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Inversion of the Configuration of Cyanohydrins by a Mitsunobu Esterification Reaction

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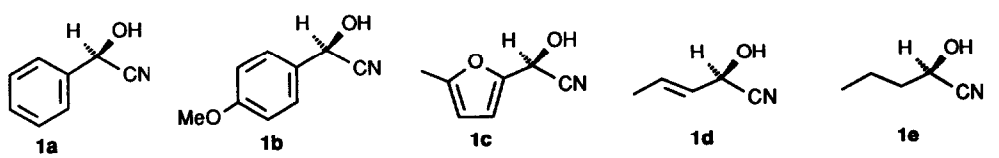
Abstract: Optically active *(R)*-cyanohydrins have been transformed into cyanohydrin esters of opposite configuration under Mitsunobu conditions and subsequently solvolyzed to *(S)*-cyanohydrins in high chemical and optical yield. The method works well for allylic and benzylic cyanohydrins. Cyanohydrins containing strongly electron donating substituents gave extensive racemization. Saturated aliphatic cyanohydrins afforded esters in which the original configuration is retained. These results are discussed in terms of the mechanism of the Mitsunobu reaction.

Chiral cyanohydrins are versatile starting materials for the synthesis of several classes of optically active compounds such as α-hydroxyacids[1] (-esters[2]), α-hydroxyketones[3], α-hydroxyaldehydes[4], ß-hydroxyamines[5] and ß-hydroxy-α-amino acids[6]. Whereas the optically active cyanohydrins possessing the *(R)*-configuration are well accessible using the enzyme mandelonitrile lyase (R-oxynitrilase[2,3,7], E.C. 4.1.2.10), synthesis of the *(S)*-enantiomers is hampered by the limited availability of the required biocatalyst (S-oxynitrilase from Sorghum) and its narrow substrate specificity[8].

It is therefore of considerable interest to find a method for the chemical conversion of *(R)*-cyanohydrins into the corresponding *(S)*-enantiomers. Effenberger et al. recently reported on their attempts to accomplish this via conversion into α-sulfonyloxynitriles[9]. As it turned out, these compounds are rather unstable and only in the case of cyanohydrins derived from saturated aliphatic aldehydes satisfactory results were obtained. With the chemically more interesting allylic and benzylic substrates, extensive racemization occurred. We now report on our results regarding the inversion of the chiral center of *(R)*-cyanohydrins under Mitsunobu[10] conditions (diethyl azodicarboxylate, triphenylphosphine, carboxylate nucleophile).

Results and Discussion

Of the five cyanohydrins tested (**1a-1e**, fig 1), only the enantiomers of *(R)*-α-hydroxybenzeneacetonitrile (**1a**) and *(R)*-α-hydroxy-4-methoxybenzeneacetonitrile (**1b**) can be obtained with the aid of the, scarcely available, S-oxynitrilase from Sorghum.



1a **1b** **1c** **1d** **1e**

Figure 1. Cyanohydrins tested in the Mitsunobu reaction.

The enantiomers of *(S)*-2-hydroxy-2-(5-methylfuryl)acetonitrile[11] (**1c**), *(R)*-2-hydroxypentenenitrile (**1d**) and *(R)*-2-hydroxypentanenitrile (**1e**) have not been reported to be accessible via biocatalysis.

First, the inversion of **1a** (e.e. 99%) under standard Mitsunobu conditions was studied employing acetic acid as proton donor and protonated nucleophile. The corresponding acetate was obtained as an oil in only moderate yield (65%). The sign of the optical rotation revealed an inversion of the configuration. HPLC analysis (Chiralcel OD) showed an e.e. of 92%.

Since the ester function is not compatible with several desirable subsequent transformations such as $LiAlH_4$[5] or DIBAL[4] reductions and Grignard reactions[3], it should be replaced by a more stable protecting group. Basic hydrolysis of the ester function is not a viable option in this case because of the base lability of the resulting cyanohydrin. Therefore solvolysis under acidic conditions was investigated, using the acetate of **1a** as a model substrate. Dilute hydrochloric acid or sulfuric acid caused no reaction at all. Applying stronger aqueous acidic conditions, such as concentrated hydrochloric acid or 20% sulfuric acid, resulted in partial hydrolysis of the cyanogroup. Best results were obtained with methanesulfonic acid[13] and with p-toluenesulfonic acid at ambient temperature in concentrations up to one equivalent in methanol.

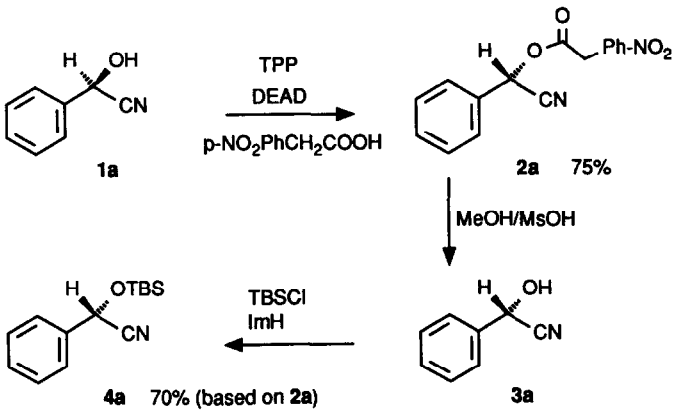
Since this Mitsunobu reaction afforded a product with some loss of optical purity, a series of carboxylic acids was investigated in order to find an ester that could be crystallized to optically pure product. The results are presented in Table I.

Table I. Formation and solvolysis of cyanohydrin esters.

cyanohydrin	entry	nucleophile RCOO⁻	yield (%)	e.e.(%)[c]	$[\alpha]_D^{20,d}$	solvolysis of ester	crystalline ester	*R/S*[e]
1a	1	CH_3	65[a]	92	-5.8	++	-	*S*
	2	C_6H_5	90[a]	92	-24.3	-	-	*S*
	3	4-$CH_3OC_6H_4$	85[a]	92	-37.0	-	-	*S*
	4	4-$NO_2C_6H_4$	76[b]	99[b]	-38.6	-	+	*S*
	5	CH_3OCH_2	95[a]	92	+7.3	++	-	*S*
	6	$C_6H_5CH_2$	95[a]	92	+10.8	+	-	*S*
	7	$(C_6H_5)_2CH$	90[a]	92	+5.1	+	-	*S*
	8	4-$NO_2C_6H_4CH_2$	75[b]	99[b]	+11.5	+	+	*S*
	9	4-$CH_3OC_6H_4CH_2$	70[a]	91	+2.9	+	-	*S*
1b	10	CH_3	90[a]	5	+1.5	++	-	*S*
	11	4-$NO_2C_6H_4$	80[b]	0	0	-	+	-
1c	12	4-$NO_2C_6H_4$	70[b]	40	+6.7	-	+	*R*[11]
1d	13	4-$NO_2C_6H_4CH_2$	75[b]	98[b]	+15.5	+	+	*S*
	14	4-$NO_2C_6H_4$	75[b]	98[b]	+10.6	-	+	*S*
1e	15	$C_6H_5CH_2$	60[a]	85	+61.2	+	-	*R*
	16	4-$NO_2C_6H_4CH_2$	70[a]	85	+51.6	+	-	*R*

a) After column chromatography. b) after crystallization. c) determined with HPLC using a Chiralcel OD column. d) (c=1, $CHCl_3$). e) configuration of major enantiomer.

As it turned out, benzoic acid and substituted benzoic acids gave excellent results (entries 2-4). The corresponding esters of opposite configuration were obtained in high chemical and optical yield. The 4-nitrobenzoate was obtained in 99% e.e. after a single crystallization. Unfortunately, all attempts to solvolyse these esters without racemization remained without success. In order to meet all criteria (good S_N2 behavior of the nucleophile, crystalline reaction product, and ester solvolysis without racemization), several substituted acetic acids were studied (entries 5-9). As can be seen in the table, some loss of optical purity occurred in all cases. Typically, e.e. values of 91-92% were found. Crystallization of the crude ester therefore remained necessary. Of the acetates studied, only the 4-nitrophenylacetate proved to be crystalline. One crystallization afforded the optically pure *(S)*-ester in 75% yield. The acetate and methoxyacetate were most readily solvolyzed. Acid catalyzed solvolysis of the 4-nitrophenylacetate (**2a**), although appreciable slower, could be performed with minimal (<2%) racemization. The inverted cyanohydrin obtained (**3a**) was converted into its *tert*-butyldimethylsilyl (TBS) ether (**4a**). The latter was shown by HPLC to have an e.e. of 96.5%.



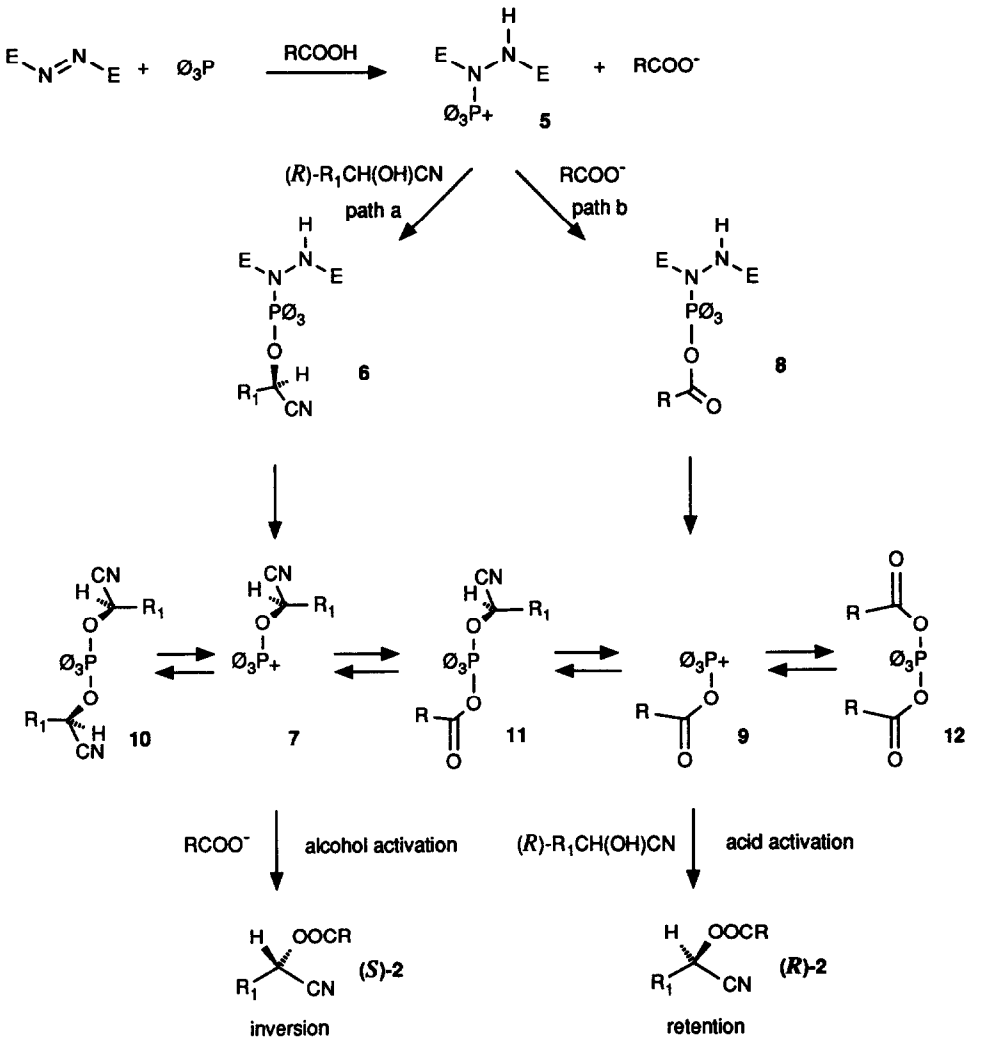
Scheme 1.

The results obtained with the other substrates (**1b-1e**) are also presented in Table I. For α-hydroxy-4-methoxybenzeneacetonitrile (**1b**) the method appeared to be of little value since both acetic acid and 4-nitrobenzoic acid (entries 10,11) gave extensive racemization. Also with cyanohydrin **1c**, derived from 5-methylfurfural considerable racemization occurred and an enantiomeric excess of only 40% was found. Apparently, the strong carbocation-stabilizing effect of the 4-methoxyphenyl and 5-methylfuryl substituents[14] causes unimolecular nucleophilic substitution (S_N1) to become a serious side reaction in these cases.

Far better results were obtained with the allylic cyanohydrin **1d** (entries 13,14). Both acids that gave crystalline esters for **1a** (4-nitrobenzoic and 4-nitrophenylacetic) did so for **1d**. In both cases the optical purity after crystallization was 98% (HPLC). As expected, only the 4-nitrophenylacetate (entry 13) could be easily solvolyzed. In order to determine its optical purity, the *(S)*-2-hydroxypentenenitrile (**3d**) obtained was converted into its UV-detectable *tert*-butyldiphenylsilyl (TBDPS) ether, which was shown to have an e.e. of 96.5% (HPLC).

Subjecting the saturated aliphatic *(R)*-cyanohydrin **1e** to the conditions of the Mitsunobu esterification yielded the 4-nitrophenylacetate as an oil. Comparison with the ester obtained from **1e** by

reaction with 4-nitrophenylacetic anhydride learned that the reaction had provided the *R*-enantiomer in 85% optical purity. This remarkable result can be rationalized by considering the mechanism of the Mitsunobu reaction[15], which is depicted in Scheme 2.



Scheme 2. Proposed reaction mechanism for retention versus inversion.

In the events leading to inversion of the configuration, the protonated azoester-triphenylphosphine complex **5** reacts with the cyanohydrin (path a) to give, via a penta coordinated intermediate **6**, the O-triphenylphosphonium activated cyanohydrin **7**. In the absence of strongly cation stabilizing substituents, activated alcohols of this type are known to react with nucleophiles by a bimolecular pathway[10,16] (S_N2), giving esters **2** with complete inversion of the configuration. If, on the other hand,

azoester complex **5** directly reacts with the carboxylate nucleophile (path b), via penta coordinated complex **8** an activated acyl intermediate **9** is formed. When **9** reacts with a molecule of the (*R*)-cyanohydrin, the ester **2** is formed with retention of the configuration.

Recent studies have indicated that under certain conditions intermediates similar to **7** and **9** are present in equilibrium with penta coordinated species of types **10**, **11** and **12**. Formed by either route (path a or b), both intermediates **7** and **9** will be available for further reaction. The product composition will therefore be determined by the relative rates of ester formation from intermediates **7** and **9**. For a given acid, the reactivity of intermediate **9** towards ester formation is approximately constant. The reactivity of intermediate **7** however, towards S_N2 displacement by carboxylate ion, will be strongly dependent on the nature of substituent R_1. It is well documented that direct nucleophilic displacement reactions take place particularly rapidly in benzylic and allylic systems.[17] As a consequence, with the benzylic and allylic substrates **1a** and **1d**, reaction of the activated alcohol is by far the faster and almost complete inversion results. In the case of the saturated aliphatic substrate **1e** the chiral center is insufficiently activated towards nucleophilic substitution and acylation of the alcohol via intermediate **9** takes over, resulting in retention.

Conclusion

A method has been developed for inverting the configuration of allylic and benzylic cyanohydrins by means of a Mitsunobu esterification, using 4-nitrophenylacetic acid as the protonated nucleophile. The inverted esters can be obtained in optically pure form by crystallization and can be subsequently solvolyzed to the free cyanohydrins under acidic conditions without or almost without loss of optical purity. The method described here is therefore complementary to the one recently described by Effenberger et al.[9], which appears to be limited to saturated aliphatic substrates. Our investigations have also clearly indicated the limitations of the Mitsunobu approach. Cyanohydrins containing strongly cation-stabilizing substituents (4-methoxyphenyl, 5-methylfuryl) give rise to extensive racemization. With cyanohydrins derived from saturated aliphatic aldehydes on the other hand, nucleophilic substitution is relatively slow and esterification via an activated acyl intermediate becomes the major pathway. The area between these limits may be fairly small, but contains cyanohydrins (allylic and benzylic) that are of special interest for subsequent chemical transformations.

Experimental

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a JEOL FX-200 instrument. Samples were measured in $CDCl_3$, with TMS as an internal standard for ^{1}H-NMR, and $CDCl_3$ as an internal standard for ^{13}C-NMR. The optical purity of the cyanohydrins was determined after conversion into their TBS or TBDPS ethers. Optical purity of esters and O-silylated cyanohydrins was determined by comparison with racemates on a analytical HPLC-instrument. The column used was a Chiralcel OD, the eluents were mixtures of n-hexane (H) and 2-propanol (I). Specific eluent ratios are presented for each compound (ratio H:I; flow rate 1mL/min). IR-spectra were recorded on a PYE UNICAM SP3 200 instrument. Optical rotations were measured using a Perkin Elmer 141 polarimeter.

(*R*)-(+)-α-hydroxybenzeneacetonitrile (1a).
Prepared as described earlier[2], e.e. 99% (determined as TBS ether, eluent H:I=99.75:0.25).

(*R*)-(+)-α-hydroxy-4-methoxybenzeneacetonitrile (1b).
Prepared as described earlier[2], e.e. 99% (determined as TBS ether, eluent H:I=99.75:0.25).

(*S*)-(+)-2-(α-hydroxyacetonitrile)-5-methylfuran (1c).
Prepared as described earlier[7c], e.e. 98% (determined as TBS ether, eluent H:I=100:0).

(*R*)-(-)-2-hydroxypentenenitrile (1d).
Prepared as described earlier[7c].
$[\alpha]_D^{20}$ - 27.1° (c=1, $CHCl_3$); e.e. 99% (determined as TBDPS ether, eluent H:I=99.75:0.25).

(*R*)-(+)-2-hydroxypentanenitrile (1e).
Prepared as described earlier[7c], e.e. 88.5% (determined as TBDPS ether, eluent H:I=99.75:0.25).

(*S*)-(+)-α-(4-nitrophenylacetoxy)-benzeneacetonitrile (2a).
To a solution of 6.7 g (50 mmol) **1a** in 75 mL of dry THF, under nitrogen, was added 14.4 g (55 mmol) triphenylphosphine and 13.6 g (75 mmol) 4-nitrophenylacetic acid. The mixture was cooled to -10 °C, after which 8.6 mL (55 mmol) of diethyl azodicarboxylate in THF (total volume 25 mL) was added dropwise in 30 min. After another 15 min at -10 °C the mixture was stirred at room temperature for 4 h, diluted with 200 mL of ether and washed with a saturated sodium bicarbonate solution (50 mL) and saturated brine (50 mL). After drying over magnesium sulfate the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography using EtOAc/hexane (3/7) as the eluent. The product was recrystallized from dichloromethane/hexane (1/1). Yield 75%. Mp 89-90 °C.
$[\alpha]_D^{20}$ + 11.5° (c=1, $CHCl_3$), e.e. 99%, eluent H:I=95:5.
^{1}H-NMR: δ(ppm) 3.84 (s, 2H, $COCH_2Ph$); 6.43 (s, 1H, $PhCHCN$); 7.44 (d, J=8.7 Hz, 2H); 7.47 (m, 5H); 8.20 (d, J=8.7 Hz, 2H). ^{13}C-NMR: δ(ppm) 168.31 (CO); 147.14 (arom); 139.61 (arom); 131.05 (arom); 130.44 (arom); 130.20 (arom); 129.12 (arom); 127.69 (arom); 123.63 (arom); 115.63 (CN); 63.45 ($CHCN$); 39.86 ($COCH_2$). IR: 3035, 2920, 2240, 1750, 1600, 1510, 1340, 1140, 750, 715 cm^{-1}.
$C_{16}H_{12}N_2O_4$: Calc. C 64.86 H 4.08 N 9.45; Found C 64.96 H 4.39 N 9.29

(*S*)-(+)-2-(4-nitrophenylacetoxy)-pentenenitrile (2d).
Prepared from **1d** following the same procedure as described for **2a**. The product was recrystallized from dichloromethane/hexane 1/1. Yield 70%. Mp 71 °C.
$[\alpha]_D^{20}$ + 15.5° (c=1, $CHCl_3$), e.e. 98%, eluent H:I=95:5.
^{1}H-NMR: δ(ppm) 1.81 (d, 3H, CH_3CH); 3.82 (s, 2H, $COCH_2Ph$); 5.58 (m, 1H, CH_3CHCH); 5.81 (d, 1H, CHCN); 6.16 (m, 1H, $CHCH_3$); 7.46 (d, J=8.7 Hz, 2H); 8.22 (d, J=8.7 Hz, 2H). ^{13}C-NMR: δ(ppm) 168.25 (CO); 146.86 (arom); 139.84 (arom); 135.84 ($CHCHCN$); 130.12 (arom); 123.34 (arom); 120.54 ($CHCH_3$); 115.19 (CN); 61.82 ($CHCN$); 39.63 ($COCH_2$); 17.26 (CH_3). IR: 3060, 2940, 2240, 1745, 1600, 1510, 1350, 1210, 1140, 970, 720 cm^{-1}.
$C_{13}H_{12}N_2O_4$: Calc. C 60.00 H 4.65 N 10.76; Found C 60.00 H 4.94 N 10.66

(*R*)-(+)-2-(phenylacetoxy)-pentanenitrile (2e).
Procedure a:
Prepared from **1e** following the same procedure as described for **2a**, using 10.2 g (75 mmol) phenylacetic acid. The crude product was purified by flash column chromatography using EtOAc/hexane (1/9) as the eluent. The product was obtained as a colorless oil. Yield 60%.
$[\alpha]_D^{20}$ + 61.2° (c=1, $CHCl_3$), e.e. 85%, eluent H:I=99.75:0.25.
Bp 137 °C 1.5 mm Hg
^{1}H-NMR: δ(ppm) 0.98 (t, 3H, CH_3CH_2); 1.49 (m, 2H, $CH_3CH_2CH_2$); 1.86 (m, 2H, CH_2CHCN); 3.69 (s,

2H, $COCH_2Ph$); 5.34 (t, 1H, CHCN); 7.31 (m, 5H, arom). ^{13}C-NMR: δ(ppm) 169.48 (CO); 132.48 (arom); 128.86 (arom); 128.33 (arom); 127.08 (arom); 116.54 (CN); 60.88 (CHCN); 40.15 ($COCH_2$); 33.67 (CH_2CHCN); 17.49 (CH_3CH_2); 12.88 (CH_3CH_2). IR: 3030, 2960, 2340, 1740, 1490, 1450, 1235, 1130, 990, 710 cm^{-1}.
$C_{13}H_{15}NO_2$: Calc. C 71.87 H 6.96 N 6.46; Found C 72.21 H 7.05 N 6.40.

Procedure b:
1 g (10 mmol) of **1e** was dissolved in 14 mL of dry pyridine and 2.8 g (11 mmol) phenylacetic anhydride was added under continuous stirring. After 5 min 0.01 g of dimethylaminopyridine was added. The mixture was allowed to react for 30 min after which it was quenched with 50 mL of ice/water. The product was extracted with dichloromethane (2x50 mL). The organic layers were washed with 6N hydrochloric acid (2x50 mL), saturated sodiumbicarbonate (50 mL), and brine (20 mL). After drying over magnesium sulfate and evaporation of the solvent *in vacuo*, **2e** was obtained as a colorless oil in 93% yield. $[\alpha]_D^{20}$ + 63.5° (c=1, $CHCl_3$), e.e. 88%. All analytical data were in agreement with the data presented above.

The esters in Table 1 were prepared following the same general procedure as for **2a**. For their HPLC analysis the following eluent ratios were used: entries 1 and 10, H:I=99.75:0.25; entries 2, 3, 5, 6, 7, and 9, H:I=99:1; entries 4 and 11, H:I=90:10; entries 12, 14, 16, H:I=95:5.

(*S*)-(-)-α-hydroxybenzeneacetonitrile (3a).
7.35 g (25 mmol) of **2a** was dissolved in a mixture of 40 mL of methanol and 100 mL of dichloromethane. 25 mmol methanesulfonic acid was added. The reaction mixture was stirred for two days at ambient temperature, after which conversion was 90% (NMR). Water was added and the product was extracted with dichloromethane (2 x 50 mL). The combined organic layers were washed with brine (2 x 25 mL), dried over magnesium sulfate, and evaporated *in vacuo*. The crude product was silylated with TBSCl.

(*S*)-(-)-α-[(*tert*-Butyldimethylsilyl)oxy]-benzeneacetonitrile (4a).
A solution of 3.5 g (50 mmol) imidazole in 75 mL of anhydrous DMF was cooled to 0 °C and 4.5 g (30 mmol) *tert*-butyldimethylsilyl chloride was added. After stirring for 15 min crude **3a** (25 mmol) 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 yellow oil which was stirred with hexane containing silica gel for 1 h, then the solid was filtered off and washed with cold hexane. Concentration of the organic solvent afforded a colorless oil. Yield 70% (based on **2a**).
$[\alpha]_D^{20}$ - 17.5° (c=1, $CHCl_3$), e.e. 96.5% (HPLC); Lit[2] $[\alpha]_D^{20}$ + 17° (c=1, $CHCl_3$) for (*R*)-enantiomer.
^{1}H-NMR: δ (ppm) 0.02 (s, 3H, CH_3Si); 0.10 (s, 3H, CH_3Si); 0.84 (s, 9H, *t*Bu); 5.38 (s, 1H, CHCN); 7.28 (m, 5H, aromatic). ^{13}C-NMR: δ (ppm) 136.31 (arom); 128.98 (arom); 128.66 (arom); 125.85 (arom); 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}.

(*S*)-(+)-2-hydroxypentenenitrile (3d).
Prepared from **2d** following the same procedure as described for **3a**. Conversion was complete and the crude product was silylated with *tert*-butyldiphenylsilyl chloride.

(*S*)-(+)-2-[(*tert*-butyldiphenylsilyl)oxy]-pentenenitrile (4d).
Prepared from **3d** following the same procedure as for **4a**, using *tert*-butyldiphenylsilyl chloride instead of *tert*-butyldimethylsilylchloride. The resulting oil was purified by flash column chromatography using dichloromethane/hexane (1/1) as the eluent. Yield 75% (based on **2d**).
$[\alpha]_D^{20}$ + 4.1° (c=1, $CHCl_3$), e.e. 96.5%; $[\alpha]_D^{20}$ - 4.2° for *R*-enantiomer with e.e. 99%[18].
^{1}H-NMR: δ (ppm) 1.09 (s, 9H, *t*Bu); 1.68 (d, 3H, $C\underline{H}_3CH$); 4.75 (d, 1H, CHCN); 5.54 (m, 1H, CHCH(O)CN); 5.70 (m, 1H, $CH_3C\underline{H}$); 7.41 (m, 6H, arom); 7.68 (m, 4H, arom). ^{13}C-NMR: δ (ppm) 135.60 (C-4); 131.90 (SiC-arom); 131.52 (SiC-arom); 131.32 (CHCOTBDPS); 130.23 (arom); 130.14 (arom); 127.81 (arom); 127.72 (arom); 125.79 (CH_3CH); 118.41 (CN); 63.28 (COTBDPS); 26.51 ($(CH_3)_3$); 19.13 (SiC); 17.29 (CH_3CH). IR: 3060, 3040, 2930, 2850, 1660, 1590, 1425, 1100, 1050, 960, 820, 740, 700 cm^{-1}.

References and notes

1. Ziegler, T.; Hörsch, B.; Effenberger, F. *Synthesis* **1990**, 575-578.
2. Brussee, J.; Loos, W.T.; Kruse, C.G.; Van der Gen, A. *Tetrahedron* **1990**, *46*, 979-986.
3. Brussee, J.; Roos, E.C.; Van der Gen, A. *Tetrahedron Lett.* **1988**, *29*, 4485-4488.
4. Jackson, W.R.; Jacobs, H.A.; Jayatilake, G.S.; Matthews, B.R.; Watson, K.G. *Aust. J. Chem.* **1990**, *43*, 2045-2062.
5. a) Brussee, J.; Döfferhoff, F.; Kruse, C.G.; Van der Gen, A. *Tetrahedron* **1990**, *46*, 1653-1658. b) Brussee, J.; Van Benthem, R.A.T.M.; Kruse, C.G.; Van der Gen, A. *Tetrahedron: Asymmetry* **1990**, *1*, 163-166. c) Brussee, J.; Van der Gen, A. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 25-26. d) Zandbergen, P.; Van den Nieuwendijk, A.M.C.H.; Brussee, J.; Van der Gen, A.; Kruse, C.G. *Tetrahedron* **1992**, *48*, 3977-3982.
6. Zandbergen, P.; Brussee, J.; Van der Gen, A.; Kruse, C.G. *Tetrahedron: Asymmetry*, **1992**, *3*, 769-774.
7. a) Becker, W.; Pfeil, E. *J. Am. Chem. Soc.* **1966**, *88*, 1299-1300. b) Effenberger, F.; Ziegler, T.; Förster, S. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 458-460. c) Zandbergen, P.; Van der Linden, J.; Brussee, J.; Van der Gen, A. *Synth. Commun.* **1991**, *21*, 1387-1391.
8. a) Effenberger, F.; Hörsch, B.; Förster, S.; Ziegler, T. *Tetrahedron Lett.* **1990**, *31*, 1249-1252. b) Smitskamp-Wilms, E.; Brussee, J.; Van der Gen, A.; Van Scharrenburg, G.J.M.; Sloothaak, J.B. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 209-215.
9. Effenberger, F.; Stelzer, U. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 873-874.
10. Mitsunobu, O. *Synthesis* **1981**, 1-28.
11. Cyanohydrin **1c** possesses a similar spatial arrangement as **1a, 1b, 1d,** and **1e.** Due to the priority rules its configuration must be assigned as *(S)*.
12. Inagaki, M.; Hiratake, J.; Nishioka, T.; Oda, J. *Bull. Inst. Chem. Res., Kyoto Univ.* **1989**, *67*, 132.
13. Loev, B. *Chem. Ind.* **1964**, 193-194.
14. Hehre, W.J.; Taagepera, M.; Taft, R.W.; Topsom, R.D. *J. Am. Chem. Soc.* **1981**, *103*, 1344-1349.
15. a) Hughes, D.L.; Reamer, R.A.; Bergan, J.J.; Grabowski, E.J.J. *J. Am. Chem. Soc.* **1988**, *110*, 6487-6491. b) Camp, D.; Jenkins, I.D. *J. Org. Chem.* **1989**, *54*, 3045-3049 and 3049-3054. c) Camp, D.; Jenkins, I.D. *Aust. J. Chem.* **1992**, *45*, 47-55.
16. Pautard-Cooper, A.; Evans, S.A., Jr. *J. Org. Chem.* **1989**, *54*, 2485-2488.
17. March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York 1992; p. 339.
18. Warmerdam, E.G.J.C. unpublished results.