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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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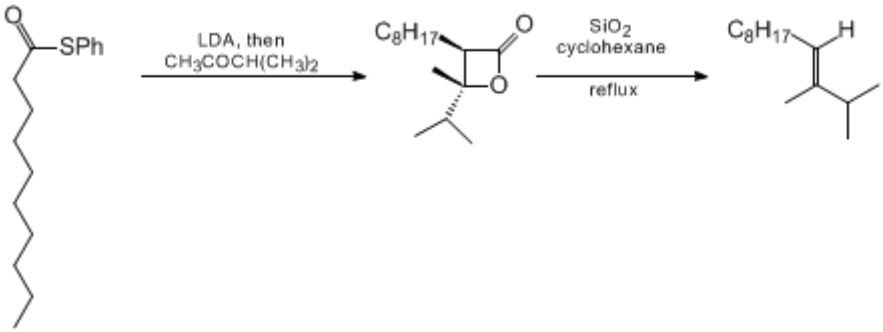
SYNTHESIS OF β-LACTONES AND ALKENES VIA THIOL ESTERS: (E)-2,3-DIMETHYL-3-DODECENE



Submitted by Rick L. Danheiser, James S. Nowick, Janette H. Lee, Raymond F. Miller, and Alexandre H. Huboux[1].
Checked by David J. Mathre and Ichiro Shinkai.

1. Procedure

A 1-L, three-necked, round-bottomed flask is equipped with a mechanical stirrer, nitrogen inlet adapter, and a 150-mL, pressure-equalizing dropping funnel fitted with a rubber septum (Note 1). The flask is charged with 225 mL of dry tetrahydrofuran (THF) (Note 2) and 26.5 mL (0.189 mol) of diisopropylamine (Note 3), and then is cooled in an ice-water bath while 70.4 mL (0.178 mol) of a 2.53 M solution of butyllithium in hexane (Note 4) is added dropwise over 5–10 min. After 10 min, the resulting solution is cooled to −78°C (Note 5) in a dry ice-acetone bath and a solution of 45.0 g (0.17 mol) of S-phenyl decanoate (Note 6) in 75 mL of dry tetrahydrofuran is added dropwise over 1 hr (the dropping funnel is washed with two 5-mL portions of tetrahydrofuran). The yellow reaction mixture is allowed to stir for 30 min at −78°C, and then 18.2 mL (0.17 mol) of 3-methyl-2-butanone (Note 7) is added via a syringe pump or funnel over 7.5 min (Note 8). After 30 min, the reaction mixture is allowed to warm gradually to 0°C over 1.5 hr (Note 9) and then is quenched by the addition of 225 mL of a half-saturated aqueous ammonium chloride solution. The resulting mixture is poured into a 1-L separatory funnel containing 150 mL of hexane and 150 mL of water. The aqueous layer is separated and washed with 50 mL of hexane. The combined organic layers are washed successively with three 200-mL portions of aqueous 10% sodium carbonate and 200 mL of saturated sodium chloride (NaCl) solution, dried over anhydrous sodium sulfate, filtered, and concentrated at reduced pressure using a rotary evaporator to afford 41.5 g of the β-lactone as a yellow oil which is used in the next step without further purification (Note 10).

A 500-mL, one-necked, round-bottomed flask, equipped with a magnetic stirring bar and a condenser fitted with a nitrogen inlet adapter, is charged with the 41.5 g of crude β-lactone prepared above, 200 mL of cyclohexane (Note 11), and 41.5 g of 230-400 mesh silica gel (Note 12). The resulting yellow mixture is heated at reflux for 1 hr (water may be observed collecting in the condenser) and then allowed to cool to room temperature. Activated charcoal (6 g) is added (Note 13), and the resulting mixture is stirred for 5 min and filtered. The residue is washed with an additional 50 mL of cyclohexane and the combined filtrates are concentrated at reduced pressure using a rotary evaporator to afford 31.5 g of a yellow oil. This crude material is applied to the top of a 4.8-cm × 30-cm column of 210 g of 230-400 mesh silica gel 60 (Note 14) and eluted with hexane (20 mL per min, 120-mL fractions) (Note 15). Concentration of fractions 3–5 using a rotary evaporator and then high vacuum (0.1 mm) affords 22.0–23.0 g (66–69% overall yield) of (E)-2,3-dimethyl-3-dodecene as a clear, colorless oil ((Note 16),(Note 17),(Note 18)).

2. Notes

1. The apparatus is oven-dried at 110°C or flame-dried under reduced pressure and maintained under an atmosphere of nitrogen during the course of the reaction.
2. Tetrahydrofuran was distilled from sodium benzophenone ketyl immediately before use. The checkers used tetrahydrofuran (E. Merck) dried over 4 Å molecular sieves and purged with dry nitrogen (water content <10 μg/mL by Karl Fischer titration).
3. Diisopropylamine was purchased from Aldrich Chemical Company, Inc., and distilled from calcium hydride prior to use. The checkers used diisopropylamine (Aldrich Chemical Company, Inc.) dried over 3 Å molecular sieves and purged with dry nitrogen (water content <35 μg/mL by Karl Fisher titration).
4. n-Butyllithium was purchased from Aldrich Chemical Company, Inc., and titrated according to the the method of Watson and Eastham.[2]
5. The checkers monitored the internal temperature of the reaction with a Teflon-coated J-type thermocouple.
6. S-Phenyl decanethioate was prepared by the following procedure:[3] [4] A 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, glass stopper, nitrogen inlet adapter, and a 50-mL pressure-equalizing addition funnel fitted with a rubber septum is charged with 250 mL of methylene chloride, 17.6 mL (0.171 mol) of thiophenol, and 13.9 mL (0.172 mol) of pyridine (Note 19). The reaction mixture is cooled in an ice-water bath and 35.4 mL (0.171 mol) of decanoyl chloride (Note 19) is added dropwise via the addition funnel over 20 min. The resulting suspension of white solid is stirred for an additional 10 min at 0°C, at room temperature for 1 hr, and then is poured into 210 mL of water. The organic phase is separated and washed, successively with 210 mL of 10% hydrochloric acid and 210 mL of saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated at reduced pressure using a rotary evaporator, then under high vacuum (0.1 mm), to provide 44.8 g of a clear, colorless oil. Distillation of this material through an 8-cm Vigreux column affords 41.7–44.0 g (93–98%) of S-phenyl decanoate as a clear, colorless oil, bp 95–125°C (0.04 mm). [Note: it appears that some of the product may decompose during the distillation based on capillary GC analysis (crude product, distilled fractions, and pot residue) and the wide temperature range for the distillation even though the pressure appeared to remain constant.]
7. 3-Methyl-2-butanone was purchased from Eastman Chemical Products, Inc. and distilled prior to use. It appeared that water was azeotropically removed during the distillation, and thus a significant fore-run was discarded.
8. The submitters employed an addition funnel and conducted the addition over 7.5 min.
9. This is best accomplished by periodically adding room temperature acetone to the cooling bath over the course of 1.5 hr. More rapid warming results in dramatically reduced yields of β-lactone.
10. A pure sample of the β-lactone was obtained by vacuum distillation through an 8-cm Vigreux column (bp 43–80°C, 0.25 mm) followed by column chromatography on silica gel and exhibited the following spectral characteristics: IR (neat) cm^{-1}: 2960, 2930, 2860, 1830, 1465, 1390, 1220, 1095, 1020, 810; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, 3 H, J = 7), 0.93 (d, 3 H, J = 7), 1.02 (d, 3 H, J = 7), 1.20–1.50 (m, 15 H), 1.50–1.65 (m, 1 H), 1.65–1.90 (m, 1 H), 1.99 (sept, 1 H, J = 7), 3.13 (t, 1 H, J = 8); ^{13}C NMR 75 MHz, $CDCl_3$) δ: 14.0, 14.9, 17.0, 17.5, 22.6, 25.0, 27.5, 29.1, 29.2, 29.4, 31.8, 37.5, 56.2, 85.0, 171.9. Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 75.17; H, 11.57. Only the trans-substituted β-lactone could be detected by NMR and NOE analysis.
11. Cyclohexane was purchased from Mallinckrodt Inc. and used without further purification.
12. Silica gel (230-400 mesh) was obtained from J. T. Baker, Inc., or E. Merck. Less silica gel (e.g., 10% wt. equiv) can be used in this step, although in this case longer reflux times are necessary to complete the decarboxylation. Note that the use of completely anhydrous silica gel (e.g., silica gel flame-dried under reduced pressure) was found to catalyze olefin isomerization in some cases and should be avoided.
13. Activated charcoal (20-40 mesh) was used as received from Matheson, Coleman, & Bell or Darco (G-60). Addition of charcoal at this stage removes reduces the amount of malodorous thiol impurities.
14. The submitters silica gel (J. T. Baker, Inc.) column (8-cm × 10-cm) was packed as a slurry in petroleum ether (Mallinkrodt Inc., bp 35–60°C). The column was eluted using petroleum ether (20 mL/min, collecting 70-mL fractions). The fractions were analyzed by capillary GC, and those containing the product (fractions 4–9) were combined.
15. Elution of the silica gel column with additional hexane afforded thiophenol (5.0 g), diphenyl disulfide (0.2 g), and BHT (0.1 g, stabilizer from the THF). Continued elution with increasing amounts of ethyl acetate (hexane:EtOAc from 100:0 to 80:20) afforded dinonyl ketone (2.4 g, 10%), S-phenyl

decanoate (0.8 g, 2%), and the enol of 2-methyl-3,5-diketotetradecane (2.4 g, 6%; the amount is probably greater).
16. Alternatively, the alkene can be purified by distillation through an 8-cm Vigreux column (Note 20) to furnish 11.8–13.0 g (53–59% overall yield) of (E)-2,3-dimethyl-3-dodecene as a clear, colorless oil, bp 52°C (0.03 mm) The yield of alkene is considerably reduced if the distillation is carried out at higher temperature.
17. The olefin thus obtained was found by ^{1}H NMR and gas chromatographic analysis to consist of a 25-27:1 mixture of E and Z isomers. The major product was identified as the trans isomer by ^{1}H NMR NOE analysis. Gas chromatographic analysis was carried out on a 0.25-mm × 30-m DB-1701-coated fused silica capillary column, column temperature 125°C, flow rate 1 mL/min, retention times: Z isomer 9.09 min, E isomer 9.30 min.
18. The product has the following spectral properties: IR (neat) cm^{-1}: 2970, 2940, 2870, 1465, 1380; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.87 (t (br), 3 H), 0.95 (d, 6 H, J = 6.5), 1.25 (s (br), 12 H), 1.55 (s, 3 H), 1.95 (m, 2 H), 2.20 (m, 1 H), 5.15 (t (br), 1 H, J = 6.9); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.3, 14.1, 21.5, 22.7, 27.8, 29.4, 29.6, 30.0, 32.0, 36.8, 122.3, 140.6; Z isomer impurity (partial) δ: 5.05 (t (br), J = 6.5), 2.8 (m), 1.60 (m), 0.95 (d). Anal. Calcd for $C_{14}H_{28}$: C, 85.71; H, 14.29. Found: C, 85.55; H, 14.38. The major product was determined to be the trans isomer by NOE analysis.
19. Methylene chloride was purchased from Mallinckrodt Inc. and used without further purification. Thiophenol was purchased from Fluka Chemical Co. and used without further purification. Pyridine was purchased from Mallinckrodt Inc. and was distilled from calcium hydride. Decanoyl chloride was purchased from the Aldrich Chemical Company, Inc., and used without further purification.
20. In order to reduce foaming, enough glass wool is added to the distillation flask just to cover the surface of the liquid.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

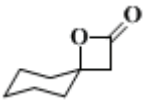
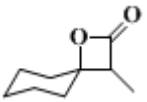
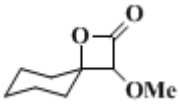
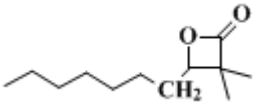
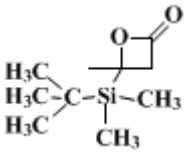
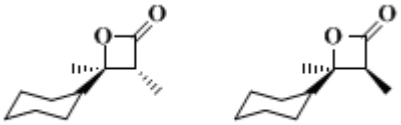
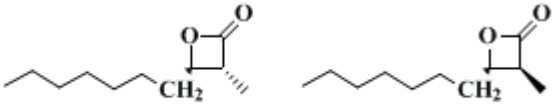
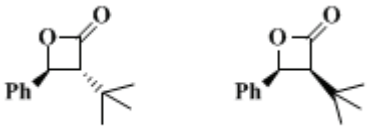
3. Discussion

The procedure described here illustrates a practical and convenient method for the synthesis of β-lactones.[3,4] In conjunction with the stereospecific decarboxylation of the β-lactone products, it provides an attractive strategy for the synthesis of substituted alkenes. The new method is based on the addition of lithium enolate derivatives of thiol esters to ketones and aldehydes at −78°C as originally described by Wemple.[5] The submitters have found that gradual warming (generally to 0°C) of the resulting aldolates produces β-lactones in good to excellent yield. The facility and generality of this spontaneous lactonization process had not been noted previously. Low-temperature quenching of the aldol addition reaction affords only the expected β-hydroxy thiol esters, although Masamune has shown that cyclization of the thiol ester aldol products can be effected as a separate operation by treatment with excess mercury(II) methanesulfonate and disodium phosphate (Na_2HPO_4) in acetonitrile.[6]

Both ketones and aldehydes, as well as acylsilanes can be employed as carbonyl substrates in the new β-lactone synthesis (Table). Reactions involving ketones are most conveniently carried out by adding the neat carbonyl compound to the thiol ester enolate solution. Under these conditions aliphatic aldehydes react to form substantial quantities of 2:1 adducts; however, formation of these side products can be suppressed simply by slowly adding the aldehyde component as a precooled (−78°C) solution to the reaction mixture. Wide variation is also possible in the thiol ester component, although a few limitations of the method have been noted. For example, α,β-unsaturated ketones such as methyl vinyl ketone and cyclohexenone fail to yield β-lactones, and attempts to generate β-lactones with severe steric crowding have also met with limited success.[3,4]

TABLE I
PREPARATION OF β-LACTONES VIA THIOL ESTERS

Entry	Carbonyl	Thiol Ester	β-Lactone	% Isolated

	Compound			Yield
1	Cyclohexanone	CH_3COSPh		86
2	Cyclohexanone	CH_3CH_2COSPh		92
3	Cyclohexanone	$MeOCH_2COSPh$		78
4	n-Octanal	$Me_2CHCOSPh$		54
5	$CH_3COSi\text{-}t\text{-}BuMe_2$	CH_3COSPh		55
6	Acetylcyclohexane	CH_3CH_2COSPh	 29:1	75
7	n-Octanal	CH_3CH_2COSPh	 2.5:1	42
8	Benzaldehyde	$t\text{-}BuCH_2COSPh$	 34:1	85

Not surprisingly, thiol ester enolates combine with ketones (and many aldehydes) to form predominantly the less sterically crowded β-lactone diastereomers, in some cases with excellent stereoselectivity. However, the stereochemical course of reactions involving aldehydes has proved to be rather complicated, and further studies are required to clarify the factors that control the stereochemical outcome of these reactions.

As described here, the new β-lactone synthesis also provides the basis for a very attractive approach to the synthesis of substituted alkenes. Since the 19th century it has been known that, upon heating, β-lactones undergo a facile [2+2] cycloreversion to generate alkenes and carbon dioxide.[7] [8] This stereospecific process[9] generally takes place at temperatures between 80° and 160°C, with the rate of reaction being highly dependent on the nature of substituents present at the C-4 (β) position of the lactone ring. The reaction often proceeds in nearly quantitative yield, and in recent years has been applied to the synthesis of a variety of types of substituted and functionalized alkenes. In this work, two experimental protocols were employed to effect the cycloreversion step. Alkenes boiling at 200°C or

lower were best generated by Kugelrohr distillation at 80–110°C from a mixture of the lactone and 10 weight % of silica gel[10] at a pressure such that the alkene product distilled as it was generated, leaving the less volatile β-lactone behind in the distillation flask. As described in the above procedure, alkenes with boiling points of ca. 250°C or greater were prepared by heating a benzene or cyclohexane solution of the requisite β-lactone at reflux in the presence of an equal weight of chromatographic silica gel.

The synthesis of β-lactones has received considerable attention[7,8] since the first representative of this class of heterocycles was prepared in 1883. Classical routes to β-lactones generally involved the cyclization of β-halocarboxylate salts[7,8] and the related "deaminative cyclization" that occurs upon diazotization of β-amino acids.[11] β-Hydroxy acids undergo a similar cyclization under Mitsunobu conditions,[12] [13] [14] and the halolactonization of α,β-unsaturated acids[15] [16] is a related process of some interest. Although these classical methods have been successfully employed for the preparation of a variety of β-lactones, their utility is often limited by side reactions including β-elimination (to form α,β-unsaturated acids) and decarboxylative elimination (to generate alkenes).

The strategy described here should find considerable use as a method for the stereoselective synthesis of alkenes. Although this olefination strategy involves one more step than the classic Wittig reaction, in many cases it may prove to be the more practical method. Finally, the scope, overall efficiency, and stereoselectivity of the β-lactone route compares favorably to the Wittig, Julia-Lythgoe, and related established strategies for the synthesis of tri- and tetrasubstituted alkenes.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 10, 339

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

silica gel

sodium benzophenone ketyl

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

ammonium chloride (12125-02-9)

acetonitrile (75-05-8)

Cyclohexanone (108-94-1)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

cyclohexane (110-82-7)

benzaldehyde (100-52-7)

acetone (67-64-1)

pyridine (110-86-1)

methylene chloride (75-09-2)

Thiophenol (108-98-5)

magnesium sulfate (7487-88-9)

Disodium Phosphate (7558-79-4)

3-methyl-2-butanone (563-80-4)

butyllithium,
n-butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

methyl vinyl ketone (78-94-4)

calcium hydride (7789-78-8)

cyclohexenone (930-68-7)

diphenyl disulfide (882-33-7)

acetylcyclohexane (823-76-7)

n-Octanal (124-13-0)

diisopropylamine (108-18-9)

(E)-2,3-Dimethyl-3-dodecene (174783-19-8)

S-phenyl decanoate

decanoyl chloride (112-13-0)

dinonyl ketone (504-57-4)

mercury(II) methanesulfonate (29526-41-8)

S-Phenyl decanethioate (51892-25-2)