Tetrahedron Vol 44, No. 4, pp. 1267 to 1272, 1988
Printed in Great Britain.

0040-4020/88 $3.00+.00

ISOXAZOLES-MEDIATED SYNTHESIS OF GEIPARVARIN AND DIHYDROGEIPARVARIN

P.G.BARALDI[a], A.BARCO[b], S.BENETTI[b], A.CASOLARI[a], S.MANFREDINI[a], G.P.POLLINI[a] and D.SIMONI[a]

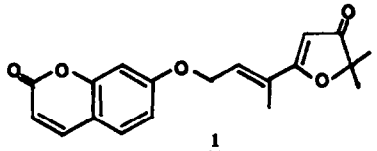
[a]Dipartimento di Scienze Farmaceutiche-Università di Ferrara

[b]Dipartimento Chimico-Università di Ferrara

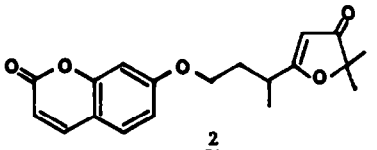
(*Received in UK* 30 *November* 1987)

Abstract - A new synthesis of geiparvarin 1 and its dihydroderivative 2, two naturally occurring antitumor agents, possessing the 3(2H)-furanone ring system central structural feature, is described. The synthetic design is based on the use of suitably substituted isoxazole derivatives, the heterocyclic ring acting as masked 1,3-diketone moiety.

Geiparvarin 1 and dihydrogeiparvarin 2 are members of a vast family of naturally occurring compounds containing the 3(2H)-furanone moiety as key central element.



1



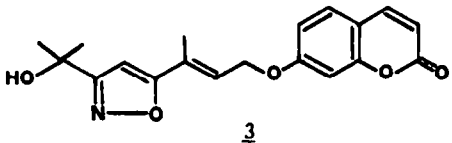
2

The presence of an uncommon system with extensive functionalization as well as the interesting biological activity[1], make these compounds challenging targets of synthesis. Consequently considerable effort has been mounted in this direction and a number of different approaches have appeared in the recent literature.[2a-h] In connection with our interest in developing new synthetic applications of 3,5-disubstituted isoxazoles as building blocks in the synthesis of natural products[3], we have recently described in preliminary form[2f] a convenient method for the synthesis of geiparvarin, featuring the use of the isoxazole template as a masked form of the 3(2H)-furanone ring system. This paper reports the details of the synthesis of 1 as well as the extension of the methodology to the preparation of the related dihydrogeiparvarin 2, a natural compound not yet synthetized, isolated from the fruit of Geijera Parviflora Lindl (Rutaceae)[4].

Our strategy is based on the well-established acid-promoted cyclodehydration[5] of an α'-hydroxy-1,3-diketone moiety as a convenient entry to 3(2H)-furanone system.

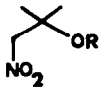
On the other hand the reductive conversion of a 3,5-disubstituted isoxazole to an 1,3-diketone is well known since the end of the last century.[6]

Accordingly we envisaged the intermediate **3**, incorporating the complete carbon atom framework of both **1** and **2**, of pivotal importance for the success of our strategy.

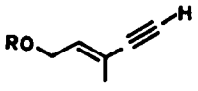


3

The isoxazole scaffold destined to become the 3(2H)-furanone part of the target compounds could be assembled through 1,3-dipolar cycloaddition between two readily available precursors, namely the primary nitroderivative **4b**, easily accessible by protection of the hydroxyl function[7] of the Henry adduct **4a** between acetone and nitromethane and the commercially available enyne **5a**.



4a R=H
4b R=SiMe$_3$

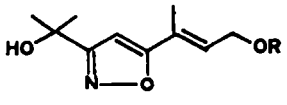


5a R=H
5b R=Ac
5c R=Me$_2$SiBu^t

The choiche of the latter is particularly valuable since it possesses three suitably located functionalities of crucial importance: i) the triple bond serves as the dipolarophile center in the highly regioselective carbon-carbon bond forming cycloaddition step to produce the isoxazole nucleus, the unactivated trisubstituted olefin being not useful as reaction partner in intermolecular cycloaddition employing aliphatic nitrile oxides; ii) the double bond, with the required E-geometry is placed in the appropriate position as in the target **1**, allowing to overcome the difficult task encountered in other approaches for its introduction, while its saturation will serve, of course, for the synthesis of **2** too; iii) finally the allylic hydroxyl function is a suitable handle for the attachment of coumarin nucleus.

Thus the nitrile oxide generated from **4b** under standard Mukaiyama conditions[8] cycloadded regio- and chemoselectively into the acetyl derivative **5b** to produce in 85% overall yield, after aqueous acetic acid removal of the trimethylsilyl protecting group, the 3,5-disubstituted isoxazole **6a**.

Removal of the acetyl protecting group by treatment at 20°C with lithium hydroxide solution (MeOH/H$_2$O; 9:1) produced **6b** in excellent yield.



6a R=Ac
6b R=H
6c R=SO$_2$Me
6d R=Me$_2$SiBu^t

The primary hydroxyl group reacted selectively with methansulfonyl chloride in the presence of triethylamine to afford the corresponding crude mesylate **6c**, which, on treatment with 7-hydroxycoumarin in the presence of lithium bromide gave rise to a 75% yield of the key intermediate **3**.

The latter has been also obtained directly from **6b** in 61% yield in a clean condensation promoted by triphenyl phosphine-diethylazodicarboxylate condensation

system.[9]

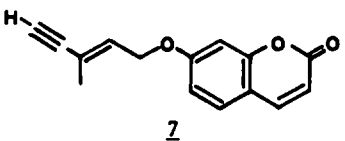
Attempts to prepare 3 by cycloaddition of the nitrile oxide derived from 4b to the alkylated coumarin 7[2c] furnished only a moderate yield of 3.

At this point the stage was set for the unmasking of the isoxazole nucleus to reveal the latent 1,3-diketone precursor of the 3(2H)-furanone system.

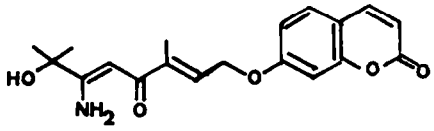
The catalytic hydrogenolysis conditions[10] commonly employed to achieve the cleavage of the labile N-O bond are unsuitable in our case, at least for the synthesis of 1, owing to the presence of a different reducible functional group.

However several types of non-hydrogenolytic methods for the ring opening of isoxazoles have been recently developed.

Among them the protocol introduced by Nitta[11] involving the use of molybdenum hexacarbonyl in wet acetonitrile, allowed the reductive cleavage of the isoxazole moiety of 3, furnishing a 92% yield of the expected enaminone 8.



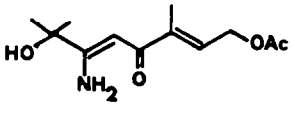
7



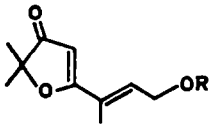
8

On exposure of 8 to acetic acid at 0°C for 4h an easy cyclodehydration took place affording 1 in 95% yield.

Application of the same sequence to 6a, namely a) $Mo(CO)_6$ promoted ring opening to give 9; b) acid-catalyzed cyclodehydration to 10a; c) basic hydrolysis of the ester group, furnished in 31% overall yield the known intermediate 10b, already taken to 1 by Raphael et al.[2c]



9



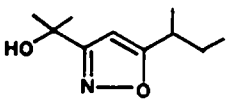
10a R=Ac

10b R=H

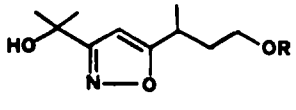
The extension of this strategy to dihydrogeiparvarin 2, a compound exhibiting significant biological activity in vitro against human carcinoma cells of the nasopharynx[4], required simply the saturation of the double bond.

This task proved more capricious than we suspected.

Attempts at achieving the saturation of the double bond of the key intermediate 3 as well as its precursors 6a and 6b were unsuccessful under different conditions, the main product isolated being 11.



11



12a R=Me_2SiBu^t

12b R=H

In order to overcome this drawback it was deemed necessary to select a different protecting group for the allylic hydroxyl function of 5, less prone than the ester group to hydrogenolysis.

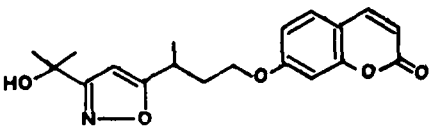
Thus we transformed 5 into the corresponding dimethyl-tert-butylsilyl ether 5c by standard procedure.

Cycloaddition between 4b and 5c proceeded without events to produce the isoxazole 6d in 82% yield after selective desilylation of the tertiary hydroxyl group by treatment with citric acid in methanol for 24h at room temperature.

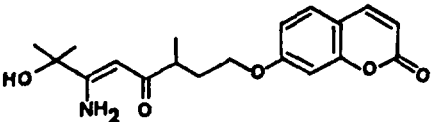
The saturation of the double bond of 6d to give 12a was cleanly accomplished by catalytic reduction over 10% Pd/C leaving the isoxazole ring untouched.

The residual protecting group was then removed by treatment with 10% aqueous hydrochloric acid to furnish the diol 12b, which was connected to the 7-hydroxycoumarin moiety through the employment of triphenylphosphine-diethylazodicarboxylate as condensation system.

The saturated analog 13 of 3 was finally converted to the target 2 in more than 90% overall yield by sequential treatment with $Mo(CO)_6$ in wet acetonitrile to cleave the heterocyclic ring followed by aqueous acetic acid promoted cyclodehydration of the derived enaminone 14.



13



14

As a conclusive remark we underline that the synthetic design to both 1 and 2 is likely to afford the opportunity of wider applicability to synthetize analogues for evaluating the biological properties, allowing to trace the profile of structure-activity relationship of this interesting class of compounds.

EXPERIMENTAL

Melting points and boiling points are uncorrected. Reaction courses and product mixtures were routinely monitored by thin-layer chromatography (TLC) on silica gel precoated F_{254} Merck plates. Infrared (IR) spectra were measured on a Perkin Elmer 297 spectrometer. Nuclear magnetic resonance (^{1}H NMR) spectra were obtained with a Brucker 200 spectrometer for solutions in $CDCl_3$ and peak positions are given in parts per million downfield from tetramethylsilane as an internal standard. All drying operations were carried out with anhydrous magnesium sulphate. Light petroleum refers to the fractions boiling range 40-60°C and ether to diethyl ether. CHN analysis was provided by Chemistry Department.

Starting materials. Compound 4b has been prepared according to known[7] directions. Compounds 5b (b.p. 65°C/18 torr) and 5c (b.p. 88°C/12 torr.) were prepared from 5a by standard procedures.

5-[(E)-3-(Acetyloxy)-1-methyl-1-propenyl]-α,α-dimethyl-3-isoxazolemethanol 6a

To a solution of 4b (10 g, 52 mmol) and 5b (21.5 g, 156 mmol) in dry benzene (30 ml) containing triethylamine (0.5 ml) phenylisocyanate (14.1 ml, 130 mmol) in benzene (10 ml) was added dropwise at room temperature, and the mixture was allowed to stand overnight. The cooled mixture (5°C) was filtered, the filtrate washed with 2% aqueous ammonia (2x50 ml) and brine (3x50 ml), dried and concentrated in vacuo. The residue crude oil dissolved in methanol (200 ml) was stirred for 0.5h with 5% HCl (50 ml). Most of methanol was removed in vacuo, the residue was poured into water (100 ml), and extracted with Et_2O (3x100 ml).

The extracts were washed with brine (2x30 ml), dried, and concentrated. The residue was flash chromatographed on silica gel (ether/light petroleum, 2:8) to give 6a as an oil (10.6 g, 85%); IR (neat): 3420, 1740, 1640, 1570 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.6 (s, 6H); 2.07 (d, 3H, J=1.2Hz); 2.1 (s, 3H); 3.35 (brs, 1H); 4.8 (d, 2H, J=6.5Hz); 6.27 (s, 1H); 6.35 (brt, 1H, J=6Hz). $C_{12}H_{17}NO_4$ requires C, 60.24; H, 7.16; N, 5.85. Found C, 60.15; H, 7.05; N, 5.76.

5-[(E)-3-Hydroxy-1-methyl-1-propenyl]-α,α-dimethyl-3-isoxazolemethanol **6b**

Lithium hydroxide monohydrate (4.2 g, 100 mmol) was added at -10°C to a stirred solution of **6a** (20 g, 83 mmol) in methanol (200 ml) containing 30 ml of water.

After 10 min. at 0°C the solution was concentrated in vacuo, the residue was poured into brine (200 ml) and extracted with ethyl acetate (3x100 ml). The dried organic extracts were evaporated in vacuo and the residue flash chromatographed on silica gel (ethyl acetate/light petroleum, 1:1) to give **6b** as an oil (16 g, 93%); IR (neat): 3350, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.6 (s, 6H), 1.95 (d, 3H, J=1.2Hz), 3.25 (br, 1H), 3.6 (brs, 1H), 4.35 (d, 2H, J=6Hz), 6.22 (s, 1H), 6.42 (brt, 1H, J=6Hz). $C_{10}H_{15}NO_3$ requires C, 60.89; H, 7.67; N, 7.10. Found C, 60.77; H, 7.58; N, 6.89.

7-[[(E)-3-(α,α-Dimethyl-3-isoxazolemethanol-5-yl)-2-butenyl]oxy]-2H-1-benzopyran-2-one **3**

To an ice-cooled solution of **6b** (0.8 g, 4 mmol) in methylene chloride (10 ml) containing triethylamine (0.5 ml, 6 mmol), methansulfonyl chloride (0.35 ml, 5 mmol) in methylene chloride (5 ml) was added dropwise with stirring. After 30 min at room temperature the mixture was treated with 2% citric acid (2.20 ml) and the organic phase separated, dried and concentrated in vacuo. The crude mesylate was immediately heated at reflux for 0.5h in acetone solution (20 ml) containing 7-hydroxycoumarin (0.65 g, 4 mmol), potassium carbonate (0.55 g, 4 mmol) and lithium bromide (0.1 g). After removal of the solvent in vacuo the residue was poured into water (50 ml) and extracted with ethyl acetate (2x50 ml). The combined extracts were washed with 5% aqueous ammonia (3x20 ml), brine (30 ml) and dried. The solvent was removed in vacuo to give **3** (1.29 g, 75%), m.p. 128-130°C/(ether); IR ($CHCl_3$): 3430, 1730, 1620, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.62 (s, 6H), 2.12 (d, 3H, J=1.2Hz), 2.32 (brs, 1H), 4.85 (d, 2H, J=6Hz), 6.3 (d, 1H, J=9Hz), 6.32 (s, 1H), 6.55 (brt, 1H, J=6Hz), 6.8-7 (m, 2H), 7.42 (d, 1H, J=8.5Hz), 7.67 (d, 1H, J=9Hz). This compound can also be prepared both by triphenylphosphine-diethylazodicarboxylate promoted condensation of **6b** and 7-hydroxy-coumarin (61% yield) or by direct cycloaddition of the nitrile oxide derived from the nitroderivative **4b** on the coumarin **7** (30% yield). $C_{19}H_{18}NO_5$ requires C, 66.85; H, 5.61; N, 4.10. Found C, 66.80; H, 5.52; N, 4.12.

7-[[(E,E)-6-Amino-7-hydroxy-3,7-dimethyl-4-oxo-2,5-octadienyl]oxy]-2H-1-benzopyran-2-one **8**

A solution of the isoxazole **3** (1 g, 6 mmol) in acetonitrile (40 ml) containing water (50 drops) was treated with molibdenumhexacarbonyl (0.81 g, 3 mmol) and heated at reflux for 1.5h with stirring. Celite (5 g) was added to the cooled solution and the resulting mixture evaporated in vacuo. The residue was flash chromatographed on silica gel (light petroleum/ethyl acetate, 4:6) to give **8** (1.94 g, 92%) m.p. 149-151°C (ethyl acetate/light petroleum, 1:2); IR ($CHCl_3$): 3480, 1730, 1620, 1560, 1520 cm^{-1} ^1H NMR ($CDCl_3$) δ 1.5 (s, 6H), 1.97 (d, 3H, J=1.2Hz), 2.35 (brs, 1H), 4.8 (d, 2H, J=6Hz), 5.4 (s, 1H), 6.27 (d, 1H, J=9Hz), 6.45 (brt, 1H, J=6Hz), 6.75-7 (m, 2H), 7.4 (d, 1H, J=8.5Hz), 7.65 (d, 1H, J=9Hz), 9.7 (br, 2H). $C_{19}H_{21}NO_5$ requires C, 66.46; H, 6.16; N, 4.08. Found C, 66.38; H, 6.23; N, 4.01.

Geiparvarin **1**

A solution of **8** (0.86 g, 2.5 mmol) in tetrahydrofuran (20 ml) was stirred at room temperature for 24h with 75% acetic acid (20 ml). The mixture was poured into brine (50 ml) and extracted with ethyl acetate (3x25 ml). Usual work-up gave geiparvarin **1** (0.77 g, 95%), m.p. 159-60°C (methanol) with spectroscopic characteristics identical to those described in the literature.[2a]

(E,E)-1-Acetyloxy-6-amino-7-hydroxy-3,7-dimethyl-4-oxo-2,5-octadiene **9**

Compound **9** was obtained as an oil in 75% yield by use of the procedure described for **8** starting from **6a**. IR (neat) 3400, 1740, 1600, 1530 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.4 (s, 6H); 1.9 (s, 3H), 2.1 (s, 3H), 3.5 (br, 1H), 4.7 (ol, 2H, J=6Hz), 5.35 (s, 1H), 6.4 (brt, 1H, J=6Hz), 6.8 (br, 1H), 10.4 (br, 1H). $C_{12}H_{19}NO_4$ requires C, 59.73; H, 7.94; N, 5.81. Found C, 59.66; H, 7.85; N, 5.73.

2,2-Dimethyl-5-(3-acetyloxy-1-methyl-1-propenyl)-3(2H)-furanone **10a**

Compound **10a** was obtained as an oil in 85% yield by acid-promoted cyclodehydration of **9** following the experimental conditions above described for **1**. IR (neat) 1740, 1690, 1640, 1560 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.4 (s, 6H), 1.95 (s, 3H), 2.1 (s, 3H), 4.65 (d, 2H, J=6Hz), 5.5 (s, 1H), 6.6 (brt, 1H, J=6Hz). $C_{12}H_{16}O_4$ requires C, 64.27; H, 7.19. Found C, 64.13; H, 7.08.

2,2-Dimethyl-5-(3-hydroxy-1-methyl-1-propenyl)-3(2H)-furanone **10b**

The 3(2H)-furanone **10b** was obtained in 50% yield m.p. 76-77°C (ether/light petroleum, 1:1) by use of the procedure described for the synthesis of **6b** starting from **10a**; its spectroscopic properties agree with the reported ones.[2c]

5-(1-Methyl-1-propyl)-α,α-dimethyl-3-isoxazolemethanol **11**

The isoxazole **6a** (2g, 8.3 mmol) in methanol was reduced at atmospheric pressure in the presence of 10% Pd/C (0.2 g) for 3h. The catalyst was filtered off through Celite and the solvent removed under reduced pressure. The crude product was purified by flash chromatography on silica gel eluent (ether/light petroleum, 1:9) to give **11** as an oil (0.96 g, 55%); IR (neat) 3470, 1600 cm^{-1}; ^1H NMR ($CDCl_3$)δ 0.95 (t, 3H, J=7.5Hz); 1.3 (d, 3H, J=7Hz); 1.6 (s, 6H); 1.3-1.6 (m, 2H), 2.9 (m, 1H), 3.4 (brs, 1H), 6.15 (s, 1H). $C_{10}H_{17}NO_2$ requires C, 65.54; H, 9.35; N, 7.64. Found C, 65.51; H, 9.27; N, 7,58.

5-[(E)-3-(t-Butyldimethylsilyloxy)-1-methyl-1-propenyl]-α,α-dimethyl-3-isoxazolemethanol **6d**

This compound was prepared from **4b** (12 mmol) and **5c** (51 mmol) in 80% yield following the above described procedure. Selective desilylation was obtained by stirring a solution of the crude cycloadduct in methanol (200 ml) in the presence of citric acid (3 g) for 12h. Most of the

methanol was removed in vacuo, the residue was partitioned between ethyl acetate (200 ml) and saturated aqueous sodium hydrogen carbonate (50 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (100 ml). The combined organic extracts were washed with brine (2x50 ml), dried, and concentrated. The residue was flash chromatographed on silica gel (ether/light petroleum, 3:7) to give **6d** as an oil (4.3 g, 82%): IR (neat) 3400, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.15 (s, 6H), 0.95 (s, 9H), 1.6 (s, 6H); 1.97 (d, 3H, J=1.1Hz); 2.6 (br, 1H), 4.3 (d, 2H, J=6Hz), 6.17 (s, 1H), 6.42 (brt, 1H, J=6Hz).

5-[3-(t-Butyldimethylsilyloxy)-1-methyl-1-propyl]-α,α-dimethyl-3-isoxazolemethanol **12a**

A solution of **6d** (3 g, 9.6 mmol) in absolute methanol was hydrogenated in the presence of 10% Pd/C (0.3 g) for 6h at room temperature. After the hydrogenation was complete, the mixture was filtered through Celite, the solvent was eliminated in vacuo and the residue flash chromatographed on silica gel (light petroleum/ether, 8:2) to give **12a** as an oil (1.95, 65%): IR (neat) 3400, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.15 (s, 6H), 0.95 (s, 9H), 1.3 (d, 3H, J=7Hz), 1.6 (s, 6H), 2.00 (m, 2H), 2.7 (br, 2H), 3.1 (m, 1H), 3.7 (t, 2H, J=6Hz), 6.05 (s, 1H).

5-(3-Hydroxy-1-methyl-1-propyl)-α,α-dimethyl-3-isoxazolemethanol **12b**

To a stirred solution of **6d** (8 g, 25 mmol) in methanol (100 ml) cooled at 0°C 5% HCl (20 ml) was added. The mixture was stirred at room temperature for 1h. Most of the methanol was removed in vacuo, and the solution was extracted with ethyl acetate, washed with brine, dried, and concentrated in vacuo to afford quantitatively **12b** as an oil (2.90 g): IR (neat) 3350, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.3 (d, 3H, J=6Hz), 1.55 (s, 6H), 2.1 (m, 2H), 2.6 (br, 1H), 3.2 (m, 1H), 3.7 (t, 2H, J=6Hz). $C_{10}H_{17}NO_3$ requires C, 60.28; H, 8.60; N, 7.03. Found C, 60.12; H, 8.51; N, 6.82.

7-[[3-(α,α-Dimethyl-3-isoxazolemethanol-5-yl)-2-butyl]oxy]-2H-1-benzopyran-2-one **13**

Diethylazodicarboxylate (0.94 ml, 6 mmol) in tetrahydrofuran (5 ml) was added dropwise to a well stirred solution of **12b** (1 g, 5 mmol) in tetrahydrofuran (25 ml) containing 7-hydroxycoumarin (0.97 g, 6 mmol) and triphenylphosphine (1.57 g, 6 mmol) under nitrogen. After being stired for 24h at room temperature the mixture was filtered and the filtrate diluted with ethyl acetate (50 ml) washed with brine (2x20 ml), dried, and evaporated under reduced pressure. The residue was carefully flash chromatographed on silica gel (ether/light petroleum, 7:3) to give **13** (1.29 g, 75%); m.p. 74-75°C (ethyl acetate/light petroleum); IR ($CHCl_3$) 3450, 1720, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.4 (d, 3H, J=6Hz); 1.6 (s, 6H), 2.2 (m, 2H), 2.6 (br, 1H), 3.2 (m, 1H), 4.0 (t, 2H, J=6Hz), 6.05 (s, 1H), 6.24 (d, 1H, J=9.5Hz), 6.7-6.9 (m, 2H), 7.32 (d, 2H, J=9Hz), 7.6 (d, 1H, J=9.5Hz). $C_{19}H_{21}NO_5$ requires C, 66.46; H, 6.16; N, 4.08. Found C, 66.31; H, 6.10; N, 3.97.

7-[[(E)-6-amino-7-hydroxy-3,7-dimethyl-4-oxo-5-octenyl]oxy]-2H-1-benzopyran-2-one **14**

Application to **13** of the procedure outlined for the synthesis of **8** provided the enaminone **14** as a solid, m.p. 91-92°C (ethyl acetate/light petroleum, 1:1) in 88% yield. IR ($CHCl_3$) 3430, 1730, 1620, 1560, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (d, 3H, J=7Hz), 1.45 (s, 6H), 1.7-2.3 (m, 2H), 2.6 (m, 1H), 3.5 (br, 1H), 4.0 (t, 2H, J=6Hz), 5.1 (s, 1H), 6.15 (d, 1H, J=9.1Hz), 6.65-6.95 (m, 2H), 7.35 (d, 1H, J=8Hz), 7.5 (d, 1H, J=9.1Hz), 9.5 (br, 2H). $C_{19}H_{23}NO_5$ requires C, 66.07; H, 6.71; N, 4.06. Found C, 66.02; H, 6.59; N, 4.12.

7-[[3-(4,5-Dihydro-5,5-dimethyl-4-oxo-2-furanyl)-2-butyl]oxy]-2H-1-benzopyran-2-one **2**

Dihydrogeiparvarin **2** was obtained in 90% yield as a solid, m.p. 122-123°C (ether/light petroleum, 1:1) by cyclodehydration of **14** under the experimental conditions as above described for **1**. Its spectroscopic properties agree with the reported ones.[4]

Acknowledgement. Financial support of this work by CNR Italy is gretefully acknowledged.

REFERENCES

1. K.Padmawinata, Acta Pharm., 1973, **4**, 1; Chem.Abstr., 1973, **97**, 75897n.
2. a) P.J.Jerris, A.B.Smith III, J.Org.Chem., 1981, **46**, 577.
   b) H.Saimoto, T.Hiyama, H.Nozaki, Bull.Chem.Soc.Jpn., 1983, **56**, 3078.
   c) R.F.W.Jackson, R.A.Raphael, J.Chem.Soc. Perkin Trans 1, 1984, 535.
   d) T.Sakai, H.Ito, A.Yamawaki, A.Takeda, Tetrahedron Lett., 1984, **25**, 2987.
   e) K.M.Chen, J.E.Semple, M.M.Joullié, J.Org.Chem., 1985, **50**, 3997.
   f) P.G.Baraldi, A.Barco, S.Benetti, M.Guarneri, S.Manfredini, G.P.Pollini, D.Simoni, Tetrahedron Lett., 1985, **26**,5319.
   g) S.H.Kang, C.Y.Hong, Ibid., 1987, **28**, 675.
   h) O.Tsuge, S.Kanemasa, H.Sugia, Chemistry Letters, 1987, 323.
3. For a review: P.G.Baraldi, A.Barco, S.Benetti, G.P.Pollini and D.Simoni, Synthesis, 1987, 857.
4. D.L.Dreyer, A.Lee, Phytochemistry, 1972, **11**, 763.
5. A.B.Smith III, P.A.Levenberg, P.F.Jerris, R.M.Scarborough Jr., P.M.Wovkulich, J.Am.Chem.Soc., 1981, **103**, 1501.
6. L.Claisen, Ber.Dtsch.Chem.Ges., 1891, **24**, 3900.
7. D.P.Curran, S.A.Scanga, C.J.Fenk, J.Org.Chem., 1984, **49**, 3474.
8. T.Mukaiyama, T.Hoshino, J.Am.Chem.Soc., 1960, **82**, 5339.
9. O.Mitsunobu, Synthesis, 1981, 1.
10 T.Wakefield, D.J.Wright, Adv.Heterocycl.Chem., 1979, **25**, 147.
11. M.Nitta, T.Kobayashi, J.Chem.Soc. Chem.Comm., 1982, 877.