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Hydroxynitrile lyase-catalyzed addition of HCN to 2-substituted cyclopentanones☆

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Abstract—A systematic investigation of the stereoselectivity of hydroxynitrile lyases (HNLs) catalyzed addition of HCN to a variety of monosubstituted cyclopentanones yielding the corresponding cyanohydrins is presented. With PaHNL from bitter almond as catalyst, the HCN addition to 2-alkyl cyclopentanones **1b–d** is highly (*R*)-selective, leading to the *cis*-(1*R*,2*S*)- and *trans*-(1*R*,2*R*)-diastereomers. The addition to the sterically less demanding methyl compound **1a** is far less selective. With MeHNL from cassava, the expected (*S*)-selectivity of the HCN addition is very high for the cyclopentanones **1c–d** with larger substituents, but only for the *cis*-(1*S*,2*R*)- and not the *trans*-(1*S*,2*S*)-diastereomers. Dynamic kinetic resolution was observed for the MeHNL-catalyzed addition of HCN to the racemic alkyl 2-oxocyclopentane carboxylates **4a** and **4b**. Continuous equilibration via keto-enol tautomerism and the preferred enzymatic conversion of the (*R*)-enantiomers of the ketones **4** results in the formation of the *cis*-(1*R*,2*S*)-diastereomers in >50% yield. The absolute configurations of the synthesized cyanohydrins were determined by X-ray crystallography of *O*-*p*-bromobenzoyl derivatives.

1. Introduction

The stereoselectivity of the hydroxynitrile lyase-catalyzed cyanohydrin formation of monosubstituted cyclic ketones is of general interest for the synthesis of biologically active compounds as well as for learning more about the stereochemistry of cyanogenesis of cyclic ketones.

4-Substituted cyclohexanone cyanohydrins, which are important precursors for potent herbicides and insecticides,[2] can be obtained as *cis*/*trans*-mixtures by chemical addition of HCN to the corresponding cyclohexanones. With hydroxynitrile lyases (HNL) as catalysts, the HCN addition is surprisingly highly stereoselective.[3] By using (*R*)-PaHNL from bitter almond (*Prunus amygdalus*) *trans*-addition almost exclusively occurred, whereas with (*S*)-MeHNL from cassava (*Manihot esculenta*) *cis*-addition is preferred.[3] Cyanohydrins of 2-substituted cyclohexanones, which are interesting precursors of various compounds with pharmacological activity,[4] can be prepared stereoselectively by applying HNLs as catalysts.[1] With PaHNL from bitter almonds, the HCN addition to the carbonyl group is (*R*)-selective, while with (*S*)-MeHNL from cassava, (*S*)-selectivity is observed.[1]

The stereoselectivity of the MeHNL-catalyzed addition of HCN to various monosubstituted cyclohexanones can be explained with the specific orientation of the cyclohexanones in the active site of the enzyme.[1,3] Since the steric requirements of cyclohexanones and cyclopentanones are markedly different, the stereochemistry of HNL-catalyzed additions to substituted cyclopentanones is of general interest in this connection. Additionally, 1-hydroxycyclopentanone carboxylic acids, which could be derived from the corresponding cyanohydrins, are biologically active building blocks in pharmaceuticals.[5] We have therefore investigated comprehensively the HNL-catalyzed addition of HCN to 2-substituted cyclopentanones. The (*R*)-PaHNL-catalyzed addition of HCN to *rac*-2-methylcyclopentanone described in a patent is the only example of this type of reaction.[6] The exact stereochemistry however of the thereby obtained cyanohydrin could not be determined.[6] Recently in a patent, the HNL-catalyzed addition of HCN to tetrahydrofuranones and tetrahydrothiophenones have been described.[7]

☆ See Ref. 1.

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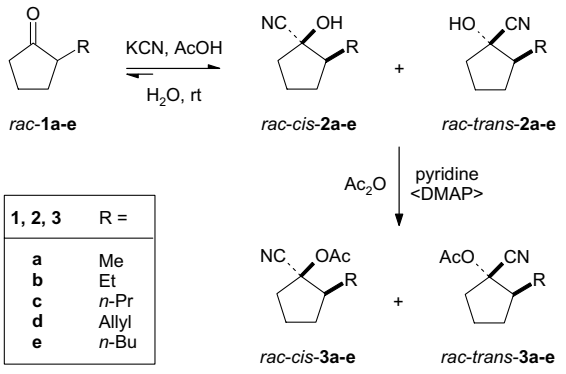
2. Results and discussion

2.1. Chemical addition of HCN to 2-alkyl substituted cyclopentanones 1

Before starting the enzyme-catalyzed reactions, we investigated the chemical addition of HCN, prepared in situ in aqueous solution from KCN with acetic acid,[8] to racemic 2-alkyl cyclopentanones *rac*-**1a–e** yielding the corresponding cyanohydrins **2a–e** (Scheme 1, Table 1).



Scheme 1.

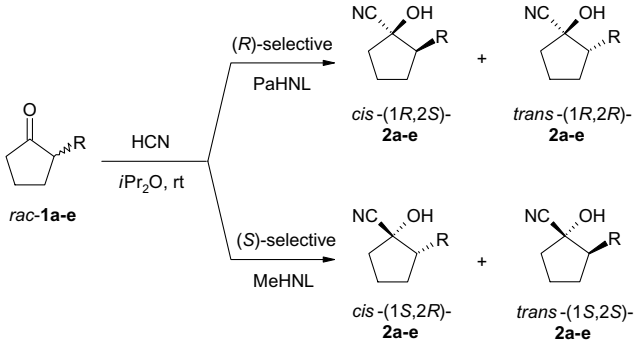
Table 1. HCN addition to racemic 2-alkyl cyclopentanones *rac*-**1a–e** to the corresponding cyanohydrins **2a–e** and subsequent acetylation to the *O*-acetyl derivatives **3a–e**

Ketones *rac*-**1** R =			Cyanohydrins **2**		*O*-Acetyl derivatives **3**	
			Yield (%)	*rac-cis*: *rac-trans*		*rac-cis*: *rac-trans*
1a	Methyl-	**2a**	88	23:77	**3a**	21:79
1b	Ethyl-	**2b**	87	31:69	**3b**	33:67
1c	*n*-Propyl-	**2c**	76	33:67	**3c**	31:69
1d	Allyl-	**2d**	74	29:71	**3d**	28:72
1e	*n*-Butyl-	**2e**	71	30:70	**3e**	28:72

The yields and *cis*/*trans* ratios presented in Table 1 are obtained as follows. The reaction mixture was stirred for 48 h and the cyanohydrins, which formed are then extracted with ether. The yields given in Table 1 are the residues obtained after evaporation of ether. Acetylation of the crude cyanohydrins *rac*-**2a–e** to the corresponding *O*-acetyl derivatives *rac*-**3a–e** was performed with acetic anhydride and pyridine, catalyzed by 4-dimethylaminopyridine (DMAP). The *O*-acetyl cyanohydrins *rac*-**3a–e** are stable and can be used for GC measurements. On an achiral phase, the *cis*/*trans*-isomers and on a chiral phase all four possible stereoisomers, can be separated chromatographically. The yields and isomer ratios of cyanohydrins **2a–e** determined by NMR spectroscopy given in Table 1 are comparable with the yields and the isomer ratios obtained for the corresponding isolated *O*-acetyl cyanohydrins **3a–e**.

2.2. (*R*)-PaHNL- and (*S*)-MeHNL-catalyzed addition of HCN to racemic 2-alkyl cyclopentanones *rac*-1a–e

The HNL-catalyzed additions of HCN to 2-alkyl cyclopentanones **1** have been performed under optimized standard conditions.[9] In order to estimate the extent of chemical addition, for each substrate the reaction was also carried out under the same conditions but without an enzyme (blank experiment). In contrast to the chemical addition, where only *cis*/*trans*-addition was expected, HNL-catalysis should cause *R*/*S*-selectivity concerning the newly formed stereogenic center at the 1-position. One should therefore expect (*R*)-selectivity by using (*R*)-PaHNL[10a] yielding the *cis*-(1*R*,2*S*) and *trans*-(1*R*,2*R*)-diastereomers and (*S*)-selectivity by applying (*S*)-MeHNL[10b] to give the *cis*-(1*S*,2*R*)- and the *trans*-(1*S*,2*S*)-diastereomer **2** as depicted in Scheme 2.



Scheme 2.

Table 2 summarizes the results of the (*R*)-PaHNL-catalyzed addition of HCN to racemic 2-alkyl cyclopentanones *rac*-**1a–e**. The cyclopentanones **1b–d** react highly (*R*)-selectively to give almost exclusively the *cis*-(1*R*,2*S*)- and *trans*-(1*R*,2*R*)-diastereomers of **2b**,**c** and **2d**, even after long reaction times. The HCN addition to methyl compound **1a** however is far less selective. In this case, the time dependent formation of the four diastereomers is interesting. Whereas the ratios of the unexpected (1*S*,2*S*)- and (1*S*,2*R*)-stereoisomers only slightly change when increasing the reaction time one observes an increase of the *trans*-(1*R*,2*R*) and decrease of the *cis*-(1*R*,2*S*)-diastereomer with longer reaction times (Table 2). These results could be due to an increasing domination of the chemical addition of HCN, where the *trans*-products are favored (Table 1). However since this *cis*- to *trans*-isomerization is not observed for the corresponding (1*S*)-stereoisomers, an (*R*)-PaHNL-catalyzed transformation of the *cis*-(1*R*,2*S*)- to the *trans*-(1*R*,2*R*)-diastereomer **2a** is more likely. As the substituents become larger, the substrate selectivity decreases (Table 2). Butyl-derivative **1e**, for example, is no longer a substrate for (*R*)-PaHNL. It is also noteworthy that even after very long reaction times (168 h), the PaHNL-catalyzed conversion rates of cyclopentanones **1** to the corresponding cyanohydrins do not exceed 80%.

Table 2. (*R*)-PaHNL-catalyzed addition of HCN to *rac*-2-alkyl cyclopentanones **1a–e**

rac-**1** R =		*t* (h)	Cyanohydrin **2**					Blank experiment	
			Conv. (%)	*cis*-(1*R*,2*S*)	*cis*-(1*S*,2*R*)	*trans*-(1*R*,2*R*)	*trans*-(1*S*,2*S*)	Conv. (%)	*cis*:*trans*
1a	Methyl-	1	6	46.2	4.0	11.5	38.3		
		5	21	45.0	5.5	12.7	36.8		
		48	59	32.1	5.5	24.9	37.5		
		168	72	30.1	7.0	29.6	33.3	8	13:87
1b	Ethyl-	1	5	47.7	2.9	48.6	0.8		
		3	15	47.4	0.8	50.9	0.9		
		8	32	44.6	0.2	54.4	0.8		
		24	60	42.9	0.2	56.2	0.7		
		147	81	47.7	0.1	50.1	2.1	8	35:65
1c	*n*-Propyl-	5	2	42.9	<0.1	56.9	<0.1		
		48	16	23.6	0.7	75.0	0.7		
		168	42	24.3	0.1	71.4	4.2		
		336	49	31.4	1.0	56.0	11.6	2	n.d.
1d	Allyl-	5	10	44.0	2.3	51.8	1.9		
		48	35	38.7	0.2	60.9	0.2		
		96	48	40.0	0.1	58.8	1.1		
		168	59	44.0	0.2	53.1	2.7		
		336	61	44.8	1.2	48.3	5.7	4	13:87
1e	*n*-Butyl-	168	<2	n.d.	n.d.	n.d.	n.d.	<2	n.d.

Table 3 summarizes the results of the (*S*)-MeHNL-catalyzed cyanohydrin formation of 2-alkyl cyclopentanones **1**.

The conversion rates are considerably faster than the rates with (*R*)-PaHNL as catalyst (Table 2). Larger substituents in the substrate also diminish the conversion rates but to a much lesser extent when compared to the (*R*)-PaHNL-catalyzed reactions (Table 2). Even **1e**, with the sterically demanding *n*-butyl residue, gives after 48 h reaction time, 47% conversion whereas with PaHNL, no reaction at all occurs. The expected (*S*)-selectivity is very high for cyclopentanones **1c** and **d** with larger substituents, but only for the *cis*-(1*S*,2*R*)-diastereomers not the *trans*-(1*S*,2*S*)-diastereomers (Table 3). Since the chemical addition, which preferentially yields *trans*-products (Table 1), can be excluded (Table 3, blank experiment) the orientation and fixation of cyclopentanones **1** in the active site of the enzyme must be the reason for these unexpected results.[11]

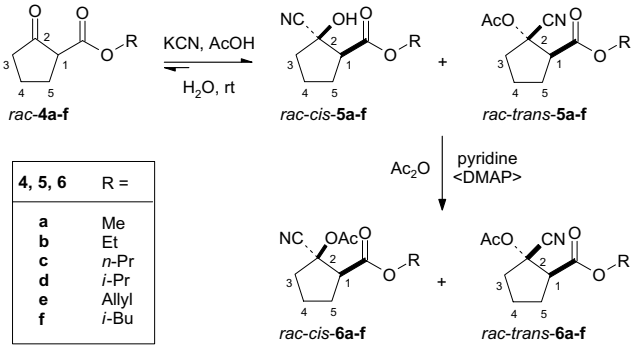
2.3. (*R*)-PaHNL- and (*S*)-MeHNL-catalyzed addition of HCN to racemic alkyl 2-oxocyclopentanecarboxylates 4

Prior to the enzyme-catalyzed reactions, we investigated the chemical addition of HCN to racemic alkyl

Table 3. (*S*)-MeHNL-catalyzed addition of HCN to *rac*-2-alkyl cyclopentanones **1a–e**

rac–**1** R =		*t* (h)	Cyanohydrin **2**					Blank experiment	
			Conv. (%)	*cis*-(1*R*,2*S*)	*cis*-(1*S*,2*R*)	*trans*-(1*R*,2*R*)	*trans*-(1*S*,2*S*)	Conv. (%)	*cis*:*trans*
1a	Methyl-	1	53	6.3	38.8	12.5	42.4		
		2	79	7.4	37.1	13.7	41.7		
		3	83	8.8	35.3	15.2	40.7		
		4	89	10.3	33.3	16.9	39.5	≪1	n.d.
1b	Ethyl-	1	43	11.8	49.3	1.6	37.4		
		3	78	14.8	47.1	2.5	35.6		
		6	89	18.2	45.0	3.7	33.1		
		8	87	19.9	44.1	4.4	31.6	≪1	n.d.
1c	*n*-Propyl-	1	10	12.3	68.7	0.7	18.3		
		5	31	13.2	66.5	0.3	20.0		
		24	44	14.5	60.9	0.3	24.3		
		48	51	14.6	60.0	0.3	25.5	<1	n.d.
1d	Allyl-	1	9	22.7	61.0	0.9	15.4		
		5	23	22.3	54.1	1.7	21.9		
		24	73	28.8	47.1	1.7	22.4		
		48	76	28.5	43.8	2.9	24.8	<1	n.d.
1e	*n*-Butyl-	24	41	15.8	61.5	0.1	22.6		
		48	47	10.7	63.0	0.1	26.2	<1	n.d.

2-oxocyclopentanecarboxylates **4a–f** affording the corresponding cyclopentanone cyanohydrins **5a–f** (Scheme 3, Table 4).



Scheme 3.

Table 4. HCN addition to racemic alkyl 2-oxocyclopentane carboxylate *rac*-**4a–f** to the corresponding cyanohydrins **5a–f** and subsequent acetylation to the *O*-acetyl derivatives **6a–f**

Ketones *rac*-**4** R =		Cyanohydrins **5**			*O*-Acetyl derivatives **6**	
			Yield (%)	*rac-cis*: *rac-trans*		*rac-cis*: *rac-trans*
4a	Methyl-	**5a**	89	45:55	**6a**	48:52
4b	Ethyl-	**5b**	90	38:62	**6b**	38:62
4c	*n*-Propyl-	**5c**	90	64:36	**6c**	64:36
4d	*iso*-Propyl-	**5d**	95	56:44	**6d**	59:41
4e	Allyl-	**5e**	86	56:44	**6e**	58:42
4f	*iso*-Butyl-	**5f**	75	59:41	**6f**	62:38

As can be seen from Table 4, *cis*- and *trans*-addition products are formed in practically equal amounts. For characterization and determining the distribution of stereoisomers for the enzyme-catalyzed reaction, the crude stereoisomeric cyanohydrin mixtures **5a–f** were transferred to the stable *O*-acetyl cyanohydrins **6a–f** (Table 4). From GCs of the *O*-acetyl derivatives **6a–f** on chiral and achiral phases in combination with NMR spectra of the cyanohydrins **5a–f**, it was possible to determine the ratios of all stereoisomers formed in the described HNL-catalyzed additions of HCN to the cyclopentanone derivatives *rac*-**4a–f**.

In the HNL-catalyzed additions of HCN to alkyl 2-oxocyclopentanecarboxylates **4**, one should expect (*R*)-selectivity by using PaHNL[10a] yielding the *cis*-(1*S*,2*R*)- and the *trans*-(1*R*,2*R*)-diastereomers **5** and (*S*)-selectivity by applying MeHNL[10b] to give the *cis*-(1*R*,2*S*)- and the *trans*-(1*S*,2*S*)-diastereomers **5** concerning the newly formed stereogenic center at the 2-position (Scheme 4).

The PaHNL-catalyzed addition of HCN to cyclopentanones **4a–f** under optimized reaction conditions have shown that only methyl ester **4a** is a reasonable substrate for PaHNL. The conversion rates for esters **4b–f** are below 10% even after long reaction times. The time dependent formations of the stereoisomers in the PaHNL-catalyzed reaction[6] of the methylester **4a** are summarized in Table 5.

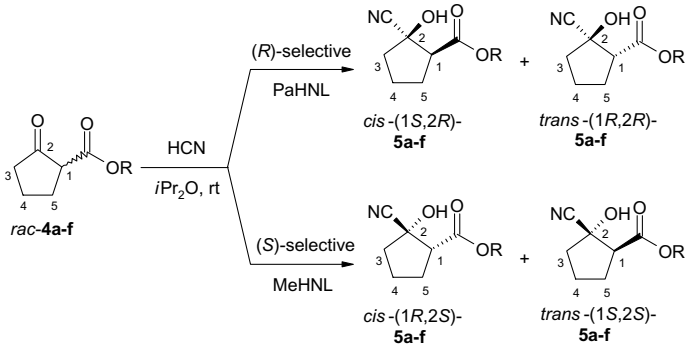
Table 5. (*R*)-PaHNL-catalyzed addition of HCN to racemic methyl 2-oxocyclopentane carboxylate *rac*-**4a**

	Cyanohydrin **5a**					
t (h)	Conv. (%)	*cis*: *trans*	*cis*-(1*S*,2*R*)	*cis*-(1*R*,2*S*)	*trans*-(1*R*,2*R*)	*trans*-(1*S*,2*S*)
1	7	83:17	80.0	2.9	9.5	7.6
5	18	77:23	73.3	3.5	12.7	10.5
7	24	72:28	68.7	3.6	14.9	12.8
24	38	56:44	49.3	6.3	22.4	22.0
36	47	45:55	36.3	8.2	28.4	27.1
168	79	41:59	30.4	10.1	29.2	30.3

In contrast to the reactions of 2-alkyl cyclopentanones **1** where practically no change in stereoisomer ratios, depending on reaction times were observed, the change in the case of the methyl 2-oxocyclopentane carboxylate **4a** was considerable. Whereas after 1 h, the expected (*R*)-selectivity was fairly high (>80%), it decreased sharply with longer reaction times. After 168 h it was almost at equilibrium between all possible stereoisomers (Table 5).

The results of the MeHNL-catalyzed additions of HCN to the cyclopentanones *rac*-**4a**,**b**,**d** are summarized in Table 6.

The conversion rates of the MeHNL-catalyzed reactions clearly show, that cyclopentanones **4** are much better



Scheme 4.

Table 6. (*S*)-MeHNL-catalyzed addition of HCN to racemic alkyl 2-oxocyclopentane carboxylate *rac*-**4**

rac-**4** R =		*t* (h)	Cyanohydrin **5**					Blank experiment	
			Conv. (%)	*cis*-(1*R*,2*S*)	*cis*-(1*S*,2*R*)	*trans*-(1*R*,2*R*)	*trans*-(1*S*,2*S*)	Conv. (%)	*cis*:*trans*
4a	Methyl-	1	28	7.9	89.1	1.1	1.9		
		3	45	7.7	91.0	0.7	0.6		
		8	53	7.1	91.2	0.8	0.9		
		28	74	7.4	88.4	2.0	2.2	4	28:72
4b	Ethyl-	1	29	5.4	90.2	0.5	3.9		
		3	54	8.2	86.5	0.2	5.1		
		8	73	13.6	79.6	0.3	6.5		
		28	86	26.2	64.8	0.9	8.1	5	31:69
4d	*i*-Propyl-	3	28	3.7	91.8	0.1	4.4		
		6	33	5.0	92.3	0.8	1.9		
		24	47	13.5	84.5	0.4	1.6	<1	n.d.

substrates for MeHNL than for PaHNL (Tables 5 and 6). The stereoselectivity of the MeHNL-catalyzed HCN-addition to racemic alkyl 2-oxocyclopentane carboxylates *rac*-**4a**,**b**, and **d** is particularly noteworthy. At conversion rates of ~50%, only one main diastereomer namely the cyanohydrins **5a**,**b** and **d** with a *cis*-(1*R*,2*S*)-configuration (Table 6) was obtained. Since starting ketones **4** are racemic, the *trans*-(1*S*,2*S*)-diastereomers **5a**,**b**, and **d** should be obtained in comparable ratios with the (*S*)-selective MeHNL as catalyst. From these results it is obvious, that the (*R*)-enantiomers of racemic ketones **4** are by far better substrates for MeHNL than the (*S*)-enantiomers and therefore the preferred formation of the (1*R*,2*S*)-configurated cyanohydrins **5** can be explained. Since β-ketoesters can easily isomerize via the tautomeric enols, the transformation of the (*S*)- into the highly reactive (*R*)-enantiomers of ketones **4** is explainable. For ethyl derivative **4b**, the amount of enol ranges from 2% to 8%, depending on the solvent.[12] The described formation is a new and interesting example of the dynamic kinetic resolution in enzyme-catalyzed reactions.[13]

2.4. Assignment of the absolute configuration of cyanohydrins 2 and 5

The structure determinations were performed on compounds **2a**, **5a**, and **5b**. The *cis*/*trans*-mixtures obtained in the HNL-catalyzed reactions were reacted with *p*-bromobenzoyl chloride to give the corresponding *O*-benzoyl derivatives, which can be separated by column chromatography. After recrystallization, the pure enantiomers *cis*-(1*S*,2*R*)-**2a**′, *trans*-(1*S*,2*S*)-**2a**′, *cis*-(1*R*,2*S*)-**5a**′, and *cis*-(1*R*,2*S*)-**5b**′ were obtained as single crystals suitable for X-ray structure determination (Figs. 1–4, Table 7).[14] The absolute configurations were elucidated from diffraction data using anomalous dispersion.

By correlation of the GC data of the *O*-acetyl derivatives on achiral and chiral phases and analyses of NMR data, an unambiguous assignment of the structures for all prepared cyanohydrins **2** and **5** was possible (see Section 4). X-ray structure determination was also performed for the pure cyanohydrin (1*R*,2*S*)-**5b** of the MeHNL-catalyzed reaction product of **4b** after recrystallization.[14]

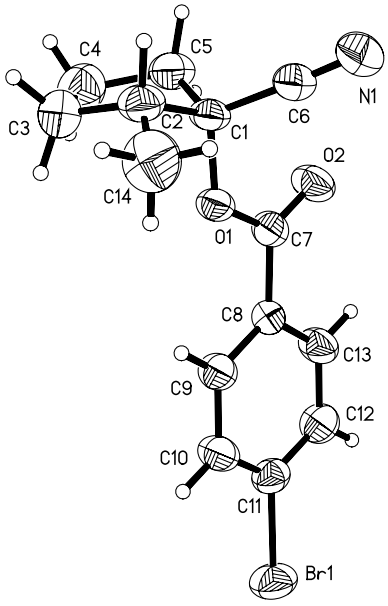


Figure 1. ORTEP view of *cis*-(1*S*,2*R*)-1-(4-bromobenzoyloxy)-2-methylcyclopentanecarbonitrile *cis*-(1*S*,2*R*)-**2a**′.

3. Conclusions

With the reactions performed it has been shown that the addition of HCN to 2-substituted cyclopentanones, to yield the corresponding cyanohydrins, can be strongly catalyzed by hydroxynitrile lyases (HNLs). The HCN-additions to racemic 2-alkyl cyclopentanones **1b**–**d**, catalyzed by PaHNL from bitter almonds, are highly (*R*)-selective yielding almost exclusively the *cis*-(1*R*,2*S*)- and *trans*-(1*R*,2*R*) stereoisomeric cyanohydrins **2b**–**d**, respectively. With the sterically less demanding methyl derivate **1a** the stereoselectivity is lower, especially for the formation of the *trans*-(1*R*,2*R*)-diastereomer. In comparison to PaHNL as catalyst, the reactions catalyzed by MeHNL from cassava were considerably faster. The expected (*S*)-selectivity with MeHNL was observed perfectly for the formation of

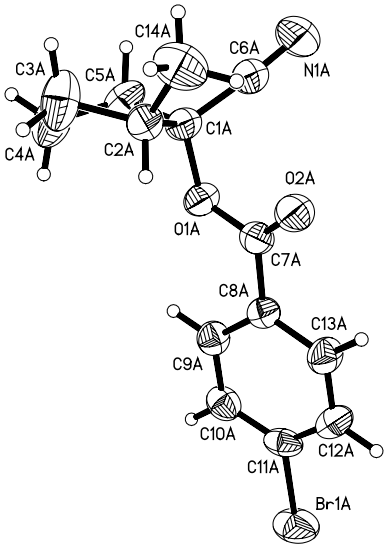


Figure 2. ORTEP view of *trans*-(1*S*,2*S*)-1-(4-bromobenzoyloxy)-2-methylcyclopentanecarbonitrile *trans*-(1*S*,2*S*)-**2a**′.

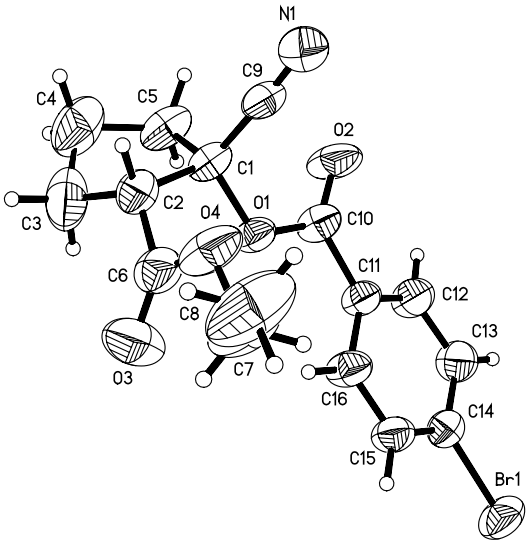


Figure 4. ORTEP view of *cis*-(1*R*,2*S*)-2-(4-bromobenzoyloxy)-2-cyanocyclopentane carboxylic acid ethyl ester *cis*-(1*R*,2*S*)-**5b**′.

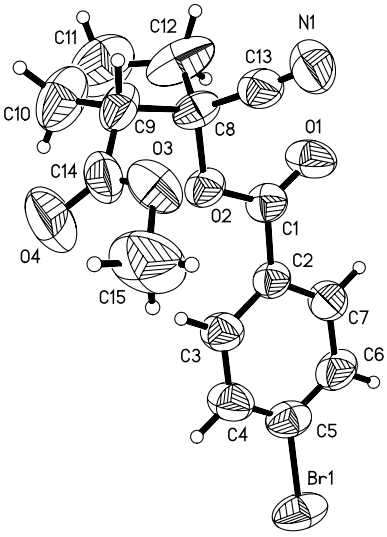


Figure 3. ORTEP view of *cis*-(1*R*,2*S*)-2-(4-bromobenzoyloxy)-2-cyanocyclopentane carboxylic acid methyl ester *cis*-(1*R*,2*S*)-**5a**′.

the *trans*-(1*S*,2*S*)- but not for the *cis*-(1*S*,2*R*)-stereoisomeric cyanohydrins **2b**–**e**.

Racemic 2-oxocyclopentane carboxylates **4a**–**f** are excellent substrates for MeHNL but not for PaHNL. In most cases, cyanohydrins **5a**–**f** with a *cis*-(1*R*,2*S*)-configuration were obtained with conversion rates of about 50%. These results can be rationalized via a fast enolization of the starting racemic β-ketoesters **4a**–**f** and a fast and preferred reaction of the (*R*)-enantiomers to the cyanohydrins **5a**–**f**.

In conclusion it is possible to selectively prepare each of the four stereoisomeric 2-substituted cyclopentanone cyanohydrins by HNL-catalyzed HCN additions to the corresponding cyclopentanone derivatives.

4. Experimental

4.1. Materials and methods

Melting points were determined on a Büchi SMP-20 and are uncorrected. Unless otherwise stated, ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 250 F (250 MHz) and ARX 500 (500 MHz) in $CDCl_3$ with TMS as the internal standard. ^{13}C NMR multiplicities were determined with DEPT experiments. Optical rotations were measured with a Perkin–Elmer polarimeter 241 LC in a thermostated glass cuvette ($l = 10$ cm). Chromatography was performed using silica gel, grain size 0.040–0.063 mm (Fluka). Diastereomeric excess: GC separations were conducted using (a) capillary glass columns (20 m) with OV 1701, carrier gas 0.4–0.6 bar hydrogen; (b) a Chiraldex B-PM (permethylated) column (30 m × 0.32 mm), carrier gas 0.6–1.0 bar hydrogen; (c) a Chiraldex B-TA and G-TA column (30 m × 0.32 mm), carrier gas hydrogen.

Cyclopentanones **1b**–**e**,[15] and **4c**–**f**[16,17] were prepared according to literature procedures. Ketones **1a**, **4a**, and **4b** are commercially available. Racemic cyanohydrins were performed according to a procedure developed by van der Gen et al.,[8] but the reaction times were always 48 h. ^{1}H and ^{13}C NMR data of the racemic cyanohydrins are reported in Tables 9 and 10. For the performance of the elemental analysis of the cyanohydrins, the *O*-acetylated cyanohydrins **3c**, **6a**, and **6c**–**6e** were used (Table 8). ^{1}H and ^{13}C NMR data of the *O*-acetylated cyanohydrins are reported in Table 11. The *O*-acetylated derivatives were prepared using acetic anhydride and dimethylaminopyridine (for conditions see determination of conversion rates and isomeric ratio). All yields are not optimized.

4.2. General procedure for the (*R*)-PaHNL-catalyzed preparation of cyclopentanone cyanohydrins 2 and 5

A solution of (*R*)-PaHNL (100 U per 100 mg support, total 200 U, 83.0 μL) was added to cellulose [Elcema-

Table 7. X-ray crystal data collection and refinement for *cis*-(1*S*,2*R*)-**2a**′, *trans*-(1*S*,2*S*)-**2a**′, *cis*-(1*R*,2*S*)-**5a**′, and *cis*-(1*R*,2*S*)-**5b**′

	cis-(1*S*,2*R*)-**2a**′	*trans*-(1*S*,2*S*)-**2a**′	*cis*-(1*R*,2*S*)-**5a**′	*cis*-(1*R*,2*S*)-**5b**′
Formula	$C_{14}H_{14}NO_2Br$	$C_{14}H_{14}NO_2Br$	$C_{15}H_{14}NO_4Br$	$C_{16}H_{16}NO_4Br$
FW	308.17	308.17	352.18	366.21
Crystal system	Orthorhombic	Monoclinic	Orthorhombic	Monoclinic
Space group	$P2_12_12_1$	$P2_1$	$P2_12_12_1$	$C2$
a (Å)	7.3146(17)	7.107(3)	7.3709(4)	29.459(6)
b (Å)	10.356(2)	12.500(5)	10.3865(5)	7.4626(14)
c (Å)	18.537(4)	15.674(5)	20.604(3)	7.7420(11)
α (°)	90	90	90	90
β (°)	90	95.85(3)	90	103.322(13)
γ (°)	90	90	90	90
V (Å^3)	1404.1(5)	1385.2(9)	1577.4(3)	1656.2(5)
Z	4	4	4	4
ρ_{calcd} (mg m^{-3})	1.458	1.478	1.483	1.469
$F(000)$	624	624	712	744
μ (mm^{-1})	2.921	2.961	3.689	2.498
θ Range (°)	2.20–26.00	2.09–25.00	4.29–68.00	2.70–27.50
Data collection[a]				
Reflections collected/unique	10966/2752	9742/4878	2678/2287	2068/2030
Data/restraints/parameters	2752/0/164	4878/1/326	2287/24/191	2030/1/200
Goodness-of-fit on F^2	1.059	1.058	1.123	1.061
Final R indices				
[$I > 2\sigma(I)$]	$R1 = 0.0362$	$R1 = 0.0393$	$R1 = 0.0602$	$R1 = 0.0541$
	$wR2 = 0.0721$	$wR2 = 0.0790$	$wR2 = 0.1687$	$wR2 = 0.1174$
R indices (all data)	$R1 = 0.0499$	$R1 = 0.0579$	$R1 = 0.0644$	$R1 = 0.0925$
	$wR2 = 0.0768$	$wR2 = 0.0845$	$wR2 = 0.1756$	$wR2 = 0.1320$
Absolute structure parameter	−0.021(12)	−0.005(8)	−0.07(5)	−0.02(3)
Largest diff.	0.359	0.383	0.560	0.431
Peak and hole (e Å^{-3})	−0.288	−0.355	−0.489	−0.273

[a] $T = 293$ K, Nicolet P3 diffractometer, Mo K_α ($l = 0.71073$) or Siemens P4 diffractometer, Cu K_α ($l = 1.54178$) radiation.

Cellulose P100PSC, Degussa: 1 g soaked in 10 mL of 0.02 M sodium citrate buffer, pH 3.3, for 2 h, and filtered off] followed by addition of diisopropyl ether (5 mL), substrate **1** or **4** (1 mmol), and anhydrous HCN[18] (150 μL, 3.9 mmol). After stirring at room temperature for the times given in Tables 2 and 5, the support was filtered off, washed twice with diethyl ether, and the combined filtrates concentrated under vacuum.

4.3. General procedure for the (*S*)-MeHNL-catalyzed preparation of cyclopentanone cyanohydrins 2 and 5

A solution of (*S*)-MeHNL (100 U per 100 mg support, total 200 U, 76.4 μL) was added to nitrocellulose [Pro-Celloidin (Fluka): 1 g (dry), soaked in 50 mL of 0.02 M sodium citrate buffer, pH 3.3, for 0.5 h; the buffer was decanted and nitrocellulose centrifuged (5700*g* for 30 min) and dried under high vacuum for 5 h], followed after 15 min by the addition of diisopropyl ether (5 mL), substrate **1** or **4** (1 mmol), and anhydrous HCN[18] (150 μL, 3.9 mmol). The reaction was performed as described above.

4.4. Blank experiment

The chemical HCN addition was performed analogously to the enzymatic reaction. However, the enzyme solution was replaced by the same volume of 0.02 M sodium acetate buffer, pH 5.4. The reaction times correspond with those of the (*R*)-PaHNL- and (*S*)-MeHNL-catalyzed reaction. ^{1}H and ^{13}C NMR data of the enzyme catalyzed and the chemically prepared cyanohydrins are identical.

Table 8. Yields and elemental analysis of racemic acetylated cyanohydrins **3** and **6**

Compound	Yield (%)	Mol. formula (mol. weight)	Calcd/found			
			C	H	N	O
rac-**3c**	52	$C_{11}H_{17}NO_2$ (195.26)	67.66 67.42	8.78 8.78	7.17 6.89	16.39
rac-**6a**	68	$C_{10}H_{13}NO_4$ (211.22)	56.87 57.02	56.87 6.22	6.63 6.53	30.30
rac-**6c**	71	$C_{12}H_{17}NO_4$ (239.27)	60.24 60.12	7.16 7.19	5.85 5.81	26.75
rac-**6d**	89	$C_{12}H_{17}NO_4$ (239.27)	60.24 60.02	7.16 7.15	5.85 5.73	26.75
rac-**6e**	51	$C_{12}H_{15}NO_4$ (237.26)	60.75 60.81	6.37 6.48	5.90 5.89	26.97
rac-**6f**	68	$C_{13}H_{19}NO_4$ (253.30)	61.64 61.77	7.56 7.53	5.53 5.45	25.27

4.5. Determination of conversion rates and isomeric ratio (acetylation)

To a solution of the crude cyclohexanone cyanohydrins **2** or **5** (10 μL) in CH_2Cl_2 (500 μL) was added acetic anhydride (50 μL) and dimethylaminopyridine (15 mg). The reaction mixture was allowed to stand at room temperature for 30 min. The mixture was then filtered through a silica gel column (3 × 0.5 cm) with CH_2Cl_2 (4 mL).

Table 9. Spectroscopic data of the 2-alkyl substituted cyanohydrins **2**

Compound	^{1}H NMR (250 MHz) (J in Hz): δ	^{13}C NMR (62.9 MHz): δ
rac-**2a**	1.15 (d, ^3J = 6.8 Hz, 0.6H, *cis*-CH_3), 1.16 (d, ^3J = 6.9 Hz, 2.4H, *trans*-CH_3), 1.41–1.49 (m, 1H, CH), 1.77–1.91 (m, 2H, 2CH), 1.98–2.30 (m, 4H, 4CH), 2.75 and 2.98 (br s, 1H, OH)	12.20 (*cis*-C^6H_3), 16.37 (*trans*-C^6H_3), 20.55 (*trans*-C^4H_2), 21.49 (*cis*-C^4H_2), 30.24 (*cis*-C^3H_2), 30.73 (*trans*-C^3H_2), 39.21 (*trans*-C^5H_2), 40.13 (*cis*-C^5H_2), 45.54 (*trans*-C^2H), 45.56 (*cis*-C^2H), 74.83 (*cis*-C^1), 78.65 (*trans*-C^1), 120.83 (*trans*-CN), 121.90 (*cis*-CN)
rac-**2b**	1.00 (d, ^3J = 7.4 Hz, 2.1H, *trans*-CH_2CH_3), 1.04 (d, ^3J = 7.4 Hz, 0.9H, *cis*-CH_2CH_3), 1.32–1.49 (m, 2H, CH_2CH_3), 1.72–2.28 (m, 7H, 7CH), 2.65 and 3.15 (br s, 1H, OH)	12.47 (*trans*-CH_2CH_3), 12.64 (*cis*-CH_2CH_3), 20.68 (*trans*-C^4H_2), 21.26, 21.32 (*cis*-C^4H_2), (*cis*-CH_2CH_3), 24.46 (*trans*-CH_2CH_3), 28.25 (*cis*-C^3H_2), 28.48 (*trans*-C^3H_2), 40.10 (*trans*-C^5H), 40.65 (*cis*-C^5H), 52.50 (*cis*-C^2H_2), 52.54 (*trans*-C^2H_2), 74.14 (*cis*-C^1), 78.28 (*trans*-C^1), 120.97 (*trans*-CN), 122.21 (*cis*-CN)
rac-**2c**	0.88–1.03 (m, 3H, $CH_2CH_2CH_3$), 1.30–1.59 (m, 4H, $CH_2CH_2CH_3$, $CH_2CH_2CH_3$), 1.60–2.51 (m, 7H, 7CH), 2.98 (br s, 1H, OH)	14.14 (*trans*-$CH_2CH_2CH_3$), 14.27 (*cis*-$CH_2CH_2CH_3$), 20.70 (*trans*-C^4H_2), 21.17 (*trans*-$CH_2CH_2CH_3$), 21.30 (*cis*-$CH_2CH_2CH_3$), 21.41 (*cis*-C^4H_2), 28.49 (*cis*-C^3H_2), 28.83 (*trans*-C^3H_2), 30.33 (*cis*-$CH_2CH_2CH_3$), 33.56 (*trans*-$CH_2CH_2CH_3$), 40.08 (*trans*-C^5H_2), 40.56 (*cis*-C^5H_2), 50.53 (*cis*-C^2H), 50.64 (*trans*-C^2H_2), 74.41 (*cis*-C^1), 78.47 (*trans*-C^1), 120.90 (*trans*-CN), 122.10 (*cis*-CN)
rac-**2d**	1.41–1.61 (m, 1H, CH), 1.66–2.59 (m, 8H, 8CH), 2.80 and 3.19 (br s, 1H, OH), 5.00–5.26 (m, 2H, $CH_2CH{=}CH_2$), 5.71–5.98 (m, 1H, $CH_2CH{=}CH_2$)	20.12 (*trans*-C^4H_2), 21.43 (*cis*-C^4H_2), 28.54 (*cis*-C^3H_2), 28.66 (*trans*-C^3H_2), 32.95 (*cis*-$CH_2CH{=}CH_2$), 35.79 (*trans*-$CH_2CH{=}CH_2$), 39.73 (*trans*-C^5H_2), 40.77 (*cis*-C^5H_2), 50.01 (*trans*-C^2H), 50.04 (*cis*-C^2H), 74.14 (*cis*-C^1), 78.46 (*trans*-C^1), 116.99 (*cis*-$CH_2CH{=}CH_2$), 117.61 (*trans*-$CH_2CH{=}CH_2$), 120.68 (*trans*-CN), 121.97 (*cis*-CN), 136.10 (*cis*-$CH_2CH{=}CH_2$), 136.13 (*cis*-$CH_2CH{=}CH_2$)
rac-**2e**	0.87–0.95 (m, 3H, $CH_2CH_2CH_2CH_3$), 1.17–1.57 (m, 6H, $CH_2CH_2CH_2CH_3$, $CH_2CH_2CH_2CH_3$, $CH_2CH_2CH_2CH_3$), 1.60–2.44 (m, 7H, 7CH), 2.48 and 2.93 (br s, 1H, OH)	13.96 (*cis*-$CH_2CH_2CH_2CH_3$), 14.00 (*trans*-$CH_2CH_2CH_2CH_3$), 20.70 (*trans*-C^4H_2), 21.42 (*cis*-C^4H_2), 22.76 (*trans*-$CH_2CH_2CH_2CH_3$), 22.88 (*cis*-$CH_2CH_2CH_2CH_3$), 27.87 (*cis*-$CH_2CH_2CH_2CH_3$), 28.56 (*cis*-C^3H_2), 28.89 (*trans*-C^3H_2), 30.21 (*trans*-$CH_2CH_2CH_2CH_3$), 30.26 (*cis*-$CH_2CH_2CH_2CH_3$), 31.12 (*trans*-$CH_2CH_2CH_2CH_3$), 40.09 (*trans*-C^5H_2), 40.57 (*cis*-C^5H_2), 50.75 (*cis*-C^2H), 50.86 (*trans*-C^2H), 74.40 (*cis*-C^1), 78.46 (*trans*-C^1), 120.96 (*trans*-CN), 122.13 (*cis*-CN)

Table 10. Spectroscopic data of the cyanohydrins **5**

Compound	^{1}H NMR (500 MHz) (J in Hz): δ	^{13}C NMR (125.8 MHz): δ
rac-**5a**	1.80–2.42 (m, 6H, 6CH), 2.94–3.06 (m, 1H, C^1H_{ax}), 3.81 (s, 1.5H, *cis*-CH_3), 3.82 (s, 1.5H, *trans*-CH_3), 4.85 (br s, 1H, OH)	19.89 (*trans*-C^4H_2), 21.66 (*cis*-C^4H_2), 24.89 (*trans*-C^5H_2), 26.92 (*cis*-C^5H_2), 38.71 (*trans*-C^3H_2), 39.32 (*cis*-C^3H_2), 52.60 (*trans*-CH_3), 52.64 (*cis*-C^1H), 52.65 (*cis*-CH_3), 55.55 (*trans*-C^1H), 72.64 (*cis*-C^2), 75.98 (*trans*-C^2), 120.11 (*trans*-CN), 120.59 (*cis*-CN), 172.09 (*trans*-COO), 173.91 (*cis*-COO)
rac-**5b**	1.30–1.35 (m, 3H, CH_2CH_3), 1.83–1.94 (m, 2H, 2CH), 1.97–2.43 (m, 4H, 4 CH), 2.94–3.15 (m, 1H, C^1H_{ax}), 3.80 (br s, 0.6H, OH), 4.23–4.31 (m, 2H, CH_2CH_3), 4.93 (br s, 0.4H, OH)	14.07 (*cis*-CH_2 CH_3), 14.15 (*trans*-CH_2CH_3), 19.97 (*trans*-C^4H_2), 21.64 (*cis*-C^4H_2), 24.98 (*trans*-C^5H_2), 26.94 (*cis*-C^5H_2), 38.81 (*trans*-C^3H_2), 39.38 (*cis*-C^3H_2), 52.72 (*cis*-C^1H), 55.57 (*trans*-C^1H), 61.77 (*trans*-CH_2CH_3), 61.87 (*cis*-CH_2CH_3), 72.68 (*cis*-C^2), 75.99 (*trans*-C^2), 120.09 (*trans*-CN), 120.65 (*cis*-CN), 171.60 (*trans*-COO), 173.52 (*cis*-COO)
rac-**5c**	0.97 (t, ^3J = 7.4 Hz, 2.0H, *cis*-$CH_2CH_2CH_3$), 1.00 (t, ^3J = 7.4 Hz, 1.0H, *trans*-$CH_2CH_2CH_3$), 1.64–2.46 (m, 8H, $CH_2CH_2CH_3$, 6CH), 2.94–3.06 (m, 1H, C^1H_{ax}), 3.87 (br s, 0.4H, OH), 4.17 (t, ^3J = 6.7 Hz, 1.3H, *cis*-$CH_2CH_2CH_3$), 4.18 (t, ^3J = 6.7 Hz, 0.7H, *trans*-$CH_2CH_2CH_3$), 4.93 (br s, 0.6H, OH)	10.28 (*cis*-$CH_2CH_2CH_3$), 10.35 (*trans*-$CH_2CH_2CH_3$), 19.90 (*trans*-C^4H_2), 21.83 (*cis*-$CH_2CH_2CH_3$), 21.89 (*trans*-$CH_2CH_2CH_3$), (*cis*-C^4H_2), 24.94 (*trans*-C^5H_2), 26.94 (*cis*-C^5H_2), 38.74 (*trans*-C^3H_2), 39.36 (*cis*-C^3H_2), 52.75 (*cis*-C^1H), 55.58 (*trans*-C^1H), 61.29 (*trans*-$CH_2CH_2CH_3$), 61.34 (*cis*-$CH_2CH_2CH_3$), 72.66 (*cis*-C^2), 75.96 (*trans*-C^2), 120.12 (*trans*-CN), 120.66 (*cis*-CN), 171.68 (*trans*-COO), 173.58 (*cis*-COO)
rac-**5d**	1.24–1.33 (m, 6H, $CH(CH_3)_2$), 1.82–2.43 (m, 6H, 6CH), 2.91–2.98 (m, 1H, C^1H_{ax}), 3.81 (br s, 0.4H, OH), 5.01 (br s, 0.6H, OH), 5.11–5.17 (m, 1H, $CH(CH_3)_2$)	20.22 (*trans*-C^4H_2), 21.59 (*cis*-C^4H_2), 21.65 (*cis*-$CH(CH_3)_2$), 21.70 (*trans*-$CH(CH_3)_2$), 21.74 (*cis*-$CH(CH_3)_2$)*, 21.78 (*trans*-$CH(CH_3)_2$)*, 25.25 (*trans*-C^5H_2), 26.82 (*cis*-C^5H_2), 38.98 (*trans*-C^3H_2), 39.43 (*cis*-C^3H_2), 52.84 (*cis*-C^1H), 55.62 (*trans*-C^1H), 69.47 (*trans*-$CH_2(CH_3)_2$), 69.71(*cis*-CH_2 $(CH_3)_2$), 72.67 (*cis*-C^2), 75.84 (*trans*-C^2), *trans*-120.19 (*trans*-CN), 120.72 (*cis*-CN), 171.22 (*trans*-COO), 173.00 (*cis*-COO)
rac-**5e**	1.78–2.52 (m, 6H, 6CH), 2.97–3.09 (m, 1H, C^1H_{ax}), 3.79 (br s, 0.5H, OH), 4.69–4.73 (m, 2H, $CH_2CH{=}CH_2$), 4.81 (br s, 0.5H, OH), 5.27–5.41 (m, 2H, $CH_2CH{=}CH_2$), 5.85–6.03 (m, 1H, $CH_2CH{=}CH_2$)	19.93 (*trans*-C^4H_2), 21.64 (*cis*-C^4H_2), 24.99 (*trans*-C^5H_2), 26.99 (*cis*-C^5H_2), 38.77 (*trans*-C^3H_2), 39.36 (*cis*-C^3H_2), 52.77 (*cis*-C^1H), 55.53 (*trans*-C^1H), 66.23 (*trans*-$CH_2CH{=}CH_2$), 66.26 (*cis*-$CH_2CH{=}CH_2$), 72.65 (*cis*-C^2), 75.91 (*trans*-C^2), 119.35 (*cis*-$CH_2CH{=}CH_2$), 119.39 (*trans*-$CH_2CH{=}CH_2$), 120.05 (*trans*-CN), 120.58 (*cis*-CN), 131.07 (*cis*-$CH_2CH{=}CH_2$), 131.36 (*trans*-$CH_2CH{=}CH_2$), 171.29 (*trans*-COO), 173.09 (*cis*-COO)
rac-**5f**	0.93–0.98 (m, 6H, $CH_2CH(CH_3)_2$), 1.80–2.47 (m, 7H, 6CH, $CH_2CH(CH_3)_2$), 2.95–3.07 (m, 1H, C^1H_{ax}), 3.86–4.06 (m, 2.5H, OH, $CH_2CH(CH_3)_2$), 4.91 (br s, 0.5H, OH)	18.94 (*cis*-$CH_2CH(CH_3)_2$), 18.96 (*cis*-$CH_2CH(CH_3)_2$)*, 19.06 (*trans*-$CH_2CH(CH_3)_2$), 19.08 (*trans*-$CH_2CH(CH_3)_2$)*trans*-C^4H_2), 21.64 (*cis*-C^4H_2), 24.91 (*trans*-C^5H_2), 26.40 (*cis*-C^5H_2), 27.47 (*trans*-$CH_2CH(CH_3)_2$), 27.64 (*cis*-$CH_2CH(CH_3)_2$), 38.69 (*trans*-C^3H_2), 39.36 (*cis*-C^3H_2), 52.80 (*cis*-C^1H), 55.59 (*trans*-C^1H), 71.41 (*cis*-C^2), 71.70 (*cis*-$CH_2CH(CH_3)_2$), 72.65 (*trans*-$CH_2CH(CH_3)_2$), 75.94 (*trans*-C^2), 120.13 (*trans*-CN), 120.65 (*cis*-CN), 171.67 (*trans*-COO), 173.49 (*cis*-COO)

* Rotamers.

Table 11. Spectroscopic data of the *O*-acetylated cyanohydrins **3** and **6**

Compound	^{1}H NMR (250 MHz) (J in Hz): δ	^{13}C NMR (62.9 MHz): δ
rac-**3c**	0.93–0.98 (m, 3H, $CH_2CH_2CH_3$), 1.26–1.53 (m, 4H, $CH_2CH_2CH_3$, $CH_2CH_2CH_3$), 1.66–1.91 (m, 3H, 3 CH), 1.93–2.67 (m, 4H, CH), 2.10–2.12 (m, 3H, $COOCH_3$)	14.10 (*trans*-$CH_2CH_2CH_3$), 14.23 (*cis*-$CH_2CH_2CH_3$), 21.05, 21.18, 21.26, 21.42 (C^4H_2, $CH_2CH_2CH_3$), 28.19, 28.83 (C^3H_2), 30.31 (*cis*-$CH_2CH_2CH_3$), 33.32 (*trans*-$CH_2CH_2CH_3$), 37.63, 37.79 (C^5H_2), 48.94, 50.80 (C^2H_2), 77.73 (*cis*-C^1), 80.89 (*trans*-C^1), 117.56 (*trans*-CN), 119.18 (*cis*-CN), 169.14 (*cis*-$COOCH_3$), 169.29 (*trans*-$COOCH_3$)
rac-**6a**	1.81–2.23 (m, 4H, 4CH), 2.08 and 2.13 (s, 3H, $OCOCH_3$), 2.25–2.33 (m, 0.5H, CH), 2.46 (t, ^3J = 7.7 Hz, 1H, CH), 2.56–2.64 (m, 0.5H, CH) 3.27 (t, ^3J = 7.8 Hz, 0.5H, CH), 3.35 (t, ^3J = 8.6 Hz, 0.5H, CH), 3.77 and 3.79 (s, 3H, $COOCH_3$)	20.79 (*cis*-$OCOCH_3$), 20.92 (*trans*-$OCOCH_3$), 21.45 (*cis*-C^4H_2), 21.97 (*trans*-C^4H_2), 25.86 (*cis*-C^5H_2), 27.00 (*trans*-C^5H_2), 38.26 (*trans*-C^3H_2), 38.31 (*cis*-C^3H_2), 52.39 (*cis*-$COOCH_3$), 52.53 (*trans*-$COOCH_3$), 53.59 (*cis*-C^1H), 54.09 (*trans*-C^1H), 76.29, 77.96 (C^2), 116.68 (*trans*-CN), 117.96 (*cis*-CN), 168.61, 168.82, 169.62, 171.19 ($COOCH_3$, $OCOCH_3$)
rac-**6c**	0.976 and 0.982 (t, $^3J_{t1} = {}^3J_{t2}$ = 7.4 Hz, 3H, $CH_2CH_2CH_3$), 1.63–2.69 (m, 8H, $CH_2CH_2CH_3$, 6CH), 2.08 and 2.13 (s, 3H, $OCOCH_3$), 3.23–3.37 (m, 1H, C^1H_{ax}), 4.04–4.23 (m, 2H, $CH_2CH_2CH_3$)	10.38 (*trans*-$CH_2CH_2CH_3$), 10.46 (*cis*-$CH_2CH_2CH_3$), 20.79 (*cis*-$OCOCH_3$), 20.92 (*trans*-$OCOCH_3$), 21.84, 21.89, 21.94 (C^4H_2), ($CH_2CH_2CH_3$), 25.72 (*cis*-C^5H_2), 26.94 (*trans*-C^5H_2), 38.26 (C^3H_2), 53.85 (*cis*-C^1H), 54.11 (*trans*-C^1H), 67.02 (*cis*-$CH_2CH_2CH_3$), 67.19 (*trans*-$CH_2CH_2CH_3$), 76.38 (*cis*-C^2), 77.96 (*trans*-C^2), 116.67 (*trans*-CN), 117.96 (*cis*-CN), 168.56, 169.13 (*cis*-COO), (*cis*-$OCOCH_3$), 168.79, 170.76 (*trans*-COO), (*trans*-$OCOCH_3$)
cis-**6d**	1.28 and 1.29 (d, $^3J_{d1} = {}^3J_{d2}$ = 6.3 Hz, 6H, $CH(CH_3)_2$), 1.82–2.25 (m, 4H, 4CH), 2.08 (s, 3H, $OCOCH_3$), 2.46 (m, ^3J = 7.6 Hz, 2H, CH), 3.30 (t, ^3J = 8.7 Hz, 1H, C^1H_{ax}), 5.07 (sept, ^3J = 6.3 Hz, 1H, $CH(CH_3)_2$)	20.76 ($OCOCH_3$), 21.55 (C^4H_2), 21.68, 21.71 ($CH(CH_3)_2$), 25.61 (C^5H_2), 38.22 (C^3H_2), 53.87 (C^1H), 69.01 ($CH(CH_3)_2$), 76.54 (C^2), 117.98 (CN), 168.52 (COO). ($OCOCH_3$)
rac-**6e**	1.82–2.34 (m, 4H, 4CH), 2.07 and 2,13 (s, 3H, $OCOCH_3$), 2,47 (t, ^3J = 7.6 Hz, 1H, CH), 2.57–2.84 (m, 1H, CH), 3.25–3.42 (m, 1H, C^1H_{ax}), 4.58–4.77 (m, 2H, $CH_2CH{=}CH_2$), 5.24–5.43 (m, 2H, $CH_2CH{=}CH_2$), 5.86–6.04 (m, 1H, $CH_2CH{=}CH_2$)	20.78 (*cis*-$OCOCH_3$), 20.92 (*trans*-$OCOCH_3$), 21.45, 21.89 (C^4H_2), 25.78, 27.00 (C^5H_2), 38.20, 39.26 (C^3H_2), 53.67, 54.01 (C^1H), 65.93, 66.16 ($CH_2CH{=}CH_2$), 76.32 (*cis*-C^2), 77.89 (*trans*-C^2), 116.62 (*trans*-CN), 117.95 (*cis*-CN), 118.70 (*cis*-$CH_2CH{=}CH_2$), 118.88 (*trans*-$CH_2CH{=}CH_2$), 131.58 (*cis*-$CH_2CH = CH_2$), 131.60 (*trans*-$CH_2CH{=}CH_2$), 168.60, 168.81, 170.41 (COO), ($OCOCH_3$)
rac-**6f**	0.96–0.99 (m, 6H, $CH_2CH(CH_3)_2$), 1.75–2.71 (m, 7H, 6CH, $CH_2CH(CH_3)_2$), 2,08 and 2,13 (s, 3H, $OCOCH_3$), 3.24–3.38 (m, 1H, C^1H_{ax}), 3.88–4.05 (m, 2H, $CH_2CH(CH_3)_2$)	19.06, 19.07 ($CH_2CH(CH_3)_2$), 20.81 (*cis*-$OCOCH_3$), 20.91 (*trans*-$OCOCH_3$), 21.53 (*cis*-C^4H_2), 21.83 (*trans*-C^4H_2), 25.70 (*cis*-C^5H_2), 26.85 (*trans*-C^5H_2), 27.62 (*trans*-$CH_2CH(CH_3)_2$), 27.70 (*cis*-$CH_2CH(CH_3)_2$), 38.23 (*trans*-C^3H_2), 38.33 (*cis*-C^3H_2), 54.01 (*cis*-C^1H), 54.14 (*trans*-C^1H), 71.57 (*cis*-$CH_2CH(CH_3)_2$), 71.63 (*trans*-$CH_2CH(CH_3)_2$), 76.33 (*cis*-C^2), 77.92 (*trans*-C^2), 116.69 (*trans*-CN), 117.97 (*cis*-CN), 168.55, 169.07 (*cis*-COO), (*cis*-$OCOCH_3$), 168.79, 170.68 (*trans*-COO), (*trans*-$OCOCH_3$)

Conversion and isomeric ratio were directly determined from the filtrate by gas chromatography.

4.6. General procedure for the preparation of the *p*-bromobenzoylated derivatives 2a′, 5a′, and 5b′

To a solution of **2a**, **5a**, or **5b** (10.70, 1.77, or 2.84 mmol, diastereomeric ratio given in Tables 3 and 6 in 1:1 pyridine/CH_2Cl_2 (20–80 mL) was added dimethylaminopyridine (ca. 0.2 equiv) and *p*-bromobenzoyl chloride (2.0 equiv), and the reaction mixture stirred for the time given. Water (20–50 mL) was then added, the layers separated, and the aqueous layer extracted with diethyl ether (3 × 50 mL). The combined extracts were washed with diluted HCl until neutral and then dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel with petroleum ether–ethyl acetate (50:1 for **2a′**, 5:1 for **5a′**, and 7:1 for **5b′**) and recrystallized.

4.6.1. *cis*-(1*S*,2*R*)-1-(4-Bromobenzoyloxy)-2-methylcyclopentanecarbonitrile *cis*-(1*S*,2*R*)-2a′. Reaction time: 14 d at room temperature, $R_f = 0.05$, yield: 33% *cis*-**2a′**, mp 73 °C (diisopropyl ether), $[\alpha]_D^{20} = +0.5$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz): δ 1.29 (d, $^3J = 6.8$ Hz, 3H, CH_3), 1.59–1.67 (m, 1H, CH), 1.78–1.90 (m, 2H, 2CH), 2.05–2.12 (m, 1H, CH), 2.43–2.56 (m, 3H, CH), 7.60–7.87 (m, 4H, H_{Ph}). ^{13}C NMR (125.8 MHz): δ 13.06 (CH_3), 21.42 (C^4H_2), 31.01 (C^3H_2), 37.40 (C^5H_2), 46.01 (C^2H), 78.79 (C^1), 118.80 (CN), 128.22, 129.01, 131.15, 132.03 (C_{Ph}), 163.90 (OCO). Anal. Calcd for $C_{14}H_{14}NO_2Br$ (308.17): C, 54.56; H, 4.58; N, 4.55; Br, 25.93; O, 10.38. Found: C, 54.56; H, 4.56; N 4.56; Br, 25.89.

4.6.2. *trans*-(1*S*,2*S*)-1-(4-Bromobenzoyloxy)-2-methylcyclopentanecarbonitrile *trans*-(1*S*,2*S*)-2a′. Reactions conditions and workup see *cis*-(1*S*,2*R*)-**2a′**, $R_f = 0.09$, yield: 35% *trans*-**2a′**, mp 76 °C (diisopropyl ether), $[\alpha]_D^{20} = +2.6$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz): δ 1.32 (d, $^3J = 7.0$ Hz, 3H, CH_3), 1.48–1.67 (m, 1H, CH), 1.81–1.97 (m, 1H, CH), 2.02–2.09 (m, 1H, CH), 2.20–2.26 (m, 1H, CH), 2.49–2.56 (m, 1H, CH), 2.67–2.73 (m, 1H, CH), 7.60–7.88 (m, 4H, H_{Ph}). ^{13}C NMR (125.8 MHz): δ 16.29 (CH_3), 21.35 (C^4H_2), 30.49 (C^3H_2), 37.49 (C^5H_2), 44.13 (C^2H), 81.93 (C^1), 117.29 (CN), 127.94, 128.99, 131.25, 131.95 (C_{Ph}), 164.16 (OCO). Anal. Calcd for $C_{14}H_{14}NO_2Br$ (308.17): C, 54.56; H, 4.58; N, 4.55; Br, 25.93; O, 10.38. Found: C, 54.63; H, 4.61; N 4.51; Br, 25.67.

4.6.3. *cis*-(1*R*,2*S*)-1-(4-Bromobenzoyloxy)-2-cyanocyclopentanecarboxylic acid methyl ester *cis*-(1*R*,2*S*)-5a′. Reaction time: 8 h under reflux, $R_f = 0.25$, yield: 61% *cis*-**5a′**, mp 108 °C (ethanol), $[\alpha]_D^{20} = -9.1$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz): δ 1.86–2.02 (m, 2H, 2CH), 2.14–2.21 (m, 1H, CH), 2.31–2.39 (m, 1H, CH), 2.53–2.66 (m, 2H, 2CH), 3.45 (t, $^3J = 8.94$ Hz, 1H, C^1H_{ax}), 3.76 (s, 3H, CH_3), 7.60–7.81 (m, 4H, H_{Ph}). ^{13}C NMR (125.8 MHz): δ 21.80 (C^4H_2), 25.90 (C^5H_2), 38.43 (C^3H_2), 52.55 (C^1H), 54.08 ($COOCH_3$), 76.89 (C^2), 117.69 (CN), 127.45, 129.36, 131.23, 132.11 (C_{Ph}), 163.33 (OCO), 169.53 ($COOCH_3$). Anal. Calcd for $C_{15}H_{14}NO_4Br$ (352.18): C, 51.16; H, 4.01; N, 3.98; Br, 22.69; O, 18.17. Found: C, 51.16; H, 4.14; N 3.83; Br, 22.53.

4.6.4. *cis*-(1*R*,2*S*)-1-(4-Bromobenzoyloxy)-2-cyanocyclopentanecarboxylic acid ethyl ester *cis*-(1*R*,2*S*)-5b′. Reaction time: 14 d at room temperature, $R_f = 0.21$, yield: 56% *cis*-**5b′**, mp 93 °C (diisopropyl ether), $[\alpha]_D^{20} = -1.9$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz): δ 1.23 (t, $^3J = 7.1$ Hz, 3H, CH_2CH_3), 1.87–2.01 (m, 2H, 2CH), 2.13–2.20 (m, 1H, CH), 2.30–2.38 (m, 1H, CH), 2.52–2.67 (m, 2H, 2 CH), 3.44 (t, $^3J = 8.9$ Hz, 1H, C^1H_{ax}), 4.19–4.25 (m, 2H, CH_2CH_3), 7.59–7.83 (m, 4H, H_{Ph}). ^{13}C NMR (125.8 MHz): δ 14.21 (CH_2CH_3), 21.76 (C^4H_2), 25.81 (C^5H_2), 38.38 (C^3H_2), 54.19 (C^1H), 61.64 (CH_2CH_3), 77.11 (C^2), 117.75 (CN), 127.51, 129.42, 131.32, 132.16 (C_{Ph}), 163.40 (OCO), 169.08 (*C*OOEt). Anal. Calcd for $C_{16}H_{16}NO_4Br$ (366.21): C, 52.48; H, 4.40; N, 3.82; Br, 21.82; O, 17.48. Found: C, 52.52; H, 4.49; N 3.76; Br, 21.73.

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14. CCDC-239154 to -239158 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Center, 12, Union Road, Cambridge CB21EZ, UK, fax: (+44) 1223 336 033 or deposit@ccdc.cam.ac.uk).
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