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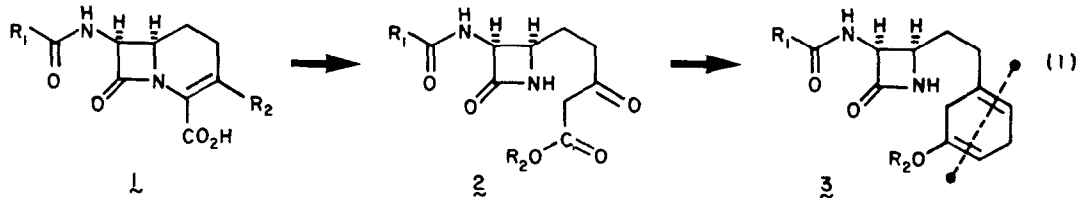
THE ASYMMETRIC SYNTHESIS OF β-LACTAM ANTIBIOTICS - II. THE FIRST ENANTIOSELECTIVE SYNTHESIS OF THE CARBACEPHALOSPORIN NUCLEUS.

David A. Evans* and Eric B. Sjogren

Department of Chemistry
Harvard University
Cambridge, Massachusetts 02138

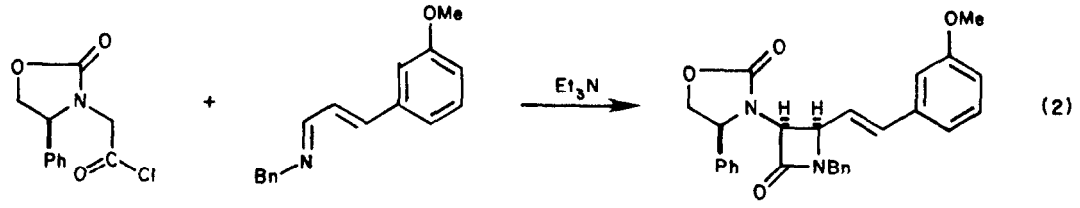
Abstract: The application of asymmetric ketene-imine cycloadditions to the first enantioselective synthesis of the carbacephalosporin nucleus is described.

The effect of nuclear substitution on the biological activity of the cephalosporin ring system has been investigated by a number of research groups.[2] These studies have resulted in the discovery of several new types of β-lactam antibiotics which include the highly active carbocephalosporins (1).[3] At present, this family of cephalosporin analogs is not directly accessible via either fermentation or the straightforward structural modification of naturally occurring β-lactam antibiotics. Accordingly, the development of practical asymmetric syntheses of the carbacephalosporin nucleus appears to be a worthwhile objective. Toward this end, we wish to report an enantioselective synthesis of the carbacephem nucleus (1) which relies upon the asymmetric ketene-imine cycloaddition reaction disclosed in the preceeding Letter.[1] An additional noteworthy facet of this project has been the successful application of dihydroanisoles as effective β-keto ester synthons.[4] In the case at hand, the dihydroanisole 3 has proven to be an effective equivalent synthon for β-keto ester 2 (eq 1).



1 2 3 (1)

Based upon the concepts described in the previous Letter, the homochiral azetidinone **4**, mp 142-143°C, may be prepared in 80% yield via the illustrated cycloadditon process (eq 2).[1] Subsequent hydrogenation of **4** (10% Pd-C, 1 atm., CH_2Cl_2) afforded a quantitative yield of **5**, mp 134-135°C, $[\alpha]_D$ +38.6 (c 2.2, $CHCl_3$).

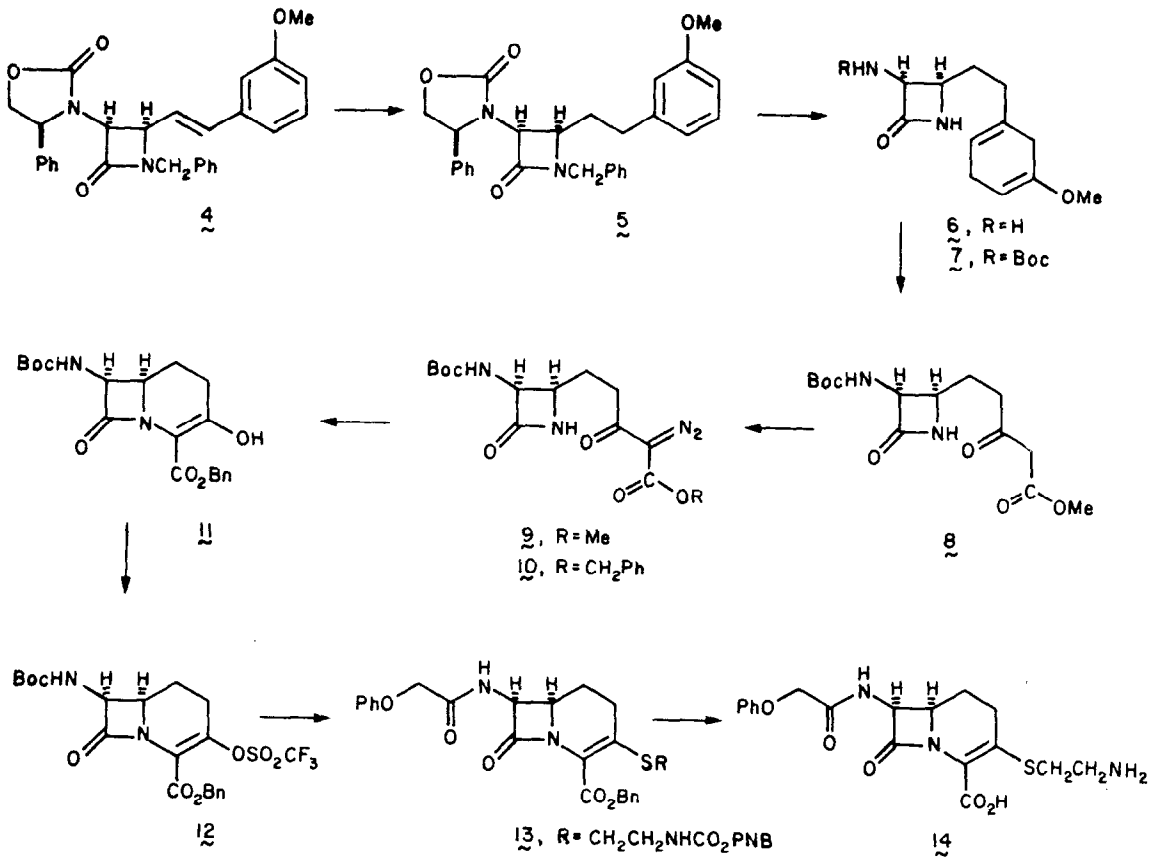


(2)

4

In the singularly most important step in the further elaboration of **5**, we have found that this intermediate can be readily transformed into the dihydroanisole **6** via dissolving metal reduction and subsequently acylated in situ to give azetidinone **7** in 74% overall yield. The dissolving metal reduction of **5** effects three significant chemical events: The oxazolidone auxiliary is removed, the anisole ring reduced, and the azetidinone nitrogen debenzylated. The development of the two-step reduction-acylation sequence leading to the conversion of **5** to **7** posed an interesting technical problem. For example, the immediate product of the dissolving metal reduction, after an ammonium acetate quench, is the carbamate salt of azetidinone **6** ($R=CO_2^-$). Under normal circumstances, acidification could be relied upon to effect carbamic acid decomposition. Nonetheless, in the present instance the acid-labile dihydroanisyl moiety imposes a significant pH constraint on this decomposition process. Fortunately, it was found that the carbamate salt **6** ($R=CO_2^-$) decomposes slowly at pH 7, and the liberated amino azetidinone **6** can be protected in situ with t-butyl pyrocarbonate to afford **7** in an overall yield (from cycloadduct **4**) of 74%. The specific conditions for the dissolving metal reduction of azetidinone **5** and the in situ acylation of **6** follow: To a solution of 79 mmol of lithium in 67 ml of 5:1 ammonia:tert-butanol at -78°C is added a 0.215 M solution of **5** (5.2 mmol) in 3:1 THF:tert-butanol. After 30 min, excess lithium is quenched with benzene, and an equimolar amount (based on lithium) of ammonium acetate is added. Upon removal of ammonia and solvent, the white residue is suspended in a 1:1 mixture of THF-water. The pH is adjusted to 7, t-butyl pyrocarbonate (1.5 equiv.) is added, and the mixture stirred overnight. The carbamate **7** is then isolated by extraction and purified by flash chromatography. Conversion of this material into the desired β-keto ester **8** was effected by ozonolysis of the olefinic bonds. Treatment of a 0.15 M solution of **7** in dichloromethane-methanol (1:1) with ozone at -78°C in the presence of Sudan III,[5] followed by reductive workup (Me_2S) afforded **8**, mp 122-123°C, $[\alpha]_D$ +48.6° (c 1.4, $CHCl_3$). The overall yield of β-keto ester **8** from the cycloadduct **4** was 62%.

Based on published precedent, we anticipated that the desired carbacephem ring system could be constructed from **9** or **10** through a rhodium-catalyzed carbene insertion.[6] However, it seemed unlikely that a methyl ester could be successfully saponified after construction of the carbacephalosporin nucleus without concomitant cleavage of the β-lactam ring. Therefore, following diazo transfer with tosyl azide (CH_3CN, Hunig's base, 94%), **9** was subjected to titanium-catalyzed transesterification in benzyl alcohol (0.14 M, 1 equiv. titanium tetrabenzyloxide, 36°C, 42 hr) to afford the benzyl ester **10** in 72% yield.[7]



In view of the other reactive functionality present in **9**, the success of this reaction is an indication of the mildness of this transesterification protocol. It is interesting to note that these conditions were less effective on the β-keto ester **8** (50%), which required higher temperatures and gave a considerable amount of a ring-opened product.

The rhodium-catalyzed carbene insertion to form **11** from **10** proved to be a sensitive reaction, but satisfactory results were obtained in refluxing alcohol-free chloroform using 1% Rh_2OAc_4 (20 min, 0.05 M). In general, the 3-hydroxy carbocephem **11** was not isolated, but trapped in situ with triflic anhydride (1 equiv., 0°C, Hunig's base) to give **12**, $[\alpha]_D$ +31.5° (c 0.5, $CHCl_3$), in 75% yield. From this triflate, a variety of C-3 and C-7 substituted carbacephalosporins can in principle be prepared. The synthesis of **14**[3e] serves to demonstrate the utility of this intermediate. Following removal of the Boc group from **12** (TFA, anisole), the derived amine salt was reacylated with phenoxyacetic anhydride (1.5 equiv., CH_2Cl_2, Hunig's base, 0°C, 90%). Treatment of this material with the p-nitrobenzyl carbamate of cysteamine[8] (CH_3CN, 0°C, Hunig's base) gave **13**, mp 173-175°C, $[\alpha]_D$ -0.9 (c 1.0, $CHCl_3$), in 84% yield. The synthesis of **14** was completed by cleavage of the benzyl ester with aluminium trichloride[9] and anisole

(8 equiv. of each, CH_2Cl_2, CH_3NO_2, 3 hr, 90%) and hydrogenolysis of the p-nitrobenzyl group (100 psi, 35 min, THF-H_2O). The zwitterionic product **14** was isolated as a white solid, $[\alpha]_D$ -4.2° (c 0.45, DMSO), in 72% yield after chromatography on HP-20 resin.

This asymmetric synthesis of carbacephalosporins provides homochiral material in relatively few steps and in good overall yield. In addition, the illustrated synthesis affords sufficient flexibility such that a range of analog structures might be readily constructed. Finally, the synthesis demonstrates the efficient manner in which dihydroanisoles serve as synthons for β-keto esters. We are currently evaluating the use of the synthon in convergent approaches to homochiral carbapenems.

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