28 (CH(CH2)CN), 43.42, 43.93 (CH2), 51.27 (OCH3), 118.37, 118.55 (CH3), 173.95 (COOCH3) ppm.
2.43 (s, 3 H, CH3), 2.73 (t, J_{HH,1H} = 7.7 Hz, 2 H, 1'-H), 4.86 (dq, J_{HH,1H} = 1.7, J_{HH,2H} = 10.4 Hz, 1 H, 10'-H2), 4.92 (dq, J_{HH,1H} = 1.7, J_{HH,2H} = 17.0 Hz, 1 H, 10'-H1), 5.73 (m, J_{HH,1H} = 6.6, J_{HH,2H} = 10.4, J_{HH,3H} = 17.0 Hz, 1 H, 9'-H) ppm. 13C NMR: δ = 10.78 (CH3), 25.13, 26.29, 28.73, 28.90, 29.29, 29.33, 32.37, 33.61 (CH3), 114.03 (C-10'), 138.94 (C-9'), 163.39, 167.02 (C-2', C-5') ppm. C_{21}H_{39}NO_3 [M]^+ 353.2930; found 353.2930.

Methyl 8-(4-Octyloxazolidin-5-yl)octanoate and Methyl 8-(5-Octyloxazolidin-4-yl)octanoate (24): A mixture of methyl 9-amino-10-hydroxystearoate/methyl 10-amino-9-hydroxyoctadecanoate (23, 1.00 g, 3 mmol)16 and paraformaldehyde (0.76 g, 25 mmol) in absolute methanol (20 mL) was stirred at room temperature for 23 h (monitored by TLC). The reaction mixture was filtered through Celite, the filter cake was washed with small portions of methanol, and the combined filtrates were concentrated to dryness, yielding a pale yellow oil (1.02 g). This was purified by column chromatography with ethyl acetate/methanol (2:1) and gave the product (0.97 g, 80%) as a pale yellow oil and as a mixture of two isomers (Rf = 0.81). 1H NMR: δ = 0.88 (s, 3 H, CH3), 1.20–1.55 (m, 24 H, CH2), 1.62 (m, 2 H, 3-H), 2.30 (t, J_{HH,1H} = 7.7 Hz, 2 H, 2-H), 2.90, 3.10 (m, 1 H, 4'-H), 3.48, 3.83 (s, 3 H, 5'-H), 3.66 (s, 3 H, OCH3), 4.47 (m, 2 H, 2-H') ppm. 13C NMR: δ = 14.07 (CH3), 22.63, 24.90, 26.77, 27.01, 27.26, 29.05, 29.13, 29.18, 29.24, 29.34, 29.54, 29.58, 26.89, 27.99, 28.99, 29.41, 31.85, 34.06 (CH3), 51.39 (OCH3), 63.11, 64.13 (C-4'), 77.00, 77.78 (C-5'), 83.35, 83.50 (C-2'), 174.19, 174.24 (COOCH3) ppm. C_{20}H_{37}O_4 (334:1) calcd. C 70.33, H 11.51, N 4.10; found C 70.52, H 11.28, N 4.13.

Methyl 8-(4-Octyloxazolidin-5-yl)imidazo-4-yl)octanoate and Methyl 8-(5-Octyloxazolidin-4-yl)octanoate (26): A mixture of methyl 9-hydroxy-10-octadecenoate/methyl 10-hydroxy-9-octadecenoate (25, 1.64 g, 5 mmol) and formamide (2 mL) was heated under nitrogen at 150 °C for 20 h (monitored by TLC). The reaction mixture was dissolved in dichloromethane and washed with water. The organic layer was dried with sodium sulfate and the solvents were evaporated to dryness. The remaining brown oil (1.7 g) was purified by column chromatography by elution with petroleum ether/ethyl acetate (1:1) followed by elution with methanol. The product (0.97 g, 58%) was obtained from the methanolic eluate (Rf = 0.63) as an orange oil and as a mixture of two isomers. 1H NMR: δ = 0.87 (t, 3 H, CH3), 1.18–1.37 (m, 16 H, CH3), 1.59 (m, 6 H, 3-H, 7-H, 12-H), 2.29 (t, J_{HH,1H} = 7.769 Hz, 2 H, 2-H), 2.52 (t, J_{HH,1H} = 7.769 Hz, 4 H, 8-H, 11-H), 3.66 (s, 3 H, OCH3), 7.59 (s, 1 H, 2'-H) ppm. 13C NMR: δ = 14.01 (CH3), 22.58, 24.81, 24.95, 28.83, 28.93, 28.98, 29.00, 29.06, 29.19, 29.30, 29.43, 29.77, 29.88, 31.79, 33.97 (CH3), 51.37 (OCH3), 130.45 (C-4', C-5'), 132.17 (C-2'), 174.24 (COOCH3) ppm. C_{20}H_{36}O_4 (336:5) calcd. C 71.38, H 10.78, N 8.32; found C 71.91, H 10.57, N 7.82.


S. Fürmeier, J. O. Metzger
Methyl 8-(5-Octyl-2-thioxo-2,3-dihydro-1H-imidazol-4-yl)octanoate (28): A solution of methyl 9-hydroxy-10-oxooctadecanoate/methyl 10-hydroxy-9-oxooctadecanoate (25, 2.00 g, 6 mmol) and ammonium thiocyanate (0.41 g, 18 mmol) in dioxane (20 mL) was heated under reflux for 5 d (monitored by TLC). After removal of the solvent in vacuo, the residue was dissolved in dichloromethane and washed with water. The organic layer was dried with sodium sulfate under reflux for 5 d (monitored by TLC). After removal of the solvent in vacuo, the residue was dissolved in dichloromethane and washed with water. The organic layer was dried with sodium sulfate and the solvents were evaporated to dryness. The residue (2.28 g) was purified by column chromatography with petroleum ether/ethyl acetate/methanol (7:3:1) and gave the product (1.71 g, 77%) as a beige, waxy solid ($R_f = 0.36$).

$^1$H NMR: $\delta = 0.87$ (t, 3 H, $CH_3$), 1.20–1.35 (m, 16 H, $CH_2$), 1.55 (m, 4 H, H-7, 12-H), 1.61 (m, 2 H, 3-H), 2.30 (m, 2 H, 2-H), 2.39 ($J_{HH} = 7.7$ Hz, 4 H, 8-H, 11-H), 3.67 (s, 3 H, OCH$_3$), 10.94, 11.02 (d, 2 H, NH) ppm. $^{13}$C NMR: $\delta = 14.02$ (CH$_3$), 22.58, 23.56, 24.80, 28.70, 28.82, 28.93, 29.13, 29.18, 29.21, 31.78, 34.00 (CH$_3$), 51.45 (OCH$_3$), 125.11, 125.19 (C-9, C-10), 156.71 (C=O), 174.27 (COOC$_2$) ppm. C$_{20}$H$_{33}$N$_2$O$_S$ (368.6): calcld. C 70.96, H 10.56, N 3.65.

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References


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