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AN ENANTIOSELECTIVE APPROACH TO CARBAPENEM ANTIBIOTICS: FORMAL SYNTHESIS OF (+)-THIENAMYCIN

David J. Hart[*,‡] and Deok-Chan Ha

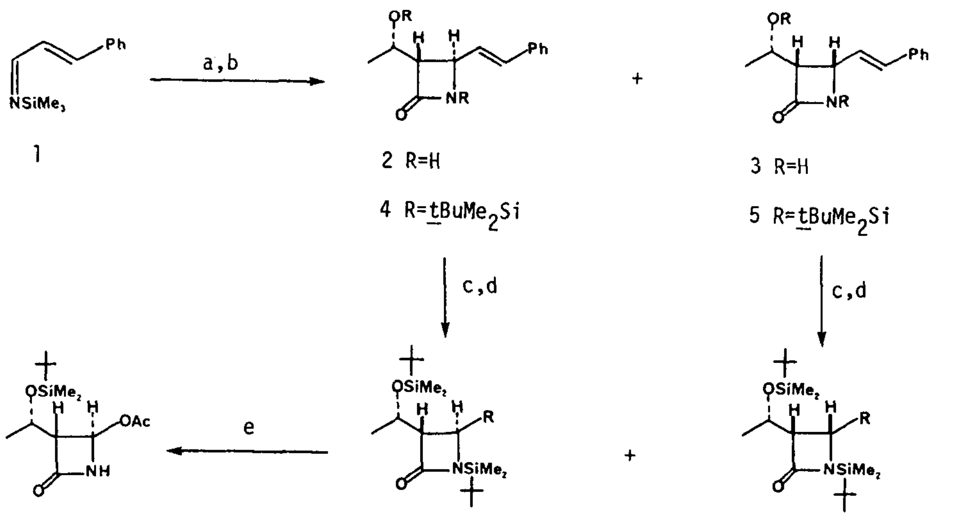
Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

Summary: An enantioselective synthesis of intermediates in syntheses of thienamycin (**15**) and epithienamycin-C (**16**) is described.

Several years ago we reported that N-trimethylsilyl imines react with ester enolates to afford 1-unsubstituted-β-lactams.[1] We also showed that ethyl β-hydroxybutyrate would serve as the ester component in this reaction, resulting in a direct route to 3-(1-hydroxyethyl)-2-azetidinones.[2] This letter presents our initial efforts to apply these observations to the area of carbapenem synthesis. Specifically, an efficient enantioselective route to β-lactam **10** and its conversion to the known thienamycin intermediate **14** is described.[3-5]

Ethyl (S)-β-hydroxybutyrate[6] was converted to the corresponding dianion (2 equiv LDA, THF, -70°C) and treated with imine **1**.[7,8] The resulting crude mixture of β-lactams **2** and **3** was treated with tert-butyldimethylsilyl chloride and triethylamine in N,N-dimethylformamide[9] to afford **4** (16%) and **5** (27%) after separation by column chromatography. Ozonolysis of **4** gave **6** (85%, mp 131-132°C) and subsequent Jones oxidation afforded acid **8** (86%, mp 105-106°C). Similar oxidative treatment of **5** gave **7** (91%) and **9** (96%, mp 146-147°C). Treatment of either **8** or **9** with lead tetraacetate[10] gave **10** (mp 79-80°C) in 81% and 80% yields, respectively. From an operational standpoint it was most convenient to subject a purified mixture of β-lactams 4 and **5** to the oxidation sequence without purification of the intermediates. In this way, **10** could be prepared from **4** + **5** in a 60% overall yield.

We have demonstrated that **10** will serve as an intermediate in a synthesis of the carbapenem antibiotic thienamycin (**15**). Thus, treatment of **10** with p-nitrobenzyl 2-diazo-3-(t-butyldimethylsiloxy)-3-butenoate and $ZnCl_2$ in dichloromethane gave diazoketone **11** (83%) which was converted to alcohol **12** [95%, mp 150°C (d)] upon exposure to methanol-aqueous hydrochloric acid.[10,12] Inversion of the C-8 stereochemistry was accomplished using the excellent method of Mitsunobu.[13,14] The resulting formate **13** (95%) was converted to the known thienamycin intermediate **14** [87%, mp 151-152°C (lit.[12] 150-152°C)] upon treatment with excess 1,2-ethanedithiol and a catalytic amount of p-toluenesulfonic and in dichloromethane-isopropanol (25°C, 96h), thus completing a formal total synthesis of thienamycin (**15**).[14,15] The use of **12** in a synthesis of the related carbapenem antibiotic epithienamycin-C (MM22381, **16**) will appear in our full account of this work.



1

2 R=H

4 R=$\underline{t}BuMe_2Si$

3 R=H

5 R=$\underline{t}BuMe_2Si$

10

6 R=CHO

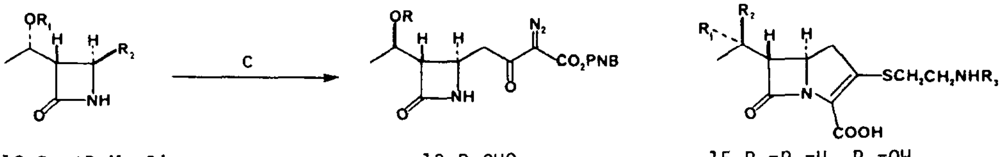
8 R=COOH

7 R=CHO

9 R=COOH

(a) $CH_3CH(OLi)CH=C(OEt)(OLi)$, THF, -70°C → 25°C, 20h (b) $\underline{t}BuMe_2SiCl$, Et_3N, DMF (c) O_3, CH_2Cl_2, -78°C then Me_2S (d) Jones Reagent (e) $Pb(OAc)_4$, AcOH

We have also examined the behavior of the dianion of ethyl β-hydroxybutyrate with N-aryl aldimines. A few of our results are reported here. Treatment of N-$\underline{p}$-methoxyphenylcinnamaldimine with the dianion of ethyl β-hydroxybutyrate in tetrahydrofuran (-70°C, then 20h at room temperature) afforded a mixture of **17** (25%, mp 160-161°C) and **18** + **19** (38%, 3:1 respectively).[16] Silylation[9] of the mixture of **18** + **19** gave **21** (72%, mp 97-98°C) and **22** (23%, mp 124-125°C) after separation by chromatography. The stereochemical assignment for **17** was established by sequential silylation to give **20** (88%), cerric ammonium nitrate oxidation,[17] and silylation to give **5** (78%). The stereochemical assignments for the trans β-lactams were confirmed by converting both **20** and **21** to **24**. Thus, ozonolysis of **21** gave **24** (86%, mp 113-115°C) and ozonolysis of **20** (90%) followed by epimerization (DBU, CH_2Cl_2, 25°C,



10 R_1=$\underline{t}BuMe_2Si$, R_2=OAc

a

11 R_1=$\underline{t}BuMe_2Si$, R_2=$CH_2C(O)C(N_2)CO_2PNB$

b

12 R_1=H, R_2=$CH_2C(O)C(N_2)CO_2PNB$

d

13 R=CHO

14 R=H

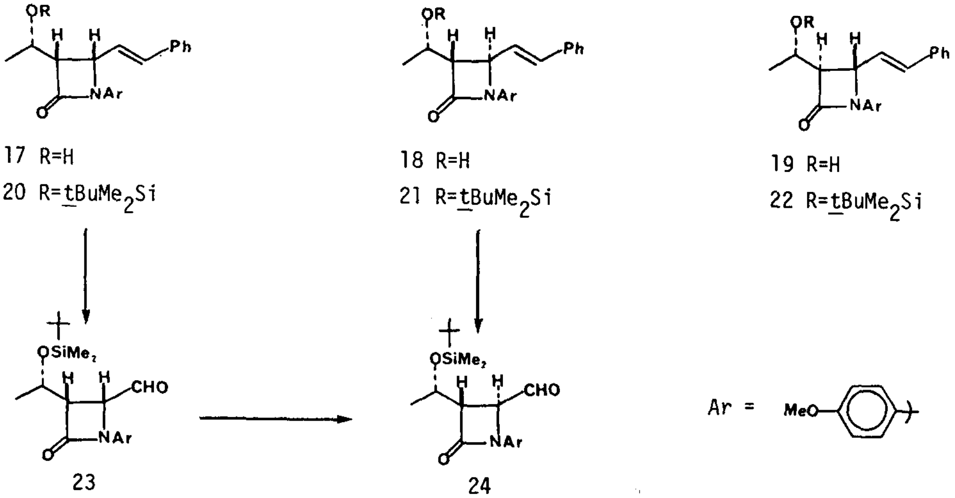
15 R_1=R_3=H, R_2=OH

16 R_1=OH, R_2=H, R_3=Ac

(a) $ZnCl_2$, $CH_2=C(OSiMe_2\underline{t}Bu)C(N_2)CO_2PNB$, CH_2Cl_2

(b) HCl, H_2O, MeOH (c) Ph_3P, HCOOH, $EtO_2CN=NCO_2Et$

(d) $HSCH_2CH_2SH$, TsOH, CH_2Cl_2, $\underline{i}PrOH$



5h) of the resulting aldehyde **23** (mp 79.5-80.5°C) also gave **24** (88%).[18] It is notable that we have not been able to isomerize **7** to **6** under identical conditions.

In summary, we have shown that the ester-imine condensation can be included in the list of enantioselective routes to carbapenem intermediates. The methods and intermediates described herein should also be useful in the synthesis of analogs such as carbacephems.

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