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On the Diastereoselectivity of Cyanide Addition to β-Hydroxyketones: One-Pot Synthesis of *syn* β-hydroxycyanohydrins and *anti* 2,4-Dihydroxyamides

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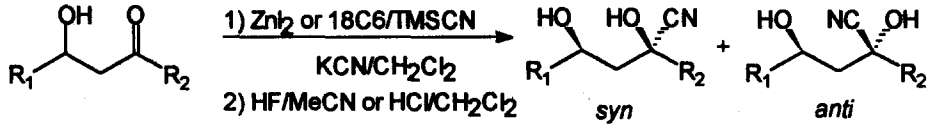
Abstract. The intrinsic stereoselectivity of the cyanide addition to β-hydroxyketones in the presence of 18-crown-6 or ZnI_2 is lower than that previously reported. However, the reaction bears a practical value in that *syn* β-hydroxycyanohydrins and *anti* 2,4-dihydroxyamides can be diastereoselectively obtained in reasonable yields in a one-pot procedure. The high d.e.'s initially reported were due to the work-up procedure, where the HCl converted much faster the *anti* β-hydroxycyanohydrin than the *syn* product into the corresponding amide. This faster conversion is explained in terms of anchimeric assistance of β-hydroxyl group. Details are given as to the configurational assignment of products by 2D NMR and molecular mechanics.

Introduction

The stereoselective production of 1,3-diols has attracted much attention in recent years because this functionality is recurrently present in a great variety of important natural products.[2] Synthesis of 1,3-diols may be achieved by addition of nuclophiles to β-hydroxyaldehydes or ketones.[3] Reduction of the latter compounds has been thoroughly studied and it can be directed to produce either *syn* or *anti* 1,3-diols depending on the reagents and conditions.[4] The addition of cyanide to β-hydroxyketones would lead to β-hydroxycyanohydrins, an attractive class of 1,3-diols whose additional nitrile function may open an entry to a number of new useful synthetic intermediates such as aminodiols and hydroxylated pyrrolidines.[5] However, the only paper to our knowledge concerning cyanide addition to β-hydroxyketones described a single example which proceeded with almost no diastereoselectivity.[6] In contrast, we have reported in preliminary communications that such an addition took place with high diastereoselectivity and reasonable chemical yields in certain conditions.[7] We hereby give full details of our recent investigations regarding addition of cyanide to β-hydroxyketones and transformation of the resulting β-hydroxycyanohydrins.

Results and Discussion

The results of the addition of CN^- to a variety of β-hydoxyketones (Scheme I, $R_1 = R_2$ = alkyl or aryl) are summarized in Table 1.



Scheme I

The listed isomer ratios of β-hydroxycyanohydrins were measured from the ^{1}H-nmr spectra of the reaction mixtures (integration of the methine carbinol protons) immediately after the corresponding reaction work-up without any further manipulation. The chemical yields refer to isolated and purified products. The configuration of the major isomer was deduced in all cases to be *syn* (Scheme I) as it will be explained in detail in the configurational assignment section.

Table 1.- Results of the addition of cyanide to several β-hydroxyketones in various conditions (see text).

			ZnI_2 reaction			18-crown-6 reaction			
			HF	HCl		HF	WS[a]/HF	HCl	
Entry	R_1	R_2	*syn:anti*[b]	d.e.(%)	yield[c]	*syn:anti*[b]	*syn:anti*	d.e.(%)	yield
1	Et	*i*-Bu	55:45(20)	90	30	60:40	58:42	90	50
2	Et	*t*-Bu	95:5	>95	82	57:43	55:45	>95	55
3	*i*-Pr	Me	-[d] (20)	>95	50	80:20(5)		>95	60
4	*i*-Pr	Et	-[d] (50)	>95	40	60:40	60:40	>95	60
5	*i*-Pr	*i*-Pr	65:35	>95	55	86:14	70:30	>95	77
6	*i*-Pr	*i*-Bu	70:30(50)	>90	30	65:35	60:40	>90	60
7	*i*-Pr	*t*-Bu	82:18	>95	78	55:45	57:43	>95	45
8	*i*-Pr	Ph	-[e]			60:40		>95	48
9	*i*-Bu	*i*-Bu	50:50(50)	90	20	50:50(50)	50:50	90	25
10	Bn	*i*-Bu	55:45(15)	>95	30	52:48(25)		90	25

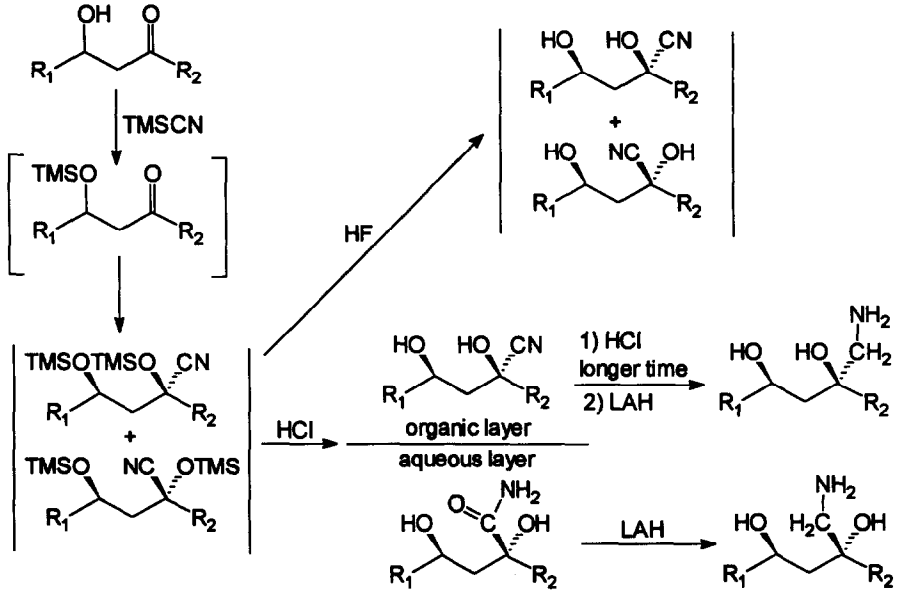
[a] Reaction without solvent. [b] Figures in parenthesis give approximate ratio (%) of unreacted β-hydroxyketone relative to cyanohydrin. [c] Isolated *syn* product. [d] Methine signals not well resolved with that of starting material. [e] No reaction.

The reactions of Table 1 were performed with TMSCN/KCN in CH_2Cl_2, in the presence of either an equivalent of ZnI_2 or a catalytic amount of 18-crown-6.[8] In the latter case, the reaction was also carried out without solvent (WS heading in Table 1). Two different work-up procedures were used (see Scheme I and experimental part) as stated in the Table under HF and HCl headings.

From the organic layer of the HCl work-up (HCl headings in Table 1) of the reaction with either ZnI_2 or 18-crown-6, we isolated almost exclusively the *syn* isomer (d.e.'s >90%; see Table 1) in an average 50% yield after purification. Thus, from a strictly practical point of view, the reaction was highly diastereoselective. But we found disturbing the fact that the diastereoselectivity was independent of the starting material and, most intriguing, of the additive considering that a different mechanism (kinetic *vs.* thermodynamic) has been proposed for cyanide addition to ketones with ZnI_2 and 18-crown-6.[8] This fact

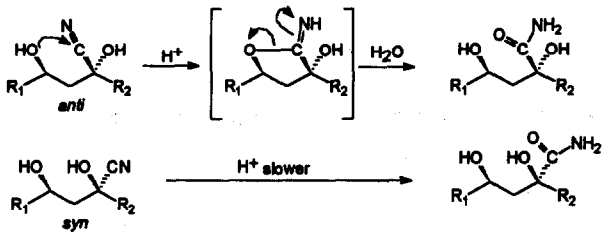
made us to question whether the high d.e.'s obtained came from the addition itself or from some kind of fortituous diastereomer isolation in the work-up procedure.

We noticed that in both cases (ZnI_2 or 18-crown-6), ^{1}H-nmr spectra of the crude reaction mixture showed, before acid treatment, the presence of a mixture of trimethylsilyl derivatives whose ^{13}C-nmr spectra contained the expected CN signals at *ca.* 121 ppm but revealed the presence of two major components in an average *ca.* 2:1 ratio. From these data we were unable to ascertain whether these compounds were TMS derivatives of *syn* and *anti* isomers or different TMS derivatives of the same isomer. To solve the problem we started looking for a different method for silyl ether cleavage to avoid any side effect. After unsuccesfully trying several methods,[9] some of which gave no reaction or decyanation, we found that the treatment of the TMS derivatives with HF in CH_3CN[10] rendered a mixture of two non-TMS-containing compounds which, after separation and purification, resulted to be *syn* and *anti* isomers of the corresponding β-hydroxycyanohydrins (Scheme II) in the ratios shown in Table 1 (HF headings).



Scheme II

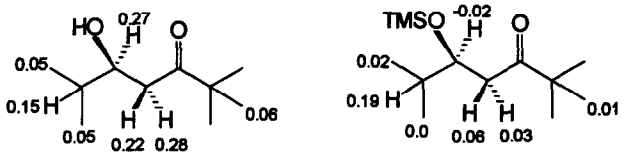
Although there were cases where the selectivity was in fact relatively high (see entries 2 and 7 for ZnI_2 and 3 and 5 for 18-crown-6 in Table 1), evidence forced us to conclude that the reaction was not in general intrinsically diastereoselective. Therefore, our previously reported high diastereoselectivity in the addition of CN^- to β-hydroxyketones must be occasioned by the HCl treatment, which caused the destruction of *anti* isomer, leaving *syn* isomer intact in the organic layer of the HCl work-up procedure. Analysis of the acid aqueous layer revealed that it contained essentially a single product, whose spectroscopic data coincided with the corresponding *anti* 2,4-dihydroxyamide (Scheme II). On the other hand, the isolated *syn* cyanohydrin was also transformed into the corresponding *syn* amide by simply prolonging its reaction time with HCl in the same conditions.



Scheme III

This configurationally dependent behavior of β-hydroxycyanohydrins towards concentrated HCl can be easily explained in terms of anchimeric assistance of remote OH group (Scheme III), which in the *anti* isomer bears an 1,3-parallel relationship to CN group and may thus facilitate hydrolysis of the latter .

The low diastereoselectivity observed with ZnI_2 contrasts with that observed in similar processes where the formation of relatively rigid chelates between C=O group and the metal accounted for high selectivities.[11] However, in our reaction TMSCN must convert first the OH group into OTMS (Scheme II) presumably hampering chelate formation. Scheme IV shows that the proton Δδ (ppm) induced by an equimolecular amount of ZnI_2 in $CDCl_3$ was much lower in the TMS derivative than in the parent β-hydroxyketone suggesting that chelation was, as anticipated, much less favorable in the silylated compound.

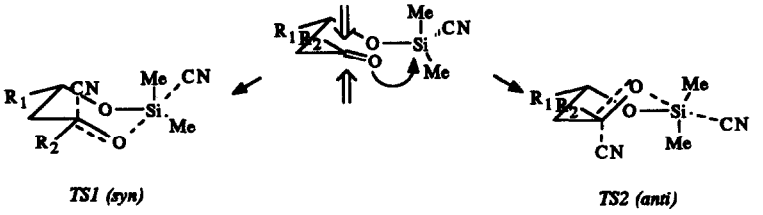


Scheme IV

On the other hand, it has been demonstrated that TIPS (triisopropylsilyl) substitution at oxygen makes this atom unable to chelate to metals.[12] In fact, no change at all was observed in the ^1H nmr spectrum of TIPS derivative of β-hydroxyketone[13] of Scheme IV upon addition of one equivalent of ZnI_2 in $CDCl_3$. Addition of TMSCN with ZnI_2 to that TIPS derivative rendered similar results (*syn:anti* ratio 85:15) compared to those obtained for the unsubstituted β-hydroxyketone (82:18, entry 7 of Table 1). We therefore concluded that ZnI_2 did not play a role as significant as initial data (entries under HCl heading in Table 1) suggested.

The addition of TMSCN to 4-*tert*-butylcyclohexanone with 18-crown-6 has been claimed to take place by thermodynamic control. The low diastereoselectivity observed in our case is thus not surprising because it should reflect the relative stabilities of the *syn* and *anti* di(trimethylsilyl)-β-hydroxycyanohydrins, which should not be very different without the possibility of hydrogen bonding formation.

We have tried to perform CN addition to β-hydroxyketones with dimethyldicyanosilane, $Me_2Si(CN)_2$ (DDS), in the hope that this reagent could transfer CN intramolecularly and increase the ratio of *anti* product, as it happened in the corresponding reductions of β-hydroxyketones with $Me_4NHB(OAc)_3$.[14] Interestingly, none of the *anti* isomer was detected in this reaction[7b] strongly suggesting intermolecular addition of cyanide in a chair-like silyl-bridged transition state (TS1 in Scheme V).

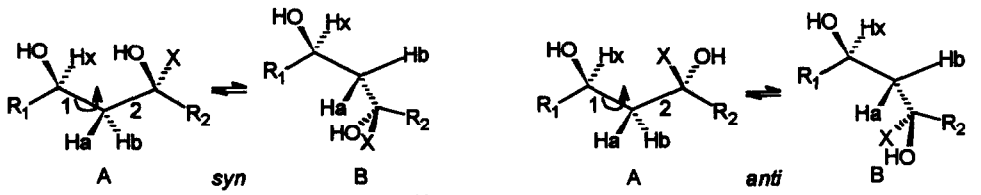


Scheme V

Reduction of cyanohydrins and amides with $LiAlH_4$ led to the corresponding 1-amino-2,4-dihydroxyderivatives (Scheme II) in good yields, although a small production of 1,3-diols (decyanation) was detected for cyanohydrin reduction. The best results were obtained with 1.2 eq. of reducing agent. The amines were used, in addition to some of the cyanhydrins themselves, to assign configurations (*vide infra*). Amides yielded lactones upon standing overnight with diluted hydrochloric acid.

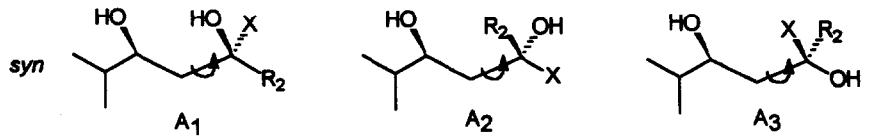
Configurational assignment

We have assigned configurations of some β-hydroxycyanohydrins and 1-amino-2,4-dihydroxyderivatives by 2D NMR COLOC experiment[15] tuned for antiperiplanar $^3J_{CH}$ (*ca.* 8 Hz) or proton detected long-range $^1H/^{13}C$ correlation,[16] on the assumption that the most stable conformers of *syn* and *anti* isomers are those labeled as A in Scheme VI.



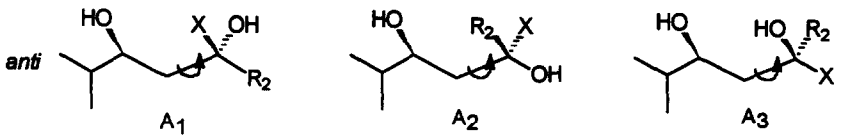
Scheme VI

Table 2.- Conformational energies as calculated by MMP2 of conformers around bond 2 of Scheme VI.



R_2	X	E(MMP2)[a]	E(MMP2)	E(MMP2)
Me	CN	**0.0**	0.9	1.0
	CH_2NH_2	**0.0**	0.7	1.3
t-Bu	CN	**0.0**	4.4	3.0
	CH_2NH_2	**0.0**	1.9	[b]

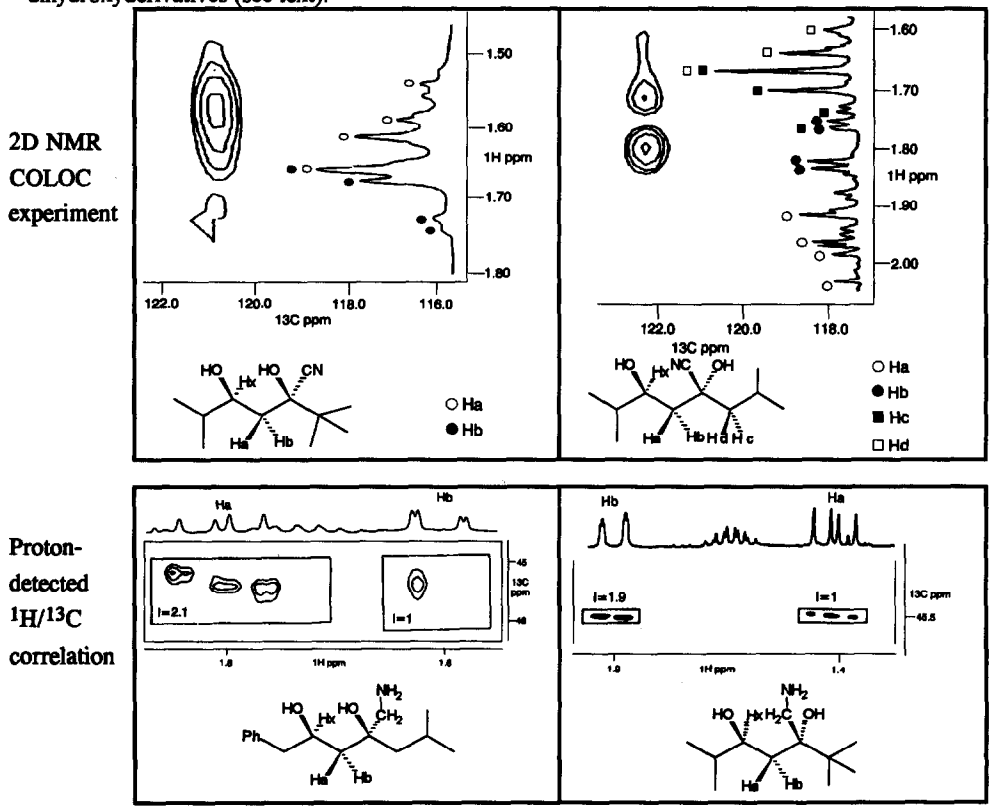
[a] Relative energy (kcal/mol). [b] Starting with an A_3 geometry, MMP2 converged to A_1 conformer.



R_2	X	E(MMP2)[a]	E(MMP2)	E(MMP2)
Me	CN	**0.0**	0.5	0.6
	CH_2NH_2	**0.0**	0.4	0.5
t-Bu	CN	**0.0**	1.7	2.4
	CH_2NH_2	**0.0**	1.5	0.9

[a] Relative energy (kcal/mol).

Figure 1.- Examples of 2D NMR spectra of β-hydroxycyanohydrins and 1-amino-2,4-dihydroxyderivatives (see text).



The observed vicinal coupling constants (*ca.* 9.5 and 2.5 Hz; *cf.* Tables 3 and 4) among Ha, Hb and Hx, typically *anti* and *gauche* respectively, are compatible with two conformers (A and B in Scheme VI) around bond 1. However, B should be much less stable because of the *gauche* interaction between R_1 and the quaternary carbon to which OH, X and R_2 groups are attached. Concerning bond 2 (Scheme VI),

MMP2 calculations[17] of some β-hydroxycyanohydrins (X=CN) and 1-amino-2,4-dihydroxyderivatives ($X=CH_2NH_2$) (Table 2) supported our hypothesis that A_1 conformers are the most stable, even in the case where R_2 is the smallest (Me).

Table 3.- ^1H NMR data of β-hydroxycyanohydrins.

En	R_1	R_2	Is.	(δ. J)Ha[a]	(δ. J)Hb[a]	(δ. J)Hx	(δ. J)R_1	(δ. J)R_2
1c	Et	*i*-Bu	*syn*	1.75 (dd) $J_{a,b}$=14.6	1.85 (dd) $J_{b,x}$=3.3	4.25 (m) $J_{a,x}$=9.8	0.96 (t, 3H, J=7), 1.47 (m, 2H)	1.03 (d, 3H, J=7.3), 1.05 (t, 3H, J=6.7), 1.62 (m, 1H),1.53 (m, 2H)
			anti	1.83 (m)	1.83 (m)	3.9 (m)	0.92 (t, 3H, J=7), 1.51 (m, 2H)	1.02 (d, 6H, J=7.3), 1.65(m, 3H)
2c	Et	*t*-Bu	*syn*	1.70 (dd) $J_{a,b}$=14.4	1.83 (dd) $J_{b,x}$=3.1	4.23 (m) $J_{a,x}$=9.5	0.90 (t, 3H, J=7), 1.55 (m, 2H)	1.04 (s, 9H)
			anti	1.90 (m)	1.90 (m)	4.12 (m)	0.95 (t, 3H, J=7), 1.55 (m, 2H)	1.05 (s, 9H)
3c	*i*-Pr	Me	*syn*	1.75 (dd) $J_{a,b}$=14.5	1.85 (dd) $J_{b,x}$=3.2	3.98 (m) $J_{a,x}$=9.9	0.87 (d, 6H, J=7.6), 1.56 (m, 1H)	1.53 (s, 3H)
			anti	2.05 (dd) $J_{a,b}$=14.5	1.87 (dd) $J_{b,x}$=3.3	3.98 (m) $J_{a,x}$=9.9	0.88 (d, 6H, J=6.7), 1.65 (m, 1H)	1.56 (s, 3H)
4c	*i*-Pr	Et	*syn*	1.79 (dd) $J_{a,b}$=14.7	1.72 (dd) $J_{b,x}$=3.2	4.01 (ddd) $J_{a,x}$=10.2	0.88 (d, 6H, J=6.7), 1.65 (m, 1H), $J_{x,CH}$=5.4	1.05 (t, 3H, J=7), 1.65 (m, 2H)
			anti	2.09 (dd) $J_{a,b}$=14.7	1.90 (dd) $J_{b,x}$=2.0	3.80 (m) $J_{a,x}$=9.9	0.92 (d, 6H, J=6.8), 1.67 (m, 1H)	1.11 (t, 3H, J=7), 1.79 (m, 2H)
5c	*i*-Pr	*i*-Pr	*syn*	1.73 (dd) $J_{a,b}$=13.4	1.90 (dd) $J_{b,x}$=3.6	4.09 (m) $J_{a,x}$=10.2	0.87 (d, 3H, J=6.7), 0.89 (d, 3H, J=6.7), 1.63 (m, 1H)	1.07 (d, 3H, J=6.8).1.09 (d, 3H, J=6.8), 1.65 (m, 1H)
			anti	2.07 (dd) $J_{a,b}$=14.8	1.97 (dd) $J_{b,x}$=3.9	3.8 (m) $J_{a,x}$=8.8	0.94 (d, 3H, J=6.8), 0.95 (d, 3H, J=6.8), 1.73 (m, 1H)	1.03 (d, 3H, J=6.8), 1.18 (d, 3H, J=6.8), 1.70 (m, 1H)
6c	*i*-Pr	*i*-Bu	*syn*	1.72 (m)	1.72 (m)	4.01 (m)	0.90 (d, 3H, J=6.8), 0.94 (d, 3H, J=6.8), 1.65 (m, 1H)	1.03 (d, 3H, J=6.7), 1.06 (t, 3H, J=6.7), 2.00 (m, 3H)
			anti	1.98 (dd) $J_{a,b}$=14.7	**1.78 (dd)** **$J_{b,x}$=2.5**	3.82 (m) $J_{a,x}$=10.0	0.91 (d, 3H, J=6.8), 0.92 (d, 3H, J=6.8), 1.95 (m, 1H)	1.02 (m, 6H), 1.66 (dd, 1H, J=5.8,14.3), 1.77 (dd, 1H, J=6.8, 14.3), 1.95 (m, 1H)
7c	*i*-Pr	*t*-Bu	*syn*	**1.69 (dd)** $J_{a,b}$=14.6	1.79(dd) $J_{b,x}$=3.2	4.12 (ddd) **$J_{a,x}$=10.0**	0.98 (d, 6H, J=6.7), 1.65 (m, 1H), $J_{x,CH}$=5.2	1.08 (s, 9H)
			anti	1.84 (dd) $J_{a,b}$=14.6	1.95(dd) $J_{b,x}$=4.0	3.77 (m) $J_{a,x}$=8.1	0.94 (d, 3H, J=6.7), 0.96 (d, 3H, J=6.7), 1.77 (m, 1H)	1.07 (s, 9H)
8c	*i*-Pr	Ph	*syn*	1.95 (m)	1.95 (m)	4.45 (m)	0.92 (d, 3H, J=6.8), 0.97 (d, 3H, J=6.8), 1.70 (m, 1H)	7.40 (m, 5H)
			anti	2.42 (dd) $J_{a,b}$=14.6	2.25 (dd) $J_{b,x}$=2.5	3.50 (m) $J_{a,x}$=9.8	0.93 (d, 3H, J=6.7), 0.99 (d, 3H, J=6.8), 1.73 (m, 1H)	7.40 (m, 5H)
9c	*i*-Bu	*i*-Bu	*syn*	1.70 (dd) $J_{a,b}$=14.8	1.80 (dd) $J_{b,x}$=4.0	4.40 (m) $J_{a,x}$=10.5	0.91 (m, 6H), 1.18 (m, 1H), 1.64 (m, 2H)	1.00 (d, 3H, J=6.6), 1.02 (t, 3H, J=6.6), 1.49 (m, 1H),2.00 (m, 2H)
			anti	2.04 (dd) $J_{a,b}$=14.7	**1.88 (dd)** **$J_{b,x}$=3.0**	4.10 (m) $J_{a,x}$=9.8	0.90 (m, 6H), 1.28 (m, 1H), 1.55 (m, 2H)	0.94 (d, 3H, J=6.6), 1.27 (m, 1H), 1.71 (m, 2H), 2.00 (m, 2H)
10c	Bn	*i*-Bu	*syn*	1.88 (m)	1.88 (m)	4.50 (m)	2.72 (dd, 1H, J=8.3,13.5), 2.85 (dd, 1H, J=4.7,13.5), 7.25, (m, 5H)	1.01 (d, 3H, J=6.7), 1.03 (t, 3H, J=6.7), 1.58 (dd, 1H, J=6.7, 14.3), 1.70 (dd, 1H, J=6.2, 14.3), 2.02 (m, 1H)
			anti	2.14 (dd) $J_{a,b}$=14.6	**1.98 (dd)** **$J_{b,x}$=3.4**	4.25 (m) $J_{a,x}$=9.1	2.83 (m, 2H), 7.25, (m, 5H)	0.98 (d, 3H, J=6.6), 1.03 (t, 3H, J=6.6), 1.64 (dd, 1H, J=6.0, 14.5), 1.74 (dd, 1H, J=6.6, 14.5), 1.87 (m, 1H)

[a] Boldfaced numbers indicate the protons correlated to CN in the 2D NMR long range correlation (see text).

In the conformations A (Scheme VI), the carbon atom of X group is always *antiperiplanar* and *gauche* relative to its β-protons, Ha and Hb, and its corresponding coupled ^{13}C signal should therefore contain two $^{3}J_{CH}$ coupling constants of *ca.* 8 (*anti*) and 2 (*gauche*) Hz. In the *syn* isomer, the higher $^{3}J_{CH}$ coupling is attained with Ha which should also display a high $^{3}J_{HH}$ (*anti*) with Hx, whereas in the *anti* isomer the proton antiperiplanar to X is Hb which should bear a smaller $^{3}J_{HH}$ coupling (*gauche*) with Hx. Therefore, in the aforementioned 2D NMR spectra, the carbon of X group of *syn* and *anti* isomers should exhibit a correlation signal of higher intensity with the β-methylene proton exhibiting the greater or the smaller vicinal coupling constant, respectively, with Hx. Figure 1 shows some examples.

Table 4.- ^{1}H NMR data of 1-amino-3,5-dihydroxyderivatives.

Ent.	R_1	R_2	Isom.	(δ. J)Ha[a]	(δ. J)Hb[a]	(δ. J)Hx	(δ. J)CH_2N	(δ. J)R_1	(δ. J)R_2
2m	Et	*t*-Bu	*syn*	**1.72 (dd)** $J_{a,b}$=14.6	1.45 (dd) $J_{b,x}$=1.7	3.75 (m) **$J_{a,x}$=10.4**	2.64, 3.07 J=13.2	0.94 (t, 3H, J=7.4) 1.48 (m, 2H)	0.90 (s, 9H)
			anti	1.47 (dd) $J_{a,b}$=14.9	**1.89 (ddd)** **$J_{b,x}$=1.3** $J_{b,CH2}$=1.3	3.72 (m) $J_{a,x}$=10.1	2.64, J=12.2 3.06, J=1.3,12.2	0.96 (t, 3H, J=7.2) 1.50 (m, 2H)	0.94 (s, 9H)
4m	*i*-Pr	Et	*syn*	**1.64 (dd)** $J_{a,b}$=14.6	1.51 (dd) $J_{b,x}$=2.7	3.56 (m) **$J_{a,x}$=9.9**	2.68, 2.81 J=12.6	0.90 (d, 3H, J=6.7) 0.92 (d, 3H, J=6.7) 1.60 (m, 1H)	0.89 (t, 3H, J=7. 1.48 (q, 2H, J=7.
			anti	1.57 (dd) $J_{a,b}$=14.9	**1.77 (dd)** **$J_{b,x}$=2.0**	3.45 (m) $J_{a,x}$=10.4	2.58, 2.72 J=12.8	0.91 (d, 3H, J=6.8) 0.93 (d, 3H, J=6.8) 1.63 (m, 1H)	0.85 (t, 3H, J=7 1.47 (q, 2H, J=7
6m	*i*-Pr	*i*-Bu	*syn*	1.71 (dd) $J_{a,b}$=14.5	1.49 (dd) $J_{b,x}$=1.7	3.53 (m) $J_{a,x}$=10.6	2.66, 2.80 J=12.6	0.88 (d, 3H, J=6.9) 0.89 (d, 3H, J=6.9) 1.35 (m, 1H)	0.92 (d, 3H, J=6. 0.93 (t, 3H, J=6. 1.35 (m, 1H) 1.70 (m, 2H)
			anti	1.52 (m)	1.52 (m)	3.75 (m)	2.62, 2.77 J=13.5	0.92 (d, 3H, J=6.8) 0.93 (d, 3H, J=6.8) 1.66 (m, 1H)	0.95 (d, 3H, J=6. 0.97 (t, 3H, J=6. 1.59 (m, 2H) 1.65 (m, 1H)
7m	*i*-Pr	*t*-Bu	*syn*	**1.71 (dd)** $J_{a,b}$=14.6	1.41(dd) $J_{b,x}$=+1.6	3.60 (m) **$J_{a,x}$=10.5**	2.60, 3.10 J=13.2	0.92 (d, 3H, J=6.7) 0.93 (d, 3H, J=6.7) 1.60 (m, 1H)	0.91 (s, 9H)
			anti	1.45 (dd) $J_{a,b}$=14.9	**1.89(ddd)** **$J_{b,x}$=1.4** $J_{b,CH2}$=1.0	3.53 (m) $J_{a,x}$=10.5	2.61, J=12.3 3.04, J=12.3, 1.0	0.93 (d, 3H, J=6.8) 0.94 (d, 3H, J=6.8) 1.66 (m, 1H)	0.95 (s, 9H)
10m	Bn	*i*-Bu	*syn*	**1.79 (dd)** $J_{a,b}$=14.6	1.57(dd) $J_{b,x}$=1.9	4.06 (m) **$J_{a,x}$=10.3**	2.62, 2.75 J=12.6	2.66 (dd, 1H, J=6.3, 13.4) 2.87 (dd, 1H, J=7, 13.4) 7.35, (m, 5H)	0.89 (d, 3H, J=6. 0.95 (t, 3H, J=6. 1.31 (m, 3H)
			anti	1.55 (m)	1.55 (m)	4.17 (m)	2.54, 2.70 J=12.6	2.65 (dd, 1H, J=6.4, 13.3) 2.86 (dd, 1H, J=7, 13.3) 7.24, (m, 5H)	0.83 (d, 3H, J=6. 0.89 (t, 3H, J=6. 1.26 (dd, 1H) 1.41 (m, 2H)

[a] Boldfaced numbers indicate the protons correlated to CH_2N in the 2D NMR long range correlation (see text).

Limitations in instrument time made us to perform the 2D NMR analysis on a number of selected cases where, in addition, the chemical shift difference between Ha and Hb be reasonable (>20 Hz) to avoid undesirable strong second-order effects. Boldfaced numbers in Tables 3 and 4 summarize the results indicating which β-proton correlated to the X carbon (Scheme VI).

Table 5.- ^{13}C NMR data of β-hydroxycyanohydrins.

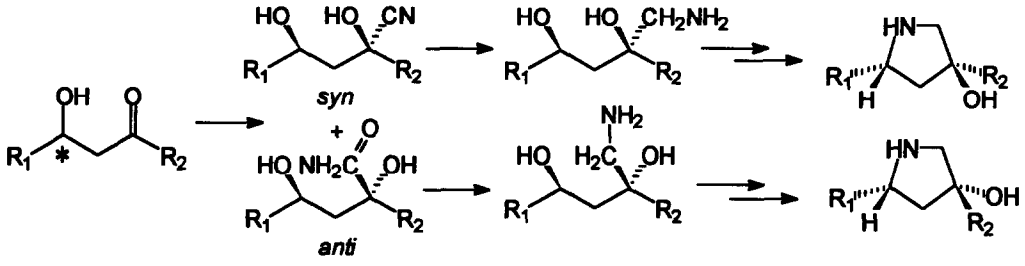
Ent.	R_1	R_2	Isom.	δC1	δC2	δC3	δCN	δR_1	δR_2
1c	Et	*i*-Bu	*syn*	72.3	49.3	72.0	121.7	9.1 (Me), 30.7 (CH_2)	23.5 (Me), 23.7 (Me), 24.3 (CH), 53.3 (CH_2)
			anti	69.6	44.8	70.2	121.0	9.5 (Me), 30.3 (CH_2)	23.7 (Me), 23.8 (Me), 24.4 (CH), 47.8 (CH_2)
2c	Et	*t*-Bu	*syn*	72.4	37.9	79.4	121.1	9.1 (Me), 30.9 (CH_2)	24.5 (Me)
			anti	70.6	39.4	75.8	122.0	10.1 (Me), 30.3 (CH_2)	24.6 (Me)
3c	*i*-Pr	Me	*syn*	75.8	42.2	69.1	121.0	17.8 (Me), 17.0 (Me), 34.0 (CH)	28.3 (Me)
			anti	75.0	42.9	68.9	121.5	17.3 (Me), 17.9 (Me), 33.8 (CH)	28.5 (Me)
4c	*i*-Pr	Et	*syn*	76.0	40.5	73.4	121.3	17.0 (Me), 18.0 (Me), 34.3 (CH)	8.1 (Me), 34.2 (CH_2)
			anti	73.0	40.8	72.3	121.7	17.2 (Me), 17.6 (Me), 33.9 (CH)	8.5 (Me), 32.7 (CH_2)
5c	*i*-Pr	*i*-Pr	*syn*	76.0	37.9	76.7	120.9	16.4 (Me), 16.9 (Me), 34.2 (CH)	17.7 (Me), 18.1 (Me), 37.4 (CH)
			anti	73.2	39.3	75.7	120.7	17.2 (Me), 17.5 (Me), 34.1 (CH)	17.2 (Me), 18.1 (Me), 36.0 (CH)
6c	*i*-Pr	*i*-Bu	*syn*	75.6	41.8	72.2	121.8	17.0 (Me), 17.9 (Me), 34.1 (CH)	23.6 (Me), 23.8 (Me), 24.4 (CH), 49.5 (CH_2)
			anti	73.3	42.6	70.1	122.2	17.3 (Me), 18.1 (Me), 34.1 (CH)	23.5 (Me), 23.9 (Me), 25.1 (CH), 47.8 (CH_2)
7c	*i*-Pr	*t*-Bu	*syn*	75.6	35.3	72.4	121.1	17.0 (Me), 18.0 (Me), 34.2 (CH)	24.5 (Me)
			anti	73.2	37.4	70.1	122.2	17.4 (Me), 18.6 (Me), 33.7 (CH)	24.4 (Me)
8c	*i*-Pr	Ph	*syn*	76.1	45.2	74.8	120.9	17.0 (Me), 17.8 (Me), 34.0 (CH)	123.0, 126.6, 130.2, 140.3
			anti	73.3	44.3	72.6	121.4	16.9 (Me), 17.8 (Me), 33.7 (CH)	124.9, 128.7, 139.4
9c	*i*-Bu	*i*-Bu	*syn*	69.2	45.2	72.1	121.7	22.1 (Me), 23.0 (Me), 24.1 (CH), 47.1 (CH_2)	23.5 (Me, 23.8 (Me), 24.4 (CH), 49.4 (CH_2)
			anti	66.9	46.0	70.4	122.1	22.0 (Me), 23.0 (Me), 24.3 (CH), 46.8 (CH_2)	23.6 (Me, 23.9 (Me), 25.0 (CH), 48.2 (CH_2)
10c	Bn	*i*-Bu	*syn*	71.7	44.3	71.8	121.5	44.6 (CH_2), 126.9, 128.7, 129.3, 136.4	23.5 (Me), 23.7 (Me), 24.4 (CH), 49.3 (CH_2)
			anti	69.6	44.0	70.4	122.0	44.8 (CH_2), 127.0, 128.8, 129.3, 136.8	23.5 (Me), 23.8 (Me), 25.0 (CH), 48.0 (CH_2)

In all the cases studied by 2D NMR, the isomer of β-hydroxycyanohydrins which survived the HCl work-up (*vide supra*) resulted to be *syn*. In the case of R_1 = *i*-Pr and R_2 = *t*-Bu the 2D NMR analysis of the "HCl-resistant" cyanohydrin (Table 3) and the corresponding amine (Table 4) gave a *syn* configuration for both compounds, assuring that reduction of CN to CH_2NH_2 did not affect, as expected, the stereochemistry of the stereocenters and that configuration of cyanohydrins and amines could be thus correlated.

It can be seen in Table 3 that the β-hydroxycyanohydrins whose configurational assignment was performed by 2D NMR on themselves or on the corresponding amines, displayed a Δδ of *ca.* -0.25 ppm for Hx in going from *syn* to *anti* isomers. This difference, which is much smaller in the corresponding amines (*cf.* Table 4), is consistent with the deshielding produced on Hx by the π electrons of CN group in 1,3-parallel arrangement to this proton in the *syn* isomer (Scheme VI). ^{13}C NMR data of β-hydroxycyanohydrins (Table 5) also shows some consistencies when going from *syn* to *anti* isomers, namely the shielding of C1 and C3 (*ca.* -2 ppm). The configurational assignment of the remaining β-hydroxycyanohydrins not analyzed by 2D NMR was based on these findings.

Conclusion

Although addition of cyanide with TMSCN to β-hydroxyketones did not result intrinsically diastereoselective, the reaction bears a practical value in that *syn* β-hydroxycyanohydrins and *anti* 2,4-dihydroxyamides can be easily isolated in reasonable yields. Starting form chiral non-racemic β-hydroxyketones[18] this reaction may be a valid entry to a number of useful optically active products as the 2,3-disubstituted-4-hydroxypyrrolidines shown in Scheme VII.



Scheme VII

Experimental Part

General. ^1H and ^{13}C NMR spectra were recorded on either Bruker AC-200 or AMX-300 instruments. IR spectra were measured on a Philips PU 9165 instrument. High resolution mass spectra (LSIMS) were obtained in a VG Autospec spectrometer located, as well as the AMX-300 NMR instrument, at the *Servicio Interdepartamental de Investigación* (SIdI) of the *Universidad Autónoma de Madrid.*

Preparation of β-hydroxyketones.- They were prepared by aldol reaction between a lithium enolate of a ketone and a aldehyde following a described procedure.[19] The crude hydroxyketones were purified by fractional distillation under reduced pressure or by column chromatography.

Numbering of hydroxyketones corresponds to the entries and R_1 and R_2 groupings of Tables 1, 3, 4 and 5.

General procedure for cyanide addition to β-hydroxyketones.- Reaction with solvent: To 5mmol of β-hydroxyketone in 10 mL of dichloromethane, 0.33 g (5 mmol) of KCN and 1.59 g (5 mmol) of ZnI_2 or a catalytic amount (5% eq.) of 18-crown-6, were added and the mixture was stirred (20 min.) under Ar at room temperature. The reaction mixture was cooled to 0°C and a solution of 1.24 g (12.5 mmol) of TMSCN in 10 mL of dichloromethane was injected and the resulting mixture was stirred overnight at 0°C. Water (10 mL) was added to the reaction mixture, the organic layer was separated, washed with water, dried (anh. Na_2SO_4) and the solvent evaporated. **Reaction without solvent:** A mixture of β-hydroxyketone (5 mmol), 0.33 g (5 mmol) of KCN and a catalytic amount (5% eq.) of 18-crown-6 was stirred at room temperature under Ar at room temperature. To this mixture, 1.24 g (12.5 mmol) of TMSCN were injected and the mixture stirred at room temperature for 30 min. Water (10 mL) and dichloromethane (25 mL) were then added to the reaction mixture which was vigorously stirred for 15 min. The organic layer was separated, washed with water, dried (anh. Na_2SO_4) and the solvent evaporated. **HCl work-up:** The crude mixture was treated with 1.5 mL of conc. HCl, diluted with 50 mL of water and stirred for no longer than 30 min. The aqueous solution was then extracted with dichloromethane (2x25 mL), the organic extracts dried (anh. Na_2SO_4) and the solvent evaporated. The resulting mixture was analyzed by ^{1}H-NMR containing mainly *syn* cyanohydrin which was purified by flash chromatography (ethyl acetate/hexane 5:1). The aqueous layer was carefully neutralyzed and extracted with dichloromethane (2x25 mL). Usual work-up of the organic extracts yielded the corresponding *anti* 2,4-dihydroxyamide. **HF work-up:** The crude product mixture was taken in acetonitrile (10 mL) and 1 mL of 40% aqueous HF solution was added. The mixture was allowed to stand at room temperature for 30 minutes and then poured into 20 mL of water. The resulting solution was extracted with dichloromethane (2x25 mL), the organic extracts dried (anh. Na_2SO_4) and the solvent evaporated. The crude product mixture was analyzed by ^{1}H-NMR and the resulting *syn* and *anti* cyanohydrins separated by flash chromatography (ethyl acetate/hexane 5:1).

^{1}H- and ^{13}C-NMR of β-hydroxycyanohydrins are collected in Tables 3 and 5, respectively.

Conversion of *syn* β-hydroxycyanohydrins into 2,4-dihydroxyamides. The β-hydroxy-cyanohydrin was stirred overnight at room temperature with a saturated solution of hydrogen chloride in ethyl ether. The organic solution was carefully washed with saturated sodium bicarbonate and worked-up as usual.

Numbering of 2,4-dihydroxyamides (followed by letter d) corresponds to the entries and R_1 and R_2 groupings of Tables 1, 3, 4 and 5.

Reduction of β-hydroxycyanohydrins and 2,4-dihydroxyamides to 2,4-dihydroxyamines. It was performed with $LiAlH_4$ following a described procedure.[8] ^{13}C data of amines are collected in Table 6.

High resolution mass spectra (HRMS) of selected β-hydroxycyanohydrins, 2,4-dihydroxyamines, 2,4-dihydroxyamides and γ-butyrolactones are indicated in Table 7.

Conversion of *syn* 2,4-dihydroxyamides into γ-butyrolactones. 2,4-Dihydroxyamide was suspended in 10% hydrochloric acid and stirred overnight at room temperature. Extraction with dichloromethane of the aqueous layer and usual work-up of the extracts yielded the corresponding γ-butyrolactone. Numbering of γ-butyrolactones (followed by letter l) corresponds to the entries and R_1 and R_2 groupings of Tables 1, 3, 4 and 5.

6-Hydroxy-2-methyl-4-octanone (1).- B.p. 75°C/0.5 mm Hg, ^{1}H NMR ($CDCl_3$) δ 0.89 (d, J=6.5Hz, 6H), 0.90 (t, J=7Hz, 3H), 1.45 (m, 2H), 2.10 (m, 1H) 2.28 (m, 2H), 2.48 (dd, J=17.5,7.2, 1H), 2.51 (dd, J=17.5,3.3, 1H), 3.67-3.76 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 212.1, 68.6, 52.3, 48.9, 29.1, 24.2, 22.2, 9.5. IR (cm^{-1}) υ 3420, 1700.

5-Hydroxy-2,2-dimethyl-3-heptanone (2).- B.p. 73°C/0.5 mm Hg, ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J=7Hz, 3H), 1.08 (s, 9H), 1.40 (dq, J=5.3,7.3Hz, 2H), 2.47 (dd, J=17.8,8.7, 1H), 2.64 (dd, J=17.8,2.9, 1H), 3.80-3.92 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 216.5, 68.5, 43.8, 42.4, 29.0, 25.7, 9.1. IR (cm^{-1}) υ 3440, 1690.

4-Hydroxy 5-methyl-2-hexanone (3).- B.p. 69°C/0.5 mm Hg, ^{1}H NMR ($CDCl_3$) δ 0.89 (d, J=4Hz, 3H), 0.90 (d, J=4Hz, 3H), 1.65 (m, 1H), 2.16 (s, 3H), 2.58 (dd, J=17.4, 3.3, 1H), 2.48 (dd, J=17.4, 8.5, 1H), 3.78 (ddd, J=3.3, 8.5, 6.1, 1H). ^{13}C NMR ($CDCl_3$) δ 210.2, 72.1, 46.9, 33.0, 30.8, 18.3,17.7. IR (cm^{-1}) υ 3440, 1700.

5-Hydroxy-6-methyl-3-heptanone (4).- B.p. 70°C/0.5 mm Hg, ^{1}H NMR ($CDCl_3$) δ 0.87 (d,J=6.7Hz, 3H), 0.90 (d,J=6.7Hz, 3H), 1.03 (t, J=7Hz, 3H), 1.65 (m, 1H), 2.45 (q, J=7Hz, 2H), 2.53 (m, 2H), 3.74-3.82 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 215.9, 72.0, 45.5, 36.6, 32.9, 18.1, 17.5, 7.2. IR (cm^{-1}) υ 3440, 1700.

5-Hydroxy-2,6-dimethyl-3-heptanone (5).- B.p. 80°C/0.5 mm Hg, ^{1}H NMR ($CDCl_3$) δ 0.89 (d,J=6.6Hz, 6H), 1.08 (d,J=6.9Hz, 6H), 1.66 (s, J=7Hz, 1H), 2.49 (dd, J=17.0, 9.0, 1H), 2.62 (dd, J=17.0, 2.6, 1H), 2.70 (m, 1H), 3.68-3.82 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 215.8, 72.0, 43.6, 41.2, 32.9, 18.2, 17.7, 17.7, 17.4. IR (cm^{-1}) υ 3480, 1700.

6-Hydroxy-2,7-dimethyl-4-octanone (6).- B.p. 76°C/0.5 mm Hg, ^{1}H NMR ($CDCl_3$) δ 0.90 (d,J=7Hz, 12H), 1.59 (m, 1H), 2.05-2.24 (m, 1H), 2.30 (m, 2H), 2.43 (dd, J=17.4, 8.9, 1H), 2.56 (dd, J=17.4, 3.3, 1H), 3.78 (ddd, J=3.3, 5.4, 8.9, 1H). ^{13}C NMR ($CDCl_3$) δ 213.9, 71.9, 52.4, 46.3, 32.8, 24.2, 22.2, 22.2, 18.1, 17.5. IR (cm^{-1}) υ.3465, 1710.

5-Hydroxy-2,2,6-trimethyl-3-heptanone (7).- B.p. 85°C/0.5 mm Hg, ^{1}H NMR ($CDCl_3$) δ 0.88 (d,J=6.7Hz, 3H), 0.90 (d,J=6.7Hz, 3H), 1.10 (s, 9H), 1.65 (o, J=6.7Hz, 1H), 2.47 (dd, J=17.6, 9.3, 1H), 2.65 (dd, J=17.6, 2.4, 1H), 3.72 (ddd, J=2.4, 5.1, 9.3, 1H). ^{13}C NMR ($CDCl_3$) δ 217.1, 71.8, 44.0, 39.6, 32.6, 25.8, 18.1, 17.3. IR (cm^{-1}) υ 3480, 1690.

3-Hydroxy-4-methyl-1-phenyl-1-pentanone (8).- ^{1}H NMR ($CDCl_3$) δ 1.02 (d,J=6.7Hz, 3H), 1.03 (d,J=6.7Hz, 3H), 1.81 (o, J=6.7Hz, 1H), 3.02 (dd, J=17.5, 9.1, 1H), 2.58 (dd, J=17.5, 2.6, 1H), 4.00 (ddd, J=2.6, 5.1, 9.1, 1H), 7.50 (m,3H), 7.95 (m,2H). ^{13}C NMR ($CDCl_3$) δ 136.9,133.4, 128.6, 128.0, 72.3, 42.0, 33.1, 18.5, 17.8. IR (cm^{-1}) υ 3500, 1680.

6-Hydroxy-2,8-dimethyl-4-nonanone (9).- B.p. 78°C/0.5 mm Hg, ^{1}H NMR ($CDCl_3$) δ 0.87 (d, J=6.5Hz, 6H), 0.86 (d, J=6.5Hz, 6H), 1.07 (m, 1H), 1.41 (m, 1H) 2.1 (dd, J=4Hz, 2H), 2.2 (m, 2H),

2.40 (dd, J=17.6, 7.9, 1H), 2.52 (dd, J=17.6, 4.0, 1H), 4.0-4.13 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 211.1, 65.2, 52.1, 49.9, 45.4, 23.9, 23.9, 22.9, 22.0, 21.6. IR (cm^{-1}) υ 3420, 1705.

Table 6.- ^{13}C NMR (DEPT) data of 2,4-dihydroxyamines.

Ent.	R_1	R_2	Isom.	δC1	δC2	δCH_2N	δR_1	dR_2
2m	Et	*t*-Bu	*syn*	70.1	40.5	42.7	10.1 (Me) 30.6 (CH_2)	24.9 (Me)
			anti	67.9	41.7	45.2	10.4 (Me) 31.3 (CH_2)	25.3 (Me)
4m	*i*-Pr	Et	*syn*	72.8	39.2	47.4	17.7 (Me) 18.8 (Me) 34.8 (CH)	7.6 (Me) 31.9 (CH_2)
			anti	72.4	38.4	48.9	17.7 (Me) 18.3 (Me) 34.2 (CH)	8.4 (Me) 30.4 (CH_2)
6m	*i*-Pr	*i*-Bu	*syn*	72.9	40.3	48.3	17.7 (Me) 18.4 (Me) 34.2 (CH)	23.6 (Me) 23.8 (Me) 24.4 (CH) 49.5 (CH_2)
			anti	72.5	40.1	49.8	17.2 (Me) 18.4 (Me) 34.2 (CH)	24.0 (Me) 24.6 (CH) 25.0 (Me) 46.9 (CH_2)
7m	*i*-Pr	*t*-Bu	*syn*	73.3	37.7	42.7	18.0 (Me) 18.6 (Me) 33.9 (CH)	25.0 (Me)
			anti	71.1	38.5	45.5	17.7 (Me) 18.9 (Me) 34.5 (CH)	25.3 (Me)
10m	Bn	*i*-Bu	*syn*	69.6	42.8	48.7	47.3 (CH_2) 126.3 128.4 128.5 129.4	23.5 (CH) 24.5 (Me) 25.0 (Me) 44.8 (CH_2)
			anti	69.0	43.3	49.6	44.6 (CH_2) 126.3 128.4 128.5 129.5	23.9 (CH) 24.7 (Me) 24.8 (Me) 47.3 (CH_2)

2-Hydroxy-1-phenyl-6-methyl-4-heptanone (10).- B.p. 85°C/0.5 mm Hg, ^1H NMR ($CDCl_3$) δ 0.89 (d, J=6.5Hz, 3H), 0.90 (d, J=6.5Hz, 3H), 2.12 (m,1H), 2.27 (d,J=7.4Hz, 2H), 2.52 (d, J=7Hz, 2H), 2.72 (dd, J=13.5, 6.3 Hz, 2H), 2.86 (dd, J=13.5, 7 Hz, 2H), 4.22-4.35 (m, 1H), 7.27 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 211.5, 129.45, 129.4, 128.6, 128.5, 126.5, 68.7, 52.5, 48.6, 42.9, 24.4, 22.5, 19.2. IR (cm^{-1}) υ 3400, 1700.

2,4-Dihydroxy-2-(2-methylpropyl)-hexanoamide (1d).- ***anti*** **isomer:** ^1H NMR ($CDCl_3$) δ 1.00 (m, 6H), 1.01 (t, 3H, J=6.8), 1.70 (m, 5H), 1.95 (dd, J=9.3, 13.7, 1H), 2.48 (dd, J= 6.8, 13.7, 1H), 4.30 (m, 1H).

Table 7.- HRMS for selected compounds.

Ent.	R_1	R_2	Compd.	Mol. formula	mw	Calcd.	Found for *syn*	Found for *anti*	Assignt.
1	Et	*i*-Bu	CN	$C_{10}H_{19}NO_2$	185	186.1494	186.1494		M^++1
						159.1385	159.1388		M^+-CN
2	Et	*t*-Bu	CN	$C_{10}H_{19}NO_2$	185	186.1494	186.1501	186.1513	M^++1
						159.1385	159.1375	159.1364	M^+-CN
			CH_2NH_2	$C_{10}H_{23}NO_2$	189	190.1807	190.1792		M^++1
						159.1395	159.1375		M^+-CH_2NH_2
			$CONH_2$	$C_{10}H_{22}NO_3$	203	204.1599	204.1574	204.1575	M^++1
						159.1395	159.1395	159.1360	M^+-$CONH_2$
4	*i*-Pr	Et	CN	$C_9H_{17}NO_2$	171	172.1338	172.1354	172.1374	M^++1
						145.1229	145.1238	145.1269	M^+-CN
			CH_2NH_2	$C_9H_{21}NO_2$	175	176.1650	176.1642		M^++1
						145.1232	145.1232		M^+-CH_2NH_2
5	*i*-Pr	*i*-Pr	CN	$C_{10}H_{19}NO_2$	185	186.1494	186.1498	186.1493	M^++1
						159.1385	159.1383	159.1386	M^+-CN
6	*i*-Pr	*i*-Bu	CN	$C_{11}H_{21}NO_2$	199	200.1651	200.1678	200.1676	M^++1
						173.1542	173.1532	173.1535	M^+-CN
7	*i*-Pr	*t*-Bu	CN	$C_{11}H_{21}NO_2$	199	200.1651	200.1669	200.1651	M^++1
						173.1542	173.1548	173.1545	M^+-CN
8	*i*-Pr	Ph	CN	$C_{13}H_{18}NO_2$	219	220.1338		220.1368	M^++1
						193.1229		193.1235	M^+-CN
9	*i*-Bu	*i*-Bu	CN	$C_{12}H_{23}NO_2$	213	214.1807	214.1844	214.1823	M^++1
						187.1698	187.1747	187.1705	M^+-CN
			γ-lactone	$C_{12}H_{22}O_3$	214	215.1647		215.1654	M^++1
						170.1671		170.1674	M^+-CO_2
10	Bn	*i*-Bu	CN	$C_{15}H_{21}NO_2$	247	248.1651	248.1699	248.1652	M^++1
						221.1542	221.1566	221.1551	M^+-CN
			CH_2NH_2	$C_{15}H_{25}NO_2$	251	252.1963		252.1958	M^++1
						251.1885	251.1901		M^+
						221.1542	221.1551	221.1546	M^+-CH_2NH_2
			$CONH_2$	$C_{15}H_{23}NO_3$	265	266.1756	266.1755		M^++1
						221.1542	221.1546		M^+-$CONH_2$
			γ-lactone	$C_{15}H_{20}O_3$	248	248.1412		248.1408	M^++1
						204.1514		204.1512	M^+-CO_2

2,4-Dihydroxy-2-(1,1-dimethylethyl)-hexanoamide (2d).- ***syn*** **isomer:** ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 3H, J=7.4), 1.00 (s, 9H), 1.60 (dq, J=6.8, 7.4, 2H), 1.83 (dd, J=9.3, 13.7, 1H), 2.60 (dd, J= 6.8, 13.7, 1H), 4.13 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 9.4 (Me), 24.8 (Me), 29.8 (CH_2), 40.2 (CH_2), 80.2 (CH), 81.6 (C), 176.1 (CO); ***anti*** **isomer:** ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3H, J=7.4), 1.10 (s, 9H), 1.55 (m, 2H), 1.88 (dd, J=9.7, 13.4, 1H), 2.11 (dd, J= 5.8, 13.4, 1H), 4.35 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 9.5 (Me), 24.7 (Me), 27.9 (CH_2), 39.6 (CH_2), 79.1 (CH), 82.4 (C), 173.3 (CO);

2,4-Dihydroxy-5-methyl-2-propylhexaneamine (4d).- ***anti*** **isomer:** ^{1}H NMR ($CDCl_3$) δ 0.90 (d, 3H, J=6.7), 1.01 (d, 3H, J=6.7), 1.03 (t, 3H, J=7), 1.73 (m, 1H), 1.73 (q, 2H, J=7), 1.93 (dd, J=10.4, 12.7, 1H), 2.29 (dd, J=5.6, 12.7, 1H), 3.88 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 7.7 (Me), 17.4 (Me), 18.6 (Me), 31.1 (CH_2), 33.2 (CH), 39.2 (CH_2), 77.2 (C), 83.3 (CH), 178.0 (CO).

2,4-Dihydroxy-5-methyl-2-(2-methylpropyl)-hexanoamide (6d).- ***anti*** **isomer:** ^{1}H NMR ($CDCl_3$) δ 0.90 (d, 3H, J=6.6), 0.95 (d, 3H, J=6.6), 0.99 (d, 3H, J=6.6), 1.04 (t, 3H, J=6.6), 1.50 (m, 1H), 1.75 (m,

1H), 1.82 (m, 3H), 1.69 (dd, J=10.3, 13.1, 1H), 2.25 (dd, J=5.2, 13.1, 1H), 4.26 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 17.5 (Me), 18.3 (Me), 23.9 (Me), 24.3 (Me), 24.6 (CH), 32.7 (CH), 40.3 (CH_2), 45.6 (CH_2), 83.4 (C), 84.5 (CH), 174.0 (CO).

2,4-Dihydroxy-2-(1,1-dimethylethyl)-5-methylhexanoamide (7d).- *syn* isomer: ^{1}H NMR ($CDCl_3$) δ 0.89 (d, 3H, J=6.6), 0.99 (d, 3H, J=6.6), 1.05 (s, 9H), 1.75 (m, 1H), 1.90 (dd, J=9.5, 13.7, 1H), 2.57 (dd, J=6.8, 13.7, 1H), 3.90 (ddd, J=5.2, 6.8, 9.5, 1H); ^{13}C NMR ($CDCl_3$) δ 17.3 (Me), 18.5 (Me), 24.7 (Me), 34.2 (CH), 38.3 (CH_2), 82.8 (C), 83.5 (CH), 175.0 (CO); ***anti* isomer:** ^{1}H NMR ($CDCl_3$) δ 0.90 (d, 3H, J=6.8), 1.01 (d, 3H, J=6.8), 1.11 (s, 9H), 1.71 (m, 1H), 1.91 (dd, J=9.7, 13.5, 1H), 2.04 (dd, J=5.9, 13.5, 1H), 4.11 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 17.4 (Me), 18.7 (Me), 24.7 (Me), 32.6 (CH), 37.7 (CH_2), 82.3 (C), 82.8 (CH), 178.0 (CO).

2,4-Dihydroxy-5-methyl-2-phenylhexanoamide (8d).- *anti* isomer: ^{1}H NMR ($CDCl_3$) δ 0.84 (d, 3H, J=6.8), 0.98 (d, 3H, J=6.8), 1.95 (m, 1H), 2.26 (dd, J=10.6, 12.4, 1H), 2.44 (dd, J=5.2, 12.4, 1H), 3.78 (m, 1H), 7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 17.4 (Me), 18.6 (Me), 32.8 (CH), 43.9 (CH_2), 79.0 (C), 82.9 (CH), 125.4, 125.5, 128.2, 128.6, 177.0 (CO).

2,4-Dihydroxy-2-(2-methylpropyl)-6-methylheptanoamide (9d).- *syn* isomer: ^{1}H NMR ($CDCl_3$) δ 0.92 (m, 6H), 0.98 (m, 6H), 1.40 (m, 2H), 1.60 (m, 2H), 1.63 (m, 2H), 1.86 (dd, J=9.4, 12.6, 1H), 2.40 (dd, J=5.6, 12.6, 1H), 4.30 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 22.3 (Me), 23.0 (Me), 24.4 (Me), 24.8 (CH), 24.7 (CH), 24.9 (Me), 42.6 (CH_2), 44.8 (CH_2), 46.3 (CH_2), 76.9 (CH), 80.2 (C), 177.0 (CO); ***anti* isomer:** ^{1}H NMR ($CDCl_3$) δ 0.95 (m, 6H), 1.05 (m, 6H), 1.45 (m, 3H), 1.47 (m, 3H), 1.98 (dd, J=9.4, 12.6, 1H), 2.48 (dd, J=5.6, 12.6, 1H), 4.41 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 22.3 (Me), 22.9 (Me), 24.2 (Me), 24.3 (CH), 24.3 (Me), 24.9 (CH), 41.6 (CH_2), 44.8 (CH_2), 45.1 (CH_2), 76.0 (CH), 80.0 (C), 179.3 (CO).

2,4-Dihydroxy-2-(2-methylpropyl)-5-phenylpentanoamide (10d).- *anti* isomer: ^{1}H NMR ($CDCl_3$) δ 0.89 (d, 3H, J=6.5), 0.98 (t, 3H, J=6.5), 1.48 (m, 1H), 1.75 (dd, J=10.1, 13.1, 1H), 1.84 (m, 2H), 2.25 (dd, J=5.2, 10.1, 1H), 2.86 (dd, 1H, J=6.1, 14.0), 2.99 (dd, 1H, J=6.8, 14.1), 4.82 (m, 1H), 7.25 (m, 5H).

3-(1,1-dimethylethyl)-3-hydroxy-5-ethyl-γ-butyrolactone (1l).- *syn* isomer: ^{1}H NMR ($CDCl_3$) δ 1.00 (t, J=7, 3H), 1.05 (s, 9H), 1.75 (m, 2H), 1.93 (dd, J=8.4, 13.9, 1H), 2.66 (dd, J=7.1, 13.8, 1H), 4.27 (m, 1H); ***anti* isomer:** ^{1}H NMR ($CDCl_3$) δ 0.96 (t, J=7.4, 3H), 1.10 (s, 9H), 1.67 (m, 2H), 1.86 (dd, J=9.6, 13.6, 1H), 2.14 (dd,J=7.1, 13.8, 1H), 4.50 (m, 1H).

3-(1,1-dimethylethyl)-3-hydroxy-5-(1-methylethyl)-γ-butyrolactone (7l).- *anti* isomer: ^{1}H NMR ($CDCl_3$) δ 0.93 (d, J=6.7, 3H), 1.04 (d, J=6.7, 3H), 1.08 (s, 9H), 1.80 (m, 1H), 1.96 (dd, J=9.7, 13.6, 1H), 2.10 (dd, J=5.8, 13.6, 1H), 4.29 (m, 1H).

3-(2-methylpropyl)-3-hydroxy-5-(2-methylpropyl)-γ-butyrolactone (9l).- *anti* isomer: ^{1}H NMR ($CDCl_3$) δ 0.95 (d, J=6.6, 3H,), 0.96 (d, J=6.6, 3H), 1.00 (d, J=6.6, 3H), 1.01 (d, J=6.6, 3H), 1.40 (m, 1H), 1.45 (m, 1H), 1.58 (dd, J=6.5, 14.5, 1H), 1.71 (dd, J=6.5, 14.5, 1H), 1.80 (m, 2H), 1.97 (dd, J=9.1, 13.0, 1H), 2.49 (dd, J=5.8, 13.0, 1H), 4.41 (m, 1H).

3-(2-methylpropyl)-3-hydroxy-5-benzyl-γ-butyrolactone (10l).- *anti* isomer: ^{1}H NMR ($CDCl_3$) δ 0.85 (d, J=6.5, 3H), 0.96 (d, J=6.5, 3H), 1.40 (m, 1H), 1.78 (m, 2H), 1.86 (dd, J=9.4, 13.6, 1H), 2.30 (dd, J=5.7, 13.6, 1H), 2.92 (dd, J=6.4, 13.7, 1H), 3.06 (dd, J=6.5, 13.7, 1H), 4.90 (m, 1H), 7.37 (m, 5H).

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