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Candida antarctica lipase A in the dynamic resolution of novel furylbenzotiazol-based cyanohydrin acetates

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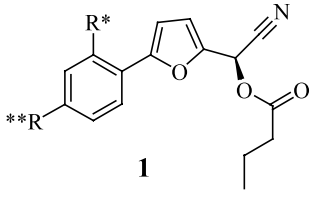
Abstract—A series of novel (*R*)-furylbenzotiazol-based cyanohydrin acetates were prepared in over 90% isolated yields from the corresponding furancarbaldehydes. The one-pot method combines a basic resin to produce hydrogen cyanide from acetone cyanohydrin, an equilibrium between the formation and decomposition of furylbenzotiazol-based cyanohydrins and the unique enantioselectivity of *Candida antarctica* lipase A, allowing the acylation of (*R*)-cyanohydrins in the presence of vinyl acetate in anhydrous acetonitrile.

1. Introduction

Heterocyclic ring systems can be commonly found in the active components of many medicines. This is not surprising since these systems present a diverse array of pharmacophores, acting as hydrogen bond donors and acceptors and also providing positive ions. Substitution of the parent heterocyclic ring with an aromatic or heteroaromatic ring system can further increase pharmacophoric diversity. Accordingly, there is a need for general heterocyclic building blocks and intermediates which fulfil one or more of the following criteria: are highly enantiopure, contain reactive functional groups through which a building block can be attached to other structural components of a final drug molecule and allow an easy transformation of the intermediate to other types of compound. Optically active cyanohydrins can fulfil all these criteria, the criterium for high enantiopurity being most challenging. We earlier worked with the preparation of highly enantiopure (*R*)-5-phenylfuran-2-ylcyanomethyl butanoates **1** through *Pseudomonas cepacia* lipase (lipase PS) catalysed dynamic kinetic resolution (Scheme 1).[1] Still based on the furyl ring as the parent heterocyclic ring,



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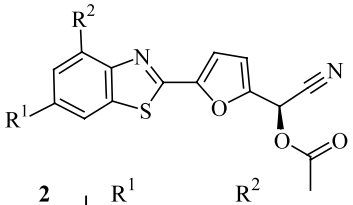

2	R^1	R^2
a	H	H
b	Cl	H
c	CH_3	H
d	H	Cl

Scheme 1.

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the focus herein is on the preparation of highly enantiopure furylbenzotiazol-based cyanohydrin acetates **2**.

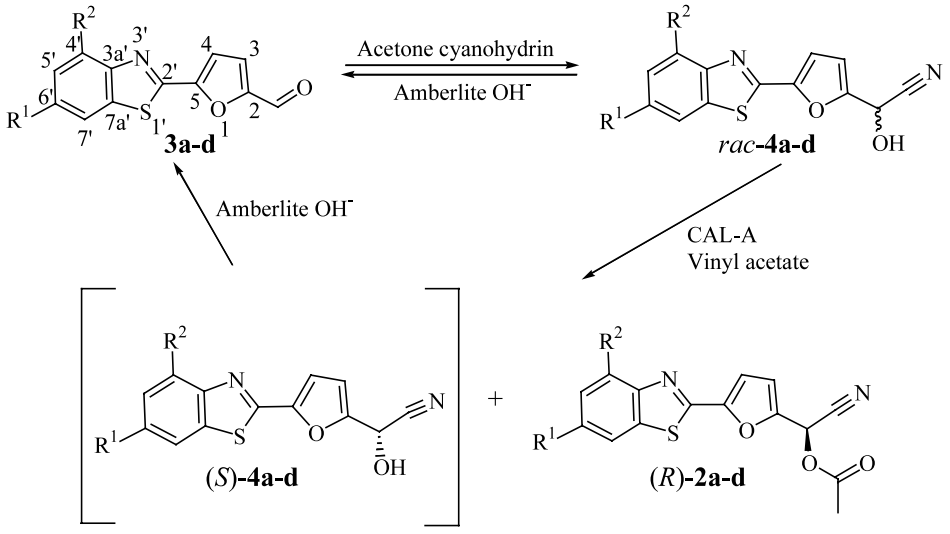
Currently, the lipase-catalysed kinetic resolution of racemic compounds with various functionalities has become an important method for the preparation of enantiopure compounds.[2] When the method is successful both enantiomers of a racemate at ca. 50% theoretical yields are simultaneously available for drug development. However, it can occur that the other enantiomer exerts a different, even harmful, physiological effect or shows lowered or no activity. Accordingly, there is a final bias toward the preparation of only one of the enantiomers, leaving behind a question about what to do with the undesired enantiomer of the kinetic resolution. To solve this problem, the principle of dynamic kinetic resolution has been previously exploited in an efficient one-pot synthesis of optically active cyanohydrin esters in the presence of a basic resin and a lipase.[1,3–5] Another elegant way has been the acylation of the free cyanohydrin enantiomer in a resolved mixture (one enantiomer as a cyanohydrin and the other as a cyanohydrin ester) under the Mitsunobu conditions, leading to the inversion of configuration and accordingly to the desired ester enantiomer with 100% theoretical yield when calculated according to the racemic starting material.[6] In the case of labile cyanohydrin substrates, however, a decrease in enantiopurity can result under the Mitsunobu conditions.

Herein we now report the preparation of novel (*R*)-cyanohydrin acetates **2a–d** from the corresponding aldehydes **3a–d** and acetone cyanohydrin (source of HCN) through effective lipase-catalysed dynamic kinetic resolution of cyanohydrins **4a–d** with vinyl acetate (achiral acyl donor) in the presence of Amberlite IRA-904 basic resin in organic solvents (Scheme 2). Vinyl acetate, one of the most commonly used acyl donors was successfully used, although it had been previously emphasized that only isopropenyl acetate was usable.[4] In this work, use is made of the lability of cyanohydrins and the stability of cyanohydrin esters. Traditional kinetic resolution provides the enantioselectivity basis for successful dynamic kinetic resolution. Accordingly, the lipase-catalysed acylation of novel cyanohydrins **4a–d** was first studied (Scheme 3).

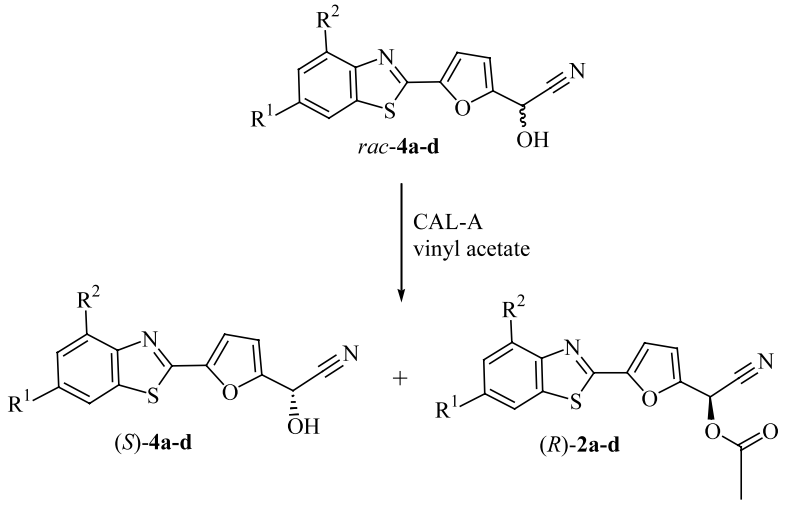
2. Results and discussion

2.1. Kinetic resolution by acylation

A large number of commercially available lipases exhibit a high degree of substrate selectivity, providing products with various levels of enantioselectivity. Potential lipases were screened for the enantioselective acylation of racemic cyanohydrin **4a** as a model substrate in vinyl acetate. Most of the lipases, including lipase PS (previously shown to have the most potential[1,3,4]), were catalytically inactive. CAL-B with minor reactivity (time needed to reach a certain conversion) and enantioselectivity (Table 1; entry 1) was also useless although successfully used for the dynamic resolution of mandelonitrile.[5] Only CAL-A was highly active and catalysed the reaction enantioselectively ($E=23\pm0.4$; entry 4). It is interesting to recognize that also in previous work this enzyme provided an excellent, very fast and environmentally benign method for the preparation of racemic cyanohydrin esters **1**.[1] The enzyme has only rarely been applied to enantioselective reactions.[7] There are, however, some interesting applications with sterically hindered substrates, including the highly enantioselective acylations of β-amino esters,[8–10] methyl pipecolinate[11] and 1-phenylethan-1,2-diol.[12] Evidently, the size of compounds **2** and/or the heteroaromatic structure of the benzotiazol ring enhance enzymatic enantioselectivity over that of compounds **1** as substrates. For good catalytic activity and enantioselectivity of CAL-A, it has been essential to use the enzyme adsorbed on Celite in the presence of sucrose (enzyme preparation).[13] In the present work, the reaction of **4a** with vinyl acetate in acetonitrile yielded an



Scheme 2. One-pot synthesis of (*R*)-(+)-**2a–d** by dynamic resolution.



Scheme 3. Kinetic resolution of racemic cyanohydrins **4a**–**d**.

Table 1. Enzymatic acylation of racemic cyanohydrin **4a** (13 mM)

Entry	Enzyme (mg ml^{-1})	Solvent	Acyl donor (mM)	Time (h)	Conv. (%)	E
1	CAL-B (50)	Vinyl acetate	Vinyl acetate	168	8	3±0.1
2	CAL-B (50)	Ethyl acetate	Ethyl acetate	168	0	–
3	CAL-B (50)	Acetonitrile	Vinyl acetate (26)	168	23	5±0.1
4	CAL-A (10)	Vinyl acetate	Vinyl acetate	12	48	23±0.4
5	CAL-A (10)	Ethyl acetate	Ethyl acetate	168	12	8±0.1
6	CAL-A (10)	Acetonitrile	Vinyl acetate (26)	24	44	62±2
7	CAL-A (10)	Acetonitrile	Vinyl acetate (39)	24	47	61±1
8	CAL-A (10)	Acetonitrile	Vinyl acetate (52)	24	48	62±1
9	CAL-A (5)	Acetonitrile	Vinyl acetate (26)	48	45	64±2
10	CAL-A (20)	Acetonitrile	Vinyl acetate (26)	12	43	24±0.7
11	CAL-A (50)	Acetonitrile	Vinyl acetate (26)	5	51	9±0.3

almost racemic product at the initial rate of $v_o = 0.07$ μmol mg^{-1} h^{-1} in the presence of the native enzyme, whereas $v_o = 0.4$ μmol mg^{-1} h^{-1} resulted when the enzyme preparation was used.

Due to the very low solubility of racemic cyanohydrin **4a** in most organic solvents, only reactions in acetonitrile and ethyl acetate were studied for further optimization. Acetonitrile proved to be most useful for CAL-A-mediated acylation with vinyl acetate (Table 1; entries 6–8), while reduced reactivity and selectivity was evident for the reaction in ethyl acetate (entry 5). The results for the acylation of **4a** in acetonitrile indicate that the concentration of vinyl acetate had no effect on reactivity or enantioselectivity (entries 6–8). On the other hand, an unexpected decrease in enantioselectivity is clear with increasing the amount of CAL-A preparation from 10 to 50 mg ml^{-1} (entries 6, 10 and 11). The explanation for this is unclear especially since reactivity increases with increasing enzyme content, excluding the possibility to mass transfer effects. When racemic cyanohydrin acetate **2a** was subjected under the enzymatic reaction conditions without an added nucleophile in the presence of 5 and 50 mg ml^{-1} of the enzyme preparation, the hydrolysis of the cyanohydrin acetate **2a** to the cyanohydrin **4a** by water coming from the seemingly dry enzyme preparation was not observed.

For the optimization of enantioselectivity, attention is often paid to the structure of an achiral acyl donor. In the terms of the two-step reaction mechanism (typical to serine hydrolases) proceeding through an acyl-enzyme intermediate (RCO-enzyme), enantiodiscrimination occurs when the intermediate reacts with a cyanohydrin as a nucleophile. Accordingly, the nature of the intermediate is changed when group R is varied. The previous results for the acylation of the amino group in amino esters indicated enhanced reactivity and enantioselectivity with increasing carbon chain R in the achiral acyl donor.[8] On this basis, higher E values can be expected for the CAL-A-catalysed acylation of **4a**–**d** if vinyl butanoate is used in the place of the acetate as an acyl donor. However, vinyl acetate has been used throughout the present work as an acyl donor due to analytical problems in detecting the enantiomers of butanoylated (or higher analogues) cyanohydrins by the used HPLC-method.

According to the above results, the reactions of **4a**–**d** with vinyl acetate in the presence of CAL-A preparation (10 mg ml^{-1}) in acetonitrile were studied. The reactions proceeded smoothly with enantioselectivities dependent on the nature of the substituents at the benzene ring (Table 2). A substituent at the position 6′

of the benzotiazol ring lowers enantioselectivity (entries 2 and 3, Table 2) compared to the unsubstituted compound (entry 1) while the substituent at the position 4′ has no effect (entry 4).

Table 2. Acylation of racemic cyanohydrins **4a–d** (13 mM) with vinyl acetate (40 mM) in acetonitrile mediated by CAL-A preparation (10 mg/ml)

Entry	Resolution products	E	Time (h)	Conversion (%)
1	(*S*)-**4a**, (*R*)-**2a**	62±2	24	44
2	(*S*)-**4b**, (*R*)-**2b**	14±0.3	24	39
3	(*S*)-**4c**, (*R*)-**2c**	48±2	24	46
4	(*S*)-**4d**, (*R*)-**2d**	64±2	24	48

2.2. Dynamic kinetic resolution and preparation of (*R*)-cyanohydrin acetates

In an efficient enzymatic dynamic kinetic resolution, the less reactive enantiomer should be rapidly racemized under the same conditions where the product of the enzyme-catalysed reaction remains stable. Moreover, the enzyme should keep its activity throughout the reaction. Under such conditions, the starting material is always practically racemic, allowing the maximal enantiopurity (as determined by the E value of the corresponding kinetic resolution) to be reached at the theoretical zero conversion for the more reactive enantiomer throughout the reaction. The use of appropriate conditions is extremely important, because ee of the product enantiomer in normal enzymatic kinetic resolution tends to decrease with increasing conversion.

In the present dynamic kinetic resolution method for the production of (*R*)-cyanohydrin acetates **2a–d** (Scheme 2), the fast equilibrium between a cyanohydrin and the corresponding aldehyde (and acetone) and hydrogen cyanide in the presence of Amberlite IRA-904 basic resin is essential. In order to demonstrate that under the reaction conditions cyanohydrins can be smoothly produced in reasonable amounts, a mixture of aldehyde **3a** (65 mol) and acetone cyanohydrin (200 mol) was equilibrated in acetonitrile in the presence of the basic resin (5 mg ml^{-1}; 0.65 mmol ml^{-1}). The equilibrium value of 8 for [**4a**]/[**3a**] in less than 2 h clearly fulfilled the requirement. To verify the enantiomeric stability of the products of the above-described kinetic resolution (Scheme 3), the resolved mixture of one of the pairs (*S*)-**4a–d** and (*R*)-**2a–d** against time was treated with the basic resin (5 mg ml^{-1}; 0.65 mmol ml^{-1}). The free (*S*)-cyanohydrins **4a–d** were racemized within less than 2 h, whereas the enantiomeric composition of (*R*)-cyanohydrin esters **2a–d** remained unaltered even after 7 days.

The amount of basic resin is critical for the dynamic resolution as previously shown for the case of mandelonitrile.[5] In the present work, acetic acid which is liberating from vinyl acetate through the reaction with the water present in the enzyme preparation can neutralize the resin, and accordingly lead to normal kinetic rather than dynamic kinetic resolution. In addition, some hydrogen cyanide is also present in spite of the fast formation of cyanohydrins from the aldehydes. That the basic resin is still active at the end of the dynamic kinetic resolution was shown by adding a new portion of acetone cyanohydrin after the dynamic resolution of **4a**. The dark brown colour appeared immediately, indicating that the base-catalysed decomposition of acetone cyanohydrin produced hydrogen cyanide followed by the base-catalysed polymerisation.[14] The dark brown color was also observed when 10 mg ml^{-1} (1.3 mmol ml^{-1}) of the resin was used instead of the normal 5 mg ml^{-1}, but in this case the enzymatic acylation was also prevented.

In the one-pot synthesis of (*R*)-cyanohydrin acetates **2a–d** by dynamic kinetic resolution, CAL-A provided reactivities that were comparable to those found in normal kinetic resolution (Table 3 compared to Table 2). More importantly, the observed ee values for the acetates **2a–d** were in accordance with the theoretical values that can be calculated from the E values in Table 2 by extrapolating to zero conversion using the equation of Chen et al.[15] The reactions were practically at 100% conversion after 48 or 72 h in the presence of 10 mg ml^{-1} of the enzyme preparation. At lower enzyme content longer reaction times were needed (entry 2, Table 3). These results indicated that the present dynamic kinetic resolution do not suffer from water effects which were previously described for the CAL-B-catalysed dynamic kinetic resolution of mandelonitrile.[5] In accordance with the high enzyme content of 50 mg/ml the very fast reaction of aldehyde **3a** gave product **2a** at ee = 57% compared to the theoretical value of 80% (entry 3), indicating that the racemization

Table 3. Dynamic kinetic resolution of racemic cyanohydrins **4a–d** (13 mM) with vinyl acetate (40 mM) in acetonitrile mediated by CAL-A preparation (10 mg ml^{-1})

Entry	Product	Conv. (%)	Isolated yield (%)	Time (h)	ee (%)	Theoretical ee (%)	$[\alpha]_D^{25}$
1	(*R*)-**2a**	>99	91	48	96	97	+17.9
2	(*R*)-**2a**[a]	>99	–	120	92[a]	97	–
3	(*R*)-**2a**[b]	>99	–	12	57[b]	80	–
4	(*R*)-**2b**	>99	92	72	84	86	+14.2
5	(*R*)-**2c**	>99	93	48	95	95	+18.2
6	(*R*)-**2d**	>99	92	48	96	97	+8.1

[a] 5 mg ml^{-1} of CAL-A preparation.
[b] 50 mg ml^{-1} of CAL-A preparation.

of **4a** was not fast enough compared to the fast enzymatic reaction as shown in Table 1 (entry 11).

2.3. Absolute configuration

The *R* absolute configurations of the enzymatically produced enantiomers of cyanohydrin esters **1** were previously reported for the lipase PS-catalysed kinetic resolution of the corresponding cyanohydrins by acylation in accordance with the *R* enantioselectivity of the lipase PS-mediated kinetic resolution of furan-2-ylhydroxyacetonitrile and with the *S* enantioselectivity of the lipase PS-catalysed acylation of mandelonitrile and related compounds (the change from *R* to *S* is due to the change in the priority order of the substituents from furanyl to phenyl-based cyanohydrins).[1,3,4] The *R* enantiopreference can also be addressed to the CAL-A-mediated acylation of furan-2-ylhydroxyacetonitrile with vinyl acetate by comparing the peak positions in the HPLC chromatograms to those observed in the case of lipase PS catalysis. As a further support, the reaction yielded the corresponding enantiomerically enriched (+)-acetic esters with $[\alpha]_D^{25}=+18.4$ (*c* 1, $CHCl_3$) (ee 67%) in accordance with the literature value of $[\alpha]_D^{25}=+24.3$ (*c* 1.6, $CHCl_3$) (ee = 98%) for the (*R*)-(+)-acetic ester.[16]

3. Conclusions

The present work describes the usefulness of a dynamic kinetic resolution method for the preparation of novel cyanohydrin acetates (*R*)-**2a**–**d**. This method exploits the reversible nature of the base-catalysed cyanohydrin formation from the corresponding aldehydes **3a**–**d** and hydrogen cyanide and the base-catalysed cyanohydrin decomposition to the aldehyde and hydrogen cyanide, leading to the effective racemization of cyanohydrins **4a**–**d** at the same time when the *R* enantiomer is selectively acylated in the CAL-A-catalysed acylation (Scheme 2). The method exploits acetone cyanohydrin as an in situ source of hydrogen cyanide. Everything takes place in one pot, allowing at least 99% of the original aldehyde to be transformed to the corresponding cyanohydrin ester (*R*)-**3a**–**d** with high enantiopurity (ee 84–96%). The possibility to avoid the separate preparation and purification of the relatively labile cyanohydrins **4a**–**d** and the handling of hydrogen cyanide are great advantages of this method.

An important aspect of the present work is that a readily available lipase can be used for the production of enantiopure cyanohydrin intermediates because of the high stability, good availability and wide substrate selectivity of the enzymes. It has been possible to show the unique nature of the CAL-A enzyme to work with sterically hindered substrates under conditions where more common lipases, such as lipase PS and CAL-B, fail.

4. Experimental

4.1. Materials and methods

Anilines, 2-furoyl chloride, vinyl acetate, trimetylsilyl cyanide, P_2S_5, $PClO_3$ and ZnI_2 were products of Aldrich or Fluka. Amberlite IRA 904 was purchased from Acros and it was conditioned as previously described.[4] All solvents were purified and dried by standard methods as required. Lipase A (CAL-A) and lipase B (CAL-B, Chirazyme L2) from *Candida antarctica* were purchased from Boehringer-Mannheim. Before use CAL-A was adsorbed on Celite (4.0 g; product from Aldrich high purity analytical grade) by dissolving the enzyme and sucrose (0.24 g) in Tris–HCl buffer (pH 7.9) and the solution was thereafter left to dry at room temperature as described previously.[13] The final lipase content in the enzyme preparation was 10% (w/w). All enzymatic reactions were performed at room temperature (23–24°C).

The ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Jeol Lambda 400 spectrometer operating at 399.78 and 100.54 MHz, respectively. ^1H spectra were referenced internally to the solvent signal (d_6-DMSO, 2.49 ppm); ^{13}C spectra to the solvent signal (d_6-DMSO, 39.50 ppm). The correct assignment of the chemical shifts was confirmed by a combination of standard CHSHF (f1-decoupled, optimized to 145 Hz $^1J_{CH}$ coupling) and COLOC (optimized to $^nJ_{CH}$ couplings of 4, 6 and 8 Hz) ^{13}C, ^1H correlation measurements. Mass spectra (MS) were taken on a VG 7070E mass spectrometer. Thin layer chromatography (TLC) was carried out using Merck Kieselgel $60F_{254}$ sheets. Spots were visualized by treatment with 5% ethanolic phosphomolybdic acid solution and heating. Preparative chromatographic separations were performed using column chromatography on Merck Kieselgel 60 (0.063–0.200 μm). Melting points were determined by hot plate method and are uncorrected. Optical rotations were measured in acetonitrile (*c* 1) on a Jasco DIP-360 polarimeter and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. HPLC analyses were conducted with a HP 1090 instrument using a CHIRACEL OD column (0.46×25 cm) and a mixture of hexane and isopropanol (80:20) as eluent at the flow rate of 1 ml min^{-1}. For good baseline separation, the unreacted cyanohydrin in the sample was derivatized with chloroacetylchloride in the presence of pyridine containing 1% 4-*N*,*N*-dimethylaminopyridine (DMAP) before injections. Retention time for 5-(benzothiazol-2-yl)-furan-2-ylcyanomethyl acetates (*R*,*S*-**2a**–**d**) and for 5-(benzothiazol-2-yl)-furan-2-ylcyanomethyl chloroacetates (*R*,*S*-**2′a**–**d**) are presented in Table 4. The deter-

Table 4. Retention time for acetates (*R*,*S*-**2a**–**d**) and chloroacetates (*R*,*S*-**2′a**–**d**)

	R_t (min)			
Compound	(*R*)-**2**	(*S*)-**2**	(*R*)-**2′**	(*S*)-**2′**
a	46.4	9.3	53.4	11.5
b	27.4	14.6	31.3	18.3
c	17.2	6.8	22.4	14.5
d	23.3	10.6	25.1	11.5

mination of E was based on equation $E=\ln[(1-c)(1-ee_S)]/\ln[(1-c)(1+ee_S)]$.[15] Using linear regression E is achieved as the slope of a line. In the case of the dynamic kinetic resolution, conversion was determined using the ^{1}H NMR spectra of the reaction mixture by integrating characteristic proton signals for all the chemical species involved (aldehydic proton for **3a–d**, proton from cyanohydrin group for **4a–d** and protons from acetate for the esters **2a–d**).

4.2. Preparation of racemic cyanohydrins and their esters

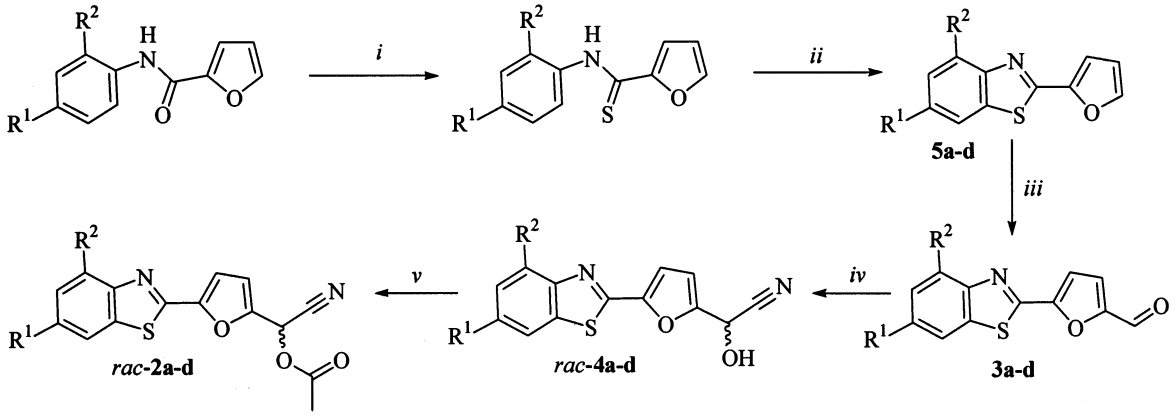
The synthesis of racemic cyanohydrins **4a–d** and esters **2a–d** was straightforward, as shown in Scheme 4. 2-Furan-2-ylbenzothiazoles were first prepared as previously described starting from furan-2-carboxylic acid phenylamides.[17,18] These products were further transformed into carbaldehydes **3a–d** using the Vilsmeier–Haack formylation method.[19] The aldehydes yielded novel racemic cyanohydrins **4a–d** via a reaction with trimethylsilylcyanide and ZnI_2, followed by desilylation with 3 M HCl.[20] Esterification for analytical purposes was performed with acetic anhydride in the presence of DMAP and triethyl amine.

4.2.1. Preparation of aldehydes 3a–d. Phosphorus oxychloride (10 ml) was added dropwise into ice-cooled dimethylformamide (30 ml), followed by addition of one of the 2-furan-2-yl benzothiazoles (**5a–d**) (100 mmol). The resulting mixture was stirred at 100°C for 2 h and then poured into ice (500 g). The pH of the reaction mass was set to 6 by addition of saturated aqueous sodium acetate solution. After 3 h the crude product was filtered, and dried. Chromatography on silica gel using dichloromethane as an eluent followed by recrystallization from ethyl acetate resulted in the formyl derivatives.

4.2.1.1. 5-(Benzothiazol-2-yl)furan-2-carbaldehyde 3a. Yield: 74%. Mp 176°C, (lit.[19] 176°C); HRMS M^+ found (M^+ calculated for $C_{12}H_7NO_2S$): 229.02068 (229.01975); MS: m/z (relative intensity) = 231 (6), 230 (15), 229 (100) [M^+], 228 (15), 227 (2), 202 (1), 201 (6), 200 (7), 174 (3), 173 (13), 172 (37), 147 (1), 146 (5), 145 (8), 140 (2), 128 (5); ^{1}H NMR: $\delta=7.53$ (ddd, $J=1.2$ Hz, $J=7.1$ Hz, $J=8.1$ Hz, 1H, (C(5′)-H), 7.57 (d, $J=3.9$ Hz, 1H, C(4)-H), 7.60 (ddd, $J=1.3$ Hz, $J=7.1$ Hz, $J=8.2$ Hz, 1H, C(6′)-H), 7.74 (d, $J=3.9$ Hz, 1H, C(3)-H), 8.10 (ddd, $J=0.6$ Hz, $J=1.2$ Hz, $J=8.2$ Hz, 1H, C(7′)-H), 8.21 (ddd, $J=0.6$ Hz, $J=1.3$ Hz, $J=8.1$ Hz, 1H, C(4′)-H), 9.73 (s, 1H, CHO); ^{13}C NMR: $\delta=113.4$ (C(4)), 122.7 (C(4′)), 123.3 (C(7′)), 124.3 (C(3)), 126.3 (C(5′)), 127.2 (C(6′)), 134.3 (C(3a′)), 151.6 (C(5)), 152.9 (C(2)), 153.2 (C(7a′)), 155.6 (C(2′)), 178.8 (CHO).

4.2.1.2. 5-(6-Chlorobenzothiazol-2-yl)furan-2-carbaldehyde 3b. Yield: 69%. Mp 213°C; HRMS M^+ found (M^+ calculated for $C_{12}H_6ClNO_2S$): 262.98001 (262.98078); MS: m/z (relative intensity) = 267 (2), 266 (5), 265 (37), 264 (18), 263 (100) [M^+], 262 (12), 237 (2), 236 (2), 235 (6), 234 (5), 209 (4), 208 (14), 207 (12), 206 (35), 182 (1), 181 (3), 180 (4), 179 (6), 174 (1), 172 (2), 171 (3), 144 (9), 142 (4); ^{1}H NMR: $\delta=7.60$ (d, $J=3.9$ Hz, 1H, C(4)-H), 7.63 (dd, $J=2.2$ Hz, $J=8.8$ Hz, 1H, C(5′)-H), 7.75 (d, $J=3.9$ Hz, 1H, C(3)-H), 8.10 (d, $J=8.8$ Hz, 1H, C(4′)-H), 8.38 (d, $J=2.2$ Hz, 1H, C(7′)-H), 9.74 (s, 1H, CHO); ^{13}C NMR: $\delta=113.9$ (C(4)), 122.4 (C(7′)), 124.2 (C(3)), 124.4 (C(4′)), 127.7 (C(5′)), 130.8 (C(6′)), 135.8 (C(3a′)), 151.1 (C(5)), 152.0 (C(7a′)), 153.0 (C(2)), 156.6 (C(2′)), 178.9 (CHO).

4.2.1.3. 5-(6-Methylbenzothiazol-2-yl)furan-2-carbaldehyde 3c. Yield: 72%. Mp 168°C, (lit.[19] 169–170°C); HRMS M^+ found (M^+ calculated for $C_{13}H_9NO_2S$): 243.03428 (243.03540); MS: m/z (relative intensity) = 246 (1), 245 (6), 244 (16), 243 (100) [M^+], 242 (14), 241 (2), 216 (1), 215 (3), 214 (10), 188 (1), 187 (4), 186 (17), 185 (3), 184 (1), 154 (4), 122 (4), 121 (15); ^{1}H NMR: $\delta=2.70$ (s, 3H, CH_3), 7.39 (m, 1H, C(5′)-H), 7.40 (m, 1H, C(7′)-H), 7.53 (d, $J=3.9$ Hz, 1H, C(4)-H), 7.73 (d, $J=3.9$ Hz, 1H, C(3)-H), 7.99 (m, Hz, 1H, C(4′)-H), 9.72 (s, 1H, CHO); ^{13}C NMR: $\delta=18.0$ (CH_3), 113.4 (C(4)), 119.9 (C(4′)), 124.3 (C(3)), 126.3 (C(7′)), 127.4 (C(5′)), 133.0 (C(6′)), 134.2 (C(3a′)), 151.6 (C(5)), 152.6 (C(7a′)), 152.8 (C(2)), 154.4 (C(2′)), 178.7 (CHO).



Scheme 4. *Reagents and conditions*: (*i*) P_2S_5/Py; (*ii*) Baker's yeast; (*iii*) $POCl_3$/DMF; (*iv*) $(CH_3)_3SiCN/CH_2Cl_2$; (*v*) Ac_2O (DMAP/Py)/CH_2Cl_2.

4.2.1.4. 5-(4-Chlorobenzothiazol-2-yl)furan-2-carbaldehyde 3d. Yield: 71%. Mp 207°C; HRMS M^+ found (M^+ calculated for $C_{12}H_6ClNO_2S$): 262.98111 (262.98078); MS: m/z (relative intensity) = 267 (2), 266 (5), 265 (37), 264 (20), 263 (100) [M^+], 262 (16), 237 (2), 236 (3), 235 (4), 234 (6), 209 (4), 208 (10), 207 (9), 206 (25), 182 (1), 181 (2), 180 (3), 179 (4), 174 (1), 172 (2), 171 (3), 144 (5), 142 (2); ^{1}H NMR: δ = 7.51 (dd, J = 8.0 Hz, J = 8.1 Hz, 1H, (C(6′)-H), 7.63 (d, J = 3.9 Hz, 1H, C(4)-H), 7.69 (dd, J = 1.0 Hz, J = 8.0 Hz, 1H, C(5′)-H), 7.75 (d, J = 3.9 Hz, 1H, C(3)-H), 8.19 (dd, J = 1.0, J = 8.1 Hz, Hz, 1H, C(7′)-H), 9.75 (s, 1H, CHO); ^{13}C NMR: δ = 114.2 (C(4)), 121.8 (C(7′)), 124.1 (C(3)), 127.0 (C(4′)), 127.1 (C(6′)), 127.2 (C(5′)), 136.0 (C(3a′)), 149.9 (C(7a′)), 151.0 (C(5)), 153.1 (C(2)), 156.8 (C(2′)), 178.9 (CHO).

4.2.2. Synthesis of racemic cyanohydrins 4a–d. To a stirred solution of one of the aldehydes (**3a**–**d**, 1 mmol) in dry dichloromethane (10 ml) a catalytic amount of ZnI_2 (3.2 mg, 10 μmol) and trimethylsilyl cyanide (119 mg, 150 μl, 1.2 mmol) were added dropwise at room temperature and the resulting mixture was stirred further at room temperature, until the entire quantity of the aldehyde was transformed. The dichloromethane was evaporated and the crude product was redissolved in 5 ml acetonitrile. The formed trimethylsilyl cyanohydrin was decomposed by adding 3 M HCl (100 μl). The solvent was evaporated and the resulted crude cyanohydrins were purified by recrystallization from ethyl acetate.

4.2.2.1. 5-(Benzothiazol-2-yl)furan-2-ylhydroxyacetonitrile *rac*-4a. Yield: 86%. Mp 139°C; HRMS M^+ found (M^+ calculated for $C_{13}H_8N_2O_2S$): 256.031143 (256.03065); MS: m/z (relative intensity) = 256 (2) [M^+], 239 (2), 231 (6), 230 (15), 229 (100), 228 (15), 227 (2), 202 (1), 201 (6), 200 (7), 174 (3), 173 (13), 172 (37), 147 (1), 146 (5), 145 (8), 140 (2), 128 (5); ^{1}H NMR: δ = 6.03 (d, J = 6.5 Hz, 1H, C(2)-CH(CN)OH), 6.85 (dd, J = 0.5 Hz, J = 3.7 Hz, 1H, C(3)-H)), 7.37 (d, J = 3.7 Hz, 1H, C(4)-H), 7.43 (d, J = 6.5 Hz, 1H, C(2)-CH(CN)OH), 7.47 (ddd, J = 1.2 Hz, J = 7.2 Hz, J = 8.2 Hz, 1H, C(5′)-H), 7.55 (ddd, J = 1.2 Hz, J = 7.2 Hz, J = 8.2 Hz, 1H, C(6′)-H), 8.04 (ddd, J = 0.6 Hz, J = 1.2 Hz, J = 8.2 Hz, 1H, C(7′)-H), 8.15 (ddd, J = 0.6 Hz, J = 1.2 Hz, J = 8.2 Hz, 1H, C(4′)-H); ^{13}C NMR: δ = 55.9 (CH(CN)OH), 111.9 (C(3)), 112.8 (C(4)), 118.1 (CH(CN)OH), 122.5 (C(4′)), 122.8 (C(7′)), 125.7 (C(5′)), 126.9 (C(6′)), 133.8 (C(3a′)), 148.5 (C(2)), 151.7 (C(5)), 153.2 (C(7a′)), 156.1 (C(2′)).

4.2.2.2. 5-(6-Chlorobenzothiazol-2-yl)furan-2-ylhydroxyacetonitrile *rac*-4b. Yield: 87%. Mp 197°C; HRMS M^+ found (M^+ calculated for $C_{13}H_7ClN_2O_2S$): 290.01025 (289.99167); MS: m/z (relative intensity) = 292 (1), 290 (3) [M^+], 273 (1), 267 (2), 266 (5), 265 (37), 264 (18), 263 (100), 262 (12), 237 (2), 236 (2), 235 (6), 234 (5), 209 (4), 208 (14), 207 (12), 206 (35), 182 (1), 181 (3), 180 (4), 179 (6), 174 (1), 172 (2), 171 (3), 144 (9), 142 (4); ^{1}H NMR: δ = 6.03 (d, J = 6.8 Hz, 1H, C(2)-CH(CN)OH), 6.86 (d, J = 0.5 Hz, J = 3.6 Hz, 1H, C(3)-H), 7.39 (d, J = 3.6 Hz, 1H, C(4)-H), 7.43 (d, J = 6.8 Hz, 1H, C(2)-CH(CN)OH), 7.58 (dd, J = 2.2 Hz, J = 8.8 Hz, 1H, C(5′)-H), 8.02 (d, J = 8.8 Hz, 1H, C(4′)-H), 8.30 (d, J = 2.2 Hz, 1H, C(7′)-H); ^{13}C NMR: δ = 55.9 (CH(CN)OH), 112.0 (C(3)), 113.3 (C(4)), 118.1 (CH(CN)OH), 122.1 (C(7′)), 123.9 (C(4′)), 127.3 (C(5′)), 130.1 (C(6′)), 135.3 (C(3a′)), 148.1 (C(2)), 152.0 (C(5)), 152.0 (C(7a′)), 157.0 (C(2′)).

4.2.2.3. 5-(6-Methylbenzothiazol-2-y)furan-2-ylhydroxyacetonitrile *rac*-4c. Yield: 87%. Mp 160°C; HRMS M^+ found (M^+ calculated for $C_{14}H_{10}N_2O_2S$): 270.04421 (270.04630); MS: m/z (relative intensity) = 270 (1) [M^+], 253 (1), 246 (1), 245 (6), 244 (16), 243 (100), 242 (14), 241 (2), 216 (1), 215 (3), 214 (10), 188 (1), 187 (4), 186 (17), 185 (3), 184 (1), 154 (4), 122 (4), 121 (15); ^{1}H NMR: δ = 2.69 (s, 3H, CH$_3$), 6.04 (d, J = 7.0 Hz, 1H, C(2)-CH(CN)OH), 6.84 (dd, J = 0.5 Hz, J = 3.6 Hz, 1H, C(3)-H), 7.34 (d, J = 3.6 Hz, 1H, C(4)-H), 7.35 (m, 1H, C(7′)-H), 7.36 (m, 1H, C(5′)-H), 7.42 (d, J = 7.0 Hz, 1H, C(2)-CH(CN)OH), 7.94 (m, 1H, C(4′)-H); ^{13}C NMR: δ = 18.0 (CH$_3$), 55.9 (CH(CN)OH), 111.9 (C(3)), 112.6 (C(4)), 118.2 (CH(CN)OH), 119.7 (C(4′)), 125.7 (C(7′)), 127.2 (C(5′)), 132.5 (C(6′)), 133.6 (C(3a′)), 148.6 (C(2)), 151.6 (C(5)), 152.5 (C(7a′)), 155.0 (C(2′)).

4.2.2.4. 5-(4-Chlorobenzothiazol-2-yl)furan-2-ylhydroxyacetonitrile *rac*-4d. Yield: 85%. Mp 191°C; HRMS M^+ found (M^+ calculated for $C_{13}H_7ClN_2O_2S$): 289.98334 (289.99167); MS: m/z (relative intensity) = 292 (1), 290 (3) [M^+], 273 (1), 267 (2), 266 (5), 265 (37), 264 (20), 263 (100), 262 (16), 237 (2), 236 (3), 235 (4), 234 (6), 209 (4), 208 (10), 207 (9), 206 (25), 182 (1), 181 (2), 180 (3), 179 (4), 174 (1), 172 (2), 171 (3), 144 (5), 142 (2); ^{1}H NMR: δ = 6.06 (d, J = 7.1 Hz, 1H, C(2)-CH(CN)OH), 6.87 (dd, J = 0.7 Hz, J = 3.7 Hz, 1H, C(3)-H)), 7.43 (d, J = 3.7 Hz, 1H, C(4)-H), 7.45 (dd, J = 7.9 Hz, J = 8.1 Hz, 1H, C(6′)-H), 7.46 (d, J = 7.1 Hz, 1H C(2)-CH(CN)OH), 7.64 (dd, J = 1.1 Hz, J = 7.9 Hz, 1H, C(5′)-H), 8.12 (dd, J = 1.1 Hz, J = 8.1 Hz, 1H, C(7′)-H); ^{13}C NMR: δ = 55.9 (CH(CN)OH), 112.0 (C(3)), 113.7 (C(4)), 118.1 (CH(CN)OH), 121.5 (C(7′)), 126.5 (C(6′)), 126.6 (C(4′)), 126.9 (C(5′)), 135.4 (C(3a′)), 148.0 (C(2)), 149.9 (C(7a′)), 152.2 (C(5)), 157.2 (C(2′)).

4.2.3. Chemical acylation of *rac*-4a–d with acetic anhydride. Acetic anhydride (79 mg, 81.8 μl, 0.5 mmol), a catalytic amount of 4-*N*,*N*-dimethylaminopyridine in pyridine (5 μl; 1% solution) and triethylamine (50.5 mg, 69.2 μl, 0.5 mmol) were added into the solution of one of the racemic cyanohydrins (*rac*-**4a**–**d**, 0.5 mmol) in dichloromethane (5 ml). After stirring for 15 min at room temperature the solvent was evaporated in *vacuum* and the crude product was purified by column chromatography using dichloromethane as an eluent. Finally the cyanohydrin esters *rac*-**2a**–**d** were recrystallized from diisopropyl ether.

4.2.3.1. 5-(Benzothiazol-2-yl)-furan-2-ylcyanomethyl acetate *rac*-2a. Yield: 67%. Mp 109°C; HRMS M^+ found (M^+ calculated for $C_{15}H_{10}N_2O_3S$): 298.041260 (298.041218); MS: m/z (relative intensity) = 300 (3), 299 (8), 298 (46) [M^+], 258 (5), 256 (87), 255 (62), 254 (2), 241 (6), 240 (18), 239 (100), 238 (8), 237 (10), 230 (3),

229 (5), 228 (10), 212 (6), 211 (19), 210 (29), 202 (2), 201 (4), 174 (4), 173 (6), 172 (12), 141 (1), 140 (6), 136 (6), 135 (6), 134 (11); ^{1}H NMR: $\delta=2.20$ (s, 3H, C(2)-CH(CN)OCOC$\underline{H}_3$), 6.99 (s, 1H, C(2)-C$\underline{H}$(CN)OCO-CH_3), 7.07 (d, $J=0.5$ Hz, $J=3.7$ Hz, 1H, C(3)-H), 7.43 (d, $J=3.7$ Hz, 1H, C(4)-H), 7.49 (ddd, $J=1.2$ Hz, $J=7.3$ Hz, $J=8.1$ Hz, 1H, C(5′)-H), 7.58 (ddd, $J=1.2$ Hz, $J=7.3$ Hz, $J=8.3$ Hz, 1H, C(6′)-H), 8.05 (ddd, $J=0.6$ Hz, $J=1.2$ Hz, $J=8.3$ Hz, 1H, C(7′)-H), 8.17 (ddd, $J=0.6$ Hz, $J=1.2$ Hz, $J=8.1$ Hz, 1H, C(4′)-H); ^{13}C NMR: $\delta=20.0$ (CH(CN)OCO$\underline{C}$H$_3$), 56.1 ($\underline{C}$H(CN)OCOCH$_3$), 112.9 (C(4)), 114.6 (CH($\underline{C}$N)-OCOCH$_3$), 115.4 (C(3)), 122.5 (C(4′)), 123.0 (C(7′)), 125.9 (C(5′)), 127.0 (C(6′)), 133.9 (C(3a′)), 146.3 (C(2)), 149.5 (C(5)), 153.1 (C(7a′)), 155.7 (C(2′)), 168.7 (CH(CN)O$\underline{C}$OCH$_3$).

4.2.3.2. 5-(6-Chlorobenzothiazol-2-yl)furan-2-ylcyanomethyl acetate *rac*-2b. Yield: 68%. Mp 151°C; HRMS M$^+$ found (M$^+$ calculated for $C_{15}H_9ClN_2O_3S$): 332.00296 (332.00224); MS: m/z (relative intensity)= 335 (2), 334 (16), 333 (7), 332 (43) [M$^+$], 294 (2), 293 (6), 292 (35), 291 (32), 290 (95), 289 (47), 288 (2), 276 (7), 275 (38), 274 (22), 273 (100), 272 (9), 264 (7), 263 (6), 262 (12), 247 (6), 246 (10), 245 (16), 244 (17), 238 (6), 237 (26), 210 (7), 209 (7), 208 (9), 207 (6), 206 (15); ^{1}H NMR: $\delta=2.20$ (s, 3H, C(2)-CH(CN)OCOC$\underline{H}_3$), 6.99 (s, 1H, C(2)-C$\underline{H}$(CN)OCOCH$_3$), 7.08 (d, $J=3.6$ Hz, 1H, C(3)-H), 7.45 (d, $J=3.6$ Hz, 1H, C(4)-H), 7.59 (dd, $J=2.1$ Hz, $J=8.8$ Hz, 1H, C(5′)-H), 8.05 (d, $J=8.8$ Hz, 1H, C(4′)-H), 8.32 (d, $J=2.1$ Hz, 1H, C(7′)-H); ^{13}C NMR: $\delta=20.0$ (CH(CN)OCO$\underline{C}$H$_3$), 56.1 ($\underline{C}$H(CN)OC-OCH$_3$), 113.4 (C(4)), 114.6 (CH($\underline{C}$N)OCOCH$_3$), 115.5 (C(3)), 122.2 (C(7′)), 124.1 (C(4′)), 127.4 (C(5′)), 130.3 (C(6′)), 135.4 (C(3a′)), 146.5 (C(2)), 149.1 (C(5)), 151.9 (C(7a′)), 156.6 (C(2′)), 168.7 (CH(CN)O$\underline{C}$OCH$_3$).

4.2.3.3. 5-(6-Methylbenzothiazol-2-yl)furan-2-ylcyanomethyl acetate *rac*-2c. Yield: 67%. Mp 125–126°C; HRMS M$^+$ found (M$^+$ calculated for $C_{16}H_{12}N_2O_3S$): 312.05621 (312.05686); MS: m/z (relative intensity)= 314 (3), 313 (8), 312 (44) [M$^+$], 272 (4), 271 (13), 270 (64), 269 (61), 255 (6), 254 (19), 253 (100), 252 (11), 251 (18), 226 (8), 225 (9), 224 (8), 223 (11), 188 (3), 187 (4), 186 (10), 185 (4), 150 (3), 149 (3), 148 (7); ^{1}H NMR: $\delta=2.20$ (s, 3H, C(2)-CH(CN)OCOC$\underline{H}_3$), 2.69 (s, 3H, C(6′)-C$\underline{H}_3$), 7.00 (s, 1H, C(2)-C$\underline{H}$(CN)OCOCH$_3$), 7.07 (dd, $J=0.4$ Hz, $J=3.6$ Hz, 1H, C(3)-H), 7.36 (m, 1H, C(5′)-H), 7.37 (m, 1H, C(7′)-H), 7.40 (d, $J=3.6$ Hz, 1H, C(4)-H), 7.96 (m, 1H, C(4′)-H); ^{13}C NMR: $\delta=18.0$ (C(6′)-$\underline{C}$H$_3$), 20.1 (CH(CN)OCO$\underline{C}$H$_3$), 56.1 ($\underline{C}$H(CN)-OCOCH$_3$), 112.6 (C(4)), 114.7 (CH($\underline{C}$N)OCOCH$_3$), 115.5 (C(3)), 119.8 (C(4′)), 125.9 (C(7′)), 127.2 (C(5′)), 132.7 (C(6′)), 133.7 (C(3a′)), 146.1 (C(2)), 149.7 (C(5)), 152.5 (C(7a′)), 154.6 (C(2′)), 168.8 (CH(CN)O$\underline{C}$OCH$_3$).

4.2.3.4. 5-(4-Chlorobenzothiazol-2-yl)-furan-2-ylcyanomethyl acetate *rac*-2d. Yield: 70%. Mp 129°C; HRMS M$^+$ found (M$^+$ calculated for $C_{15}H_9ClN_2O_3S$): 332.00247 (332.00224); MS: m/z (relative intensity)= 335 (2), 334 (13), 333 (6), 332 (34) [M$^+$], 294 (2), 293 (6), 292 (37), 291 (32), 290 (100), 289 (45), 288 (2), 276 (5), 275 (27), 274 (13), 273 (71), 272 (2), 264 (7), 263 (5), 262 (11), 247 (5), 246 (5), 245 (13), 244 (9), 238 (8), 237 (40), 210 (6), 209 (9), 208 (8), 207 (6), 206 (13); ^{1}H NMR: $\delta=2.20$ (s, 3H, C(2)-CH(CN)OCOC$\underline{H}_3$), 7.01 (s, 1H, C(2)-C$\underline{H}$(CN)OCOCH$_3$), 7.09 (dd, $J=0.4$ Hz, $J=3.5$ Hz, 1H, C(3)-H), 7.48 (dd, $J=8.0$ Hz, $J=8.1$ Hz, 1H, C(6′)-H), 7.50 (d, $J=3.5$ Hz, 1H, C(4)-H), 7.67 (dd, $J=1.1$ Hz, $J=8.0$ Hz, 1H, C(5′)-H), 8.15 (dd, $J=1.1$ Hz, $J=8.1$ Hz, 1H, C(7′)-H); ^{13}C NMR: $\delta=20.1$ (CH(CN)OCO$\underline{C}$H$_3$), 56.1 ($\underline{C}$H(CN)OCOCH$_3$), 113.8 (C(4)), 114.6 (CH($\underline{C}$N)OCOCH$_3$), 115.6 (C(3)), 121.6 (C(7′)), 126.7 (C(4′)), 126.8 (C(6′)), 127.0 (C(5′)), 135.5 (C(3a′)), 146.7 (C(2)), 149.1 (C(5)), 149.9 (C(7a′)), 156.9 (C(2′)), 168.8 (CH(CN)O$\underline{C}$OCH$_3$).

4.3. Kinetic resolution of racemic cyanohydrins *rac*-4a–d

In a typical small scale experiment, one of the cyanohydrins **4a–d** (13 mol) and vinyl acetate (3.4 mg, 3.6 l, 40 mol) were dissolved in dry organic solvent (1 ml). CAL-A preparation (10 mg, corresponding to 1 mg of the enzyme) was added. Samples (20 l) were taken after 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168 h and diluted with the same solvent (80 l) as the mobile phase for HPLC (Table 2).

4.4. One-pot synthesis of cyanohydrin esters (*R*)-(+)-3a–d

One of the aldehydes **3a–d** (65 mol), acetone cyanohydrin (17 mg, 18 l, 200 mol) and vinyl acetate (17 mg, 18 l, 200 mol) were added in dry acetonitrile (5 ml). To this solution Amberlite IRA 904 ($^-$OH form, 5 mg (0.0065 mmol $^-$OH) ml^{-1}) and immobilised CAL-A (10 mg ml^{-1}) were added. The reaction mixture was stirred at room temperature for 48–72 h. The enzyme and the resin were filtered off and washed with acetonitrile (2×5 ml). Solvents were distilled off from the filtrate and the residue was purified by column chromatography on silica gel with dichloromethane yielding (*R*)-(+)-**2a–d** (Table 3).

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