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TETRAHEDRON: *ASYMMETRY*

Stereoselective synthesis of biologically active tetronic acids[1]

Franz Effenberger * and Jana Syed †

Institut für Organische Chemie der Universität Stuttgart, Pfaffenwaldring 55, D-70569 Stuttgart, Germany

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Abstract

(4*R*)-3-Amino-4-trimethylsilyloxy-2-alkenoates (*R*)-**3**, obtained from O-trimethylsilyl protected optically active cyanohydrins (*R*)-**1** via the Blaise reaction, are hydrolyzed under mildly acidic conditions to give optically active tetronic acids (*R*)-**4** without racemization. From the follow-up reactions of (*R*)-**4** investigated, only methylation with diazomethane afforded the biologically active tetronic acid derivative (*R*)-**5a** without racemization whereas acylation and reductive alkylation, respectively, resulted in partial racemization or failed on the whole.

Tetronic acid derivatives and their metabolites are widespread in nature, whereof vitamin C and penicillic acid are undoubtedly the most important.[2] Natural 4-ylidenetetronic acid derivatives known as pulvinic acids have been found as pigments in lichens and higher fungi.[3] Tetronic acid derivatives are interesting because of their antibiotic,[4] antitumor,[5] anticoagulant,[6] antiepileptic,[7] antifungal,[4b,8] insecticidal,[9] analgesic[10] and antiinflammatory[10b,11] properties. In recent times tetronic acid derivatives have also become important as HIV-1 protease inhibitors.[12] Most of the investigated tetronic acids with chiral centres are applied only as racemates.[5c,6b,c,7,8a,13]

Optically active tetronic acid derivatives were synthesized mostly by Dieckmann cyclizations starting from 'chiral pool' compounds such as (*S*)-lactic acid, (*S*)-mandelic acid, (*S*)-malic acid or (*R,R*)-tartaric acid.[14] For the preparation of 5-aryl-3-hydroxytetronic acids, which are very sensitive to racemization, O-protected mandelaldehydes were used as starting materials.[15] The enantioselective synthesis of 5-substituted 3-methyltetronic acids, starting from chiral ethyl 2-methyl-3-(1-phenylethoxy)acrylate, was achieved by optical induction with very high enantiomeric excesses.[16]

Only two papers have been published on the synthesis of chiral tetronic acids starting from optically active cyanohydrins. In the first one, the Blaise reaction was applied to the O-protected optically active cyanohydrin from trifluoroacetaldehyde.[17] Acidic workup of the addition products gave the corresponding trifluoromethyl tetronic acid derivatives.[17] The optical purity of the obtained products

* Corresponding author. E-mail: franz.effenberger@po.uni-stuttgart.de

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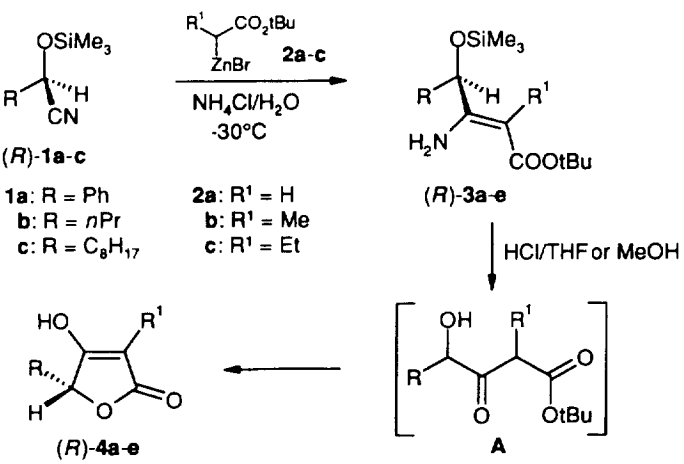
was not determined.[17] In the second publication, which appeared very recently,[18] the synthesis of four chiral 5-substituted 3-methyltetronic acids is described.

In the preceding paper, the synthesis of (4*R*)-3-amino-4-hydroxyalkenoates by Blaise reaction with (*R*)-cyanohydrins is described.[1] We have now used these γ-hydroxy esters for the preparation of the corresponding chiral tetronic acid derivatives. In follow-up reactions the possibilities of the preparation of specially substituted tetronic acid derivatives with known biological activities were investigated.

1. Hydrolysis and cyclization of (*R*)-*tert*-butyl 3-amino-4-trimethylsilyloxyalkenoates (*R*)-3 to (*R*)-tetronic acids (*R*)-4

The (*R*)-enaminoesters (*R*)-**3**, derived from O-trimethylsilylated (*R*)-cyanohydrins (*R*)-**1** by Blaise reaction with the Reformatsky reagents **2**,[1] were lactonized under acid catalysis in tetrahydrofuran (THF) or methanol with removal of the O-protecting group via intermediates **A** to (*R*)-tetronic acids (*R*)-**4** (Scheme 1, Table 1).



3, 4	R	R¹
a	Ph	H
b	*n*Pr	H
c	*n*Pr	Me
d	*n*Pr	Et
e	C_8H_{17}	H

Scheme 1.

Table 1
Acid-catalyzed cyclization of (*R*)-enaminoesters **3** to (*R*)-tetronic acids **4**

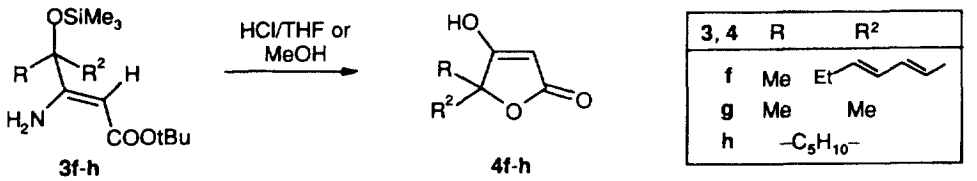
(*R*)-**3**		react.	HCl	(*R*)-tetronic acids **4**				
	ee (%)	time (h)	(% ic)		yield (%)	*ee* (%)[a]	*ee* (%)[b]	$[\alpha]_D^{23}$ (*c*, EtOH)
a	>95	100	20	**a**	55	78	93	-191.0 (1.0)
b	94	23	10	**b**	40	94	96	+9.2 (0.6)
c	72	21	10	**c**	69	88	95	+13.4 (0.6)
d	76	24	10	**d**	48	-	94	+31.7 (0.6)
e	n.d.	65	20	**e**	70	79	79	+68.1 (0.4)[c]
f	-	110	20	**f**	64	-	-	-
g	-	72	20	**g**	88	-	-	-
h	-	29	20	**h**	62	-	-	-

[a] *ee*-Value of crude products. [b] *ee*-Value after recrystallization; determined from acetylated products by gc on chiral β-cyclodextrin phase Bondex-unβ-5,5-Et-105. [c] In dichloromethane.

The lactonization of the aliphatic enaminoesters (*R*)-**3b–d** proceeded without racemization. After recrystallization the (*R*)-tetronic acids (*R*)-**4b–d** were isolated with high *ee* values of 94–96% (Table 1). (*R*)-**3a**, however, was cyclized to (*R*)-4-hydroxy-5-phenyl-2(5H)-furanone (*R*)-**4a** with partial racemization. The enantiomeric excess could be increased to 93% by recrystallization. Only the 5-octyltetronic acid derivative (*R*)-**4e** was obtained, also after recrystallization, with only 79% *ee* (Table 1).

While hydrolysis of the enamino group is finished after just 1 hour, the cyclization, especially of sterically hindered intermediates **A**, requires a reaction time of several days. In the case of **3a**, using a 10% HCl/diethyl ether system as a milder hydrolysis medium, we were able to isolate intermediate **A** (R=Ph, R^1=H) in 55% yield after 4 hours reaction time.

Also the enaminoesters **3f–h**, derived from the corresponding O-protected ketone cyanohydrins, were converted under acid catalysis to tetronic acids **4f–h** with good yields (Scheme 2, Table 1).

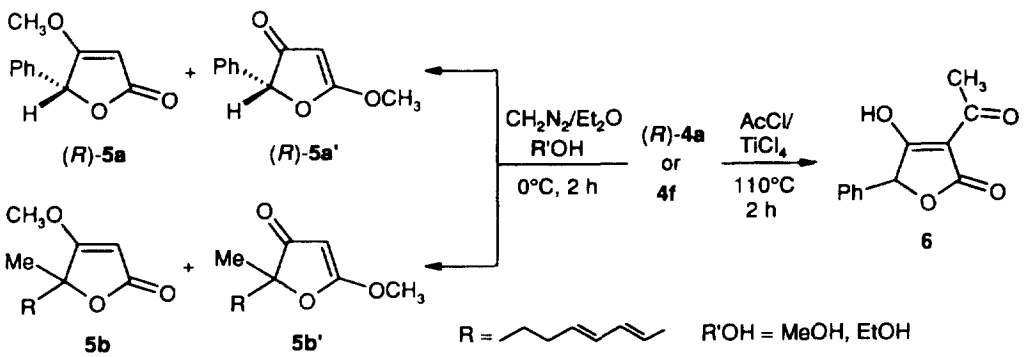


Scheme 2.

Tetronic acid derivatives are known to exist as solids and in alcoholic solution in their enol form.[2b] For solutions of **4** in chloroform we have found the enol form to be dominant for tetronic acids (*R*)-**4a,c,d** and **4g,h** while the keto form predominates in derivatives (*R*)-**4b,e** and **4f** (see Experimental).

2. Follow-up reactions of tetronic acids 4 to compounds of known biological activity

O-Methylation, α-acylation and α-alkylation of (*R*)-tetronic acids (*R*)-**4** should offer an approach to optically active derivatives which are of pharmacological interest and are known so far only as racemates. As starting compounds for the follow-up reactions we have applied (*R*)-**4a** and **4f**. In Scheme 3 both methylation and acylation of these derivatives are illustrated.



Scheme 3.

Methylation was examined first with racemic tetronic acid **4a**. **4a** was reacted with methanolic HCl solution (1%) according to literature-known procedures[19] to give the 4-methoxy substituted derivative **5a** in 47% yield. Methylation of the caesium salt of **4a** with iodomethane gave compound **5a** in 50% yield. In this case, methylation at the 3-position also occurred to give 4-methoxy-3-methyl-5-phenyl-2(5H)-furanone in 10% yield besides **5a**.

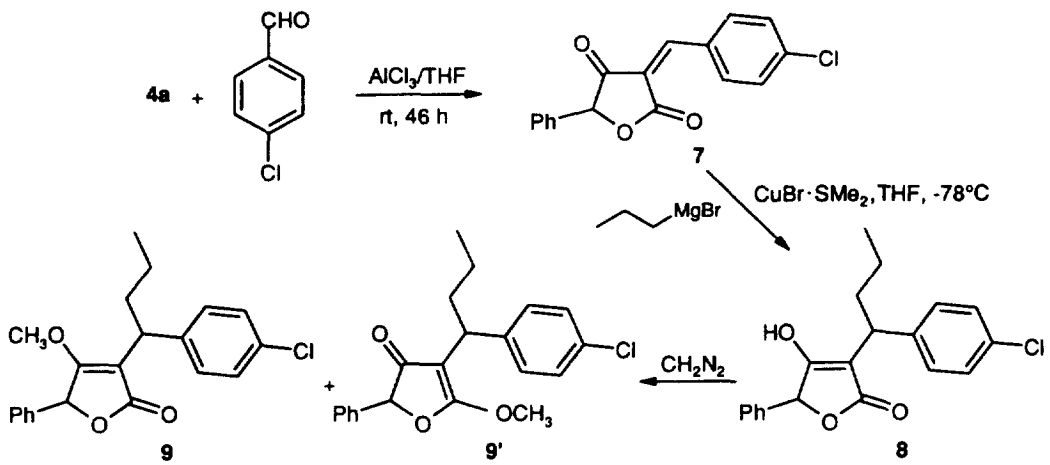
Methylation with diazomethane in diethyl ether/methanol at 0°C, giving the best results with racemic **4a**, was also used for (*R*)-**4a** (93% *ee*) (Scheme 3). By this procedure we are able to obtain optically active (*R*)-**5a** without any racemization in 62% yield and 93% *ee*, which, in racemic form, is known to be more than 30 times as active as the natural antibiotic penicillic acid.[20] The isomeric 2-O-methylated (*R*)-**5a**′ formed as a by-product in 14% yield, could be separated readily by chromatography on silica gel.

Under analogous conditions the methylated tetronic acids **5b** and **5b**′ were obtained (Scheme 3). After chromatographic separation, **5b**′ was isolated in 18% yield while the yield of the desired **5b** (37%) is clearly lower than that of (*R*)-**5a**.

Acetylation of (*R*)-**4a** appeared to open an access to optically active α-acetyl-γ-phenyltetronic acid **6**, which has been synthesized so far in racemic form as an antitumor agent.[5c] The reaction of (*R*)-**4a**, based on the Friedel–Crafts acylation of racemic **4a** described by Andresen et al.,[21] with acetyl chloride in the presence of $TiCl_4$ gave compound **6** in 45% yield, but with complete racemization (Scheme 3). On the other hand, all attempts failed to prepare **6** in pure form by conversion of **4a** with acetic anhydride in the presence of triethylamine and 4-dimethylaminopyridine and subsequent Fries rearrangement.

As a further pharmacologically potent tetronic acid we have chosen 3-[1-(4-chlorophenyl)butyl]-5-phenyltetronic acid derivative **8**,[6a,c] which should be accessible by direct alkylation of γ-phenyltetronic acid **4a**. However, neither the alkylation of **4a** with α-(*n*-propyl)-*p*-chlorobenzyl alcohol[22] in the presence of $BF_3 \cdot Et_2O$ in dioxane nor the sodium iodide assisted reaction of the lithium salt of **4a** with α-(*n*-propyl)-*p*-chlorobenzyl bromide[23] in THF/tetramethylenediamine has been successful.

The alternative route to tetronic acid derivative **8**, based on a known methodology,[12b] is outlined in Scheme 4. The reaction sequence involves an aldol condensation with *p*-chlorobenzaldehyde to intermediate **7** and subsequent addition of propylmagnesium bromide to give compound **8**.



Scheme 4.

The aldol condensation in THF in the presence of a twofold excess of $AlCl_3$ (based on **4a**) gave compound **7** as a yellow fluorescent oil in 88% crude yield. **7** was reacted without purification with the Grignard reagent at −78°C in THF under catalysis by a $CuBr \cdot SMe_2$ complex to give regioselectively tetronic acid derivative **8** as a congealing yellow oil in 90% crude yield. In contrast to intermediate **7**, derivative **8** is stable. We were not able to obtain **8** in pure form by this procedure because impurities could not be separated either by distillation or by chromatography, and recrystallization was not successful.

For characterization, compound **8** was derivatized with diazomethane as described above to give the corresponding 4-O- and 2-O-methylated derivatives **9** and **9**′ in 24% and 14% yield (based on

4a), respectively, after chromatography on silica gel. As stated by ^{1}H NMR spectra, all tetronic acid derivatives **8** and **9**, **9′** exist in a diastereomeric ratio of 1:1.

3. Experimental

3.1. Materials and methods

$AlCl_3$ was purchased from Aldrich, *p*-chlorobenzaldehyde, $TiCl_4$ and $CuBr \cdot SMe_2$ complex from Fluka, and Celite 503 from Roth. (4*R*)-*tert*-butyl 3-amino-4-trimethylsilyloxy-2-alkenoates **3** were prepared according to methods described elsewhere.[1] All solvents were purified and dried as described in the literature. Melting points were determined on a Büchi SMP-20 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC 250 F with TMS as an internal standard. Optical rotations were determined in a Perkin–Elmer polarimeter 241 LC. Preparative column chromatography was performed with glass columns of different sizes packed with silica gel S, grain size 0.032–0.063 mm (Riedel-de Haen). GC for the determination of enantiomeric excess: Carlo Erba HRGC 5300 Mega Series with FID, Carlo Erba Mega Series integrator, 0.4–0.5 bar hydrogen, column 20 m, phase OV 1701 or PS086 with bonded β-cyclodextrin Bondex-un-5.5-Et-105. High resolution mass spectra were obtained with a Varian MAT 711 electron impact spectrometer by using the peak-matching method.

3.2. Acid-catalyzed cyclization of (R)-3a–e to (R)-tetronic acids (R)-4a–e; general procedure

Aqueous HCl (20%, 2 and 15 ml for **3e,a**; 10%, 20–38 ml) was added to an ice-cold solution of (*R*)-**3a–d** (3.1–7.5 mmol) in THF or (*R*)-**3e** (2.8 mmol) in methanol under a nitrogen atmosphere, and the reaction mixture was stirred at room temperature for the given time (Table 1). The reaction mixture was saturated with NaCl and extracted several times with diethyl ether. The combined extracts were dried ($MgSO_4$), concentrated, and the crude products (*R*)-**4** recrystallized from ethyl acetate/petroleum ether (**4a,b,d**), from ethyl acetate (**4c**), and from *n*-hexane (**4e**).

3.3. Determination of enantiomeric excesses of (R)-4a–e

Pyridine (5 μl) and acetic anhydride (20 μl) were added to a solution of **4** (5 mg) in 200 μl dichloromethane. The reaction mixture was heated to 60°C for 2 h and then filtered through a silica gel column (0.5×3 cm) with 5 ml dichloromethane. The enantiomeric excess was determined by gas chromatography directly from the filtrate on Bondex-unβ-5.5-Et-105.

3.4. Acid-catalyzed cyclization of 3f–h to tetronic acids 4f–h; general procedure

Aqueous 20% HCl (3–15 ml) was added to an ice-cold solution of **3** (6.8–25.6 mmol) in THF or methanol (for **3h**) under an N_2 atmosphere, and the reaction mixture was stirred for the time given in Table 1. The tetronic acids **4** were worked up as follows: **4f**: the reaction mixture was set to pH 8 with sat. Na_2CO_3 solution and extracted with ethyl acetate. The aqueous phase was again acidified with HCl and extracted several times with ethyl acetate. The combined organic phases were dried ($MgSO_4$) and concentrated to yield **4f** as an orange oil;[24] **4g**[25]: as described above (Section 3.2); **4h**[25]: after removal of methanol *in vacuo*, the residual aqueous phase was extracted several times with ethyl acetate. The

combined extracts were dried ($MgSO_4$), concentrated and the product (white crystals) washed with ethyl acetate and dried.

3.5. *Methylation of* (R)-**4a** *to 4-O- and 2-O-methylated furanones* (R)-**5a** *and* (R)-**5a′**

A solution of 0.2 M diazomethane in diethyl ether was added dropwise to a solution of (*R*)-**4a** (105.3 mg, 0.6 mmol) in 8 ml diethyl ether/2.6 ml methanol at 0°C. The reaction mixture was stirred for a further 2 h at 0°C. After removal of the solvent, the crude product was chromatographed on silica gel with petroleum ether:ethyl acetate (65:35) to give (*R*)-**5a** and (*R*)-**5a′**.

(*R*)-**5a**: 71.2 mg (62%) as white crystals, m.p. 77–78°C, 93% *ee*; ^{1}H NMR ($CDCl_3$) δ=3.80 (s, 3H, OCH_3), 5.16 (d, *J*=1.3 Hz, 1H, CH), 5.70 (d, *J*=1.3 Hz, 1H, CH), 7.20–7.40 (m, 5H, Ph). Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.60; H, 5.45.

(*R*)-**5a′**: 16 mg (14%) as white crystals; ^{1}H NMR ($CDCl_3$) δ=4.05 (s, 3H, OCH_3), 4.86 (s, 1H, CH), 5.53 (s, 1H, CH), 7.36–7.43 (m, 5H, Ph).

Physical and ^{1}H NMR data of tetronic acids **4**

Compd	m.p. (°C)	^{1}H NMR (250 MHz, $CDCl_3$, δ)
(*R*)-**4a**[a]	154-156	enol:keto=3.6:1; 3.30 (d, *J* = 22.0 Hz, 1 H, keto 3-C*H*$_a$H$_b$), 3.39 (d, 1 H, keto 3-CH$_a$*H*$_b$), 5.17 (d, *J* = 1.0 Hz, 1 H, enol 3-CH), 5.72 (d, *J* = 0.5 Hz, 1 H, enol 5-CH), 5.76 (s, 1 H, keto 5-CH), 7.32-7.44 (m, 10 H, 2 Ph), 9.40 (broad s, 1 H, OH)
(*R*)-**4b**	65-68	enol:keto=1:1.3; 0.96 and 0.97 (each t, *J* = 7.3 Hz, 3 H, CH_3), 1.44-2.00 (m, 8 H, 2 $(CH_2)_2$), 3.14 (dd, *J* = 22.5, 1.0 Hz, 1 H, keto 3-C*H*$_a$H$_b$), 3.24 (d, *J* = 22.5 Hz, 1 H, keto 3-CH$_a$*H*$_b$), 4.76 (dd, *J* = 4.7, 7.6 Hz, 1 H, keto 5-CH), 4.85 (dd, *J* = 3.7, 7.4 Hz, 1 H, enol 5-CH), 5.03 (s, 1 H, enol 3-CH), 11.7 (broad s, 1 H, OH)
(*R*)-**4c**	104-107	enol:keto=1:0; 0.95 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.36-1.68 (m, 3 H, $CH_3CH_2CH_aH_b$), 1.74 (s, 3 H, CH_3), 1.90-2.10 (m, 1 H, $CH_3CH_2CH_aH_b$), 4.78 (broad dd, 1 H, 5-CH), 10.70 (broad s, 1 H, OH)
(*R*)-**4d**[b]	70-73	enol:keto =22:1; 0.95 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.06 (t, *J* = 7.5 Hz, 3 H, CH_3), 1.40-1.54 (m, 2 H, $CH_3CH_2CH_2$), 1.57-1.65 (m, 1 H, keto 3-C*H*$_a$H$_b$), 1.90-2.00 (m, 1 H, keto 3-CH$_a$*H*$_b$), 2.23 (q, *J* = 7.5 Hz, 2 H, CH_3CH_2), 4.77 (dd, *J* = 3.3, 7.6 Hz, 1 H, enol 5-CH), 10.20 (broad s, 1 H, OH)
(*R*)-**4e**	93-95	enol:keto =1:1; 0.88 (broad t, *J* = 6.5 Hz, 6 H, 2 CH_3), 1.20-1.55 (m, 24 H, 2 $(CH_2)_6$), 1.60-1.90 (m, 4 H, 2 CH_2), 3.13 (dd, *J* = 23.0, 1.1 Hz, keto 3-C*H*$_a$H$_b$), 3.23 (dd, *J* = 23.0, 0.5 Hz, 1 H, keto 3-CH$_a$*H*$_b$), 4.75 (dd, *J* = 4.6, 7.5 Hz, 1 H, keto 5-CH), 4.84 (dd, *J* = 3.7, 7.4 Hz, 1 H, enol 5-CH), 5.00 (s, 1 H, enol 5-CH), 11.20 (broad s, 1 H, OH)
4f	-	enol:keto=0:1; 1.01 (t, *J* = 7.4 Hz, 3 H, CH_3), 1.59 (s, 3 H, CH_3), 2.07-2.18 (m, 2 H, CH_2CH), 3.15 (d, *J* = 22.3 Hz, 1 H, 3-C*H*$_a$H$_b$), 3.30 (d, 1 H, 3-CH$_a$*H*$_b$), 5.55 (d, *J* = 15.4 Hz, 1 H, =CH), 5.88 (dt, *J* = 6.2, 15.2 Hz, 1 H, CH_2CH=), 6.01 (dd, *J* = 15.2, 10.0 Hz, 1 H, =C*H*-CH), 6.36 (dd, *J* = 15.4, 10.0 Hz, 1 H, CH-C*H*=)
4g	145-147[c]	enol:keto=1:0; 1.37 (s, 6 H, CH_3), 4.79 (s, 1 H, CH), 12.60 (broad s, 1 H, OH)
4h	198-201[c]	enol:keto=1:0; 1.20-1.79 (m, 10 H, $(CH_2)_5$), 4.78 (s, 1 H, CH), 12.60 (broad s, 1 H, OH)

[a] In CD_3CN. [b] 500 MHz. [c] See Ref.[25]

Elemental analytical data of compounds (R)-4b-4e

Compd	Mol. formula (Mol. weight)	Calculated/found C	H	Compd	Mol. formula (Mol. weight)	Calculated/found C	H
(*R*)-**4b**	$C_7H_{10}O_3$[a]	59.14	7.09	(*R*)-**4d**	$C_9H_{14}O_3$	63.51	8.29
	(142.2)	58.78	6.97		(170.2)	63.12	8.03
(*R*)-**4c**	$C_8H_{12}O_3$	61.53	7.74	(*R*)-**4e**	$C_{12}H_{20}O_3$	67.89	9.49
	(156.2)	61.54	7.65		(212.3)	67.54	9.34

[a] MS (EI, 70 eV): Calcd 142.06264. Found: 142.06264.

3.6. *Methylation of **4f** to 4-O- and 2-O-methylated furanones **5b** and **5b′***

A solution of 0.4 M diazomethane in diethyl ether was added dropwise to a solution of **4f** (830 mg, 4.27 mmol) in dry diethyl ether and 25 ml dry ethanol at 0°C. After stirring for a further 2 h at 0°C, solvents were removed, and the crude product was chromatographed on silica gel with petroleum ether:ethyl acetate (1:1) to give **5b** and **5b′**.

5b:[26] 325 mg (37%) as a light yellow oil; ^{1}H NMR ($CDCl_3$) δ=1.00 (t, *J*=7.5 Hz, 3H, CH_3), 1.56 (s, 3H, CH_3), 2.11 (dq, *J*=7.3 Hz, 2H, CH_2CH), 3.88 (s, 3H, OCH_3), 4.96 (s, 1H, CH), 5.56 (d, *J*=15.4 Hz, 1H, =CH), 5.83 (dt, *J*=6.3, 15.2 Hz, 1H, CH_2CH), 6.00 (dd, *J*=10.0, 15.2 Hz, 1H, =CH–CH), 6.34 (dd, *J*=10.1, 15.4 Hz, 1H, CH–CH=).

5b′: 164.2 mg (18%) as white solid; ^{1}H NMR ($CDCl_3$) δ=0.99 (t, *J*=7.4 Hz, 3H, CH_3), 1.56 (s, 3H, CH_3), 2.10 (dq, *J*=7.0 Hz, 2H, CH_2CH), 3.99 (s, 3H, OCH_3), 4.70 (s, 1H, CH), 5.60 (d, *J*=15.4 Hz, 1H, =CH), 5.81 (dt, *J*=6.4, 15.1 Hz, 1H, CH_2CH), 6.00 (dd, *J*=10.4, 15.1 Hz, 1H, =CH–CH), 6.33 (dd, *J*=10.2, 15.4 Hz, 1H, CH–CH=).

3.7. *α-Acylation of (R)-**4a** to tetronic acid derivative **6** according to Andresen et al.*[21]

A mixture of (*R*)-**4a** (273 mg, 1.55 mmol), acetyl chloride (119 μl, 1.7 mmol) and $TiCl_4$ (350 μl, 3.3 mmol) was stirred at room temperature for 5 min followed by heating to 110°C for 3 h. The reaction mixture was then poured into an ice-cold 4 N solution of HCl and extracted with chloroform. The combined organic phases were extracted with a solution of Na_2CO_3 (10%). The aqueous phase was acidified with conc. HCl and extracted several times with chloroform. The combined extracts were dried ($MgSO_4$), concentrated, and the remaining crystals recrystallized from ethyl acetate/petroleum ether to give 152 mg (45%) racemic **6** as white crystals, m.p. 104–105°C.

3.8. *Preparation of tetronic acid derivative **8***

(a) According to Chrusciel et al[12b] *p*-chlorobenzaldehyde (0.8 g, 5.7 mmol) and $AlCl_3$ (1.42 g, 10.6 mmol) were added to a solution of **4a** (0.96 g, 5.4 mmol) in 38 ml THF, and the reaction mixture was stirred for 46 h at room temperature in the absence of light. After addition of $Na_2CO_3 \cdot 10H_2O$ (1.1 g Na_2CO_3 and 1.9 ml H_2O) followed by anhydrous Na_2CO_3 (1.1 g), the reaction mixture was stirred for 10 min and then filtered through a short Celite column. The filtrate was concentrated *in vacuo*, and the residue taken up in 40 ml ethyl acetate and filtered once more through a Celite column. The filtrate was concentrated and dried under high vacuum to give 1.42 g crude **7** as a fluorescent yellow oil. **7** was converted without further purification.

(b) At −78°C a 0.5 M solution of propylmagnesium bromide in THF, prepared from propyl bromide (3.16 g, 25.8 mmol) and Mg (0.63 g, 25.9 mmol) in 53 ml THF, was added dropwise to a mixture of **7** (2.19 g, 7.3 mmol) and the catalyst CuBr·SMe_2 (151.1 mg, 0.74 mmol) in 50 ml dry THF. The reaction mixture was stirred for 2 h. After addition of a 5% solution of acetic acid in *n*-hexane (15 ml) and stirring for a further 10 min at −78°C, the reaction mixture was allowed to warm to room temperature. Then ethyl acetate and 1 N HCl were added. The organic phase was separated, washed with sat. NaCl solution, dried ($MgSO_4$), concentrated and dried under high vacuum to give 1.7 g (90%, based on **4a**) of crude **8** as an orange oil. For characterization, **8** was methylated with diazomethane as described above to give derivatives **9** and **9′**.

9: 24% yield, light yellow congealing oil, diastereomeric ratio 1:1; ^{1}H NMR ($CDCl_3$) δ=0.95 (t, *J*=7.2 Hz, 6H, $2CH_3$), 1.22–1.43 (m, 4H, $2CH_2$), 1.92–2.09 (m, 2H, 2 2-C$H_a$$H_b$), 2.09–2.24 (m, 2H, 2 2-C$H_a$$H_b$), 3.66 and 3.67 (each s, 3H, OCH_3), 3.81 and 3.82 (each t, *J*=8.1 Hz, 1H, 2CH), 5.71 (s, 2H, 2CH–O), 7.20–7.42 (m, 10H, 2Ph). Anal. Calcd for $C_{21}H_{21}ClO_3$: C, 70.68; H, 5.93; Cl, 9.94. Found: C, 70.46; H, 6.00; Cl, 10.12.

9′: 14%, colourless oil, diastereomeric ratio 1:1; ^{1}H NMR ($CDCl_3$) δ=0.88 and 0.90 (each t, *J*=7.3 Hz, 3H, CH_3), 1.15–1.31 (m, 4H, $2CH_3CH_2$), 1.81–2.12 (m, 4H, $2CH_2$), 3.57 and 3.58 (each t, *J*=8.0 Hz, 1H, 2CH), 4.08 (s, 6H, $2OCH_3$), 5.41 and 5.43 (each s, 1H, 2CH–O), 7.19–7.40 (m, 10H, 2Ph). Anal. Calcd for $C_{21}H_{21}ClO_3$: C, 70.68; H, 5.93; Cl, 9.94. Found: C, 70.61; H, 5.96; Cl, 9.74.

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