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BIO-ORGANIC SYNTHESIS OF OPTICALLY ACTIVE CYANOHYDRINS AND ACYLOINS

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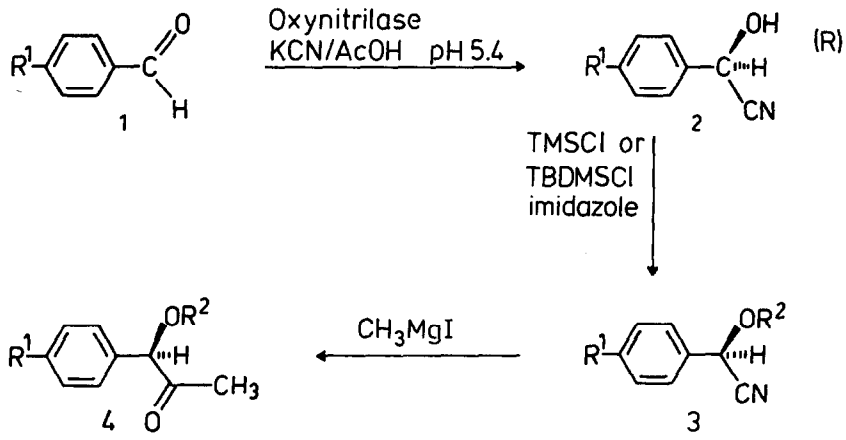
Abstract: Chiral acyloins of high optical purity have been obtained in good yields by enzyme catalyzed formation of optically active cyanohydrins, followed by hydroxyl protection and reaction with a Grignard reagent.

Cyanohydrins are expedient starting materials for the preparation of several important classes of compounds such as α-hydroxyacids, α-hydroxyketones (acyloins), and β-aminoalcohols, which play a vital role in organic synthesis[1]. The simplest method to prepare cyanohydrins or O-protected cyanohydrins consists of the addition of hydrogen cyanide or trimethylsilylcyanide to an aldehyde or ketone[2-5]. Optically active cyanohydrins can be obtained with the aid of chiral catalysts, e.g.: titanium(IV) alkoxides[6], boryl compounds[7], synthetic dipeptides[8-10], and the enzyme oxynitrilase[11,12] (E.C. 4.1.2.10). These catalysts have to be synthesized from optically active compounds or, in the case of oxynitrilase, the enzyme has to be isolated and purified[13,14]. Very few optically active O-protected cyanohydrins have thus far been described in literature[15]. We now report a simple procedure for the preparation of multigram quantities of *(R)*-(+)-benzaldehydecyanohydrin (**2a**) and *(R)*-(+)-4-methoxybenzaldehydecyanohydrin[16] (**2b**), using the enzyme oxynitrilase as present in a crude extract of almond flour, and conversion of these cyanohydrins into chiral acyloins, after safeguarding the chiral centre by silylation of the hydroxyl group.

Optically active cyanohydrins: Extracts from small portions (40-80 g) of ground defatted almonds are used without additional purification for the conversion of 30-50 g of aldehyde. In the case of benzaldehyde (**1a**), a 95% conversion is attained after a total reaction time of 40 min at 0°C. Using a diastereomeric shift reagent, the optical purity of the reaction product was determined by NMR to be at least 98%.

The reaction of 4-methoxybenzaldehyde (**1b**) with hydrogen cyanide at pH 5.4 is much slower, both with or without biocatalysis. Optimal conditions were found at a conversion of 85% and an e.e. of 78% after 20 h reaction time. Nearly optically pure (e.e. 99%) 4-methoxybenzaldehydecyanohydrin (**2b**) could be obtained from this mixture in good yield (65.5%) by a single crystallization. The mother liquor showed no remaining optical activity. Thus, it may be concluded that enantiomerically pure cyanohydrins can be obtained rapidly and in sizable quantities by this simple procedure. Another advantage of the present process lies in the use of a potassium cyanide/acetic acid buffer rather than free hydrogen cyanide.



	R1	R2
1a.	H	-
1b.	OCH3	-
2a.	H	-
2b.	OCH3	-
3a.	H	TMS
3b.	OCH3	TMS
3c.	H	TBDMS
3d.	OCH3	TBDMS

	R1	R2
4a.	H	H
4b.	OCH3	H
4c.	H	TBDMS
4d.	OCH3	TBDMS

TMS: trimethylsilyl
TBDMS: *t*-butyldimethylsilyl

Optically active hydroxy-protected cyanohydrins: Silylation of the hydroxyl function was found to proceed with little or no racemization and in excellent yields (90-100%) by using trimethylsilylchloride or *t*-butyldimethylsilylchloride in the presence of imidazole. Attempts to establish the enantiomeric excess directly remained unsuccessful. However, after conversion of the silylated cyanohydrins into the corresponding acyloins (**4**) (see below), the e.e. before purification was shown by NMR analysis to be more than 92%.

Optically active α-hydroxyketones: Grignard reactions on unprotected cyanohydrins require a large excess of Grignard reagent and in general give poor yields [17,18]. Next to these complications, substantial racemization may occur[19]. We could circumvent these problems by protecting the hydroxyl function, thereby also fixing the chiral centre, before carrying out reactions on the nitrile group. Trimethylsilyl ethers are usually stable under Grignard conditions, but hydrolysis readily occurs during work-up. If protected α-hydroxyketones are desired, use of a more acid-stable substituent such as *t*-butyldimethylsilyl is indicated. In this way we succeeded in preparing both protected (**4c,d**) and unprotected (**4a,b**) optically active α-hydroxyketones in good yields and with high e.e.'s. The crude protected acyloins had a chemical purity of about 85% (GLC, NMR). The optical purity was determined by NMR to be between 92% and 99% e.e. After flash chromatography, the chemically pure silylated acyloins were obtained in 80% yield. Although the e.e.'s did not change, this purification caused a dramatic increase in the optical rotation (e.g. for **4d**

from 39° to 61°). As it turned out, the unprotected acyloin (**4b**) showed a large negative optical rotation(-343°). As a consequence, traces of unprotected acyloin in the crude product strongly influence the optical rotation.

The optically active O-protected α-hydroxyketones described here form excellent starting materials for the synthesis of a range of compounds with a second, neighbouring, chiral center, such as 1,2-diols and β-aminoalcohols. Such conversions are presently being studied and will be reported separately.

Experimental:

^{1}H NMR spectra were recorded on a JEOL PS-100 or, in the case of e.e. determinations, on a JEOL FX-200 and a Bruker AM-400 instrument. Samples were measured in CDCl3. The optical purity of the cyanohydrins was determined with the aid of tris-[3-(heptafluoropropylhydroxymethylene)-d-camphorato] europium III [Eu(hfc)3]. Under optimized conditions at 400 MHz, racemic **2a** gave two signals with baseline separation for the benzylic proton. E.e's of the (protected) α-hydroxyketones were determined by preparing diastereomeric hydrazones with (*S*)-(-)-1-amino-2-(*t*-butyldimethylsilyloxymethyl)-pyrrolidon (SASP). To samples, dissolved in CDCl3, one equivalent of SASP and mol. sieves were added. After 4 h at 60°C, the samples were filtered and measured at 200 MHz. The e.e. of optically active acyloins was determined by integration of the benzylic proton signals. These values were confirmed by measurements at 400 MHz, using (-)-2,2,2-trifluoro-1-(9-anthryl)-ethanol as a chiral cosolvent. Optical rotations were measured with a Perkin Elmer 141 polarimeter.

Oxynitrilase extract. The brown skin of sweet almonds was stripped easily after immersing the seeds in hot water (80°C). Grinding, defatting with ether, and drying gave a flour which retained its activity for at least several months when stored under nitrogen at 0°C. 70 g Of the almond flour thus obtained was mixed with 500 mL of water and the pH was adjusted to 7.4 with 1N NH4OH. After standing overnight the mixture was centrifugated (3500 rpm, 5 min.) and the supernatant (225 mL) was adjusted to pH 5.4 with 50% AcOH. The precipitate of accompanying proteins was subsequently removed by centrifugation. The pale yellow extract was used without further purification.

(R)-(+)-α-Hydroxybenzeneacetonitrile (2a). To a solution of **1a** (35 g, 0.33 Mol) in 150 mL of EtOH was added, under argon, 170 mL of the enzyme extract and the mixture was cooled to 0°C. 400 mL of a 1N KCN/HOAc buffer (pH 5.4) was mixed with 150 mL of EtOH, cooled to 0°C, and added dropwise to the magnetically stirred mixture in 20 min. After stirring for another 20 min, the reaction mixture was extracted with ether (3x300 mL). The combined organic layers were washed with 10% NaCl (3x30 mL). Drying and evaporation under reduced pressure afforded 43 g (98%) of colorless oil which crystallized upon standing at -5°C. $[\alpha]_D^{20}$ of the crude product: + 40° (c=1, CHCl3). Lit. (13) + 49° (c=5, CHCl3). NMR analysis showed 94% cyanohydrin, 4% benzaldehyde and traces of EtOH and AcOH. The amount of *S*-enantiomer in the crude product was less than 1%.

(R)-(+)-α-Hydroxy-4-methoxybenzeneacetonitrile (2b). To a solution of 45 g (0.33 Mol) of 4-methoxybenzaldehyde in 160 mL of ethanol was added, under argon, 225 mL of the enzyme extract. The mixture was cooled to 0°C and 400 mL of a 1N KCN/HAc buffer, mixed with 160 mL of ethanol and cooled to 0°C, was added dropwise in 10 h with the aid of a peristaltic pump. After stirring for another 10 h, the mixture was worked up as described for (**2a**). The resulting white solid (52.2 g) consisted of a mixture of **2b** (85%, e.e. 78%) and **1b**. This mixture was dissolved in 110 mL of methylene chloride under gentle warming. Light petroleum 40-60 (90 mL) was slowly added. After cooling to 4°C the resulting crystals were filtered. Yield 35.3 g (65.5%). Mp 79-81°C. $[\alpha]_D^{20}$ +49° (c=1, CHCl3). NMR: δ(ppm) 3.76 (s, 3H, OMe); 4.50 (s, 1H, OH); 5.38 (s, 1H, CH); 6.86 (d, 2H, arom); 7.35 (d, 2H, arom). E.e. ≥99%.

(R)-(+)-α-[(Trimethylsilyl)oxy]-benzeneacetonitrile (3a). A solution of 4.2 g imidazole (60 mMol) in 75 mL of dry DMF was cooled to 0°C and 4.9 g trimethylsilylchloride (45 mMol) was added. After stirring for 15 min, 4 g **2a** (30 mMol) was added and the resulting mixture was stirred for 1 h at room temperature, poured into 150 mL of water, and extracted with ether. Work-up gave 6.1 g (99%) of a pale yellow oil. $[\alpha]_D^{20}$ +25° (c=1, CHCl3). NMR: δ(ppm) 0.03 (s, 9H, Me3-Si); 5.25 (s, 1H, CH); 7.16 (m, 5H, arom). Chemical purity: 90% (NMR, GLC).

(R)-(+)-α-[(Trimethylsilyl)oxy]-4-methoxybenzeneacetonitrile (3b). Procedure as for 3c. NMR: δ(ppm) 0.16 (s, 9H, Me3-Si); 3.75 (s, 3H, OMe); 5.36 (s, 1H, CH); 6.84 (d, 2H, arom); 7.31 (d, 2H, arom). Chemical purity: 96% (NMR, GLC). $[\alpha]_D^{20}$ +22° (c=1, $CHCl_3$).

(R)-(+)-α-[(t-Butyldimethylsilyl)oxy]-benzeneacetonitrile (3c). This compound was prepared similarly to 3a, using *t*-butyldimethylsilylchloride. Yield: 99% of pale yellow oil. NMR: δ(ppm) 0.02 (s, 3H, Me-Si); 0.10 (s, 3H, Me-Si); 0.84 (s, 9H, *t*-Bu-Si); 5.38 (s, 1H, CH); 7.28 (m, 5H, arom). Chemical purity: 95% (NMR, GLC). $[\alpha]_D^{20}$ +16° (c=1, $CHCl_3$).

(R)-(+)-α-[(t-Butyldimethylsilyl)oxy-4-methoxybenzeneacetonitrile (3d). Procedure as for 3a. NMR: δ(ppm) 0.09 (s, 3H, Me-Si); 0.17 (s, 3H, Me-Si); 0.90 (s, 9H, *t*-Bu-Si); 3.75 (s, 3H MeO); 5.36 (s, 1H, CH); 6.83 (d, 2H, arom); 7.29 (d, 2H, arom). Chemical purity: 98% (NMR, GLC). M.p.-2°C. $[\alpha]_D^{20}$ +15° (c=1, $CHCl_3$).

(R)-(-)-1-Hydroxy-1-phenyl-2-propanone (4a). To a solution of 9.6 g CH_3MgI (58 mMol) in 150 mL of ether was added dropwise a solution of 6.0 g 3a (29 mMol) in 50 mL of ether. The mixture was stirred and refluxed for 4 h, cooled and poored onto 120 g of ice, containing 5 mL of conc. H_2SO_4. After stirring for 8 h the layers were separated and the water layer extracted twice with 40 mL of ether. Work-up afforded 3.1 g (71 %) of 4a. NMR: δ(ppm) 2.07 (s, 3H, Me); 4.30 (s, 1H, OH); 5,09 (s, 1H, CH); 7.34 (m, 5H, arom). $[\alpha]_D^{20}$ -393° (c=1, $CHCl_3$). E.e. 95 %.

(R)-(-)-1-Hydroxy-1-(4-methoxyphenyl)-2-propanone (4b). Prepared from 3b (1.5 g; 6.4 mMol) by the same procedure described for 4a. Work-up afforded 0.9 g (78%) of 4b. NMR: δ(ppm) 2.01 (s, 3H, Me); 3.73 (s, 3H MeO); 4.30 (s, 1H, OH); 4.96 (s, 1H, CH); 6.82 (d, 2H, arom); 7.15 (d, 2H, arom). $[\alpha]_D^{20}$ -343° (c=1, $CHCl_3$). E.e. 96 %.

(R)-(+)-1-[(t-Butyldimethylsilyl)oxy]-1-phenyl-2-propanone (4c). Prepared from 3c as described for 4a, with the exception that the acidified water layer is extracted directly. Yield: 96% of colorless oil. Chemical purity 84% (GLC, NMR). E.e. 92%. $[\alpha]_D^{20}$ +39° (c=1, $CHCl_3$). Flash chromatography (CH_2Cl_2/MeOH, 95:5) afforded a chemically pure product in 80% yield. E.e. 92%. $[\alpha]_D^{20}$ +61° (c=1, $CHCl_3$). NMR: δ(ppm) -0.13 (s, 3H, Me-Si); -0.04 (s, 3H, Me-Si); 0.85 (s, 9H, *t*-Bu-Si); 1.99 (s, 3H, Me); 4.93 (s, 1H, CH); 7.23 (m, 5H, arom).

(R)-(+)-1-[(t-Butyldimethylsilyl)oxy]-1-(4-methoxyphenyl)-2-propanone (4d). Procedure as for 4c. Yield 92%, chemical purity 86% (GLC, NMR). E.e. 99%. $[\alpha]_D^{20}$ +45° (c=1, $CHCl_3$). Flash chromatography afforded a chemically pure product in 80% yield. $[\alpha]_D^{20}$ +60° (c=1, $CHCl_3$). NMR: δ(ppm) -0.05 (s, 3H, Me-Si); 0.04 (s, 3H, Me-Si); 0.88 (s, 9H, *t*-Bu-Si); 2.06 (s, 3H, Me); 3.72 (s, 3H, MeO); 4.91 (s, 1H, CH); 6.80 (d, 2H, arom); 7.26 (d, 2H, arom).

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