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A Highly Refined Version of the α-Keto Ester Based Carbapenem Synthesis: The Total Synthesis of Meropenem.

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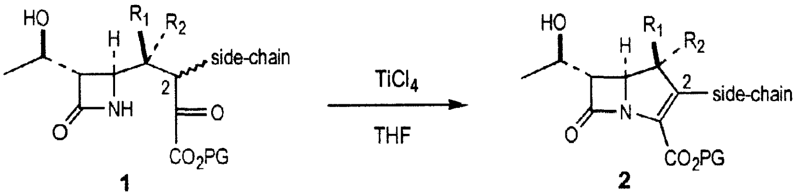
Abstract: *The α-keto ester based carbapenem synthesis has been refined so that all deprotections and the ring forming cyclization can be carried out in a single step.*

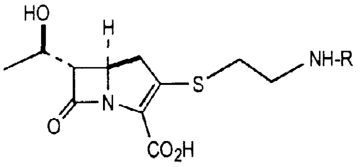
As discussed in previous papers, we have been evaluating new ways to synthesize the carbapenem ring system.[1] One approach has shown particular promise and versatility: the intramolecular condensation of an α-keto ester with a β-lactam nitrogen (i.e. **1** → **2**).



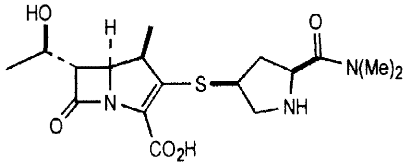
R_1 = H or Me, R_2 = H PG = protecting group

Scheme 1

This mode of ring formation was successfully applied to the formal total synthesis of thienamycin **3**:[1c] a naturally occurring compound that has inspired many synthetic analogs. These carbapenems constitute a broad class of structures characterized by having a side-chain connected at C-2 with sulfur. An important member of this class is meropenem **5**,[2] a potent antibacterial,[3] and the only other carbapenem to make its way to the market since imipenem **4** was introduced in 1985.



3 Thienamycin R = H
4 Imipenem R = CH=NH } (Merck)



5 Meropenem (Zeneca)

Figure 1

In this paper, we describe our efforts to streamline the α-keto ester based carbapenem synthesis using meropenem as a model. We began by preparing meropenem using our established[1c] procedure (**Scheme 2**).

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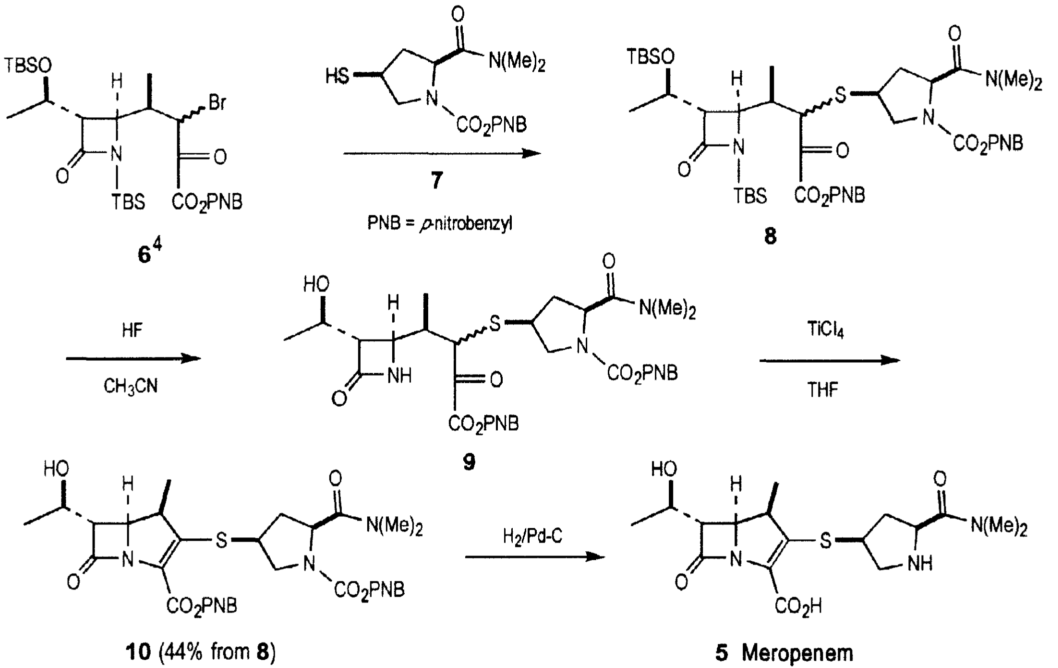
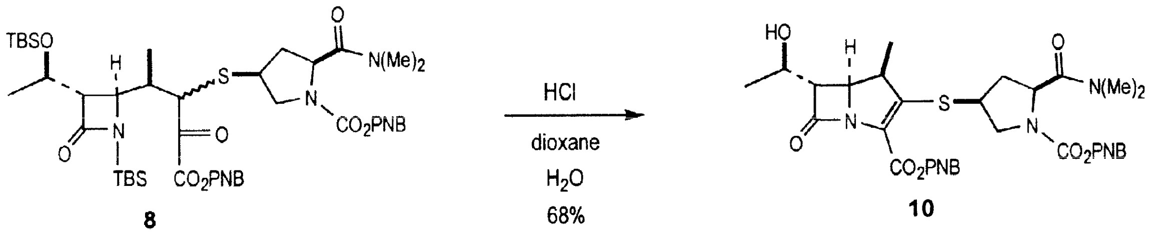


Scheme 2

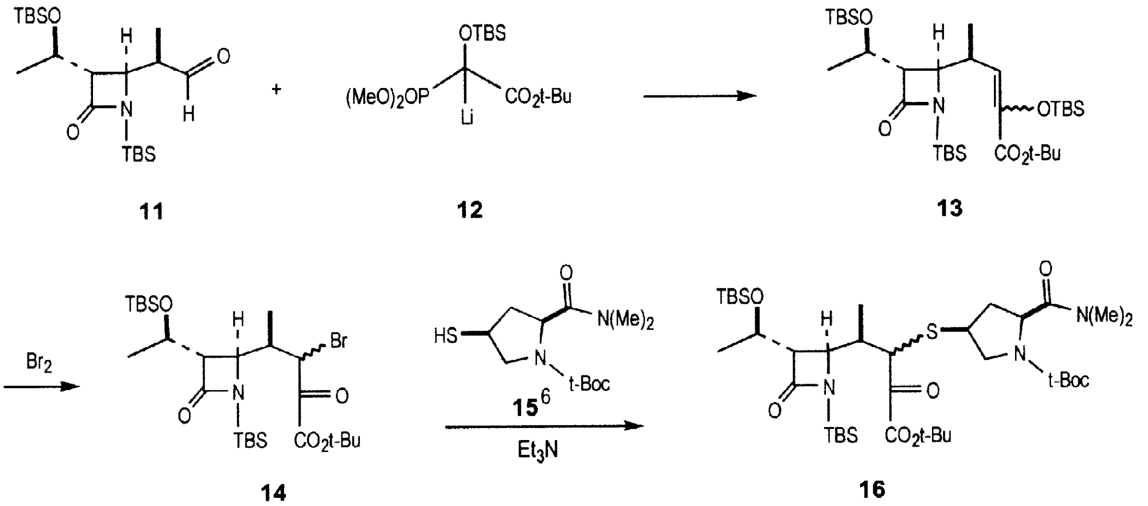
Seeking to enhance the practicality of this sequence, we set out to consolidate steps where possible and determine whether a mineral acid could be used for the cyclization instead of $TiCl_4$. Our ultimate hope was to find conditions under which the TBDMS group deprotections (e.g., **8** → **9**) and cyclization (e.g., **9** → **10**) could be carried out in a single operational step.

It should be noted that no isolable cyclocondensation products related to carbapenem **10** were ever observed during the high-yielding double desilylation of **8** with 10% (5 molar) HF. In contrast, it was gratifying to find that both deprotection and cyclization could be achieved with HCl in ethereal solvents over a wide range of acid concentrations. Yields of the carbapenem product varied widely, depending on the exact conditions employed. After considerable experimentation, a carefully defined protocol was established to ensure optimal reaction efficiency. Surprisingly, better results for the deprotection-cyclization sequence were obtained when the HCl concentration was high and reaction time relatively short. While carbapenem was observed to form at much lower acid concentration, 4.2 M HCl in dioxane (containing 10% water) was found to be ideal. Hence, α-keto ester **8** afforded carbapenem **10** in 68% yield[5] (**Scheme 3**). Notwithstanding case-by-case variation in optimal reaction time, we found these conditions to be reliable for the general class of substrates whose C-2 side-chains are attached by sulfur.



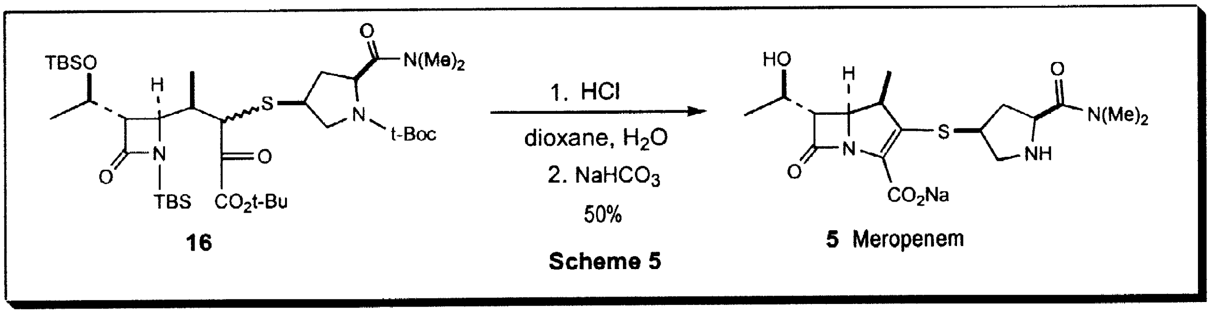
Scheme 3

Having achieved our initial goal, we then chose to address a long-standing problem in the field of carbapenem synthesis: C-3 carboxylate deprotection. We cautiously set out to test the possibility of adding two more reactions to the double TBS deprotection-cyclization procedure: removal of the C-3 carboxylate and N-pyrrolidine protecting groups. This required an intermediate in which the two p-nitrobenzyloxy-based protecting groups present in **8** were replaced with acid labile ones. Thus, a cyclization substrate with a t-butyl protected ester and t-boc protected pyrrolidine was prepared (i.e., compound **16**, **Scheme 4**).



Scheme 4

We were pleased to find that, upon treating compound **16** with HCl (30-60 minutes, under the conditions used to transform **8** into **10**) followed by neutralization with $NaHCO_3$, meropenem was formed as its sodium salt **5**. However, the product mixture contained a substantial amount of uncyclized material. By extending the reaction time to 2.5 hours, the reaction was found to go to completion and a 50% yield of the desired meropenem sodium salt was obtained[7] (**Scheme 5**).



Scheme 5

Using meropenem as a model, we have been able to improve the key steps of the α-keto ester based carbapenem synthesis. The earlier synthesis, requiring deprotection with HF, cyclization with $TiCl_4$, then deprotection with H_2/Pd-C, was successfully transformed into an efficient one-pot procedure employing common reagents.

Acknowledgments: The authors wish to thank Drs. Stanley A. Lang and Ving J. Lee for facilitating these studies.

References and Notes

1. a) Feigelson, G. B. *Tetrahedron Lett.* **1995**, *36*, 7407. b) Ziegler, C. B.; Curran, W. V.; Feigelson, G. B.; Bitha, P.; Fabio, P.; Strohmeyer, T.; Short, K.; Lin, Y-I *Tetrahedron* **1994**, *50*, 12085. c) Feigelson, G. B. *Tetrahedron Lett.* **1993**, *34*, 4747.

2. The original method for preparing meropenem is described in Sunagawa, M.; Matsumura, H.; Inoue, T.; Fukasawa, M.; Kato, M. *J. Antibiotics* **1990**, *43*, 519.

3. For a review of meropenem's microbiological properties see: a) Fish, D. N.; Singletary, T. J. *Pharmacotherapy* **1997**, *17*, 644. b) Blumer, J. L.; *Int. J. Antimicrob. Agents* **1997**, *8*, 73.

4. Compound **6** was prepared in analogy to the sequence shown in **Scheme 4.** Compound **11** was prepared by treating 3S,4S-3[(R)-1-t-butyldimethylsilyloxyethyl]-4-[(R)-1-formylethyl] azetidin-2-one (Takasago, Int., Rockleigh, NJ) with TBSCl and Et$_3$N in DMF.

5. Preparation of protected meropenem **10** from α-keto ester **8**: To 1.62 mL of 4.7M HCl in dioxane was added 0.180 mL of water. The solution was allowed to cool to room temperature (RT) after which α-keto ester **8** (50 mg, .053 mmol) was added in a single portion. The reaction was stirred at RT for 30 min then carefully added to a rapidly stirring mixture of EtOAc and saturated NaHCO$_3$. The mixture was then diluted with water, partitioned, and the organic layer was washed once with brine. The combined aqueous layers were then back extracted with EtOAc and the combined organics dried over anhyd. MgSO$_4$. The crude product thus obtained was flash chromatographed over silica gel with 10% MeOH in EtOAc. Protected meropenem **10** was obtained in 68% yield (25 mg). ^{1}H NMR consistent with published data[3]: (CDCl3) δ 8.22 (d, 4H), 7.64 (d, 2H), 7.51 (d, 1H), 7.43 (d, 1H), 5.49 (d, 1H), 5.24 (d, 1H), 5.20 (br s, 2H), 4.73 (m, 1H), 4.25 (m, 2H), 3.67 (m, 1H), 3.52 (m, 1H), 3.38 (m, 1H), 3.26 (m, 1H), 3.10, 2.98, 2.97, 2.95 (4s, 6H), 2.72 (1H, m), 1.93 (m, 1H), 1.36 (d, 3H), 1.25 (d, 3H).

6. Prepared as described in Brands, K. M. J.; Marchesini, G.; Williams, J. M.; Dolling, U.-H.; Reider, P. J. *Tetrahedron Lett.* **1996**, *37*, 2919.

7. Preparation of meropenem sodium salt **5** from α-keto ester **16**: To 1.86 mL of 4.7 M HCl in dioxane was added 0.2 mL of water and the mixture was allowed to cool to RT. This solution was added to α-keto ester **16** (50 mg, .064 mmol) and the reaction was stirred at RT for 2.5 hours. The reaction mixture was then quenched by carefully adding it to ice cold NaHCO$_3$ (ca. 730 mg) in water. The resulting pH was checked to assure slight basicity. The solution was then concentrated *in vacuo* and chromatographed on reverse phase support (MCI CHP20, water then 10% EtOH in water). Sodium salt **5** was obtained as an off-white solid: 13 mg (50%). ^{1}H NMR identical to commercial meropenem sodium salt (Zeneca) obtained by constituting Merrem® with D$_2$O: δ 4.11 (m, 3H), 3.73 (m, 1H), 3.28 (m, 2H), 3.13 (dd, 1H), 3.02 (dd, 1H), 2.94 (s, 3H), 2.86 (s, 3H), 2.68 (m, 1H), 1.53 (m, 1H), 1.17 (d, 3H), 1.08 (d, 3H). HRMS (MH$^+$) 384.1583.