Recycling numbers of photocatalyst are listed in Table I.

Thus, the major problems involved in the chemical reduction of keto carboxylate were solved by the use of the present "keto carboxylate photoreducing micelle". Undesirable hydration of NADH in aqueous solution was successfully avoided by using **2** as a potential electron-transport catalyst, and insufficient reactivity of **2b** was solved by using a micelle and also by introduction of a substituent in **2a**.

The presently prepared artificial system capable of catalytic production of biologically important molecules is concluded to drive the following overall reaction in a single functionalized particle:

$$RCOCOX + 2Na_2S_2O_3 + 2H_2O \xrightarrow{h\nu} RCHOHCOX + Na_2S_4O_6 + 2NaOH \quad (4)$$

Stereocontrolled Synthesis of a *cis*-Carbapenem Antibiotic (−)-Carpetimycin A

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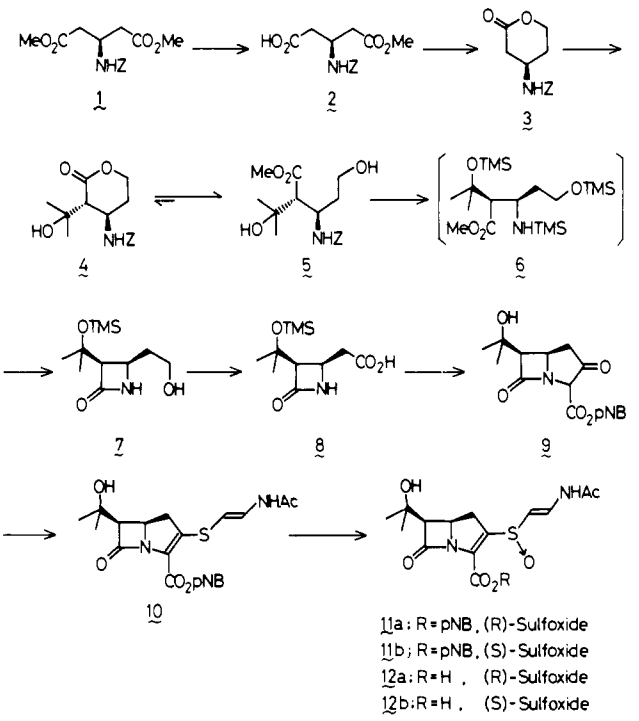
The synthetic control of absolute stereochemistry of (+)-thienamycin and related, naturally occurring, trans-substituted carbapenem antibiotics has been developed by a number of unique approaches.[1] However, there is no successful report for the chiral synthesis of naturally occurring cis-substituted carbapenem antibiotics[2] and only racemic 6-epi-PS-5 was synthesized.[3] We now report a stereocontrolled synthesis of (−)-carpetimycin A that employs an efficient conversion of a trans-substituted δ-lactone to a cis-substituted β-lactam, starting from (*S*)-3-[(benzyloxycarbonyl)amino]-4-(methoxycarbonyl)butyric acid (**2**; Z = $COOCH_2Ph$) prepared by an enzyme-mediated hydrolysis[4] of the prochiral ester **1** as shown in Scheme I. Thus, δ-lactone **3** was obtained by reduction of **2** with $NaBH_4$ followed by cyclization with Ac_2O–py in 65% yield (two steps), $[\alpha]^{20}_D$ +4.70° (*c* 1.66, $CHCl_3$).[5] Incorporation of the hydroxyisopropyl group occurred in a completely stereocontrolled manner by treatment of the enolate anion (LDA, 2.2 equiv) of **3** with acetone (excess) in THF at −78 °C for 1 h. After workup and column chromatography

Scheme I



on SiO_2 (CH_2Cl_2:Et_2O = 10:1), hydroxyisopropyl lactone **4** was obtained in 77% yield [oil; R_f 0.40 (CH_2Cl_2:Et_2O = 1:1); $[\alpha]^{20}_D$ −3.17° (*c* 1.15, $CHCl_3$)]. The trans stereochemistry of **4** was strongly suggested by ^1H NMR[6] and proved by eventual conversion to the natural *cis*-carbapenem **12**. No other isomer was detected either by TLC, HPLC, or ^1H NMR.

Then, the next crucial conversion of δ-lactone **4** to cis-monocyclic β-lactam **7** was studied. The δ-lactone **4** easily undergoes a retroaldol type reaction with usual bases and even the THP or Me_3Si derivatives of **4** did not afford the expected hydrolyzed products by base-catalyzed reaction. However, acid-catalyzed cleavage of δ-lactone **4** proceeded smoothly. The δ-lactone **4** was opened with methanol in the presence of a catalytic amount of hydrochloric acid, and an equilibrium of the opened ester **5** and **4** was established at room temperature within 12 h.[7] After usual workup, the mixture of methyl *syn*-3-[(benzyloxycarbonyl)amino]-5-hydroxy-2-[(1-hydroxy-1-methyl)ethyl]pentanoate[8] (**5**) and **4** (about 3:1) was separated by column chromatography on SiO_2, and recovered **4** was again subjected to the same procedures [**5**: 88% total yield oil; $[\alpha]^{20}_D$ +39.3° (*c* 0.50, $CHCl_3$); R_f 0.25 (CH_2Cl_2: Et_2O 1:1)]. After removal of *N*-Z group by catalytic hydrogenolysis, the resultant amino ester was fully silylated with Me_3SiCl[9] (Et_3N, Et_2O, 25 °C, 2 h) to afford **6**. The reaction mixture was directly subjected to a Grignard-mediated cyclization[10] (*t*-BuMgCl (1.5 equiv), Et_2O, 25 °C, 12

(1) (a) From L-aspartic acid: Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6161. (b) From penicillin: Karady, S.; Amato, J. S.; Reamer, R. A.; Weinstock, L. M. *Ibid.* **1981**, *103*, 6765. (c) From chiral sugar templates: Ikota, N.; Yoshino, O.; Koga, K. *Chem. Pharm. Bull.* **1982**, *30*, 1929. Chida, N.; Miyashita, M.; Yoshikoshi, A. 25th Symposium on the Natural products, Tokyo, Abstracts, 1982 p 108. (d) By a chemicoenzymatic approach: Okano, K.; Izawa, T.; Ohno, M. *Tetrahedron Lett.* **1983**, *24*, 217.

(2) (a) Carpetimycins or C-19393 H_2 and S_2: Nakayama, M.; Iwasaki, A.; Kimura, S.; Mizoguchi, T.; Tanabe, S.; Murakami, A.; Watanabe, I.; Okuchi, M.; Ito, H.; Saino, Y.; Kobayashi, F.; Mori, T. *J. Antibiot.* **1980**, *33*, 1338. Harada, S.; Shinagawa, S.; Nozaki, Y.; Asai, M.; Kishi, T. *Ibid.* **1980**, *33*, 1425. (b) Olivanic acids (MM22380 and MM22382) or epithienamycin A and B. See: Cooper, R. D. G. *Top. Antibiot. Chem.* **1979**, *3*, 118–123 and references cited therein.

(3) (a) Bateson, J. H.; Hickling, R. I.; Roberts, P. M.; Smale, T. C.; Southgate, R. *J. Chem. Soc., Chem. Commun.* **1980**, 1084. (b) Kametani, T.; Huang, S.-P., Nagahara, T.; Ihara, M. *Heterocycles* **1981**, *16*, 65. (c) Recently, a synthesis of racemic 5,6-*cis*-carbapenems related to C-19393 H_2 was presented at the 4th International Conference on Organic Synthesis, Tokyo, 1982. Natsugari, H.; Matsushita, Y.; Tamura, N.; Yoshioka, K.; Ochiai, M., Abstracts, p 111.

(4) Ohno, M.; Kobayashi, S.; Iimori, T.; Wang, Y.-F.; Izawa, T. *J. Am. Chem. Soc.* **1981**, *103*, 2405. It was found that enzymes of microbial origin *Flavobacterium lutescens* gave the better optical yield (98% ee), and a detailed study of the enzymatic process will be soon published in *Agric. Biol. Chem.*

(5) Recently, a practical synthesis of (±)-thienamycin was extensively developed by the Merck group, utilizing δ-lactones obtained from acetone dicarboxylate derivatives. See: Melillo, D. G.; Liu, T.; Reamer, R. A.; Shinkai, I. *Tetrahedron Lett.* **1981**, *22*, 913.

(6) The methine proton at the α-position to the carbonyl group of **6** showed a doublet signal at δ 2.59 (100 MHz, $CDCl_3$) with $J_{2,3}$ = 7.0 Hz.

(7) In our hands, the acid-catalyzed cleavage of **6** in benzyl alcohol did not afford the expected benzyl ester in good yield. See: Melillo, D. G.; Shinkai, I.; Liu, T.; Ryan, K.; Sletzinger, M. *Tetrahedron Lett.* **1980**, *21*, 2783.

(8) For the such stereochemical descriptors as syn and anti, see: Masamune, S.; Kaiho, T.; Gravey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5521.

(9) It was necessary to protect the *tert*-hydroxyl group for further transformation, since if the hydroxyl was free, bicyclic δ-lactone A was formed as

A

a major product during the oxidation of the primary alcohol. When the *tert*-butyldimethylsilyl group was used instead of the trimethylsilyl group, the silyl ether was found to resist conventional deprotection procedures after homologation of carboxylic acid to the β-keto ester.

(10) Birkofer, L.; Schramm, J. *Liebigs Ann. Chem.* **1975**, 2195.

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Table I. Antibacterial Activity of Synthetic Carpetimycins (μg/mL)

compd	*S. aureus* 209P JC-1	*E. coli* NIHJ JC-2	*P. aeruginosa* NCTC 10490
natural	0.78	0.1	3.13
12a	0.39	0.1	3.13
12b	0.78	1.56	12.5

h), after filtration to remove the triethylamine hydrochloride, followed by selective removal of *N*- and *O*-(primary)silyl groups with 1% AcOH (MeOH, 25 °C, 24 h), to give monocyclic β-lactam **7** [mp 127–129 °C; $[\alpha]^{20}_D$ +43.4° (*c* 1.00, $CHCl_3$)] in 58% yield. The cis stereochemistry of **7** was clearly demonstrated by ^1H NMR (H_3, δ 3.17, $J_{3,4}$ = 5.0 Hz). Oxidation of **7** with Sarett reagent (CrO_3 in pyridine, 25 °C, 15 h) afforded acid derivative **8** [mp 133–134 °C; $[\alpha]^{20}_D$ +53.1° (*c* 1.50, CH_3COCH_3)] in 66% yield after purification on SiO_2 column chromatography (CH_2Cl_2:Et_2O = 10:1). The keto ester was prepared by using Masamune's procedure[11] (carbonyl diimidazole, THF, 25 °C, 45 min, and magnesium salt of the mono-*p*-nitrobenzyl ester of malonic acid, THF, 25 °C, 12 h) in 77% yield [oil; R_f 0.60 (Et_2O); $[\alpha]^{20}_D$ +56.2° (*c* 0.63, $CHCl_3$)]. The construction of the bicyclic system was completed according to the excellent procedure by the Merck group.[1a] Thus, the bicyclic keto ester **9** was obtained in three steps [81% overall yield, (1) diazo exchange with TsN_3, Et_3N, CH_3CN, 25 °C, 2 h; (2) removal of *O*-silyl protecting group with 1 N HCl, MeOH, 25 °C, 45 min (3) $Rh_2(OAc)_4$, C_6H_6, reflux, 1 h], showing $[\alpha]^{20}_D$ +108.50° (*c* 0.50, $CHCl_3$) and R_f 0.65 (Et_2O).

The final phase of the synthesis was accomplished by conversion of **9** to the vinyl phosphate[1a] followed by direct treatment with NaI (4.6 equiv) and powdered silver (*E*)-2-acetamido-1-ethenethiolate (4 equiv) in DMF (25 °C, 1 h → 4 °C, 41 h)[3b] to give compound **10** in 40% yield from **9** (two steps) [oil; R_f 0.20 (Et_2O:CH_2Cl_2 = 1:1); $[\alpha]^{20}_D$ -92.2° (*c* 0.58, $CHCl_3$)].

The (acetamidoethenyl)thio derivative **10** was oxidized with MCPBA (1.1 equiv) in CH_2Cl_2 (−30 → −5 °C, 70 min), and after workup and purification with preparative silica gel TLC (CH_3COCH_3:C_6H_6 = 2:1), (*R*)-sulfoxide **11a** [oil; R_f 0.09 (CH_2Cl_2:MeOH = 20:1); $[\alpha]^{20}_D$ −77.6° (*c* 0.55, $CHCl_3$:MeOH = 10:1)] and (*S*)-sulfoxide **11b** [oil; R_f 0.11 (CH_2Cl_2:MeOH = 20:1); $[\alpha]^{20}_D$ +22.1° (*c* 0.55, $CHCl_3$:MeOH = 10.1)] were obtained in 45 and 47% yield, respectively.[12] Catalytic hydrogenolysis of **11a** (H_2, 40 psi, 10% Pd/C, phosphate buffer solution–dioxane at pH 6.8) gave **12a** identical in all respects with natural carpetimycin A, and similarly **12b**[13] was obtained by the catalytic hydrogenolysis.[14]

Some typical antibacterial activities of **12a** and **12b** are shown in Table I.

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Supplementary Material Available: Listings of physical properties of new compounds (3 pages). Ordering information is given on any current masthead page.

(11) Brooks, D. W.; Lu, L. D.-L.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 72.
(12) This isomer was confirmed to be identical with an authentic sample derived from natural carpetimycin A in all respects (IR, NMR, TLC, HPLC, optical rotation).
(13) Unnatural carpetimycin A (**12b**) showed $[\alpha]^{25}_D$ −83.3° (*c* 0.30, H_2O) and UV_{max} (H_2O) 248.5 nm (ε 10400), 284.5 (ε 7800).
(14) All materials described here gave satisfactory elementary analysis and MS, IR, and NMR spectra consistent with their structures.

Titanium-Induced Cyclization of Keto Esters: A New Method of Cycloalkanone Synthesis

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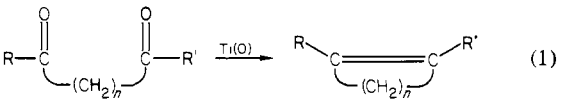
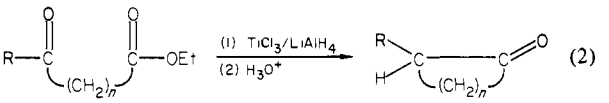
Several years ago, we reported a new and general method for the synthesis of cycloalkenes.[1,2] Treatment of diketones or keto aldehydes with an activated Ti(0) reagent, prepared by reduction of $TiCl_3$ with a Zn–Cu couple, effects an intramolecular coupling reaction leading to the cycloalkene. The reaction (eq 1) gives high



(1)

yields on all ring sizes four through seventeen, and we have recently demonstrated the utility of the method in natural-product synthesis by carrying out efficient syntheses of the 15-membered-ring diterpene flexibilene[3] and the 11-membered-ring sesquiterpene humulene.[4]

We now report an extension of the dicarbonyl coupling reaction to the synthesis of cycloalkanones by titanium-induced cyclization of keto esters. The basic idea behind this work was that, if we were to begin the coupling reaction with a substrate of higher oxidation state (keto *ester* rather than diketone), we might also end up with a product of higher oxidation state (cycloalkanone rather than cycloalkene; eq 2).



(2)

The reaction does indeed occur exactly as desired, and some of our results are presented in Table I. As can be seen, we have successfully prepared rings of size four through fourteen. All ring sizes were produced in synthetically useful yields, although the medium-sized rings, eight through eleven, show a slight diminution in yield compared with both smaller and larger rings. It should be pointed out that the results shown in the table were obtained by carrying out the keto ester coupling reaction using $TiCl_3$/$LiAlH_4$ in the presence of triethylamine as the reagent, rather than $TiCl_3$/Zn–Cu; consistently higher yields were obtained by doing so.

In a representative procedure, a black slurry of the titanium coupling reagent was prepared by adding $LiAlH_4$ (114 mg, 3.0 mmol) to a stirred suspension of $TiCl_3$ (925 mg, 6.0 mmol) in 40 mL dry dimethoxyethane (DME) under an argon atmosphere. The mixture was stirred for 10 min at room temperature, triethylamine (0.17 mL, 1.20 mmol) was added, and the mixture was refluxed for 1.5 h. Methyl 13-oxotetradecanoate (154 mg, 0.60 mmol) in 20 mL of DME was then added to the refluxing slurry over a 24-h period via syringe pump. After a further 3-h reflux period, the reaction mixture was cooled to room temperature, diluted with 12 mL of ether, and quenched by cautious addition of 6 mL of methanol and 6 mL of water. The mixture was further diluted with a pentane/ether mixture, passed rapidly through Florisil, washed with brine, dried ($MgSO_4$), and concentrated at the rotary evaporator. The crude product was then stirred for 3 h in dilute ethanolic/aqueous HCl, reisolated, and purified by chromatography on silica gel to yield 2-methylcyclotridecanone: mp 33–34 °C; 60% yield; IR 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50 (d, 3 H, *J* = 6 Hz); mass spectrum calcd for $C_{14}H_{26}O$ 210.1984, found 210.1969.

(1) McMurry, J. E.; Kees, K. L. *J. Org. Chem.* **1977**, *42*, 2655.
(2) McMurry, J. E.; Fleming, M. P.; Kees, K. L.; Krepski, L. R. *J. Org. Chem.* **1978**, *43*, 3255.
(3) McMurry, J. E.; Matz, J. R.; Kees, K. L.; Bock, P. A. *Tetrahedron Lett.* **1982**, *23*, 1777.
(4) McMurry, J. E.; Matz, J. R. *Tetrahedron Lett.* **1982**, *23*, 2723.

0002-7863/83/1505-1660$01.50/0