Chemoselective Enzymatic Hydrolysis of Aliphatic and Alicyclic Nitriles

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Mild and selective hydrolysis of aliphatic and alicyclic nitriles leading to carboxylic acids and amides was achieved under neutral conditions by an immobilized enzyme preparation from *Rhodococcus* sp. This method is particularly useful for the transformation of compounds containing other acid- or base-sensitive groups.

Chemical transformation of nitriles into carboxylic acids or amides is of synthetic importance owing to the ease with which the desired organic nitrile usually can be obtained. Synthetic routes to these compounds providing a method for one-carbon-homologation include the reaction of cyanide with organic halides, arenes, aldehydes and olefins, as well as the Sandmeyer reaction. However, the chemical hydrolysis of nitriles usually requires rather harsh conditions. Such media are often incompatible with other hydrolysable or acid/base sensitive groups within the molecule and in these cases neutral hydrolytic conditions would be a clear advantage. Chemical hydration under neutral conditions has been conducted, albeit with varying degrees of success. Often relatively expensive and elaborate reagent systems are required, for example platinum,[1] palladium[2] and cobalt complexes.[3] In addition, 'reduced copper'[4] and manganese dioxide[5] have also been applied. Furthermore, elevated reaction temperatures are usually necessary. Biocatalysis is playing an increasingly important role in synthetic organic chemistry due to the very mild reaction conditions normally required and the usually high chemo-, regio- and stereo-selectivity with which such transformations take place. In this respect, the ability of enzymes to hydrolyse nitriles, in particular employed as whole microorganisms, is well established[6–9] and a range of both aromatic and aliphatic nitriles as well as dinitriles have been successfully hydrolysed. Indeed, monohydrolysis of dinitrile substrates, not possible using conventional means, has been demonstrated.[6,10,11] Most recently, optically active products have also been obtained.[12,13]

The mechanism of these enzyme systems have been investigated[14–16] and two distinct pathways are believed to be operating: firstly, the stepwise hydrolysis of the nitrile into an amide *via* a nitrile hydratase followed by transformation of the latter into a carboxylic acid by an amidase (path A) and secondly, the direct conversion of the nitrile into a carboxylic acid *via* a nitrilase (path B). However, the handling of viable microorganisms requires special equipment and skill for their cultivation which are not always at hand in synthetic organic laboratories. Recently a ready to use immobilized nitrilase complex derived from *Rhodococcus* sp. became available.† This preparation consists of both the hydratase and amidase systems.[6] Preliminary communications[17–19] have shown that a number of aromatic and aliphatic mono- and di-nitriles can be successfully hydrolysed using this immobilized enzyme. Herein we report investigations on the selectivity of enzymatic hydrolysis of aliphatic and alicyclic nitriles either bearing other hydrolysable groups, such as cyano esters **1a–5a** and **18a**, cyano acetals **6a**, **7a** and epoxide **8a**, or being prone to side reactions such as elimination or aldol-type reactions under the conditions of conventional nitrile hydrolysis, for example hydroxy nitriles **9a–12a**, **14a–17a** and **19a–21a** as well as oxo nitriles **22a–24a**.

† Immobilized nitrilase complex SP 409 from Novo Industri A/S, Denmark. The batch used in this study had a nitrile hydratase activity of 391 HPU g^{-1} (substrate proprionitrile) and an amidase activity of 159 APU g^{-1} (substrate propionamide).

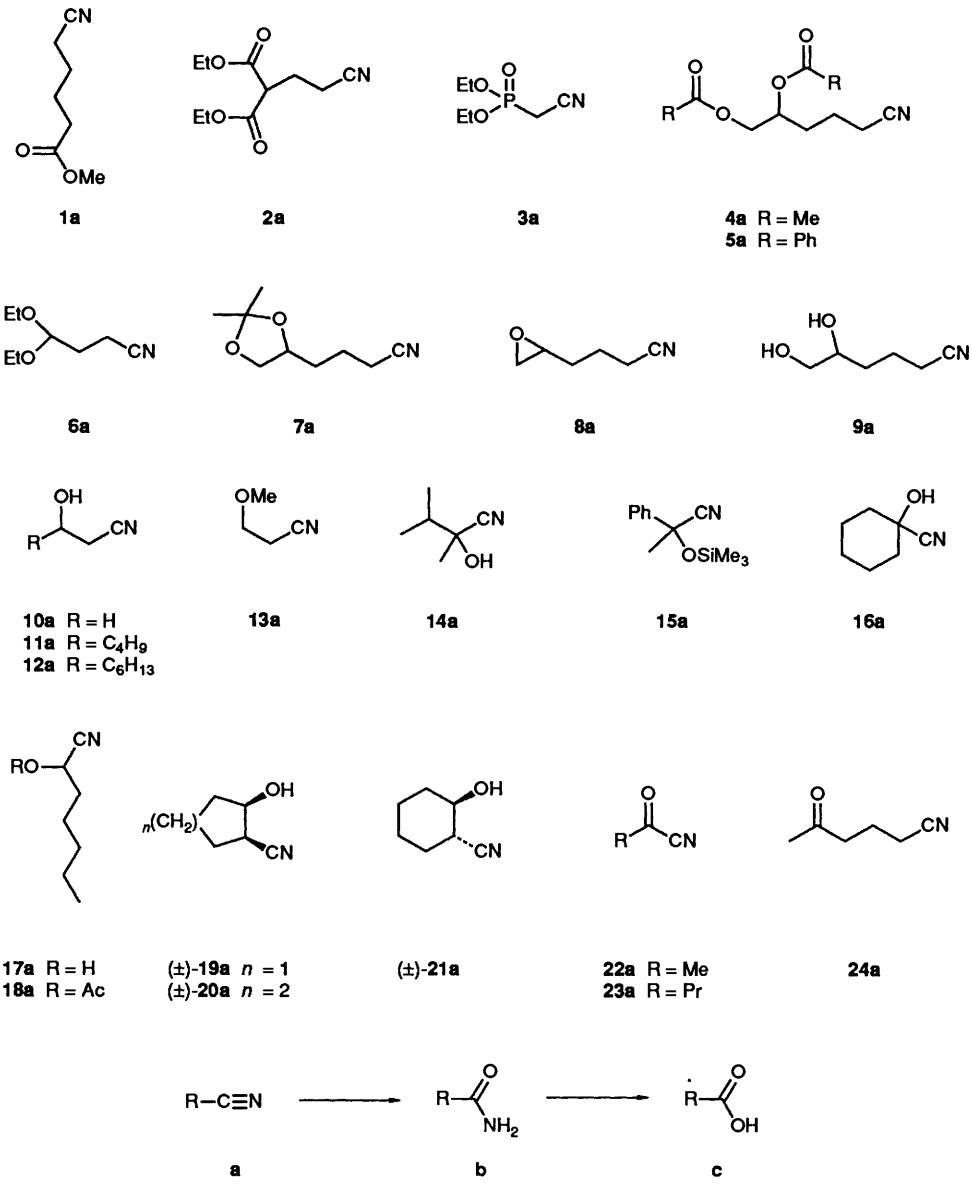
Table 1 Enzymatic hydrolysis of nitriles

Substrate	Conditions[a]	Product(s)	Yield (%)[b]
1a	5 (6)	Adipic acid	68
2a	5 (48)	**2c**	92
3a	5 (168)	**3c**	41
4a	4 (72)	**9a**	11
		9c	28
5a	10 (312)	No reaction	—
6a	5 (24)	**6c**	46
7a	1 (72)	**7c**	41
8a	4 (20)	**9c**	62
9a	4 (72)	**9c**	50
10a	5 (24)	**10c**	63
11a	5 (24)	**11c**	62
12a	5 (1)	**12b**	26
		12c	39
12a	5 (24)	**12c**	83
13a	5 (48)	**13c**	52
14a	10 (168)	**14c**	12
15a	10 (168)	Decomp.	—
16a	10 (120)	Decomp.	—
17a	Z0 (48)	**17c**	< 10
18a	10 (48)	**17a**	85
		17c	< 10
19a	5 (72)	**19c**	50
20a	5 (30)	**20c**	85
21a	5 (48)	**21c**	47
22a	5 (120)	Decomp.	—
23a	5 (40)	Butyric acid	25
24a	5 (24)	**24c**	68

[a] Equivalents of immobilized enzyme (w/w), reaction time (h). [b] Not optimized.

Results and Discussion

Generally, the biotransformations were carried out using a 4- to 5-fold excess of biocatalyst† (w/w) *versus* substrate. Only in those cases where no reaction could be observed with this amount, a 10-fold equivalent was employed. Since a large proportion of the catalyst consists of the macroscopic carrier, the actual amount of enzyme(s) is very low. Generally, complete conversion of the nitrile into the carboxylic acid was observed for all entries of Table 1. The only exceptions were substrate **5a**, **15a–17a** and **18a**, where an exceedingly slow reaction occurred, and **3a**, where the incomplete conversion came to a standstill after 7 days. Depending on the substrate structure the reaction time ranged from 6 h, **1a**, to 7 days, **3a**. In some cases, **9a–12a**,



Scheme 1

the formation of a minor second product—most likely the corresponding amide—could be observed by TLC during the course of the reaction. However, the small quantities involved allowed the isolation and characterisation of an amide only in case of **12b**.

Surprisingly, the hydrolysis of the nitrile **1a** gave adipic acid rather than its expected hemi-ester **1c** and for compounds **4a** and **18a** fast deacylation also occurred, leading to product mixtures. These undesired side reactions can be attributed to an ester hydrolase activity present in the enzyme preparation. For the other ester substrates investigated, **2a** and **3a**, no ester cleavage was detected as in the case for heteroaromatic nitriles containing an ester moiety.[20]

Lack of reactivity observed for some substrates may be due to several reasons. For substrate **5a**, the insolubility of the crystalline compound in the aqueous medium was probably the reason for its non-acceptance by the biocatalyst. Attempts to improve the solubility by adding either water-miscible or -immiscible organic cosolvents to the reaction medium such as methanol, ethanol, dimethyl sulfoxide or toluene, turned out to cause rapid deactivation of the enzyme(s). This point clearly represents a major drawback of this approach. On the other hand, liquid but likewise water-insoluble lipophilic substrates (*e.g.* **2a–4a**, **7a**, **8a** and **24a**), which could be easily dispersed in the medium by vigorous shaking, were successfully transformed.

The cyanohydrins **14a–17a** exhibited low stability in aqueous solution and for all of these compounds the corresponding aldehyde or ketone could be detected in increasing amounts during the course of the reaction. Consequently, the slow and insufficient formation of the α-hydroxy acids **14a**, **16a** and **17a** is a result of the competing reaction rates for enzymatic nitrile hydrolysis *versus* a retro-cyanohydrin reaction. Moreover, free cyanide produced by decomposition of the cyanohydrins[21] has been reported to act as an inhibitor of nitrile hydratase from *Rhodococcus* sp.[16] The cyanohydrin ester **18a** was rapidly deacylated to yield **17a**.

Variable yields of products can be attributed to several factors: Tedious purification by chromatography and significant adsorption onto the carrier. For the α-oxo nitriles **22a** and **23a** the expected products could not be isolated due to hydrolytic decomposition of the starting material in the aqueous medium leading to butyric acid as sole product for **23a**. Similarly, hydrolysis of the epoxy nitrile **8a** gave the dihydroxy acid **9c**

presumably due to non-enzymatic hydrolysis of the intermediate epoxy acid **8c** in the aqueous reaction medium.

In conclusion, the immobilized nitrilase complex proved to be a valuable biocatalyst for the hydrolysis of nitriles under mild conditions for a variety of substrates bearing acid- or base-sensitive functional groups.

Experimental

M.p.s were determined on a Büchi-Tottoli apparatus and are uncorrected. Column chromatography was performed on silica gel Merck 60, 230–400 mesh, and TLC on silica gel Merck 60, F_{254}. NMR spectra were recorded on a Bruker MSL 300. Chemical shifts (δ) are reported in ppm with TMS as internal standard; J values are recorded in Hz. IR spectra were determined on a Beckman IR-33 spectrophotometer. GLC analyses were performed on a Dani 8500 chromatograph with a DB 1701 capillary column (25 m × 0.25 mm, 0.25 μm film, N_2) equipped with FID.

Compounds **1a**, **2a**, **3a**, **6a**, **10a**, **13a**, **16a**, **22a**, **23a** and **24a** were commercially obtained or prepared according to literature procedures as listed below. Complete experimental data on compounds **11a**,[22] **12a**, **19a**, **20a**,[23] **14a**, **14c**,[24] **15a**,[25] **17a**, **17c**,[26] **21a**[27] and **24c**[28] were previously reported.

Hex-5-enenitrile.[29]—To a solution of tetrabutylammonium cyanide (2.70 g, 10 mmol) in anhydrous dichloromethane (45 cm^3), 5-bromopent-1-ene (0.80 cm^3, 6.7 mmol) was added and the mixture refluxed under dry nitrogen. After 10 h the yellow solution was diluted with dichloromethane (100 cm^3), washed with water (2 × 100 cm^3) and dried (Na_2SO_4). It was then filtered through a plug of silica gel (5 × 2.5 cm) and the resulting colourless filtrate was concentrated under reduced pressure to give hex-5-enenitrile as a syrup (0.51 g, 80%), b.p. 59 °C/19 Torr; ν_{max}(film)/cm^{-1} 2240 (CN); δ_H($CDCl_3$) 1.76 (2 H, m, $J_{2,3}$ 7.2, $J_{3,4}$ 7.2, 3-H), 2.22 (2 H, q, $J_{4,5}$ 7.2, 4-H), 2.35 (2 H, t, 2-H), 5.09 (2 H, m, 6-H) and 5.75 (1 H, m, 5-H); δ_C($CDCl_3$) 136.2 (C-5), 119.6 (C-1), 116.7 (C-6), 32.4 (C-2), 24.6 (C-4) and 16.4 (C-3).

(±)-5,6-*Diacetoxyhexanenitrile* **4a**.—5,6-Dihydroxyhexanenitrile **9a** (0.74 g, 5.7 mmol) was acetylated under standard conditions (acetic anhydride, pyridine) to afford **4a** (1.04 g, 85%) as a pale yellow syrup; ν_{max}(film)/cm^{-1} 2245 (CN); δ_H($CDCl_3$) 1.64 (4 H, m, 3-H and 4-H), 1.93 and 1.95 (6 H, 2 s, MeCO), 2.30 (2 H, t, $J_{2,3}$ 6.4, 2-H), 3.93 (1 H, dd, $J_{5,6}$ 6.1, $J_{6,6'}$ 12.0, 6-H), 4.12 (1 H, dd, $J_{5,6'}$ 3.7, 6'-H) and 4.95 (1 H, m, 5-H); δ_C($CDCl_3$) 170.5 (C=O), 119.1 (C-1) 70.2 (C-5), 64.5 (C-6), 29.5 (C-2), 21.1 (C-4), 20.7 (CH_3), 20.5 (CH_3) and 16.7 (C-3) (Found: C, 56.1; H, 7.2; N, 6.5. $C_{10}H_{15}NO_4$ requires C, 56.3; H, 7.1; N, 6.6%).

(±)-5,6-*Dibenzoyloxyhexanenitrile* **5a**.—5,6-Dihydroxyhexanenitrile **9a** (0.58 g, 4.5 mmol) was benzoylated under standard conditions to afford **5a** (1.38 g, 91%), m.p. 82–83 °C; ν_{max}(Nujol)/cm^{-1} 2244 (CN); δ_H($CDCl_3$) 1.77–2.10 (4 H, m, 3-H and 4-H), 2.46 (2 H, t, $J_{2,3}$ 6.9, 2-H), 4.50 (1 H, dd, $J_{5,6}$ 6.3, $J_{6,6'}$ 12.0, 6-H), 4.60 (1 H, dd, $J_{5,6'}$ 3.8, 6'-H), 5.55 (1 H, m, 5-H) and 7.4–8.2 (10 H, m, ArH); δ_C($CDCl_3$) 166.3 (C=O), 166.2 (C=O), 133.5, 133.4, 129.9 and 128.8 (Ar), 119.2 (C-1), 71.2 (C-5), 65.5 (C-6), 30.2 (C-2), 21.6 (C-4) and 17.2 (C-3) (Found: C, 70.9; H, 5.9; N, 4.0. $C_{20}H_{19}NO_4$ requires C, 71.2; H, 5.7; N, 4.2%).

(±)-4-(3-*Cyanopropyl*)-2,2-*dimethyldioxolane*[30] **7a**.—Acetalization of 5,6-dihydroxyhexanenitrile **9a** (1.46 g, 12.6 mmol) with 2,2-dimethoxypropane (13.1 g, 126 mmol) and toluene-*p*-sulfonic acid as catalyst afforded **7a** (1.1 g, 52%); b.p. 105 °C/30 Torr; ν_{max}(film)/cm^{-1} 2240 (CN); δ_C($CDCl_3$) 119.27 (CN), 108.66 (C-2), 74.81 (C-5), 68.85 (C-4), 32.15 (C-1'), 26.63 (CH_3), 25.33 (CH_3), 21.80 (C-3') and 16.73 (C-2').

(±)-5,6-*Epoxyhexanenitrile*[30] **8a**.—To a mixture of hex-5-enenitrile (1.46 g, 15.4 mmol) and disodium hydrogen phosphate (3 g, 21.1 mmol) in CH_2Cl_2 (35 ml), *m*-chloroperbenzoic acid (2.6 g, 15.4 mmol) was added portionwise. The mixture was stirred for 60 h after which the solids were filtered off and washed with CH_2Cl_2. The supernatants were combined, washed with aqueous sodium hydrogen carbonate (2.5%) and dried (Na_2SO_4). Evaporation and Kugelrohr distillation afforded **8a** (0.6 g, 35%); b.p. 82 °C/22 Torr; ν_{max}(film)/cm^{-1} 2245 (CN), 1260 (epoxide); δ_H($CDCl_3$) 1.5–1.65 (1 H, m) and 1.75–2.00 (3 H, m, 3-H and 4-H), 2.40–2.60 (3 H, m, 2-H and 5-H) and 2.75–3.00 (2 H, m, 6-H); δ_C($CDCl_3$) 119.2 (CN), 50.66 (C-5), 46.04 (C-6), 30.68 (C-2), 21.69 (C-4) and 16.20 (C-3).

(±)-5,6-*Dihydroxyhexanenitrile*[30] **9a**.—To a stirred solution of hex-5-enenitrile (1.71 g, 18 mmol), in acetone–water (10:1; 165 cm^3), 4-methylmorpholine 4-oxide monohydrate (9.71 g, 72 mmol) and a catalytic amount of osmium tetroxide were added at room temperature. After 24 h Na_2S was added to the mixture to destroy the catalyst. The upper layer of the mixture was decanted and the lower black layer was extracted with acetone (5 × 100 cm^3). The organic phases were combined and evaporated. Column chromatography afforded **9a** (2.04 g, 88%) as a pale yellow syrup; ν_{max}(film)/cm^{-1} 2245 (CN); δ_H(CD_3OD) 1.5–1.9 (4 H, m, 3-H and 4-H), 2.53 (2 H, t, $J_{2,3}$ 6.9, 2-H), 3.47 (m, 2 H, 6-H) and 3.63 (m, 1 H, 5-H); δ_C(CD_3OD) 121.4 (C-1), 72.5 (C-5), 67.3 (C-6), 33.4 (C-2), 23.1 (C-4) and 17.5 (C-3).

(±)-cis-2-*Hydroxycyclopentanecarbonitrile*[23] **19a**. δ_C($CDCl_3$) 120.59 (CN), 72.99 (C-2), 36.40 (C-1), 33.59 (C-3), 28.00 (C-5) and 21.90 (C-4).

(±)-cis-2-*Hydroxycyclohexanecarbonitrile* **20a**. This compound was synthesized according a literature procedure:[23] δ_H see ref. 31; δ_C($CDCl_3$) 121.2 (CN), 66.45 (C-2), 36.19 (C-1), 31.60 (C-3), 26.67 (C-6), 22.82 (C-4) and 22.01 (C-5).

General Procedure for the Enzymatic Hydrolysis of Nitriles.—Substrate and immobilized enzyme respectively were suspended in phosphate buffer (0.1 mol dm^{-3}, pH = 7.0; 50 cm^3) and the mixture was shaken at 200 rpm at room temperature. The biocatalyst was removed by either filtration or centrifugation when TLC or GLC had indicated that all the starting material had been converted into, in most cases, a single more polar product. The resulting solution was evaporated to dryness, resuspended in toluene and again evaporated. The residue was stirred with anhydrous methanol (20–40 cm^3) and the suspension was filtered and the filtrate concentrated under reduced pressure. The product was further purified by silica gel chromatography if necessary. The following compounds were thus obtained:

1,1-*Diethyl* 3-*hydrogen propane*-1,1,3-*tricarboxylate* **2c** (530 mg, 92%) from **2a** (530 mg); ν_{max}(Nujol)/cm^{-1} 1740–1750 (ester C=O), 1720–1735 (acid C=O); δ_H([$^2H_6$]-DMSO) 1.21 (6 H, t, J 7.1, CH_3CH_2), 1.98 (4 H, m, 2-H and 3-H), 3.55 (1 H, t, $J_{1,2}$ 7.3, 1-H), 4.14 (4 H, q, CH_3CH_2) and 4.50 (1 H, br s, D_2O exchangeable, CO_2H); δ_C([$^2H_6$]-DMSO) 175.5 (CO_2H), 169.4 (CO_2Et), 60.9 (CH_3CH_2), 51.1 (C-1), 34.1 and 25.4 (C-2 and C-3) and 14.1 (CH_3CH_2) (Found: C, 51.4; H, 7.1. $C_{10}H_{16}O_6$ requires C, 51.7; H, 6.9%).

Diethylphosphonoacetic acid[32] **3c** (220 mg, 41%) from **3a** (500 mg).

4,4-*Diethoxybutanoic acid* [33] **6c** (280 mg, 46%) from **6a** (500 mg); ν_{max}(film)/cm^{-1} 1710 (C=O); δ_H($CDCl_3$) 1.12 (6 H, t, J 7.2, CH_3), 1.82 (2 H, dxt, J 7.2 and 7.5, 3-H), 2.27 (2 H, t, J 7.2, 2-H), 3.42 (2 H, m, CH_2O), 3.58 (2 H, m, CH_2O), 4.46 (1 H, t,

J 7, 4-H) and 8.25 (1 H, br s, D_2O exchangeable, CO_2H); $\delta_C(CDCl_3)$ 179.2 (C-1), 102.20 (C-4), 61.52 (CH_2O), 30.45 (C-2), 29.23 (C-3) and 15.29 (CH_3).

(±)-4-(2,2-*Dimethyldioxolan*-4-*yl*)*butanoic acid*[34] **7c** (45 mg, 41%) from **7a** (100 mg); ν_{max}(film)/cm^{-1} 1716 (C=O); $\delta_H(CDCl_3)$ 1.36 and 1.41 (3 H, s, CH_3), 1.50–1.90 (4 H, m, 3-H and 4-H), 2.42 (2 H, m, 2-H), 3.53 (1 H, m, 4′-H), 4.0–4.2 (2 H, m, 5′-H) and 10.05 (1 H, br s, D_2O exchangeable, CO_2H); $\delta_C(CDCl_3)$ 179.0 (C-1), 109.13 (C-2′), 75.81 (C-4′), 69.42 (C-5′), 33.95 (C-2), 33.02 (C-4), 25.80 and 27.07 (CH_3) and 21.18 (C-3).

(±)-5,6-*Dihydroxyhexanoic acid*[34] **9c** (73 mg, 50%) from **9a** (133 mg); ν_{max}(film)/cm^{-1} 1715 (C=O); $\delta_H([^2H_6]$-DMSO) 1.15–1.90 (4 H, m, 3-H and 4-H), 2.12 (2 H, t, $J_{2.3}$ 7.3, 2-H), 3.30 (2 H, m, 6-H), 3.43 (1 H, m, 5-H) and 4.44 (3 H, br s, D_2O exchangeable, OH, CO_2H); $\delta_C([^2H_6]$-DMSO) 179.9 (C-1), 73.2 (C-5), 67.5 (C-6), 36.3 (C-2), 34.2 (C-4) and 22.8 (C-3).

3-*Hydroxypropionic acid*[35] **10c** (370 mg, 63%) from **10a** (560 mg); ν_{max}(film)/cm^{-1} 1700 (C=O); $\delta_H([^2H_6]$-DMSO) 2.25 (2 H, t, $J_{2.3}$ 6.3, 2-H), 3.60 (2 H, t, 3-H) and 5.73 (2 H, br s, D_2O exchangeable, OH, CO_2H); $\delta_C([^2H_6]$-DMSO) 175.9 (C-1), 58.4 (C-3) and 39.6 (C-2).

(±)-3-*Hydroxyheptanoic acid*[36] **11c** (390 mg, 62%) from **11a** (550 mg); m.p. 40–41 °C (from light petroleum); ν_{max}(Nujol)/cm^{-1} 1710 (C=O); $\delta_H([^2H_6]$-DMSO) 0.91 (3 H, t, $J_{6.7}$ 6.4, 7-H), 1.34 (6 H, m, 4-H through 6-H), 2.23 (1 H, dd, $J_{2.2'}$ 14.9, $J_{2.3}$ 7.8, 2-H), 2.31 (1 H, dd, $J_{2'.3}$ 5.1, 2′-H), 3.81 (1 H, m, 3-H) and 4.18 (2 H, br s, D_2O exchangeable, OH, CO_2H); $\delta_C[^2H_6]$-DMSO) 174.3 (C-1), 67.5 (C-3), 43.3 (C-2), 36.8 (C-4), 27.6 and 22.5 (C-5 and C-6) and 14.3 (C-7).

(±)-3-*Hydroxynonanamide* **12b** (60 mg, 26% after 1 h) from **12a** (207 mg); m.p. 66–68 °C (from MeOH–CH_2Cl_2); ν_{max}(Nujol)/cm^{-1} 1655 (C=O); $\delta_H([^2H_6]$-DMSO) 0.86 (3 H, t, $J_{8.9}$ 6.2, 9-H), 1.30 (10 H, m, 4-H through 8-H), 2.13 (2 H, d, $J_{2.3}$ 6.4, 2-H), 3.67 (1 H, m, 3-H), 4.61 (1 H, d, $J_{3.OH}$, 5.2, OH), 6.79 (1 H, s, NH_2) and 7.25 (1 H, s, NH_2); $\delta_C[^2H_6]$-DMSO) 173.5 (C-1), 67.6 (C-3), 43.5 (C-2), 37.1 (C-4), 31.5, 29.0, 25.2 and 22.3 (C-5 through C-8) and 14.1 (C-9) (Found: C, 62.7; H, 10.8; N, 7.9. $C_9H_{19}NO_2$ requires C, 62.4; H, 11.1; N, 8.1%).

(±)-3-*Hydroxynonanoic acid*[37] **12c** (470 mg, 83% after 24 h) from **12a** (500 mg); $\delta_C([^2H_6]$-DMSO) 174.4 (C-1), 67.6 (C-3), 43.4 (C-2), 37.3 (C-4), 31.6, 29.1, 25.4 and 22.4 (C-5 through C-8) and 14.2 (C-9).

3-*Methoxypropanoic acid*[38] **13c** (320 mg, 52%) from **13a** (500 mg); ν_{max}(film)/cm^{-1} 1716 (C=O); $\delta_H(CDCl_3)$ 2.5 (2 H, t, $J_{2.3}$ 7, 2-H), 3.65 (3 H, s, CH_3), 3.75 (2 H, t, 3-H) and 10.15 (1 H, br s, D_2O exchangeable, CO_2H); $\delta_C(CDCl_3)$ 176.74 (C-1), 67.92 (CH_3), 58.48 (C-3) and 34.89 (C-2).

(±)-cis-2-*Hydroxycyclopentanecarboxylic acid*[23] **19c** (580 mg, 50%) from **19a** (1 g); $\delta_C(CDCl_3)$ 177.9 (CO_2H), 73.34 (C-2), 50.10 (C-1), 34.70 (C-3), 26.27 (C-5) and 22.11 (C-4).

(±)-cis-2-*Hydroxycyclohexanecarboxylic acid*[39] **20c** (980 mg, 85%), from **20a** (1.0 g); $\delta_H([^2H_6]$-DMSO) 1.15–2.00 (8 H, m, 3-H through 6-H), 2.48 (1 H, m, 1-H), 4.21 (1 H, br s, 2-H) and 7.88 (2 H, br s, D_2O exchangeable, OH and CO_2H); $\delta_C(CDCl_3)$ 180.18 (CO_2H), 67.40 (C-2), 46.61 (C-1), 31.61 (C-3), 24.59 (C-6), 23.99 (C-4) and 20.42 (C-5).

(±)-trans-2-*Hydroxycyclohexanecarboxylic acid*[40] **21c** (43 mg, 47%) from **21a** (80 mg); $\delta_C([^2H_6]$-acetone) 176.57 (CO_2H), 71.38 (C-2), 52.08 (C-1), 35.24 (C-3), 29.01 (C-6), 25.60 (C-5) and 25.07 (C-4).

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