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SYNTHESIS OF OPTICALLY ACTIVE SILYL PROTECTED CYANOHYDRINS.

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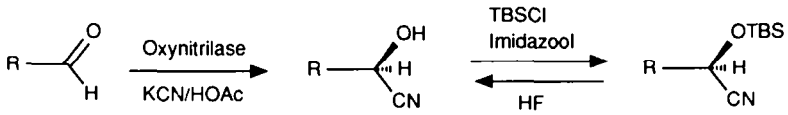
Abstract: Mandelonitrile lyase as present in a crude extract of almond flour has been tested for the synthesis of several chiral cyanohydrins. Silylated cyanohydrins of benzaldehyde, 4-methoxybenzaldehyde, piperonal, 5-methylfurfural, butyraldehyde and crotonaldehyde were obtained in good yield and high enantiomeric excess (>93%) after treatment with silyl chlorides and imidazole in DMF.

Cyanohydrins are versatile starting materials for the synthesis of several classes of compounds such as α-hydroxyacids (-esters), vicinal diols, α-hydroxyketones, ethanolamines and amino acids. Optically active cyanohydrins can be obtained with the aid of chiral catalysts, e.g.: titanium(IV) alkoxides[1], boryl compounds[2], synthetic dipeptides[3], enzymes for resolution[4,5], and with the enzyme mandelonitrile lyase (oxynitrilase) (E.C. 4.1.2.10) for direct synthesis[6-8]. Resolution by reaction with a chiral protective group has been reported[9]. However, in the latter case deprotection under basic conditions is not possible on account of the instability of the cyanohydrin and acid hydrolysis afforded the α-hydroxy ester.



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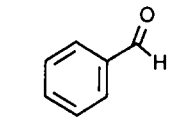
The possibility to catalyze cyanohydrin formation by the mandelonitrile lyase enzyme in purified form has been tested for a substantial number (62) of aldehydes[10-12]. About half of these were accepted by the enzyme but, except for benzaldehyde cyanohydrin, no enantiomeric excess was determined in these studies. More recently Effenberger et al.[7] have tested 9 aldehydes, both in water/ethanol and water/ethyl acetate systems. After converting the cyanohydrins into diastereomeric esters the e.e. was determined by gas chromatography. In our endeavours towards the synthesis of chiral building blocks and/or enantiomerically pure biologically active compounds, we have tested 12 aldehydes in our previously described mandelonitrile lyase catalyzed system[8]. In this system a crude extract of almond flour is used, rather than a purified enzyme. Also, a potassium cyanide/acetic acid buffer is applied to avoid the use of free hydrocyanic acid. In this way, the

process is less laborious, less costly, and safer to operate.

The aldehydes were first tested under standard conditions (see experimental). Conversion and e.e. were determined by NMR, using $Eu(Hfc)_3$ as a chiral shift reagent. The results are presented in Table I.

Table I. Enzyme Catalyzed Formation of Cyanohydrins under Standard Conditions.

aldehyde.	conv.(%)	e.e.(%)	aldehyde.	conv.(%)	e.e.(%)
a.	81	94	g.	86	55
b.	55	93	h.	96	0
c.	50	93	i.	100	92
d.	83	0	j.	95	67
e.	0	-	k.	99	69
f.	0	-	l.	25	78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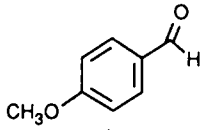
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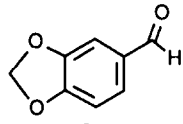
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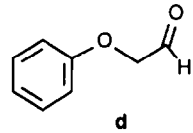
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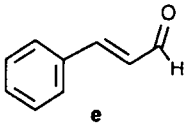
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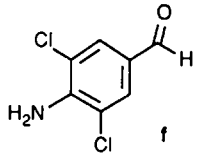
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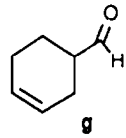
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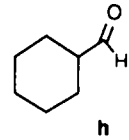
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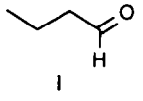
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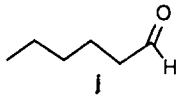
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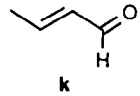
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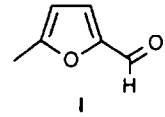
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Out of the twelve aldehydes tested, *E*-Cinnamaldehyde (**1e**) and 4-amino-3,5-dichlorobenzaldehyde (**1f**) were neither converted enzymatically nor chemically. Cyclohexanecarboxaldehyde (**1h**) and 2-phenoxyethanal (**1d**) likewise were not accepted by the enzyme but under the reaction conditions used, rapid non-enzyme-catalyzed conversion to the cyanohydrin occurred.

From literature data[6-11] and the results presented here one can postulate that mandelonitrile lyase will accept as substrates: 1. straight chain aliphatic aldehydes with up to six carbon atoms which may be substituted at the α-position with one methyl group. 2. α,ß-unsaturated aldehydes which may also be substituted at the α-position. 3. aromatic aldehydes which may be substituted mainly at para- and/or meta-positions.

4. heteroaromatic aldehydes such as 2-furancarboxaldehyde or 2-thiophencarboxaldehyde. It should be noted that, except for the aliphatic aldehydes and **1g**, all these compounds possess an α,ß-unsaturation.

Cyanohydrins prepared with the aid of mandelonitrile lyase possess a positive rotation, except those prepared from acyclic α,ß-unsaturated aldehydes.

Those aldehydes that had shown good affinity to the enzyme were tested under various reaction conditions in order to optimize the formation of optically active cyanohydrins with respect to the enantiomeric excess, even if this went at cost of the chemical yield. These results are presented in Table II.

Optimal conditions for benzaldehyde (**1a**) and 4-methoxybenzaldehyde (**1b**) have been described in a previous report[8]. Purification by means of distillation, crystallization or chromatography is not possible, except in the case of 4-methoxybenzaldehyde cyanohydrin (**2b**) which can be obtained nearly optically pure by a single crystallization from an optimized solvent system. Derivatization often leads to decomposition or racemization. However, silylation of the hydroxyl function was found to proceed with little or no racemization and in excellent yields by using *tert*-butyldimethylsilyl chloride (TBSCl) in the presence of a suitable proton acceptor.

Different proton acceptors were tested, e.g.: triethylamine, pyridine, imidazole, and dimethylaminopyridine (DMAP). Silylation in the presence of triethylamine was accompanied by extensive decomposition and racemization. With pyridine, no reaction occurred at all. Imidazole and DMAP however gave excellent results.

Other silyl chlorides such as trimethylsilyl-, *tert*-butyldiphenylsilyl-, and thexyldimethylsilyl chloride gave results comparable to those obtained with TBSCl.

Table II. Enzyme Catalyzed Formation of Cyanohydrins under Optimized Conditions.

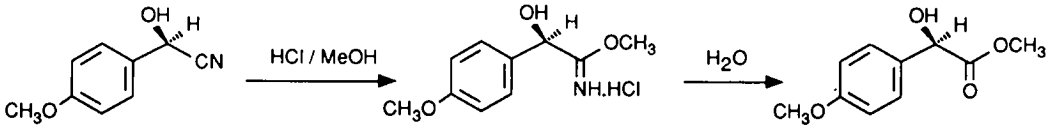
aldehyde.	conv.(%)	e.e.(%)	aldehyde.	conv.(%)	e.e.(%)
a.	95	99	i.	98	93
b.	85	99*	k.	94	95
c.	50	93	l.	65	95

* After crystallization, yield 67%.

Silylated cyanohydrins are stable and can be purified by flash chromatography or even by distillation at reduced pressure. In this way the, protected cyanohydrins, none of which had been reported earlier in an optically active form, were obtained in good yields and high e.e.'s. The enantiomeric excess could not be established at this point. However, after conversion of the silylated cyanohydrins **3a** and **3b** into the corresponding acyloins[8] or by removal of the protecting group with aqueous HF in acetonitrile (**3a,b,i,k**) to give the original cyanohydrins, it could be confirmed that no racemization had occurred during silylation. It should be noted that a similar desilylation of **3c** and **3l** is not possible without decomposition of the acid-sensitive methylenedioxy- or furan moiety, respectively.

The configuration of (+)-benzaldehyde cyanohydrin (**2a**) is known to be *R*. For (+)-4-methoxybenzaldehyde

cyanohydrin (**2b**) we could establish the configuration to be *R* as well, by conversion into (*R*)-(-) methyl 4-methoxymandelate (**5b**) of known absolute configuration[13].



2b **4b** **5b**

Cyanohydrins **2c,i,k** and **l** are assumed to have likewise the *R*-configuration because of their analogy with **2a** and **2b** in method of preparation.

Experimental.

-- ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a JEOL FX-200 or, in case of e.e. determinations, on a Bruker AM-400 instrument. Samples were measured in $CDCl_3$. The optical purity of the cyanohydrins was determined with the aid of tris-[3-(heptafluoropropylhydroxymethylene)-d-camphorato]-europium(III) [Eu(hfc)$_3$]. Under optimized conditions at 400 MHz, racemic cyanohydrins gave two signals with baseline separation for the proton at the α-carbon atom. The e.e. of optically active cyanohydrins was determined by integration of these signals.
-- IR-spectra were recorded on a PYE UNICAM SP3 200 instrument.
-- MS-spectra were recorded on a TSQ Triple Quad instrument.
-- Optical rotations were measured using a Perkin Elmer 141 polarimeter.

Chemicals.

Except in the case of **1d**, commercially available products were used. Aldehydes were distilled in an inert atmosphere prior to use.

2-Phenoxyethanal. (**1d**).
A mixture of 9.4 g (0.1 mol) phenol and 19.7 g (0.1 mol) 2-bromoacetaldehyde dimethylacetal in an ethanolic sodium ethoxide solution (2.3 g Na in 40 mL of absolute ethanol) was refluxed for 92 h. The solvent was evaporated and the residue was poured into cold water (200 mL) and extracted with ether (3 x 200 mL). The combined organic layers were washed three times with 2N NaOH and evaporated under reduced pressure. The residual oil was dissolved in 225 mL of THF. Aqueous 5% HCl (150 mL) was added and the mixture was heated to reflux. After 3 h, 250 mL of water was added, and the mixture was extracted with three 250 mL portions of ether. The combined ether layers were washed three times with 20 mL portions of a 10% NaCl solution, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residual oil was distilled to give 7.5 g (55%) 2-phenoxyethanal.
Bp 106-108 °C (3 mm Hg).
^{1}H NMR δ(ppm) 4.45 (s, 2H, CH_2); 6.89 (m, 3H, aromatic); 7.27 (m, 2H, aromatic); 9.74 (s, 1H, CHO).

Enzyme catalyzed formation of cyanohydrins.

1. Standard conditions.

The mandelonitrile lyase extract used was prepared as described previously[8].
To a solution of 15 mmol aldehyde in 5 mL of ethanol was added, under argon, 15 mL of the enzyme extract and the mixture was cooled to 0°C. 20 mL of a 1N KCN/HOAc buffer (pH 5.4) was mixed with 10 mL of ethanol, cooled to 0°C and added dropwise to the magnetically stirred mixture in 1.5 h. After stirring for another 3.5 h at 0°C, the reaction mixture was extracted with ether (3 x 25 mL). The combined ether layers were washed with a 10% NaCl solution (3 x 5 mL). Drying over magnesium sulfate and evaporation

of the solvent afforded the crude product, which was used for the e.e. determinations.

2. Optimized experiments.

For (*R*)-(+)-α-Hydroxybenzeneacetonitrile (**2a**) and (*R*)-(+)-α-Hydroxy-4-methoxybenzeneacetonitrile (**2b**), see previous report[8].

(*R*)-(+)-α-Hydroxy-1,2-benzodioxole-5-acetonitrile. (**2c**).
To a solution of 50 mmol piperonal in 25 mL of ethanol was added, under argon, 75 mL of the enzyme extract and the mixture was cooled to 0°C. 60 mL of a 1N KCN/HOAc buffer (pH 5.4) was mixed with 25 mL of ethanol, cooled to 0°C, and added dropwise to the magnetically stirred mixture in 1.5 h. After stirring for another 3.5 h, the reaction mixture was extracted with ether (3 x 50 mL). The combined organic layers were washed with a 10% NaCl solution (3 x 10 mL). Drying and evaporation of the solvent afforded a yellow oil. NMR analysis showed 45% cyanohydrin, 54% aldehyde and traces of acetic acid.
$[\alpha]_D^{20}$ + 23° (c=1, $CHCl_3$) crude product.
e.e. 93%

(*R*)-(+)-2-Hydroxypentanenitrile. (**2i**).
The procedure was the same as described above, except that 100 mmol of butyraldehyde and 125 mL of the enzyme extract was used. 120 mL 1N KCN/HOAc buffer was added in 1.5 h and stirring was continued for 1.5 h. The resulting colourless oil consisted of a mixture of the cyanohydrin (98%), aldehyde (2%) and traces of acetic acid.
$[\alpha]_D^{20}$ + 23° (c=1, $CHCl_3$) crude product.
e.e. 93%

(*R*)-(-)-2-Hydroxy-3-(*E*)-pentenenitrile. (**2k**).
Procedure as for **2c**, except that 70 mmol crotonaldehyde and 125 mL of the enzyme extract was used. 80 mL 1N KCN/HOAc buffer was added in 1.5 h and stirring was continued for 0.5 h. NMR analysis of the resulting oil showed 94% cyanohydrin, 5% aldehyde and traces of acetic acid.
$[\alpha]_D^{20}$ - 21° (c=1, $CHCl_3$) crude product.
e.e. 95%

(*R*)-(+)-2-(α-Hydroxyacetonitrile)-5-methylfuran. (**2l**).
The procedure was the same as described above, except that 105 mmol of 5-methylfurfural and 85 mL of the enzyme extract was used. 200 mL 1N KCN/HOAc buffer was added in 1.5 h and stirring was continued for 2 h. The resulting oil consisted of a mixture of the cyanohydrin (65%), aldehyde (33%) and traces of acetic acid.
$[\alpha]_D^{20}$ + 45° (c=1, $CHCl_3$) crude product.
e.e. 95%

3. Protection of the hydroxyl function.

(*R*)-(+)-α-[(*tert*-Butyldimethylsilyl)oxy]-4-methoxybenzeneacetonitrile. (**3b**).
A solution of 4.2 g (60 mmol) imidazole in 75 mL of anhydrous DMF was cooled to 0°C and 5.3 g (35 mmol) *tert*-butyldimethylsilyl chloride was added. After stirring for 15 min, 4.9 g (30 mmol) of **2b** was added and the resulting mixture was stirred for 1 h at room temperature, poured into 150 mL of water, and extracted with ether. Work-up gave a pale yellow oil which was purified by flash column chromatography using dichloromethane/hexane (75/25) as eluent.
Yield: 71% (after chromatography).
$[\alpha]_D^{20}$ + 16° (c=1, $CHCl_3$); n_D^{20} 1.4923
^{1}H NMR: δ(ppm) 0.09 (s, 3H, CH_3-Si); 0.17 (s, 3H, CH_3-Si); 0.90 (s, 9H, t-C_4H_9-Si); 3.75 (s, 3H, CH_3O); 5.36 (s, 1H, CH-CN); 6.83 (d, 2H, aromatic, J=8 Hz); 7.29 (d, 2H, aromatic, J=8 Hz).
^{13}C NMR: 160.13 (C-4); 128.57 (C-1); 127.49 (C-2,6); 119.31 (CN); 114.08 (C-3,5); 63.54 (COTBS); 55.13 (OCH_3); 25.40 ($(CH_3)_3$); 17.99 (SiC); -5.22 ($(CH_3)_2$Si).

IR: 2920, 1605, 1505, 1460, 1250, 1080, 840 cm^{-1}
MS: 251 $[M+H-HCN]^+$, 146$[M-OTBS]^+$
$C_{15}H_{23}NO_2Si$: Calc. C 64.94 H 8.36 N 5.05; Found C 64.40 H 8.34 N 4.98

(*R*)-(+)-α-[(*tert*-Butyldimethylsilyl)oxy]-benzeneacetonitrile. (**3a**).
Procedure as for **3b**. Purified by flash column chromatography using dichloromethane/hexane (75/25) as eluent.
Yield: 79% (after chromatography).
$[\alpha]_D^{20}$ + 17° (c=1, $CHCl_3$); n_D^{20} 1.4834
^1H NMR: δ(ppm) 0.02 (s, 3H, CH_3-Si); 0.10 (s, 3H, CH_3-Si); 0.84 (s, 9H, t-C_4H_9-Si); 5.38 (s, 1H, CH-CN); 7.28 (m, 5H, aromatic)
^{13}C NMR: 136.31 (C-1); 128.98 (C-4); 128.66 (C-3,5); 125.85 (C-2,6); 119.02 (CN); 63.74 (COTBS); 22.32 ($(CH_3)_3$); 17.90 (SiC); -5.34 ($(CH_3)_2Si$).
IR: 2920, 1670, 1460, 1260, 1195, 1100, 940, 840 cm^{-1}
MS: 280 $[M+H+MeOH]^+$, 248 $[M+H]^+$, 221 $[M+H-HCN]^+$
$C_{14}H_{21}NOSi$: Calc. C 67.97 H 8.55 N 5.66; Found C 68.06 H 8.45 N 5.50

(*R*)-(+)-α-[(*tert*-Butyldimethylsilyl)oxy]-1,2-benzodioxole-5-acetonitrile. (**3c**).
The crude cyanohydrin **2c** was converted into the TBS ether as described for **3b**.
Purification was done by flash column chromatography using dichloromethane/hexane (75/25) as eluent.
Yield: 52% (after chromatography).
$[\alpha]_D^{20}$ + 17° (c=1, $CHCl_3$); n_D^{20} 1.5007
^1H NMR: δ(ppm) 0.13 (s, 3H, CH_3-Si); 0.21 (s, 3H, CH_3-Si); 0.93 (s, 9H, t-C_4H_9-Si); 5.40 (s, 1H, CH-CN); 6.00 (s, 2H, CH_2); 6.89 (m, 3H, aromatic)
^{13}C NMR: 148.34 and 148.16 (C-1 and C-2); 130.38 (C-5); 119.87 (C-4); 119.19 (CN); 108.24 and 106.67 (C-3 and C-6); 63.74 (COTBS); 25.46 ($(CH_3)_3$); 18.08 (SiC); -5.70 ($(CH_3)_2Si$).
IR: 2940, 1490, 1450, 1250, 1085, 1040, 940, 840, 780 cm^{-1}
MS: 324 $[M+H+MeOH]^+$, 292 $[M+H]^+$, 265 $[M+H-HCN]^+$
$C_{15}H_{21}NO_3Si$: Calc. C 61.82 H 7.26 N 4.81; Found C 61.60 H 7.36 N 4.74

(*R*)-(+)-2-[(*tert*-Butyldimethylsilyl)oxy]-pentanenitrile. (**3i**).
The crude cyanohydrin **2i** was converted into the TBS ether as described for **3b**.
The resulting oil was purified by distillation (Bp 106-108 °C, 3 mm Hg).
Yield: 85% (after distillation)
$[\alpha]_D^{20}$ + 48° (c=1, $CHCl_3$); n_D^{20} 1.4270
^1H NMR: δ(ppm) 0.14 (s, 3H, CH_3-Si); 0.19 (s, 3H, CH_3-Si); 0.91 (s, 9H, t-C_4H_9-Si); 0.97 (t, 3H, CH_3, J= 7 Hz); 1.55 (m, 2H, CH_2-CH); 1.75 (m, 2H, CH_2-CH_3); 4.43 (s, 1H, CH-CN)
^{13}C NMR: 119.75 (CN); 61.41 (COTBS); 38.08 (CH_2COTBS); 25.23 ($(CH_3)_3$); 17.73 (SiC); 17.58 (CH_3CH_2); 13.14 (CH_3CH_2); -5.69 ($(CH_3)_2Si$).
IR: 2920, 1460, 1250, 1120, 830, 780 cm^{-1}
MS: 246 $[M+H+MeOH]^+$, 214 $[M+H]^+$, 187 $[M+H-HCN]^+$
$C_{11}H_{23}NOSi$: Calc. C 61.91 H 10.86 N 6.56; Found C 61.56 H 10.44 N 7.16

(*R*)-(+)-2-[(*tert*-Butyldimethylsilyl)oxy]-3-(E)-pentenenitrile. (**3k**).
The crude cyanohydrin **2k** was converted into the TBS ether as described for **3b**.
The resulting oil was purified by flash column chromatography using dichloromethane/hexane (75/25) as eluent.
Yield: 74% (after chromatography).
$[\alpha]_D^{20}$ + 11° (c=1, $CHCl_3$); n_D^{20} 1.4402
^1H NMR: δ(ppm) 0.15 (s, 3H, CH_3-Si); 0.17 (s, 3H, CH_3-Si); 0.91 (s, 9H, t-C_4H_9-Si); 1.76 (d, 3H, CH_3, J= 6 Hz); 4.89 (d, 1H, CH-CN, J= 6 Hz); 5.57 (m, 1H, CH-CHCN); 5.92 (m, 1H, CH-CH_3)
^{13}C NMR: 130.23 (CHCOTBS); 126.20 (CH_3CH); 118.46 (CN); 62.23 (COTBS); 25.29 ($(CH_3)_3$); 17.84 (SiC); 17.08 (CH_3CH); -5.31 ($(CH_3)_2Si$).
IR: 2940, 1670, 1470, 1260, 1095, 1005, 970, 840, 780, 670 cm^{-1}
MS: 244 $[M+H+MeOH]^+$; 212 $[M+H]^+$; 185 $[M+H-HCN]^+$
$C_{11}H_{21}NOSi$: Calc. C 62.50 H 10.01 N 6.63; Found C 62.10 H 9.87 N 6.46

(*R*)-(+)-2-{-α-[(*tert*-Butyldimethylsilyl)oxy]acetonitrile}-5-methylfuran, (**3l**).
The crude cyanohydrin **2l** was converted into the TBS ether as described for **3b**.
Crystallization from methanol/water afforded the pure ether.
Yield: 81% (after crystallization)
$[\alpha]_D^{20}$ + 24° (c=1, $CHCl_3$)
Mp 40-41°C
^{1}H NMR: δ(ppm) 0.13 (s, 3H, CH_3-Si); 0.15 (s, 3H, CH_3-Si); 0.91 (s, 9H, t-C_4H_9-Si); 2.30 (s, 3H, CH_3); 5.49 (s, 1H, CH-CN); 5.95 (d, 1H, CH, J=3 Hz); 6.38 (d, 1H, CH, J=3 Hz)
^{13}C NMR: 153.77 (C-2); 146.53 (C-5); 117.33 (CN); 110.29 (C-3); 106.61 (C-4); 58.02 (COTBS); 25.41 ($(CH_3)_3$); 18.08 (SiC); 13.43 (5-CH_3); -5.22 ($(CH_3)_2$Si).
IR: 2920, 1355, 1095, 840, 780 cm^{-1}
MS: 251 $[M]^+$, 194 $[M\text{-}t\text{-}C_4H_9]^+$, 120 $[M\text{-}OTBS]^+$
$C_{13}H_{21}NO_2Si$: Calc. C 62.11 H 8.42 N 5.57; Found C 62.22 H 8.35 N 5.55

4. Deprotection of the hydroxyl function.

(*R*)-(+)-α-Hydroxy-4-methoxybenzeneacetonitrile, (**2b**).

20 mmol of **3b** was dissolved in 25 mL of MeCN and 2 mL of a 40% aqueous HF solution was added. The mixture was warmed gently to 45 °C. After stirring for 5 h, 50 mL of water was added and the mixture was extracted with ether (3 x 25 mL), the combined organic layers were washed with a 10% NaCl solution (2 x 5 mL), dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. Since the formed TBSF also evaporated, the pure cyanohydrin remained.
$[\alpha]_D^{20}$ + 49° (c=1, $CHCl_3$)
e.e. >99%
^{1}H NMR: δ(ppm) 3.76 (s, 3H, CH_3O); 4.50 (s, 1H, OH); 5.38 (s, 1H, CH); 6.86 (d, 2H, aromatic, J= 9 Hz); 7.35 (d, 2H, aromatic, J=9 Hz)
^{13}C NMR: 160.51 (C-4); 128.25 (C-2,6); 127.43 (C-1); 119.02 (CN); 114.43 (C-3,5); 63.07 (COH); 55.36 (OCH_3).
IR: 3400, 2240, 1610, 1505, 1020, 820 cm^{-1}
MS: 169 $[M+H+MeOH\text{-}HCN]^+$, 137 $[M+H\text{-}HCN]^+$

(*R*)-(+)-α-Hydroxybenzenacetonitrile, (**2a**).
Procedure as for **2b**.
$[\alpha]_D^{20}$ + 45° (c=1, $CHCl_3$); Lit[7] $[\alpha]_D^{20}$ + 49° (c=5,$CHCl_3$).
e.e. >99%
^{1}H NMR: δ(ppm) 4.46 (br, 1H, OH); 5.44 (s, 1H, CH(OH)CN); 7.42 (m, 5H, aromatic)
^{13}C NMR: 135.14 (C-1); 129.71 (C-4); 129.12 (C-3,5); 126.70 (C-2,6); 119.16 (CN); 63.22 (COH).
IR: 3400, 2930, 2240, 1680, 1030 cm^{-1}
MS: 166 $[M+H+MeOH]^+$; 139 $[M+H+MeOH\text{-}HCN]^+$; 107 $[M+H\text{-}HCN]^+$

(*R*)-(+)-2-Hydroxypentanenitrile, (**2i**).
Procedure as for **2b**.
$[\alpha]_D^{20}$ + 24° (c=1, $CHCl_3$)
e.e. 93%
^{1}H NMR: δ(ppm) 0.99 (t, 3H, CH_3, J= 7 Hz); 1.54 (m, 2H, CH_2-CH(OH)CN); 1.84 (m, 2H, CH_2-CH_3); 2.90 (br., 1H, OH); 4.49 (t, 1H, CH-CN, J= 7 Hz).
^{13}C NMR: 119.98 (CN); 60.53 (COH); 36.62 (CH_2COH); 17.61 (CH_3CH_2); 13.03 (CH_3).
IR: 3400, 2930, 2240, 1630, 1460, 1070 cm^{-1}
MS: 132 $[M+H+MeOH]^+$; 105 $[M+H\text{-}MeOH\text{-}HCN]^+$; 73 $[M+H\text{-}HCN]^+$

(*R*)-(-)-2-Hydroxy-3-(*E*)-pentenenitrile, (**2k**).
Procedure as for **2b**.
$[\alpha]_D^{20}$ - 22° (c=1, $CHCl_3$)
e.e. 95%
^{1}H NMR: δ(ppm) 1.80 (d, 3H, CH_3, J= 6 Hz); 3.05 (br., 1H, OH); 4.94 (d, 1H, CH-CN, J= 6 Hz); 5.62 (m,

1H, CH-CH(OH)CN); 6.09 (m, 1H, CH-CH_3)
^{13}C NMR: 132.10 ($CH_3\underline{C}HCH$); 124.65 ($CH_3\underline{C}H$); 118.41 (CN); 61.00 (COH); 17.03 (CH_3).
IR: 3400, 2240, 1670, 1420, 1080, 1030, 970 cm^{-1}
MS: 103 [M+H+MeOH-HCN]$^+$; 71 [M+H-HCN]$^+$

The TBS ethers of piperonal cyanohydrin (**3c**) and 5-methylfurfural cyanohydrin (**3l**) could not be deprotected in this way because of the presence of other acid-sensitive groups in these compounds.

(*R*)-(-) methyl 4-methoxymandelate. (**5b**).
Prepared by a slightly modified literature method[9].
A solution of 3.26 g (20 mmol) (*R*)-(+)-4-methoxybenzaldehyde cyanohydrin (**2b**) in 1.28 g (40 mmol) of anhydrous MeOH and 25 mL of anhydrous ether was cooled in ice. HCL gas was dried over concentrated H_2SO_4 and passed into the solution until 1.83 g (50 mmol) was absorbed. After standing overnight at 5°C, the solution was allowed to warm to 15°C. The crystals were filtered and directly washed with dry ether. Yield: 4.4 g (95%) of (*R*)-(-)-4-methoxy-mandelimidate HCL salt (**4b**). mp 123-124°C (dec). $[\alpha]_D^{20}$ -192.0° (c=1, MeOH).
4 g (17.3 mol) of **4b** was dissolved in 23 mL of water to give a clear solution which turned turbid after a few minutes. After 30 min at 5°C, the crystals were filtered, washed with a small amount of water and dried. Yield: 2.87 g (82%) of (*R*)-(-)-methyl-4-methoxymandelate (**5b**). mp 63-64°C. $[\alpha]_D^{20}$ -143° (c=1, MeOH), $[\alpha]_{546}^{20}$ -165° (c=1, EtOH). (Lit.[13] $[\alpha]_{546}$ -152° (EtOH). mp 60-61°C).
^{1}H NMR: δ(ppm) 3.60 (br, 1H, OH); 3.75 (s, 3H, $COOCH_3$); 3.80 (s, 3H, CH_3O); 5.10 (s, 1H, CH); 6.86 (d, 2H, J=9Hz, arom.); 7.32 (d, 2H, J= 9Hz, arom.).

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