J. Iran. Chem. Soc., Vol. 4, No. 1, March 2007, pp. 46-58.

JOURNAL OF THE
Iranian
Chemical Society

Preparation and Reactions of Optically Active Cyanohydrins Using the (*R*)-Hydroxynitrile Lyase from *Prunus amygdalus*[1]

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(Received 13 August 2006, Accepted 7 October 2006)

Cyanuration of 2-naphthaldehyde (**1**) and 5-methyl-2-furaldehyde (**2**) yielded the racemic 2-hydroxy-2-(β-naphthyl)ethanenitrile (*R,S*)-**3** and 2-hydroxy-2-(5-methyl-2-furyl)ethanenitrile (*R,S*)-**5**, respectively. The same reaction can be completed by using acetone cyanohydrin (**4**) as a transcyanating agent. The optically active (*R*)-**3** and (*S*)-**5** could be respectively obtained by hydrocyanation of **1** and **2** using (*R*)-hydroxynitrile lyase (*R*)-PaHNL [EC 4.1.2.10] from almonds (*Prunus amygdalus)* as a chiral catalyst. Cyanohydrins **3** and **5** in their racemic and optically active forms undergo a number of transformations which involve either the hydroxyl group or the cyanide function. Moreover, derivatization of **3** and **5** with (*S*)-Naproxen®chloride (*S*)-**14** gave the respective diastereoisomers. The optical activity of (*R*)-**3** and (*S*)-**5** as well as their derivatives were recorded. The postulated structures for the new products were supported with compatible elementary and spectroscopic (IR, ^{1}H NMR, ^{13}C NMR, MS, and single crystal X-Ray crystallography) analyses. The antimicrobial activity of some selected racemic new products and their respective optically active analogues were also undertaken.

Keywords: Aldehydes, Cyanohydrins, Enzymes, Stereochemistry

INTRODUCTION

Cyanohydrins are expedient starting materials and valuable key building blocks for the preparation and one step synthesis of several classes of compounds such as α-hydroxy- carboxylic acids [1-7] which play a vital role in organic synthesis [8-10]. Optically active cyanohydrins are also versatile intermediates in organic synthesis and have received considerable amount of interest particularly during the last two decades [1-3,11-13]. A number of methods for the preparation of optically pure cyanohydrins have been developed using various chiral catalysts [14,15], such as cyclic dipeptides [16,17], as well as chiral complexes with titanium [18,19]. Aluminum [20] and boron [21]. The enantioselective synthesis of cyanohydrins has also been performed enzymatically by means of hydroxynitrile lyases (oxynitrilases) from different plant sources [3,22]. This approach is rather precise, clean and cheap. It entails a high degree of stereoselectivity leading to optically pure chiral cyanohydrins [1,23-26]. The preparation and reactions of racemic and optically active cyanohydrins derived from 2-naphthaldehyde (**1**) and 5-methyl-2-furaldehyde (**2**) is the

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[1]This paper is dedicated to Professor Dr. M. Sidky.

theme of the present study. Products obtained from **2** may be of particular importance since biological activities of many substances are associated with or enhanced by the presence of a furan nucleus in their molecules [27].

A comparative study on the antimicrobial activity of some newly prepared racemic products and their optically active analogous was undertaken. This might be of a particular significance in the light of the well-established correlation between biological activity and stereochemical aspects [28].

EXPERIMENTAL

Materials and Methods

The reactions of air-sensitive reagents were carried out in flame-dried glassware under an atmosphere of dry argon. Solvents were rigourously dried according to literature procedures. Aldehydes **1** and **2** are commercially available and were purified directly before use. Racemic cyanohydrins were prepared according to known procedure [44]. The chemical purity of the obtained crude cyanohydrins was measured by the analysis of their ^{1}H NMR spectra.

Chromatography was performed using silica gel, grain size 0.040-0.063 (Merck). The (*R*)-hydroxynitrilase (HNL) was extracted [45] and assayed [46] according to established references. Naproxen is commercially available and naproxen chloride is prepared according to a procedure developed by Solis *et al*. [37]. Melting points were recorded on an electrothermal melting point apparatus and were uncorrected. pH measurements were made on Precisa Digital pH-Meter pH 900 with Ag/AgCl electrode. The optical rotations were recorded on Perkin Elmer Polarimeter 241 LC and/or Carl Zeiss 212503 Polarimeter: $[\alpha]_{D/25} = \alpha/c.d$, Path length (d) = 10 cm, concentration (c) = 10 mg ml^{-1}, α is the measured angle of rotation and $[\alpha]$ is the specific rotation expressed in (°.L)/(Gk.dm). A Shimadzu UV-2401 PC UV-Vis Recording Spectrophotometer was used in assay of the enzyme. The infrared spectra were recorded either neat or on KBr using Bruker Vector 22 Spectrophotometer and/or JASCO FT/IR-300E Fourier Transform Infrared Spectrophotometer. ^{1}H NMR spectra were recorded on Varian Gemini MHz 200 at 200 MHz and/or JEOL JNM-EX 270 at 270 MHz. ^{13}C NMR spectra were recorded on Varian Gemini 200 operating at 50 MHz and the chemical shifts were given in δ ppm units downfield from TMS. Mass spectra were recorded on Finnigan SSQ 7000 Spectrometer at 70 eV. X-ray crystallography was performed on Kappa-CCD Single Crystal Diffractometer Enraf nonius FR 590.

Preparation of the Racemic Cyanohydrins 3 and 5; General Procedure

In a three necked flask equipped with a mechanical stirrer and a dropping funnel, a saturated solution of sodium metabisulphite (125 g in 170 ml water) was added dropwise to a mixture of aldehyde **1** or **2** (0.25 mol) and potassium cyanide solution (0.25 mole in 50 ml of freshly distilled water). During the initial stages of addition, the reaction mixture was cooled by adding crushed ice in several portions through the third neck. After completion of addition (30 min), the reaction mixture was stirred for further 6 h at r.t. then extracted with diethyl ether (3 × 100 ml). The combined ethereal extracts were washed with water (2 × 50 ml), dried over anhydrous sodium sulfate and filtered. The ether filtrate was evaporated under reduced pressure to leave a residue which was dried well *in vacuo* to afford the crude racemic cyanohydrins **(*R,S*)-3** and **(*R,S*)-5**. The crude products were found to be sufficiently pure (^{1}H NMR) and were reacted directly without further purification.

(*R,S*)-2-Hydroxy-2-(β-naphthyl)ethanenitrile (*R,S*)-3. Yellow crystals; m.p.: 112 °C; yield 85%, chemical purity 91%. Molecular formula (Molecular weight): $C_{12}H_9NO$ (183.21).

(*R,S*)-2-Hydroxy-2-(5-methyl-2-furyl)ethanenitrile (*R, S*)-5. Brown oil; yield 95%, chemical purity 87%. Molecular formula (Molecular weight): $C_7H_7NO_2$ (137.14).

Preparation of the Racemic Cyanohydrins 3 and 5 Using Acetone Cyanohydrin (4) as a Transcyanating Agent

To a stirred solution of aldehyde **1** or **2** (0.01 mol) in diisopropyl ether (20 ml), acetone cyanohydrin [44] (0.015 mol, 1.2 ml) was added followed by sodium hydroxide (15 ml of 1 M solution) at r.t. After stirring for 4 h, the crude products were worked-up as described previously.

(*R,*S)-2-Hydroxy-2-(β-naphthyl)ethanenitrile (*R,S*)-3. m.p.: 109 °C; yield 72%, chemical purity 89% (determined by HPLC).

(*R,S*)-2-Hydroxy-2-(5-methyl-2-furyl)ethanenitrile (*R, S*)-5. Yield 77%, chemical purity 81% (determined by HPLC).

General Procedure for the Preparation of Optically Active Cyanohydrins (R)-3 and (S)-5

(1) To a solution of potassium cyanide (0.2 mol, 13 g) in distilled water (30 ml) and isopropyl ether (50 ml), was added orthophosphoric acid (0.2 mol, 13.7 ml) dropwise with stirring within 5 min at 0 ºC. After completion of addition, the reaction mixture was stirred for further 10 min. After removal of the cooling bath, the ethereal layer was separated and used directly in the following step.

(2) To a mixture of aldehyde **1** or **2** (0.1 mol) and the crude enzyme extract in diisopropyl ether (30 ml) was added the ethereal HCN solution (prepared in the first step) dropwise with stirring at 0 °C. After completion of addition (30 min), the reaction mixture was stirred for further 16 h. The cooling bath was removed and the reaction mixture was stirred vigorously with an excess of saturated sodium chloride solution (200 ml) and diisopropyl ether (100 ml) for 30 min. The ethereal layer was separated, washed with distilled water (2 × 50 ml) and dried over anhydrous sodium sulfate. After filtration, the ether solution was evaporated under reduced pressure to leave a residue which was dried well *in vacuo* to afford the respective crude optically active cyanohydrins.

(*R*)-(+)-2-Hydroxy-2-(β-naphthyl)ethanenitrile (*R*)-3. $[\alpha]_{D/25}$ = +74.4 (c 1.0, $CHCl_3$); m.p.: 114 ºC; yield 93%, chemical purity 93%.

(*S*)-(+)-2-Hydroxy-2-(5-methyl-2-furyl)ethanenitrile, (*S*)-5. $[\alpha]_{D/25}$ = +45.6 (c 1.0, $CHCl_3$); yield 92%, chemical purity 88%.

Preparation of (R)-3 and (S)-5 Using Acetone Cyanohydrin as Transcyanation Agent

To a stirred mixture of aldehyde **1** or **2** (0.01 mol) and the crude enzyme extract in diisopropyl ether (5 ml) was added acetone cyanohydrin [44] (**4**) (0.015 mol, 1.2 ml) at r.t. After stirring for 4 h, the product was isolated as described previously.

(*R*)-(+)-2-Hydroxy-2-(β-naphthyl)ethanenitrile (*R*)-3. $[\alpha]_{D/25}$ = +73.9 (c 1.0, $CHCl_3$); m.p.: 112 ºC; yield 74%, chemical purity 90%.

(S)-(+)-2-Hydroxy-2-(5-methyl-2-furyl)ethanenitrile (*S*)-5. $[\alpha]_{D/25}$ = +46.8 (c 1.0, $CHCl_3$); yield 79%, chemical purity 85%.

General Procedure for the Reaction of Cyanohydrins 3 and 5 with Acetic Anhydride

A mixture of **3** and/or **5** (0.02 mol), pyridine (0.04 mol, 3.2 ml) and acetic anhydride (0.4 mol, 5 ml) in methylene chloride (100 ml) was stirred for 12 h at r.t. The organic layer was separated, washed with 5% sulfuric acid (2 × 25 ml), distilled water (2 × 25 ml) saturated sodium bicarbonate solution (2 × 25 ml) and dried over anhydrous sodium sulfate. Removal of the volatile materials under reduced pressure followed by chromatography on silica gel with petroleum ether 40-60 °C/acetone (98:2 v/v) afforded the pure acetylated cyanohydrins.

(*R,S*)-2-Acetoxy-2-(β-naphthyl)ethanenitrile (*R,S*)-6. Colorless oil; yield 97%. Anal. Calcd. for $C_{14}H_{11}NO_2$ (225.25): C (74.65), H (4.92), N (6.22)%. Found: C (74.37), H (5.21), N (6.41)%. IR (neat, cm^{-1}): 3050 (C-H, aromatic), 2950 (C-H, aliphatic), 1750 (C=O, ester), 1210 (C-O, stretching), 2100 (CN). ^{1}H NMR ($CDCl_3$, δ ppm): 2.2 (s, 3H, C<u>H</u>$_3$), 6.6 (s, 1H, C<u>H</u>CN), 8.05-7.55 (m, 7H, aromatics). MS: m/z (relative intensity%): 225 (27.64) $[M]^{+\cdot}$, 183 (39.34) $[M^{+\cdot} - {}^{\cdot}C(O)CH_2]^+$, 155 (100) [β-naphthyl-C≡O]$^+$, 127 (68.43) [naphthyl cation].

(*R*)-(+)-2-Acetoxy-2-(β-naphthyl)ethanenitrile (*R*)-6. $[\alpha]_{D/25}$ = +30 (c 1.0, $CHCl_3$); yield 75%. For further characterization see above.

(*R,S*)-2-Acetoxy-2-(5-methyl-2-furyl)ethanenitrile (*R, S*)-7. Yellow oil; yield 80%. Anal. Calcd. for $C_9H_9NO_3$ (179.18): C (60.33), H (5.06), N (7.82)%. Found: C (60.08), H (5.20), N (8.02)%. IR (neat, cm^{-1}): 3050 (C-H, furan), 2960-2850 (C-H, aliphatic), 2260 (CN), 1750 (C=O,ester), 1600, 1510 (C=C, furan), 1220 (C-O, stretching). ^{1}H NMR ($CDCl_3$, δ ppm): 2.19 (s, 3H, =CC<u>H</u>$_3$), 2.24 (s, 3H, OCOC<u>H</u>$_3$), 6.33 (s, 1H, C<u>H</u>CN), 5.96 (d, J_{HH} = 4.8 Hz, 1H, furan), 6.48 (d, J_{HH} = 4.20 Hz, 1H, furan). MS: m/z (relative intensity%): 179 (14.9) $[M]^{+\cdot}$, 120 (100%) $[M^{+\cdot} - {}^{\cdot}OC(O)CH_3]^+$.

(S)-(+)-2-Acetoxy-2-(5-methyl-2-furyl)ethanenitrile (*S*)-7. $[\alpha]_{D/25}$ = +150 (c 1.0, $CHCl_3$); yield 85%. For further characterization see above.

Reaction of Cyanohydrins (R,S)-3, (R)-3, (R,S)-5 and/or (S)-5 with 3,4-Dichlorophenyl-isocyanate (8); General Procedure

A solution of isocyanate **8** (0.01 mol, 1.9 g) in dry toluene (20 ml) was added dropwise by a syringe to a solution of the cyanohydrin (0.01 mol), and triethylamine (10 µl) in dry toluene (10 ml) at 0 °C under dry argon atmosphere. After stirring the reaction mixture for 48 h at r.t., the volatile materials were evaporated under reduced pressure. The residual material was collected and crystallized from methylene chloride to give the racemic and/or optically active forms of the iminooxazolidinone derivatives **10** and **12**.

(*R,S*)-3-N-(3,4-Dichlorophenyl)-4-imino-5-(β-naphthyl)-2-oxazolidinone (*R,S*)-10. Yellow crystals; m.p.: 142 °C (CH_2Cl_2); yield 84%. Anal. Calcd. for $C_{19}H_{12}Cl_2N_2O_2$ (371.22): C (61.47), H (3.26), Cl (19.1), N (7.55)%. Found: C (61.79), H (3.09), Cl (18.78), N (7.71)%. IR (KBr, cm^{-1}): 3300 (N-H), 3100 (C-H, aromatic), 1780 (C=O, lactone), 1660 (C=N), 1610, 1590, 1550 (C=C, aromatic), 1120 (C-O, stretching), 805 (Cl-C-aromatic). ^{1}H NMR (DMSO, δ ppm): 6.37 (s, 1H, C<u>H</u>-O), 6.38-8.10 (m, 10H, aromatic), 9.4 (NH, D_2O-exchangeable). MS: m/z (relative intensity%): 370 (100) and 374 (18.1) $[M]^{+\cdot}$, 342 (2.0) and 346 (0.2) $[M^{+\cdot} - CO]^{+\cdot}$, 325 (94) and 329 (24) $[M^{+\cdot} - CO_2]^{+\cdot}$, 299 (85.7) and 303 (10.65) $[M^{+\cdot} - (NC^{\cdot} + CO_2)]^+$, 188 (19.1) and 192 (0.6) $[C_7H_3Cl_2NO]^+$, 166 (47.5) [β-naphthyl-CHCN]$^+$, 155 (92.9) [β-naphthyl-C≡O]$^+$, 127 (91.6) [β-naphthyl cation], 145 (41.3) and 149 (1.7) $[C_6H_3Cl_2]^+$.

(*R*)-(+)-3-N-(3,4-Dichlorophenyl)-4-imino-5-(β-naphthyl)-2-oxazolidinone (*R*)-10. $[\alpha]_{D/25}$ = +125 (c 1.0, $CHCl_3$); m.p.: 144 °C; yield 46%. For further characterization see above.

(*R,S*)-3-N-(3,4-Dichlorophenyl)-4-imino-5-(5-methyl-2-furyl)-2-oxazolidinone (*R,S*)-12. Brown crystals; m.p.: 179 °C (CH_2Cl_2); yield 48%. Anal. Calcd. for $C_{14}H_{10}Cl_2N_2O_3$ (325.15): C (51.72), H (3.16), Cl (21.81), N (8.61)%. Found: C (51.43), H (3.31), Cl (22.09), N (8.74)%. IR (KBr, cm^{-1}): 3320 (N-H), 3100 (C-H, aromatic), 1700 (C=O, ester), 1640 (C=N), 1610, 1560, 1480 (C=C, aromatic and furan), 1120 (C-O, stretching), 810 (Cl-C, aromatic). ^{1}H NMR (DMSO, δ ppm): 2.14 (s, 3H, C<u>H</u>$_3$), 6.10 (s, 1H, C<u>H</u>O), 6.20-8.33 (m, 5H, aromatics and furans), 10.80 (NH, D_2O-exchangeable). ^{13}C NMR (DMSO, δ ppm): 14.97 (<u>C</u>H$_3$), 68.15 (<u>C</u>H-C=NH), 152.79 (-<u>C</u>=NH), 154.71 (-<u>C</u>=O). MS: m/z (relative intensity %): $M^{+\cdot}$ (not recorded), 296 (5.52) and 300 (0.5) $[M^{+\cdot} - CO]^+$, 187 (100) and 191 (11.7) $[C_7H_5Cl_2N_2]^+$, 161 (36.13) and 165 (3.2) $[C_6H_5Cl_2N]^{+\cdot}$, 109 (67.59) [H$_3$C-furyl-C≡O]$^+$, 81 (4.64) [CH$_3$-furyl]$^+$.

(*S*)-(+)-3-N-(3,4-Dichlorophenyl)-4-imino-5-(5-methyl-2-furyl)-2-oxazolidinone (*S*)-12. $[\alpha]_{D/25}$ = +144; m.p.: 182 °C; yield 41%. For further characterization see above.

Reaction of Cyanohydrins (R,S)-3, (R)-3, (R,S)-5 and (S)-5 with Naproxen Chloride (14)

A solution of Naproxen chloride (*S*)-**14** [37] in 10 ml dry methylene chloride was added dropwise by a syringe to a solution of the cyanohydrin (0.01 mol) and pyridine (0.01 mol, 0.85 ml) in 10 ml dry methylene chloride with stirring at 0 °C under dry argon atmosphere. The reaction mixture was stirred for further 3 h at r.t. An additional volume of methylene chloride (30 ml) was added, then the reaction mixture was washed with a saturated solution of sodium carbonate (3 × 20 ml), distilled water (3 × 20 ml) and dried over anhydrous sodium sulfate. After filtration, the volatile materials were removed under reduced pressure and the residues were chromatographed to afford the pure products (*1`R,2S*)-**15** and (*1`S,2S*)-**16**.

(*1`R,2S*)-(+)-1`-β-Naphthylcyanomethyl-2-(6-methoxy-β-naphthyl)propionate (*1`R,2S*)-15. $[\alpha]_{D/25}$ = + 112.5 (c 1.0, $CHCl_3$); colourless crystals; m.p.: 150 °C; yield 80% (after chromatography on silica gel with petroleum ether 60-80 °C/acetone 95:5 (v/v)). Anal. Calcd. for $C_{26}H_{21}NO_3$ (395.46): C (78.97), H (5.36), N (3.54)%. Found: C (78.69), H (5.57), N (3.62)%. IR (KBr, cm^{-1}): 2960-2850 (C-H, aliphatic), 2240 (CN), 1750 (C=O, ester), 1640 (C=N), 1630, 1600 (C=C, aromatic), 1130 (C-O, stretching). ^{1}H NMR (DMSO, δ ppm):1.5 (d, J_{HH} = 10 Hz, 3H, C<u>H</u>$_3$CH-), 3.85 (s, 3H, OC<u>H</u>$_3$), 4.18 (q, J_{HH} = 10 Hz, 1H, CH$_3$C<u>H</u>), 6.90-8.10 (m, 13H, aromatics). ^{13}C NMR (DMSO, δ ppm): 19.93 (C-<u>C</u>H$_3$), 45.84 (O<u>C</u>H$_3$), 56.98 (<u>C</u>HCH$_3$), 65.18 (<u>C</u>HCN), 107.59 (CN), 135.17 (Ar-<u>C</u>-CHCH$_3$), 136.35 (Ar-<u>C</u>-CH-CN), 159.15 (Ar-<u>C</u>-OCH$_3$), 174.2 (O-<u>C</u>=O), 129.48, 129.84, 130.72, 134.93 (4C, the fused carbon atoms in the naphthalene nuclei), 118.6, 120.66, 125.93, 127.93, 127.93, 128.41, 128.74, 129.05, 129.24, 130.09, 130.9, 131.19, 134.1 (aromatics). MS: m/z (relative intensity%): 395 (23) $[M]^{+\cdot}$, 185 (100) $[C_{13}H_{13}O]^+$, 166 (49.4) [β-naphthyl-CHCN]$^+$, 127 (4.9) [naphthyl cation].

(*1`S,2S*)-(+)-1`-(5-Methyl-2-furyl)cyanomethyl-2-(6-methoxy-β-naphthyl)propionate (*1`S,2S*)-16. $[\alpha]_{D/25}$ = +102.0 (c 1.0, $CHCl_3$); brown oil; yield 80% (after chromatography on silica gel with petroleum ether 60-80 ºC/acetone 98:2 (v/v)). Anal. Calcd for $C_{21}H_{19}NO_4$ (349.39): C (72.19), H (5.48), N (4.01)%. Found: C (71.92), H (5.62), N (4.19)%. IR (neat, cm^{-1}): 3059 (C-H, aromatic), 2966, 2936, 2847 (C-H, aliphatic), 2207 (CN), 1710 (C=O, ester), 1604, 1456 (C=C, aromatic), 1026 (C-O, stretching). ^1H NMR ($CDCl_3$, δ ppm): 1.58 (d, J_{HH} = 11 Hz, 3H, $C\underline{H}_3CH$), 2.14 (s, 3H, $C\underline{H}_3$-furyl), 3.86 (s, 3H, OCH_3), 3.91(q, J_{HH} = 11 Hz, 1H, $C\underline{H}CH_3$), 6.41 (s, 1H, $C\underline{H}CN$), 7.10-8.54 (m, 8H, aromatics and furans).

General Procedure for the Reaction of Cyanohydrins (R,S)-3, (R)-3, (R,S)-5 and (S)-5 with Dialkylphosphorothio-chloridates 17a,b

A solution of the cyanohydrin (0.01 mol) in dry acetonitrile (100 ml) was stirred with dry potassium carbonate (5 g) for 1 h at r.t., under dry argon atmosphere. The appropriate thiochloridate **17a** or **17b** (0.01 mol) was added and the mixture was refluxed for 5 h. After removal of the inorganic materials by filteration, the volatile materials were removed from the filtrate under reduced pressure. The residual material was collected and chromatographed on silica gel by eluting with petroleum ether/acetone 99:1 (v/v) to give the corresponding pure thiophosphate esters (**18a**, **18b**, and **19**) as yellow to brown colored oils.

(*R,S*)-2-(Dimethylthiophosphoryloxy)-2-(β-naphthyl) ethanenitrile (*R,S*)-18a. Yellow oil; yield 92%. Anal. Calcd. for $C_{14}H_{14}NO_3PS$ (307.31): C (54.72), H (4.59), N (4.56), P (10.08), S (10.43)%. Found: C (54.98), H (4.41), N (4.49), P (10.31), S (10.29). IR (neat, cm^{-1}): 3057 (C-H, aromatic), 2825, 2763, 2715 (C-H, aliphatic), 2289 (CN), 1226 (C=C, aromatic), 1261 (C-O, stretching), 1021 (P-O-CH_3). ^1H NMR ($CDCl_3$, δ ppm): 3.78 (d, J_{HP} = 19.0 Hz, 6H, $P(S)(OC\underline{H}_3)_2$), 7.38 -8.22 (m, 8H, aromatics and $C\underline{H}CN$). MS: m/z (relative intensity%): 307 (14.88) $[M]^+$, 166 (94) [β-naphthyl-$CHCN]^+$, 155 (86.84) [β-naphthyl-$C{\equiv}O]^+$, 127 (100) [β-naphthyl cation].

(*R*)-2-(Dimethylthiophosphoryloxy)-2-(β-naphthyl) ethanenitrile (*R*)-18a. $[\alpha]_{D/25}$ = +52.4; yield 81%. For further characterization see above.

(*R,S*)-2-(Diethylthiophosphoryloxy)-2-(β-naphthyl) ethanenitrile (*R,S*)-18b. Yellow oil; yield 96%. Anal. Calcd. for $C_{16}H_{18}NO_3PS$ (335.36): C (57.30), H (5.41), N (4.18), P (9.24), S (9.56)%. Found: C (57.67), H (5.20), N (8.89), S (9.77)%. IR (neat, cm^{-1}): 3059 (C-H, aromatic), 2957, 2925, 2855 (C-H, aliphatic), 2270 (CN), 1461 (C=C, aromatics). ^1H NMR ($CDCl_3$, δ ppm): 0.88 (t, J_{HH} = 7 Hz, 3H, $OCH_2C\underline{H}_3$), 1.24 (t, J_{HH} = 7 Hz, 3H, $OCH_2C\underline{H}_3$), 3.95 (q, J_{HH} = 7 Hz, 2H, $OC\underline{H}_2CH_3$), 4.25 (q, J_{HH} = 7 Hz, 2H, $OC\underline{H}_2CH_3$), 7.11 (s, 1H, $C\underline{H}CN$), 7.15-8.58 (m, 7H, aromatics). MS: m/z (relative intensity%): 335 (87) $[M]^+$, 307 (8.6) $[M^+ - C_2H_4]^+$, 279 (13.4), $[M^+ - 2C_2H_4]^+$, 182 (4.6) $[C_{12}H_8NO]^+$, 166 (100) [β-naphthyl-$CHCN]^+$, 155 (15.7) [β-naphthyl-$C{\equiv}O]^+$, 127 (12) [β-naphthyl cation], 97 (12.4) $[P(S)(OH)_2]^+$.

(*R*)-(+)-2-(Diethylthiophosphoryloxy)-2-(β-naphthyl) ethanenitrile (*R*)-18b. $[\alpha]_{D/25}$ = +57.8; yellow oil; yield 80%. For further characrterization see above.

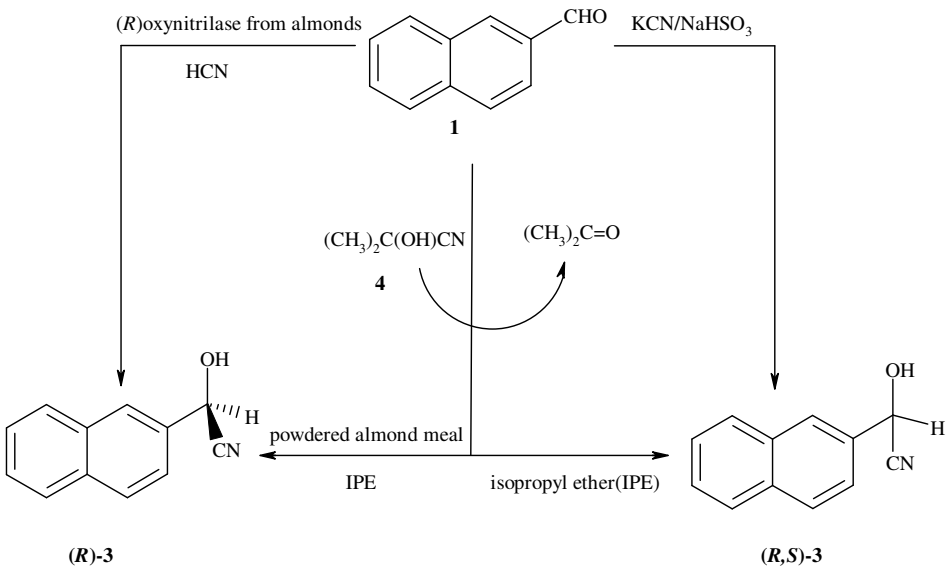
(*R,S*)-2-(Diethylthiophosphoryloxy)-2-(5-methyl-2-furyl)ethanenitrile (*R,S*)-19. Brown oil; yield 44%. Anal. Calcd. for $C_{11}H_{16}NO_4PS$ (289.29): C (45.67, H (5.58), N (4.84), P (10.71), S (11.08)%. Found: C (45.47), H (5.79), N (5.18), P (10.52), S (11.30)%. IR (neat, cm^{-1}): 3060 (C-H, furan), 2960, 2920, 2850 (C-H, aliphatic), 2217 (C≡N), 1600, 1580, 1540 (C=C, furan), 1280 (C-O, stretching), 1023 (P-O-C_2H_5) [41].

(*S*)-(+)-2-(Diethylthiophosphoryloxy)-2-(5-methyl-2-furyl)ethanenitrile (*S*)-19. $[\alpha]_{D/25}$ = + 32.0 (c 1, $CHCl_3$); yield 60%. For further characterization see above.

General Procedure for the Conversion of Cyanohydrins (R,S)-3, (R)-3, (R,S)-5 and (S)-5 into their Respective α-Hydroxycarboxylic Acids

A solution of the cyanohydrin (0.03 mol) in concentrated hydrochloric acid (50 ml) was stirred for 16 h at r.t., and then refluxed for 5 h. The reaction mixture was poured onto distilled water, then extracted with methylene chloride (3 × 25 ml). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and evaporated *in vacuo* to yield the α-hydroxycarboxylic acids (*R,S*)-**20,** (*R*)-**20**, (*R,S*)-**21** and (*R*)-**21**.

(*R,S*)-2-Hydroxy-2-(β-naphthyl)acetic acid (*R,S*)-20. Yellow crystals; m.p.: 220 ºC (CH_2Cl_2); yield 89%. Anal. Calcd. for $C_{12}H_{10}O_3$ (202.21): C (71.28), H (4.98)%. Found: C (71.21), H (5.15)%. IR (KBr, cm^{-1}): 3360, 3000 (OH), 1690



Scheme 1

(C=O), 1600 (C=C, aromatic) and 1280 (C-O, stretching). ^{1}H NMR (DMSO, δ ppm): 5.10 (d, J_{HH} = 6 Hz, 1H, exocyclic C<u>H</u>), 6.20 (1H, OH D_2O-exchangeable), 7.30 (1H, OH, D_2O exchangeable), 7.20-8.15 (m, 7H, aromatics). MS: m/z (relative intensity%): 202 (62) $[M]^{+\cdot}$, 185 (3.9) $[M^{+\cdot} - HO^{\cdot}]^+$, 157 (100) $[M^{+\cdot} - HOOC^{\cdot}]^+$, 127 (44.1) [β-naphthyl cation], 75 (3.3) [hydroxyacetic acid cation].

(*R*)-2-Hydroxy-2-(β-naphthyl)acetic acid (*R*)-20. $[\alpha]_{D/25}$ = -13.0 (c 1.0, $CHCl_3$); m.p.: 222 ºC (CH_2Cl_2); yield 78%. For further characterization see above.

(*R,S*)-2-Hydroxy-2-(5-methyl-2-furyl)acetic acid (*R,S*)-21. Yellow oil; yield 88%. Anal. Calcd. for $C_7H_8O_4$ (156.14): C (53.84), H (5.16)%. Found: C (54.03), H (4.92)%. IR (neat, cm^{-1}): 3400 (OH), 1780 (C=O), 1630 (C=C, aromatic), 1050 (C-O, stretching). ^{1}H NMR (DMSO, δ ppm): 2.18 (s, 3H, C<u>H</u>$_3$), 6.85 (s, 1H, C<u>H</u>-OH), 7.18 (d, J_{HH} = 2.5 Hz, 1H, C<u>H</u>-furan), 7.42 (d, J = 2.5 Hz, 1H, C<u>H</u>-furan) 8.85 (bs, OH, D_2O exchangeable).

(*R*)-(+)-2-Hydroxy-2-(5-methyl-2-furyl)acetic acid (*R*)-21. $[\alpha]_{D/25}$ = +83.3 (c 1.0, $CHCl_3$); yellow oil; yield 70%. For further characterization see above.

RESULTS AND DISCUSSION

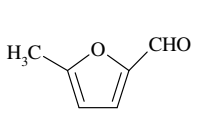
Chemistry

It has been now found that treatment of 2-naphthaldehyde (**1**) with aqueous potassium cyanide in presence of a saturated solution of sodium bisulphite yields 2-hydroxy-2-(β-naphthyl)-ethanenitrile (*R,S*)-(**3**) in an 85% yield. Formation of (*R,S*)-**3** from **1**can also be completed by using acetone cyanohydrin (**4**) as a transcyanating agent (Scheme 1) [29,30].

The IR-spectrum of (*R,S*)-**3** (KBr, cm^{-1}) showed strong absorption bands at 3418 (OH), 2248 (CN) and at 1625, 1597 (C=C, aromatic). Its ^{1}H NMR spectrum (DMSO, δ ppm) showed signals at 5.9 (1H, CH-CN, s) and at 8.20-7.20 (7H, aromatics, m). Similarly, (*R*)-2-hydroxy-2-(β-naphthyl) ethanenitrile (*R*)-**3** could be obtained by hydrocyanation of **1** directly using (*R*)-oxynitrilase from almonds [EC 4.1.2.10] which is a rich source of this enzyme [31] or by using acetone cyanohydrin (**4**) as a transcyanating agent in the presence of powdered defatted almond meal as a catalyst. This meal provides an inexpensive catalyst, the use of which eliminates the need to purify and immobilize the enzyme [30]. The isolated yield of (*R*)-**3** is 93%. It forms yellow crystals; $[\alpha]_{D/25}$ = +74.4.

Under similar experimental conditions, 2-hydroxy-2-(5-methyl-2-furyl)ethanenitrile (*R,S*)-**5** and (*S*)-**5** were respectively obtained by the non-enzyme and enzyme catalyzed cyanuration of 5-methyl-2-furaldehyde (**2**). The (*R*) and (*S*) assignments for **3** and **5** as well as their corresponding

derivatives are based on the Cahn-Ingold-Prelog (CIP) priority rules [32].



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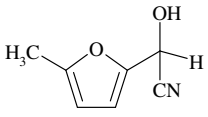
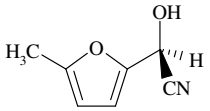


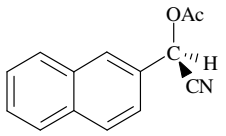
(*R,S*)-**5**



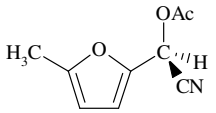
(*S*)-**5**

The IR-spectrum of compound **5** (neat, cm^{-1}) showed absorption bands at 3409 (OH), 2251 (CN), 1559, 1519 (C=C, furan) and 1216 (C-O, stretching). The isolated yield of (*S*)-**5** is 92%. It forms a brown oil; $[\alpha]_{D/25}$ = +45.6. Both of racemic and optically active forms of cyanohydrins **3** and **5** undergo a number of transformations which involve either the hydroxyl group or the cyano-function in their molecules.

(A) Reactions of the hydroxyl group. Acetylation of (*R*)-**3** and (*S*)-**5** with acetic anhydride yielded (*R*)-(+)-2-acetoxy-2-(β-naphthyl)ethanenitrile (*R*)-**6** and (*S*)-(+)-acetoxy-2-(5-methyl-2-furyl)ethanenitrile (*S*)-**7**, respectively.



(*R*)-**6**

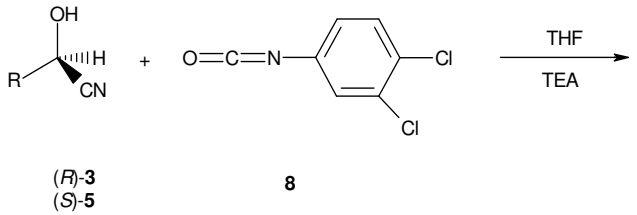


(*S*)-**7**

Treatment of (*R*)-**3** with 3,4-dichlorophenylisocyanate (**8**) in THF in presence of a few drops of triethylamine (TEA) yielded a yellow crystalline substance formulated as (*R*)-(+)-3-*N*-(3,4-dichlorophenyl)-4-imino-5-(β-naphthyl)-2-oxazolidinone (*R*)-**10**. Similarly, (*S*)-(+)-3-*N*-(3,4-dichlorophenyl)-4-imino-5-(5-methyl-2-furyl)-2-oxazolidinone (*R*)-**12** was obtained upon reacting (*S*)-**5** with isocyanate **8** (Scheme 2).

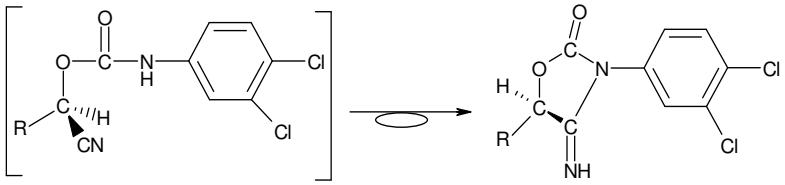
Structural reasonings for (*R*)-**10** are:

i. Compatible elementary and molecular weight determination



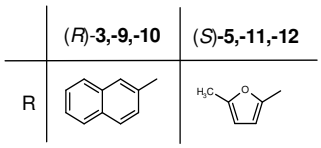
(*R*)-**3**
(*S*)-**5**

8



(*R*)-**9**
(*S*)-**11**

(*R*)-**10**
(*S*)-**12**



Scheme 2

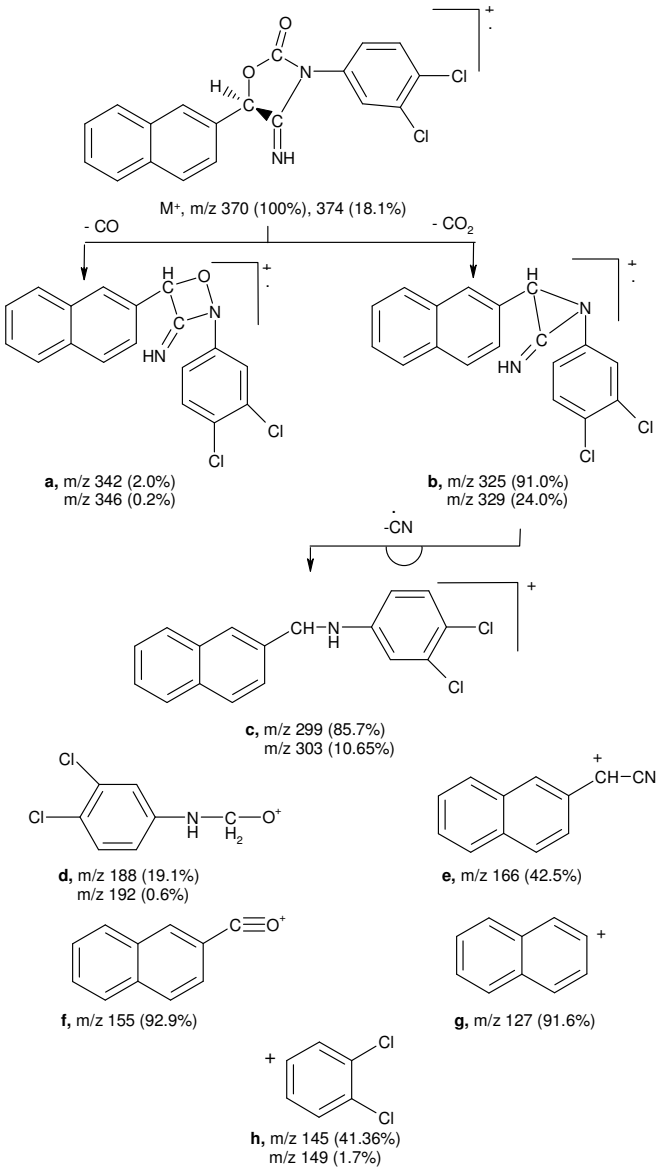
(MS) corresponded to $C_{19}H_{12}Cl_2N_2O_2$.

ii. Its IR-spectrum (KBr, cm^{-1}) showed strong absorption bands at 3330 (NH), 3100 (CH, aromatic), 1780 (C=O, lactone), 1610, 1590, 1550 (C=C, aromatic), 1120 (C-O, stretching) and 805 (Cl-C, aromatic). The spectrum revealed the absence of (CN) group absorption around 2200 cm^{-1}. On the other hand, it showed a strong band at 1670 due to the C=N group absorption.

iii. The ^1H NMR spectrum (DMSO, δ ppm) revealed the presence of signals at 6.37 (1H, CH-O, s), 8.19-7.54 (10H, aromatics, m) and 8.78 (NH, D_2O, exchangeable).

iv. The ^{13}C NMR spectrum (DMSO, δ ppm) showed signals at 160.90 (C=O), 153.9 (-C=NH) and 79.36 (CH-O). The aromatic carbon atoms (16 C) gave signals at 132.81, 131.99, 131.09, 130.13, 128.66, 128.34, 127.77, 127.67, 127.14, 127.02, 126.59, 126.20, 126.14, 124.05, 114.00, and 113.80.

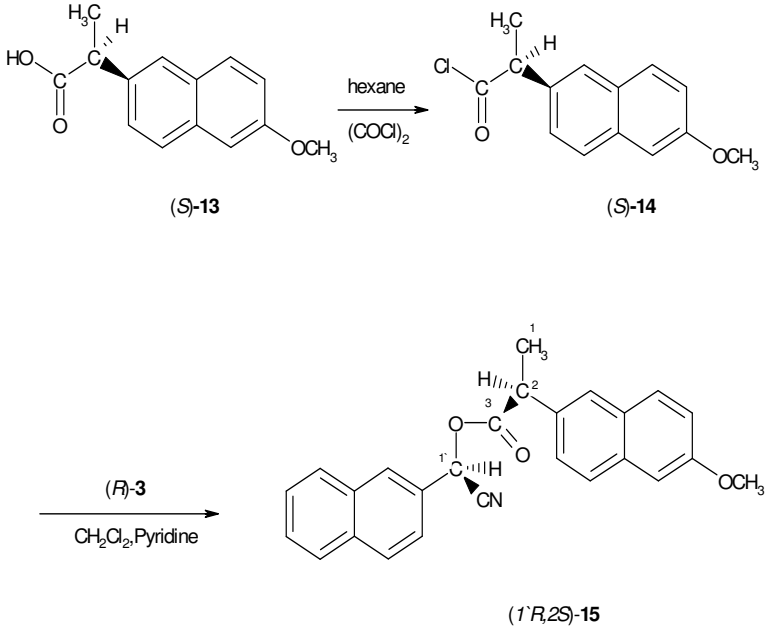
v. The mass spectrum of compound (*R*)-**10** revealed the molecular ion peak at m/z 370 (374). Successive loss of neutral CO and CO_2 molecules from M^+ produces radical cations **a** and **b** at m/z 342 (346) and m/z 325 (329), respectively. This behavior is frequently observed in the mass spectra of cyclic carbonyl compounds and anhydrides (lactones) [33]. Molecular rearrangement of ion **b** followed by ejection of CN-radical, produces ion **c** at m/z 299 (303). The spectrum also disclosed the presence of ion peaks at m/z 188 (192) (cation **d**), 166 (cation **e**), 155 (cation **f**), 127 (cation **g**) and 145 (149) (cation **h**) which are expected from cleavage of M^+ and its fragments under electron bombardment (Scheme 3).



Scheme 3

Apparently, the reaction of cyanohydrins (*R*)-**3** and (*S*)-**5** with **8** proceeds to give the respective carbamic acid esters (*R*)-**9** and (*S*)-**11** which undergo then molecular rearrangement to give the final products (*R*)-**10** and (*S*)-**12**, respectively. In this connection, it is worthy to report that the new products (*R*)-**10** and (*S*)-**12** supplement to an important chemotype class of compounds, namely the oxazolidinones. They are broadly known as potent antimicrobial agents [34,35], due to their activity against numerous multidrug-resistant strains of pathogenic and Gram-Positive microorganisms [36].

The use of (*S*)-Naproxen®(**13**) as a derivatizing agent to determine the optical purity of organic compounds [37] and as a chiral resolving agent for converting racemates to a mixture of diastereoisomers [38,29], is very well known. In the present study, it has been found that derivati-zation of (*R*)-**3** with (*S*)-Naproxen chloride (*S*)-**14** proceeds in methylene chloride in the presence of pyridine to give the respective diastereoisomer, namely, (*1`R,2S*)-(+)-1`-β-naphthylcyano-methyl-2-(6-methoxy-β-naphthyl)propionate (*1`R,2S*)-**15**. Naproxen® (**13**) could be obtained by extraction with chloroform from

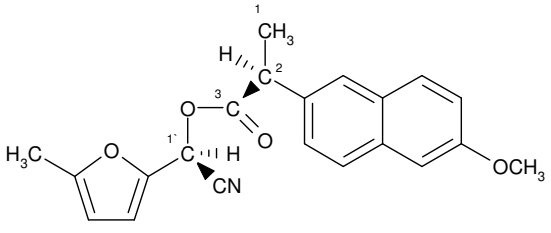


(*S*)-**13** (*S*)-**14** (*1`R,2S*)-**15**

Scheme 4

commercially available tablets [37]. Treatment of **13** with oxalyl chloride in hexane yields the acid chloride (**14**) (Scheme 4) [37].

The diastereoisomer (*1`R,2S*)-**15** was also mainly isolated and identified upon chiral resolution of the racemate mixture (*R,S*)-**3** with (S)-**14** in hexane. The diastereoisomer (*1`S,2S*)-**16**, namely, (*1`S,2S*)-(+)-1`-(5-methyl-2-furyl)cyanomethyl-2-(6- methoxy-β-naphthyl) propionate was similarly obtained by reacting (*S*)-**5** with (*S*)-Naproxen chloride (*S*)-**14** in hexane and/or upon treatment of a solution of the racemate mixture (*R,S*)-**5** with (*S*)-**14**.



(*1s`,2s*)-**16**

Elementary and molecular weight determination (MS) for (1`*R*,2*S*)-**15** corresponded to $C_{26}H_{21}NO_3$. Structural reasonings for (1`*R*,2*S*)-**15** are:

i. Its IR spectrum (KBr, cm^{-1}) disclosed the presence of strong absorption bands at 2960-2850 (CH, aliphatic), 1750 (C=O, ester), 1630, 1600 (C=C, aromatic) and 1130 (C-O, stretching).

ii. Its ^1H NMR spectrum (DMSO, δ ppm) showed signals at 1.15 (d, J_{HH} = 10 Hz, 3H, $C\underline{H}_3$-CH-), 3.85 (s, 3H, OCH_3), 4.18 (q, J_{HH} = 10 Hz, 1H, CH_3-C<u>H</u>) and 6.90-8.10 (m, 13H, aromatics).

iii. The ^{13}C NMR spectrum (DMSO, δ ppm) of (*1`R,2S*)-**15** showed signals at 19.93 (C-<u>C</u>H_3), 45.84 (OCH_3), 56.98 (<u>C</u>H-CH_3), 65.18 (<u>C</u>H-CN), 107.59 (CN), 135.17 (Ar-<u>C</u>-CH-CH_3), 136.35 (Ar-<u>C</u>-CH-CN), 159.15 (Ar-<u>C</u>-OCH_3) and 174.2 (O-C=O). The fused C-atoms in the naphthalene nuclei (4C) appeared as signals at 129.48, 129.84, 130.72, 134.93. The carbon atoms in the same rings (13C) gave signals at 118.60, 120.66, 125.93, 127.83, 127.93, 128.41, 128.74, 129.05, 129.24, 130.09, 130.90, 131.19, 134.10.

iv. The mass spectrum of (*1`R,2S*)-**15** showed the molecular ion peak at m/z 395 (23%).

v. The absolute structural configuration of the diastereoisomer (*1`R,2S*)-**15** was also confirmed by X-ray crystallographic analysis (Fig. 1).

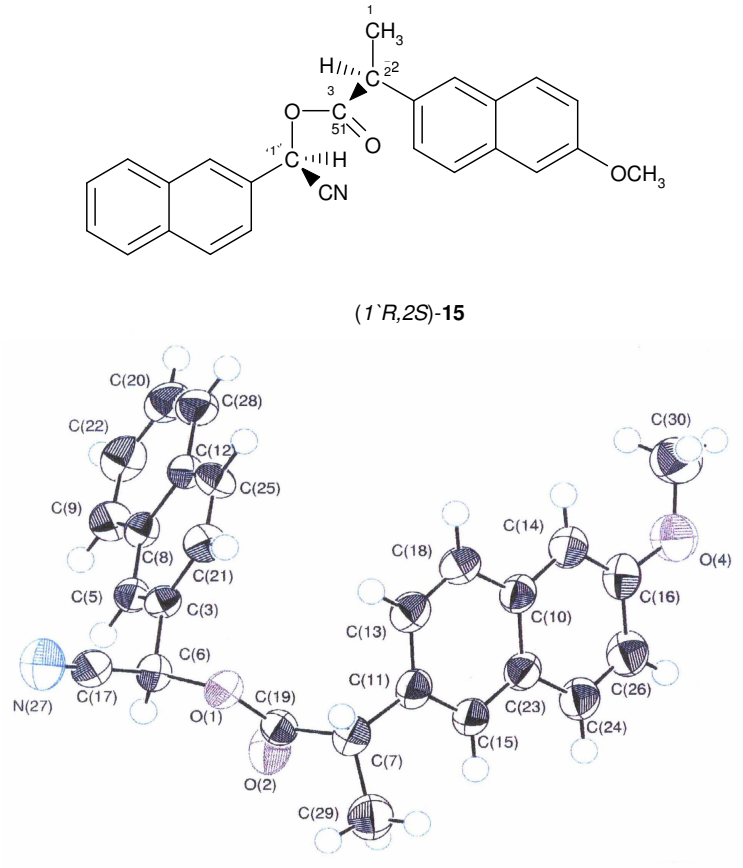


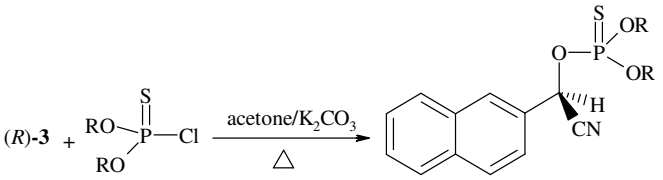
Fig. 1. ORTEP diagram of the compound of (*1`R,2S*)-**15**.

Table 1. X-ray Crystal Data Collection and Refinement for (*1`R,2S*)-**15**

Formula	$C_{26}H_{21}NO_3$	ρcalc (mg m^{-3})	1.275
F.W.	395.458	F (000)	416
Crystal system	Monoclinic	Data collection[a]	
Space group	H-M $P2_1$	Reflections collected/unique	1700/1122
a (Å)	10.5730(5)	Data/restraints/parameters	1122/0/271
b (Å)	6.0662(2)	Goodness-of-fit on F^2	1.297
c (Å)	16.0782(11)	Final R indices	
α (º)	90.00	[I > 3σ (I)]	$R1 = 0.032$
			$wR2 = 0.062$
β (º)	92.369(2)	*R* indices (all data)	$R1 = 0.059$
			$wR2 = 0.070$
γ (º)	90.00		
V (Å³)	1030.34(9)		
Z	2		

[a]*T* = 298 K, KappaCCD single crystal diffractometer, Mo K_a (*l* = 0.71073).

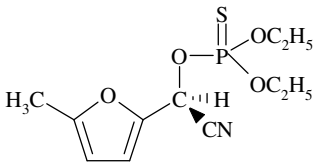
Many compounds incorporating the *O*-dialkylthiophosphoryl moiety in their molecules (phosphorothiolates) are of marked biological significance particularly for their application as pesticides [40]. Therefore, preparation of the dialkylthiophosphoryl esters of cyanohydrins (*R*)-**3** and (*S*)-**5** was undertaken. Thus, reacting (*R*)-**3** with dimethylphosphorothiochloridate (**17a**) in boiling acetone in the presence of anhydrous potassium carbonate yielded 2-(dimethylthiophosphoryloxy)-2-(β-naphthyl)-ethanenitrile (*R*)**-18a**. Under the same conditions, (*R*)**-3** reacted with diethylphosphorothiochloridate (**17b**) to afford 2-(diethylthio-phosphoryloxy)-2-(β-naphthyl)-ethanenitrile (*R*)**-18b**.



17a, R = CH_3
17b, R = C_2H_5

(*R*)**-18a**, R = CH_3
(*R*)**-18b**, R = C_2H_5

Similarly, the reaction of cyanohydrin (*S*) **-5** with **17b** yielded 2-(diethylthiophosphoryloxy)-2-(5-methyl-2-furyl) ethanenitrile (*S*)**-19**.



(*S*)-**19**

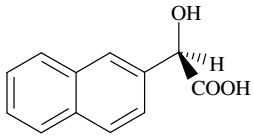
Structural reasonings for (*R*)**-18a** are:

i. Its IR-spectrum (neat, cm^{-1}) showed bands at 3057 (CH, aromatic), 2825, 2763, 2715 (CH, aliphatic) 2289 (CN), 1626 (C=C, aromatic), 1261 (C-O, stretching) and at 1021 (P-O- CH_3) [41].

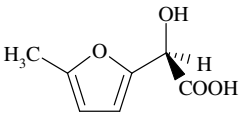
ii. The ^1H NMR spectrum ($CDCl_3$, δ ppm) showed signals at 3.78 (6H, P(S)$(OCH_3)_2$, d, J_{HH} = 19.6 Hz), 7.38-8.22 (8H, aromatics and C<u>H</u>CN, m).

iii. The mass spectrum of (*R*)**-18a** showed the molecular ion peak at m/z 307 (14.8%).

(B) Reactions of the cyanide function. Upon heating (*R*)-(+)-2-(β-naphthyl)ethanenitrile (*R*)-**3** with concentrated hydrochloric acid, it yielded (*R*)-(-)-2-hydroxy-2-(β-naphthyl) acetic acid *(R)*-**20**. Under the same conditions, acid hydrolysis of (*S*)-**5** aforded (*R*)-(+)-2-hydroxy-2-(5-methyl-2-furyl) acetic acid (*R*)-**21**.



(*R*)-**20**



(*R*)-**21**

Compatible elementary and molecular weight determination (MS) for (*R*)-**20** corresponded to $C_{12}H_{10}O_3$. Structural reasonings for (*R*)-**20** are:

i. Its IR-spectrum (KBr, cm^{-1}) disclosed the presence of absorption bands at 3360, (OH), 1690 (C=O), 1600 (C=C, aromatic), and 1280 (C-O, stretching).

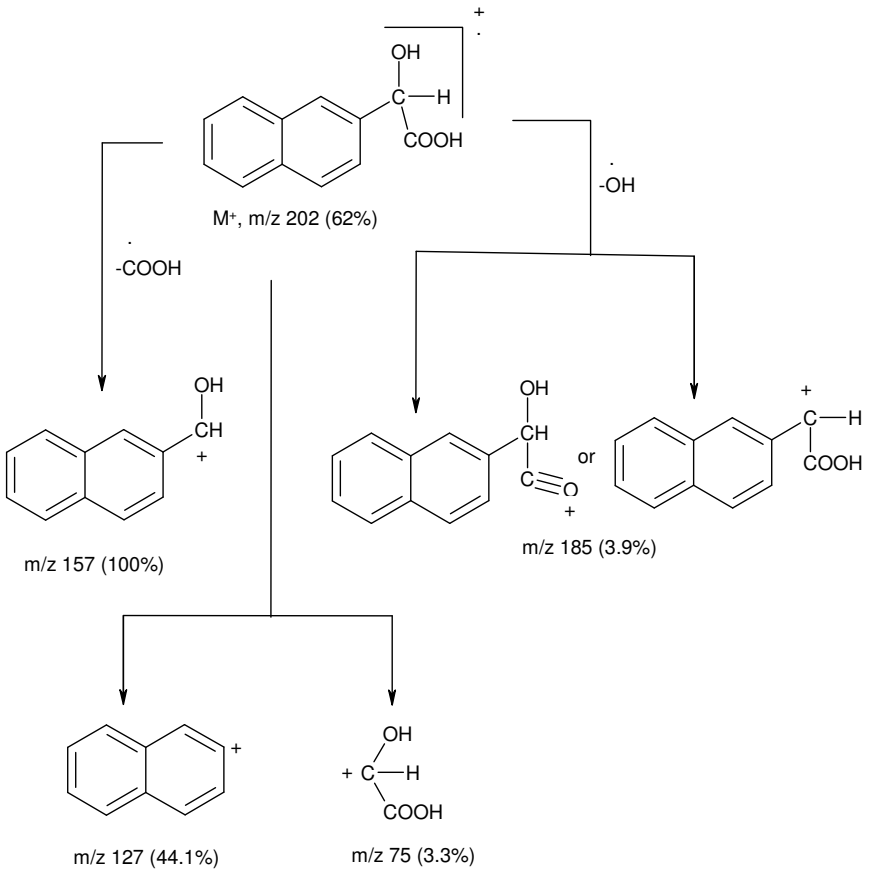
ii. Its ^1H NMR spectrum (DMSO, δ ppm) showed signals at 5.10 (1H, exocyclic CH, d, J_{HH} = 6 Hz); simplified to a singlet upon deuteration), 6.2 (OH, D_2O-exchangeable), 7.30 (OH, D_2O-exchangeable) and 7.20-815 (7H, aromatics, m).

iii. The mass spectrum of (*R*)-**20** showed the molecular ion peak at m/z 202. Loss of OH radical from M^+ yields the cation at m/z 185. Meanwhile, loss of COOH-radical from M^+ affords the cation at m/z 157. The spectrum also showed ion peaks at m/z 127 (β-naphthyl-cation) and at m/z 75 which corresponds to the cation of hydroxyacetic acid (Scheme 5).

The racemic analogues (*R,S*)**-6, -7, -10, -12, -15, -16, -18a,b, -19, -20**, and **-21** were likewise obtained by reacting cyanohydrins (*R,S*)**-3** and (*R,S*)**-5** with the appropriate reagents (Experimental).

Biological Results

Compound (*R,S*)-**12** inhibited the growth of all tested organisms. It exhibited high inhibitory effect against *Escherichia coli and Bacillus subtillus* equivalent to the effect



Scheme 5

of Chloramphenicol; probably due to the presence of the oxazolidinone ring (which has antimicrobial activity) [34,35] and the furan ring. The mode of action of (*R,S*)-**12** has been found to inhibit protein synthesis in the intial stage [43]. Due to this novel mechanism of action, oxazolidinones are not cross resistant with other types of antibiotics [43]. Compound (*R*)-**10** exhibited comparatively low inhibitory activity toward all the organisms tested when compared with (*R,S*)-**12** probably due to the absence of the furan ring in its molecule. Compounds (*R,S*)-**20** and (*R*)-**20** exhibited the lowest inhibitory activity toward all the tested organisms compared to other compounds.

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