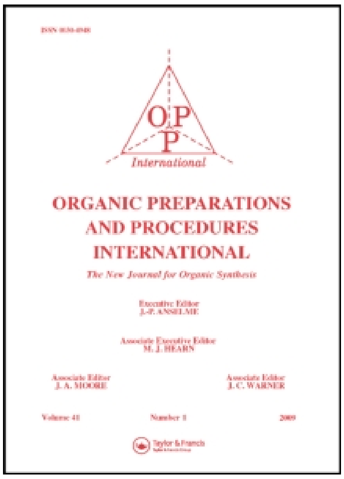

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SYNTHESIS OF A DIBENZYLBUTYROLACTONE LIGNAN EXTRACTIVE OF CINNAMOMUM CAMPHORA

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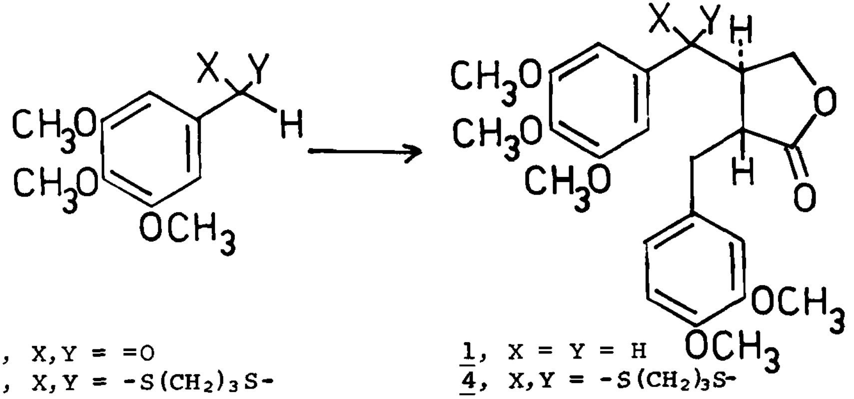
A useful review of the dibenzylbutyrolactone group of lignans has recently appeared.[1] Of the more than thirty compounds reported to occur naturally, the most recent, isolated from the heartwood of Cinnamomum camphora Sieb., has been formulated[2] as (-)-trans-2-(3,4-dimethoxybenzyl)-3-(3,4,5-trimethoxybenzyl)butyrolactone (1). We now report a synthesis of the



2, X,Y = =O
3, X,Y = $-S(CH_2)_3S-$

1, X = Y = H
4, X,Y = $-S(CH_2)_3S-$

(±)-form of this product, both as part of a general programme of lignan synthesis and more particularly since the reported pmr spectrum (particularly the MeO group chemical shifts) appeared incompatible with the proposed structure. The pathway adopted now appears to be of general applicability, and has been followed for the synthesis of (±)-podorhizol,[3] (±)-parabenzlactone[4] and (±)-hinokinin.[4]

2-(3,4,5-Trimethoxyphenyl)-1,3-dithiane (3), readily prepared from the parent aldehyde (2), was converted in a "one-pot" reaction to 2-(3,4-dimethoxybenzyl)-3-[2-(3,4,5-trimethoxyphenyl)-1,3-dithianyl]butanolide (4) by sequential addition of n-butyllithium, butenolide, 3,4-dimethoxybenzyl bromide and tetramethylethylenediamine. Desulphurisation of 4 so obtained as an oil in 76% yield, proceeded smoothly with Raney nickel to give the required butyrolactone 1 quantitatively.

The pmr spectrum of the (±)-lactone exhibited methoxyl signals at δ 3.82 and 3.85 in contrast to the values (δ 3.28 and 3.32) reported for the (-)-natural product. A direct comparison of the spectra (the natural product spectrum kindly provided by Professor Hiroi) confirmed their identity, however, with the reported high field values being an overlooked typographical error.

EXPERIMENTAL

Pmr spectra are reported for $CDCl_3$ solutions.

2-(3',4',5'-Trimethoxyphenyl)1,3-dithiane (3). - Propane-1,3-dithiol (3.0 g) and p-toluenesulphonic acid monohydrate (ca. 100 mg) was added to a solution of 3,4,5-trimethoxybenzaldehyde (5.0 g) in chloroform (50 ml). The mixture was stirred for 4 hr., then washed with 20% aqueous sodium hydroxide solution (50 ml), brine (2 x 50 ml) and water. Evaporation of the dried (Na_2SO_4) solution gave a light yellow oil, which crystallized from methanol, yielding the dithiane (3) as needles (6.81 g), mp 84-85°, δ 1.75-2.03 (m, $CH_2(CH_2S-)_2$) 2.83-3.06 (m, $-SCH_2$), 3.85 (s, OMe), 5.13 (s, -SCHS-), 6.75 (H-2′ and 6′).

Anal. Calcd. for $C_{13}H_{18}O_3S_2$: C, 54.52; H, 6.33

Found: C, 54.54; H, 6.44%.

2-(3′,4′-Dimethoxybenzyl)-3-(3″,4″,5″-trimethoxybenzyl)butanolide (1). - n-Butyllithium (2.4 ml, 2.3 M solution in hexane) was added to a solution of the dithiane (3) (1.50 g) in tetrahydrofuran (75 ml) at -78° under nitrogen and stirred for 1hr. A solution of butenolide (500 mg) in tetrahydrofuran (10 ml) was then added with stirring and the temperature allowed to rise to 0° over 1 hr. The mixture was re-cooled to -78° and a solution of 3,4-dimethoxybenzyl bromide (1.33 g) in tetrahydrofuran (10 ml) added, followed by tetramethylethylenediamine (1 ml). After this had been allowed to warm to room temperature over 1 hr., it was stirred for an additional 12 hr., then quenched with saturated aqueous ammonium chloride solution (100 ml). The organic layer was washed with brine and water, dried (Na_2SO_4) and evaporated to give 2-(3′,4′-dimethoxybenzyl)-3-[2-(3″,4″,5″-trimethoxyphenyl)1,3-dithianyl]butanolide (4) as an oil (2.07 g), δ 1.80-2.03 (m, $CH_2(CH_2S-)_2$), 2.52-2.93 (m, $-SCH_2$ and H-3), 3.05-3.25 (m, $ArCH_2$ and H-2), 3.87 (s, OMe), 3.90 (s, OMe), 4.61 (dd, J 5, 10 Hz, H-4), 6.45 (dd, J 1.5, 8 Hz, H-6′), 6.62 (d, J 1.5 Hz, H-2′), 6.75

(d, J 8 Hz, H-5′) and 7.02 (s, H-2″ and 6″).

Without further purification, the thiane (4) (886 mg) was dissolved in ethanol and heated under reflux with Raney nickel (ca. 100 mg) for 9 hr. Filtration and evaporation gave a residual oil, which on crystallization from methylene chloride-petroleum ether gave (±)-trans-2-(3,4-dimethoxybenzyl)-3-(3,4,5-trimethoxybenzyl)-butyrolactone (1) as prisms (700 mg), mp 125-126°, δ 2.55 (m, $ArCH_2$), 2.90 (m, H-2 and 3), 3.82 (s, OMe), 3.85 (s, OMe), 3.80-4.25 (m, H-4), 6.20 (s, H-2″ and 6″) and 6.73 (m, H-2′,5′ and 6′), λ (EtOH) 229 (log 4.18) and 280 mμ (log 3.51).

Anal. Calcd. for $C_{23}H_{28}O_7$: C, 66.33; H, 6.78

Found: C, 66.41; H, 6.73%.

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