Tetrahedron Letters, Vol.31, No.13, pp 1921-1924, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

A Concise Formal Approach to the Oxacephem Skeleton from an Intramolecular Peterson Type olefination of N-[bis(trimethylsilyl)methyl]-β-lactams.

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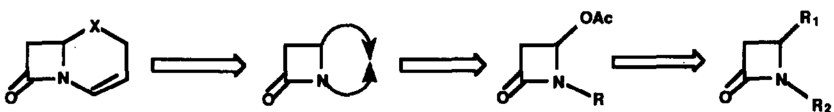
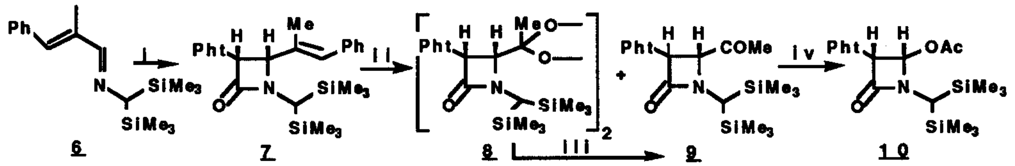
Abstract: A convenient synthesis of precursors of bicyclic β-lactam compounds from 4-acetoxy-1-(bistrimethylsilylmethyl)azetidin-2-ones prepared in few steps from the acid chloride-imine approach is described. A novel method to construct a bicyclic β-lactam ring system through an intramolecular Peterson type alkenation catalyzed by fluoride ion is also made.

Since the discovery of nonclassical β-lactam antibiotics[1], much attention has been focused on the exploration of new synthetic approaches to these and related systems[2]. In compounds like cephalosporins, the increased chemical reactivity seems to be associated with the presence of a double bond in conjugation with the nitrogen atom of the β-lactam ring[3]. A similar relationship exists in the new family of the synthetic β-lactam antibiotics which derive from 1-oxacephem 1[4] (X:O). The main strategies (figure 1) toward β-lactam synthesis usually involve first the construction of an appropriately substituted monocyclic β-lactam 4 with the correct stereochemistry at C_3-C_4 of the β-lactam ring, followed by chemical manipulations at N_1 and C_4 and subsequent ring closure to form the bicyclic ring system 1 in the last step of the synthesis[2,5]. From this strategy, 4-acetoxyazetidin-2-ones of type 3 are recognized as the most useful intermediates for synthetic work in β-lactam chemistry. The replacement of the acetoxy group by a variety of nucleophiles provides an easy access to a wide variety of bicyclic β-lactam precursors[6]. The most direct access to 4-acetoxyazetidin-2-ones is the addition of chlorosulfonyl isocyanate (CSI) to the corresponding vinyl acetate. Following this approach, Nayler et al.[7] reported a total synthesis of oxacephalosporins which involves substitution of the acetoxy group by alcohols, followed by an intramolecular Wittig reaction. However, apart from the low yields reported and the lack of stereoselectivity in the cycloaddition step, CSI is reactive towards several functional groups and such a process to introduce substituents at C_3 position is not usually feasible[8]. We wish to report a new entry to bicyclic β-lactams through our recently developed acid chloride-imine methodology, which involves the use of Schiff bases derived from bis(trimethylsilyl)methylamine[9] and an intramolecular Peterson-type olefination to produce the bicyclic ring system.



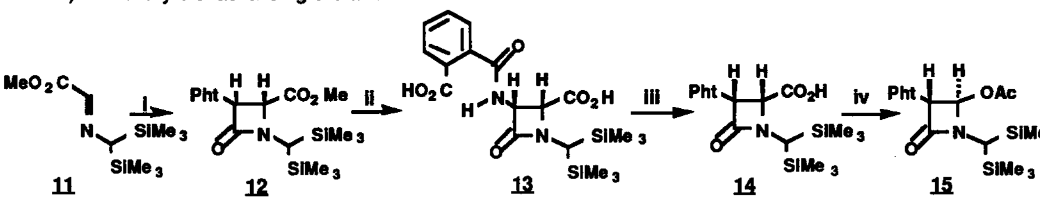
1 2 3 4

First, the access to 4-acetoxyazetidin-2-ones of type 3 was examined from the imine 6 following our protocol[10](Scheme 1). Thus, reaction between phthalimidoacetyl chloride 5 and this imine in the presence of triethylamine furnished the β-lactam 7 in 77% as single *cis* isomer. The β-lactam 7 thus prepared was then subjected to low temperature ozonolysis followed by dimethylsulphide workup, to give the 4-acetyl-β-lactam 9 in 53% yield together with a small amount of the dimeric product 8 in 13% yield. Subsequent Baeyer-Villiger oxidation of 9 with m-chloroperbenzoic acid (mCPBA; molar ratio, 1:4) in boiling benzene for 3h gave the desired acetoxy derivative 10 (m.p: 144-146ºC) in quantitative yield with retention of configuration at C_3-C_4 of the β-lactam ring. Although 8 can be transformed into the methyl ketone 9 by thermal decomposition in boiling chlorobenzene, better overall yield could be obtained when the above approach was tested from the glyoxalate imine 11 (Scheme 2).



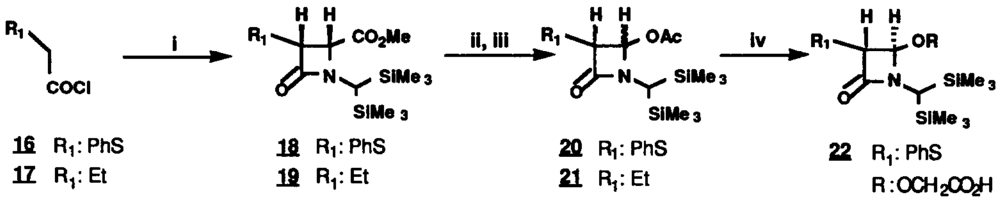
Scheme 1. Reagents and Conditions: i) $PhtCH_2COCl$ 5 NEt_3, CH_2Cl_2,r.t. 5h, ii) O_3, CH_2Cl_2, -78ºC, then, Me_2S. iii) Chlorobenzene, reflux, 1hr. iv) mCPBA, C_6H_6, reflux., 3hr.

Thus, the imine 11 prepared from methyl glyoxalate and bis(trimethylsilyl)methylamine, was allowed to react with phthalimidoacetyl chloride 5 under standard conditions[11]. After workup, the β-lactam 12 was isolated in 80% yield as a single *cis* isomer. Saponification of the methyl ester in 12 lead to the carboxylic acid 13 with concomitant opening of the phthalimido group. Treatment of the crude compound 13 with twofold excess of thionyl chloride in the presence of triethylamine, followed by aqueous workup, produced the expected β-lactam 14 in 80% overall yield. As expected, the oxidative acetoxy-decarboxy substitution[12] proceeded smoothly to furnish the desired 4-acetoxy derivative 15 (m.p: 170-172ºC) in 70% yield as a single *trans* isomer.



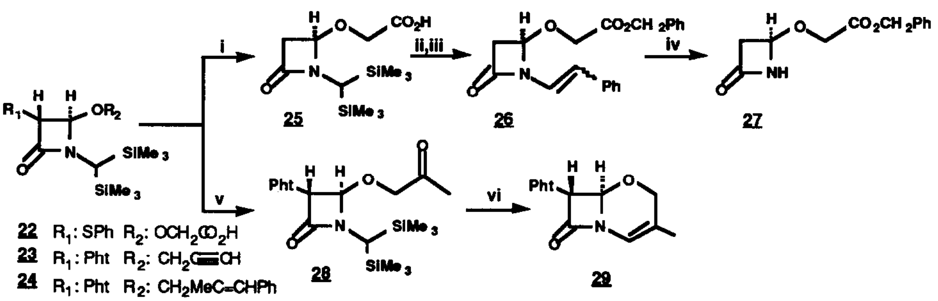
Scheme 2. Reagents and Conditions: i) Pht-CH_2COCl 5, Et_3N, CH_2Cl_2,2h, r.t., ii) LiOH, THF-H_2O, 60min, r.t., iii) Cl_2SO, Pyridine, CH_2Cl_2, 0ºC, 1h, iv) $Pb(OAc)_4$, Pyridine, C_6H_6, 50ºC, 30min.

The extension of this method is shown in Scheme 3. For instance, reaction between phenythioacetyl chloride 16 and the imine 11 in a molar ratio 2:1, in boiling methylene chloride, produced the β-lactam 18 (m.p: 113-115ºC) in 82%yield as single *cis* isomer. Under similar conditions, but using benzene as solvent, butanoyl chloride 17 afforded the *cis*-β-lactam 19 (b.p: 130-135ºC/0.02torr) in 98%yield. Particularly noteworthy is the fact that reaction between 17 and the imine 6, under the described conditions did not lead to the formation of the corresponding β-lactam[13]. Therefore, from this approach, a wider range of C_3 substituted β-lactams suitable for further chemical elaboration can be obtained in excellent yields. It is also worth of noting that only the *cis* isomer was formed in the cycloaddition reaction by using the bulky (bistrimethylsilyl)methyl group in the starting imines[14]. The β-lactam 18 thus obtained, upon saponification and further oxidative acetoxy-decarboxy substitution, furnished the corresponding acetoxy derivative 20 in 80% yield as a mixture of *cis* and *trans* isomers in a 6:94 ratio. Similarly, 19 produced a mixture of *cis* and *trans* isomers of 21 (83% yield) in a 20:80 ratio, respectively.



Scheme 3. Reagents and conditions: i) 11, NEt_3, C_6H_6 or CH_2Cl_2, reflux, 12h. ii) LiOH, THF-H_2O,60min, r.t. iii) $Pb(OAc)_4$, pyridine, C_6H_6, 50°C, 30min. iv) $Me_3SiOCH_2CO_2SiMe_3$, $TfOSiMe_3$cat., CH_2Cl_2, r.t., 1.5h. then, H_3O^+.

At this stage, we examined the conversion of these 4-acetoxyazetidin-2-ones to suitable β-lactam building-blocks. For example, the β-lactam **22**, obtained in 76%yield by reaction between **20** and trimethylsilyl trimethylsilyloxyacetate (1:2.5 molar ratio) under trimethylsilyl triflate as catalyst[15], was subjected to tributyltin hydride reduction to afford **25** in 73% yield. Compound **25** was esterified and further treated with benzaldehyde under tris(dimethylamino)sulphonium difluorotrimethylsiliconate (TASF) catalysis, and the resulting N-vinyl-β-lactam **26** was transformed into **27** in 70% yield as precursor of oxacephalosporins[1]. The wide utility of these N-[bis(trimethylsilyl)methyl-β-lactams can be further shown in the formation of oxacephalosporin **29** from the precursor **28** through an intramolecular Peterson type olefination. Thus, compound **23** obtained in 80% yield by treatment of **10** with trimethylsilyloxy-1-propyne (1:2.5 molar ratio) under trimethylsilyl triflate catalyst, was subjected to hydration[16] with mercuric oxide in acetone-water to afford **28** in 70% yield. Alternatively, **15** upon treatment with trimethylsilyloxy 2-methyl-1-phenyl propene, under the same conditions as above, gave **24** as a syrup, which was directly subjected to low temperature ozonolysis, to afford **28** in 40% overall yield. As expected, in all cases the substitution reaction of the acetoxy group occurs stereospecifically leading to the corresponding alkoxy compounds as single *trans* isomers.



Scheme 4. Reagents and Conditions. i) N,O-bis(trimethylsilyl)acetamide (BSA), Me_3SiCl cat. 30min, r.t., CH_2Cl_2, then, n-Bu_3SnH, AIBN cat., toluene, reflux. ii) $PhCH_2Br$, NEt_3, CH_3CN, r.t., 6h. iii) PhCHO(5equiv.), TASF cat., THF, r.t., 60min. iv) ref. 9, v) HgO, H_2O-Me_2CO, H_2SO_4cat, reflux, 10min vi) TASF, THF, reflux, 1.5hr

Compound **28** was then subjected to treatment with TASF in boiling tetrahydrofuran to furnish the bicyclic compound **29**[17] in 28% overall yield from **10**[18]. Attempted intramolecular cyclization of **28** to **29** under usual Peterson reaction conditions, by using either lithium diisopropylamide or n-butyllithium, was unfruitful. Particularly noteworthy is that this type of intramolecular alkenation represents the first example of a regioselective generation of a carbanion through a modified Peterson methodology[19].

In conclusion, the presently described synthesis constitutes a tactically new approach for the construction of bicyclic β-lactam compounds, which may be readily extended to further applications in heterocyclic chemistry. Such extensions are now underway in our laboratory and we wish to report our results in due course.

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(Received in UK 5 February 1990)