HETEROCYCLES, Vol. 73, 2007, pp. 191 - 195. © The Japan Institute of Heterocyclic Chemistry
Received, 21st June, 2007, Accepted, 9th August, 2007, Published online, 10th August, 2007. COM-07-S(U)25

DIASTEREOSELECTIVE APPROACH TO AN HIV PROTEASE INHIBITOR INTERMEDIATE USING A CATION-EXCHANGE RESIN MEDIATED MANNICH-TYPE REACTION

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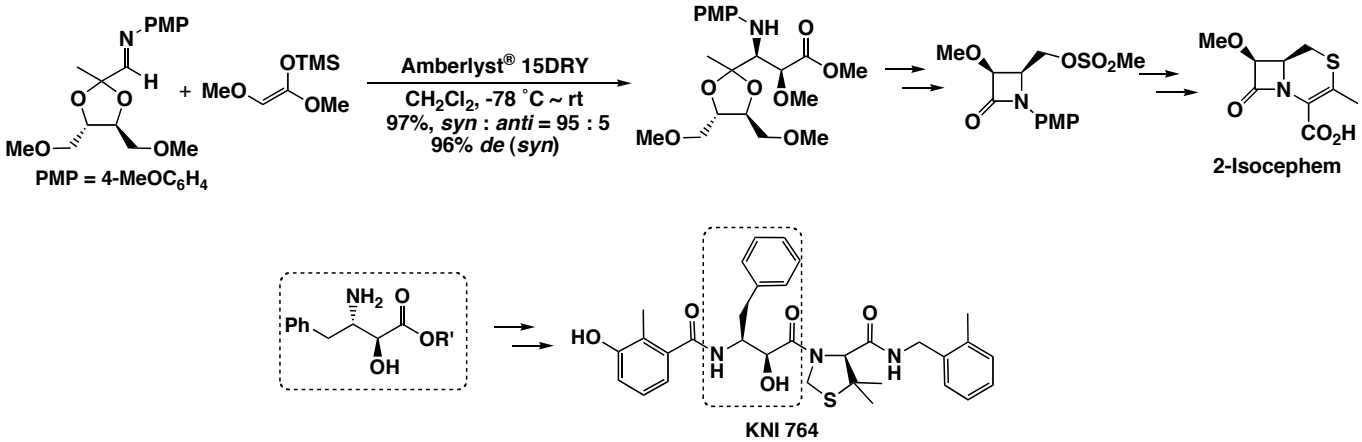
Abstract –Mannich-type reaction of ketene silyl acetals with a chiral imine proceeded smoothly to give β-amino esters in good yields with high diasetereoselectivity under the influence of a cation-exchange resin, and the subsequent functional group transformations gave an HIV protease inhibitor intermediate.

Our continuous interests in the stereodivergent construction of the β-lactam rings using a chiral imine led to a new approach to 2-isocephem intermediate in a highly stereoselective manner.[1] During these investigations cation-exchange resins have been found to be excellent activators for Mannich-type reaction of ketene silyl acetals with imines, which after cyclization lead to the stereodivergent synthesis

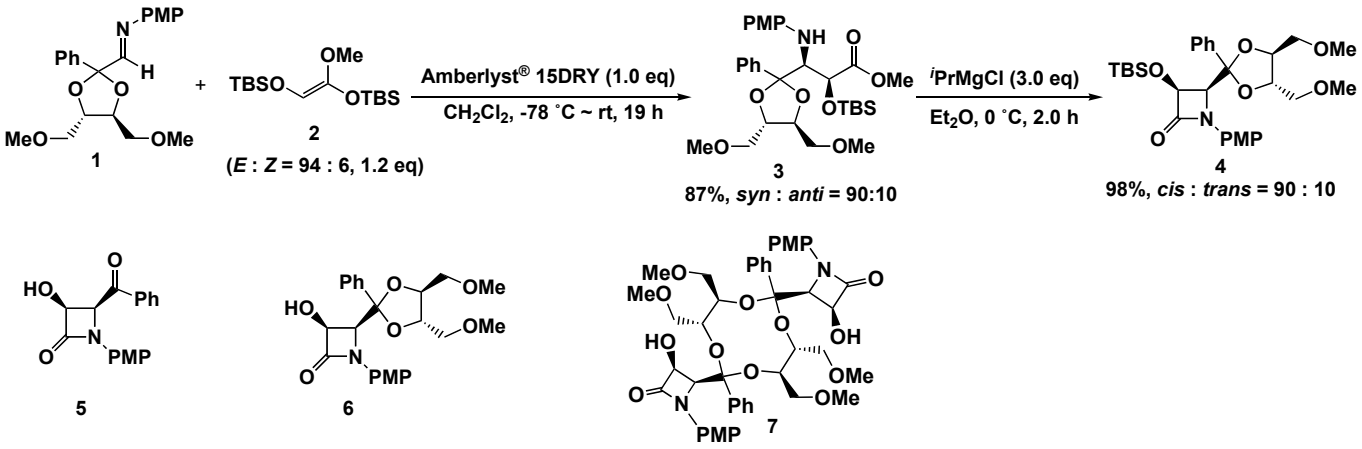


Scheme 1

This paper is dedicated to the memory of Professor Ivar Ugi who passed away on 27th September, 2005.

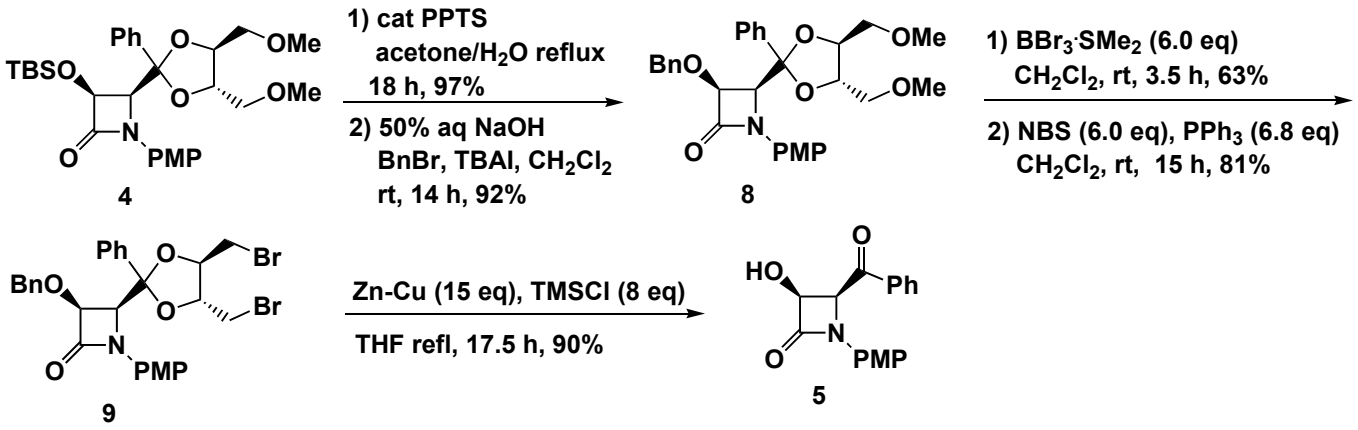
of β-lactams.[2] Use of ion-exchange resins offers several advantages in organic synthesis, *e.g.*, simplification of reaction procedures, easy separation of products without discharging harmful waste water, repeated use, and so on. In our previous report, a cation-exchange resin, in particular Amberlyst® 15DRY, having a large surface area (45 m^2 /g), was found to be one of the most useful resins that promoted Mannich-type reaction, where the addition reactions proceeded with high chemoselectivity in the presence of two kinds of imines and/or nucleophiles. This time we used a cation-exchange resin promoted Mannich-type reaction for the synthesis of a key component for the construction of HIV protease inhibitor (**KNI 764**)[3] using the chiral imine (**1**).

The starting chiral imine (**1**) was prepared from (2*S*,3*S*)-1,4-dimethoxy-2,3-butanediol in 3 steps.[4] The initial Mannich-type reaction proceeded with the ketene silyl acetal (**2**) to give the adduct (**3**) in 87% yield. Cyclization into the β-lactam (**4**) was readily carried out under the influence of isopropylmagnesium bromide in 98% yield.[5] However, we have encountered much difficulty to remove the chiral ketal group. Although a variety of hydrolysis conditions were examined, we obtained either the desilylated product (**6**) or the dimerized cyclic ether (**7**), and the desired ketone (5) was not obtained at all.



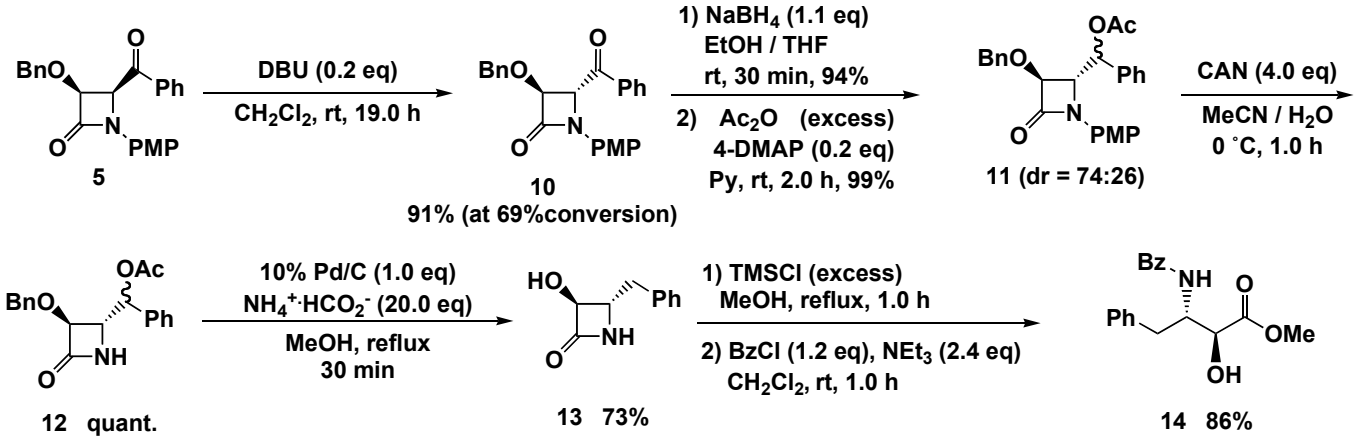
Scheme 2

We therefore turned our attention to the removal of the ketal group using a multi-step procedure. First, the TBS group was replaced with a benzyl group via hydrolysis with PPTS in refluxing acetone/water followed by benzylation with BnBr under the phase-transfer catalysis conditions in good overall yield.[6] Bis-bromination was readily carried out first by cleavage of the methyl ether with BBr_3 followed by NBS-PPh_3 treatment. Reductive elimination of the ketal was conducted with Zn-Cu in the presence of TMSCl in refluxing THF, and the desired ketone (**5**) was obtained in good overall yield.



Scheme 3

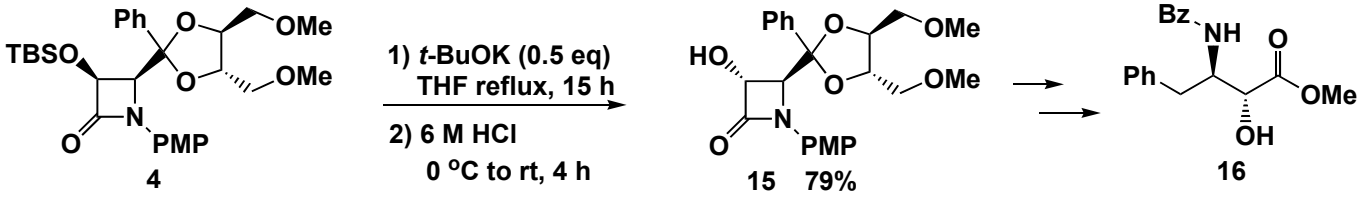
For the synthesis of the desired hydroxyaminoester (**14**) epimerization of the benzoyl group was needed. This was readily carried out using DBU as a base, and the *trans*-β-lactam (**10**) was obtained. Further functional group transformations were conducted as follows: The phenyl ketone (**10**) was reduced to the alcohol (a 74:26 mixture of diastereomers), which in turn acetylayed to give the acetate (**11**). The PMP group was removed with CAN in MeCN/water in quantitative yield. Hydrogenolysis of the acetate with cat Pd/C-ammonium formate gave 4-benzyl-3-hydroxy-β-lactam (**13**), which upon methanolysis and *N*-benzoylation gave the desired methyl ester (**14**)[3j-m,7] in good overall yield.



Scheme 4

In conclusion, we have found that an ion-exchange resin promoted Mannich-type reaction of the ketene silyl acetal derived from glycolate with a chiral imine offers a useful method for β-amino ester, which upon treatment with isopropyl Grignard reagent gives β-lactam. Appropriate functional group transformations provide a rapid approach to an HIV protease inhibitor intermediate. Since we have succeeded in the epimrization of the 3-TBSO group of the β-lacam (**4**) under the influence of *t*-BuOK in

refluxing THF,[8] the enantiomer (**16**) of the ester (**14**) may also be prepared using the same procedures. These transformations are under active investigation in our laboratories.



Scheme 5

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5. The following example represents a procedure for the synthesis of β-lactam (**4**): To a suspension of Amberlyst® 15DRY (43.0 mg, 0.2 mmol on the sulfonic acid portion, washed EtOH and dried in vacuo at 100 °C) and the imine (**1**) (74.0 mg, 0.2 mmol) in CH_2Cl_2 (0.5 mL) was added a solution of ketene silyl acetal (**2**) (76.0 mg, 0.24 mmol) in CH_2Cl_2 (0.6 mL) at -78 °C under an argon atmosphere. After being stirred at at -78 °C for 2 h, the reaction mixture was allowed to stand at rt for 12 h. Then, triethylamine (1.1 mL) was added at -78 °C. The suspension was filtrated through a Celite pad. The filtrate was concentrated in vacuo to afford a crude oil. Purification by silica gel column

chromatography (*n*-hexane / Et_2O = 1/1, as an eluent) gave the adduct (**3**) (101.2 mg, 87%) as a pale yellow oil. Examination by HPLC indicated the formation of diastereomers in a 90:10 *(syn*:*anti*) ratio. Cyclization into β-lactam (**4**): To a solution of the adduct (**3**) (623.0 mg, 1.08 mmol) in Et_2O (28.5 mL) was added a THF solution of ^{i}PrMgBr (4.20 mL, 3.25 mmol, 0.733 M in THF) at 0 ºC, and the mixture was stirred at 0 ºC for 2 hr. Sat. aqueous NaCl (20 mL) was added to the mixture. After extracting with Et_2O followed by a usual work-up, a crude oil was purified by silica gel column chromatography (*n*-hexane / AcOEt = 5/1, as an eluent) gave the β-lactam (**4**) (572.2 mg, 98%) as a colorless oil. Examination by HPLC indicated the formation of diastereomers in a 90:10 *cis*:*trans*) ratio. Rf = 0.40 (*n*-hexane : Et_2O = 1 : 1); ^{1}H-NMR (500 MHz, $CDCl_3$) δ : 0.14 (s, 3H), 0.15 (s, 3H), 1.07 (s, 9H), 3.28 (dd, *J* = 4.9, 10.4 Hz, 1H), 3.33-3.35 (m, 4H), 3.58 (s, 3H), 3.60 (dd, *J* = 4.9, 10.7 Hz, 1H), 3.69 (dd, *J* = 5.8, 10.7 Hz, 1H), 3.77 (ddd, *J* = 4.9, 6.7, 11.9 Hz, 1H), 3.98 (s, 3H), 4.13 (ddd, *J* = 4.9, 5.8, 11.9 Hz, 1H), 4.91 (d, *J* = 5.5 Hz, 1H), 5.02 (d, *J* = 5.5 Hz, 1H), 7.03-7.06 (m, 2H), 7.47-7.50 (m, 3H), 7.72-7.74 (m, 2H), 7.81-7.83 (m, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ : -5.5, -5.0, 18.4, 25.8, 55.4, 59.0, 59.5, 63.9, 72.7, 73.4, 75.0, 77.5, 79.5, 110.2, 113.8, 119.4, 126.7, 127.7, 128.2, 131.4, 140.2, 156.0, 167.3.

6. Although the ketene *t*-butyldimethylsilyl acetal derived from methyl benzyloxyacetate could be used for the initial Mannich type reaction with the imine (**1**), the subsequent cyclization into β-lactam was not facile as in the case with the TBS derivative (**2**), and therefore, replacement of the TBS group was conducted in the present synthesis (Scheme 3).
7. Methyl (2*S*,3*S*)-3-(benzamido)-2-hydroxy-4-phenylbutanoate (**14**): White crystals; Mp 183-184 ºC; Rf = 0.45 (CH_2Cl_2 : MeOH = 20 : 1) ^{1}H-NMR (500 MHz, $CDCl_3$) δ : 2.92 (dd, *J* = 6.7, 14.0 Hz, 1H), 2.98 (dd, *J* = 7.9, 14.0 Hz, 1H), 3.58 (d, *J* = 5.2 Hz, 1H), 3.60 (s, 3H), 4.44 (dd, *J* = 3.1, 5.2 Hz, 1H), 4.85 (dddd, *J* = 3.1, 6.7, 7.9, 8.5 Hz, 1H), 6.45 (d, *J* = 8.5 Hz, 1H), 7.20-7.23 (m, 1H), 7.25-7.31 (m, 4H), 7.39-7.42 (m, 2H), 7.47-7.50 (m, 1H), 7.66-7.68 (m, 2H). ^{13}C-NMR (126 MHz, $CDCl_3$) δ : 35.4, 52.7, 53.3, 72.0, 126.8, 126.9, 128.5, 128.6, 129.4, 131.7, 134.0, 136.8, 167.4, 173.0.
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