nicated for 3 min in a standard low-power laboratory ultrasonicator and then filtered through glass wool into a 5-mm NMR tube for analysis. As control experiments, each of the salts **2a**–**d** was treated in the same way in the absence of **1**. In each case, no detectable amounts of the salts were solubilized.

Homogeneous Complexation A mixture of 5.0 mg of macrocycle **1** (9.7 μmol) and 5.15 mg of perchlorate salt **2a** (19.4 μmol) in 0.5 mL of acetone-d_6 in a 5-mm NMR tube was sonicated to give a homogeneous solution and then analyzed by NMR spectroscopy. A similar mixture was made up from 5.0 mg of **1** and 4.81 mg of bromide salt **2c**. For comparison acetone-d_6 solutions of salts **2a** and **2c** were also prepared in the absence of **1**.

Acknowledgment. This work was supported by the Office of Naval Research.

Synthesis of (+)-Lasalocid Aldehyde

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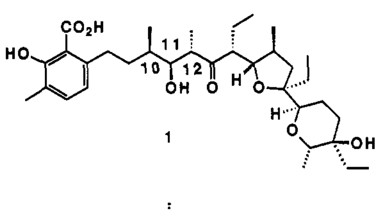
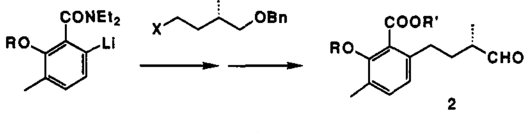
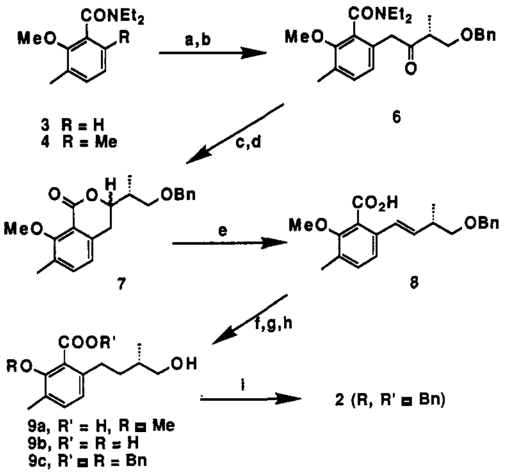
In connection with our studies of the effect of stereochemistry and substitution on the ionophoric properties of the polyether antibiotics, we recently suggested that the diastereomer of lasalocid A (**1**)[1] which is epimeric at C10, C11, and C12 is as well preorganized for binding cations as lasalocid A itself.[2] In preparation for synthesizing that diastereomer, we needed a source of the aldehydic lasalocid precursor (**2**), which is enantiomeric with the natural series. While the enantiomers of **2** have been prepared previously,[3] we felt that a more practical route to **2** might be available using the metalated salicylic acid derivative shown below.





We began by metalating[4] the methyl ether of *N*,*N*-diethyl-3-methylsalicylamide[5] (**3**) using *sec*-butyllithium (THF/TMEDA, −78 °C). A variety of electrophiles including alkyl bromides and carbonyl compounds added smoothly to the resulting aryllithium. However, in the case of alkylation, the resulting highly hindered amide could not be hydrolyzed. With aldehyde electrophiles, the amide was readily cleaved using the internal alcohol nucleophile to give an intermediate γ-lactone,[6] but reduction of the benzylic lactone oxygen was problematic. Catalytic hydrogenolysis with Raney Ni, Pd, or Pt gave only the starting lactone, and Birch reduction resulted when dissolving metal conditions were used. While a neighboring benzylic alcohol group facilitated hydrolysis of our amide, the more remote terminal hydroxyl (as in **9**) did not provide the necessary assistance.

Scheme I[a]



[a] (a) (i) *s*-BuLi, TMEDA; (ii) CH_3I; (b) (i) *n*-BuLi; (ii) (*R*)-methyl 3-(benzyloxy)-2-methylpropionate (**5**); (c) $NaBH_4$; (d) CSA; (e) DBU (f) H_2, 30% Pd/C; (g) BBr_3; (h) K_2CO_3, BnBr; (i) $(COCl)_2$, DMSO.

To allow amide hydrolysis and formation of a fully reduced side chain, we chose an alternative pathway via a homobenzylic alcohol which could assist in the amide hydrolysis and then be removed by a subsequent elimination. Therefore, we alkylated the above aryllithium with methyl iodide to give **4** (96%). A second deprotonation using *n*-BuLi (THF, −78 °C) followed by acylation with 1 equiv of the benzyl ether of commercial methyl (*R*)-3-hydroxy-2-methylpropionate (**5**) then gave adduct **6** in 46% yield (81% based on consumed **4**).[7] The highly acidic nature of the benzyl ketone substructure of **6** was important for several reasons. In particular, the strongly basic conditions employed immediately deprotonated **6** upon its formation, thus suppressing elimination of the terminal benzyloxy group and epimerization of the chiral methine. However, the anion of starting **4** also functioned as the base in deprotonating **6**, and thus only a 50% conversion of **4** could be achieved. We were unable to improve the conversion using additional quantities of *n*-BuLi or other bases. An alternative scheme using the aldehydic analogue of **5** avoided a subsequent reduction step but provided lower yields of the coupled product. We therefore proceeded using **6** (Scheme I).

Conversion of the keto amide **6** to an intermediate δ-lactone (**7**) with loss of diethylamine was effected in 72% yield by reduction ($NaBH_4$, MeOH) and acidic lactonization (camphorsulfonic acid, $PhCH_3$). The ~1:1 mixture of diastereomeric lactones was subjected to elimination conditions by heating overnight at 135 °C with DBU in butyronitrile to give styrene **8**. Catalytic hydrogenation (30% Pd/C, EtOH) removed the benzylic ether and saturated the olefin to provide **9a**. Demethylation (BBr_3, CH_2Cl_2) then gave the free salicylic acid derivative **9b**.

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Finally, we protected **9b** for elaboration to C-10 lasalocid derivatives by protection of the aromatic hydroxyl and carboxylic acid using benzyl bromide and potassium carbonate. Dibenzyl **9c** was thus prepared in 67% overall yield from **7**. Swern oxidation provided the desired aldehyde (**2**) in 86% yield.

Finally, to confirm that the sequence had not resulted in significant loss of enantiomeric purity, the Mosher ester of **9c** (as prepared above and by borohydride reduction of **2** (R,R′ = Bn)) was compared with the diastereomeric ester prepared from the known retroaldol product[8] of benzyl lasalocid. The ^{1}H NMR ($CDCl_3$) spectrum clearly distinguished these diastereomeric esters of the primary alcohols and indicated <5% racemization had occurred in the synthesis of **2**.[9]

Experimental Section

^{1}H NMR spectra were recorded on a 400-MHz Varian VXR-4000 FT spectrometer in $CDCl_3$ and are reported in parts per million. Infrared spectra were recorded as neat films on a Perkin-Elmer 983 spectrophotometer. High-resolution mass spectra were determined under chemical ionization conditions by The Midwest Center for Mass Spectrometry. Optical rotations were measured on a JASCO DIP-181 digital polarimeter. All products were homogeneous by TLC and judged to be >90% pure by 400-MHz ^{1}H NMR spectroscopy.

***N*,*N*-Diethyl-3,6-dimethyl-2-methoxybenzamide (4).** To a stirred solution of **3** (11.2 g, 50.7 mmol) and TMEDA (11.5 mL, 76.1 mmol) in 300 mL of dry THF at −78 °C under N_2 was added 1.4 M *sec*-butyllithium in cyclohexane (54.3 mL, 76.1 mmol) over 5 min, and stirring was continued for 1 h. Methyl iodide (6 mL, 96 mmol) was added, and stirring was continued for 1 h at −78 °C. The reaction was worked up with saturated NH_4Cl, extracted with ether (1 × 100 mL) and CH_2Cl_2 (2 × 100 mL), and dried over $MgSO_4$. Flash chromatography of the combined extracts (20% EtOAc/petroleum ether) yielded 11.4 g (96%) of **4** as an oil: ^{1}H NMR δ 7.04 (d, 1 H, J = 8.9 Hz, ArH), 6.85 (d, 1 H, J = 8.9 Hz, ArH), 3.75 (s, 3 H, OCH_3), 3.59 (m, 2 H, NCH_2), 3.19 (m, 2 H, NCH_2), 2.22 (s, 3 H), 2.20 (s, 3 H), 1.26 (t, 3 H, J = 10.0 Hz, NCH_2CH_3), 1.02 (t, 3 H, J = 9.5 Hz, NCH_2CH_3); IR 1632, 1290, 1261, 1124, 1063 cm^{-1}; HRMS (m/e) found 235.1574, calculated for $C_{14}H_{21}O_2N$ 235.1573.

(*R*)-*N*,*N*-Diethyl-6-(4-(benzyloxy)-3-methyl-2-oxobutyl)-2-methoxy-3-methylbenzamide (6). To a stirred solution of **4** (4.1 g, 17.4 mmol) in 125 mL of THF at −78 °C under N_2 was added 2.5 M *n*-butyllithium in hexanes (7.7 mL, 19.3 mmol) dropwise. The burgundy-colored solution was stirred 30 min. A solution of (*R*)-methyl 3-(benzyloxy)-2-methylpropionate (**5**, 4.0 g, 19.2 mmol) in 20 mL of THF was added until the solution lost its color, and the mixture was stirred an additional 15 min. Workup with 1.5 mL of acetic acid and 150 mL of water, extraction with ether (1 × 50 mL) and CH_2Cl_2 (2 × 100 mL), and drying of the combined extracts over $MgSO_4$ gave 3.3 g of **6** (46%, 81% based on consumed **4**) as an oil after flash chromatography (20% EtOAc/petroleum ether): ^{1}H NMR δ 7.31 (m, 5 H, ArH), 7.11 (m, 1 H, ArH), 6.83 (m, 1 H, ArH), 4.49 (m, 2 H, $PhCH_2$), 3.73 (s, 3 H, OCH_3), 3.55 (m, 5 H), 3.08 (m, 4 H), 2.26 (s, 3 H, $ArCH_3$), 1.23 (m, 3 H, NCH_2CH_3), 1.08 (m, 6 H, NCH_2CH_3, $CHCH_3$); IR 1716, 1626, 1292, 1261 cm^{-1}; $[\alpha]^{25}_D$ = −38.5° (c, 0.0065, CCl_4); HRMS (m/e) found 411.2397, calculated for $C_{25}H_{33}O_4N$ 411.2409.

3-(2-(Benzyloxy)-1-methylethyl)-3,4-dihydro-8-methoxy-7-methylisocoumarin (7). To a stirred solution of **6** (840 mg, 2.03 mmol) in 20 mL of MeOH at 0 °C was added $NaBH_4$ (156 mg, 4.11 mmol). After stirring 30 min, the reaction was quenched with 10% sodium potassium tartrate and stirred for 10 min at room temperature, and the methanol was distilled under reduced pressure. Extraction with CH_2Cl_2 (3 × 50 mL), drying over $MgSO_4$, and flash filtration through silica gel yielded the diastereomeric alcohols. The mixture of alcohols was dissolved in 10 mL of toluene, racemic camphorsulfonic acid (500 mg, 2.15 mmol) was added, and the mixture was refluxed for 24 h. Removal of solvent under reduced pressure and flash chromatography (5% EtOAc/petroleum ether) yielded 500 mg of **7** (72%) as an oil: ^{1}H NMR δ 7.30 (m, 6 H, ArH), 6.88 (m, 1 H, ArH), 4.50 (m, 3 H, $PhCH_2$, $ArCH_2CH$), 3.79 (s, 1 H, OCH_3), 3.55 (m, 2 H, $PhCH_2OCH_2$), 2.85 (m, 2 H, $ArCH_2$), 2.30 (s, 3 H, $ArCH_3$), 2.15 (m, 1 H, $CHCH_3$), 1.12 (m, 3 H, $CHCH_3$); IR 1728, 1483, 1453, 1406 cm^{-1}; HRMS (m/e) found 340.1676, calculated for $C_{21}H_{24}O_4$ 340.1674.

(*S*)-6-(4-(Benzyloxy)-3-methyl-1(*E*)-butenyl)-2-methoxy-3-methylbenzoic Acid (8). To a stirred solution of **7** (479 mg, 1.41 mmol) in 7 mL of butyronitrile was added 14 mL of DBU. The mixture was heated at 135 °C overnight. Acidification of the dark brown solution with 50 mL of 1 N HCl, extraction with ethyl acetate (4 × 20 mL), drying over $MgSO_4$, and flash chromatography (70% EtOAc, petroleum ether) yielded **8** as a thick oil: ^{1}H NMR δ 7.25 (m, 7 H, ArH), 6.68 (d, 1 H, J = 15.2 Hz, ArH), 6.10 (dd, 1 H, J = 15.2, 6.5, Hz, $ArCHCH$), 4.57 (s, 2 H, $PhCH_2O$), 3.82 (s, 3 H, OCH_3), 3.43 (m, 2 H, $BnOCH_2$), 2.69 (m, 1 H, $CHCH_3$), 2.32 (s, 3 H, $ArCH_3$), 1.13 (d, 3 H, J = 6.3 Hz); IR 3300 (br), 1721, 1458, 1261 cm^{-1}; $[\alpha]^{25}_D$ = −7.9° (c 0.0076, CCl_4); HRMS (m/e) found 340.1689, calculated for $C_{21}H_{24}O_4$ 340.1674.

(*S*)-2-Methoxy-3-methyl-6-(4-hydroxy-3-methylbutyl)benzoic Acid (9a). To a flask containing **8** (product from the previous step) in 15 mL of ethanol was added a catalytic amount (ca. 5%) of 30% Pd/C, fitted with a hydrogen-filled balloon, and stirred vigorously overnight. Filtration through Celite and solvent removal yielded **9a** as a thick oil: ^{1}H NMR δ 7.19 (d, 1 H, J = 8.8 Hz, ArH), 6.94 (d, 1 H, J = 8.8 Hz, ArH), 3.85 (s, 3 H, OCH_3), 3.58 (m, 2 H, CH_2OH), 2.73 (m, 2 H, $ArCH_2$), 2.31 (s, 3 H, $ArCH_3$), 1.72 (m, 2 H, $ArCH_2CH_2$), 1.52 (m, 1 H, $CHCH_2OH$), 0.99 (d, 3 H, J = 6.3 Hz, $CHCH_3$); IR 3300, 1701, 1486, 1458, 1409, 1383 cm^{-1}; $[\alpha]^{25}_D$ = −2.2° (c 0.0137, CCl_4); HRMS (m/e) found 252.1360, calculated for $C_{14}H_{20}O_4$ 252.1361.

(*S*)-3-Methyl-6-(4-hydroxy-3-methylbutyl)salicylic Acid (9b). To a stirred solution of **9a** (from the previous step) in 15 mL of CH_2Cl_2 at −78 °C under N_2 was added 2.8 mL of 1 M BBr_3 in CH_2Cl_2. The reaction was stirred 30 min at −78 °C, followed by another 30 min at room temperature. Workup with 5 mL of TFA and 50 mL of methanol, stirring for 30 min, and flash chromatography (30% EtOAc/petroleum ether) afforded **9b** as a waxy solid: ^{1}H NMR δ 7.20 (d, 1 H, J = 8.3 Hz, ArH), 6.54 (d, 1 H, J = 8.3 Hz, ArH), 3.63 (d, 2 H, J = 5.8 Hz, CH_2OH), 2.93 (m, 2 H, $ArCH_2$), 2.21 (s, 3 H, $ArCH_3$), 1.70 (m, 2 H, $ArCH_2CH_2$), 1.45 (m, 1 H, $CHCH_2OH$), 0.99 (d, 3 H, J = 6.0 Hz, $CHCH_3$); IR 3300 (br), 1653, 1417, 1247 cm^{-1}; $[\alpha]^{25}_D$ = −4.9° (c 0.0070, $CHCl_3$); HRMS (m/e) found 238.1201, calculated for $C_{13}H_{18}O_4$ 238.1205.

(*S*)-Benzyl 2-(Benzyloxy)-3-methyl-6-(4-hydroxy-3-methylbutyl)benzoate (9c). To a solution of **9b** (from the previous step) in 10 mL of dry acetone was added 1 g of potassium carbonate and 0.6 mL of benzyl bromide. The stirred mixture was refluxed under N_2 overnight. The reaction mixture was cooled, 25 mL of water was added, and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). Drying over $MgSO_4$ and flash chromatography (20% EtOAc/petroleum ether) yielded 395 mg of **9c** (67% from **7** over four steps) as an oil: ^{1}H NMR δ 7.35 (m, 10 H, ArH), 7.17 (d, 1 H, J = 8.5 Hz, ArH), 6.92 (d, 1 H, J = 8.5 Hz, ArH), 5.29 (s, 2 H, CO_2CH_2Ph), 4.89 (s, 2 H, $ArOCH_2Ph$), 3.39 (m, 2 H, CH_2OH), 2.53 (m, 2 H, $ArCH_2$), 2.29 (s, 3 H, $ArCH_3$), 1.61 (m, 2 H, $ArCH_2CH_2$), 1.38 (m, 1 H, $CHCH_2OH$), 0.88 (d, 3 H, $CHCH_3$, J = 6.7 Hz); IR 3200 (br), 1724, 1452, 1276, 1255, 1134 cm^{-1}; $[\alpha]^{25}_D$ = −4.6° (c 0.0069, CCl_4); HRMS (m/e) found 418.2150, calculated for $C_{27}H_{30}O_4$ 418.2144.

(*S*)-Benzyl 2-(Benzyloxy)-3-methyl-6-(3-methyl-4-oxobutyl)benzoate (2, R, R′ = Bn). To a solution of oxalyl chloride (19.6 μL, 224 μmol) in 1 mL of CH_2Cl_2 at −78 °C under N_2 was added DMSO (23.8 μL, 336 μmol). After stirring 3 min, a solution of **9c** (47.0 mg, 112 μmol) in 1 mL of CH_2Cl_2 was added dropwise. After 15 min, triethylamine (78 μL, 560 μmol) was added dropwise, and the mixture was stirred another 15 min at −78 °C. The reaction was warmed to 0 °C and stirred for 20 min, and 10 mL of water was added. Extraction with CH_2Cl_2 (3 × 15 mL), drying over $MgSO_4$, and flash chromatography (5% EtOAc/petroleum ether) afforded 40.3 mg of **2** (R, R′ = Bn) (86%) as an oil: ^{1}H

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[8] The authentic aldehyde derived by thermal retroaldol of benzyl lasalocid[3a] was reduced ($NaBH_4$, MeOH, −20 °C) and benzylated (Bu_4NOH, BnBr, THF/H_2O). See also Westley, J. W.; Evans, R. H.; Williams, T.; Stempel, A. *J. Chem. Soc., Chem. Commun.* **1970**, 71.

[9] We acknowledge the support of NIH Grant HL25634.

NMR δ 9.50 (d, 1 H, CHO, J = 1.6 Hz), 7.35 (m, 10 H, ArH), 7.17m (d, 1 H, J = 8.4 Hz, ArH), 6.90 (d, 1 H, J = 8.4 Hz, ArH), 5.28 (s, 2 H, CO_2CH_2Ph), 4.89 (s, 2 H, $ArOCH_2Ph$), 2.54 (m, 2 H, $ArCH_2$), 2.29 (s, 3 H, $ArCH_3$), 2.20 (m, 1 H, C*H*CHO), 1.93 (m, 1 H), 1.55 (m, 1 H), 1.03 (d, 3 H, J = 6.5 Hz, $CHCH_3$); IR 1726, 1455, 1277, 1255, 1134 cm^{-1}; $[\alpha]^{25}_{D}$ = +8.3° (c 0.0145 CCl_4); HRMS (m/e) found 416.1986, calculated for $C_{27}H_{28}O_4$ 416.1987.

Supplementary Material Available: ^1H NMR spectra of compounds **2**, **3**, **6–8**, and **9a–c** (10 pages). Ordering information is given on any current masthead page.

A New Preparation of Ethyl 3-Oxo-4-pentenoate: A Useful Annelating Reagent

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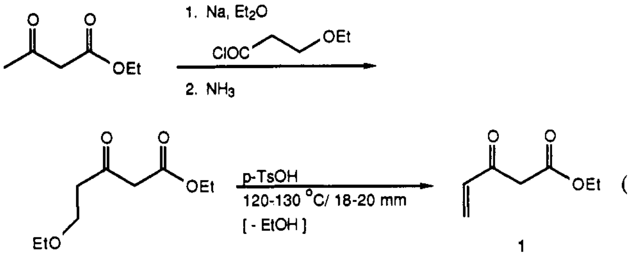
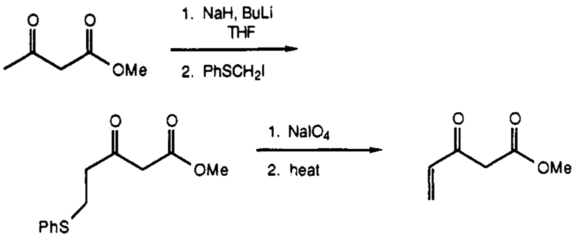
Received February 17, 1989

As part of a continuing project directed toward the total synthesis of several terpenes, we required large amounts of the well-known annelating reagent ethyl 3-oxo-4-pentenoate (**1**, Nazarov's reagent).[1] The synthesis and use of this compound as an annelating agent have been reported in the literature many times.[2-9] We required a facile, short, and efficient synthesis of **1**, readily providing large quantities.

In 1953, Nazarov reported the preparation of ethyl 3-oxo-4-pentenoate (**1**) as shown in eq 1. The last step of this synthesis required the elimination of ethanol through acid catalysis. Groups prior to us have termed this step “capricious”,[10] and indeed, we were unable to obtain more than 100 mg of **1** by this method. Furthermore, attempted elimination of HCl from ethyl 5-chloro-3-oxo-pentanoate[11] in an analogous manner also failed.[12] The synthesis of methyl 3-oxo-4-pentenoate by Stork and Guthikonda[4] (64–68% for three steps) required as the last step a retro-Diels–Alder reaction of pentadiene through a special high-temperature apparatus (quartz-packed column at 600 °C). Trost and Kunz[6] later reported preparation of the methyl ester of **1** wherein the last step involved elimination of a sulfoxide as shown in eq 2 (60–76% for three steps). Also, (iodomethyl)phenylsulfide utilized here must be prepared from thioanisole requiring two steps (89%). In our hands, the elimination occurred smoothly, but polymerization proceeded promptly.

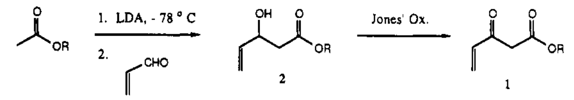


(1)



(2)

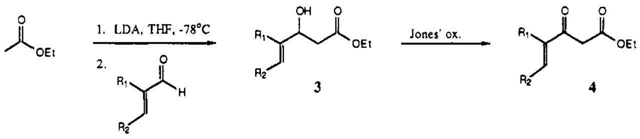
Table I



entry	R	solvt	% yield of 2 (scale)	% yield of 1 (scale)
1	**a**, Me	THF	71 (100 mmol)	48 (50 mmol)
2	**b**, Et	THF	79 (100 mmol)	58 (50 mmol)
3	**b**, Et	Et_2O	^{a} (300 mmol)	53^b
4	**c**, i-Pr	THF	76 (100 mmol)	76 (50 mmol)
5	**d**, t-Bu	THF	74 (100 mmol)	64 (50 mmol)
6	**e**, bornyl	Et_2O	95 (100 mmol)	59 (50 mmol)

^{a} Compound **2b** was not purified in this case, rather the oxidation carried out on crude material. ^{b} The percent yield in this case is for two steps.

Table II



entry	compd	% yield of 3 (scale)	% yield of 4 (scale)
1	**a**, $R_1 = CH_3$, $R_2 = H$	89 (100 mmol)	42 (50 mmol)
2	**b**, $R_1 = H$, $R_2 = CH_3$	89 (100 mmol)	54 (50 mmol)

We wish to report a facile (two step) and efficient synthesis of several esters of 3-oxo-4-pentenoate. It is well-known that the one-step preparation of β-keto esters is a difficult task since acylation of an ester enolate generates a product that contains protons more acidic than the starting materials, often resulting in bisacylation.[13] Indeed, our attempts to acylate lithioethyl acetate using acryloyl chloride failed to provide more than minute quantities of ethyl 3-oxo-4-pentenoate.

As shown in a study by Smith and Levenberg,[14] β-keto esters can be synthesized readily by oxidation of the corresponding β-hydroxy esters. We therefore prepared a series of β-hydroxy esters (**2a–e**, Table I) to explore oxidation to Nazarov's reagent and analogues. Typically, the ester enolate (100 mmol, LDA, THF, −78 °C) was reacted with acrolein to provide in all cases good yields of β-hy-

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[11] Prepared by the reaction of lithioethyl acetate with 3-chloropropionyl chloride.

[12] This has been done successfully to prepare *tert*-butyl 3-oxo-4-pentenoate, see: Ohta, S.; Shimabayashi, A.; Hatano, S.; Okamoto, M. *Synthesis* **1983**, 715.

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