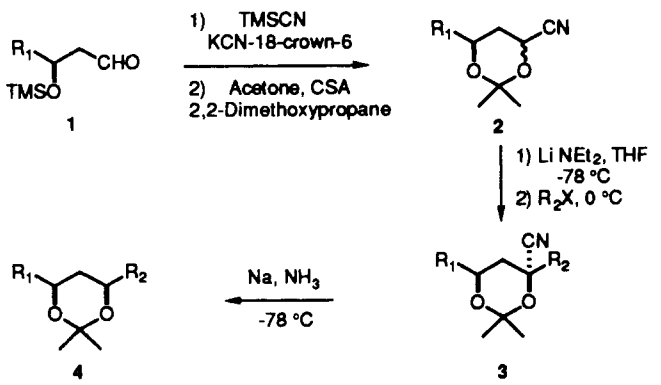
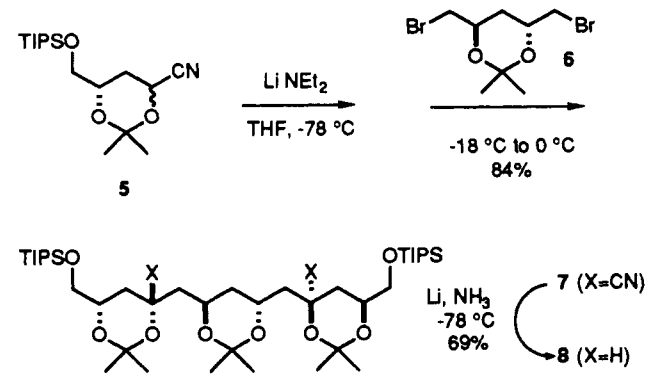
Scheme I



Scheme II



without any loss of stereochemistry at the secondary methyl centers (entries 6, 7).[9] Isolated olefins are not affected by this procedure (entry 4), and allylic ethers are tolerated if lithium di-*tert*-butylbiphenylide in THF is used in the reductive decyanation (entry 9). Even compounds with an intervening quaternary centers give good results (entry 8). The example presented in Scheme II illustrates the potential of this procedure in polyene macrolide antibiotics synthesis. Reaction of scalemic dibromide **6**[10] with 2.8 equiv of the cyanohydrin anion derived from scalemic **5** gives the dialkylated product **7** in 84% yield. Reductive decyanation with lithium in ammonia gives a 69% yield of **8**, which has the correct relative stereochemistry for C15 to C27 of roxaticin.[11] This new method will dramatically simplify the synthesis of complex polyol chains.

What factors determine the stereochemistry of these reductive decyanation? The reductive decyanation of protected cyanohydrins has not been reported, but the reductive decyanation of tertiary nitriles is a well-studied reaction which has been known for over 50 years.[12] Reductive decyanation proceeds by fragmentation of a nitrile radical anion to give cyanide anion and an alkyl radical which is subsequently reduced and protonated to give an alkane. In the reduction of axial cyanohydrin **3** the proton is introduced into an axial position, which is due to either stereochemical retention or preferential formation of the axial anion. Cohen and Sinay have shown that reduction of 2-tetrahydropyranyl radicals produces axial anions,[13] which presumably reflects the greater stability of the axial rather than the equatorial radical,[14] whereas Fabre has shown that reductive decyanation of aminonitriles proceeds largely with retention of configuration.[15] To distinguish between preferential formation of an axial anion and stereochemical retention we prepared cyanohydrin acetonide **3** (R_1 = *i*-Pr, R_2 = *n*-C_5H_{11}) and its epimer as a 52:48 mixture from the corresponding ketone.[16] Reduction of this mixture with sodium in liquid ammonia gave *syn*-1,3-diol acetonide **4** (R_1 = *i*-Pr, R_2 = *n*-C_5H_{11}) as a single isomer[17] in 87% yield, demonstrating that the axial anion is formed preferentially from both cyanohydrin epimers. The syn stereochemistry observed in reductive decyanations reflects the configuration preference for axial anomeric radicals and not a retention of configuration.

Acknowledgment. Support has been provided by the Searle Scholars Program, the Petroleum Research Fund, and the National Institutes of Health (GM43854-01).

Supplementary Material Available: Full spectral data for all new compounds and detailed experimental procedures for compounds **2**, **3**, **4** (entry 1), **5**, **7**, and **8** (11 pages). Ordering information is given on any current masthead page.

(9) In entry 6, aldehyde **1** and acetonide **4** are both present as 10:1 mixtures at the methyl center. In entry 7, aldehyde **1** and acetonide **4** are both present as 15–17:1 mixtures at the methyl center.

(10) **6** was prepared in optically pure form by hydrogenating 1,5-dichloro-2,4-pentanedione with $[(S\text{-BINAP})RuCl_2]_2Et_3N$ catalysis and treating the resulting diol sequentially with (i) KOH/Et_2O, (ii) Li_2NIBr_4, and (iii) acetone, 2,2-dimethoxypropane, CSA. Full experimental details will be published separately.

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(12) Walter, L. A.; McElvain, S. M. *J. Am. Chem. Soc.* **1934**, *56*, 1614–1616. Arapakos, P. G. *J. Am. Chem. Soc.* **1967**, *89*, 6794–6796. Arapakos, P. G.; Scott, M. K. *Tetrahedron Lett.* **1968**, 1975–1976. Arapakos, P. G.; Scott, M. K.; Huber, F. E., Jr. *J. Am. Chem. Soc.* **1969**, *91*, 2059–2062. Fabre, C.; Salem, M. H. A.; Welvart, Z. *Bull. Soc. Chim. Fr.* **1975**, 178–182. Bunnelle, W. H.; Shevlin, C. G. *Tetrahedron Lett.* **1989**, *30*, 4203–4206.

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(14) Descotes, G. *J. Carbohydr. Chem.* **1988**, *7*, 1–20.

(15) Fabre, C.; Welvart, Z. *C. R. Acad. Sci. Paris* **1970**, *270*, 1887–1889. Bonin, M.; Romero, J. R.; Grierson, D. S.; Husson, H.-P. *Tetrahedron Lett.* **1982**, *23*, 3369–3372.

(16) 2-Hydroxy-3-methyl-5-decanone was converted to **3** (R_1 = *i*-Pr, R_2 = *n*-C_5H_{11}) and its epimer as follows: (i) BSA, CH_3CN; (ii) TMSCN, KCN–18-crown-6; (iii) acetone, 2,2-dimethoxypropane, CSA.

(17) The ratio was 99.0:1.0 syn to anti (see ref 8).

Photocatalytic One-Step Syntheses of Cyclic Imino Acids by Aqueous Semiconductor Suspensions

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Summary: Optically active cyclic imino acids, pipecolinic acid and proline, are readily obtained from α,ω-diamino carboxylic acids and their N_ω-substituted derivatives by the photoirradiation of aqueous suspensions of TiO_2 or CdS loaded with platinum oxides under Ar at room temperature.

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Few successful cases of the application of semiconductor photocatalysis have appeared in the literature, despite its potential as a specific and unique synthetic tool.[1] Previously we reported the room-temperature photocatalytic conversion of aliphatic diamines to cyclic secondary amines in an aqueous suspension of platinized TiO_2.[2] This paper describes an application of photocatalytic cyclization to the room-temperature one-step synthesis of optically active cyclic imino acids **3** and **4** from the α,ω-diamino carboxylic acids[3] **1** and **2**, as a practical and economical nonenzymatic route to useful synthons for heterocyclic compounds.

Upon illumination (>300 nm, high-pressure Hg arc) onto an oxygen-free suspension of TiO_2 loaded with PtO_2,[4] proline (**3**) and pipecolinic acid (**4a**) were obtained from L-ornithine (**1a**) and L-lysine (**2a**), respectively (Table I). A lower molecular weight homologue, L-2,4-diaminobutanoic acid (**5**), did not give a 4-membered-ring imino acid, but a degradation product, β-alanine. H_2 and NH_3 were commonly detected in the experiments shown in the table. Minor amounts of CO_2 and cyclic secondary amines were observed, suggesting that a photo-Kolbe reaction proceeds simultaneously.[5] The TiO_2 suspensions gave 2S (i.e. L) isomers that retain their original configuration despite the variation of loaded noble metals, whereas CdS[6] and ZnS gave 2*R* (i.e. D) products in excess.

$$R^1OOCCH(NH_2)(CH_2)_nNHR^2 \rightarrow$$

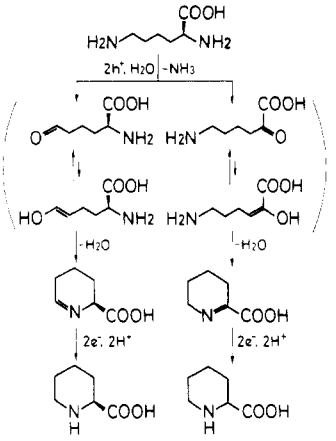
L-**1a–c** (n = 3)
L-**2a–g** (n = 4)

$$R^1OOC\underbrace{CH(CH_2)_nNH} + R^2NH_2$$

3 (n = 3, R^1 = H)
4a (n = 4, R^1 = H)
4b (n = 4, R^1 = CH_3)

MS analysis (FAB ionization) of **4a** from L-$^{15}N_\alpha$-**2a** (Cambridge Isotope Laboratories, 99% ^{15}N) in TiO_2–PtO_2 suspension showed the content of ^{15}N-**4a** to be 64, 53, and 62% at initial pH's (pH_i) of 6, 10, and 13, respectively. These values were quite close to the optical purities (68, 57, and 13% ee L), except in the case of the strongly alkaline (pH_i 13) suspension.[7] This result indicates that the incorporation of α- and ϵ-amino groups into **4a** leads to L (retaining the original configuration) and racemeic products, respectively, and also suggests the mechanism shown in Scheme I. This mechanism consists of oxidation of the amino group followed by hydrolysis into carbonyl derivatives, intramolecular condensation between the carbonyl

Scheme I



group and residual amino group, and reduction of Schiff bases.[2]

We performed a second isotope experiment by measuring the deuterium distribution of **4a** obtained from a D_2O suspension by ^1H NMR spectroscopy.[8] Assuming two possibilites for deuterium incorporation in **4a** (i.e., via reduction of the Schiff bases to result in deuteration at the α- and ϵ-, and N-positions and via keto–enol tautomerization of the α-keto acid or δ-aldehyde resulting in deuteration at the β- or δ-positions), the composition of **4a** via the δ-aldehyde can be estimated from the deuterium content at the ϵ-position to be 48%.[9] The coincidence with the optical purity measured by HPLC (52%) further supports this reaction mechanism. The marked difference in optical purity of **4a** obtained from TiO_2 and from CdS should arise from the difference in primary reaction paths; TiO_2 and CdS give L-rich and racemic[10] products via an ω-aldehyde and α-keto acid, respectively, although the cause of the difference is still obscure at present.[11] The difference in adsorption sites between metal oxides and sulfides might account for this alternative reaction pathway. Molecular structural and spectroscopic studies on the surface adsorption are in progress.

The above results lead to a strategy for producing optically pure cyclic imino acids through the preferential oxidation of ω-amino groups (rather than α-amino) in the substrates. We attempted to activate the ω-amino group by N_ω-substitution. As seen in the table, the N_ω-substi-

(1) Fox, A. M. *Acc. Chem. Res.* **1983**, *16*, 314 and references therein. For example (unusual Kolbe reaction): Kraeutler, A. J.; Bard, A. J. *J. am. Chem. Soc.* **1978**, *100*, 5985. (epoxidation and oxidative cleavage of olefins) (a) Kanno, T.; Oguchi, T.; Sakuragi, H.; Tokumaru, K. *Tetrahedron Lett.* **1980**, *21*, 467. (b) Sackett, D. D.; Fox, M. A. *J. Phys. Org. Chem.* **1988**, *1*, 103. (oxidative coupling of amines) Yanagida, S.; Azuma, T.; Kawakami, H.; Kizumoto, H.; Sakurai, H. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1487.

(2) Nishimoto, S.; Ohtani, B.; Yoshikawa, T.; Kagiya, T. *J. Am. Chem. Soc.* **1983**, *105*, 7180.

(3) Enantioselective stoichiometric synthesis of L-**4a** from L-**2a**, for example: (a) Fujii, T.; Miyoshi, M. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 1341–1342. (b) Miyazaki, K.; Yasutake, A.; Aoyagi, H.; Izumiya, N. *Mem. Fac. Sci. Kyushu Univ., Ser. C* **1980**, *12*, 165–172. (c) Beck, M. T.; Katho, A.; Dozsa, L. *Inorg. Chim. Acta* **1981**, *55*, L55–L56. (d) Katho, A.; Bodi, Z.; Beck, M. T. *Inorg. Chim. Acta* **1984**, *84*, 145–150.

(4) Mechanical mixing of TiO_2 (or CdS) and PtO_2 powders in an agate mortar provides fairly active photocatalyst. Photoinduced deposition of platinum onto TiO_2 is also a means to prepare a catalyst suitable for the present reaction. Details will be described elsewhere.

(5) No evidence was obtained to distinguish two pathways; decarboxylation into α,ω-diamines followed by deaminocyclization and decarboxylation of **3** and **4a**.

(6) Although CdS by itself could induce the photocatalytic cyclization as in the case of ZnS, PtO_2 loading increases the reaction rate.

(7) In the control experiment at high pH, **4a** was also decomposed by the photocatalytic reaction and the residual **4a** was partly reacemized, presumably due to the base-catalyzed dark reaction. Since the pH of the reaction mixture increases due to NH_3 liberation, prolonged irradiation might decrease the yield and/or optical purity of **4a**. Actually, buffered TiO_2 suspension (pH 4) gave improved optical purity of **4a** (70% ee L), which was higher than that from the unbuffered suspension (pH_i 4) (60% ee L).

(8) To minimize the contamination of H atom, the catalyst (TiO_2–PtO_2) and **2a** (hydrochloride) were mixed with D_2O (CEA, >99.8% D) and evaporated. This treatment was repeated twice. NaOD in D_2O (CEA, >99%) was added to adjust D^+ concentration to pD_i = 10. Deuterium distribution was estimated from a ^1H NMR spectrum on the assumption that C_γ remains undeuterated (Scheme I).

(9) As suggested in the scheme, one of two ϵ-H atoms (equatorial) of **4a** remained undeuterated, while 48% of an axial ϵ-H was substituted by deuterium. The ^1H NMR peak assignment was based on the previous report: Kristensen, I.; Larsen, P. O.; Olsen, C. E. *Tetrahedron* **1976**, *32*, 2799.

(10) Excess D isomer in the CdS systems is attributable to transamination between the α-keto acid and substrate L-**2a** to yield D-**2a** and α-keto acid, in the dark.

(11) A difference in the photocatalytic products from α-hydroxy carboxylic acid by TiO_2 and CdS has been reported: Harada, H.; Sakata, T.; Ueda, T. *J. Phys. Chem.* **1989**, *93*, 1542–1548. In agreement with the present results, the CdS-based catalyst led to the production of α-keto acids, while the TiO_2-based catalyst gave decarboxylated products.

Table I. Photocatalytic Syntheses of Cyclic Imino Acids from L-α,ω-Diamino Carboxylic Acids

	$R^1OOCCH(NH_2)(CH_2)_nNHR^2$										
	R^1	n	R^2	conc, mM	catalyst	pH_i	time, h	conv, %	product	yield,[a] %	% ee, config
1a	H	3	H	20	TiO_2–PtO_2	9.8	41	100	**3**	43[b]	27, L
1b	H	3	C(=NH)NH_2	20	TiO_2–PtO_2	2.7	40	100	**3**	31	97, L
1c	H	3	$CONH_2$	20	TiO_2–PtO_2	6.5	17	100	**3**	32	89, L
2a	H	4	H	20	TiO_2–PtO_2	9.7	44	100	**4a**	33[b]	47, L
2a	H	4	H	40	CdS[c]–PtO_2	9.7	24	59	**4a**	24	17, D
2a	H	4	H	40	CdS[d]–PtO_2	9.7	24	42	**4a**	12	13, D
2a	H	4	H	40	ZnS	9.7	24	100	**4a**	7	20, D
2b	H	4	C(=NH)NH_2	20	TiO_2–PtO_2	5.7	24	85	**4a**	43	96, L
2c	H	4	$CONH_2$	20	TiO_2–PtO_2	7.3	17	89	**4a**	38	92, L
2d	H	4	$COOC(CH_3)_3$	8	TiO_2–PtO_2	4.6	41	80	**4a**	11	100, L
2e	H	4	$COCH_3$	20	TiO_2–PtO_2	5.8	24	68	**4a**	17	98, L
2f	H	4	CHO	20	TiO_2–PtO_2	6.6	47	50	**4a**	8	56, L
2g	CH_3	4	H	20	TiO_2–PtO_2	4.5	48	53	**4b**	16	75, L
5	H	2	H	20	TiO_2–PtO_2	2.0	40	100	β-Ala[e]	22	–

[a] HPLC yield based on feed, unless otherwise stated. [b] Isolated yield. [c] Supplied from Katayama Chemicals. [d] Furuuchi Chemicals. [e] β-Alanine.

tuted amino acids gave **3** and **4a** with fairly high or almost quantitative optical purity. An exception was the *N*-formyl derivative (**2f**) yielding only 56% ee L **4a**. Liberation of guanidine and urea, observed respectively from N_ω-amidino and carbamoyl derivatives, indicates a C–N_ω bond cleavage by the photocatalytic process. The marked decrease in chemical yield from the *tert*-butoxycarbonyl and acetyl derivatives is attributed to the predominant formation of an α-keto acid which undergoes intermolecular condensation and/or further decomposition instead of cyclization into the Schiff base, owing to the less reactive secondary ω-amino group. Thus, N_ω substitution by a relatively hydrophilic group might improve the optical purity with a reasonable yield. In another approach, esterification of the α-carboxylic acid of **2a** was also effective for improving the optical purity (**2g**), while reducing reactivity.

In conclusion, we have demonstrated the facile photocatalytic synthesis of cyclic imino acids from α,ω-diamino carboxylic acids, via a redox-combined mechanism with either α-keto acid or ω-aldehyde intermediates. Further improvements through surface modification of the catalysts are underway.

Thermal Hetero [3 + 2] Cycloaddition Approach to Functionalized Tetrahydrofurans

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Summary: A purely thermal [3 + 2] cycloaddition between a ketal of 2-methylenecyclopropanone **1** and a carbonyl compound takes place to give an acetal of α-methylene γ-lactone **2** in good to excellent yield, providing a strategically new entry to substituted tetrahydrofurans.

Substituted tetrahydrofurans and γ-lactones are among the most common structures in biologically active compounds.[1] We report here a strategically novel synthesis of five-membered oxygen heterocycles that relies upon a single-step, thermal hetero [3 + 2] cycloaddition[2] of a methylenecyclopropanone ketal **1**[3] with carbonyl compounds (Scheme I, reaction a).

Several features of the reaction are noteworthy. (1) The reaction is purely thermal and proceeds under relatively mild conditions (80–130 °C) either neat or in a variety of solvents. (2) The cycloaddition is virtually free of side reactions, and good to excellent yields of cycloadducts are obtained by using stoichiometric amounts of reactants. (3) The cycloaddition exhibits striking regioselectivity, giving predominantly (>90%) an acetal of α-methylene γ-lactone **2** rather than the ketene acetal **3**, which would be the product expected from the reaction mode analogous to the previously observed cycloaddition of **1** with electron-deficient olefins[3] (Scheme I, reaction b). (4) The adduct **2**–an intriguing protected α-methylene γ-lactone–not only gives the parent lactone upon hydrolysis, but provides access to a variety of synthetically and biologically important structures.[4]

The experimental procedure is very simple: heating a mixture of **1** (509 mg, 3.30 mmol) and benzaldehyde (318 mg, 3.00 mmol) in toluene (2.2 mL) at 80 °C for 11 h

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(1) Cf.: Oliver, E. J.; Fischer, H. D. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Eds.; Springer: Wien, 1979; p 47. Westley, J. W. *Polyether Antibiotics: Naturally Occurring* Acid *Ionophores*; Marcel Dekker: New York, 1982; Vols I, II.

(2) (a) Trost, B. M.; Bonk, P. J. *J. Am. Chem. Soc.* **1985**, *107*, 1778. (b) Trost, B. M.; Bonk, P. J. *J. Am. Chem. Soc.* **1985**, *107*, 8277. (c) Trost, B. M.; King, S. A.; Schmidt, T. *J. Am. Chem. Soc.* **1989**, *111*, 5902. (d) Little, R. D.; Bode, H.; Stone, K. J.; Wallquist, O.; Dannecker, R. *J. Org. Chem.* **1985**, *50*, 2400. (e) Danheiser, R. L.; Kwasigroch, C. A.; Tsai, Y.-M. *J. Am. Chem. Soc* **1985**, *107*, 7233. (f) Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.* **1986**, *108*, 6695. (g) For our previous route via homoenolate chemistry, see: Nakamura, E.; Oshino, H.; Kuwajima, I, *J. Am. Chem. Soc.* **1986**, *108*, 3745. (h) For 1,3-dipolar cycloaddition routes, see: Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*; John Wiley & Sons: New York, 1984; Vols. 1 and 2. See ref 3 for [3 + 2] synthesis of five-membered carbocycles. (i) See ref 3 for [3 + 2] cycloaddition approaches to cyclopentanes.

(3) Yamago, S.; Nakamura, E. *J. Am. Chem. Soc* **1989**, *111*, 7285.

(4) See the supplementary material for some transformations.

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