

A Simple Method for the Synthesis of Lignan Skeleton.¹⁾ Syntheses of (±)-Parabenzlactone and (±)-Hinokin

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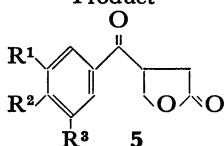
The reaction of 2-aryl-2-lithio-1,3-dithianes with 2-butenolide followed by quenching with benzyl halides gave lignan skeleton in fairly good yield.

In connection with the total synthesis of a novel class of antileukemic lignan lactone, steganacin (**1**),²⁾ we needed the efficient synthetic method for constructing the *seco*-lactone skeleton (**2**). We have studied the addition of 2-aryl-2-lithio-1,3-dithianes to 2-butenolide, hoping to find a new method leading to **2**. Although synthetic applications of 2-lithio-1,3-dithianes as an acyl anion equivalent had been widely explored,³⁾ little investigation existed for the Michael addition of it to α,β -unsaturated lactones, when we started on this project. Since then Ziegler and Schwartz⁴⁾ reported the synthesis of lignans by means of a conjugate addition of aryl dithiane anion to 2-butenolide. In this paper we wish to report on the results of our own independent studies which based on the essentially the same idea as theirs.

Results and Discussion

Treatment of 2-aryl-1,3-dithianes (**3**)⁵⁾ in THF with butyllithium at -40°C followed by addition of 2-butenolide at -78°C gave the Michael addition products (**4**). Concerning the effect of substituents, it was shown that the addition was facilitated by the presence of electron-releasing groups **4b**—**4e**, as shown in Table 1. Neither 2-lithio-1,3-dithiane nor 2-lithio-2-

TABLE 2. DESULFURIZATION OF DITHIANE LACTONES

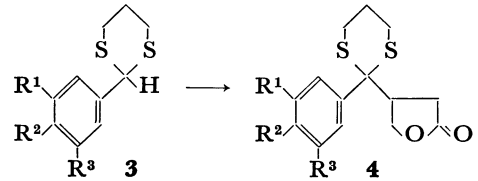
 Product 5	Condition		Mp (°C)	Yield (%)
	Temp (°C)	Time (min)		
b ; R ¹ =R ² =H; R ³ =OMe	rt	60	68.5—69.5	80
c ; R ¹ =R ² =OMe; R ³ =H	40	30	118—119.5	67
d ; R ¹ =R ² =-OCH ₂ O-; R ³ =H	50	30	118—119	100
e ; R ¹ =R ² =R ³ =OMe	0→rt	45	93—95	61
f ; R ¹ =OBz; R ² =OMe; R ³ =H	rt	60	150—151	72

aryl-1,3-dithiolane added to 2-butenolide. Desulfurization of **4** with *N*-chlorosuccinimide and silver nitrate gave β -aroyl- γ -lactones (**5**), as shown in Table 2.

Attempted alkylation of **4d** with lithium cyclohexylisopropylamide and piperonyl bromide (THF-HMPA, -78°C , 2 h) led to the recovery of the starting material.* We then carried out indirect alkylation. Treatment of the lactone **4d** with dimethyl carbonate and sodium hydride without solvent gave the α -carbomethoxy lactone (**6**). The NMR spectrum showed peaks at 3.94 ppm (d, $J=9.0$ Hz) due to $-\text{CO}-\text{CH}-\text{CO}_2\text{Me}$, suggesting the *trans* configuration of substituents. This was alkylated with piperonyl bromide to give the trisubstituted lactone (**7**) in 74% yield from **4d**. The IR spectrum of **7** showed the presence of a γ -lactone (1780 cm^{-1}) and an ester group (1750 cm^{-1}). The NMR spectrum of **7** showed signals at 3.00 (H_e, dd, $J=8.2$ and 11.3 Hz), 3.31 (H_c, H_d, AB_q, $J=16.1$ Hz), 3.92 (H_b, t, $J=8.2$ and 10.2 Hz) and 4.55 ppm (H_a, dd, $J=10.2$ and 11.3 Hz). Hydrolysis of the ester **7** with ethanolic potassium hydroxide followed by acidification gave the bis-benzyl-substituted lactone (**8**) in 80% yield. The IR spectrum of **8** showed a characteristic band at 1770 cm^{-1} . The NMR spectrum of **8** showed signals at 2.91 (H_c, m), 3.86 (H_b, q, $J=8.2$ and 9.8 Hz), 4.54 (H_a, q, $J=4.2$ and 9.8 Hz), 5.86 ($-\text{OCH}_2\text{O}-$, q, $J=2$ Hz) and 5.96 ppm ($-\text{OCH}_2\text{O}-$, q, $J=2$ Hz). The characteristic feature of the NMR spectrum is the non-equivalence of both methylenedioxy groups, probably due to the stretched and rather rigid *trans* orientation⁶⁾ of the two methylenedioxy benzyl residue to avoid the steric repulsion of large 1,3-dithiane group and to the presence of hindered rotation.

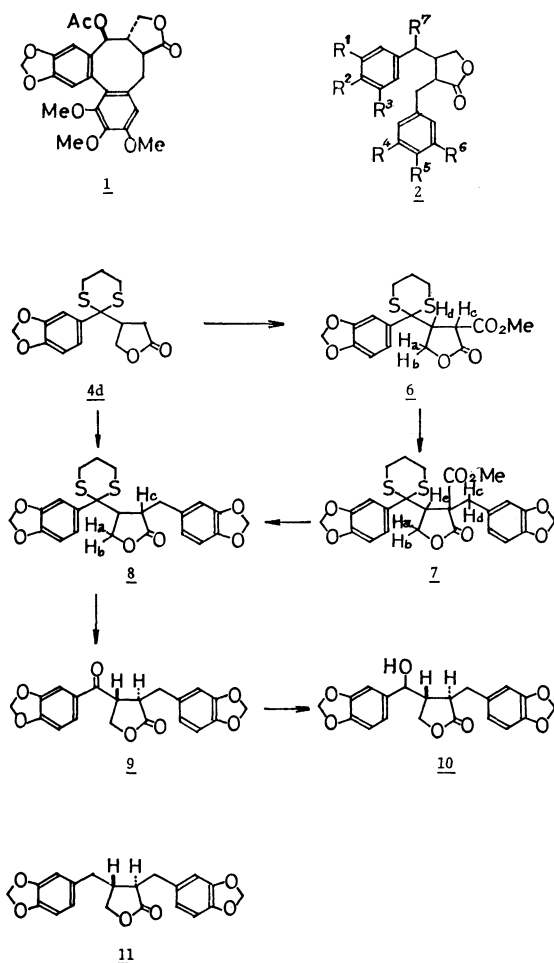
We have also observed that the intermediate lactone enolate generated by the Michael addition can be

TABLE 1. FORMATION OF DITHIANE LACTONES

 Dithiane 3	Product	
	Mp (°C)	Yield (%) ^{a)}
a ; R ¹ =R ² =R ³ =H	109—110	13
b ; R ¹ =R ³ =H; R ² =OMe	98.5—100	88
c ; R ¹ =R ² =OMe; R ³ =H	130—131	71
d ; R ¹ =R ² =-OCH ₂ O-; R ³ =H	158.5—160	78
	(lit, ⁴⁾ 154—155	
e ; R ¹ =R ² =R ³ =OMe	161—163	68
f ; R ¹ =OBz; R ² =OMe; R ³ =H	130—131.5	79

a) Isolated yield.

* Ziegler and Schwartz⁴⁾ alkylated **4d** with lithium diisopropylamide and 3,4,5-trimethoxybenzyl chloride in THF-HMPA at -78°C for 3 h and then at room temperature for 18 h.



trapped with piperonyl bromide to give **8** in 78% yield. Cleavage of the dithioketal group of **8** gave the keto lactone **9**. The NMR spectrum ($\text{CDCl}_3\text{-C}_6\text{D}_6$ 1:1) of **9** showed three protons multiplet between 2.52–3.36 ppm (Fig. 1). The multiplets centered at 2.76 and 3.30 ppm were assigned as H_A and H_B , and H_X , respectively. Two benzylic protons forming the AB part of an ABXY system with $J_{AY}=J_{BY}=0$ Hz and the proton α to the lactone carbonyl forming the X part. Analysis of the spectrum revealed the following coupling constants: $|J_{AB}|=14.2$ Hz; $|J_{AX}|=3.4$ Hz; $|J_{BX}|=9.0$ Hz; and $|J_{XY}|=8.5$ Hz. As the coupling constants of flexible five-membered ring might be of little diagnostic value, we then carried out equilibration experiments. Equilibration of **9** with potassium *t*-butoxide in *t*-butyl alcohol gave unchanged material, suggesting the thermodynamically more stable, *trans* stereochemistry of the two substituents at the lactone ring. The keto lactone **9**

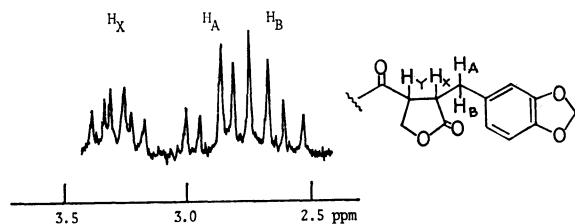


Fig. 1 The NMR spectrum of **9** in $\text{CDCl}_3\text{-C}_6\text{D}_6$ (1:1).

Fig. 1. The NMR spectrum of **9** in $\text{CDCl}_3\text{-C}_6\text{D}_6$ (1:1).

was identical with oxo-parabenzlactone⁷⁾ (IR, UV, NMR, and TLC) derived from natural (–)-parabenzlactone by means of Jones' oxidation.

Reduction of **9** with NaBH_4 or $\text{Zn}(\text{BH}_4)_2$ gave (±)-parabenzlactone (**10**), which was identical with the natural product⁷⁾ (IR, UV, NMR, and TLC). Since it has been known that the reduction with $\text{Zn}(\text{BH}_4)_2$ does not change the configuration at the lactone ring,⁸⁾ the synthetic parabenzlactone also takes the *trans* stereochemistry. Thus the synthesis unambiguously established the *trans* stereochemistry of (–)-parabenzlactone which accords with the conclusion derived from CD experiments.⁹⁾

Reductive desulfurization of **8** with Raney Ni gave the amorphous lactone (**11**), whose IR and NMR spectra were superimposable with those of (–)-hinokinin.⁹⁾

Experimental

All the melting points are uncorrected. The IR spectra were measured with JASCO IRA-1 spectrophotometer. The NMR spectra were recorded in CDCl_3 , with TMS as the internal standard, using JEOL PS-100 spectrophotometer.

General Procedure for the Preparation of Dithiane Lactones **4**.

Butyllithium (6.5 ml of a 15% hexane solution, 0.0105 mol) was added to a solution of 2-aryl-1,3-dithiane **3** (0.01 mol) in THF (30 ml) and HMPA (0.01 mol) at -75°C under nitrogen atmosphere. The mixture was stirred for an additional hour at -40°C . After cooling at -75°C , the mixture was treated with 2-butenolide (1.26 g; 0.015 mol) in 3 ml of THF, stirred for two hours at -75°C , and then treated with 10% hydrochloric acid. Extractive work-up and chromatography on silicic acid gave pure dithiane lactone.

Dithiane Lactone 4a. IR (Nujol) 1780, 1770 (sh), 1600, 1490, 1180, 770, and 710 cm^{-1} ; NMR (CDCl_3) 1.84 (m, 2), 2.16–3.12 (m, 6), 4.0–4.42 (m, 2), 7.2–7.48 (m, 3), and 7.84–7.94 (m, 2); Found: C, 60.05; H, 5.82%. Calcd for $\text{C}_{14}\text{H}_{16}\text{O}_2\text{S}_2$: C, 59.97; H, 5.75%.

Dithiane Lactone 4b. IR (CHCl_3) 1775, 1605, and 1025 cm^{-1} ; NMR (CDCl_3) 1.7–2.0 (m, 2), 2.21–3.16 (m, 7), 3.84 (s, 3), 4.04–4.44 (m, 2), 6.90 (m, 2), and 7.82 ppm (m, 2); Found: C, 58.06; H, 5.84%. Calcd for $\text{C}_{15}\text{H}_{18}\text{O}_3\text{S}_2$: C, 58.03; H, 5.84%.

Dithiane Lactone 4c. IR (CHCl_3) 1775, 1600, 1590, and 1025 cm^{-1} ; NMR (CDCl_3) 1.8–2.04 (m, 2), 2.29–3.24 (m, 7), 3.97 (s, 6), 4.10–4.52 (m, 2), 6.94 (d, 1, $J=9$ Hz) and 7.49–7.60 ppm (m, 2); Found: C, 56.55; H, 5.94%. Calcd for $\text{C}_{16}\text{H}_{20}\text{O}_4\text{S}_2$: C, 56.44; H, 5.92%.

Dithiane Lactone 4d. IR (Nujol) 1775, 1500, 1040, and 930 cm^{-1} ; NMR ($\text{CDCl}_3\text{-DMSO-}d_6$) 1.8–2.01 (m, 2), 2.24–3.16 (m, 7), 4.06–4.46 (m, 2), 6.02 (s, 2), 6.80 (d, 1, $J=9$ Hz), and 7.31–7.48 ppm (m, 2); Found: C, 55.51; H, 4.95%. Calcd for $\text{C}_{15}\text{H}_{16}\text{O}_4\text{S}_2$: C, 55.53; H, 4.97%.

Dithiane Lactone 4e. IR (Nujol) 1780, 1500, 1585, and 1130 cm^{-1} ; NMR (CDCl_3) 1.96 (m, 2), 2.28–3.22 (m, 7), 3.91 (s, 9), 4.11–4.61 (m, 2), and 7.28 (s, 2); Found: C, 55.06; H, 5.99%. Calcd for $\text{C}_{17}\text{H}_{22}\text{O}_5\text{S}_2$: C, 55.11; H, 5.99%.

Dithiane Lactone 4f. IR (CHCl_3) 1770, 1600, 1585, and 1020 cm^{-1} ; NMR (CDCl_3) 1.80–2.02 (m, 2), 2.26–3.20 (m, 7), 3.90 (s, 3), 4.08–4.50 (m, 2), 5.17 (s, 2), 6.92 (d, 1, $J=8$ Hz), and 7.30–7.56 (m, 8).

General Procedure for the Desulfurization of Dithiane Lactones **4**.

To a mixture of NCS (0.004 mol) and silver nitrate (0.0045 mol) in 4 ml of CH_3CN and 2 ml of water was added a solution of **4** (0.001 mol) in CH_3CN . The mixture was stirred under

the condition shown in Table 2, then poured into sat NaCl soln and extracted with ether. The extract was washed with NaHSO₃ soln and NaCl soln and dried. Evaporation and chromatography gave pure β -aroyl- γ -lactone 5.

β -(4-Methoxybenzoyl)butyrolactone 5b. IR (CHCl₃) 1770, 1670, 1595, 1570, 1210, and 1025 cm⁻¹; NMR (CDCl₃) 2.56—3.10 (m, 2), 3.86 (s, 3), 4.12—4.64 (m, 3), 6.94 (m, 2), and 7.87 ppm (m, 2); Found: C, 65.46; H, 5.49%. Calcd for C₁₁H₁₂O₄: C, 65.44; H, 5.49%.

β -(3,4-Dimethoxybenzoyl)butyrolactone 5c. IR (CHCl₃) 1775, 1670, 1590, 1585, 1260, and 1020 cm⁻¹; NMR (CDCl₃) 2.60—3.15 (m, 2), 3.93 (s, 3), 3.96 (s, 3), 4.27—4.70 (m, 3), 6.94 (d, 1, *J*=9 Hz), and 7.44—7.61 (m, 2); Found: C, 62.37; H, 5.68%. Calcd for C₁₃H₁₄O₅: C, 62.39; H, 5.64%.

β -(3,4-Methylenedioxybenzoyl)butyrolactone 5d. IR (Nujol) 1780, 1680, 1620, and 1040 cm⁻¹; NMR (CDCl₃) 2.57—3.12 (m, 2), 4.08—4.64 (m, 3), 6.04 (s, 2), 6.84 (d, 1, *J*=8 Hz) and 7.35—7.50 ppm (m, 2); Found: C, 61.40; H, 4.28%. Calcd for C₁₂H₁₀O₅: C, 61.54; H, 4.30%.

β -(3,4,5-Trimethoxybenzoyl)butyrolactone 5e. IR (CHCl₃) 1780, 1680, 1590, 1030, and 1000 cm⁻¹; NMR (CDCl₃) 2.90 (m, 2), 3.93 (s, 9), 4.48 (m, 3), and 7.16 ppm (s, 2).

β -(3-Benzoyloxy-4-methoxybenzoyl)butyrolactone 5f. IR (CHCl₃) 1775, 1670, 1590, 1580, 1260, and 1020 cm⁻¹; NMR (CDCl₃) 2.55—3.12 (m, 2), 3.91 (s, 3), 4.20—4.62 (m, 3), 5.20 (s, 2), 6.89 (d, 1, *J*=9 Hz), 7.27—7.42 (m, 6), and 7.46 ppm (d, 1, *J*=9 Hz); Found: C, 69.84; H, 5.49%. Calcd for C₁₉H₁₈O₅: C, 69.93; H, 5.56%.

Carbomethoxylation of 4. To 0.275 g (0.0057 mol) of 50% mineral oil dispersion of NaH (twice washed with anhyd. hexane) suspended in 5 ml of dry Me₂CO₃ was added 713 mg of 4 in 11 ml of Me₂CO₃ and 5 ml of anhyd. THF, and the mixture was refluxed for 10 h. After the excess reagent had been destroyed with MeOH, the mixture was poured into water and extracted with CHCl₃. The organic layer was washed with NaHCO₃ soln, dried and evaporated to give 813 mg (97%) of the carbomethoxy lactone 6, mp 168—170 °C (from EtOH), IR (Nujol) 1770 and 1735 cm⁻¹; NMR (CDCl₃) 1.94 (m, 2), 2.72 (m, 4), 3.58 (m, 1, H_d), 3.68 (s, 3), 3.94 (d, 1, *J*=9 Hz, H_c), 4.32 (q, 1, *J*=8 and 10 Hz), 6.82 (d, 1, *J*=9 Hz), and 7.44 ppm (m, 2); Found: C, 53.35; H, 4.72%. Calcd for C₁₇H₁₈O₆S₂: C, 53.39; H, 4.74%.

Alkylation of 6. To a soln of 654 mg (0.00171 mol) of 6 in 30 ml of DME was added 115 mg (0.00239 mol) of NaH mineral oil dispersion (50%) under a nitrogen atmosphere. Several drops of dried *t*-BuOH were added, the mixture was stirred for 40 min at room temp, then a soln of 386 mg (0.00171 mol) of piperonyl bromide in 7 ml of DME was added and the resulting mixture was refluxed for 3 h. After removal of the solvent under reduced pressure, water was added to this mixture and extracted with ether. The crude product was chromatographed over neutral Al₂O₃ (Act II), and elution with C₆H₆-ether (95:5) afforded 674 mg (76%) of 7, mp 206—208 °C (from EtOH), IR (CHCl₃) 1780, 1750, 1610, and 940 cm⁻¹; NMR (CDCl₃) 1.91 (m, 2), 2.64 (m, 4), 3.00 (q, 1, *J*=8.2 and 8.5 Hz, H_c), 3.31 (q, 2, *J*=15 Hz, H_c, H_d), 3.81 (s, 3), 3.92 (q, 1, *J*=8.2 and 10 Hz, H_b), 4.55 (q, 1, *J*=8.5 and 10 Hz, H_a), 5.91 (s, 2), 6.06 (s, 2), and 6.74—7.56 ppm (m, 6); Found: C, 58.04; H, 4.67%. Calcd for C₂₅H₂₄O₈S₂: C, 58.12; H, 4.68%.

Decarboxylation of 7. Hydrolysis of 7 (260 mg) with 1 M ethanolic KOH (15 ml) at 50 °C for an hour followed by acidification with acetic acid gave 8 (205 mg; 80%), mp 153—155 °C (from EtOH); IR (CHCl₃) 1770, 1610, and 940 cm⁻¹; NMR (CDCl₃) 1.84 (m, 2), 2.56 (m, 7), 2.96 (m, 1, H_c), 3.86 (q, 1, *J*=8.2 and 10 Hz, H_b), 4.54 (q, 1, *J*=4.2 and 10 Hz, H_a), 5.86 (q, 2, *J*=2.0 Hz) and 5.96 ppm (q, 2, *J*=2.0 Hz);

Found: C, 60.12; H, 4.83%. Calcd for C₂₃H₂₂O₆S₂: C, 60.24; H, 4.84%.

One-pot Synthesis of 8. Butyllithium (3.3 ml of a 15% hexane soln, 5.29 × 10⁻³ mol) was added to a soln of 3d (1.211 g; 5.04 × 10⁻³ mol) in THF (25 ml) at -78 °C under nitrogen atmosphere. The mixture was stirred for 1.5 h at -40 °C. After cooling at -78 °C, the mixture was treated with 2-butenolide (0.423 g; 5.04 × 10⁻³ mol) in 5 ml of abs. THF. After stirring for 2 h at -60 °C, the mixture was treated with 10% HCl. Extractive work-up and chromatography on silicic acid and elution with C₆H₆-AcOEt (95:5) gave pure 8 in 77% yield.

Equilibration of 8. The lactone 8 (50 mg) was added to a 3% soln of *t*-BuOK in *t*-BuOH (10 ml). The mixture was stirred for 5 h at 60 °C and then for 12 h at room temp. After quenching the reaction with dil HCl, extractive work-up gave the starting material (TLC, NMR, and IR).

Desulfurization of 8. To a mixture of NCS (0.567 g; 97%; 4.12 × 10⁻³ mol) and silver nitrate (0.787 g; 4.63 × 10⁻³ mol) in 4 ml of CH₃CN and 2 ml of water was added a soln of 8 (474 mg; 1.03 × 10⁻³ mol) in 6 ml of CH₃CN. The mixture was heated for 30 min at 50 °C, then poured into sat. NaCl soln and extracted with ether. The extract was washed with NaHSO₃ soln and NaCl soln and dried. Evaporation of the solvent gave the keto lactone 9, (370 mg; 100%), mp 140—142 °C (from EtOH); IR (CHCl₃) 1780, 1675, 1610, and 940 cm⁻¹; NMR (CDCl₃) 2.92 (m, 2, AB part of ABXY system), 3.38 (m, 1, X part of ABXY system), 3.79—4.40 (m, 3), 5.84 (s, 2), and 6.01 ppm (s, 2). This compound was identical with the oxo-parabenzlactone derived from natural (-)-parabenzlactone⁹ by oxidation with Jones' reagent (IR, NMR, UV and TLC).

Reduction of 9. (a) To a chilled (0 °C) soln of 9 (36 mg; 9.78 × 10⁻⁵ mol) in 5 ml of MeOH and 5 ml of THF was added 4 mg (9.78 × 10⁻⁵ mol) of NaBH₄. The mixture was stirred for 40 min and then the excess reagent was destroyed with few drops of acetic acid. The solvent was removed *in vacuo* (50 °C), the residue was diluted with water and worked up by extraction with CHCl₃ giving 10 (16 mg), mp 156—158 °C (from MeOH). This was identical with natural parabenzlactone⁹ (IR, NMR, and TLC).

(b) To a soln of 9 (60 mg; 1.63 × 10⁻⁴ mol) in 2.5 ml of dry C₆H₆ was added 1.63 × 10⁻⁴ mol of zinc borohydride⁹ in 11.2 ml of abs ether. After 24 h at room temp the mixture was treated with water and then with dil acetic acid. Extractive work-up gave an oil (65 mg), which was purified by chromatography on silicic acid. Elution with AcOEt-C₆H₆ (1:4) gave pure 10 (50 mg).

Reductive Desulfurization of 8. The mixture of 8 (150 mg) and 2 g of Raney Ni (W-2) in 50 ml of abs EtOH was refluxed overnight. Filtration of the catalyst and evaporation of the solvent gave 11 as a viscous oil. The IR and NMR spectra of 11 were superimposable with those of (-)-hinokinin.⁹

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