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1,3-Dipolar cycloaddition approach to pyrrolidine analogues of C-nucleosides related to pseudouridine

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ABSTRACT

Pyrrolidine analogues of C-nucleosides related to pseudouridine have been synthesized by 1,3-dipolar cycloaddition reactions of uracil-5 and 2,4-dimethoxypyrimidine-5 nitrones with allyl alcohol and methyl acrylate, and subsequent reductive cleavage of the isoxazolidine cycloadducts. The dimethoxy derivatives have been easily deprotected to the corresponding uracils bearing the pyrrolidine ring instead of a sugar moiety. The regio and stereoselectivity of the reactions are discussed.

1. Introduction

During the last decades nucleoside analogues have constituted a great and continuous interest due to their important role as anticancer and antiviral agents.[1] Several modifications have been made to both the heterocyclic base and the sugar moiety in the search for effective and selective derivatives. The most notable modifications are found in the sugar part with its replacement by acyclic moieties or carbo or other heterocyclic rings. Since the base moiety should preserve the base-pairing functionalities, only minor modifications of bases are usually present in biologically active nucleosides analogues. Besides the variations in the sugar and base parts, important modifications result from varying their connection as in the C-nucleosides, where the typical C–N glycosidic bond is replaced by a nonhydrolyzable C–C bond.

The most abundant natural C-nucleoside is pseudouridine, a C-5 linked uridine. Although the biological role of pseudouridine is not fully understood, its wide distribution in natural RNA and the genetic information invested in its formation, lead to the reasonable conjecture that this modified nucleoside is an important even essential constituent of RNA in the biological contexts in which it normally exists.[2]

The biological significance of pseudouridine has resulted in studies aimed at the synthesis of analogues with modified sugar moieties.[3] In particular, pyrrolidino pseudouridine derivatives have aroused considerable interest, and the influence of their incorporation into oligonucleotides on duplex and triplex stability has been studied.[4] Two methods have been mainly applied for their synthesis, Staudinger–aza-Wittig cyclization of γ-azido ketones,[4a] or palladium (0)-mediated coupling of 2-pyrrolines and 5-iodouracil.[4b]

In the context of our ongoing research on the synthesis of modified nucleosides,[5] and in continuation of our work on isoxazolidine analogues of pseudouridine,[6] we report in this paper a new route for the synthesis of pyrrolidino analogues of pseudouridine relying on the 1,3-dipolar cycloaddition with subsequent reductive ring cleavage.

2. Results and discussion

As key compounds for our synthesis we have chosen the uracil nitrones **2** and **14**, which can be readily prepared from the corresponding aldehydes **1** and **13**. The dioctyl derivatives have been chosen for the purposes of higher solubility and enhanced hydrophobicity, whereas the dimethoxy derivatives are protected forms of uracil. Nitrones are important synthons and their huge synthetic potential 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, and natural and modified pyrrolizidine and indolizidine alkaloids.[7] The most widely used reaction of nitrones is the 1,3-dipolar cycloaddition with alkenes to give isoxazolidines. Suitably substituted isoxazolidines can be further transformed to azaheterocycles via

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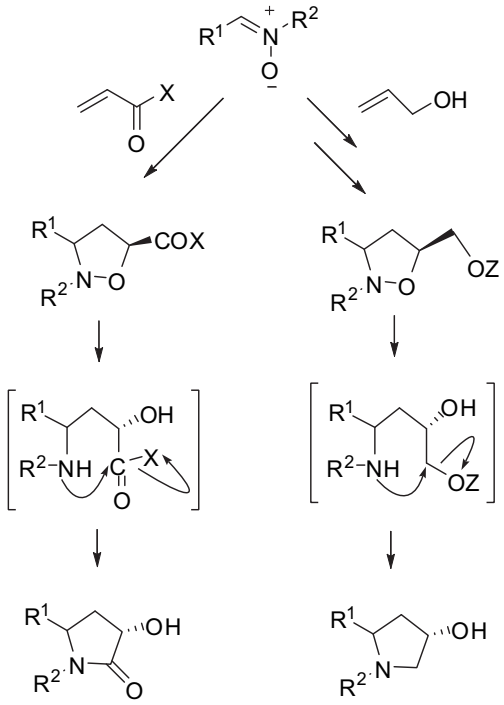
reductive cleavage of the N–O bond. Common appropriate substituents for these transformations are carbonyl derivatives or activated hydroxymethyl groups, which usually preexist in the alkene moiety. The N–O cleavage of the 5-substituted isoxazolidine cycloadduct and concomitant nucleophilic displacement of X or OZ groups give access to pyrrolidones or pyrrolidines, respectively (Scheme 1).

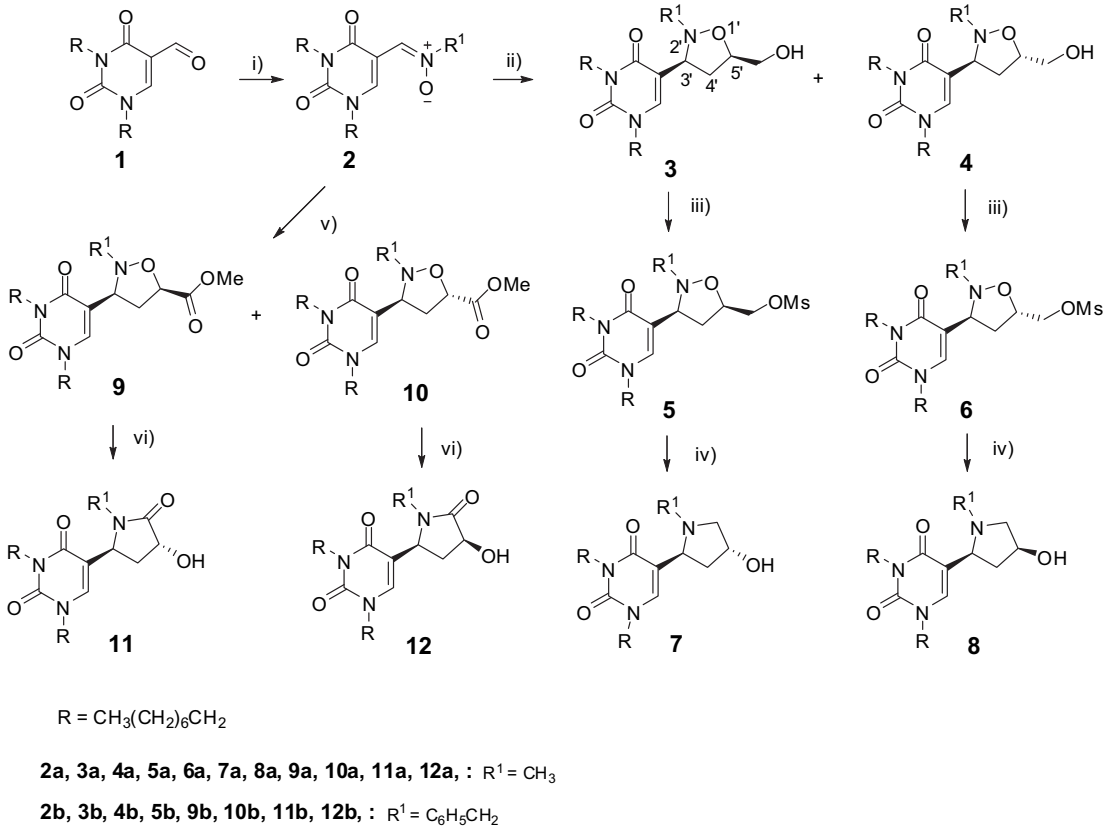


Scheme 1. Formation of pyrrolidones and pyrrolidines via 1,3-dipolar cycloaddition reactions of nitrones.

Uracil nitrones have been already successfully used by us[6] and others[3h] for the synthesis of isoxazolidine analogues of pseudouridine. Having in hand these successful cycloadditions, we proceeded to the synthesis of pyrrolidino uracils applying the 1,3-cycloaddition approach of the nitrones **2** and **14**. As alkenes we have chosen allyl alcohol and methyl acrylate bearing the appropriate functional groups for further manipulation and formation of the pyrrolidine ring after the reductive cleavage of the N–O bond. As depicted in Scheme 2 nitrones **2a** and **2b** reacted with allyl alcohol to give the stereoisomeric isoxazolidines **3** and **4** in a ratio 1.8:1 and 2.8:1 and total yields 85% and 75%, respectively. For the reaction with nitrone **2a** it was possible to separate the two stereoisomers **3a** and **4a** by column chromatography, whereas for the reaction with nitrone **2b** only the major isomer **3b** was obtained in a pure form. The hydroxymethyl isoxazolidines **3a**, **4a**, and **3b** were transformed to the corresponding mesyl derivatives **5a**, **6a**, and **5b**, which upon catalytic hydrogenation over Pd/C gave the hydroxypyrrolidines **7** and **8**. The reduction step proceeded almost quantitatively as shown by TLC. The resulted pyrrolidines were relatively unstable and they partially decomposed upon column chromatography. However, it was possible to obtain pyrrolidines **7a** and **8a** in satisfactory pure form after removal of the mesyl residues, by extraction with sodium carbonate solution. In the case of the reduction of **5b**, where debenzylation is also expected to take place during the catalytic step, it was not possible to isolate the corresponding pyrrolidine, although several attempts were made to trap it as its hydrochloride salt or its trifluoroacetyl derivative. As an alternative to the formation of the pyrrolidine ring we performed the cycloaddition reactions of the nitrones **2a** and **2b** with methyl acrylate. The reactions were performed in both neat acrylate (reflux) and toluene (heating with a fivefold excess solution of acrylate). In both cases the reactions were quantitative and gave an unseparable mixture of the two 5-substituted carboxymethyl isoxazolidines **9** and **10** (in ratio **9a**/**10a** 1:1.3 and **9b**/**10b** 1:1.7) containing also small amounts about 10% of the 4-carboxymethyl derivatives, as it was shown from the ^{1}H NMR spectrum of the crude reaction mixture. The reactions in neat acrylate were shorter but contaminated by large amounts by acrylate polymers, whereas reactions in toluene were cleaner and the obtained mixture of isomers could be used in one pot for the next reduction step after evaporation of the solvents. Catalytic hydrogenation over Ra/Ni gave the expected pyrrolidones **11** and **12**, which could be separated with column chromatography.

The same reaction sequence was also followed for the dimethoxypyrimidine nitrones **14a** and **14b** as shown in Scheme 3. Nitrone **14a** reacted with allyl alcohol to give the two stereoisomers **15a** and **16a** in a ratio 1.5:1 and 89% total yield. Nitrone **14b** gave the two isomers **15b** and **16b** as an unseparable mixture in a ratio 2:1 (determined by ^{1}H NMR) and 85% yield. Upon reaction with mesylchloride in pyridine the obtained cycloadducts were transformed to their mesyl derivatives. From the mixture of **15b** and **16b** the mesylates **17b** and **18b** were obtained separately. Catalytic hydrogenation of **17a**, **18a**, **17b**, and **18b** over Pd/C gave almost quantitatively the corresponding pyrrolidines **19a**, **20a**, **19b**, and **20b**. It should be mentioned that in the case of the benzyl derivatives **17b** and **18b**, debenzylation also takes place during the catalytic hydrogenation step. Demethylation of the resulted pyrrolidines upon reflux with methanol/hydrochloric acid solution gave the pyrrolidino uracils **21a**, **22a**, **21b**, and **22b** as their hydrochlorides. Following the alternative procedure for the formation of the pyrrolidine ring by cycloaddition to methyl acrylate and subsequent reduction, nitrone **14a** gave the two isomers **25a** and **26a** in a ratio of 1:1.8 and total yield 85% and it was possible to isolate in pure form only the major isomer **26a**. Nitrone **14b** gave the isomers **25b** and **26b** in a ratio of 1:2 and 82% total yield. However, it was not possible to separate the two isomers after reduction nor in the former cycloaddition step. Pyrrolidinone **26a** was quantitatively demethylated to the corresponding uracil **27a** by heating with sodium iodide in an acetic acid solution.

The structure elucidation of the obtained products was made on the basis of their elemental analysis and their spectroscopic data. All the compounds give molecular ion peaks in the mass spectra and the expected chemical shifts in the ^{1}H and ^{13}C NMR spectra. In particular, the discrimination between the stereoisomeric pairs of cycloadducts was based on the characteristic pattern of the 4-H protons of isoxazolidine ring. It has been testified in a series of analogous derivatives,[6,8] that the difference in the chemical shifts of the 4-H isoxazolidine protons is remarkably larger in the stereoisomers with a cis arrangement of the 3- and 5-isoxazolidine substituents than that with a trans arrangement, probably as a result of the shielding effect of both substituents on the same proton. Indeed, the $\Delta\delta$ between the chemical shifts of 4-H of the *cis*-isoxazolidines **3a**, **3b**, **15a**, **15b** ranges between 0.70 and 0.90 ppm, whereas that of the *trans*-isoxazolidines **4a**, **4b**, **16a**, **16b** between 0.28 and 0.44 ppm. Analogous regularities are also observed in the ^{1}H NMR spectra of the pyrrolidones **11**, **12**, **25**, and **26**. In the cis derivatives **12a**, **12b**, **26a**, **26b** the $\Delta\delta$ between the chemical shifts of the methylene protons ranges between 0.74 and 0.90 ppm, whereas that of the trans derivatives **11a**, **11b**, **25a**, **25b** between 0.00 and 0.22 ppm. The above general trends were further supported by NOE measurements performed on compounds **3b** and **26a**. Thus, in the isoxazolidine **3b** trans to the substituents low field 4′-H (δ 2.88) exhibits large mutual NOE enhancements with both 3′-H (δ 4.15) and 5′-H (δ 4.43) (10% enhancement of both 3′-H and 5′-H upon saturation of 4′-H, and 7% and 8% enhancement of 4′-H upon saturation of 3′-H and 5′-H, respectively). These findings



Scheme 2. Reagents and conditions: (i) $NH_2OH{\cdot}HCl$ or $PhCH_2NHOH{\cdot}HCl$, Na_2CO_3, $EtOH/H_2O$, rt, 24 h; (ii) $CH_2{=}CHCH_2OH$, reflux, 48 h; (iii) mesylchloride, pyridine, rt, 1–2 h; (iv) H_2, Pd/C, CH_3OH, rt, 48 h; (v) $CH_2{=}CHCO_2CH_3$, toluene, 80 °C, 48 h; (vi) H_2, Ra/Ni, CH_3OH, rt, 24 h.

indicate the cis desposition of 3′-H and 5′-H being cis to the same 4′-H. Analogous results were obtained from NOE measurements on pyrrolidone **26a**. Saturation of the low field methylene 3′-H proton (δ 2.75) causes 7% and 8% enhancements to 2′-H (δ 4.42) and 4′-H (δ 4.62) and mutually saturation of 2′-H and 4′-H causes 8% and 9% enhancement of 3′-H.

The reactions of nitrones **2** and **14** with allyl alcohol and methyl acrylate show opposite stereoselectivities. With allyl alcohol the major products are the cycloadducts with a cis arrangement of 3′ and 5′ substituents, whereas with methyl acrylate those with a trans arrangement. *cis* Cycloadducts are formed from an *exo* approach of the dipolarophile and *trans* cycloadducts from an *endo* approach assuming *Z*-configuration of the nitrone as it has been proved for aldonitrones.[3h] *exo* Transition states are favored by stereochemical factors, whereas *endo* transition states by secondary interactions. The observed stereoselectivities are in accordance with the known superiority of the methoxycarbonyl group in manifestation of secondary orbital interactions.[9]

In conclusion, the 1,3-dipolar cycloaddition reactions of 5-uracil or 5-dimethoxypyrimidine nitrones emerge as a convenient route for the construction of the pyrrolidine ring at the 5-position of uracil. By applying appropriately substituted nitrones and alkenes, a variety of new pyrrolidine analogues of pseudouridine with different substituents and geometry can be prepared.

3. Experimental

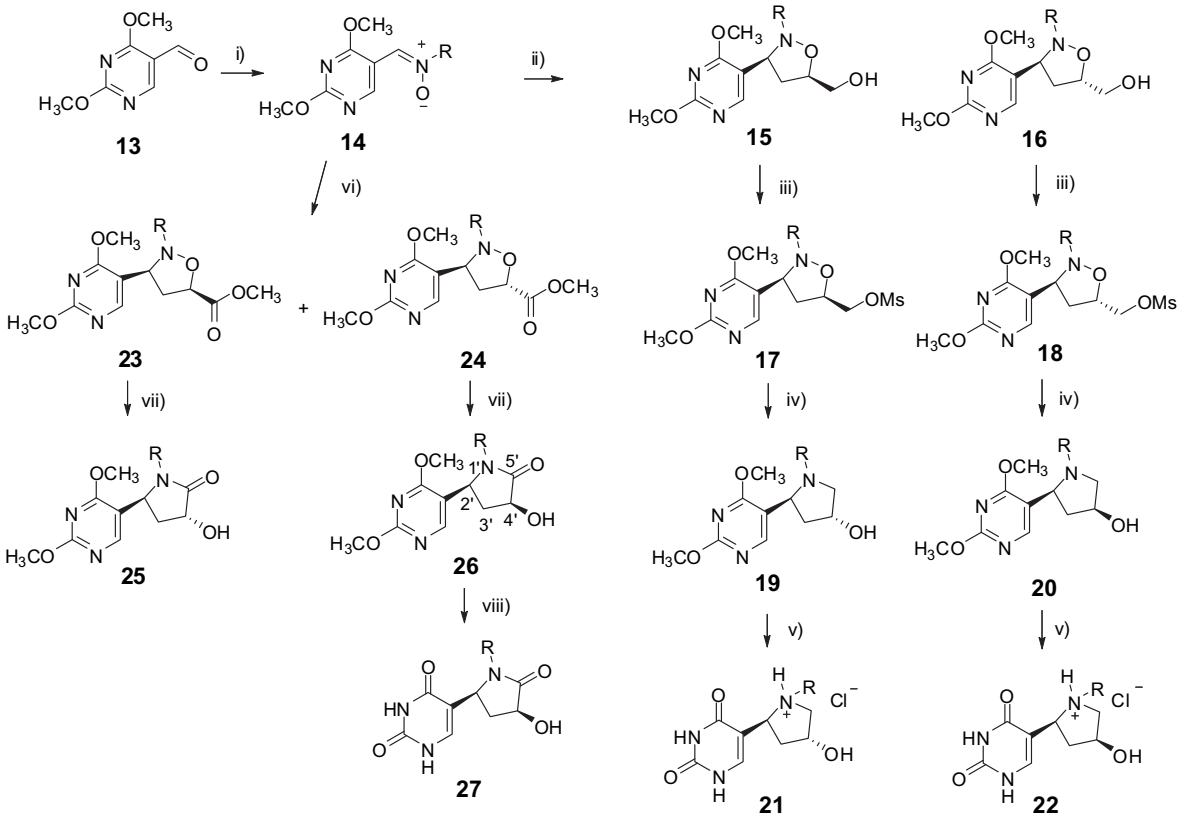
3.1. General

Mps are uncorrected and were determined on a Kofler hot-stage microscope. IR spectra were recorded on a Perkin–Elmer 297 spectrometer. ^{1}H NMR spectra were recorded at 300 MHz on a Bruker AVANCE^{III} 300 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, unless otherwise stated. Mass spectra were performed on a Shimadzu LCMS-2010EV instrument under electrospray ionization conditions. High resolution mass spectra (HRESI) were obtained with a 7 T APEX II spectrometer. Microanalyses were performed on a Perkin–Elmer 2400-II element analyser. Column chromatography was carried out on Merck Kieselgel (particle size 0.063–0.200 mm) and solvents were distilled before use. The synthesis of the aldehydes **1** and **13** and nitrones **2a** and **14a** was made according to previously described procedures.[5c,6]

3.2. Synthesis of nitrones 2b and 14b

General procedure. An aqueous solution (2.5 ml) of benzylhydroxylamine hydrochloride (2 mmol) and sodium carbonate (1.5 mmol) was added to an ethanolic solution (5 ml) of the aldehyde **1** or **13** (1 mmol) and the reaction mixture was stirred at room temperature for 24 h. After the ethanol was evaporated, water was added and the mixture was extracted with methylene chloride. After drying and evaporation of the solvent from the organic layer, the residue nitrones were obtained by column chromatography with eluents hexane/ethyl acetate 2:1 and ethyl acetate for nitrones **2b** and **14b**, respectively.

*3.2.1. N-Benzyl-C-(1,3-dioctyl-5-uracil)nitrone (**2b**).* This compound was obtained in 80% yield as a white solid, mp 50–53 °C; IR (Nujol): ν_{max} 3070, 3030, 2920, 2850, 1690, 1635, 1460, 1340, 1190, 1140, 1115 cm^{-1}; ^{1}H NMR: δ 0.87 (t, J=6.4 Hz, 6H, $CH_2CH_2(CH_2)_5CH_3$), 1.20–1.45 (m, 20H, $CH_2CH_2(CH_2)_5CH_3$), 1.55–1.77 (m, 4H, $CH_2CH_2(CH_2)_5CH_3$), 3.75 (t, J=6.8 Hz, 2H, $CH_2CH_2(CH_2)_5CH_3$), 3.97



13a, 14a, 15a, 16a, 17a,18a, 19a, 20a, 21a, 22a, 23a, 24a, 25a, 26a, 27a : R = CH_3

13b, 14b, 15b, 16b, 17b, 18b, 23b, 24b, 25b, 26b: R= $C_6H_5CH_2$

19b, 20b, 21b, 22b: R = H

Scheme 3. Reagents and conditions: (i) $NH_2OH{\cdot}HCl$ or $PhCH_2NHOH{\cdot}HCl$, Na_2CO_3, EtOH/H_2O, rt, 24 h; (ii) $CH_2{=}CHCH_2OH$, reflux, 48 h; (iii) mesylchloride, pyridine, rt, 1–2 h; (iv) H_2, Pd/C, CH_3OH, rt, 48 h; (v) CH_3OH, 6 M aqueous HCl, reflux, 3 h; (vi) $CH_2{=}CHCO_2CH_3$, toluene, 80 °C, 48 h; (vii) H_2, Ra/Ni, CH_3OH, rt, 24 h; (viii) CH_3COOH, NaI, 90 °C, 1 h.

(t, J=7.6 Hz, 2H, C$H_2$$CH_2(CH_2)_5CH_3$), 4.98 (s, 2H, C$H_2$Ph), 7.35–7.48 (m, 5H, Ph–H), 7.84 (s, 1H, CH=N(O)), 9.88 (s, 1H, 6-H); ^{13}C NMR: δ 13.7 (CH_3), 22.2, 26.0, 26.5, 27.1, 28.6, 28.7, 28.8, 28.9, 31.3 and 31.4 (CH_2 (CH_2)$_6CH_3$), 41.4 and 50.2 ($CH_2(CH_2)_6CH_3$), 69.8 (CH_2Ph), 105.3 (C-5), 127.2, 128.5, 128.6 and 128.8 (C–Ph), 132.8 (CH=N(O)), 142.3 (C-6), 149.4 (C-2), 161.1 (C-4); MS (m/z, %): 492 [(M+Na)$^+$, 100]. Anal. Calcd for $C_{28}H_{43}N_3O_3$: C, 71.61; H, 9.23; N, 8.95. Found: C, 71.74; H, 8.99; N, 8.82.

*3.2.2. N-Benzyl-C-(1,3-dimethoxy-5-pyrimidine)nitrone (**14b**).* This compound was obtained in 88% yield as a white solid mp 96–98 °C; IR (Nujol): ν_{max} 3085, 3045, 3000, 2920, 2850, 1570, 1550, 1460, 1330, 1235, 1210, 1165, 1055, 1015 cm^{-1}; ^{1}H NMR: δ 4.01 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 5.04 (s, 2H, CH_2Ph), 7.32–7.50 (5H, Ph–H), 7.64 (s, 1H, CH=N(O)), 10.18 (s, 1H, 6-H); ^{13}C NMR: δ 54.4 and 55.3 (OCH_3), 71.0 (CH_2Ph), 107.5 (C-5), 125.7, 129.0, 129.1 and 129.2 (C–Ph), 133.2 (CH=N(O)), 157.9 (C-6), 165.1 and 167.9 (C-2 and C-4); MS (m/z, %): 273 [(M)$^+$, 30%]. Anal. Calcd for $C_{14}H_{15}N_3O_3$: C, 61.53; H, 5.53; N, 15.38. Found: C, 61.48; H, 5.71; N, 15.34.

3.3. Reactions of nitrones 2 and 14 with allyl alcohol

General procedure. A solution of the nitrone **2** or **14** (0.5 mmol) and allyl alkohol (4 ml) was heated to reflux and the reaction was monitored by TLC until consumption of the nitrone. After two days only traces of the nitrone were detected in the TLC. The heating was stopped and after evaporation of the excess allyl alcohol the residue was chromatographed on a silica gel column with hexane/ethyl acetate (1:2 for the reaction of **2a**, 2:1 for the reaction of **2b**, 1:5 for the reaction of **14a**, 1:2 for the reaction of **14b**) as the eluent. From the reactions with the methyl nitrones **2a** and **14a** the two diastereoisomeric products **3a**, **4a** and **15a**, **16a**, respectively, were obtained separately. From the reaction with the benzyl nitrone **2b** the major isomer **3b** was obtained separately and the minor **4b** only as a mixture with the major one, whereas from the reaction of the benzyl nitrone **14b** the two isomers **15b**, **16b** were obtained as a mixture. In the cases of mixtures the given yields were calculated from their ratio as it was determined from their proton NMR.

*3.3.1. (3′RS,5′SR)-5-(5′-Hydroxymethyl-2′-methyl isoxazolidin-3′-yl)-1,3-dioctyluracil (**3a**).* This compound was obtained from nitrone **2a** in 55% yield as an oil; IR (liquid film): ν_{max} 3400, 3060, 2920, 2850, 1690, 1640, 1460, 1370, 1240, 1055 cm^{-1}; ^{1}H NMR: δ 0.85–0.92 (m, 6H, CH_3), 1.14–1.41 (m, 20H, CH_2CH_2(CH_2)$_5CH_3$), 1.50–1.75 (m, 4H, $CH_2CH_2(CH_2)_5CH_3$), 1.97 (dt, J=12.6, 6.4 Hz, 1H, 4′-H), 2.2 (br, 1H, OH), 2.68 (s, 3H, N–CH_3), 2.87 (dt, J=12.6, 8.3 Hz, 1H, 4′-H), 3.59 (dd, J=11.9, 5.2 Hz, 1H, CH_2OH), 3.69–3.80 (m, 3H, $CH_2CH_2(CH_2)_5CH_3$ and CH_2OH), 3.85–3.96 (m, 3H, $CH_2CH_2(CH_2)_5CH_3$ and 3′-H), 4.33–4.43 (m, 1H, 5′-H), 7.35 (s, 1H, 6-H); ^{13}C NMR: δ 14.0 (CH_3), 22.6, 26.5, 27.0, 27.5, 29.0, 29.1, 29.2, 31.7 and 31.8 (CH_2(CH_2)$_6CH_3$), 38.0 (C-4′), 41.6, 44.0 and 50.0 ($CH_2(CH_2)_6CH_3$ and N–CH_3), 64.1 and 64.9 (C-3′ and

CH_2OH), 76.9 (C-5′), 112.1 (C-5), 139.2(C-6), 150.8 (C-2), 162.7 (C-4); MS (*m*/*z*, %): 452 [$(M+H)^+$, 100%]. Anal. Calcd for $C_{25}H_{45}N_3O_4$: C, 66.48; H, 10.04; N, 9.30. Found: C, 66.26; H, 10.21; N, 9.25.

*3.3.2. (3′RS,5′RS)-5-(5′-Hydroxymethyl-2′-methyl isoxazolidin-3′-yl)-1,3-dioctyluracil (**4a**).* This compound was obtained from nitrone **2a** in 30% yield as an oil; IR (liquid film): ν_{max} 3450, 3050, 2920, 2850, 1675, 1630, 1450, 1340, 1250, 1230, 1030 cm^{-1}; ^1H NMR: δ 0.80–0.95 (m, 6H, CH_3), 1.17–1.41 (m, 20H, $CH_2CH_2(CH_2)_5CH_3$), 1.52–1.70 (m, 4H, $CH_2CH_2(CH_2)_5CH_3$), 1.90 (br, 1H, OH), 2.14 (ddd, *J*=12.4, 8.0, 5.2 Hz, 1H, 4′-H), 2.58 (dt, *J*=12.4, 8.0 Hz, 1H, 4′-H), 2.71 (s, 3H, *N*–CH_3), 3.63 (dd, *J*=12.0, 5.1 Hz, 1H, CH_2OH), 3.71–4.02 (m, 6H, $CH_2CH_2(CH_2)_5CH_3$, CH_2OH and 3′-H), 4.12–4.21 (m, 1H, 5′-H), 7.33 (s, 1H, 6-H); ^{13}C NMR: δ 14.0 (CH_3), 22.6, 26.5, 27.0, 27.6, 29.0, 29.1, 29.2, 31.6 and 31.7 ($CH_2(CH_2)_6CH_3$), 37.3 (C-4′), 41.6, 49.9 and 53.5 ($CH_2(CH_2)_6CH_3$ and *N*–CH_3), 63.9 (C-3′ and CH_2OH), 78.2 (C-5′), 112.1 (C-5), 139.2 (C-6), 150.9 (C-2), 162.6 (C-4), 166.7 (C=O); MS (*m*/*z*, %): 452 [$(M+H)^+$, 100%]. Anal. Calcd for $C_{25}H_{45}N_3O_4$: C, 66.48; H, 10.04; N, 9.30. Found: C, 66.48; H, 9.87; N, 9.50.

*3.3.3. (3′RS,5′SR)-5-[(2′-Benzyl-5′-hydroxymethyl)isoxazolidin-3′-yl]-1,3-dioctyluracil (**3b**).* This compound was obtained from nitrone **2b** in 55% yield as an oil; IR (liquid film): ν_{max} 3450, 3050, 2920, 2850, 1675, 1630, 1450, 1330, 1210, 1110, 1020 cm^{-1}; ^1H NMR: δ 0.80–0.98 (m, 6H, CH_3), 1.15–1.43 (m, 20H, $CH_2CH_2(CH_2)_5CH_3$), 1.50–1.75 (m, 4H, $CH_2CH_2(CH_2)_5CH_3$), 2.01 (dt, *J*=12.6, 6.4 Hz, 1H, 4′-H), 2.30 (br, 1H, OH), 2.88 (dt, *J*=12.6, 8.4 Hz, 1H, 4′-H), 3.57 (dd, *J*=11.6, 5.5 Hz, 1H, CH_2OH), 3.63–3.78 (m, 3H, $CH_2CH_2(CH_2)_5CH_3$ and CH_2OH), 3.84–3.93 (m, 3H, $CH_2CH_2(CH_2)_5CH_3$ and $CH_2C_6H_5$), 4.05 (d, *J*=13.7 Hz, 1H, $CH_2C_6H_5$), 4.15 (dd, *J*=8.4, 6.4 Hz, 1H, 3′-H), 4.39–4.49 (m, 1H, 5′-H), 7.27–7.32 (m, 5H, $CH_2C_6H_5$), 7.39 (s, 1H, 6-H); ^{13}C NMR: δ 14.0 (CH_3), 22.5, 26.4, 26.8, 26.9, 27.5, 29.1, 29.2, 31.6 and 31.7 ($CH_2(CH_2)_6CH_3$), 37.7 (C-4′), 41.8, and 49.9 ($CH_2(CH_2)_6CH_3$), 61.2, 61.9 and 64.5 (C-3′, $CH_2C_6H_5$ and CH_2OH), 77.3 (C-5′), 112.5 (C-5), 127.4, 128.7, 128.8 and 136.8 ($CH_2C_6H_5$), 139.4 (C-6), 150.8 (C-2), 162.5 (C-4); MS (*m*/*z*, %): 550 [$(M+Na)^+$, 100]. Anal. Calcd for $C_{31}H_{49}N_3O_4$: C, 70.55; H, 9.36; N, 7.96. Found: C, 70.33; H, 9.21; N, 8.07.

*3.3.4. (3′RS,5′RS)-5-[(2′-Benzyl-5′-hydroxymethyl)isoxazolidin-3′-yl]-1,3-dioctyluracil (**4b**).* This compound was obtained from nitrone **2b** in 20% yield only as a mixture with **3b**; ^1H NMR: δ 0.80–0.98 (m, CH_3), 1.15–1.45 (m, $CH_2CH_2(CH_2)_5CH_3$), 1.50–1.80 (m, $CH_2CH_2(CH_2)_5CH_3$), 2.01 (dt, *J*=12.6, 6.4 Hz, 4′-H of **3b**), 2.17 (ddd, *J*=12.4, 7.8, 4.8 Hz, 4′-H of **4b**), 2.58 (dt, *J*=12.4, 7.8 Hz, 4′-H of **4b**), 2.88 (dt, *J*=12.6, 8.4 Hz, 4′-H of **3b**), 3.51–3.80 (m, $CH_2CH_2(CH_2)_5CH_3$ and CH_2OH), 3.84–3.93 (m, $CH_2CH_2(CH_2)_5CH_3$ and $CH_2C_6H_5$), 4.05 (d, *J*=13.7 Hz, $CH_2C_6H_5$), 4.10–4.20 (m, 3′-H and 5′-H of **4b**), 4.39–4.49 (m, 5′-H of **3b**), 7.20–7.40 (m, $CH_2C_6H_5$ and 6-H).

*3.3.5. (3′RS,5′SR)-5-(5′-Hydroxymethyl-2′-methylisoxazolidin-3′-yl)-2,4-dimethoxypyrimidine (**15a**).* This compound was obtained from nitrone **14a** in 53% yield as an oil; IR (liquid film): ν_{max} 3600–3100, 2950, 2910, 2860, 1595, 1565, 1460, 1390, 1200, 1075, 1015 cm^{-1}; ^1H NMR: 2.07 (ddd, *J*=12.4, 8.5, 5.6 Hz, 1H, 4′-H), 2.62 (s, 3H, *N*–CH_3), 2.70 (br, 1H, OH), 2.77 (dt, *J*=12.4, 8.5 Hz, 1H, 4′-H), 3.65–3.71 (m, 2H, CH_2OH), 3.80 (t, *J*=8.5 Hz, 1H, 3′-H), 3.98 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 4.30–4.39 (m, 1H, 5′-H), 8.31 (s, 1H, 6-H); ^{13}C NMR: δ 38.3 (C-4′), 43.4 (*N*–CH_3), 54.0 and 54.7 (OCH_3), 64.5 and 65.3 (C-3′ and CH_2OH), 77.0 (C-5′, detected by DEPT), 112.8 (C-5), 156.5 (C-6), 164.7 (C-2), 168.9 (C-4); MS (*m*/*z*, %): 278 [$(M+Na)^+$, 100]. Anal. Calcd for $C_{11}H_{17}N_3O_4$: C, 51.76; H, 6.71; N, 16.46. Found: C, 51.54; H, 6.82; N, 16.65.

*3.3.6. (3′RS,5′RS)-5-(5′-Hydroxymethyl-2′-methylisoxazolidin-3′-yl)-2,4-dimethoxypyrimidine (**16a**).* This compound was obtained from nitrone **14a** in 36% yield as an oil; IR (liquid film): ν_{max} 3600–3100, 2990, 2910, 2860, 1595, 1560, 1450, 1390, 1230, 1050 cm^{-1}; ^1H NMR: δ 2.10 (br, 1H, OH), 2.23 (dt, *J*=12.1, 8.0 Hz, 1H, 4′-H), 2.51 (ddd, *J*=12.1, 9.5, 6.7 Hz, 1H, 4′-H), 2.62 (s, 3H, *N*–CH_3), 3.62 (dd, *J*=12.0, 4.8 Hz, 1H, CH_2OH), 3.72–3.86 (m, 2H, CH_2OH and 3′-H), 3.99 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 4.25–4.35 (m, 1H, 5′-H), 8.30 (s, 1H, 6-H); ^{13}C NMR: δ 38.0 (C-4′), 43.6 (*N*–CH_3), 54.0 and 54.7 (OCH_3), 63.6 and 64.5 (C-3′ and CH_2OH), 77.5 (C-5′), 112.9 (C-5), 156.8 (C-6), 164.7 (C-2), 169.0 (C-4); MS (*m*/*z*, %): 278 [$(M+Na)^+$, 100]. Anal. Calcd for $C_{11}H_{17}N_3O_4$: C, 51.76; H, 6.71; N, 16.46. Found: C, 51.58; H, 6.65; N, 16.66.

*3.3.7. (3′RS,5′SR)-5-[(2′-Benzyl-5′-hydroxymethyl)isoxazolidin-3′-yl]-2,4-dimethoxypyrimidine (**15b**) and (3′RS,5′RS)-5-[(2′-benzyl-5′-hydroxymethyl)isoxazolidin-3′-yl]-2,4-dimethoxypyrimidine (**16b**).* These compounds were obtained from nitrone **14b** as a oily mixture in a ratio 2:1 and 85% total yield and they were characterized only by their ^1H NMR spectrum; ^1H NMR: δ 1.98 (br, OH), 2.05 (ddd, *J*=12.7, 7.7, 5.7 Hz, 4′-H of **15b**), 2.21 (dt, *J*=12.2, 7.6 Hz, 1H, 4′-H of **16b**), 2.58 (ddd, *J*=12.2, 8.1, 6.9 Hz, 1H, 4′-H of **16b**), 2.81 (dt, *J*=12.7, 8.3 Hz, 4′-H of **15b**), 3.62 (dd, *J*=12.0, 4.8 Hz, 1H, CH_2OH), 3.54–4.01 (overlapped s and m, OCH_3, $CH_2C_6H_5$, CH_2OH and 3′-H of **16b**), 3.99 (s, OCH_3), 4.01 (s, OCH_3), 4.08 (apparent t, Σ*J*=16 Hz, 3′-H of **16b**), 4.22–4.31 (m, 1H, 5′-H of **16b**), 4.33–4.41 (m, 1H, 5′-H of **15b**), 7.19–7.37 (m, $CH_2C_6H_5$), 8.41 (s, 6-H of **16b**), 8.43 (s, 6-H of **15b**).

3.4. Mesylation reactions of hydroxymethyl isoxazolidines, 3, 4, 15, 16

General procedure. Hydroxymethyl isoxazolidine **3** or **4** or **15** or **16** (2 mmol) was dried by addition and evaporation with dry toluene three times. Next, it was dissolved in dry pyridine (3 ml) and mesylchloride (2.4 mmol) was added under an argon atmosphere at 0 °C. The reaction mixture was stirred at room temperature until the completion of the reaction (1–2 h). Then the pyridine was evaporated and the residue was chromatographed on a silica gel column with a mixture of hexane/ethyl acetate (2:1 for the reactions of **3a**, **4a**, 1:1 for the reactions of **3b**, **15a**, **16a**, **15b**, **16b**) as the eluent.

*3.4.1. (3′RS,5′SR)-5-[2′-Methyl-5′-((methylsulfonyloxy)methyl)isoxazolidin-3′-yl]-1,3-dioctyluracil (**5a**).* This compound was obtained from **3a** in 87% yield as an oil; IR (liquid film): ν_{max} 2920, 2845, 1690, 1650, 1455, 1350, 1175, 1060 cm^{-1}; ^1H NMR: δ 0.80–0.95 (m, 6H, CH_3), 1.17–1.40 (m, 20H, $CH_2CH_2(CH_2)_5CH_3$), 1.55–1.75 (m, 4H, $CH_2CH_2(CH_2)_5CH_3$), 1.91 (dt, *J*=12.8, 6.2 Hz, 1H, 4′-H), 2.68 (s, 3H, *N*–CH_3), 2.89–2.96 (m, 1H, 4′-H), 3.05 (s, 3H, SO_2CH_3), 3.61–3.95 (m, 5H, $CH_2CH_2(CH_2)_5CH_3$ and 3′-H), 4.18 (dd, *J*=11.0, 4.5 Hz, 1H, $CH_2OSO_2CH_3$), 4.31 (dd, *J*=11.0, 7.0 Hz, 1H, $CH_2OSO_2CH_3$), 4.45–4.61 (m, 1H, 5′-H), 7.32 (s, 1H, 6-H); ^{13}C NMR: δ 13.97, 13.98 (CH_3), 22.5, 22.6, 26.5, 27.0, 27.5, 29.0, 29.1, 29.2, 31.6 and 31.7 ($CH_2(CH_2)_6CH_3$), 37.7 and 38.1 (C-4′ and SO_2CH_3), 41.5, 44.0 and 50.0 ($CH_2(CH_2)_6CH_3$ and *N*–CH_3), 64.2 and 64.9 (C-3′ and $CH_2OSO_2CH_3$), 74.2 (C-5′), 111.6 (C-5), 139.5 (C-6), 150.9 (C-2), 162.5 (C-4); MS (*m*/*z*, %): 552 [$(M+Na)^+$, 100]. Anal. Calcd for $C_{26}H_{47}N_3O_6S$: C, 58.95; H, 8.94; N, 7.93. Found: C, 58.88; H, 8.69; N, 8.01.

*3.4.2. (3′RS,5′RS)-5-[2′-Methyl-5′-(methylsulfonyloxy)methyl)isoxazolidin-3′-yl]-1,3-dioctyluracil (**6a**).* This compound was obtained from **4a** in 85% yield as an oil; IR (liquid film): ν_{max} 2920, 2845, 1695, 1640, 1455, 1350, 1170, 1080 cm^{-1}; ^1H NMR: δ 0.85–0.95 (m, 6H, CH_3), 1.17–1.40 (m, 20H, $CH_2CH_2(CH_2)_5CH_3$), 1.52–1.77 (m, 4H, $CH_2CH_2(CH_2)_5CH_3$), 2.28 (ddd, *J*=12.6, 8.2, 5.5 Hz, 1H, 4′-H), 2.56 (dt, *J*=12.6, 7.6 Hz, 1H, 4′-H), 2.72 (s, 3H, *N*–CH_3), 3.09 (s, 3H, SO_2CH_3), 3.70–3.80 (m, 2H, $CH_2CH_2(CH_2)_5CH_3$), 3.85–3.98 (m, 3H, $CH_2CH_2(CH_2)_5CH_3$ and 3′-H), 4.22–4.44 (m, 3H, $CH_2OSO_2CH_3$ and 5′-H), 7.31 (s, 1H, 6-H); ^{13}C NMR: δ 14.0 (CH_3), 22.6, 26.5, 27.0, 27.6, 29.0, 29.1, 29.2, 31.6 and 31.7 ($CH_2(CH_2)_6CH_3$), 37.6 and 37.8 (C-4′

and SO_2CH_3), 41.6, 44.9 and 50.0 ($CH_2(CH_2)_6CH_3$ and N–CH_3), 64.2 and 64.9 (C-3′ and $CH_2OSO_2CH_3$), 74.2 (C-5′), 111.4 (C-5), 139.6 (C-6), 150.9 (C-2), 162.4 (C-4); MS (m/z, %): 552 [(M+Na)$^+$, 100]. Anal. Calcd for $C_{26}H_{47}N_3O_6S$: 58.95; H, 8.94; N, 7.93. Found: C, 58.79; H, 8.66; N, 7.97.

*3.4.3. (3′RS,5′SR)-5-[2′-Benzyl-5′-((methylsulfonyloxy)methyl)isoxazolidin-3′-yl]-1,3-dioctyluracil (**5b**).* This compound was obtained from **3b** in 95% yield as an oil; IR (liquid film): ν_{max} 3030, 3015, 2915, 2845, 1695, 1650, 1455, 1355, 1175, 1080 cm^{-1}; ^{1}H NMR: δ 0.80–0.95 (m, 6H, CH_3), 1.17–1.40 (m, 20H, $CH_2CH_2(CH_2)_5CH_3$), 1.50–1.72 (m, 4H, $CH_2CH_2(CH_2)_5CH_3$), 1.89 (dt, J=12.8, 6.2 Hz, 1H, 4′-H), 2.76 (s, 3H, SO_2CH_3), 2.96 (dt, J=12.8, 8.5 Hz, 1H, 4′-H), 3.60–4.01 (m, 6H, $CH_2CH_2(CH_2)_5CH_3$, $CH_2C_6H_5$ and 3′-H), 4.05–4.18 (m, 2H, $CH_2C_6H_5$ and $CH_2OSO_2CH_3$), 4.32 (dd, J=11.2, 7.2 Hz, 1H, $CH_2OSO_2CH_3$), 4.51–4.59 (m, 1H, 5′-H), 7.27–7.32 (m, 5H, $CH_2C_6H_5$), 7.37 (s, 1H, 6-H); ^{13}C NMR: δ 14.1 (CH_3), 22.5, 26.5, 27.0, 27.6, 29.1, 29.2, 31.7 and 31.8 ($CH_2(CH_2)_6CH_3$), 37.4 and 38.0 (C-4′ and SO_2CH_3), 41.6, and 50.0 ($CH_2(CH_2)_6CH_3$), 60.9, 61.7 and 70.4 (C-3′, $CH_2C_6H_5$ and $CH_2OSO_2CH_3$), 74.5 (C-5′), 111.7 (C-5), 127.6, 128.4, 128.9 and 136.8 ($CH_2C_6H_5$), 139.7 (C-6), 150.8 (C-2), 161.0 (C-4); MS (m/z, %): 628 [(M+Na)$^+$, 100]. Anal. Calcd for $C_{32}H_{51}N_3O_6S$: C, 63.44; H, 8.49; N, 6.94. Found: C, 63.28; H, 8.67; N, 6.72.

*3.4.4. (3′RS,5′SR)-5-[2′-Methyl-5′-((methylsulfonyloxy)methyl)isoxazolidin-3′-yl]-2,4-dimethoxypyrimidine (**17a**).* This compound was obtained from **15a** in 84% yield as white solid, mp 154–156 °C; IR (Nujol): ν_{max} 3015, 2995, 2920, 2845, 1590, 1550, 1450, 1380, 1350, 1170, 1070 cm^{-1}; ^{1}H NMR: δ 1.98 (ddd, J=12.3, 8.2, 5.1 Hz, 1H, 4′-H), 2.62 (s, 3H, N–CH_3), 2.84 (dt, J=12.3, 8.2 Hz, 1H, 4′-H), 3.07 (s, 3H, SO_2CH_3), 3.76 (t, J=8.2 Hz, 1H, 3′-H), 3.99 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 4.16 (dd, J=10.5, 3.3 Hz, 1H, $CH_2OSO_2CH_3$), 4.43 (dd, J=10.5, 7.6 Hz, 1H, $CH_2OSO_2CH_3$), 4.46–4.55 (m, 1H, 5′-H), 8.26 (s, 1H, 6-H); ^{13}C NMR: δ 37.5 and 38.4 (SO_2CH_3 and C-4′), 43.2 (N–CH_3), 53.9 and 54.7 (OCH_3), 64.4 (C-3′), 70.26 ($CH_2OSO_2CH_3$), 74.0 (C-5′), 112.2 (C-5), 156.6 (C-6), 164.8 (C-2), 168.8 (C-4); MS (m/z, %): 356 [(M+Na)$^+$, 100]. Anal. Calcd for $C_{12}H_{19}N_3O_6S$: C, 43.23; H, 5.74; N, 12.60. Found: C, 42.95; H, 5.54; N, 12.45.

*3.4.5. (3′RS,5′RS)-5-[2′-Methyl-5′-((methylsulfonyloxy)methyl)isoxazolidin-3′-yl]-2,4-dimethoxypyrimidine (**18a**).* This compound was obtained from **16a** in 85% yield as a white solid, mp 143–145 °C; IR (Nujol): ν_{max} 3000, 2960, 2920, 2845, 1595, 1560, 1465, 1390, 1350, 1175, 1075 cm^{-1}; ^{1}H NMR: δ 2.41 (dt, J=12.5, 7.9 Hz, 1H, 4′-H), 2.49 (ddd, J=12.5, 8.1, 6.8 Hz, 1H, 4′-H), 2.63 (s, 3H, N–CH_3), 3.01 (s, 3H, SO_2CH_3), 3.80 (br m, 1H, 3′-H), 3.99 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 4.29 (dd, J=11.2, 5.7 Hz, 1H, $CH_2OSO_2CH_3$), 4.37 (dd, J=11.2, 3.2 Hz, 1H, $CH_2OSO_2CH_3$), 4.39–4.48 (m, 1H, 5′-H), 8.28 (s, 1H, 6-H); ^{13}C NMR: δ 37.8 and 38.2 (SO_2CH_3 and C-4′), 43.7 (N–CH_3), 54.1 and 54.8 (OCH_3), 63.9 (C-3′), 69.6 ($CH_2OSO_2CH_3$), 74.4 (C-5′), 112.3 (C-5), 156.8 (C-6), 164.8 (C-2), 169.0 (C-4); MS (m/z, %): 356 [(M+Na)$^+$, 100]. Anal. Calcd for $C_{12}H_{19}N_3O_6S$: C, 43.23; H, 5.74; N, 12.60. Found: C, 43.33; H, 5.47; N, 12.85.

*3.4.6. (3′RS,5′SR)-5-[2′-Benzyl-5′-((methylsulfonyloxy)methyl)isoxazolidin-3′-yl]-2,4-dimethoxypyrimidine (**17b**).* This compound was obtained from the mixture of **15b** and **16b** in 56% yield as an oil; IR (liquid film): ν_{max} 3060, 3020, 2920, 2845, 1590, 1550, 1455, 1380, 1320, 1170, 1075 cm^{-1}; ^{1}H NMR: δ 1.90 (ddd, J=12.7, 7.9, 4.8 Hz, 1H, 4′-H), 2.58 (s, 3H, SO_2CH_3), 2.88 (dt, J=12.7, 8.4 Hz, 1H, 4′-H), 3.77 (d, J=13.6 Hz, 1H, $CH_2C_6H_5$), 3.93 (d, J=13.6 Hz, 1H, $CH_2C_6H_5$), 3.98–4.10 (overlapped s and m, 8H, OCH_3 and $CH_2OSO_2CH_3$), 4.37–4.53 (m, 2H, 3′-H and 5′-H), 7.23–7.38 (m, 5H, $CH_2C_6H_5$), 8.40 (s, 1H, 6-H); ^{13}C NMR: δ 37.0 and 38.0 (C-4′ and SO_2CH_3), 54.2 and 55.0 (OCH_3), 60.1, 61.8 and 70.6 (C-3′, $CH_2C_6H_5$ and $CH_2OSO_2CH_3$), 74.4 (C-5′), 112.7 (C-5), 127.5, 128.3, 128.9 and 136.9 ($CH_2C_6H_5$), 156.1 (C-6), 164.5 (C-2), 168.9 (C-4); MS (m/z, %): 432 [(M+Na)$^+$, 100]. Anal. Calcd for $C_{18}H_{23}N_3O_6S$: C, 52.80; H, 5.66; N, 10.26. Found: C, 53.07; H, 5.87; N, 10.46.

*3.4.7. (3′RS,5′RS)-5-(2′-Benzyl-5′-methylsulfonyloxy methyl isoxazolidin-3′-yl)-2,4-dimethoxypyrimidine (**18b**).* This compound was obtained from the mixture of **15b** and **16b** in 29% yield as an oil; IR (liquid film): ν_{max} 3060, 3025, 2920, 2845, 1595, 1555, 1450, 1390, 1350, 1175, 1070 cm^{-1}; ^{1}H NMR: δ 2.33 (ddd, J=12.4, 8.1, 7.3 Hz, 1H, 4′-H), 2.54 (ddd, J=12.4, 8.1, 6.8 Hz, 1H, 4′-H), 2.95 (s, 3H, SO_2CH_3), 3.87–4.16 (overlapped s and m, 9H, OCH_3, $CH_2OSO_2CH_3$ and 3′-H), 4.30–4.47 (m, 3H, 5′-H and $CH_2C_6H_5$), 7.21–7.36 (m, 5H, $CH_2C_6H_5$), 8.41 (s, 1H, 6-H); ^{13}C NMR: δ 37.6 and 38.0 (C-4′ and SO_2CH_3), 54.1 and 54.8 (OCH_3), 60.9, 61.0 and 69.9 (C-3′, $CH_2C_6H_5$ and $CH_2OSO_2CH_3$), 74.6 (C-5′), 112.8 (C-5), 127.4, 128.2, 128.8 and 136.9 ($CH_2C_6H_5$), 156.8 (C-6), 164.9 (C-2), 168.7 (C-4); MS (m/z, %): 432 [(M+Na)$^+$, 100]. Anal. Calcd for $C_{18}H_{23}N_3O_6S$: C, 52.80; H, 5.66; N, 10.26. Found: C, 51.97; H, 5.78; N, 10.37.

3.5. Reduction of mesyl derivatives

General procedure. The mesyl ester **5**, or **6**, or **17**, or **18** (0.1 mmol) was dissolved in methanol (3 ml), a catalytic amount of Pd/C was added and the reaction mixture was stirred for two days under a hydrogen atmosphere. Next, the crude reaction mixture was passed over Celite and concentrated. The residue was dissolved in methylene chloride and extracted two times with saturated sodium carbonate solution. The organic layer was dried and concentrated to give the pyrrolidines **7**, **8**, **19**, **20** in satisfactory pure forms.

*3.5.1. (2′RS,4′SR′)-5-(4′-Hydroxy-1′-methylpyrrolidin-2′-yl)-1,3-dioctyluracil (**7a**).* This compound was obtained in 95% yield as an oily solid; IR (liquid film): ν_{max} 3600–3100, 2920, 2845, 1685, 1635, 1455, 1355, 1090, 1040 cm^{-1}; ^{1}H NMR: δ 0.80–0.96 (m, 6H, CH_3), 1.18–1.42 (m, 20H, $CH_2CH_2(CH_2)_5CH_3$), 1.52–1.76 (m, 4H, $CH_2CH_2(CH_2)_5CH_3$), 1.90–2.90 (overlapped m and s, 8H, N–CH_3, 3′-H, 5′-H, OH), 3.55–3.81 (m, 3H, $CH_2CH_2(CH_2)_5CH_3$ and 2′-H), 3.87–415 (m, 3H, $CH_2CH_2(CH_2)_5CH_3$ and 4′-H), 7.02 (s, 1H, 6-H); ^{13}C NMR: δ 13.8, 13.85 (CH_3), 22.4, 22.5, 26.4, 26.8, 27.4, 28.9, 29.0, 29.1, 31.5 and 31.6 ($CH_2(CH_2)_6CH_3$), 38.6, 41.4, 48.2 and 49.4 (C-3′, N–CH_3) and ($CH_2(CH_2)_6CH_3$), 60.5, 63.1 and 68.9 (C-2′, C-4′ and C-5′), 113.0 (C-5), 139.0 (C-6), 151.0 (C-2), 163.7 (C-4); HRESIMS for $C_{25}H_{45}N_3O_3K$ (M+K)$^+$: calcd 474.3098, found 474.3095.

*3.5.2. (2R′S′,4R′S″)-5-(4′-Hydroxy-1′-methylpyrrolidin-2′-yl)-1,3-dioctyluracil (**8a**).* This compound was obtained in 96% yield as an oil; IR (liquid film): ν_{max} 3600–3500, 2925, 2860, 1685, 1630, 1455, 1350, 1080, 1030 cm^{-1}; ^{1}H NMR: δ 0.80–0.94 (m, 6H, CH_3), 1.17–1.42 (m, 20H, $CH_2CH_2(CH_2)_5CH_3$), 1.56–1.73 (m, 4H, $CH_2CH_2(CH_2)_5CH_3$), 1.83 (dd, J=14.2, 4.5 Hz, 1H, 3′-H), 2.29 (s, 3H, N–CH_3), 2.39 (dd, J=9.9, 3.6 Hz, 1H, 5′-H), 2.48 (br, 1H, OH), 2.56 (ddd, J=14.2, 10.5, 6.4, 1H, 3′-H), 2.99–3.19 (m, 2H, 2′-H and 5′-H), 3.61–3.80 (m, 2H, $CH_2CH_2(CH_2)_5CH_3$), 3.89–3.95 (m, 2H, $CH_2CH_2(CH_2)_5CH_3$), 4.25 (dd, J=5.9, 3.6 Hz, 1H, 4′-H), 7.15 (s, 1H, 6-H); ^{13}C NMR: δ 13.95, 14.0 (CH_3), 22.5, 22.6, 26.5, 27.0, 27.5, 29.0, 29.15, 29.2, 31.7 and 31.8 ($CH_2(CH_2)_6CH_3$), 40.4, 41.4, 41.6 and 49.8 (C-3′, N–CH_3) and ($CH_2(CH_2)_6CH_3$), 63.7, 65.2 and 70.6 (C-2′, C-4′and C-5′), 113.2 (C-5), 139.8 (C-6), 151.1 (C-2), 162.8 (C-4); HRESIMS for $C_{25}H_{45}N_3O_3Na$ (M+Na)$^+$: calcd 458.3359, found 458.3360.

*3.5.3. (2′RS,4′SR′)-5-(4′-Hydroxy-1′-methylpyrrolidin-2′-yl)-2,4-dimethoxypyrimidine (**19a**).* This compound was obtained in 96% yield as an oily solid; IR (liquid film): ν_{max} 3500–3100, 2920, 2845, 1595, 1520, 1470, 1380, 1320, 1075, 1020 cm^{-1}; ^{1}H NMR: δ 1.93 (ddd, J=13.3, 9.2, 7.7 Hz, 1H, 3′-H), 2.13 (ddd, J=13.5, 7.2, 3.0 Hz, 1H, 3′-H), 2.22 (s, 3H, N–CH_3), 2.32 (dd, J=10.0, 6.5 Hz, 1H, 5′-H), 2.49 (br, 1H,

OH), 3.58 (dd, *J*=10.0, 7.2 Hz, 1H, 5′-H), 3.67 (dd, *J*=9.2, 7.2 Hz, 1H, 2′-H), 3.96 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 4.45–4.53 (m, 1H, 4′-H), 8.25 (s, 1H, 6-H); ^{13}C NMR: δ 40.3 (*N*–CH_3), 43.3 (C-3′), 53.6 and 54.4 (OCH_3), 60.5, 65.1 and 69.5 (C-2′, C-4′ and C-5′), 115.2 (C-5), 156.4 (C-6), 164.2 (C-2), 169.2 (C-4); HRESIMS for $C_{11}H_{17}N_3O_3Na$ $(M+Na)^+$: calcd 262.1168, found 262.1164.

*3.5.4. (2′RS,4′RS′)-5-(4′-Hydroxy-1′-methylpyrrolidin-2′-yl)-2,4-dimethoxypyrimidine (**20a**).* This compound was obtained in 97% yield as an oily solid; IR (liquid film): ν_{max} 3500–3100, 2925, 2845, 1585, 1550, 1450, 1370, 1310, 1070, 1015 cm^{-1}; ^{1}H NMR: δ 1.73 (dd, *J*=14.2, 7.4 Hz, 1H, 3′-H), 2.22 (s, 3H, *N*–CH_3), 2.39 (dd, *J*=10.1, 4.2 Hz, 1H, 5′-H), 2.61 (ddd, *J*=14.2, 9.1, 6.3 Hz, 1H, 3′-H), 2.73 (br, 1H, OH), 3.14 (d, *J*=10.1, 1H, 5′-H), 3.22 (dd, *J*=9.1, 7.4 Hz, 1H, 2′-H), 3.99 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 4.23–4.29 (m, 1H, 4′-H), 8.27 (s, 1H, 6-H); ^{13}C NMR: δ 40.2 (*N*–CH_3), 43.0 (C-3′), 53.9 and 54.6 (OCH_3), 62.2, 65.5 and 70.5 (C-2′, C-4′ and C-5′), 115.3 (C-5), 156.7 (C-6), 164.4 (C-2), 168.9 (C-4); HRESIMS for $C_{11}H_{17}N_3O_3Na$ $(M+Na)^+$: calcd 262.1168, found 262.1164.

*3.5.5. (2′RS,4′SR′)-5-(4′-Hydroxypyrrolidin-2′-yl)-2,4-dimethoxypyrimidine (**19b**).* This compound was obtained in 98% yield as an oil; IR (liquid film): ν_{max} 3600–3100, 2920, 2845, 1595, 1560, 1465, 1380, 1200, 1070, 1015 cm^{-1}; ^{1}H NMR: δ 1.87 (ddd, *J*=13.5, 9.4, 7.3 Hz, 1H, 3′-H), 2.19 (dd, *J*=13.5, 6.4 Hz, 1H, 3′-H), 2.55 (br, 2H, NH, OH), 3.02 (d, *J*=11.9 Hz, 1H, 5′-H), 3.28 (dd, *J*=11.9, 4.3 Hz, 1H, 5′-H), 3.97 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 4.46–4.56 (m, 2H, 2′-H and 4′-H), 8.25 (s, 1H, 6-H); ^{13}C NMR: δ 41.6 (C-3′), 53.7, 53.9, 54.7 and 55.4 (C-2′, C-5′ and OCH_3), 72.6 (C-4′), 116.7 (C-5), 155.4 (C-6), 164.5 (C-2), 168.9 (C-4); HRESIMS for $C_{10}H_{16}N_3O_3$ $(M+H)^+$: calcd 226.1192, found 226.1188.

*3.5.6. (2′RS,4′RS′)-5-(4′-Hydroxypyrrolidin-2′-yl)-2,4-dimethoxypyrimidine (**20b**).* This compound was obtained in 95% yield as an oil; IR (liquid film): ν_{max} 3600–3100, 2940, 2830, 1590, 1565, 1460, 1350, 1190, 1070, 1010 cm^{-1}; ^{1}H NMR: δ 1.74–1.83 (m, 1H, 3′-H), 2.44–2.55 (m, 1H, 3′-H), 2.99–3.20 (m, 2H, 5′-H), 3.45 (br, 2H, NH, OH), 3.97 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 4.19 (t, *J*=7.2 Hz, 1H, 2′-H), 4.45 (br, 1H, 4′-H), 8.33 (s, 1H, 6-H); ^{13}C NMR: δ 40.9 (C-3′), 54.0, 54.4, 54.7 and 55.6 (C-2′, C-5′ and OCH_3), 71.8 (C-4′), 115.4 (C-5), 156.3 (C-6), 164.7 (C-2), 168.7 (C-4); HRESIMS for $C_{10}H_{16}N_3O_3$ $(M+H)^+$: calcd 226.1192, found 226.1187.

3.6. Demethylation reaction of pyrrolidines 19 and 20

General procedure. A solution of pyrrolidine **19** or **20** (0.2 mmol) in methanol (1 ml) and hydrochloric acid (2 ml, 6 M) was heated under reflux for 3 h. After the solvents were evaporated to dryness, the residue was dissolved in a small volume of methanol and the demethylated uracil derivatives were precipitated as their hydrochloride salts by addition of diethyl ether.

*3.6.1. (2′RS,4′SR′)-5-(4′-Hydroxy-1′-methylpyrrolidin-2′-yl)-uracil hydrochloride (**21a**).* This compound was obtained as a pale green solid in 78% yield, mp 240–245 °C under dec; IR (Nujol): ν_{max} 3600–3100, 2915, 2840, 1700–1630, 1450, 1370, 1220, 1070 cm^{-1}; ^{1}H NMR (DMSO-d_6, 50 °C): δ 2.01–2.18 (br m, 1H, 3′-H), 2.50–260 (br m, 1H, 3′-H), 2.70 (s, 3H, *N*–CH_3), 3.80–4.00 (br m, 2H, 5′-H), 4.41–4.70 (m, 2H, 2′ and 4′-H), 7.92 (s, 1H, 6-H), 10.01 (br, 1H, NH), 11.14 (br, 2H, NH); ^{13}C NMR (DMSO-d_6): δ 36.8 (C-3′), 40.2 (*N*–CH_3), 61.1 (C-5′), 61.9 and 65.8 (C-2′ and C-4′), 101.2 (C-5), 142.5 (C-6), 148.5 (C-2), 161.8 (C-4); HRESIMS for $C_9H_{14}N_3O_3$ $(M+H)^+$: calcd 212.1035, found 212.1032.

*3.6.2. (2′RS,4′RS′)-5-(4′-Hydroxy-1′-methylpyrrolidin-2′-yl)-uracil hydrochloride (**22a**).* This compound was obtained as a white solid in 85% yield, mp 279–282 °C; IR (Nujol): ν_{max} 3600–3100, 2900, 2830, 1710–1630, 1450, 1365, 1245, 1205, 1070 cm^{-1}; ^{1}H NMR (DMSO-d_6, 50 °C): δ 2.02–2.20 (br m, 1H, 3′-H), 2.58–2.66 (br m, 1H, 3′-H), 2.75 (s, 3H, *N*–CH_3), 3.40–3.58 (br m, 2H, 5′-H), 4.40–4.60 (m, 2H, 2′ and 4′-H), 7.89 (s, 1H, 6-H), 10.01 (br, 1H, NH), 11.17 (br, 2H, NH); ^{13}C NMR (DMSO-d_6): δ 38.3 (C-3′), 39.2 (*N*–CH_3), 62.8 (C-5′), 62.7 and 67.00 (C-2′ and C-4′), 104.3 (C-5), 144.2 (C-6), 150.6 (C-2),163.9 (C-4); HRESIMS for $C_9H_{13}N_3O_3Na$ $(M+Na)^+$: calcd 234.0855, found 234.0851.

*3.6.3. (2′RS,4′SR′)-5-(4′-Hydroxypyrrolidin-2′-yl)-uracil hydrochloride (**21b**).* This compound was obtained as an oily solid in 82% yield; IR (Nujol): ν_{max} 3600–3100, 2920, 2850, 1710–1620, 1455, 1375, 1250, 1205, 1075, 1040, 1015 cm^{-1}; ^{1}H NMR (DMSO-d_6, 50 °C): δ 2.13 (dd, *J*=14.3, 6.5 Hz, 1H, 3′-H), 2.23 (ddd, *J*=14.3, 11.2, 4.5 Hz, 1H, 3′-H), 3.07 (br m, 1H, 5′-H), 3.44 (dd, *J*=14.0, 4.1 Hz, 1H, 5′-H), 4.40–4.50 (br m, 1H, 4′-H), 4.63 (dd, *J*=11.2, 6.5 Hz, 1H, 2′-H), 7.66 (s, 1H, 6-H), 8.98 (br, 1H, NH), 9.60 (br, 1H, NH), 11.12 (br, 2H, NH); ^{13}C NMR (DMSO-d_6): δ 37.2 (C-3′), 52.7 (C-5′), 54.3 and 68.8 (C-2′ and C-4′), 106.1 (C-5), 141.8(C-6), 150.8 (C-2), 163.8 (C-4); HRESIMS for $C_8H_{12}N_3O_3$ $(M+H)^+$: calcd 198.0879, found 198.0882.

*3.6.4. (2′RS,4′RS′)-5-(4′-Hydroxypyrrolidin-2′-yl)-uracil hydrochloride (**22b**).* This compound was obtained as an oily solid in 80% yield; IR (Nujol): ν_{max} 3600–3100, 2915, 2840, 1700–1620, 1460, 1370, 1280, 1080, 1045, 1015 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.98–2.08 (m, 1H, 3′-H), 2.32–2.42 (m, 1H, 3′-H), 2.94–3.09 (br m, 1H, 5′-H), 3.16–3.27 (br m, 1H, 5′-H), 4.37–4.52 (m, 2H, 2′ and 4′-H), 7.62 (s, 1H, 6-H), 8.74 (br, 1H, NH), 9.35 (br, 1H, NH), 11.18 (br, 1H, NH), 11.38 (br, 1H, NH); ^{13}C NMR (CD_3OD/$CDCl_3$): δ 36.9 (C-3′), 53.9 (C-5′), 56.3 and 70.1 (C-2′ and C-4′), 108.4 (C-5), 143.2 (C-6), 152.6 (C-2),165.6 (C-4); HRESIMS for $C_8H_{11}N_3O_3Na$ $(M+Na)^+$: calcd 220.0698, found 220.0693.

3.7. One pot reaction of nitrones 2 and 14 with methyl acrylate and reduction over Ra/Ni

General procedure. A solution of nitrone **2** or **14** (0.5 mmol) and methyl acrylate (2.5 mmol) in toluene was heated at 80 °C for two days. After the solvent was evaporated, the residue was dissolved in methanol (5 ml). A catalytic amount of Ra/Ni was added and the reaction mixture was stirred under a hydrogen atmosphere at room temperature for one day. The crude reaction mixture was passed over Celite and after evaporation of the solvent, the residue was chromatographed on a silica gel column with a mixture of hexane/ethyl acetate (1:1 for the reaction of **2a**, 2:1 for the reaction of **2b**) and a mixture of dichloromethane/methanol 30:1 for the reaction of **14a**.

*3.7.1. (2′R′S′,4S′R′)-5-(4′-Hydroxy-1′-methyl-5′-oxopyrrolidin-2′-yl)-1,3-dioctyluracil (**11a**).* This compound was obtained from nitrone **2a** in 35% yield as an oil; IR (liquid film): ν_{max} 3500–3100, 2920, 2845, 1685, 1650, 1455, 1375, 1230, 1075 cm^{-1}; ^{1}H NMR: δ 0.87–0.91 (m, 6H, CH_3), 1.20–1.40 (m, 20H, $CH_2CH_2(CH_2)_5CH_3$), 1.52–1.78 (m, 4H, $CH_2CH_2(CH_2)_5CH_3$), 2.29–2.47 (m, 2H, 3′-H), 2.83 (s, 3H, *N*–CH_3), 3.25 (br s, 1H, OH), 3.61–3.81 (m, 2H, $CH_2CH_2(CH_2)_5CH_3$), 3.93 (t, *J*=7.5 Hz, 2H, $CH_2CH_2(CH_2)_5CH_3$), 4.51 (d, *J*=8.7 Hz, 1H, 2′-H), 4.58 (t, *J*=8.4 Hz, 1H, 4′-H), 6.86 (s, 1H, 6-H); ^{13}C NMR: δ 14.04 and 14.06 (CH_3), 22.5, 22.6, 26.5, 27.0, 27.5, 28.6, 29.1, 29.15, 29.2, 29.7, 31.7 and 31.8 ($CH_2(CH_2)_6CH_3$ and *N*–CH_3), 34.6 (C-3′), 41.6, 50.1, 55.7 and 69.7 ($CH_2(CH_2)_6CH_3$, C-3′ and C-4′), 111.0 (C-5), 138.6 (C-6), 150.8 (C-2), 161.8 (C-4), 175.4 (C-5′); MS (*m*/*z*, %): 472 [$(M+Na)^+$, 100]. Anal. Calcd for $C_{25}H_{43}N_3O_4$: C, 66.78; H, 9.64; N, 9.35. Found: C, 66.68; H, 9.42; N, 9.08.

*3.7.2. (2′RS,4′RS)-5-(4′-Hydroxy-1′-methyl-5′-oxopyrrolidin-2′-yl)-1,3-dioctyluracil (**12a**).* This compound was obtained from nitrone

2a in 45% yield as an oil; IR (liquid film): ν_{max} 3500–3100, 2920, 2845, 1690, 1640, 1455, 1370, 1240, 1080 cm^{-1}; ^1H NMR: δ 0.87–0.91 (m, 6H, CH_3), 1.19–1.40 (m, 20H, $CH_2CH_2(CH_2)_5CH_3$), 1.51–1.75 (m, 4H, $CH_2CH_2(CH_2)_5CH_3$), 1.89 (dt, J=14.1, 4.7 Hz, 1H, 3′-H), 2.10 (br s, 1H, OH), 2.71–2.87 (overlapped s and m, 4H, N–CH_3 and 3′-H), 3.72–3.80 (m, 2H, $CH_2CH_2(CH_2)_5CH_3$), 3.93 (t, J=7.5 Hz, 2H, $CH_2CH_2(CH_2)_5CH_3$), 4.38 (dd, J=8.3, 4.7 Hz, 1H, 2′-H), 4.58 (dd, J=8.3, 4.7 Hz, 1H, 4′-H), 7.26 (s, 1H, 6-H); ^{13}C NMR: δ 14.03 and 14.05 (CH_3), 22.5, 22.6, 26.5, 27.0, 27.5, 28.0, 29.1, 29.15, 29.2, 29.7, 31.7 and 31.8 ($CH_2(CH_2)_6CH_3$ and N–CH_3), 34.6 (C-3′), 41.7, 50.2, 54.9 and 69.5 ($CH_2(CH_2)_6CH_3$, C-3′ and C-4′), 111.1 (C-5), 141.4 (C-6), 150.6 (C-2), 162.4 (C-4), 174.9 (C-5′); MS (m/z, %): 472 [(M+Na)$^+$, 100]. Anal. Calcd for $C_{25}H_{43}N_3O_4$: C, 66.78; H, 9.64; N, 9.35. Found: C, 66.63; H, 9.35; N, 9.22.

*3.7.3. (2′R′S′,4S′R′)-5-(1′-Benzyl-4′-hydroxy-5′-oxopyrrolidin-2′-yl)-1,3-dioctyluracil (**11b**).* This compound was obtained from nitrone **2b** in 31% yield as an oil; IR (liquid film): ν_{max} 3500–3100, 3055, 3020, 2930, 2850, 1700–1630, 1455, 1355, 1270, 1110, 1080 cm^{-1}; ^1H NMR: δ 0.82–0.98 (m, 6H, CH_3), 1.18–1.45 (m, 20H, $CH_2CH_2(CH_2)_5CH_3$), 1.50–1.72 (m, 4H, $CH_2CH_2(CH_2)_5CH_3$), 2.26 (dt, J=12.9, 9.0 Hz, 1H, 3′-H), 2.44 (dd, J=12.9, 8.3 Hz, 1H, 3′-H), 3.20 (br s, 1H, OH), 3.51–3.72 (m, 2H, $CH_2CH_2(CH_2)_5CH_3$), 3.83 (t, J=7.1 Hz, 2H, $CH_2CH_2(CH_2)_5CH_3$), 4.15 (d, J=14.1 Hz, 1H, $CH_2C_6H_5$), 4.34 (d, J=9.0 Hz, 1H, 2′-H), 4.68–4.79 (m, 2H, $CH_2C_6H_5$ and 4′-H), 6.68 (s, 1H, 6-H), 7.15–7.38 (m, 5H, $CH_2C_6H_5$); ^{13}C NMR: δ 14.1 (CH_3), 22.6, 26.5, 27.0, 27.5, 29.1, 29.2, 31.7 and 31.8 ($CH_2(CH_2)_6CH_3$), 34.2 (C-3′), 41.5, 45.6, 49.9, 54.2 and 69.2 ($CH_2(CH_2)_6CH_3$, $CH_2C_6H_5$, C-3′ and C-4′), 110.6 (C-5), 127.9, 128.2, 128.7 and 135.7 ($CH_2C_6H_5$), 139.7 (C-6), 150.7 (C-2), 161.4 (C-4), 175.5 (C-5′); MS (m/z, %): 548 [(M+Na)$^+$, 100]. Anal. Calcd for $C_{31}H_{47}N_3O_4$: C, 70.82; H, 9.01; N, 7.99. Found: C, 70.53; H, 8.87; N, 8.02.

*3.7.4. (2R′S′,4R′S′)-5-(1′-Benzyl-4′-hydroxy-5′-oxopyrrolidin-2′-yl)-1,3-dioctyluracil (**12b**).* This compound was obtained from nitrone **2b** in 54% yield as an oil; IR (liquid film): ν_{max} 3500–3100, 3060, 3030, 2925, 2850, 1700–1630, 1460, 1355, 1275, 1120, 1080 cm^{-1}; ^1H NMR: δ 0.82–0.98 (m, 6H, CH_3), 1.18–1.40 (m, 20H, $CH_2CH_2(CH_2)_5CH_3$), 1.50–1.65 (m, 4H, $CH_2CH_2(CH_2)_5CH_3$), 1.93 (dt, J=13.6, 4.7 Hz, 1H, 3′-H), 2.73 (dt, J=13.6, 8.5 Hz, 1H, 3′-H), 3.47–3.61 (m, 2H, $CH_2CH_2(CH_2)_5CH_3$), 3.83 (t, J=7.7 Hz, 2H, $CH_2CH_2(CH_2)_5CH_3$), 4.22 (d, J=14.5 Hz, 1H, $CH_2C_6H_5$), 4.44 (dd, J=8.5, 4.7 Hz, 1H, 2′-H), 4.48–4.60 (m, 2H, $CH_2C_6H_5$ and 4′-H), 5.10 (br s, 1H, OH), 7.03 (s, 1H, 6-H), 7.10–7.30 (m, 5H, $CH_2C_6H_5$); ^{13}C NMR: δ 14.1 (CH_3), 22.6, 26.4, 26.9, 27.4, 29.1, 29.2, 31.7 and 31.9 ($CH_2(CH_2)_6CH_3$), 34.3 (C-3′), 41.7, 45.5, 50.0, 53.8 and 69.6 ($CH_2(CH_2)_6CH_3$, $CH_2C_6H_5$, C-3′ and C-4′), 110.6 (C-5), 127.6, 128.2, 128.6 and 136.4 ($CH_2C_6H_5$), 142.0 (C-6), 150.4 (C-2), 162.2 (C-4), 174.9 (C-5′); MS (m/z, %): 548 [(M+Na)$^+$, 100]. Anal. Calcd for $C_{31}H_{47}N_3O_4$: C, 70.82; H, 9.01; N, 7.99. Found: C, 70.63; H, 8.92; N, 8.05.

*3.7.5. (2′RS,4′SR′)-5-(4′-Hydroxy-1′-methyl-5′-oxopyrrolidin-2′-yl)-2,4-dimethoxypyrimidine (**25a**).* This compound was obtained from nitrone **14a** only as mixture with **26a** in 28% yield; ^1H NMR: δ 2.01 (dt, J=13.2, 7.7 Hz, 3′-H of **26a**), 2.36–2.42 (m, 3′-H of **25a**), 2.69 (s, N–CH_3 of **26a**), 2.75 (overlapped s and m, N–CH_3 of **25a** and 3′-H of **25b**), 3.99 (s, OCH_3), 4.00 (s, OCH_3), 4.01 (s, OCH_3), 4.02 (s, OCH_3), 4.30 (br, OH), 4.42 (t, ΣJ=16.2 Hz, 2′-H of **26a**), 4.55 (t, ΣJ=16 Hz, 2′-H of **25a**), 4.59–4.68 (m, 4′-H of **25a** and **26a**), 7.96 (s, 6-H of **25a**), 8.17 (s, 6-H of **26a**).

*3.7.6. (2′RS,4′RS′)-5-(4′-Hydroxy-1′-methyl-5′-oxopyrrolidin-2′-yl)-2,4-dimethoxypyrimidine (**26a**).* This compound was obtained from nitrone **14a** in 52% yield as solid; mp 277–280 °C; IR (Nujol): ν_{max} 3600–3100, 3055, 3020, 2930, 2850, 1655, 1450, 1365, 1200, 1075 cm^{-1}; ^1H NMR: δ 2.01 (dt, J=13.2, 7.7 Hz, 1H, 3′-H), 2.69 (s, 3H, N–CH_3), 2.75 (dt, J=13.2, 8.5, 7.2 Hz, 1H, 3′-H), 4.00 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 4.42 (t, ΣJ=16.2 Hz, 1H, 2′-H), 4.62 (t, ΣJ=14.9 Hz, 1H, 4′-H), 8.17 (s, 1H, 6-H); ^{13}C NMR: δ 28.1 (N–CH_3), 35.2 (C-3′), 53.8, 54.2 and 54.9 (C-2′ and OCH_3), 69.3 (C-4′), 112.4 (C-5), 157.7 (C-6), 165.2 (C-2), 169.0 (C-4), 175.3 (C-5′); MS (m/z, %): 276 [(M+Na)$^+$, 100]. Anal. Calcd for $C_{11}H_{15}N_3O_4$: C, 52.17; H, 5.97; N, 16.59. Found: C, 52.30; H, 5.90; N, 16.47.

*3.7.7. (2′RS,4′SR′)-5-(1′-Benzyl-4′-hydroxy-5′-oxopyrrolidin-2′-yl)-2,4-dimethoxypyrimidine (**25b**) and (2′RS,4′RS′)-5-(1′-benzyl-4′-hydroxy-5′-oxopyrrolidin-2′-yl)-2,4-dimethoxypyrimidine (**26b**).* These compounds were obtained from nitrone **14b** as a oily mixture in a ratio 1: 2 and 85% total yield and they were characterized only by their ^1H NMR spectrum; ^1H NMR: δ 2.11 (dt, J=12.0, 8.1 Hz, 3′-H of **26b**), 2.26–2.42 (m, 3′-H of **25b**), 2.71 (ddd, J=12.0, 9.4, 7.4 Hz, 3′-H of **26b**), 3.75 (d, J=14.6 Hz, $CH_2C_6H_5$), 3.88 (s, OCH_3), 3.88 (s, OCH_3), 3.92 (s, OCH_3), 4.00 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 4.45–4.55 (m, 2′-H of **25b** and 2′-H and 4′-H of **26b**), 4.62 (t, ΣJ=16.1 Hz, 4′-H of **25b**), 4.87 (d, J=14.6 Hz, $CH_2C_6H_5$), 4.89 (d, J=14.6 Hz, $CH_2C_6H_5$), 5.05 (br, OH), 6.96–7.00 (m, $CH_2C_6H_5$), 7.11–7.15 (m, $CH_2C_6H_5$), 7.21–7.29 (m, $CH_2C_6H_5$), 7.89 (s, 6-H of **25b**), 8.03 (s, 6-H of **26b**).

3.8. Demethylation reaction of pyrrolidone 26a

Pyrrolidone **26a** (51 mg, 0.2 mmol) was heated with sodium iodide (0.1 g) in glacial acetic acid (3 ml) at 100 °C for 1 h. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column with 20% methanol in methylene chloride as the eluent to give (2′*RS*,4′*RS*′)-5-(4′-hydroxy-1′-methyl-5′-oxopyrrolidin-2′-yl)-uracil (**27a**) (40 mg, 90% yield) as a solid, mp 249–251 °C; IR (Nujol): ν_{max} 3600–3100, 3055, 3020, 2920, 2845, 1700–1620, 1455, 1375, 1275, 1215, 1080 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.78 (dt, J=12.0, 7.4 Hz, 1H, 3′-H), 2.40–2.47 (overlapped s and m, 4H, N–CH_3 and 3′-H), 4.07 (t, ΣJ=15.4 Hz, 1H, 2′-H), 4.29 (t, ΣJ=14.3, 1H, 4′-H), 5.50 (br, 1H, OH), 7.35 (s, 1H, 6-H), 10.05 (br, 2H, NH); ^{13}C NMR (DMSO-d_6): δ 27.9 (N–CH_3), 34.9 (C-3′), 53.68 (C-2′), 69.1 (C-4′), 109.8 (C-5), 141.1 (C-6), 151.1 (C-2), 163.7 (C-4), 173.9 (C-5′); MS (m/z, %): 248 [(M+Na)$^+$, 100]. Anal. Calcd for $C_9H_{11}N_3O_4$: C, 48.00; H, 4.92; N, 18.66. Found: C, 47.71; H, 6.10; N, 18.50.

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.01.020.

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