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A CONVENIENT APPROACH TO HYDROXYETHYLENE DIPEPTIDE ISOSTERES AS BUILDING BLOCKS FOR ENZYME INHIBITORS

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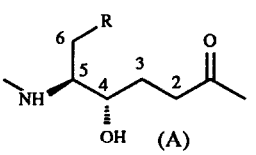
Abstract: γ-Lactones **6**, **7**, **8**, **10** and the ester **9**, precursors to the hydroxyethylene dipeptide isostere unit, were synthesized stereoselectively in two or three steps from α-amino-ketones in good yield Peptides containing these isosteres are potent inhibitors of certain aspartyl proteinases. Alkylation of the (3*S*,4*S*)-substituted γ-lactone **6** afforded exclusively cis-alkylation, with regard to C-2 and C-4

Introduction

In recent years there has been a growing interest in certain enzyme inhibitors as new therapeutic agents One class of proteolytic enzymes that has received particular attention are aspartyl proteinases[1] which include the blood pressure regulating enzyme renin[2] and the replication of the human immunodeficiency virus regulating enzyme HIV-1-proteinase [3] These enzymes have, as the catalytic system, two aspartyl groups in the active site and cleave the substrate[4] between two internal hydrophobic amino acid residues (Leu^{10}-Val^{11}) Series of potent synthetic peptide inhibitors of these aspartyl proteinases have been reported that contain a dipeptide mimic, known as hydroxyethylene dipeptide isosteres [5a]

In the course of our work on inhibitors of HIV-1-protease we discovered, besides other groups that the replacement of peptide bonds by the dipeptide analogues (A) (homostatine) can impart greater activity, enhanced selectivity and metabolic stability, in relation to statine analogues



(A)

Figure 1 Unit of (4*S*,5*S*)-5-amino-6-alkyl-4-hydroxy-hexanoic acid

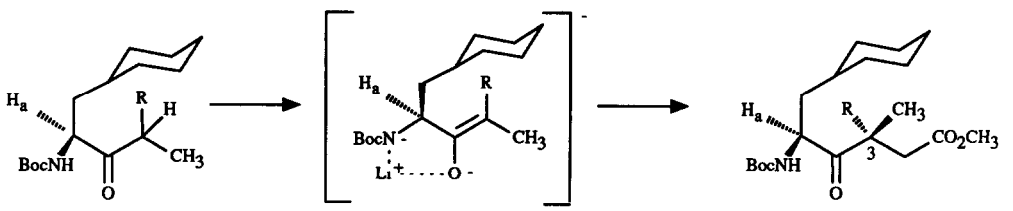
Compounds in which the replacement unit has been the "naked" homostatine[6] (unsubstituted at the C-atoms 2 and 3), indeed showed a high metabolic stability, but no successful antihypertensive or HIV-1-protease inhibiting activity.

It has been known that a substituent at C-atom 2 (e. g (2*S*)-isopropyl or (2*S*)-benzyl) improves the biological activity dramatically Several syntheses of these hydroxyethylene isosteres have been reported,[7, 8, 9] but the majority exhibits serious shortcomings in stereochemical control To date no derivatives with a substiuent at C-3 are described in the literature

Results and Discussion

Considering previous experiences of others, we aimed at the lactones **6**, **7**, and **8** (see schemes 2 and 3) Besides this, the additional alkylation of **6** leads to the lactone **10** (see Scheme 4) After opening these different lactones by LiOH[11] or primary amines[12], the resulting δ-amino acids can be introduced into certain inhibitors of aspartyl proteinases

Scheme 1



1 R = H
2 R = CH_3

3a R = H
b R = CH_3

4 R = H
5 R = CH_3

Our key intermediates, the α-amino ketones **1**, **2** can be easily prepared in large scale (50 - 500 g) starting from amino acids following the route of H Rapoport [13]

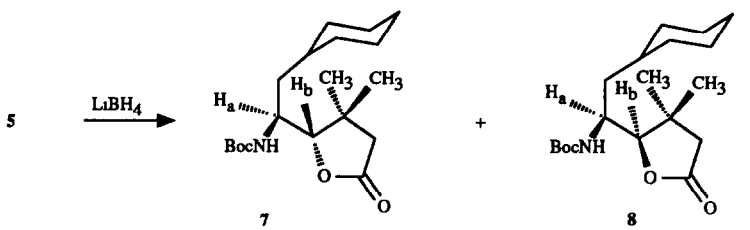
With these optically pure N-Boc-α-amino ketones in hand, we began our investigation of enolization and alkylation conditions in order to control the alkyl branch stereochemistry at the new stereocentre (in case of **4** at C-3) Enolization of ketone **1** with the sterically hindered base lithium diisopropyl amide (LDA) in tetrahydrofuran and trapping this enolate with methyl bromoacetate resulted in formation of a single compound In the case of the mono methylated compound **4** the (3*S*,5*S*) diastereomer was the predominant one, but traces of the (3*R*,5*S*)-configurated isomer can be seen We found that addition of certain Lewis acids ($ZnBr_2$, $ClTi(O\text{-}iPr)_3$ and $LiClO_4$) avoided the formation of this side product (< 4 %) This result can be explained by means of a strong chelation control in the transition state of the enol intermediate, and a "clean" backside (*si*-side) attack of the electrophil These observations support our speculation that the intermediate Z-enolate **3a** appears to be the thermodynamic enolate This observation is in full agreement with a theroretical paper published by K N Houk[14] and an experimental work on the synthesis of the cyclosporin amino acid (2S,3R,4R,6E)-3-hydroxy-4-methyl-2-(methylaminol-6-octenoic acid (MeBmt) [15]

The desired γ-keto-ester preserved the optical integrity at C-5 That means that the enolization went exclusively into the alkyl side chain, and not in the direction of the nitrogen atom.
Following the same procedure, alkylation of the isopropyl ketone **2** gave the dimethylated derivative **5** as colorless oily product in 64% yield It should be mentioned that similar alkylation of the corresponding methyl ketone afforded only traces of the C-3-unsubstituted product [13c]

Interesting are some remarkable differences in The NMR spectra of **4** and **5** While H_a in **4** resonated at δ = 4 11 (m), and NH at δ = 7 26 (d, J = 7 3 Hz) the corresponding signals in **5** were registered at δ = 4 58 (m) and δ = 6 94 (d, J = 8 82 Hz) From the different coupling constants and chemical shifts it can be seen that the torsion angle between the neighbouring C-5-H_a and NH-bonds is rather different in both compounds The additional methyl substituent at C-3 obviously has a strong influence on the conformation in solution and therefore it is expected that also the carbonyl group in **4** is quite differently oriented compared to ketone **5** If this is the case, the following reduction of **4** and **5** should lead to different stereoselectivities

Completion of the synthesis of 3-alkyl-4-hydroxy-5-amino acids from the amino ketones requires a stereoselective reduction of the keto group In our first attempt we reduced the dimethylated keto ester **5** in order to get information about the stereoselectivity of different reduction conditions and the stereochemical assignment of the resulting lactones (see Scheme 2)

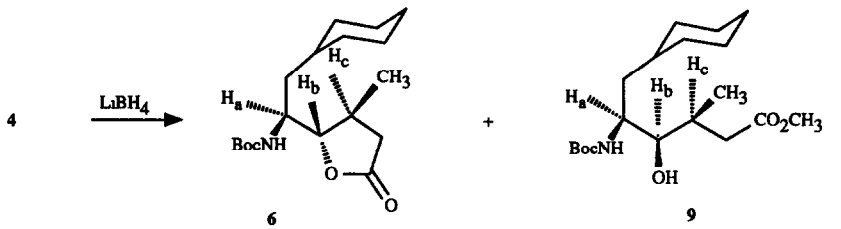
Scheme 2



Various reducing agents ($NaBH_4$, $LiBH_4$, $LiAl(OR)_3$, Selectride etc) and reaction conditions, including microbiological reductions were tried in order to achieve a stereoselective reduction of the carbonyl group, but in every case we isolated a mixture of the diastereomeric lactones **7** and **8** in a ratio of about 1 1 However, both lactones can easily be separated by column chromatography on silica gel and were recrystallized from n-hexane The diastereomeric purity of these compounds was secured by NMR measurements in DMSO-d_6 and proved to be higher than 96 % de The stereochemistry of the newly generated stereo centre at C-4 was determined by means of elucidation of the coupling constants of H_a and H_b [19] In the case of **7** we found a constant of $J_{a,b}$ = 9 7 Hz which means that the resulting hydroxy group is anti-configurated to the α-amino group The isomeric lactone **8** shows a coupling constant of $J_{a,b}$ = 5 4 Hz according to a syn order of the hydroxy- and to the amino group

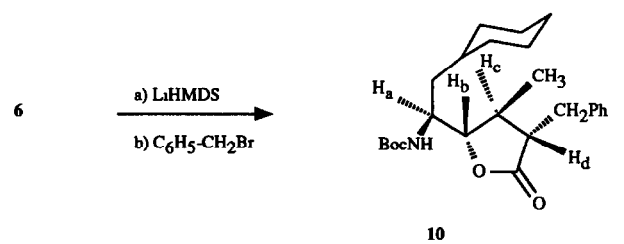
In contrast to keto-ester **5** the reduction of the mono methyl ketone **4** with $LiBH_4$ in 2-propanol supplied lactone **6** and the ring opened δ-amino-ester **9** in a ratio of 1 5 (see Scheme 3). The spectral data confirm the stereochemistry (**6** IR 1779, 1713, 1680 cm^{-1}, ^{1}H-NMR. $J_{a,b}$ = 9 8 Hz, $J_{b,c}$ = 5 0 Hz, **9** IR 3424, 1746, 1685 cm^{-1}, ^{1}H-NMR. $J_{a,b}$ = 9 Hz, $J_{b,c}$ = 2 1 Hz) Although **9** has the undesired relative stereochemistry, the finding that this compound is the major product is in full accordance with particular items of the literature [15,16]

Scheme 3



In the last step, we investigated the alkylation of the dianion of **6**, generated with 2 equiv of lithium hexamethyldisilazide [17] (see Scheme 4) Best results were achieved with benzyl bromide which, upon reaction with the dianion resulted in a 24% yield of the cis lactone **10** (cis regarding C-2 and C-4) The relative configuration of **10** was firmly established by the coupling constants of H_c ($J_{c,d}$ = 5 6 Hz, see experimental section) Only traces of a side product, presumably the trans-isomer, could be detected and no amount of dialkylated material was formed The high cis-stereoselectivity of our 3-methyl lactone **6** in contrast to the unsubstituted lactones is explained by a transition state of **6** in which the front-side (*re*-side) of the ketone enolate is shielded by the methyl group, so that only backside (*si*-side) attack of the alkylation reagent occurs This hypothesis is supported by the observation that an alkylation of the dimethylated lactones **7** and **8** is not possible

Scheme 4



Synthesis of peptides containing the hydroxyethylene isosteres derived from lactones **6**, **7**, **8**, **10** and their biological activity will be reported elsewhere

Experimental

^{1}H-NMR spectra were obtained by using a Bruker AC 200, Bruker WM 250, and Bruker AM 500 spectrometer with TMS as internal standard IR spectra were obtained using a Perkin Elmer 397, Bruker IFS 48, Bruker IFS 66, Bruker IFS 88 spectrometer UV spectra were obtained using UV/VIS spectrophotometers Lambda 5 and Lambda 2 Optical rotations were obtained with Perkin-Elmer 241 polarimeter
The melting points are uncorrected and were obtained in open capillaries on a Mettler FP 61 melting point apparatus
Solvents and reagents were commercially available and used after distillation All reactions were performed under helium atmosphere Solvents were removed by means of a rotary evaporator
Chromatography was performed using 0 063 - 0 002 mm silica gel (E Merck, Si60) Analytical thin-layer chromatography was performed on Si60, F254 silica gel plates using phosphomolybdic acid for visualization
HPLC was performed using RP18 LiChrosorb 250-4 5 µm (E Merck), detection - 215 nm, and flow rate 1 ml/min

(4*S*)-4-tert-Butoxycarbonylamino-5-cyclohexylpentan-3-one (1) and (4*S*)-4-tert-butoxycarbonylamino-2-methyl-5-cyclohexylpentan-3-one (2) Following the procedure of Weinert[18] and Rapoport[13] N-Boc-cyclohexyl-alanyl-N-methyl-N-methoxy-amide was treated with the corresponding Grignard compound The desired amino ketones were purified by chromatography and subsequent crystallization from n-hexane

1 Yield 66 %, mp 71 7°C, $[\alpha]_D^{20}$ = +34 3° (c = 0 45, $CHCl_3$), IR(KBr) 3326, 2920, 1725, 1694, 1680, 1533, 1367, 1314, 1168 cm^{-1}, ^{1}H-NMR (DMSO-d_6) δ = 0 91 (3 H, t, J = 7 2 Hz, CH_3), 1 37 (9 H, s, tBu), 2 46 (2 H, m, $J_{2,2'}$ = -18 0 Hz, $J_{2',CH3}$ = 7 0 Hz, $J_{2,CH3}$ = 7 0 Hz, CH_2), 3 96 (1 H, m, $J_{Ha,5}$ = 5 7 Hz, $J_{Ha,5'}$= 9 7 Hz, J_{HaNH} = 7 9 Hz, H_a), 7 15 (1 H, d, J = 7 9 Hz, NH) Anal Calcd for $C_{16}H_{29}NO_3$ (283 4) C, 67 81, H, 10 31, N, 4.94, O, 16 94 Found C, 68 90, H, 10 32, N, 5 20, O, 16 50

2 Yield 53 %, mp 126 2°C, $[\alpha]_D^{20}$ = + 44 5° (c = 1 0, $CHCl_3$) IR(KBr)· 3323, 2921, 1715, 1678, 1536 cm^{-1}, ^{1}H-NMR($CDCl_3$) δ = 1 11 (6 H, d, CH_3), 1 46 (9 H, s, tBu), 2 80 (1 H, m, CH), 4 52 (1 H, m, H_a), 5 03 (1 H, d, J = 8 4 Hz, NH), anal calcd for $C_{17}H_{31}NO_3$ (297 4) C, 68 65, H, 10 51, N, 4 71, O, 16 14, found C, 68 1, H, 10 40, N, 4 80, O, 16 3

(5*S*)-5-tert-Butoxycarbonylamino-6-cyclohexyl-3,3-dimethyl-4-oxohexanoic acid methylester (5) To a solution of 90 mmol LDA in THF at -70°C was added dropwise a solution of 8 9 g (30 mmol) **2** in 200 ml abs THF The mixture was allowed to stir at this temp for 2 h Then, a solution of 8 3 ml (90 mmol) freshly distilled methyl bromoacetate in 20 ml abs THF was added dropwise over a 30 min period When the addition was complete, the mixture was allowed to warm up to 0°C The reaction was quenched by the addition of 2 N HCl (~ pH 5) and extracted with dichloromethane The organic phase was separated, washed with brine, dried over anhydrous Na_2SO_4, and evaporated to give 18 g of a colorless oil Purification of the crude product on silica gel with petroleumether-methyl tert butyl ether = 4 1 afforded

9 5 g **5** as an oil HPLC-purity· 96 6 % (eluent acetonitrile· H_2O = 7 3, detection at 200 nm) $[\alpha]_D^{20}$ = -10 9° (c = 0 94, $CHCl_3$), IR(Kap) 3360, 2925, 1741, 1704, 1502 cm^{-1}, ^{1}H-NMR(DMSO-d_6) δ = 1 14 (3 H, s, CH_3), 1 27 (3 H, s, CH_3), 1 37 (9 H, s, tBu), 2 85 (2 H, dd, CH_2), 3 53 (3 H, s, OCH_3), 4 58 (1 H, m, H_a), 6 94 (1 H, d, J = 8 82 Hz, NH), anal calcd for $C_{20}H_{35}NO_5$ (369 5) C, 65 01; H, 9 55; N, 3.79, O, 21 65, found· C, 64 60, H, 9 48, N, 4 10, O, 22 8 %

(3*S*,5*S*)-5-tert-Butoxycarbonylamino-6-cyclohexyl-3-methyl-4-oxohexano ic acid methylester (4) Starting from **1** the procedure for preparation of **4** corresponds to the synthesis of **5**, except before treating the enolate of the α-amino ketone with methyl bromoacetate, the addition 1 mol equiv of chlorotriisopropoxytitanium is necessary to obtain a high yield of desired oily γ-keto-ester **4** Yield 39 %, $[\alpha]_D^{20}$ = -34 3° (c =0 95, $CHCl_3$), IR(Kap) 2925, 1749, 1712,1510 cm^{-1}, ^{1}H-NMR(DMSO-d_6) δ = 1.0 (3 H, s, CH_3), 1 37 (9 H, s, tBu), 2.27 (1 H, $J_{2,2'}$= -16 4 Hz, $J_{2,3}$ = 6 8 Hz, H_2), 2 58 (1 H, $J_{2',3}$ = 7 2 Hz, $H_{2'}$), 3 21 (1 H, m H_3), 3 56 (3 H, s, OCH_3), 4 11 (1 H, m, H_a), 7 26 (1 H, d, J = 7.3 Hz, NH), anal calcd for $C_{19}H_{33}NO_5$ (355 5) C, 64,18, H, 9 37; N, 3 94, O, 22 50; found C, 63 5, H, 9.04; N, 4 00, O, 23 50 %

(5*S*)-5-[(1*S*)-1-tert-Butoxycarbonylamino-2-cyclohexylethyl]-4,4-dimethyltetrahydrofuran-2-one (7) and (5*R*)-5-[(1*S*)-1-tert-butoxycarbonylamino-2-cyclohexylethyl]-4,4-dimethyl-tetrahydrofuran-2-one (8) To a stirring solution of 7.1 g (19 mmol) **5** in 150 ml 2-propanol at -20°C 3 5 g lithium borohydride was added in portions After stirring an additional 30 min period at 0°C, the reaction was quenched by the addition of 2 N HCl, and extracted with dichloromethane The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated to give 7 4 g of an oil Silica gel purification of the crude mixture with a hexane-methyl-tert butyl ether (2 1) eluant gave 2 8 starting material, 1 3 g (20 %) **7** and 1 37 g (21 %) **8**

7 mp 149 1°C (from n-hexane), $[\alpha]_D^{20}$ = - 69 2° (c = 0 45, $CHCl_3$), IR(KBr) 3340, 2929, 1788, 1681, 1528 cm^{-1}, ^{1}H-NMR(DMSO-d_6). δ = 0 99 (3 H, s, CH_3), 1 12 (3 H, s, CH_3), 1.39 (9 H, s, tBu), 2 4 (2 H, dd, CH_2), 3 67 (1 H, m, H_a), 3 93 (1 H, d, $J_{Hb,Ha}$ = 9 7 Hz, H_b), 6 82 (1 H, d, J = 9.55 Hz, NH), anal calcd for $C_{19}H_{33}NO_4$ (399 5) C, 67 22, H, 9 80, N, 4 13, O, 18 85, found C, 67 6, H, 9 49, N, 4 5, O, 19 3 %

8 mp 113 6°C (from n-hexane), $[\alpha]_D^{20}$ = -7 10° (c, 0 36, $CHCl_3$), IR(KBr) 3425, 2922, 1775, 1713, 1498 cm^{-1}, ^{1}H-NMR(DMSO-d_6) δ = 1 03 (3 H, s, CH_3), 1 11 (3 H, s, CH_3), 1 38 (9 H, s, tBu), 2 34 (2 H, dd, CH_2), 3 80 (1 H, m, H_a), 3 95 (1 H, d, $J_{Hb,Ha}$ = 5 4 Hz, H_b), 6 63 (1 H, d, J = 9 5 Hz, NH), anal calcd for $C_{19}H_{33}NO_4$ (339 5) C, 67 22, H, 9 80, N, 4 13, O, 18 85, found C, 66 6, H, 9 49, N, 4 00, O, 18 6 %

(4*S*,5*S*)-5-[(1*S*)-1-tert-Butoxycarbonylamino-2-cyclohexylethyl]-4-methyltetrahydrofuran-2-one (6) and (3*S*,4*R*,5*S*)-5-tert-butoxycarbonylamino-6-cyclohexyl-4-hydroxy-3-methylhexanoic acid methyl ester (9) To a solution of 1 g (2 8 mmol) of **4** in 25 ml abs 2-propanol 0.2 g lithium borohydride was added portionwise at -50°C After being stirred for 30 min, the mixture was poured onto ice cold 2 N HCl and extracted several times with diethyl ether The organic layer was separated, dried over Na_2SO_4, and evaporated to an oil Purification of the crude oil by silica gel chromatography with a dichloromethane/tert-butylmethyl ether (95 5) eluant afforded 16 8 % **6** and 69 9 % **9**

6· mp 166 2°C (from n-pentane), $[\alpha]_D^{20}$ = -75 8° (c = 0 99, $CHCl_3$), IR(KBr) 3360, 2927, 1779, 1713, 1680, 1528 cm^{-1}, ^{1}H-NMR(DMSO-d_6) δ = 0 91 (3 H, s, CH_3), 1.36 (9 H, s, tBu), 2 09 (1 H, dd, CH_2), 2 83 (1 H, dd, CH_2), 3.68 (1 H, m, $J_{Hb,Ha}$ = 9.6 Hz, $J_{Ha,NH}$ = 9 9 Hz, H_a), 4 21 (1 H, dd, $J_{Ha,Hb}$ = 9 8 Hz, $J_{Hb,Hc}$ = 5 0 Hz, H_b), 6 81 (1 H, d, NH), anal calcd for $C_{18}H_{31}NO_4$ (325 4) C, 66 41, H, 9.62, N, 4.30, O, 19 66, found C, 66 70, H, 9.41; N, 4 30, O, 20 20 %

9 mp 111 1°C (from n-pentane), $[\alpha]_D^{20}$ = -4 5° (c = 0.94, $CHCl_3$), IR(KBr)· 3424, 2925, 1746, 1685, 1520 cm^{-1}, ^{1}H-NMR(DMSO-d_6) δ = 0 77 (3 H, d, J = 7 0 Hz, CH_3), 1 36 (9 H, s, tBu), 3 06 (1 H, m, $J_{Hb,Ha}$ = 9 0 Hz, $J_{Hc,Hb}$ = 2 1 Hz, $J_{Hb,OH}$ = 6 7 Hz, H_b), 3 39 (1 H, m, H_a), 3 56 (3 H, s, OCH_3), 4 54 (1 H, d, OH), 6 40 (1 H, d, J = 10 1 Hz, NH), anal calcd for $C_{19}H_{35}NO_5$ (357.5) C, 63 82, H, 9 89, N, 3 92, O, 22 37, found C, 64 10, H, 9 66, N, 4 00, O, 21 90 %

(3*S*,4*S*,5*S*)-3-Benzyl-5-[(1*S*)-tert-butoxycarbonylamino-2-cyclohexylethyl]-tetrahydrofuran-2-one (10) To a suspension of lithium hexamethyldisilazide, prepared at 0°C by the dropwise addition of 4 1 mmol of a 1 6 M solution of n-butyllithium in hexane, to 0 87 ml (4 2 mmol) of hexamethyldisilazane in 2 ml of abs THF was added dropwise a solution of 0 58 g (1 8 mmol) of **6** in 1 5 ml of abs THF at -78°C After 15 min a solution of 0 24 ml (2 03 mmol) freshly distilled benzyl bromide in 1 ml abs THF was added, and the mixture was allowed to warm up to -40°C within 2h After quenching with 2 N HCl the mixture was poured onto ice water, and extracted several times with tert butylmethyl ether The organic layer was separated and washed with brine, dried over Na_2SO_4 and evaporated to an oil which was purified on silica gel with an n-hexane/methyl tert butyl ether (2 1) eluant

9 Yield 24 1 % The chemical purity was determined by HPLC (Eluant acetonitrile/H_2O = 70 30) and was 98 8 %, mp 169 2°C (from n-pentane), $[\alpha]_D^{20}$ = -5 1° (c = 0 99, $CHCl_3$), IR(KBr) 3360, 2922, 1773, 1680, 1530 cm^{-1} ^{1}H-NMR(DMSO-d_6) δ = 0 83 (3 H, d, CH_3), 1 36 (9 H, s, tBu), 2 26 (1 H, m, $J_{Hd,Hc}$ = 5 6 Hz, $J_{Hc,Hb}$ = 6 8 Hz, H_c), 2 65 (1 H, m, H_d), 2 81 (1 H, dd, CH_2), 2 95 (1 H, dd), 3 66 (1 H, m, H_a), 4 27 (1 H, dd, $J_{Hb,Ha}$ = 8 6 Hz, H_b), 6 79 (1 H, d, J = 9 4 Hz, NH), 7 27 (5 H, m, arom H), anal calcd for $C_{25}H_{37}NO_4$ (415 6) C, 72 24, H, 8 99, N, 3 37, O, 15 40, found C, 72 00, H, 8 92, N, 3 60, O, 15 40 %

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