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Asymmetric Synthesis of Tetronic Acids by Blaise Reaction of Protected Optically Active Cyanohydrins

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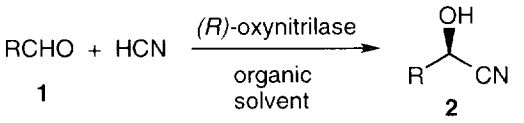
Abstract: An asymmetric synthesis of tetronic acids is described, involving the Blaise reaction of Reformatsky reagents with silyl-protected optically active cyanohydrins, which were prepared by an enzyme-catalysed method. Copyright © 1996 Elsevier Science Ltd

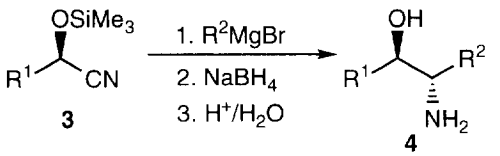
The asymmetric enzyme-catalysed synthesis of cyanohydrins from aldehydes **1** and hydrogen cyanide has received much attention in recent years.[1] The *(R)*-cyanohydrins **2** can be prepared using *(R)*-oxynitrilase, which is readily available from almonds (Scheme 1), and the *(S)*-enantiomers are also accessible using the *(S)*-oxynitrilase from *Sorghum bicolor*. The *(R)*-oxynitrilase from almonds accepts a wide variation in the structure of the aldehyde; however it has only recently become a practical synthetic method. This is as a result of the the use of organic solvents, in which high enantioselectivities areachieved.[1] Previously, water or water-ethanol mixtures were used, in which the competing chemical reaction results in low enantioselectivities. Immobilising the enzyme on an insoluble support also has advantages of ease of product isolation when working in organic solvents.[2]



Scheme 1

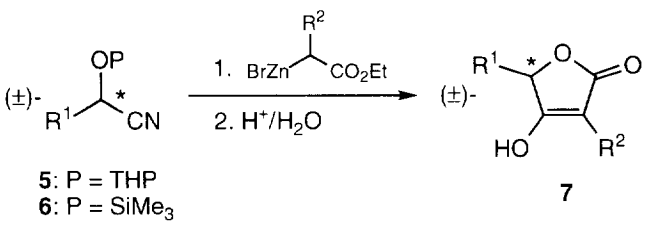
The *(R)*-cyanohydrins **2** obtained in this way have been used as intermediates for the preparation of a variety of compounds, particularly α-hydroxycarboxylic acids and 2-amino alcohols.[1] Generally, the nitrile is simply subjected to a functional group transformation, and so the final product has little more structural complexity than that of the intermediate cyanohydrin. Also, in this approach the cyanohydrin is necessarily formed by the reaction of a one-carbon nucleophile (cyanide), and so again, there is only a small increase in structural complexity over that of the starting material aldehyde. An attractive way to elaborate the cyanohydrins therefore would be to form a new carbon-carbon bond to the nitrile carbon atom, using a carbon-centred nucleophile which itself contains an additional functional group. Grignard reagents have been added to

optically active O-silyl cyanohydrins **3**, and the intermediates reduced to 2-amino alcohols **4** (Scheme 2)[3]. This achieves carbon-carbon bond formation to simple alkyl groups, which however, lack extra functionality.



Scheme 2

The reaction of Reformatsky reagents with nitriles (the Blaise reaction[4]) gives β-keto esters after hydrolytic work-up. This reaction has also been applied to racemic O-tetrahydropyranyl[5] and O-silyl[6] cyanohydrins **5** and **6**, and in these cases the protecting group is also removed during hydrolytic work-up, and lactone formation occurs to give the tetronic acid **7** (Scheme 3).

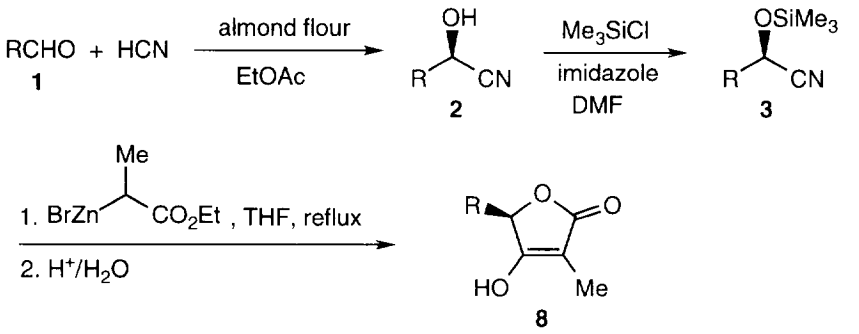


5: P = THP
6: P = $SiMe_3$

Scheme 3

It appeared attractive to us to apply the Blaise reaction to optically active O-protected cyanohydrins, since this would result in new carbon-carbon bond formation to the nitrile, and would also introduce additional functionality. The products would be optically active tetronic acids, where the single stereogenic centre in the ring would be derived from the enzymic step. Tetronic acids are of interest[7] because of their occurrence in natural products, and there are few general methods for their synthesis in optically active form,[8] especially in the case of 5-monosubstituted examples such as **7**. There has been one isolated report of a Blaise reaction on a single optically active fluorinated O-silyl cyanohydrin;[9] however the enantiomeric excesses of the products were not determined.

In this paper, we report the results of some Blaise reactions on optically active O-silyl cyanohydrins, and show that the tetronic acid products can be obtained without racemisation. The *(R)*-oxynitrilase catalysed formation of the *(R)*-cyanohydrins **2** was carried out using the procedure of Brussee *et al.*,[10] which uses almond flour as a convenient and inexpensive source of *(R)*-oxynitrilase, avoiding the need for purification of the enzyme, and also serving as the insoluble support for immobilisation (Scheme 4). Both commercially available almond meal,[11] and also flour which we prepared ourselves from almonds[12] were used, and both were equally effective. Ethyl acetate was used as the organic solvent, and the handling of neat liquid hydrogen cyanide was avoided by its use as a dilute solution in ethyl acetate, prepared by treatment of an aqueous solution of sodium cyanide with acetic acid, followed by extraction into the organic solvent.[10]



Scheme 4

The cyanohydrins prepared **2**[13] are shown in Table 1, and were chosen to be representative of alkyl, branched alkyl, α,β-unsaturated, and aryl groups on the aldehyde. The enantiomeric excesses of the cyanohydrins were determined by formation of the Mosher esters,[14] followed by capillary gas chromatography, and are consistent with those obtained in the literature,[10] for those examples which are already known. The corresponding racemic cyanohydrins **9** were also prepared by literature methods as indicated in Table 2 (except for (±)-mandelonitrile, which is commercially available), both for calibration of the determination of e.e., and for the preparation of racemic tetronic acids **7**.

Table 1 Synthesis of Optically Active Cyanohydrins and Tetronic Acids

	Aldehyde **1**	*(R)*-Cyanohydrin **2**		TMS ether **3**	*(R)*-Tetronic Acid **8**	
Entry	RCHO	% Yield	% e.e.[a]	% Yield	% Yield	% e.e.[c]
a	PhCHO	97	>99[b]	80	25	91
b	n-PrCHO	98.5	95	69	36	99
c	CH_3CH=CHCHO	74	94	57	29	97
d	i-PrCHO	83	85	60	27	89

a. by derivatisation as the Mosher ester, followed by capillary GC.
b. by 500 MHz ^1H nmr in the presence of $Eu(hfc)_3$.
c. by derivatisation as the acetate ester, followed by capillary GC on a chiral Cyclodex B column.

Both the optically active and the racemic cyanohydrins were then converted to their O-trimethylsilyl ethers **3** and **6**, using standard conditions. The Blaise reactions were then carried out (Scheme 4) using ethyl bromopropionate and zinc-copper couple, prepared from zinc dust using the method of Legoff.[15] Isolation of the tetronic acids was achieved by adding the reaction mixture to ice-sulfuric acid and stirring at room temperature for 48 hours to complete hydrolysis and cyclisation, followed by extraction and flash chromatography. The tetronic acids **7** and **8** were obtained in moderate yields of 25-38% (see Tables 1 and 2), which are however, comparable to those in the literature for Blaise reactions of racemic aliphatic protected cyanohydrins.[5,6] The enantiomeric purities of the optically active tetronic acids were determined by

derivatisation as the acetates (Ac_2O-DMAP-pyridine) followed by capillary GC on a chiral Cyclodex B column. In each case, the enantiomeric excess of the tetronic acid **8** was comparable to that of the cyanohydrin **2** from which it was derived, showing that little or no racemisation had occurred.

Table 2 Synthesis of Racemic Cyanohydrins and Tetronic Acids

	Aldehyde **1**	(±)-Cyanohydrin **9**		TMS ether **5**	(±)-Tetronic Acid **7**
Entry	RCHO	Method	% Yield	% Yield	% Yield
a	PhCHO		–	85	33
b	n-PrCHO	ref. 5	42	73	31
c	CH_3CH=CHCHO	ref. 5	78	75	38
d	i-PrCHO	ref. 16	82	75	26

In conclusion, we have shown that optically active cyanohydrins can be protected and then subjected to the Blaise reaction, giving optically active tetronic acids without racemisation. We are currently applying this method to the synthesis of some optically active tetronic acid-containing natural products.

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