complex formation or extensive coupling with other low frequency modes. See W. M. Scovell and T. G. Spiro, *Inorg. Chem.*, **13**, 304 (1974), for a comparison of $[S(CO)_3Fe]_2$ and $[(CH_3S)(CO)_3Fe]_2$.
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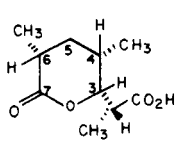
A Stereocontrolled Synthesis of the (±) Djerassi–Prelog Lactonic Acid

Sir:

The lactonic acid[1,2] **1** is a key degradation product of the macrolide antibiotic methymycin. Its structure was established by Djerassi,[3] while the stereochemical assignments were completed by Rickards.[4] Significantly, **1** retains the structural fragment C-1 through C-7 and four of the six chiral centers of the aglycone methynolide, and this fact has been exploited in the total synthesis of the latter by Masamune.[5]



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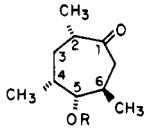
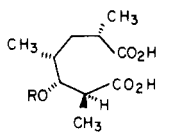
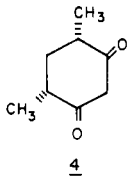


2 R = CH_2OCH_3
2a R = H



3 R = CH_2OCH_3
3a R = H

We now report a stereocontrolled and efficient synthesis of *rac*-**1**. A strategy involving the construction of the cycloheptanone **2** and its oxidative fragmentation to the diacid precursor **3** was considered an ideal route to the lactone **1**. *cis*-4,6-Dimethyl cyclohexane-1,3-dione (**4**) was used to provide the cis geometry of the 2,4-methyl groups in **2**. A single stereoisomer



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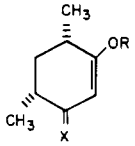
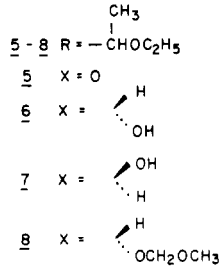


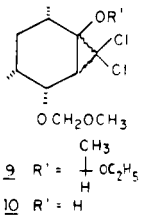


5 X = O
6 X = H, OH
7 X = OH, H
8 X = H, OCH_2OCH_3

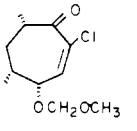
of **4** was obtained by the reaction of butanone with methyl methacrylate[6] (NaOMe, benzene, 0 °C, 6 h), mp 110–113 °C, in 30% yield: mass spectrum *m/e* 140 (M^+); IR ($CHCl_3$) 5.8, 5.9, 6.55 μ; NMR ($CDCl_3$) δ 1.2 (6 H, d, *J* = 6 Hz, $-CHCH_3$), 3.45 (2 H, s, $COCH_2CO$). The stereochemistry of **4** was established by its periodate oxidation[7] to afford the known *meso*-2,4-dimethylglutaric acid.[8] Reaction of **4** with ethyl vinyl ether (hydrochloric acid catalysis, room temperature, 12 h), gave the acetal **5**, bp 98–100 °C (~0.2 mm), in 83% yield: IR (neat) 6.0, 6.27 μ (Fermi resonance); NMR (CCl_4) δ 5.2 (1 H, m, -C=CH).

The desired cis axial alcohol **6** was obtained from **5** by reduction with lithium Selectride[9] (THF, 0 °C, 1.5 h), followed by oxidative workup, as a single isomer in 94% yield: IR (neat) 3.0, 6.08 μ (enol ether); NMR (CCl_4) δ 4.85 (1 H, d, *J* = 8 Hz, -C=CH). The expected stereochemical assignment for **6** was supported by the reduction of **5** with lithium aluminum hydride (THF, 0 °C, 1.5 h) when an isomeric alcohol **7** was obtained: NMR (CCl_4) δ 4.6 (1 H, s, -C=CH). The alcohol **6**, when treated with chloromethyl methyl ether in the presence of ethyl diisopropylamine (0 °C, 12 h) afforded the acetal **8**, bp 90–91 °C (0.5 mm), in 85% yield: mass spectrum *m/e* 285 (M^+); IR (neat) 6.08 μ (=C—O); NMR ($CDCl_3$) δ 3.38 (3 H, s, OCH_3), 4.7 (2 H, AB, J_{AB} = 4 Hz, $-OCH_2O$), 4.95 (1 H, d, *J* = 7 Hz, -C=CH).

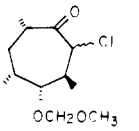
The stage was now set for the addition of a methylene equivalent to **8**, and the subsequent ring expansion to a cycloheptenone. This was done by the addition of dichlorocarbene ($CHCl_3$, 50% aqueous NaOH, benzyl triethylammonium chloride[10]). The reaction afforded the *gem*-dichlorocyclopropyl compound[11] **9** in 97% yield. Treatment of **9** with



9 R' = $CH(CH_3)OC_2H_5$
10 R' = H



11

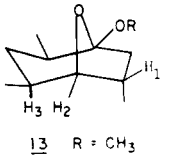


12

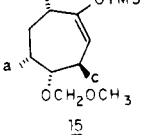
aqueous acetic acid (90%), containing sodium acetate, transformed it smoothly, via **10**, to the chloroenone **11** (82% yield, bp 107 °C (0.06 mm)) as a thick oil with a characteristic odor: mass spectrum: *m/e* 232 (M^+); IR (neat) 5.92, 6.35 μ; NMR ($CDCl_3$) δ 0.95 (3 H, d, *J* = 6 Hz, CH_3 at C-5), 1.2 (3 H, d, *J* = 6 Hz, CH_3 at C-7) 3.2 (3 H, s, OCH_3), 4.7 (2 H, s, OCH_2O), 6.8 (1 H, d, *J* = 4 Hz, -C=CH).

The last methyl group was introduced by the addition of lithium dimethylcuprate to **11** (ether, 0 °C, 1.5 h). The chloroketone **12** was obtained as a mixture epimeric at C-2, bp 103–105 °C (0.05 mm), in 97% yield: NMR ($CDCl_3$) δ 5.28 (1 H, 2 d, *J* = 3 Hz, H at C-2). Reductive dehalogenation of **12** with chromous perchlorate[12] (DMF, 0 °C, 6 h) afforded the cycloheptanone[13] **2** as a colorless oil, bp 78–80 °C (0.05 mm), in 62% yield: mass spectrum *m/e* 214 (M^+); IR (neat), 5.85 μ; ^1H NMR ($CDCl_3$) δ 0.9 (3 H, d, *J* = 8 Hz, CH_3 at C-4), 1.1 (6 H, d, *J* = 8 Hz, CH_3 at C-2 and C-6), 3.4 (3 H, s, OCH_3), 4.7 (2 H, AB, J_{AB} = 4 Hz, OCH_2O); ^{13}C NMR ($CDCl_3$) δ 16.77 (CH_3 at C-4), 19.33 (CH_3 at C-6), 21.41 (CH_3 at C-2), 33.33 (C-3), 33.57 (C-6), 33.62 (C-4), 41.41 (C-7), 55.68 (OCH_3) 83.84 (C-5), 96.32 ($-OCH_2O$), 215.8 (C=O).

Support for the assignment at C-5 and C-6 was derived from NMR studies on the ketal **13**, obtained from **2** with dilute hydrochloric acid, followed by methanol and acid, via the alcohol **2a** which is in equilibrium with the hemiketal **14**. Examination of the molecular models of **13** reveals dihedral angles of 0° between H-1 and H-2 and 90° between H-2 and H-3. As expected, the NMR spectrum of **13** exhibits H-2 as a doublet at δ 4.35 (*J* = 7 Hz) coupled to H-1 (irradiation of H-1 collapses H-2 into a singlet, whereas irradiation of H-3 has no effect on the H-2 signal). The configurations of the methyl at



13 R = CH_3
14 R = H



15

C-6 and methoxyl at C-5 in **13**, and therefore of the methyl and alkoxy groups in **2**, clearly follow from the above NMR results.[14] Conclusive evidence for these stereochemical assignments was provided by transformation of **2** to the (±) Djerassi–Prelog lactone. The ketone **2** was converted by trapping the kinetic enolate (LDA, THF, 0 °C) with trimethylchlorosilane[15] to the silyl enol ether **15**, bp 84 °C (0.05 mm), in 84% yield: mass spectrum *m/e* 286 (M^+); IR (neat) 6.02 μ (C=CHOTMS); NMR ($CDCl_3$) δ 0.2 (9 H, s, $SiCH_3$), 0.9 (3 H,

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d, J = 6 Hz, CH_3[b]), 1.1. (6 H, d, J = 7.5 Hz, CH_3[a] and CH_3[c]), 3.4 (H, s, OCH_3), 4.5 (1 H, d, J = 6 Hz, -C=CH), 4.65 (2 H, s, OCH_2O). Ozonolysis of **15** in acetone (−78 °C), followed by oxidation of the ozonide (CrO_3), afforded, presumably via **3a**, (±) Djerassi-Prelog lactonic acid (**1**) which was crystallized from ethanol, mp 114–115 °C,[16] in 26% yield from **15**. The spectral data (IR, NMR) were completely identical with those of an authentic sample[5] of the (±) Djerassi-Prelog lactonic acid.[17]

Acknowledgment. We express our thanks to Professor Carl Djerassi for a sample of the (+)-lactonic acid derived from methymycin and to Professor S. Masamune for a sample of his synthetic (±) material and its spectra. We also thank the National Institutes of Health and the National Science Foundation for the support of this work.

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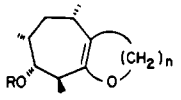
(13) The cycloheptanone **2** merits attention as a potential precursor for bicyclic systems of the type I and II which could undergo oxidative fragmentation to afford macrolides. For construction of macrolides using this type of approach, see (a) I. J. Borowitz, V. Bandurco, M. Heyman, R. D. G. Rigby,



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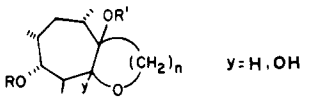

II

and S. N. Ueng, *J. Org. Chem.*, **38**, 1234 (1973); (b) J. R. Mahajan, G. A. L. Ferreira, and H. C. Araujo, *J. Chem. Soc., Chem. Commun.*, 1078 (1972); (c) T. Wakamatsu, K. Akasaka, and Y. Ban, *Tetrahedron Lett.*, 2751 (1977).
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(15) G. Stork and P. F. Hudrlik, *J. Am. Chem. Soc.*, **90**, 4462, 4464 (1968).
(16) A sample of (±)-lactonic acid, provided by Professor Masamune, had mp 113–114 °C (reported[5] mp 119–120 °C) and, when this was mixed with our sample, the mixture melting point was not depressed.
(17) We have recently become aware of another stereospecific construction which also uses a cycloheptenone intermediate; cf. J. D. White and Y. Fukuyama, *J. Am. Chem. Soc.*, **101**, 226 (1979).

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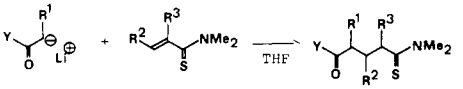
1,4-Addition Reactions of Lithium Enolates to α,β-Unsaturated Thioamides

Sir:

1,4-Addition reactions of organometallic compounds to α,β-unsaturated carbonyl compounds constitute one of the fundamental processes;[1] especially those with kinetically formed enolates are valuable to prepare the functionalized molecules desirable for the further transformations to natural and unnatural products. Therefore, owing to the unsuccessful 1,4 addition of lithium enolates or enolate copper reagents, studies have been focused on the modifications of Michael-type acceptors.[2]

In connection with the recently reported 1,4-addition reaction of organolithium, -magnesium, and -sodium compounds to α,β-unsaturated thioamides,[3] we have found that α,β-unsaturated thioamides serve as excellent Michael acceptors for various enolates. We report here the 1,4-addition reaction of lithium enolates of symmetrical and unsymmetrical ketones, ester, amides, and sodium ethyl acetoacetate to α,β-unsaturated thioamides (eq 1) and the very easy transformation of the thus obtained δ-carbonylthioamides to the corresponding δ-carbonyl esters (Table I).



(1)

1 2 3

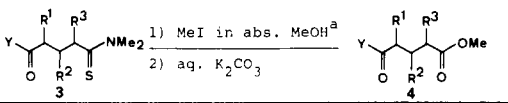
1a: R^1 = H, Y = NMe_2
1b: R^1 = Me, Y = NMe_2
1c: R^1 = H, Y = $OCMe_3$
1d: R^1 = H, Y = CMe_3
1e: R^1 = H, Y = Ph
1f: R^1 = H, Y = $CHMe_2$
1g: R^1-Y = $-(CH_2)_2CHMe-$
1h: R^1-Y = $-(CH_2)_3CHMe-$
1i: R^1-Y = $-(CH_2)_4-$
1j: R^1 = H, Y = $NaCHCO_2C_2H_5$

2a: R^2 = Me, R^3 = H
2b: R^2 = Ph, R^3 = H
2c: R^2 = H, R^3 = Me
2d:

2e: R^2 = MeCH=CH-, R^3 = H

The efficiency of the present 1,4-addition reaction is augmented by the ease with which it is performed, as typified in the following example (Table II, entry 7). To a THF (3 mL) solution of *tert*-butyl α-lithioacetate (**1c**), prepared from *tert*-butyl acetate (1.5 mmol) and lithium diisopropylamide (LDA, 1.5 mmol), was added a THF (1 mL) solution of *N,N*-dimethylthiocrotonamide (**2a**, 1 mmol) at −20 °C under argon. After the mixture was allowed to warm gradually to ambient temperature over a 30-min period, the reaction was quenched with CH_3OH and extracted with EtOAc. After this was dried over Na_2SO_4 and the solvent was evaporated, the faintly yellow residue was subjected to column purification (silica gel, benzene–ethyl acetate gradient) to give *N,N*-dimethyl-3-methyl-4-carbo-*tert*-butoxythiobutanamide (**3h**) in 93% yield: bp 135~140 °C (0.001 mmHg) (Kugelrohr); NMR (CCl_4) δ 1.05 (d, J = 5 Hz, 3 H), 1.25 (s, 9 H), 2.0~3.0 (m,

Table I. Conversion of Thioamides to Esters



3 4

Reactant[b]	Product[c] (% yield)[d]				
3	4	Y	R^1	R^2	R^3
3a	4a (91)	NMe_2	H	Me	H
3b	4b (83)	NMe_2	H	Ph	H
3h	4h (100)	O^tBu	H	Me	H
3i	4i (86)	O^tBu	H	Ph	H
3k	4k (92)	^tBu	H	Me	H
3r	4r (71)	$-(CH_2)_4-$		Me	H

[a] 4–16 equiv of MeI was used. [b] For the structures of *3a–r*, see Table II. [c] All new compounds showed satisfactory spectral (IR, NMR, mass) and analytical results (within ±0.3% for C and H (and N for **4a** and **4b**)). [d] Isolated yields.

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