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STUDIES ON STRUCTURALLY SIMPLE α,β-BUTENOLIDES. IV. BEHAVIOUR OF PROTOANEMONIN AS ELECTROPHILE TOWARDS ALCOHOLS AND THIOLS.

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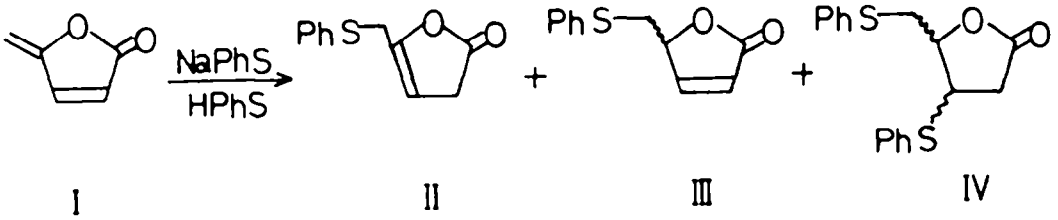
Abstract - Protoanemonin, reacts in different ways with thiolate and alkoxide anions. Thus, while the very soft nucleophile benzenethiolate attacks exclusively the olefinic carbons of 1, alkoxides always attack the carbonyl group in the first step of the reaction. In intermediate cases, when neither very hard nor very soft nucleophiles are used, regioselectivity is not observed. Mechanisms are discussedto explain this differential reactivity.

INTRODUCTION

In a recent paper[1], we have reported the behaviour of protoanemonin, 1, as acceptor towards PhS^-/PhSH in a 1,6-conjugate addition, to give compounds 2, 3 and 4. (Scheme 1).



Scheme 1

This behaviour of protoanemonin itself was not known. Previously, only the reaction of a few γ-ylidene-α,β-butenolides (excluding 1) with nucleophiles had been reported[2].

An extension of this study seemed necessary to account for the vesicant properties of protoanemonin[3], which might be related to its reactivity towards different nucleophiles present in the skin, mainly residual groups of aminoacids (-SH, -OH $-NH_2$, etc.).

On the other hand, potential carcinogenic activity of several unsaturated lactones has been correlated with the rate of reaction with cysteine[4] and glutathione[5]. It has been suggested that carcinogenic lactones might react enzymatically in the body tissues with thiols to give open chain thioester derivatives.

Therefore, we decided to carry out a systematic study of the reactivity of the protoanemonin, 1, with several kinds of nucleophiles. In this paper we explore the reaction of 1 with propanethiolate and phenylmethanethiolate, sulfur nucleophiles less soft than benzenethiolate, and three alkoxides (methoxide, n-butoxide and tert-butoxide), as hard nucleophiles.

RESULTS

Reaction with thiolates

Reaction of 1 with thiols in the presence of a catalytic amount of the corresponding thiolate is very fast and affords a complex mixture of products. Aside from much polymeric material, several compounds could be identified in the fractions resulting from column chromatography. This identification was important from the point of view of the mechanism of the reaction, but it was not intended to have preparative purposes.

Thus, reaction of 1 with one equivalent of propanethiol and a catalytic amount of lithium propanethiolate in dimethoxyethane at room temperature for ten minutes, afforded a crude material (20% weight loss) in which, after silica gel chromatography, four compounds could be identified by their ^{1}H NMR, IR and mass spectra. These compounds, never purified completely, were (see Scheme 2):

- 4-propylthio-5-propylthiomethyltetrahydrofuran-2-one, 4, (in ~10% yield). Its lactone structure was supported by IR (1790 cm^{-1}) and the presence of two PrS groups by mass spectrometry (M^+ = 248). One of the propylthio groups was bound to the exocyclic methylene carbon atom of 1 (m/z: 89 -PrSCH$_2$- and 159 (M^+-89), which excludes direct bonding of PrS to the ring) and the other at C-4 of the tetrahydrofuranone ring (a double triplet at δ 4.4 for the proton at C-5).
- S-Propyl cis-4-oxo-2-pentenethioate, 5, (~5%). This thioester was mainly identified by its IR (absorption at 1710 (CH_3CO-) and 1680 cm^{-1} (-COSPr)) and its ^{1}H NMR spectrum that showed, besides the propyl and methyl protons, two doublets at δ 6.09 and 7.20 (J = 15.1 Hz) corresponding clearly to a pair of cis olefinic protons.
- a γ-lactone (10%) (IR: carbonyl absorption at 1790 cm^{-1}) tentatively identified as 7a or 9a on the basis of its mass spectrum, which displayed again two PrS groups, but none of them linked to the exocyclic methylene carbon atom of 1 (absence of M^+ - PrSCH$_2$ peak). In its ^{1}H NMR spectrum, the presence of a three-proton singlet at δ 1.5 confirmed the latter point, while the absence of any absorption at δ 4.0 (characteristic for the C-5 proton in γ-lactones) gave support to our assumption that one of the PrS groups should be linked there. The position (C-3 or C-4) of the second PrS group could not be ascertained from the available spectral data.
- An open-chain thioester (IR: 1710 for ketone, 1685 for thioester; MS:m/z 248; ^{1}H NMR: a one-methyl singlet at 2.2 δ and several broad absorptions in the region 1.29 - 3.8 δ), tentatively identified as 6a or 10a. (~9%).

Reaction of 1 with one equivalent of phenylmethanethiol and a catalytic amount of lithium phenylmethanethiolate under conditions closely parallel to those described above gave likewise a saturated lactone, 7b or 9b, with 5-methyl-4-phenylmethylthio-5H-furan-2-one, 9, among other unidentified substances. The unsaturated lactone 11 was identified by its spectral properties. IR: 1780 cm^{-1} (γ-lactone); ^{1}H NMR ($CDCl_3$): δ 1.35 (d, J = 7 Hz, 3H, C_5-Me), 4.88 (dq, J_d = 7 Hz, J_q 1.2 Hz, 1H, C_5-H), 5.14 (d, J 1.2 Hz, 1H, C_3-H), 4.07 (s, 2H, PhCH$_2$-S) and 7.32 (m, 5H, C_6H_5).

Reaction with alkoxides

All the experiments were carried out by addition of the appropriate alcohol, containing a trace of sodium alkoxide, to a solution of 1 in the same alcohol used as reactant. Table 1 summarizes the experiments performed.

Thus, while reaction of 1 with 10 equivalents of methanol and catalytic sodium methoxide in dimethoxyethane did not take place, 1 reacted smoothly in methanol as solvent and sodium methoxide, giving methyl 2-methoxy-4-oxopentanoate, 6b, 5-methoxy-5-methyl-5H-furan-2-one, 8a, [(^{1}H NMR in $CDCl_3$: δ1.66 (s, 3H), 3.26 (s, 3H), 6.13 (d, J = 5.3 Hz, 1H), 7.15 (d, J = 5.3 Hz, 1H); IR: 1780 cm^{-1})] and methyl 3-methoxy-4-oxopentanoate, 10b. Butenolide 8a seems to be an intermediate in the formation of the open-chain ester 10b, since a longer addition time (total time had no influence) left unaltered the proportion of ester 6b in the crude reaction mixture, while the ratio 10b/8a increased. Moreover, a mixture containing butenolide 8a and ester 10b was submitted to the reaction conditions, yielding, after a few minutes, only the ester 10b.

Protoanemonin (1), also reacted with sodium n-butoxide in n-butanol to afford n-butyl 2-n-

butoxy-4-oxopentanoate, 6c, and 5-n-butoxy-5-methyl-5H-furan-2-one (8b). In this case the butenolide 8b did not form the open-chain ester 10b on further action of sodium n-butoxide in n-butanol.

Table 1. Reactions of protoanemonin with alkoxides

Reactant[b]	Equivalents of ROH	Reaction conditions[a] Solvent	Total[c] time	Addition time (c)	Yield (%)	Crude compos.[d] 6	8	10
MeO^-/MeOH	Excess	MeOH	10	5	45	18	40	42
"	"	"	40	10	55	18	12	70
"	"	"	20	15	40	20	traces	80
n-BuO-/n-BuOH	"	n-BuOH	60	10	48	10	90	--

(a) All experiments were carried out under argon, at room temp.
(b) The alkoxides were always used in catalytic quantities.
(c) In minutes.
(d) % Molar ratio calculated from ^1H NMR spectra.

Finally, starting material was quantitatively recovered after treatment of protoanemonin with tert-butanol under catalysis by sodium tert-butoxide.

Assignment of structures of both isomeric methyl esters 6b and 10b was made on the basis of their ^{13}C NMR spectra. Data corresponding to observed and calculated[6] chemical shifts are given in Table 2. Comparison of these data with those of n-butyl ester 6c confirmed the proposed structure for the latter.

Table 2. ^{13}C NMR chemical shifts for esters 6b, 6c and 10b in $CDCl_3$

Compound	Chemical shift (δ)	C_1	C_2	C_3	C_4	C_5	$\delta_{C_2}-\delta_{C_3}$	Δ[a]	$\delta_{C_4}-\delta_{C_1}$	Δ
10b	Observed	170.6	36.2	83.1	208.7	25.7	46.9	1.6	38.1	0.4
	Calculated[b]	173.3	37.5	86.0	211.8	20.9	48.5		38.5	
6b	Observed	172.2	76.2	46.0	204.4	30.4	30.2	3.2	32.2	0.3
	Calculated	175.7	75.2	48.2	207.6	27.1	27.0		31.9	
6c	Observed	172.1	75.1	46.2	204.7	30.7	28.9	1.8	32.6	0.7
	Calculated	175.7	79.8	50.7	207.6	27.1	29.1		31.9	

(a) Absolute difference $(\delta_{C_i}-\delta_{C_j})_{obs}-(\delta_{C_i}-\delta_{C_j})_{calc}$; (b) see ref. 6

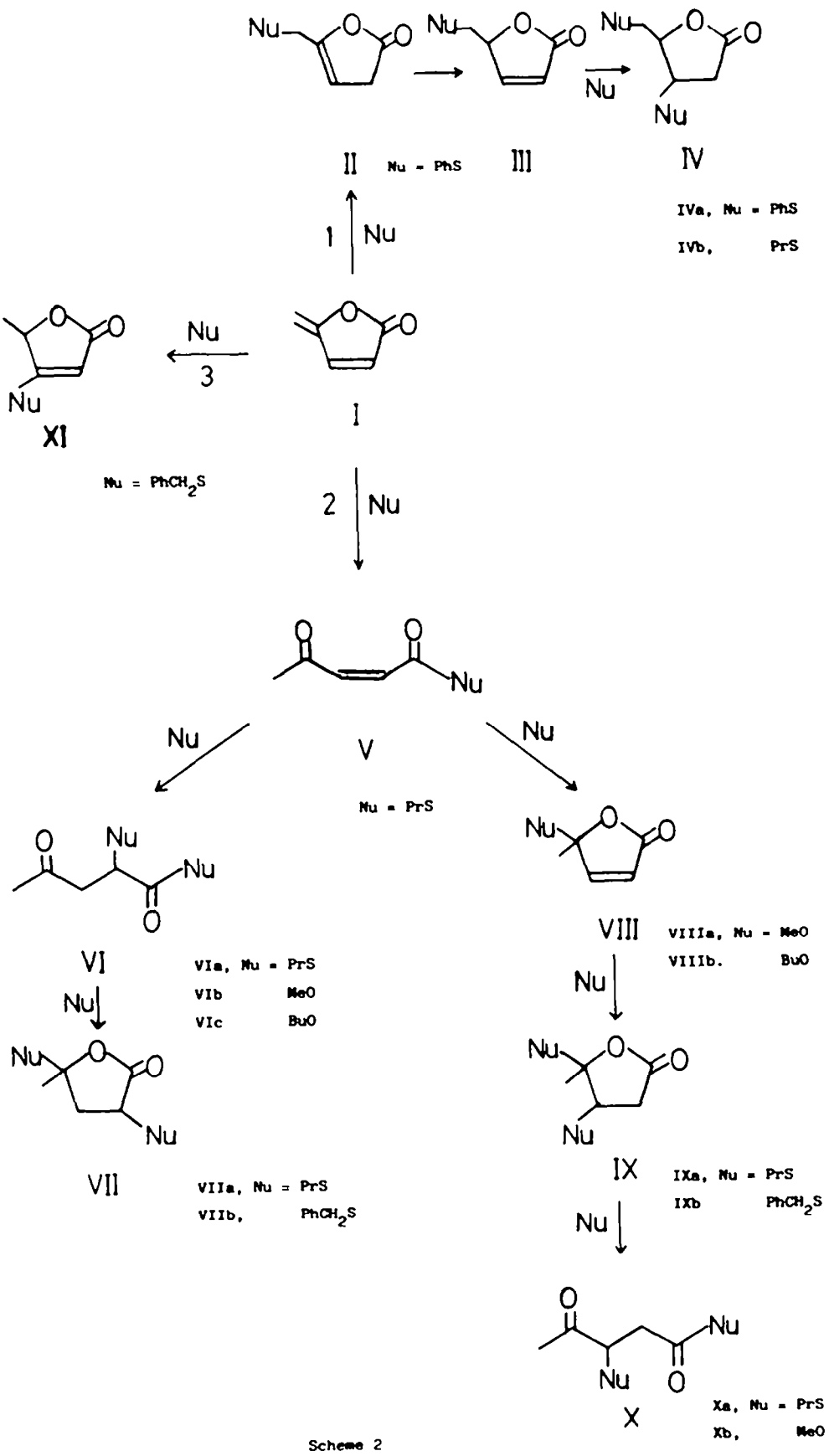
DISCUSSION

Scheme 2 shows pathways to explain the formation of the identified products. Pathway 1 leads to products formed through an initial attack of the nucleophile to the exocyclic methylene carbon atom of 1 (1,6-conjugate addition). Pathway 2 produces compounds resulting from an initial attack to the carbonyl carbon and having a common precursor, the α,β-unsaturated-γ-ketoester 5 (ring opening), which was detected only when PrS^- was used as nucleophile.

Formation of butenolide 11 (pathway 3) can be justified through a 1,4-conjugate addition since protoanemonin, as an enol lactone, should have also an electronic deficiency at C-4: the intermediate forms 11 through a furan-2-ol structure (Scheme 3).

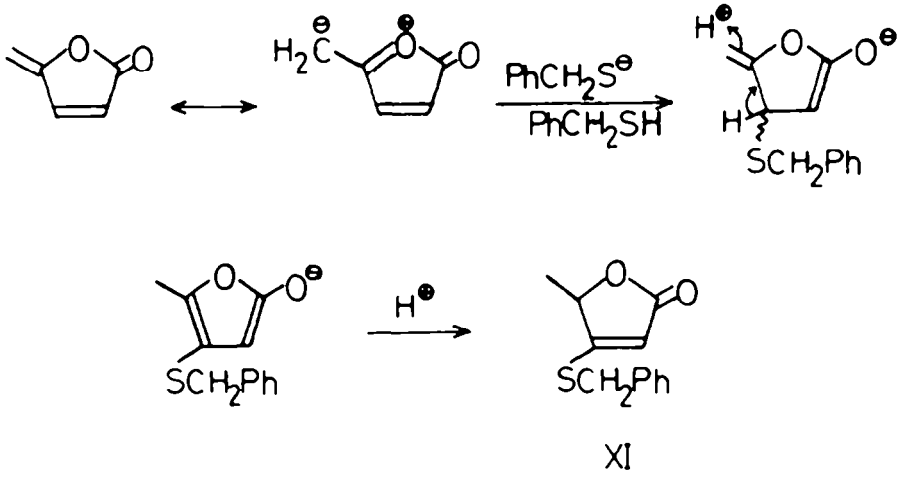
The α,β-unsaturated-γ-ketoester 5 can undergo further transformation in two different ways:

i) Michael addition of a second equivalent of nucleophile, giving the α-substituted-γ-ketoester 6, followed by catalytic ring closure initiated by attack of the nucleophile to the ketone carbonyl, leading to a 3,5-disubstituted saturated lactone 8 (Scheme 4, equation 1).


II Nu = PhS
III
IV
IVa, Nu = PhS
IVb, PrS
1 Nu
Nu
3
XI
Nu = PhCH2S
I
2 Nu
V
Nu = PrS
VI
VIa, Nu = PrS
VIb MeO
VIc BuO
VII
VIIa, Nu = PrS
VIIb, PhCH2S
VIII
VIIIa, Nu = MeO
VIIIb. BuO
IX
IXa, Nu = PrS
IXb PhCH2S
X
Xa, Nu = PrS
Xb, MeO

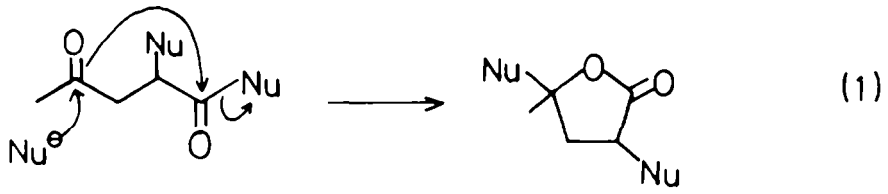
Scheme 2

ii) Ring closure, through a mechanism like that proposed for the formation of lactone 7, would afford a butenolide, 8, that could undergo a Michael addition, giving a 4,5-disubstituted saturated lactone, 9. Ring-opening by attack of the nucleophile to the carbonyl of 9, and elimination of Nu from C-5, would yield the β-substituted-γ-ketoester 10 (Scheme 4, equation 2).

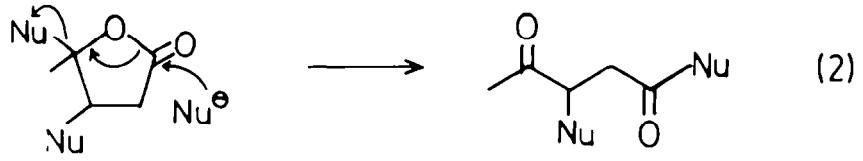


XI

Scheme 3



VI VII

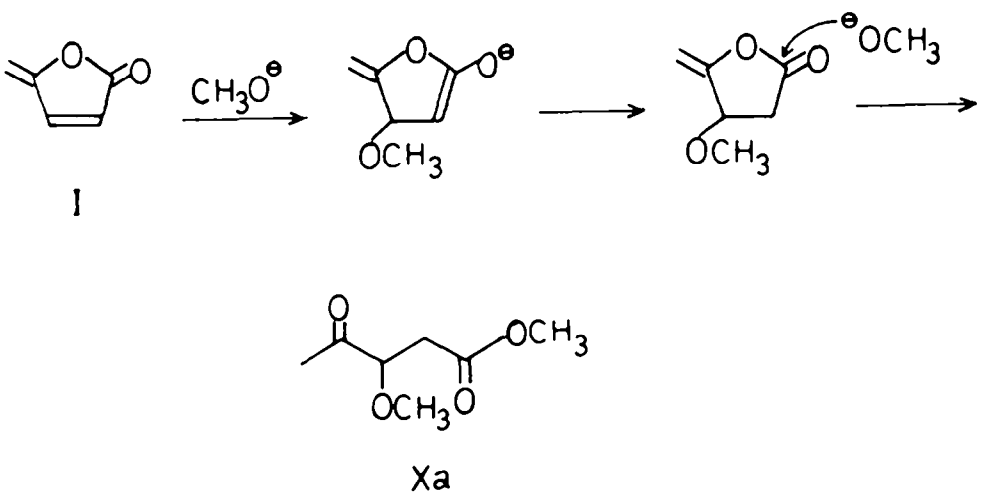


IX X

Scheme 4

Our results indicate that protoanemonin reacts differently at its three electrophilic centers, acting as an internal probe in a kind of measure of the hardness of the nucleophile used. At least this is true for the extreme cases, where a great regioselectivity is observed. While the softest, PhS^-, gives only cyclic products (irrespective of the counterion, sodium or lithium) arising from initial 1,6-conjugate addition (open-chain products have never been detected), the hardest nucleophiles, MeO^- and $n\text{-}BuO^-$, give products that can only be accounted for by initial attack to the lactone carbonyl, through a common precursor 5. This assumption is based on the constant ratio found for 6b and 8a+10b (see Table 2) when MeO^- is used and also supported by the role of butenolide 8a as the intermediate leading to 10b. This rules out an alternative mechanism to explain the formation of 10b starting by a 1,4-conjugate addition, which furthermore would not ex-

plain the formation of 8a (Scheme 5)



Scheme 5

Although 5 was not detected when hard nucleophiles were used, we have been able to identify it when the nucleophile was PrS^-, which has a nucleophilic strength intermediate between PhS^- and MeO^-. In fact in this case both 1,6- and carbonyl addition took place, giving all the products arising from pathways 1 and 2. The analogous $PhCH_2S^-$ nucleophile also gave a very complex mixture of compounds from which we have been able to detect compound 11 (Scheme 2, pathway 3). Probably with these nucleophiles all three pathways were operative, but the analytical conditions for the final mixtures prevented the observation of all their products. The information that we have is then complementary.

In conclusion, protoanemonin reacts smoothly with nucleophiles, through several pathways that involve different mechanisms and presumably also different rates. The products found are the results of competition of such processes in consuming the added nucleophile. The effect of this competition is much more evident when neither very hard not very soft nucleophiles are used.

Studies on the reacttion of 1 with nucleophiles bearing a negative charge on carbon, nitrogen and phosphorus are in progress.

EXPERIMENTAL

The GC-MS spectra were recorded with a Hewlett-Packard apparatus, model 5985 B, working at 70 eV. The infrared spectra were recorded on a Perkin-Elmer Spectrophotometer, model 720. The 80 MHz ^1H NMR and 20 MHz ^{13}C NMR spectra were recorded on a Bruker Spectrometer, model WP 80 SY; chemical shifts are given in parts per million relative to TMS (δ scale).

Reaction of protoanemonin (1) with sodium benzenethiolate/benzenethiol - See ref. 1.

Reaction of 1 with lithium propanethiolate/propanethiol -

A tipycal experiment was run as follows:

to a solution of propanethiol (274 mg, 3.6 mmol) in anhydrous dimethoxyethane (10 ml), a 1,6 M ethereal methyllithium (0.22 ml, 0.34 mmol) was added under argon atmosphere. The resulting mixture was added dropwise, under argon, to a stirred solution of protoanemonin (1) (350 mg, 3.6 mmol) in anhydrous dimethoxyethane (15 ml). After ten minutes, the reaction mixture was diluted with CH_2Cl_2 and washed with water. The aqueous layer was extracted (CH_2Cl_2) and the combined organic extracts were dried (Na_2SO_4) and the solvent evaporated at reduced pressure. The residue (500 mg) was chromatographed on silica gel eluting with mixture of hexane-EtOAc (from 95:5 to 1:9 ratio) affording fractions in which the following compounds were identified:

S-Propyl 4-oxo-2-propylthiopenthanethioate (6a) or its isomer S-propyl 4-oxo-3-propylthiopenthanethioate, (10a). ^1H NMR ($CDCl_3$), 0.88 (t, J = 7 Hz; 6H); 1.29-1.67 (m, 4H); 2.2 (s, 3H) and 2.4-3.8 (m, 7H); IR ($CHCl_3$), 3040, 3000, 2950, 1710, 1685, 1460, 1400, 1360, 1300, 1210, 1200, 1160, 1080 and 1020 cm^{-1}; MS, m/z (%) 248 (M^+, 7), 205 (11), 177 (55), 172 (70), 163 (18), 145 (15), 131 (7), 103 (43), 97 (71), 89 (10), 72 (12) and 43 (100).

S-Propyl cis-4-oxo-2-pentenethioate (5), a major compound in one fraction of the chromatography, could not be isolated. ^{1}H NMR ($CDCl_3$), 0.88 (t, J = 7 Hz; 3H); 1.29–1.67 (m, 2H); 2.2 (s, 3H); 6.09 (d, J = 5.1 Hz; 1H) and 7.20 (d, J = 5.1 Hz; 1H); IR (film), 1710 and 1680 cm^{-1}.

5-Methyl-3,5-dipropylthiotetrahydrofuran-2-one (7a), or its isomer 5-methyl-4,5-dipropylthiotetrahydrofuran-2-one (9a). It was not possible to purify it completely. ^{1}H NMR ($CDCl_3$), 0.88 (t, J = 7 Hz; 6H); 1.35–1.60 (m, 4H); 1.50 (s, 3H); 2.32–2.85 (m, 6H) and 3.7 (dd, J = 8.2 Hz, J' = 6.4 Hz; 1H); IR ($CHCl_3$), 1790 cm^{-1}; GC-MS, m/z (%) 172 (M^+ - PrSH, 10), 130 (6), 129 (7), 115 (6), 102 (11), 97 (12), 85 (55), 71 (10), 57 (36) and 43 (100).

4-Propylthio-5-propylthiomethyltetrahydrofuran-2-one (4b), identified in a fraction by the following spectroscopic data: ^{1}H NMR ($CDCl_3$), 4.4 (dt, J = 6.4, J' = 4.7 Hz; 1H); IR ($CHCl_3$), 1790 cm^{-1}; GC-MS, m/z (%) 248 (M^+, 5), 172 (M^+ - PrSH, 100), 159 (M^+ - $PrSCH_2$, 47), 145 (30), 131 (28), 117 (55),89 (40), 55 (35) and 43 (55).

Reaction of 1 with lithium phenylmethanethiolate/phenylmethanethiol - Operating as described above, reaction of protoanemonin (1), (160 mg, 1.6 mmol) with lithium phenylmethanethiolate (0.16 mmol) and phenylmethanethiol (207 mg, 1.67 mmol) in anhydrous dimethoxyethane, afforded 330 mg of a crude material that was chromatographed on silica gel begining with hexane-EtOAc (85:15) and ending with 100 % EtOAc as eluent. Among other unidentified substances, the following compounds were detected:

5-Methyl-3,5-diphenylmethylthiotetrahydrofuran-2-one (7b), or its isomer 5-methyl-4,5-diphenylmethylthiotetrahydrofuran-2-one (9b). ^{1}H NMR ($CDCl_3$), 1.53 (s, 3H); 2.0–3.0 (m, 3H); 3.70 (s, 2H); 3.75 (s, 2H) and 7.14–7.38 (m, 10 H); IR (film), 1780 cm^{-1}.

5-Methyl-4-phenylmethylthio-5H-furan-2-one (11). ^{1}H NMR ($CDCl_3$) 1.35 (d, J = 7 Hz; 3H); 4.07 (s, 2H); 4.88 (dq, J = 7 Hz, J' = 1.2 Hz; 1H); 5.64 (d, J = 1.2 Hz; 1H) and 7.32 (m, 5H); IR (film), 1780 cm^{-1}; GC-MS, m/z (%) 220 (M^+, 3), 180 (0.8), 151 (10), 91 (100), 65 (17) and 43 (19).

Reaction of 1 with sodium methoxide/methanol - To a stirred solution of protoanemonin (1), (430 mg, 4.5 mmol) in 2.5 ml of absolute methanol containing traces of sodium methoxide was added, under Ar, over 10 min. The mixture was allowed to stand for 30 min, then diluted with $CHCl_3$ and washed with water. The aqueous layer was extracted with $CHCl_3$ and the combined organic extracts were dried (Na_2SO_4) and the solvent was removed at reduced pressure. The crude (350 mg) contained compounds 6b, 7a and 10b in 70:12:18 ratio, calculated from its ^{1}H NMR spectrum. Column chromatography on silica gel with CH_2Cl_2–ether (4:1) as eluent afforded the following products:

Methyl 2-methoxy-4-oxopentanoate, 6b. ^{1}H NMR ($CDCl_3$), 2.17 (s, 3H); 2.82 (d, J = 6.3 Hz, 2H); 3.44 (s, 3H); 3.75 (s, 3H); 4.23 (t, J = 6.3 Hz; 1H); ^{13}C NMR ($CDCl_3$), 30.4, 46.0, 51.9, 58.6, 76.3, 172.2 and 204.2; IR (film), 3050, 3010, 2880, 1750, 1720, 1450, 1360, 1270, 1200, 1160, 1130 and 800 cm^{-1}; MS, m/z (%) 160 (M^+, 0.3), 145 (0.4), 128 (15), 117 (15), 101 (46), 85 (5), 75 (9), 59 (14) and 43 (100).

Methyl 3-methoxy-4-oxopentanoate (10b). ^{1}H NMR ($CDCl_3$), 2.26 (s, 3H); 2.70 (d,J = 5.8 Hz; 2H); 3.44 (s, 3H); 3.72 (s, 3H) and 4.00 (t, J = 5.8 Hz; 1H); ^{13}C NMR ($CDCl_3$), 25.7, 36.2, 51.6, 58.4, 83.1, 170.6 and 200.7; IR (film), 3020, 2980, 2850, 1740, 1720, 1440, 1360, 1260, 1200, 1160, 1010 and 800 cm^{-1}; MS, m/z (%) 160 (M^+, 0.2), 130 (10), 120 (6), 117 (32), 97 (19), 87 (8), 75 (100), 59 (31) and 43 (34).

5-Methyl-5-methoxy-5H-furan-2-one (7a), it was obtained from the chromatography contaminated by 6b and 10b. ^{1}H NMR ($CDCl_3$), 1.66 (s, 3H); 3.26 (s, 3H); 6.13 (d, J = 5.3 Hz; 1H); 7.15 (d, J = 5.3 Hz; 1H); IR (film), 1780 cm^{-1}; MS, m/z (%) 129 (M^+, 0.6), 113 (61), 97 (100), 85 (20), 69 (15), 54 (21), 43 (45).

Reaction of 1 with sodium n-butoxide - To a stirred solution of protoanemonin (1),(211 mg, 2.2 mmol) in 2 ml of anhydrous n-butanol, 2 ml of n-butanol containing traces of sodium n-butoxide was added under Ar, over 10 min. The mixture was allowed to stand for 1 hour, then diluted with CH_2Cl_2 and washed with water. The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts were dried (Na_2SO_4). The solvent was removed at reduced pressure to afford 187 mg of a crude, that chromatographed on silica gel afforded 140 mg of 8b and 25 mg of 6a.

5-n-butoxy-5-methyl-5H-furan-2-one (8b). ^{1}H NMR ($CDCl_3$), 0.86 (m, 3H); 1.23–1.58 (m, 6H); 1.63 (s, 3H); 3.17–3.53 (m, 2H); 6.13 (d, J = 5.3 Hz, 1H); 7.15 (d, J = 5.3 Hz); ^{13}C NMR ($CDCl_3$), 13.6, 19.0, 23.8, 31.5, 63.7, 109.0, 123.7, 154.5 and 170.0; IR (film), 2960, 2940, 2880, 1770, 1380, 1340, 1270, 1180, 1100 and 800 cm^{-1}; MS, m/z (%) 155 (M^+ -15, 5), 127 (4), 11 (2), 97 (100), 69 (4), 57 (5) and 43 (23).

n-Butoxy 2-butoxy-4-oxopentanoate (6a). ^{1}H NMR ($CDCl_3$), 0.75–1.00 (m, 6H); 1.20–1.70 (m, 8H); 2.13 (s, 3H); 2.74 (d, J = 5.3 Hz, 1H); 2.75 (d, J = 7 Hz; 1H); 3.25–3.63 (m, 2H), 4.09 (t, J = 6.6 Hz; 2H); 4.22 (dd, J = 7 Hz, J' = 5.3 Hz; 1H); ^{13}C NMR ($CDCl_3$), 13.5, 13.7, 19.1, 19.2, 30.7 (two peaks), 31.7, 46.2, 64.9, 71.1, 72.1 and 204.7; IR (film), 3020, 2980, 2900, 1740, 1715, 1460, 1400, 1360, 1260, 1210, 1160, 1120, 1080, 1020 and 910 cm^{-1}; MS, m/z (%) 244 (M^+, 0.6), 201 (1.1), 187 (1), 172 (12), 143 (37), 129 (18), 87 (100), 73 (7), 57 (28) and 43 (75).

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