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A NEW SYNTHESIS OF 14-TETRADECANOLIDE FROM CYCLODODECANONE.

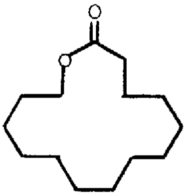
Jean Pierre GENET* and Philippe KAHN

Laboratoire de Chimie Organique de Synthèse
Equipe de Recherche Associée au C.N.R.S.
Université Pierre et Marie Curie
8, rue Cuvier - 75005 Paris.

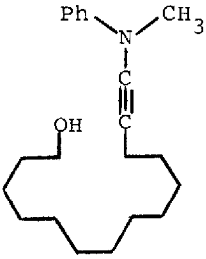
Summary : The ω-hydroxy ynamine (2) is cyclized to the ketene N,O-acetal (3) which gives, on hydrolysis, natural 14-tetradecanolide (1).

Synthesis of macrolides is a current problem of intensive investigation. One direct route to macrocyclic lactones uses appropriate acyclic precursors such as ω-hydroxy acids and various methods for activation of acid derivatives have been devised for this purpose[1].

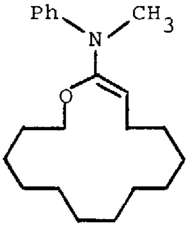
In this paper, we report the use of an ynamine moiety as the activated form of an acid in a new synthesis of 14-tetradecanolide (1), a natural macrolide recently isolated[2] from *Ferula galbaniflua*. The lactone formation involves the intramolecular addition[3] of the ω-hydroxy ynamine (2) which leads to the ketene N,O-acetal (3), the hydrolysis of which gives the 15-membered lactone[4] (1).



(1)

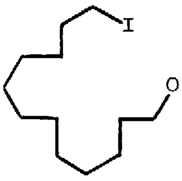


(2)

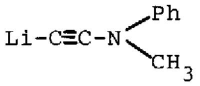


(3)

The synthesis of the ω-hydroxy ynamine (2) from cyclododecanone is shown in scheme I. A key step involves the alkylation of the protected 12-iodododecanol (4), $Z = -CH_2-\overset{Br}{\overset{|}{C}}=CH_2$ by N-methyl N-phenyl aminoethynyl lithium (5) according to the method of Ficini and Barbara[5].



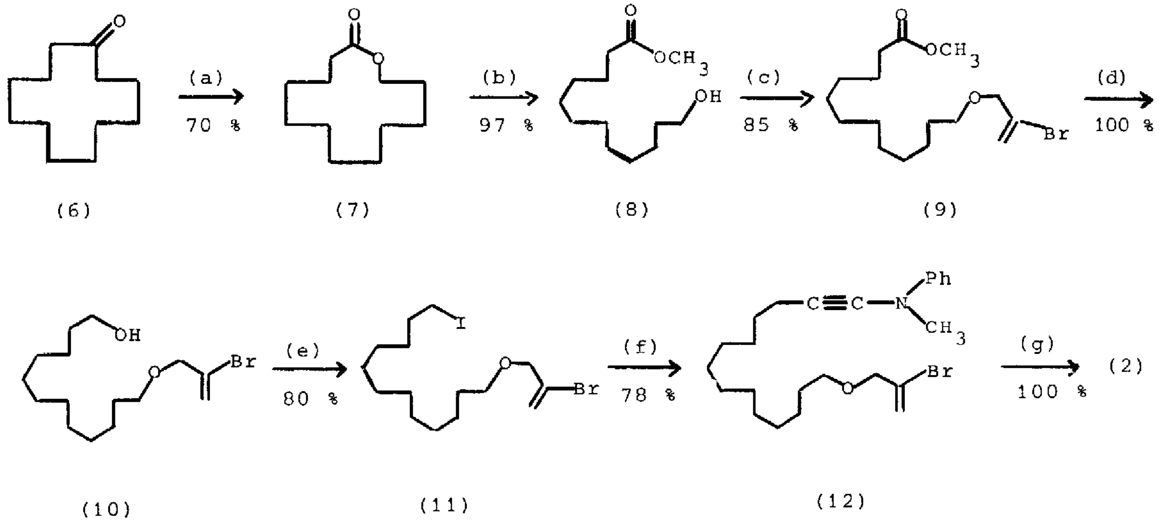
(4)

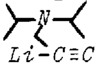


(5)

The protection of the hydroxyl group of 12-iodododecanol(4),(Z = H), is achieved by using its bromopropenyl ether (4), ($Z = CH_2-CBr=CH_2$). This protecting group[6] is normally stable to base and is suitable for the alkylation step (11) ⟶ (12), (scheme I). However, it can be easily and quantitatively removed by β-elimination[7] after halogen metal exchange reaction with t-butyllithium. Under these conditions the hydroxyynamine is stable[8].

SCHEME I



(a) MCPBA, CH_2Cl_2, reflux 20 h ; (b) HCl/MeOH, 3 h, 25°C ; (c) 2,3 dibromopropene,  18 h, 150°C ; (d) $LiAlH_4$, Et_2O, 2 h then H_2O ; (e) $(PhO)_3\overset{\oplus}{P}MeI^{\ominus}$, DMF ; (f) $Li-C{\equiv}C-N{<}^{Ph}_{Me}$, HMPA, THF, 70°C, 3 h then NH_4Cl-NH_4OH ; (g) tBuLi, THF, -78°C ⟶ 25°C, H_2O.

The lactone[9] (7) was synthesized from cyclododecanone (6) by Baeyer-Villiger reaction in refluxing dichloromethane with an excess of MCPBA (20 h). The 13-membered lactone (7) was isolated in 90 % yield[10] [bp : 90°C/15 mm ; IR (film) : 1725 cm^{-1} ; NMR ($CDCl_3$)$-CH_2-\underset{\overset{\Vert}{O}}{C}-$, 2.33 (t) ; $O-CH_2-$, 4.13 (t)].

Methanolysis of (7) with methanol-hydrogen chloride gave methyl 12-hydroxydodecanoate[11] (8) in 97 % yield, [IR (film) : 3400, 1730 cm^{-1} ; NMR ($CDCl_3$) : 3.68 (s,3H) and 3,58 (t,2H), 2.18 (t,2H), J = 7 Hz].

The protection of the alcohol (8) was achieved (150°C, 18 h)[12] with 2,3-dibromopropene in the presence of diisopropylethylamine as hydrogen bromide trap. The protected alcohol (9) was isolated in 85 % yield [IR (film) : 1735 cm^{-1} ; NMR (C_6D_6 : 5.73 (s,1H), 5.41 (s,1H), 3.8 (s,2H)]. The reduction of (9) with lithium aluminium hydride afforded quantitatively (10), bp : 120°C/0,1.

Treatment of (10) with methyltriphenoxyphosphonium iodide[13] gave cleanly the iodide (11) in 80 % yield, m/e : 430. The alkylation of (11) with (N-methyl N-phenyl amino)ethynyl lithium (5) was performed in HMPA-THF at 70°C for 3 h, and the mixture was then quenched at -40°C with ammonium chloride-ammonia. The ynamine (12) was isolated in 78 % yield [bp : 160°C/0,2 mm ; IR (film) : 2240, 1635, 1600 cm^{-1}]. Treatment of (12) with t-butyllithium (2 eq.) in THF at -78°C, then 15 min. at room temperature, followed by hydrolysis with NH_4Cl/NH_4OH at 40°C gave quantitatively the hydroxy ynamine (2) [IR (film) : 3400, 2240, 1600 cm^{-1}].

The cyclization of (2) was run in ether (0,01M) with BF_3 etherate as catalyst. Direct hydrolysis with 3N HCl afforded, after chromatography on silicagel, 14-tetradecanolide (1) in 30 % yield [IR (film) : 1730 cm^{-1}; NMR ($CDCl_3$) : 4.02 (m), CH_2-O ; 2.20 (m), $CH_2-\underset{\overset{\Vert}{O}}{C}$; Mass spectrum (70 ev) : $M^{\ddagger} = 226$ (9,3 %)]. The physical data are identical to litterature[4a].

We would like to express our sincere thanks to Professor J. FICINI for stimulating discussions.

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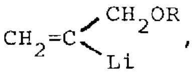
7) For a study of organometallic species such  $CH_2{=}C{<}^{CH_2OR}_{Li}$, see : J. Ficini, J.C. Depezay, Bull. Soc. Chim. France, 3878 (1966) ; J. Ficini, J.C. Depezay, Tetrahedron Letters, 937 (1968) ; J.C. Depezay, Thesis, Paris (1969).

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