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A Non-Catalyzed Ring-Opening Aminolysis Reaction of Sesquiterpene Lactones

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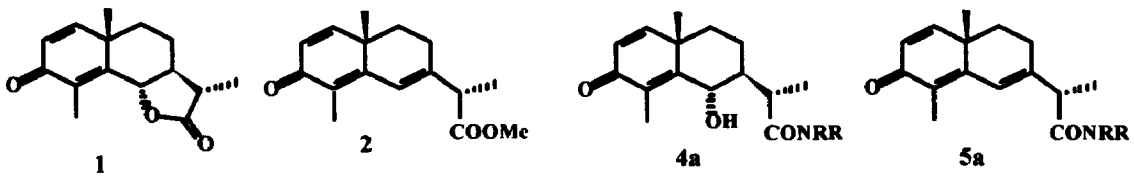
Abstract: Santonin (1) and other sesquiterpene lactones (6-10) react cleanly with pyrrolidine at room temperature to afford γ-hydroxyalkylamides, which by elimination with mesyl chloride in pyridine-benzene at 80°C give unsaturated alkylamides.

As part of our current synthetic programme related to natural sesquiterpenes with biological activity, we have previously synthesized the trienone **2** from santonin (**1**) [1] This trienone is a key intermediate to the C_8 oxyfunctionalization of the eudesmane framework and consequently to the synthesis of 8,12-eudesmanolides [1,2] It has been also used in the synthesis of (+)-8-oxo-β-cyperone derivatives.[3]

We have considered alternative methods for the preparation of the system of 1,4,6-trien-3-one present in **2** and we describe here a non-catalyzed ring-opening aminolysis reaction of santonin (**1**) by nucleophilic attack by pyrrolidine (**3a**). By dehydration of the resulting γ-hydroxyalkylamide **4a** the 1,4,6-trien-3-one system **5a** was obtained.



1 **2** **4a** **5a**

In general, aminolysis of lactones requires long reaction times at high temperaures when amines[4-5] are used as nucleophiles. Metalic (Li, Al, Sn) amides[6-8] are useful reagents, but are not compatible with sensitive functionality. Recently an aluminum chloride mediated aminolysis of 5-7 membered lactones has been reported [9]

In our method the aminolysis was conveniently carried out in benzene and excess of amine (20 eq) at room temperature. The product was isolated by evaporation of the solvent and the excess of amine As Table 1 shows the reaction with pyrrolidine is quantitative and the facility of the ring-opening aminolysis reaction seems to be determined by steric factors rather than electronic factors Thus, whilst the less hindered cyclic amines, including the lower basicity morpholine (at 60°C), react with santonin (**1**) in the indicated conditions, the non-cyclic amines need for acid catalysis.[9]

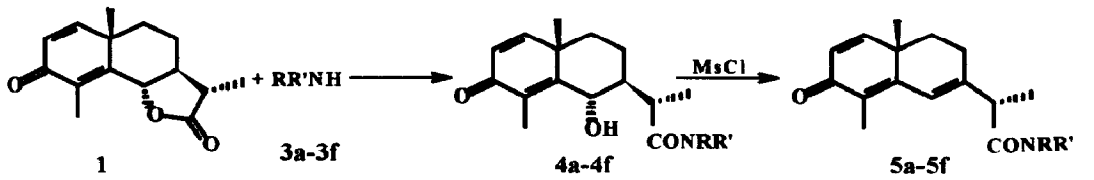
The elimination of the resulting hydroxyl group at C_6 was achieved with excess of mesyl chloride in pyridine-benzene at 80°C The reaction runs well giving the alquene with *N,N*-dialkylamides, although

relactonization was observed in some cases. With *N*-alkylamides, the elimination was complicated by mesylation on the nitrogen atom and intramolecular replacement of the mesylate by the oxygen of the amido group

In summary, the best results of aminolysis-elimination were obtained with pyrrolidine, obtaining compound **5a**, with the 1,4,6-trien-3-one system, with a 70% overall yield from santonin (**1**).[10] Consequently pyrrolidine was chosen to test the scope of the aminolyis-elimination of other sesquiterpene lactones As Table 2 shows the aminolysis was quantitative in all cases and the overall yield was good in the cases where a conjugated carbonyl system was obtained [11] Furthermore the elimination occurs spontaneously during the aminolysis reaction, without treatment with mesyl chloride, when a C_8 carbonyl group was present because of the greater acidity of the H_7 [12] In the cases (entries d, e) where a carbonyl group there was not present, the yields were lower, specially in the entry e where the reaction occurs with double bond migration [13]

In conclusion, santonin (**1**) and other sesquiterpene lactones (**6-10**) react cleanly with pyrrolidine at room temperature to afford γ-hydroxyalkylamides, which by elimination with mesyl chloride in pyridine-benzene at 80°C give unsaturated alkylamides **5a** and **16-19** respectively

Table 1. Aminolysis -Elimination of Santonin (**1**) with Several Amines



1 **3a-3f** **4a-4f** **5a-5f**

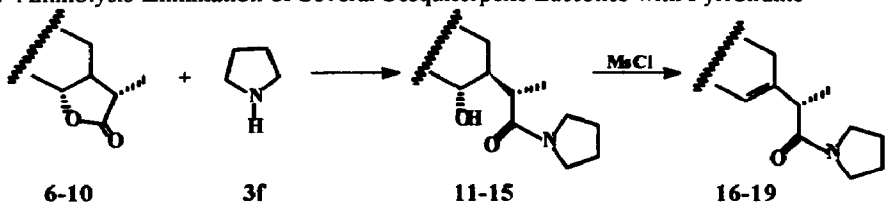
		AMINOLYSIS				ELIMINATION	
Entry	Amine (**3a-3f**)	Method[a]	T(°C)	t(h)	yield of **4a-4f**[b]	t(h)	yield of **5a-5f**[c]
a		non-catalyzed	r t	3 5	100%	5 5	78%
b		non-catalyzed	60	48	92%(8%)	7	57%(34%)
c		non-catalyzed	60	48	69%(31%)	7	24%(60%)
d	Et_2NH	catalyzed	r t	0.75	82%	3 5	85%
e		catalyzed	r.t	6	83%	5.5	13%
f		catalyzed	r t	8	45%(15%)	5 5	30%

[a] Non-catalyzed refers to our method. Catalyzed refers to literature method[9] (2.5 eq of amine, 1.25 eq. of $AlCl_3$ in CH_2ClCH_2Cl).

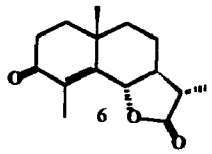
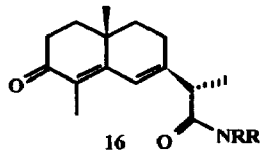
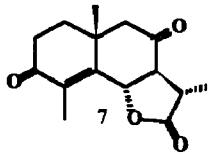
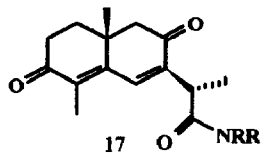
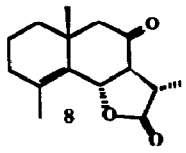
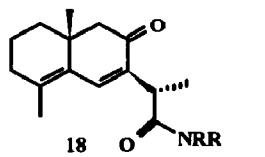
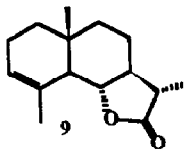
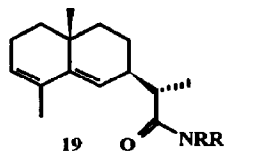
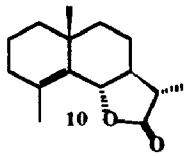
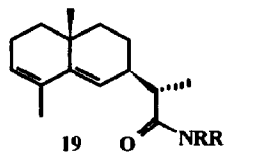
[b] Recovered santonin (**1**) in parenthesis (by ^1H NMR)

[c] Recovered santonin (**1**) in parenthesis (isolated)

Table 2 Aminolysis-Elimination of Several Sesquiterpene Lactones with Pyrrolidine



6-10 **3f** **11-15** **16-19**

	AMINOLYSIS			ELIMINATION		
Entry	Sustrate	t(h)	yield of **11-15**	t(h)	Product **16-19**	yield of **16-19**[a]
a		4	100%	5.5		78%
b		1	-	-		98%
c		20	-	-		98%
d		18	100%	5 5		65%(22%)
e		30	100%	7		20%(17%)

[a] Recovered starting product in parenthesis

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10. Compound (**5a**): m.p. 79-82°C (Hexane-EtOAc); $[\alpha]_D^{26}$ +357.3 ($CHCl_3$); MS *m/e* 300 (M^++1, 75), 299 (M^+,75), 284 (35), 201 (19), 98 (100); IR (KBr) 1645-1641, 1609, 831 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.14 (3H, s, H_{14}), 1.33 (3H, d, J 7.0 Hz, H_{13}), 1.54 (1H, ddd, J 6.6, 11.0, 13.0 Hz, $H_{9\alpha}$), 1.75 (1H, ddd, J 1.6, 5.6, 13.0 Hz, $H_{9\beta}$), 1.8-2.0 (4H, m, $2CH_2CH_2N$), 1 92 (3H, brs, H_{15}), 2.26 (1H, brddd, J 1.6, 6.6, 18.0 Hz, $H_{8\alpha}$), 2.43 (1H, dddd, J 1 8, 5.6, 11.0, 18.0 Hz, $H_{8\beta}$), 3.36 (1H, q, J 7 0 Hz, H_{11}), 3.3-3.5 (4H, m, $2CH_2N$), 6.21 (1H, d, J 9.8 Hz, H_2), 6 48 (1H, brs, J 1.8 Hz, H_6), 6 70 (1H, d, J 9 8 Hz, H_1); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 186.5 (C_3), 170.7 (C_{12}), 154 7 (C_1), 153.5, 145 9, 128.2 (C_4, C_5, C_7), 126.9 (C_2), 121.6 (C_6), 46.4, 46.0 (CH_2N), 46.3 (C_{11}), 37.3 (C_{10}), 31.9 (C_9), 26.0 (C_8), 25.0 (C_{14}), 24.0, 23.6 (CH_2CH_2N), 16.4 (C_{13}), 9 9 (C_{15}).

11. Compound (**16**): m.p. 90-92°C (Hexane-EtOAc); $[\alpha]_D^{26}$ +470 8 $CHCl_3$), MS *m/e* 302 (M^++1, 35), 301 (M^+, 76), 286 (3), 204 (10), 98 (100); IR (KBr) 1640, 1620, 850 cm^{-1}, ^1H NMR (200 MHz, $CDCl_3$) δ 1.09 (3H, s, H_{14}), 1.32 (3H, d J 6.9 Hz, H_{13}), 1.49 (1H, dt, J 5.9, 13.2 Hz, $H_{9\alpha}$), 1.81 (3H, s, H_{15}), 1 6-2.0 (7H, m, $2H_1$, $H_{9\beta}$, $2CH_2CH_2N$), 2.2-2.4 (2H, m, $2H_8$), 2 42 (1H, ddd, J 2.9, 4.4, 17.9 Hz, H_2), 2.63 (1H, ddd, J 6.5, 13.3, 17.9 Hz, $H_{2'}$), 3.35 (1H, q, J 6.9 Hz, H_{11}), 3 4-3 6 (4H, m, $2CH_2N$), 6.37 (1H, brs, H_6); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 198.8 (C_3), 170 7 (C_{12}), 154 8, 148.5, 127 1 (C_4, C_5, C_7), 121 4 (C_6), 46.7 (C_{11}), 46.3, 45 9 (CH_2N), 36.6, 36.0 (C_1, C_9), 33.6 (C_2), 32.8 (C_{10}), 26.0 (C_8), 23.9, 23.5 (CH_2CH_2N), 21.0 (C_{14}), 16.3 (C_{13}), 10.1 (C_{15})

12. Compound (**17**): an oil, $[\alpha]_D^{20}$ +289 5 ($CHCl_3$), MS *m/e* 316 (M^++1, 45), 315 (M^+, 21), 298 (18), 246 (15), 217 (9), 98 (100); IR (NaCl) 1665, 1579, 921 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.27 (3H, s, H_{14}), 1 35 (3H, d, J 7.2 Hz, H_{13}), 1 94 (3H, s, H_{15}), 1 7-2.1 (6H, m, $2H_1$, $2CH_2CH_2N$), 2 34 (1H, d, J 15.4 Hz, H_9), 2.51 (1H, d, J 15.4 Hz, $H_{9'}$), 2.4-2.6 (2H, m, $2H_2$), 3 0-3.2 (4H, m, $2CH_2N$), 3 45 (1H, brq, J 7.2 Hz, H_{11}), 7.24 (1H, brs, H_6); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 198.1, 197 8 (C_3, C_8), 180 1 (C_{12}), 151.8, 144.2, 133.0 (C_4, C_5, C_7), 134 7 (C_6), 52 2 (C_9), 44.5 ($2CH_2N$), 42 7 (C_{11}), 37 1 (C_{10}), 35.4 (C_1), 33.3 (C_2), 24.3 ($2CH_2CH_2N$), 23.4 (C_{14}), 16 8 (C_{13}), 10 7 (C_{15})

Compound (**18**): an oil, $[\alpha]_D^{24}$ +164 ($CHCl_3$), MS *m/e* 301 (M^+,3), 203 (13), 187 (2), 98 (100), IR (NaCl) 1660, 1620, 910 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.06 (3H, s, H_{14}), 1.26 (3H, d, J 7.2 Hz, H_{13}), 1.4-1.5 (2H, m, $2H_1$), 1.80 (3H, brs, H_{15}), 1.8-2.0 (4H, m, $2CH_2CH_2N$), 2.0-2.2 (2H, m, $2H_3$), 2.21 (1H, d, J 15.4 Hz, H_9), 2.32 (1H, d, J 15 4 Hz, $H_{9'}$), 3 15 (4H, brt, J 7 0 Hz, $2CH_2N$), 3 43 (1H, brq, J 7.2 Hz, H_{11}), 7.21 (1H, brs, H_6); ^{13}C NMR (50.3 Hz, $CDCl_3$) δ 199 8 (C_8), 180.3 (C_{12}), 138 7, 136 6, 132.7 (C_4, C_5, C_7), 137.4 (C_6), 52 9 (C_9), 44 5 ($2CH_2N$), 40.9 (C_{11}), 37 4 (C_1), 36 2 (C_{10}), 33 2 (C_3), 24.7 (C_{14}), 24.3 ($2CH_2CH_2N$), 19.3 (C_{15}), 17 9 (C_2), 16 8 (C_{13})

13. Compound (**19**): an oil, $[\alpha]_D^{20}$ +16.8 ($CHCl_3$), MS *m/e* 288 (M^++1, 55), 287 (M^+, 91), 272 (39), 188 (67), 160 (100), 98 (43); IR (NaCl) 1629, 866 cm^{-1}, ^1H NMR (200 MHz, $CDCl_3$) δ 0.94 (3H, s, H_{14}), 1 11 (3H, d, J 6.4 Hz, H_{13}), 1.68 (3H, brs, H_{15}), 1 8-2 0 (4H, m, $2CH_2CH_2N$), 2.0-2 15 (1H, m, H_2), 2.15-2.35 (1H, m, $H_{2'}$), 2 38 (1H, dq, J 6.2, 8 8 Hz, H_{11}), 2 4-2 6 (1H, brm, H_7), 3.2-3 4 (4H, m, $2CH_2N$), 5.21 (1H, brs, H_6), 5.49 (1H, brs, H_3)

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