Enzyme-catalyzed Reactions, Part 39[+]

A Convenient Synthesis of Optically Active 5,5-Disubstituted 4-Amino- and 4-Hydroxy-2(5*H*)-furanones from (*S*)-Ketone Cyanohydrins

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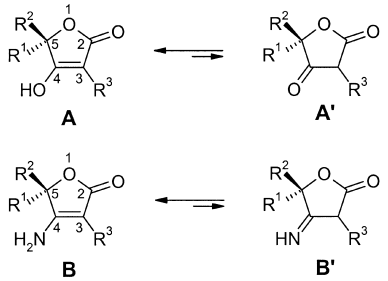
Abstract: (*S*)-Ketone cyanohydrins (*S*)-**2** are accessible by enantioselective HCN addition to ketones **1** by using hydroxynitrile lyase from *Manihot esculenta* ((*S*)-MeHNL) as a biocatalyst. Acylation of (*S*)-**2** gave the corresponding (*S*)-acyloxynitriles (*S*)-**3**, which can be cyclized by LHMDS to give 5,5-disubstituted (*S*)-4-amino-2(5*H*)-furanones (*S*)-**4** and (*S*)-**5**. Different substituents (H, Me, OBn, OH) in the 3-position of the furanones were introduced by selecting the appropriate acylating agent, which in the case of benzyloxyacetyl chloride led to the novel structure type of 4-amino-3-hydroxyfuranones (*S*)-**5**. For the synthesis of 5,5-disubstituted (*S*)-tetronic acids (*S*)-**8**, ketone cyanohydrins (*S*)-**2** were first transformed into the corresponding 2-hydroxy esters (*S*)-**6**. Acylation of (*S*)-**6** gave 2-acyloxy esters (*S*)-**7**, which, by treatment with LHMDS or LDA, afforded tetronic acids (*S*)-**8** in high yields and enantiomeric excesses. By debenzylation of benzyloxy acetoxy derivatives (*S*)-**8e**,**f**, the new vitamin C analogues (*S*)-**9a**,**b** were generated. All the described tetronic acid and aminofuranone derivatives were obtained in good chemical yields and without racemization with respect to the starting cyanohydrins (*S*)-**2**. In many cases the enantiomeric purity could be enriched by simple recrystallization (e.g. (*S*)-**4a** from 69% *ee* to >99% *ee*).

Keywords: aminofuranones · cyanohydrins · enzyme catalysis · tetronic acids

Introduction

Tetronic acid derivatives and their metabolites are widespread in nature, the best known examples of which are undoubtedly vitamin C and penicillic acid.[1] Tetronic acids **A** (Scheme 1) are of substantial interest owing to their versatile pharmacological applications.[2] The special redox behaviour of vitamin C is found in nature only in vitamin C itself and in the macrolide antibiotic chlorothricin.[3] Much synthetic effort has been made to find routes to new compounds that exhibit the vitamin C redox system. The best known compound with these properties is undoubtedly the *aci*-reductone 4-(4-chlorophenyl)-2-hydroxytetronic acid, which exhibits also antilipidemic and antiaggregatory properties.[4] The nitrogen analogues of tetronic acids, 4-amino-2(5*H*)-furanones **B** (Scheme 1), also show physiological activity and are precursors to defoliants, plant growth retardants[5a,b] and antihypertensive agents.[5a,c] Among the 5,5-disubstituted tetronic acid derivatives (**A** with R^1,$R^2 \neq H$), the mycotoxin (−)-vertinolide from *Verticillium intertextum* has been investigated intensively in recent years with respect to both its synthesis and its stereochemistry.[6] Due to the wide spectrum of their biological activities, syntheses of optically active 4-aminofuranones, tetronic acids and their derivatives have gained increasing importance.



Scheme 1. Structure of tetronic acids (**A**, **A′**) and of the amino analogues 4-aminofuranones (**B**, **B′**).

Optically active tetronic acids have been prepared mainly by Dieckmann cyclization, starting, for example, from (*S*)-lactic acid, (*S*)-mandelic acid or other compounds from the "chiral pool".[4a, 7] The first synthesis of optically active 5-substituted 3-methyltetronic acids, starting from (*R*)-cyanohydrins by using the Blaise reaction, has recently been

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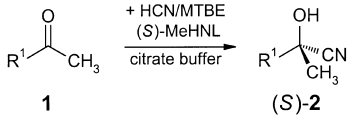
published.[8] We have also described the preparation of optically active tetronic acids through the Blaise reaction starting from (*R*)-cyanohydrins.[9]

While optically active 5-monosubstituted tetronic acids are now readily available by the procedures mentioned,[7–9] little is known about the syntheses of the important 5,5-disubstituted tetronic acids.[6] Racemic 5,5-disubstituted tetronic acids have been prepared from the corresponding 2-acyloxycarboxylic acids by cyclization in the presence of strong base.[3a] In addition, one example for the synthesis of a chiral 5,5-disubstituted 4-aminofuranone (**B** with $R^1 = CH_3$, $R^2 = C_9H_{19}$, $R^3 = H$), starting from (*S*)-2-cyano-2-undecyl acetate, by ring closure with lithium hexamethyldisilazanide has been described in the literature.[10] The optically active cyanohydrin acetate used in the reaction was obtained in this case by kinetic resolution of the racemic cyanohydrin acetate with cells of *Pichia miso*.[10] This synthetic route is restricted to ketone cyanohydrin acetates. Furthermore the microbial resolution gives only moderate yields (39%). We therefore investigated a general method for the preparation of optically active 5,5-disubstituted tetronic acids and 5,5-disubstituted 4-aminofuranones, in which the 3-position in both types of compounds can be varied by the choice of the acylating agent, starting from optically active ketone cyanohydrins.

Results and Discussion

Synthesis of ketone cyanohydrins (*S*)-2: Optically active cyanohydrins are easily synthesized by hydroxynitrile lyase (HNL)-catalyzed HCN addition to aldehydes and prochiral ketones.[11] Investigations of the substrate acceptance of recombinant (*S*)-hydroxynitrile lyase from *Manihot esculenta* ((*S*)-MeHNL) have shown that methyl ketones are accepted as substrates by the enzyme.[12] Scheme 2 exhibits the (*S*)-MeHNL-catalyzed HCN addition to ketones **1** to give (*S*)-ketone cyanohydrins (*S*)-**2**. The enzyme-catalyzed reaction



MTBE = methyl *tert*-butyl ether

Scheme 2. Preparation of (*S*)-ketone cyanohydrins (*S*)-**2** by (*S*)-MeHNL-catalyzed addition of HCN to methyl ketones **1**.

was performed in aqueous citrate buffer (pH 4.0). A solution of HCN in methyl *tert*-butyl ether was added dropwise to a solution of enzyme and ketone **1** in the buffer, whereby a stable emulsion was formed.[13] By using this procedure a low HCN concentration was maintained, and the chemical addition which would lead to the formation of racemic (*RS*)-**2** was minimized. The results obtained are summarized in Table 1.

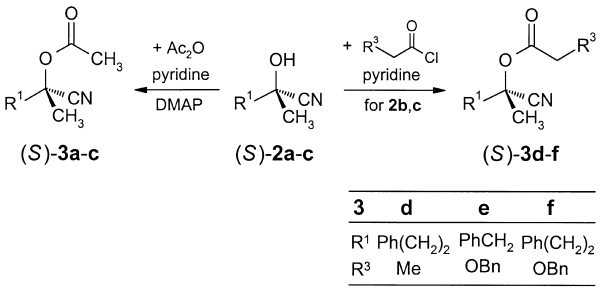
Table 1. Preparation of (*S*)-ketone cyanohydrins (*S*)-**2** by (*S*)-MeHNL-catalyzed HCN addition to ketones **1** in citrate buffer/methyl *tert*-butyl ether.

	t [h]		Yield [%]	*ee* [%][a]	α_D^{20} (*c* in $CHCl_3$)
1a	1.0	**2a**	85	69	−2.1 (1.10)
1b	1.0	**2b**	97[b]	98	−2.1 (2.80)[c]
1c	0.5	**2c**	93[b]	90	−4.8 (2.20)

[a] Determined by gas chromatography after acetylation. [b] Yield of crude product at 87% conversion each. [c] See also ref. [13].

The reference compound (*R*)-**2a**,[14] which is required for determining the configuration of the cyanohydrin (*S*)-**2a** obtained, was prepared by a slightly modified procedure developed by Brussee et al.,[15] by using almond meal as an enzyme source. In this case HCN was generated from KCN with sulfuric acid. (*R*)-**2a** was obtained in 83% yield with 98% *ee* ($[\alpha]_D^{20} = +4.7$ ($c = 1.2$ in $CHCl_3$)).

Synthesis of (*S*)-4-amino-2(5*H*)-furanones (*S*)-4: As already mentioned above, 5-methyl-5-undecyl-4-aminofuranone was synthesized from (*S*)-2-cyano-2-undecyl acetate by using a strong base.[10] Since the substituents of a compound are known to change its biological activity considerably, we have investigated the possibility of introducing substituents in the 3-position of aminofuranones **B** (Scheme 1) by varying the *O*-acyl group in the cyanohydrins (*S*)-**3** (Scheme 3). A prerequisite for this desired structural variation is a racemization-free acylation of cyanohydrins (*S*)-**2**.



Scheme 3. Acylation of (*S*)-ketone cyanohydrins (*S*)-**2a–c** to (*S*)-acyloxynitriles (*S*)-**3a–c** and **3d–f**.

As shown in Scheme 3, (*S*)-**3a–c** were prepared from (*S*)-**2a–c** by the addition of acetic anhydride in the presence of pyridine with DMAP as a catalyst. The results are summarized in Table 2. The acetylation of the cyanohydrins (*S*)-**2a–c** proceeded without racemization. The corresponding (*S*)-2-acetoxynitriles, (*S*)-**3a–c**, were isolated in good chemical yields. Also the reference compound (*R*)-**3a** was obtained from (*R*)-**2a** in high enantiomeric excess and chemical yield under the same reaction conditions (Table 2).

The reaction of (*S*)-**2c** with propionyl chloride ($R^3 = CH_3$)/pyridine as well as reactions of (*S*)-**2b,c** with benzyloxyacetyl chloride ($R^3 = OBn$)/pyridine gave the corresponding acylation products (*S*)-**3d–f**. In general, acylation of sterically demanding tertiary cyanohydrins turned out to be more difficult with bulkier acylation agents than acetic anhydride. Larger excesses of acylating agents, higher reaction temper-

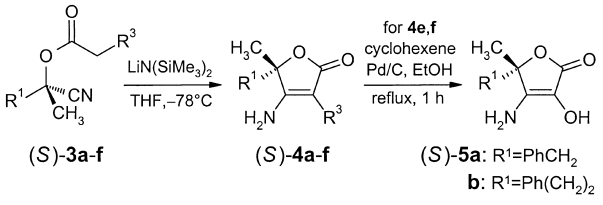
Table 2. Preparation of 2-acyloxynitriles **3a–f** from cyanohydrins **2a–c** and subsequent cyclization to 4-amino-2(5*H*)-furanones **4a–f**.

	Yield [%]	*ee* [%][a]	α_D^{20} (*c* in $CHCl_3$)		Yield [%]	α_D^{20} (*c* in MeOH)	M.p. [°C]
(*S*)-**3a**	83	69	−25.9 (2.00)	(*S*)-**4a**	47	−25.0 (1.10)	91
(*S*)-**3b**	89	97	−23.5 (0.90)[b]	(*S*)-**4b**	65	−51.6 (1.86)	176
(*S*)-**3c**	79	90	−45.0 (2.00)	(*S*)-**4c**	71	−15.0 (2.60)	155–157
(*S*)-**3d**	24	90	−40.5 (2.00)	(*S*)-**4d**	60	−12.6 (3.40)	111–112
(*S*)-**3e**	65	–	−11.9 (2.00)	(*S*)-**4e**	95	−69.0 (0.40)	145
(*S*)-**3f**	78	–	−33.0 (2.00)	(*S*)-**4f**	83	−47.6 (2.00)	135
(*R*)-**3a**	83	98	+33.5 (2.00)	(*R*)-**4a**	74	+25.2 (1.05)	91

[a] Determined directly by gas chromatography. [b] $\alpha_D^{20} = -18.1$ ($c = 1.7$ in $CHCl_3$), 72% *ee*.[13]

atures and prolonged reaction times were therefore required to complete conversion (see experimental section).

The base-induced ring closure[5a, 10] of 2-acyloxynitriles (*S*)-**3a–d** was carried out under conditions described in the literature[5a] to give the corresponding 4-amino-2(5*H*)-furanones (*S*)-**4a–d** (Scheme 4). The ring closure was effected with strong bases such as lithium diisopropyl amide (LDA) or lithium hexamethyldisilazanide ($LiN(SiMe_3)_2$) in THF at −78 °C (Scheme 4).



3, 4	a	b	c	d	e	f
R^1	*n* Bu	$PhCH_2$	$Ph(CH_2)_2$	$Ph(CH_2)_2$	$PhCH_2$	$Ph(CH_2)_2$
R^3	H	H	H	Me	OBn	OBn

Scheme 4. Preparation of 5,5-disubstituted (*S*)-4-amino-2(5*H*)-furanones (*S*)-**4a–f** and (*S*)-**5a**,**b** starting from (*S*)-2-acyloxynitriles (*S*)-**3a–f** by intramolecular nitrile addition of an ester enolate.

In accordance with the literature[5a] we observed that $LiN(SiMe_3)_2$ was more efficient for cyclization than LDA, resulting in higher yields. The 4-amino-2(5*H*)-furanones (*S*)-**4a–d** could be isolated in good yields without racemization (Table 2). In case of (*S*)-**4a**, which was prepared from (*S*)-**3a** (only 69% *ee*), the enantiomeric excess could be enriched by crystallization from petroleum ether/ethyl acetate to >99%, as confirmed by X-ray crystallography and comparison of the optical rotation value of (*R*)-**4a**, prepared from (*R*)-**3a** (98% *ee*) (Table 2).

Crystals of (*S*)-**4a** have been analyzed by X-ray crystallography[16, 17] (Figure 1).

As can be seen from Figure 1b, the packing of the crystal structure is stabilized by a network of intermolecular hydrogen bonds. Both water and the NH_2 group of the aminofuranone act as hydrogen donors, while the carbonyl group is the hydrogen acceptor (distance CO···NH_2 2.939 Å, CO···H_2O 2.828 Å; angle 172.5° and 161.3°).

Ring closure of 2-acyloxynitriles (*S*)-**3e**,**f** in the presence of strong base gives a novel structure type of benzyl-protected 4-amino-3-hydroxy tetronic acids (*S*)-**4e**,**f**, which are obtained as stable and crystalline compounds. Debenzylation of (*S*)-**4e**,**f** using Pd/C and cyclohexene in EtOH leads to unstable

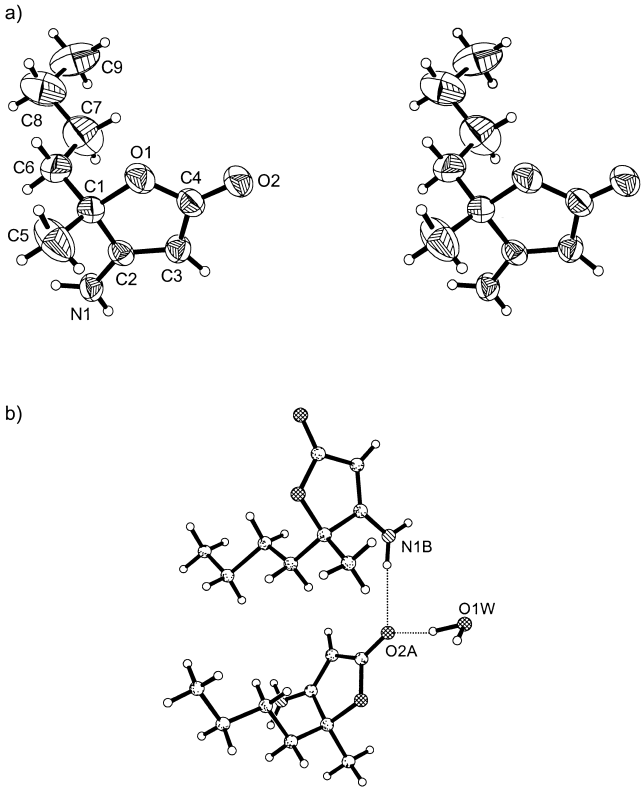


Figure 1. a) Stereoplot of (*S*)-4-amino-5-butyl-5-methyl-2(5*H*)-furanone (*S*)-**4a** with thermal ellipsoids; b) structure showing hydrogen bonds.

4-amino-3-hydroxy tetronic acids (*S*)-**5a**,**b**, which, on exposure to air, turn dark red.

Synthesis of (*S*)-tetronic acids (*S*)-7: Nonchiral 5,5-disubstituted tetronic acids have been previously prepared by ring closure of 2-acetoxy carboxylates in the presence of strong base.[3a] By this route the preparation of optically active tetronic acids, starting from (*S*)-ketone cyanohydrins (*S*)-**2**, should be possible.

Hydrolysis of aldehyde cyanohydrins to the corresponding α-hydroxycarboxylic acids with concentrated HCl is known to proceed readily without any racemization.[11] As expected, the hydrolysis of ketone cyanohydrins is more difficult. Under stronger reaction conditions (higher temperature, concentrated HCl) the corresponding α-hydroxycarboxylic acids are accessible in good yields.[10, 18] Optically active tertiary α-hydroxycarboxylic acids, which are difficult to prepare by other routes, are useful intermediates for the synthesis of many optically active natural products.[18, 19]

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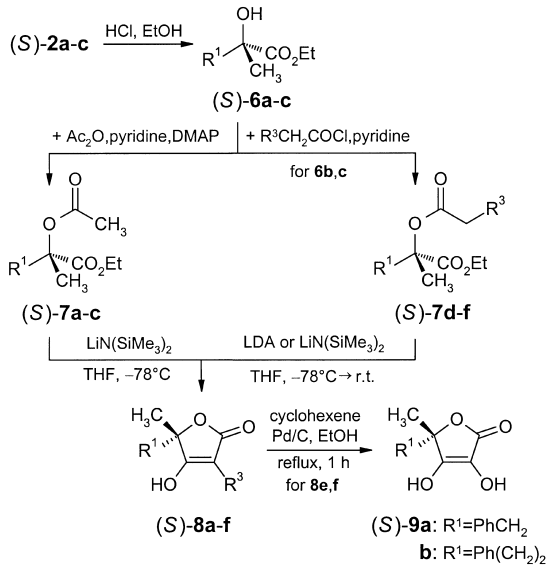
Since the cyclization of α-hydroxycarboxylic acid derivatives to tetronic acids can only be performed with esters but not with the carboxylic acids, the cyanohydrins (*S*)-**2a–c** were converted directly in the corresponding hydroxy esters (*S*)-**6a–c** through the Pinner reaction by treatment with HCl in ethanol at 90–100 °C for 16 hours (Scheme 5, Table 3). The



8	a	b	c	d	e	f
R^1	*n* Bu	$PhCH_2$	$Ph(CH_2)_2$	$Ph(CH_2)_2$	$PhCH_2$	$Ph(CH_2)_2$
R^3	H	H	H	Me	OBn	OBn

Scheme 5. Preparation of 5,5-disubstituted (*S*)-tetronic acids (*S*)-**8a–f** and (*S*)-**9a,b** starting from (*S*)-2-acyloxy esters (*S*)-**7a–f** (prepared by Pinner reaction of (*S*)-**2a–c** to ethyl esters (*S*)-**6a–c**, and subsequent acylation) by intramolecular ester addition of an ester enolate.

2-hydroxy esters (*S*)-**6** were acetylated with acetic anhydride/pyridine and DMAP, as described above, to yield the corresponding 2-acetoxycarboxylates (*S*)-**7a–c** (Scheme 5, Table 3). As in the case of tertiary cyanohydrins, the acylation of tertiary hydroxy esters (*S*)-**6c** with propionyl chloride/pyridine and (*S*)-**6b,c** with benzyloxyacetyl chloride/pyridine required long reaction times. Compounds (*S*)-**7d–f** were obtained in 64–80% yield. The Pinner reaction was expected to occur without racemization (Table 3). The enantiomers of the α-hydroxyesters (*S*)-**6** can be separated by gas chromatography. All attempts failed, however, to separate the enantiomers of **7** by gas chromatography in order to determine their enantiomeric purity.

The cyclization of compounds (*S*)-**7a–c** to give the tetronic acid derivatives (*S*)-**8a–c** (Scheme 5) was performed under the reaction conditions described above for the preparation of the aminofuranones (*S*)-**4**, by using $LiN(SiMe_3)_2$ (2.2 equiv) in THF at −78 °C (Table 3). In order to obtain complete conversion of (*S*)-**7d** to (*S*)-**8d**, employment of the stronger base, LDA, and warming to room temperature was necessary.

Cyclization of compounds (*S*)-**7e,f** led to 3-benzyl-protected 3,4-dihydroxy tetronic acids (*S*)-**8e,f**. Debenzylation finally gave the vitamin C analogues (*S*)-**9a,b**.

Table 3 shows that 5,5-disubstituted tetronic acids (*S*)-**8a–f** are accessible in good to excellent chemical yields. After workup, compounds (*S*)-**8b,c** were obtained directly as amorphous powders in an analytically pure form, while (*S*)-**8a** and (*S*)-**8d** were isolated as oils which crystallized after some time. Compounds (*S*)-**8e,f** were obtained as oils and directly debenzylated to yield the crystalline dihydroxy tetronic acids (*S*)-**9a,b**. In the case of (*S*)-**8c** and (*S*)-**9a,b** we succeeded in the separation of the two enantiomers by gas chromatography on a chiral column after derivatization with diazomethane according to a published method.[9a] The obtained *ee* value of 90% for both (*S*)-**8c** and (*S*)-**9b** could be improved by recrystallization to 93% *ee* and 95% *ee*, respectively, with good yields. In the case of (*S*)-**9a**, the enantiomeric purity was greater than 99% after one recrystallization. All tetronic acids, (*S*)-**8a–f** and (*S*)-**9a,b**, exist in their enol form as can be seen from the ^{13}C NMR spectra.

Conclusion

(*S*)-Methyl ketone cyanohydrins (*S*)-**2**, which are easily synthesized by (*S*)-MeHNL-catalyzed addition of HCN to methyl ketones **1**, are important chiral building blocks for a variety of biologically active compounds. In the present publication, the stereoselective synthesis of optically active 5,5-disubstituted 4-amino- and 4-hydroxy-2(5*H*)-furanones (*S*)-**4**, (*S*)-**5**, (*S*)-**8** and (*S*)-**9**, which are the frameworks of many natural products, for example, vitamin C or vertinolide, is described. A great variety of substituents in the 3- and 5-positions of the furanones (*S*)-**4** and (*S*)-**8** can be conveniently introduced by varying the starting ketones and by selection of appropriate agents for the acylation of the cyanohydrins (*S*)-**2** and α-hydroxy esters (*S*)-**6**, respectively.

Table 3. Ethyl hydroxycarboxylates (*S*)-**6a–c** from cyanohydrins (*S*)-**2a–c** by Pinner reaction, subsequent acylation to (*S*)-**7a–f** and intramolecular ester condensation to (*S*)-tetronic acids (*S*)-**8a–f**.

	Yield [%]	*ee* [%][a]	α_D^{20} (*c* in $CHCl_3$)		Yield [%]	α_D^{20} (*c* in $CHCl_3$)		Yield [%]	α_D^{20} (*c* in MeOH)
(*S*)-**6a**	76	69	+2.0 (1.80)	(*S*)-**7a**	66	−3.0 (2.00)	(*S*)-**8a**	92	+14.2 (2.40)
(*S*)-**6b**	83	97	+33.2 (2.00)	(*S*)-**7b**	70	−29.7 (1.10)	(*S*)-**8b**	67	+36.9 (1.94)
(*S*)-**6c**	79	90	+29.6 (2.40)	(*S*)-**7c**	80	−5.3 (2.40)	(*S*)-**8c**	89	+48.7 (1.54)[b]
(*S*)-**6c**				(*S*)-**7d**	64	−5.8 (4.00)	(*S*)-**8d**	79	+36.3 (3.00)
(*S*)-**6b**				(*S*)-**7e**	75	−27.2 (1.00)	(*S*)-**8e**	84	−47.0 (1.00)[c]
(*S*)-**6c**				(*S*)-**7f**	80	−2.2 (2.40)	(*S*)-**8f**	90	+4.8 (4.00)

[a] Enantiomeric excesses were determined directly by GC on a Chiraldex G-DM phase and correspond with those of starting material (*S*)-**2**. [b] Enantiomeric excess was determined by GC on a Chiraldex B-DM phase after derivatization with diazomethane analogous to ref. [9a] to be 90% *ee*; the value was enhanced to 93% *ee* after one recrystallization from toluene. [c] In $CHCl_3$.

Some of the newly synthesized 5,5-disubstituted (*S*)-4-aminofuranones (*S*)-**4** and (*S*)-**5** and (*S*)-tetronic acids (*S*)-**8** and (*S*)-**9**, could be of interest as chiral intermediates in stereoselective synthesis and for applications as biologically active compounds.

Optically active tertiary 2-hydroxy esters (*S*)-**6**, also important chiral starting materials in stereoselective synthesis and which are hardly accessible by other routes, can be obtained in good chemical yields and enantiomeric excesses from the respective cyanohydrins (*S*)-**2**.

Experimental Section

General methods: Melting points were determined on a Büchi SMP-20 apparatus and are uncorrected. ^{1}H NMR spectra were recorded with TMS as an internal standard on a Bruker AC250F (250 MHz) or a Bruker ARX500 (500 MHz) instrument. Specific rotations were measured on a Perkin-Elmer polarimeter 241LC. Preparative column chromatography was carried out on columns packed with silica gel S (Riedel-de Haen, grain size 0.032–0.063 mm). Enantiomeric excesses were determined by GC by using: a) Hewlett-Packard 5890 II with FID, hydrogen 5.4 mL min^{-1} or 2.2 mL min^{-1}, glass column (30 m × 0.32 mm), phases Chiraldex B-DM cyclo or OV 1701 PF 035 (ICT), and b) Hewlett-Packard 6890 with FID, hydrogen 3 mL min^{-1}, capillary column (30 m), phase Astec 71130 B-TA (ICT). Mass spectral analyses were performed on a Finnigan MAT95 (Auto-CI) spectrometer. The following compounds were prepared according to known procedures; anhydrous HCN,[20] (*R*)-2-hydroxy-2-methylhexanenitrile ((*R*)-**2a**).[14]

General procedure for (*S*)-MeHNL-catalyzed preparation of cyanohydrins (*S*)-2: The respective ketone **1** (100 mmol) was added to a solution of (*S*)-MeHNL (65000 Units) in sodium citrate buffer (80 mL, 50 mM, pH 4.0) at 0 °C, and a solution of HCN (6.0 mL, 150 mmol) in methyl *tert*-butyl ether (80 mL) was added dropwise over 1 h with vigorous stirring, whereby a stable emulsion resulted. After being stirred for the time given in Table 1 (GC and TLC control), methyl *tert*-butyl ether (250 mL) was added, and the reaction solution was saturated with ammonium sulfate. The organic phase was decanted, and the aqueous phase extracted several times with methyl *tert*-butyl ether. The combined organic phases were dried ($MgSO_4$) and concentrated, and any remaining solvent was removed under high vacuum. Cyanohydrins **2** were treated directly and fully characterized as acetylated nitriles **3**.

(*S*)-2-Hydroxy-2-methylhexanenitrile ((*S*)-2a): ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 0.95$ (t, $J = 7.1$ Hz, 3H; CH_3), 1.32–1.60 (m, 4H; CH_2), 1.60 (s, 3H; CH_3), 1.73–1.83 (m, 2H; CH_2), 3.34 (br s, 1H; OH).

(*S*)-2-Hydroxy-2-methyl-3-phenylpropanenitrile ((*S*)-2b): ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.64$ (s, 3H; CH_3), 2.99 (AB system, q, $J =$ 13.7 Hz, 2H; $PhCH_2$), 3.61 (br s, 1H; OH), 7.25–7.39 (m, 5H; Ph).

(*S*)-2-Hydroxy-2-methyl-4-phenylbutanenitrile ((*S*)-2c): ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.64$ (s, 3H; CH_3), 2.00–2.10 (m, 2H; 3-CH_2), 2.77–3.00 (m, 2H; $PhCH_2$), 3.12 (br s, 1H; OH), 7.16–7.34 (m, 5H; Ph).

General procedure for the Pinner reaction of (*S*)-2 to give ethyl hydroxycarboxylates (*S*)-6: A solution of the respective **2** (30 mmol) in saturated alcoholic HCl (50 mL) was heated in a closed pressure vessel to 90–100 °C for 16 h to produce a white precipitate. The vessel was opened after cooling, and the reaction mixture poured into diethyl ether (40 mL) with stirring. Water was added to dissolve the precipitate, and the organic phase was separated. The aqueous phase was extracted three times with small volumes of diethyl ether. The combined organic phases were washed with saturated $NaHCO_3$ solution, dried (Na_2SO_4) and concentrated. The residue was fractionally distilled in vacuo to yield **6** as colourless oils.

Ethyl (*S*)-2-hydroxy-2-methylhexanoate ((*S*)-6a): B.p. 82 °C (15 Torr); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 0.89$ (t, $J = 7.1$ Hz, 3H; CH_2CH_3), 1.05–1.83 (m, 9H; OCH_2CH_3, 3 CH_2), 1.39 (s, 3H; CH_3), 3.38 (br s, 1H; OH), 4.24 (q, $J = 7.1$ Hz, 2H; OCH_2CH_3); MS: *m*/*z* (%): 175.1 (14) $[M-H]^+$, 157.0 (26), 101 (100); HRMS calcd for $C_9H_{19}O_3$ 175.1334, found 175.1332.

Ethyl (*S*)-2-hydroxy-2-methyl-3-phenylpropionate ((*S*)-6b): B.p. 68 °C (0.01 Torr); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.26$ (t, $J = 7.1$ Hz, 3H; OCH_2CH_3), 1.49 (s, 3H; CH_3), 2.91 (AB system, d, $J = 13.5$ Hz, 1H; $PhCH^AH^B$), 3.07 (AB system, d, $J = 13.5$ Hz, 1H; $PhCH^AH^B$), 3.08 (s, 1H; OH), 4.15 (q, $J = 7.1$ Hz, 2H; OCH_2CH_3), 7.18–7.30 (m, 5H; Ph); elemental analysis calcd (%) for $C_{12}H_{16}O_3$ (208.3): C 69.21, H 7.74; found C 69.08, H 7.80.

Ethyl (*S*)-2-hydroxy-2-methyl-4-phenylbutyrate ((*S*)-6c): B.p. 90 °C (0.01 Torr); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.29$ (t, $J = 7.1$ Hz, 3H; OCH_2CH_3), 1.44 (s, 3H; CH_3), 1.97 (AB system, m, 1H; 3-CH^AH^B), 2.08 (AB system, m, 1H; 3-CH^AH^B), 2.46 (AB system, m, 1H; $PhCH^AH^B$), 2.78 (AB system, m, 1H; $PhCH^AH^B$), 3.32 (s, 1H; OH), 4.20 (q, $J = 7.1$ Hz, 2H; OCH_2CH_3), 7.16–7.29 (m, 5H; Ph); elemental analysis calcd (%) for $C_{13}H_{18}O_3$ (222.3): C 70.24, H 8.16; found C 70.12, H 8.19.

General procedure for the acetylation of (*S*)-2 and (*S*)-6 to give 2-acetoxynitriles (*S*)-3a–c and esters (*S*)-7a–c: A solution of **2** (30 mmol) or **6** (25 mmol), pyridine (3.95 g, 50 mmol), acetic anhydride (5.10 g, 50 mmol) and catalytic amounts of 4-(dimethylamino)pyridine (DMAP) in dichloromethane (40 mL) was heated to reflux for 10–15 min (GC control). The reaction mixture was concentrated, and the residue was taken up in diethyl ether, washed with HCl (10%), saturated $NaHCO_3$ and NaCl solutions and dried ($MgSO_4$). The solvent was removed and the residue was distilled in vacuo to yield products **3** or **7**.

(*R*)-2-Acetoxy-2-methylhexanenitrile ((*R*)-3a): B.p. 100 °C (10 Torr); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 0.94$ (t, $J = 6.9$ Hz, 3H; CH_3), 1.34–1.69 (m, 4H; CH_2), 1.73 (s, 3H; CH_3), 1.78–2.06 (m, 2H; CH_2), 2.09 (s, 3H; $COCH_3$); elemental analysis calcd (%) for $C_9H_{15}NO_2$ (169.2): C 63.88, H 8.93, N 8.28; found C 63.62, H 8.87, N 8.20.

(*S*)-2-Acetoxy-2-methylhexanenitrile ((*S*)-3a): Data correspond to those of (*R*)-**3a**.

(*S*)-2-Acetoxy-2-methyl-3-phenylpropanenitrile ((*S*)-3b): B.p. 92 °C (0.01 Torr); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.70$ (s, 3H; CH_3), 2.09 (s, 3H; $COCH_3$), 3.25 (AB system, q, $J = 13.7$ Hz, 2H; $PhCH_2$), 7.27–7.40 (m, 5H; Ph); MS: *m*/*z* (%): 204.1 (10) $[M-H]^+$, 143.0 (100), 91.0 (50); HRMS calcd for $C_{12}H_{14}NO_2$ 204.1025, found 204.1033.

(*S*)-2-Acetoxy-2-methyl-4-phenylbutanenitrile ((*S*)-3c): B.p. 122 °C (0.01 Torr); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.78$ (s, 3H; CH_3), 2.07 (s, 3H; $COCH_3$), 2.20 (AB system, m, 1H; 3-CH^AH^B), 2.30 (AB system, m, 1H; 3-CH^AH^B), 2.83 (AB system, m, 2H; $PhCH_2$), 7.20–7.32 (m, 5H; Ph); elemental analysis calcd (%) for $C_{13}H_{15}NO_2$ (217.3): C 71.87, H 6.96, N 6.45; found C 72.02, H 7.05, N 6.16.

Ethyl (*S*)-2-acetoxy-2-methylhexanoate ((*S*)-7a): B.p. 97 °C (12 Torr); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 0.91$ (t, $J = 6.7$ Hz, 3H; CH_2CH_3), 1.23–1.39 (m, 4H; 2 CH_2), 1.25 (t, $J = 7.1$ Hz, 3H; OCH_2CH_3), 1.55 (s, 3H; CH_3), 1.72–1.94 (m, 2H; CH_2), 2.05 (s, 3H; $COCH_3$), 4.18 (q, $J = 7.1$ Hz, 2H; OCH_2CH_3); elemental analysis calcd (%) for $C_{11}H_{20}O_4$ (216.3): C 61.09, H 9.32; found C 60.88, H 9.19.

Ethyl (*S*)-2-acetoxy-2-methyl-3-phenylpropionate ((*S*)-7b): B.p. 92 °C (0.01 Torr); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.21$ (t, $J = 7.1$ Hz, 3H; OCH_2CH_3), 1.49 (s, 3H; CH_3), 2.06 (s, 3H; $COCH_3$), 3.03 (AB system, d, $J = 13.8$ Hz, 1H; $PhCH^AH^B$), 3.29 (AB system, d, $J = 13.8$ Hz, 1H; $PhCH^AH^B$), 4.16 (q, $J = 7.1$ Hz, 2H; OCH_2CH_3), 7.16–7.35 (m, 5H; Ph); MS: *m*/*z* (%): 251 (28) $[M-H]^+$, 190 (100), 135 (60); HRMS calcd for $C_{14}H_{19}O_4$ 251.1283, found 251.1286.

Ethyl (*S*)-2-acetoxy-2-methyl-4-phenylbutyrate ((*S*)-7c): B.p. 124 °C (0.01 Torr); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.26$ (t, $J = 7.1$ Hz, 3H; OCH_2CH_3), 1.64 (s, 3H; CH_3), 2.05 (s, 3H; $COCH_3$), 2.07–2.25 (AB system, m, 2H; 3-CH^AH^B), 2.60–2.73 (AB system, m, 2H; $PhCH^AH^B$), 4.19 (q, $J = 7.1$ Hz, 2H; OCH_2CH_3), 7.17–7.29 (m, 5H; Ph); elemental analysis calcd (%) for $C_{15}H_{20}O_4$ (264.3): C 68.16, H 7.63; found C 68.37, H 7.64.

General procedure for the acylation of (*S*)-2b,c and (*S*)-6b,c to give 2-acyloxynitriles (*S*)-3d–f and ester (*S*)-7d–f: Propionyl chloride (4.37 mL, 50 mmol) was slowly added to a solution of **2c** or **6c** (25.6 mmol) and pyridine (3.95 g, 50 mmol) in dichloromethane (50 mL), and the reaction mixture was heated to 60 °C for 24 h (GC control). In the case of benzyloxyacetyl chloride, a solution of **2b–c** or **6b–c** (46 mmol) and benzyloxyacetyl chloride (92 mmol) in pyridine (100 mL) was stirred at 60 °C for 12 h. The reaction mixture was taken up in diethyl ether and washed several times with aq. HCl (10%) and saturated $NaHCO_3$ and NaCl

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solutions. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified either by distillation in vacuo (**3d** and **7d**) or by chromatography on silica gel with petroleum ether/ethyl acetate to yield the products as colourless oils.

(*S*)-2-Propionyloxy-2-methyl-4-phenylbutanenitrile ((*S*)-3d): B.p. 120 °C (0.01 Torr); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.15$ (t, $J = 7.6$ Hz, 3H; $COCH_2CH_3$), 1.79 (s, 3H; CH_3), 2.17–2.36 (m, 2H; $PhCH_2CH_2$), 2.34 (q, $J = 7.6$ Hz, 2H; $COCH_2CH_3$), 2.78–2.91 (m, 2H; $PhCH_2CH_2$), 7.20–7.32 (m, 5H; Ph); elemental analysis calcd (%) for $C_{14}H_{17}NO_2$ (231.3): C 72.70, H 7.41, N 6.06; found C 72.49, H 7.50, N 5.98.

(*S*)-2-Benzyloxyacetoxy-2-methyl-3-phenylpropanenitrile ((*S*)-3e): SiO_2, eluent: petroleum ether/ethyl acetate 8:2, $R_f = 0.37$; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.74$ (s, 3H; CH_3), 3.27 (AB system, q, $J = 13.8$ Hz, 2H; $PhCH_2$), 4.10 (s, 2H; $PhCH_2O$), 4.60 (s, 2H; $COCH_2O$), 7.21–7.49 (m, 10H; Ph); elemental analysis calcd (%) for $C_{19}H_{19}NO_3$ (309.4): C 73.77, H 6.19, N 4.53; found C 73.48, H 6.37, N 4.58.

(*S*)-2-Benzyloxyacetoxy-2-methyl-4-phenylbutanenitrile ((*S*)-3f): SiO_2, eluent: petroleum ether/ethyl acetate 9:1, $R_f = 0.27$; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.81$ (s, 3H; CH_3), 2.12–2.35 (m, 2H; $PhCH_2CH_2$), 2.78–2.89 (m, 2H; $PhCH_2CH_2$), 4.06 (s, 2H; $PhCH_2O$), 4.63 (s, 2H; $COCH_2O$), 7.17–7.37 (m, 10H; Ph); elemental analysis calcd (%) for $C_{20}H_{21}NO_3$ (323.4): C 74.28, H 6.55, N 4.33; found C 74.16, H 6.65, N 4.43.

Ethyl (*S*)-2-propionyloxy-2-methyl-4-phenylbutyrate ((*S*)-7d): B.p. 132 °C (0.01 Torr); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.15$ (t, $J = 7.6$ Hz, 3H; $COCH_2CH_3$), 1.26 (t, $J = 7.1$ Hz, 3H; OCH_2CH_3), 1.64 (s, 3H; CH_3), 2.00–2.39 (m, 2H; $PhCH_2CH_2$), 2.33 (q, $J = 7.6$ Hz, 2H; $COCH_2CH_3$), 2.59–2.72 (m, 2H; $PhCH_2CH_2$), 4.18 (q, $J = 7.1$ Hz, 2H; OCH_2CH_3), 7.16–7.31 (m, 5H; Ph); elemental analysis calcd (%) for $C_{16}H_{22}O_4$ (278.3): C 69.04, H 7.97; found C 68.89, H 8.07.

Ethyl (*S*)-2-benzyloxyacetoxy-2-methyl-3-phenylpropionate ((*S*)-7e): SiO_2, eluent: petroleum ether/ethyl acetate 8:2, $R_f = 0.33$; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.21$ (t, $J = 7.1$ Hz, 3H; OCH_2CH_3), 1.54 (s, 3H; CH_3), 3.19 (AB system, q, $J = 13.9$ Hz, 2H; $PhCH_2$), 4.10 (s, 2H; $PhCH_2O$), 4.18 (q, $J = 7.1$ Hz, 2H; OCH_2CH_3), 4.62 (s, 2H; $COCH_2O$), 7.14–7.36 (m, 10H; Ph); elemental analysis calcd (%) for $C_{21}H_{24}O_5$ (356.4): C 70.77, H 6.79; found C 70.53, H 6.91.

Ethyl (*S*)-2-benzyloxyacetoxy-2-methyl-4-phenylbutyrate ((*S*)-7f): SiO_2, eluent: petroleum ether/ethyl acetate 9:1, $R_f = 0.24$; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.27$ (t, $J = 7.1$ Hz, 3H; OCH_2CH_3), 1.69 (s, 3H; CH_3), 2.09–2.28 (m, 2H; $PhCH_2CH_2$), 2.59–2.73 (m, 2H; $PhCH_2CH_2$), 4.11 (s, 2H; $PhCH_2O$), 4.21 (q, $J = 7.1$ Hz, 2H; OCH_2CH_3), 4.64 (s, 2H; $COCH_2O$), 7.15–7.39 (m, 10H; Ph); elemental analysis calcd (%) for $C_{22}H_{26}O_5$ (370.4): C 71.33, H 7.07; found C 71.31, H 7.10.

General procedure for the preparation of (*S*)-4-amino-2(5*H*)-furanones (*S*)-4: A solution of **3** (10 mmol) in THF (20 mL) was added dropwise over 15 min to a solution of $LiN(SiMe_3)_2$ in THF (20 mL) at −78 °C. The $LiN(SiMe_3)_2$ solution was prepared from hexamethyldisilazane (3.3 mL, 16 mmol) in THF (20 mL) at 0 °C under nitrogen atmosphere by addition of a 1.6 M solution of *n*-BuLi in hexane (10 mL, 16 mmol) using a syringe and stirring for 15 min. After 2 h (TLC monitoring), a saturated NH_4Cl solution was added to quench the reaction, and the reaction mixture was allowed to warm to room temperature. The organic phase was separated, and the aqueous phase was extracted twice with diethyl ether (30 mL each). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel with petroleum ether/ethyl acetate (3:7 or 2:8) ((*R*)-**4a**, (*S*)-**4b** and (*S*)-**4d**) or crystallized.

(*R*)-4-Amino-5-butyl-5-methyl-2(5*H*)-furanone ((*R*)-4a): Colourless crystals; ^{1}H NMR (250 MHz, [D$_6$]DMSO): $\delta = 0.85$ (t, $J = 7.0$ Hz, 3H; CH_3CH_2), 0.93–1.29 (m, 4H; CH_2), 1.34 (s, 3H; CH_3), 1.67 (t, $J = 7.8$ Hz, 2H; CH_2), 4.38 (s, 1H; CH=), 7.00 (brs, 2H; NH_2); elemental analysis calcd (%) for $C_9H_{15}NO_2$ (169.2): C 63.88, H 8.93, N 8.28; found C 63.83, H 9.04, N 8.25.

(*S*)-4-Amino-5-butyl-5-methyl-2(5*H*)-furanone ((*S*)-4a): Crystallized from petroleum ether/ethyl acetate (1:5) as colourless single crystals; ^{1}H NMR data correspond with those of (*R*)-**4a**; elemental analysis calcd (%) for $C_9H_{15}NO_2 \cdot 1/4\,H_2O$ (173.7): C 62.22, H 8.70, N 8.06; found C 62.30, H 8.92, N 8.03.

Crystallographic data: crystal size, $0.5 \times 0.5 \times 0.3$ mm; *T*, 293 K; space group, $P4_12_12$; crystal system, tetragonal; $a = b = 9.6240(9)$, $c = 44.421(7)$ Å; $\alpha = \beta = \gamma = 90°$; $V = 4114.3(9)$ Å^3; $Z = 16$; $\rho_{calcd} = 1.122$ g cm^{-3}; $\theta - 2\theta$-scan; 2θ range, 46°; reflections collected, 3277; independent reflections, 2863; reflections observed [$I > 2\sigma(I)$], 1895; *R*1(obs. data), 0.0743; *wR*2(all data), 0.2714; GOF (F^2, all data), 1.093; residual electron density, 0.380 e Å^{-3}; the structure was solved by direct methods; [16] refinement method, full matrix least-squares on F^2; diffractometer, Nicolet P3, graphite monochromator, $Mo_{K\alpha}$ ($\lambda = 0.71073$ Å) radiation.

(*S*)-4-Amino-5-benzyl-5-methyl-2(5*H*)-furanone ((*S*)-4b): Colourless crystals; ^{1}H NMR (500 MHz, [D$_6$]DMSO): $\delta = 1.38$ (s, 3H; CH_3), 2.99 (s, 2H; $PhCH_2$), 4.17 (s, 1H; CH=), 7.14–7.24 (brs, and m, 7H; NH_2, Ph); elemental analysis calcd (%) for $C_{12}H_{13}NO_2$ (203.3): C 70.92, H 6.45, N 6.89; found C 71.06, H 6.50, N 6.88.

(*S*)-4-Amino-5-methyl-5-(2-phenyl)ethyl-2(5*H*)-furanone ((*S*)-4c): Crystallized from ethyl acetate as colourless crystals; ^{1}H NMR (500 MHz, [D$_6$]DMSO): $\delta = 1.14$ (s, 3H; CH_3), 1.95–2.04 (m, 2H; $PhCH_2CH_2$), 2.31–2.51 (m, 2H; $PhCH_2CH_2$), 4.48 (s, 1H; CH=), 7.13–7.30 (brs, and m, 7H; NH_2, Ph); elemental analysis calcd (%) for $C_{13}H_{15}NO_2$ (217.3): C 71.87, H 6.96, N 6.45; found C 71.88, H 6.96, N 6.23.

(*S*)-4-Amino-3,5-dimethyl-5-(2-phenyl)ethyl-2(5*H*)-furanone ((*S*)-4d): White needles; ^{1}H NMR (500 MHz, [D$_6$]DMSO): $\delta = 1.37$ (s, 3H; CH_3), 1.55 (s, 3H; CH_3), 1.95–2.01 (m, 2H; $PhCH_2CH_2$), 2.24–2.44 (m, 2H; $PhCH_2CH_2$), 6.73 (s, 2H; NH_2), 7.15–7.28 (m, 5H; Ph); elemental analysis calcd (%) for $C_{14}H_{17}NO_2$ (231.3): C 72.70, H 7.41, N 6.06; found C 72.96, H 7.62, N 5.78; MS (70 eV, EI): *m*/*z* (%): 231.1 (12) [*M*]$^+$, 127.1 (100), HRMS calcd for $C_{14}H_{17}NO_2$ 231.1259, found 231.1259.

(*S*)-4-Amino-3-benzyloxy-5-benzyl-5-methyl-2(5*H*)-furanone ((*S*)-4e): White microcrystals; m.p. 145 °C; ^{1}H NMR (500 MHz, [D$_6$]DMSO): $\delta = 1.37$ (s, 3H; CH_3), 2.98 (s, 2H; $PhCH_2$), 4.47 (s, 2H; $PhCH_2O$), 6.67 (brs, 2H; NH_2), 7.14–7.35 (m, 10H; Ph); elemental analysis calcd (%) for $C_{19}H_{19}NO_3$ (309.4): C 73.77, H 6.19, N 4.53; found C 73.96, H 6.26, N 4.45.

(*S*)-4-Amino-3-benzyloxy-5-methyl-5-(2-phenyl)ethyl-2(5*H*)-furanone ((*S*)-4f): Crystallized as colourless crystals from MTBE/ethyl acetate (9:1); m.p. 135 °C; ^{1}H NMR (250 MHz, [D$_6$]DMSO): $\delta = 1.33$ (s, 3H; CH_3), 1.84–2.26 (m, 4H; $PhCH_2CH_2$), 4.93 (AB system, q, $J = 11.6$ Hz, 2H; $PhCH_2O$), 6.62 (brs, 2H; NH_2), 7.06–7.47 (m, 10H; Ph); elemental analysis calcd (%) for $C_{20}H_{21}NO_3$ (323.4): C 74.28, H 6.55, N 4.33; found C 74.36, H 6.69, N 4.31.

General procedure for the preparation of (*S*)-tetronic acids (*S*)-8a–c and 8e–f: A solution of **7a–c**, **7e** and **7f** (10 mmol) in THF (20 mL) was added dropwise over 15 min to a solution of $LiN(SiMe_3)_2$ in THF (20 mL) [prepared as described above] at −78 °C. After 2 h (TLC monitoring), water (30 mL) was added to quench the reaction, and the reaction mixture was allowed to warm to room temperature. The organic phase was separated and extracted twice with saturated $NaHCO_3$ solution (30 mL each). The combined aqueous phases were adjusted to pH 1 with conc. HCl and extracted three times with ethyl acetate (30 mL each). The combined extracts were dried (Na_2SO_4) and concentrated to give analytically pure products **8**.

(*S*)-5-Butyl-4-hydroxy-5-methyl-2(5*H*)-furanone ((*S*)-8a): M.p. 78 °C; ^{1}H NMR (250 MHz, [D$_6$]DMSO): $\delta = 0.66$ (t, $J = 6.8$ Hz, 3H; CH_2CH_3), 0.80–1.12 (m, 4H; CH_2), 1.17 (s, 3H; CH_3), 1.47 (m, 2H; CH_2), 6.46 (s, 1H; CH=), 12.48 (brs, 1H; OH); ^{13}C NMR (63 MHz, [D$_6$]DMSO): $\delta = 13.50$, 21.70, 22.95, 24.47, 35.27 (CH_3, CH_2), 83.19 (C–O–), 86.96 (CH=), 171.88, 183.70 (C=O,C–OH); elemental analysis calcd (%) for $C_9H_{14}O_3$ (170.2): C 63.51, H 8.29; found C 63.58, H 8.35.

(*S*)-5-Benzyl-4-hydroxy-5-methyl-2(5*H*)-furanone ((*S*)-8b): M.p. 115 °C; ^{1}H NMR (500 MHz, [D$_6$]DMSO): $\delta = 1.43$ (s, 3H; CH_3), 2.90 (AB system, d, $J = 13.9$ Hz, 1H; $PhCH^AH^B$), 3.02 (AB system, d, $J = 13.9$ Hz, 1H; $PhCH^AH^B$), 7.14–7.26 (m, 5H; Ph), 12.69 (brs, 1H; OH); ^{13}C NMR (126 MHz, [D$_6$]DMSO): $\delta = 23.48$ (CH_3), 42.35 ($PhCH_2$), 83.79 (C–O–), 88.28 (CH=), 127.85, 128.18, 130.36, 135.46 (Ph), 172.05, 183.40 (C=O,C–OH); elemental analysis calcd (%) for $C_{12}H_{12}O_3$ (204.2): C 70.57, H 5.92; found C 70.57, H 5.98.

(*S*)-4-Hydroxy-5-methyl-5-(2-phenyl)ethyl-2(5*H*)-furanone ((*S*)-8c): M.p. 145 °C; yield 1.95 g (89%), 90% *ee*; recrystallization from toluene gave 1.67 g (78%), 93% *ee*; ^{1}H NMR (500 MHz, [D$_6$]DMSO): $\delta = 1.42$ (s, 3H; CH_3), 1.95 (m, 2H; $PhCH^AH^B$), 2.40 (AB system, dt, $J_1 = 12.2$, $J_2 = 5.2$ Hz, 1H; $PhCH_2CH^AH^B$), 2.50 (AB system, dt, $J_1 = 12.2$, $J_2 = 5.2$ Hz, 1H; $PhCH_2CH^AH^B$), 4.91 (s, 1H; CH=), 7.17–7.29 (m, 5H; Ph), 12.75 (brs, 1H;

OH); ^{13}C NMR (126 MHz, [D$_6$]DMSO): $\delta = 23.55$ (CH_3), 29.25 (PhCH$_2$*C*H$_2$), 38.10 (Ph*C*H$_2$), 83.64 (C–O–), 87.81 (CH=), 126.28, 128.49, 128.74, 141.30 (Ph), 172.49, 184.16 (C=O,C–OH); elemental analysis calcd (%) for $C_{13}H_{14}O_3$ (218.3): C 71.54, H 6.47; found C 71.52, H 6.48.

(*S*)-3-Benzyloxy-5-benzyl-4-hydroxy-5-methyl-2(5*H*)-furanone ((*S*)-8e): Yellow resin; ^{1}H NMR (250 MHz, CDCl$_3$): $\delta = 1.44$ (s, 3H; CH_3), 3.00 (AB system, q, $J = 14$ Hz, 2H; PhC*H*$_2$), 4.66 (AB system, q, $J = 11.2$ Hz, 2H; PhC*H*$_2$O), 7.15–7.46 (m, 10H; Ph); ^{13}C NMR (63 MHz, CDCl$_3$): $\delta =$ 22.99 (CH_3), 42.86 (PhCH$_2$), 68.00 (PhCH$_2$O), 81.30 (C–O–), 120.46 (PhCH$_2$O*C*=), 127.12, 128.14, 128.46, 128.49, 128.53, 130.16, 134.39, 136.53 (Ph,PhCH$_2$OC=), 163.14, 169.14 (C=O,C–OH); HRMS (70 eV, EI): calcd for $C_{19}H_{18}NO_4$ 310.1205, found 310.1200.

(*S*)-3-Benzyloxy-4-hydroxy-5-methyl-5-(2-phenyl)ethyl-2(5*H*)-furanone ((*S*)-8f): Pale yellow resin; ^{1}H NMR (250 MHz, [D$_6$]DMSO): $\delta = 1.35$ (s, 3H; CH_3), 1.81–2.30 (m, 4H; PhC*H*$_2$C*H*$_2$), 5.03 (AB system, q, $J = 11.6$ Hz, 2H; PhC*H*$_2$O), 7.06-7.45 (m, 10H; Ph), 12.10 (brs, 1H; OH); ^{13}C NMR (63 MHz, [D$_6$]DMSO): $\delta = 23.57$ (CH_3), 28.33 (PhCH$_2$*C*H$_2$), 37.39 (Ph*C*H$_2$CH$_2$), 71.99 (PhCH$_2$O), 79.98 (C–O–), 117.82 (PhCH$_2$O*C*=), 125.75, 127.96, 128.06, 128.24, 136.74, 140.79 (Ph), 163.72, 168.13 (C=O,C–OH); elemental analysis calcd (%) for $C_{20}H_{20}O_4$ (324.4): C 74.06, H 6.21; found C 73.93, H 6.49.

(*S*)-4-Hydroxy-3,5-dimethyl-5-(2-phenyl)ethyl-2(5*H*)-furanone ((*S*)-8d): A solution of (*S*)-**7d** (4.1 g, 14.7 mmol) in THF (40 mL) was added dropwise over 15 min to a solution of LDA (3.47 g, 32.4 mmol) in THF (40 mL) at $-78\,^\circ$C. The stirred reaction mixture was allowed to warm to room temperature (12 h). Water (50 mL) and methyl *tert*-butyl ether (50 mL) were added to quench the reaction. The organic phase was separated and extracted twice with saturated $NaHCO_3$ solution (50 mL each). The combined aqueous phases were washed twice with methyl *tert*-butyl ether (50 mL each), acidified with conc. HCl to pH 1 and extracted three times with ethyl acetate (50 mL each). The combined extracts were dried (Na_2SO_4) and concentrated to give analytically pure (*S*)-**8d** as a yellow oil, which solidifies slowly. M.p. 124 °C; ^{1}H NMR (500 MHz, [D$_6$]DMSO): $\delta = 1.40$ (s, 3H; CH_3), 1.62 (s, 3H; CH_3), 1.96–2.03 (m, 2H; PhCH$_2$C*H*$_2$), 2.30–2.44 (m, 2H; PhC*H*$_2$CH$_2$), 7.15–7.28 (m, 5H; Ph), 11.80 (brs, 1H; OH); ^{13}C NMR (126 MHz, [D$_6$]DMSO): $\delta = 6.56$, 23.66 (CH_3), 29.25 (PhCH$_2$CH$_2$), 38.08 (PhCH$_2$), 82.32 (C–O–), 94.92 (CH=), 126.24, 128.48, 128.70, 141.37 (Ph), 173.73, 176.77 (C=O,C–OH); elemental analysis calcd (%) for $C_{14}H_{16}O_3$ (232.3): C 72.39, H 6.94; found C 72.15, H 7.05.

General procedure for the preparation of (*S*)-amino-hydroxy-2(5*H*)-furanones (*S*)-5 and (*S*)-dihydroxy-2(5*H*)-furanones (*S*)-9: A solution of the respective benzyloxy derivative **4e**,**f** or **8e**,**f** (10 mmol), cyclohexene (30 mL, 300 mmol) and 10% Pd/C (0.5 g) in EtOH (150 mL) was refluxed under nitrogen for 1 h. The reaction mixture was filtered, and the filtrate was concentrated and dried in vacuo to give the products **5** and **9**. Products **9** were purified by recrystallization.

(*S*)-4-Amino-5-benzyl-3-hydroxy-5-methyl-2(5*H*)-furanone ((*S*)-5a): Colourless resin, which turns dark red on exposure to air; yield: 100%; $[\alpha]_D^{20} = -83.3$ ($c = 0.06$ in MeOH); ^{1}H NMR (250 MHz, [D$_6$]DMSO): $\delta =$ 1.38 (s, 3H; CH_3), 2.98 (s, 2H; PhCH$_2$), 6.09 (brs, 2H; NH_2), 7.12–7.27 (m, 5H; Ph), 7.42 (brs, 1H; OH); ^{13}C NMR (63 MHz, [D$_6$]DMSO): $\delta = 24.59$ (CH_3), 42.49 (PhCH$_2$), 79.23 (C–O–), 113.31 (O–*C*=), 126.35, 127.57, 129.89, 135.51 (Ph), 150.33, 168.21 (C=O,C–OH); HRMS (70 eV, EI): calcd for $C_{12}H_{13}NO_3$ 219.0895, found 219.0894.

(*S*)-4-Amino-3-hydroxy-5-methyl-5-(2-phenyl)ethyl-2(5*H*)-furanone ((*S*)-5b): Colourless resin, which turns dark red on exposure to air; yield: 100%; $[\alpha]_D^{20} = -20.5$ ($c = 4.0$ in MeOH); ^{1}H NMR (250 MHz, [D$_6$]DMSO): $\delta =$ 1.39 (s, 3H; CH_3), 1.90–2.09 (m, 2H; PhCH$_2$C*H*$_2$), 2.24–2.45 (m, 2H; PhC*H*$_2$CH$_2$), 6.11 (brs, 2H; NH_2), 7.15–7.49 (m, 5H; Ph), 7.63 (brs, 1H; OH); ^{13}C NMR (63 MHz, [D$_6$]DMSO): $\delta = 24.77$ (CH_3), 28.8 (PhCH$_2$CH$_2$), 38.45 (Ph*C*H$_2$), 79.23 (C–O–), 112.96 (O–*C*=), 125.79, 128.08, 128.32, 141.27 (Ph), 151.05, 168.75 (C=O,C–OH); HRMS (70 eV, EI): calcd for $C_{13}H_{15}NO_3$ 233.1052, found 233.1053.

(*S*)-5-Benzyl-3,4-dihydroxy-5-methyl-2(5*H*)-furanone ((*S*)-9a): Crystallized from toluene/ethyl acetate (7:3); yield: 65%; m.p. 194–196 °C; $[\alpha]_D^{20} = -11.2$ ($c = 1.0$ in MeOH), >99% *ee*; ^{1}H NMR (250 MHz, [D$_6$]DMSO): $\delta = 1.41$ (s, 3H; CH_3), 2.98 (AB system, q, $J = 14.1$ Hz, 2H; PhCH$_2$), 7.11–7.28 (m, 5H; Ph), 8.21, 11.28 (brs each, 1H; OH); ^{13}C NMR (63 MHz, [D$_6$]DMSO): $\delta = 23.78$ (CH_3), 42.17 (PhCH$_2$), 80.07 (C–O–), 117.25 (O–*C*=), 126.64, 127.81, 130.04, 135.23 (Ph), 156.25, 168.79 (C=O,C–OH); elemental analysis calcd (%) for $C_{12}H_{12}O_4$ (220.2): C 65.45, H 5.49; found C 65.31, H 5.50.

(*S*)-3,4-Dihydroxy-5-methyl-5-(2-phenyl)ethyl-2(5*H*)-furanone ((*S*)-9b): Crystallized from toluene/THF (20:1); yield: 89%; m.p. 216 °C; $[\alpha]_D^{20} =$ +29.9 ($c = 2.0$ in MeOH), 95% *ee*; ^{1}H NMR (250 MHz, [D$_6$]DMSO): $\delta =$ 1.39 (s, 3H; CH_3), 1.88–2.02 (m, 2H; PhCH$_2$C*H*$_2$), 2.28–2.46 (m, 2H; PhC*H*$_2$CH$_2$), 7.14–7.29 (m, 5H; Ph), 8.45, 11.33 (brs each, 1H; OH); ^{13}C NMR (63 MHz, [D$_6$]DMSO): $\delta = 23.69$ (CH_3), 28.82 (PhCH$_2$CH$_2$), 37.88 (Ph*C*H$_2$), 79.86 (C–O–), 116.7 (O–*C*=), 125.79, 128.01, 128.29, 140.92 (Ph), 157.02, 169.16 (C=O,C–OH); elemental analysis calcd (%) for $C_{13}H_{14}O_4$ (234.2): C 66.66, H 6.02; found C 66.46, H 5.97.

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