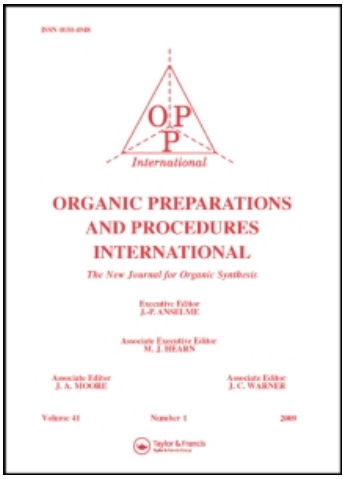

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A CONVENIENT SYNTHESIS OF 7-HYDROXY-3-HYDROXYMETHYL-4-PHENYL-2-NAPHTHOIC ACID, LACTONE FORM

Joseph F. Payack[a]; Dean R. Bender[a]
[a] Department of Process Research, Merck Research Laboratories, Division of Merck & Co., Inc., Rahway, NJ

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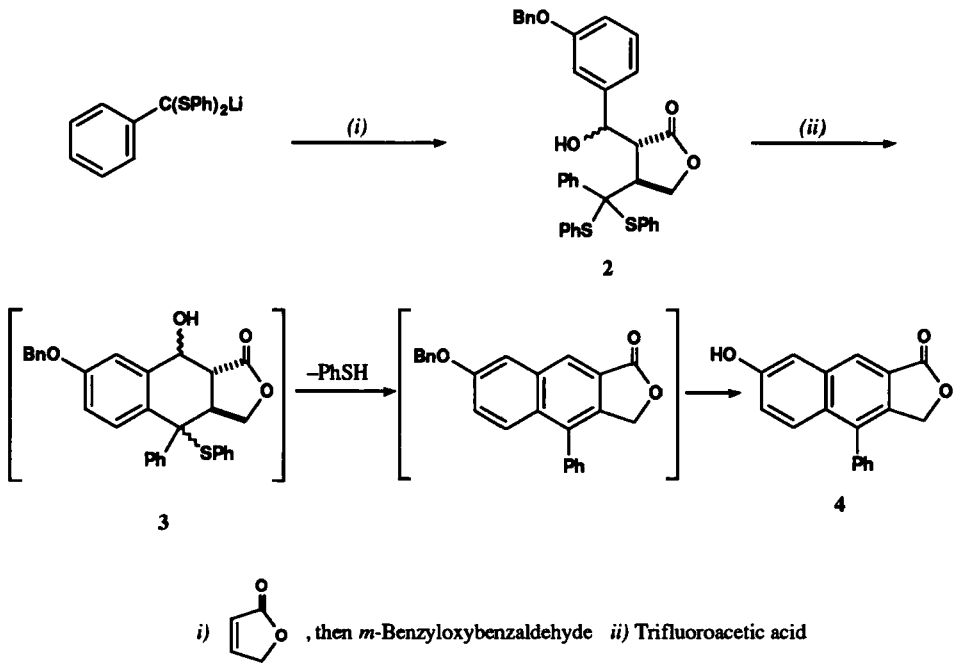
Joseph F. Payack* and Dean R. Bender

Department of Process Research
Merck Research Laboratories, Division of Merck & Co., Inc.
P. O. Box 2000, Rahway, NJ 07065

1-Arylnaphthalene lignans have become interesting synthetic targets due to their wide range of biological activity.[1] We became interested in the synthesis of 7-hydroxy-3-hydroxymethyl-4-phenyl-2-naphthoic acid, lactone form (**4**) in connection with ongoing research in our laboratories. Previously reported procedures[2] for preparing compounds of this type include Diels-Alder reaction of 1-arylisobenzofurans,[3] tandem conjugate addition-aldol reaction involving aryl cyanohydrin anions



i) , then *m*-Benzyloxybenzaldehyde *ii)* Trifluoroacetic acid

with butenolide,[4] and tandem reaction of thioacetal anions with butenolide.[5] These methods require multiple steps, utilize polyoxygenated aromatic nuclei or, if a mono oxygenated ring is used, provide no regioselectivity for the desired 7-hydroxy analog.[6] We present here a concise and convenient two-step route to **4** based on tandem 1,4-conjugate addition of benzaldehyde bis(phenylthio)acetal anion to butenolide, and trapping the resulting enolate with 3-benzyloxybenzaldehyde. The crude butyrolactone is then cyclized, aromatized, and debenzylated with trifluoroacetic acid (TFA) to provide **4** in good yield with no purification necessary.

The anion of benzaldehyde bis(phenylthio)acetal (**1**) was generated at -78° by dropwise addition of *n*-BuLi to a solution of **1** in dry THF. The yellow suspension was then treated dropwise with 2(5H)-furanone (butenolide) giving a pale yellow solution. After 1.5 hr, the enolate was trapped by the addition of a suspension of 3-benzyloxybenzaldehyde in THF. After a further 2 hrs at -78°, the reaction mixture was quenched by the addition of dilute aqueous acetic acid. Aqueous work-up afforded lactone **2** in 72% yield as a crude foam which assayed (HPLC) as 68 weight percent of a ~2:1 mixture of two diastereomers, which could not be separated on silica or reverse phase chromatography. The tandem addition gives the *trans*-alkylated product, with the alcohol from the second alkylation being formed with only partial stereoselectivity. Athough these diastereomers could be separated from by-products *via* flash chromatography (silica, 20% ethyl acetate/hexanes), this difficult chromatography may be avoided by submitting the crude product directly to the next step, which destroys all the stereocenters and permits purification by simple crystallization.

Heating a solution of **2** to 60° for 1 hr in a mixture of TFA/thioanisole provided **4** in ~70% assay yield (HPLC). The mechanism of this reaction is believed to involve acid-catalyzed removal of

thiophenol, with the resulting cation alkylating *para* to the benzyloxy moiety; no *ortho* alkylation was observed. HPLC studies have indicated that at room temperature, **2** is converted to a mixture of aryltetralin diastereomers **3**, which slowly aromatize by elimination of water and thiophenol. At 60° the aromatization is rapid, with the added benefit of debenzylation of the phenol occurring under the reaction conditions. Reactions carried out in the absence of thioanisole as a cation scavenger resulted in only a 40% assay yield of **4** accompanied by a 20-30% yield of ring-benzylated **4**, formed *via* nucleophillic attack of the naphthalene by benzyl cation; anisole was not an effective scavenger. The product was isolated by evaporation of TFA, followed by addition of ethyl acetate to the resulting yellow suspension, which resulted in the crystallization of most of the product as a pale yellow solid in 55% yield and 95% purity (HPLC).

This two-step process produces **4** efficiently in 40% overall yield, with one crystallization providing highly pure material. Efforts are underway to expand the scope of this method to produce a variety of aryl naphthalene compounds.

EXPERIMENTAL SECTION

NMR spectra were run in $CDCl_3$ (**2**) or DMSO-d_6 (**4**) and the ^1H and ^{13}C spectra were measured at 250 and 62.9 MHz. The melting point was determined in an open capillary apparatus, and was uncorrected. Reactions and products were assayed by HPLC using a Zorbax RX C_8 25x0.46 cm reverse phase column, eluent 20:80 H_2O (0.1% H_3PO_4): acetonitrile, 1.5 mL/min, UV detection at 270 nm. THF was dried over 3Å seives. Benzaldehyde bis(phenylthio)acetal was prepared according to the method of Fujita *et al.*[7] All other reagents were purchased from Aldrich and were used as received.

3-(α-Hydroxy-3-benzyloxybenzyl)-4-[α,α-bis(phenylthio)benzyl]butyrolactone (2).- To a stirred solution of benzaldehyde bis(phenylthio)acetal (46.6 g, 151 mmol) in THF (500 mL) chilled to -73° (internal temp) was added *n*-BuLi (65.1 mL, 2.34M in hexanes, 152 mmol) over 15 min. The resulting yellow suspension was stirred 30 min at -70°, then 2(5H)-furanone (butenolide, 13.0 mL, 182 mmol) was added over 3 min. The pale yellow solution was stirred for 1.5 hr at -70°, then a slurry of 3-benzyloxybenzaldehyde (32.3 g, 152 mmol) in THF (150 mL) was added over 3 min. The solution was stirred for a further 2 hrs at -70°, and then was quenched with acetic acid (18.3 g glacial acetic acid in 100 mL H_2O). The mixture was allowed to warm to room temperature, and then isopropyl acetate (900 mL) and H_2O (600 mL) were added. The aqueous phase was extracted with another portion of isopropyl acetate (200 mL) then the combined organic phase was washed with saturated aqueous $NaHCO_3$ (2x200 mL) and H_2O (3x500 mL). The organic phase was evaporated to give 96.2 g of crude **2** as a foam (a mixture of diastereomers which assayed (HPLC) as 68% by weight), in a weight percent corrected yield of 65.4 g (72%). The material was used without further purification. ^1H NMR major isomer: δ 7.75–6.65 (m, 24H), 5.18 (d, 1H, J = 3.5), 4.69 (dd, 1H, J = 9.8; 2.0), 4.04 (dd, 1H, J = 9.8; 8.1), 3.31 (dd, 1H, J = 3.5; 2.4), 2.97 (ddd, 1H, J = 8.1; 2.0; 2.4). Minor: δ 7.75–6.65 (m, 24H), 5.05 (d, 1H, J = 4.9), 4.56 (dd, 1H, J = 10.0; 2.2), 3.64 (dd, 1H, J = 10.0; 8.1), 3.48 (dd, 1H, J = 4.9; 2.2), 3.10 (ddd, 1H, J = 8.0; 2.2; 2.2).

7-Hydroxy-3-hydroxymethyl-4-phenyl-2-naphthoic Acid Lactone Form (4).- To a mixture of crude **2** (96.2 g of 68 weight percent material: 65.0 g) and thioanisole (200 mL) was added TFA (500 mL). The mixture was stirred to dissolve **2**, and then was heated at 60° for 1 hr. The dark amber solution was cooled to room temperature and the TFA was evaporated leaving a solution of **4** in thioanisole. The solution was co-distilled with toluene (2x100 mL) to azeotropically remove traces of TFA giving a suspension of crystals. Ethyl acetate (325 mL) was added, and the crystals were collected and washed with ethyl acetate (2x50 mL), and then dried in vacuo (60°) to give 16.6 g (55%) of **4** as a pale yellow solid, mp. 258-260°. IR (mull) 1725 cm^{-1}. ^1H NMR: δ 10.12 (s, 1H, OH), 8.42 (s, 1H), 7.46-7.64 (m, 7H), 7.27 (dd, 2H, *J* =9.2, 2.4), 5.32 (s, 2H). ^{13}C NMR: δ 170.65 (lactone carbonyl), 155.70, 135.69, 135.53, 135.06, 133.15, 129.29, 128.78, 128.59, 128.11, 126.65, 123.63, 122.82, 122.10, 110.58, 69.17(CH_2).

Anal. Calcd for $C_{18}H_{12}O_3$: C, 78.25; H, 4.38. Found: C, 77.99; H, 4.27

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