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The Oxidation Induced Rearrangement of Carbapenems to Carbacephams

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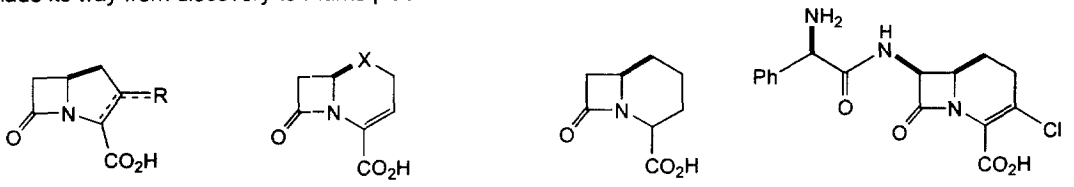
Abstract: *Upon dihydroxylation, carbapenems with an exocyclic vinyl sulfone at C-2 were found to rearrange to 2-keto-3-hydroxy carbacephams. These products could then be converted into the corresponding carbacephems.*

Cephalosporins **2** are unquestionably among the most important therapeutic antibacterial agents on the market. Amazingly, even with three to four generations of cephalosporins in use, research in this area continues. Over the past few years, the literature has indicated a growing interest in a closely related area - the preparation and biological evaluation of the structurally analogous carba-cephalosporins (carbacephems) **3**.[1] While this structural type has not yet been isolated from natural sources, certain variants have demonstrated quite respectable antibacterial profiles. One carbacephem in particular, loracarbef **5**, has made its way from discovery to marketplace.[2]



1 Carbapenem

2 X = S, Cephalosporin (cephem)
3 X = CH_2, Carbacephem

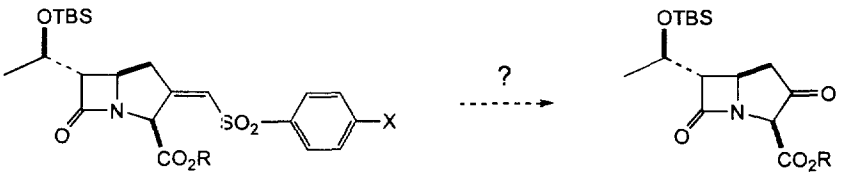
4 Carbacepham

5 Loracarbef (Lilly)

Figure 1

The methods used to assemble the carbacephem ring system are largely analogous to those used for the construction of carbapenems **1**: most involve appending a six-membered ring onto a β-lactam. The ring-forming reactions employed vary and include; carbene insertions,[3] Dieckmann reactions,[4] aldol[5] and tricarbonyl condensations,[6] and Wittig reactions.[7]

In connection with a carbapenem program, we pursued the conversion of readily available aryl sulfone bearing carbapenems **6a/b**,[8] into well-known β-keto ester carbapenem intermediate **7a/b** (**Scheme 1**).



6a R = PMB (p-methoxybenzyl), X = H
6b R = PNB (p-nitrobenzyl), X = F

7a/b

Scheme 1

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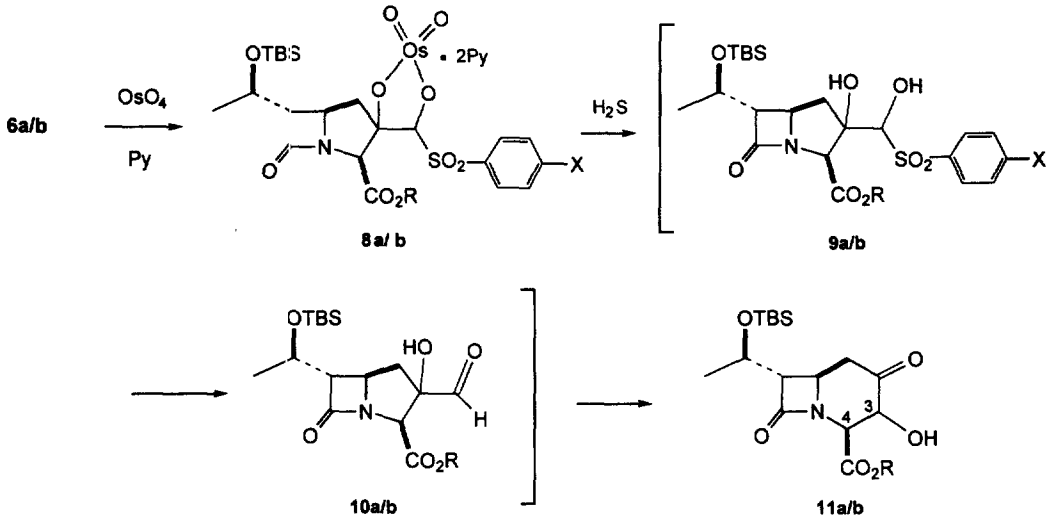
PII: S0040-4039(98)00510-3

Attempts to oxidatively cleave the exocyclic double-bond under a variety of conditions gave mainly decomposition. Eventually, osmium tetroxide, known for its ability to form stable osmate esters of electron deficient olefins, was brought to bear on this problem.

Osmylation of phenyl sulfone substrate **6a** in pyridine gave a single brown spot by thin layer chromatography; an observation consistent with the formation of an osmate ester-pyridine complex such as **8a**. While initially encouraged, subsequent reaction with hydrogen sulfide in the presence of periodate gave a compound that was neither diol **9a** nor hydroxy aldehyde **10a**.

The only isolable product proved to be the ring expanded α-hydroxy ketone **11a:** a compound considered even more interesting than the sought-after 2-ketocarbapenem. The formation of this product can be explained by rearrangement of the initially formed diol **9a** to α-hydroxy aldehyde **10a** followed by ring-expansion to **11a** (**Scheme 2**). Spectroscopic data suggested that only one stereoisomer formed at C-3.

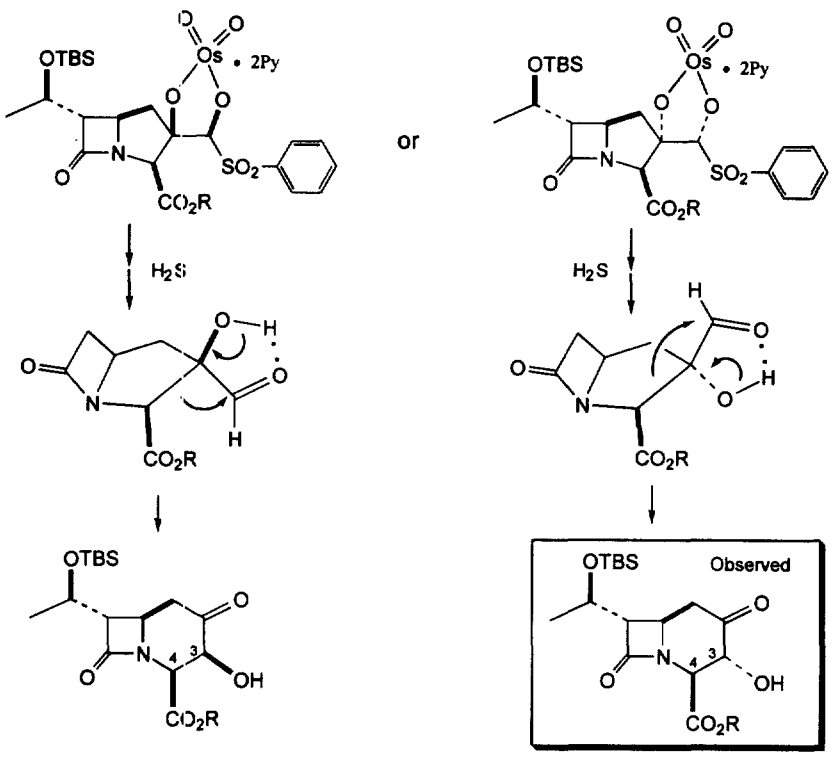


Scheme 2

The stereochemical relationship between the groups at C-3 and C-4 was deduced as *trans* from the established stereochemistry[8a] at C-4 and the large coupling constant ($J_{3,4}$ = 9.5 Hz) between protons at each of these centers. Mechanistic deconstruction of the product allows for confirmation that the oxidation took place from the anticipated, less hindered, α-face of the bicyclic ring-system (**Scheme 3**).

This result constitutes *the first example of a carbapenem being transformed into a carbacepham.* Further, the α-hydroxy ketone substitution that arises in this sequence has potential as a starting point for the elaboration of novel structural variants.

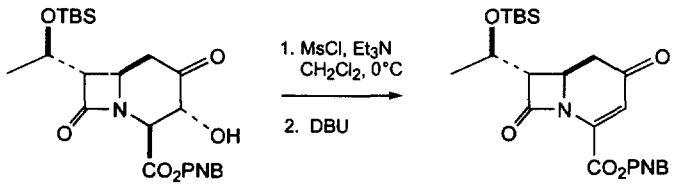
The osmylation induced rearrangement was also attempted on *p*-fluorophenyl sulfone bearing carbapenem **6b** (possessing the more practical *p*-nitrobenzyl carboxyl protecting group). The desired rearrangement occurred as anticipated to afford **11b**. Reaction condition refinements made it possible to improve the initially observed yield of carbacepham **11b** from 28% to 52%.[9]



Scheme 3

Transformations on 3-hydroxy-2-keto-carbacephams

Of particular interest was the possibility of using the C-3 hydroxyl group formed in the rearrangement as a means to introduce a double-bond between C-3 and C-4: an important structural feature associated with the traditional cephalosporins. Indeed, mesylation of **11b** and treatment with base affords the enone **12b** in 62% overall yield (**Scheme 4**):

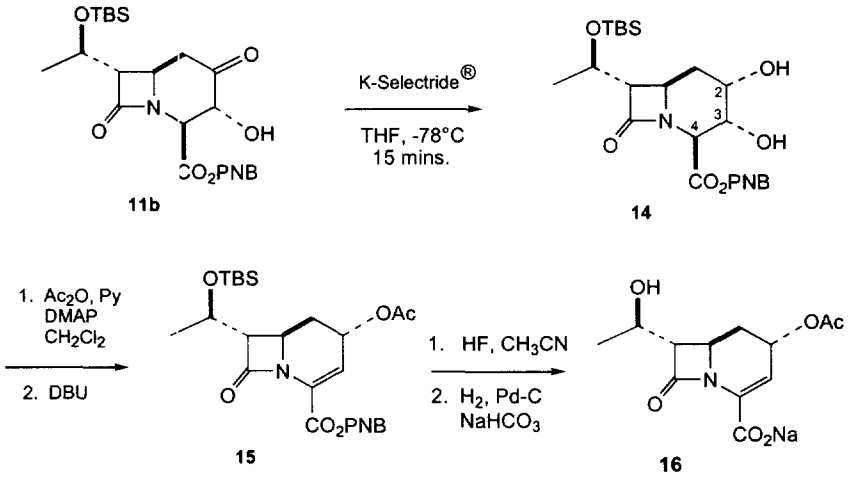


11b **12b** (62%)

Scheme 4

Hydroxy-ketone **11b** was found to undergo a number of other transformations including formation of diol **14**[10] upon reduction with two equivalents of K-selectride®. Confirmation of the structure was achieved via exhaustive acetylation (Ac_2O, Py, CH_2Cl_2, DMAP). Proton NMR coupling constants ($J_{2,3}$ = 3.1Hz) support exclusive formation of the *cis* diol.

With the diacetate of **14** in hand, it was of interest to determine whether the 3-acetoxy group could be eliminated directly to provide the 3,4 double-bond. Elimination proved to be facile as did the two step deprotection sequence used to convert compound **15**[10] into sodium salt **16**.



Scheme 5

Thus, dihydroxylation of vinyl sulfone bearing carbapenems provides access to the carbacepham ring-system. Further, the functionality that emerges is useful for double-bond (carbacephem) formation.

Acknowledgment Thanks to Dr. Carl B. Ziegler, Jr. for helpful discussions during the course of this study.

References and Notes

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8. Compounds **6a/b** are chiral as they were both derived from [3S-[3a(S*),4β]]-4-(acetoxy)-3-[1-[[1,1-(dimethylethyl)dimethylsilyl]oxy]-2-azetidinone: a) Ziegler, C. B., Jr., W. V. Curran, Feigelson, G. B., Bitha, P., Fabio, P., Strohmeyer, Short, K., Lin, Y-i. *Tetrahedron* **1994**, *50*, 12085. b) Ziegler, C. B.; Curran, W. V.; Feigelson, G. US patent 5,068,232.
9. Preparation of Compound **11b**: Sulfone **5b** (2.0 g) in 10 mls pyridine is treated with 10 mls of 10% OsO_4 in THF solution. After 70 mins., the reaction is diluted with EtOAc and stirred vigorously for one minute with sat'd $NaHSO_3$ solution. After partitioning, the organic layer is washed with water, brine, and then dried over $MgSO_4$. The crude osmate ester is dissolved in 150 mls of $CHCl_3$ and then H_2S is bubbled through for ca. one minute. After filtering through silica gel with 10% EtOAc in hexanes, the dark crystalline mass is recrystallized from THF/$CHCl_3$/hexanes. Yields: 0.824 g off-white crystals (52%). ^1H NMR ($CDCl_3$) δ 8.24 (d, 2H), 7.6 (d, 2H), 5.41 (ABq, 2H), 4.62 (m, 1H), 4.21 (m, 1H), 3.8 (d, 1H), 3.66 (br s, 1H), 2.96 (dd, 1H), 2.69 (dd, 1H), 1.2 (d, 3H).
10. **14**: ^1H NMR ($CDCl_3$) δ 7 86 (d, 2H), 7.03 (d, 2H), 5.07 (q, 2H), 4.0 (d, 1H), 4.95 (m, 1H), 3.85-3.65 (m, 3H), 2.47 (br s, 1H), 1.9 (m, 1H), 1.05 (d, 3H); **15**: ^1H NMR ($CDCl_3$) δ 8.19 (d, 2H), 7.6 (d, 2H), 6.3 (d, 1H), 5.4 (m, 1H), 5.3 (ABq, 2H), 4.23 (m, 1H), 3.73 (m, 1H), 2.3 (br d, 1H), 2.04 (s, 3H), 1.6 (dd, 1H), 1.22 (d, 3H).