

Simple Synthesis of Benzofuranoid Neolignans from *Myristica fragrans*

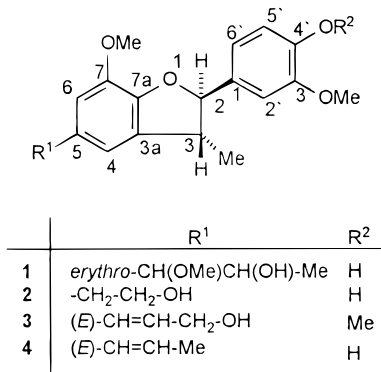
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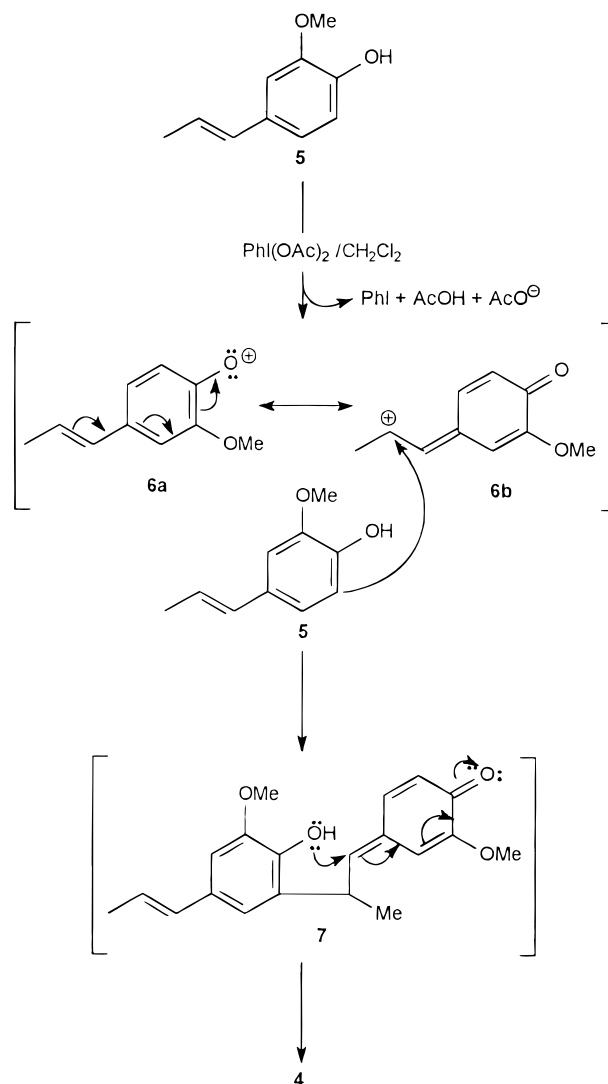
The total synthesis of four neolignans—fragnasols A (**1**), B (**2**), and C (**3**) and dehydrodiisoeugenol (**4**)—starting from the readily available phenol derivative isoeugenol (**5**) was accomplished. The key step of the synthesis of these natural products is a novel type of dimerization of **5** into **4** with iodobenzene diacetate.

Neolignans possessing a 2,3-dihydrobenzo[*b*]furan skeleton are a prominent subgroup of the naturally occurring O-heterocycles owing to their complex biological activities.^{1–5} The mace of *Myristica fragrans* Houtt. (Myristicaceae) is a commonly used spice and has been applied as a remedy for strengthening the stomach and expelling the “wind-evil” in Chinese medicine. Its methanolic extract has also been found to be useful for preventing dental caries due to its antibacterial activity against *Streptococcus mutans*.⁶ From this source fragnasols A (**1**), B (**2**),⁷ and (–) C (**3**)⁸ have been isolated, along with dehydrodiisoeugenol (**4**), which is known as one of the major and most active phenolic constituents of this plant.



In a continuation of our study on the synthesis of benzofuranoid-type neolignans with potential biological activity,^{9–11} herein we report the total synthesis of fragnasols A (**1**), B (**2**), and C (**3**) and dehydrodiisoeugenol (**4**), starting from the commercially available isoeugenol (**5**), using the hypervalent iodine reagent, iodobenzene diacetate (IDA).¹² In a previous paper¹³ we reported that the oxidation of *o*- or *p*-substituted phenols to the corresponding semi-quinol derivatives by IDA in nucleophilic solvents such as alcohols occurred via a phenoxenium ion intermediate. Therefore, it seemed to be obvious to suppose that the phenoxenium ion **6a** (stabilized in its quinone–methide form, **6b**) can also be generated from isoeugenol (**5**) with IDA in dry dichloromethane as depicted in Scheme 1. Moreover, in the absence of nucleophilic solvent, the latter intermediate presumably reacts smoothly with **5**, owing to its high electrophilic character, to form the C–C bond of the 2,3-dihydrobenzo[*b*]furan skeleton of **4**. The resulting quinone–methide-type intermediate **7** could then be transformed into dehydrodiisoeugenol (**4**) by the thermodynamically

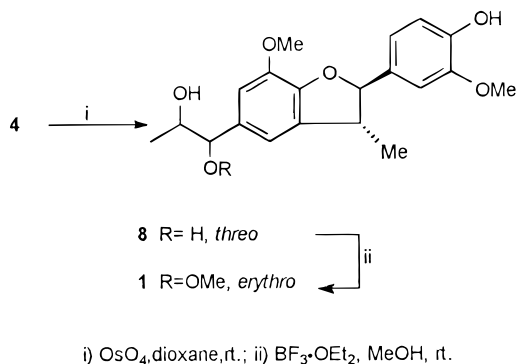
Scheme 1. Mechanism of the Dimerization of Isoeugenol (**5**) by IDA



controlled addition of its phenolic hydroxyl group at the quinone–methide moiety.

In full accordance with the above-mentioned assumption, transformation of isoeugenol (**5**) with IDA in dry dichloromethane at room temperature resulted only in one product, accompanied by some polymerization based on TLC monitoring of the reaction mixture. Isolation of this product in crystalline form (mp, 129–132 °C) was executed by flash chromatography on Si gel in a moderate yield

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Scheme 2. Synthesis of *rac*-Fragnasol A (**1**)

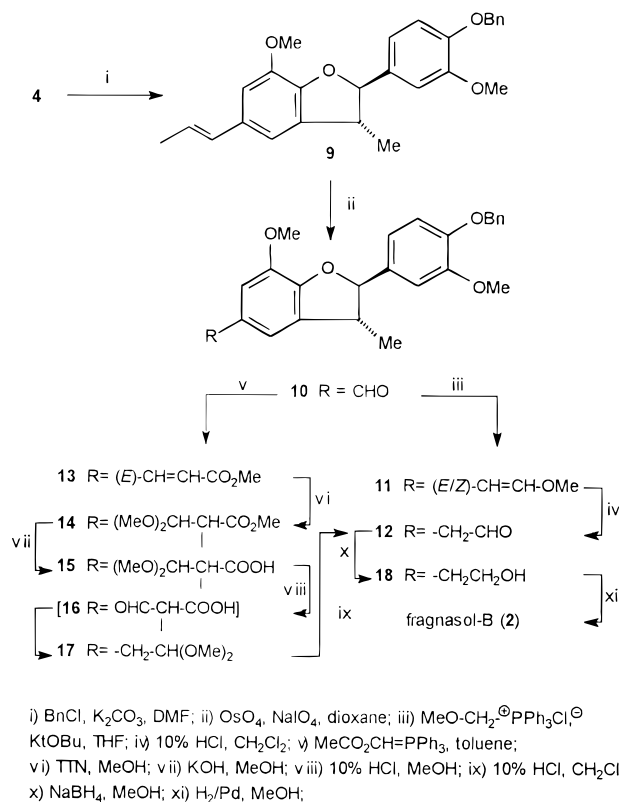
(35%) and its structure was proved to be identical with that of dehydrodiisoeugenol (**4**) by means of ¹H and ¹³C NMR measurements. The coupling constant for C-2H and C-3H (*J* = 9.45 Hz) clearly showed that the adjacent 2-aryl and 3-methyl substituents are *trans* oriented. It is to be noted that **4** has been isolated also from *Magnolia kachira-chiari*,¹⁴ and prepared¹⁵ from **5** via the corresponding quinone-methide radical intermediate generated by FeCl₃.

The synthesis of fragnasol A (**1**) could be achieved in two steps starting from dehydrodiisoeugenol (**4**) (Scheme 2). In the first step its unsaturated side-chain of *E*-geometry was hydroxylated with OsO₄ in dioxane at room temperature to give the corresponding *threo*-diol derivative **8** in a satisfactory yield (49%), due to the well-known stereospecific *syn* addition of this reagent¹⁶ at the double bond of **4**. The benzylic hydroxyl group of **8** was susceptible to solvolysis, with inversion of configuration in the presence of methanol/boron trifluoride etherate at room temperature, to afford fragnasol A (**1**). The spectroscopic data (¹H and ¹³C NMR) of our synthetic product (isolated by preparative TLC) were found to be identical with those of the natural substance.

Dehydrodiisoeugenol (**4**) served as a suitable starting material for the synthesis of fragnasol B (**2**), as well (Scheme 3). According to our previous observations,¹⁷ the phenolic hydroxyl group of **4** required protection prior to the oxidative cleavage at the side-chain. Thus, **4** was benzylated with benzyl chloride in the presence of potassium carbonate in dry DMF to result in **9** with 61% yield, and subsequently oxidized to **10** with sodium metaperiodate in the presence of a catalytic amount of OsO₄. To introduce a hydroxymethyl group at the aldehyde functional group of **10**, and thus to construct the side-chain of **2**, the methyl vinyl ether derivative **11** was prepared by the Wittig reaction of **10** with methoxymethyltriphenylphosphonium chloride¹⁸ in THF at 0 °C in the presence of potassium *tert*-butoxide. As expected, the Wittig reaction furnished a 2:3 mixture of the *cis/trans* vinyl ethers (**11**) according to the ¹H NMR spectrum of the products isolated by means of flash chromatography.

The hydrolysis of the enol ether of **11** was readily achieved by treatment with hydrochloric acid in dichloromethane to give quantitative conversion to the corresponding phenylacetaldehyde derivative **12**, which could also be synthesized from **10** in a five-step method described below.

First, **10** was transformed into **13** by Wittig reaction with methyl carboxymethylene-triphenylphosphorane¹⁹ in a good yield (63%). Rearrangement of **13** with thallium(III) nitrate (TTN) under the conditions described by McKillop et al.²⁰ furnished the dimethylacetal (**14**) in 54% yield. Saponification of **14** with sodium hydroxide in methanol (**14** → **15**), followed by hydrolysis of the dimethyl acetal (**15** →

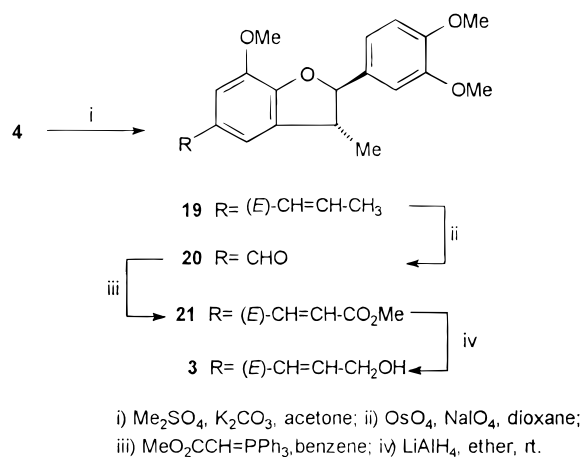
Scheme 3. Synthesis of *rac*-Fragnasol B (**2**)

16) under mild acidic condition in methanol did not result in **12** directly. Spontaneous decarboxylation of the β-oxo-carboxylic acid derivative **16** furnished the dimethyl acetal (**17**). Hydrolysis of **17** in the absence of methanol under mild conditions (10% HCl-CH₂Cl₂, room temperature) afforded the aldehyde **12** in high yield. The dimethyl acetal **14** could not be directly transformed into **12** under basic conditions (**14** → **15** → **16** → **12**). Only the first step of this process occurred, even though cleavage of the dimethylacetal of aldehydes carrying an active hydrogen at α-position is well-documented.²¹ In this case, however, the stability of the dimethylacetal function of **14** can be explained by the lack of an electron-withdrawing effect caused by a very rapid hydrolysis of the ester group to the sodium salt of **15**.

Finally, transformation of **12** into fragnasol B (**2**) could be achieved by means of a good-yielding (67%) two-step procedure involving reduction of the aldehyde to the corresponding alcohol (**12** → **18**) and its catalytic hydrogenation to remove the benzyl protecting group (**15** → **2**). The spectroscopic data of our synthetic product were identical with those of fragnasol B (**2**) reported by Hattori et al.⁷

Starting from **4**, the synthesis of racemic fragnasol C (**3**) could also be accomplished in four steps (Scheme 4). First, **4** was methylated with dimethyl sulfate in the presence of potassium carbonate in dry acetone, giving **19** (85%). The side-chain of **19** was cleaved with NaIO₄-OsO₄ in a good yield (80%) as described for **10**. The resulting aldehyde **20** was transformed into **21** with the Wittig methodology (see Experimental Section).

Reduction of the α,β-unsaturated ester function of **21** to the allyl alcohol moiety of **3** preserving the *trans*-geometry at the side-chain, could be accomplished with lithium aluminum hydride in dry THF at room temperature. Identification of our synthetic product with fragnasol C (**3**) was accomplished by comparison of spectroscopic data.

Scheme 4. Synthesis of *rac*-Fragnasol C (3)

Experimental Section

General Experimental Procedures. Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The analytical and preparative TLC were performed on plates Kieselgel 60 F₂₅₄ (Merck). Isoeugenol and the reagents were purchased from Sigma-Aldrich. For workup the solutions were dried (MgSO₄) and concentrated in vacuo. The ¹H and ¹³C NMR spectra were recorded on Bruker WP-200 and Bruker WP-360 (marked by an asterisk*) spectrometers with TMS as internal standard in CDCl₃. The chemical shifts are given in δ (ppm) and the spin-spin coupling constants (*J*) in hertz. HRMS were recorded in EI mode at 70 eV on a VG 7035 MS spectrometer.

(±)-2-(4-Hydroxy-3-methoxyphenyl)-3-methyl-7-methoxy-5-[(*E*)-1-propenyl]-2,3-dihydrobenzo[*b*]furan, *rac*-dehydrodiisoeugenol (4). To a stirred solution of 5 (4 g, 24.39 mmol) in dichloromethane (75 mL) was added dropwise a solution of IDA (2.5 g, 7.55 mmol) in dichloromethane (100 mL) at room temperature within 4 h and stirring was continued at room temperature for 48 h. Subsequently, the same amount of IDA in dichloromethane (100 mL) was added within 4 h. After stirring the reaction mixture at room temperature for 2 h, 3 g of solid NaHCO₃ was added, and stirring was continued for 5 h. Subsequently, NaHCO₃ was filtered off, and the solvent was evaporated to give a yellow oil, whose purification by flash chromatography on Si gel (*n*-hexane-ethyl acetate, 6:1) resulted in 4 (1.4 g, 35%) as white needles with mp 129–132 °C; lit.¹⁵ mp 132–133 °C (EtOH); ¹H NMR* δ 1.37 (3H, d, *J*_{3,Me} = 6.76, C-3-Me), 1.86 (3H, dd, *J*_{2',3'} = 6.55, *J*_{1',3'} = 1.37, H-3'), 3.45 (1H, m, *J*_{2,3} = 9.45, *J*_{3,3Me} = 6.76, H-3), 3.87 (3H, s, OMe), 3.89 (3H, s, OMe), 5.10 (1H, d, *J*_{2,3} = 9.45, H-2), 5.64 (1H, s, OH), 6.10 (1H, m, *J*_{2',3'} = 6.55, *J*_{1',2'} = 15.69, H_{2'}'), 6.36 (1H, dd, *J*_{1'',2''} = 15.69, *J*_{1',3'} = 1.37, H-1'), 6.7–7.1 (5H, m, Ar-H); ¹³C NMR* δ 17.56 (C-3 Me), 18.31 (C-3''), 45.59 (C-3), 55.95 (2 OMe), 93.74 (C-2), 108.93 (C-6), 109.33 (C-5'), 113.31 (C-2'), 114.07 (C-4), 119.92 (C-2''), 123.43 (C-6'), 130.93 (C-1'), 132.10 (C-5), 132.19 (C-3a), 133.27 (C-1'), 144.14 (C-4'), 145.78 (C-7a), 146.59 (C-3'), 146.66 (C-7); HRMS *m/z* 326.1514 (calcd for C₂₀H₂₂O₄, 326.1518).

(±)-threo-1-[2-(4-Hydroxy-3-methoxyphenyl)-3-methyl-7-methoxy-2,3-dihydrobenzo[*b*]furan-5-yl]-1,2-propanediol (8). A solution of 4 (240 mg, 0.9 mmol) and OsO₄ (230 mg, 0.9 mmol) in dry dioxane (10 mL) was stirred at room temperature. After 2 h, a solution of NaHSO₃ in water (10 mL) was added and stirring was continued at room temperature for 1 h. Subsequently, the product was extracted with ether (2 × 20 mL), and the organic layer was washed with an aqueous solution of D-sorbitol (2 × 20 mL), and dried. Evaporation of the solvent yielded 200 mg of an oil, which was purified by flash chromatography on Si gel (ethyl acetate-toluene, 3:1) furnished 5 (133 mg, 49%) as a colorless thick oil: ¹H NMR δ 1.10 (3H, d, *J*_{3,Me} = 6.29, C-3 Me), 1.38 (3H, d, *J*_{2',3'} = 6.77, H-3'), 2.51 (1H, br s, C-1' OH), 2.65 (1H, br s,

C-2 OH), 3.47 (1H, m, *J*_{2,3} = 9.59, *J*_{3,Me} = 6.29, H-3), 3.88 (3H, s, OMe), 3.89 (3H, s, OMe), 3.89 (1H, m; *J*_{2',3'} = 6.77, *J*_{2',1'} = 7.49, H-2''), 4.34 (1H, d, *J*_{2',1'} = 7.49, H-1''), 5.11 (1H, d, *J*_{2,3} = 9.59, H-2), 5.68 (1H, br s, C-4' OH), 6.70–7.10 (5H, m, Ar-H), ¹³C NMR* δ 16.83 (Me), 18.22 (C-3''), 44.85 (C-3), 55.28 (OCH₃), 55.38 (OCH₃), 71.59 (C-2''), 78.98 (C-1''), 93.12 (C-2), 108.24 (C-6), 109.67 (C-6'), 113.44 (C-3, C-4), 119.22 (C-2'), 131.21 (C-1', C-5), 132.61 (C-7), 133.92 (C-3a), 143.47 (C-7a), 145.15 (C-4'), 145.97 (C-3'); HRMS *m/z* 360.1569 (calcd for C₂₀H₂₄O₆, 360.1573).

(±)-erythro-1-[2-(4-Hydroxy-3-methoxyphenyl)-3-methyl-7-methoxy-2,3-dihydrobenzo[*b*]furan-5-yl]-1-methoxy-2-propanol, *rac*-fragnasol A (1). To a stirred solution of 8 (110 mg, 0.35 mmol) in dry methanol (5 mL) was added 0.1 mL of BF₃·OEt₂ at room temperature. After 12 h, the mixture was diluted with 5 mL of water, and the product was extracted with dichloromethane (2 × 10 mL) and dried. Evaporation of the solvent gave an oil (50 mg), which was purified by preparative TLC (toluene-ethyl acetate, 1:1) to obtain 1 (15 mg, 13%) as a colorless oil: ¹H NMR δ 1.01 (3H, d, *J* = 5.58, H-3'), 1.39 (3H, dd, *J* = 2.63, *J*_{2,3} = 6.89, C-3-Me), 3.27 (3H, s, C-1'' OMe), 3.48 (1H, m, H-3), 3.9 (6H, s, OMe), 3.9 (1H, m, H-2''), 4.0 (1H, d, *J*_{1',2'} = 5.25, H-1''), 5.12 (1H, d, *J*_{2,3} = 9.52, H-2), 5.67 (1H, br s, C-4' OH), 6.6–7.1 (5H, m, Ar-H); ¹³C NMR δ 17.37 (C-3-Me), 18.14 (C-3''), 45.57 (C-3), 56.0 (OMe), 56.6 (OMe), 71.5 (C-2''), 88.0 (C-1''), 93.9 (C-2), 108.9 (C-2'), 110.7 (C-6), 114.0 (C-5'), 115.0 (C-4), 119.9 (C-6'), 131.8 (C-5), 133.2 (C-3a, C-1'), 144.2 (C-7), 145.8 (C-4'), 146.7 (C-3'), 147.3 (C-7a); HRMS *m/z* 374.1731 (calcd for C₂₁H₂₆O₆, 374.1729).

(±)-2-(4-Benzyloxy-3-methoxyphenyl)-3-methyl-7-methoxy-5-[(*E*)-1-propenyl]-2,3-dihydrobenzo[*b*]furan (9). A mixture of 4 (1 g, 3.06 mmol), potassium carbonate (5 g), and benzyl chloride (0.5 mL) in dry DMF (20 mL) was stirred at 100 °C. After 5 h the reaction mixture was diluted with water (100 mL) and extracted with dichloromethane (2 × 25 mL). The organic layer was washed with brine (2 × 20 mL) and dried. Evaporation of the solvent yielded an oil (900 mg), whose purification by flash chromatography on Si gel (*n*-hexane-ethyl acetate, 3:1) resulted in 9 (750 mg, 61%) as a thick oil: ¹H NMR δ 1.37 (3H, d, *J*_{3,Me} = 6.76, C-3-Me), 1.86 (3H, dd, *J*_{2',3'} = 6.55, *J*_{1',3'} = 1.37, H-3'), 3.45 (1H, m, *J*_{2,3} = 9.45, *J*_{3,Me} = 6.76, H-3), 3.87 (3H, s, OMe), 3.88 (3H, s, OMe), 5.10 (1H, d, *J*_{2,3} = 9.51, H-2), 5.14 (2H, s, OCH₂-), 6.10 (1H, m, *J*_{1',2'} = 15.69, *J*_{2',3'} = 6.55, H-2''), 6.36 (1H, dd, *J*_{1'',2''} = 1.37, *J*_{1',2'} = 15.69, H-1''), 6.57–7.10 (5H, s, Ar-H), 7.20–7.50 (5H, s, OCH₂-Ph); ¹³C NMR δ 17.66 (C-3-Me), 18.32 (C-3''), 45.49 (C-3), 55.91 (C-7-OMe), 56.03 (C-3'-OMe), 71.02 (OCH₂-), 93.54 (C-2), 109.26 (C-6), 110.12 (C-5'), 113.29 (C-2'), 113.76 (C-4), 119.09 (C-2''), 123.42 (C-6'), 127.21, 127.76, 128.48 (OCH₂-Ph), 130.90 (C-1'), 132.18 (C-3a, C-5), 133.25 (C-1'), 144.14 (C-4'), 145.78 (C-7a), 146.59 (C-3'), 146.66 (C-7); HRMS *m/z* 416.1983 (calcd for C₂₇H₂₈O₄, 416.1987).

(±)-2-(4-Benzyloxy-3-methoxyphenyl)-5-formyl-3-methyl-7-methoxy-2,3-dihydrobenzo[*b*]furan (10). A solution of 9 (750 mg, 1.87 mmol) and OsO₄ (80 mg, 0.31 mmol) in dry dioxane (50 mL) was stirred at room temperature for 24 h. Subsequently, a solution of sodium periodate (900 mg) in water (100 mL) was added, and after 24 h the reaction mixture was extracted with ether, and the organic layer was washed with an aqueous solution of D-sorbitol and NaHSO₃. The solution was dried and evaporation of the solvent gave an oil (500 mg), which was purified by flash chromatography on Si gel (*n*-hexane-ethyl acetate, 4:1) to afford 10 (386 mg, 50%) as a colorless thick oil: ¹H NMR δ 1.44 (3H, d, *J*_{3,Me} = 6.80, C-3-Me), 3.61 (1H, m, *J*_{2,3} = 9.14, *J*_{3,Me} = 6.80, H-3), 3.88 (3H, s, OMe), 3.94 (3H, s, OMe), 5.17 (2H, s, OCH₂-), 5.25 (1H, d, *J*_{2,3} = 9.51, H₂), 6.80–7.10 (5H, m, Ar-H), 7.20–7.50 (5H, m, OCH₂-Ph), 9.85 (1H, s, CHO); ¹³C NMR δ 17.89 (C-3-Me), 44.86 (C-3), 56.10 (OMe), 71.06 (OCH₂-), 94.76 (C-2), 110.14 (C-6), 111.85 (C-5'), 113.92 (C-2'), 119.16 (C-4), 119.98 (C-6'), 127.21, 127.85, 128.53 (CH₂-Ph), 131.49 (C-3a), 132.25 (C-5), 133.63 (C-1'), 136.97 (C-4'), 144.96 (C-7a), 148.63 (C-3'), 149.98 (C-7), 190.53 (C-1''); HRMS *m/z* 404.1626 (calcd for C₂₅H₂₄O₅, 404.1623).

(±)-2-(4-Benzyloxy-3-methoxyphenyl)-3-methyl-7-methoxy-5-[(*E/Z*)-2-methoxy-1-ethenyl]-2,3-dihydrobenzo[*b*]-

furan (11). To a stirred solution of methoxymethyltriphenylphosphonium chloride¹⁸ (500 mg, 1.46 mmol) in dry THF (10 mL) was added potassium *tert*-butoxide (150 mg) at 0 °C. After 30 min a solution of **10** (216 mg, 0.53 mmol) in dry THF (30 mL) was added and stirring was continued at 0 °C for 30 min. Subsequently, the solvent was evaporated to give an oil (270 mg), whose purification by flash chromatography on Si gel (*n*-hexane–ethyl acetate, 6:1) afforded **11** (115 mg, 50%) as a colorless oil: ¹H NMR δ 1.36 (3H, d, *J*_{3,Me} = 6.76, C-3–Me), 3.45 (1H, m, H-3), 3.66 (3H, s, *trans*-OMe), 3.76 (3H, s, *cis*-OMe), 3.80 (6H, s, 2 OMe), 5.15 (2H, s, OCH₂–), 5.0–5.40 (2H, m, H-2, H-2''), 5.80 (1H, d, *J*_{1'',2''} = 12.90, H-1''), 6.05 (1H, d, *J*_{1'',2''} = 6.92, H-1'), 6.65–7.15 (5H, m, Ar–H), 7.20–7.60 (5H, m, OCH₂Ph); ¹³C NMR* δ 17.68 (C-3–Me), 45.60 (C-3), 55.07 (Ar–OMe), 56.54 (vinyl–OMe), 71.12 (OCH₂), 93.42 (C-2), 105.41 (C-2'' *trans*), 105.88 (C-2'' *cis*), 110.26 (C-6), 112.01 (C-5'), 112.58 (C-2'), 113.93 (C-4), 119.11 (C-6'), 127.25, 127.77, 128.49 (OCH₂Ph), 129.58 (C-3a), 129.87 (C-7a), 133.42 (C-1'), 137.15 (C-a), 144.25 (C-4'), 146.17 (C-1'' *cis*), 147.57 (C-1'' *trans*), 148.27 (C-3'), 149.90 (C-7); HRMS *m/z* 432.1935 (calcd for C₂₇H₂₈O₅, 432.1936).

(±)-2-[2-(4-Benzylloxy-3-methoxyphenyl)-3-methyl-7-methoxy-2,3-dihydrobenzo[*b*]furan-5-yl]-ethanal (12). (A) A solution of **11** (100 mg, 0.23 mmol) in dichloromethane (20 mL) was stirred with 10% HCl (40 mL) at room temperature. After 30 min, the organic layer was washed with saturated aqueous NaHCO₃ and dried. Evaporation of the solvent gave **12** (80 mg, 82%) as a colorless oil.

(B) The solution of **17** (15 mg, 0.03 mmol) and 10% HCl (5 mL) in dichloromethane (20 mL) was stirred at room temperature for 30 min. Subsequently, the organic layer was washed with saturated aqueous NaHCO₃ and dried. Evaporation of the solvent gave **12** (10 mg, 74%) as a colorless oil: ¹H NMR δ 1.37 (3H, d, *J*_{3,Me} = 6.94, C-3–Me), 3.48 (1H, m, H-3), 3.64 (2H, d, *J*_{1'',2''} = 2.56, H-1''), 3.87 (6H, s, OMe), 5.12 (1H, d, *J*_{2,3} = 9.51 Hz, H-2), 5.15 (2H, s, OCH₂), 6.58–7.5 (10H, m, Ar–H), 9.74 (1H, t, *J*_{1'',2''} = 2.56, CHO); HRMS *m/z* 418.1776 (calcd for C₂₆H₂₆O₅, 418.1780).

(±)-Methyl-(E)-3-[2-(4-benzylloxy-3-methoxyphenyl)-3-methyl-7-methoxy-2,3-dihydrobenzo[*b*]furan-5-yl]propanoate (13). The stirred solution of **10** (340 mg, 0.81 mmol) and methyl carboxymethyltriphenylphosphorane²⁰ (340 mg) in dry toluene (50 mL) was heated at 100 °C for 12 h. Subsequently, the solvent was evaporated, and the residue (650 mg) was purified by flash chromatography on Si gel (toluene–ethyl acetate, 4:1) to obtain **13** (275 mg, 63%) as a colorless oil: ¹H NMR δ 1.39 (3H, d, *J*_{3,Me} = 6.78, C-3–Me), 3.49 (1H, m, *J*_{2,3} = 9.63, *J*_{3,Me} = 6.78, H-3), 3.79 (3H, s, ester–OMe), 3.87 (3H, s, OMe), 3.90 (3H, s, OMe), 5.15 (2H, s, CH₂), 5.16 (1H, d, *J*_{2,3} = 9.63, H-2), 6.31 (1H, d, *J*_{1'',2''} = 15.88, H-2''), 6.81–7.05 (5H, m, Ar–H), 7.26–7.48 (5H, m, OCH₂Ph), 7.65 (1H, d, *J*_{1'',2''} = 15.88, H-1''); ¹³C NMR* δ 17.75 (C-3–Me), 45.12 (C-3), 51.52 (ester–OMe), 56.05 (OMe), 71.03 (OCH₂), 94.02 (C-2), 110.12 (C-5'), 111.48 (C-2'), 113.86 (C-4), 115.54 (C-6), 116.54 (C-6'), 119.10 (C-2''), 127.21, 127.80, 128.49, 137.0 (CH₂Ph), 132.68 (C-5), 133.75 (C-1'), 144.45 (C-3a), 145.08 (C-1''), 148.44 (C-7a), 149.75 (C-4'), 149.90 (C-3' and C-7), 167.71 (COOMe); HRMS *m/z* 460.1883 (calcd for C₂₈H₂₈O₆, 460.1885).

(±)-Methyl-2-[2-(4-benzylloxy-3-methoxyphenyl)-3-methyl-7-methoxy-2,3-dihydrobenzo[*b*]furan-5-yl]-3,3-dimethoxypropanoate (14). To a solution of **13** (240 mg, 0.52 mmol) in dry methanol (30 mL) was added thallium(III) nitrate (250 mg, 0.52 mmol) with stirring at room temperature, and stirring was continued for 1.5 h. Subsequently, brine (0.5 mL) was added to the reaction mixture, and it was filtered out to water (100 mL). The product was extracted with dichloromethane (2 × 20 mL). The organic layer was washed with saturated aqueous NaHCO₃ and dried. Evaporation of the solvent yielded 200 mg of an oil, which was purified by flash chromatography on Si gel (*n*-hexane–ethyl acetate, 3:1) to give a diastereomeric mixture of **14** (148 mg, 54%) as a colorless oil: ¹H NMR* δ 1.37 (3H, dd, *J*_{3,Me} = 6.71, *J* = 0.92, C-3–Me), 3.23 (3H, s, OMe), 3.46 (3H, s, OMe), 3.48 (1H, m, *J*_{2,3} = 9.69, *J*_{3,Me} = 6.71, H-3), 3.69 (3H, s, OMe), 3.83 and 3.85 (1H, d, *J*_{3'',2''} = 5.42 (H-3''), 3.87 (3H, s, OMe), 3.88 (3H, s, OMe), 4.92

and 4.94 (1H, d, *J*_{3'',2''} = 5.42, H-2''), 5.1 (1H, d, *J*_{2,3} = 9.69, H-2), 5.15 (2H, s, CH₂), 6.76–6.9 (5H, m, Ar–H), 7.22–7.48 (5H, m, CH₂Ph); ¹³C NMR* δ 17.36 (C-3–Me), 45.54 (C-3), 52.04 (ester–OMe), 53.19 and 53.52 (acetal–OMe), 55.30 and 55.08 (C-3'') 56.03 (OMe), 71.01 (CH₂), 93.61 (C-2), 105.15 and 105.39 (C-1''), 110.13 (C-6), 112.05 (C-2'), 113.73 (C-5'), 115.95 (C-6'), 119.14 (C-4), 127.21, 127.76, 128.47, 137.04 (CH₂Ph), 127.65 (C-5), 133.06 (C-1'), 133.24 (C-7), 144.04 (C-3a), 147.04 (C-7a), 148.24 (C-4'), 149.80 (C-3'), 171.90 (COOMe); HRMS *m/z* 538.2564 (calcd for C₃₁H₃₈O₈, 538.2566).

(±)-2-[2-(4-Benzylloxy-3-methoxyphenyl)-3-methyl-7-methoxy-2,3-dihydrobenzo[*b*]furan-5-yl]-3,3-dimethoxypropionic Acid (15). To a stirred solution of **14** (148 mg, 0.28 mmol) in methanol (10 mL) was added a solution of potassium hydroxide (50 mg) in water (2 mL) at 60 °C. After 8 h the reaction mixture was acidified with 10% hydrogen chloride solution (50 mL) and extracted with dichloromethane (2 × 20 mL). The organic layer was washed with saturated sodium hydrogen carbonate solution and dried. Evaporation of the solvent gave an oil (180 mg), which was purified by flash chromatography (toluene–ethyl acetate, 4:1) to furnish a diastereomeric mixture of **15** (120 mg, 83%) as a colorless oil: ¹H NMR δ 1.37 (3H, d, *J*_{2,3} = 6.75, C-3–Me), 3.25 (3H, s, OMe), 3.47 (3H, s, OMe), 3.48 (1H, m, H-3), 3.88 (6H, s) + 2H (d + d), OMe + H-2''), 4.91 (1H, d, *J* = 3.67, H-3''), 4.95 (1H, d, *J* = 3.68, H-3'), 5.09 (1H, d, *J* = 9.76, H-2), 5.15 (2H, s, OCH₂), 6.7–7.6 (10H, m, Ar–H); ¹³C NMR* δ 17.37 (C-3–Me), 45.57 (C-3), 53.61 and 53.28 (acetal–OMe), 55.42 and 55.01 (C-3''), 56.09 (OMe), 71.05 (CH₂), 93.72 (C-2), 104.82 and 105.07 (C-2''), 110.15 (C-6), 112.27 (C-2'), 113.76 (C-5'), 116.17 (C-6'), 119.20 (C-4), 127.21, 127.80, 128.47, 137.07 (CH₂Ph), 127.06 (C-5), 133.02 (C-1'), 133.40 (C-7), 144.16 (C-3a), 147.29 (C-7a), 148.29 (C-4'), 149.84 (C-3'), 175.69 (COOH); HRMS *m/z* 524.2412 (calcd for C₃₀H₃₆O₈, 524.2410).

(±)-2-(4-Benzylloxy-3-methoxyphenyl)-3-methyl-7-methoxy-5-(2,2-dimethoxyethyl)-2,3-dihydrobenzo[*b*]furan (17). A solution of **15** (110 mg, 0.21 mmol) in methanol (5 mL) was stirred at 70 °C in the presence of 10% HCl (1 mL) for 1 h. Subsequently, the reaction mixture was diluted with water (10 mL) and extracted with dichloromethane (2 × 20 mL). The organic layer was washed with water (2 × 20 mL) and saturated aqueous NaHCO₃ (2 × 20 mL) and dried. Evaporation of the solvent gave an oil (60 mg), which was purified by preparative TLC (toluene–ethyl acetate, 4:1) to furnish **17** (30 mg, 33%) as a colorless oil: ¹H NMR δ 1.36 (3H, d, *J*_{3,Me} = 6.72, C-3–Me), 2.87 (2H, d, *J*_{1'',2''} = 5.56, H-1''), 3.36 (3H, s, OMe), 3.5 (3H, s, OMe), 3.5 (1H, m, H-3), 3.88 (6H, s, OMe), 4.54 (1H, t, *J* = 5.56, H-2''), 5.08 (1H, d, *J*_{2,3} = 9.61, H-2), 5.16 (2H, s, OCH₂), 6.6–7.9 (10H, m, Ar–H); HRMS *m/z* 480.2510 (calcd for C₂₉H₃₆O₆, 480.2511).

(±)-2-[2-(4-Benzylloxy-3-methoxyphenyl)-3-methyl-7-methoxy-2,3-dihydrobenzo[*b*]furan-5-yl]-ethanol (18). To a stirred solution of the aldehyde (**12**) (25 mg, 0.06 mmol) in dry methanol (2 mL) was added NaBH₄ (5 mg) at room temperature. Subsequently, after 30 min 500 mg of Si gel was added to the reaction mixture, and stirring was continued for a further 30 min. Then the Si gel was filtered off, and evaporation of the solvent yielded **18** (22 mg, 88%) as a colorless oil: ¹H NMR δ 1.37 (3H, d, *J*_{3,Me} = 6.56, C-3–Me), 2.82 (2H, t, *J*_{1'',2''} = 6.11, H-2''), 3.5 (1 H, m, H), 3.85 (2H, t, *J* = 6.11, H-1''), 3.87 (6H, s, OMe), 5.08 (1H, d, *J* = 9.92, H-2), 5.15 (2H, s, OCH₂), 6.6–7.7 (10H, m, Ar–H); HRMS *m/z* 436.2251 (calcd for C₂₇H₃₂O₅, 436.2249).

(±)-2-[2-(4-Hydroxy-3-methoxyphenyl)-3-methyl-7-methoxy-2,3-dihydrobenzo[*b*]furan-5-yl]ethanol, *rac*-Fragransol B(2). A solution of **18** (22 mg, 0.052 mmol) in dry methanol (5 mL) was hydrogenated in the presence of Pd/C (15 mg) at room temperature. The usual workup gave **2** (15 mg, 76%) as a colorless oil: ¹H NMR δ 1.37 (3H, d, *J* = 6.94, C-3–Me), 2.83 (2H, t, *J* = 6.58, H-2''), 3.45 (1H, m, H-3), 3.88 (6H, s, OMe), 3.9 (2H, t, H-1''), 5.1 (1H, d, *J* = 9.84, H-2), 5.63 (1H, br s, C-4'-OH), 6.6–7.1 (5H, m, Ar–H); ¹³C NMR δ 17.56 (C-3–Me), 39.1 (C-2''), 45.6 (C-3), 56.0 (OMe), 63.8 (C-1''), 93.6 (C-2), 109.1 (C-2'), 112.8 (C-6), 114.3 (C-5'), 116.3 (C-4), 119.8

(C-6') 132.2 (C-5, C-1'), 135.0 (C-3a), 144.2 (C-7), 145.8 (C-4'), 146.7 (C-7a, C-3'); HRMS m/z 346.1778 (calcd for $C_{20}H_{26}O_5$, 346.1780).

(±)-2-(3,4-Dimethoxyphenyl)-3-methyl-7-methoxy-5-[(E)-1-propenyl]-2,3-dihydrobenzo[b]furan (19). To a stirred mixture of **4** (150 mg, 0.46 mmol) and potassium carbonate (200 mg) in dry acetone (5 mL) was added dimethyl sulfate (0.1 mL) at 60 °C, and after 2 h the reaction mixture was diluted with water (15 mL). After 12 h, the reaction mixture was extracted with dichloromethane (2×10 mL) and dried. Evaporation of the solvent gave **19** (133 mg, 85%) as a colorless oil: $^1\text{H NMR}$ δ 1.37 (3H, d, $J_{3,\text{Me}}$ = 6.76, C-3-Me), 1.86 (3H, dd, $J_{2'',3''}$ = 6.55, $J_{1'',3''}$ = 1.37, H-3''), 3.45 (1H, m, $J_{2,3}$ = 9.45, $J_{3,\text{Me}}$ = 6.76, H-3), 3.87 (9H, s, 3 OMe), 5.12 (1H, d, $J_{2,3}$ = 9.44, H-2), 6.11 (1H, m, $J_{2'',3''}$ = 6.55, $J_{1'',2''}$ = 15.69, H-2''), 6.36 (1H, dd, $J_{1'',2''}$ = 15.69, $J_{1'',3''}$ = 1.37, H-1''), 6.70–7.10 (5H, m, Ar-H); $^{13}\text{C NMR}$ δ 17.66 (C-3-Me), 18.39 (C-3''), 45.61 (C-3), 55.95 (OMe), 93.69 (C-2), 109.29 (C-6), 109.54 (C-5'), 110.82 (C-2'), 113.30 (C-4), 119.25 (C-2''), 123.52 (C-6'), 130.94 (C-1''), 132.24 (C-3a, C-5), 133.29 (C-1'), 149.16 (C-7, C-3', C-4', C-7a); HRMS m/z 374.1731 (calcd for $C_{21}H_{26}O_6$, 374.1729); HRMS m/z 356.1985 (calcd for $C_{22}H_{28}O_4$, 356.1987).

(±)-2-(3,4-Dimethoxyphenyl)-5-formyl-3-methyl-7-methoxy-2,3-dihydrobenzo[b]furan (20). A solution of **19** (287 mg, 0.84 mmol) and OsO_4 (50 mg, 0.197 mmol) in dry dioxane (15 mL) was stirred at room temperature for 2 h. Subsequently, a solution of sodium periodate (361 mg) in water (10 mL) was added, and after 12 h the reaction mixture was extracted with ether. The organic layer was washed with an aqueous solution of D-sorbitol and NaHSO_3 and dried. Evaporation of the solvent gave **20** (222 mg, 80%) as white needles with mp 109–111 °C: $^1\text{H NMR}$ δ 1.45 (3H, d, $J_{3,\text{Me}}$ = 6.76, C-3-Me), 3.62 (1H, m, $J_{2,3}$ = 9.45, $J_{3,\text{Me}}$ = 6.76, H-3), 3.88 (3H, s, OMe), 3.89 (3H, s, OMe), 3.95 (3H, s, OMe), 5.27 (1H, d, $J_{2,3}$ = 9.45, H-2), 6.80–7.50 (5H, m, Ar-H), 9.85 (1H, s, CHO), $^{13}\text{C NMR}$ δ 17.79 (C-3-Me), 44.80 (C-3), 55.94 (OMe), 56.06 (OMe), 94.83 (C-2), 109.51 (C-6), 111.03 (C-7), 111.87 (C-2'), 131.49 (C-4), 131.66 (C-3a), 133.65 (C-1'), 144.96 (C-5), 149.3 (C-4'), 149.52 (C-3'), 153.22 (C-7a), 190.53 (CHO); HRMS m/z 328.1312 (calcd for $C_{19}H_{20}O_5$, 328.1310).

(±)-Methyl-(E)-3-[2-(3,4-dimethoxyphenyl)-3-methyl-7-methoxy-2,3-dihydrobenzo[b]furan-5-yl]propenoate (21). To a stirred solution of **20** (222 mg, 0.68 mmol) in dry benzene (25 mL) was added methyl carboxymethylene-triphenylphosphorane¹⁹ (340 mg, 1.01 mmol) at 60 °C. After 12 h the solvent was evaporated to give an oil (280 mg), whose purification by flash chromatography on Si gel (toluene–ethyl acetate, 4:1) resulted in **21** (241 mg, 93%) as white needles with mp 66–68 °C: $^1\text{H NMR}$ δ 1.41 (3H, d, $J_{3,\text{Me}}$ = 6.76, C-3-Me), 3.50 (1H, m, $J_{2,3}$ = 9.33, $J_{3,\text{Me}}$ = 6.76, H-3), 3.80 (3H, s, COOMe), 3.87 (9H, s, 3 OMe), 5.19 (1H, d, $J_{2,3}$ = 9.33, H-2), 6.32 (1H, d, $J_{1'',2''}$ = 16, H-2''), 6.80–7.10 (5H, m, Ar-H), 7.66 (1H, d, $J_{1'',2''}$ = 16, H-1''); $^{13}\text{C NMR}$ δ 17.69 (C-3-Me), 45.21 (C-3), 51.55 (ester-OMe), 55.95 (3 OMe), 94.21 (C-2), 109.53 (C-5'), 110.97 (C-2'), 111.49 (C-4), 115.86 (C-6), 116.56 (C-6'), 119.23 (C-2''), 128.49 (C-3a, C-7), 132.11 (C-1'), 133.79 (C-4', C-3'), 145.10 (C-1''), 149.26 (C-5), 167.71 (COOMe), HRMS m/z 384.1575 (calcd for $C_{22}H_{24}O_6$, 384.1572).

(±)-3-[2-(3,4-Dimethoxyphenyl)-3-methyl-7-methoxy-2,3-dihydrobenzo[b]furan-5-yl]-2-propen-1-ol, rac-frag-nasol C (3). To a stirred solution of LiAlH_4 (15 mg) in dry THF (3 mL) was added a solution of **21** (100 mg, 0.26 mmol) in 2 mL of dry THF at room temperature. After 30 min, a few milligrams of $\text{Na}_2\text{SO}_4 \times 10\text{H}_2\text{O}$ was added to the reaction mixture. After filtration, the solvent was evaporated to give **3** (74 mg, 80%) as a colorless oil: $^1\text{H NMR}$ δ 1.39 (3H, d, J = 6.68; C-3-Me), 3.48 (1H, m, H-3), 3.87 (3H, s, OMe), 3.88 (3H, s, OMe), 3.89 (3H, s, OMe), 4.31 (2H, d, J = 5.95, H-1''), 5.14 (1H, d, J = 9.5, H-2), 6.25 (1H, dt, J = 15.9 and 5.95, H-2''), 6.57 (1H, d, J = 15.9, H-3''), 6.83–7.0 (5H, m, Ar-H); $^{13}\text{C NMR}$ δ 17.52 (C-3-Me), 45.39 (C-3), 55.83 (3 OMe), 93.69 (C-2), 109.43 (C-5'), 109.84 (C-2'), 110.79 (C-6), 114.09 (C-6'), 119.13 (C-4), 126.29 (C-2''), 130.80 (C-5), 131.25 (C-1'), 132.42 (C-7, C-1''), 133.31 (C-3a), 144.14 (C-7a), 147.26 (C-4), 149.08 (C-3'); HRMS m/z 356.1619 (calcd for $C_{21}H_{26}O_5$, 356.1623).

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References and Notes

- Nagai, M.; Noguchi, M.; Iizuka, T.; Otani, K.; Kamata, K. *Biol. Pharm. Bull.* **1996**, *19*, 228–232.
- Fukuyama, Y.; Mizuta, K.; Nakagawa, K.; Qin, W.; Wa, X. *Planta Med.* **1986**, 502–504.
- Sih, C. J.; Ravikumar, P. R.; Huang, F.; Buckner, C. Whitlock, H. *J. Am. Chem. Soc.* **1976**, *98*, 5412–5413.
- Nikaido, T.; Ohmoto, T.; Kinoshita, T.; Sankawa, H.; Nishibe, S.; Hisada, S. *Chem. Pharm. Bull.* **1981**, *29*, 3586–3592.
- Kamata, K.; Itzuka, T.; Nagai, M.; Kasuya, Y. *Gen. Pharmacol.* **1993**, *24*, 977–981.
- Hattori, M.; Hada, S.; Watahiki, A.; Ihara, H.; Shu, Y.-Z.; Kakiuchi, N.; Mizuno, T.; Namba, T. *Chem. Pharm. Bull.* **1986**, *34*, 3885–3893.
- Hada, S.; Hattori, M.; Tezuka, Y.; Kikuchi, T.; Namba, T. *Phytochemistry* **1988**, *27*, 563–568.
- Hattori, M.; Yang, X.-W.; Shu, Y.-Z.; Kakiuchi, N.; Tezuka, Y.; Kikuchi, T.; Namba, T. *Chem. Pharm. Bull.* **1988**, *36*, 648–653.
- Antus, S.; Bauer, R.; Gottsegen, Á.; Seligmann, O.; Wagner, H. *Liebigs. Ann. Chem.* **1987**, 357–360.
- Antus, S.; Gottsegen, Á.; Kolonits, P.; Wagner, H. *Liebigs. Ann. Chem.* **1989**, 593–594.
- Antus, S.; Baitz-Gács, E.; Gottsegen, Á.; Seligman, O.; Wagner, H. *Liebigs Ann. Chem.* **1990**, 495–497.
- Leffler, J. E.; Story, L. J. *J. Am. Chem. Soc.* **1967**, *89*, 2333–2338.
- Kürti, L.; Herczegh, P.; Simonyi, M.; Antus, S.; Pelter, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 379–380.
- Li, W. S.; El-Feraly, F. S. *Proc. Nat. Sci. Coun. Repub. China* **1981**, 145–149.
- Leopold, B. *Acta Chem. Scand.* **1950**, *4*, 1523–1537.
- Baran, J. S. *J. Org. Chem.* **1960**, *25*, 257–258.
- Tőkés, A. L.; Litkei, Gy.; Gulácsi, K.; Antus, S.; Baitz-Gács, E.; Szántay, Cs.; Darkó, L. L. *Tetrahedron* **1999**, *55*, 9283–9296.
- Schow, S. R.; McMorris, T. C. *J. Org. Chem.* **1979**, *44*, 3760–3769.
- Hercouet, A.; Le Corre, M. *Tetrahedron Lett.* **1979**, 2995–2998.
- Taylor, E. C.; Robey, R. L.; Lin, K.-T.; Favre, B.; Bozimo, H. T.; Conley, R. E.; Chiang, C.-S.; McKillop, A.; Ford, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 3037–3038.
- Antus, S.; Boross, F.; Nógrádi, M. *Liebigs Ann. Chem.* **1978**, 107–117.

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