Stereoselective Access to Tetrahydropyranylacetic Acid Derivatives. Simple Synthesis of (+)-(*S,S*)-(*cis*-6-Methyltetrahydropyran-2-yl)acetic Acid

Valentine Ragoussis,* Vassiliki Theodorou

Laboratory of Organic Chemistry, University of Athens, Panepistimiopolis, Zografou, G-157-71 Athens, Greece

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The reaction of the lactols **1a–1d**, with malonic acid in hot dimethyl sulfoxide, in the presence of piperidinium acetate as catalyst, gives the corresponding (tetrahydrofuran-2-yl)acetic acids **2a,c** and (tetrahydropyran-2-yl)acetic acids **2b,d** in high yield (65–75%). While the synthesis of the (6-methyltetrahydropyran-2-yl)acetic acid **(2d)** is highly stereoselective (cis/trans ratio 20:1), no stereoselection was observed with the (5-methyltetrahydrofuran-2-yl)acetic acid **(2c)** (cis/trans ratio 1:1). This reaction was applied for the synthesis of natural (+)-(*S,S*)-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid **(7)**, minor constituent of the glandular secretion of the civet cat.

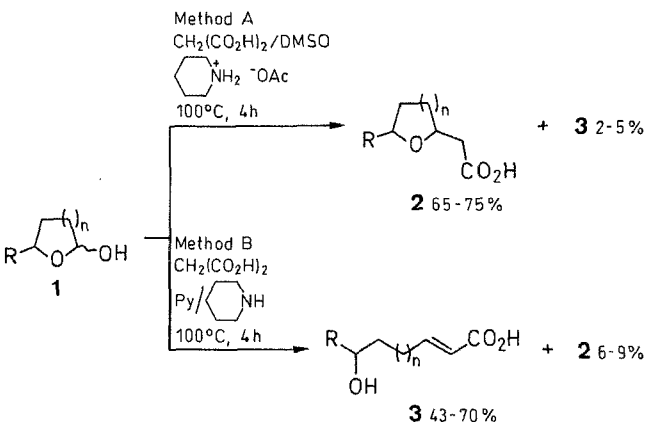
The synthesis of a wide range of biological important natural products containing oxacyclic subunits such as polyether antibiotics,[1,2] polyene mycotoxins[3] etc, has led to the development of a number of procedures for the construction of substituted tetrahydrofurans[4] and tetrahydropyrans.[5] While there are several notable examples of stereocontrolled synthesis of disubstituted 2,5-tetrahydrofurans[6] and 2,6-tetrahydropyrans,[7] a simple and effective approach to such ring systems is still lacking.

We present a very simple synthesis of tetrahydrofuranylacetic acids and tetrahydropyranylacetic acids, by condensation of an hydroxyaldehyde with malonic acid. This reaction was applied successfully to the synthesis of natural (*cis*-6-methyltetrahydropyran-2-yl)acetic acid **(7)**, in optically pure form.

In 1961[8] it was observed that the reaction of 5-hydroxypentanal with malonic acid leading to 7-hydroxyhept-2-enoic acid, gives also a small amount of the tetrahydropyranylacetic acid. Recently it has been reported that the course of the condensation of an aldehyde with malonic acid may be dramatically changed by changing the solvent.[9] Therefore, we investigated the reaction of 5-hydroxypentanal and 4-hydroxybutanal with malonic acid in various, mainly polar aprotic solvents[10] in order to improve the yields of the tetrahydrofuranyl and tetrahydropyranyl derivatives. Indeed, the reaction of the 4-hydroxybutanal **(1a)** or 5-hydroxypentanal **(1b)** with two equivalents of malonic acid in hot (100°C) dimethyl sulfoxide, in the presence of piperidinium acetate as catalyst, gave the cyclic products **2a** and **2b** almost exclusively (Scheme 1). The same condensation, in pyridine–piperidine solution (Verley–Doebner modification of the Knoevenagel condensation[11]), yielded mainly the α,β-unsaturated acids **3a** and **3b**. The results are reported in Table 1.

The starting materials **1a** and **1b** are readily available. 4-Hydroxybutanal **(1a)** was easily prepared from the 2,3-dihydropyran by hydration[12] and 5-hydroxypentanal **(1b)** is commercially available.

The stereochemistry of this reaction was studied in the formation of the simplest 2,5-disubstituted tetrahydrofuran **2c** and 2,6-disubstituted tetrahydrofuran **2d** derivatives from the methyl hydroxyaldehydes **1c** and **1d**,



1-3	n	R
a	1	H
b	2	H
c	1	Me
d	2	Me

Scheme 1

respectively. The hydroxyaldehydes **1c** and **1d**, were obtained in good yield by partial reduction of the corresponding lactones by lithium aluminum hydride in diethyl ether.[13]

The reaction of the lactol **1c** with malonic acid gave, as expected, the (5-methyltetrahydrofuran-2-yl)acetic acid **(2c)**, in good yield (Table 1). Although the cyclic structure of the product was evident from the IR (ν = 1710 cm^{-1}) and ^1H NMR (absence of olefinic protons), detailed GCMS analysis revealed the presence of the two isomers (cis and trans) in a ratio of 1:1, exhibiting identical mass spectra. In contrast, the lactol **1d** gave, almost exclusively (*cis*-6-methyltetrahydropyran-2-yl)acetic acid **(2d)** (cis/trans ratio determined by GC, 20:1), under the same conditions. The trans-isomer as well as the unsaturated acid **3d**, were easily removed from the distilled reaction product by crystallization from hexane and thus, the cis-isomer was obtained with very high purity (Table 2).

The condensation described represents a very simple, one-step stereoselective synthesis, of the (*cis*-6-methyltetrahydropyran-2-yl)acetic acid **(2d)**. This heterocyclic acid, is found in trace quantities (2 mg/kg) in Civet, the perfume material, secreted by the scent gland of the civet cat *Viverra civetta*.[14,15] The natural occurrence, isolation, confirmation of structure[14] and determination of the absolute stereochemistry[14,15] of (*cis*-6-methyltetrahydropyran-2-yl)acetic acid, have been reported in 1979. Several syntheses of the racemic form[16] as well as of the optically active natural enantiomer[5,7a,17] have been reported in recent years. Nevertheless, as far as we are aware, none of the reported syntheses is as simple and efficient as the one described in this paper.

Table 1. The Condensation of Lactols **1a–d** with Malonic Acid

Substrate	Method	Products (Yield %)	
1a	A	**2a** (66)[c]	**3a** (5)[a]
1a	B	**2a** (6)[a]	**3a** (70)[c]
1b	A	**2b** (71)[c]	**3b** (2)[a]
1b	B	**2b** (9)[b]	**3b** (43)[b]
1c	A	**2c** (65)[c]	**3c** (3)[a]
1d	A	**2d** (75)[c]	**3d** (< 2)[a]

[a] Product not isolated; GC yield.
[b] Result of Lit.[8].
[c] Product isolated by distillation or column chromatography.

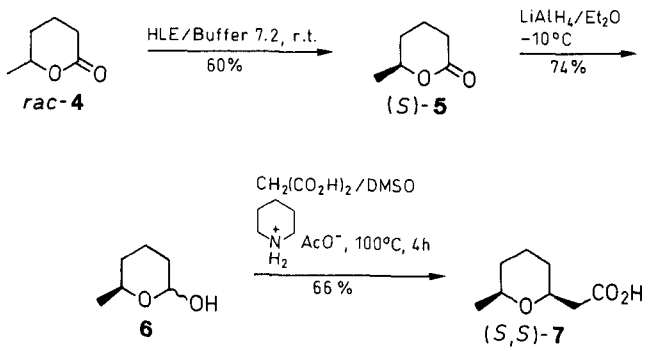
were measured with a Hewlett Packard 5970 spectrometer, interfaced on a Hewlett Packard 5890A gas chromatograph, equipped with an SE-30 capillary column (12 m × 0.25 mm i.d.). Optical rotations were determined at 20–25 °C, on a Perkin-Elmer 141 polarimeter. Analytical TLC was carried out on Merck silica gel $60F_{254}$ precoated aluminum sheets, with mixtures of Et_2O/light petroleum ether and spots were visualized with I_2 or with 40% methanolic H_2SO_4 and heating at 100 °C. Column chromatography was carried out on Merck silica gel (0.05–10.2 mm). Petroleum ether refers to that fraction boiling in the range 40–60 °C. DMSO, piperidine and pyridine were of reagent grade purity, from freshly opened containers and dried over 3Å molecular sieves. Piperidinium acetate was formed, from equimolecular quantities of piperidine and AcOH. Horse liver esterase (HLE) acetone powder was purchased from Sigma and 5-hydroxypentanal from Janssen Chimica.

Table 2. Characterization of Products **2a–d** and **3a**

Product	mp (°C) (solvent)	Lit. mp (°C)	IR (CCl_4) ν (cm^{-1})	^1H NMR (CCl_4/TMS) δ, J (Hz)	MS m/z (%)
2a	oil	oil[19]	2980, 2880, 1710, 1420, 1300, 1070	1.55 (m, 1H), 1.80–2.10 (m, 3H), 2.52 (dd, 2H), 3.70–3.90 (m, 2H), 4.25 (m, 1H)	129 (1), 112 (8), 102 (47), 84 (38), 71 (92), 56 (18), 55 (22), 43 (100)
2b	54–56 (hexane)	55–57[20]	2938, 2858, 2848, 1712, 1440, 1301, 1174, 1087, 940	1.50 (m, 6H), 2.45–2.5 (dd, 2H), 3.45 (m, 1H), 3.70 (m, 1H), 3.95–4.00 (two s, 1H)	144 (1), 115 (25), 102 (71), 85 (65), 84 (60), 60 (20), 55 (50), 41 (100)
2c	oil	oil[23]			144 (1), 143 (1), 129 (12), 111 (30), 102 (100), 85 (62), 56 (51), 55 (53)
2d(*cis*)	52 (hexane)	52–53[14]	2975, 2936, 1715, 1443, 1295, 1090, 1070, 1040	[a]1.20 (d, 3H, J = 6), 1.25–1.35 (m, 2H), 1.60–1.90 (m, 4H), 2.52 (dd, 1H, J = 16, 5), 2.57 (dd, 1H, J = 16, 7), 3.55 (m, 1H), 3.75 (m, 1H)	158 (2), 143 (4), 140 (4), 125 (10), 116 (10), 115 (19), 102 (46), 99 (18), 98 (17), 97 (16), 89 (22), 86 (22), 81 (26), 71 (28), 70 (18), 60 (30), 55 (100), 45 (82), 43 (95), 42 (99)
3a	62–63 (hexane)	oil[22]	3400, 2945, 1700, 1655, 1285, 1060	1.75 (m, 2H), 2.37 (m, 2H), 3.69 (t, 2H, J = 6), 5.85 (d, 1H, J = 14), 7.10 (dt, 1H, J = 14, 6)	

[a] Recorded on a Bruker 200 MHz in $CDCl_3$.

Because (−)-(*S*)-5-hexanolide (**5**) (Scheme 2) is readily available in excellent enantiomeric excess, by an enzymatic resolution of its racemate **4**,[18] the synthesis of the natural optical isomer **7**, was carried out. The (−)-(5)-hexanolide (**5**) was reduced by lithium aluminum hydride in diethyl ether,[13] to the corresponding lactol **6**, which was converted as described above, to the natural (+)-(*S,S*)-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid (**7**), in excellent chemical yield and high enantiomeric excess.



Scheme 2

Melting points were measured with a Büchi 510 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1750 IR Fourier Transform spectrophotometer. ^1H NMR spectra were recorded on a Varian EM360 instrument (60 MHz). Mass spectra

Tetrahydrofuranyl- and Tetrahydropyranylacetic Acids 2a–d; General Procedure:

Method A: To a stirred solution of piperidine (0.5 mmol) and AcOH (0.5 mmol) in DMSO (30 mL), was added malonic acid (50 mmol). To the resulting clear solution, the lactol **1** (25 mmol) was added and the mixture was stirred at r.t. for 30 min. Then it was heated at 100 °C under stirring, until the evolution of CO_2 had stopped (3–4 h). The mixture was poured into H_2O (100 mL) and extracted with Et_2O (3 × 50 mL). The organic layer was washed once with a sat. aq NaCl (50 mL), dried (Na_2SO_4) and the solvent was concentrated in vacuo. The residue was purified, either by distillation or/and by column chromatography.

(±)-*Tetrahydrofuran-2-ylacetic Acid* (**2a**):

Compound **2a** was obtained from 4-hydroxybutanal (**1a**; 4.0 g, 0.045 mol) by the general procedure and was purified by column chromatography (petroleum ether/Et_2O, 3:7) to afford a colorless oil (3.8 g, 66%). The ^1H NMR spectrum of this compound was identical with the spectrum of an authentic sample.

(±)-*Tetrahydropyran-2-ylacetic Acid* (**2b**):

Compound **2b** was obtained from 5-hydroxypentanal (**1b**; 4.0 g, 0.039 mol) by the general procedure and was purified by distillation (bp 115–120 °C/1.5 Torr). Crystallization from hexane gave colorless crystals (4.0 g, 71%); mp 54–56 °C. The spectroscopic data of this compound were consistent with the reported in Lit.[21].

(±)-(*5-Methyltetrahydrofuran-2-yl*)*acetic Acid* (**2c**):

The mixture of the two isomers **2c**, was obtained from lactol **1c** (4.0 g, 0.039 mol) by the general procedure and purified by column chromatography (petroleum ether/Et_2O, 3:7) to afford a colorless oil (3.65 g, 65%). The IR and ^1H NMR spectra were consistent with

those of the Lit.[23] GCMS analysis gave two products in a ratio of 1:1 with identical mass spectra.

(±)-*(cis-6-Methyltetrahydropyran-2-yl)acetic Acid* (**2d**):

The compound **2d**, was obtained from the lactol **1d** (5.0 g, 0.043 mmol) by the general procedure and was purified by distillation (bp 125–145°C/1 Torr) to give a colorless oil which solidified. Recrystallization from hexane gave colorless crystals (5.1 g, 75%); mp 52°C. The spectroscopic data of this compound were consistent with that reported.[7a,7d]

(*E*)-6-Hydroxyhex-2-enoic Acid (3a):

Method B: Compound **3a** was obtained from the 4-hydroxybutanal (**1a**; 1.6 g, 0.018 mol) by the classical Knoevenagel condensation[11] and was purified by column chromatography (petroleum ether/Et_2O, 1:9) to give a colorless crystalline solid. Recrystallization from hexane gave pure **3a** (1.65 g, 70%); mp 62–63°C. The spectroscopic data of this compound were consistent with that reported.[22a]

(+)-(*S,S*)-(6-Methyltetrahydropyran-2-yl)acetic Acid (7):

a: Enzymatic resolution of the racemic 5-hexanolide **4** by horse liver esterase, according to the described procedure,[18] gave the (−)-(*S*)-5-hexanolide (**5**), as a colorless oil $[\alpha]_D^{25}$ −42.0° (*c* = 2, EtOH) [Lit.[18] $[\alpha]_D^{20}$ −41.7° (*c* = 2.2, EtOH)].

b: Reduction of the lactone **5** (2.15 g, 0.019 mol), by a solution of $LiAlH_4$ in Et_2O (23 mL, 0.25 M) at −10°C,[13] gave the lactol **6** (1.6 g, 74%), which was used in the next step without further purification.

c: Condensation of the lactol **6** (1.6 g, 0.013 mol) with malonic acid according to the general procedure, gave the title compound **7**, which was purified by column chromatography (petroleum ether/Et_2O, 3:7) to give a colorless oil (1.45 g, 66%); $[\alpha]_D^{25}$ +43.0° (*c* = 2, benzene) [Lit.[7] $[\alpha]_D^{20}$ +43.85° (*c* = 2.52, benzene); all spectral data were identical with those of the racemic compound **2d**.

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