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A [3+2] Nitrile Oxide Cycloaddition Approach to (-)-Pyrenophorin, and Rosefuran.

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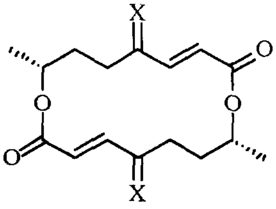
Abstract: [3+2] Nitrile oxide cycloaddition chemistry has been conveniently applied as carbon-carbon bond forming reaction for the assemblage of the functionalized carbon atom fragments required for the synthesis of two simple but different targets such as the macrolide antibiotic (-)-pyrenophorin **1** and rosefuran **2**, a trace component of the high prized oil of rose. In both cases, an intermediate 3,5-disustituted isoxazoline ring system has been used as serviceable precursor of the the salient structural feature of the targets, namely a γ-oxoacrylate moiety, common to many biologically active compounds, and a β,γ-dihydroxyketone functionality, easily converted by mild acid treatment to rosefuran.

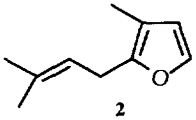
The 1,3-dipolar cycloaddition of nitrile oxides to olefinic and acetylenic compounds to form isoxazolines and isoxazoles respectively, followed by reductive N-O bond cleavage to reveal the number of functionalities contained in masked form in these versatile heterocycles, represents an important tool in synthetic organic chemistry.[1] Research in these laboratories centered on the use of [3+2]-nitrile oxide cycloaddition chemistry as a tool for the assemblage of functionalized carbon chains led us to discover an efficient methodology for the construction of carbon frameworks having a γ-oxoacrylate moiety as salient structural feature, recently applied to the synthesis of bioactive compounds isolated from *Melodorum fruticosum* Lour.[2]

Our own methodology allowed the creation of the γ-oxoacrylate unit in a safely masked form, simply by trapping the nitrile oxide, generated *in situ* from a suitable precursor with methyl acrylate in the cycloaddition step utilized as carbon-carbon bond forming reaction. In the meantime, we have also observed the easy formation of furans by mild acid treatment of aliphatic β,γ-dihydroxyketones, further demonstrating that 1,2-azoles produced by nitrile oxide cycloaddition chemistry are especially suited intermediates in natural product synthesis.[3] As a part of our continuous interest in [3+2] nitrile oxide cycloaddition chemistry, we describe in this paper the synthesis of two simple but different targets, such as (-)-pyrenophorin **1**, a dilactone antifungal antibiotic produced by the plant pathogenic fungi *Pyrenophora avenae* and *Stemphylium radicinum*,[4] and rosefuran **2**, a trace component of the high prized oil of rose.[5]



1 $X = O$

11 $X = -OCH_2CH_2O-$



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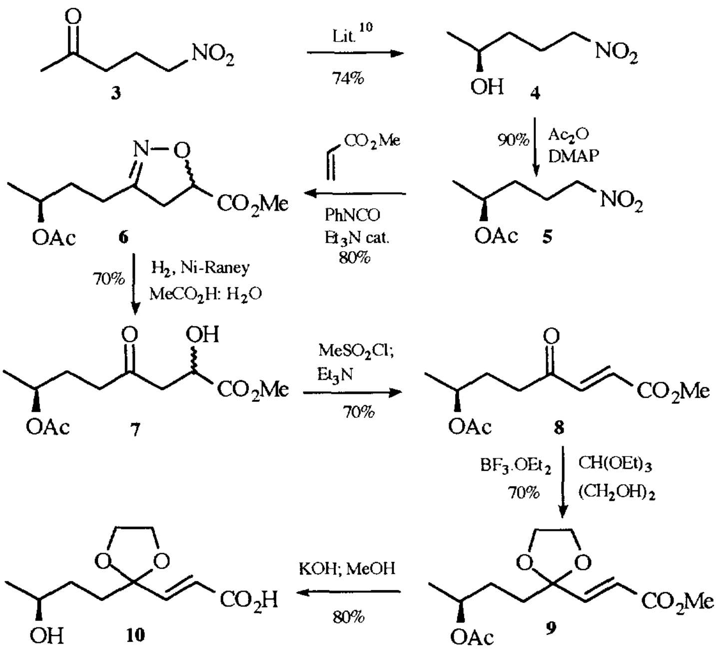
The common theme is represented by the use of 3,5-disubstituted isoxazoline ring system intermediates as serviceable precursors.

A. Enantioselective synthesis of 3-[2-(3-(S)-Hydroxybutyl)-1,3-dioxolan-2-yl]-2-propenoic Acid 10: a formal synthesis of (-)-pyrenophorin.

The widespread occurrence of the γ-oxo-α,β-unsaturated acrylate fragment as structural unit in a variety of biologically active natural compounds[4] has led to the development of a variety of synthetic approaches.[6] In particular, (-)-pyrenophorin **1**, a 16-membered ring dilactone derived by head-to-tail dimerization of two identical C_8 hydroxy acid subunits, has revealed a testing ground to demonstrate the validity of the methodology employed. Thus, while elegant and ingenious applications of carbanionic chemistry[7] as well as the elaboration of 3,5-disubstituted isoxazoles[8] has been developed for the construction of suitably protected C_8 hydroxy acid subunits in racemic form, with the unpleasant consequence that the subsequent dimerization led to formation of a 1:1 mixture of racemic and meso pyrenophorin **1**, only few approaches to the natural 8R,16R isomer **1** through dimerization of enantiomerically pure C_8 hydroxy acid subunits have been reported.[7,9-11]

We describe in this paper the formal synthesis of (-)-**1** through the easy adaptation of our own strategy to the enantioselective synthesis of a suitably protected subunit **10**, which has been already converted to the natural target.[7] As summarized in the Scheme I, the required eight carbon atom skeleton has been constructed by coupling of two fragments of five and three carbon atoms through a dipolar [3+2]-cycloaddition, the starting fragments being **3**,[12] which incorporates both the primary nitro group as nitrile oxide precursor and a suitably placed prochiral carbonyl group required for introducing the correct chirality, and methyl acrylate respectively.

SCHEME I



Submitting **3** to the action of Baker's yeast following the conditions carefully described by Guarna et al.,[13] an easy enzymatic reduction took place affording the known (S)-5-nitro-2-pentanol **4** in 99% e.e (74% yield), which was subsequently transformed into the corresponding acetyl derivative **5** by treatment with acetic anhydride/triethylamine system in the presence of 4-dimethylaminopyridine in 90% yield.

The stage was set for performing the key cycloaddition step, which was accomplished generating the nitrile oxide from the primary nitro group of **3** under classical Mukaiyama conditions[14] (phenyl isocyanate and catalytic triethylamine) in benzene solution in the presence of methyl acrylate to furnish an 80% yield of the 3,5-disubstituted isoxazoline **6**, as an unseparable mixture of diastereomers at the newly created chiral center. Reductive hydrolysis of the isoxazoline ring system with Raney Ni in aqueous acetic acid under a hydrogen atmosphere to reveal the β-hydroxy carbonyl function gave rise to **7**, immediately dehydrated by action of methansulfonyl chloride/triethylamine system to give **8**, which contains the complete γ-keto acrylate function. After protection of the carbonyl function of **8** as cyclic ethylene ketal **9** by treatment with ethylene glycol, triethyl orthoformate in the presence of boron trifluoride/ether complex, the latter underwent saponification of ester groups by alkaline hydrolysis to provide the hydroxy acid **10** upon acidification.

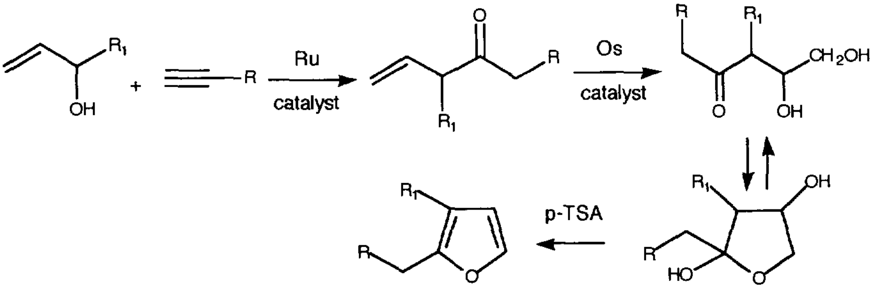
When combined with the efficient cyclodimerization to the protected pyrenophorin **11** with triphenyl phosphine/diethylazodicarboxylate (Mitsunobu method) according to Gerlach's procedure[15] and subsequent aqueous acid removal of the protecting groups, the synthesis of **10** represents the formal synthesis of (–)-pyrenophorin **1**, which compares well with the published ones in term of steps and overall yields, with the additional merit of using simple reactions and inexpensive chemicals.

B. Synthesis of Rosefuran.

Since its first synthesis in 1968,[16] rosefuran **2** has become the target of considerable synthetic attention and a number of synthetic routes, which are both of practical importance due to its olfactive properties, as well as useful tests for the development of new methodologies for furan synthesis have been reported.[17]

Trost and Flygare[17] have recently developed an elegant and practical synthesis of **2** entailing on the formation of furan ring systems by mild acid-promoted cyclization of aliphatic β,γ-dihydroxyketones, in turn assembled by ruthenium-catalyzed addition of simple acetylenes and allylic alcohols, followed by dihydroxylation of the derived β,γ-unsaturated ketones, as summarized in the following Scheme II.

SCHEME II

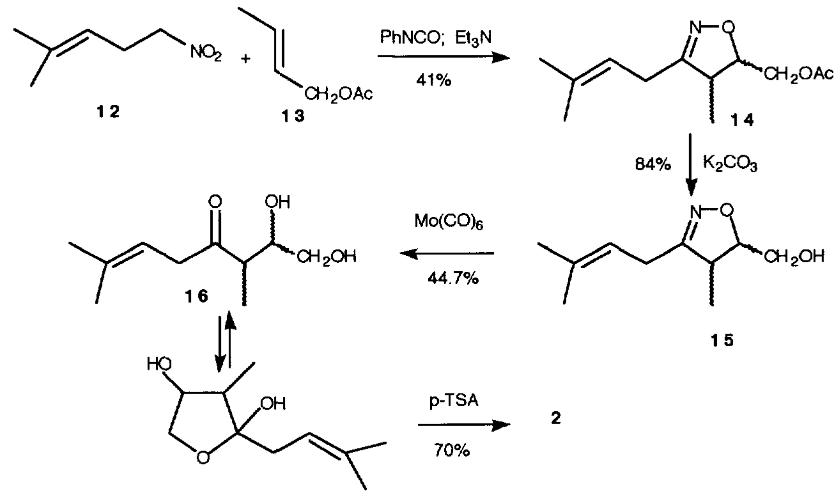


The acid lability of aliphatic β,γ-dihydroxyketones[18] has been accounted for the equilibrium to a lactol, which loses two moles of water to give the furan ring systems, which we also observed previously.[2]

Thus, we envisaged that polyfunctional compounds such as aliphatic β,γ-dihydroxyketones could be simply prepared by demasking the β-hydroxyketone moiety incorporated in a 5-hydroxymethylsubstituted isoxazoline ring system, in turn easily available through [3+2] nitrile oxide cycloaddition chemistry.

As summarized in Scheme III, our approach to **2** entailed on the [3+2] cycloaddition of the nitrile oxide generated under classical Mukaiyama conditions[14] from the known primary nitrocompound **12**,[19] containing in addition the felicitously placed required unsaturation, into the suitably protected crotyl alcohol **13** to afford the key 3,4,5-trisubstituted isoxazoline **14** in moderate yield.

SCHEME III



Saponification of the acetate easily occurred at room temperature by treatment with methanolic potassium carbonate to provide the free alcohol **15** in 84% yield. The stage was set for demasking the required α,β-dihydroxyketone moiety contained in **15**, which was conveniently accomplished by means of molybdenum hexacarbonyl in wet acetonitrile, owing to the presence of an unsaturation, leading to the formation of **16** in 44.7% yield. As anticipated, its exposure to catalytic p-toluenesulfonic acid in methylene chloride easily proceeded with the formation of **2** in 70% yield.

A major benefit of our sequence has been offered by the choice of a starting material already incorporating the trisubstituted double bond, its generation by dehydration of the corresponding tertiary alcohol as in most of the synthetic routes leading invariably to the formation of mixtures of **2** and its isomer, isorosefuran .

In summary, the assemblage of functionalized carbon atom fragments required for enantioselective approach of the subunit required for the formal synthesis of (-)-pyrenophorin **1**, as well as a new approach to rosefuran **2**, a commercially important target, illustrates once more the power of [3+2] nitrile oxide cycloaddition chemistry for the joining of carbon-carbon bonds required for the construction of natural products.

Experimental.

General remarks. Melting points were determined on a Büchi-Tottoli apparatus and are uncorrected. Infrared (IR) spectra were measured on a Perkin-Elmer Model 297. Nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker AC-200 spectrometer for solutions in $CDCl_3$ unless otherwise noted and peak positions are given in parts per millions downfield from tetramethylsilane as an internal standard. Coupling constants are given in Hz. Optical rotation were measured on a Perkin-Elmer 241 polarimeter. Organic solutions were dried over anhydrous magnesium sulphate and evaporated with a rotary evaporator. Light petroleum refers to the fractions boiling range 40-60°C and ether to diethyl ether. Flash-chromatography was carried out with Merck silica gel (230-400 mesh). All reactions were carried out under N_2 atmosphere. Elemental analyses were effected by the microanalytical laboratory of Dipartimento di Chimica, University of Ferrara.

Materials. The enantioselective reduction of 5-nitro-2-pentanone **3**, prepared through Al_2O_3-catalyzed[9] Michael addition of nitromethane to 3-buten-2-one, to (S)-5-nitro-2-pentanol **4** with Baker's yeast was accomplished according to the protocol described by Guarna et al.,[10] while 1-nitro-4-methyl-3-pentene **12** has been prepared by treatment of the commercially available bromide with sodium nitrite in DMSO as described in the literature.[19] Crotyl alcohol has been transformed into the corresponding acetate **13** by treatment with Ac_2O in the presence of pyridine in essentially quantitative yield.

(S)-5-nitro-2-pentanol acetate 5. A cooled (0°C) solution of (S)-5-nitro-2-pentanol **4** (5g, 37mmol) in CH_2Cl_2 (30ml) was treated with Ac_2O (4.25ml, 45mmol), triethylamine (6.5ml, 45mmol) and 4-dimethylaminopyridine (0.52g, 4.2mmol) and the mixture stirred at room temperature for 10min. The reaction mixture was washed with brine (30ml), dried and evaporated. The residue was chromatographed through a flash silica gel column (eluent ether : light petroleum 1:4) to give **5** (5.92g, 90%) as a pale yellow oil, $[\alpha]^{22}_D = +6$ (c 1.77, $CHCl_3$); IR: 1750, 1560 cm^{-1}; ^{1}H NMR: δ 1.25 (d, 3H, J=6.1), 1.65 (m, 2H), 2.01-2.06 (m, 2H), 2.05 (s, 3H), 4.41 (t, 2H, J=7), 4.93 (m, 1H). (Found: C, 47.89; H, 7.43; N, 7.87. $C_7H_{13}NO_4$ requires C, 47.99; H, 7.48; N, 8.0).

Methyl 3-[3-(S)-acetyloxybutyl]-4,5-dihydroisoxazole-5-carboxylate 6. To a solution of **5** (4g, 23mmol) and methyl acrylate (12.5ml, 138mmol) in dry benzene (15ml) containing triethylamine (0.5ml, 3.4mmol), phenylisocyanate (6ml, 57mmol) in benzene (5ml) was added dropwise and the reaction mixture stirred at room temperature overnight. The solid precipitated was removed by filtration and the filtrate was concentrated under vacuum.The residue was subjected to flash chromatography (eluent: ether : light petroleum 2:1) yielding **6** (4.4g, 80%) as a pale orange oil: IR: 1720-1700, 1620 cm^{-1}; ^{1}H NMR: δ 1.25 (d, 3H, J=6.3), 1.88 (m, 2H), 2.0 (s, 3H), 2.39 (m, 2H), 3.24 (d, 2H, J=8.7), 3.72 (s, 3H), 4.96 (m, 2H). (Found: C, 54.19; H, 7.01; N, 5.59. $C_{11}H_{17}NO_5$ requires C, 54.31; H, 7.04; N, 5.76).

Methyl 7(S)-Acetyloxy-2-hydroxy-4-oxo-octanoic acid 7. A solution of **6** (2g, 8.2mmol) in methanol (50ml) containing AcOH (4ml) and water (0.5ml) was hydrogenated in the presence of W2-Ni-Raney for 12h in a Parr apparatus. After filtration through Celite and removal of most of the solvent under vacuum, the residue was extracted with AcOEt (2x30ml), dried and concentrated. The residue was purified by flash chromatography (eluent: ether : light petroleum 4:1) to give **7** (1.4g, 70%) as colorless oil: IR: 3450, 1750-1720 cm^{-1}; ^{1}H NMR: δ 1.22 (d, 3H, J=6.3), 1.75-1.95 (m, 2H), 2.0 (s, 3H), 2.50 (t, 2H, J=7.3), 2.90 (m, 2H), 3.79 (s, 3H), 4.50 (m, 1H), 4.89 (m, 1H). (Found: C, 53.59; H, 7.27. $C_{11}H_{18}O_6$ requires C, 53.65; H, 7.37).

Methyl 7(S)-Acetyloxy-4-oxo-2-octenoic acid 8. Triethylamine (1.9ml, 13.2mmol) and methansulfonyl chloride (1.02ml, 13.2mmol) were successively added to an ice-cooled (0°C) solution of **7** (1g, 4mmol) in CH_2Cl_2 (40ml) and the mixture stirred at room temperature for 1h. After cooling at 0°C, a second portion of triethylamine (1.90ml, 13.2mmol) was added and the mixture stirred at room temperature for 1h. Water (20ml) was added, the organic phase separed, dried and evaporated. The residue was purified by flash chromatography (eluent ether : light petroleum 1:3) to give **8** (0.65g, 70%), as yellow oil, $[\alpha]^{22}_D = +1.6$ (c 0.8, $CHCl_3$); IR: 1720-1740, 1670 cm^{-1}; ^{1}H NMR: δ 1.25 (d, 3H, J=6.2), 1.9 (m, 2H), 2.02 (s, 3H), 2.69 (t, 2H, J=7.2), 3.82 (s, 3H), 4.91 (m, 1H), 6.68 (d, 1H, J=16), 7.08 (d, 1H, J=16). (Found: C, 61.89; H, 7.43. $C_{11}H_{16}O_5$ requires C, 62.04; H, 7.44).

Methyl 3-[2-(3-(S)-acetyloxy)butyl]-1,3-dioxolan-2-yl]-2-propenoate 9. A solution of **8** (0.6g, 2.6mmol) in dry benzene (15ml) containing ethylene glycol (0.24ml, 4mmol) and triethyl orthoformate (0.45ml, 2.7mmol), and two drops of $BF_3.Et_2O$ was refluxed for 24h. The cooled mixture was washed with saturated $NaHCO_3$, extracted with ether, dried and evaporated. The residue was purified by flash chromatography (eluent: ether : light petroleum 1:2) to give **9** (1.22g, 80%) as colorless oil, $[\alpha]^{22}_D = -5.4$ (c 0.52, $CHCl_3$); IR: 1750, 1670 cm^{-1}; ^{1}H NMR: δ 1.20 (d, 3H, J=6.1), 1.5-1.8 (m, 4H), 2.02 (s, 3H), 3.76 (s, 3H), 3.8-4.0 (m, 4H), 4.91 (m, 1H), 6.08 (d, 1H, J=16), 6.72 (d, 1H, J=16). (Found: C, 57.29; H, 7.43. $C_{13}H_{20}O_6$ requires C, 57.34; H, 7.4).

3-[2-(3-(S)-Hydroxybutyl)-1,3-dioxolan-2-yl]-2-propenoic Acid 10. A solution of **9** (1g, 4mmol) in methanol (25ml) was allowed to stand at room temperature for 3.5h with 2N KOH solution (12.5ml). The cooled (-5°C) reation mixture was acidified and rapidly extracted with AcOEt (2x20ml). The organic extracts were washed with brine, dried and concentrated. The residue was purified by flash cromatography (eluent: chloroform : acetic acid 9.5:0.5) to afford **10** (0.69g, 80%) as a light yellow oil, $[\alpha]^{22}_D = +14.8$ (c 0.44, $CHCl_3$); IR: 3450, 1700 cm^{-1}; ^{1}H NMR: δ 1.20 (d, 3H, J=6.1), 1.6 (m, 2H), 1.9 (m, 2H), 3.95 (m, 4H), 5.20 (bs, 2H), 6.07 (d, 1H, J=16), 6.81 (d, 1H, J=16) (Found: C, 61.89; H, 7.43. $C_{13}H_{20}O_6$ requires C, 62.04; H, 7.44).

4,5-Dihydro-3-[(3-methyl-2-buten)-yl]-4-methyl-5-isoxazolemethanol acetate 14. To a solution of **12** (0.7g, 5.4mmol) and crotyl acetate **13** (12.5ml, 138mmol) in dry benzene (10ml) containing triethylamine (0.1ml), phenylisocyanate (1.46ml, 13.5mmol) in benzene (2ml) was added dropwise and the reaction mixture stirred at room temperature for 36h. The solid precipitated was removed by filtration and the filtrate was concentrated under vacuum.The residue was subjected to flash chromatography (eluent: ether : light petroleum 1:2) yielding **14** (0.5g, 41%) as an oil: IR: 1750, 1610 cm^{-1}; ^{1}H NMR: δ 1.28 (d, 3H, J=6.3), 1.67 (s, 3H), 1.77 (s, 3H), 2.07 (s, 3H), 3.1 (m, 3H), 4.0-4.3 (m, 2H), 4.45 (m, 1H), 5.18 (bt, 1H). (Found: C, 64.05; H, 8.01; N, 6.19. $C_{12}H_{19}NO_3$ requires C, 63.98; H, 8.5; N, 6.22).

4,5-Dihydro-3-[(3-methyl-2-buten)-yl]-4-methyl-5-isoxazolemethanol 15. A solution of **14** (0.5g, 2.23mmol) in methanol (5ml) was allowed to stand at room temperature for 18h with saturated K_2CO_3 solution (2.5ml). Most of the solvent was evaporated in vacuum and the reaction mixture extracted with Et_2O (2x20ml), dried and concentrated. The residue was purified by flash cromatography (eluent: ether : light petroleum 2:1) to afford **15** (0.32g, 84%) as an oil; IR: 3400, 1610 cm^{-1}; ^{1}H NMR: δ 1.28 (d, 3H, J=6.3), 1.67 (s, 3H), 1.74 (s, 3H), 2.45 (bs, 1H), 2.8-3.3 (m, 3H), 3.5-3.9 (m, 2H), 4.45 (m, 1H), 5.18 (bt, 1H). (Found: C, 64.41; H, 9.63. $C_{10}H_{17}NO_2$ requires C, 64.49; H, 9.74).

1,2-Dihydroxy-3,7-dimethyl-6-octen-4-one 16. A solution of **15** (0.32g, 1.75mmol) in acetonitrile (15ml) containing 15 drops of water was treated with molybdenum hexacarbonyl (0.5g, 1.9mmol) and refluxed for 2h. The cooled mixture was filtered through Celite and the filtrate evaporated. The residue was purified by chromatography on Florisil (eluent ether, then EtOAc) to give **16** (0.14g, 44%), as an oil; IR: 3400, 1730, 1610 cm^{-1}; ^{1}H NMR: δ 1.31 (d, 3H, J=6.3), 1.64 (s, 3H), 1.77 (s, 3H), 2.4-3.0 (m, 1H), 3.0 (bs, 1H), 3.3 (d, 2H, J=7), 3.92 (d, 1H, J=5), 4-4.2 (m, 2H), 4.4 (m, 1H), 5.2 (bt, 1H). (Found: C, 61.89; H, 7.43. $C_{10}H_{18}O_3$ requires C, 62.04; H, 7.44).

Rosefuran 2. A solution of **16** (0.14g, 0.75mmol) in CH_2Cl_2 (3ml) was treated with p-toluenesulfonic acid hydrate (0.013g, 0.07mmol) and stirred at room temperature for 30 min. The mixture was evaporated and the residue purified by flash chromatography (eluent: light petroleum) to give **2** (0.07g, 70%) as colorless oil; ^{1}H NMR: δ 1.64 (s, 3H), 1.77 (s, 3H), 1.96 (s, 3H), 3.28 (d, 2H, J=7), 5.21-5.30 (m, 1H), 6.16 (d, 1H, J=1.7), 7.22 (d, 1H, J=1.6). (Found: C, 79.89; H, 9.33. $C_{10}H_{14}O$ requires C, 79.96; H, 9.38).

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