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.

Acknowledgment. This work was financially supported in part by a Grant-in-Aid Special Project Research. We express our cordial thanks to Dr. H. Tani of Tokyo Research Laboratories, Kowa Co., Ltd., for the generous donation of the authentic samples of **11a** and natural carpetimycin A, for the experimental help at the final stage of hydrogenolysis of **11a** and **11b**, and for the determination of the antibacterial activity of the synthetic samples **12a** and **12b**.

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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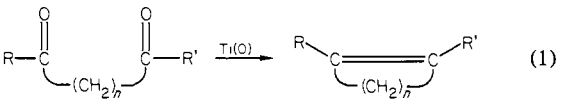
Received November 15, 1982

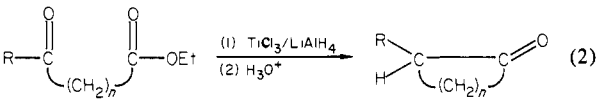
Several years ago, we reported a new and general method for the synthesis of cycloalkenes.[1,2] Treatment of diketones or keto aldehydes with an activated Ti(0) reagent, prepared by reduction of $TiCl_3$ with a Zn-Cu couple, effects an intramolecular coupling reaction leading to the cycloalkene. The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

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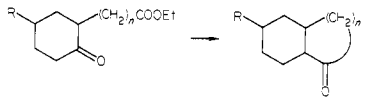
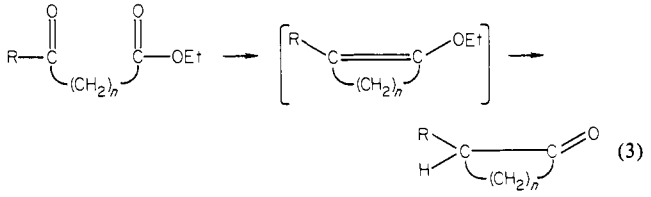
Table I. Synthesis of Cycloalkanones by Titanium-Induced Cyclizati on of Keto Esters

entry	keto ester	cycloalkanone	ring size	isolated yield, %
				
1	R = *tert*-butyl; $n = 1$		4	57
2	R = H; $n = 2$		5	75
3	R = H; $n = 3$		6	80
4	R = H; $n = 4$		7	82
5	R = H; $n = 5$		8	52
6	R = H; $n = 6$		9	50
7	R = H; $n = 11$		14	54
				
8	R = CH_3; $n = 8$		10	50
9	R = CH_3CH_2; $n = 9$		11	45
10	R = CH_3CH_2; $n = 10$		12	63
11	R = CH_3; $n = 11$		13	60

The mechanism of this titanium-induced keto ester cyclization appears to be an exact analogue of the diketone coupling.[2] Thus, an initial pinacol-type coupling reaction forms the carbon–carbon bond,[5] followed by deoxygenation to yield an enol ether, and acidic hydrolysis to yield the final ketone product (eq 3). Evidence for



(3)

this proposed mechanism comes from the fact that the enol ether can indeed be isolated if the acidic step is eliminated from the workup.

The finding that enol ethers are initial reaction products opens up a host of possibilities for further exploration; for example, does the coupling reaction occur with keto trialkylsilyl esters to yield enol silyl ethers? We are actively pursuing this and other possibilities.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their support of this research.

Registry No. $TiCl_3$, 7705-07-9; $LiAlH_4$, 16853-85-3; ethyl 5-*tert*-butyl-2-oxocyclohexaneacetate, 4857-18-5; ethyl 2-oxocyclohexanepropanoate, 4095-02-7; ethyl 2-oxocyclohexanebutanoate, 84751-60-0; ethyl 2-oxocyclohexanepentanoate, 84751-61-1; ethyl 2-oxocyclohexanehexanoate, 84751-62-2; ethyl 2-oxocyclohexaneheptanoate, 41301-64-8; ethyl 2-oxocyclohexanedodecanoate, 84751-63-3; methyl 10-oxoundecanoate, 18993-09-4; methyl 11-oxotridecanoate, 84751-64-4; methyl 12-oxotetradecanoate, 74515-89-2; methyl 13-oxotetradecanoate, 18993-10-7; 2-*tert*-butylbicyclo[4.2.0]octan-7-one, 84751-65-5; octahydro-1*H*-inden-1-one, 29927-85-3; octahydro-1(2*H*)-naphthalenone, 4832-16-0; decahydro-5*H*-benzacycloheptenone-5-one, 84751-66-6; decahydrobenzocycloocten-5(6*H*)-one, 84751-67-7; dodecahydro-5*H*-benzocyclononen-5-one, 84751-68-8; hexadecahydrobenzocyclotetradecen-5-(6*H*)-one, 84751-69-9; 2-methylcyclodecanone, 73674-38-1; 2-ethylcycloundecanone, 26644-85-9; 2-ethylcyclododecanone, 1138-00-7; 2-methylcyclotridecanone, 63662-71-5.

Supplementary Material Available: Analytical data and structures for entries in Table I (4 pages). Ordering information is given on any current masthead page.

(5) Intramolecular pinacol-type couplings of keto esters have been observed previously by using sodium in ammonia as the reducing agent, but the products of such couplings are mixtures of ketones and α-hydroxy ketones, yields are not good, and the reactions are limited to the formation of five- through seven-membered rings. See: Gutsche, C. D.; Tao, I. Y. C.; Kozma, J. *J. Org. Chem.* **1967**, *32*, 1782.

Rotational Excitation in the Carbon Monoxide Product of Ketene Photodissociation

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Received November 1, 1982

The consequences of photodissociation reactions, vis-à-vis the distribution of available energy among products' degrees of freedom, has been the subject of much recent study.[1] Infrared fluorescence[2,3] and laser absorption[4,5] methods have been employed in characterizing vibrational energy disposal, while in the case of rotational energy disposal, laser-induced fluorescence has proved useful in some cases.[6,7]

We report here the application of an infrared fluorescence method in probing rovibrational energy release to carbon monoxide, formed upon the photodissociation of ketene. Our data are in qualitative accord with published data on the CO vibrational energy distribution for this chemistry[8] but additionally demonstrate that rotational energy release is a dominant feature of the reaction dynamics. This result has important bearing on the problem of elucidating the nature of the potential surface for ketene photofragmentation.

The spectroscopy and photofragmentation of ketene have been extensively studied. Lee and co-workers[9] have found that photodissociation at 308 nm yields only $CH_2(^1A_1)$. Lin and coworkers[8] have determined a vibrational temperature for CO formed upon ketene photodissociation at 193 nm where again the CH_2 product is formed in the $^1A_1$ state. Little information is available on the rotational energy disposal associated with this chemistry. Although ^{14}C-labeling experiments have provided evidence of isomerization channels available to photoactivated ketene,[10] these are apparently not coupled to the fragmentation channel.[10,11] Detailed ab initio studies of the ketene photodissociation problem have been reported,[12,13] but the nature of the relevant potential surface has not been conclusively established.

In our experiments, ketene flowed through an aluminum fluorescence cell equipped with quartz windows through which an ArF* (193 nm) laser beam is propagated. The cell has a CaF_2 window for viewing IR radiation at 90° relative to the direction of propagation of the UV laser. A cold gas filter (CGF) cell, a 4.7-μm band-pass filter and a 1-μm long-pass filter are interposed between the cell and an IR detector. An InSb detector with a 7-μm cutoff is employed. Its output is processed by using a boxcar averager. The detection system risetime is ≲1 μs, and the laser pulse width is ca. 15 ns.

Irradiation of ketene at 193 nm (ca. 4 mJ/cm^2) yields intense IR fluorescence[14] at 4.7 μm due to CO. Fluorescence decay curves were recorded at several pressures of pure ketene between 0.04 and 4.5 torr and for dilute mixtures of ketene in argon. In every case, decay curves were obtained with the CGF cell both evacuated

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(14) Under our experimental conditions, IR fluorescence intensity is found to vary linearly with laser intensity.

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