Water as the medium of choice for the 1,3-dipolar cycloaddition reactions of hydrophobic nitrones

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1,3-Dipolar cycloadditions of different hydrophobic nitrones **1**, **2**, **3**, **4** with acrylates **5** and **6** were studied in both homogenous organic solutions and aqueous suspensions. Reactions in water suspensions showed great rate accelerations over homogenous solutions. Small changes were also observed to the stereoselectivities of the reactions. Hydrophobic interactions are invoked for the observed behaviour.

Introduction

Although life the most complex form of organic compounds requires the construction of chemical bonds in an aqueous environment, water as a solvent was ruled out from organic reactions during the preceding decades. This notion of using organic solvents for organic reactions arising mainly from the reactivity and solubility considerations has been changed in 1980 by the pioneering work of Breslow and Rideout, who demonstrated that Diels–Alder reactions would be greatly accelerated in aqueous medium.[1] Since then many other reactions were studied in this medium and there has been a rapidly growing attention directed toward the development of organic reactions in water.[2,3] The use of water as a solvent has obvious environmental and economic advantages relative to other solvents. From the standpoint of green chemistry and its 12 principles[4] water is the solvent of choice, being both cheap and non toxic. Furthermore using water as a solvent offers also many advantages, such as simple operation and high efficiency in many organic reactions that involve water-soluble substrates, reagents and renewable materials such as carbohydrates without the laborious derivatizations. Additionally, in many cases due to hydrophobic effects[5] using water as a solvent not only accelerates reaction rates but also enhances reaction selectivities. In the first decades of the studies of organic reactions in water either organic cosolvents or substrate modifications were usually employed as it was assumed that a minimum solubility is required for efficient reaction. However, recently Sharpless *et al.* showed substantial rate accelerations when insoluble reactants are stirred in aqueous suspension in emulsion conditions and they termed these reactions as "on-water" reactions.[6]

Among the organic transformations which appear to benefit from aqueous media Diels–Alder reactions are protagonists, whereas the closely related 1,3-dipolar cycloaddition reactions have been studied to a much lower extent summarized in a recently appeared review.[7] The 1,3-dipolar cycloadditions as Diels–Alder reactions are six π-electron concerted reactions and they have wide applications in organic chemistry for the synthesis of five membered heterocyclic rings. Of particular importance for synthetic purposes are the 1,3-dipolar cycloaddition reactions of nitrones which can lead to a variety of products by further manipulations of the initially formed isoxazolidine ring. The huge synthetic potential of nitrones is testified by the vast number of publications employing nitrones in the construction of a variety of compounds with biological interest as carbohydrate mimics, modified nucleosides, natural and modified pyrrolozidine and indolizidine alkaloids.[8] However, in spite of their well-documented utility, there are only scattered reports dealing with the performance of 1,3-dipolar cycloaddition reactions of nitrones in aqueous media.[9] Pure hydrophobic accelerations have been testified only for the 1,3-dipolar cycloadditions of *C,N*-diphenylnitrone,[9a–c] whereas in other cases surfactant[9d,e] or "on water" organocatalysis[9f] are invoked. Also, the reaction between both a water soluble unprotected sugar derived nitrone and a dipolarophile has been reported recently for the synthesis of a new disaccharide mimic.[9g]

In connection with our previous studies on nitrone cycloadditions,[10] we present in this paper the 1,3-dipolar cycloaddition reactions of several hydrophobic nitrones in aqueous suspensions with the aim to expand the use of water as solvent in nitrone chemistry and in synthetic schemes involving them.

Results and discussion

For the purposes of our study we have chosen nitrones **1**, **2**, **3** and **4** (Scheme 1). Nitrone **1** is a typical acyclic hydrophobic nitrone and it was easily formed from the corresponding *n*-decanal. Although unstable it was possible to give cycloaddition products. Nitrone **2** was prepared starting from thymine and it has been used for the synthesis of pseudouridine analogues.[10e] Compound **3** works as a masked nitrone since it exists in equilibrium with the cyclic hydroxylamine form with the equilibrium shifted to the hydroxylamine site. It was prepared starting from D-ribose and it has been used for the synthesis of new triyhdroxypyrrolizidines.[10h] Nitrone **4** is a chiral cyclic nitrone and it was prepared starting also from D-ribose.[11] It has been successfully used for the synthesis of enantiopure pyrroli-

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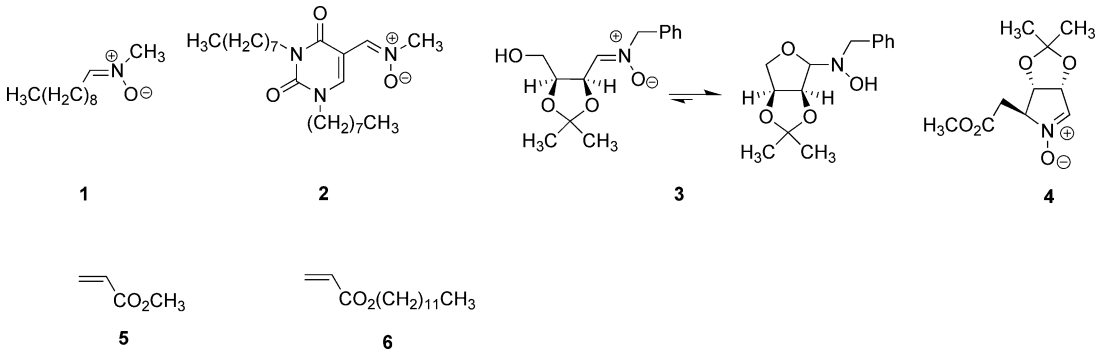


Scheme 1 Reacting nitrones and alkenes.

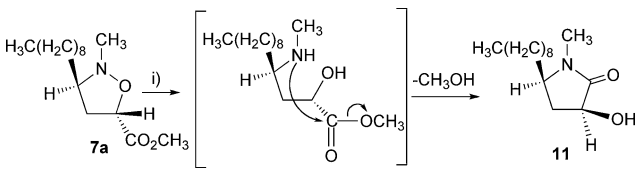
dine and pyrrolizidine derivatives,[10f] aza-*C*-disaccharides[10i] and modified nucleosides.[10g] As dipolarophiles there have been used the commercially available strong dipolarophiles methyl acrylate (**5**) and the more hydrophobic dodecyl acrylate (**6**).

All the reactions were conducted in both homogenous organic solutions and water suspensions with vigorous stirring at the same temperature employing a five fold excess of the dipolarophile. The reactions were monitored with TLC until the consumption of the starting nitrone. The reaction products were analysed by ^{1}H NMR or/and column chromatography.

The reactions of the nitrone **1** with the alkenes **5** and **6** were performed in methylene chloride solution and water suspension at ambient temperature. From the reactions there were obtained two products which were assigned as 5-substituted stereoisomers **7a** and **8a** from the reaction with methyl acrylate and **7b** and **8b** from the reaction with dodecyl acrylate (Scheme 2). The major isomers **7** were obtained in a pure form after column chromatography, whereas the minor ones **8** only as mixtures with **7**. The reaction conditions the yield and the ratio of the isomers, as determined by ^{1}H NMR examination of the column fractions, are given in Table 1. Both the obtained cycloadducts **7** and **8** were assigned as 5-substituted isoxazolidines on the basis of their characteristic 5-H chemical shifts at the regions δ 4.49–4.61 and 4.12–4.22 for the **7** and **8** isomers respectively. However the assignment of the stereochemistry was not possible from their ^{1}H NMR spectra, in which the most peaks appear as broads due probably to dynamic effects of the isoxazolidine ring. Although the broadening was somehow reduced at elevated temperature the net result was not satisfactory. Thus, the major isomer **7a** was transformed to hydroxy lactame **11** according to a well documented procedure[10a] including initial reductive cleavage of the isoxazolidine ring and subsequent recyclization with retention of the stereochemistry of chiral centres 3 and 5 (Scheme 3).

Table 1 Reaction conditions, yields and ratio of the products of the reactions of nitrone **1**

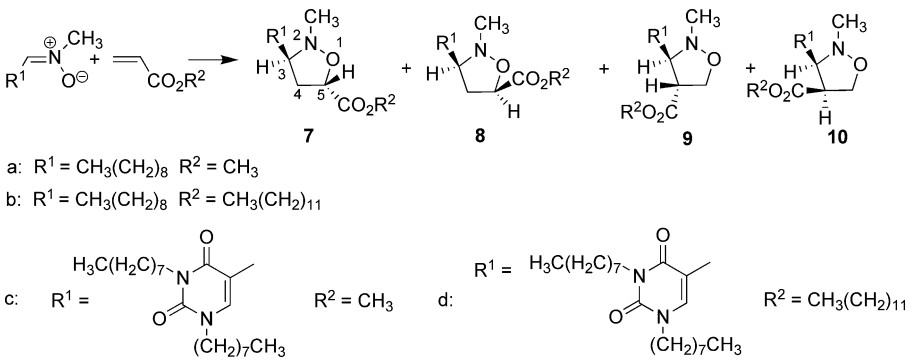
Dipolarophile	Media	Temp. (°C)	Time (days)	Yield (%)	Ratio of isomers **7**/**8**
5	Methylene chloride	25	6	71	77 : 23
5	Water	25	1	72	73 : 27
6	Methylene chloride	25	6	68	82 : 18
6	Water	25	1	69	76 : 24



Scheme 3 (i) H_2, Raney Ni, CH_3OH, RT, 2 days.

NOE measurements performed on compound **11** indicate a *cis* relationship between the 3-H and 5-H as depicted in Fig. 1. This finding reveals the structure of the starting isoxazolidine as **7a**.

The reactions of nitrone **2** with the alkenes **5** and **6** were performed in toluene solution, water suspension and water with



Scheme 2 Reactions of nitrones **1** and **2**.

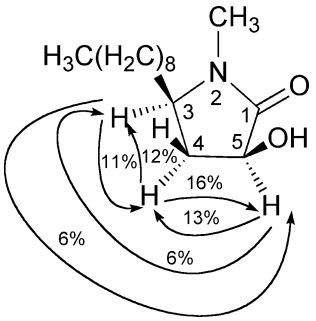


Fig. 1 NOE enhancements measured on compound **11**.

lithium chloride additive (Scheme 2). The reaction of nitrone **2** with methyl acrylate gave a mixture of the four isomeric isoxazolidines **7c**, **8c**, **9c** and **10c**, which could be identified by their characteristic peaks in the ^{1}H NMR spectra of the reaction mixture. In particular, the two 5-carboxymethyl substituted isoxazolidines **7c** and **8c** were identified and differentiated on the basis of the characteristic pattern of their 4-H methylene protons. Thus, in the *cis* isomer **8c** the two methylene protons exhibit a larger difference in their chemical shifts ($\Delta\delta$ = 0.73 ppm) than those of **7c** ($\Delta\delta = 0.32$ ppm) in accordance with analogous isoxazolidine isomers.[10a] Furthermore in compound **8c** the *cis* to the aromatic ring upfielded 4-H^1 at δ 2.37 has smaller coupling constants with both 3-H and 5-H ($J_{4H^1\,3H}$ = $J_{4H^1\,5H}$ = 5.5 Hz) than the other 4-H^2 at δ 3.10 ($J_{4H^2\,3H}$ = 8.9 Hz, $J_{4H^2\,5H}$ = 8.2 Hz). These correlations indicate that 4-H^1 and 4-H^2 are *trans* and *cis* to both 3-H and 5-H respectively and consequently 3-H and 5-H are *cis* to each other. The differentiation of the two 4-carboxymethyl isoxazolidines **9c** and **10c** was based on the chemical shift of the carboxymethyl protons which in the isomer **9c** is considerably upfielded at δ 3.52 due to the protection of the aromatic ring. In the case of the reaction of nitrone **2** with dodecyl acrylate only the two 5-substituted isomeric isoxazolidines **7d** and **8d** could be identified in the reaction mixture and also in the fractions obtained after column chromatography. The ring protons of **7d** and **8d** show the same ^{1}H NMR pattern with that of **7c** and **8c** respectively. The reaction conditions the yields and the ratio of the isomers are given in Table 2.

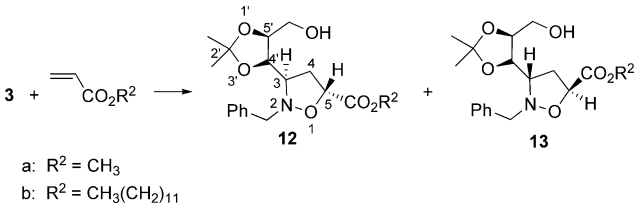
The reactions of nitrone **3** with the alkenes **5** and **6** were also performed in toluene solution and water suspensions (Scheme 4). With both alkenes there were isolated two products which were assigned as **12** and **13** resulting from *endo-Re*

Table 2 Reaction conditions, yields and ratio of the products of the reactions of nitrone **2**

Dipolarophile	Media	Temp. (°C)	Time (h)	Yield (%)	Ratio of isomers **7/8/9/10**
5	Toluene	80	53	100	50 : 38 : 10 : 2
5	Water	80	6	100	49 : 41 : 9 : 1
5	Water + 3M LiCl	80	5	100	48 : 42 : 9 : 1
6	Toluene	80	60	94	57 : 43 : 0 : 0
6	Water	80	5	95	52 : 48 : 0 : 0
6	Water + 3M LiCl	80	5	95	50 : 50 : 0 : 0

Table 3 Reaction conditions, yields and ratio of the products of the reactions of nitrone **3**

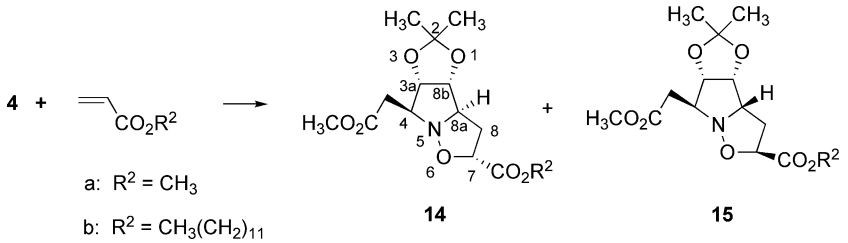
Dipolarophile	Media	Temp. (°C)	Time (h)	Yield (%)	Ratio of isomers **12/13**
5	Toluene	80	144	60	66 : 34
5	Water	80	6	65	66 : 34
6	Toluene	80	144	65	62 : 38
6	Water	80	12	70	62 : 38



Scheme 4 Reactions of nitrone **3**.

and *exo-Re* transition states respectively. The assignment of structures **12a** and **13a** has been described in a previous paper,[10h] whereas structures **12b** and **13b** were assigned in analogy with them. The most characteristic feature in the ^{1}H NMR spectra of compounds **12** and **13** is the pattern of 4-H and 5-H isoxazolidine protons. Thus, in the ^{1}H NMR of compound **12b** the one of 4-H appears at δ 2.77 (ddd, J = 13.1, 8.9, 7.7 Hz), the other one at δ 3.00 (dd, J = 13.1, 8.9 Hz) and the 5-H at 4.62 (t, J = 8.9 Hz), in close resemblance with the corresponding protons of **12a** [δ 2.77 (ddd, J = 13.1, 8.7, 7.1 Hz, one of 4-H), 2.97 (dd, J = 13.1, 8.7 Hz, one of 4-H), 4.63 (t, J = 8.7 Hz, 5-H)]. The same similarities are observed in the spectra of **13a** and **13b**. Thus the one of 4-H of **13b** appears at δ 2.75 (ddd, J = 12.6, 5.5, 1.3 Hz), the other 4-H at δ 2.88 (ddd, J = 12.6, 10.3, 8.2 Hz) and the 5-H at 4.80 (dd, J = 10.3, 5.5 Hz), whereas the corresponding protons of **13a** appear at δ 2.75 (ddd, J = 13.4, 5.8, 1.5 Hz, one of 4-H), 2.85 (ddd, J = 13.4, 10.3, 8.4 Hz, one of 4-H), 4.79 (dd, J = 10.3, 5.8 Hz, 5-H). The reaction conditions the yields and the ratio of the isomers as determined after column chromatography are given in Table 3.

The reactions of nitrone **4** with the alkenes **5** and **6** were performed in methylene chloride solution, water suspension and water with lithium chloride additive (Scheme 5). With both alkenes there were isolated two products which were assigned as **14** and **15** resulting from *exo-Re* and *exo-Si* transitions states. The assignment of **14a** and **15a** has been described previously,[10f] whereas structures **14b** and **15b** were assigned on the basis of the resemblance of their NMR spectra with those of **14a** and **15a** respectively. The most characteristic similarity is the ^{1}H NMR pattern of 8-H protons. In compounds **14** the two 8-H appear at δ 2.67 (ddd, J = 13.7, 9.2, 1.5 Hz) and 2.91 (ddd, J = 13.7, 7.9, 4.7 Hz) for **14a** and 2.67 (ddd, J = 13.2, 9.2, 1.5 Hz) and 2.90 (ddd, J = 13.2, 7.5, 4.9 Hz) for **14b**. In the isomers **15** the two 8-H appear at δ 2.46-2.62 (m overlapped with $CH_2CO_2CH_3$) and 2.93 (ddd, J = 12.8, 9.6, 3.3 Hz) for **15a** and 2.45-2.73 (m overlapped with $CH_2CO_2CH_3$) and 2.91 (ddd, J = 12.8, 9.2, 3.6 Hz) for **15b**. The reaction conditions the yields and the ratios of the isomers as determined after column chromatography are given in Table 4.



Scheme 5 Reactions of nitrone **4**.

Table 4 Reaction conditions, yields and ratio of the products of the reactions of nitrone **4**

Dipolarophile	Media	Temp. (°C)	Time (h)	Yield (%)	Ratio of isomers **14**/**15**
5	Methylene Chloride	25	12	95	67 : 33
5	Water	25	5	98	75 : 25
5	Water + 3M LiCl	25	3	98	78 : 22
6	Methylene chloride	25	60	80	58 : 42
6	Water	25	5	89	62 : 38
6	Water + 3M LiCl	25	5	95	64 : 36

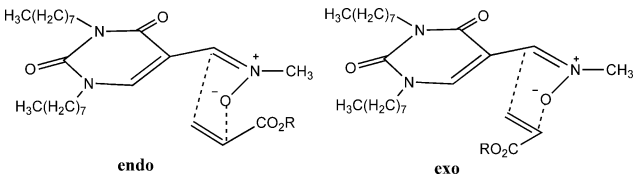
Tables 1, 2, 3 and 4 reveal that the reactions of all the used nitrones **1**, **2**, **3** and **4** with both the dipolarophiles **5** and **6** show considerable rate enhancement on changing the solvent from an organic one to water. In all cases studied the required time for the completion of the reaction was much shorter, when water was used as the medium. Since the used nitrones are almost totally insoluble in water the reactions may be characterized as "on water reactions". The considerable rate accelerations in reactions carried out under these conditions over those in organic solvents are not fully understood and are not explained by a unifying theory. Among others hydrophobic effects are usually invoked for their explanation. Our findings can be also attributed at least partially to hydrophobic effects. Although the decrease of the reactions time with the more hydrophobic alkene **6** was not larger than that with methyl acrylate as it was expected, the addition of LiCl " a salting out" agent caused a small farther decrease enhancing the hydrophobic nature of the effect of water. The most impressive results were observed with nitrone **3**, in which the reaction time was reduced from 144 h to 6 h with alkene **5** and to 12 h with alkene **6**. As it has been already mentioned compound **3** is a masked nitrone of low reactivity being in equilibrium with the cyclic hydroxylamine. In this case besides the hydrophobic effect the water may be shift the equilibrium to the more polar open nitrone structure.

The polarity of water is not expected to be the reason for rate enhancements, since it is known that polar solvents slow the rate of nitrone cycloadditions.[12] This was testified for our own experiments by performing some of our reactions in alcohol solutions. Thus, the reactions of nitrone **4** with alkenes **5** and **6** in methanol at RT were finished after 25 and 70 hours respectively, whereas the reactions of nitrone **2** with alkenes **5** and **6** in propanol were not finished even after heating at 80 °C for 7 days.

The observed regioselectivity and stereoselectivity of the reactions are in accordance with the known behaviour of the reactions of acyclic nitrones with acrylates,[10a–c,13] in which 5-substituted isoxazolidines with *trans* 1,3-substituents usually predominate. The stereoselectivity of the nitrone cycloadditions is related to the transition states leading to the possible stereoisomers. In the reactions of acyclic nitrones assuming that they react *via* their *Z*-form as it is generally accepted for acyclic aldonitrones,[14] *trans* and *cis* 1,3-isoxazolidines result from an *endo* and *exo* transition state respectively. Secondary interactions favour the *endo* approach, whereas steric factors the *exo* approach, the former one predominates in the reactions with acrylates giving *trans* 1,3-substituted isoxazolidines as the major products as it happens with the reactions of the nitrones **1** and **2** and with the asymmetric nitrone **3**, where only the two *trans* isoxazolidines were obtained resulting from the *endo* approach of the dipolarophile to the *Re* and *Si* face of this nitrone. Analogous stereoselectivity shows and the cyclic asymmetric nitrone **4**. In this case the two *trans* 1,3-isoxazolidines **14** and **15** result from an *exo* transition state to the *E*-form of the nitrone as it holds for cyclic nitrones

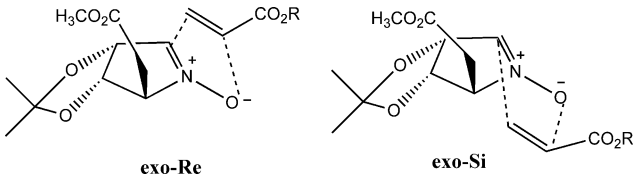
Concerning the regioselectivity of the reactions it is not influenced by the water medium. With the exception of the reaction of nitrone **2** with methyl acrylate only 5-substituted isoxazolidines were detected in all cases. Some, although small, remarkable changes are observed in the stereoselectivity of the reactions. The influence of the water on the stereoselectivity of the reactions can be related to the magnitude and the geometry of the transition state. In Diels Alder reactions the preference for *endo* attack in water is attributed mainly to hydrophobic effects which favour the most compact *endo* transition state with a smaller exposed non polar surface, although the operation of polar effects which increase the charge transfer interaction resulting from secondary orbital overlap in the *endo* transition state is not excluded.[15] More recently hydrophobic effects have been proposed as a method to determine transition state geometries.[16]

Contrary to the behaviour of Diels–Alder reactions, 1,3-dipolar cycloaddition reactions of nitrones **1** and **2** in water and especially with the more bulky ester **6** show a small tendency to favour the minor isomer coming from an *exo* transition state. An examination of the transition states by molecular models as depicted in scheme 6 for the nitrone **2** shows that in this case the *exo* transition state is more compact that the *endo*. The stereoselectivity of nitrone **3** does not show any influence by the medium. Both *endo* transition states leading to the two isomers



Scheme 6 Transition states for the reactions of nitrone **2**.

show the same compactness as it comes out from molecular models. On the contrary the stereoselectivity of the nitrone **4** shows a remarkable influence by the water which favours the formation of the major isomer **14**. Although both isomers **14** and **15** come from *exo* transition states, the *exo-Re* transition state having the two ester groups at the same site of the plane seems to be more compact than the *exo-Si* transition state as depicted in scheme 7.



Scheme 7 Transition states for the reactions of nitrone **4**.

Conclusions

In conclusion, the 1,3-dipolar cycloaddition reactions of several nitrones derived from sugars or nucleic bases or simple alkyl nitrones as **1**, **2**, **3**, **4** have been proved to be much faster in aqueous suspensions than in homogenous organic media revealing water as the medium of choice for the reactions of a variety of nitrones. From the standpoint of economic and environmental purposes this is of considerable importance taking into account the utility of nitrones as synthons in many synthetic schemes. Furthermore, small effects were observed in the stereoselectivities of the reactions explained on the basis of hydrophobic interactions which favour the more compact transition states.

Experimental section

General information

IR spectra were recorded on a Perkin-Elmer 297 spectrometer. ^{1}H NMR spectra were recorded at 300 MHz on a Bruker 300 AM spectrometer and ^{13}C NMR spectra at 75.5 MHz on the same spectrometer, and are quoted relative to tetramethylsilane as internal reference, in deuteriochloroform solutions. High resolution mass spectra (HRESI) were obtained with a 7 T APEX II spectrometer. Column chromatography was carried out on Merck Kieselgel (particle size 0.063-0.200 mm) and solvents were distilled before use. All reactions were monitored by TLC using Merck Kiesegel 60 F_{254} plates. In the case of water suspensions the TLC was done after a micro-extraction of 0,1 mL of the suspension with 1 mL Et_2O. Visualisation of the reaction components was achieved by using UV fluorescence (254 nm) or/and by spraying the TLC plates with a solution of 0.5% *p*-anisaldehyde in methanol/acetic acid/sulfuric acid 20 : 2 : 1 solution followed by charring on a hot plate for a few minutes. Methyl acrylate **5** and dodecyl acrylate **6** were supplied by Aldrich. Nitrones **2**,[10e] **3**,[10h] and **4**[11] were prepared as previously described.

N-[(1*Z*)-decylidene]-*N*-methylamine oxide (1)

Methylhydroxylamine hydrochloride (0.585 g, 7 mmol) and triethylamine (0.810 g, 8 mmol) were added to a solution of decanal (0.545 g, 3.5 mmol) in methylene chloride (5 mL) and the reaction mixture was stirred at room temperature and was monitored by TLC. After 24 h there was a small amount of the starting aldehyde but the reaction was stopped since longer reaction times resulted in more by-products as it was tested. The solvent was evaporated, water was added (10 mL) and the mixture was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over Mg_2SO_4 and the solvent was removed in vacuo. Flush column chromatography of the residue (ethyl acetate/methanol 95:5, *Rf* = 0.20) furnished **1** as a pale yellow oil (0,300 g, 1,6 mmol, 46% yield). Compound **1** was decomposed upon staying and treatment, so it was identified only from its NMR spectra and it was used immediately for the cycloaddition reactions without further purification. ^{1}H NMR ($CDCl_3$): δ = 0.86 (t, J = 7.4 Hz, 3H, CH_3), 1.15-1.41 (m, 12H, $CH_2CH_2(CH_2)_6CH_3$), 1.44-1.51 (m, 2H, $CH_2CH_2(CH_2)_6CH_3$), 2.41 (q, 2H, J = 6.2 Hz $CH_2CH_2(CH_2)_6CH_3$), 3.65 (s, 3H, CH=N(CH_3)O), 6.73 (t, J = 6.2 Hz, 1H, C*H*=N(CH_3)O); ^{13}C NMR ($CDCl_3$): δ 13.4 (CH_3), 22.0, 24.8, 26.2, 28.6, 28.7, 29.8, 29.9 and 31.2 ((CH_2)$_8$$CH_3$), 51.5 (N-$CH_3$), 140.2 (*C*H=N($CH_3$)O).

Cycloaddition reactions of nitrone 1

1,3-Dipolar cycloadditions of nitrone 1 in methylene chloride solutions. A solution of the nitrone **1** (0.092 g, 0.5 mmol) and the alkene **5** or **6** (2.5 mmol) in methylene chloride (10 mL) was allowed to stay at room temperature and it was monitored by TLC until the consumption of the nitrone. After that the solvent was evaporated and the residue was chromatographed with hexane/ethyl acetate 2 : 1 and 7 : 1 for the reactions with esters **5** and **6** respectively. From the column there were obtained in order of elution a mixture of **7** and **8** and after that pure **7**. The total yields of **7** and **8** and their ratio are given in Table 1.

1,3-Dipolar cycloadditions of nitrone 1 in aqueous suspensions. A suspension of the nitrone **1** (0.092 g, 0.5 mmol) and the alkene **5** or **6** (2.5 mmol) in water (10 mL) was allowed to stay at room temperature under vigorous stirring. The reaction was monitored by TLC until the consumption of the nitrone. After that, the reaction mixture was extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried over Mg_2SO_4 and the solvent was removed *in vacuo*. Then the same as above procedure was followed.

Methyl (3*RS*,5*SR*)-2-methyl-3-nonylisoxazolidine-5-carboxylate (7a)

This compound was obtained as an oil; *Rf* = 0.61 (hexane–ethyl acetate 2 : 1); ^{1}H NMR ($CDCl_3$): δ = 0.89 (t, J = 7.1 Hz, 3H,

CH_3), 1.18-1.38 (br m, 14H, $(CH_2)_7CH_3$), 1.45–1.62 (br m, 2H, $CH_2(CH_2)_7CH_3$), 2.14–2.33 (m, 1H, 4-H), 2.48–2.59 (m, 1H, 4-H), 2.71 and 2.75 (br s, overlapped with m, 4H, N-CH_3 and 3-H), 3.77 and 3.78 (s, 3H, OCH_3), 4.49–4.61 (m, 1H, 5-H); ^{13}C NMR ($CDCl_3$): δ 14.0 (CH_3), 22.6, 26.7, 29.2, 29.4, 29.6, 31.8, 32.0 and 32.4 (($CH_2)_8CH_3$), 39.4 (br, C-4), 43.8 and 44.5 (brs, N-CH_3), 52.2 (OCH_3), 67.5 and 68.5 (C-3), 73.6 and 74.7 (C-5), 172.3 (C=O); IR (neat): ν = 1740 (C=O) cm^{-1}; HRMS (ESI): m/z calcd for $C_{15}H_{30}NO_3$: 272.2225 [M+H]$^+$; found: 272.2220.

Methyl (3*RS*,5*RS*)-2-methyl-3-nonylisoxazolidine-5-carboxylate (8a)

This compound was isolated as a mixture with **7a**. ^{1}H NMR ($CDCl_3$): δ = 0.89 (t, J = 7.1 Hz, CH_3), 1.18–1.38 (br m, $(CH_2)_7CH_3$), 1.45-1.62 (br m, $CH_2(CH_2)_7CH_3$), 2.14–2.33 (m, 4-H), 2.48-2.59 (m, 4-H), 2.71, 2.72 and 2.75 (br s, overlapped with m, N-CH_3 and 3-H), 3.72 and 3.73 (s, OCH_3 of **8a**), 3.77 and 3.78 (s, OCH_3 of **7a**), 4.12–4.22 (m, 5-H of **8a**), 4.49-4.61 (m, 5-H of **7a**); ^{13}C NMR ($CDCl_3$): δ 14.0 (CH_3), 22.6, 26.7, 29.2, 29.4, 29.5, 29.6, 29.7, 31.8, 32.0 and 32.4 (($CH_2)_8CH_3$), 39.4 (br, C-4), 43.8 and 44.5 (brs, N-CH_3), 50.1 (OCH_3 of **8a**), 52.2 (OCH_3 of **7a**), 67.0 and 67.7 (C-3 of **8a**), 67.5 and 68.5 (C-3 of **7a**), 73.6, 74.7 and 74.9 (C-5), 172.3 (C=O of **7a**), 172.8 (C=O of **8a**).

Dodecyl (3*RS*,5*SR*)-2-methyl-3-nonylisoxazolidine-5-carboxylate (7b)

This compound was isolated as an oily white solid with melting point < 25 °C; Rf = 0.23 (hexane–ethyl acetate 7 : 1); ^{1}H NMR ($CDCl_3$): δ = 0.89 (t, J = 7.1 Hz, 6H; CH_3), 1.18–1.42 (m, 32H, 3-$CH_2(CH_2)_7CH_3$ and $OCH_2CH_2(CH_2)_9CH_3$), 1.50–1.75 (m, 4H, 3-$CH_2(CH_2)_7CH_3$ and $OCH_2CH_2(CH_2)_9CH_3$), 2.28 (ddd, J = 12.2, 9.2, 7.9 Hz, 1H, 4-H), 2.52 (ddd, J = 12.2, 6.7, 5.5 Hz, 1H, 4-H), 2.75 and 2.65–2.80 (br s, overlapped with br m, 4H, N-CH_3 and 3-H), 4.14 (t, J = 6.7 Hz, 2H, $OCH_2CH_2(CH_2)_9CH_3$), 4.45–4.56 (br m, 1H, 5-H); ^{13}C NMR ($CDCl_3$): δ 14.1 (CH_3), 22.6, 25.8, 26.7, 28.5, 29.2, 29.25, 29.3, 29.4, 29.5, 29.6, 29.7, 31.8 and 32.5, (3-($CH_2)_8CH_3$ and $OCH_2(CH_2)_{10}CH_3$)), 39.4 (br, C-4), 44.6 (br, N-CH_3), 65.4 ($OCH_2CH_2(CH_2)_9CH_3$), 67.5 (br, C-3), 75.0 (C-5), 172.1 (C=O); IR (KBr disk): ν = 1737 (C=O) cm^{-1}; HRMS (ESI): m/z calcd for $C_{26}H_{51}NO_3Na$: 448.3767[M+Na]$^+$; found: 448.3760.

Dodecyl (3*RS*,5*RS*)-2-methyl-3-nonylisoxazolidine-5-carboxylate (8b)

This compound was isolated as a mixture with **7b**; ^{1}H NMR ($CDCl_3$): δ = 0.89 (t, J = 6.5 Hz, CH_3), 1.19-1.46 (m, 3-$CH_2(CH_2)_7CH_3$ and $OCH_2CH_2(CH_2)_9CH_3$), 1.55-1.72 (m, 3-$CH_2(CH_2)_7CH_3$ and $OCH_2CH_2(CH_2)_9CH_3$), 2.17 (ddd, J = 12.2, 7.9, 6.1 Hz, 4-H of **8b**), 2.28 (ddd, J = 12.2, 9.2, 7.9 Hz, 4-H of **7b**), 2.47–2.61 (m, 4-H of **8a** and **8b**), 2.48–2.82 (br ss overlapped with br m, N-CH_3 and 3-H), 4.08–4.20 (m, $OCH_2CH_2(CH_2)_9CH_3$ and 5-H of **8b**), 4.45–4.56 (br m, 1H, 5-H of **7b**); ^{13}C NMR ($CDCl_3$): δ 14.1 (CH_3), 22.6, 25.7, 25.8, 25.9, 26.1, 26.7, 26.9, 28.5, 29.1, 29.2, 29.25, 29.3, 29.4, 29.5, 29.6, 29.7, 29.8, 30.0, 31.8, 32.2 and 32.5, (3-($CH_2)_8CH_3$ and OCH_2 $(CH_2)_{10}CH_3$)), 39.2 and 39.4 (br, C-4), 43.7 and 44.6 (br, N-CH_3), 65.0 and 65.4 ($OCH_2CH_2(CH_2)_9CH_3$), 67.5 and 68.3 (br, C-3), 73.5 and 75.0 (C-5), 172.1 and 172.3 (C=O).

Reduction of isoxazolidine 7a

A catalytic amount of Raney Ni (about 20 mg) was added to a previously degassed solution of isoxazolidine **7a** (0,054 g, 0.2 mmol) in MeOH (5 mL) under a hydrogen atmosphere (balloon). The mixture was stirred for about 2 days and then the crude reaction mixture was passed through Celite, concentrated and purified by column chromatography on silica gel using hexane–ethyl acetate 2 : 1 as the eluent to furnish 0.040 g (yield 83%) of compound **11**.

(3*SR*,5*RS*)-3-Hydroxy-1-methyl-5-nonylpyrrolidin-2-one (11)

This compound was obtained as an oil; Rf = 0.25 (hexane–ethyl acetate 2 : 1); ^{1}H NMR ($CDCl_3$): δ = 0.89 (t, J = 7.1 Hz, 3H; CH_3), 1.15–1.45 (br m, 14H, $(CH_2)_7CH_3$), 1.60–1.80 (br m, 2H, $CH_2(CH_2)_7CH_3$), 2.07 (dt, J = 12.2, 8.1 Hz, 1H, 4-H), 2.20 (ddd, J = 12.2, 8.1, 3.2 Hz, 1H, 4-H), 2.84 (s, 3H, N-CH_3), 3.28 (br s, 1H, OH), 3.51 (m, 1H, 5-H), 4.39 (t, J = 8.1 Hz, 1H, 3-H); ^{13}C NMR ($CDCl_3$): δ 14.1 (CH_3), 22.6, 24.8, 28.2, 29.3, 29.5, 29.6, 31.8, 32.0, 32.8 and 33.1(($CH_2)_8CH_3$, C-4 and N-CH_3), 57.6 (C-5), 70.0 (C-3), 174.4 (C=O); IR (neat): ν = 3.340 (OH), 1675 (C=O) cm^{-1}; HRMS (ESI): m/z calcd for $C_{14}H_{27}NO_2Na$: 264.1939 [M+Na]$^+$; found: 264.1935.

Cycloaddition reactions of nitrone 2

1,3-Dipolar cycloadditions of nitrone 2 in toluene solutions. A solution of the nitrone **2** (0.196 g, 0.5 mmol) and the alkene **5** or **6** (2.5 mmol) in toluene (10 mL) was heated in an oil bath with temperature controlled at 80 °C and it was monitored by TLC until the consumption of the nitrone. After that, the solvent was evaporated and the residue was chromatographed with hexane–ethyl acetate 2 : 1 and 5 : 1 for the reactions with esters **5** and **6** respectively. From the reaction with the ester **5** the column furnished an unseparable mixture of the four isomers **7c**, **8c**, **9c** and **10c**, whereas from the reaction with the ester **6** there were obtained in order of elution pure **7d**, mixture of **7d** with **8d** and pure **8d**. The total yields of the products and their ratio are given in Table 2

1,3-Dipolar cycloadditions of nitrone 2 in aqueous suspensions. A suspension of the nitrone **2** (0.196 g, 0.5 mmol) and the alkene **5** or **6** (2.5 mmol) in 10 mL of water or LiCl (3M) aqueous solution was heated in an oil bath with temperature controlled at 80 °C under vigorous stirring. The reaction was monitored by TLC until the consumption of the nitrone. After that, the reaction mixture was extracted with methylene chloride (3 × 20 mL). The combined organic layers were dried over Mg_2SO_4 and the solvent was removed in vacuo. Then the same as the above procedure was followed.

Methyl (3*S*,5*S*)-3-(1′,3′-dioctyl-2′,4′-dioxo-1′,2′,3′,4′-tetrahydropyrimidin-5′-yl)-2-methylisoxazolidine-5-carboxylate (7c) and methyl (3*S*,5*R*)-3-(1′,3′-dioctyl-2′,4′-dioxo-1′,2′,3′,4′-tetrahydropyrimidin-5′-yl)-2-methylisoxazolidine-5-carboxylate (8c) and methyl (3*S*,4*S*)-3-(1′,3′-dioctyl-2′,4′-dioxo-1′,2′,3′,4′-tetrahydropyrimidin-5′-yl)-2-methylisoxazolidine-4-carboxylate (9c) and methyl (3*S*,4*R*)-3-(1′,3′-dioctyl-2′,4′-dioxo-1′,2′,3′,4′-tetrahydropyrimidin-5′-yl)-2-methylisoxazolidine-4-carboxylate (10c)

These compounds were obtained as a mixture. ^{1}H NMR ($CDCl_3$): δ = 0.89 (t, J = 6.8 Hz, 3H, CH_3), 1.18–1.40 (m, $CH_2CH_2(CH_2)_2(CH_2)_5CH_3$), 1.52–1.73 (m, $CH_2CH_2(CH_2)_5CH_3$), 2.37 (dt, J = 12.8, 5.5 Hz, 4-H of **8c**), 2.56 (ddd, J = 13.4, 7.8, 4.3 Hz, 4-H of **7c**), 2.63 (s, N-CH_3 of **9c**), 2.68 (s, N-CH_3 of **8c**), 2.72 (s, N-CH_3 of **10c**), 2.75 (s, N-CH_3 of **7c**), 2.92 (ddd, J = 13.4, 7.8, 6.4 Hz, 4-H of **7c**), 3.10 (ddd, J = 12.8, 8.9, 8.2 Hz, 4-H of **8c**), 3.52 (s, $COOCH_3$ of **9c**), 3.61-4.00 (overlapped m and s, $COOCH_3$, $CH_2CH_2(CH_2)_5CH_3$, 3-H, 4-H of **9c** and **10c**), 4.08 (dd, J = 6.4, 4.3, 3-H of **7c**), 4.13-4.29 (m, 5-H of **9c** and **10c**), 4.47 (t, J = 7.8 Hz, 5-H of **7c**), 4.71 (dd, J = 8.2, 5.5 Hz, 5-H of **8c**), 7.31 (s, 6′-H of **9c**), 7.35 (s, 6′-H of **7c**), 7.38 (s, 6′-H of **10c**), 7.41 (s, 6′-H of **8c**); HRMS (ESI): m/z calcd for $C_{26}H_{45}NO_3Na$: 502.3257 $[M+Na]^+$; found: 502.3249.

Dodecyl (3*S*,5*S*)-3-(1′,3′-dioctyl-2′,4′-dioxo-1′,2′,3′,4′-tetrahydropyrimidin-5′-yl)-2-methylisoxazolidine-5-carboxylate (7d)

This compound was isolated as an oil; *R*f = 0.33 (hexane–ethyl acetate 5 : 1); ^{1}H NMR ($CDCl_3$): δ = 0.77-0.97 (m, 9H, CH_3), 1.12-1.40 (m, 38H, $NCH_2CH_2(CH_2)_5CH_3$ and $OCH_2CH_2(CH_2)_9CH_3$), 1.49–1.74 (m, 6H, $NCH_2CH_2(CH_2)_5CH_3$ and $OCH_2CH_2(CH_2)_9CH_3$), 2.57 (ddd, J = 12.8, 8.5, 3.7 Hz, 1H, 4-H), 2.80 (s, 3H, N-CH_3), 2.89 (ddd, J = 12.8, 8.2, 7.3 Hz, 1H, 4-H), 3.60–4.27 (m, 7H, 3-H, $OCH_2CH_2(CH_2)_9CH_3$ and $NCH_2CH_2(CH_2)_5CH_3$), 4.44 (dd as t, ΣJ = 15.8, 1H, 5-H), 7.36 (s, 1H, 6′-H); ^{13}C NMR ($CDCl_3$): δ 14.1 (CH_3), 22.6, 22.7, 25.8, 26.4, 26.5, 27.0, 27.6, 28.5, 29.1, 29.2, 29.3, 29.4, 29.5, 29.6, 31.7, 31.8 and 31.9, ($NCH_2(CH_2)_6CH_3$ and $OCH_2(CH_2)_{10}CH_3$)), 38.7 (C-4), 41.5, 45.7 and 50.00 (N-CH_3 and $NCH_2(CH_2)_6CH_3$), 63.5 and 65.7 (C-3 and $OCH_2(CH_2)_{10}CH_3$), 76.1 (C-5), 111.6 (C-5′), 139.7 (C-6′), 150.9 (C-2′), 162.5 (C-4′), 171.9 (C=O); IR (neat): ν = 1736, 1703, 1664, 1642 (C=O) cm^{-1}; HRMS (ESI): m/z calcd for $C_{37}H_{67}NO_3Na$: 656.4978 $[M+Na]^+$; found: 656.4967.

Dodecyl (3*S*,5*R*)-3-(1′,3′-dioctyl-2′,4′-dioxo-1,2,3,4-tetrahydropyrimidin-5′-yl)-2-methylisoxazolidine-5-carboxylate (8d)

This compound was isolated as an oily white solid with melting point < 25 °C; *R*f = 0.26 (hexane–ethyl acetate 5 : 1); ^{1}H NMR ($CDCl_3$): δ = 0.80–0.99 (m, 9H, CH_3), 1.15-1.45 (m, 38H, $NCH_2CH_2(CH_2)_5CH_3$ and $OCH_2CH_2(CH_2)_9CH_3$), 1.50-1.71 (m, 6H, $NCH_2CH_2(CH_2)_5CH_3$ and $OCH_2CH_2(CH_2)_9CH_3$), 2.36 (dt, J = 12.9, 5.1 Hz, 1H, 4-H), 2.73 (s, 3H, N-CH_3), 3.10 (ddd, J = 12.9, 9.0, 8.3 Hz, 1H, 4-H), 3.68–4.18 (m, 7H, 3-H, $OCH_2CH_2(CH_2)_9CH_3$ and $NCH_2CH_2(CH_2)_5CH_3$), 4.69 (dd, J = 9.0, 5.1 Hz, 1H, 5-H), 7.43 (s, 1H, 6′-H); ^{13}C NMR ($CDCl_3$): δ 14.1 (CH_3), 22.6, 22.7, 25.7, 26.5, 27.0, 27.6, 28.5, 29.1, 29.2, 29.3, 29.5, 29.6, 31.7, 31.8 and 31.9, ($NCH_2(CH_2)_6CH_3$ and OCH_2 $(CH_2)_{10}CH_3$)), 39.4 (C-4), 41.5, 44.6 and 50.00 (N-CH_3 and $NCH_2(CH_2)_6CH_3$), 63.2 and 65.5 (C-3 and $OCH_2(CH_2)_{10}CH_3$), 74.5 (C-5), 111.7 (C-5′), 140.2 (C-6′), 150.9 (C-2′), 162.7 (C-4′), 171.5 (C=O); IR (KBr disk): ν = 1737, 1703, 1663, 1642 (C=O) cm^{-1}; HRMS (ESI): m/z calcd for $C_{37}H_{67}NO_3Na$: 656.4978 $[M+Na]^+$; found: 656.4969.

Cycloaddition reactions of nitrone 3

1,3-Dipolar cycloadditions of nitrone 3 in toluene solutions. A solution of the nitrone **3** (0.123 g, 0.5 mmol) and the alkene **5** or **6** (2.5 mmol) in toluene (10 mL) was heated in an oil bath with temperature controlled at 80 °C and it was monitored by TLC until the consumption of the nitrone. After that the solvent was evaporated and the residue was chromatographed with hexane–ethyl acetate 2 : 1 and 4 : 1 for the reactions with esters **5** and **6** respectively. From the column there were obtained in order of elution pure **12**, mixture of **12** with **13** and pure **13**. The total yields of the products and their ratio are given in Table 3.

1,3-Dipolar cycloadditions of nitrone 3 in aqueous suspensions. A suspension of the nitrone **3** (0.123 g, 0.5 mmol) and the alkene **5** or **6** (2.5 mmol) in 10 mL of water was heated in an oil bath with temperature controlled at 80 °C under vigorous stirring. The reaction was monitored by TLC until the consumption of the nitrone. After that, the reaction mixture was extracted with methylene chloride (3 × 20 mL). The combined organic layers were dried over Mg_2SO_4 and the solvent was removed *in vacuo*. Then the same as above procedure was followed.

Dodecyl (3*R*,5*R*)-2-benzyl-3-[(4′*R*,5′*S*)-5′-(hydroxymethyl)-2′,2′-dimethyl-1′,3′-dioxolan-4′-yl]isoxazolidine-5-carboxylate (12b)

This compound was isolated as an oil; *R*f = 0.37 (hexane–ethyl acetate 4 : 1); ^{1}H NMR ($CDCl_3$): δ = 0.89 (t, J = 6.1 Hz, 3H CH_3), 1.21-1.35 (m, 18H, $OCH_2CH_2(CH_2)_9CH_3$), 1.35 (s, 3H, 2′-CH_3), 1.42 (s, 3H, 2′-CH_3), 1.60-1.72 (m, 2H, $OCH_2CH_2(CH_2)_9CH_3$), 2.77 (ddd, J = 13.1, 8.9, 7.7 Hz, 1H, 4-H), 3.00 (dd, J = 13.1, 8.9 Hz, 1H, 4-H), 3.35 (ddd, J = 12.8, 7.3, 4.3 Hz, 1H, CH_2OH), 3.63–3.74 (m, 2H, CH_2OH and 3-H), 3.81 (d, J = 12.8 Hz, 1H, $CH_2C_6H_5$), 3.90-4.03 (m, 2H, 4′-H and OH), 4.19 (t, J = 6.7 Hz, 2H, $OCH_2CH_2(CH_2)_9CH_3$), 4.24 (d, J = 12.8 Hz, 1H, $CH_2C_6H_5$), 4.36 (ddd, J = 9.7, 5.5, 4.3 Hz, 1H, 5′-H), 4.62 (t, J = 8.9 Hz, 1H, 5-H), 7.31–7.46 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$): δ 14.1 (CH_3), 22.6, 25.4, 25.8, 28.1, 28.5, 29.2, 29.3, 29.5, 29.55, 29.6 and 31.9 (OCH_2 $(CH_2)_{10}CH_3$ and 2′-CH_3), 33.3 (C-4), 59.2, 62.1, 64.7, 65.8, 75.3, 77.3 and 77.4 ($OCH_2(CH_2)_{10}CH_3$, CH_2OH, $CH_2C_6H_5$, C-3, C-5, C-4′ and C-5′), 108.7 ($C(CH_3)_2$), 127.9, 128.6, 129.9 and 135.7 (C_6H_5), 172.5 (C=O); IR (neat): ν = 3356 (OH), 1735 (C=O) cm^{-1}; HRMS (ESI): m/z calcd for $C_{29}H_{47}NO_3Na$: 528.3301 $[M+Na]^+$; found: 528.3299.

Dodecyl (3*R*,5*S*)-2-benzyl-3-[(4′*R*,5′*S*)-5′-(hydroxymethyl)-2′,2′-dimethyl-1′,3′-dioxolan-4′-yl]isoxazolidine-5-carboxylate (13b)

This compound was isolated as an oil; *R*f = 0.26 (hexane–ethyl acetate 4 : 1); ^{1}H NMR ($CDCl_3$): δ = 0.89 (t, J = 6.7 Hz, 3H CH_3), 1.23-1.33 (m, 18H, $OCH_2CH_2(CH_2)_9CH_3$),

1.33 (s, 3H, 2′-CH_3), 1.40 (s, 3H, 2′-CH_3), 1.59–1.72 (m, 2H, $OCH_2CH_2(CH_2)_9CH_3$), 2.75 (ddd, J = 12.6, 5.5, 1.3 Hz, 1H, 4-H), 2.88 (ddd, J = 12.6, 10.3, 8.2 Hz, 1H, 4-H), 3.35–3.46 (m, 1H, CH_2OH), 3.56-3.74 (m, 3H, CH_2OH, 3-H and OH), 3.84 (d, J = 12.8 Hz, 1H, $CH_2C_6H_5$), 3.98 (d, J = 12.8 Hz, 1H, $CH_2C_6H_5$), 4.10–4.26 (m, 3H, 4′-H and $OCH_2CH_2(CH_2)_9CH_3$), 4.31-4.39 (m, 1H, 5′-H), 4.80 (dd, J = 10.3, 5.5 Hz, 1H, 5-H), 7.29–7.45 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$): δ 14.1 (CH_3), 22.7, 25.4, 25.8, 28.0, 28.5, 29.2, 29.3, 29.5, 29.55, 29.6, 29.6 and 31.9 ($OCH_2(CH_2)_{10}CH_3$ and 2′-CH_3), 33.1 (C-4), 59.6, 60.5, 63.4, 65.8, 75.1, 76.2 and 77.2 ($OCH_2(CH_2)_{10}CH_3$, CH_2OH, $CH_2C_6H_5$, C-3, C-5, C-4′ and C-5′), 108.3 ($C(CH_3)_2$), 128.5, 129.6, 129.9 and 135.2 (C_6H_5), 170.8 (C=O); IR (neat): ν = 3441 (OH), 1742 (C=O) cm^{-1}; HRMS (ESI): m/z calcd for $C_{29}H_{47}NO_3Na$: 528.3301 [M+Na]$^+$; found: 528.3292.

Cycloaddition reactions of nitrone 4

1,3-Dipolar cycloadditions of nitrone 4 in methylene chloride solutions. A solution of the nitrone **4** (0.115 g, 0.5 mmol) and the alkene **5** or **6** (2.5 mmol) in methylene chloride (10 mL) was allowed to stay at room temperature and it was monitored by TLC until the consumption of the nitrone. After that, the solvent was evaporated and the residue was chromatographed with hexane–ethyl acetate 2 : 1 and 3 : 1 for the reactions with esters **5** and **6** respectively. From the column there were obtained in order of elution pure **14**, mixture of **14** with **15** and pure **15**. The total yields of the products and their ratio are given in Table 4.

1,3-Dipolar cycloadditions of nitrone 4 in aqueous suspensions. A suspension of the nitrone **4** (0.115 g, 0.5 mmol) and the alkene **5** or **6** (2.5 mmol) in 10 mL of water or LiCl (3M) aqueous solution was allowed to stay at room temperature under vigorous stirring. The reaction was monitored by TLC until the consumption of the nitrone. After that, the reaction mixture was extracted with methylene chloride (3 × 20 mL). The combined organic layers were dried over Mg_2SO_4 and the solvent was removed *in vacuo*. Then the same as above procedure was followed.

Dodecyl (3a*S*,4*S*,7*R*,8a*R*,8b*R*)-4-(2-methoxy-2-oxoethyl)-2,2-dimethyl hexahydro[1,3]dioxolo[3,4]pyrrolo[1,2-*b*]isoxazole-7-carboxylate (14b)

This compound was isolated as an oil; *R*f = 0.25 (hexane–ethyl acetate 3 : 1); ^{1}H NMR ($CDCl_3$): δ = 0.88 (t, J = 6.7 Hz, 3H, CH_3), 1.23–1.33 (overlapped s and m, 21H, $OCH_2CH_2(CH_2)_9CH_3$ and 2-CH_3), 1.52 (s, 3H, 2-CH_3), 1.58–1.73 (m, 2H, $OCH_2CH_2(CH_2)_9CH_3$), 2.67 (ddd, J = 13.2, 9.2, 1.5 Hz, 1H, 8-H), 2.78 (dd, J = 15.7, 6.4 Hz, 1H, $CH_2CO_2CH_3$), 2.90 (ddd, J = 13.2, 7.5, 4.9 Hz, 1H, 8-H), 3.10 (dd, J = 15.7, 8.3 Hz, 1H, $CH_2CO_2CH_3$), 3.65–3.76 (overlapped s and m, 4H, 4-H and CH_3O), 3.81 (dd, J = 7.5, 1.5 Hz, 1H, 8a-H), 4.11 (t, J = 6.8 Hz, 2H, $OCH_2CH_2(CH_2)_9CH_3$), 4.46-4.56 (m, 2H, 7-H and 8b-H), 4.74 (t, J = 6.8 Hz, 1H, 3a-H); ^{13}C NMR ($CDCl_3$): δ 14.1 (CH_3), 22.7, 25.2, 25.7, 25.8, 26.0, 27.4, 28.4, 29.2, 29.3, 29.5, 29.6 and 31.9 (OCH_2 $(CH_2)_{10}CH_3$ and 2-CH_3), 34.5 and 37.9 ($CH_2CO_2CH_3$ and C-8), 51.8 (CH_3O), 65.5, 69.4, 70.4 and 74.1 ($OCH_2(CH_2)_{10}CH_3$, C-4, C-7 and C-8a), 85.9 and 88.1 (C-3a and C-8b), 114.9 ($C(CH_3)_2$), 171.5 and 171.7 (C=O); IR (neat): ν = 1742 (C=O) cm^{-1}; HRMS (ESI): m/z calcd for $C_{25}H_{43}NO_7Na$: 492.2937 [M+Na]$^+$; found: 492.2933.

Dodecyl (3a*S*,4*S*,7*S*,8a*S*,8b*R*)-4-(2-methoxy-2-oxoethyl)-2,2-dimethylhexahydro[1,3]dioxolo[3,4]pyrrolo[1,2-*b*]isoxazole-7-carboxylate (15b)

This compound was isolated as an oil; *R*f = 0.13 (hexane–ethyl acetate 3 : 1); ^{1}H NMR ($CDCl_3$): δ = 0.88 (t, J = 6.8 Hz, 3H, CH_3), 1.18–1.36 (overlapped s and m, 21H, $OCH_2CH_2(CH_2)_9CH_3$ and 2-CH_3), 1.51 (s, 3H, 2-CH_3), 1.58–1.72 (m, 2H, $OCH_2CH_2(CH_2)_9CH_3$), 2.45–2.73 (m, 3H, $CH_2CO_2CH_3$ and 8-H), 2.91 (ddd, 1H, J = 12.8, 9.2, 3.6 Hz, 8-H), 3.69 (s, 3H, CH_3O), 3.82–3.90 (m, 2H, 4-H and 8a-H), 4.14 (t, J = 6.8 Hz, 2H, $OCH_2CH_2(CH_2)_9CH_3$), 4.56–4.76 (m, 3H, 3a-H, 7-H and 8b-H); ^{13}C NMR ($CDCl_3$): δ 14.1 (CH_3), 22.7, 24.5, 25.8, 26.6, 28.5, 29.2, 29.4, 29.5, 29.6 and 31.9 (OCH_2 $(CH_2)_{10}CH_3$ and 2-CH_3), 33.9 and 36.9 ($CH_2CO_2CH_3$ and C-8), 51.8 (CH_3O), 65.5, 67.0, 67.7 and 75.6 ($OCH_2(CH_2)_{10}CH_3$, C-4, C-7 and C-8a), 80.7 and 85.6 (C-3a and C-8b), 113.3 ($C(CH_3)_2$), 171.3 and 171.7 (C=O); IR (neat): ν = 1742 (C=O) cm^{-1}; HRMS (ESI): m/z calcd for $C_{25}H_{43}NO_7Na$: 492.2937 [M+Na]$^+$; found: 492.2931.

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