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A New Synthetic Route to Macrocycles : Synthesis of Large Ring Enaminolactones

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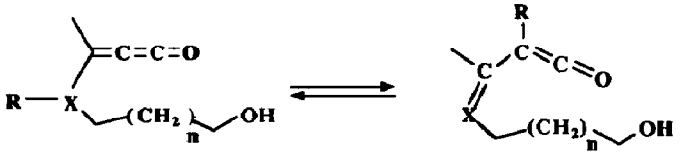
Abstract : *Macrocyclic enaminolactones 5 are prepared in three steps from commercialy available chloroalcohols 1. The cyclization step is performed by intramolecular nucleophilic addition of the hydroxy group to an aminomethyleneketene generated by thermolysis.*

Macrocycles and particularly macrolides which sometimes contain an α,β–unsaturated lactone moiety[1] have attracted interest over a number of years and synthetic methods towards these large ring cycles have been described.[2-4] Macrolides generaly occur in nature and many of them have biological activity such as antibiotic,[5] antiviral[6-8] or cytotoxic properties.[9]

The synthesis of macrocycles can be carried out from either linear or cyclic precursors : in the past few years this has been done by increasing the size of smaller cycles using silylated compounds,[10] and by Wittig[11] or Ullmann reactions.[12] Enzymatic Baeyer-Villiger reaction have also been applied to the formation of seven membered lactones.[13]

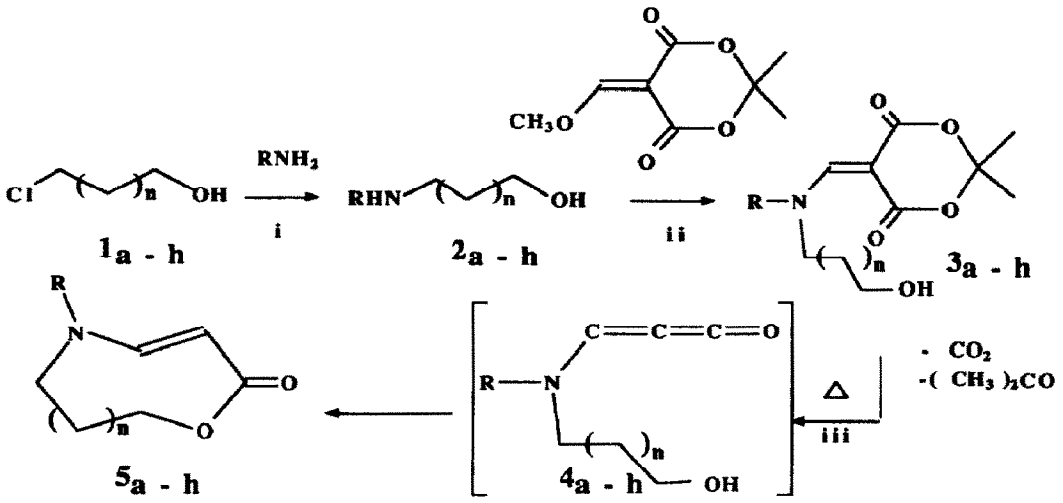
More recently , Quinkert and coworkers have obtained optically active macrocyclic lactones or lactams by photo-lactonization or lactamization of ortho-quinol acetates : [14,15] the cyclization was based on an intramolecular nucleophilic attack of hydroxy or amino group respectively on the photochemically generated dieneketene intermediate which is a vinylogue of **4'** (X = CH). Owing to the present interest in macrolides, we decided to investigate such a strategy and we present here our results concerning a general synthesis of a new class of macrocycles (β-enaminolactones) based on the reactivity of methyleneketenes.[16] The key step involves the cyclization of ω-hydroxyalkylamino methyleneketenes **4** (X = N) which are formally the tautomeric forms of iminoketenes **4'** (X = N when R = H). Intermediates **4** are easily generated by thermal decomposition[17] of the



4 **4'**

corresponding Meldrum acid derivatives (5-(ω-hydroxyalkylaminomethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione **3**). This new methodology supposes the preliminary synthesis of secondary alkylamines **2** bearing a hydroxygroup at the ω- position.

Aminoalcohols **2** were prepared from commercialy available chloroalcohols **1** : a large excess of amine (10 or 15 equivalents) was slowly added to a solution of methylamine in ethanol (**2 a, b** , R = CH_3) or aniline in toluene (**2 c-h**, R = Ph), and the mixture was stirred at 25 ° or 110 ° C respectively for 15 or 24 hours. After



R = Me, n = 0, 1

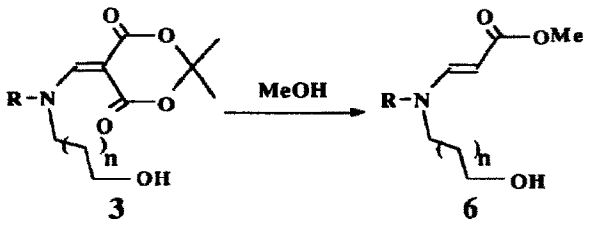
R = Ph, n = 0, 1, 4, 6, 8, 9

i = 10 eq of aniline or methylamine per mole of 1 in toluene ;

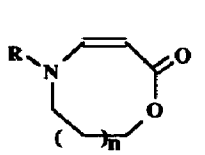
ii = 1 eq of methoxymethylene Meldrum acid derivative per mole of 2, acetonitrile as solvent ;

iii = thermolysis : temperature range, 400 ° - 500° C ; pressure : 16 torr.

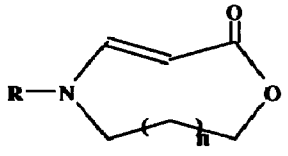
extraction, aminoalcohols **2** were isolated by distillation or recristallization, but could also be immediately transformed into Meldrum acid derivatives **3 a-h** in good yieds without previous purification . In the second step, substitution of the alkoxy group of 5-methoxymethylene-2,2-dimethyl-1,3-dioxane-4, 6-dione [18] by the amino group of **2** was performed under reflux in acetonitrile for 8 hours. It should be mentioned that when the mixture was maintained much longer at 80 ° C , the Meldrum's acid ring could be cleaved by methanol formed during the reaction and thus the corresponding enaminoesters **6** were exclusively obtained. Similar monodecarboxylating transesterifications leading to β-enaminoesters have already been reported in basic or acid conditions ;[19, 20] these have also been reported in a neutral medium.[21]



The cyclization was achieved by thermolysis of Meldrum acid derivatives **3 a-h** between 400 and 500 ° C under flow conditions [16] : in all cases, enaminolactones **5 a-h** were obtained . These results can be rationalized by assuming the formation of the methyleneketene intermediates **4 a-h** generated from **3 a-h** by thermal extrusion of carbon dioxide and acetone.[17] Intramolecular nucleophilic addition of the terminal hydroxy group to the ketene moiety of the heterocumulene affords medium-ring lactones **5 a-d** with only the Z double bond configuration (n = 0, 1; R = CH_3 or Ph, $J_{2,3}$ = 9,5-10 Hz) whereas for the larger ring derivatives **5 e-h** (n = 4, 6, 8, 9 , R = Ph) the ethylenic bond is exclusively E ($J_{2,3}$ = 13-13,5 Hz).



5 a,b R: Me n: 0,1
5 c,d R: Ph n: 0,1



5 e-h R: Ph n: 4,6,8,9

Isolated yields of 2, 3 and 5

R	Me	Me	Ph	Ph	Ph	Ph	Ph	Ph
n	0	1	0	1	4	6	8	9
(%) 2	(1)	40	(1)	64	89	98	92	94
(%) 3	95	90	92	57	81	99	97	97
(%) 5	60	35	57	56	22	36	75	54

(1) : commercialy available

In summary, this three step sequence provides a stereospecific synthetic access to large sized enaminolactones, a novel class of macrocycles, with relatively good yields.

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