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SYNTHESIS OF A NEW C_2-SYMMETRIC MOLECULE WITH DIMERIC HYDROXYETHYLENE ISOSTERIC MOIETY

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Abstract: As part of our studies directed toward the development of new HIV protease inhibitors, a new type of C_2-symmetric molecule having a dimeric hydroxyethylene isosteric moiety is synthesised by Cu(II)-mediated dimerisation of the sodium enolate of an amino acid-derived methylketo copound.

Protease inhibitors are becoming an important class of drugs for treating HIV infected patients.[1] Among the various types of protease inhibitors of particular importance are those with C_2- or pseudo-C_2-symmetric structures.[2] After the pioneering work from Abbott,[3] a large variety of structural types of C_2- and pseudo-C_2-symmetric inhibitors of HIV protease have been reported.[4] Here we report the synthesis of a new class of C_2-symmetric molecule, {Boc-Val-Phe-ψ[CH(OH)CH_2]-}$_2$ (**1**), having a dimeric hydroxyethylene isosteric moiety where the spacing between adjacent hydrogen bond-donating (NH) groups is seven bond lengths and the other functional groups are strategically placed in order to achieve the expected binding with the protease. The concept of mechanism-based inhibitor design where the scissile P1-P1' bond is replaced by a nonhydrolysable isostere with tetrahedral geometry is coupled here synergistically with structure-based design concept incorporating C_2 symmetry into the molecule.

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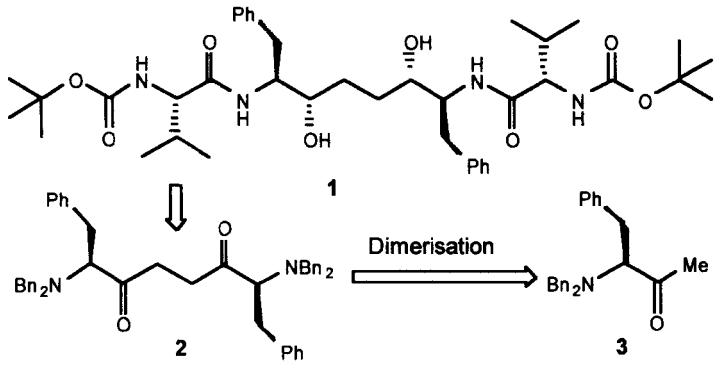
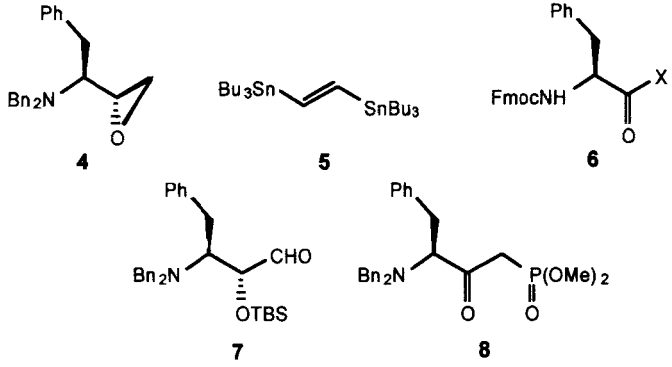
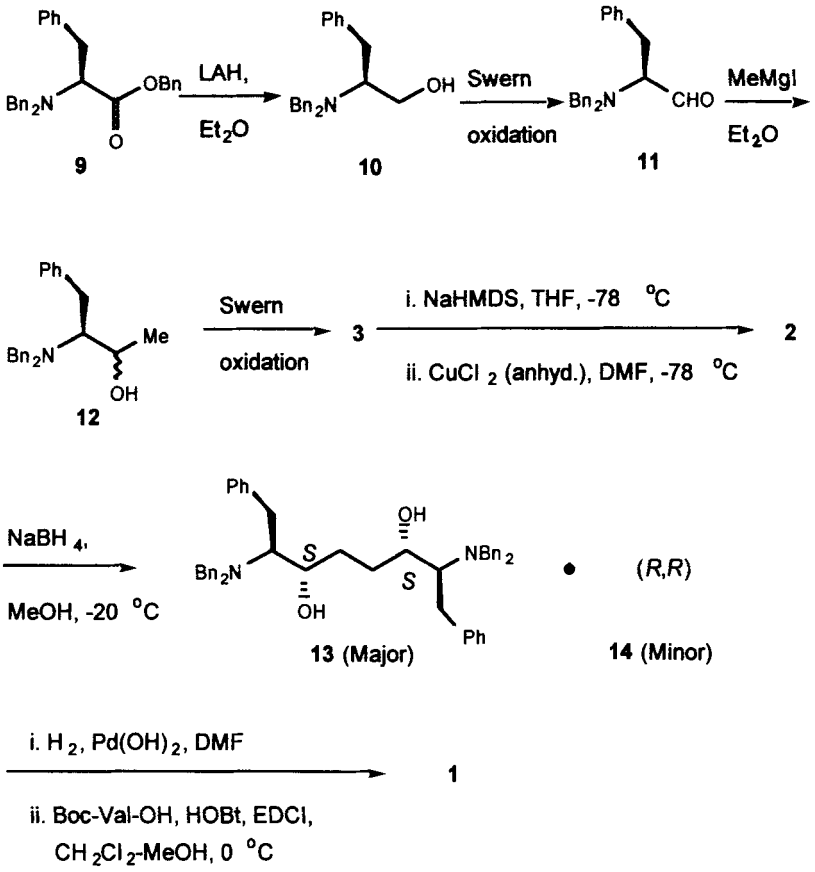


Retrosynthetic dissection revealed the requirement of a precursor like **2**, a 1,4-diketo compound which can be obtained from a suitably functionalised amino acid **3**. The lithium enolate of **3** (Scheme 1) when reacted with epoxide **4**,[5] the expected epoxide opening did not take place. Palladium-catalysed coupling of distannylethene **5**[6] with two molecules of amino acid halide **6** did not yield the targetted 1,4-diketone.[7] Olefination of aldehyde **7**[8] with ketophosphonate **8** was also unsuccessful. All these failures prompted us to device an alternate approach which involves Cu^{2+}-induced oxidative electron transfer process in the enolate of methylketo compounds leading to the formation of radical intermediates which on dimerisation furnish the required 1,4-diketo compounds.[9]





Scheme 1. Synthesis of **1**

The starting material used by us was **3** which was prepared in four steps from *N,N*-dibenzylphenylalanine benzyl ester **9**[10] (Scheme 1): LAH reduction to *N,N*-dibenzylphenylalaninol **10** (95% yield), Swern oxidation to aldehyde **11**, addition of MeMgI to get **12** (90% from **10**) and finally Swern oxidation to the methylketone **3** (96% yield). The sodium enolate of **3** was generated using sodium

hexamethyldisilazide at -78 °C. When this enolate was treated with anhydrous cupric chloride, the desired 1,4-diketo compound **2** was formed in about 90-92% yield (based on recovered starting material). The C_2-symmetric nature of the molecule was clearly evident in the NMR where only one half of the molecule was seen. The mass which was taken at the diol stage also supported the dimeric structure. Reduction of this diketo compound **2** with $NaBH_4$ in MeOH at -20 °C led to the formation of diastereomeric mixture (~3:1) of alcohols in 90% yield. The major one was assigned with (*S,S*) stereochemistry (**13**) on the basis of reported works.[11] Nonavailability of better diastereoselective bulky reducing agent like lithium selectride did not permit us to get exclusively one isomer in this step. The mixture of isomers (**13** and **14**) was hydrogenated to get the free diamine which was coupled at both ends with Boc-Val-OH using 1-hydroxybenzotriazole (HOBt) and 1-(3-dimethylaminopropyl)-3-ethylcarbo-diimide hydrochloride (EDCI) to get the targetted dimeric product **1** (65% yield in two steps).

Thus a Cu^{2+}-induced oxidative dimerisation of amino acid-derived methylketo compound led to the synthesis of a dimeric hydroxyethylene isosteric moiety, which has a potential application in the development of new HIV protease inhibitors. With the availability of methods to synthesize 2,5-disubstituted pyrrolidines from 1,4-diketones by reductive amination,[12] or from 1,4-diols by tosylation (or mesylation) followed by trearment with amine,[13] our synthesis of **1** and **2** open up the possibility of the synthesis of different new classes of C_2-symmetric molecules which may have interesting as well as useful biological properties. Further work is under progress.

Experimental

General Procedures. NMR spectra were recorded on Varian Gemini 200 instrument or Unity 400 instruments. IR spectra were recorded on Shimadzu IR-

470 and Perkin-Elmer 283 B instruments. MS were recorded on VG MICROMASS 70-70H and VG Auti Spec M Spectrometers under electron impact (EI), chemical ionization (CI) or liquid secondary ion mass spectrometric (LSIMS) techniques.

All reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) with UV light, I_2, 7% ethanolic phosphomolybdic acid-heat and 2.5% ethanolic anisaldehyde (with 1% AcOH and 3.3% conc. H_2SO_4)-heat as developing agents. Acme, India, silica gel (finer than 200 mesh) was used for flash column chromatography. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.

***N,N*-Dibenzylphenyl alaninol (10)**: To a solution of *N,N*-dibenzylphenyl alanine benzyl ester **9**[10] (535 mg, 1.23 mmol) in dry ether (10 ml) LAH (0.093 g, 2.46 mmol) was added portionwise with stirring under nitrogen atmosphere at 0 °C. The reaction mixture was allowed to come to room temperature in 1 h time. It was then cooled again to 0 °C and quenched by dropwise addition of saturated Na_2SO_4 solution (4 ml) with stirring until white solids precipitated out. The clear solution was decanted out and the solids washed with EtOAc (2x15 ml). The combined organic layer was washed with brine (10 ml), dried (Na_2SO_4) and concentrated in vacuo. Column chromatography (SiO_2, 10-15% EtOAc in petroleum ether eluant) gave pure *N,N*-dibenzylphenyl alaninol **10** (387 mg, 95% yield) as a syrupy liquid. R_f = 0.6 (silica, 30% EtOAc in petroleum ether). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.45 - 7.08 (m, 15H, aromatic), 4.06 and 3.48 (ABq, 4H, NC*H*$_2$Ph), 3.62 and 3.4 (m, 2H, -C*H*$_2$OH), 3.22 (dd, *J* 10, 4 Hz, 1H, -CHC*H*$_2$Ph), 3.05 (m, 1H, -NC*H*-), 2.4 (dd, *J* 10 Hz, -CHC*H*$_2$Ph).

***N,N*-Dibenzylphenyl alaninal (11)**: To a solution of oxalyl chloride (0.15 ml, 1.76 mmol) in CH_2Cl_2 (5 ml) under nitrogen atmosphere at -78 °C, DMSO (0.27 ml, 3.74 mmol) was added slowly and dropwise. After stirring for 15 min. at -78 °C, *N,N*-dibenzylphenyl alaninol **10** (387 mg, 1.17 mmol) in CH_2Cl_2 (2 ml) was added to it. The reaction mixture was stirred at -78 °C for 0.5 h followed by the addition of Et_3N (0.82 ml, 5.85 mmol). After stirring at the same temperature for further 0.5 h it was allowed to come to room temperature in 1 h time followed by quenching with saturated NH_4Cl (10 ml). It was extracted with EtOAc (2x10 ml). The combined organic extracts were washed with brine (10 ml), dried (Na_2SO_4) and concentrated in vacuo. The resulting syrupy liquid was directly used in the next step.

Methyl carbinol 12: To a solution of the above aldehyde **11** in dry ether (10 ml) at 0 °C under nitrogen atmosphere was slowly adeed MeMgI (1.17 ml, 2M solution in ether, 2.34 mmol). After stirring for 15 min. at 0 °C it was allowed to come to room temperature and stirred for an additional hour followed by quenching with saturated NH_4Cl solution (10 ml). It was extracted with EtOAc (2x10 ml). The combined organic extracts were washed with brine (10 ml), dried (Na_2SO_4) and concentrated in vacuo. Column chromatography (SiO_2, 8-12% EtOAc in petroleum ether eluant) gave pure methyl carbinol **12** (363 mg, 90% from **10**, single isomer) as a syrupy liquid. R_f = 0.4 (silica, 20% EtOAc in petroleum ether). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.36-7.12 (m, 15H, aromatic), 3.94 (dq, *J* 6.6 Hz, 1H, C*H*OH), 3.8 and 3.62 (ABq, 4H, NC*H*2Ph), 3.08 (dd, *J* 12.8, 6.6 Hz, 1H, PhC*H*2CH-), 2.96 (q, *J* 6.6 Hz, 1H, NC*H*-), 2.82 (dd, *J* 12.8, 6.6 Hz, 1H, PhC*H*2CH), 1.22 (d, *J* 6.6 Hz, 3H, C*H*3).

Methyl Ketone 3: The methyl carbinol **12** (350 mg, 1.014 mmol) was oxidised in the same way as described above to get the ketone **3** (334 mg, 96% yield) as a

syrupy liquid. R_f = 0.7 (silica, 15% EtOAc in petroleum ether). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.4-7.0 (m, 15H, aromatic), 3.75 and 3.52 (ABq, 4H, NCH_2Ph), 3.46 (dd, *J* 9, 4.5 Hz, 1H, NC*H*CO), 3.1 (dd, *J* 13.5, 9 Hz, 1H, PhCH_2CH), 2.82 (dd, *J* 13.5, 4.5 Hz, 1H, PhCH_2CH), 2.04 (s, 3H, COCH_3).

1,4-Diketo compound 2: To a solution of the methyl ketone **3** (275 mg, 0.802 mmol) in dry THF (2 ml) under nitrogen atmosphere at -78 °C, sodium hexamethyldisilazide (0.88 ml, 1M sol. in THF, 0.88 mmol) was added dropwise. After stirring at the same temperature for 0.5 h, freshly dried anhydrous cupric chloride (118 mg, 0.88 mmol), dissolved in dry DMF (2 ml), was added to the reaction mixture drop by drop. The solution immediately turned green. It was stirred at -78 °C for 1 h followed by slow warm up to room temperature in 2 h time. Then it was quenched with sat. NH_4Cl solution (5 ml). The aqueous layer was extracted with EtOAc (2x10 ml). The combined organic extracts were washed with brine (10 ml), dried (Na_2SO_4) and concentrated in vacuo. Column chromatography (SiO_2, 2-3% EtOAc in petroleum ether eluant) separated the unreacted starting material (110 mg) and the pure diketo compound **2** (152 mg, 92% yield) was obtained as a syrupy liquid. R_f = 0.5 (silica, 5% EtOAc in petroleum ether). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.4-7.0 (m, 15H, aromatic), 3.8 and 3.55 (ABq, 4H, NCH_2Ph), 3.52 (m, 1H, NC*H*CO), 3.2-2.8 (m, 4H, PhCH_2, COCH_2).

Diol 13 (and **14**): To a solution of the diketo compound **2** (150 mg, 0.22 mmol) in methanol (10 ml) under nitrogen atmosphere at -20 °C, sodium borohydride (67 mg, 1.76 mmol) was added portionwise. After stirring at the same temperature for 2 h, the reaction mixture was quenched by adding saturated NH_4Cl solution (10 ml). The aqueous layer was extracted with EtOAc (2x10 ml). The combined

organic extracts were washed with brine (10 ml), dried (Na_2SO_4) and concentrated in vacuo. Column chromatography (SiO_2, 8-10% EtOAc in petroleum ether eluant) gave dihydroxy compounds **13** and **14** as a mixture of isomers (~3:1, 136 mg, 90% yield). R_f = 0.45 (silica, 20% EtOAc in petroleum ether). IR (KBr): ν 3400, 3100, 3000, 2900, 2825, 1600, 1500, 1450 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, major isomer **13**): δ 7.4-7.05 (m, 15H, aromatic), 3.85 and 3.33 (ABq, 4H, NC*H*$_2$Ph), 3.49 (t, *J* 7 Hz, 1H, C*H*OH), 2.97 (dd, *J* 14.1, 7.5 Hz, 1H, PhC*H*$_2$CH), 2.78 (dd, *J* 7.5, 5 Hz, 1H, NC*H*CHOH), 2.67 (dd, *J* 14.1, 5 Hz, 1H, PhC*H*$_2$CH), 1.7-1.4 (m, 2H, C*H*$_2$). MS (LSIMS): calcd. for $C_{48}H_{52}N_2O_2$ (M^+): 689, found *m/z* 689 (M^+).

{Boc-Val-Phe-ψ[CH(OH)CH$_2$]-}$_2$ (1): The mixture of diols **13** and **14** (130 mg, 0.19 mmol) was dissolved in DMF (5 ml) and $Pd(OH)_2$ on carbon (20%, 100 mg) was added into it. It was then hydrogenated under atmospheric pressure using a H_2 balloon for 5 h. The reaction mixture was then filtered through a short pad of celite and the filter cake washed with MeOH (2x10 ml). The filtrate and washings were combined and concentrated in vacuo. The residue was azeotroped with dry toluene (2x5 ml) and dries under vacuum. To a solution of Boc-Val-OH (87 mg, 0.4 mmol) in dry CH_2Cl_2 (2 ml) at 0 °C under nitrogen atmosphere was added sequentially HOBt (54 mg, 0.4 mmol) and EDCI (77 mg, 0.4 mmol). After stirring for 15 min. at the same temperature, the above diamine dissolved in dry DMF (2 ml) was added to it. The reaction mixture was slowly allowed to come to room temperature and stirred for 16 h. It was then diluted with EtOAc (10 ml) and washed with saturated NH_4Cl (10 ml), brine (10 ml), dried (Na_2SO_4) and concentrated in vacuo. Column chromatography (SiO_2, 2% MeOH in CH_2Cl_2 eluant) gave **1** (90 mg, 65% yield) as a mixture of isomers (~3:1). R_f = 0.4 (silica, 10% MeOH in CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$, major isomer): δ 7.8 (br s,

1H, Phe-N*H*), 7.2-7.08 (m, 5H, aromatic), 5.0 (d, *J* 11 Hz, 1H, BocN*H*), 3.9 (dd, *J* 11, 6.7 Hz, 1H, Val-α*H*), 3.4 (m, 1H, C*H*OH), 3.3 (m, 1H, NC*H*CHOH), 3.02 (m, 2H, PhCH_2CH), 1.8-1.2 (m, 3H, CH_2, C*H*), 1.25 (s, 9H, Boc), 0.81 (d, *J* 6.7 Hz, 6H, Val-CH_3). MS (LSIMS): calcd. for $C_{40}H_{62}N_4O_8$ (M^+): 728, found *m/z* 728 (M^+, 90%), 628 (M^+-Boc, 70%).

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