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APPLICATION OF ß-LACTAMS IN THE SYNTHESIS OF SUBSTANCE P ANTAGONISTS: PREPARATION OF 2-AZABICYCLO[3.3.1]NONANE RING SYSTEMS

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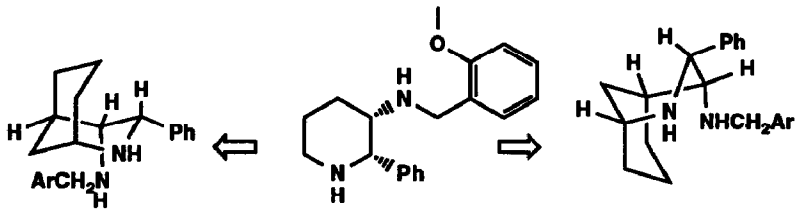
Abstract: Intramolecular ureidomercuration of ß-aminoacids synthesized from appropriate ß-lactams provides an expeditious route to the synthesis of 2-aza-bicyclo[3.3.1]nonane ring systems. Synthesis of the locked-in chair conformer **2** of CP-99,994 is described.

Substance P (SP), an eleven amino acid peptide,[1] is implicated in the pathogenesis of diverse diseases such as arthritis, asthma, and inflammatory bowel disease.[2] Research in our laboratory has been focused on the application of a *structure based strategy* for the identification of non-peptidic SP antagonists; in this regard we disclosed the rationale behind the discovery of CP-99,994 (**1**) as the most potent SP antagonist.[3,4] The identification of **1** (CP-99,994) presented us with an opportunity to examine its binding conformation to the SP receptor. An interesting feature of **1** is that the piperidine ring can adopt either a chair or a boat conformation when bound to the receptor. We proposed that these conformations can be locked-in by creating a three carbon bridge as in **2** or **3**. We herein report the synthesis of **2** which utilizes intramolecular ureidomercuration as one of the key steps.



2 **1** **3**

The *pharmacophore-driven synthetic strategy* we have developed for the synthesis of SP antagonists suggests that **2** and **3** would originate from **4a** and **4b** *via* the intramolecular ureidomercuration reaction followed by reductive work-up;[5] **4a** and **4b** have opposite configurations at the C-5 chiral center. Thus we surmised that the diastereomeric mixture **4** would serve as a critical intermediate for the synthesis of both ring systems of **2** and **3**. In line with our analysis **4** could be synthesized from **5** by functional group transformations. Compound **5** can be derived by the application of the Hart ß-lactam synthesis.[6] The primary concern was the relative ease of 6-exo (N-Cbz to C-7) vs. 7-endo (N-Cbz to C-8) mode of cyclization with **4**. There is also a possibility that if the transition state leading to these cyclizations is sterically hindered, the addition of solvent to the activated double bond may become a competing reaction. Furthermore, two interesting stereochemical implications must be noted

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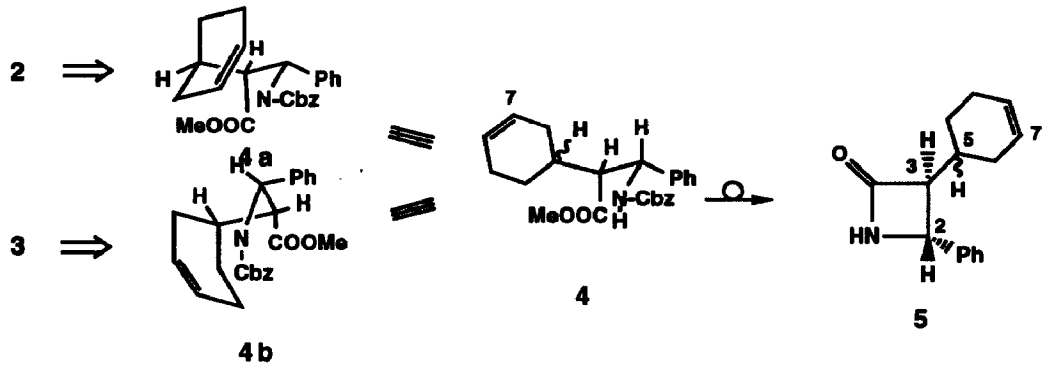
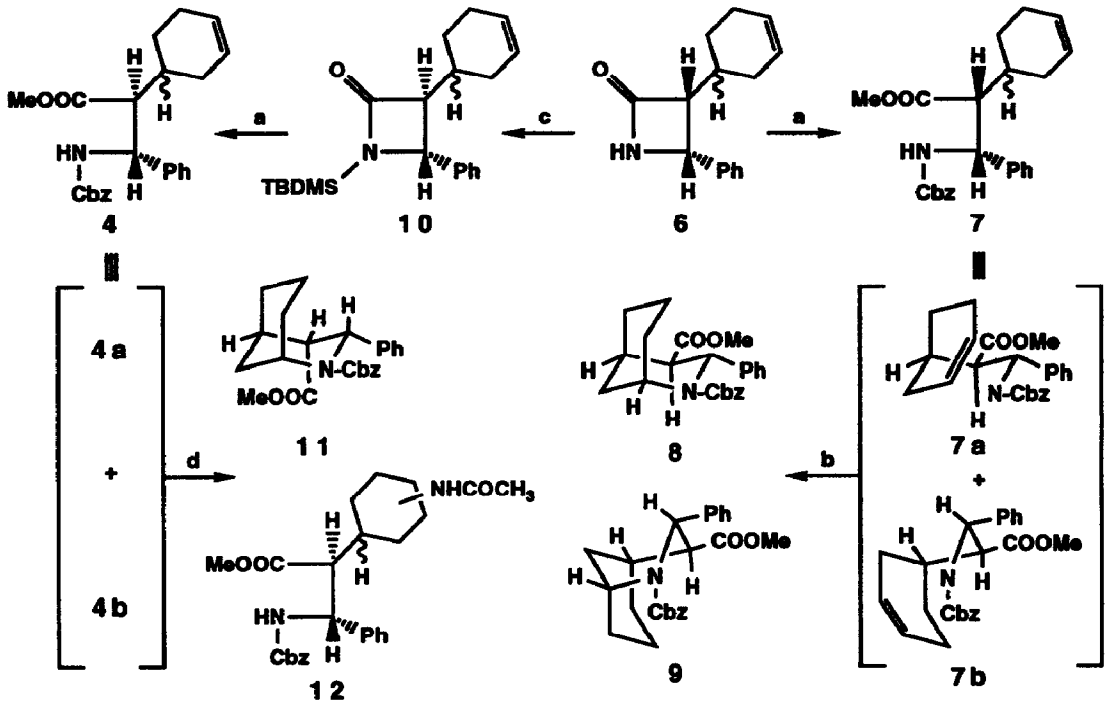
in the conversion of **5** to **2** and **3**: (1) the *trans* ß-lactam **5** would be required to generate the *cis* stereochemistry in **2** and **3**; (2) the formation of the frozen chair or boat analog is governed by the stereochemistry at C-5.

Scheme I



Scheme II



Reagents: (a) 1. 5% MeOH, H_2SO_4, reflux; 2. CbzCl, aq. $KHCO_3$, EtOAc, 25°C; (b) 1. $Hg(OCOCF_3)_2$, CH_3NO_2, 25°C; 2. $NaBH_4$, C_2H_5OH; (c) 1. TBDMS-OTf, $EtNiPr_2$, 0°C; 2. LDA, THF, -78°C; 3. AcOH, -78°C; (d) $Hg(OCOCF_3)_2$, CH_3CN, 25°C; 2. $NaBH_4$, C_2H_5OH

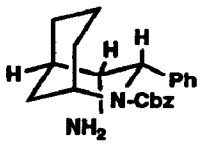
Treatment of anion of 3-cyclohexenylmethyl acetate (LDA, THF, -78°C) with N-trimethylsilyl benzaldimine afforded after acidic work-up the *cis* ß-lactam **6** in quantitative yield; assignment of the *cis* stereochemistry in **6** is in agreement with that observed by Hart *et al.* and ^{1}H-NMR analysis ($J_{2,3}$ = 4 Hz). As expected the isomeric ratio at C-5 was 1:1. The *cis* stereochemistry of the ß-lactam **6** would dictate that its conversion to **5** would involve an additional isomerization step. At this stage, we decided to postpone the latter reaction until the feasibility of the intramolecular mercury-cyclization reaction with **7** had been established. Exposure of **6** to 5% H_2SO_4 in refluxing methanol followed by N-protection (Cbz-Cl, $KHCO_3$) afforded **7** in 91% yield. Treatment of **7** with mercury bistrifluoroactate in nitromethane at room temperature followed by reductive workup with sodium borohydride provided a 1:1.4 mixture of **8** and **9** in 61% yield. The structures of **8** and **9** were established by single crystal X-ray analysis of their derivatives. Of particular significance was the lack of side products arising either from the 7-endo mode of cyclization or by intermolecular hydration of the double bond.

It was indeed gratifying that the key intramolecular mercury cyclization of **7** was successful. However, for our objective, this success had to be duplicated with **4**. Thus **4** was synthesized from **6** *via* a four step sequence: (1) protection of the *cis*-ß-lactam **6** (TBDMS-OTf, Et_3N, CH_2Cl_2) (2) isomerization to yield **5** (LDA, THF, AcOH) (3) methanolysis (5% H_2SO_4 in MeOH) and (4) protection of the amino group (Cbz-Cl, $KHCO_3$). Interestingly the column chromatography after step 2 changed the isomeric ratio at C-5 from 1:1 to 1:3. With **4** in hand, we next investigated intramolecular ureidomercuration; the latter reaction proved much more difficult than originally anticipated. Unfortunately, **4** resisted cyclization under identical or even more forceful conditions than those developed for **7**; the starting material was recovered unchanged. Finally after considerable experimentation, it was found that use of acetonitrile was crucial for the success of the reaction. Treatment of **4** with mercury bistrifluoroacetate in acetonitrile at room temperature followed by reductive work-up with sodium borohydride provided **11** in 15-20% yield; the major product was **13**. The formation of **13** is reminiscent of products formed in the Ritter reaction via participation of acetonitrile.[7] The structure of **11** was established by single crystal X-ray analysis of its derivative.

The observed reactivity pattern in the mercury cyclization of **7** and **4** can be understood in terms of non-bonding interaction in the transition state conformations **4a**, **4b**, **7a** and **7b**. The conformations **4a** and **7a** leading to the formation of frozen chair ring systems **8** and **11** have less severe gauche interactions between the carbomethoxy and the cyclohexene groups. However the situation is different for the conformations **4b** and **7b** expected to produce frozen boat ring systems. Conformation **4b** has a very severe eclipsoid interaction between the carbomethoxy and the cyclohexene groups which becomes worst as the nitrogen approaches C-7. Interestingly, when the stereochemistry is *trans* as in **7b** the eclipsoid interaction is replaced by the less severe gauche interaction. The upshot of such different long range interactions in **4b** and **7b** is that **4b** does not participate in the intramolecular ureidomercuration, but instead the trapping of the mercury-double bond complex of **4b** by the solvent acetonitrile becomes a competitive pathway leading to the formation of **13**.

In line with our objective, the chair cyclized product **11** was converted to **2** via a straightforward sequence of reactions. The stereospecific elaboration of the carbomethoxy group into an amino group was achieved via a two step sequence: (1) conversion of the carbomethoxy group to a carboxamide (trimethylaluminum, ammonium chloride, 50°C)[8] (2) oxidation of the carboxamide to an amino group *via* Hoffmann degradation ([*I,I*-bis(trifluoroacetoxy)iodo]benzene, CH_3CN, 25°C) to yield **13** in 53% overall yield.[9] Reductive amination of **13**

with o-methoxybenzaldehyde followed by cleavage of the Cbz group afforded **2**. Similarly **8** and **9** were converted to **14** and **15**.



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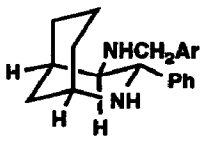

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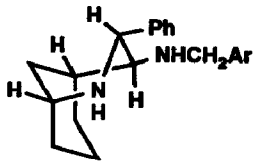

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In conclusion the intramolecular ureidomercuration of the functionalized ß-lactams provides an expeditious route to the synthesis of 2-aza-bicyclo[3.3.1]nonane ring systems. The biological activity of these compounds will be reported in due course.

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