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Stereoselective Synthesis of Cis-Substituted Azetidinones from Penicillin: a Formal Total Synthesis of Loracarbef[1]

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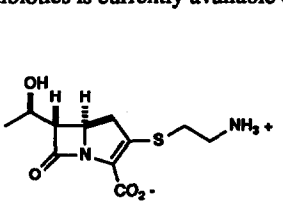
Abstract: A new method for the synthesis of chiral azetidinones bearing a carbon-carbon bond at the 4-position is described. The preparation involves a stereoselective alkylation-reduction of a silylated 4-phenylsulfonyl azetidinone. The utility of this method was demonstrated by a formal total synthesis of loracarbef.

Due to the clinical utility of non-classical β-lactam structures such as the carbapenems (thienamycin 1[2]), monobactams (azetreonam 2[3]), and carbacephems (loracarbef 3[4]), much attention has been focused on the development of economically practical, large-scale syntheses of these derivatives. In particular, the carbacephem class of antibiotics is currently available only via total synthesis.[5]



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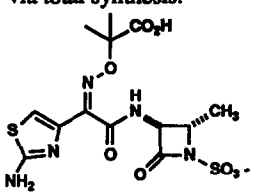

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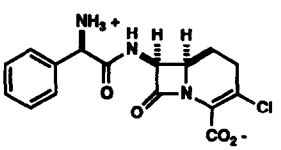


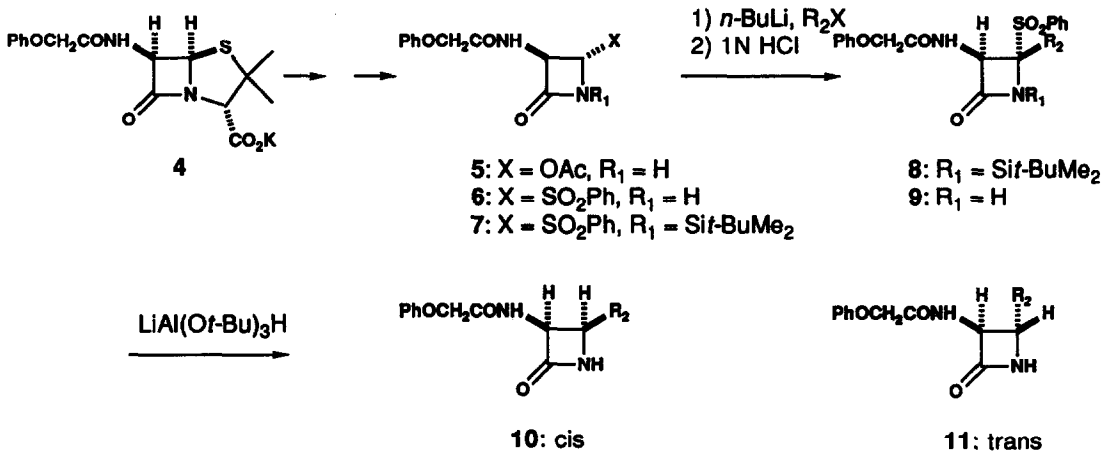
3

A particularly attractive approach to the large scale preparation of these antibiotics involves the use of the fermentation-derived penicillin nucleus as a starting material. This approach has the advantage of beginning with an inexpensive, readily-available starting material which contains a preformed β-lactam ring having the correct absolute configuration necessary for biological activity. A key element of this approach has been the development of carbon-carbon bond forming reactions at the 5-position of the penicillin nucleus. One of the more formidable challenges in this area relates to control of the relative configuration of the resulting two sp^3 hybridized carbons contained within the azetidinone ring. This issue is especially important for the synthesis of amido-substituted bicyclic systems as the biological activity of these substances is strictly dependent upon the stereochemistry of these two centers. While a number of methods for direct carbon-carbon bond formation of azetidinone dervivatives have been reported,[6] to our knowledge no general method for the preparation of cis-substituted derivatives from penicillin has been disclosed.[7]

We report herein a new alkylation/reduction sequence for cis-stereoselective carbon-carbon bond formation at the 5-position of the penicillin nucleus. This sequence provides a general method for the preparation of cis-substituted azetidinones from penicillin precursors and has been applied to a formal total synthesis of loracarbef.

The synthetic sequence (outlined in Scheme 1) commenced with the conversion of the commercially available potassium salt of penicillin-V (**4**) to the acetoxyazetidinone **5** utilizing known methodology.[8] Displacement with sodium phenylsulfinate (DMF, RT, 81%) afforded the sulfonyl derivative **6**.[9] The silyl-protected sulfone derivative **7** (TBDMSCl, DIPEA, THF, 77%) served as a general alkylation substrate for carbon-carbon bond introduction. Alkylation of this derivative was accomplished by dianion formation with 2.5 equivalents of *n*-butyllithium (THF, -78 °C), followed by addition of a slight excess of alkylating agent (1.1 to 2.0 equivalents, -23 °C) to afford the alkylation products **8**. The alkylation was highly stereoselective for the beta-alkylated products shown.[10,11] Reductive removal of the phenyl sufonyl moiety was accomplished in two steps. The silyl protecting group was removed with 1N aqueous hydrochloric acid in tetrahydrofuran at room temperature. The desilylated derivatives **9** could be purified by recrystallization or trituration, or used directly in the next step without purification. Replacement of the sulfone group by hydrogen was accomplished with high preference for the cis (**10**) versus trans (**11**) products by treatment lithium tri-*tert*-butoxyaluminohydride in tetrahydrofuran at 0 °C (Table 1).[12]

Scheme 1



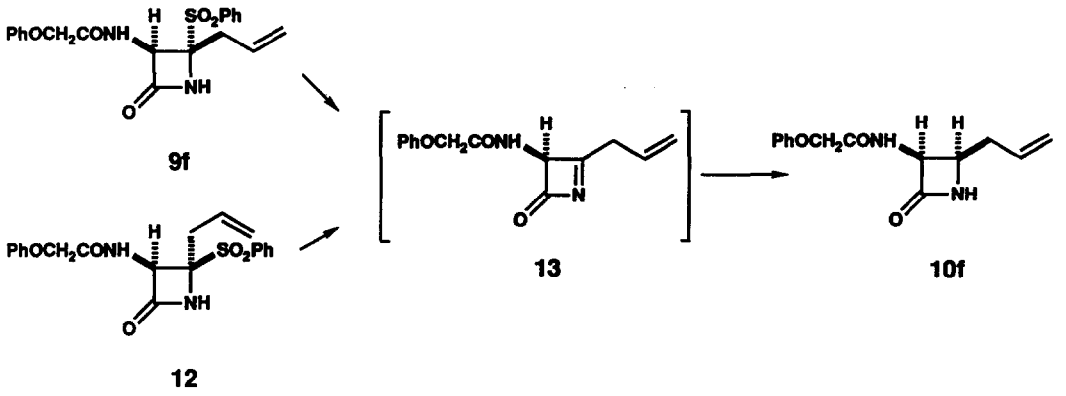
A plausible mechanism for the above sequence would involve azetidinone nitrogen-assisted elimination of the phenyl sulfone moiety to afford an acylimine species such as **13**, followed by hydride delivery from the least sterically hindered alpha-face. Evidence for such a mechanism is given by the fact that independent reduction of either **9f** or **12** under identical conditions provided the identical cis isomer **10f** in 51% and 61% yields, respectively (Scheme 2). The utility of this methodology was further demonstrated by a formal total synthesis of the carbacephalosporin antibiotic, loracarbef (Scheme 3). The butenyl derivative **10g** was oxidized under Krapcho conditions[13] ($KMnO_4$, HOAc, acetone/H_2O, 70%) to afford the carboxylic acid derivative **14**,[14] which has previously been converted to loracarbef.[5d]

In summary, we have developed a general method for the cis-stereoselective replacement of the carbon-sulfur bond of penicillin with a carbon-carbon bond while preserving the chirality of the amide-bearing azetidinone carbon. Application of this methodology to other antibiotic targets is currently under investigation.

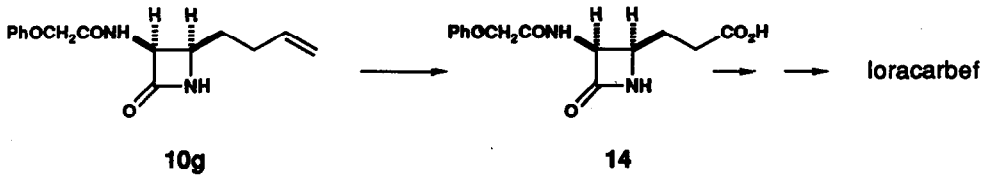
Table 1

Alkylating agent	Yield of Alkylation Product 8	cis 10 /trans 11	Yield of Reduction Product 10 from 8 (R_2 =)
a) CH_3I	69%	92/8	CH_3- (53%)
b) $PhCH_2Br$	57%	89/11	$PhCH_2$- (41%)
c) $nC_{12}H_{25}Br$	65%	93/7	$nC_{12}H_{25}$- (74%)
d) FCH_2CH_2Br	45%	91/9	FCH_2CH_2- (56%)
e) $MeOCH_2CH_2Br$	57%	93/7	$MeOCH_2CH_2$- (68%)
f) CH_2=$CHCH_2Br$	58%	91/9	CH_2=$CHCH_2$- (36%)
g) CH_2=$CHCH_2CH_2Br$	47%	94/6	CH_2=$CHCH_2CH_2$- (78%)
h) CH_2=$CHCH_2CH_2CH_2Br$	68%	93/7	CH_2=$CHCH_2CH_2CH_2$- (57%)
i) Me_3SiCl	23%	>95/5	Me_3Si- (11%)

Scheme 2



Scheme 3



Acknowledgements. We thank the physical chemistry department for providing analytical and spectral data. We gratefully acknowledge Bennie Foster for the large-scale preparation of compound **7**. We are also grateful to process research and development for the preparation of kilogram quantities of acetoxyazetidinone intermediate **5** and an authentic sample of chiral acid **14**.

References and notes

† deceased

1. This paper is dedicated to the memory of David A. Hall.

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6. a) For a review, see: Kametani, T.; Fukumoto, K.; Ihara, M. *Heterocycles*, **1982**, *17*, 463. See also: b) Kametani, T.; Nakayama, A.; Itoh, A.; Honda, T. *Heterocycles*, **1983**, *20*, 2355; c) Fujimoto, K.; Iwano, Y.; Hirai, K. *Bull. Chem. Soc. Jpn.*, **1986**, *59*, 1363, and references cited therein; d) Fliri, H.; Mak, C.-P. *J. Org. Chem.*, **1985**, *50*, 3438, and references cited therein; e) Blaszczak, L. C.; Armour, H. K.; Halligan, N. G. *Tetrahedron Lett.*, **1990**, *31*, 5693.

7. A preliminary account of this work was given at the 201st National Meeting of the American Chemical Society, Atlanta, GA, April 1991.

8. Blaszczak, L. C. U.S. Patent No. 4,771,135, 1988.

9. Clauβ, K.; Grimm, D.; Prossel, G. *Liebigs Ann. Chem.*, **1974**, 539.

10. The relative stereochemistry of the alkylation product **8g** was unequivocally established by x-ray crystallography.

11. Due to the complexity of the reaction mixtures, the major product of the alkylation reaction (the beta-product) was normally the only product isolated. However, in the case of **8f**, a minor amount (< 5%) of the alpha product **12** was isolated.

12. Sodium borohydride has been used to reduce acetoxyazetidinones; Pfaendler, H. R.; Hoppe, H. *Heterocycles*, **1985**, *23*, 265.

13. Krapcho, A. P.; Larson, J. R.; Eldridge, J. M. *J. Org. Chem.*, **1977**, *42*, 3749.

14. For **14**: ^{1}H NMR: (300 MHz, $(CH_3)_2SO$-d_6) δ 12.15 (br s, 1H), 8.92 (d, J = 8 Hz, 1H), 8.38 (s, 1H), 7.3 (m, 2H), 6.92 (m, 3H), 5.08 (dd, J = 8, 4 Hz, 1H), 4.57 (ABq, 2H), 3.64 (m, 1H), 2.2 (m, 2H), 1.65 (m, 2H). IR: (KBr) 3321, 1744, 1715, 1665, 1533, 1489, 1235, 1193, and 1181 cm^{-1}. OR: (DMSO) +205.5 degrees @ 365 nm (for authentic **14**, OR: (DMSO) +238.4 degrees @ 365 nm). Anal: ($C_{14}H_{16}N_2O_5$) C, H, N.

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