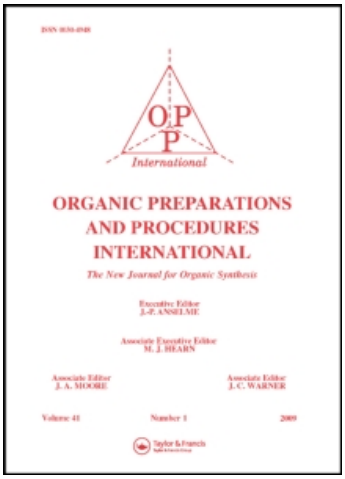


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

SYNTHESIS OF (±)-ISO-OTOBAPHENOL

Pralhad A. Ganeshpure[a]; Robert Stevenson[a]
[a] Department of Chemistry, Brandeis University, Waltham, MA, USA

To cite this Article Ganeshpure, Pralhad A. and Stevenson, Robert(1981) 'SYNTHESIS OF (±)-ISO-OTOBAPHENOL', Organic Preparations and Procedures International, 13: 5, 323 — 330
To link to this Article: DOI: 10.1080/00304948109356134
URL: http://dx.doi.org/10.1080/00304948109356134

ORGANIC PREPARATIONS AND PROCEDURES INT. 13(5), 323-330 (1981)

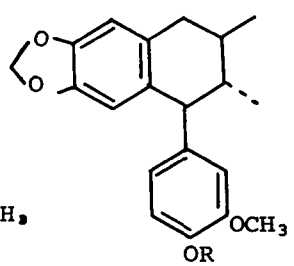
SYNTHESIS OF (±)-ISO-OTOBAPHENOL

Pralhad A. Ganeshpure and Robert Stevenson*

Department of Chemistry, Brandeis University,

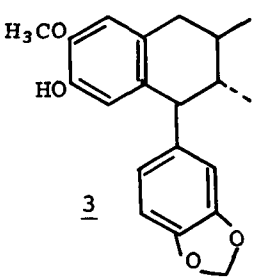
Waltham, MA 02254 U.S.A.

The myristicaceous genus Virola is of interest as a source of hallucinogenic snuffs and potential therapeutic reagents. From the wood of the species Virola carinata (Benth.) Warb., reportedly used to treat "carate" (a disease causing blotched skin discolouration),[1] there has recently been isolated a product identified as 2S,3R-dimethyl-6,7-methylenedioxy-1S-(4-hydroxy-3-methoxyphenyl)-1,2,3,4-tetrahydronaphthalene (1) and named iso-otobaphenol.[2] The structural isomer, otobaphenol (3) had been isolated a decade earlier from Myristica otoba.[3]



1 R = H

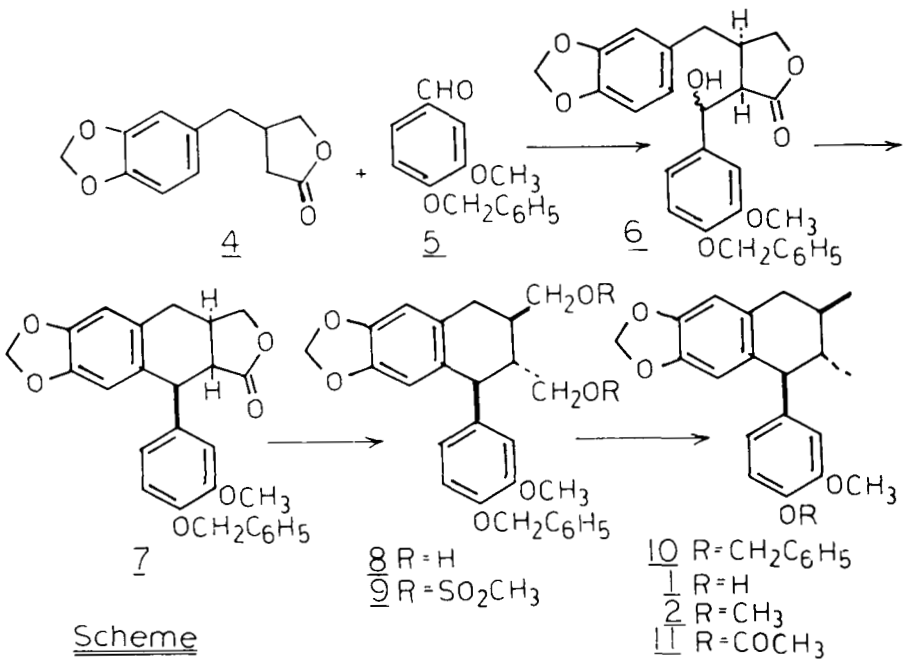
2 R = CH3



3

The constitution of (1) was established by the PMR spectrum and conversion to the known monomethyl ether derivative, (-)-galcatin (2). We report here a short synthesis of

(±)-iso-otobaphenol, required for pharmacological evaluation, as outlined in the Scheme. Due to recent improvements in preparative methods for β-benzyl-γ-butyrolactones[4-8] and their α-hydroxylation,[6,9] the procedure is particularly useful for the synthesis of all-trans-1-aryl-2,3-disubstituted tetrahydronaphthalene lignans.[10]



Scheme

The lithium enolate of the β-benzylbutyrolactone (4),[8] prepared by the action of lithium di-isopropylamide in tetrahydrofuran, reacted with O-benzylvanillin (5) to give in over 90% yield a mixture of the epimeric alcohols (6) in an approximately 1:1 ratio, as determined from the integrated p.m.r. spectrum. Ample precedent for this result exists[6,8,10]

with analogous reactants. With trifluoroacetic acid at room temperature, (6) underwent smooth cyclization to the aryltetralin trans-lactone (7), reduction of which with lithium aluminium hydride gave the diol (8). Employment of a standard procedure for conversion of a hydroxymethyl to a methyl group, by methanesulphonylation [to (9)] and lithium aluminium hydride reduction, gave (±)-iso-otobaphenol benzyl ether (10), which on debenzylation by catalytic hydrogenolysis yielded (±)-iso-otobaphenol (1). This product was further characterized for identification by p.m.r. spectrum comparison by formation of the acetate (11) and methyl ether (2) derivatives. The latter compound, corresponding to (±)-galcatin had already been synthesized.[11]

EXPERIMENTAL

Pmr spectra were determined in $CDCl_3$ solutions using TMS as internal standard, and melting points (capillary) were determined using a Gallenkamp apparatus.

trans-2-(4-Benzyloxy-3-methoxy-α-hydroxybenzyl)-3-(3,4-methylenedioxybenzyl)-γ-butyrolactones (6). — A solution of 3-(3,4-methylenedioxybenzyl)butyrolactone (4)[8] (2.20 g, 10 mmol) in dry tetrahydrofuran (10 ml) was injected to a stirred solution of lithium di-isopropylamide, (prepared from di-isopropylamine (1.21 g) and n-butyl lithium (2.55 M, 4.7 ml)) in tetrahydrofuran (30 ml) at -78° under nitrogen. The mix-

ture was stirred at this temperature for 30 min., then warmed to -20°. A solution of O-benzylvanillin (5)[12] (2.42 g, 10 mmol) in tetrahydrofuran (10 ml) was injected with stirring at -20° for 1 hour, followed by acidification with dilute hydrochloric acid and extraction with ethyl acetate. Evaporation of the washed and dried extract gave the epimeric hydroxybenzyl-lactones (6) as a pale yellow solid (4.3 g), δ 4.82 (d, J = 8 Hz) and 5.28 (d, J = 3 Hz) corresponding to the ArCHOH proton in approximately equal integrated intensity. This product was used for subsequent cyclization without further purification.

6,7-Methylenedioxy-r-1,c-3-hydroxymethyl-1-(4-benzyloxy-3-methoxyphenyl)-1,2,3,4-tetrahydronaphthalene-t-2-carboxylic Acid Lactone (7). - To a stirred solution of trifluoroacetic acid (13 ml) in dichloromethane (117 ml) was added a solution of the epimeric lactones (6)(3.0 g) in dichloromethane (20 ml). Evaporation of solvents after stirring 3 hr. at room temperature gave a solid, which crystallized from chloroform-methanol to give the all-trans-lactone (7) as soft felted needles (2.16 g), m.p. 240-241°, δ 2.43-2.72 (m, H-2 and 3), 2.87-3.02 (br.d, H-4), 3.86 (s, OMe), 3.93-4.17 (m, $-CH_2O$), 4.43-4.63 (m, H-1), 5.14 (s, OCH_2Ph), 5.89 (s, OCH_2O) and 6.36-7.58 (m, ten ArH).

Anal. Calcd. for $C_{27}H_{24}O_6$: C, 72.96; H, 5.44

Found: C, 72.61; H, 5.47%.

6,7-Methylenedioxy-r-1-(4-benzyloxy-3-methoxyphenyl)-t-2,c-3-bishydroxymethyl-1,2,3,4-tetrahydronaphthalene (8). — To a stirred suspension of lithium aluminium hydride (1.2 g) in tetrahydrofuran (25 ml) was added dropwise a solution of lactone (7)(1.82 g) in the same solvent (70 ml) over 10 min. under nitrogen. The mixture was refluxed for 1 hr., then stirred at room temperature for a further 2 hr. Ethyl acetate (10 ml) was then added slowly, followed by saturated aqueous ammonium chloride solution. Extraction with chloroform and evaporation of the washed and dried extract yielded a solid, which was recrystallized from chloroform-benzene to give the diol (8)(1.47 g), m.p. 169-171°, δ 1.73-2.02 (m, H-2 and 3), 2.55-2.82 (m, H-4), 3.37-3.97 (m, H-1 and C-3 and 4 CH_2OH), 3.83 (s, OMe), 5.13 (s, OCH_2Ph), 5.84 (s, OCH_2O) and 6.22-7.55 (ten ArH).

Anal. Calcd. for $C_{27}H_{28}O_6$: C, 72.30; H, 6.29

Found: C, 72.36; H, 6.40%.

6,7-Methylenedioxy-r-1-(4-benzyloxy-3-methoxyphenyl)-t-2,c-3-dimethyl-1,2,3,4-tetrahydronaphthalene (10). — Methanesulphonyl chloride (ca. 0.5 ml) was added to a solution of the diol (8)(538 mg) in dry pyridine (10 ml) at 0°, and the mixture stirred at room temperature for 2 hr. Ice was then added, and after 1 hour, extraction with chloroform and evaporation of the washed (dil. HCl and H_2O) and dried extract gave the crude di-methanesulphonate (9) as a glassy solid,

δ 2.95 and 3.03 (CH_3SO_2-O groups), which was dissolved in dry tetrahydrofuran (30 ml) and added dropwise over 10 min. to a stirred suspension of lithium aluminium hydride (500 mg) in the same solvent (20 ml) under nitrogen. After being stirred at room temperature for 30 min. and refluxed for 3 hr., the product was isolated in the usual way, and crystallized from chloroform-methanol to give (±)-iso-otobaphenol benzyl ether (10) as needles (394 mg), m.p. 149-150°, δ 0.83 (d, J = 5.5 Hz, C-2 Me), 1.04 (d, J = 5.5 Hz, C-3 Me), 1.39-1.81 (m, H-2 and 3), 2.56-2.71 (m, H-4), 3.38 (br.d., J = 9 Hz, H-1), 3.83 (s, OMe), 5.14 (s, OCH_2Ph), 5.83 (s, OCH_2O), 6.16 (s, H-8), 6.55 (s, H-5), 6.62 (d, J = 2 Hz, H-2′), 6.64 (dd, J = 8,2 Hz, H-6′), 6.85 (d, J = 8 Hz, H-5′) and 7.32-7.55 (m, five ArH).

Anal. Calcd. for $C_{27}H_{28}O_4$: C, 77.86; H, 6.78

Found: C, 77.69; H, 6.82%.

(±)-Iso-otobaphenol (1). — A solution of the benzyl ether (10) (315 mg) in ethyl acetate (20 ml) was stirred under hydrogen with palladium-carbon (10%, 50 mg) and perchloric acid (1 drop) for 20 hr. at atmospheric pressure. After filtration, and washing of the filter with hot ethyl acetate, the combined filtrate and washings were evaporated to give a solid, which was crystallized from diethyl ether-hexane to yield (±)-iso-otobaphenol (1) as long needles (200 mg), m.p. 142-143°, δ^{13} 0.85 (d, J = 6 Hz, C-2 Me), 1.06 (d, J = 6 Hz, C-3 Me),

1.38-1.81 (m, H-2 and 3), 2.57-2.70 (m, H-4), 3.37 (br.d, J = 9 Hz, H-1), 3.82 (s, OMe), 5.50 (s, OH), 5.80 (s, OCH_2O), 6.15 (s, H-8), 6.52 (s, H-5), 6.53 (d, J = 2 Hz, H-2′), 6.63 (dd, J = 8,2 Hz, H-6′) and 6.85 (d, J = 8 Hz, H-5′).

Anal. Calcd. for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79

Found: C, 73.57; H, 6.90%.

(±)-Iso-otobaphenol Acetate (11). – Acetylation of the phenol (1) with pyridine and acetic anhydride at room temperature for 4 hours yielded the acetate (11) as glistening plates, m.p. 132-133° from methanol, δ^{13} 0.87 (d, J = 6 Hz, C-2 Me), 1.06 (d, J = 6 Hz, C-3 Me), 1.34-1.76 (m, H-2 and 3), 2.31 (s, $OCOCH_3$), 2.59-2.70 (m, H-4), 3.46 (br.d, J = 10.5 Hz, H-1), 3.77 (s, OMe), 5.82 (s, OCH_2O), 6.16 (s, H-8), 6.53 (s, H-5), 6.65 (d, J = 2 Hz, H-2′), 6.69 (dd, J = 8.5, 2 Hz, H-6′) and 6.96 (d, J = 8.5 Hz, H-5′).

Anal. Calcd. for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57

Found: C, 71.68; H, 6.70%.

(±)-Iso-otobaphenol Methyl Ether [(±)-Galcatin] (2). – Methylation of iso-otobaphenol (1) with methyl iodide and potassium carbonate in acetone gave (±)-galcatin as prisms, m.p. 135-136° (lit.[11] m.p. 136-137°) from diethyl ether-hexane, δ 0.85 (d, J = 6 Hz, C-2 Me), 1.06 (d, J = 6 Hz, C-3 Me), 1.36-1.84 (m, H-2 and 3), 2.59-2.71 (m, H-4), 3.39 (d, J = 8.5 Hz, H-1), 3.82 (s, OMe), 3.87 (s, OMe), 5.81 (s, OCH_2O), 6.14 (s, H-8), 6.53 (s, H-5), 6.56 (d, J = 2 Hz, H-2′), 6.67 (dd,

J = 8,2 Hz, H-6′) and 6.81 (d, J = 8 Hz, H-5′).

REFERENCES

1. R. E. Schultes and B. Holmstedt, Lloydia, 34, 61 (1971).
2. O. R. Gottlieb, J. G. S. Maia and M. N. De S. Ribeiro, Phytochemistry, 15, 773 (1976).
3. F. Kohen, I. Maclean and R. Stevenson, J. Chem. Soc.(C) 1775 (1966).
4. J. Rothe and H. Zimmer, J. Org. Chem. 24, 586 (1959) and earlier cited papers.
5. J. L. Herrman, M. H. Berger and R. H. Schlessinger, J. Amer. Chem. Soc., 95, 7923 (1973).
6. F. E. Ziegler and J. A. Schwartz, J. Org. Chem., 43, 985 (1978).
7. Y. Asano, T. Kamikawa and T. Tokoroyama, Bull. Chem. Soc. Japan, 49, 3232 (1976).
8. E. Brown, J.-P. Robin and R. Dhal, J.C.S. Chem. Comm. 556 (1978).
9. P. A. Grieco and K. Hiroi, J.C.S. Chem. Comm., 892 (1972).
10. E. Brown, M. Loriot and J.-P. Robin, Tetrahedron Letters, 1389 (1979).
11. S. M. Adjangba and D. Billet, Bull. Chem. Soc. France, 1970 (1962).
12. Commercial sample (Aldrich Chemical Co.).
13. The n.m.r. spectral results are in excellent agreement with those reported for natural (1) and (11), except for the C-2 Me signal of (1) which was inadvertently designated as a singlet.

Acknowledgment.— This work was supported by a grant from the National Institutes of Health.

(Received December 26, 1980)