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A New Method for the Synthesis of 2-Carboxymethyl-2-hydroxy-tetrahydropyrans

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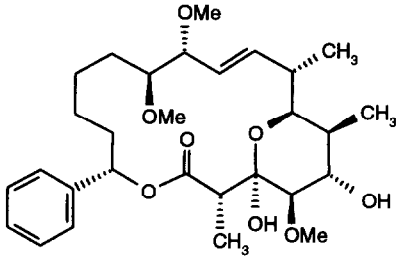
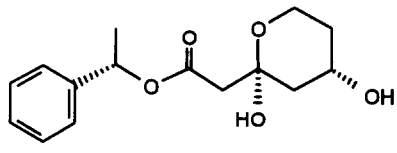
Abstract: A simple synthesis of the title compounds **5** from diketene, and the aldehyde **3** is described.

2-Carboxymethyl-2-hydroxy-tetrahydropyrans are structural units which are to be found in various natural products including the ionophore antibiotics[1], the toxin pederin[2], and the cytotoxic and fungicidal macrolide soraphen A.[3] We were interested in the notion that the biological activity of soraphen A may be invoked by simpler acyclic analogs which contain the 2-carboxymethyl-2-hydroxy-tetrahydropyran moiety.



Soraphen A



Model Compounds

The synthesis of such structures has been reported using either a direct method, via addition of an ester enolate to a δ-lactone[4], or via its ϕ-hydroxy-β-ketoester tautomer **5a**.[5] Thus one of the many known syntheses of β-ketoesters may be used if it is compatible with the protected ϕ-hydroxy group.

The titanium tetrachloride induced reaction between diketene **2**, aldehyde and alcohol found by Mukaiyama combines reactive and inexpensive reagents to yield β-ketoesters in one step[6]. We have found that by using suitably protected β-hydroxyaldehydes **3** under the conditions described by Mukaiyama, the desired compounds **4** were isolated in good yields. Removal of the protecting group then allowed the molecule to close to the hemiacetal structure **5b**.

Scheme 1. Synthesis of Compounds **5**

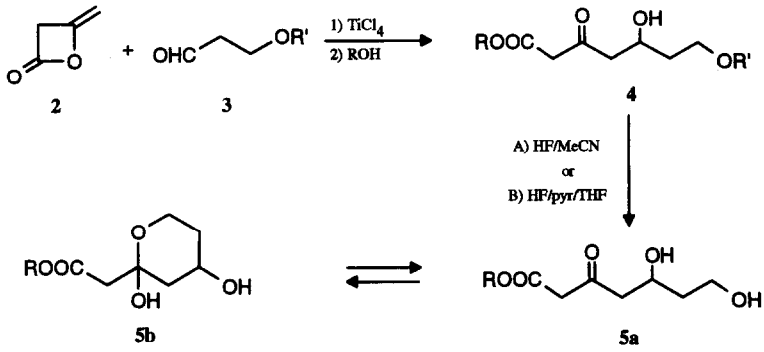
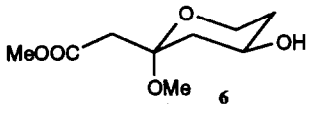


Table 1. Yields of the Processes from Scheme 1.

R'	R	4(%)	Method	5(%)
$ThxMe_2Si$	tBu	55	A	54
$ThxMe_2Si$	Et	52	A	50
$ThxMe_2Si$	Me	a		
$tBuPh_2Si$	Me	68	A	23
$tBuPh_2Si$	Et	73	A	25
			B	65
$tBuPh_2Si$	tBu	75	A	40
			B	69
$tBuPh_2Si$	PhCH2	62	B	76
$tBuPh_2Si$	PhCHMe	60	B	72
$tBuPh_2Si$	PhCHEt	59	B	76

a) **6** (16%) was formed in this reaction.



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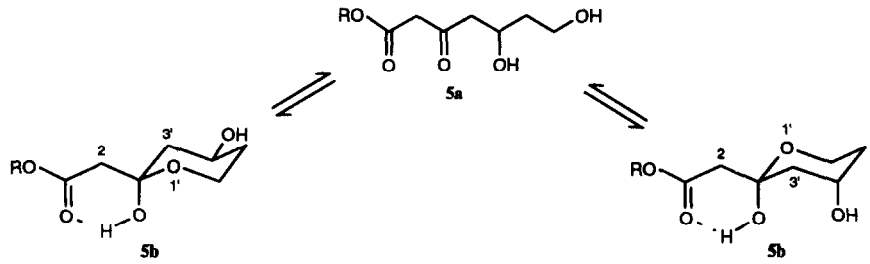
The requisite protected β-hydroxy-aldehydes were prepared by iBu_2AlH reduction of the corresponding β-hydroxynitriles[7]. We thought initially that use of chiral titanium complexes[8] might make a synthesis of optically active products possible, but it transpired that titanium compounds less active than $TiCl_4$ were ineffective as catalysts. $CpTiCl_3$ did not bring about a reaction at temperatures below 0°C, and did

not yield the desired product above this temperature. Using $TiCl_4$ however the reaction is finished after a few minutes at -78°C.

It became clear from the rather moderate yields found with the $ThxMe_2Si$[9] protecting group (Entries 1 and 2), and the formation of the acetal **6** when methanol was used as the alcohol component (Entry 3), that the $ThxMe_2Si$ group was too labile for the acidic conditions under which the condensation was carried out. The more tenacious $tBuPh_2Si$ group presented no problem, and high yields of the β-ketoesters were isolated.

The conditions used for cleaving the protecting group proved to be important. HF/pyridine[10] (B) resulted in higher yields of **5** than the more acidic HF/acetonitrile[11] (A), particularly for the removal of the $tBuPh_2Si$ group.

The compounds isolated were mixtures of slowly interconverting hemiacetal (**5b**) and hydroxyketone (**5a**) tautomers, wherein the hemiacetal form dominates. The two hemiacetal (**5b**) tautomers have either an axial or an equatorial hydroxy group at C(4'), and both have a hydrogen bond between the anomeric hydroxyl and the carbonyl of the ester, which is evidenced by a long range coupling between the hydroxyl proton at C(2') and an axial proton on C(3'). This contrasts with the hydrogen bond in soraphen A itself, formed between the anomeric hydroxyl and the hydroxyl in the tetrahydropyran ring.



Scheme 2. Tautomerisation of Compounds **5**.

None of the compounds described here showed either fungicidal activity or an ability to inhibit fungal acetyl-CoA-carboxylase[12], at concentrations up to 300 times the IC_{50} of soraphen A.

In summary, three readily available and inexpensive materials are condensed in one simply performed step, followed by a deprotection step, affording a high yield convergent synthesis of 2-carboxymethyl-2-hydroxy-tetrahydropyrans.

EXPERIMENTAL

General:- The NMR measurements were made on a Varian Unity 500, or XL300, or a Bruker AM400 NMR spectrometer at room temperature in $CDCl_3$. IR measurements were made on a Perkin-Elmer 1420. THF was dried by distillation from sodium/benzophenone. Glassware was dried with a flame and cooled under nitrogen. We thank Dr. T. Allmendinger for the detailed procedure for the preparation of the aldehydes 3[7].

A- Preparation of the aldehydes 3

3-Thexyldimethylsilyloxy-propionaldehyde (**3**; R' = $ThxMe_2Si$)

a) A solution of 3-hydroxy-propionitrile (3.24g, 45.6mmol) in CH_2Cl_2 (15ml) was added slowly to a solution of DBU (8.27g, 54 mmol) and thexyldimethylchlorosilane (9g, 50 mmol) in CH_2Cl_2 (25ml). After 18 hrs at room temperature the mixture was washed with water, HCl (0.1M), and $NaHCO_3$ (sat.). After drying (Na_2SO_4), filtration, evaporation of the solvent,and bulb to bulb distillation (120°C / 4.10^{-1} mbar), 3-thexyldimethylsilyloxy-propionitrile was isolated in 99% yield. NMR (250 MHz): δ = 0.0 (s, Me_2-Si); 0.75 (m, Thx); 1.48 (m, Thx); 2.40 (t, J=6Hz, 2H-C(2)); 3.70 (t, J=6Hz, 2H-C(3)). IR: 2260 cm^{-1} (CN).

b) A solution of iBu_2Al (1M in CH_2Cl_2, 65 ml, 65 mmol) was added slowly to a solution of 3-thexyldimethylsilyloxy-propionitrile (9.6g, 45 mmol) in toluene (80 ml) under argon at -60°C. After 2 hrs at this temperature the reaction was warmed to -30°C and MeOH (2,5 ml) was added. The mixture was then poured into a cold saturated solution of NH_4Cl, acidified with H_2SO_4 (1M) and stirred for 30 minutes. After separation of the two phases, the aqueous phase was reextracted twice with toluene. The combined organic phase was washed with Na_2CO_3 (satd) and NaCl (satd), dried with $MgSO_4$, and chromatographed on silica (EtOAc / hexane 1:5). (Yield 60%). NMR (250 MHz): δ = 0.0 (s, Me_2-Si); 0.75 (m, Thx); 1.49 (m, Thx); 2.49 (dt, J_t=6Hz, J_d=3Hz, 2H-C(2)); 3.87 (t, J=6Hz, 2H-C(3)); 9.7 (t, J=3Hz, H-C(1)). IR: 1730cm^{-1} (C=O).

3-Tert.butyldiphenylsilyloxy-propionaldehyde (**3**; R' = $tBuMe_2Si$).

a) Imidazole (13.62g, 200 mmol) was added to a solution of 3-hydroxypropionitrile (7.6g, 106 mmol) and tert.butyldiphenylchlorosilane (25 ml, 97 mmol) in DMF (70 ml) under argon at 0°C, and the mixture left at room temperature for 16 hrs. The mixture was extracted between water, hexane, and ether, the organic phase dried (Na_2SO_4), and the solvent evaporated to yield 3-tert.butyldiphenylsilyloxy-propionitrile in quantitative yield. NMR (250 MHz): δ = 1.1 (s, tBu); 2.58 (t, J=6Hz, 2H-C(2)); 3.85 (t, J=6Hz, 2H-C(3)); 7.38-7.48 and 7.65-7.70 (2m, Ph). IR: 2260cm^{-1} (CN).

b) A solution of iBu_2Al (1M in CH_2Cl_2, 160 ml, 160 mmol) was added slowly to a solution of 3-tert.butyldiphenylsilyloxy-propionitrile (40g, 130 mmol) in toluene (200ml) under argon at -70°C. After 3 hrs at -40°C, MeOH (2,5 ml) was added. The mixture was then poured into a cold saturated solution of NH_4Cl (300ml), acidified with H_2SO_4 (1M) and stirred for 30 minutes. After separation of the two phases, the aqueous phase was reextracted twice with toluene. The combined organic phase was washed with Na_2CO_3 (satd) and NaCl (satd), dried with $MgSO_4$, and chromatographed on silica (EtOAc / hexane 1:4). (Yield 80%). NMR (250 MHz): δ = 1.05 (s, tBu); 2.60 (dt, J_d=2Hz, J_t=6Hz, 2H-C(2)); 4.0 (t, J=6Hz, 2H-C(3)); 7.30-7.53 and 7.60-7.72 (2m, Ph); 9.81 (t, J=3Hz, H-C(1)). IR: 1730 cm^{-1} (C=O).

B-General procedure for the preparation of the esters 4.

$TiCl_4$ (0.7 ml, 6.4 mmol) was added in one part to a rapidly stirred solution of the aldehyde **3** (6.4 mmol) and freshly distilled diketene (1.08g, 12.8 mmol) in CH_2Cl_2 (40 ml) under argon at -78°C. After 5 minutes stirring at this temperature the alcohol (60 mmol) was added and the mixture stirred at -10°C et -20°C. The reaction was followed by tlc. After completion of the reaction the mixture was poured into a cold solution of K_2CO_3 (50 ml, 4.4mM, aq.). The organic phase was washed with Na_2CO_3 (satd) and NaCl (satd), dried with $MgSO_4$, and chromatographed on silica

5-Hydroxy-3-oxo-7-thexyldimethylsilyloxy-heptanoic acid t.butyl ester (**4**; R = t.Bu; R' = $ThxMe_2Si$)

Eluant : EtOAc / hexane 1:3. Yield 55%. NMR (500 MHz): δ = 0.06 (s, Me-Si); 0.07 (s, Me-Si); 0.82 (m, Thx); 1.43 (s, tBu-Si); 1.57 (m, H-C(6)); 1.61-1.68 (m, H-C(6), Thx); 2.64 (dd, J=17.5, 5Hz, H-C(4)); 2.67 (dd, J=17.5, 7.5Hz, H-C(4)); 3.35 (s, 2H-C(2)); 3.50 (d, J=2.5Hz, OH); 2.76 (m, 2H-C(7)); 4.24 (m, H-C(5)). IR: 1710 cm^{-1} (C=O ester); 1735 cm^{-1} (C=O ketone); 3480 cm^{-1} (OH).

5-Hydroxy-3-oxo-7-thexyldimethylsilyloxy-heptanoic acid ethyl ester (**4**; R = Et; R' = $ThxMe_2Si$)

Eluant : EtOAc / hexane 1:7. Yield 52%. NMR (250 MHz): δ = 0.01 (s, 2Me-Si); 0.76 (m, Thx); 1.18 (t, J=7Hz, Me); 1.45-1.62 (m, 2H-C(6), Thx); 2.62 (m, 2H-C(4)); 3.38 (s, 2H-C(2)); 3.41 (d, J=2.5Hz, OH); 3.70 (m, 2H-C(7)); 4.09 (q, J=7Hz, CH_2CH_3); 4.19 (m, H-C(5)). IR: 1710 cm^{-1} (C=O ester); 1730 cm^{-1} (C=O ketone); 3460 cm^{-1} (OH).

5-Hydroxy-3-oxo-7-t.butyldiphenylsilyloxy-heptanoic acid methyl ester (**4**; R = Me; R' = $t.BuPh_2Si$)

Eluant : EtOAc / hexane 1:3. Yield 68%. NMR (400 MHz): δ = 1.05 (s, tBu); 1.72 (m, 2H-C(6)); 2.68 (dd, J=17.5, 5Hz, H-C(4)); 2.75 (dd, J=17.5, 7.5Hz, H-C(4)); 3.40 (d, J=2.5Hz, OH); 3.51 (s, 2H-C(2)); 3.73 (s, OMe); 3.85 (m, 2H-C(7)); 4.37 (m, H-C(5)); 7.34-7.47 and 7.61-7.70 (2m, Ph). IR: 1740 cm^{-1} (C=O); 3500 cm^{-1} (OH).

5-Hydroxy-3-oxo-7-t.butyldiphenylsilyloxy-heptanoic acid ethyl ester (**4**; R = Et; R' = $t.BuPh_2Si$)

Eluant : EtOAc / hexane 2:5. Yield 73%. NMR (500 MHz): δ = 1.05 (s, tBu); 1.28 (t, J=7.5Hz, Me); 1.68(m, H-C(6)); 1.76 (m, H-C(6)); 2.69 (dd, J=17.5, 5Hz, H-C(4)); 2.75 (dd, J=17.5, 7.5Hz, H-C(4)); 3.44 (d, J=2.5Hz, OH); 3.49 (s, 2H-C(2)); 3.85 (m, 2H-C(7)); 4.19 (q, J=7.5Hz, CH_2Me); 4.37 (m, H-C(5)); 7.37-7.46 and 7.64-7.69 (2m, Ph).

5-Hydroxy-3-oxo-7-t.butyldiphenylsilyloxy-heptanoic acid t.butyl ester (**4**; R = t.Bu; R' = $t.BuPh_2Si$)

Eluant : EtOAc / hexane 1:7. Yield 75%. NMR (250 MHz): δ = 1.05 (s, tBu-Si); 1.46 (s, tBu-O); 1.72 (m, 2H-C(6)); 2.72 (m, 2H-C(4)); 3.40 (s, 2H-C(2)); 3.48 (d, J=2.5Hz, OH); 3.85 (m, 2H-C(7)); 4.37 (m, H-C(5)); 7.30-7.50 and 7.60-7.70 (m, Ph). IR: 1730 cm^{-1} (C=O); 3500 cm^{-1} (OH).

5-Hydroxy-3-oxo-7-t.butyldiphenylsilyloxy-heptanoic acid benzyl ester (**4**; R = CH_2Ph; R' = $t.BuPh_2Si$)

Eluant : EtOAc / hexane 1:3. Yield 62%. NMR (250 MHz): δ = 1.05 (s, tBu); 1.71 (m, 2H-C(6)); 2.70 (m, 2H-C(4)); 3.43 (d, J=2.5Hz, OH); 3.55 (s, 2H-C(2)); 3.72-3.90 (m, 2H-C(7)); 4.36 (m, H-C(5)); 5.18 (s, $C\underline{H}_2Ph$); 7.30-7.50 and 7.60-7.70 (m, Ph). IR: 1715 cm^{-1} (C=O ester); 1745 cm^{-1} (C=O ketone); 3480 cm^{-1} (OH):

5-Hydroxy-3-oxo-7-t.butyldiphenylsilyloxy-heptanoic acid α–methylbenzyl ester (**4**; R = CHMePh; R' = $t.BuPh_2Si$)

Eluant : EtOAc / hexane 1:3. Yield 60%. NMR (400 MHz): δ = 1.04 (s, tBu); 1.55 (d, J=6Hz, Me); 1.69 (m, 2H-C(6)); 2.68 (m, 2H-C(4)); 3.39 (d, J=2.5Hz, OH); 3.5 (s, 2H-C(2)); 3.83 (m, 2H-C(7)); 4.35 (m, H-C(5)); 5.93 (q, J=7.5Hz, C<u>H</u>-Me); 7.27-7.47 and 7.62-7.70 (m, Ph). IR: 1715 cm^{-1} (C=O ester); 1735 cm^{-1} (C=O ketone); 3500 cm^{-1} (OH).

5-Hydroxy-3-oxo-7-t.butyldiphenylsilyloxy-heptanoic acid α-ethylbenzyl ester (**4**; R = CHEtPh; R' = t.BuPh_2Si)

Eluant : EtOAc / hexane 1:3. Yield 59%. NMR (500 MHz): δ = 0.90 (t, J=7.5Hz, Me); 1.05 (s, tBu); 1.62 (m, H-C(6)); 1.71 (m, H-C(6)); 1.85 (m, CH-Me); 1.96 (m, CH-Me); 2.66 (m, 2H-C(4)); 3.41 (d, J=2.5Hz, OH); 3.50 (s, 2H-C(2)); 3.83 (m, 2H-C(7)); 4.34 (m, H-C(5)); 5.70 (t, J=7.5Hz, CH-Ph); 7.28-7.48 and 7.61-7.69 (m, Ph). IR: 1735 cm^{-1} (C=O); 3500cm^{-1} (OH).

(4'-Hydroxy-2'-methoxy-tetrahydropyran-2'-yl)-acetic acid methyl ester **6**.

Yield 16%. NMR (500 MHz): δ= 1.47-1.55 (m, H_{ax}-C(5'), HO); 1.58 (dd, J=13, 12Hz, H_{ax}-C(3')); 1.90 (m, H_{eq}-C(5')); 2.31 (ddd, J=13, 5, 2Hz, H_{eq}-C(3')); 2.64 (d, J=15Hz, H-C(2)); 2.77 (d, J=15Hz, H-C(2)); 3.24 (s, MeO-C(2')); 3.60 (ddd, J=13, 12, 2Hz, H_{ax}-C(6')); 3.70 (s, MeOCO); 3.76 (m, H_{eq}-C(6')); 4.08 (dddd, J=12, 12, 5, 5Hz, H_{ax}-C(4')).

C General procedure for the preparation of the products 5(a+b).

Method A[11].

The ester **4** (0.45 mmol) was dissolved in 2 ml of a solution of HF:H_2O:MeCN (2:3:95 vol%). After 60 min. at room temperature, Na_2CO_3 (satd, 2ml) was added, the mixture was extracted with CH_2Cl_2, dried with $MgSO_4$, and chromatographed on silica (EtOAc / hexane 2:1).

Method B[10].

The ester **4** (0.2 mmol) was dissolved in 1ml of a solution of HF/pyr/THF (prepared from 60-70% HF/pyridine (7.8g), pyridine(18.8ml), and THF(60ml)). The reaction was stirred for ca 30-60 min. (tlc), taken up in CH_2Cl_2, washed with water, HCl (2M), water once more, and dried with $MgSO_4$. Chromatography on silica (EtOAc 100%) afforded the product.

(2',4'-Dihydroxy-tetrahydro-pyran-2'-yl)-acetic acid t.butyl ester (**5**, R = tBu)

Yields:- From **4** (R' = ThxMe_2Si), 54% method A. From **4** (R' = t.BuPh_2Si), 40% method A, 69% method B.
Tautomer A. (C(4')-OH in an equatorial position). NMR (500 MHz): δ=.1.27 (m, H_{ax}-C(3')); 1.47 (s, tBu); 1.52 (m, H_{ax}-C(5')); 1.91 (dddd, J=12, 4, 4, 2Hz, H_{eq}-C(5')); 2.12 (ddd, J=12, 4, 2Hz, H_{eq}-C(3')); 2.51 (d, J=15Hz, H-C(2)); 2.56 (d, J=15Hz, H-C(2)); 3.72 (ddd, J=12, 5, 2Hz, H_{eq}-C(6')); 3.95 (ddd, J=13, 12, 2Hz, H_{ax}-C(6')); 4.17 (m, H-C(4')); 5.12 (d, J=2.5Hz, HO-C(2')). IR: 1710cm^{-1} (C=O); 3450cm^{-1} (OH).
Tautomer B. (C(4')-OH in an axial position) NMR (500 MHz): δ= 1.47 (s, tBu); 1.64 (ddd, J=15, 2.5, 2.5Hz, H_{ax}-C(3')); 1.70 (m, H_{eq}-C(5')); 1.80 (dddd, J=14, 14, 6, 3Hz, H_{ax}-C(5')); 1.98 (ddd, J=14,3,3Hz, H_{eq}-C(3')); 2.48 (d, J=15Hz, H-C(2)); 2.51 (d, J=15Hz, H-C(2)); 3.65 (dd, J=12, 6Hz, H_{eq}-C(6')); 3.94 (d, J=10Hz, HO-C(4')); 4.10 (m, H-C(4')); 4.28 (ddd, J=12.5, 12.5, 2.5Hz, H_{ax}-C(6')); 5.57 (d, J=2.5Hz, HO-C(2')). IR: 1710cm^{-1} (C=O); 3450cm^{-1} (OH).

(2',4'-Dihydroxy-tetrahydropyran-2'-yl)-acetic acid ethyl ester (**5**, R = Et)

Yields:- From **4** (R' = ThxMe_2Si), 50% method A. From **4** (R' = t.BuPh_2Si), 25% method A, 65% method B.
Tautomer A. (C(4')-OH in an equatorial position)NMR (500 MHz): δ= 1.29 (t, J=7Hz, Me); 1.32 (m, H_{ax}-C(3')); 1.50 (m, HO-C(4'), H_{ax}-C(5')); 1.90 (dddd, J=12, 4, 4, 2Hz, H_{eq}-C(5')); 2.15 (ddd, J=12, 4, 2Hz, H_{eq}-C(3')); 2.58 (d, J=15Hz, H-C(2)); 2.66 (d, J=15Hz, H-C(2)); 3.73 (ddd, J=12, 5, 2Hz, H_{eq}-C(6')); 3.94 (ddd, J=13, 12, 2Hz, H_{ax}-C(6')); 4.14 (m, H-C(4')); 4.21 (q, J=7Hz, CH_2Me); 4.96 (d, J=2.5Hz, HO-C(2')).

Tautomer B. (C(4')-OH in an axial position) NMR (500 MHz): δ= 1.29 (t, J=7Hz, Me); 1.66-1.72 (m, H_{eq}-C(5'), H_{ax}-C(3')); 1.81 (dddd, J=14, 14, 6, 3Hz, H_{ax}-C(5')); 2.00 (ddd, 14, 3, 3Hz, H_{eq}-C(3')); 2.57 (d, J=15Hz, H-C(2)); 2.60 (d, J=15Hz, H-C(2)); 3.65 (dd J=12, 6Hz, H_{eq}-C(6')); 3.85 (d, J=10Hz, HO-C(4')); 4.14 (m, H-C(4')); 4.21 (q, J=7Hz, C<u>H</u>$_2$Me); 4.28 (ddd, J=12.5, 12.5, 2.5Hz, H_{ax}-C(6')); 5.44 (d, J=2.5Hz, HO-C(2')).

<u>(2',4'-Dihydroxy-tetrahydro-pyran-2'-yl)-acetic acid methyl ester</u> (**5**, R = Me)

Yield From **4** (R' = $tBuPh_2Si$), 23% method A.
Tautomer A. (C(4')-OH in an equatorial position) NMR (500 MHz): δ = 1.31 (ddd, J=12.5, 12.5, 2.5Hz, H_{ax}-C(3')); 1.50 (m, H_{ax}-C(5'), HO-C(4')); 1.91 (dddd, J=12, 4, 4, 2Hz, H_{eq}-C(5')); 2.15 (ddd, J=12, 4, 2Hz, H_{eq}-C(3')); 2.60 (d, J=15Hz, H-C(2)); 2.68 (d, J=15Hz, H-C(2)); 3.73 (m, H_{eq}-C(6')); 3.72 (s, MeO); 3.94 (ddd, J=13, 12, 2Hz, H_{ax}-C(6')); 4.16 (m, H-C(4')); 4.85 (d, J=2.5Hz, HO-C(2')).
Tautomer B. (C(4')-OH in an axial position) NMR (500 MHz): δ = 1.69 (m, Heq-C(5'), H_{ax}-C(3')); 1.81 (dddd, J=14, 14, 6, 3Hz, H_{ax}-C(5')); 2.01 (ddd, J=14, 3, 3Hz, H_{eq}-C(3')); 2.58 (d, J=15Hz, H-C(2)); 2.63 (d, J=15Hz, H-C(2)); 3.65 (dd, J=12, 6Hz, H_{eq}-C(6')); 3.72 (s, MeO); 3.80 (d, J=10Hz, HO-C(4')); 4.16 (m, H-C(4')); 4.27 (ddd, J=12.5, 12.5, 2.5Hz, H_{ax}-C(6')); 5.34 (d, J=2.5Hz, HO-C(2')).

<u>(2',4'-Dihydroxy-tetrahydro-pyran-2'-yl)-acetic acid benzyl ester</u> (**5**, R = CH_2Ph).

From **4** (R' = $tBuPh_2Si$), 76% method B.
Tautomer A. (C(4')-OH in an equatorial position) NMR (500 MHz): δ= 1.32 (ddd, J=12.5, 12.5, 2.5Hz, H_{ax}-C(3')); 1.51 (m, HO-C(4'), H_{ax}-C(5')); 1.92 (dddd, J=12, 4, 4, 2Hz, H_{eq}-C(5')); 2.15 (ddd, J=12, 4, 2Hz, H_{eq}-C(3')); 2.65 (d, J=15Hz, H-C(2)); 2.74 (d, J=15Hz, H-C(2)); 3.73 (ddd, J=12, 5, 2Hz, H_{eq}-C(6')); 3.95 (ddd, J=13, 12, 2Hz, H_{ax}-C(6')); 4.17 (m, H-C(4')); 4.83 (d, J=2.5Hz, HO-C(2')); 5.16 (d, J=12.5Hz, C<u>H</u>-Ph); 5.23 (d, J=12.5Hz, C<u>H</u>-Ph); 7.31-7.40 (m, Ph). IR: 1720 cm^{-1} (C=O); 4370 cm^{-1} (OH).
Tautomer B. (C(4')-OH in an axial position) NMR (500 MHz): δ= 1.70 (m, H_{eq}-C(5'), H_{ax}-C(3')); 1.81 (dddd, J=14, 14, 6, 3Hz, H_{ax}-C(5')); 2.02 (ddd, J=14, 3, 3Hz, H_{eq}-C(3')); 2.64 (d, J=15Hz, H-C(2)); 2.68 (d, J=15Hz, H-C(2)); 3.66 (dd, J=12, 6Hz, H_{eq}-C(6')); 3.80 (d, J=10Hz, HO-C(4')); 4.17 (m, H-C(4')); 4.28 (ddd, J=12.5, 12.5, 2.5Hz, H_{ax}-C(6')); 5.17 (d, J=12.5Hz, C<u>H</u>-Ph); 5.22 (d, J=12.5Hz, C<u>H</u>-Ph); 5.31 (d, J=2.5Hz, HO-C(2')); 7.31-7.40 (m, Ph). IR: 1720 cm^{-1} (C=O); 4370 cm^{-1} (OH).

<u>(2',4'-Dihydroxy-tetrahydro-pyran-2'-yl)-acetic acid (±) α methylbenzyl ester</u> (**5**, R = CHMePh).

From **4** (R' = $tBuPh_2Si$), 72% method B. The product was a mixture of two pairs of diastereomers, each of which consists of two tautomers.
Diastereomer A Tautomer A (C(4')-OH in an equatorial position) NMR (400 MHz): δ = 1.31 (ddd, J=12.5, 12.5, 2.5Hz, H_{ax}-C(3')); 1.44 (d, J=5Hz, HO-C(4')); 1.50 (m, H_{ax}-C(5')); 1.56 (m, Me); 1.89 (dddd, J=12, 4, 4, 2Hz, H_{eq}-C(5')); 2.15 (ddd, J=12, 4, 2Hz, H_{eq}-C(3')); 2.64 (d, J=15Hz, H-C(2)); 2.72 (d, J=15Hz, H-C(2)); 3.67 (m, H_{eq}-C(6')); 3.89 (ddd, J=13, 12, 2Hz, H_{ax}-C(6')); 4.15 (m, H-C(4')); 4.78 (d, J=2.5Hz, HO-C(2')); 5.96 (q, J=7.5Hz, C<u>H</u>-Ph); 7.28-7.39 (m, Ph). IR: 1715 cm^{-1} (C=O); 3460 cm^{-1} (HO).
Diastereomer A Tautomer B (C(4')-OH in an axial position) NMR (400 MHz): δ = 1.56 (m, Me); 1.64-1.73 (m, H_{eq}-C(5'), H_{ax}-C(3')); 1.81 (dddd, J=14, 14, 6, 3Hz, H_{eq}-C(5')); 1.98 (ddd, J=14, 3, 3Hz, H_{eq}-C(3')); 2.57 (d, J=15Hz, H-C(2)); 2.65 (d, J=15Hz, H-C(2)); 3.67 (m, H_{eq}-C(6')); 3.82 (d, J=10Hz, HO-C(4')); 4.15 (m, H-C(4')); 4.28 (ddd, J=12.5, 12.5, 2.5Hz, H_{ax}-C(6')); 5.35 (d, J=2.5Hz, HO-C(2')); 5.95 (q, J=7.5Hz, C<u>H</u>-Ph); 7.28-7.39 (m, Ph). IR: 1715 cm^{-1} (C=O); 3460 cm^{-1} (OH).
Diastereomer B Tautomer A (C(4')-OH in an equatorial position) NMR (400 MHz): δ = 1.30 (ddd, J=12.5, 12.5, 2.5Hz, H_{ax}-3'); 1.45 (d, J=5Hz, HO-C(4')); 1.51 (m, H_{ax}-C(5')); 1.57 (d, J=7.5Hz, Me); 1.90 (dddd, J=12, 4, 4, 2Hz, H_{eq}-C(5')); 2.12 (ddd, J=12, 4, 2Hz, H_{eq}-(3')); 2.57 (d, J=15Hz, H-C(2)); 2.71 (d, J=15Hz, H-C(2)); 3.74 (ddd, J=12, 5, 2Hz, H_{eq}-(6')); 3.94 (ddd, J=13, 12, 2Hz, H_{ax}-C(6')); 4.15 (m, H-C(4')); 4.89 (d, J=2.5Hz, HO-C(2')); 5.95 (q, J=7.5Hz, C<u>H</u>-Ph); 7.27-7.39 (m, Ph). IR: 1715 cm^{-1} (C=O); 3460 cm^{-1} (HO).

Diastereomer B Tautomer B (C(4')-OH in an axial position). NMR (400 MHz): δ = 1.57 (d, J=7.5Hz, Me); 1.64-1.73 (m, H_{eq}-C(5'), H_{ax}-C(3')); 1.79 (dddd, J=14, 14, 6, 3Hz, H_{eq}-C(5')); 1.20 (ddd, J=14, 3, 3Hz, H_{eq}-C(3')); 2.64 (s, 2H-C(2)); 3.60 (dd, J=12.5, 5Hz, H_{eq}-C(6')); 3.79 (d, J=10Hz, HO-C(4')); 4.10-4.26 (m, H-C(4'), H_{ax}-C(6')); 5.27 (d, J=2.5Hz, HO-C(2')); 5.96 (q, J=7.5Hz, CH-Ph); 7.27-7.39 (m, Ph). IR: 1715 cm^{-1} (C=O); 3460 cm^{-1} (HO).

(2',4'-Dihydroxy-tetrahydro-pyran-2'-yl)-acetic acid (±) α ethylbenzyl ester.(**5**, R = CHEtPh).

From **4** (R' = $tBuPh_2Si$), 76% method B. The product was a mixture of two pairs of diastereomers, each of which consists of two tautomers.

Diastereomers A and B. Tautomers A (C(4')-OH in an equatorial position). NMR (500 MHz): δ= 0.89 (t, J=7.5Hz, Me); 1.31 (m, H_{ax}-C(3')); 1.43-1.54 (m, HO-C(4'), H_{ax}-C(5')); 1.80-2.00 (m, CH_2Me, H_{eq}-C(5')); 2.13 (m, H_{eq}-C(3')); 2.59 (m, 2H-C(2)); 3.68 (m, H_{eq}-C(6')); 3.89 (m, H_{ax}-C(6')); 4.15 (m, H-C(4')); 4.75 and 4.90 (2d, J=2.5Hz, HO-C(2')); 5.73 (m, CHPh); 7.27-7.37 (m, Ph).

Diastereomers A and B Tautomers B (C(4')-OH in an axial position). NMR (500 MHz): δ= 0.89 (t, J=7.5Hz, Me); 1.64-1.72 (m, H_{eq}-C(5'), H_{ax}-C(3')); 1.75-2.00 (m, H_{ax}-C(5'), CH_2Me, H_{eq}-C(3')); 2.54-2.65 (m, 2H-C(2)); 3.58 (m, H_{eq}-C(6')); 3.79 (d, J=10Hz, HO-C(4')); 3.84 (d, J=10Hz, HO-C(4')); 4.15 (m, H-C(4')); 4.26 (m, H_{ax}-C(6')); 5.24 and 5.35 (2d, J=2.5Hz, HO-C(2')); 5.73 (m, CH-Ph); 7.27-7.37 (m, Ph).

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