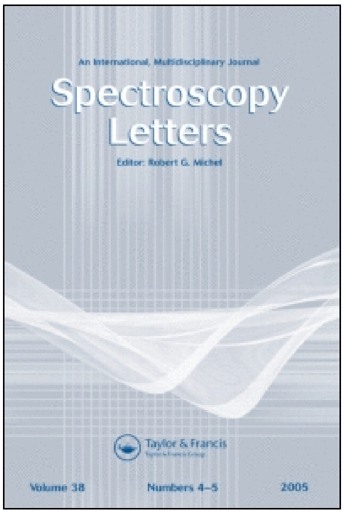

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2D NMR STUDIES OF THE STRUCTURES OF THE STEREOSELECTIVE ADDUCTS OF THE DEHYDROCOSTUS LACTONE WITH PYRIMIDINE DERIVATIVES.

KEY WORDS: 2D NMR, NOESY, dehydrocostus lactone pyrimidine derivatives.

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ABSTRACT

Analysis of ^1H-^1H n.O.e. effects observed for the adducts on C-13 (10-18) of dehydrocostus lactone and different pyrimidine derivatives shown that H-7 and H-11 protons are in trans position. The NOESY cross peaks analysis and x-ray molecular structure of adduct 10 are in excellent agreement with the experimental data. Complete assignments of the ^{13}C signals of some adducts based on 1D and 2D ^1H and ^{13}C NMR techniques are reported.

INTRODUCTION

It is well known that sesquiterpenic lactones posseses interesting chemical and biological properties[1,2]. Some of them may cause allergic contact dermatitis in experimental animals as well as in humans. Much effort has been expended to clarify the mechanism of the biological action of this class of allergens in the view of specific theraphy [3,4].

With this in mind, in this paper we described the Michael addition of pyrimidine derivatives (2-9) to the exocyclic methylene (C-13) of the dehydrocostus lactone. Dehydrocostus lactone (1) is a natural product isolated from different plant species[5-7] and whose structure has been previously well established[8-10].

We also report the correct stereochemistry at the site of the nucleophilic attack, the complete proton assignment as well as the detailed analysis of the 500 MHz ^1H-^1H dipolar correlation (NOESY) spectra[11] of the adducts (10-18) and the ^{13}C assignments of some products herein described altogether with the x-ray ellipsoid perspective drawing for compound 10.

Results and Discussion

Addition of pyrimidine derivatives to dehydrocostus lactone under basic conditions (see experimental) provided stereoselectively adducts derived from N-alkylation (10-16), S-alkylation (17) or C-alkylation (18), (see schemes 1 and 2).

The complete ^1H and ^{13}C assignments of these molecules was achieved by means of the proton-carbon correlations methods. An HMQC experiment[12] allowed the identification of all the protonated carbons and then HMBC spectrum[13-14] permited sufficient long range correlations to be observed for complete assignments. The assignments given in experimental part, are self consistent and unambiguous and these will be fully described. The ^1H and ^{13}C resonances were identified through interative interpretation of NOESY, COSY, HMQC and HMBC spectra.

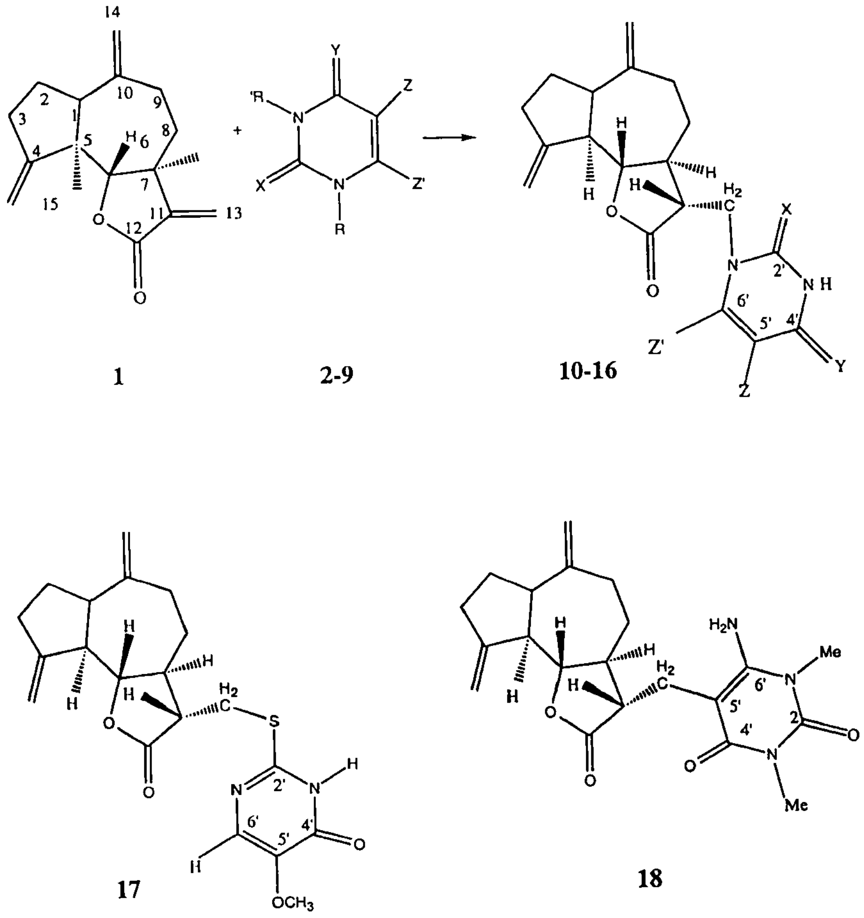
The chemical shift multiplets for H-7, H-11 and 13-CH_2 of the adducts 10-18 lie in the range of 2.70-5.00 ppm in $CDCl_3$ solution recorded at 500 MHz and the network of dipolar coupled nuclei is not very extended. This appears to hold true for the interactions of H-6 with H-8 and H-11 which are detected in all NOESY spectra. Since H-6β and H-7α are known to be with trans relationship, we were able through the coupling constant between H-7/H-11 as well as the dipolar cross peaks between H-6/H-11, H-6/H-8, H-13/H-7, H-7/H-1 and H-7/H-5 to support the

Pyrimidine	R	R'	X	Y	Z	Z'	Compound
2	H	H	O	O	H	H	10
3	H	H	O	O	CH_3	H	11
4	H		O	NH_2	H	H	12
5	H	H	O	O	F	H	13
6	H	H	O	O	Br	H	14
7	H	H	O	O	nPr	H	15
8	H	H	S	O	OCH_3	H	16
8	H	H	S	O	OCH_3	H	17
9	CH_3	CH_3	O	O	H	NH_2	18

Scheme 1

assignment where H7/H-11 are in *trans* relationship[15]. Such consideration was also supported by the x-ray crystallographic studies.

If we select as a model the compound 10 to initiate the chemical shift assignment on the ${}^{1}H$ NMR spectrum, the proton signals of H-13, H-13' and H-6 were observed in $CDCl_3$ solution completely overlapped (see experimental). However, we ascertained that the chemical shift dispersion in $C_6D_6/CDCl_3$ mixture solution allows one to differentiate these protons multiplets. In fact, in this solvents system, the H-7 and H-11 signals are centered at $\delta=1.77$ and $\delta=2.02$ respectively. The value of ${}^{3}J_{7\text{-}11}$= 12.5 Hz suggested that both protons are in *trans* relationship. Then we decided to perform phase-sensitive NOESY experiment recorded in the above mentioned solvent mixture in order to ascertain the configuration of the new stereocenter created for the adduct 10. The resulting cross peaks relative to the diagonal, shown some important connectivities. We observed cross peaks between H-7 with H-5 and also with one of the CH_2-13 geminal protons (δH-13=3.58, ${}^{3}J_{11\text{-}13}$=4.0 ; δH-13'=3.55, ${}^{3}J_{11\text{-}13'}$= 5,5). One of the C-13 methylene protons, namely the proton showing shorter ${}^{3}J_{11\text{-}13}$ value (4.0 Hz) showed an intense n.O.e. cross peaks with H-11 and significant interaction with H-6'. The other geminal proton showing ${}^{3}J_{11\text{-}13}$=5.5 Hz, present cross peak with H-7. The



1 2-9 10-16

17 18

Scheme 2

uracil proton H-6' (δ=7.07) showed a strong n.O.e cross peaks with H-5'(δ=5.45, dd J=8.0, 2.0).

The long range ^{1}H-^{13}C correlation spectrum (HMBC) allow us to distinguish among the different carbonyls groups on the structure of the adducts as well as between the five sp^3 methylene groups present. For example, for compound **16** (see experimental), the assignments of

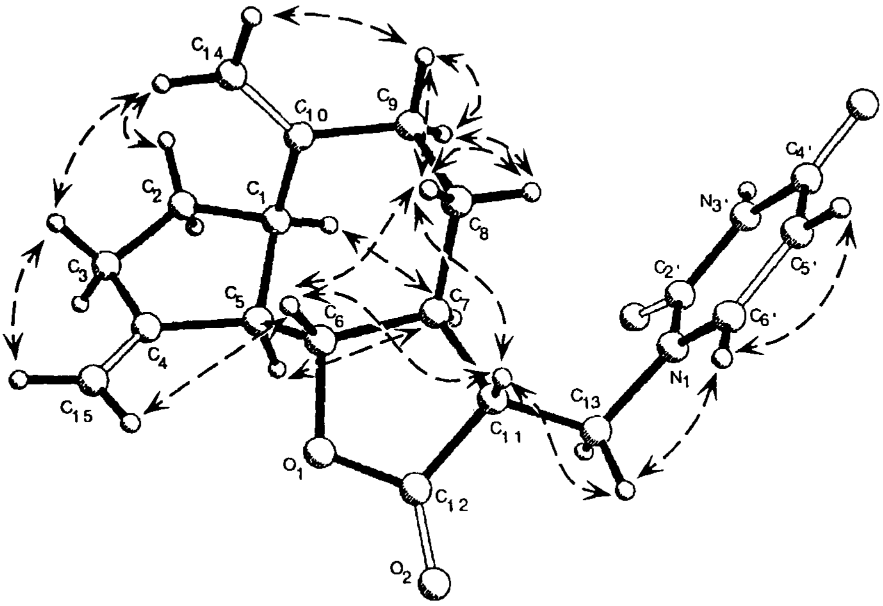


Figure 1. - Selected NOESY data from the spectrum recorded in $CDCl_3/C_6D_6$ for 13-(1-uracil) dehydrocostunolide (<u>10</u>)

the quaternary carbons C2', C4' and C5' was achieved using the long range correlations with H-13/C2', H-13'/C2' (δH_{13}=4.68, ^2J=-14.0, $^3J_{11-13}$= 3.0; $\delta H_{13'}$=4.20, $^3J_{11-13}$=7.5). At the same time, we were able to observe the correlations between H-13/C-12 and H-13'/C-12. In addition H6'(δ=7.34) correlate strongly with both C4' (δ=172.1) and C2'(δ=156.2) and finally C5' (δ=140.4) correlate well with the OMe protons at δ=3.78.

The methylene groups at C-2, C-3, C-8, C-9 and C-13 were well distinguish by HMQC correlations. For example, C-2 δ=30.1) correlates with protons at δ=1.94 and 1.86 (H-2 and H-2'). C-3 (δ=32.5) correlates with the multiplet centered at δ=2.50 (H-3 and H-3'). C-8 (δ=32.5) also correlates with protons at δ=2.48 and 1.40 (H-8 and H-8'), C-9 (δ=37.4) correlates with the protons at δ=2.48 and 2.03. Finally the carbon signal at δ=52.7 correlates with the H-13 and H-13' at δ=4.68 and 4.20 respectively.

With respect to C-7 and C-11, they could be correlated with the appropiate protons only by HMBC spectrum since the H-7 signal was shifted to higher field after the Michael addition. In this way, H-11 (δ=2.91) correlates with the C-13 and C-7 signals at δ=52.7 and 45.3 respectively.

The proton chemical shifts of CH_2-13 enabled us to differentiate between the structures of the compound **16** (δH-13=4.68, δH-13'=4.20) and compound **17** (δH-13=3.64, $^3J_{11\text{-}13}$=5.5, δH-13'=3.45, ^2J=-14.5, $^3J_{11\text{-}13}$=5). In addition, they were also differentiated by the ^{13}C chemical shift from -N-CH_2-13 of compound **16** which was observed at lower field (δ=52.7) than that observed for S-CH_2-13 (δ=29.0) of compound **17**.

The quaternary carbons of **17** at C-12, C-4', C-2' and C-5' were assigned by their long range ^1H-^{13}C correlation. In this way, we observed that the signals due to H-13 and H-13' (δH-13=3.64, ; δH13'=3.45 correlated with the C-12 carbonyl signal at δ=176.1, as well as C-2' (δ=150.2). The singlet for the OMe protons at δ=3.83 correlates with C-5' singlet at δ=144.4. The proton H-6' (δ=7.40) correlates with C-4' (δ=159.3), C-2' (δ=150.2) and C-5' (δ=144.4).

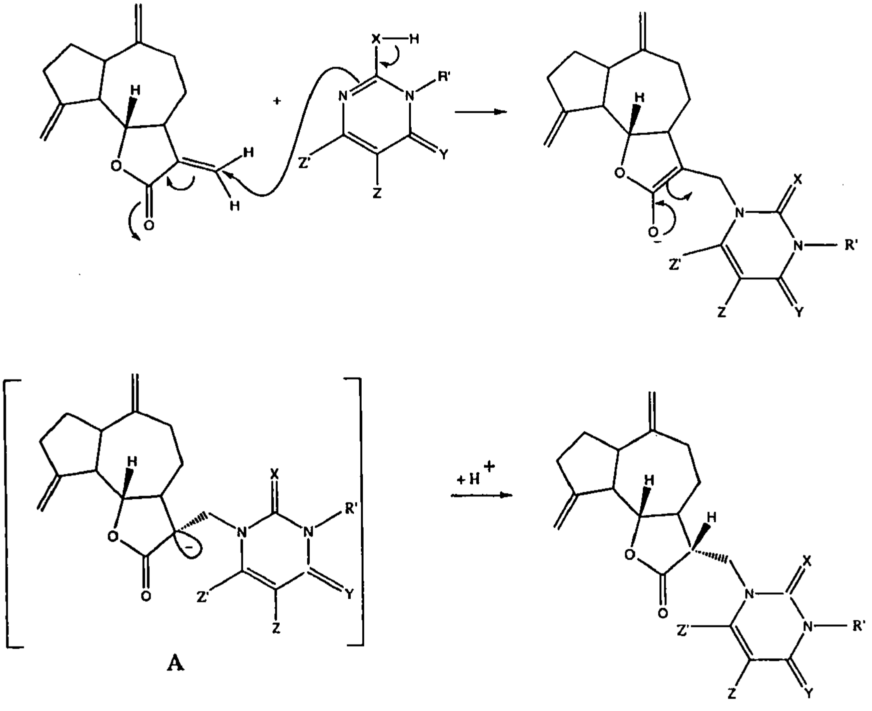
The compound **18** which correspond to C-alkylation adduct (see experimental) was recently described[16] and it will not be discussed here.

In asymmetric induction reactions, it is assumed that under kinetic control, the stereoselectivity arise from the transition state of lower energy, which provide the prefered diasteromer. In the structure A shown on scheme 3, if H-6 / H- 11 are placed in *cis* -relationship they will be produce a less energetic stereoisomer than that expected for the trans arrangement.

Recently, has been described the adduct between alantolactone[17] with the dipeptide (Z)-L-Cys-L-Ala-OMe, whose structure shown that H-7 and H-11 protons are in the *cis* relationship, which is different to our findings.

EXPERIMENTAL

Mass spectra were recorded on instruments JEOL JMS-AX505 HA and JEOL-JMS -10217. The IR spectra were performed on instruments Nicolet FX-SX and Nicolet 55-X.



Scheme 3

For initial ^1H and ^{13}C spectra, the sample was dissolved in 0.5 ml of $CDCl_3$ and the probe temperature was set at 298K. The ^1H chemical shifts are referenced to TMS. For ^{13}C reference, the centre peak of the 1:1:1 multiplet of $CDCl_3$ was assigned the value of 77.0 ppm. The experiments were performed on a Varian Unity 300 operating at observation frequency of 300 MHz for ^1H and 75.0 MHz for ^{13}C.

High resolution spectra were recorded on a Varian Unity 500 operating at 500.3 MHz for ^1H and 125.0 MHz for ^{13}C. The experiments were performed using an inverse detection 5 mm probe. The COSY,NOESY, HMQC and HMBC spectrum were recorded using the standard Varian Unity programs.

General Procedures. The pyrimidine derivatives herein used were purchased from Aldrich Chemical Co. and they were used as were received. Solvents and other reagents were purchased from Aldrich or Fluka.

The desired addition was performed under two different reaction conditions:

Method A. To a solution (THF) of 5 mmol of the corresponding pyrimidine derivative , 1 ml of aqueousTriton B (40%) in 10 ml of a mixture THF/H_2O (9:1), 230 mg of dehydrocostus lactone (1) in 5 ml of THF were added. The mixture was stirred for 3h at room temperature. Usual work up followed by flash column chromatography (silica gel, Kieselgel 60 230-400 mesh, Merck) afforded compounds 10-18.

Method B. To a solution of 290 mg of dehydrocostus lactone (1) (1mmol) in 5 ml of methylene chloride, 2 mmol of the corresponding pyrimidine derivative, 0.5 ml of 2.5 M aqueous sodium hydroxide an 50 mg of Aliquat 336 were added. The reaction was stirred at room temperature for 24h. After the usual work up, the residue was purified by flash column chromatography (silica gel) to yield derivatives 10-18 .

13-[1'-uracil] dehydrocostunolide lactone. (10)

mp 204-206° C. NMR ^{1}H. δ ppm: 2.87 (H-1), 1.94 (H-2), 1.86 (H-2), 2.50 (H-3, H-3), 2.78 (H-5), 4.00 (H-6), 2.11 (H-7), 1.35 (H-8), 2.35 (H-8), 2.03 (H-9), 2.48 (H-9), 2.58(H-11), 4.05(H-13), 4.00(H-13), 4.78 (H-14) 4.88 (H-14), 5.03 (H-15), 5.13 (H-15) , 5.69 (H-5'), 7.47 (H-6').

NMR ^{13}C, δ ppm: 47.0 (C-1), 30.1 (C-2), 32.3 (C-3), 149.5 (C-4), 51.8 (C-5), 85.9 (C-6), 45.2 (C-7), 32.5 (C-8), 37.4 (C-9), 151.4 (C-10), 45.8 (C-11), 176.0 (C-12), 47.6 (C-13), 112.2 (C-14), 109.3 (C-15), 151.1 (C-2'), 163.0 (C-4'), 102.4 (C-5'), 145.6 (C-6')

MS: M^+ 342, $C_{19}H_{22}O_4N_2$ .M^+-18, m/z 324, (M^+-112) m/z 230 (100%) . .

IR, cm^{-1}: 3390, 3036, 2939, 1766, 1713, 1690.

13-[1'-(5'-methyl uracil)] dehydrocostunolide lactone (11).

mp 91-93°C. NMR^{1}H, δ ppm: 2.87 (H-1), 1.86 (H-2), 1.94 (H-2), 2.49 (H-3), 2.51 (H-3), 2.78 (H-5), 4.00 (H-6), 2.11 (H-7), 1.35 (H-8), 2.35 (H-8), 2.03 (H-9), 2.48 (H-9) 2.57 (H-11), 4.00 (H-13), 4.06 (H-13), 4.78 (H-14), 4.89 (H-14), 5.06 (H-15), 5.16 (H-16), 1.91 (Me-C5'), 7.30 (H-6'), 8.10 (N_3,H).

MS M^+ m/z 356 , $C_{20}H_{24}N_2O_4$, (M^+-18) m/z 338, (M^+-126) m/z 230 (100%) m/z 184. IR. cm^{-1} 3394, 2933, 1766, 1705 .

13-[1'-cytosyl] dehydrocostunolide lactone. (12)

mp 200°C, dec. NMR ^1H, δ, ppm: 2.85 (H-1), 1.85 (H-2), 1.90 (H-2), 2.40 (H-3), 2.74 (H-5), 3.95 (H-6),1.90 (H-7), 1.25 (H-8), 2.30 (H-8), 2.45 (H-9), 1.80 (H-9), 2.90 (H-11), 3.79 (H-13), 3.97 (H-13), 4.70 (H-14), 4.81 (H-14), 4.96 (H-15), 5.01 (H-15), 7.07 (NH_2-4'), 5.65 (H-5'), 7.57 (H-6').

MS, M^+ m/z 341 $C_{19}H_{23}O_3N_3$. (M^+-1) m/z 342 (100%), (M^+-121) m/z 230.

IR cm^{-1} 3453, 3374, 1762.

13-{1'-(5'-fluorouracil)] dehydrocostunolide lactone. (13)

mp 82-84° C. NMR ^1H, δ ppm: 2.88 (H-1), 1.84 (H-2), 1.92 (H-2), 2.55 (H-3,H-3), 2.79 (H-5), 4.01 (H-6), 2.10 (H-7), 1.34 (H-8), 2.34 (H-8), 2.03 (H-9), 2.50 (H-9), 2.59 (H-11), 4.80 (H-14), 4.90 (H-14), 5.06 (H-15), 5.16 (H-15), 7.63 (H-6'). MS. M^+ m/z 360 $C_{19}H_{21}O_4N_2F$, (M^+-18) m/z 342, (M^+-130 m/z 230 (100%) IR cm^{-1} 3383, 2927, 1766, 1722, 1705.

13-{1'-(5'-bromouracil)] dehydrocostunolide lactone (14).

mp 107-108°C. NMR ^1H, δ ppm: 2.87 (H-1), 1.85 (H-2), 1.94 (H-2), 2.49 (H-3), 2.57 (H-3), 2.80 (H-5), 4.01 (H-6), 2.11 (H-7), 1.37 (H-8), 2.33 (H-8), 2.03 (H-9), 2.50 (H-9), 2.60 (H-11), 4.02 (H-13), 4.07 (H-13), 4.78 (H-14), 4.89 (H-14), 5.05 (H-15), 5.15 (H-15), 7.85 (H-6'), 9.03 NH.

MS M^+ m/z 420, 422. $C_{19}H_{21}O_4N_2Br$. (M^+-18) m/z 402, 404, (M^+-190) m/z 230 (100%) IR cm^{-1} 2939, 1766, 1697, 1624.

13-[1'-(5'-propil uracil)] dehydrocostunolide lactone. (15)

mp 71-73°C, NMR ^1H δ ppm: 2.88 (H-1), 1.94 (H-2), 2.00 (H-2), 2.50 (H-3), 2.52 (H-3), 2.77 (H-5), 3.99 (H-6), 2.11 (H-7), 1.34 (H-8), 1.96 (H-8), 2.03 (H-9) 2.48 (H-9), 2.57 (H-11), 4.01 (H-13), 4.07 (H-13), 4.78 (H-14), 4.88 (H-14), 5.05 (H-15), 5.15 (H-15), 7.24 (H-6'), 0.93 Me, 1.55 CH_2, 2.30 CH_2.

MS M^+ m/z 384 $C_{22}H_{28}O_4N_2$. (M^+-18) m/z 366, (M^+-29) m/z 355) m/z 230 (100%). IR cm^{-1} 3458, 3025, 2951, 1770, 1758, 1699.

13-[1'-(5'-metoxi-2'-tiouracil)] dehydrocostunolide lactone.(16)

mp 92-94° C. NMR^1H δ ppm: 2.87 (H-1), 1.86 (H-2), 1.94 (H-2), 2.50 (H-3, H-3), 2.78 (H-5), 4.03 (H-6), 2.20 (H-7), 1.40 (H-8), 2.48 (H-8), 2.03 (H-9), 2.48 (H-9), 2.91 (H-11), 4.20 (H-13), 4.68 (H-13), 4.77 (H-14), 4.88 (H-14), 5.04 (H-15), 5.13 (H-15), 3.78 (MeO-5'), 7.34 (H-6').

RMN ^{13}C δ ppm: 47.0 (C-1), 30.1 (C-2), 32.5 (C-3), 151.4 (C-4), 51.9 (C-5), 86.2 (C-6), 45.3 (C-7), 32.5 (C-8), 37.4 (C-9), 149.4 (C-10), 46.5 (C-11), 176.9

(C-12), 52.7 (C-13), 112.2 (C-14), 109.2 (C-15), 156.2 (C-2'), 172.1 (C-4'), 140.4 (C-5'), 125.6 (C-6'), 52.0 (O-Me).

MS M^+ m/z 388 $C_{20}H_{24}O_4N_2S$, (M^+-33) m/z 355, (M^+-158) m/z 230 (100%), (M^+-230) m/z 158 . IR cm^{-1} 3373, 2929, 1763, 1708, 1642.

13-[2'-(5'-methoxy-2'tiouracil)] dehydrocostunolide lactone (17).

mp 119-121° C. NMR ^1H ,δ ppm: 2.83 (H-1), 1.84 (H-2), 1.93 (H-2), 2.46 (H-3), 2.52 (H-3), 2.81 (H-5), 3.95 (H-6), 2.24 (H-7), 1.33 (H-8), 2.35 (H-8), 1.97 (H-9), 2.45 (H-9), 2.70, (H-11), 3.44 (H-13), 3.64 (H-13), 4.76 (H-14), 4.85 (H-14), 5.03 (H-15), 5.17 (H-15), 3.83 (MeO-5'), 7.40 (H-6').

NMR ^{13}C, δ ,ppm: 47.1 (C-1), 30.1(C-2), 32.7 (C-3), 151.5 (C-4), 50.4 (C-5), 85.4 (C-6), 46.1 (C-7), 32.4 (C-8), 37.3 (C-9), 149.6 (C-10), 47.1 (C-11), 176.1 (C-12), 29.0 (C-13), 112.0 (C-14), 109.2(C-15), 150.2 (C-2'), 159.3 (C-4'), 144.4 (C-5'), 131.0 (C-6'), 56.4 (MeO-5').

MS, M^+ m/z 388 $C_{20}H_{24}O_4N_2S$; (M^+-158) m/z 230; (M^+-230) m/z 158 (100%). IR cm^{-1}: 3361, 1767, 1608, 1268.

13-[5'-(6'-amino-1', 3'- N,N dimethyluracil)] dehydrocostunolide lactone (18).

mp 204-206°C, RMN ^1H, δ ppm: 2.68 (H-1), 1.87 (H-2), 1.94 (H-2), 2.49 (H-3), 2.52 (H-3), 2.80 (H-5), 3.98 (H-6), 2.15 (H-7), 2.51 (H-8), 1.30 (H-8), 2.00 (H-9), 2.68 (H-9), 2.37 (H-11), 2.71 (H-13), 2.77 (H-13), 4.74 (H-14), 4.87 (H-14), 5.03 (H-15), 5.13 (H-15), 3.45 (NMe-1'), 3.33 (NMe-3'), 5.62 (NH_2-6'). RMN ^{13}C , δ ppm: 47.3 (C-1), 30.1 (C-2), 32.5 (C-3), 151.9 (C-4), 51.7 (C-5) 87.1 (C-6), 46.8 (C-7), 32.6 (C-8), 38.1 (C-9), 150.2 (C-10), 49.2 (C-11), 181.9 (C-12), 22.2 (C-13), 111.5 (C-14), 108.8 (C-15), 29.2 ($N_{1'}$-Me), 151.4 (C-2'), 28.2 ($N_{3'}$-Me), 163.1 (C-4'), 85.8 (C-5'), 152.0 (C-6').

MS M^+ m/z 385 $C_{21}H_{27}O_4N_3$ (M^+-155) m/z 230, (M^+-217) m/z 168 (100%). IR cm^{-1}: 3502, 3352, 2925, 1747, 1625.

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