the nature of the rehybridization of the bridgehead atoms.

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Supplementary Material Available: Preparation of bicyclo[2.2.2]octane-1,4-dialdehyde, experimental details for **4**, and characterization of important intermediates (1 page). Ordering information is given on any current masthead page.

Photoreduction of Keto Carboxylic Acid Derivatives to Oxyacid Derivatives Catalyzed by ZnTPPS-Quinolinium-3-carboxamide-CTAB Micelle

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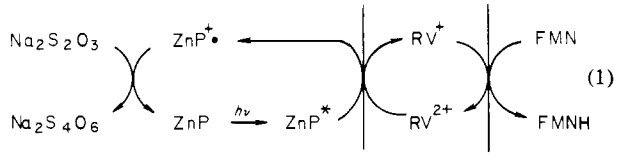
Reduction of keto carboxylates or other carbonyl compounds via biomimetic or synthetic organic approaches has been the subject of many investigations.[1] Especially important is the reduction of carbonyl compounds in an *aqueous solution* "induced" by an electron-transport species such as NAD or certain artificial NAD equivalents, in consideration that the enzymatic reductions are carried out in an aqueous solution mediated by NAD(P) in the presence of a dehydrogenase.[2] However, the reductions under such conditions have seldom been successful by the use of an artificial NAD equivalent, due to problems of either (1) undesirable side reactions[3] and/or (2) insufficient reactivity[1] of NADH or its artificial equivalent under the conditions.[4] In the present paper we report that efficient endoergonic reduction of benzoylformic acid derivatives takes place photochemically with $Na_2S_2O_3$ in the presence of a specifically functionalized micelle.

Very efficient charge separation can be achieved in two-phase systems[5] or multiphase systems. Further extension of the successful charge separation to the efficient electron fixation at the reduction end leads to the FMNH production via an artificial photosynthesis of bacteria type (see eq 1).



(1)

Thus, a micellar system consisting of ZnTPPS (ZnTPP *p*-tetrasulfonate, 2×10^{-6} M) as a photocatalyst, quinolinium-3-carboxamide (**2**) (7×10^{-5} M) as an electron acceptor, $Na_2S_2O_3$ (0.02 M) as an electron source, and CTAB (5×10^{-3} M) was prepared and degassed under vacuum followed by Ar substitution. The aqueous micellar solution was irradiated by a 500-W tungsten lamp (>370 nm, with a Toshiba UV-37 filter, with water cooling).

Table I. Recycling of Photocatalyst[a]

substrate	$PhCOCO_2Me$	$PhCH_2COCO_2Me$	isatin
ZnTPPS, M	1.1×10^{-6}	1.8×10^{-6}	5.1×10^{-5}
obsd recycling[d]	82	60[d]	2.1
theor recycling[c]	330	64	30

[a] Substrate = 1.4×10^{-3} M, $[ZnTPPS]_0 = 2.9 \times 10^{-6}$, $[2a]_0 = 2.1 \times 10^{-5}$ M, $[Na_2S_2O_3]_0 = 0.18$ M, CTAB, 0.12 M, $h\nu$ (>370 nm). [b] Electron utilized for reduction/ZnTPPS used. [c] Based on ZnTPPS consumed. [d] Recovery of the starting keto carboxylate was poor.

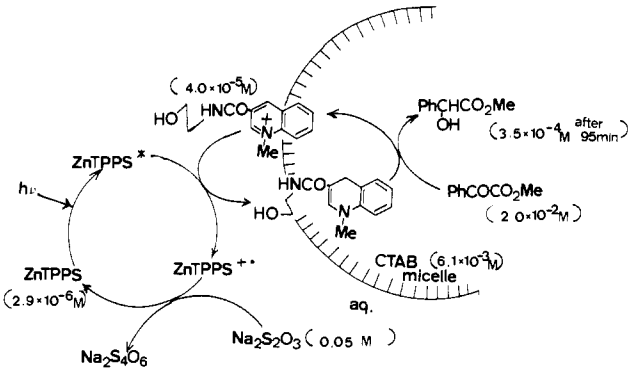
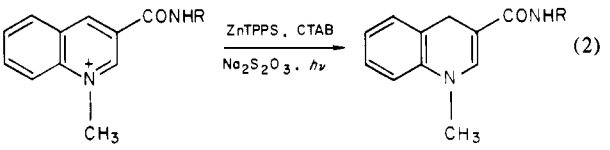


Figure 1. Benzoylformate photoreducing micelle.

After 10 min of irradiation practically quantitative conversion of **2** to the corresponding dihydro derivative, **3**, was observed (eq 2).



(2)

2a, R = CH_2CH_2OH
b, R = H

3

In an interesting contrast, no detectable amount of **3** was formed from the irradiation of the homogeneous solution of **2** under the corresponding conditions (without CTAB). Therefore, it is evident that phase transfer of **3** from an aqueous to a hydrophobic region is necessary and important for the effective production of the NADH equivalent. The following observations are noteworthy: (a) a recycling number of the photocatalyst (reduction equivalent/catalyst used) was found to be ca. 70; (b) no appreciable decomposition of the photocatalyst was observed; (c) the present reduction is an energetically uphill conversion by 15-18 kcal/mol, and reduction of **2** to **3** with $Na_2S_2O_3$ does not occur without irradiation.

The presently prepared dihydroquinoline **3a** incorporated in the photosynthesizing micelle was used for the reduction of benzoylformates. Thus, methyl benzoylformate was reduced to the corresponding mandelate in a good yield (eq 3 and Table I) and

$$PhCOCO_2Me + \mathbf{3a} \rightarrow PhCHOHCO_2Me + \mathbf{2a} \quad (3)$$

with a reasonable rate. However, dihyroquinoline **3b**, having no substituent on the amide nitrogen, showed only slow rate and very poor yield of mandelate.

On the basis of these observations, full construction of a "keto carboxylate photoreducing micelle" was successfully made as shown in Figure 1. Recycling numbers of the photocatalyst and the electron-transport catalyst were excellent, and a remarkable amount of methyl mandelate was accumulated in the micelle as shown in Figure 1. The methyl mandelate formed was extracted with ether (3×2 mL) from the aqueous solution, analyzed by HPLC, and purified. Interestingly, under the conditions, the observed steady-state concentration of **3a** was low, suggesting that the reduction of the benzoylformate with **3a** in the micelle was quite fast. Other keto carboxylic acid derivatives were similarly reduced with $Na_2S_2O_3$ by the present "photoreducing micelle".

(1) (a) Reviews: D. S. Sigman, J. Hajodu, and D. J. Creighton, "Bioorganic Chemistry", E. Tamelen, Ed., Academic Press, 1978, Vol. 4, p 385; R. J. Kill and D. A. Widdowson, ibid., p 239. (b) Y. Ohnishi, K. Kagami, and A. Ohno, *J. Am. Chem. Soc.* **97**, 4766 (1975). (c) J. G. der Vries and R. M. Kellog, *ibid.*, **101**, 2759 (1979). (d) S. Akabori, S. Sakurai, Y. Izumi, and Y. Fujii, Nature (*London*) **178**, 323 (1956). (e) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, Inc., Englewood Cliffs, NJ, 1971. (f) W. S. Knowles, M. J. Sabacky, B. D. Vineyard, and D. J. Weinkauff, *J. Am. Chem. Soc.*, **97**, 2568 (1975).

(2) C. H. Wong and G. M. Whitesides, *J. Am. Chem. Soc.*, **104**, 3542 (1982).

(3) S. Shinkai, H. Hamada, Y. Kusano, and O. Manabe, *J. Chem. Soc., Perkin Trans. 2*, 699 (1979).

(4) S. Shinkai, H. Hamada, T. Ide, and O. Manabe, *Chem. Lett.*, 685 (1978).

(5) S. C. Wallace, M. Oratzel, and J. K. Thomas, *Chem. Phys. Lett.*, **23**, 359 (1973).

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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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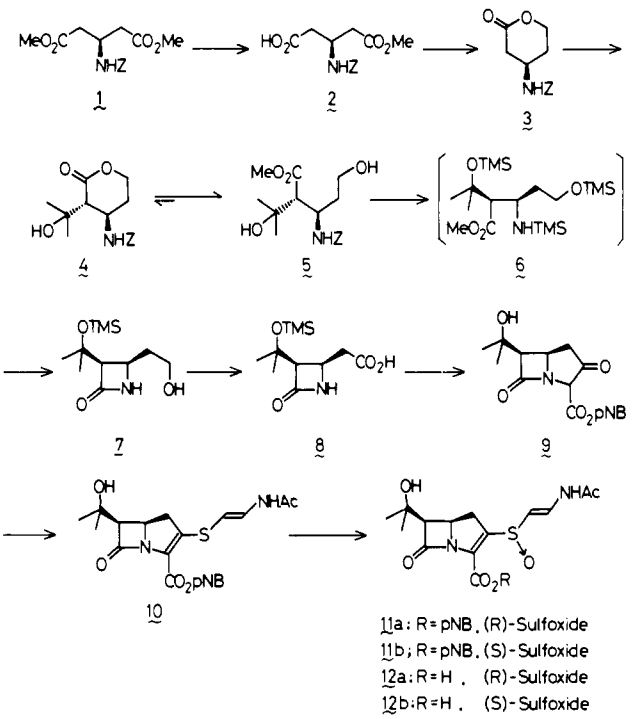
The synthetic control of absolute stereochemistry of (+)-thienamycin and related, naturally occurring, trans-substituted carbapenem antibiotics has been developed by a number of unique approaches.[1] However, there is no successful report for the chiral synthesis of naturally occurring cis-substituted 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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