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Studies in ANF Potentiation. Synthesis of Rigid Bicyclic Analogs of Cyclopentyl Glutaryl Derivatives

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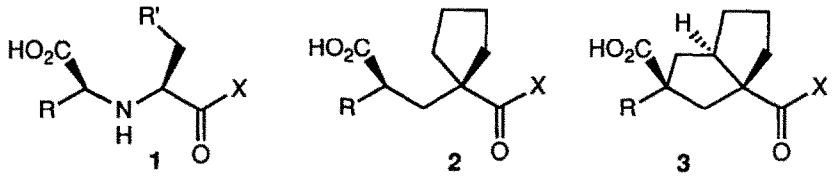
Abstract: The synthesis of bicyclic NEP inhibitors represented by the structure **3** is described. These compounds were weaker NEP inhibitors than the cycloalkyl glutaryl derivatives **2**. It is suggested that the minimum energy conformation adopted by compound **3** does not correspond to the bio-active conformation occupied by compound **2**.

The Atrial Natriuretic Factors (ANF) are peptide hormones with powerful vasodilatory, diuretic, and natriuretic effects.[1-4] *In vivo* levels of ANF suffer from short half-life due to receptor-mediated clearance[5-8] as well as degradation by neutral endopeptidase (NEP, EC 3.4.24.11).[9,10] Studies todate indicate that ANF potentiation *via* neutral endopeptidase inhibition[11,12] may provide a novel therapeutic approach for the treatment of hypertension and congestive heart failure.[13]

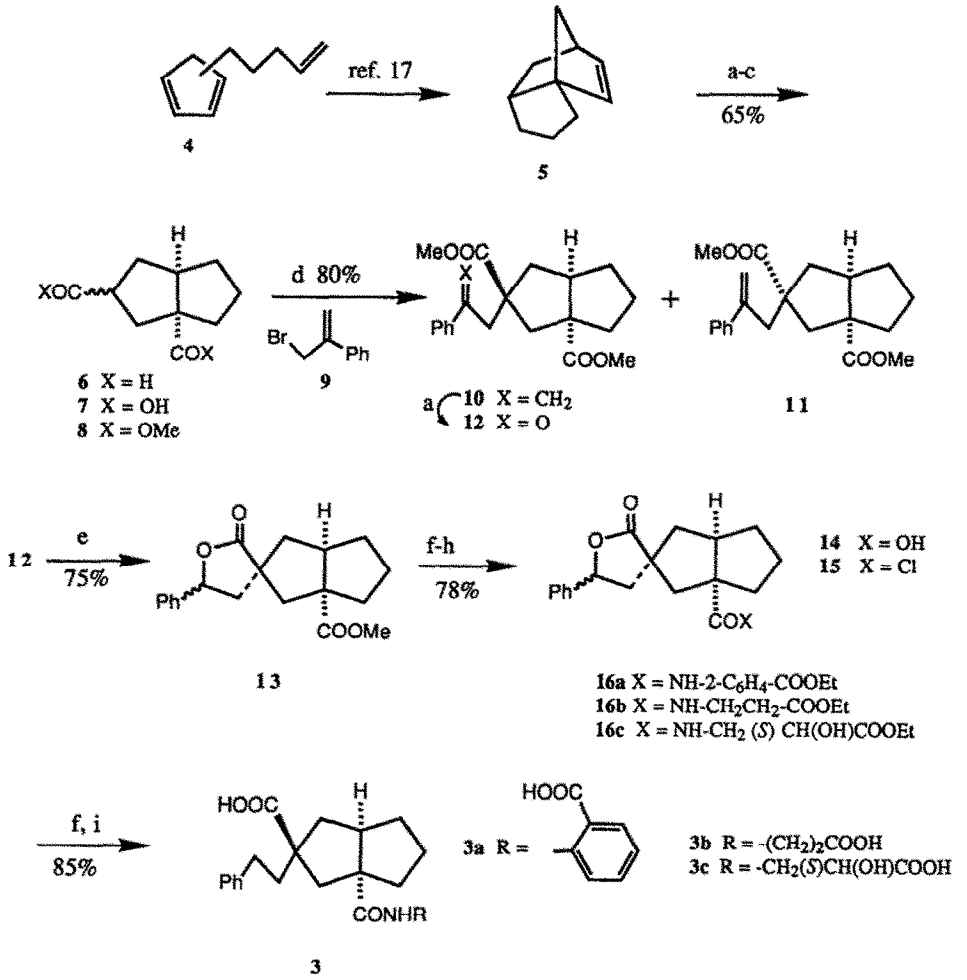
Carboxyalkyl peptides of the general structure **1** were shown to potentiate ANF activity and express antihypertensive effects[14]. Subsequently, workers at Pfizer reported that conformationally constrained deaza analogs of type **2** are potent inhibitors of NEP *in vivo* [15,16]. In view of these results, we wish to report our efforts in a novel series of bicyclic compounds represented by the diquinane structure **3**. This class of compounds could be viewed as rigid, conformationally restrained analogs of cyclopentyl glutaryl peptides **2**.



The synthesis of compound **3** starts with the tricyclic alkene **5** which was prepared according to the literature procedure[17]. Compound **5** was subjected to ozonolysis at -78° C in dichloromethane to yield the dialdehyde **6** which, without purification, was subjected to Jones oxidation[18] to yield the dicarboxylic acid **7**. Esterificiation of the dicarboxylic acid **7** was achieved using carbonyldiimidazole in dry methanol to give the diester **8** as a mixture of diastereomers in 65% overall yield from compound **5**. Direct alkylation of the ester enolate derived from compound **8** using phenylethyl bromide was found to be difficult due to competing elimination of phenylethyl bromide to styrene. However, this problem was circumvented using an indirect, but efficient, protocol shown in the scheme. Alkylation of the anion of compound **8**, generated using lithium diisopropyl amide in a solution of tetrahydrofuran:dimethylpropenylurea (DMPU) (3:1, v/v), using bromomethyl

styrene (**9**)[19], yielded compounds **10** and **11** in 4:1 ratio in 80 % yield. As expected from the topology of the diquinane ring system, the major product **10** resulted from the approach of the electrophile from the convex face of the bicyclic system. The stereochemistry of **10** was confirmed by 2-D NMR and NOE studies. Ozonolyis of

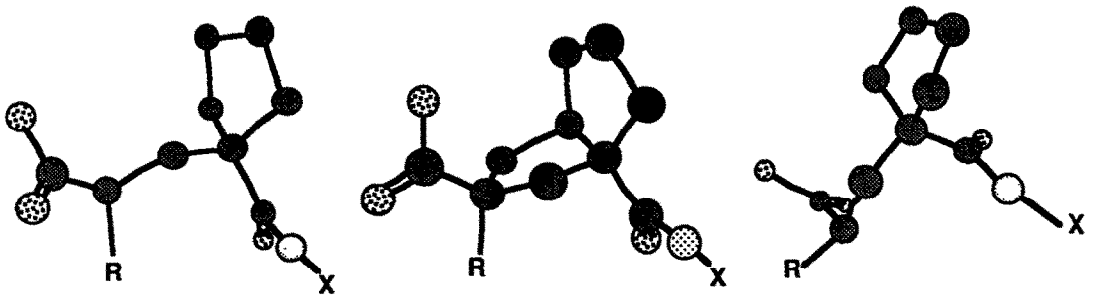
Scheme



(a) (i) O_3/CH_2Cl_2/-78°C; (ii) Dimethyl sulfide/RT. (b) Jones Reagent/acetone/RT. (c) Carbonyl diimidazole (excess)/ MeOH (dry). (d) (i) LDA/THF/-40°C; (ii) DMPU (1/3 vol of THF)/-40°C/45 min/**9**. (e) $NaBH_4$/i-PrOH-MeOH (1:1)/-7°C. (f) LiOH/THF-H_2O/H_2O_2. (g) $SOCl_2$/PhH/reflux. (h) 2-$EtOOCC_6H_4NH_2$(4 eq) → **16a** (i) H_2/Pd-C/EtOAc → **3a**.

styrene **10** followed by sodium borohydride reduction in ethanol at -7°C yielded the lactone **13** in 75% overall yield.[20]

Saponification of the tertiary carboxylic ester group followed by thionyl chloride treatment yielded the acid chloride **15**. This was coupled with various amino acids to give the corresponding amides. Some representative examples (**16a - 16c**) are shown in the scheme. In cases where optically pure amino acids were employed, diastereomers were often separable by flash chromatography. Saponification of the carboxylic ester followed by hydrogenolysis of the lactone smoothly yielded the final products (**3a - 3c**) in high overall yield[21].



A	B	C
2	3	2

These compounds were tested against neutral endopeptidase (NEP) activity[22] *in vitro* as well as *in vivo*. Compounds of the general structure **3** were much less potent inhibitors of NEP than corresponding compounds of the type **2** (equivalent R and X). The rigid diquinane system **B** represents a constrained analog of conformer **A** of glutaramide **2**[23]. Thus we infer from the low activity that either conformer **A** is not the bio-active conformer or the "extra" methylene of diquinane system hinders binding to NEP. The observed low NEP activity of the diquinane derivatives is consistent with the hypothesis that the binding mode of glutaramide derivatives such as **2** may be represented by conformer **C**[24], similar to that observed for N-(1-carboxy-3-phenylpropyl)-L-leucyl-L-tryptophan (CLT) bound to thermolysin.[25]

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20. Temperature was maintained at -7° C using ethanol-water (1:4 v/v ratio)-dry ice mixture. Higher temperature yielded products arising from reduction of lactone.

21. All the intermediates and final products were characterized by spectroscopic methods. Representative physical data is as follows. **8** (major, more polar, diastereomer): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.68 (s, 3H), 3.69 (s, 3H), 2.75 - 2.95 (m, 2H), 1.20 - 2.45 (m, 10H); IR (CCl_4) 1740 cm^{-1}; MS (CI/isobutane) m/e 227 $(M+1)^+$. **10**: ^{1}HNMR (300 MHz, $CDCl_3$) δ 7.20 - 7.35 (m, 5H), 5.20 (s, 1H), 5.00 (s, 1H), 3.71 (s, 3H), 3.19 (s, 3H), 3.0 (m, 1H), 2.80 (d, 14.5Hz, 1H), 2.74 (d, 14.5 Hz, 1H), 2.60 (d, 14.0 Hz, 1H), 1.90 (d, 14.0 Hz, 1H), 1.35 - 2.05 (m, 8H); IR (CCl_4) 1740 cm-1; MS (EI) m/e 342 (M^+). **13**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 - 7.45 (m, 5H), 5.40 (m, 1H), 3.72(s, 1.4 H), 3.64 (s, 1.6H), 3.05 - 1.55 (m, 13 H); IR (CH_2Cl_2) 1760 cm^{-1}, 1720 cm^{-1}; MS (EI) m/e 314 (M^+). **3a**: ^{1}HNMR (300 MHz, $CDCl_3$) δ 11.11 (s, 1H), 8.72 (d, 8.5 Hz, 1H), 8.15 (dd, 6.4 Hz, 1.4 Hz, 1H), 7.65 (m, 1H), 7.05 - 7.20 (m, 6 H), 3.25 (m, 1H), 2.78 (d, 13.5 Hz, 1H), 2.58 (m, 2H), 1.20 - 2.20 (m, 11H); IR (CH_2Cl_2) 3450 cm^{-1} -2450 cm^{-1}(broad), 1690 cm^{-1}; MS (FAB) m/e 422 $(M+1)^+$.

22. See reference 11 for testing methods.

23. Conformers **A**, **B** and **C** were constructed using Sybyl 5.5 (tripos Associates) and Macro Model ver. 3.5 (Columbia) to search and minimize structures with MM2 force field.

24. Conformer **C** is similar to that previously proposed schematically to represent binding interactions of compound **2** with NEP.[15]

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