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Bicyclo[3.2.0]hept-2-en-6-one cyanohydrins: preparations by chemical hydrocyanation, and enantio- and diastereoselective biotransformation by the hydroxynitrile lyase from *Prunus amygdalus* in the form of almond meal

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Abstract

The first enantioselective enzyme-catalyzed addition of the elements of hydrogen cyanide to a complex ketone, namely bicyclo[3.2.0]hept-2-en-6-one **4**, provides access to a valuable single enantiomer of a bicyclic ketone. The preparation of cyanohydrins from bicyclic ketones **1–4** is documented. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: cyanohydrins; enzymes; enzyme reactions; bicyclic aliphatic compounds; cyclobutanones.

Cycloaddition of dichloroketene and cyclopentadiene furnishes 7,7-dichlorobicyclo[3.2.0]hept-2-en-6-one **1**.[1–5] Hydrodechlorination of this ketone affords the 7-*endo*-chloroketone **2**[6,7] which may be equilibrated to the 7-*exo*-chloro compound **3**.[7] Dihydrodechlorination of ketone **1** gives ketone **4**.[7–9] The hydrocyanation of ketones **1–4**, in the presence and absence of a hydroxynitrile lyase, is reported below.

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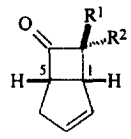

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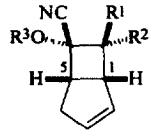
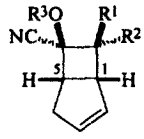
3 $R^1 = Cl$; $R^2 = H$
4 $R^1 = R^2 = H$





5 $R^1 = R^2 = Cl$; $R^3 = H$
6 $R^1 = R^3 = H$; $R^2 = Cl$
7 $R^1 = Cl$; $R^2 = R^3 = H$
8 $R^1 = R^2 = R^3 = H$
9 $R^1 = Cl$; $R^2 = H$; $R^3 = COCH_3$
10 $R^1 = R^2 = H$; $R^3 = COCH_3$

11
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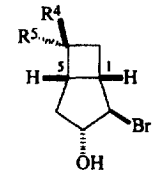
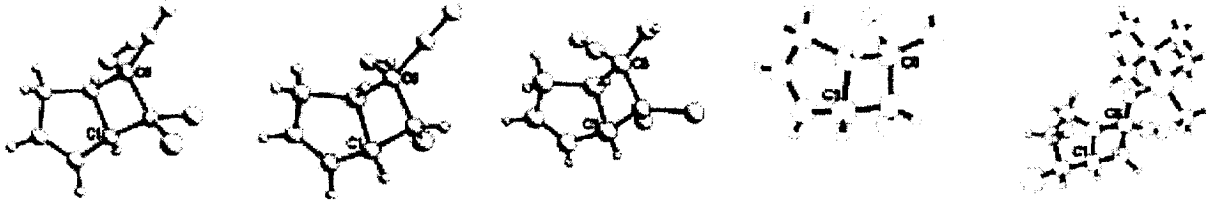


17 $R^4 = CN$; $R^5 = OTBS$

18 R^4, $R^5 = O$

1. Chemical hydrocyanation and stereochemistry elucidation

Treatment of dichloroketone **1** with potassium cyanide in aqueous acetic acid gave two cyanohydrins **5** (35%) and **11** (60%). The stereochemical assignment at C-6 was elucidated by X-ray analysis (Fig. 1).



5 **6** **11** **12** **17**

Figure 1. Crystal structures of cyanohydrins **5**, **6**, **11** and **12**, and derivative **17**

The major product obtained on chemical hydrocyanation of monochloroketone **2** was temperature-dependant. Reaction of ketone **2** with potassium cyanide in aqueous acetic acid at 20°C furnished only cyanohydrin **6** (69%): running the same reaction at 60°C favoured formation of diastereoisomer **12** (69%) with cyanohydrins **6**, **7** and **13** as minor products. The hypothesis that cyanohydrin **12** was the thermodynamically most stable product of a series of equilibria was tested by heating cyanohydrin **6** to 60°C in $KCN/H_2O/CH_3CO_2H$; NMR analysis clearly showed the presence of cyanohydrins **6** (4%), **7** (6%), **12** (84%) and **13** (5%). The stereochemistry of cyanohydrins **6** and **12** was established by X-ray crystallography (Fig. 1).

The ketones **3** and **4** reacted with KCN in aqueous acetic acid at room temperature to give the corresponding cyanohydrins **7**:**13** and **8**:**14** in the ratio 2:3 and approximately 2:1, respectively. All four cyanohydrins **7**, **8**, **13** and **14** were converted into the corresponding acetates **9**, **10**, **15** and **16**. In addition, cyanohydrin **8** was protected as the *tert*-butyldimethylsilyl (TBS) ether and then reacted with 1,3-dibromo-5,5-dimethylhydantoin (bromodan) in aqueous acetone to afford crystalline bromohydrin **17** which was subjected to X-ray crystallography (Fig. 1).

The stereochemistry of the remainder of the series was defined by ^1H NMR spectroscopy. Thus, the chemical shifts of the 7-*exo*-chloro compounds **7**, **9**, **13** and **15** followed the patterns established by the 7-dihydro compounds **8**, **10**, **14** and **16** with respect to the effects on the change of OH to $OCOCH_3$ and of the inversion of C-6 configuration. For example, the signal due to 7-*endo*-H was observed at higher

field for compound **9** (δ 3.98) than for stereoisomer **15** (δ 4.55). Almost exactly the same effect was observed for the analogous pair of cyanohydrins **10** and **16** (Δδ 0.52), the relative stereochemistry of which had been established.

2. Biotransformations

The employment of hydroxynitrile lyases (HNLs) for the preparation of optically active cyanohydrins is well known.[10–12] The utilization of meal from almonds (*Prunus amygdalus*) is popular methodology[13–16] since the meal is readily available, cheap, simple to use and contains large amounts of an HNL which accepts a large range of aldehydic substrates. Whilst biotransformations of methyl ketones have been successful,[17–19] only poor results have been obtained with ethyl ketones,[18] and there have been no reports of biotransformations of structurally more complex ketones. Furthermore, although the influence on HNL selectivity of stereocentres already present in substituted aldehydes has been addressed,[20] there have been no reports of effective resolutions of carbonyl compounds by this method.

Hence we were pleased to find that racemic bicycloheptenone (±)-**4** was transformed by almond meal in a biphasic system consisting of diisopropyl ether, aqueous buffer and acetone cyanohydrin over 5 days to give cyanohydrin (+)-(1*S*,5*S*)-**8** (26% conversion). In the absence of almond meal no cyanohydrin was observed. The absolute stereochemistry was established by two independent routes. Firstly, treatment of the cyanohydrin (+)-**8** with bromodan in aqueous acetone gave ketone (+)-**18**, a compound documented previously.[21] Secondly, (1*S*,5*S*)-bicyclo[3.2.0]hept-2-en-6-one (+)-**4** was found to be biotransformed more rapidly than the (1*R*,5*R*)-enantiomer (−)-**4** (41% versus 6% conversion after 3 days): single enantiomers of ketone **4** are available by fractional crystallization of amine bisulphite salts.[22]

The enantiomeric excess of cyanohydrin (+)-**8** was determined by ^{1}H NMR spectroscopy using (*R*)-*tert*-butyl-phenyl-phosphinothioic acid, a chiral solvating agent established for the analysis of chiral alcohols, amines and thiols.[23] This represents, to the best of our knowledge, the first effective method of enantiomeric excess determination for unprotected cyanohydrins apart from sparse examples using Eu(hfc)$_3$.[24,25] Using this methodology the enantiomeric excess was judged to be 85% and chiral GC (Lipodex D) confirmed this result.

In parallel experiments almond meal did not catalyze the formation of cyanohydrin from ketone **1**: in a control experiment, the background reaction was found to be relatively fast. In contrast ketone **3** was biocatalytically converted to cyanohydrins **7** and **13** (ratio 1:3) in 93% yield after 5 days, with no background reaction: disappointingly the major product was racemic and the minor product exhibited only 26% ee by the ^{1}H NMR method. Similarly ketone **2** was converted to cyanohydrin **6**: stopping the reaction at 25% conversion ensured no background reaction but nevertheless yielded racemic cyanohydrin.

These experiments demonstrate that the bicycloheptenone (+)-**4** is the first complex ketone to undergo biotransformation with the hydroxynitrile lyase from almond meal. It is probable that the compact nature and the reactivity of the strained cyclobutanone ring assists the biocatalytic process. Cyanohydrin (+)-**8** may be converted in one-step either to ketone (+)-**4** or ketone (+)-**18**,[26] useful building blocks for prostaglandins and other chemicals.[22,27,28]

3. Experimental

3.1. Typical procedure for chemical hydrocyanation

To a stirred solution of racemic ketone **4** (4.20 g, 38.8 mmol) in acetic acid (19 ml) was added dropwise a solution of potassium cyanide (5.72 g, 0.117 mmol) (caution) in water (19 ml). After stirring for 70 h at room temperature, the mixture was extracted into ether (3×40 ml). The ethereal layer was dried with magnesium sulphate and the solvent removed in vacuo. Purification by flash column chromatography using 15% ethyl acetate in hexane as eluent yielded two diastereomeric oils (4.88 g, 93%) in a ratio of 69:31 respectively; firstly 6-*endo*-hydroxy-bicyclo[3.2.0]hept-2-ene-6-carbonitrile **8** was obtained as a colourless oil; R_f (*p*-anisaldehyde or $KMnO_4$) (15% ethyl acetate in hexane) 0.23; ν_{max}/cm^{-1} (film) 3417s (O-H), 3057m, 2943s and 2851m (C-H), 2237w (C≡N); δ_H (400 MHz, $CDCl_3$) 5.90–5.87 (1H, m, 3-H), 5.85–5.81 (1H, m, 2-H), 3.53–3.46 (1H, ddddd appears as ddbq, $J_{5,4\text{-}exo}$ 9.1, $J_{5,1}$ 7.5, $J_{5,4\text{-}endo} \approx J_{5,7\text{-}exo} \approx J_{5,7\text{-}endo} \approx 1.6$, 5-H), 3.32–3.24 (1H, m, 1-H), 3.10–3.03 (1H, ddd, $J_{7\text{-}exo,7\text{-}endo}$ 13.4. $J_{7\text{-}exo,1}$ 8.3, $J_{7\text{-}exo,5}$ 1.6, 7-*exo*-H), 2.82–2.74 (1H, ddddd appears as ddq, $J_{4\text{-}endo,4\text{-}exo}$ 17.8, $J_{4\text{-}endo,3}$ 3.0, $J_{4\text{-}endo,1} \approx J_{4\text{-}endo,2} \approx J_{4\text{-}endo,5} \approx 1.9$, 4-*endo*-H), 2.57–2.48 (1H, ddddd appears as ddq, $J_{4\text{-}exo,4\text{-}endo}$ 17.8, $J_{4\text{-}exo,5}$ 9.1, $J_{4\text{-}exo,1} \approx J_{4\text{-}exo,2} \approx J_{4\text{-}exo,3} \approx 1.9$, 4-*exo*-H), 2.49 (1H, s, OH), 2.08–2.02 (1H, ddd, $J_{7\text{-}endo,7\text{-}exo}$ 13.4, $J_{7\text{-}endo,1}$ 4.0, $J_{7\text{-}endo,5}$ 1.2, 7-*endo*-H); δ_C (100 MHz, $CDCl_3$) 133.76 and 132.93 (CH, C-2 and C-3), 121.94 (CN), 65.92 (C, C-6), 46.66 (CH, C-1 or C-5), 43.10 (CH_2, C-4 or C-7), 39.94 (CH, C-1 or C-5), 32.04 (CH_2, C-4 or C-7); *m/z* (EI) 135 (M^+, 3%), 120 (3), 106 (4), 95 (4), 79 (13), 66 (100), 57 (20); C_8H_9NO (M^+) requires: 135.068414, found: 135.06890 (+3.6 ppm); elemental analysis found (requires)/%: C 71.40 (71.09), H 6.75 (6.71), N 10.32 (10.36); secondly 6-*exo*-hydroxy-bicyclo[3.2.0]hept-2-ene-6-carbonitrile **14** was isolated as a colourless oil; R_f ($KMnO_4$) (15% ethyl acetate in hexane) 0.17; ν_{max}/cm^{-1} (film) 3416s (O-H), 3058m, 2942s and 2851m (C-H) 2239m (C≡N); δ_H (400 MHz, $CDCl_3$) 5.88–5.84 (1H, m, 3-H), 5.84–5.80 (1H, m, 2-H), 3.34–3.26 (1H, m, 1-H), 3.10–3.05 (1H, m, 5-H), 2.79–2.66 (3H, m, 4-*exo*-H, 4-*endo*-H and OH), 2.63–2.58 (1H, ddd, $J_{7\text{-}exo,7\text{-}endo}$ 13, $J_{7\text{-}exo,1}$ 8.5, $J_{7\text{-}exo,5}$ 1, 7-*exo*-H), 2.57–2.50 (1H, ddd, $J_{7\text{-}endo,7\text{-}exo}$ 13, $J_{7\text{-}endo,1}$ 4, $J_{7\text{-}endo,5}$ 1, 7-*endo*-H); δ_C (100 MHz, $CDCl_3$) 133.07 and 131.95 (CH, C-2 and C-3), 120.09 (CN), 70.91 (C, C-6), 48.95 (CH, C-1 or C-5), 42.50 (CH_2, C-4 or C-7), 38.65 (CH, C-1 or C-5), 36.68 (CH_2, C-4 or C-7); *m/z* (EI) 135 (M^+, 31%), 120 (43), 106 (50), 92 (27), 79 (69), 66 (100), 53 (53); C_8H_9NO (M^+) requires: 135.068414, found: 135.06890 (+3.5 ppm); elemental analysis found (requires)/%: C 70.93 (71.09), H 6.74 (6.71), N 10.34 (10.36).

3.2. Typical biotransformation procedure

To a ketone (5 mmol) was added almond meal (0.75 g) which had been pre-swollen with a buffer solution of disodium hydrogencitrate (1.1 ml, 0.02 M, pH 5.5) for 15 minutes, diisopropyl ether (10.4 ml) and acetone cyanohydrin (0.593 ml, 6.5 mmol) (caution), and the reaction mixture stirred at room temperature in a sealed flask under constant pressure. The reaction mixture was filtered, the residue further eluted with ether (20 ml), and the filtrate was concentrated in vacuo and purified by flash column chromatography. Data for (+)-**8**: 85% ee (by ^1H NMR spectroscopy using (*R*)-*tert*-butyl-phenyl-phosphinothioic acid as chiral solvating agent); >95% de (cyanohydrin **14** not observed); $[\alpha]_D^{22}$ (*c* 3.00, methanol) +27.3.

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