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ASYMMETRIC SYNTHESIS OF TERTIARY 2-SUBSTITUTED 5-OXOTETRAHYROFURAN-2-CARBOXYLIC ACIDS

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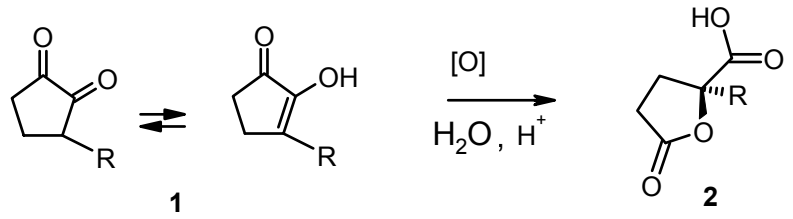
Abstract – 3-Substituted 1,2-cyclopentanediones **1** were transformed to 2-substituted 5-oxotetrahydrofuran-2-carboxylic acids **2** using a catalytic process with 0.2-0.3 equivalent of Ti(O*i*Pr)$_4$/tartaric ester/*t*BuOOH complex in up to 72% isolated yield and up to 94% *ee*. Different functional groups in the 3-alkyl substituent of **1** like, hydroxy, ether, Boc-amino and ester groups are tolerated. Boc-aminomethyl substituents lead to β-amino acid analogues and Boc-aminoethyl substituent to γ-amino acid analogues as well as spiro-lactone-lactams. A direct, two-step procedure for homocitric acid synthesis is described.

INTRODUCTION

Chiral 2-substituted 5-oxotetrahydrofuran-2-carboxylic acids are common structural units in various bioactive natural compounds like lycoperdic acid,[1] aspernolides,[2] monatins,[3] methylisocitrate,[4] sartorymensins,[5] and other compounds with potential pharmacological[6] and other applications.[3] The particular biomedicinal interest may have spiro-lactone-lactam structures.[5,6f,14]

A very simple method for diastereoselective In catalyzed synthesis of tertiary lactone structures has been described by Kumar.[7] There are several methods describing the synthesis of chiral tertiary γ-lactone structures, including enzymatic desymmetrization of parent esters for the synthesis of tertiary butenolides[8] and protein kinase C ligands.[9] In many cases chemical synthesis from natural chiral compounds is used, (e.g for the synthesis of lycoperdic acid).[10] There are a few examples of the asymmetric chemical synthesis of related structures by using the chiral auxiliaries in the synthesis of crobarbatic acid and its homologues,[11] and other chiral γ-butyrolactones.[12] Also, chiral reagents[6c] or catalysts[6g,13] have been used.

We have previously developed a method for the synthesis of enantiomerically enriched 2-alkyl-5-oxotetrahydrofuran-2-carboxylic acids **2**[15] by using the asymmetric oxidation of 3-alkyl-1,2-cyclopentanediones **1** with a stoichiometric amount of Ti(O*i*Pr)$_4$/tartaric ester/*t*BuOOH complex[16] (Scheme 1).

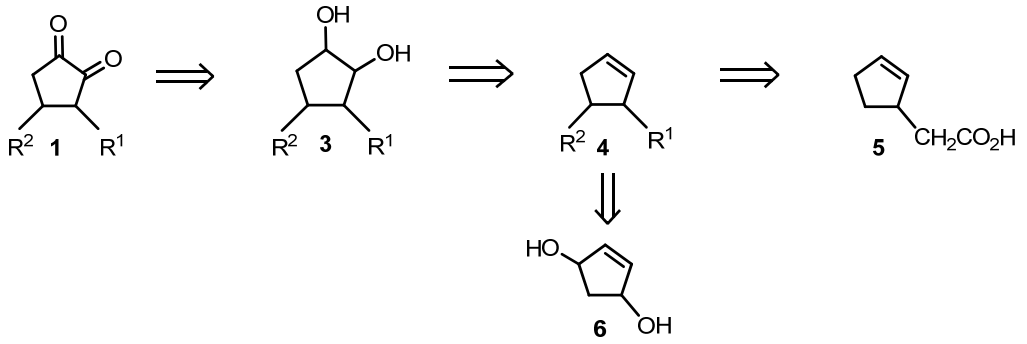


Scheme 1. General scheme for synthesis 2-alkyl-5-oxotetrahydrofuran-2-carboxylic acids **2**

Herein we describe our attempts to develop a catalytic version of the asymmetric oxidation process and broaden of the scope of the reaction by using functionalized substituents in substrate **1**, in order to obtain chiral synthons for natural compound synthesis. Using this strategy, homocitric acid lactone and spiro-lactone-lactam were synthesized.

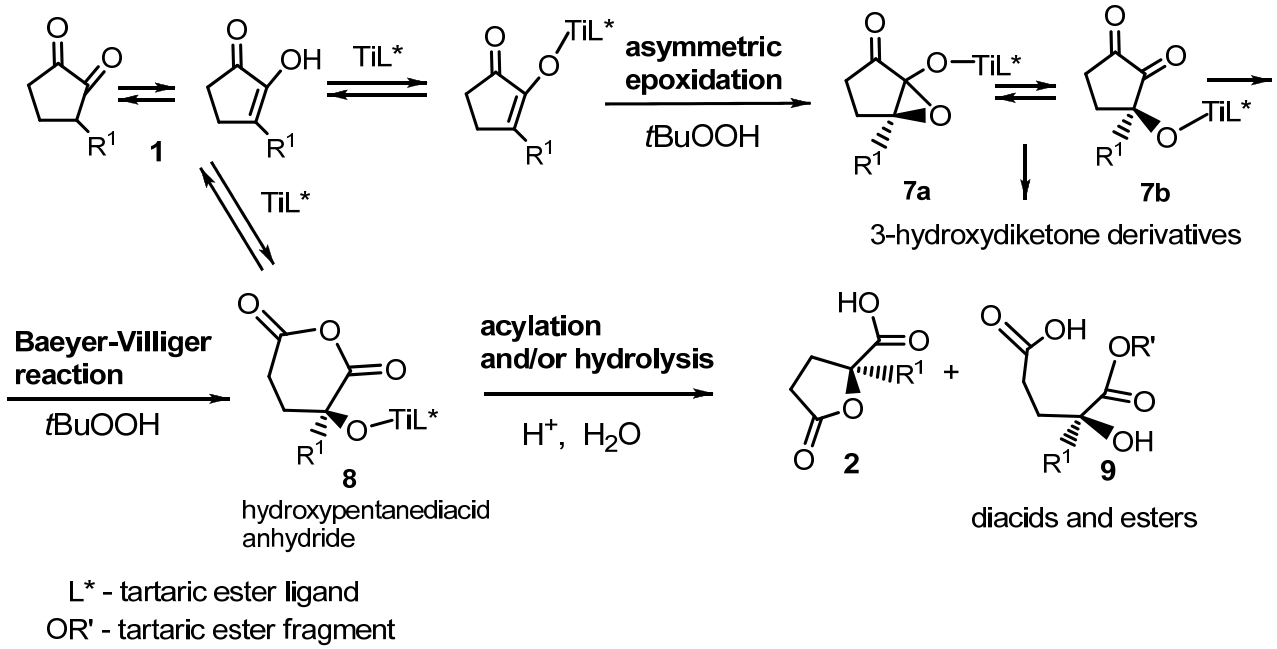
RESULTS AND DISCUSSION

The starting 3-substituted-1,2-cyclopentanediones **1** are easily accessible compounds: the preparation of compound **1a** (**a** R^1 = Bn) has been described by us earlier;[18] diketones **1b** (**b** R^1 = Me) and **1c** (**c** R^1 = Et) are commercially available. Other compounds were prepared from 3-substituted cyclopentenes by dihydroxylation, followed by Swern oxidation of the resulted diols by using our common protocols[17] (Scheme 2). In many cases the most convenient starting compound for 3-substituted cyclopentenes **4** (R^2 = H) was cyclopenten-3-acetic acid **5** (for compounds **1d-1h**; **d** R^1 = CH_2CH_2OH; **e** R^1 = CH_2CH_2OBn; **f** R^1 = CH_2NHBoc; **g** R^1 = CH_2CH_2NHBoc; **h** R^1 = CH_2CO_2tAm). Compound **1i** (R^1 = Bn, R^2 = $OSiMe_2t$Bu) was prepared from commercially available *cis*-4-cyclopentene-1,3-diol **6** by mono-acylation, protection of the OH group and Grignard replacement of the acetate, followed again by a standard reaction sequence cited above.



Scheme 2. Retrosynthetic sequence for 3-substituted 1,2-cyclopentanediones **1**

We have previously shown that the oxidation of 1,2-cyclopentanediones **1** consists of three steps: epoxidation (α-hydroxylation), *in situ* Baeyer-Villiger reaction of the resulted intermediate and acylation (Scheme 3).[19] The products that may be isolated are hydroxy diketones from intermediates **7**, dioxygenated products - diacids and diacid esters **9**, and after hydrolysis and acylation lactone carboxylic acids **2**.



Scheme 3. The formal reaction cascade

Ti species participate in all steps of the cascade, catalyzing not only the oxidation but also the epoxide re-arrangement and acylation reactions. It is obvious that titanium is complexed to both, the products and the reagent. It is straightforward from Scheme 3 that a prerequisite for a catalytic reaction is the existence of equilibrium between Ti that is complexed with reaction products **8** and the substrate **1**, allowing the Ti-catalyst to enter the next catalytic cycle.

We made mixtures of the substrate **1a** (Figure 1, D) with Ti(O*i*Pr)$_4$ in CH_2Cl_2 at different substrate/Ti ratios and recorded the NMR spectra of the resulted solutions. The experimental NMR data show that Ti(O*i*Pr)$_4$ forms with substrate **1a** with a ratio of 1:2 in single clearly distinguishable complex, the spectrum of which is presented in Figure 1, A. Adding of the oxidation reagent, *t*BuOOH to the complex not only initiates the oxidation reaction, but also changes the initial complex, releasing free substrate **1a** to the reaction medium (Figure 1, B and C). These results may indicate that the complexes of Ti with *t*BuOOH and the reaction products are more stable than these with substrate **1a**.

Having this discouraging information, we made an attempt to perform the oxidation of 3-benzyl-1,2-cyclopentanedione **1a** with *t*BuOOH in the presence of various amounts of Ti(O*i*Pr)$_4$, keeping the ratio of Ti to (+)-diethyl tartrate constant in 1:1.6 . The reaction was quenched with basic

water to hydrolyze the formed esters to diacids, and then subjected to acidic treatment to lactonize the hydroxy diacids. The obtained results are presented in Table 1.

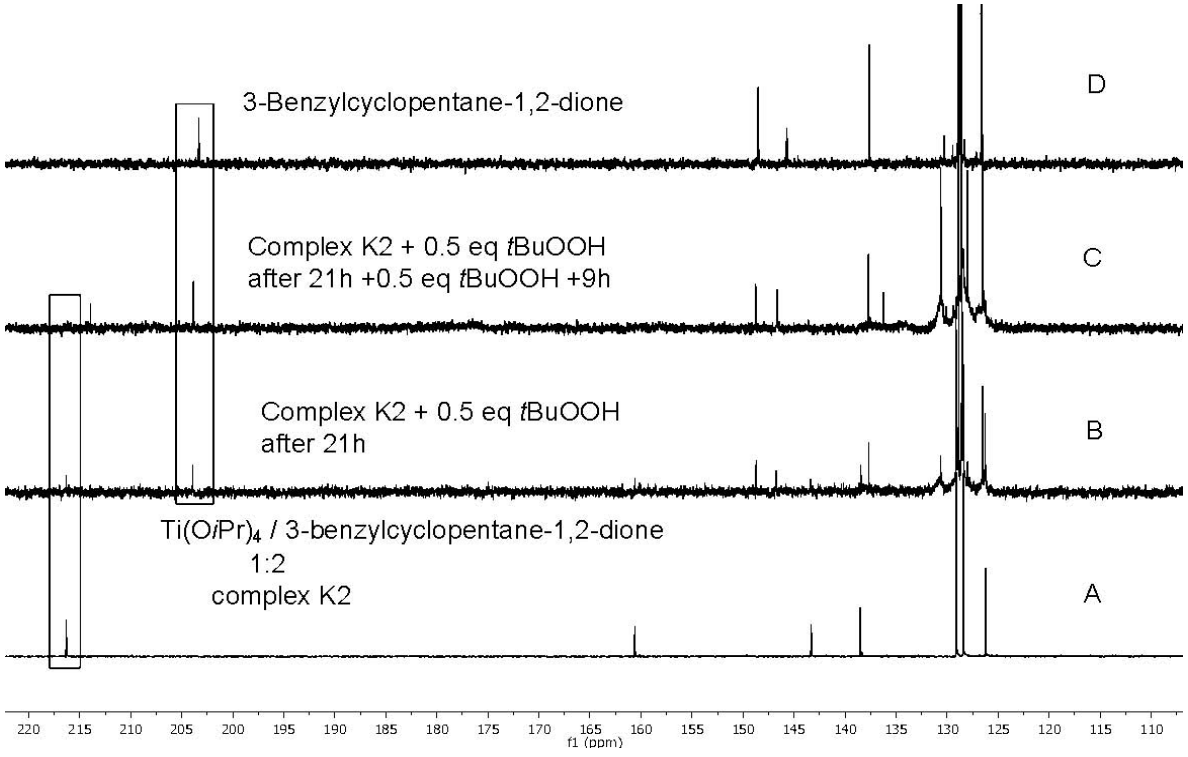


Figure 1. ^{13}C NMR spectra of the substrate **1a**, its complex with Ti(O*i*Pr)$_4$ and *t*BuOOH

Table 1. Catalytic conditions for the oxidation of 3-benzylcyclopentane-1,2-dione **1a**

Entry	Ti(OiPr)$_4$ (eq)	(+)-DET (eq)	*t*BuOOH (eq)	Yield (%)	*ee* (%)
1	1	1.6	2.5[a]	83	96
2	0.5	0.8	2.5[a]	78	93
3	0.5	0.1	2.5[b]	42	25
4	0.3	0.48	2.5[a]	71	91
5	0.3	0.48	2.5[b]	72	93
6	0.2	0.32	2.5[b]	69	91
7	0.1	0.16	2.5[a]	26	68

[a] *t*BuOOH contains ~4% of water
[b] anhydrous *t*BuOOH was used

The data reveal that by reducing the amount of Ti (together with (+)-diethyl tartrate) to 0.5 equivalents towards substrate **1a** from the initial 1:1 amount, a slight reduction of the yield and stereoselectivity occurs (Table 1, Entries 1 and 2). Further reduction of the Ti/substrate ratio to 0.3 caused some additional reduction in the yield and stereoselectivity (Table 1, Entries 4, 5). Even at 0.2 ratio 69% yield and 91% *ee* were obtained. Also, we observed that anhydrous reaction conditions are preferable for the non-stoichiometric process, affording slightly better selectivity 91% *vrs* 93% (Table 1, Entries 4 and 5).

Reduction of the substrate Ti/**1a** ratio from 1 to 0.2 causes 5% reduction in the stereoselectivity and 14% in the yield. Keeping in mind that reduction of the catalyst fivefold may considerably simplify separation of the products, this result may be acceptable for some industrial purposes.

It is clearly seen that 0.1 eq of Ti is not sufficient for an efficient and selective process, causing already a considerable loss in the yield and stereoselectivity. Also, it is not possible to change the ratio of Ti/tartaric ester by reducing the amount of the chiral ligand because of drastic reduction in stereoselectivity and yield (Table 1, Entry 3).

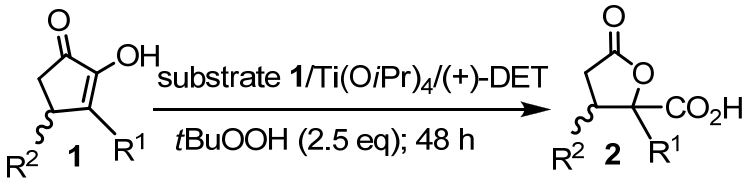
We applied the found conditions (0.3 equivalents of $Ti(O\textit{i}Pr)_4$ and 0.48 equivalents of chiral ligand (+)-DET towards substrate) for oxidation of differently substituted substrates **1**. The formed lactone carboxylic acids were isolated and their stereoisomeric purities were determined by means of chiral HPLC. The obtained results are presented in Table 2, together with a reference of the corresponding values for a stoichiometric process.

The asymmetric oxidation method of 3-substituted 1,2-diones with Ti/tartaric ester/*t*BuOOH complex is quite universal: different functional groups like alkyl, benzyl, hydroxyl, ether, Boc-amino and ester groups are tolerated. In most cases the stoichiometric process affords the isolated yield of lactone acid ~ 70% or higher. The most remarkable feature of the process is its toleration of strong electron donating groups like Boc-aminoalkyl and ester groups. In both cases high selectivity with satisfactory yield was obtained (Table 2, Entries 8-10). The aminomethyl lactone acid **1f** has once before been detected and characterized by MS.[20] According to the best of our knowledge, aminoethyl lactone acid as well as its Boc-derivative have not been synthesized before.

The catalytic process with 0.3 Ti/substrate ratio affords slightly lower yields and selectivity than the stoichiometric process. However, in all cases the yields and the enantiomeric purities of the products are satisfactory also for the catalytic process (yield ~60% or higher and *ee* ~90%).

The racemic substrate **1i** reveals very high stereoselectivity for the oxidation of the enol double bond for both enantiomers: the resulted diastereomers had high enantiomeric purities. It means that the configuration of the protected OH group did not influence the stereoselectivity of oxidation: both enantiomers reacted with similar rate and the observed ratio of diastereomers was 1:1.

Table 2. Synthesis of substituted lactone carboxylic acids **2** from 3-substituted cyclopentane-1,2-diones **1**



a R^2 = H; R^1 = -Bn;
b R^2 = H; R^1 = -Me;
c R^2 = H; R^1 = -Et;
d R^2 = H; R^1 = $-CH_2CH_2OH$;
e R^2 = H; R^1 = $-CH_2CH_2OBn$;
f R^2 = H; R^1 = $-CH_2NHBoc$;
g R^2 = H; R^1 = $-CH_2CH_2NHBoc$;
h R^2 = H; R^1 = $-CH_2CO_2tAm$;
i R^2 = $-OSiMe_2tBu$; R^1 = -Bn;

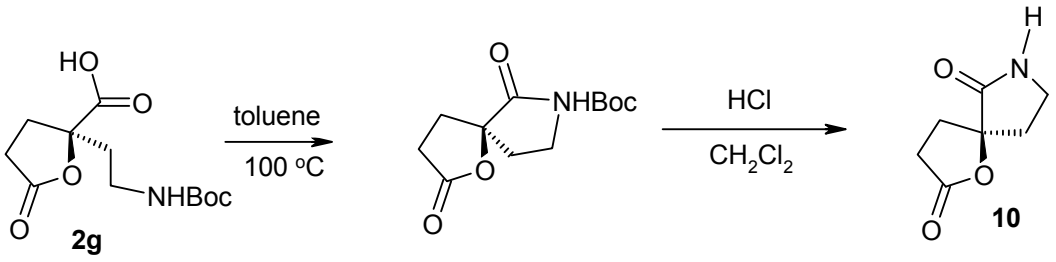
No	**1**	Lactone acid **2**			
		Yield %		*ee* %	
		Stoichiometric[a]	Catalytic[b]	Stoichiometric[a]	Catalytic[b]
1	a	83[6c]	72	96	93
2	a[c]	62[6c]	63	92	91
3	a[d]	nd	68	nd	92
4	b	75	69	94	94
5	c	72	nd	93	nd
6	d	80[e]	75[g]	95	90[g]
7	e	71[6c]	69	95	94
8	f	47	38	98	92
9	g	69	66	98	92
10	h	nd	58	nd	94
11	i	54[f]	52[f]	95/97	95/95

[a]Ratio of substrate/ $Ti(OiPr)_4$/(+) DET/ *t*BuOOH 1:1:1.6;2.5; reaction time 48 h
[b]Ratio of substrate/ $Ti(OiPr)_4$/(+) DET/ *t*BuOOH 1:0.3:0.5:2.5; reaction time 48 h
[c]Reaction time 2 h
[d]Reaction time 4 h
[e]Spirodilactone was obtained[17b]
[f]2 diastereomers at 1:1 ratio
[g] *t*BuOOH contained 4% of water

The direct cascade oxidation of 3-substituted 1,2-cyclopentanediones opens an attractive approach for the short and direct synthesis of different chiral compounds of interest. Earlier we have used a stoichiometric oxidation process for the synthesis of a natural compound homocitric acid by using hydroxyethyl-substituted diketone **1d** or acetic ester substituted diketone **1h**.[21] Now we have applied an improved protocol that enables the obtaining of homocitric acid in a two-step process using catalytical reaction conditions. Thus, diketone **1h** was subjected to asymmetric oxidation by using a standard catalytic

procedure with 0.3 equivalents of Ti(O*i*Pr)$_4$, to afford lactone acid **1h** in 58% yield and 94% *ee* (Table 2, Entry 10). After acidic hydrolysis of the *t*-amyl ester with conc. HCl, homocitric acid was obtained in 88% yield.

Lactone acids **2f** and **2g** are prospective candidates for the synthesis of analogues of β- and γ-amino acid analogues, correspondingly. We transformed lactone acid **2g** to spiro-γ-lactone-γ-lactam **10** by lactamization of **2g**, followed by removal of the Boc-group, in 59% overall yield (Scheme 4).



Scheme 4. Spiro-γ-lactone-γ-lactam **10** from lactone acid **2g**

The obtained structure may serve as a new chiral synthon for further transformations. This type of skeleton is known in many bioactive compounds.

EXPERIMENTAL

General

^{1}H and ^{13}C spectra were recorded in deuterated solvents on a Bruker AMX-500 or Avance II 400 spectrometer. Deuterated solvent peaks were used as references. 2D FT methods were used for the full assignment of ^{1}H and ^{13}C chemical shifts. Mass spectra were measured on a Shimadzu GCMS – QP 2010 spectrometer using EI (70 eV). IR spectra were recorded on a Perkin-Elmer Spectrum BX FTIR spectrometer. Elemental analyses were performed on a Perkin-Elmer 2400 Analyzer. Optical rotations were measured using a Krüss Optronic GmbH polarimeter P 3002 or Anton Paar GWB polarimeter MCP 500. High resolution mass spectra were obtained on an Accurate-Mass Q-TOF LC/MS instrument Agilent Technologies 6450 UHD by using AJ-ESI ionization. TLC was performed using DC-Alufolien Kieselgel 60 F_{254} (Merck) silica gel plates. For column chromatography silica gel KSK 40-100 μm and 100-160 μm was used. All reactions sensitive to oxygen or moisture were conducted under argon atmosphere in oven-dried glassware. Commercial reagents were generally used as received. THF was distilled from $LiAlH_4$ before use. CH_2Cl_2 was distilled from CaH_2 and stored over 3Å molecular sieve pellets. DMF and *t*AmOH was distilled from CaH_2.

(2-Cyclopent-2-enylmethyl)carbamic acid *tert*-butyl ester 4f

For the synthesis of compound **4f** one-pot Curtius rearrangement was used.[22] To a solution of cyclopent-2-enylacetic acid **5** (1.134 g, 9 mmol), NaN_3 (2.046 g, 33 mmol), TBAB (435 mg, 1.35 mmol) and zinc triflate (108 mg, 0.297 mmol) in THF (90 mL) at 45 °C di-*tert*-butyl dicarbonate (2.364 g, 9.9 mmol) was added. The reaction mixture was stirred at 45 °C for 20 h. The mixture was cooled to room temperature and 20% aqueous solution of $NaNO_2$ (75 mL) and EtOAc (80 mL) was added. After stirring for 20 min at room temperature the layers were separated and the aqueous phase was extracted with EtOAc (2x50 mL). The combined extracts were washed with saturated NH_4Cl (2x40 mL), with saturated aqueous $NaHCO_3$ (50 mL), with brine (50 mL) and dried (Na_2SO_4). The solvents were removed under reduced pressure and the residue was purified by flash chromatography (silica gel, petroleum ether/ EtOAc 25:1 to 10:1) giving **4f** as a white solid (1.225 g, 69%); mp 46-48 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.82 (qd, *J*=3x2.2 and 5.6 Hz, 1H, H-3), 5.62 (qd, *J*=3x2.2 and 5.6 Hz, 1H, H-2), 4.57 (bs, 1H, NH), 3.17 and 3.06 (m, 2H, H-6), 2.87 (m, 1H, H-1), 2.37 and 2.31 (m, 2H, H-4), 2.01 (tdd, *J*=2x8.8, 5.2 and 13.6 Hz, 1H, H-4), 1.51 (tdd, *J*=2x5.9, 9.2 and 13.6 Hz, 1H, H-4), 1.44 (s, 9H, H-9); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.13 (C-7), 132.75 (C-2), 131.85 (C-3), 79.01 (C-8), 46.00 (C-6), 44.81 (C-1), 32.02 (C-3), 28.39 (C-9), 26.93 (C-4); IR (KBr, cm^{-1}): 3339, 3959, 2983, 2865, 1682, 1538, 1437, 1391, 1365, 1276, 1253, 1174, 1141, 1081, 989; MS (*m/z*): 198, 182, 141, 130, 124, 97, 80, 67, 57 (base); HRMS: Calcd for $C_{11}H_{19}NO_2Na$ $[M+Na]^+$ 220.1308, found 220.1317.

(2-Cyclopent-2-enylethyl)carbamic acid *tert*-butyl ester 4g

To a solution of 2-cyclopent-2-enyl-ethanol[17a] (2.24 g, 20mmol) in CH_2Cl_2 (100 mL), Et_3N (3.9 mL, 28 mmol) and methanesulfonyl chloride (1.856 mL, 24 mmol) at 0 °C were added and the mixture was stirred for 3.5 h at 0 °C. Water (200 mL) and 1N HCl solution (4 mL) were then added and the aqueous phase was extracted with CH_2Cl_2 (1x80 mL and 1x60 mL). The combined extracts were washed with brine (80 mL), dried on Na_2SO_4, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (silica gel, petroleum ether/ EtOAc 5:1) giving 3.61 g (95%) of methanesulfonic acid 2-cyclopent-2-enylethyl ester. The mixture of obtained ester (1.71 g, 9 mmol) and NaN_3 (1.024 g, 15.75 mmol) in DMF (13.5 mL) was stirred for 2 h at 50 °C and for 1.5 h at 70 °C. After cooling water (80 mL) was added and the mixture extracted with petroleum ether (80 mL), the extract was dried over Na_2SO_4. The solvent was removed under reduced pressure to yield a crude azide (1.138 g). For the conversion of azide functionality to Boc protected amine a literature procedure was used.[23] To the azide (1.138 g, 8.3 mmol) in the mixture of THF (40 mL) and water (40 mL), triphenylphosphine (4.364 g, 16.6 mmol) was added and the mixture was stirred for 2.5 h at room temperature. Then, the reaction was cooled to 0 °C, Et_3N (1.83 mL, 13.3 mmol) and di-*tert*-butyl dicarbonate (2.69 g, 12.7 mmol) were added dropwise. After stirring for 5.5 h at room temperature, water (40 mL) and Et_2O (40 mL) were added, the layers were separated and the aqueous phase was extracted with Et_2O (2x40 mL). The combined extracts were washed with brine (40 mL),

dried (Na_2SO_4) and the solvent was removed. The residue was dissolved in pentane (25 mL), the precipitate was removed by filtration and the filtrate was concentrated. Flash chromatography (silica gel, petroleum ether/acetone 100:1 to 25:1) afforded **4g** as a colorless oil (1.446 g, 76% from methanesulfonic acid 2-cyclopent-2-enylethyl ester), which physical and spectroscopic properties correspond to the data given in literature.[24]

Cyclopent-2-enylacetic acid 1,1-dimethylpropyl ester 4h

Cyclopent-2-enylacetic acid methyl ester was synthesized according to literature procedure[26] from cyclopent-2-enylacetic acid **5**. For the synthesis of compound **4h** transesterification process was used.[27] To a solution of cyclopent-2-enylacetic acid methyl ester (1.54 g, 10 mmol) in *t*AmOH (5.45 mL), Li-pieces (7 mg, 1 mmol) was added and the mixture was heated at 130 °C for 1.5 h. Then the temperature was raised to 140 °C and MeOH/*t*AmOH azeotropic mixture (1 mL) was removed. The reaction was cooled, *t*AmOH (1 mL) was added and the mixture was again heated at 130 °C for 1.5 h, followed by removal of azeotrope. This procedure was repeated four times. Finally, the volatiles were removed at 140-150 °C and the reaction mixture was cooled. Water (5 mL) was added and extracted with petroleum ether (3x6 mL), the extracts were washed with water (5 mL), dried ($MgSO_4$) and concentrated. Flash chromatography (silica gel, petroleum ether/Et_2O 60:1 to 50:1) afforded **4h** as a colourless oil (1.2 g, 61%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.73 (qd, J=3x2.2 and 5.6 Hz, 1H, H-3), 5.65 (qd, J=3x2.2 and 5.6 Hz, 1H, H-2), 3.04 (m, 1H, H-1), 2.34 and 2.28 (m, 2H, H-4), 2.29 (dd, J=6.8 and 14.7 Hz, 1H, H-6), 2.19 (dd, J=8.1 and 14.7 Hz, 1H, H-6), 2.10 (m, 1H, H-5), 1.76 (q, J=7.5 Hz, 2H, H-10), 1.45 (m, 1H, H-5), 1.41 (s, 6H, H-9), 0.87 (t, J=7.5 Hz, 3H, H-11); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.21 (C-7), 133.90 (C-2), 131.12 (C-3), 82.47 (C-8), 42.24 (C-1), 41.73 (C-6), 33.44 (C-10), 31.80 (C-4), 29.53 (C-5), 25.53 (C-9), 8.16 (C-11); IR (neat, cm^{-1}): 3053, 2975, 2852, 1730, 1462, 1368, 1265, 1145, 1061, 948, 836, 724; MS (*m/z*): 181, 167, 126, 109, 108, 79, 71, 70, 67 (base), 66, 55, 43, 41, 39.

General procedure for the synthesis of 1,2-cyclopentanediones 1f-i

(2-Cyclopent-2-enylmethyl)carbamic acid *tert*-butyl ester **4f** (2.23 g, 11.3 mmol) was dissolved in a *t*BuOH/H_2O mixture 3:1 (38 mL), fiber bound OsO_4 catalyst (7.5% OsO_4, 38 mg, 0.0113 mmol) and NMO (50 wt. % solution in water, 3.1 mL, 14.7 mmol) were added. The reaction mixture was stirred at 60 °C for 8 days (1-4 days for the other alkenes), the catalyst was filtered off, rinsed with EtOAc (3x10 mL) and aqueous solution of 10% $Na_2S_2O_3$ (40 mL) was added. The aqueous layer was extracted with EtOAc (2x50 mL and 1x30 mL), the combined extracts were washed with brine (40 mL), dried (Na_2SO_4) and the solvents were removed under reduced pressure. Purification of the residue by flash chromatography (silica gel, petroleum ether/acetone 10:2 to 10:4) afforded 1.855 g, (71%) of the diol **3f**. The same procedure was used for diols **3g-i**. Thus, diols **3g** (2.153 g, 91%), **3h** (1.05 g, 84%) and **3i** (2.493 g, 92%) were obtained from

alkenes **4g** (2.015 g, 9.5 mmol), **4h** (1.05 g, 5.4 mmol) and **4i**[28] (2.419 g, 8.4 mmol), respectively. The diols were oxidized as followed: to a solution of DMSO (1.81 mL, 23 mmol) in CH_2Cl_2 (108 mL), TFAA (3.25 mL, 19 mmol) was added dropwise at -60 °C. The mixture was stirred for 10 min followed by the addition of the above diol (1.855 g, 8 mmol) in a DMSO/ CH_2Cl_2 mixture 1:2 (8 mL). After stirring for 1.5 h at -60 °C, Et_3N (7.4 mL, 53 mmol) was added at -60 °C and the mixture was stirred for 1.5 h at that temperature. Then the reaction mixture was warmed to ca. 5 °C, poured into a cold 1N HCl solution (220 mL) and the aqueous layer was extracted with CH_2Cl_2 (2x80 mL). The combined extracts were washed with water (200 mL), dried (Na_2SO_4) and the solvent was evaporated. The residue was dissolved in CH_2Cl_2 (80 mL), K_2CO_3 (373 mg, 2.7 mmol) was added and the mixture was stirred for 21 h at room temperature. Then, 1N HCl solution (45 mL) was added, stirred for 10 min and the aqueous layer was extracted with CH_2Cl_2 (2x40 mL). The combined extracts were washed with water (50 mL), dried ($MgSO_4$) and the solvent was evaporated. The residue was purified by flash chromatography (silica gel, petroleum ether/ EtOAc 10:5 to 10:6) giving the target compound.

(2-Hydroxy-3-oxocyclopent-1-enylmethyl)carbamic acid *tert*-butyl ester 1f

Obtained as a white solid (1.458 g, 80%); mp 134-136 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (bs, 1H, OH), 5.29 (bs, 1H, NH), 4.07 (bd *J*=6.0Hz, 2H, H-6), 2.47 (m, 2H, H-5, 2.42 (m, 2H, H-4), 1.43 (s, 9H, H-9); ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.76 (C-3), 156.54 (C-7), 149.47 (C-2), 142.99 (C-1), 80.07 (C-8), 38.71 (C-6), 31.91 (C-4), 28.23 (C-9), 23.92 (C-5); IR (KBr, cm^{-1}): 3365, 3337, 2988, 1703, 1684, 1664, 1523, 1410, 1398, 1368,1283, 1251, 1192, 1164, 1111; MS (*m/z*): 171, 154, 127, 111, 110, 84, 82, 57 (base). Anal. Calcd for $C_{11}H_{17}O_4N$: C, 58.14; H, 7.54; N, 6.16. Found: C, 58.10; H, 7.59; N, 6.15.

[2-(2-Hydroxy-3-oxocyclopent-1-enyl)ethyl]carbamic acid *tert*-butyl ester 1g

Diketone **1g** was obtained from diol **3g** (1.114 g, 4.55 mmol) as a white solid (0.722 g, 66%), which physical and spectroscopic properties correspond to the data given in literature.[25]

(2-Hydroxy-3-oxocyclopent-1-enyl)acetic acid 1,1-dimethylpropyl ester 1h

Diketone **1h** was obtained from diol **3h** (1.48 g, 6.43 mmol) as a white solid (0.766 g, 53%), mp 71-72 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.85 (s, 1H, OH), 3.38 (s, 2H, CH_2CO), 2.53 (m, 2H, H-5), 2.43 (m, 2H, H-4), 1.75 (q, *J*=7.3Hz, 2H, CH_2CH$_3$), 1.42 (s, 6H, $(CH_3)_2$), 0.86 (t, *J*=7.3Hz, 3H, CH_2CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.16 (C-3), 168.80 (COO), 150.04 (C-2), 138.61 (C-1), 84.24 (O*C*(Me)$_2$), 35.42 (*C*H$_2$CO), 33.36 (*C*H$_2$CH$_3$), 32.01 (C-4), 25.36 (OC(*Me*)$_2$ and C-5), 8.09 (*C*H$_3$CH$_2$).; IR (KBr, cm^{-1}): 3316, 2979, 2938, 2885, 1727, 1700, 1665, 1465, 1415, 1386, 1346, 1193, 1150, 1007, 844, 696; MS (*m/z*): 226, 156, 139, 111, 71, 55, 43 (base); HRMS: Calcd for $C_{12}H_{18}O_4Na$ $[M+Na]^+$ 249.1097, found 249.1101.

3-Benzyl-4-(*tert*-butyldimethylsilanyloxy)-2-hydroxycyclopent-2-enone 1i

Dikeone **1i** was obtained from diol **3i** (2.075 g, 6.4 mmol) as a white solid (1.532g, 75%) , mp 92-96 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.15 (m, 5H, Bn), δ 6.22 (s, 1H, OH), δ 4.67 (m, 1H, H-4), δ 3.76 (dd, J = 186.1, 14.4 Hz, 2H, Bn-CH_2), δ 2.74 and 2,27 (both dd, J = 19.5 Hz, 2H, 5-H), δ 0.90 (s, 9H, *t*Bu), δ 0.03 (s, 6H, 2 CH_3), ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.19 (C-1), 149.56 (C-2), 145.17 (C-3), 137.80 (*s*Bn), 129.13 (*o*-Bn), 128.71 (*m*-Bn), 126.66 (*p*-Bn), 66.97 (C-4), 43.35 (C-5), 31.18 (Bn-CH_2), 25.87 (*t*Bu CH_3), 18.10 (*t*Bu C), -4.30 (CH_3), -4.85 (CH_3).; IR (KBr, cm^{-1}): 3248, 3084, 1711, 1671, 1601, 1454, 1256, 1112, 1072, 835, 778, 757, 696; MS (*m/z*, %):186, 158 (base), 129, 115, 105, 91, 77, 66, 51, 41; Anal. Calcd for $C_{18}H_{26}O_3Si$: C, 67.88; H, 8.23. Found: C, 67.76; H, 8.30.

General procedure for catalytic asymmetric oxidation of 1,2-cyclopentanediones 1a-i

To a solution of Ti(O*i*Pr)$_4$ (0.18 mL, 0.6 mmol) and 4Å powdered molecular sieves (200 mg) in CH_2Cl_2 (5 mL), (+)-DET (0.164 mL, 0.48 mmol) was added at -20 °C and the mixture was stirred for 15 min. Then, cyclopentanedione (2 mmol) in CH_2Cl_2 (3.0 mL) was added and the reaction mixture was stirred for 30 min. Next *t*BuOOH (0.85 mL, 5 mmol, 5.85M solution in decane) was added and the reaction was kept at -20 °C for 48 h. Water (6.0 mL) was added and the mixture was stirred for 1 h at room temperature, then 1.8 mL of 30% aqueous NaOH in saturated aqueous NaCl solution was added and the mixture was again stirred at room temperature for an additional 1 h. The CH_2Cl_2 layer was removed and the mixture was acidified with 1M HCl solution (pH=1-2) and extracted with EtOAc. The combined extracts were dried over $MgSO_4$ and the solvent was evaporated. The residue was dissolved in CH_2Cl_2 (40 mL) and concentrated HCl solution (0.4 mL) was added (in the case of **2h** a catalytic amount of *p*TsOH was used as the acid and for **2f, 2g, 2i** thermal cyclization in toluene was used) and the mixture was stirred for 2 h at room temperature. Then, 20 mL of water was added and the CH_2Cl_2 layer was separated. The water layer was extracted with EtOAc and the combined extracts were dried over $MgSO_4$. After evaporation of the solvents, the residue was purified by flash chromatography to give the corresponding γ-lactone acids **2**. Lactone acid **1a-e** correspond to the data given in literature.[15b,15c,16b]

(2*R*)-2-(*tert*-Butoxycarbonylaminomethyl)-5-oxotetrahydrofuran-2-carboxylic acid 2f

Lactone acid **2f** was obtained as a white solid (196 mg, 38%); mp 138-139 °C; $[\alpha]_D^{22}$ +9.3 (c 2.3, $CHCl_3$-MeOH 1:1); *ee* 92%; ^{1}H NMR (500 MHz, $CDCl_3$+CD_3OD): δ 3.61 and 3.56 (2d, J = 14.6 Hz, 2H, H-6), 2.64 (td, J = 2x9.7 and 18.1 Hz, 1H, H-4,), 2.54 (ddd, J = 4.0, 9.9 and 18,1 Hz, 1H, H-4), 2.36 (ddd, J = 4.0, 9.7 and 13.5 Hz, 1H, H-3), 2.27 (ddd, J = 9.7, 9.9 and 13.5 Hz, 1H, H-3), 1.38 (s, 9H, H-9); ^{13}C NMR (125 MHz, $CDCl_3$+CD_3OD): δ 177.07 (C-5), 172.34 (COOH), 156.85 (C-7), 86.07 (C-2), 80.28 (C-8), 44.69 (C-6), 28.29 (C-9), 28.26 (C-3), 28.21 (C-4); IR (KBr, cm^{-1}): 3386, 2984, 2939, 2613, 1797, 1785, 1748, 1656, 1537, 1464, 1392, 1290, 1260, 1185, 1161, 1098956, 922. 854, 774; HRMS: Calcd. for

$C_{11}H_{16}NO_6$ $[M-H]^-$ 258.0983, found 258.0990.

(2*R*)-2-(2-*tert*-Butoxycarbonylaminoethyl)-5-oxotetrahydrofuran-2-carboxylic acid 2g

Cyclopentanedione **1g** (237 mg, 0.98 mmol) was oxidized according to general procedure to give **2g** as a white solid (177 mg, 66%); mp 139-141 °C; $[\alpha]_D^{25}$ -14.0 (c 2.51, MeOH); *ee* 92%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.99 (bt, J = 5.7 Hz, 1H, NH), 3.29 and 3.18 (2m, 2H, H-7), 2.70 and 1.69 (2m, 2H, H-6), 2.53 and 2.52 (2m, 2H, H-4), 2.49 and 2.15 (2m, 2H, H-3), 1.43 (s, 9H, H-10); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.93 (C-5), 174.93 (COOH), 158.33 (C-8), 83.66 (C-2), 81.61 (C-9), 36.91(C-7), 36.70 (C-6), 32.99 (C-3), 27.98 (C-10), 27.72 (C-4); IR (KBr, cm^{-1}): 3406, 2982, 2591, 1784, 1526, 1370, 1254, 1174, 1197, 1029, 901, 865, 780; HRMS: Calcd. for $C_{12}H_{18}NO_6$ $[M-H]^-$ 272.1140, found 272.1142.

(2*R*)-2-(1,1-Dimethylpropoxycarbonylmethyl)-5-oxotetrahydrofuran-2-carboxylic acid 2h

Lactone acid **2h** was obtained as a white solid (301 mg, 58%); mp 38-40 °C; $[\alpha]_D^{25}$ -18.3 (c 4.74, $CHCl_3$); *ee* 94%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.91 (br s, 1H, OH), 3.11 and 2.86 (2d, 2H, J = 16.8 Hz, CH_2CO), 2.76-2.53 (m, 3H, H-4, H-3), 2.36-2.28 (m, 1H, H-3), 1.75 (q, J = 7.5 Hz, 2H, CH_2CH_3), 1.39 (s, 6H, $(CH_3)_2$), 0.85 (t, J = 7.5 Hz, CH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.84 (C-5), 175.56 (COOH), 167.81 (CH_2CO), 85.33 ($OC(CH_3)_2$), 82.91 (C-2), 42.84 (CH_2CO), 33.33 (CH_2CH_3), 31.41 (C-3), 27.82 (C-4), 25.52 (CH_2CH_3), 25.50 (CH_2CH_3), 8.25 (CH_3CH_2); IR (KBr, cm^{-1}): 3445, 2981, 2945, 2886, 2595, 1786, 1730, 1464, 1388, 1371, 1187, 1152, 1069, 947, 842; HRMS: Calcd. for $C_{12}H_{17}O_6$ $[M-H]^-$ 257.1031, found 257.1040.

(2*S*,3*R*)-2-Benzyl-3-(*tert*-butyldimethylsilanyloxy)-5-oxotetrahydrofuran-2-carboxylic acid 2i and (2*S*,3*S*)-2-Benzyl-3-(*tert*-butyldimethylsilanyloxy)-5-oxotetrahydrofuran-2-carboxylic acid 2i'

Cyclopentanedione **1i** (414 mg, 1.3 mmol) was oxidized according to the general procedure to give **2i** and **2i'** as white solids in 1:1 ratio (238 mg, 52%). **2i**: mp 99-102 °C; $[\alpha]_D^{25}$ -23.5 (c 2.07, $CHCl_3$); *ee* 95%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.10 (m, 5H, Bn), 4.52-4.34 (m, 1H, H-3), 3.28 (dd, J = 81.6, 14.5 Hz, 2H, Bn-CH_2), 2.46 and 2.25 (2dd, J = 24.2 Hz, 2H, H-4), 0.87 (s, 9H, *t*-Bu), 0.09 (d, J = 23.5 Hz, 6H, 2 Si-CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.36 (C-5), 170.51 (COOH), 133.99 (*p*-Bn), 130.54 (*m*-Bn), 128.67 (*o*-Bn), 127.49 (*s*-Bn), 91.04 (C-2), 72.44 (C-3), 40.12 (Bn-CH_2), 38.03 (C-4), 25.44 (*t*-Bu CH_3), 17.79 (*t*-Bu C), -4.74 (Si-CH_3), -5.20 (Si-CH_3). IR (KBr, cm^{-1}): 3034, 2860, 1498, 1262, 1082, 781. Anal. Calcd for $C_{18}H_{26}O_5Si$: C, 61.69; H, 7.48. Found: C, 61.65; H, 7.52.

2i': mp 110-113 °C; $[\alpha]_D^{25}$ -13.3 (c 0.72, $CHCl_3$); *ee* 95%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.13 (m, 5H, Bn), 4.77-4.63 (m, 1H, H-3), 3.43 – 3.08 (m, 2H, Bn-CH_2)), 2.81 and 2.39 (2dd, J = 19.1Hz, 2H, H-4), 0.96 (s, 9H), 0.20 (d, J = 15.4 Hz, 6H, 2 Si-CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.13 (C-5), 171.66 (COOH), 134.73 (*p*-Bn), 130.08 (*m*-Bn), 127.83 (*o*-Bn), 126.67 (*s*-Bn), 91.58 (C-2), 72.96 (C-3), 38.44 (C-4), 37.52 (Bn-CH_2), 25.22 (*t*-Bu CH_3), 17.74 (*t*-Bu C), -5.39 (Si-CH_3), -5.50 (Si-CH_3). IR (KBr, cm^{-1}):

3483, 1770, 1705, 1497, 1254, 1085, 833, 706; HRMS: Calcd. for $C_{18}H_{27}O_5Si$ $[M+H]^+$ 351.1622, found 351.1631.

(*R*)-1-Oxa-7-azaspiro[4.4]nonane-2,6-dione 10

(2*R*)-2-(*tert*-Butoxycarbonylamino-methyl)-5-oxotetrahydrofuran-2-carboxylic acid **2g** (76 mg, 0.26 mmol) was dissolved in toluene and boiled at reflux for 9 h. After cooling, the toluene was removed under reduced pressure and the residue was purified by flash chromatography (silica gel, petroleum ether/acetone 10:2) giving Boc-protected spirolactam (46 mg). To the solution of obtained protected compound (46 mg, 0.18 mmol) in CH_2Cl_2 (10 mL) concentrated HCl solution (0.1 mL) was added and the mixture was stirred for 23 hours at room temperature. Then, 6 mL of water was added and the water layer was extracted several portions with CH_2Cl_2, dried (Na_2SO_4) and concentrated. Flash chromatography (silica gel, petroleum ether/ acetone 10:5 to 10:6) gave **10** as a white solid (24 mg, 59%) from lactone acid **2g**; mp 158-160 °C; $[\alpha]_D^{22}$ +124.2 (c 2.63, $CHCl_3$); *ee* 92%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (br s, 1H, NH), 3.53-3,47 (m, 1H, H-8), 3.39-3.33 (m, 1H, H-8), 2.97-2.88 (m, 1H, H-3) ,2.61-2.50 (m, 3H, H-3, H-4, H-9), 2.28-2.11 (m, 2H, H-9, H-4); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.11 (C-2), 174.83 (C-6), 84.81 (C-5), 38.84 (C-8), 33.45 (C-9), 29.82 (C-4), 28.74 (C-3); IR (KBr, cm^{-1}): 3253, 2966, 1776, 1717, 1672, 1459, 1437, 1301, 1257, 1197, 1179, 1138, 1113, 1076, 1053, 1012, 982, 912, 769, 690; MS (*m/z*): 155, 137, 127, 113, 110, 100, 98, 84, 70, 56 (base), 55; HRMS: Calcd. for $C_7H_{10}NO_3$ $[M+H]^+$ 156.0655, found, 156.0651.

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