The Total Synthesis of Cephalosporin C

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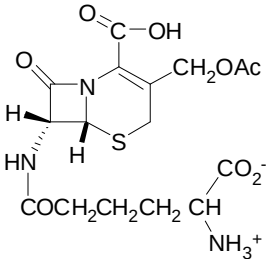


Cephalosporin C

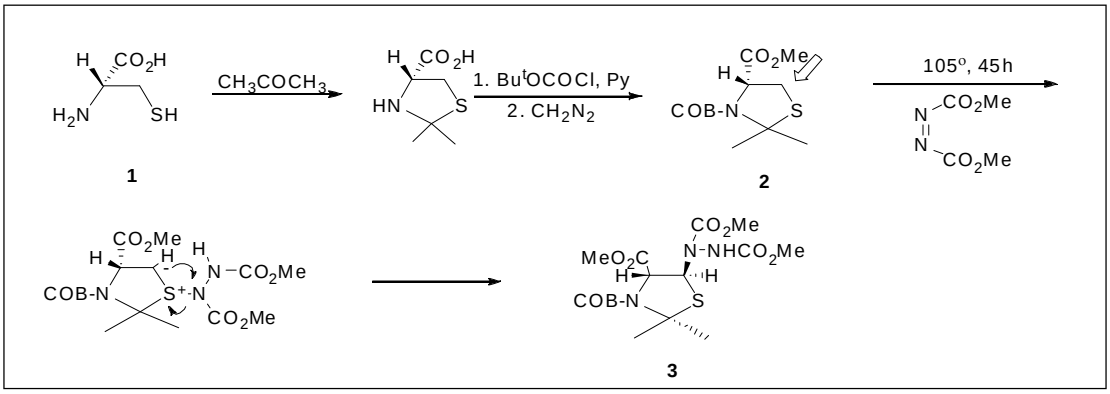
The Nobel Prize in Chemistry for 1965 has been awarded for contributions to the art of chemical synthesis. It gives me much pleasure to record here my gratification with the citation, which properly signalizes an exciting and significant aspect of synthetic activity. But that aspect is one which is more readily – and I dare say more effectively – exemplied and epitomized than it is articulated and summarized. Having here this morning the responsibility of delivering a lecture on a topic related to the work - for which the Prize was awarded, I have chosen to present an account of an entirely new and hitherto unreported investigation [namely, the total synthesis of Cephalosporin C] which, I hope, will illuminate many facets of the spirit of contemporary work in chemical synthesis.

– *R B Woodward* in his Nobel Lecture, Dec 11, 1965.

The total synthesis of Cephalosporin C is yet another example where Woodward identifies an anchor from which he never wavered, in spite of enormous problems. The anchor here was L (+) cysteine (**1**). The choice of **1** was indeed ingenious! Not only does **1** contain half of the carbon framework but one of the chiral centres too.

Compound **1** was transformed to the key intermediate **2** by normal procedure. Not only did these protocols protect all the active centres of **1**, they also enhanced the activity of the -CH_2- group, on which the whole synthetic strategy was pledged. Innumerable rational procedures to introduce a functional group failed. Success was finally achieved by an entirely novel path with MeOOC-N=N-COOMe leading to **3**, which can be rationalized by initial acceptance by sulfur eventually leading to an S-N shift (*Scheme* 1).

Keywords
Cephalosporin C.

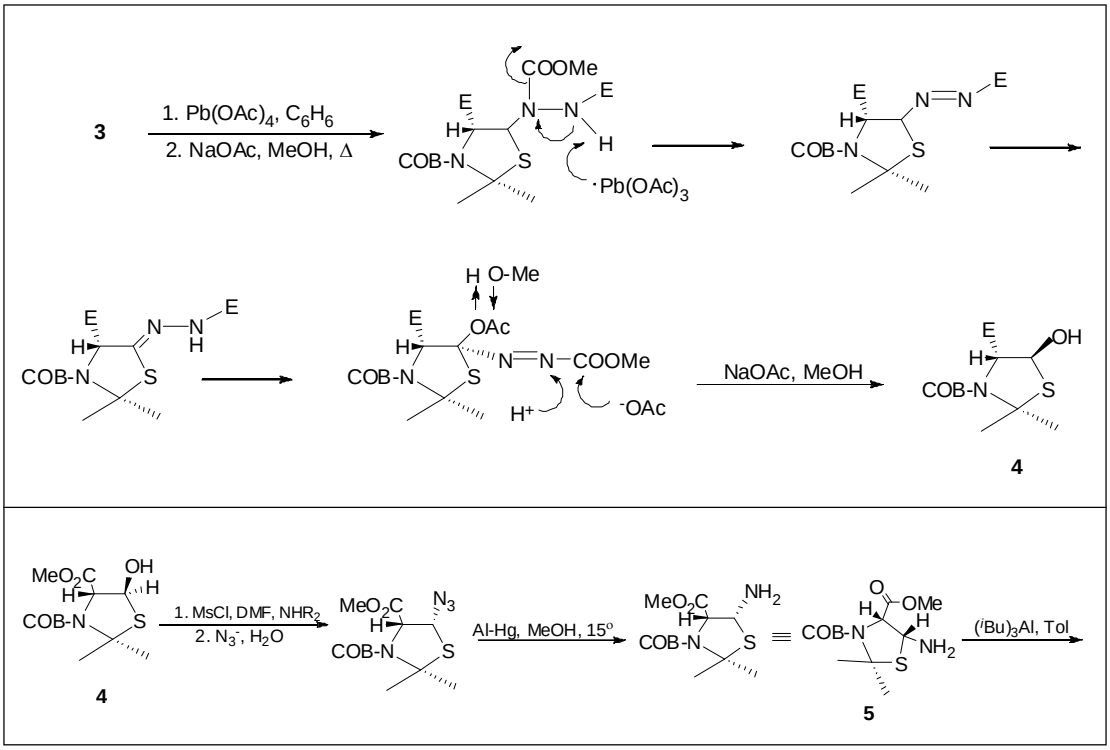


Scheme 1.

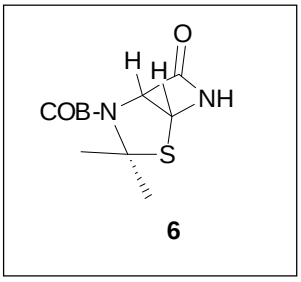
The transformation of **3** to **4** involving the specific replacement of β-N(E)−NHE with β-OH, reflects the deep understanding of reaction mechanisms (*Scheme* 2).

The transformation of **4** to the α-amino group , well placed to form the desired β-lactam was accomplished without much impediments (*Scheme* 3).

Scheme 2 (top).
Scheme 3 (bottom).



However, the desired peptide bond leading to the β-lactam **6** (*Structure* 1), proved very difficult. Woodward felt that there was a need to enhance the activity of the -C=O unit and this he achieved in an ingenious manner using $(^{i}Bu)_3$ Al in toluene!



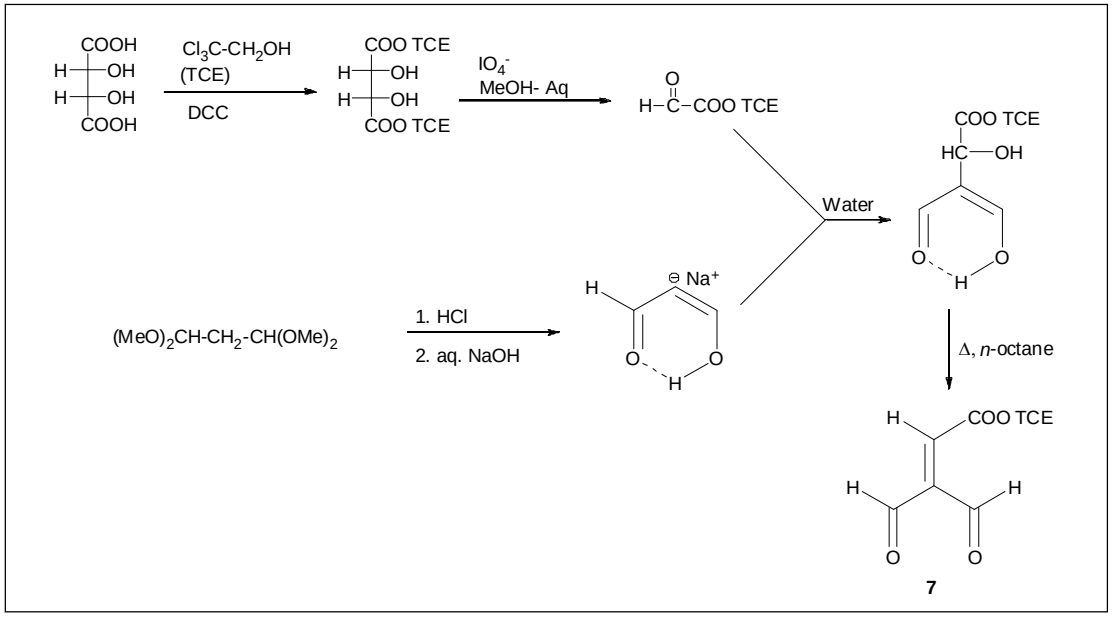
Structure 1.

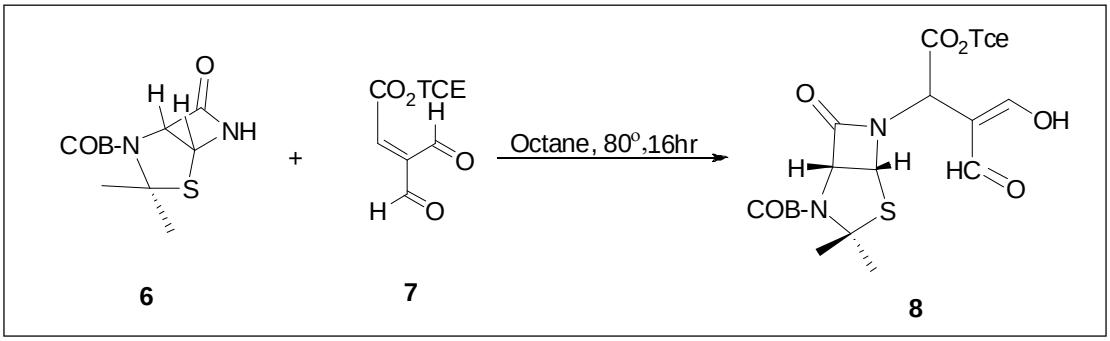
The next challenge was to attach the remaining framework of cephalosporin C, taking advantage of the NH grouping present in the fragile **6**. A strongly electrophilic partner had to be created and the chosen target was the olefin **7** endowed with three electrophilic substituents. Here again Woodward chose to start with simple partners, *d*-tartaric acid and 1,1,3,3-tetra methoxy propane (*Scheme* 4).

Scheme 4 belies the fact that compound **7** and some of the precursors are nasty customers, highly lacrimatory and need handling with great care! The desired union of **6** and **7** was smoothly accomplished on heating with *n*-octane leading to **8** (*Scheme* 5).

The time had come now to fire the 'magic bullet' (TFA) to generate the entire cephalosporin C skeleton! That memorable night (8 pm in Basel, Switzerland) **8** was treated with TFA. The

Scheme 4.





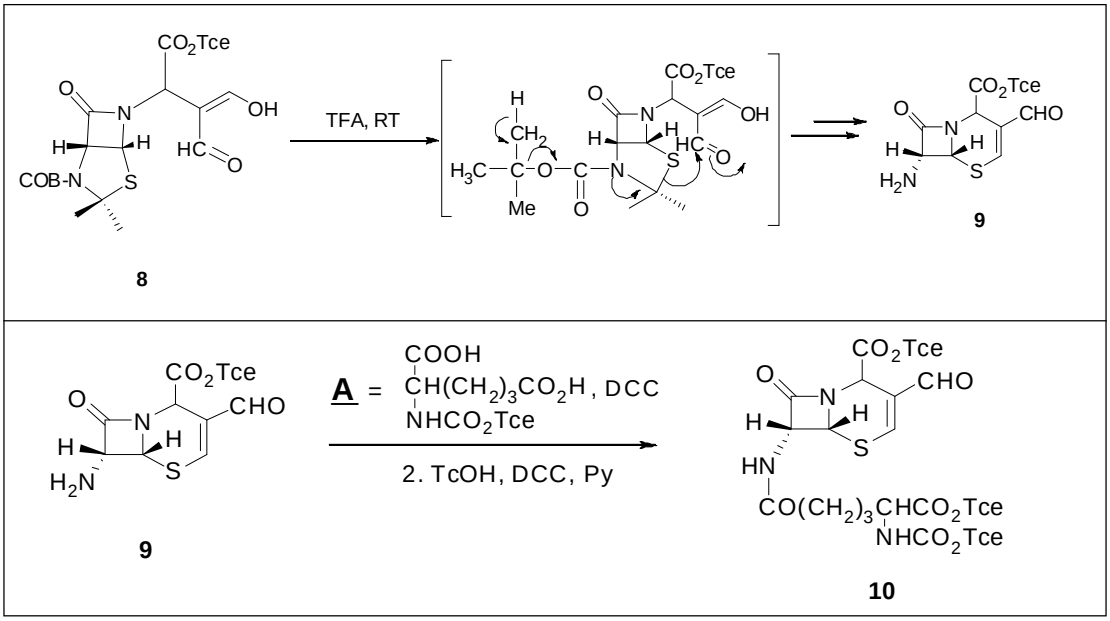
Scheme 5 .

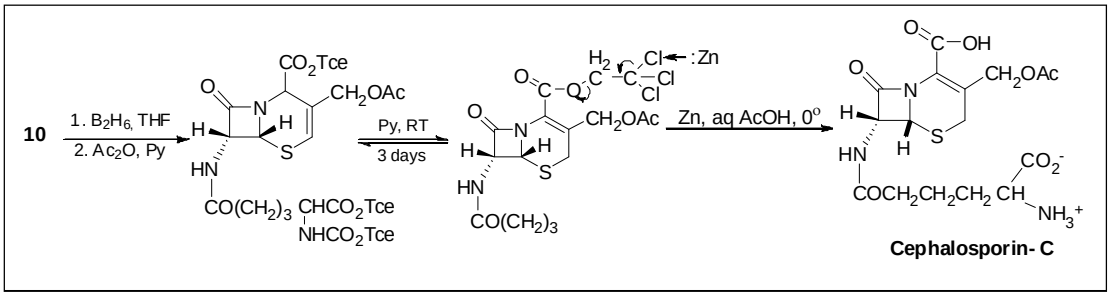
cascade of reactions that followed and constantly monitored by RB from Boston, involved removal of the BOC group; the freed nitrogen lone pair swung in to free the S from its shackles which in turn attacked the proximate-CHO, leading to loss of water on one hand and hydrolysis of Schiff's base on the other to yield **9**! (*Scheme* 6.)

It may be noted that **6** + **7** addition generates a new chiral centre as a mixture of epimers. However this centre becomes a tertiary one in the final product and hence of no major consequence.

Scheme 6 (top).
Scheme 7 (bottom).

A sequence of amidation of **9** with **A** followed by chromatography gave **10**, a heavily protected cephalosporin C! (*Scheme* 7.)





Scheme 8.

Diborane reduction of **10** (-CHO ! CH_2OH), acetylation, equilibration to $\alpha\beta$ ($\beta\gamma \rightleftharpoons \alpha\beta$:: 3 : 1) (Py, RT) and TCE deprotection (Zn, aq. AcOH) afforded cephalosporin C identical in all respects to the natural antibiotic (*Scheme* 8).

Suggested Reading

[1] R B Woodward, Recent Advances in the Chemistry of Natural Products, *Nobel Lectures*, 1965.