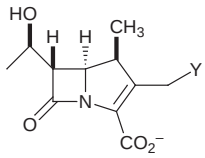
A stereoselective synthesis of a 2-functionalized-methyl-1β-methylcarbapenem key intermediate *via* decarboxylation

Woo-Baeg Choi, Jaemoon Lee, Joseph E. Lynch,*† R. P. Volante, Paul J. Reider and Robert A. Reamer

Process Research, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA

An efficient synthesis of a key intermediate 2a for the synthesis of 2-functionalized methyl-1β-methylcarbapenem antibiotics 1 has been realized *via* a stereoselective decarboxylation reaction.

The emergence of multiple drug resistant bacteria and the alarming increase in the number of infections resulting from these organisms have clearly demonstrated an urgent need for new antimicrobial agents. Methicillin resistant *Staphylococcus aureus* (MRSA) is one of the more common of these infectious agents and in the early 1990s accounted for about 20% of the bacterial cultures isolated in hospitals.[1] MRSA remains a challenging target of antimicrobial research programs throughout the pharmaceutical industry. 2-Functionalized-methyl-1β-methylcarbapenem antibiotics **1** have drawn much attention due their potent activity against a variety of pathogens including MRSA.[2] However, the lack of an efficient synthesis of these carbapenems has hindered their development as clinical candidates. The 2-hydroxymethyl-1β-methyl ketone **2a** is a key intermediate in the synthesis of **1** and several syntheses of **2a** in variously protected forms have appeared in the literature.[2a,3]



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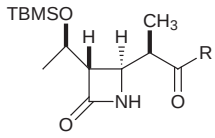
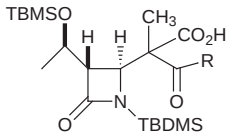
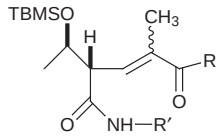


2a R = CH_2OH
b R = OH
c R = CH_2OBn
d R = OCH_3



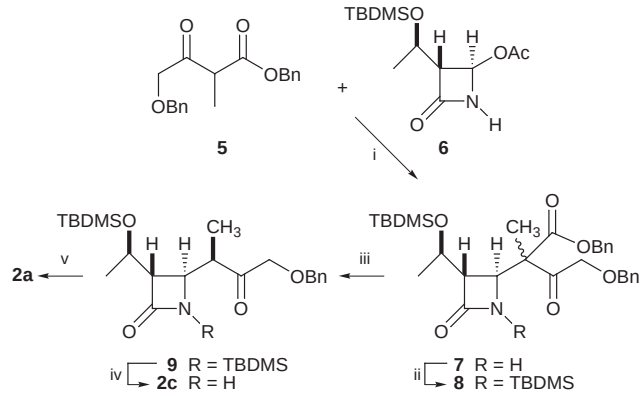
3a R = CH_2OH
b R = OH
c R = CH_2OBn
d R = OCH_3



4a R = CH_2OBn, R′ = TBDMS
b R = OCH_3, R′ = TBDMS
c R = CH_2OBn, R′ = H

Some time ago, we (and others) reported that the malonic acid **3b** underwent a highly stereoselective decarboxylation/protonation to give the 1β-methyl carboxylic acid **2b**.[4a,b] We envisioned that the keto acid **3a** or **3c** should undergo a similar decarboxylation to give **2a** or **2c**, respectively.

After several unsuccessful attempts to generate the requisite β-keto acid **3a** *via* aqueous ester saponification, we adjusted our strategy to allow preparation of a β-keto acid in a nonpolar solvent *via* hydrogenolysis of a suitable benzyl ester. Benzyl 4-benzyloxy-2-methyl-3-oxobutyrate **5** was prepared by the Claisen condensation of benzyl propionate (2 equiv. + 2 equiv. LDA) and methyl *O*-benzylglycolate in 80% yield (Scheme 1). The acetoacetate **5** was then coupled with acetoxyazetidinone **6** (K_2CO_3 in DMF at 45 °C, 1 h) to give *ca*. 2:1 diastereomeric mixture **7** in 85–90% yield. *N*-silylation of **7** was carried out using TBDMSOTf and Et_3N in DMF to give **8** in quantitative yield. In our previous work on the malonic acid series we had



Scheme 1 *Reagents and conditions*: i, K_2CO_3, DMF, 45 °C, 1 h; ii, Et_3N, TBDMSOTf, DMF; iii, HCO_2H, EtOAc, 5% Pd/C, 30 psi H_2, room temp., 1 h; iv, Bu^n_4NF, CH_2Cl_2, 0 °C; v, 10% Pd/C, EtOH, 45 psi H_2

observed a remarkable diastereospecificity in the decarboxylation reaction.[4d] We found that only the (1*R*)-ester **3d** underwent decarboxylation to give **2d**. The (1*S*)-diastereomer underwent decarboxylation only under forcing conditions resulting in ring cleavage and giving **4b** as a major product. We were concerned that such diastereospecificity would be problematic with the 2:1 mixture of diastereomers **8**. We thus separated the two isomers of **8** (silica gel chromatography) and investigated the decarboxylation of each isomer individually. Each benzyl ester **8** was subjected to hydrogenolysis conditions (3 equiv. HCO_2H, 5% Pd/C, 30 psi, room temp., 1 h) in EtOAc. Surprisingly both isomers cleanly gave **9** as a single stereoisomer (> 99:1 β:α).[5] Encouraged by the individual results, the 2:1 mixture of **8** was subjected to hydrogenolysis/decarboxylation to give the desired β-methyl product **9** in 95% yield along with 3–4% of **4a**. *N*-desilylation of **9** was achieved using TBAF in CH_2Cl_2 at 0 °C giving **2c** in 85% yield.[6] Debenzylation of **2c** was accomplished under more vigorous hydrogenolysis conditions in EtOH (10% Pd/C, 45 psi H_2, 1 h) to give **2a** in 90% yield.[7,8]

Although the malonic acid series demonstrated a stereospecific decarboxylation,[4d] this was not an issue in the decarboxylation of **8** (*via* **3c**). This could be due to the greater stability of the enol intermediate and the corresponding lower transition state energy *vs.* the ketene acetal intermediate in the malonic acid series. The greater selectivity in the protonation step may be a result of the lower reaction temperature (20 °C for **2a** *vs.* 80 °C for **2b**) as well as the relative energetics of the two systems.

The Authors thank Dr Mark Greenlee for helpful suggestions during the preparation of this manuscript.

Notes and References

† E-mail: joe_lynch@merck.com

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5 The crude product was filtered through Celite, washed with aq. Na_2CO_3 and analyzed by ^{1}H NMR spectroscopy. The major isomer of **8** cleanly gave a >99:1 β:α mixture of **9**, while the minor isomer of **8** gave the same 99:1 β:α mixture of **9** along with 7–10% ring opened by-product **4a**.

6 During the desilylation, 7–10% of **4c** was formed.

7 The C-1 configuration was determined by conversion of **2a** to the known acetate [ref. 3(*a*)]. The spectroscopic data of the acetate were found to be identical to those reported.

8 *Selected data* for **2a**: $\delta_H(CDCl_3)$ 6.43 (br s, 1 H), 4.38 (d, *J* 19.4, 1 H), 4.25 (d, *J* 19.4, 1 H), 4.15 (m, 1 H), 3.85 (dd, *J* 1.9, 5.0, 1 H), 3.25 (br s, 1 H), 2.93 (dd, *J* 1.9, 4.6, 1 H), 2.84 (1 H, m), 1.19 (d, *J* 7.0, 3 H), 1.16 (d, *J* 6.3, 3 H), 0.85 (s, 9 H), 0.06 (s, 3 H), 0.04 (s, 3 H); $\delta_C(CDCl_3)$ 211.8, 168.5, 67.9, 65.3, 61.8, 51.4, 44.7, 25.8, 22.6, 17.9, 12.4, −4.3, −4.9.

Received in Corvallis, OR, USA, 1st June 1998; 8/04125C