Pergamon

Tetrahedron Letters, Vol. 38, No. 6, pp. 1037-1040, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(96)02496-3

Synthesis of γ-and δ-Lactones Derived from 4-Quinolone-3-Carboxylic Acid

Claire Clémencin-Le Guillou, Sylviane Giorgi-Renault, Jean-Charles Quirion, Henri-Philippe Husson

Laboratoire de Chimie Thérapeutique associé au CNRS, Faculté des Sciences Pharmaceutiques et Biologiques, Université René Descartes, 4, Avenue de l'Observatoire, 75270 Paris Cedex 6, France *

Abstract : New quinolones **3**, **6** and **9** annelated to either a 5-membered or a 6-membered lactone were designed as hybrids of antibacterial 4-quinolones and antitumor epipodophyllotoxin derivatives. They were synthezised using ethyl 2-ethenyl-4-hydroxy-1,2-dihydroquinoline-3-carboxylate **2** as a key intermediate. © 1997, Published by Elsevier Science Ltd. All rights reserved.

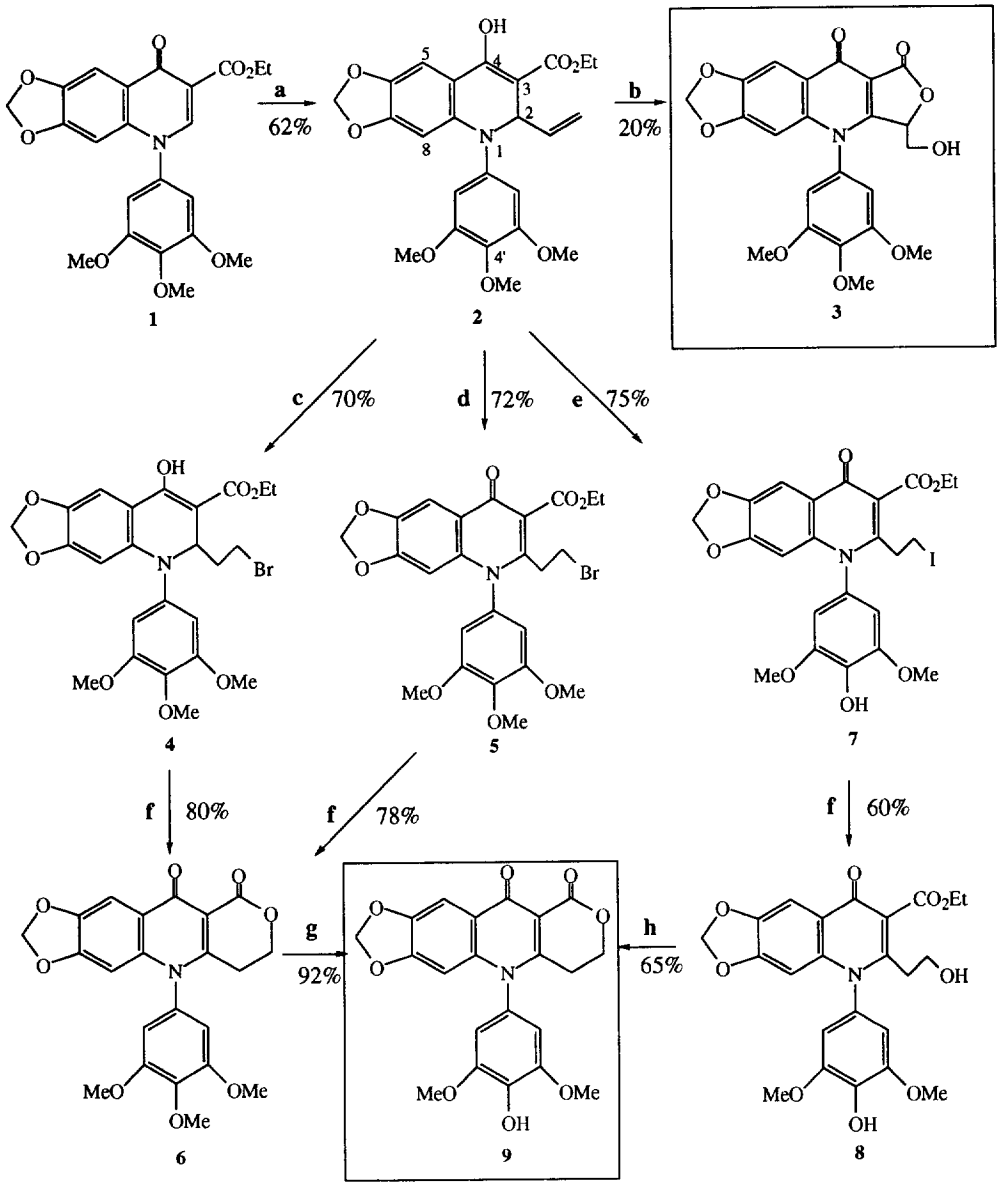
Topoisomerases are enzymes critical for maintaining and controlling the conformations required for DNA replication and transcription.[1] They are found in both eukaryotic and prokaryotic cells and represent targets for a wide variety of chemotherapeutic agents. There are many topoisomerase II inhibitors that demonstrate useful antitumor activity (e.g., amsacrine or semisynthetic glycosidic derivatives of 4'-*O*-demethylepipodophyllotoxin such as etoposide and teniposide)[2], and it has been suggested that increased topoisomerase II-mediated DNA cleavage may explain the activity of these antitumor agents.[3] While quinolone-based inhibitors (e.g., oxolinic acid, pefloxacin...) of bacterial topoisomerase II also known as DNA gyrase, have long been used as antibacterial agents [4], recent studies have identified some quinolones which also inhibit mammalian topoisomerase II [5] and thus quinolones have become viable lead compounds in the development of cancer chemotherapeutic agents.

We thus became interested in the synthesis of *N*-aryl quinolones annelated at the 2,3-positions to a lactone. The compounds which we have designed, are related to quinolones and to epipodophyllotoxin derivatives. In these hybrids, we have chosen to maintain the units that seem to be important for activity: the *N*-1-substituted-4-quinolone nucleus of cytotoxic quinolones[5], a 1,3-benzodioxo ring, a 3,4,5-trimethoxyphenyl system (or better the corresponding 4-*O*-demethyl derivative) as well as the lactone function of the epipodophyllotoxins.[6] To the best of our knowledge, only one *N*-substituted quinolone with a 6-membered lactone has been prepared by cyclisation of the corresponding ethyl 1-cyclopropyl-2-ethenyl-6,7,8-trifluoro-4-quinolone-3-carboxylate in acidic medium.[7]

Herein we report our first results dealing with the synthesis of this skeleton. The key intermediate of the scheme is the 1,2-dihydroquinoline **2** substituted at C-2 and C-3 by a vinyl chain and a carboxylate respectively. The lactone nucleus could thus be obtained by reaction of the 3-ester function with a hydroxylated chain derived from the vinyl group.

Quinolone **1** [8] was prepared from 2-bromo-4,5-methylenedioxybenzoic acid by the classical method currently used for the preparation of the ethyl 1,4-dihydro-4-oxoquinoline-3-carboxylates bearing an *N*-1 aryl substituent.[4] The vinyl group was introduced by a 1,4-addition reaction at C-2 with vinyl cuprate to give the key intermediate **2** in 62% yield.[8,9]

* Fax : + 33 1 43 29 14 03



Reagents : **(a)** vinylmagnesium bromide, CuI, -70°C, 6h. **(b)** $KMnO_4$, H_2O / acetone, 0°C-20°C, 36h. **(c)** TMSBr 3.5 eq, CH_2Cl_2, 0°C, 4h. **(d)** HBr (gas), CH_2Cl_2, rt, 48h or TMSBr 3.5 eq, CH_2Cl_2, rt, 24h. **(e)** TMSI 3.5 eq, CH_2Cl_2, rt, 24h. **(f)** Ag_2O, H_2O / acetone, 60°C, 3h. **(g)** TMSI 1.4 eq, CH_2Cl_2, rt, 4h. **(h)** NaH 60%, THF, 3h, reflux.

Scheme

With the desired substituted intermediate in hand, we first investigated the possibility of creating a lactone ring *via* a 2-dihydroxylated chain. Reaction of **2** with $KMnO_4$ in aqueous acetone afforded lactone **3** (20%) and quinolone **1** as the major product (75%). Despite variation in the experimental conditions, it was not

possible to increase the yield of **3**. The formation of **1** may result from the cleavage of the cyclic manganate ester intermediate, whereas **3** is one of the two possible lactones that could be obtained by cyclization of the intermediate diol resulting from the dihydroxylation of the vinyl chain of **2** followed by oxidation into a quinolone system. Under these conditions, the formation of the 6-membered lactone was not observed. The structure of **3** was deduced from the ^1H NMR spectrum by the disappearance of the signals of the ethoxy group and the vinyl chain and by the appearance of an ABX system. The two shielded protons of this system were coupled with a triplet which disappeared upon addition of D_2O, indicating the presence of a hydroxymethyl side chain. The ^{13}C NMR spectrum of **3** showed a methine signal and a methylene signal which confirmed the proposed structure.[10]

In order to create a 6-membered lactone, we first tried Kiely's method.[7] Dihydro-compound **2** was oxidized into the corresponding quinolone which was treated with HCl in acetic acid to give the 3-carboxylic acid without cyclization to the lactone. Previously, in order to obtain the 4'-*O*-demethyl derivative of **2**, we treated the latter with TMSI. Indeed, TMSI has been used for selective *O*-demethylation of hindered ether without cleavage of methylenedioxy group, ester function or lactone ring in epipodophyllotoxin series.[11] Surprisingly, quinolone **7** was obtained by "iodide" addition, demethylation and oxidation reactions in one pot and in excellent yield.

With these results in hand, we reasoned that we could elaborate a rapid synthesis of the 6-membered lactone by sequential treatment of **2** with TMSI then Ag_2O. Silver oxide could deplace iodine giving a hydroxy ester which might undergo spontaneous lactonization.[12] Treatment of **7** with Ag_2O afforded the hydroxy ester **8** which cyclized into lactone **9** after formation of the alcoholate. Thus, the desired lactone **9** [13] was synthezised in 3 steps from **2** but only in 27% overall yield.

For this reason, we then investigated an alternative preparation of **9** from **2** using anhydrous HBr in the first step. This agent is currently used in the epipodophyllotoxine series for 4'-*O*-demethylation.[14] In our case, side chain bromination and oxidation were observed, giving quinolone **5** which had not been demethylated. The same compound was obtained by reaction of TMSBr [15] with **2** at room temperature. In contrast, when the reaction was carried out at 0°C for only 4 h. , it was possible to isolate the 4-hydroxy-1,2-dihydroquinoline **4** in good yield. When treated with Ag_2O, both the bromo derivatives **4** and **5** led directly the quinolone lactone **6** without isolation of the intermediate hydroxy ester. It should be noted that in the case of compound **4** a concomitant oxidation of the heterocyclic system occurred. Lactone **9** was then obtained in good yield by demethylation of **6** with TMSI. Whatever the chosen experimental conditions for the first step, the second strategy represents an efficient method for preparing the desired quinolone lactone **9** in only 3 steps and in 51% overall yield starting from **2**. This scheme compares favorably with the previous strategy.[7]

The biological activity of these quinolone lactones will be reported in due course.

Acknowledgements : The authors would like to thank Dr. D. Bouzard and Dr. P. Rémuzon for helpful discussions. C. Clémencin-Le Guillou was supported by a fellowship from La Ligue Nationale Contre le Cancer.

References and Notes

1. D'Arpa, P.; Liu, F.L. *Biochim. Biophys. Acta.* **1989**, *989*, 163-177.
2. Potmesil, M.; Kohn, K.W. *DNA Topoisomerase in Cancer*; Oxford University Press : New York, **1991**.

3. Liu, F.L. *Ann. Rev. Biochem.* **1989**, *58*, 351-375.
4. Bouzard, D. *Recent progress in the chemical synthesis of antibiotics.* Lukacs, G.; Ohno, M.; Springer Verlag, Berlin, **1990**, p.249-283.
5. a) Elsea, S. H.; Osheroff, N.; Nitiss, J. L. *J. Biol. Chem.* **1992**, *267*, 13150-13153. b) Robinson, M. J.; Martin, B. A.; Gootz, T. D.; McGuirk, P. R.; Melinda, M.; Sutcliffe, J. A.; Osheroff, N. *J. Biol. Chem.* **1991**, *266*, 14585-14592. c) Wentland, M. P.; Lesher, G. Y.; Reuman, M.; Gruett, M. D.; Singh, B.; Aldous, S. C.; Dorff, P. H.; Rake, J. B.; Coughlin, S. A. *J. Med. Chem.* **1993**, *36*, 2801-2806. d) Kuo, G. H.; Eissenstat, M. A.; Wentland, M. P.; Robinson, R. G.; Klingbeil, K. M.; Danz, D. W.; Coughlin, S. A. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 399-404. e) Wentland, M. P.; Aldous, S. C.; Gruett, M. D.; Perni, R. B.; Powles, R. G.; Danz, D. W.; Klingbeil, K. M.; Peverly, A. D.; Robinson, R. G.; Corbett, T. H.; Rake, J. B.; Coughlin, S. A. *Ibid.* **1995**, *5*, 405-410. f) Eissenstat, M. A.; Kuo, G. H.; Weaver, J. D.; Wentland, M. P.; Robinson, R. G.; Klingbeil, K. M.; Danz, D. W.; Corbett, T. H.; Coughlin, S. A. *Ibid.* **1995**, *5*, 1021-1026.
6. Jardine, I. *Anticancer agents based on natural product model.* Cassady, J. M.; Douras, J. Eds ; Academic Press, NewYork, **1980**, p.319-351.
7. Kiely, J. S.; Huang, S.; Lesheski, L. E. *J. Heterocycl. Chem.* **1989**, *26*, 1675-1681.
8. All new compounds have been fully characterized and their spectral data are in accord with the proposed structures.
9. Compound **2** exists in $CDCl_3$ as a mixture of keto-ester and enol-ester in a 16/84 ratio.
10. **3** : amorphous; MS (CI), m/z : 442 (MH^+). ^1H NMR (DMSO-d_6, 500 MHz) δ(ppm) : 3.00 (ddd, J=12.7 Hz, 5.7 Hz, 2.8 Hz, CH_2OH), 3.61 (ddd, J=12.7 Hz, 5.7 Hz, 1.7 Hz, CH_2OH), 3.82 (s, OMe), 3.83 (s, OMe), 3.84 (s, OMe), 5.11 (t, J=5.7 Hz, OH), 5.40 (dd, J=2.8 Hz, 1.7 Hz, CH), 6.22 (m, OCH_2O), 6.55 (s, H-5 or H-8), 7.02 (d, J=2 Hz, H-2' and H-6'), 7.66 (s, H-5 or H-8). ^{13}C NMR (DMSO-d_6, 125.77 MHz) δ(ppm) : 57.34 (OMe), 57.46 (OMe), 59.85 (CH_2OH), 61.96 (OMe), 78.89 (CH), 98.67 (Ar), 103.48 (Ar), 103.99 (OCH_2O), 106.85 (Ar), 107.33 (Ar), 105.82, 124.03, 132.31, 139.79, 140.36, 147.40, 153.19, 154.71, 155.17, 164.56, 167.86, 171.70 (Cq).
11. Klein, L. L.; Yeung, C. M.; Chu, D. T.; McDonald, E. J.; Clement, J. J.; Plattner, J. J. *J. Med. Chem.* **1991**, *34*, 984-992.
12. Perrone, E.; Alpegiani, M.; Bedeschi, A.; Giudici, F.; Foglio, M.; Franceschi, G. *Tetrahedron Lett.* **1983**, *24*, 3283-3286.
13. **9** : mp. > 270°C (cyclohexane - ether). MS (ES), m/z : 412 (MH^+), 434 (MNa^+). ^1H NMR ($CDCl_3$, 300 MHz) δ(ppm) : 2.67 (t, J=6 Hz, CH_2), 3.92 (s, 2OMe), 4.20 (t, J=6 Hz, OCH_2), 5.95 (s, OCH_2O), 6.14 (s, H-5 or H-8), 6.90 (s, H-2' and H-6'), 7.30 (s, H-5 or H-8). ^{13}C NMR ($CDCl_3$, 75.45 MHz) δ(ppm) : 27.68 (CH_2), 56.39 (2OMe), 60.72 (OCH_2), 97.74 (Ar), 101.77 (Ar), 102.99 (OCH_2O), 105.55 (C-2' and C-6'), 104.92, 122.40, 132.75, 137.85, 138.66, 145.62, 151.31, 154.33, 155.88, 161.79, 172.18 (Cq).
14. Lee, K. H.; Imakura, Y.; Haruna, M.; Beers, S. A.; Thurston, L. S.; Dai, H. J.; Chen, C. H. *J. Nat. Prod.* **1989**, *52*, 606-611.
15. Bhatt, M. V.; Kulkarni, S. U. *Synthesis.* **1983**, 249-282.

(*Received in France* 22 *November* 1996; *accepted* 20 *December* 1996)