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.

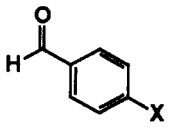
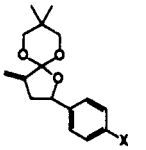
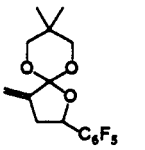
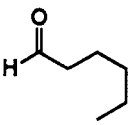
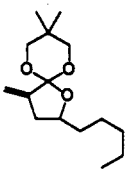
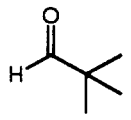
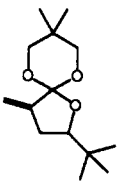
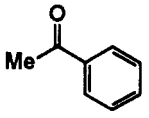
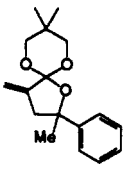
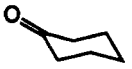
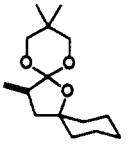
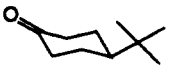
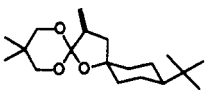
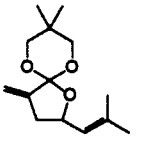
(2) (a) Trost, B. M.; Bonk, P. J. *J. Am. Chem. Soc.* **1985**, *107*, 1778. (b) Trost, B. M.; Bonk, P. J. *J. Am. Chem. Soc.* **1985**, *107*, 8277. (c) Trost, B. M.; King, S. A.; Schmidt, T. *J. Am. Chem. Soc.* **1989**, *111*, 5902. (d) Little, R. D.; Bode, H.; Stone, K. J.; Wallquist, O.; Dannecker, 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.

0022-3263/90/1955-5553$02.50/0

Table I. Cycloaddition of 1 with Carbonyl Compounds[a]

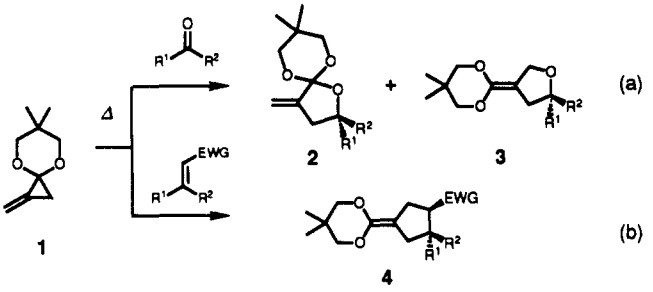
entry	carbonyl compound (equiv)	conditions: temp, °C	conditions: time, h	major product	% yield of 2[b] (2:3)[c]
1	 X = H (0.91)	80	11		84 (89:11)
2	X = OMe (1.1)	80	20		82 (87:13)
3	X = Cl (1.1)	80	8		81 (87:13)
4	C_6F_5CHO (0.91)	80	4		75 (92:8)
5	 (1.1)	100	30		84 (96:4)
6	 (0.91)	100	63		86 (96:4)
7	 (1.1)	100	30		81 (93:7)
8	 (0.83)	130	18		56[d] (96:4)
9	 (0.83)	100	62		81[e] (~98:2)
10	(0.77)	80	50[f]		74[e] (~94:6)
11	$(CH_3)_2C{=}CHCHO$ (1.1)	80–100	19		49[g] (95:5)

[a] The reaction was carried out in benene or toluene except in entry 9 (without solvent). [b] Isolated yield. Yields are based on 1 except in entries 1, 4, 6, and 8–10 wherein they are based on the carbonyl compounds. [c] Determined by ^1H NMR in the experiments performed in benzene-d_6 or toluene-d_8. In entries 9, 10, and 11, the ratios were estimated by capillary GLC. [d] 74% yield when 2 equiv of 1 was used. [e] The product consisted of a 80:20 mixture of two diastereomers (the major isomer is shown). See the supplementary material for structure determination. [f] The reaction was carried out under high pressure (13–14 kbar) in CH_2Cl_2. [g] A cycloadduct (4) due to addition to the olefin also formed in 25% yield.

followed by chromatographic purification on silica gel gives 656 mg (84%) of the cycloadduct **2** (R^1 = Ph, R^2 = H). The reaction can be carried out either neat or in a variety of solvents, e.g., aromatic hydrocarbons, ethers, haloalkanes, and nitriles. We observed a moderate solvent effect, with the rate of reaction increasing as the solvent was changed from cyclohexane, to toluene, and to acetonitrile. The rate of the cycloaddition can be enhanced under high pressure (13–14 kbar). The reactions accompanies the formation of a small amount of a readily separable isomeric cycloadduct **3** (**2**:**3** ratio of >96:4) (Table I, entries 5–11). With some aromatic aldehydes, the ratio may become worse (ca. ~87:13, entries 1–3), yet still remains synthetically acceptable. The isomeric ratio is generally insensitive to the structure of the carbonyl compounds (cf. entry 6) or to the reaction pressure (13–14 kbar).

Table I summarizes the results of our study of th cycloaddition. The reactions were very clean, and the cycloaddition products normally accounted for >90% of the total conversion of the starting carbonyl compounds. Aromatic carbonyl compounds (entries 1–4 and 7 reacted

Scheme I

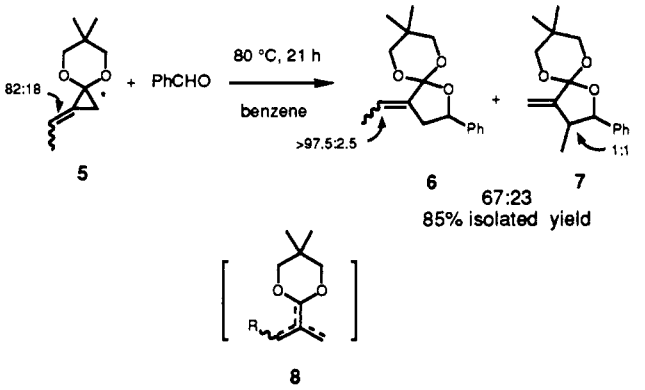


faster with 1 than aliphatic derivatives (entries 5, 6, and 8–10). Aldehydes reacted smoothly below 100 °C, while more sterically encumbered ketones reacted more slowly, requiring higher temperatures (100–130 °C). In these latter cases, use of high pressure proved particularly rewarding as shown in entry 10 for the cycloaddition of 4-*tert*-butylcyclohexanone, which was complete at 80 °C under 13–14 kbar of pressure. This cycloaddition took place selectively from the electronically favored axial direction,[5] and the stereoselectivity (80:20) remained unchanged under high-pressure conditions (cf. entries 9 and 10).

Whereas the cycloaddition of α,β-unsaturated *ketones* took place highly rgioselectively on the olefin[3] (Scheme I, reaction b), the cycloaddition to α,β-unsaturated *aldehydes* gave a product mixture due to competing cycloadditions to the carbonyl and the olefinic groups[3] (entry 11). The relative rates of these two paths, as examined for several enals, were found to fall in a range of 1:2 to 2:1.

Brief studies of competitive kinetic experiments confirmed the nucleophilic nature of this cycloaddition.[6] Thus, the rate of the cycloaddition doubled as the aldehyde acceptor was changed first from *p*-anisaldehyde to benzaldehyde, and then again on changing to *p*-chlorobenzaldehyde. Perfluorobenzaldehyde (entry 4) was the most reactive among the carbonyl compounds examined.

The reaction of an ethylidene compound **5** brings up the important issue of the regiochemical course of the cycloaddition. Thus, **5**,[7] prepared through the same synthetic sequence used for **1**,[3] was subjected to the reaction with benzaldehyde. Most interestingly, the reaction predominantly gave an ethylidene lactone acetal **6**[7] (57% isolated yield) together with a methylene lactone **7** (28%). The formation of **6** requires that the starred C–C bond in **5** be cleaved *prior to* the coupling with the aldehyde. An important consequence of such a cleavage is the formation of a trimethylenemethane **8** (R = Me).[8] A mechanistic



possibility that the present cycloaddition proceeds through a trimethylenemethane[9] is certainly consistent with a variety of experimental observations including the acceptor-dependent dichotomy of the reaction paths (i.e., C=O vs C=C; Scheme I). This fascinating mechanism is being actively investigated.

Acknowledgment. We thank the Ministry of Education, Science, and Culture for financial support (Grant-in-Aid for Scientific Research). We thank Prof. B. M. Trost for providing authentic spectra for structural assignments.

Supplementary Material Available: Physical data for the cycloadducts and structural assignment of the adduct in entries 9 and 10 in Table I (9 pages). Ordering information is given on any current masthead page.

(5) The trimethylenemethane-type intermediate by Trost gives a cycloadduct due to an equatorial approach of the reagent (ref 2a).

(6) (a) The nucleophilic nature of **1** has also been ascertained in the cycloaddition to olefins (ref 3). (b) Attempted cycloaddition of **1** to a benzaldehyde imine failed.

(7) The compounds **5** and **6** consisted of one major geometrical isomer. The stereochemistry has not been determined yet.

(8) (a) Interconversion between a methylenecyclopropane and a trimethylenemethane is a well-established process. Cf.: Ullmann, E. F. *J. Am. Chem. Soc.* **1960**, *82*, 505. Gajewski, J. J. *J. Am. Chem. Soc.* **1971**, *93*, 4450. Doering, W. v. E.; Birladeanu, L. *Tetrahedron* **1973**, *29*, 449. Gilbert, J. C.; Butler, J. R. *J. Am. Chem. Soc.* **1970**, *92*, 2168. Gilbert, J. C.; Higley, D. P. *Tetrahedron Lett.* **1973**, 2075. Kirmse, W. Murawski, H.-R. *J. Chem. Soc., Chem. Commun.* **1977**, 122. Salinaro, R. F.; Berson, J. A. *J. Am. Chem. Soc.* **1982**, *104*, 2228. Goldschmidt, Z.; Finkel, D. *J. Chem. Soc., Perkin Trans. 1* **1983**, 45. Buchwalter, S. L. *Tetrahedron* **1984**, *40*, 5097. Creary, X.; Mehrsheikh-Mohammadi, M. E. *J. Org. Chem.* **1986**, *51*, 2664. LeFevre, G. N.; Crawford, R. J. *J. Org. Chem.* **1986**, *51*, 747. Baldwin, J. E.; Ghatlia, N. D.; Lundbäck, K. M. O. *Acta Chem. Scad. B* **1987**, *41*, 698. Molchanov, A. P.; Kostikov, R. R. *Zh. Org. Khim*, **1988**, *24*, 949. (b) Theoreticl studies: Hehre, W. J.; Salem, L.; Wilcott, M. R. *J. Am. Chem. Soc.* **1974**, *96*, 4328. Feller, D.; Tanaka, K.; Davidson, E. R.; Borden, W. T. *J. Am. Chem. Soc* **1982**, *104*, 967. Skancke, A.; Schaad, L. J.; Hess, B. A., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 5315. Review: Akiba, K. J. *Synth. Org. Chem. Soc. Jpn.* **1973**, *31*, 635. (c) Very facile degenerate rearrangement of a suitably labeled derivative of **1** suggests facile generation of **8** under the present conditions: unpublished results.

(9) Berson's trimethylenemethane species (Berson, J. A. *Acc. Chem. Res.* **1978**, *11*, 486) undergoes cycloaddition only to benzaldehyde and to a tricarbonyl compound: Little, R. D. *Chem. Rev.* **1986**, *86*, 875.

1,2-Functionalization of α,β-Epoxycycloalkanones

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Summary: For 1,2-functionalization, α,β-epoxy cycloalkanones were treated with 2.1 equiv of 2-lithio-2-(trimethylsilyl)-1,3-dithiane to give high yields of *trans*-2-dithianyl-3-dithianylidene-1-cycloalkanols, which were oxidatively hydrolyzed with an excess of halogenating agents in alcohols to the corresponding acetal esters.

Our synthetic approaches to aglycons of anthracyclines such as daunomycinone (**1**) and adriamycinone (**2**)[1] involve

(1) For representative reviews, see: (a) Kelly, T. R., Ed. *Tetrahedron* **1984**, *40*, 4539–4793. (b) Krohn, K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 790.

0022-3263/90/1955-5555$02.50/0