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

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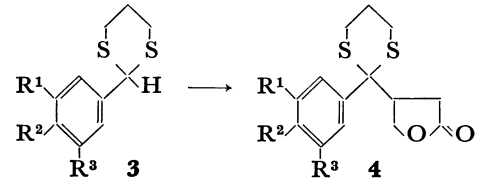
The reaction of 2-aryl-2-lithio-1,3-dithianes with 2-butenolide followed by quenching with benzyl halides gave lignan skeleton in fairly good yield.

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 Schwartz[4] 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-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.

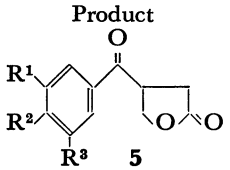
Table 1. Formation of dithiane lactones



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; $R^1=R^2=-OCH_2O-$; $R^3=H$	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.

Table 2. Desulfurization of dithiane lactones

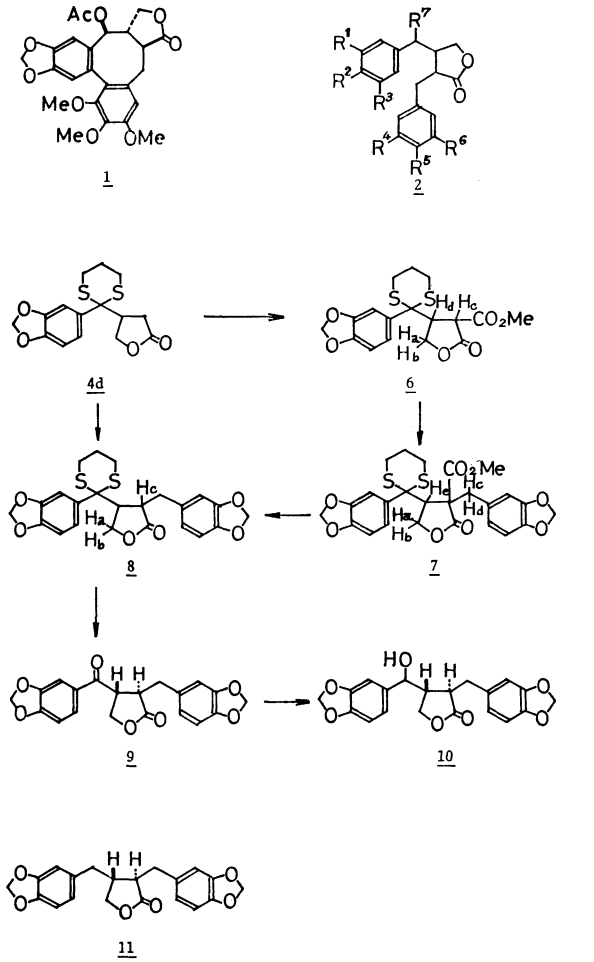


Product **5**	Condition Temp (°C)	Time (min)	Mp (°C)	Yield (%)
b; $R^1=R^3=H$; $R^2=OMe$	rt	60	68.5— 69.5	80
c; $R^1=R^2=OMe$; $R^3=H$	40	30	118 —119.5	67
d; $R^1=R^2=-OCH_2O-$; $R^3=H$	50	30	118 —119	100
e; $R^1=R^2=R^3=OMe$	0→rt	45	93 — 95	61
f; $R^1=OBz$; $R^2=OMe$; $R^3=H$	rt	60	150 —151	72

Attempted alkylation of **4d** with lithium cyclohexyl-isopropylamide 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 $-CO-\underline{C}H-CO_2Me$, 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 ($-OCH_2O-$, q, J=2 Hz) and 5.96 ppm ($-OCH_2O-$, 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* orientation[6] 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

* Ziegler and Schwartz[4] 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 ($CDCl_3$–C_6D_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** was identical with oxo-parabenzlactone[7] (IR, UV, NMR, and TLC) derived from natural (−)-parabenzlactone by means of Jones' oxidation.

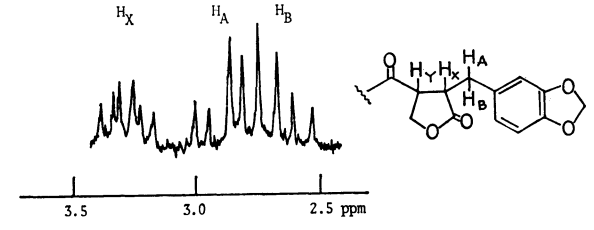


Fig. 1 The NMR spectrum of 9 in $CDCl_3$-C_6D_6 (1:1).

Fig. 1. The NMR spectrum of **9** in $CDCl_3$–C_6D_6 (1: 1).

Reduction of **9** with $NaBH_4$ or $Zn(BH_4)_2$ gave (±)-parabenzlactone (**10**), which was identical with the natural product[7] (IR, UV, NMR, and TLC). Since it has been known that the reduction with $Zn(BH_4)_2$ 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 $C_{14}H_{16}O_2S_2$: 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 $C_{15}H_{18}O_3S_2$: 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 $C_{16}H_{20}O_4S_2$: C, 56.44; H, 5.92%.

Dithiane Lactone **4d**. IR (Nujol) 1775, 1500, 1040, and 930 cm^{-1}; NMR ($CDCl_3$–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 $C_{15}H_{16}O_4S_2$: 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 $C_{17}H_{22}O_5S_2$: 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 withNaHSO$_3$ soln and NaCl soln and dried. Evaporation and chromatography gave pure β-aroyl-γ-lactone **5**.

β-(4-Methoxybenzoyl)butyrolactone ***5b***. IR ($CHCl_3$) 1770, 1670, 1595, 1570, 1210, and 1025 cm^{-1}; NMR ($CDCl_3$) 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 $C_{11}H_{12}O_4$: C, 65.44; H, 5.49%.

β-(3,4-Dimethoxybenzoyl)butyrolactone ***5c***. IR ($CHCl_3$) 1775, 1670, 1590, 1585, 1260, and 1020 cm^{-1}; NMR ($CDCl_3$) 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 $C_{13}H_{14}O_5$: C, 62.39; H, 5.64%.

β-(3,4-Methylenedioxybenzoyl)butyrolactone ***5d***. IR (Nujol) 1780, 1680, 1620, and 1040 cm^{-1}; NMR ($CDCl_3$) 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 $C_{12}H_{10}O_5$: C, 61.54; H, 4.30%.

β-(3,4,5-Trimethoxybenzoyl)butyrolactone ***5e***. IR ($CHCl_3$) 1780, 1680, 1590, 1030, and 1000 cm^{-1}; NMR ($CDCl_3$) 2.90 (m, 2), 3.93 (s, 9), 4.48 (m, 3), and 7.16 ppm (s, 2).

β-(3-Benzyloxy-4-methoxybenzoyl)butyrolactone ***5f***. IR ($CHCl_3$) 1775, 1670, 1590, 1580, 1260, and 1020 cm^{-1}; NMR ($CDCl_3$) 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 $C_{19}H_{18}O_5$: 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 Me_2CO_3 was added 713 mg of **4** in 11 ml of Me_2CO_3 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 $CHCl_3$. The organic layer was washed with $NaHCO_3$ 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 ($CDCl_3$) 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 $C_{17}H_{18}O_6S_2$: 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 Al_2O_3 (Act II), and elution with C_6H_6–ether (95: 5) afforded 674 mg (76%) of **7**, mp 206—208 °C (from EtOH), IR ($CHCl_3$) 1780, 1750, 1610, and 940 cm^{-1}; NMR ($CDCl_3$) 1.91 (m, 2), 2.64 (m, 4), 3.00 (q, 1, J=8.2 and 8.5 Hz, H_e), 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 $C_{25}H_{24}O_8S_2$: 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 ($CHCl_3$) 1770, 1610, and 940 cm^{-1}; NMR ($CDCl_3$) 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 $C_{23}H_{22}O_6S_2$: 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 C_6H_6–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 CH_3CN and 2 ml of water was added a soln of **8** (474 mg; 1.03×10^{-3} mol) in 6 ml of CH_3CN. 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 $NaHSO_3$ 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 ($CHCl_3$) 1780, 1675, 1610, and 940 cm^{-1}; NMR ($CDCl_3$) 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 (−)-parabenzlactone[7] 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 $NaBH_4$. 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 $CHCl_3$ giving **10** (16 mg), mp 156—158 °C (from MeOH). This was identical with natural parabenzlactone[7] (IR, NMR, and TLC).

(b) To a soln of **9** (60 mg; 1.63×10^{-4} mol) in 2.5 ml of dry C_6H_6 was added 1.63×10^{-4} mol of zinc borohydride[8] 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–C_6H_6 (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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