hexane/2-propanol (95:5) at a flow rate of 2.0 mL/min, back pressure <1000 psi. The ratio could be determined directly by integration of the peak areas of interest.

Sulfones (1c–3c). To a solution of sulfides **1a–3a** (30 mg) in *tert*-butyl alcohol/saturated aqueous $MgSO_4$ (500 μL:500 μL) was added an excess of $KMnO_4$, and the purple reactions were stirred at room temperature for 4 h. The sulfones were isolated by preparative TLC on silica plates, which, when eluted with Et_2O, gave R_fs of ca. 0.9, and were easily separable from both contaminating sulfide and sulfoxide.

Acknowledgment. We thank Mr. David O'Krongly and Dr. Robert Corcoran for assistance in obtaining ^1H NMR data. The support and shared interest of Professor Ronald Breslow is gratefully acknowledged. This work was performed at Columbia University while the author held an NIH Postdoctoral Fellowship.

Registry No. **1a**, 622-63-9; (±)-**1b**, 67529-34-4; (*R*)-**1b**, 1519-40-0; (*S*)-**1b**, 62961-00-6; **1c**, 7569-34-8; **2a**, 30506-33-3; (±)-**2b**, 88315-70-2; (*R*)-**2b**, 88336-00-9; (*S*)-**2b**, 88336-01-0; **2c**, 34545-14-7; **3a**, 88315-69-9; (±)-**3b**, 88315-71-3; (*R*)-**3b**, 88336-02-1; (*S*)-**3b**, 88336-03-2; **3c**, 88315-72-4; **4**, 585-34-2; **5**, 3972-64-3; cyclodextrin, 1269-70-4; *p*-methylthiophenol, 106-45-6; *p*-*tert*-butylthiophenol, 2396-68-1.

(19) Based on both an examination of CPK molecular models and the results of Bender and co-workers (*J. Am. Chem. Soc.* **1967**, *89*, 3242), which indicate a greatly enhanced rate of hydrolysis for *m*-*tert*-butylphenyl acetate as compared to the para isomer.
(20) The binding of *tert*-butylhydroperoxide (Matsui and co-workers, *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1909) and of aromatics to cyclodextrins is well documented.
(21) Gilman, H.; Beaber, N. J. *J. Am. Chem. Soc.* **1925**, *47*, 1449.
(22) Ruechardt, C.; Eichler, S. *Chem. Ber.* **1962**, *95*, 1921.

Studies on the Intramolecular Claisen Condensation; Facile Synthesis of Tetronic Acids

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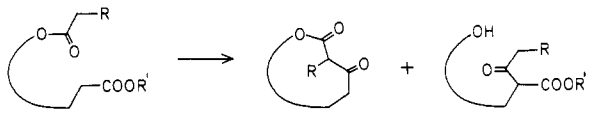
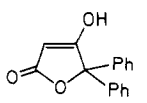
Received May 31, 1983

An ester of an acyloxy carboxylic acid can in principle give both a cyclic (**2**) and an acyclic (**3**) product in the intramolecular Claisen condensation. Disregarding re-



1 *2* *3*

actions of compounds that have additional anion-stabilizing groups, e.g., acetoacetates, few examples have however been reported of cyclizations of the type **1** → **2**. In 1956 Haynes and Stanners[1] treated α-acetoxy esters with (diisopropylamino)magnesium bromide and obtained, e.g., γ,γ-dimethyl- and γ,γ-diphenyltetronic acid (**4**) in yields

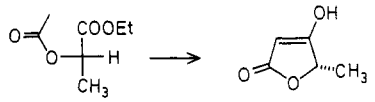


4

of 46% and 85%, respectively. Ireland and Thompson[2] recently improved the former yield to 95% by using lithium diisopropylamide as base.

(1) Haynes, L. J.; Stanners, A. H. *J. Chem. Soc.* **1956**, 4103-4106.
(2) Ireland, R. E.; Thompson, W. J. *J. Org. Chem.* **1979**, *44*, 3041-3052.

We now report some attempted intramolecular Claisen diester condensations using lithium bis(trimethylsilyl)-amide as base. Rathke and Lindert[3] found that this base smoothly deprotonates esters of acetic acid in THF at −78 °C but reacts markedly more slowly with esters of the higher carboxylic acids, and we therefore started with esters of acetoxy carboxylic acids in order to optimize the formation of the cyclic product **2**. Thus, when ethyl 2-(*S*)-acetoxypropanoate was added to 2.4 equiv of lithium bis(trimethylsilyl)amide in THF (−78 °C),[4] hydrolytic workup after 1 h gave (+)-γ-methyltetronic acid (**5**)[5] in a

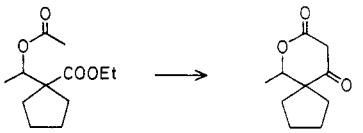


5

yield better than 95%. The analogous reaction using lithium diisopropylamide as base yielded a complex mixture containing only traces of **5**, and much of the starting ester was recovered (VPC, ^1H NMR). It seems reasonable to assume that the cause of the recovery of the starting ester is that it was transformed into its dianion by lithium diisopropylamide.

Similar treatment of ethyl 3-acetoxybutanoate and dimethyl 2-acetoxybutanedioate with lithium bis(trimethylsilyl)amide gave ethyl crotonate and dimethyl fumarate, respetively, as major products. In view of the

steric requirements of this base,[3] we interpret the result as being due to a selective deprotonation of the acetoxy group, followed by a cyclic (internal base) elimination of acetate ion. It is evident that the elimination leading to the α,β-unsaturated ester was faster than the formation of both the five- and the six-membered ring lactone. When elimination is prohibited, as in **6**, ring closure to the lactone **7** occurs. However, while the formation of **5** was essen-



6 *7*

tially complete within 30 min at −78 °C, only ca. 20% of **7** had been formed after 70 min at this temperature (VPC). In another run, the components were mixed at −78 °C (30 min) and the temperature was then raised to ca. −50 °C. It was found (VPC) that a reaction time of 3 h was necessary to complete the formation of **7**.

From an experiment with the γ-acetoxy ester **8**, we conclude that the formation of a seven-membered ring lactone is not a favored process. The use of 2.3 equiv of lithium bis(trimethylsilyl)amide (−78 °C, 2 h) led to a mixture of several compounds. The least polar component (**9**)[6] was obtained in a yield of 15% after chromatography on silica gel.

Application of the tetronic acid synthesis to tartaric acid would give optically pure carbohydrate-like C_6 compounds.

(3) Rathke, M. W.; Lindert, A. *J. Am. Chem. Soc.* **1971**, *93*, 2318-2320.
(4) This order of addition was used in all experiments.
(5) The levorotatory form of this compound, mp 115 °C, $[\alpha]_{546}$ −21° (*c* 0.5, H_2O), is a metabolite of *Penicillium Charlesii* G. Smith[13] and was shown to have the *R* configuration by a synthesis of **5** from ethyl (*S*)-lactate in low yield.[14]
(6) Duus, F.; Lawesson, S.-O. *Tetrahedron* **1971**, *27*, 387-399.

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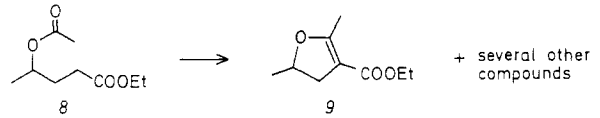
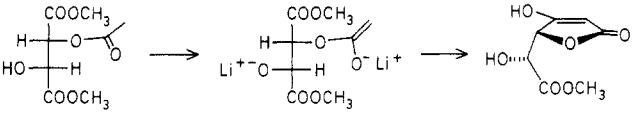


8 9

However, initially attempted syntheses from the diacetate or the acetate benzoate of dimethyl (*R,R*)-tartrate led to deep red crude reaction products from which no cyclized products could be isolated; benzoic acid was obtained from the latter starting material (ca. 50% yield). It seems reasonable to assume that these two starting esters, like dimethyl 2-acetoxybutanedioate (see above), undergo elimination faster than they undergo ring closure.

On the other hand, when the monoacetate **10**[7] was treated with 3.5 equiv of lithium bis(trimethylsilyl)amide in THF (-78 °C, 1 h), ring closure occurred, and after hydrolysis, **11** crystallized during workup (78% yield).



10 11

This difference in reactivity between **10** and the diacetate of dimethyl tartrate can be rationalized by assuming that the base rapidly converts the α-hydroxy group of **10** into a lithium oxido group which then prevents 1,2-elimination of the β-acetoxy group by lowering the acidity of the α hydrogen. The use of a lithium oxido group to prevent 1,2-elimination of an adjacent group has, to the best of our knowledge, not been reported before.

Experimental Section

Tetrahydrofuran (THF) was freshly distilled over $LiAlH_4$. An atmosphere of N_2 was used in all reactions involving amide bases. NMR spectra were recorded by using a JEOL JNM-FX 100 instrument. Unless otherwise stated, chemical shifts are related to internal tetramethylsilane.

General Procedure. Synthesis of 4-Hydroxy-5(*S*)-methyl-2(5*H*)-furanone ((*S*)-γ-Methyltetronic Acid) (5). A solution of lithium bis(trimethylsilyl)amide (15 mmol) in THF (40 mL) was prepared from the commercially available (Aldrich) 1 M solution in THF or from butyllithium (15 mmol) in ether (13 mL) and hexamethyldisilazane (20 mmol) in THF (30 mL, 15 min, ca. 10 °C). The solution of the base was cooled to -78 °C, and a solution of ethyl 2(*S*)-acetoxypropanoate[8] (1.00 g, 6.29 mmol) in THF (40 mL) was added with stirring over a period of 30 min. The reaction mixture was kept at -78 °C for 1 h and then poured into 2 M HCl (20 mL). The two layers were separated, the aqueous layer was washed once with EtOAc, the combined organic layers were dried with NaCl(s) and concentrated, and CH_2Cl_2 was added. Drying with Na_2SO_4 and evaporation of the solvent left a solid residue (0.76 g, 107%), mp 103-108 °C, which on ^1H NMR analysis proved to be almost pure γ-methyltetronic acid; estimated yield, >95%. Recrystallization from EtOAc-light petroleum ether gave 0.50 g (70%; 83% on the 4-g scale); mp 112-115 °C; $[\alpha]^{22}_D$ +19.3°; $[\alpha]^{22}_{546}$ +23.9° (*c* 0.5, H_2O).[5] ^1H and ^{13}C NMR spectra show that **5** in $CDCl_3$ is a mixture (≈3:7) of keto and enol forms: ^1H NMR ($CDCl_3$) δ 11.5 (very broad), 5.06 (s, olefinic H), 4.92 (q, 1 H), 3.23 (α-H of keto form), 1.53 (d, 3 H). In $(CD_3)_2SO$ only the enol form was observed: ^{13}C NMR, 183.3, 173.1, 87.2, 74.9, and 17.8 ppm (calibrated against solvent signal, 39.6 ppm); these shifts are similar to those obtained with CD_3OD as solvent.[9] This solvent dependence was somewhat unexpected since the usual experience is that the enol form decreases as the solvent polarity increases.

2-Methyl[tetrahydropyran-3-spirocyclopentane]-4,6-dione (7). Ethyl acetoacetate was alkylated with 1,4-dibromobutane[10] and the product reduced with sodium borohydride.[11] The resulting secondary alcohol was acetylated with acetic anhydride-/4-(dimethylamino)pyridine[12] to obtain ethyl 1-(1-acetoxyethyl)cyclopentane-1-carboxylate (**6**) in a yield of 51%; bp 80-82 °C (2 mmHg); ^1H NMR ($CDCl_3$) δ 5.22 (q, 1 H), 4.12 (q, 2 H), 2.3-1.4 (m, 11 H, including a 3-H singlet at 2.02), 1.24 (t, 3 H), 1.17 (d, 3 H).

The intramolecular Claisen condensation of **6** was carried out according to the general procedure, but the reaction mixture was kept at -50 to -55 °C for 3 h before hydrolysis. Workup as above and crystallization from ether-light petroleum ether gave a 76% yield of **7**: mp 76-79 °C; ^1H NMR ($CDCl_3$) δ 4.58 (q, 1 H), 3.58 and 3.42 (AB spectrum, 2 H, J_{AB} = 20.0 Hz), 2.2-1.4 (m, 8 H), 1.38 (d, 3 H); ^{13}C NMR ($CDCl_3$, 77.17 ppm) 204.8, 167.6, 78.9, 58.3, 44.4, 32.8, 29.6, 26.3 (double intensity, probably two carbons), 16.3 ppm. Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.92; H, 7.62.

Methyl 2-Deoxy-L-*threo*-hex-2-enarate 1,4-Lactone (11). Monoacetate **10**[7] (1 g) was allowed to react with lithium bis(trimethylsilyl)amide (3.5 equiv) according to the general procedure. After hydrolysis, the organic layer was separated and the aqueous layer extracted twice with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and the solvents evaporated. More ethyl acetate was added and then evaporated. After a further addition of ethyl acetate, the solution was concentrated to about 2 mL. On addition of methylene chloride (ca. 10 mL) **11** crystallized (78% yield). After recrystallization from THF-methylene chloride it showed the following: mp 126-130 °C; $[\alpha]^{22}_D$ +95° (*c* 0.5, H_2O); ^1H NMR [$(CD_3)_2SO$ + 2 drops of 40% DCl in D_2O] δ 5.10 (d, 1 H, *J* = 2.0 Hz), 4.49 (d, 1 H, *J* = 2.0 Hz), 3.71 (s, 3 H); ^1H NMR [$(CD_3)_2SO$] δ 6.0 (broad, 1 H), 4.94 (s, 1 H), 4.79 (s, 1 H), 4.41 (s, 1 H), 3.69 (s, 3 H); ^{13}CNMR [$(CD_3)_2SO$] 178.6, 173.2, 171.6, 89.6, 79.6, 68.1, 52.2 ppm (calibrated against solvent signal, 39.6 ppm). Anal. Calcd for $C_7H_8O_6$: C, 44.69; H, 4.29. Found: C, 44.54; H, 4.28.

Acknowledgment. This work has been supported by the National Swedish Board For Technical Development.

Registry No. **5**, 22886-01-7; **6**, 88377-35-9; **7**, 88377-36-0; **10**, 36065-06-2; **11**, 88377-37-1; ethyl 2(*S*)-acetoxypropanoate, 20918-91-6; ethyl acetoacetate, 141-97-9; 1,4-dibromobutane, 110-52-1.

(7) Hungerbühler, E.; Seebach, D.; Wasmuth, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 958-960.
(8) Commercially available ethyl (*S*)-lactate was acetylated according to Fryzuk, M. D.; Bosnich, B. *J. Am. Chem. Soc.* **1978**, *100*, 5491-5494.
(9) Jacobsen, J. P.; Reffstrup, T.; Boll, P. M. *Acta Chem. Scand., Ser. B* **1977**, *B31*, 756-760.
(10) Goldsworthy, L. J. *J. Chem. Soc.* **1934**, 377-378.
(11) Barnett, J. E. G.; Kent, P. W. *J. Chem. Soc.* **1963**, 2743-2747.
(12) Steglich, W.; Höfle, G. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 981.
(13) Clutterbuck, P. W.; Raistrick, H.; Reuter, F. *Biochem. J.* **1935**, *29*, 1300-1309.
(14) Boll, P. M.; Sörensen, E.; Balieu, E. *Acta Chem. Scand.* **1968**, *22*, 3251-3255.

Improved Selectivity in the Preparation of Some 1,1-Difunctionalized 3-Cyclopentenes. High-Yield Synthesis of 3-Cyclopentenecarboxylic Acid

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Received July 29, 1983

Although 3-cyclopentenecarboxylic acid (**3**, eq 1) has frequently been used as a starting material in synthesis,[1]

(1) (a) Grubs, E. J.; Lee, D. J.; Bellettini, A. G. *J. Org. Chem.* **1966**, *31*, 4069. (b) Wilt, J. W.; Massie, S. N.; Dabek, R. B. *Ibid.* **1970**, *35*, 2803. (c) Portoghese, P. S.; Lattin, D. L. *J. Heterocycl. Chem.* **1972**, *9*, 395. (d) David, S.; Lepine, M. C.; Lubineau, A. *Bull. Soc. Chim. Fr.* **1972**, 3580. (e) Givens, R. S.; Rademacher, D. R.; Kongs, J.; Dikerson, J. *Tetrahedron Lett.* **1974**, 3211. (f) Williams, T. R.; Sirvio, L. M. *J. Org. Chem.* **1980**, *45*, 5082. (g) Rastetter, W. H.; Phillion, D. P. *Ibid.* **1981**, *46*, 3204. (h) David, F. *Ibid.* **1981**, *46*, 3512. (i) Paulsen, H.; Maass, U. *Chem. Ber.* **1981**, *114*, 346. (j) Cremer, S. E.; Blankenship, C. *J. Org. Chem.* **1982**, *47*, 1626.

0022-3263/84/1949-0928$01.50/0