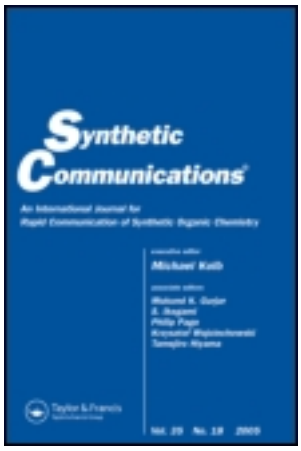


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Convenient Synthesis of Protoanemonin

Caroline Crey [a], Pascal Dumy [a], Jean Lhomme [a] & Mitsuharu Kotera [a]

[a] LEDSS-UMR5616 Associé au CNRS, BP53, Université Joseph Fourier, Grenoble, France

Published online: 16 Aug 2006.

To cite this article: Caroline Crey , Pascal Dumy , Jean Lhomme & Mitsuharu Kotera (2003) A Convenient Synthesis of Protoanemonin, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 33:21, 3727-3732, DOI: 10.1081/SCC-120025181

To link to this article: http://dx.doi.org/10.1081/SCC-120025181

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

SYNTHETIC COMMUNICATIONS®
Vol. 33, No. 21, pp. 3727–3732, 2003

A Convenient Synthesis of Protoanemonin

Caroline Crey, Pascal Dumy, Jean Lhomme, and Mitsuharu Kotera*

LEDSS-UMR5616 Associé au CNRS, BP53, Université Joseph Fourier, Grenoble, France

ABSTRACT

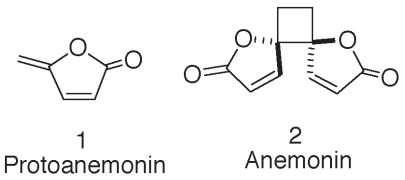
A new convenient synthesis of protoanemonin (**1**) starting from 2-deoxy-D-ribose (**3**) is described. A key step in the sequence is the successive β- and δ-eliminations of 3,5-di-*O*-*p*-toluoyl-2-deoxy-D-ribono-1,4-lactone (**6**).

Key Words: Protoanemonin; Synthesis; β- and δ-eliminations.

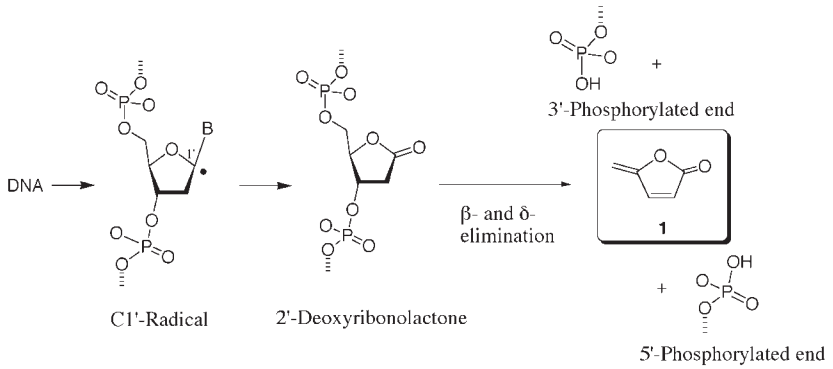
Protoanemonin [5-methylene-2-(5*H*)-furanone **1**] is the antibacterial principle of many plants belonging to Ranunculaceae family (e.g., buttercup).[1] This dieno γ-lactone is not stable and dimerizes spontaneously to

*Correspondence: Mitsuharu Kotera, LEDSS-UMR5616 Associé au CNRS, BP53, Université Joseph Fourier, 38041 Grenoble, France; Fax: 33.4.76.51.49.46; E-mail: mitsu.kotera@ujf-grenoble.fr.

DOI: 10.1081/SCC-120025181 0039-7911 (Print); 1532-2432 (Online)



Scheme 1.

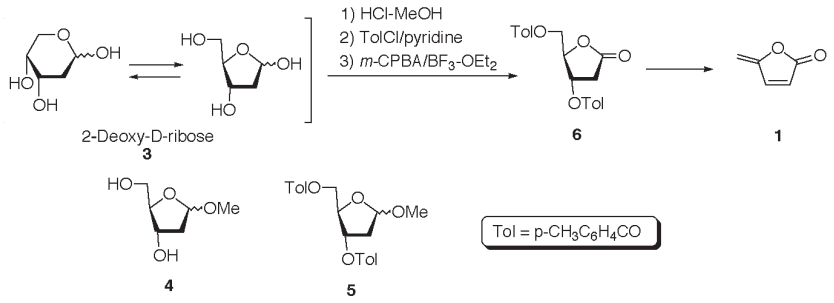


Scheme 2.

anemonin **2** via a head to head [2 + 2] cycloaddition in a regio and stereospecific manner.[2,3] Protoanemonin **1** has also shown to be synthetically useful as a C5 synthon for its reactivity particularly as a dienophile in Diels-Alder cycloadditions[4–7] (Sch. 1).

On the other hand, protoanemonin [5-methylene-2-(5*H*)-furanone **1**] is the by-product resulting from the cleavage of the 2-deoxyribonolactone lesion in DNA.[8–11] This abasic lesion is produced in a variety of DNA oxidative damaging processes including UV light and γ-irradiation or the action of chemical agents such as the ene-diyne antibiotic neocarzinostatin or metal complexes. This lactone lesion is alkali labile and is subject to successive β- and δ-elimination reactions leading to strand cleavage and formation of protoanemonin **1** (Sch. 2).

Several synthetic methods to prepare protoanemonin (**1**) have been reported in the literature.[12–16] In the two methods described earlier, levulinic acid was used as starting material. Although these methods have been widely used, they involve several tedious separation steps and some problems of reproducibility have been reported. More recently, Font and co-workers developed a method using photo-oxygenation of 5-hydroxymethylfurfuril.



Scheme 3.

In the course of our study of the 2-deoxyribonolactone lesion in DNA, protoanemonin **1** was required repeatedly as an authentic sample for analysis.[17,18] Because of the unstability of **1**, none of the above preparative methods was appropriate in this context, we thus devised a new efficient method to prepare protoanemonin **1** starting from 2-deoxy-D-ribose **3** (Sch. 3).

The lactone **6** was prepared from **3** using a three step procedure carried out successively without purification in a 58% overall yield. In the first stage of the transformation (**3**–**4**), glycosilation was achieved with methanolic hydrogen chloride prepared by adding acetyl chloride to methanol. The resulting mixture of the methylfuranoside anomers (**4**) was acylated by treatment with *p*-toluoyl chloride in pyridine to give **5**. The lactone **6** was obtained by oxidation of the methoxy sugar **5** by *m*-chloroperbenzoic acid in the presence of a catalytic amount of boron trifluoride etherate. This lactone **6** is a stable crystalline solid and can be stored at room temperature without special precaution.

Upon treatment of lactone **6** with 5 equiv. of NEt_3 at room temperature overnight, successive β- and δ-eliminations took place cleanly to afford protoanemonin **1** with 80% yield. The IR and NMR spectra of **1** were identical to those described in the literature.

In summary, we developed a new safe, convenient, and rapid synthetic entry to protoanemonin **1** by successive β- and δ-eliminations from the stable lactone **6**.

EXPERIMENTAL

All chemicals and solvents were used as purchased. All preparations were carried out in a hood. Melting points were measured on a

REICHERT THERMOVAR apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded on BRUKER AV300 spectrometers. NMR spectra were referenced to the residual solvent peak; chemical shifts δ in ppm; apparent scalar coupling constants J in Hz. IR spectra were recorded on Nicolet Impact 400. Elemental analyses were performed by "Service central d'analyse du CNRS."

3,5-Di-*O*-*p*-toluoyl-2-deoxy-D-ribono-1,4-lactone (6)

To a solution of 5.0 g (37.0 mmol) of 2-deoxy-D-ribose **3** in MeOH (60 mL) was added 1% methanolic hydrogen chloride (10 mL; prepared by adding 1.7 mL of acetyl chloride to 100 mL of MeOH). The reaction mixture was stirred at room temperature for 25 min and neutralized by adding solid sodium bicarbonate (2 g). After filtration, the methanol was removed by repeated coevaporation with pyridine (1×25 mL and 2×10 mL) under reduced pressure. The residual syrup was dissolved in pyridine (30 mL), cooled to 0°C and *p*-toluoylchloride (11 mL; 80 mmol) was added dropwise. The solution was stirred under argon at room temperature overnight. The reaction mixture was evaporated and diluted with $NaHCO_3$ saturated aqueous solution and extracted three times with CH_2Cl_2. The combined organic layers were washed with NH_4Cl saturated aqueous solution, then with KH_2PO_4 (5% aqueous solution), dried on $MgSO_4$ and evaporated.

To the resulting syrup in CH_2Cl_2 (60 mL) was added BF_3-Et_2O (1.6 mL, 10.9 mmol) and *m*CPBA (13.8 g, 80.0 mmol). The mixture was stirred overnight under argon. The solution was diluted in $NaHCO_3$ 0.5 M and stirred during 15 min. The mixture was extracted with CH_2Cl_2 (1×100 mL and 2×50 mL). The combined organic layers were washed with $NaHCO_3$ 0.5 M (50 mL) and dried on $MgSO_4$. After evaporation and recrystallization from hot AcOEt/cyclohexane (20:80; v/v) (100 mL), the lactone (**6**) was obtained as a white crystal in 52% yield. M.p.: 110–112°C. IR (KBr): $\nu = 1792, 1719, 1610, 1269, 1174, 1100, 753\ cm^{-1}$. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.89$ (m, 4H), 7.25 (m, 4H), 5.59 (m, 1H, H-3), 4.95 (m, 1H, H-4), 4.61 (m, 2H, H-5), 3.18 (dd, 1H, H-2, $J = 18$ and 7 Hz), 2.81 (dd, 1H, H-2′, $J = 18$ and 2 Hz), 2.42 (s, 6H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.7$ (two peaks, CH_3), 35.1 (C-2), 63.7 (C-5), 71.7 (C-3), 82.6 (C-4), 125.9, 126.3, 128.4, 129.4 (two peaks), 129.7, 129.8, 144.4, 144.8 (arom C), 165.8, 165.9 (C=O), 174.0 (C=O lactone). Anal. calcd. for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47. Found: C, 68.14; H, 5.58.

Protoanemonin (1)

To a solution of (**6**) (2.0 g; 5.0 mmol) in CH_2Cl_2 (25 mL), was added NEt_3 (2.73 g; 27.0 mmol). The mixture was stirred at room temperature overnight, washed with Na_2CO_3 1 M (4 × 20 mL) and dried on molecular sieves 4 Å. Column chromatography on silica gel (pentane/CH_2Cl_2; 1/2 as eluent) of the residual syrup afforded pure protoanemonin in 80% yield. IR (KBr): $\nu = 1781$, 1750, 1647, 1561, 1285, 1122, 1069, 972, 874, 823, 727 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.41$ (d, 1H, H-3, $J = 5$ Hz), 6.24 (d, 1H, H-2, $J = 5$ Hz), 5.24 (m, 1H, $=CH_E\underline{H_Z}$), 4.90 (d, 1H, $=C\underline{H_E}H_Z$, $J = 3$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 98.4$ ($=\underline{C}H_2$), 122.0 (C-4), 143.9 (C-3), 155.3 (C-5), 170.1 (C-2). Anal. calcd. for ($C_5H_4O_2$): C, 62.50; H, 4.20. Found: C, 61.72; H, 4.18.

REFERENCES

1. *The MERCK INDEX*, 12th Ed.; 8078.
2. Moriarty, R.M.; Romain, C.R.; Karle, I.L.; Karle, J. The structure of anemonin. J. Am. Chem. Soc. **1965**, *87*, 3251–3252.
3. Lustig, E.; Moriarty, R.M. Estimation of the angle of twist for a cyclobutane derivative by nuclear magnetic resonance. J. Am. Chem. Soc. **1965**, *87*, 3252–3253.
4. Bruckner, R. The synthesis of γ-alkylidenebutenolides. Current Organic Chemistry **2001**, *5*, 679–718.
5. Branchadell, V.; Font, J.; Moglioni, A.G.; Ochoa de Echagueen, C.; Oliva, A.; Ortuno, R.M.; Veciana, J.; Vidal-Gancedo, J. A biradical mechanism in the Diels-Alder reactions of 5-methylene-2(5*H*)-furanones: experimental evidence and theoretical rationalization. J. Am. Chem. Soc. **1997**, *119*, 9992–10003.
6. Tanaka, K.; Uchiyama, F.; Sakamoto, K.; Inubushi, Y. Stereocontrolled total synthesis of (±)-coriamyrtin. J. Am. Chem. Soc. **1982**, *104*, 4965–4967.
7. Roussel, C.; Fihi, R.; Ciamala, K.; Audebert, P.; Vebrel, J. Revisiting the addition of nitriloxides on protoanemonin. A new access to (2*E*)-3-(3′-arylisoxazol-5′-yl)propenoic acids. New J. Chem. **2000**, *24*, 471–476.
8. Chen, C.-h.B.; Milne, L.; Landgraf, R.; Perrin, D.M.; Sigman, D.S. Artificial nucleases. Chem. Bio. Chem. **2001**, *2*, 735–740.
9. Fujimoto, K.; Ikeda, Y.; Ishihara, S.; Saito, I. Deoxyribonolactone formation in photoirradiation of 5-bromouracil-containing oligo-

nucleotides by direct C1′ hydrogen abstraction. Tetrahedron Lett. **2002**, *43*, 2243–2245.
10. Pratviel, G.; Pitie, M.; Perigaud, C.; Gosselin, G.; Bernadou, J.; Meunier, B. Identification of sugar degradation intermediates in a metalloporphyrin-mediated DNA cleavage resulting from hydroxylation at C-5′. J. Chem. Soc., Chem. Commun. **1993**, 149–151.
11. Bose, R.N.; Moghaddas, S.; Mazzer, P.A.; Dudones, L.P.; Joudah, L.; Stroup, D. Oxidative damage of DNA by chromium(V) complexes: relative importance of base vs. sugar oxidation. Nucleic Acids Res. **1999**, *27*, 2219–2226.
12. Shaw, E. Synthesis of protoanemonin. Tautomerism of acetylacrylic acid and penicillic acid. J. Am. Chem. Soc. **1946**, *68*, 2510–2513.
13. Grundmann, C.; Kober, E. An improved synthesis of protoanemonin. J. Am. Chem. Soc. **1955**, *77*, 2332–2333.
14. Tsuboi, S.; Wada, H.; Mimura, S.; Takeda, A. A facile synthesis of γ-alkylidene-α,β-unsaturated γ-lactones. Chem. Lett. **1987**, 937–938.
15. Iovel, I.; Gol'dberg, Y.; Shimanska, M. A novel synthesis of protoanemonin by the catalytic vapor-phase oxidation of silvan. J. Chem. Soc., Chem. Commun. **1990**, 1079–1080.
16. Alibes, R.; Font, J.; Mula, A.; Ortuno, R.M. Studies on structurally simple α,β-butenolides. XI. A new and convenient synthesis of protoanemonin. Synth. Commun. **1990**, *20*, 2607–2615.
17. Roupioz, Y.; Lhomme, J.; Kotera, M. Chemistry of the 2-deoxyribonolactone lesion in oligonucleotides: cleavage kinetics and products analysis. J. Am. Chem. Soc. **2002**, *124*, 9129–9135.
18. Kotera, M.; Roupioz, Y.; Defrancq, E.; Bourdat, A.-G.; Garcia, J.; Coulombeau, C.; Lhomme, J. The 7-nitroindole nucleoside as a photochemical precursor of 2′-deoxyribonolactone: access to DNA fragments containing this oxidative abasic lesion. Chem.-Eur. J. **2000**, *6*, 4163–4169.

Received in the UK November 19, 2002