Tetrahedron Vol 33, pp 285 to 288 Pergamon Press 1977 Printed in Great Britain

SYNTHESIS OF TETRAHYDROFURAN LIGNANS, (±)-GALBELGIN AND (±)-GRANDISIN

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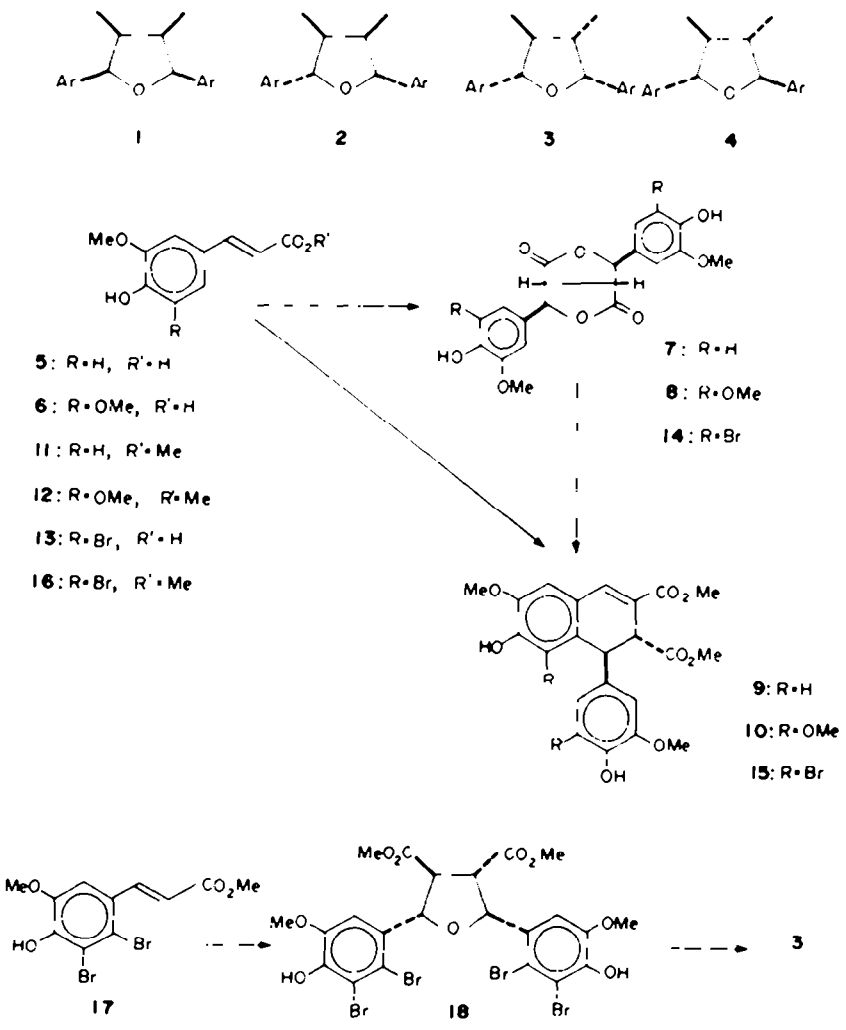
(*Received in USA* 6 *April* 1976; *Received in UK for publication* 16 *August* 1976)

Abstract—A stereoselective synthesis procedure for lignans of the all-*trans* $\alpha\alpha'$-diaryl-$\beta\beta'$-dimethyltetrahydrofurans is described. The lignans, galbelgin (4) and grandisin (37) were synthesized by routine reduction of the tetrahydrofuran dicarboxylic esters (24 and 34), obtained by mild acid treatment of the readily available diaryl dilactones (23 and 33).

$\alpha\alpha'$-Diaryl-$\beta\beta'$-dimethyltetrahydrofurans are now a well recognized class of lignans. Of the six possible stereoisomeric forms in which such structures can exist, four have been found naturally occurring. These are the *cis*-meso (1, tetrahydrofuroguaiacin B dimethyl ether[1]), the *trans*-meso (2, galgravin[2]), the *r*-2, 3*c*, 4*t*, 5*c* form (3, (+)-veraguensin[3]) and the all-*trans* *r*-2, 3*t*, 4*c*, 5*t* form (4, (−)-galbelgin[4]) in each example of which the aryl symbol represents the 3,4-dimethoxyphenyl moiety. The synthesis of both meso forms was reported by Haworth,[5] 1 by catalytic hydrogenation of the diveratryldimethyl furan, and 2 by acid-catalyzed equilibration of 1. More recently we have described a synthesis of (±)-veraguensin (3) by an oxidative phenolic coupling of a bromo-ferulic acid derivative.[6] In an extension of these studies, a procedure for the synthesis of the remaining all-*trans* group (e.g. 4) has been devised.

It has been established[7] that ferric chloride oxidation of

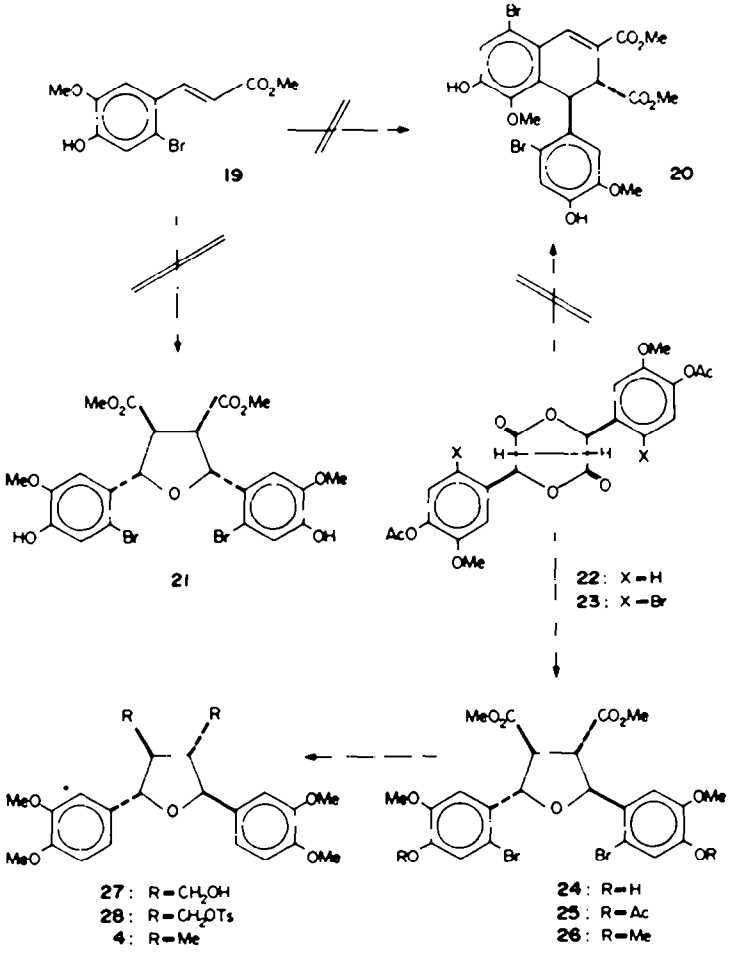


ferulic acid (5) or sinapic acid (6) yields the corresponding dilactone (7 or 8) which rearranges with methanolic hydrogen chloride to give the aryldihydronaphthalene esters (9 or 10); these esters could also be obtained in one step by oxidation of the respective methyl cinnamate esters (11 and 12).[8] Furthermore, the phenolic coupling of 5-bromoferulic acid was unexceptional in giving the dilactone (14), and the diester (15) was readily obtained by rearrangement of 14 or direct oxidation of methyl 5-bromoferulate (16). In contrast, ferric chloride oxidation of methyl 5,6-dibromoferulate (17) yielded the tetrahydrofuran (18) whose structure was established by conversion to (±)veraguensin (3). With this background, it was anticipated that ferric chloride oxidation of methyl 6-bromoferulate (19) might yield either the aryldihydronaphthalene (20), desired in connection with other synthetic work,[6] or the tetrahydrofuran (21). In sequel, neither was a principal oxidation product,[9] leading us to examine the behaviour of the dibromo-dilactone (23) toward the standard acid-catalysed condition of rearrangement to the aryl dihydronaphthalene in the hope of effecting the change 23 → 20.

The readily available dilactone[10] (7) on acetylation gave the diacetate (22) which on treatment with thallium triacetate followed by bromine gave the dibromodilactone (23) with spectrometric data in accordance[7] with this structure. On treatment with methanolic hydrogen chloride at room temperature, the dilactone was converted to a tetrahydrofuran (24), characterized as the diacetate (25). The structure and stereochemistry of this product, involving configurational retention at all chiral centers was established by conversion to (±)-galbelgin (4). Formation of the tetramethyl ether (26) by diazomethane treatment, followed by reduction with lithium aluminium hydride to reduce the ester functions and hydrogenolyze the bromine atoms gave the diol (27) whose di-*p*-toluenesulphonate derivative (28) with lithium aluminium hydride gave (±)-galbelgin (4), identified by comparison of the published spectrometric data.[3,4,11] It was unnecessary to isolate or purify any of the intermediates (26–28), the essential completion of each step being ascertained by appropriate spectra determination.

The recently reported isolation from *Litsea grandis* of a product named (−)-grandisin and for which the structure (37) was proposed[12] prompted a synthesis of the (±)-form by a similar procedure. The dehydrodisinapic acid dilactone (29), readily obtained[7,13] by ferric chloride oxidation of sinapic acid, gave the hexamethoxy-dilactone (30) on treatment with diazomethane. As anticipated, however, from earlier work on the synthesis of thomasidioic acid,[7] treatment of 30 with methanolic hydrogen chloride gave the aryl dihydronaphthalene diester (31). It was proposed to overcome this obstacle by suitable deactivation of the aryl ring and one simple solution follows.

The dehydrodisinapic acid dilactone diacetate (32) on bromination in acetic acid yielded the dibromide (33), which on heating with hydrogen chloride in dioxan-methanol yielded the required intermediate tetrahydrofu-



ran (**34**). Parenthetically, it might be added that the dibromide (**35**) obtained in the same way from the dimethyl ether derivative (**30**) did not undergo a similar clean acid-catalyzed rearrangement, being unchanged on standing overnight at room temperature, and yielding products other than the tetrahydrofuran (**36**) under reflux conditions. The conversion of tetrahydrofuran (**34**) to (±)-grandisin (**37**) was achieved in the same manner as for galbelgin, by diazomethane treatment to (**36**) followed by successive treatment with LAH, *p*-toluenesulphonyl chloride and LAH.

EXPERIMENTAL

M.ps were determined with either a Gallenkamp or Fisher-Johns apparatus and are uncorrected. NMR spectra were determined for $CDCl_3$ solns with TMS as internal reference on a Varian A60 spectrometer.

r - 1H - 2c,6c - *Bis* - (4' - *acetoxy* - 3' - *methoxyphenyl*) - 3,7 - *dioxabicyclo* - [3,3,0] - *octane* - 4,8 - *dione* (**22**)

Ac_2O (20 ml) was added to a soln of **7** (6.0 g) in pyridine (20 ml), warmed at *ca.* 65° for 30 min, cooled, poured into ice-water and filtered. Recrystallization of the ppt from acetone–MeOH gave the *diacetate* (**22**) as spiked needles (6.68 g, m.p. 228–230°) raised to m.p. 231–232° on recrystallization for analysis (Found: C, 61.15; H, 4.80. $C_{24}H_{22}O_{10}$ requires: C, 61.27; H, 4.72%). NMR spectrum: δ 2.30 s (6, OAc), 3.61 s (2, H-1 and 5), 3.87 s (6, OMe), 5.91 s (2, H-2 and 6) and 6.82–7.20 m (6, ArH).

r - 1H - 2c,6c - *Bis* - (4' - *acetoxy* - 2' - *bromo* - 5' - *methoxyphenyl*) - 3,7 - *dioxabicyclo* - [3,3,0] - *octane* - 4,8 - *dione* (**23**)

Thallium triacetate (3.7 g) and **22** (3.7 g) were dissolved in hot AcOH (200 ml) and a soln of Br_2 in AcOH (*ca.* 1 g/ml) added until the halogen colour persisted. Acetone was then added to remove excess Br_2, followed by water until the hot soln clouded. The product which separated on cooling was dissolved in hot AcOH, filtered and recrystallized to give the *dibromo dilactone diacetate* (**23**) as clusters of needles (4.4 g in two crops), m.p. 235–236° (Found: C, 45.78; H, 3.15. $C_{24}H_{20}Br_2O_{10}$ requires: C, 45.88; H, 3.21%). NMR spectrum: δ 2.28 s (6, OAc), 3.58 s (2, H-1 and 5), 3.82 s (6, OMe), 6.07 s (2, H-2 and 6), 6.85 s (2, H-2') and 7.32 s (2, H-5').

r - 2,*t* - 5 - *Bis*(2' - *bromo* - 4' - *hydroxy* - 5' - *methoxyphenyl*) - *tetrahydrofuran* - t - 3,*c* - 4 - *dicarboxylic acid dimethyl ester* (**24**)

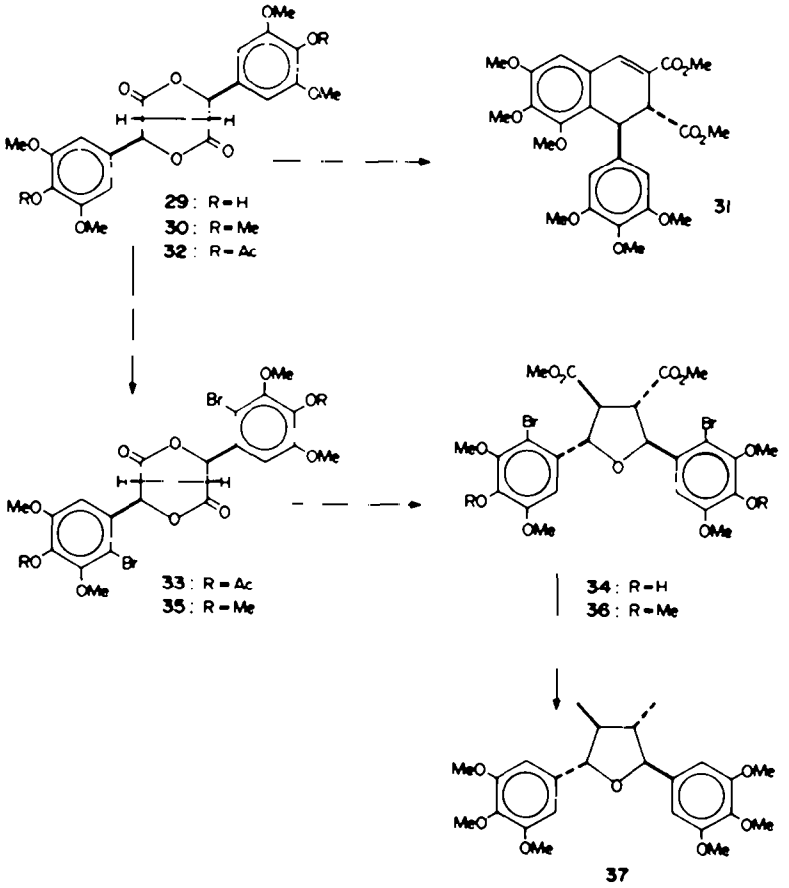
A soln of HCl in MeOH (3%, 50 ml) was added to a soln of **23** (2.43 g) in dioxan (35 ml). The mixture was allowed to stand at room temp. for 48 hr, poured into water (100 ml), extracted with chloroform (3 × 50 ml) and the dried extract evaporated to give the crude product (2.5 g) which was crystallized from ether–hexane yielding the *bisphenol* (**24**) as prisms (1.16 g), m.p. 179–180° (Found: C, 45.01; H, 3.79. $C_{22}H_{22}Br_2O_8$ requires: C, 44.77; H, 3.76%). NMR spectrum: δ 3.70 s (6, CO_2Me), 3.95 s (6, OMe), 3.59–3.92 m (2, H-3 and 4), 5.77–5.90 m (2, H-2 and 5), 7.12 s and 7.17 s (ArH).

r - 2,*t* - 5 - *Bis*(4' - *acetoxy* - 2' - *bromo* - 5' - *methoxyphenyl*) - *tetrahydrofuran* - t-3,*c* - 4 - *dicarboxylic acid dimethyl ester* (**25**)

Ac_2O (5 ml) was added to a soln of **24** (120 mg) in pyridine (5 ml), the mixture heated at *ca.* 80° for 30 min, poured on to ice and extracted with ether. The residue from the washed and dried extract was crystallized from MeOH–acetone to give the *dibromo diacetate* (**25**) as prisms (70 mg, m.p. 182–183°) raised to 185–185.5° for analysis (Found: C, 46.64; H, 3.95. $C_{26}H_{24}Br_2O_{12}$ requires: C, 46.31; H, 3.89%). NMR spectrum δ 2.29 s (6, OAc) 3.64 s (6, CO_2Me), 3.89 s (6, OMe), H-3 and 4 (indistinct, partly hidden), 5.88–5.98 m (2, H-2 and 5), 7.23 s and 7.26 s (ArH).

r - 2,*t* - 5 - *Bis* - (2' - *bromo* - 4',5' - *dimethoxyphenyl*) - *tetrahydrofuran* - t - 3,*c* - 4 - *dicarboxylic acid dimethyl ester* (**26**)

Excess diazomethane in ether was added to a soln of **24** (400 mg) in THF (5 ml) and MeOH (5 ml) at 0°, stirred overnight at



room temp., the solvents evaporated and the residue (440 mg) in ether filtered through alumina to give the *tetramethyl ether* (**26**) as an oil (360 mg) which was not obtained crystalline. The analytical sample was obtained as a glass (softens *ca.* 55° and liquid at 65°) by high vacuum sublimation. (Found: C, 46.78; H, 4.17. $C_{24}H_{24}Br_2O_8$ requires: C, 46.62; H, 4.24%). NMR spectrum: δ 3.67 s (6, CO_2Me), H-3 and 4 (indistinct, partly hidden), 3.85 s and 3.90 s (OMe groups), 5.73–5.85 m (2, H-2 and 5), 6.97 s (2, H-2') and 7.13 s (2, H-5').

r - 2,t - 5 - *Bis* - (3',4' - *dimethoxyphenyl*) - t -3,c - 4 - *dimethyl-tetrahydrofuran*

(±)-*Galbelgin* (**4**). Excess LAH was added to a soln of **26** (500 mg) in THF (*ca.* 30 ml), the mixture allowed to stand at room temp. for 30 min and worked up by addition of EtOAc and water, decantation and evaporation of the dried organic extract to give the crude diol (**27**, 400 mg). A soln of *p*-toluenesulphonyl chloride (1.3 g) in pyridine (7 ml) was added to the diol in the same solvent (7 ml) at −12°, the mixture stored at this temp. overnight, poured into water, worked up via ether in the usual way to yield the residual **28** (500 mg) which without purification was re-treated with LAH as above. The product (240 mg) was dissolved in benzene and filtered through a column (7.5 × 1 cm) of alumina (Laporte, type H, deactivated). Evaporation of the eluate (100 ml) gave (±)-galbelgin (in 30% overall yield from **26**) as jagged prisms, m.p. 124–127° (lit.[11] m.p. 124–128°) on crystallization from MeOH, and with concordant NMR spectrum.[3,11]

r - 1H - 2c,6c - *Bis* - (3',4',5' - *trimethoxyphenyl*) - 3,7 - *dioxabicyclo* - [3,3,0] - *octane* - 4,8 - *dione* (**30**)

To a soln of **29**[7] (1.5 g) in THF (200 ml) and MeOH (500 ml) was added excess ethereal diazomethane, and the mixture stirred overnight at room temp. Removal of the solvent and crystallization of the residue from aqueous MeOH gave the *hexamethoxydilactone* (**30**) in 94% yield as clusters of needles, m.p. 202–203°, λ(KBr) 5.64 μ. (Found: C, 60.60; H, 5.65. $C_{24}H_{26}O_{10}$ requires: C, 60.75; H, 5.52%). NMR spectrum: δ 3.62 s (2, H-1 and 5), 3.78 s (6, 4'-OMe), 3.85 s (12, 3' and 5'-OMe), 5.85 s (2, H-2 and 6) and 6.50 s (4, ArH).

Treatment of dilactone (**30**) *with hydrogen chloride in methanol.* HCl was bubbled through a suspension of the hexamethoxydilactone (100 mg) in MeOH (25 ml) until soln was complete (*ca.* 20 min), the mixture refluxed for 1.5 hr, concentrated to 10 ml, then poured into ice-water. The ppt (60 mg) had an NMR spectrum identical to that reported[7] for **31**.

r - 1H - 2c,6c - *Bis* - (2' - *bromo* - 3',4',5' - *trimethoxyphenyl*) - 3,7 - *dioxabicyclo* - [3,3,0] - *octane*-4,8 - *dione* (**35**).

To a soln of **30** (500 mg) in AcOH (25 ml) was added a soln of Br_2 (375 mg) in the same solvent (0.35 ml). When the colour faded, water was added and the ppt crystallized from CH_2Cl_2–MeOH to give the *dibromide* (**35**) as needles (610 mg), m.p. 261–263°, λ(KBr) 5.59 μ. (Found: C, 45.38; H, 3.86. $C_{24}H_{24}Br_2O_{10}$ requires: C, 45.59; H, 3.83). NMR spectrum: δ 3.53 s (2, H-1 and 5), 3.85 s and 3.90 s (18, ArOMe), 6.08 s (2, H-2 and 6) and 6.62 s (2, ArH).

A soln of the dilactone (50 mg) was suspended in MeOH (20 ml) and HCl bubbled through until soln was complete. Aqueous dilution yielded a ppt shown to be unchanged starting material by NMR spectrum examination. The lactone was also recovered unchanged after being allowed to stand overnight at room temp. in 3% methanolic HCl. When heated under reflux for 18 hr with saturated methanolic HCl, neither starting material, nor THF product was present in the product mixture.

r - 1H - 2c,6c - *Bis* - (4' - *acetoxy* - 2' - *bromo* - 3',5' - *dimethoxyphenyl*) - 3,7 - *dioxabicyclo* - [3,3,0] - *octane* - 4,8 - *dione* (**33**)

To a soln of **32**[7] (3.4 g) and NaOAc (1.7 g) in AcOH (70 ml) at room temp. was added a soln of Br_2 (2.14 g) in the same solvent (2.0 ml). Aqueous dilution precipitated a solid which was recrystallized from CH_2Cl_2–MeOH as clusters of needles (3.25 g), m.p. 204–206°. An analysis sample of the *diacetate dibromide* (**33**) had m.p. 208–209°, λ(KBr) 5.58 (lactone) and 5.63 μ (ester). (Found: C, 45.26; H, 3.46. $C_{28}H_{28}Br_2O_{12}$ requires: C, 45.37; H, 3.51%). NMR spectrum: δ 2.33 s (6, OAc), 3.57 s (2, H-1 and 5), 3.82 s and 3.85 s (12, ArOMe), 6.10 s (2, H-2 and 6), and 6.67 s (2, ArH).

r - 2,t - 5 - *Bis* - (2' - *bromo* - 4' - *hydroxy* - 3',5' - *dimethoxyphenyl*) - *tetrahydrofuran* - t - 3,c - 4 - *dicarboxylic acid dimethyl ester* (**34**)

A saturated soln of HCl in MeOH (40 ml) was added to a soln of **33** (880 mg) in dioxan (8 ml), the mixture warmed to the b.p., then allowed to stand overnight at room temp. Dilution with water, extraction with ether and evaporation of the washed and dried extract yielded a residue (727 mg) which crystallized from ether-hexane (3:1) to give *the tetrahydrofuran* (**34**) as clusters of needles (250 mg), m.p. 92–94° (dec). The NMR spectrum indicated the presence of ether as solvent of crystallization, and drying of the sample *in vacuo* at 78° for 3 hr and room temp. overnight, converted the crystalline form to an amorphous glass. (Found: C, 43.93; H, 4.05. $C_{24}H_{26}Br_2O_{11}$ requires: C, 44.13; H, 4.03%). NMR spectrum: δ *ca.* 3.60 m (2, H-3 and 4, partly hidden), 3.67 s (6, CO_2Me), 3.90 s and 3.95 s (12, ArOMe), 5.92 m (2, H-2 and 5) and 7.03 s (2, ArH).

r - 2,t - 5 - *Bis* - (2' - *bromo* - 3',4',5' - *trimethoxyphenyl*) - *tetrahydrofuran* - t - 3,c - 4 - *dicarboxylic acid dimethyl ester* (**36**)

Treatment of **34** in THF with ethereal diazomethane and crystallization of the product from ether-hexane gave the *tetrahydrofuran hexamethyl ether* (**36**) (in 28% overall yield from **33**) as elongated prisms, m.p. 122–123°. (Found: C, 46.21; H, 4.38. $C_{26}H_{30}Br_2O_{11}$ requires: C, 46.04; H, 4.46%). NMR spectrum: δ *ca.* 3.58 m (2, H-3 and 4, partly hidden), 3.63 s (6, CO_2Me), 3.85 s (12, ArOMe, 3.88 s (6, ArOMe), 5.96 m (2, H-2 and 5) and 6.98 s (2 ArH).

r - 2,t - 5 - *Bis* - (3',4',5' - *trimethoxyphenyl*) - t - 3,c - 4 - *dimethyltetrahydrofuran*

(±)-*Grandisin* (**37**). Excess LAH was added to a soln of **36** (2.65 g) in THF (250 ml) and the mixture stirred at room temp for 30 min. Work up in the usual way gave the debrominated diol (1.80 g) which was dissolved in pyridine (15 ml) and added to a soln of *p*-toluenesulphonyl chloride (6 g) in the same solvent (15 ml) at −12°. The mixture was maintained at this temp. overnight, diluted with water, extracted with chloroform, and the washed and dried extract evaporated to give the crude ditosylate (2.5 g) which was dissolved in THF, stirred with LAH for 30 min at room temp. and worked up in the usual way to give crude (±)-grandisin (1.3 g). It was purified by TLC (silica gel HF-254, 1.75 mm layer, using benzene-ether (5:1)). The zone R_f 0.57 was eluted with acetone, and a solution of the extract in ether filtered through a short column of alumina. Recrystallization of the evaporated filtrate from ether-hexane gave (±)-grandisin (**37**) as needles (240 mg), m.p. 128–130°, (lit.[11] m.p. 128–129°) with concordant NMR spectrum.[11]

Acknowledgement—The award of a Research Grant (GM-19566) from the U.S. Public Health Service is gratefully acknowledged.

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