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Synthesis of Melodienone and 7-Hydroxy-6-hydromelodienone, two Heptenes from *Melodorum Fruticosum*.

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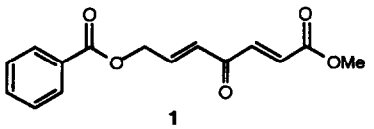
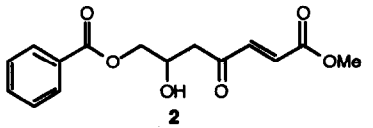
Abstract: An unified approach to the construction of the seven carbon atom framework of the title compounds, having a γ-oxoacrylate moiety as common structural feature, utilizing an intermolecular [3+2] cycloaddition of the nitrile oxide generated from a malic acid derived C-4 aldehyde fragment with methyl acrylate, is described.

Recently, McLaughlin et al.[1,2] have isolated from *Melodorum fruticosum* Lour.(Annonacee) several new bioactive compounds with slight to significant cytotoxic activity to human tumor cell lines, which were named heptenes, owing to their novel seven-carbon atom skeleton.

Interestingly, the examination of the structures of two members of this family, trivially named melodienone **1** and 7-hydroxy-6-hydromelodienone **2**, revealed common structural similarities, including a C(1)-C(4) fragment of their skeleton incorporated into a γ-oxoacrylate moiety and a primary hydroxyl group at C(7) esterified with a benzoic acid residue, which seems to be of crucial importance for the integrity of these structures.



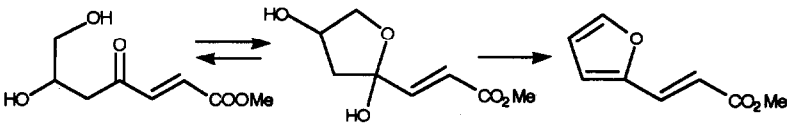
1



2

In fact, the free primary hydroxyl group is suitably located for intramolecular addition to the carbonyl group to produce the corresponding hemiketal, which may in turn give rise to the corresponding 3-(2-furyl)-acrylic acid ester by dehydration,[3] as outlined in the Scheme I.

SCHEME I



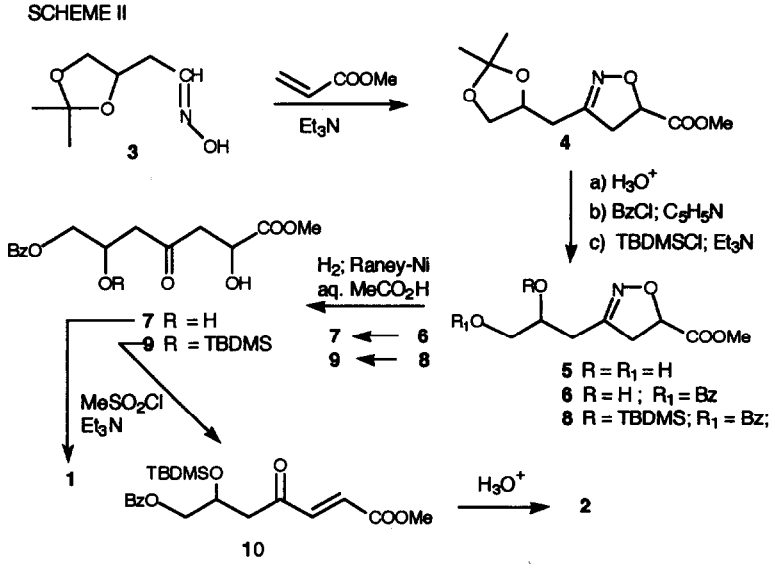
These compounds differ for the substitution pattern at the C(5)-C(6) frame, where the conjugated double bond defining the dienone moiety of **1**, is saturated in **2**, which bears an additional free secondary hydroxyl group at C(6). The presence of an array of different functionalities combined with the interesting biological properties, make these compounds challenging targets for synthesis, which may also serve to confirm unequivocally their structures, assigned on the basis of spectroscopic data.

To this end, we have developed a common synthetic strategy involving the assemblage of the seven carbon atom skeleton of both **1** and **2** by coupling two fragments of four and three carbon atoms respectively through a dipolar [3+2]-cycloaddition of the nitrile oxide derived from a C-4 aldehyde component, easily available from malic acid with the C-3 fragment represented by methyl acrylate.

The approach based to a large extent on our previous experiences on nitrile oxide chemistry,[4,5] was designed not only to form the key carbon-carbon bond between the two fragments but especially to delay until the final stage the problematic introduction of the γ-oxoacrylate moiety, safely masked into the derived 3,5-disubstituted heterocyclic compound.

The synthesis of this deceptively simple molecules began with the oxime **3** of the known[6] aldehyde, readily available from malic acid dimethyl ester in a four-step sequence involving the regioselective reduction of the ester bearing the α-hydroxyl group, followed by ketalization with acetone/p-toluesulfonic acid of the generated 1,2-diol moiety, reduction of the remaining ester group and final Swern oxidation. Treatment of **3** under the well established Torsell protocol[7] generated the required 1,3-dipole which was trapped with methyl acrylate to

SCHEME II



afford a 78% yield of the key intermediate **4**, as unseparable mixture of diastereomers at the newly created chiral center. Removal of the acetonide protecting group by aqueous acid treatment of **4** led quantitatively to the diol **5**. Selective protection of the primary hydroxyl group was possible by benzoylation with benzoyl chloride in pyridine in the presence of 4-dimethylaminopyridine and compound **6** with a free secondary hydroxyl group, a common intermediate for both **1** and **2**, was obtained.

Thus, the synthesis of **1** was easily completed by reductive hydrolysis of the isoxazoline ring system* with Raney Ni in aqueous acetic acid under a hydrogen athmosphere to reveal the β-hydroxy carbonyl function giving rise to **7**, easily converted to melodienone **1** by double dehydration promoted by methansulfonyl choride-triethylamine system. On the other hand, the completion of the synthesis of **2**, required an additional protection-deprotection operation for preserving the secondary hydroxyl group of **6**, before the reductive cleavage of the isoxazoline ring. Thus, after transformation of **6** into the corresponding tert-butyl-dimethylsilyl ether **8** by standard procedure, the stage was set to uncover the functionality masked in the heterocyclic ring system, which was smoothly cleaved as before by hydrogenolysis/hydrolysis with hydrogen in aqueous acetic acid to produce the intermediate β-hydroxy ketone **9**, which underwent easy dehydration by treatment with methansulfonyl chloride-triethylamine system to afford **10** with the required γ-oxoacrylate moiety. Final deprotection of the secondary hydroxyl group of **10** by acid treatment provided the target **2** as a nicely crystalline compound with physical and spectroscopic properties identical to the reported ones[2] when the synthetic sequence was performed starting from racemic malic acid, but with a different melting point, m.p.77-78°C (lit.[2]: m.p. 96-97°C) and $[\alpha]^{23}_{D}$= -15.4 (c 0.9,.$CHCl_3$) when natural (S)-malic acid was used instead.

Rather puzzlingly, no optical rotation has been given in the literature for **2**, although all the products described in the original papers were carefully characterized. These findings support the hypothesis put forward by the Authors[2] that **2** might be an extraction artifact rather than a natural product, probably arising by the hydration of **1**, partial or complete racemization at the chirogenic center of the natural compound appearing less likely.

In summary, we described herein a methodology which allows an efficient construction of the functionalized seven carbon atom of a new class of bioactive compounds, which may be relevant for the preparation of compounds having a γ-oxoacrylate moiety, a salient structural feature commonly featuring antitumoral compounds.[8]

Experimental.

General remarks. Melting points were determined on a Büchi-Tottoli apparatus and are uncorrected. Reaction courses and product mixtures were routinely monitored by thin-layer chromatography (TLC) on silica gel coated plates F_{254} (Merck). Infrared (IR) spectra were measured on a Perkin-Elmer Model 297. Nuclear magnetic resonance (^1H 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 rotations were measured on a Perkin-Elmer polarimeter 241. 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.

1,3-Dioxolane-2,2-dimethyl-4-acetaldehyde oxime 3.

Hydroxylamine hydrochloride (2.17g, 31.2mmol) and sodium bicarbonate (3.9g, 54mmol) in water (100ml) were added to a solution of 1,3-dioxolane-2,2-dimethyl-4-acetaldehyde[6] (4.5g, 31.2mmol) in ethanol (10ml) and the mixture stirred overnight at room temperature, then extracted with dichloromethane (3x25ml). The dried organic extracts were concentrated, and the residue purified by flash chromatography (eluent: ether : light petroleum 1:1) to give the oxime **3** (3.2 g, 65%), as colorless oil: IR (neat): 3400, 3000-2800 cm^{-1}; ^1H NMR: δ 1.37 (s, 3H), 1.43 (s, 3H), 2.5 (m, 1H), 2.7 (m, 1H), 3.6 (m, 1H), 4.1 (1H, dd, J=6, J=8.2), 4.3 (m, 1H), 6.9-7.5 (t, 1H), 9.3-9.8 (sb, 1H). (Found: C, 58.59; H, 8.91; N, 9.67. $C_7H_{13}O_3N$ requires C, 58.72; H, 9.15, N, 9.78).

Methyl 3-[(2,3-O-isopropylidene)-2,3-dihydroxyprop-1-yl]-4,5-dihydroisoxazole-5-carboxylate 4.

A solution of **3** (4.1g, 25.7mmol) in dry $CHCl_3$ (20ml) was added to a suspension of N-chlorosuccinimide (3.41g, 25.7mmol) in $CHCl_3$ (20ml) containing pyridine (0.12ml, 16.1mmol) and the mixture stirred at room temperature for 30min. The addition of methyl acrylate (2.9ml, 33mmol) was followed by dropwise addition of triethylamine (3.8ml, 26mmol) diluted with $CHCl_3$ (10ml). After the mixture was being stirred for 20min at room temperature, water (25ml) was added, the organic phase separed, dried and concentrated in vacuum. The residual oil was purified by flash chromatography (eluent: ether : light petroleum 8:2) to afford **4** (4.1 g, 65%) as a colorless oil: IR (neat): 1740 cm^{-1}; ^1H NMR: δ 1.35 (s, 3H), 1.40 (s, 3H), 2.6 (m, 2H), 3.3 (m, 2H),3.65 (dd, 1H, J=6.5, J=8.3), 3.8 (s, 3H), 4.1 (dd, 1H, J=6, J=8.3), 4.3 (m, 1H), 5.0 (dd, 1H, J=7.9, J=9). (Found: C, 54.19; H, 6.91; N, 5.67. $C_{11}H_{17}O_5N$ requires C, 54.31; H, 7.04, N, 5.76).

Methyl 3-(2,3-dihydroxyprop-1-yl)-4,5-dihydroisoxazole-5-carboxylate 5.

A solution of **4** (1g, 41.15mmol) in methanol (20ml) was added for 30min at room temperature in the presence of *p*-toluenesulfonic acid (0.2mg). Most of the solvent was evaporated in vacuum, the residue was partitioned between water and CH_2Cl_2 (20ml of each), the organic phase separed, dried and concentrated. The residue was purified by flash chromatography (eluent: CH_2Cl_2 : MeOH 9:1) to give **5** (0.58g, 70%), as a colorless oil: IR (neat): 3600-3300, 1740 cm^{-1}; ^1H NMR: δ 2.5 (m, 2H), 3.2-3.7 (m, 3H), 3.8 (s, 3H), 3.9-4.2 (m, 2H), 5.0 (dd, 1H, J=12.1, J=7.3). (Found: C, 47.19; H, 6.31; N, 6.67. $C_8H_{13}O_5N$ requires C, 47.29; H, 6.45, N, 6.89).

Methyl 3-(2-hydroxy-3-benzoyloxyprop-1-yl)-4,5-dihydroisoxazole-5-carboxylate 6.

Benzoyl chloride (0.31ml, 3.94mmol) was added to a solution of **5** (0.8g, 3.94mmol) in CH_2Cl_2 (30ml) containing pyridine (0.31ml, 3.94mmol) and 4-dimethylaminopyridine (0.2mg) and the mixture stirred for 24h at room temperature. Evaporation of the volatiles in vacuum was followed by flash chromatography of the residue (eluent: EtOAc : light petroleum 1:1) to give **6** (0.99g, 82%) as an oil: IR (neat): 3500, 1740 cm^{-1}; ^1H NMR: δ 2.7 (m, 2H), 3.3 (m, 3H), 3.8 (s, 3H), 4.4 (m, 3H), 5.0 (dd, 1H, J=12, J=7.2), 7.4-7.7 (m, 3H), 8.1 (m, 2H). (Found: C, 58.59; H, 5.43; N, 4.45. $C_{15}H_{17}O_6N$ requires C, 58.63; H, 5.58; N, 4.56).

(Methyl 2,6-Dihydroxy-7-benzoyloxy-4-oxoheptanoic acid 7.

A solution of **6** (0.7g, 2.27mmol) in methanol (20ml) containing AcOH (1.3ml) and water (0.5ml) was hydrogenated in the presence of W2 Ni-Raney for 4h in a Parr apparatus. After filtration through Celite and removal of most of the solvents in vacuum, the residue was extracted with AcOEt (2x20ml), dried and concentrated. The residue was purified by flash chromatography (eluent: CH_2Cl_2 : MeOH 9.5 :0.5) to afford **7**

(0.49g, 70%) as an homogeneous oil: IR (neat): 3600, 1780 cm^{-1}; ^1H NMR: δ 2.8 (m, 2H), 3.0 (m, 2H), 3.7-3.9 (m, 2H), 3.8 (s, 3H), 4.4 (m, 2H), 4.51 (m, 2H), 7.3-7.7 (m, 3H), 8.1 (m, 2H). (Found: C, 57.89; H, 5.47. $C_{15}H_{18}O_7$ requires C, 58.06; H, 5.85).

Methyl 7-Benzoyloxy-4-oxo-2,5-heptadienoic acid 1 (Melodienone).

Triethylamine (0.43ml, 3mmol) and methansulfonyl chloride (0.23ml, 3mol) were successively added to an ice-cooled (0°C) solution of **7** (0.28g, 0.9mmol) in CH_2Cl_2 (20ml) and the mixture stirred at room temperature for 1h. After cooling at 0°C, a second portion of triethylamine 0.42ml, 3mmol) was added and the mixture stirred at room temperature for 30min. Water (20ml) was added, the organic phase separed, dried and evaporated. The residue was purified by flash chromatography (eluent ether : light petroleum 3:7) to give **1** (0.15g, 60%) as a solid m.p. 68-69°C (pentane).[lit.[1] m.p. 69-70°C].(Found: C, 65.64; H, 5.07. $C_{15}H_{14}O_5$ requires C, 65.69; H, 5.14).

Methyl 3-[2-[[(1,1-Dimethylethyl)dimethylsilyl]-oxy]-3-benzoyloxypropyl]-4,5-dihydroisoxazole-5-carboxylate 8.

To an ice-cooled (0°C) solution of **6** (0.5g, 1.78mmol) in CH_2Cl_2 (20ml) were successively added 2,6-lutidine (0.41ml, 3.57mmol) and TBDMS (0.81ml, 3.57mmol) in CH_2Cl_2 (10ml) and the mixture stirred at room temperature for 1h. Water (20ml) was added, the organic phase separed, dried and evaporated in vacuum. The residue was purified by flash chromatography (eluent: EtOAc : light petroleum 1:1) to give **8**, (0.63g, 93%) as a colorless oil: IR: 1720-1740 cm^{-1}; ^1H NMR: δ 0.1 (s, 6H), 0.9 (s, 9H), 2.7 (m, 2H), 3.0 (m, 2H), 3.8 (s, 3H), 4.1-4.5 (m, 2H), 4.5 (m, 1H), 5.0 (m, 1H), 7.3-7.8 (m, 3H), 8.1 (m, 2H). (Found: C, 59.69; H, 7.33; N, 3.32. $C_{21}H_{31}O_6NSi$ requires C, 59.83; H, 7.41; N, 3.32).

Methyl 7-Benzoyloxy-6-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-hydroxy-4-oxoheptanoic acid 9.

This compound was obtained from **8** (0.6g, 1.41mmol) using the same procedure as above described for **7**. The final purification was effected by flash chromatography (eluent: EtOAc : light petroleum 3:7) giving **9** (0.4g, 73%) as colorless oil: IR: 3600-3300, 1740-1720 cm^{-1}; ^1H NMR: δ 0.1 (s, 6H), 0.85 (s, 9H), 2.8 (m, 2H), 3.0 (m, 2H), 3.3 (d, 1H, J=4.1), 3.8 (s, 3H), 4.1-4.4 (m, 2H), 4.6 (m, 2H), 7.3-7.7 (m, 3H), 8.1 (m, 2H). (Found: C, 59.29; H, 7.43. $C_{21}H_{32}O_7Si$ requires C, 59.41; H, 7.6).

Methyl 7-Benzoyloxy-6-(1,1-dimethyl)dimethylsilyloxy-4-oxo-2-heptenoic acid 10.

Triethylamine (0.25ml, 1.78mmol) and methansulfonyl chloride (0.13ml, 1.78mol) were successively added to an ice-cooled (0°C) solution of **9** (0.3g, 0.71mmol) in CH_2Cl_2 (20ml) and the mixture stirred at room temperature for 1h. After cooling at 0°C, a second portion of triethylamine (0.25ml, 1.78mmol) was added and the mixture stirred at room temperature for 30min. Water (20ml) was added, the organic phase separed, dried and evaporated. The residue was purified by flash chromatography (eluent ether : light petroleum 2:8) to give **10** (0.2g, 70%), as colorless oil: IR: 1680, 1720 cm^{-1}; ^1H NMR: δ 0.05 (s, 3H), 0.1 (s, 13H), 0.85 (s, 9H), 2.8-3.1 (m, 2H), 3.8 (s, 3H), 4.2-4.4 (m, 2H), 4.6 (m, 1H), 6.7 (d, 1H, J=16), 7.1 (d, 1H, J=16), 7.3-7.7 (m, 3H), 8.1 (m, 2H). (Found: C, 61.89; H, 7.43. $C_{21}H_{30}O_6Si$ requires C, 62.04; H, 7.44).

Methyl 7-Benzoyloxy-6-hydroxy-4-oxo-2-heptenoic acid 2.

To a solution of **10** (0.1g, 0.8mmol) in methanol (3ml) was added a 1% methanolic solution of 6M HCl (10ml) and mixture stirred for 3h at room temperature. After evaporation of the solvent in vacuum, the residue was purified by flash chromatography (eluent: EtOAc : light petroleum 3:7) to yield **2** (0.06g, 80%) as a crystalline solid, m.p. 96-97° C (ether : n-pentane 1:1), lit.[2] m.p. 96-97°C; IR: 3600-3300, 1720-1690 cm^{-1}; ^1H NMR: δ

3.0 (m, 2H), 3.3 (d, 1H, J=4.2), 3.8 (s, 3H), 4.4 (m, 2H), 4.6 (m, 1H), 6.7 (d, 1H, J=16), 7.1 (d, 1H, J=16), 7.3-7.7 (m, 3H), 8.1 (m, 2H). (Found: C, 61.59; H, 5.43. $C_{15}H_{16}O_6$ requires C, 61.64; H, 5.52).

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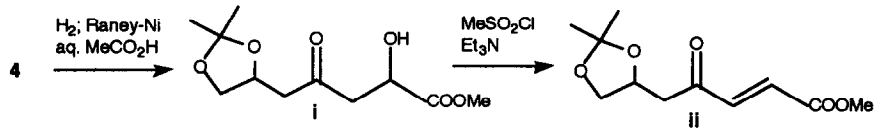
References and Notes.

1. Jung, J. H.; Pummangura, S.; Chaichantipyuth, C; Patarapanich, C.; Fanwick, P. E.; Chang, C.-J.; McLaughlin, J. L., *Tetrahedron*, **1990**, *46*, 5043-5054.
2. Jung, J. H.; Chang, C.-J.; McLaughlin, J. L.; Pummangura, S.; Chaichantipyuth, C; Patarapanich, C., *J. Nat. Prod.*, **1991**, *54*, 500-505.
3. The formation of substituted furan derivatives promoted by acetic acid acid on similarly substituted substrates has been recently reported: Paquette, L. A.; Doherty, A. M.; Raynen, C. M., *J. Am. Chem. Soc.*, **1992**, *114*, 3910-3926.
4. De Simoni, G.; Tacconi, G.; Barco, A.; Pollini, G. P., "*Natural Products Synthesis Through Pericyclic Reactions*", A.C.S.- Washington; 1983.
5. Baraldi, P. G.; Barco, S. Benetti, S.; Pollini, G. P.; Simoni, D., Synthesis, **1987**, 857-869.
6. Hanessian, S.; Ugolini, A.; Therien, M., *J. Org. Chem.*, **1983**, *48*, 4427-4430.
7. Larsen, K. E.; Torsell, K. B., *Tetrahedron*, **1984**, *40*, 2985-2988.
* Interestingly, when the γ-oxoacrylate moiety was unmasked from the isoxazoline nucleus of **4** through the intermediates **i** and **ii**, attempts to remove the acetal protecting group from the latter by mild acid treatment (catalytic p-toluenesulfonic acid in methanol at room temperature) led to the isolation of 3-(2-furyl)-acrylic acid methyl ester in 75% yield along the pathway indicated in the Scheme I, thus supporting the crucial importance of the benzoyl group for the survival of the structures **1** and **2**.



8. Machinaga, N.; Kibayashi, C., *Tetrahedron Lett.*, **1993**, *34*, 841-844 and references quoted therein.

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