EtOH) [natural:[8] mp 124-125 °C, $[\alpha]^{22.5}_D$ -92° (EtOH)], in 84% overall yield. This route constitutes the first enantiocontrolled synthesis of the natural product.

On the other hand, oxidation of the lactol **14** by silver carbonate on Celite[9] gave the lactone **17**, $[\alpha]^{32}_D$ -69.9° (*c* 0.30, $CHCl_3$), in 88% yield, which was transformed into lactam **18**, $[\alpha]^{31}_D$ -72.4° (*c* 1.47, $CHCl_3$), in 76% yield on heating at 180 °C with aqueous methylamine in a sealed tube. Upon exposure to diisobutylaluminum hydride at -78 °C followed by lithium aluminum hydride in refluxing THF, 18 furnished (-)-esermethole[1,10] (**21**), $[\alpha]^{34}_D$ -134° (*c* 0.41, benzene) [lit.[3a] $[\alpha]_D$ -129° (*c* 0.33, benzene)], directly in 34% yield, presumably via the carbinolamines **19** and **20**. Since **21** has previously been transformed into natural (-)-physostigmine (**2**) in two steps[3a] via (-)-eseroline (**22**),[1,2] this sequence constitutes a formal synthesis of the natural product.

Acknowledgment. We are grateful to Professors Keiichiro Fukumoto and Kozo Shishido for a sample of physovenine.

(8) Robinson, B. *J. Chem. Soc.* **1964**, 1503.
(9) Fetizon, M.; Golfier, M.; Louis, J.-M. *Tetrahedron* **1975**, *31*, 171.
(10) Enantiomeric excess was determined to be ≥98% by HPLC [CHIRACEL OJ, ^{i}PrOH-hexane (1:9)]. Spectral data (IR, ^{1}H NMR, and MS) and TLC were identical with those of an authentic material.[3a,b]

Supplementary Material Available: Experimental details and spectroscopic data (IR and ^{1}H NMR) for compounds **1**, **4**, **7-10**, **15**, **17**, **18**, and **21** (6 pages). Ordering information is given on any current masthead page.

Articles

β-Lactams from Ester Enolates and Silylimines: Enantioselective Synthesis of the *trans*-Carbapenem Antibiotics (+)-PS-5 and (+)-PS-6

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A new synthetic route to the antibiotics (+)-PS-5 and (+)-PS-6 is described. The preparation involves a fully stereocontrolled reaction between the enantiomerically pure *N*-trimethylsilylimine of lactic or mandelic aldehyde and the lithium enolate of the *tert*-butyl butanoate or *tert*-butyl isovalerate, respectively. Conversion of the azetidinones obtained to 4-acetoxy derivatives via oxidative cleavage of the hydroxyethyl or hydroxybenzyl side chain and introduction of the necessary appendage in the position 4 of the azetidinone ring, followed by assemblage of the bicyclic ring system, afforded the natural *trans*-carbapenems (+)-PS-5 and (+)-PS-6.

Introduction

The control of absolute stereochemistry is a central problem in the synthesis of biologically significant enantiomers of natural products. Of the large volume of literature on the synthesis of enantiomerically pure 3- and 4-disubstituted azetidin-2-ones as well as their corresponding bicyclic derivatives, the approach that leads to products of high enantiomeric purity either involves the use of an enantiomerically pure auxiliary, which is subsequently cleaved, or of an enantiomerically pure building block, which is retained in the target compound.[1]

The cycloaddition reaction of ester enolates with aldimines has proved to be an effective method for preparing β-lactams.[2] Recently, in fact, we and others[3] have demonstrated the synthetic usefulness of this reaction in the synthesis of thienamycin, using (*S*)-ethyl 3-hydroxybutanoate as the chiral nucleophilic component in the cycloaddition[4] (Chart I). However, there are some β-lactam antibiotics bearing no stereogenic centres in the C-3 side chain of the azetidinone ring. For instance, the carbapenems (+)-PS-5 and (+)-PS-6 have an ethyl and isopropyl group, respectively, in this position. In these case,[5] in order to prepare enantiomerically pure compounds, the asymmetry can be incorporated in the electrophilic partner

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(1) (a) Liebeskind, L. S.; Welker, M. E.; Goedken, V. *J. Am. Chem. Soc.* **1984**, *106*, 441. (b) Liebeskind, L. S.; Welker, M. E.; Fengl, R. W. *J. Am. Chem. Soc.* **1986**, *108*, 6328. (c) Hart, D. J.; Lee, C. S.; Pirkle, M. H.; Hyon, M. H.; Tsipouras, A. *J. Am. Chem. Soc.* **1986**, *108*, 6054. (d) Furukawa, M.; Okawara, T.; Noguchi, Y.; Terawaki, Y. *Chem. Pharm. Bull.* **1978**, *26*, 260. (e) Broadley, K.; Davies, S. G. *Tetrahedron Lett.* **1984**, 1743. (f) Evans, D. E.; Sjogren, E. B. *Tetrahedron Lett.* **1986**, 3119. For recent reviews on the synthesis of carbapenem β-lactam antibiotics, see: (g) Durckheimer, W.; Blumbach, J.; Lattrell, R.; Scheunemann, K. H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 180. (h) Koppel, G. A. In *Small ring Heterocycles - Azetidines, β-lactams, Diazetidine and Diaziridines*; Hassner, A., Ed.; John Wiley: New York, 1983; Part 2, pp 248-301. (i) Nagara, T.; Kametani, T. *Heterocycles* **1987**, *25*, 729. (j) Labia, R.; Morin, C. *J. Antibiot.* **1984**, *37*, 1103. (k) Ratcliffe, R. W.; Albers-Schonberg, G. In *Chemistry and Biology of Beta Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic Press; New York, 1982; Vol. 2.

(2) For an excellent review on this topic, see: Hart, D. J.; Ha, D. C. *Chem. Rev.* **1989**, *89*, 1447. See also: Brown, M. J. *Heterocycles* **1989**, *29*, 2225.

(3) (a) Cainelli, G.; Panunzio, M. *Il Farmaco.* **1991**, *46*, 177. (b) Cainelli, G.; Contento, M.; Giacomini, D.; Panunzio, M. *Tetrahedron Lett.* **1985**, *26*, 937. (c) Cainelli, G.; Panunzio, M.; Basile, T.; Bongini, A.; Giacomini, D.; Martelli, G. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2637. (d) Georg, G. I.; Akgun, E. *Tetrahedron Lett.* **1990**, *31*, 3276. (e) Guanti, G.; Narisano, E.; Banfi, L. *Tetrahedron Lett.* **1987**, *28*, 4335. (f) Iimori, T.; Shibasaki, M. *Tetrahedron Lett.* **1985**, *26*, 1523. (g) Chiba, T.; Nakai, T. *Tetrahedron Lett.* **1985**, *26*, 4647. (h) Chiba, T.; Nagatsuma, M.; Nakai, T. *Chem. Lett.* **1985**, 1343.

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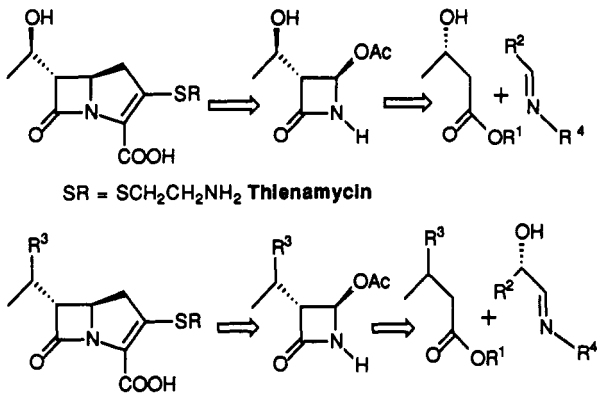
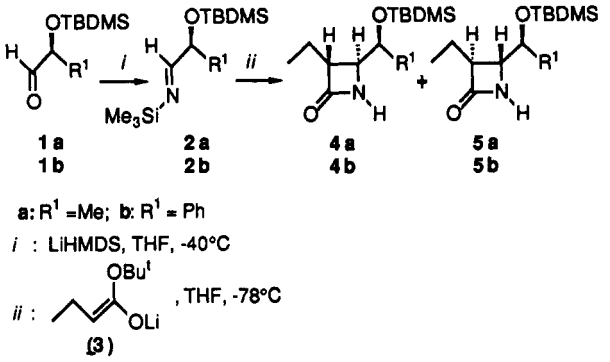
Chart I



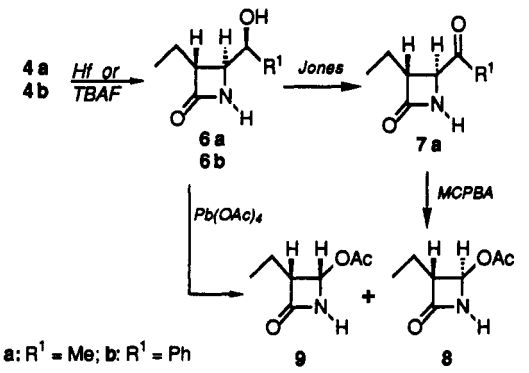
Scheme I



of the cycloaddition reaction using a chiral imine (Chart I).

Chiral imines can be, in principle, obtained starting from chiral aldehydes[6] or from chiral amines.[7] Obviously, the closer the inducing stereocenter is to the reaction site, the better the stereocontrol is expected to be. Imines obtained from protected α-hydroxy aldehydes appear to be especially useful. The hydroxy group thus incorporated into the C-4 side chain of the azetidinone ring is available for further transformations, which allow the introduction of the necessary ring appendage for the bicyclic annelation.

Scheme II



In a preliminary communication,[8] we have recently demonstrated the usefulness of this approach, using the *N*-(trimethylsilyl)imine of (*S*)-lactaldehyde for the preparation of the natural carbapenem (+)-PS-5. In this paper we wish to report further developments of our strategy and its application to the synthesis of (+)-PS-5 and (+)-PS-6.

Synthesis of (+)-PS-5

Our synthesis of this carbapenem starts from the (*S*)-lactaldehyde **1a** protected as the *tert*-butyldimethylsilyl ether.[9] Treatment of **1a** with 1 equiv of lithium hexamethyldisilylamide (LiHMDS) in THF at −40 °C gave the *N*-(trimethylsilyl)imine **2a**. No racemization could be detected during this reaction.[10] Treatment, in situ, of the imine **2a** at −78 °C with 1 equiv of lithium *tert*-butyl butanoate (**3**), obtained by metalation of the corresponding ester[11] with 1 equiv of LDA, affords the β-lactams **4a** and **5a** in 61% yield and 96:4 ratio (Scheme I).

The trans relationship of the C_3H and C_4H in **4a** and **5a** has been established by their ^1H NMR coupling constants of 2.5 Hz, consistent with the assigned trans configuration.[12] Moreover, the absolute configuration of the predominant isomer **4a**, has been determined by completing a formal total synthesis of (+)-PS-5.

For this purpose we next turned to converting the 4-hydroxyethyl substituent into an acetic acid residue, a group that has proved to be quite versatile in carbapenem synthesis since various types of carbon chains required to construct the five-membered ring fused with the β-lactam

(4) For a recent review on thienamycin synthesis, see: Georg, G. I. In *Studies in Natural Product Chemistry*, Vol. 4; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1989; p 431.

(5) For reading review, see: Palomo, C. In *Recent Progress in the Chemical Synthesis of Antibiotics*; Verlag: Berlin, 1990; p 565. See also: (a) ref 1c. (b) Georg, G. I.; Kant, J. *J. Org. Chem.* **1988**, *53*, 692. (c) Corbett, F. D.; Eglington, J. A. *J. Chem. Soc., Chem. Commun.* **1980**, 1083. (d) Palomo, C.; Cossio, F. P.; Arrieta, A.; Odriozola, J. M.; Oiarbide, M.; Ontoria, M. J. *J. Org. Chem.* **1989**, *54*, 5736. (e) Bateson, J. H.; Hickling, R. I.; Smale, T. C.; Southgate, R. *J. Chem. Soc. Perkin Trans. 1* **1990**, 1793. (f) Manhas, M. S.; Ghosh, M.; Bose, A. K. *J. Org. Chem.* **1990**, *55*, 575. (g) Kametani, T.; Honda, T.; Nakayama, A.; Sasakai, Y.; Mochizuki, T.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2228. (h) Hart, D. J.; Ha, D.-C. *J. Antibiot.* **1987**, *40*, 309. (i) Chiba, T.; Nakai, T. *Chem. Lett.* **1987**, 2187. (j) Wasserman, H. H.; Han, W. T. *Tetrahedron Lett.* **1984**, *25*, 3747. (k) Okano, K.; Izawa, T.; Ohno, M. *Tetrahedron Lett.* **1983**, *24*, 217. (l) Hatanaka, M.; Nitta, H.; Ishimaru, T. *Tetrahedron Lett.* **1984**, *25*, 2387. (m) Cecchi, R.; Consonni, P.; Depaoli, A.; Favara, D.; Omodei-Salè, A. *Gazz. Chim. Ital.* **1984**, *114*, 225. (n) Bateson, J. H.; Hickling, R. I.; Roberts, P. M.; Smale, T. C.; Southgate, R. *J. Chem. Soc., Chem. Commun.* **1980**, 1084. (o) Hsiao, C.-N.; Ashburn, S. P.; Miller, M. J. *Tetrahedron Lett.* **1985**, *26*, 4855. (p) Koskinen, A. M. P.; Ghiaci, M. *Tetrahedron Lett.* **1990**, *31*, 3209. (q) Tanner, D.; Somfai, P. *Tetrahedron* **1988**, *44*, 619. (r) Favara, D.; Omodei-Salè, A.; Consonni, P.; Depaoli, A. *Tetrahedron Lett.* **1982**, *23*, 3105. (s) See ref 1f.

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(7) (a) Ojima, I.; Inaba, S. *Tetrahedron Lett.* **1980**, *21*, 2077; (b) 2081. (c) Yamamoto, Y.; Nishii, S.; Maruyama, K.; Komatsu, T.; Ito, W. *J. Am. Chem. Soc.* **1986**, *108*, 7777. (d) Yamamoto, Y.; Ito, W. *Tetrahedron* **1988**, *44*, 5415. (e) Takahashi, H.; Suzuki, Y.; Inagaki, H. *Chem. Pharm. Bull.* **1982**, *30*, 3160. (f) Suzuki, Y.; Takahashi, H. *Chem. Pharm. Bull* **1983**, *31*, 1659. (g) Takahashi, H.; Chida, Y.; Suzuki, T.; Yanara, S.; Suzuki, Y.; Masuda, C. *Chem. Pharm. Bull* **1983**, *31*, 1659. (h) Takahashi, H.; Suzuki, Y.; Hori, T. *Chem. Pharm. Bull.* **1983**, *31*, 2183.

(8) Gainelli, G.; Panunzio, M.; Giacomini, D.; Martelli, G.; Spunta, G. *J. Am. Chem. Soc.* **1988**, *110*, 6879.

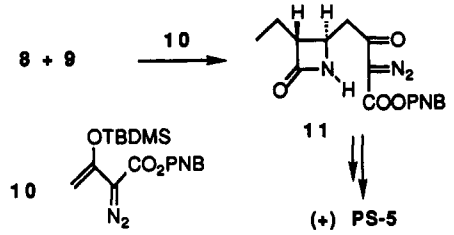
(9) Hirama, M.; Nishizaki, I.; Shigemoto, T.; Ito, S. I. *J. Chem. Soc., Chem. Commun.* **1986**, 393.

(10) The imine **2a** was decomposed at −40 °C to give the (*S*)-lactaldehyde **1a** presenting spectral data (IR, ^1H NMR, and $[\alpha]_D$) identical with those of the authentic sample.

(11) Kaiser, E. M.; Woodruff, R. A. *J. Org. Chem.* **1970**, *35*, 1198.

(12) (a) Bouffard, F. A.; Christensen, B. G. *J. Org. Chem.* **1981**, *46*, 2208. (b) Bouffard, F. A.; Johnston, D. B. R.; Christensen, B. G. *J. Org. Chem.* **1980**, *45*, 1130.

Scheme III



can be readily introduced at position 4 by its substitution with different nucleophiles.[13]

Two different methods for converting **4a** into acetoxy derivative 8 were studied (Scheme II). In the first method, treatment of **4a** with aqueous hydrogen fluoride in acetonitrile[14] gave the alcohol **6a**, which, upon oxidation by chromic acid in ether/water,[15] afforded the methyl ketone **7a** in 76% overall yield. Bayer–Villiger oxidation of this ketone with *m*-chloroperbenzoic acid afforded the expected *trans*-acetoxy derivative 8 in 72% yield as single isomer. Alternatively, direct oxidation of the side chain to the acetoxy derivative has been performed by heating **6a** with lead tetraacetate in benzene at reflux.[16] This fragmentation reaction lacks stereospecificity since a 30/70 cis/trans mixture of 8 and 9 is obtained in 61% yield. This second alternative appears to be more valuable since the lack of stereoselectivity of the fragmentation reaction is unimportant because the C_4 stereocenter completely equilibrated to the trans isomer in the next step of the synthesis.

We have found that better yields and, most notably, complete stereoselectivity could be obtained starting from mandelic aldehyde **1b** with the hydroxy functionality protected as silyl ether. The preparation of the corresponding *N*-(trimethylsilyl)imine **2b** was achieved by reduction of (*S*)-ethyl [(*tert*-butyldimethylsilyl)oxy]-mandelate with 1 equiv of diisobutylaluminum hydride (DIBAH) (89% yield) and subsequent elaboration of the aldehyde thus obtained following the previously described protocol. The imine **2b**, upon treatment with 1 equiv of the lithium *tert*-butylbutanoate, gave the β-lactam **4b** in 84% yield as single isomer. No traces of the trans diastereoisomer **5b** or the cis isomers could be detected (HPLC and 200-MHz ^1H and ^{13}C NMR spectra). Taking into account the previous results, we next converted this

Chart II

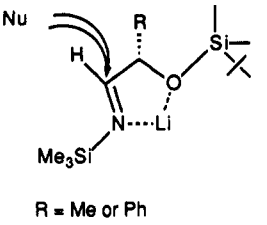


Chart III

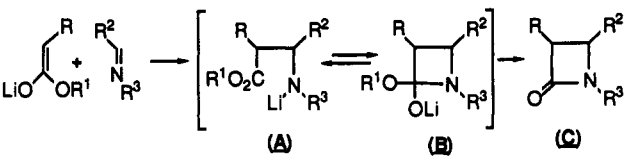
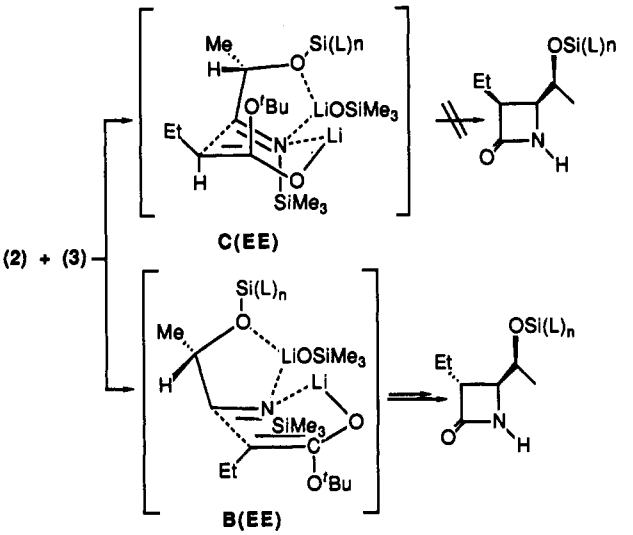


Chart IV



compound to the 4-acetoxy derivatives 8 and 9 in a 30/70 ratio and 63% overall yield by sequential treatment of **4b** with tetrabutylammonium fluoride and lead tetraacetate. The azetidinones 8 and 9 thus obtained were identical in all respect with those arising from lactaldehyde (Scheme II).

Since these azetidinones have already been converted into the carbapenem (+)-PS-5 via introduction of the correct side chain followed by rhodium acetate mediated ring closure, this synthesis constitutes a formal total synthesis of (+)-PS-5 (Scheme III).[5r]

With regard to the stereochemistry, the condensation leads in all cases to a total trans diastereoselection in C_3–C_4 bond formation and a to very high degree of C_4–$C_{4'}$ diastereoselection with the *N*-(trimethylsilyl)imine of the lactaldehyde, whereas a complete diastereoselectivity is observed when mandelic aldehyde is used.

The excellent 1,2-like induction[17] at the C_4 stereocenter may be explained by assuming a coplanarity between the oxygen and the nitrogen of the imine due to the chelating effect of the lithium cations present in the reaction medium. The enolate would then attack from the less hindered face of the diastereotopic plane of the imine group (Chart II).

The formation of the β-lactam ring from an ester enolate and an imine is generally assumed to be multistage. In

(13) For comprehensive reviews on the use of the 4-acetoxyazetidinone in the synthesis of β-lactam antibiotics, see: (a) Kametani, T.; Fukumoto, K.; Ihara, M. *Heterocycles* **1982**, *17*, 463. (b) Reference 1i. (c) Davies, D. E.; Storr, R. C. In *Comprehensive Heterocyclic Chemistry*; Lwowski, W., Ed.; Pergamon: New York, 1984; Vol. 7, p 237. (d) Nagao, Y. In *Perspective in the Organic Chemistry of Sulfur*; Zwanenburg, B., Klunder, A. J. H., Eds.; Elsevier: New York, 1987; p 57. For the synthesis of thienamycin, see: (e) Reider, P. J.; Grabowski, E. J. J. *Tetrahedron Lett.* **1982**, *23*, 2293. (f) Karaday, S.; Amato, J. S.; Reamer, R. A.; Weinstock, L. M. *J. Am. Chem. Soc.* **1981**, *103*, 6765. (g) Attrill, R. P.; Barrett, A. G. M.; Quayle, P.; Van der Westhuizen, J. *J. Org. Chem.* **1984**, *49*, 1679. (h) Ueda, Y.; Roberge, G.; Vinet, V. *Can. J. Chem.* **1984**, *62*, 2936. For the synthesis of β-methylcarbapenems, see: (i) Kim, C. U.; Luh, B.; Partyka, R. A. *Tetrahedron Lett.* **1987**, *28*, 507. (j) Shirai, F.; Nakai, T. *J. Org. Chem.* **1987**, *52*, 5492. (k) Endo, M.; Droghini, R. *Can. J. Chem.* **1988**, *66*, 1400. For the synthesis of penems, see: (m) Miyadera, T. *J. Synth. Org. Chem. Jpn.* **1983**, *41*, 1168. (n) Alpeggiani, M.; Battistini, C.; Bedeschi, A.; Franceschi, G.; Perrone, E.; Zarini, F. *Pure Appl. Chem.* **1987**, *59*, 467. (o) Sheppard, A.; Miller, M. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2519.

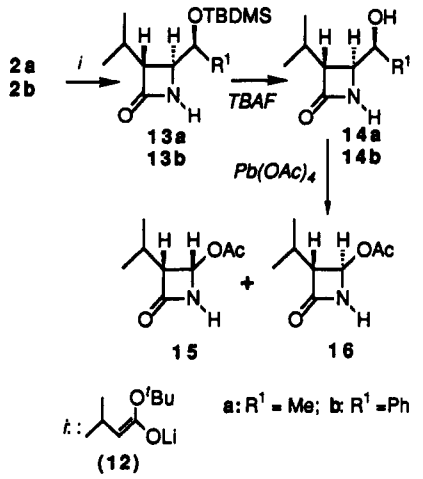
(14) Newton, R. F.; Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, 3981.

(15) Brown, H. C.; Garg, P. C.; Liu, K. T. *J. Org. Chem.* **1971**, *36*, 387. For general review, see: *Chromium Oxidations in Organic Chemistry*; Cainelli, G., Cardillo, G., Eds.; Springer: Berlin, 1984.

(16) Amorosa, M.; Caglioti, L.; Cainelli, G.; Immer, H.; Keller, J.; Werli, H.; Mihailovic, M. L.; Schaffner, K.; Arigoni, D.; Jeger, O. *Helv. Chim. Acta* **1962**, *45*, 2674.

(17) Seebach, D.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 654.

Scheme IV



the first step the addition of the enolate to the imine gives rise to an acyclic amino ester intermediate (A) in equilibrium with the corresponding four-membered cyclic structure B. Elimination of the alkoxy group from the cyclic species furnishes the end product C (Chart III).

In our case a very interesting feature of the cycloaddition reaction is the trans diastereoselectivity observed in the formation of the C_3–C_4 bond. Recent studies from our and other research groups on the ester enolate–aldimine cycloaddition show that a predominant cis diastereoselectivity is observed when the α-imine substituent is not sterically demanding, whereas when a bulky branched substituent is present in the α-position of the azomethine carbon, trans diastereoselectivity became predominant.

Ample literature suggests that treatment of esters with LDA affords the *E* enolate[18] and that the imine should exist predominantly as the trans geometric isomer.[1c] Moreover, we can assume that under the conditions used, the reaction proceeds under kinetic control.[3c] Keeping fixed the structure of the imine and of the enolate and using the Evans transition-state descriptors,[19] two possible transition-state models, chair-like transition state C(EE) and boat-like transition state B(EE), can be invoked to rationalize the stereochemical outcome of the cycloaddition[20] (Chart IV).

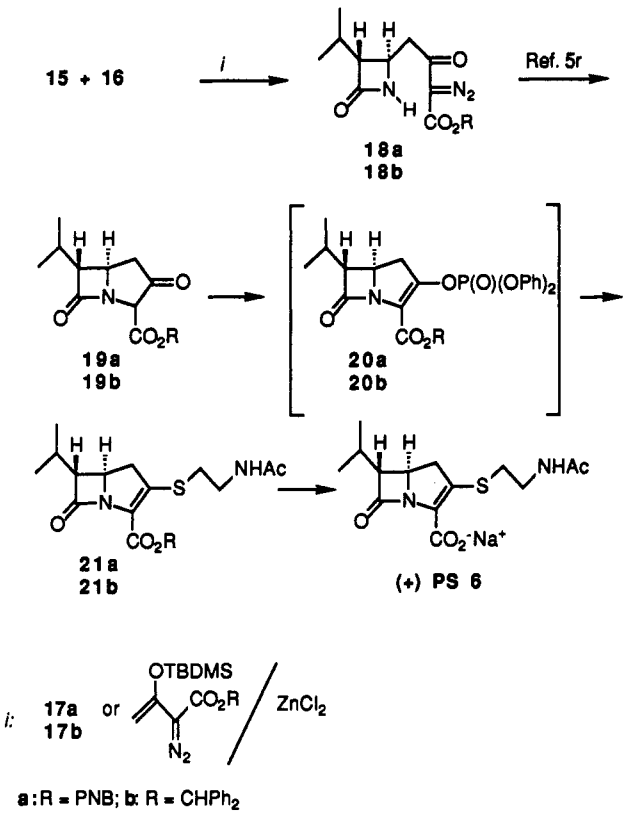
In the chair-like transition state C(EE), leading to the cis β-lactam, an important 1:3 diaxial nonbonded interaction between the *tert*-butoxy group of the enolate and the imine side chain can be observed. In the boat-like transition state B(EE), leading to the trans β-lactam, the *tert*-butoxy group and the imine substituent are remote from each other. Moreover the 1:4 apical interaction between the *tert*-butoxy group of the ester and the trimethylsilyl group appears to be of moderate degree since the two groups are far away because of the N–Si bond length. All these speculations suggest that the boat-like transition state B(EE) corresponds to the lowest energy and leads to the formation of the *trans*-azetidinones **4a** and **5a**.

(18) (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. (b) Heathcook, C.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066. (c) Seebach, D.; Amstutz, R.; Lanbe, T.; Schweizer, B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1985**, *107*, 5403.

(19) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Topics in Stereochemistry*; Allinger, N. L., Eliel, E. L., Wilm, S. H., Eds.; Wiley: New York, 1982; Vol. 13, pp 1–117.

(20) The nitrogen long pair coordinates the two lithium cations arising from the preparation of the enolate and of the imine (interaction between a double occupied orbitals and an appropriate combination of the empty orbitals of the two lithium atoms).

Scheme V



Synthesis of the Carbapenem (+)-PS-6

As expected, substituting the lithium enolate of the *tert*-butyl butanoate **3** for the lithium enolate of *tert*-butyl isovalerate **12** in the aforementioned sequence produces a key intermediate in the preparation of the carbapenem (+)-PS-6 (Scheme IV).

Reaction of silylimine **2a** of the (*S*)-lactaldehyde with lithium *tert*-butyl isovalerate (**12**) furnished the *trans*-azetidinone **13a** as single isomer in 61% yield. Azetidinone **13a** was further processed to the (3*R*,4*R*)-3-isopropyl-4-acetoxyazetidin-2-one (**15**) and its epimer **16** in a 20/80 mixture and 48% yield following the one-step fragmentation reaction with lead tetraacetate described above. Once again, starting from the *N*-(trimethylsilyl)imine of mandelic aldehyde **2b** gave better yields (70%) and total diastereoselectivity in the production of the azetidinone **13b**.

With the completion of the efficient synthesis of **15** and **16** from **13b** via a fragmentation reaction with lead tetraacetate in 70% yield and a 30/70 ratio, we next turned to the elaboration of the acetates **15** and **16** of the natural carbapenem (+)-PS-6.

Scheme V reports the procedure used. In this context the acetoxy derivatives were readily transformed to the corresponding β-keto ester **18a** by reaction with the silyl enol ether **17a**.

The keto ester **18a** thus obtained as a single isomer underwent the rhodium-catalyzed cyclization to give the bicyclic derivative **19a** in quantitative yield. Introduction of the thioamide side chain resulted in the formation of the β-lactam **21a**. Elimination of the *p*-nitrobenzyl group by catalytic reduction of **21a** gave the target in 21% yield. Better yields were obtained by starting from the corresponding benzhydryl ester **18b**. Thus, treatment of **15** and **16** with the silyl enol ether **17b** gave rise to **18b** as a single trans isomer. Elaboration of **18b** by treatment with rhodium acetate gave the bicyclic derivative **19b** in quantitative yield. Treatment of this substrate with diphenyl

phospochloridate in acetonitrile in the presence of Huing's base and 4-(dimethylamino)pyridine as catalyst followed by reaction of the intermediate phosphate with *N*-acetylcysteamine in the presence of Hunig's base gave the product **21b** protected as the benzhydryl ester. Finally, removal of the benzhydryl group by $AlCl_3$[21] furnished the natural carbapenem (+)-PS-6. This product was identified by comparison of its physical and spectral data with those reported in the literature.[22]

Conclusions

We have succeeded in exploiting the synthetic utility of *N*-(trimethylsilyl)imines in the preparation of natural occurring β-lactam antibiotics. We have, indeed, demonstrated that the cycloaddition reaction of lithium enolates and enantiomerically pure α-hydroxy *N*-(trimethylsilyl)-imines, easily obtained from the corresponding aldehydes, constitutes a useful methodology for the completely enantio- and diastereoselective synthesis of enantiomerically pure azetidinones. Particularly promising in terms of stereospecificity and yields is the use of the mandelic aldehyde. The radical fragmentation with lead tetraacetate avoiding the two-step oxidation procedure with chromium trioxide and *m*-chloroperbenzoic acid allows a three-step preparation of homochiral 4-acetoxyazetidinones, useful intermediates in the synthesis of penems and carbapenems.

Experimental Section

General. For purification of crude reaction mixtures, flash chromatography using 70–230-mesh silica gel was used: the composition of the eluting solution is given in brackets. Analytical thin layer chromatography was performed by using precoated silica gel F-254 plates; products were observed by using ultraviolet light, iodine, or phosphomolybdate spot tests. THF and diethyl ether were predried over CaH_2 and distilled from sodium benzophenone under an argon atmosphere prior to use. Methylene chloride, ethyl acetate, and methanol were distilled from CaH_2. After workup, the organic layers were dried over $MgSO_4$. Acetone was distilled over $KMnO_4$. NMR data were obtained as $CDCl_3$ solutions on FT 80, EM 390, VXR 200, or Gemini 300 spectrometers, chemical shifts are reported in parts per million (ppm) from internal tetramethylsilane, and coupling constants (*J*) are reported in hertz. IR spectra were obtained as chloroform solutions, unless otherwise stated, and are reported in cm^{-1}. Optical rotations were taken in chloroform at 25 °C. Melting points are uncorrected. Mass spectra were recorded at an ionization energy of 70 eV. Elemental analyses were taken at Dipartimento di Chimica Organica, Università degli Studi di Firenze.

(*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-*N*-(trimethylsilyl)propanimine (2a). To (*S*)-2-[(*tert*-butyldimethylsiloxy]-propanal[9] (1.88 g, 10 mmol) in THF (15 mL) at −78 °C was added 10 mL of a 1 M solution in THF of LiHMDS. The mixture was stirred at −40 °C for 40 min and the resulting cold solution of *N*-(trimethylsilyl)imine was used directly in the preparation of the β-lactams **4a** and **5a**.

(*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-2-phenylethanal (1b). To a solution of ethyl [(*tert*-butyldimethylsilyl)oxy]mandelate[23] (5 g, 17 mmol) in ether (50 mL) was added diisobutylaluminum hydride (DIBAH) in hexane (25.5 mL, 1 M) by a side arm at −78 °C. After being stirred at the same temperature for 15 min, the mixture was poured in ice–water and extracted with ethyl acetate. The solvent was dried and the residue chromatographed (hexane–ethyl acetate 9:1) to give **1b** (4 g, 88%) as an oil: $[\alpha]^{25}_D$ = +5.5° (neat); IR (film) 1740; ^{1}H NMR (200 MHz) − 0.05 (s, 3), 0.05 (s, 3), 0.90 (s, 9), 4.95 (d, 1, *J* = 2), 7.3 (5, Ar), 9.45 (d, 1, *J* = 2); ^{13}C NMR (200 MHz) 199.40, 136.60, 128.69, 128.33, 126.40, 80.00, 25.71, 16.27, −4.66.

(*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-2-phenyl-*N*-(trimethylsilyl)ethanimine (2b). To a solution of LiHMDS in THF (10 mL, 1 M) at −78 °C was added a solution of **1b** (2.5 g, 10 mmol) in THF (5 mL). The mixture was stirred at −78 °C for 10 min, and the resulting cold solution of *N*-(trimethylsilyl)imine **2b** was used as such in the following reaction: IR (THF) 1695; ^{1}H NMR (90 MHz) 0.12 (s, 6), 0.15 (s, 3), 1.05 (s, 9), 5.15 (d, 1, *J* = 5.4), 7.45 (m, 5, Ar), 8.25 (d, 1, *J* = 5.4).

(3*R*,4*S*)-3-Ethyl-4-[(*S*)-1-[(*tert*-butyldimethylsilyl)oxy]-ethyl]-2-azetidinone (4a) and (3*S*,4*R*)-3-Ethyl-4-[(*S*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-2-azetidinone (5a). To a solution of diisopropylamine (1.01 g, 10 mmol) in THF (20 mL) was added *n*-butyllithium in hexane (4 mL, 10 mmol) at −78 °C. The solution was stirred for 10 min followed by addition of *tert*-butyl butanoate (1.44 g, 10 mmol) in THF (5 mL) at a rate such that the temperature did not exceed −60 °C. The solution was stirred for 1 h followed by addition of (trimethylsilyl)imine **2a** via cannula over a 5-min period. The mixture was stirred at −78 °C for 15 min, the cold bath was removed, and the mixture was allowed to warm to room temperature followed by stirring overnight. The solution was diluted with 100 mL of ethyl acetate and washed sequentially with 50 mL of a saturated solution of NH_4Cl and 50 mL of water. The combined aqueous washes were extracted with 100-mL portions of ethyl acetate. The combined organic layers were dried and concentrated in vacuo. The residue was purified (hexane–ethyl acetate 70:30) to give 1.51 g of the β-lactam **4a** and 0.060 g of the β-lactam **5a** in a 96/4 ratio and 61% overall yield.

β-Lactam 4a: mp 49 °C; $[\alpha]^{25}_D$ = +23.5° (*c* 1.2, $CHCl_3$); IR 3400, 1765; ^{1}H NMR (300 MHz) 0.070 (s, 3), 0.075 (s, 3), 0.88 (s, 9), 1.03 (t, 3), 1.15 (d, 3), 1.75 (m, 2), 2.71 (dt, 1, *J* = 2.5, 7), 3.18 (dd, 1, *J* = 2.5, 8), 3.75 (quintet, 1, *J* = 8), 5.96 (bs, 1, NH); ^{13}C NMR (80 MHz) ($CDCl_3$) 168.8, 68.9, 57.8, 52.4, 23.7, 19.3, 18.1, 15.9, 9.47; MS *m/z* 257. Anal. Calcd for $C_{13}H_{27}NO_2Si$: C, 60.65; H, 10.57; N, 5.44. Found: C, 60.89; H, 10.53; N, 5.38.

β-Lactam 5a: ^{1}H NMR (300 MHz) 0.070 (s, 3), 0.075 (s, 3), 0.88 (s, 9), 1.05 (m, 6), 1.75 (m, 2), 2.85 (dt, 1, *J* = 2.5, 7), 3.15 (dd, 1, *J* = 2.5, 5), 3.85 (m, 1), 6.55 (bs, 1); MS *m/z* 257. Anal. Calcd for $C_{13}H_{27}NO_2Si$: C, 60.65; H, 10.57; N, 5.44. Found: C, 60.60; H, 10.50; N, 5.32.

(3*R*,4*S*)-3-Ethyl-4-[(*S*)-[(*tert*-butyldimethylsilyl)oxy]-phenylmethyl]-2-azetidinone (4b). This product was obtained in 84% yield according the procedure described for the azetidinones **4a** and **5a** from *N*-(trimethylsilyl)imine **2b** (10 mmol) and lithium *tert*-butyl butanoate. **4b**: mp 113–114 °C; $[\alpha]^{25}_D$ = +48.4° (*c* 1.26, $CHCl_3$); IR (Nujol) 3240, 1765; ^{1}H NMR (200 MHz) −0.2 (s, 3), 0.00 (s, 3), 0.45 (t, 3), 0.85 (s, 9), 1.4 (m, 2), 2.70 (m, 1), 3.33 (dd, 1, *J* = 7.44, 2.2), 4.50 (d, 1, *J* = 7.44), 6.66 (bs, 1, NH), 7.23 (m, 5, Ar); ^{13}C NMR (200 MHz) 170.63, 140.63, 128.10, 127.82, 126.30, 77.87, 60.40, 54.19, 25.51, 20.83, 17.83, 10.66, −4.85, −5.23; MS *m/z* 262 (M − 57), 246, 221. Anal. Calcd for $C_{18}H_{29}NO_2Si$: C, 67.66; H, 9.15. Found: C, 67.92; H, 9.18.

(3*R*,4*S*)-3-Ethyl-4-[(*S*)-1-hydroxyethyl]-2-azetidinone (6a). **4a** (0.257 g, 1 mmol) was dissolved in acetonitrile (5 mL) containing 0.5 mL of a 40% aqueous solution of HF. TLC monitoring was carried out by spotting aliquots directly onto a silica gel plate. When deprotection was complete (90 min), acetonitrile was removed and the residue oil purified (ethyl acetate) to give **6a** (0.138 g, 97%): $[\alpha]^{25}_D$ = +41.8° (*c* 1.4, $CDCl_3$); IR 3420, 1760; ^{1}H NMR (200 MHz) 1.0 (t, 3), 1.5 (d, 3, *J* = 6), 1.70 (m, 2), 2.70 (m, 1), 3.15 (dd, 1, *J* = 2.5, 8), 3.75 (quintet, 1, *J* = 8), 4.1 (bs, 1, OH), 7.2 (bs, 1, NH); ^{13}C NMR (200 MHz) 171.98, 69.82, 59.96, 54.50, 21.19, 19.66, 11.43; MS *m/z* 143, 125.

(3*R*,4*S*)-3-Ethyl-4-[(*S*)-hydroxymethylphenyl]-2-azetidinone (6b). To a solution of the β-lactam **4b** (0.1 g, 0.31 mmol) in dry THF (2 mL) was added in one portion a THF solution of tetrabutylammonium fluoride (0.62 mL 1 N) at 0 °C. TLC monitoring was carried out by spotting aliquots directly onto a silica gel plate (hexane–ethyl) acetate 1:1). When deprotection was complete (90 min), THF was removed and the residue oil was purified on a short column (ethyl acetate) to yield 0.06 g (95%) of the β-lactam **6b**: $[\alpha]^{25}_D$ = +35.7° (*c* 2.2, $CHCl_3$); IR 3420, 1765; ^{1}H NMR (90 MHz) 0.50 (t, 3), 1.5 (m, 2), 2.75 (m, 1), 3.40 (dd,

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(23) The (*S*)-ethyl [(*tert*-butyldimethylsilyl)oxy]mandelate, $[\alpha]^{25}_D$ = +41.2° (*c* 1.5, $CHCl_3$), was prepared by a standard procedure from ethyl (*S*)-mandelate [$BuMe_2SiCl$, imidazole, dimethylformamide (DMF), 94%].

1, J = 7.44, 2.2), 4.4 (bs, 1, OH), 4.50 (d, 1, J = 7.44), 7.2 (bs, 1, NH), 7.35 (m, 5, Ar); ^{13}C NMR (200 MHz) 171.59, 140.51, 128.75, 128.51, 126.50, 77.17, 60.02, 54.73, 21.05, 10.88; MS m/z 205 (M^+), 162, 133. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.45; H, 7.40; N, 6.75.

(3*R*,4*S*)-3-Ethyl-4-acetyl-2-azetidinone (7a). Diethyl ether, 20 mL, and **6a** were (0.286 g, 2 mmol) placed in a 100-mL three-necked flask fitted with a stirrer, a condenser, and an additional funnel. Chromic acid solution[15] (1.2 mL) was added to the stirred solution over 15 min. After 2 h at room temperature, the upper ether layer was separated and the aqueous phase was extracted with three 30-mL portions of CH_2Cl_2. The combined organic extracts were washed with saturated $NaHCO_3$ solution and water and then dried. The solvent was removed and the residue chromatographed (ethyl acetate) to give **7a** as solid (0.214 g, 76%): mp 82–83 °C; $[\alpha]^{25}_D$ = +15.6° (c 9.3, $CHCl_3$); IR 3420, 1780, 1730; ^{1}H NMR (90 MHz) 1.15 (t, 3), 1.85 (m, 2), 2.3 (s, 3), 3.1 (m, 1), 3.95 (d, 1, J = 3), 6.7 (bs, 1, NH); ^{13}C NMR (80 MHz) 205.7, 169.5, 59.9, 58.0, 25.6, 21.5, 11.2; MS m/z 141, 126, 112, 98. Anal. Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.79; H, 7.83; N, 10.1.

(3*R*,4*R*)-3-Ethyl-4-acetoxy-2-azetidinone (8) from 7a. To a solution of **7a** (0.2 g, 1.42 mmol) in dry ethyl acetate was added *m*-chloroperbenzoic acid (0.35 g, 2 mmol) in one portion, and the mixture was stirred at 50 °C for 3 h until disappearance of the starting material. The solution was diluted with 50 mL of ethyl acetate and washed with a cooled solution of 5% $NaHCO_3$. The organic layers were dried, the solvent removed, and the oily residue was chromatographed (hexane–ethyl acetate 1:1) to give 8 (0.16 g, 72%): $[\alpha]^{25}_D$ = +100° (c 1.62, $CHCl_3$); IR 3420, 1785, 1745; ^{1}H NMR (90 MHz) 1.1 (t, 3), 1.8 (m, 2), 2.15 (s, 3), 3.15 (dt, 1, J = 1.5, 6), 5.6 (d, 1, J = 1.5), 7.3 (bs, 1, NH); ^{13}C NMR (80 MHz) 171.0, 168.5, 77.8, 59.2, 20.7, 19.7, 11.1; MS m/z 157 (M^+). Anal. Calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.73; H, 7.09; N, 8.85.

(3*R*,4*R*)-3-Ethyl-4-acetoxy-2-azetidinone (8) and (3*R*,4*S*)-3-Ethyl-4-acetoxy-2-azetidinone (9) from 6b. To a solution of **6b** (0.139 g., 0.63 mmol) in 5 mL of anhyd benzene was added lead tetraacetate (0.66 g, 1.5 mmol) in one portion under an inert atmosphere of argon. The solution was stirred, under reflux, until complete disappearance of the starting material (1 h, TLC monitoring, hexane–ethyl acetate 1:1). The mixture was diluted with ethyl acetate and poured into a cold solution of 10% HCl (10 mL). The aqueous layer was extracted with ethyl acetate, dried, and evaporated to give a yellow oil, which was purified by chromatography (ethyl acetate–hexane 1:1) to give 0.056 g (53%) of a 72/28 mixture of 8 and 9.

9: IR 3420, 1785, 1750; ^{1}H NMR (200 MHz) 1.15 (t, 3), 1.75 (m, 2), 2.10 (s, 3), 3.30 (m, 1), 5.9 (d, 1, J = 4.3), 7.2 (bs, 1, NH); ^{13}C NMR (200 MHz) 171.2, 169.61, 75.5, 57.7, 20.86, 19.80, 11.87; MS m/z 157 (M^+).

β-Lactams 8 and 9 from 6a. These compounds were prepared from **6a** and lead tetraacetate according to the above described procedure in 61% yield as a 70/30 trans/cis mixture.

(3*R*,4*R*)-3-Ethyl-4-[3-diazo-2-oxo-3-[[(*p*-nitrobenzyl)oxy]carbonyl]propyl]-2-azetidinone (11). This product was obtained in 62% yield from the β-lactams 8 and 9 according to the literature procedure.[13h] **11**: mp 110–111 °C; $[\alpha]^{25}_D$ = +63.9° (c 1.14, $CHCl_3$); IR 3405, 2120, 1760, 1730; ^{1}H NMR (300 MHz) 1.02 (t, 3), 1.77 (m, 2), 2.82 (dt, 1, J = 1.5, 4), 3.36 (ddd, 2, J = 18, 4, 9), 3.8 (m, 1), 5.38 (s, 2), 6.33 (s, 1), 7.60 (d, 2, J = 9), 8.25 (d, 2, J = 9); ^{13}C NMR (300 MHz) 189.85, 170.23, 160.55, 146.80, 141.87, 128.63, 123.82, 65.41, 57.97, 49.62, 45.35, 21.24, 11.15, 5.97. Anal. Calcd for $C_{16}H_{16}N_4O_6$: C, 53.33; H, 4.48; N, 15.55. Found: C, 53.43; H, 4.43; N, 15.30.

(3*R*,4*S*)-3-Isopropyl-4-[(*S*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl]-2-azetidinone (13a). This product was obtained as single trans isomer in 61% yield from lithium *tert*-butyl isovalerate and *N*-(trimethylsilyl)imine of the (*S*)-lactaldehyde following the procedure described for the preparation of the azetidinones **4a** and **5a**. **13a**: $[\alpha]^{25}_D$ = +22.9° (c 1.966, $CHCl_3$); IR 3425, 1765; ^{1}H NMR (200 MHz) 0.047 (s, 3), 0.054 (s, 3), 0.88 (s, 9), 0.98 (d, 3, J = 7), 1.05 (d, 3, J = 7), 1.15 (d, 3, J = 6.2), 2.06 (octet, 1, J = 7), 2.58 (dt, 1, J = 7.6, 2.2), 3.22 (dd, 1, J = 7.6, 2.2), 3.75 (quintet, 1, J = 7.6), 5.9 (bs, 1, NH); ^{13}C NMR (200 MHz) 170.31, 71.3, 59.9, 58.1, 27.6, 25.8, 20.6, 20.2, 20.2, 18.0, −4.3, −4.6; MS m/z 271 (M^+), 228, 171. Anal. Calcd for $C_{14}H_{29}NO_2Si$: C, 61.94; H, 10.77; N, 5.16. Found: C, 61.71; H, 10.74; N, 5.28.

(3*R*,4*S*)-3-Isopropyl-4-[(*S*)-[(*tert*-butyldimethylsilyl)oxy]phenylmethyl]-2-azetidinone (13b). This product was obtained according to the procedure described for azetidinone **4b** in 70% yield. **13b**: mp 62–63 °C; $[\alpha]^{25}_D$ = +44.2° (c 1.5, $CHCl_3$); IR 3425, 1765; ^{1}H NMR (200 MHz) −0.20 (s, 3), 0.02 (s, 3), 0.53 (d, 3, J = 6.7), 0.73 (d, 3, J = 6.7), 0.86 (s, 9), 1.75 (octet, 1, J = 6.7), 2.62 (ddd, 1, J = 7.8, 2.2, 2.2), 3.41 (dd, 1, J = 7.44, 2.2), 4.50 (d, 1, J = 7.44), 5.98 (bd, 1, J = 2.2, NH), 7.3 (m, 5, Ar); ^{13}C NMR (200 MHz) 170.05, 140.84, 128.32, 128.10, 126.59, 78.36, 59.60, 58.60, 27.28, 25.68, 19.71, 19.62, 18.03, −4.63, −5.08; MS m/z 318 (M^+ − 15), 290, 276, 221. Anal. Calcd for $C_{19}H_{31}NO_2Si$: C, 68.42; H, 9.37; N, 4.20. Found: C, 68.15; H, 9.37; N, 4.10.

(3*R*,4*S*)-3-Isopropyl-4-[(*S*)-1-hydroxyethyl]-2-azetidinone (14a) was prepared in 98% yield from **13a** according to the procedure described for the preparation of compound **6a**. **14a**: $[\alpha]^{25}_D$ = +31.2° (c 2.106, $CHCl_3$); IR 3420, 1765; ^{1}H NMR (200 MHz) 1.05 (d, 3, J = 7), 1.11 (d, 3, J = 7), 1.25 (d, 3, J = 6), 2.00 (octet, 1, J = 7), 2.65 (ddd, 1, J = 2.2, 7, 2.2), 3.25 (dd, 1, J = 2.2, 6), 3.75 (quintet, 1, J = 6), 3.9 (bs, 1, OH), 7.2 (bd, 1, J = 2.2, NH); ^{13}C NMR (200 MHz) 171.4, 70.0, 59.9, 58.2, 27.6, 20.5, 20.13, 20.08; MS m/z 157 (M^+), 114. Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 60.89; H, 9.63; N, 8.75.

(3*R*,4*S*)-3-Isopropyl-4-[(*S*)-hydroxymethylphenyl]-2-azetidinone (14b) was prepared in 90% yield from **13b** according to the procedure described for compound **6b**. **14b**: $[\alpha]^{25}_D$ = +29.4° (c 1.766, $CHCl_3$); IR 3420, 1765; ^{1}H NMR (200 MHz) 0.5 (d, 3, J = 7), 0.7 (d, 3, J = 7), 1.7 (octet, 1, J = 7), 2.60 (ddd, 1, J = 2.2, 7, 2.2), 3.4 (dd, 1, J = 2.2, 7.5), 4.5 (d, 1, J = 7.5), 4.55 (bs, 1, OH), 7.0 (bd, 1, J = 2.2, NH), 7.3 (5, Ar); ^{13}C NMR (200 MHz) 171.11, 140.61, 128.63, 128.44, 126.64, 77.42, 59.8, 58.00, 27.28, 19.7, 19.63; MS m/z 176 (M^+ − 43), 133. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.38. Found: C, 71.47; H, 7.83; N, 6.30.

(3*R*,4*S*)-3-Isopropyl-4-acetoxy-2-azetidinone (15) and (3*R*,4*R*)-3-Isopropyl-4-acetoxy-2-azetidinone (16) from 14a. To a solution of **14a** (1.5 g, 9.55 mmol) in anhyd benzene (40 mL) were added $CaCO_3$ (0.6 g) and lead tetraacetate (8.5 g, 19.1 mmol) in one portion under an inert atmosphere of argon. The solution was stirred, under reflux, until complete disappearance of the starting material (4 h, TLC monitoring, hexane ethyl–acetate 1:1). The mixture was poured into a cold solution of 10% HCl (30 mL). The aqueous layer was extracted with ethyl acetate, dried, and evaporated to give a yellow oil, which was purified (ethyl acetate–hexane 1:1) to give 0.8 g (48% yield) of a 20/80 mixture of 15 and 16, which was further elaborated without separation of diastereoisomers.

15: IR 3420, 1785, 1750; ^{1}H NMR (200 MHz) 1.04 (d, 3, J = 7), 1.15 (d, 3, J = 7), 2.1 (m, 4), 3.0 (dd, 1, J = 4.3, 8), 5.95 (d, 1, J = 4.3), 7.3 (bs, 1, NH); ^{13}C NMR (200 MHz) 171.22, 168.36, 75.50, 61.70, 25.70, 21.53, 20.13, 19.65; MS m/z 171 (M^+), 128. Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 55.91; H, 7.67; N, 8.26.

16: mp 74–76 °C; IR 3420, 1785, 1750; ^{1}H NMR (200 MHz) 1.04 (d, 3, J = 7), 1.15 (d, 3, J = 7), 2.1 (m, 4), 3.0 (dd, 1, J = 1.5, 8), 5.7 (d, 1, J = 1.5), 7.3 (bs, 1, NH); ^{13}C NMR (200 MHz) 171.22, 168.36, 76.69, 64.41, 26.48, 20.85, 20.13, 19.65; MS m/z 171 (M^+), 128. Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.22; H, 7.57; N, 8.27.

(3*R*,4*S*)-3-Isopropyl-4-acetoxy-2-azetidinone (15) and (3*R*,4*R*)-3-Isopropyl-4-acetoxy-2-azetidinone (16) from 14b. Starting from **14b** a 60% of a mixture of 15 and 16 in a 30/70 ratio was obtained by following the procedure described for 8 and 9.

(3*R*,4*R*)-3-Isopropyl-4-[3-diazo-2-oxo-3-[[(*p*-nitrobenzyl)oxy]carbonyl]propyl]-2-azetidinone (18a). This product was obtained from 15 and 16 in 56% yield by following the procedure described for compound 11. **18a**: mp 107 °C; $[\alpha]^{25}_D$ = +60.3° (c 1.13, $CHCl_3$); IR 3420, 2140, 1765, 1730, 1660, 1530, 1355; ^{1}H NMR (200 MHz) 0.99 (d, 3, J = 6.7), 1.08 (d, 3, J = 6.7), 2.05 (octet, 1, J = 6.7), 2.65 (dd, 1, J = 1.5, 8), 3.05 (dd, 1, J = 15.2, 8), 3.35 (dd, 1, J = 15.2, 4.5), 3.75 (m, 1), 5.4 (s, 2), 6.55 (s, 1), 7.6 (d, 2, J = 9), 8.25 (d, 2, J = 9); ^{13}C NMR (200 MHz) 190.1, 169.6, 160.7, 145.9, 141.9, 128.8, 124.1, 65.6, 63.3, 48.0, 45.7, 27.8, 20.3, 19.9; MS m/z 346 (M^+ − 28). Anal. Calcd for $C_{17}H_{18}N_4O_6$: C, 54.54; H, 4.85; N, 17.69. Found: C, 54.75; H, 4.83; N, 8.25.

(2*R*,5*R*,6*R*)-*p*-Nitrobenzyl 6-Isopropyl-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (19a). A mixture of **18a** (0.4 g, 1.07 mmol) and rhodium tetraacetate (3 mg) in 40 mL of dry benzene was heated at reflux for 30 min until disappearance of starting material (TLC, benzene–acetone 80:20). The mixture was filtered through Celite and the Celite was washed with dichloromethane. The filtrate was concentrated in vacuo to give 0.35 g of a colorless oil, which was used as such in the following reaction: IR 1760, 1530, 1355; ^{1}H NMR (200 MHz) 1.04 (d, 3, J = 7), 1.15 (d, 3, J = 7), 2.2 (octet, 1, J = 7), 2.4 (dd, 1, J = 18.6, 7.7), 2.90 (dd, 1, J = 18.6, 6.8), 3.05 (dd, 1, J = 1.5, 6.0), 3.9 (ddd, 1, J = 1.5, 6.8, 7.7), 4.8 (s, 1), 5.3 (m, 2), 7.54 (d, 2, J = 8.7), 8.3 (d, 2, J = 8.7); MS m/z 346 (M^+). Anal. Calcd for $C_{17}H_{18}N_2O_6$: C, 58.96; H, 5.24; N, 8.42. Found: C, 59.05; H, 5.23; N, 8.32.

(5*R*,6*R*)-*p*-Nitrobenzyl 3-[(2-Acetamidoethyl)thio]-6-isopropyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (21a). A solution of the β-lactam **19a** (0.44 g, 1.27 mmol), *N*,*N*-diisopropylethylamine (0.24 mL, 1.38 mmol), diphenyl phosphochloridate (0.28 mL, 1.38 mmol), and a catalytic amount of 4-(dimethylamino)pyridine in 20 mL of acetonitrile were mixed at 0 °C. After 1 h *N*,*N*-diisopropylethylamine (0.24 mL, 1.38 mmol) and *N*-acetylcysteamine (0.164 g, 1.38 mmol) were added. The reaction mixture was allowed to react during 18 h. A white precipitate was formed. The precipitate, containing mostly the β-lactam **21a**, was filtered; the mother liquor was evaporated and the resulting white solid was washed several times with methanol. The solvent was removed and the combined precipitate was chromatographed over a short column (benzene–acetone 8:2) in order to remove unreacted enol phosphate (28%). A white solid, which became yellow on standing (0.33 g, 58%), was obtained: mp 103–105 °C; IR 3440, 1785, 1680; $[\alpha]^{25}_D$ = +41.5° (*c* 0.869, $CHCl_3$); ^{1}H NMR (200 MHz) 1.03 (d, 3, J = 7), 1.10 (d, 3, J = 7), 2.0 (s, 3), 2.1 (m, 1), 2.9–3.8 (complex pattern, 7), 4.02 (dt, 1, J = 3, 9), 5.4 (q, 2, J = 15), 6.4 (bt, 1, NH), 7.7 (d, 2, J = 9), 8.25 (d, 2, J = 9); MS m/z 447 (M^+).

(5*R*,6*R*)-Sodium 3-[(2-Acetamidoethyl)thio]-6-isopropyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate ((+)-PS-6). A solution of **21a** (0.1 g, 0.224 mmol) in THF (20 mL) containing 0.2 g (0.224 mmol) of $NaHCO_3$ in 1 mL of H_2O was saturated with argon, and then 10% palladium on carbon (65 mg) was added. The atmosphere over the solution was evacuated and replaced with hydrogen gas twice. The mixture was stirred at room temperature under an atmosphere of hydrogen for 4 h. The palladium on carbon was removed by filtration and the solvent was evaporated under vacuum. Filtration through XAD4 resin and eluting with H_2O, followed by freeze-drying of the fraction containing the target, gave 0.016 g (21% yield) of (+)-PS-6 as a white solid.

(3*R*,4*R*)-3-Isopropyl-4-[3-diazo-2-oxo-3-[(benzhydryloxy)carbonyl]propyl]-2-azetidinone (18b). This product was obtained in 45% yield from a mixture of **15** and **16** according the procedure described for **18a**, utilizing as enol ether the ester **17b**. **18b**: $[\alpha]^{25}_D$ = +55.7° (*c* 1.80, $CHCl_3$); IR 3420, 2143, 1753, 1716, 1651; ^{1}H NMR (200 MHz) 0.93 (d, 3, J = 7), 1.02 (d, 3, J = 7), 2.0 (m, 1), 2.6 (dd, 1, J = 1.5, 8), 3.05 (dd, 1, J = 18.0, 9.5), 3.35 (dd, 1, J = 18.0, 3.5), 3.75 (m, 1), 6.1 (s, 1), 6.97 (s, 1), 7.32 (m, 10); ^{13}C NMR (200 MHz) 190.38, 169.73, 160.34, 139.15, 128.80, 128.47, 127.02, 78.34, 63.30, 48.05, 45.70, 27.76, 20.33, 19.33. Anal. Calcd for $C_{23}H_{23}N_3O_4$: C, 68.13; H, 5.72; N, 10.36. Found: C, 67.99; H, 5.64; N, 10.25.

(2*R*,5*R*,6*R*)-Benzhydryl 6-Isopropyl-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (19b). This product was obtained in quantitative yield as described for the β-lactam **19a**. **19b**: $[\alpha]^{25}_D$ = +124.4° (*c* 1.58, $CHCl_3$); mp 53–55 °C, IR 1763; ^{1}H NMR (200 MHz) 1.04 (d, 3, J = 7), 1.15 (d, 3, J = 7), 2.15 (m, 1), 2.4 (dd, 1, J = 19, 7.6), 2.8 (dd, 1, J = 19, 6.8), 3.9 (dt, 1, J = 1.5, 7.2), 4.8 (s, 1), 6.9 (s, 1), 7.35 (m, 10, Ar); ^{13}C NMR (200 MHz) 207.06, 174.26, 164.21, 139.09, 139.02, 128.50, 128.40, 128.20, 127.95, 127.22, 126.65, 78.82, 67.98, 64.19, 52.42, 41.20, 28.21, 20.41, 19.80; MS m/z 334 [M^+ – $CH(CH_3)_2$]. Anal. Calcd for $C_{23}H_{23}NO_4$: C, 73.19; H, 6.14; N, 3.71. Found: C, 73.49; H, 6.16; N, 3.80.

(5*R*,6*R*)-Benzhydryl 3-[(2-acetamidoethyl)thio]-6-isopropyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (21b) was obtained in 85% yield from **19b**, following the procedure described for the preparation of **21a**. **21b**: IR 3450, 1755, 1668, 1520; ^{1}H NMR (200 MHz) 1.02 (d, 3, J = 7), 1.10 (d, 3, J = 7), 1.93 (s, 3), 2.01 (m, 1), 2.5–3.5 (complex pattern, 7), 3.96 (dt, 1, J = 2.5, 9), 6.2 (bt, 1, NH), 6.9 (s, 1), 7.3 (m, 10, Ar); ^{13}C NMR (200 MHz) 177.60, 170.66, 160.46, 146.65, 140.28, 140.11, 128.46, 128.36, 127.86, 127.36, 127.13, 127.01, 78.08, 66.92, 53.68, 40.43, 39.89, 31.63, 28.69, 23.03, 20.65, 19.98. Anal. Calcd for $C_{27}H_{30}N_2O_4S$: C, 67.76; H, 6.32; N, 5.85. Found: C, 68.11; H, 6.34; N, 5.93.

(5*R*,6*R*)-Sodium 3-[(2-Acetamidoethyl)thio]-6-isopropyl-7-oxo-1-azabicyclclo[3.2.0]hept-2-ene-2-carboxylate ((+)-PS-6). To a stirred solution of **21b** (150 mg, 0.31 mmol) in anisole (2.4 mL) and CH_2Cl_2 (0.6 mL) at –50 °C was added $AlCl_3$ (100 mg, 0.78 mmol). The reaction mixture was stirred for 30 min at the same temperature, quenched with aqueous 5% $NaHCO_3$ (3 mL) at the same temperature, and partitioned between ethyl acetate and water. The resulting inorganic precipitates were removed by filtration and the filtrate was passed through an XAD4 column, eluting with deionized water, followed by freeze-drying to give 40 mg (40% yield) of (+)-PS-6 with physical and spectral data identical with those reported in the literature.[24]

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