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A CONVERGENT SYNTHESIS OF A NOVEL NON-PEPTIDYL GROWTH HORMONE SECRETAGOGUE, L-692,429

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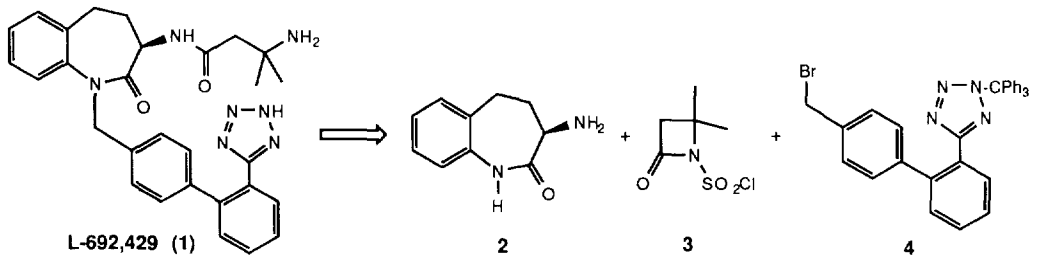
Abstract : A practical, convergent synthesis of L-692,429 (**1**) from three key intermediates -- the 3-aminobenzlactam **2**, the β-lactam **3** and the biphenyltetrazole **4** is described. The mechanism of the coupling reaction in which **3** is used as a β-aminoacid equivalent is also presented.

Growth hormone (GH) treatment has been shown to have beneficial clinical effects in elderly people, GH deficient children and severely burned victims. The problems associated with GH treatment are many: limited supply, associated risk of contamination, inconvenience of subcutaneous injection and the cost. Use of a growth hormone secretagogue is an attractive alternative for treatment with growth hormone itself.[1] L-692,429 is a prototype, non-peptidyl growth hormone secretagogue discovered in the Basic Chemistry and Basic Animal Science departments of Merck Research Laboratories.[2]

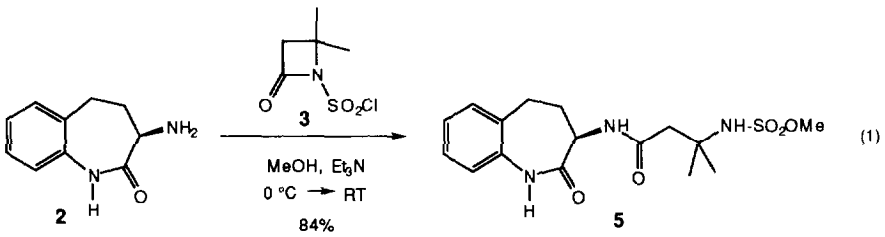
This paper discusses a practical, convergent synthesis of L-692,429 using the 3-aminobenzlactam **2**,[3] the β-lactam **3** and the biphenyltetrazole **4** (SCHEME I).

SCHEME I



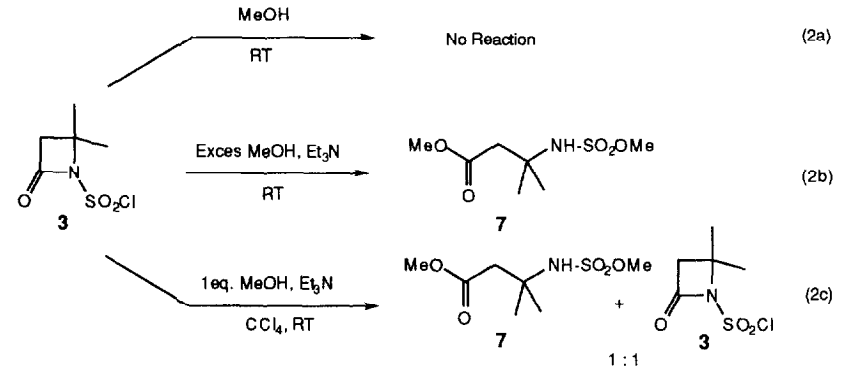
Construction of the top portion of the target (**1**) is achieved via the use of a β-lactam as a β-aminoacid equivalent (eq 1).[4] The coupling reaction is carried out by the addition of the β-lactam **3** in methanol to a solution of the amine **2** and triethylamine in methanol at 0 °C. After aqueous workup and crystallization, the product **5** is isolated in 99.5 area% purity and 84% yield. This procedure has several advantages over the one employing the β-aminoacid itself.[5] a) The β-lactam **3** is readily prepared in one step from isobutylene and chlorosulfonyl isocyanate.[6] b) The reaction uses environmentally benign solvents and inexpensive reagents.

c) This approach results directly in methoxysulfonyl (MOS) protected amine. d) The product **5** is readily isolated by crystallization in excellent purity and high yield.

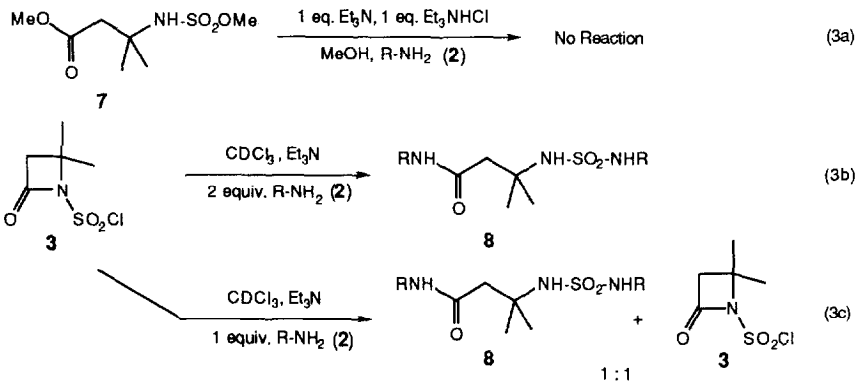


The structure of the coupled product **5** has been confirmed by ^{1}H & ^{13}C NMR as well as IR spectral data.[7] Under these reaction conditions, the alternative attack of the amine **2** on the sulfonyl group was not observed.[8] In an effort to understand the mechanism of this efficient coupling reaction, several control experiments were carried out and the results are presented in SCHEMES II & III.

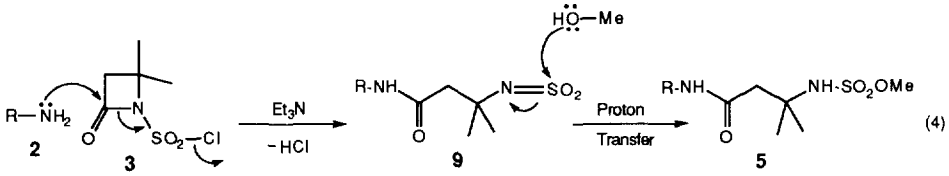
SCHEME II



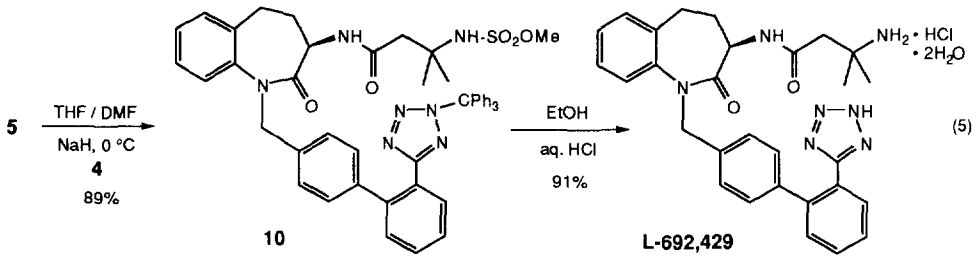
SCHEME III



As shown in eq. 2b & 3b, the β-lactam **3** reacts with two equivalents of methanol or the amine **2** in the presence of triethylamine to give **7** or **8** respectively. When only one equivalent of methanol (or the amine) is available, **7** (or **8**) and the starting β-lactam **3** are observed in 1:1 ratio, indicating that the second step is much faster than the first one. Further, as shown in eq. 3a, compound **7** is not an intermediate in the formation of compound **5**. Based on these observations, the following reaction pathway (eq. 4) is proposed for the coupling reaction. Of the two available nucleophiles (the amine **2** and methanol), the more nucleophilic amine **2** initially attacks the carbonyl group of the β-lactam **3** to give a highly reactive intermediate **9**, which in a fast step reacts with the excess methanol (solvent) present to give the desired product **5**.



To complete the synthesis of **1**, compound **5** is treated with sodium hydride and the bromide **4**[9] in 12:1 THF:DMF at 0 °C. For complete conversion, 1.8 to 2.0 equivalents of sodium hydride was required. Under these conditions, no racemization was observed. With more than 2.0 equivalents of sodium hydride, significant (10 to 20%) racemization was observed. Deprotection of both the trityl and methoxysulfonyl protecting groups is achieved by treating an ethanolic solution of compound **10** with 6N hydrochloric acid at 70 °C for 5 hours. After an extractive workup, the final product is crystallized as its hydrochloride salt dihydrate in 91% yield, 99.8 %ee[10] and 99.6 area% purity.



Acknowledgment: The authors thank Professor Barry M. Trost for consultations on the mechanism of the β-lactam coupling reaction, W.R. Schoen for early discussions on this project, G. Spencer for providing the biphenyltetrazole **4**, J.D. Armstrong and W.-B. Choi for providing the aminobenzlactam **2**, R.A. Reamer and L.M. DiMichele for nmr spectral assignments and N. Grinberg and R. Stringham for analytical support.

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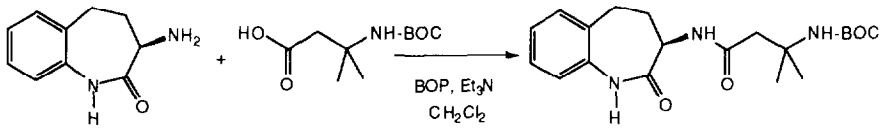
1. Schoen, W.R.; Wyvratt, M.J. Jr.; Smith, R.G. Growth hormone secretagogues. In *Annual Reports in Medicinal Chemistry Vol. 28*, Bristol, J.A. Ed.; Academic Press: San Diego, California, 1993; p. 177.

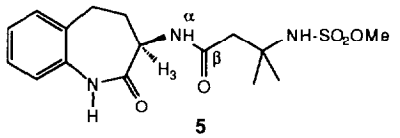
2. Smith, R.G.; Cheng, K.; Schoen, W.R.; Pong, S.-S.; Hickey, G.; Jacks, T.; Butler, B.; Chan, W.W.-S.; Chaung, L.-Y.P.; Judith, F.; Taylor, J.; Wyvratt, M.J.; Fisher, M.H. *Science* **1993**, *260*, 1640.
3. An asymmetric synthesis of the 3-aminobenzlactam **2** has been recently reported from our laboratories. Armstrong, III, J.D.; Eng, K.K.; Keller, J.L.; Purick, R.M.; Hartner, F.W., Jr.; Choi, W.-B.; Askin, D.; Volante, R.P. *Tetrahedron Lett.* **1994**, *35*, 3239.
4. Graf, R. *Liebigs Ann. Chem.* **1963**, *661*, 111. For recent applications concerning the use of a β-lactam as a β-aminoacid equivalent, see: Chen, S.H.; Wei, J-M.; Farina, V. Tetrahedron Lett. **1993**, *34*, 3205, and references therein.
5. Schoen, W.R.; Pisano, J.M.; Prendergast, K.; Wyvratt, M.J., Jr.; Fisher, M.H.; Cheng, K.; Chan, W.W.-S.; Butler, B.; Smith, R.G.; Ball, R.G. *J. Med. Chem.* **1994**, *37*, 897. In this case, the coupling was carried out using 3-aminobenzlactam **2** and *N*-BOC protected dimethyl-β-alanine as shown below.



2

This coupling reaction was not amenable to large scale synthesis due to several factors: a) high cost of BOP reagent, b) use of 1.5 equivalents of BOP reagent (~4 times the weight of **2**) making the product isolation difficult, c) use of methylene chloride and d) release of HMPA from BOP. Moreover, the preparation of *N*-BOC protected dimethyl-β-alanine required 4 steps.

6. Graf, R. Organic Synthesis Coll. Vol. **5**, 673. A modified procedure was used (see ref. 5).
7. The alternative possibility **6** (from initial amine attack on the sulfonyl) is ruled out based on long range, inverse detection, correlation experiments. Correlations were observed for H_3 & H_α to C_β; no correlation was observed for methoxy to a carbonyl indicating the absence of -$COOCH_3$ group. Further, in the IR spectrum, carbonyl absorption bands are observed at 1680 cm^{-1} and 1650 cm^{-1} (typical of amides and not of an ester).



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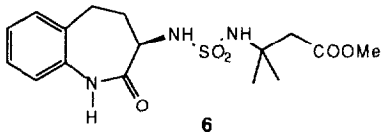

6

8. Amines containing electron withdrawing groups react at the sulfonyl group leaving the β-lactam intact. Graf, R. *Angew. Chem. Internat. Ed.* **1968**, *7*, 172.
9. Shuman, R.F.; King, A.O.; Anderson, R.K. U.S. Patent # 5,039,814 (1991).
10. Enantiomeric purity assay is carried out using Ultron ES-OVM column (retention times: *S* enantiomer -- 13 minutes and *R* enantiomer **1** -- 16 minutes). The *S* enantiomer (L-692,428) is prepared following the same sequence starting from the *S* enantiomer of the 3-aminobenzlactam **2**.

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