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ASYMMETRIC SYNTHESIS OF β-LACTAMS AND *N*-BENZOYL-3-PHENYLISOSERINES VIA THE STAUDINGER REACTION

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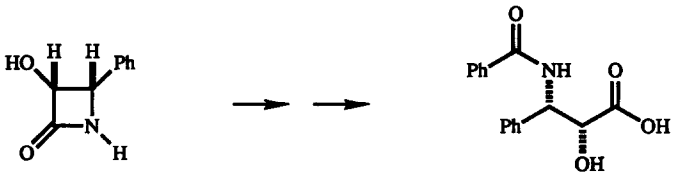
Abstract: Reaction of benzaldimine **5** derived from 2,3,4,6-tetra-O-acetyl-β-D-galactoseamine with acid chloride **6** yields cis β-lactam **7** as a single diastereoisomer. Hydrolysis of β-lactam **7** followed by *N*-benzoylation provides access toward *N*-benzoyl-(2*S*,3*R*)-3-phenylisoserine **9**. *N*-Benzoyl-3-phenylisoserines are important building blocks for the semi-synthesis of the anti-cancer agent taxol.

Several research groups have by now independently recognized[2,3,4] that optically active 3-hydroxy-4-phenyl-2-azetidinone **1** is an excellent precursor for the synthesis of *N*-benzoyl-(2*R*,3*S*)-3-phenylisoserine **2** and related α-hydroxy β-amino acids (**Scheme 1**).

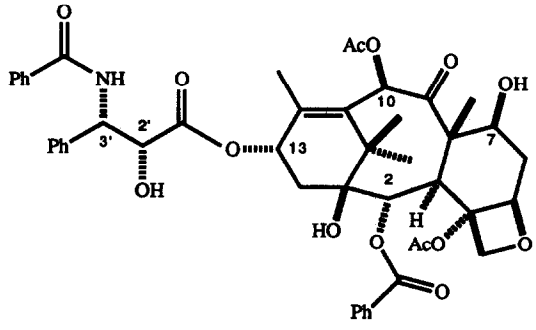
Scheme 1



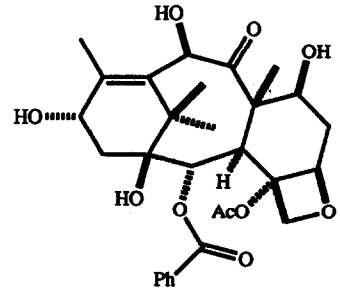
1 **2**

N-Benzoyl-3-phenylisoserine **2** can be utilized for the semi-synthesis of the potent anti-tumor agent taxol. Taxol **3**, a complex diterpene which has been isolated in small quantities from the bark of *Taxus brevifolia*, is currently considered the most exciting lead in cancer chemotherapy.[5] Taxol is in phase II clinical trials in the United States. Activity against cisplatin refractory advanced ovarian cancer has been established.[5] Widespread concern has been voiced that the very slow growing trees may be threatened by extinction should taxol prove to be highly effective in cancer chemotherapy.[6]

A recent report has detailed that a more readily available taxol precursor can be isolated from the needles of *Taxus baccata*.[6] Extraction of the fresh needles yields 10-deacetylbaccatin III **4** in up to 1 g/kg. Of note is that the harvest does not threaten the survival of the species. 10-Deacetylbaccatin III **4** has been converted to taxol *via* coupling[6] to *N*-benzoyl-3-phenylisoserine **2** and a derivative of **1**.[3] SAR studies of derivatives of **3** have revealed that the *N*-benzoyl-3-phenylisoserine side chain at C-13 of the taxol molecule is of crucial importance for the antitumor activity of taxol.[7] Asymmetric syntheses of **2** have been achieved *via* the Sharpless epoxidation,[8] the Sharpless dihydroxylation[9] reaction, and the ester enolate imine condensation.[2] Other approaches to obtain optically active **2** involve the separation[3] of diastereoisomers derived from **1** and the resolution of a derivative of **2** by enzymatic hydrolysis.[10]



Taxol **3**



10-Deacetylbaccatin III **4**

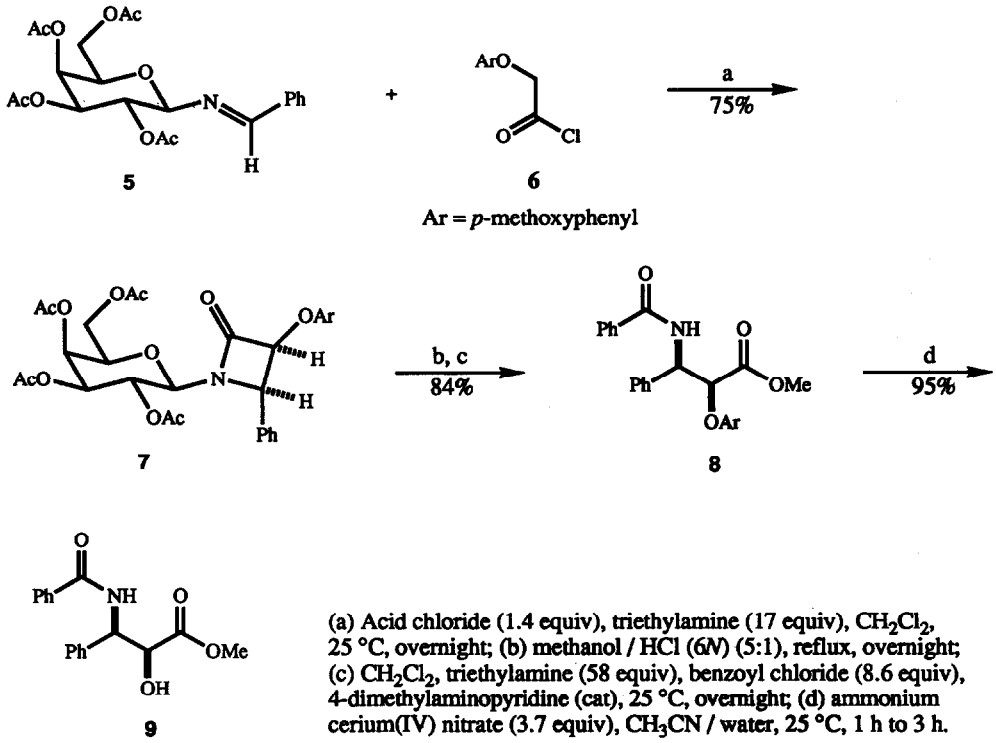
We now wish to report on our preliminary studies towards the asymmetric synthesis of β-lactams and phenylisoserines of type **1** and **2** *via* the Staudinger reaction[11,12] (**Scheme 2**). Reaction between galactose imine **5**[13] and acid chloride **6** in the presence of triethylamine gave a single diastereoisomer **7** (as shown by NMR) with cis stereochemistry at the β-lactam ring in 75% yield. Hydrolysis of **7** with hydrochloric acid (6*N*) in methanol followed by benzoylation of the crude reaction product gave the *N*-benzoyl-3-phenylisoserine derivative **8** in 84% yield. Oxidative dearylation[14] of **8** with ammonium cerium (IV) nitrate (CAN) produced phenylisoserine methyl ester **9** ($[\alpha]_D$ + 48.3°, *c* 0.575, $CHCl_3$) in 95% yield.[15]

Comparison of the optical rotation of **9** with published data[8] revealed that we had obtained an optically pure sample of the 2*S*,3*R* phenylisoserine methyl ester **9**. However, phenylisoserine **9** is enantiomeric to the desired phenylisoserine **2**, necessary for the conversion to taxol. We are therefore planning to utilize imines[13] derived from D-arabinose and L-fucose toward the synthesis of the desired phenylisoserine isomer **2** with 2*R*, 3*S* stereochemistry.

It should be pointed out that β-lactam **7** possesses the correct absolute stereochemistry at the β-lactam ring as necessary for the synthesis of β-lactam antibiotics.[16] Preliminary results[17] in our laboratories have indicated that the sugar moiety of **7** can be removed hydrolytically while keeping the β-lactam ring system intact.

Thus, the Staudinger reaction involving optically active imines of type **5** should be a very promising approach not only for the synthesis of optically active phenylisoserines but also for the synthesis of optically active precursors for the synthesis of β-lactam antibiotics. These studies are currently underway in our laboratories.

Scheme 2



(a) Acid chloride (1.4 equiv), triethylamine (17 equiv), CH_2Cl_2, 25 °C, overnight; (b) methanol / HCl (6*N*) (5:1), reflux, overnight; (c) CH_2Cl_2, triethylamine (58 equiv), benzoyl chloride (8.6 equiv), 4-dimethylaminopyridine (cat), 25 °C, overnight; (d) ammonium cerium(IV) nitrate (3.7 equiv), CH_3CN / water, 25 °C, 1 h to 3 h.

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(15) All compounds exhibited spectroscopic data in agreement with their structural assignments. The addition of the acid chloride **6** to imine **5** was performed at 0 °C. Compounds **7**, **8**, and **9** were purified by column chromatography. β-Lactam **7** could not easily be separated from the starting imine and was therefore subjected to hydrolysis containing a small impurity of imine **5**.

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