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A NOVEL SYNTHESIS OF (-)-CARPETIMYCIN A[1]

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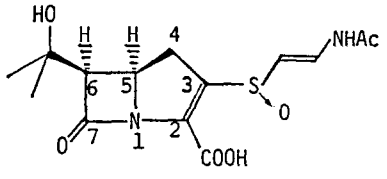
Summary: A stereoselective synthesis of the known synthetic intermediate (13) for (-)-carpetimycin A (1) has been achieved starting from the monocyclic β-lactam (8b) by the novel use of the direct aldol condensation of 8b with acetone via the titanium enolate.

Carpetimycin A (1),[2] the representative *cis*-carbapenem antibiotic, exhibits not only a highly potent, broad spectrum antibacterial activity, but also a strong β-lactamase inhibitory activity. In this communication we wish to report a novel synthesis of the key intermediate (13) for (-)-carpetimycin A (1).

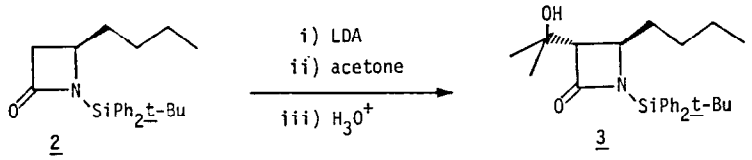


1: (R)-Sulfoxide

Carpetimycin A (1) possesses the thermodynamically unstable *cis*-substituent at the 6-position with the 5,6-relative stereochemistry, indicating that the direct introduction of a 1-hydroxy-1-methylethyl moiety on a readily available β-lactam ring might be hard to be used for the total synthesis of 1. In fact, the aldol condensation of 2 with acetone (LDA in ether) provides the *trans*-β-lactam (3) exclusively (Scheme 1)[3] and furthermore the introduction of the *cis*-side chain at the 6-position in total syntheses of 1 already reported[4] have been achieved by the use of other methods than the direct aldol condensation of a β-lactam ring with acetone. Nevertheless we expected that the direct aldol condensation of a readily available β-lactam with acetone under the well-suited conditions would provide a *cis*-β-lactam in a stereoselective manner.

One strategy we envisioned was based on observations that the MEM protecting group could nicely coordinate to a metal cation.[5] These observations suggested the following matters. In the aldol condensation of 4 with acetone, a metal cation would be coordinated by the neighboring MEM group, thus the metal cation being located on the β-face of the molecule, and furthermore the aldol condensation would proceed *via* the tightly coordinated 6-membered transition state like 5 to allow the predominant formation of the *cis*-β-lactam (6)(Scheme 11).

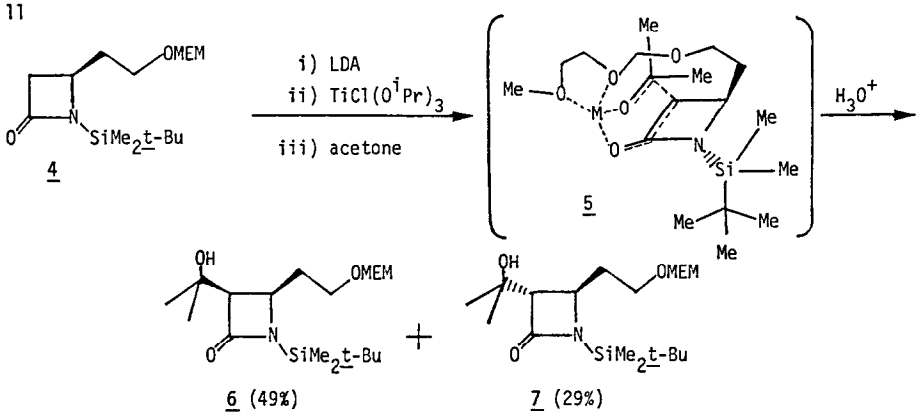
Scheme I



2 3

(exclusive formation)

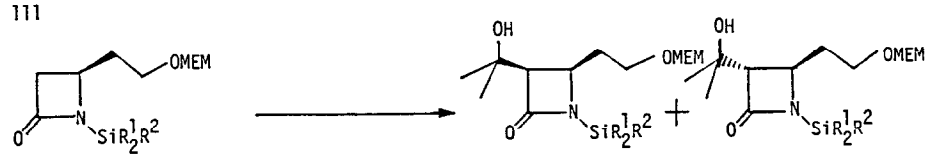
Scheme II



4 5

6 (49%) 7 (29%)

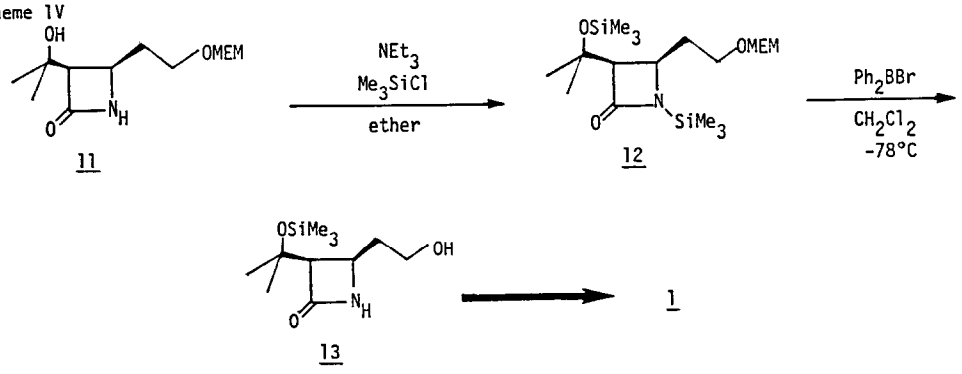
Scheme III



8 a; R^1-R^2=CH_2Ph
b; R^1=Ph, R^2=t-Bu

9a (55%) 10a (23%)
9b (59%) 10b (22%)

Scheme IV



11 12 13

The optically pure β-lactam intermediate (4)[6] for the aldol condensation was readily prepared by the known synthetic procedure.[7] In the first place the aldol condensation was carried out *via* the lithium enolate (LDA in ether), however, resulting in the highly stereoselective but undesirable formation of the *trans*-β-lactam (7) in a ratio of 1 (*trans*: 7) to <0.07 (*cis*: 6) (85% yield).[8] After several unfruitful attempts, finally it was found that the titanium enolate in ether easily derived from the lithium enolate and triisopropoxychlorotitanium gave the much better result.[9] Namely, under these conditions the desired *cis*-β-lactam (6)[6] was obtained as a major product in 49% yield along with the *trans*-β-lactam (7)[6] (29%) and recovery of the starting material (4) (11%). In order to obtain the higher stereoselectivity, we next investigated the aldol condensation of both 8a[6] and 8b[6] in expectation of more efficient shield of the α-face of the molecule by the bulkier silyl protecting group. As was expected the better results were obtained in the both cases [from 8a, *cis* (9a)[6] : *trans* (10a)[6] = 2.4 (55%) : 1 (23%), 20% recovery of 8a; from 8b, *cis* (9b)[6] : *trans* (10b)[6] = 2.8 (59%) : 1 (22%), 18% recovery of 8b],[10,11] providing a sufficient amount of the *cis*-β-lactam (9a and 9b) for further transformation to (-)-carpetimycin A (1) (Scheme III). Although the stereoselectivity of the present aldol condensation is not very satisfactory, the results obtained above are worthy of note.

Conversion of the aldolization product (9b) to the known key intermediate (13) for (-)-carpetimycin A synthesis was performed as follows (Scheme IV): Treatment of 9b with a fluoride anion gave the deprotected β-lactam (11)[6] (100%), which was followed by trimethylsilylation with trimethylsilyl chloride and triethylamine in ether at reflux temperature[12] to afford 12[6] (~100%). Chemoselective removal of both the MEM ether and one trimethylsilyl ether was achieved by treatment of 12 with diphenylboron bromide (3 molar equiv)[13] in methylene chloride at -78 °C for 1 hr to provide the known key intermediate (13)[4a,6] for the synthesis of carpetimycin A (1) in 71% yield, $[\alpha]_D^{20}$ +43.2 ° (*c* 1.00, $CHCl_3$) [lit. 4a, $[\alpha]_D^{20}$ +43.4 °(*c* 1.00, $CHCl_3$)], mp 131-133 °C (lit. 4a, 127-129 °C).

Thus, a stereoselective synthesis of (-)-carpetimycin A (1) utilizing the novel, direct aldol condensation of 8b with acetone *via* the titanium enolate as a key step has been achieved for the first time.

Acknowledgments: The authors are grateful to Dr. T. Iimori, Sagami Chemical Research Center, for valuable discussions.

References and Notes

1) This paper is dedicated to Professor Shun-ichi Yamada on the occasion of his 70th birthday.

2) (a) M. Nakayama, A. Iwasaki, S. Kimura, T. Mizoguchi, S. Tanabe, A. Murakami, I. Watanabe, M. Okuchi, H. Ito, Y. Saino, F. Funakoshi, and T. Mori, *J. Antibiot.*, 33, 1338 (1980); (b) S. Harada, S. Shinagawa, Y. Nozaki, M. Asai, and T. Kishi, *ibid.*, 33, 1425 (1980).

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4) (a) T. Iimori, Y. Takahashi, T. Izawa, S. Kobayashi, and M. Ohno, *J. Am. Chem. Soc.*, 105, 1659 (1983); (b) H. Natsugari, Y. Matsushita, N. Tamura, K. Yoshioka, M. Ochiai, *J. Chem. Soc., Perkin Trans., I*, 403 (1983); (c) M. Ihara, F. Konno, K. Fukumoto, and T. Kametani, *Heterocycles*, 20, 2181 (1983).

5) (a) A.I. Meyers and P.J. Reider, *J. Am. Chem. Soc.*, 101, 2501 (1979); (b) M. Yamazaki, M. Shibasaki, and S. Ikegami, *J. Org. Chem.*, 48, 4402 (1983).

6) Selected physical data are as follows: 4, NMR($CDCl_3$) δ4.60(s, 2H), 3.40∿3.80(m, 7H), 3.32(s, 3H), 3.10 (dd, J=15,5 Hz, 1H), 2.56(dd, J=15,3 Hz, 1H), 1.99∿2.36(m, 1H), 1.45∿1.87(m, 1H), 0.99(s, 9H), 0.24(s, 6H), 5; 4.77(s, 2H), 3.50∿4.03(m, 8H), 3.47(s, 3H), 3.09(broad s, 1H), 2.26∿2.85(m, 1H), 1.80∿2.20(m, 1H), 1.46(s, 3H), 1.39(s, 3H), 1.00(s, 9H), 0.26(s, 3H), 0.23(s, 3H), 7; 4.70(m, 2H), 3.45∿3.77(m, 7H), 3.37(s, 3H), 2.95(d, J=2 Hz, 1H), 2.34(broad s, 1H), 1.96∿2.39(m, 1H), 1.55∿1.93(m, 1H), 1.30(s, 6H), 0.97(s 9H), 0.23(s, 3H), 0.20(s, 3H), 8a; 6.77∿7.37(m, 15H), 4.50(s, 2H), 3.50(s, 4H), 3.33(s, 3H), 2.63∿3.40(m, 5H), 2.37(s, 6H), 0.80∿1.73(m, 2H), 9a; 6.77∿7.27(m, 15H), 4.53(s, 2H), 3.50(s, 4H), 3.30 (s, 3H), 3.10∿3.47(m, 4H), 2.83(broad s, 1H), 2.37(s, 6H), 1.40(s, 3H), 1.33(s, 3H), 0.80∿1.73(m, 2H), 10a; 6.80∿7.33(m, 15H), 4.53(s, 2H), 3.50(s, 4H), 3.33(s, 3H), 3.10∿3.43(m, 3H), 2.77(d, J=2.2 Hz, 1H), 2.37(s, 6H), 2.17(broad s, 1H), 0.80∿1.73(m, 2H), 1.07(s, 6H), 8b; 7.60∿7.82(m, 4H), 7.27∿7.57(m, 6H), 4.43(s, 2H), 3.33(s, 3H), 3.03∿3.68(m, 8H), 2.77(dd, J=15,3 Hz, 1H), 1.20∿1.45(m, 2H), 1.20(s, 9H), $[\alpha]_D^{20}$ -70.70 °(c 3.17, $CHCl_3$), 9b; 7.57∿7.86(m, 4H), 7.27∿7.56(m, 6H), 4.16(s, 2H), 3.15(s, 3H), 1.87 ∿3.83(m, 11H), 1.37(s, 3H), 1.26(s, 3H), 0.99(s, 9H), $[\alpha]_D^{20}$ -44.73 °(c 2.11, $CHCl_3$), 10b; 7.60∿7.83(m, 4H), 7.30∿7.60(m, 6H), 4.44(s, 2H), 3.36(s, 3H), 3.13∿3.70(m, 7H), 3.06(d, J=3 Hz, 1H), 2.63(broad s, 1H), 2.46∿2.90(m, 2H), 1.39(s, 6H), 1.20(s, 9H), 11; 6.65(broad s, 1H), 4.63(s, 2H), 3.43∿4.00(m, 8H), 3.38(s, 3H), 3.23(d, J=5.4 Hz, 1H), 1.90∿2.50(m, 2H), 1.47(s, 3H), 1.32(s, 3H), $[\alpha]_D^{20}$ +68.14 °(c 1.62, $CHCl_3$), 12; 4.67(s, 2H), 3.43∿3.82(m, 7H), 3.37(s, 3H), 3.18(d, J=6 Hz, 1H), 2.38∿2.82(m, 1H), 1.52∿ 2.12(m, 1H), 1.48(s, 3H), 1.35(s, 3H), 0.28(s, 9H), 0.13(s, 9H), $[\alpha]_D^{20}$ +8.38 °(c 2.10, $CHCl_3$), 13; 6.16(broad s, 1H), 3.52∿3.98(m, 4H), 3.15(dd, J=5.1,1.2 Hz, 1H), 1.88∿2.43(m, 2H), 1.33(s, 3H), 1.50 (s, 3H), 0.13(s, 9H).

7) According to the report by Ohno et al. [*J. Am. Chem. Soc.*, 103, 2406 (1981)], j was synthesized. Conversion of j to requisite 4 was carried out as follows; i. *t*-$BuMe_2SiCl$-Et_3N in DMF (∿100%), ii. $LiAlH_4$ in THF (∿100%), iii. MEM chloride-$(i\text{-}Pr)_2EtN$ in CH_2Cl_2 (∿100%). The β-lactams (8a and 8b) were also obtained efficiently by the same procedure described above using either Ph_2*t*-BuSiCl or $(PhCH_2)_3SiCl$ instead of *t*-$BuMe_2SiCl$.

8) The ratio of the products was determined by the GLC analysis.

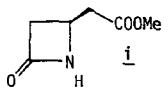
9) For titanium enolates, see: M.T. Reetz and R. Peter, *Tetrahedron Lett.*, 22, 4691 (1981).

10) General procedure for the aldol condensation: The temperature was maintained at -78 °C throughout the reaction. To a stirred solution of 8b (882 mg, 2 mM) in ether (24 ml) was added LDA (5 mM, *ca.* 10 ml ether solution). After stirring for 0.5 hr, $TiCl(O\text{-}i\text{-}Pr)_3$ (4.4 mM) was injected *via* syringe. Stirring was continued for additional 0.5 hr to generate the titanium enolate, to which was added acetone (6.0 mM). After stirring for 0.5 hr, the reaction was quenched with satd. NH_4Cl aq.. Extraction and evaporation afforded the oily residue, which was purified to give 9b (593 mg, 59%), 10b (215 mg, 22%) and 8a (160 mg).

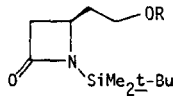
11) Other β-lactams such as ii, iii, iv, v and vi gave the less satisfactory results in the selectivity of the aldol condensation. The unsatisfactory result was also obtained by the use of THF as a solvent.

12) The reaction was carried out in a sealed tube.

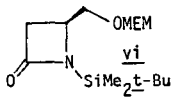
13) Y. Guindon, C. Yoakim, and H.F. Morton, *J. Org. Chem.*, 49, 3912 (1984).



i



ii: R=THP
iii: R=MOM
iv: R=$SiMe_2$*t*-Bu
v: R=H



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