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Synthesis of Amino 1,3-Diols. Ring Opening of N-Acyl Activated Lactams with Carbon Nucleophiles

S. Klutchko [a], J. M. Hamby [a], M. Reily [a], M. D. Taylor [a] & J. C. Hodges [a]
[a] Parke-Davis Pharmaceutical Research Division Warner-Lambert Company, Ann Arbor, Michigan, 48105
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SYNTHESIS OF AMINO 1,3-DIOLS. RING OPENING OF N-ACYL ACTIVATED LACTAMS WITH CARBON NUCLEOPHILES

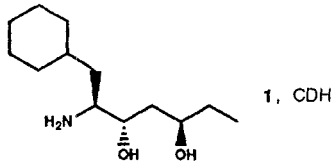
Sylvester Klutchko*, James M. Hamby, Michael Reily, Michael D. Taylor, and John C. Hodges

Parke-Davis Pharmaceutical Research Division
Warner-Lambert Company, Ann Arbor, Michigan 48105

Abstract: A synthesis of 6-amino-7-cyclohexyl-3,5-heptanediol **1** (CDH) and related amino 1,3-diols involving a nucleophilic ring opening of N-acyl activated lactams is described. Stereochemical proof of the 1,3-diol moiety is also presented.

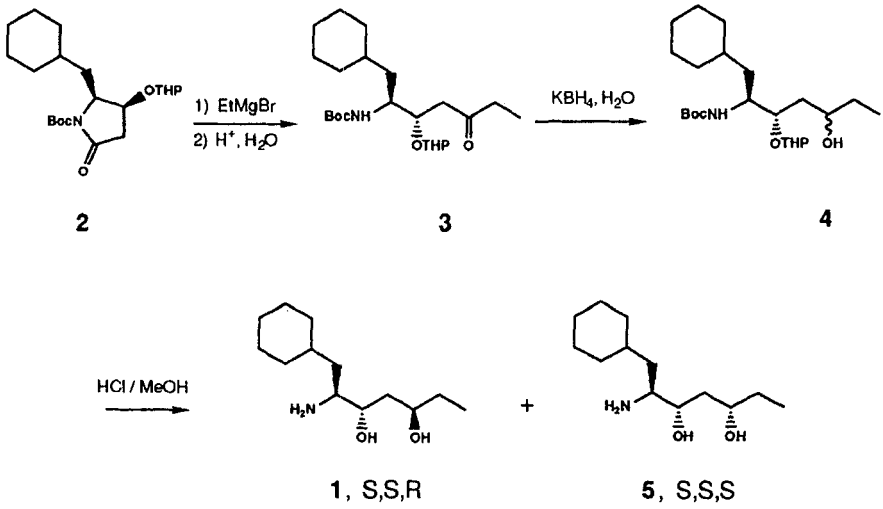
We have previously reported on the stereospecific synthesis of the renin inhibitor transition state analogs statine and ACHPA by a nucleophilic ring opening of N-Boc-lactams with hydroxide ion or amines.[1] A modification of this reaction has now been developed wherein carbon nucleophiles, such as Grignard reagents, have been used to open the lactam ring[2-4], resulting in carbon chain elongation. The method was useful in the synthesis of the amino 1,3-diol **1** (CDH) which, in our work, was an important P1-P1' building block for incorporation into renin inhibitors[5,6] and other aspartic protease inhibitors[7].

* To whom correspondence should be addressed

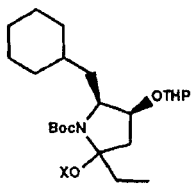


The reaction sequence leading to the amino diol product **1** began with the blocked 4-hydroxylactam **2**[1] (Scheme I). The ring opening with ethylmagnesium bromide was accomplished at 5° C in tetrahydrofuran. Treatment with citric acid solution gave the pure ketone **3** in 60% yield. Reduction of **3** with potassium borohydride in aqueous methanol gave the mixture of diastereomeric alcohols **4**. Removal of the Boc and THP groups of **4** with hydrogen chloride - methanol resulted in a mixture of amino 1,3-diols **1** and **5** which were easily separated by silica gel chromatography using an ammonia -methanol - chloroform eluant system (see experimental).

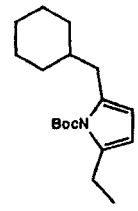
Scheme I



Prior to reprotonation in the work-up, the ketone **3** (Scheme I) probably exists in the ring-closed form **6** as indicated by its inability to react with a second equivalent of the Grignard reagent to the carbonyl group. Apparently the



6, X = MgBr
7, X = H



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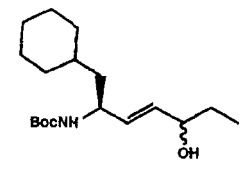

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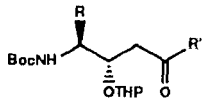
initial generation of the magnesium bromide complex **6** of the cyclic form precludes the addition of a second mole of reagent. Upon acidification of **6**, the ketone **3** was formed and, although it may exist in equilibrium with the closed form **7**, it undergoes the expected borohydride reduction ring opening. Potassium borohydride in aqueous methanol was the preferred method of reduction, preventing ß-elimination of the OTHP group to the vinyl alcohol **9.** When sodium borohydride in absolute ethanol (anhydrous condition) was used the β-elimination product was observed by MS and NMR. The major by-product in the Grignard reaction was the N-Boc-2,5-disubstituted pyrrole **8,** isolated in low yield.

The ring opening of lactams was performed with other carbon nucleophiles such as isopropylmagnesium chloride, phenylmagnesium bromide, vinylmagnesium bromide and lithio-1,3-dithiane with similar results when either the alkyl group adjacent to N was cyclohexylmethyl or isobutyl. The resulting keto amides **10 - 15** were obtained in varying yields, the best being ca. 80% for the

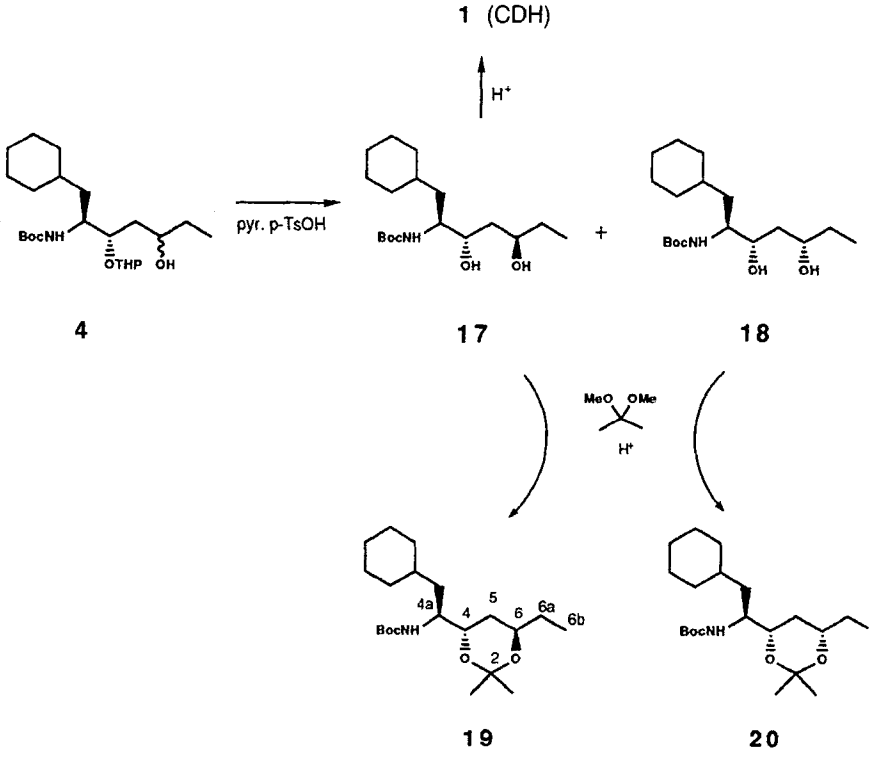
ethyl and vinyl Grignard reagents. The vinyl ketone **15** was somewhat unstable and was converted to its dimethylamine Michael addition product **16** in 92% yield.



	R	R'	% Yield
10,	i-Bu	Et	81
11,	i-Bu	i-Pr	18
12,	CH_2c-Hex	*i-Pr*	*28*
13,	CH_2c-Hex	Ph	44
14,	CH_2c-Hex	2-(1,3-dithiane)	59
15,	CH_2c-Hex	vinyl	78
16,	CH_2c-Hex	$(CH_2)_2N(CH_3)_2$	92

The stereochemistry of CDH, **1**, was established on the basis of comparison of ^{13}C and ^{1}H chemical shifts in the NMR of the corresponding ketal derivatives **19** and **20** (Scheme II). CDH was assigned the *S,S,R* configuration (from left to right as drawn) and its isomer **5** the *S,S,S*. The ketals were prepared from the N-Boc aminodiols **17** and **18.** The stereochemical proof of CDH was conclusive in that the intermediate **17** was common to the preparation of both CDH and the ketal **19** on which stereochemistry was determined. The synthesis of ketals **17** and **18** involved a mild, selective removal of the THP group of **4** (mixture of diastereomers) with pyridinium p-toluenesulfonate in ethanol to give the N-Boc amino diols **17** and **18**. After separation by chromatography, **17** and **18** were converted to the cyclic ketals **19** and **20** with 2,2-dimethoxypropane and

Scheme II



pyridinium p-toluenesulfonate as a mild catalyst leaving the N-Boc group unaffected.

The stereochemistry of the ketals was deduced by comparing ^{13}C and ^{1}H chemical shifts for assigned atoms listed in Table I. Compound **19** was assigned the *S,S,R* configuration (as drawn) and compound **20** the *S,S,S* based on the following observations:

1) The chemical shifts of the 4 and 6 ring protons appear at higher field in **19**. This can be caused by α and γ shielding influence of the 6 or the 4 axial substituent[8],

suggesting that these groups are trans about the 1,3-dioxane ring and that the configuration about C6 is *R* in **19**.

2) The difference in chemical shifts for the ring methyl carbon and proton resonances is large for **20** and small for **19**. This is consistent with a single ring conformation[9] in the former compound which is stabilized by diequatorial substitution at the 4 and 6 positions. Multiple ring conformations lead to an averaging of the chemical shifts for the same nuclei in **19**.

3) The 11 Hz vicinal ^{1}H-^{1}H coupling between H6 and the H5ax in **20** proves that these protons are diaxial. The derived configuration about carbon 6 is therefore *S* in this compound.

Table I

Selected 300 MHz ^{1}H and 75 MHz ^{13}C NMR data for **19** and **20** in DMSO-d_6 at 80° C[a].

	Compound 19		Compound 20	
Atom	^{13}C	^{1}H	^{13}C	^{1}H
2a	24.8	1.24	19.8	1.27
2a'	25.0	1.25	30.1	1.35
4	68.0	3.71	70.6	3.76
4a		3.49	51.2	1.48
4b	33.6	1.20	37.8	1.23
4b'		1.35		1.33
5ax	33.7	1.40	31.9	1.10
5eq		1.60		1.40
6	67.8	3.59	69.5	3.70
6a		1.35	19.8	1.40
6a'		1.45		1.40
6b	9.1	0.85	9.0	0.85

a. Chemical shifts are relative to TMS.

Experimental

Melting points were determined with a Thomas-Hoover capillary melting point apparatus, which was calibrated against known standards. IR spectra were run on a Nicolet MX-1 spectrometer. NMR spectra were run on a Varian XL 200, Bruker AM 250 or IBM WP 100SY spectrometer using Me_4Si as an internal standard. Mass spectra were run on a Finnigan 4500 instrument. Elemental analyses check to within 0.4% of calculated values except where indicated otherwise. The stereodescriptors (*R* and *S*) that precede the chemical names indicate the stereochemistry from left to right as the structures are drawn in this manuscript.

(*S,S,RS*)-[1-(Cyclohexylmethyl)-4-oxo-2-[(tetrahydro-2H-pyran-2-yl)oxy]hexyl]carbamic acid, 1,1-dimethylethyl ester (*RS* is the pyran center), 3.

A solution of 15.2 g (0.04 mol) of **2** in 200 ml of dry tetrahydrofuran was cooled to 5° C. Under nitrogen and with stirring, 27.5 ml (0.055 mol) of 2 M ethylmagnesium bromide in tetrahydrofuran was added over a period of five minutes, preventing the temperature from rising above 12° with mild cooling. After stirring at 10° for one-half hour, the reaction solution was poured, under nitrogen, into a stirred mixture of 300 g of ice and water. Saturated citric acid (200 ml) and 300 ml of ether were added. The organic layer was separated, washed well with water, dried (magnesium sulfate) and concentrated to give 15.8 g of crude **3**. Silica gel chromatography, eluting with hexane and then with 2:1 hexane-ethyl acetate, gave 9.4 g (57%) of pure non-crystalline product; tlc (silica gel, 2:1 hexane-ethyl acetate) showed one spot, Rf 0.6 (visualized with ninhydrin plus heat); ms (CI), m/z 412 (M + 1); nmr ($CDCl_3$) δ 0.70-1.90 (m,31H), 2.30-2.50 (m,2H), 2.55-2.95 (m,2H), 3.30-3.60 (m,1H), 3.60-3.90 (m,2H), 4.10-4.30 (m,1H), 4.35-4.80 (m,2H). Anal. ($C_{23}H_{41}NO_5$) C,H,N.

N-Boc-pyrrole derivative 8: The above chromatography for the purification of **3** yielded 0.40 g of a fast moving oil which was identified by nmr and ms as the pyrrole **8**; ms (CI) 292 (M+1); nmr ($CDCl_3$) δ 0.75-1.00 (m,3H), 1.00-1.30 (m,6H), 1.30-1.90 (m,14H), 2.65 (d,2H), 2.80 (q,2H), 5.80 (m,2H). Anal. Calcd for $C_{18}H_{29}NO$: C, 74.18; H, 10.03; N, 4.81. Found: C, 72.94; H, 9.94; N, 3.15.

***(S,S,RS,RS)*-[1-(Cyclohexylmethyl)-4-hydroxy-2-[(tetrahydro-2H-pyran-2-yl)oxy]hexyl]carbamic acid, 1,1-dimethylethyl ester (pyran and 4-hydroxy centers are *RS*), 4.**

A solution of 1.24 g (0.023 mol) of potassium borohydride in 15 ml of water was added over a ten minute period with mild cooling, keeping temperature at 25°, to a solution of 9.30 g (0.023 mol) of **3** in 100 ml of methanol and 2 ml of water. After 2 hours at room temperature traces of solid were filtered and 10 ml of acetone was added. After 15 minutes the solution was concentrated at reduced pressure to remove the methanol. Water (20 ml) was added and the product was extracted into 100 ml of ether. The solution was dried (potassium carbonate) and concentrated to give 8.80 g (93%) of non-crystalline product **4;** tlc (silica gel, 2:1 hexane-ethyl acetate) double spot Rf 0.4-0.5; ms (CI), m/z 414 (M + 1); nmr ($CDCl_3$) δ 0.70-1.05 (m,3H), 1.05-2.00 (m,28H), 2.00-2.50 (m,1H), 3.40-4.10 (m,4H), 4.10-4.90 (m,2H). Anal. ($C_{23}H_{43}NO_5$) C,H,N.

***(S,S,R)*-6-Amino-7-cyclohexyl-3,5-heptanediol, 1, (CDH) and *(S,S,S)*-6-amino-7-cyclohexyl-3,5-heptanediol, 5.**

From 4: A solution of 7.80 g (0.019 mol) of mixed isomers **4** in 100 ml of methylene chloride and 50 ml of methanol was cooled to 5° and saturated with hydrogen chloride gas. After standing six hours at room temperature the solution was concentrated at reduced pressure to remove most of the solvent and hydrogen chloride. Water (80 ml) was added to the residue. To remove insoluble gum, added "celite" and charcoal and filtered. The filtrate was cooled in an ice bath and 40% potassium hydroxide was added to pH 9. Then solid potassium carbonate was added to "salt-out" the oily amino diol mixed diastereomers. Extraction into 150 ml of ether and concentration gave 3.18 g (72%) of mixed isomers. Diastereomers were separated by silica gel chromatography as follows: The column was prepared with 1% methanol-chloroform saturated with ammonia. Eluted with 2% methanol-chloroform/ammonia to 10% methanol-chloroform/ammonia obtaining pure fast isomer, compound **5**, *(S,S,S)* which crystallized; mp 68 - 71°; tlc (silica gel, 1:10 methanol-chloroform saturated with NH_3) one spot, Rf 0.5 (visualized with ninhydrin); ms (EI), m/z 230 (M + 1); nmr ($CDCl_3$) δ 0.80-1.10 (m,4H,hydrocarbon CH), 1.10-2.85 (m,20H,hydrocarbon CH,OH,NH_2), 2.58-2.72 (m,1H,H-6), 3.40-3.55 (m,1H,H-5), 3.75-3.90 (m,1H,H-3). Anal. ($C_{13}H_{27}NO_2$) C,H,N. On further elution of the column the pure slow isomer **1**

(S,S,R) was obtained; mp 92 - 94°; tlc (same system as above) one spot, Rf 0.4; ms (EI), m/z 230 (M+1); nmr ($CDCl_3$) δ 0.70-1.85 (m,20H,hydrocarbon CH), 2.10-2.60 (br.s.,4H,NH,OH), 2.65-2.80 (m,1H,H-6), 3.50 (q,1H,H-5), 3.70-3.90 (m,1H,H-3). Anal. ($C_{13}H_{27}NO_2$) C,H,N.

Compound 1 from 17: A solution of 2.25 g (0.0068 mole) of the slow isomer (**17**) in 25 ml of methylene chloride was treated with 25 ml of methanolic HCl (0.029 g/ml HCl, 0.020 mole). The mixture was stirred at ambient temperature for 23 hours. The solvents were evaporated and the residue was triturated with ether. The solid was collected and dried to give 1.86 g (100%) of the 3-R isomer **1** hydrochloride. The free base was made by partitioning the HCl salt between ethyl acetate and saturated sodium bicarbonate. This gave 1.50 g (100 %) of **1** which was identical to CDH, **1,** isolated above (from **4**) by ms, nmr and tlc.

***(S,S,RS)*-[1-(2-Methylpropyl)-4-oxo-2-[(tetrahydro-2H-pyran-2-yl)oxy]hexyl]carbamic acid, 1,1-dimethylethyl ester, 10.**

Compound **10** was prepared from the isobutyl lactam analog[1] of **2** and ethylmagnesium bromide by the same procedure that was used for compound **3**; yield, 81%; nmr ($CDCl_3$) δ 0.90-1.00 (m,6H), 1.00-1.90 (m,26H), 2.40-2.55 (m,2H), 2.60-2.70 (m,2H), 2.85-2.95 (m,1H), 3.30-5.00 (m,6H); ir (film) 1714 cm^{-1}. Anal. ($C_{20}H_{37}NO_5$) C,H,N.

***(S,S,RS)*-[5-Methyl-1-(2-methylpropyl)-4-oxo-2-[(tetrahydro-2H-pyran-2-yl)oxy]hexyl]carbamic acid, 1,1-dimethylethyl ester, 11.**

Compound **11** was prepared from the isobutyl lactam analog[1] of **2** and isopropylmagnesium chloride by a procedure similar to that used for compound **3**; yield,18%; ms (CI), m/z 386 (M+1); nmr ($CDCl_3$) δ 0.80-0.95 (m,6H), 1.00-1.20 (m,6H), 1.25-1.90 (m,18H), 2.50-3.00 (m,3H), 3.20-4.80 (m,6H). Anal. ($C_{21}H_{39}NO_5$) C,H,N.

***(S,S,RS)*-[1-(Cyclohexylmethyl)-5-methyl-4-oxo-2-[(tetrahydro-2H-pyran-2-yl)oxy]hexyl]carbamic acid, 1,1-dimethylethyl ester, 12.**

Compound **12** was prepared from the lactam **2** and isopropylmagnesium chloride by a procedure similar to that used for compound **3**; yield, 28%; ms (EI), m/z 426.2 (M + 1); nmr ($CDCl_3$) δ 0.70-1.90 (m,34H), 2.40-3.00 (m,3H), 3.30-3.60 (m,1H), 3.60-3.90 (m, 2H), 4.10-4.30 (m, 1H), 4.50-4.70 (m, 2H); *ir* (film), 1715 cm^{-1} (C=O). Anal. ($C_{24}H_{43}NO_5 \cdot 0.5\ H_2O$) C,H,N.

***(S,S,RS)*-[1-(Cyclohexylmethyl)-4-oxo-4-phenyl-2-[(tetrahydro-2H-pyran-2-yl)oxy]butyl]carbamic acid, 1,1-dimethylethyl ester, 13.**

Compound **13** was prepared from **2** and phenylmagnesium bromide according to the procedure for compound **3**; yield, 44%; ms (CI) m/z 460 (M+1); nmr ($CDCl_3$) δ 0.70-1.00 (m,2H), 1.00-1.90 (m,25H), 3.00-4.00 (m,5H), 4.00-4.90 (m,3H), 7.30-7.55 (m,3H), 7.80-7.95 (m, 2H); ir (KBr pellet) 1675 cm^{-1}. Anal. ($C_{27}H_{41}NO_5$) C,H,N.

***(S,S,RS)*-[1-(Cyclohexylmethyl)-4-(1,3-dithian-2-yl)-4-oxo-2-[(tetrahydro-2H-pyran-2-yl)oxy]butyl]carbamic acid, 1,1-dimethylethyl ester, 14.**

A solution of 12.4 g (0.10 mole) of 97% 1,3-dithiane in 200 ml of tetrahydrofuran was cooled to -30° C. A quantity of 62.5 ml (0.10 mole) of 1.6 M n-butyllithium in hexane was added with stirring under nitrogen over a period of 10 minutes. After 15 minutes, a solution of 42.0 g (0.011 mole) of **2** in 200 ml of tetrahydrofuran was added over a period of 10 minutes at -30° C. The reaction solution was allowed to warm to room temperature. After another hour the solution was poured (under nitrogen) into a stirred mixture of 500g of ice and water. Saturated citric acid solution (200 ml) and ether (600 ml) were added. The aqueous layer was separated and the organic phase was dried (magnesium sulfate), filtered and concentrated to give the product as a gum. Silica gel chromatography eluting with from 1 to 30% ethyl acetate-hexane gave 29.30 g (59%) of **14** ; tlc (2:1 hexane-ethyl acetate, silica gel) Rf 0.7. Recrystallization from ethyl acetate gave pure product; mp 129-131° C; ms (CI) m/z 502 (M+1); nmr ($CDCl_3$) δ 0.75-1.00 (m,3H), 1.00-1.90 (m,27H), 1.95-2.10 (m,2H), 2.50-2.65 (m,2H), 2.90-3.25 (m,3H), 3.25-3.50 (m,1H), 3.70-3.90 (m,2H), 4.00-4.10 (m,1H), 4.30-4.90 (m,3H). Anal. ($C_{25}H_{43}NO_5S_2$) C,H,N.

***(S,S,RS)*-[1-(Cyclohexylmethyl)-4-oxo-2-[(tetrahydro-2H-pyran-2-yl)oxy]-5-hexenyl]carbamic acid, 1,1-dimethylethyl ester, 15.**

Compound **15** was prepared from **2** and vinylmagnesium bromide according to the procedure for compound **3**; yield, 78%; ms (FAB) m/z 540 (M+thioglycerol+Na); nmr ($CDCl_3$) δ 0.75-1.05 (m,3H), 1.05-1.95) (m,26H), 2.75-2.90 (m,1H), 2.90-3.55 (m,1H), 3.60-3.90 (m,2H), 4.05-4.30 (m,1H), 4.40-4.70 (m,2H), 5.70-5.90 (t,1H), 6.10-6.40 (m,2H); ir (film) 1618 (w) and 1708 (s) cm^{-1}. Anal. ($C_{23}H_{39}NO_5$) C,H,N.

***(S,S,RS)*-[1-(Cyclohexylmethyl)-6-(dimethylamino)-4-oxo-2-[(tetrahydro-2H-pyran-2-yl)oxy]hexyl]carbamic acid, 1,1-dimethylethyl ester, 16.**

A solution of 7.00 g (0.017 mole) of the vinyl ketone **15** in 75 ml of absolute ethanol was treated with dimethylamine gas, allowing the temperature to rise to 40°. After one-half hour the solvent and excess amine were evaporated to give 7.10 g (92%) of **16** as a gum; tlc (1:10 methanol-chloroform, silica gel), one spot Rf 0.3-0.4; ms (CI) 455 (M+1);
nmr ($CDCl_3$) δ 0.75-1.05 (m,2H), 1.05-1.90 (m,23H), 2.25 (s,7H), 2.50-2.95 (m,7H), 3.30-3.55 (m,2H), 3.60-3.90 (m,2H), 4.05-4.25 (m,1H), 4.40-4.70 (m,2H). Anal. ($C_{25}H_{46}N_2O_5$) C,H,N.

***(S,S,R)*-[1-(Cyclohexylmethyl)-2,4-dihydroxyhexyl]carbamic acid, 1,1-dimethylethyl ester 17 and *(S,S,S)*-[1-(Cyclohexylmethyl)-2,4-dihydroxyhexyl]carbamic acid, 1,1-dimethylethyl ester 18.**

A solution of 14.10 g (0.034 mole) of the mixed diastereomers **4** in 140 ml of ethanol was treated with 0.86 g (0.0034 mole) of pyridinium p-toluenesulfonate. The solution was heated at 55° for 3 hours and evaporated at reduced pressure. The residue was taken up in ethyl acetate and washed twice with water. The organic phase was dried over magnesium sulfate, filtered, and evaporated at reduced pressure to give 13.74 g of diastereomers. These were separated by flash chromatography (silica gel, 5-40% ethyl acetate-hexane) to give 4.72 g of a slow isomer **17** and 5.72 g of a fast isomer **18** as crystalline solids. Recrystallization of the slow isomer from ethyl acetate-petroleum ether gave pure **17**; tlc (1:1 ethyl acetate-hexane) Rf 0.4 (visualized with ninhydrin plus heat); mp 135-137°; ms (CI) m/z 330 (M+1); ir (KBr pellet) 1717 cm^{-1}; nmr ($CDCl_3$) δ; 0.75-1.10 (m,5H,hydrocarbon CH), 1.10-1.90 (m,22H,hydrocarbon CH), 2.55 (br.s.,1H,OH), 3.00 (d,1H,OH), 3.55-3.75 (m,1H,H-2), 3.75-3.95 (m,2H,H-1,H-4), 4.70 (d,1H,NH). Anal. ($C_{18}H_{35}NO_4$) C,H; N, Calcd, 4.25; Found, 3.73.

Recrystallization of the fast isomer from hexane gave pure **18**; tlc (same system) Rf 0.6; mp 98-100°; ms (CI) m/z 330 (M+1); ir (KBr pellet) 1689 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.75-1.10 (m,5H,hydrocarbon CH), 1.10-1.90 (m,22H,hydrocarbon CH), 2.90 (br.s.,1H,OH), 3.50-3.70 (m,1H,H-2), 3.75-4.00 (m,*H-1,H-4,OH*), 4.75 (d,1H,NH).Anal. ($C_{18}H_{35}NO_4$) C,H,N.

***(S,S,R)*-[2-Cyclohexyl-1-(6-ethyl-2,2-dimethyl-1,3-dioxan-4-yl)ethyl]carbamic acid, 1,1-dimethylethyl ester 19 and *(S,S,S)*-[2-Cyclohexyl-1-(6-ethyl-2,2-dimethyl-1,3-dioxan-4-yl)ethyl]carbamic acid, 1,1-dimethylethyl ester 20.** (Acetone ketals of compounds **17** and **18** respectively).

Compound 19. A solution of 0.30 g (0.91 mmoles) of diol **17** (slow isomer) in 5 ml of 2,2-dimethoxypropane was treated with 0.023 g (0.92 mmoles) of pyridinium p-toluenesulfonate. The mixture was heated with stirring at 50° for 3 hours. The solvent was evaporated at reduced pressure and the residue was dissolved in ethyl acetate. The solution was washed with water and saturated sodium bicarbonate solution, dried (magnesium sulfate), filtered and concentrated. The residue was purified via flash silica gel chromatography eluting with 10% ethyl acetate-hexane; wt 0.20 g (60%) of pure ketal **19**; ms (CI) m/z 370 (M+1); nmr, see Table for proton assignments.

Compound 20. Compound **20** was prepared from diol **18** by the same procedure used to prepare **19** above; ms (FAB) m/z 370.4; nmr, see Table for proton assignments.

Acknowledgement

We wish to thank F. MacKellar and his associates in the analytical department for elemental analyses and spectra.

References

1. Klutchko, S., O'Brien, P., and Hodges, J. C., Synth. Commun., 1989, 19, 2573.
2. Ohta, T., Nozoe, S., et al, Chem. Lett., 1987, 2091.
3. Giovannini, A., Savoia, D., and Umani-Ronchi, A., J. Org. Chem.,1989, 54, 228.
4. Ezquerra, J., deMendoza, J., Pedregal, C., and Ramirez, C., Tetrahedron Lett., 1992, 33, No. 38, 5589-5590.
5. Patt, W.C., Hamilton, H.W., Taylor, M.D., Ryan, M.J., Taylor, D.G., Connolly, C.J.C., Doherty, A.M., Klutchko, S.R., Sircar, I., Steinbaugh, B.A., Batley, B.L., Painchaud, C.A., Rapundalo, S.T., Michniewicz, B.M., and Olson, S.C., J. Med. Chem., 1992, 35, 2562-2572.
6. Hamby, J. M., Hodges, J. C., and Klutchko, S., 1990, WO Patent Appl. 90 07,521.

7. Rao, C., Scarborough, P.E., Lowther, W.T., Kay, J., Batley, B., Rapundalo, S., Klutchko, S., Taylor, M.D., Dunn, B.M., Structure-function Database for Active Site Binding to Aspartic Proteinases, in Advances in Experimental Medicine and Biology, Vol. 306. Dunn, B.M., ed.; Plenum Press: New York, 1991; pp143-147.
8. Fresenius et al, "Table of Spectral Data for Structure Determination of Organic Compounds", Second Edition, Springer-Verlag, 1989, p. C55.
9. Jones, A. J., Eliel, E.L., Grant, D.M., Knoeber, M.C., and Bailey, W.F., J. Am. Chem. Soc., 1971, 93, 4772.

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