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AN ENANTIOSELECTIVE ROUTE TO AN INTERMEDIATE OF THE CARBAPENAM SYSTEM FROM THE CHIRAL γ-BUTYROLACTONE

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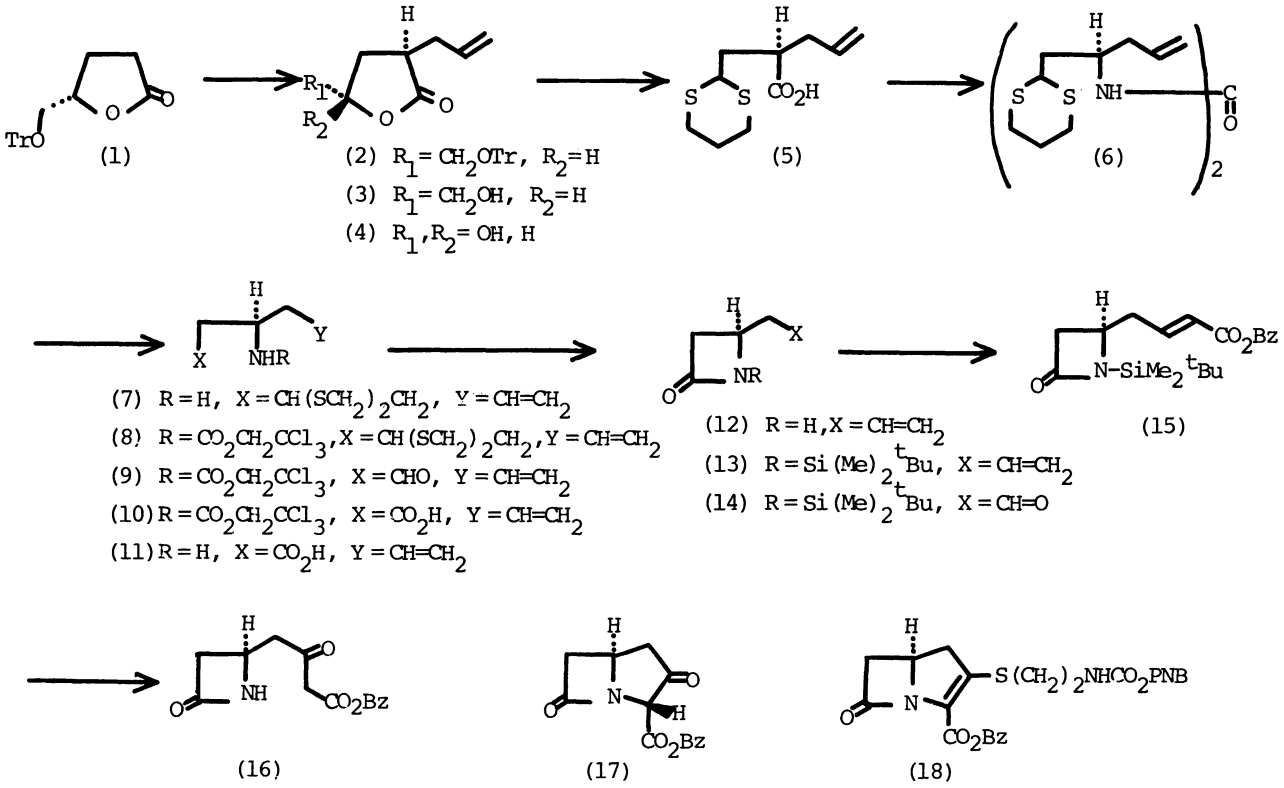
A new enantioselective synthesis of the keto ester(16) containing β-lactam ring system has been developed using the chiral lactone(1) as a starting material.

Recently we established the enantioselective syntheses of the corynanthe[1], the iboga[2], and the aspidosperma[3] indole alkaloids, and the gibbane derivatives[4] using the chiral lactone[5](1) which is easily accessible from L-glutamic acid[6] or D-mannitol[8]. We now report here another utility of the same synthon[8](1) as a starting material for the enantioselective synthesis of the β-lactam antibiotics relating to thienamycin[9], which is naturally occurring carbapenam derivative with interesting biological activities.

The chiral allyllactone[1,3](2), obtained stereoselectively from (1), was detritylated(conc HCl-MeOH), saponified(KOH-MeOH), and cleft($NaIO_4$, pH 8-9), to give the ω-hydroxylactone[10](4) in 79% overall yield after acid work-up(pH 5-6). Treatment of (4) with propane-1,3-dithiol in the presence of boron trifluoride etherate gave the carboxylic acid(5), $[\alpha]_D$ -5.50° (c=6.00,$CHCl_3$), in 86% yield. Curtius-Schmidt type rearrangement of (5) using diphenylphosphoryl azide(DPPA)[11] in the presence of triethylamine in boiling benzene afforded none of the expected amine(7) but the urea derivative[12](6) in good yield. Upon saponification with potassium hydroxide in boiling ethylene glycol, (6) gave the volatile amine(7) which was immediately converted into the carbamate(8), mp 62.5-64°C, $[\alpha]_D$ -6.20° (c=2.00,$CHCl_3$), using 2,2,2-trichloroethyl chloroformate under the standard conditions(pyridine,room temperature). Overall yield of (8) from (5) was 72%.



Scheme

Hydrolysis of (8) with an excess of methyl iodide in the presence of sodium hydrogen carbonate in aqueous acetonitrile[13] gave 92% yield of the aldehyde(9), $[\alpha]_D$ +1.66°(c=14.86, $CHCl_3$), which was then oxidized with pyridinium dichromate(PDC)(DMF, room temperature) to give the carboxylic acid(10), $[\alpha]_D$ +0.64°(c=26.40, $CHCl_3$), in quantitative yield. After removal of the amine protecting group of (10) using zinc in aqueous methanol, the resulting amino acid(11) was transformed into the β-lactam(12), $[\alpha]_D$ -3.41°(c=8.20, $CHCl_3$), in yield of 76% from (10) by employing the procedure developed by Ohno and co-workers[14].

The resulting lactam(12), after silylation using dimethyl-t-butylsilyl chloride in the presence of triethylamine, was converted into the aldehyde(14)(OsO_4(0.01 equiv), $NaIO_4$(2.2 equiv),aqTHF, 0°C[15]), and subsequently into the α,β-unsaturated ester(15), $[\alpha]_D$ -25.1°(c=4.8, $CHCl_3$), ($(EtO)_2POCH_2CO_2CH_2C_6H_5$, NaH, THF) in an exellent overall yield(90%). Treatment of (15) with t-butylhydroperoxide (1.1 equiv) in the presence of disodium tetrachloropalladate(0.2 equiv) in aqueous acetic acid at 55°C furnished 56%

yield of the known keto ester(16), $[\alpha]_D$ +22.9°(c=1.8, benzene)(lit[17] $[\alpha]_D$ +43.2°(c=0.37)), which has been synthesized in both chiral[17] and racemic[18-20] forms by fundamentally different sequence, with spontaneous desilylation.

Since both optical active[17] and racemic[18-20] forms of the keto ester(16) have been converted into the carbapenam ring systems, (17)[17-20] and (18)[18], excellently, the present approach consists an alternative enantioselective synthesis of these compounds. Limiting to the enantioselective synthesis of the keto ester(16) itself, the present method does not possess apparent advantage over that previously reported[17] as the latter method involved lesser number of steps. However, the present method would be more advantageous in the enantioselective synthesis of a variety of biologically interesting carbapenam derivatives in particular containing a functional group at 5 position, since stereoselective disubstitution at 2 position of the lactone(1) may be carried out in highly efficient manners.[3,4,21]

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