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Synthesis of natural γ-lactones and a dilactone pyrrolizidine alkaloid via the reactions of 2-propenyl-1,3-dithiane

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Abstract. The crotyllithium generated from 2-propenyl-1,3-dithiane reacts exclusively at the γ-carbon with many aldehydes to give the homoallylic alcohols having the anti configuration. Hydrolyses of the addition products yield β,γ-disubstituted γ-lactones such as whiskey lactone and an insect pheromone eldanolide. The homoallylic alcohols are resolved by catalysis with lipases and the method is applicable to syntheses of optically active γ-lactones. The addition reaction of the dithio-substituted crotyllithium and ethyl pyruvate in the presence of zinc chloride gave, however, the syn product. The product is regioselectively elaborated to an 11-membered dilactone pyrrolizidine alkaloid, crobarbatine, by esterification of retronecine at the allylic hydroxyl group and macrocyclization subsequently to hydrolysis of the ketenedithioacetal moiety. Regioselective reactions of the crotyllithium with acetals, orthoesters, aliphatic aldimines and three- to six-membered cyclic ethers are carried out by mediation of boron trifluoride.

We have studied the electrophilic reactions of dithio-substituted crotyllithium generated from (*E*)-2-propenyl-1,3-dithiane (Table 1).[1] Dithiane **1** having *E*-configuration is readily prepared by condensation of crotonaldehyde and 1,3-propanedithiol in the presence of magnesium perchlorate. The conventional method using promoters $BF_3{\cdot}Et_2O$/HOAc yields **1** as a mixture of *E*- and *Z*-isomers (86:14).[2] Deprotonation of **1** with BuLi in THF solution gives the desired crotyllithium **1L**, which reacts at the α-site with halogenalkanes, but reacts at the γ-site with aldehydes. The regioselectivity in reactions of the crotyllithium and ketones is dependent on the nature of respective ketones, *i.e.* occurring at the α-site with modest size ketones but at the γ-site with bulky and unsaturated ketones (except 2-cyclopentenone).

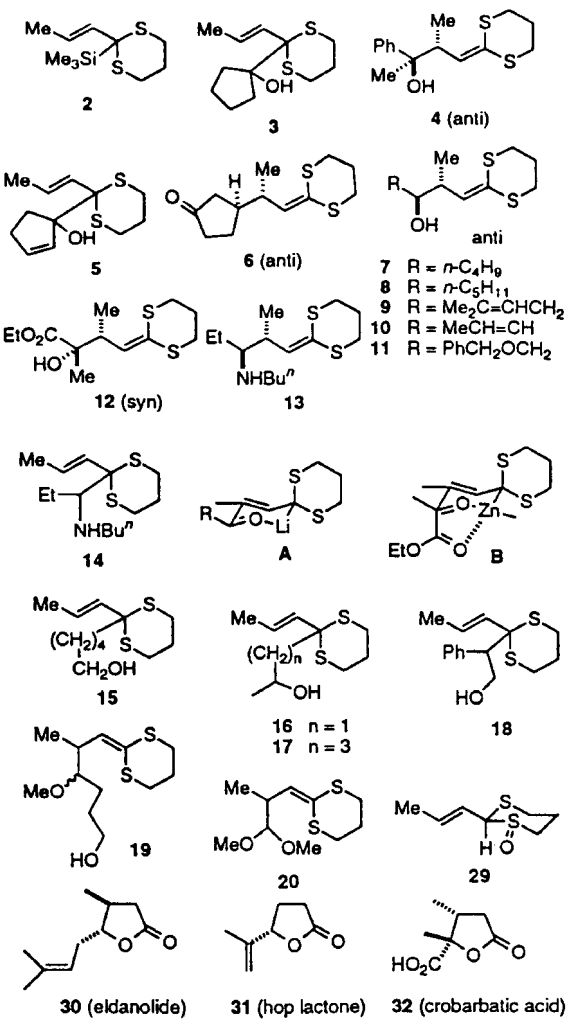
Comparison experiments on the reactivity of aldehydes and ketones are carried out (Fig. 1).[1c] A THF solution of crotyllithium **1L** is treated with a 1:1 mixture of butanal and 2-butanone at –78 °C for 2 min. The reaction was quenched, and the product mixture is found to contain 98% of α-adduct **22** from the ketone and 2% of γ-adduct **21** from the aldehyde. Similar reaction also reveals that the α-addition of 3-pentanone was much faster than the γ-addition of propanal. This result is in agreement with the HSAB principle, *i.e.* the hard-hard interaction between the α-carbon of **1L** and the carbonyl carbon of ketone is faster than the soft-soft interaction between the γ-carbon of **1L** and the carbonyl carbon of aldehyde.[3]

The influence of cosolvent HMPA and reaction temperature on the regiochemistry is studied.[1c] The α-addition products increase in the presence of HMPA, whereas the γ-addition products increase at higher reaction temperature (25 °C). The (1,2)-adducts derived from the reaction of **1** with 2-cyclopentenone and 2-cyclohexenone are isolated by means of liquid chromatography. The (1,2)-adducts have been reported to be unstable, and feasible to undergo alkoxy-Cope rearrangements in prolonged reaction time to give corresponding (1,4)-adducts.[2] The reaction of crotyllithium **1L** with α,β-unsaturated aldehydes afford allyl alcohols such as **23**, which undergo alkoxy-Cope rearrangements on treatment with KH (Fig. 2). The overall reactions can be visualized as the α-(1,4)-additions of vinylogous dithiane **1** to α,β-unsaturated aldehydes.

TABLE 1. Some typical reactions of crotyllithium **1L** with electrophiles.

Electrophile	Conditions	Products (yield/ %)
Me_3SiCl	A	**2** (98)
cyclopentanone	A	**3** (85)
acetophenone	A	**4** (91, anti/syn = 76/24)
2-cyclopentenone	A	**5** (89)
2-cyclopentenone	B	**6** (89, anti/syn = 90/10)
pentanal	A	**7** (93, anti)
hexanal	A	**8** (92, anti)
$Me_2C{=}CHCH_2CHO$	A	**9** (90, anti)
$MeCH{=}CHCHO$	A	**10** (88, anti/syn = 84/16)
$PhCH_2OCH_2CHO$	A	**11** (90, anti/syn = 78/22)
$MeCOCO_2Et$	A	**12** (86, anti/syn = 48/52)
$MeCOCO_2Et$	C	**12** (88, anti/syn = 15/85)
$MeCOCO_2Et$	D	**12** (85, anti/syn = 4/96)
$EtCH{=}NBu^n$	A	**13** (73, anti/syn = 34/66)
$EtCH{=}NBu^n$	E	**14** (90)
hexahydropyran	E	**15** (78)
2-methyloxirane	E	**16** (95)
2-methylfuran	E	**17** (84)
2-phenyloxirane	E	**18** (50) + isomer (30)
2-methoxyfuran	E	**19** (52)
$HC(OMe)_3$	E	**20** (87)

Condition **A**: THF, −78 °C; **B**: THF, 25 °C; **C**: THF, 1 equiv $ZnCl_2$, −78 °C; **D**: THF, 1 equiv $ZnCl_2$, −100 °C; **E**: Et_2O, 1 equiv BF_3, −78 °C



The γ-addition of crotyllithium **1L** with an aliphatic aldehyde occurs stereoselectively to give the product of anti configuration. The γ-adducts obtained from the reactions of α,β-unsaturated aldehydes are also in favor of the anti-configuration (anti/syn ≥ 3/1). The γ-adducts are prone to cyclization to give corresponding spirodithianes such as **25** by catalysis with mineral acids (HCl, HOAc or SiO_2). Hydrolyses of the γ-adducts in the presence of $HgCl_2$ give corresponding γ-lactones, *i.e.* the adducts of anti configuration giving trans lactones whereas the adducts of syn configuration giving cis lactones. Though a ketenedithioacetal is generally hydrolyzed with difficulty, facile hydrolysis of the γ-adduct appears to be facilitated by assistance of the neighboring hydroxyl group.

A chelate model **A** with the chair-like transition state can account for the high regioselectivity and anti selectivity in the reaction of crotyllithium **1L** with aldehydes.[4] The dithioacetal substituent plays an important role in obtaining high stereoselectivity by preventing crotyllithium **1L** from *E*/*Z* isomerization. The ketenedithioacetal moiety in the γ-adduct functions as a masked carboxyl group. Using this method, crotyllithium **1L** reacts with pentanal and 4-methyl-3-pentenal, respectively, to give the γ-anti-products **7** and **9**. Subsequent hydrolyses of these products culminate in the syntheses of a whiskey lactone **27** and an insect pheromone eldanolide **30** in nearly 70% yields.[1b]

Crotyllithium **1L** reacts exclusively at the γ-site with aldimines, but predominantly at the α-site with aliphatic aldimines in the presence of BF_3.[1f] Crotyllithium **1L** reacts also regioselectively at the α-site with acetals,

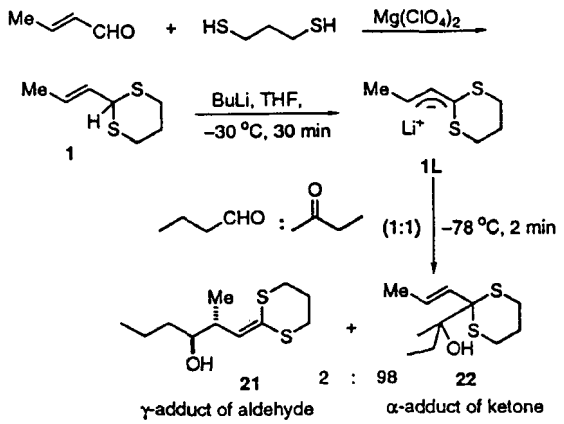


Fig. 1 Comparison experiment of reactivities of aldehyde and ketone toward crotyllithium 1L.

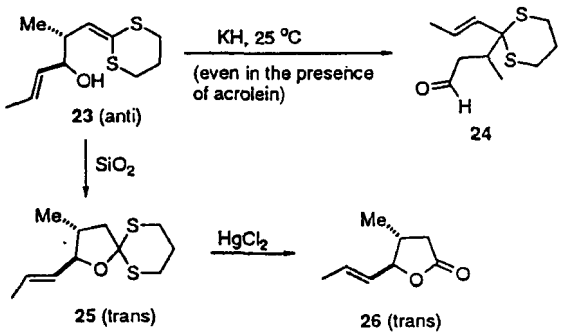


Fig. 2 Alkoxy-Cope rearrangement and cyclization of the γ-adduct of 2-propenyl-1,3-dithiane and α,β-unsaturated aldehyde.

orthoesters and three- to six-membered cyclic ethers in the presence of BF_3,[1e] whereas the corresponding reactions with acetals and orthoesters give γ-substitution products such as **19** and **20**.[5] The ring-opening reactions of 2-methyloxirane and 2-methylfuran occur at the less hindered α'-carbons, giving **16** and **17**, whereas the reaction of 2-phenyloxirane occurs preferably at the benzylic carbon, giving **18**.

Asymmetric oxidation of dithiane **1** by using a modified Sharpless reagent gives about 55% enantiomeric excess of (−)-trans-2-propenyl-1,3-dithiane 1-oxide **29**.[6a] Asymmetric oxidation of 2-propenyl-1,3-dithiolane yields the corresponding (+)-trans-1-oxide in 72% ee, which is recrystallized (Et_2O/ petroleum ether) in the optically pure form.[6b] Aldehydes react with the crotyllithium of **29**, however, at the α-site and predominantly on the face syn to the sulfinyl group.

The homoallylic alcohols obtained by the γ-additions of dithiane **1** (or related dithio-substituted analogues) with aldehydes are resolved by enzymatic methods (Fig. 3).[7] The homoallylic alcohol (±)-**7** is converted to

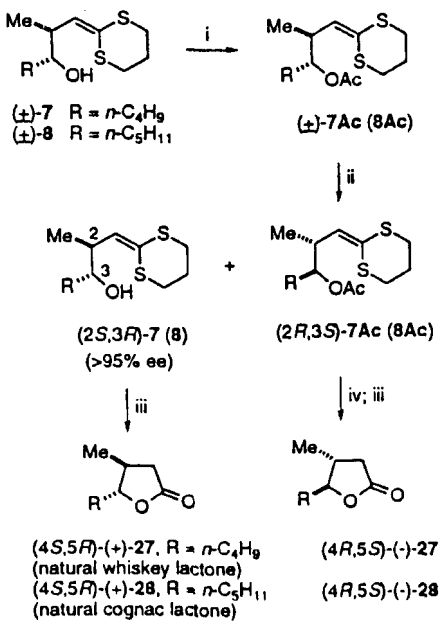


Fig. 3 Preparation of optically active γ-lactones.
(i) Ac_2O, Et_3N, cat. DMAP, CH_2Cl_2, 25 °C, 1 h; 98%.
(ii) lipase, DMF, phosphate buffer (pH 7.5).
(iii) $HgCl_2$, aq. MeOH (10%), reflux, 5 h; 92%.
(iv) KOH, aq. MeOH, 25 °C, 3 h.

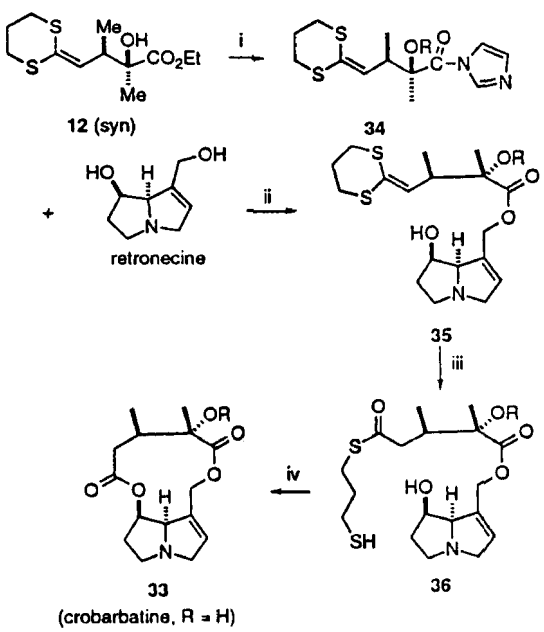


Fig. 4 Synthesis of crobarbatine.
(i) NaH, RX, THF, reflux, 99%;
t-BuOK, THF, H_2O, rt, 99%; $(Im)_2C{=}O$, THF, rt, 99%.
(ii) 0.2 equiv NaH, THF, rt, 84%.
(iii) conc. HCl, CH_2Cl_2, rt, 100%.
(iv) CF_3CO_2Ag, DMAP, THF, reflux, 55%.

the corresponding acetate, which is subjected to lipase-catalyzed hydrolysis to give the optically active alcohol having the (2*S*,3*R*)-configuration. Subsequent treatment with $HgCl_2$ affords the natural whiskey lactone (+)-**27**. Cognac lactone **28**, hop lactone **31** and other optically active γ-lactones are prepared by similar procedures.

While crotyllithium **1L** reacts with most aldehydes to give exclusively anti addition products, its reactions with (benzyloxy)acetaldehyde, D-glyceraldehyde acetonide and ethyl pyruvate give mixtures of anti and syn addition products.[1d] The reaction with ethyl pyruvate in THF at -78 °C gives the anti and syn products in a ratio of 48:52. The syn selectivity was greatly increased to 85% in the presence of a 1-equiv amount of zinc chloride. Lowering the reaction temperature to −100 °C finally leads to 96% of syn adduct. A double chelate transition state **B** due to the strong chelate ability of zinc cation and oxygen atom can account for the syn selectivity. The syn product is treated with $HgCl_2$, followed by saponification, to give crobarbatic acid **32**, a degradative product of the 11-membered dilactone pyrrolizidine alkaloid, crobarbatine **33** (R = H).

Kinetic resolution of the ethyl carboxylate **12** by enzymatic hydrolysis fails.[8] The reaction of crotyllithium **1L** and (−)-8-phenylmenthyl pyruvate is not stereoselective, even in the presence of a divalent counterion such as Mg^{2+} or Zn^{2+}. Synthesis of crobarbatine is pursued (Fig. 4).[9] The hydroxyl group in the adduct **12** (syn) is protected as a benzyl ether, and the ester group is activated as an imidazolide, giving **34**. Retronecine reacts with **34** at the more reactive allylic hydroxyl group to give the ester **35**. Upon treatment with concentrated hydrochloric acid, the ketenedithioacetal moiety is converted to a thioester, which is suitable for the macrolactonization by assistance of Cu^+ or Ag^+ ion.

Acknowledgements

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