Simple Synthesis of Benzofuranoid Neolignans from *Myristica fragrans*

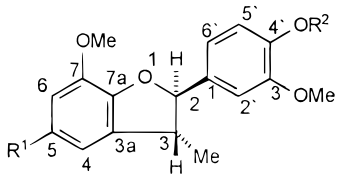
László Juhász, László Kürti, and Sándor Antus*

Department of Organic Chemistry, Lajos Kossuth University, P.O. Box 20, H-4010 Debrecen, Hungary

Received July 2, 1999

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.

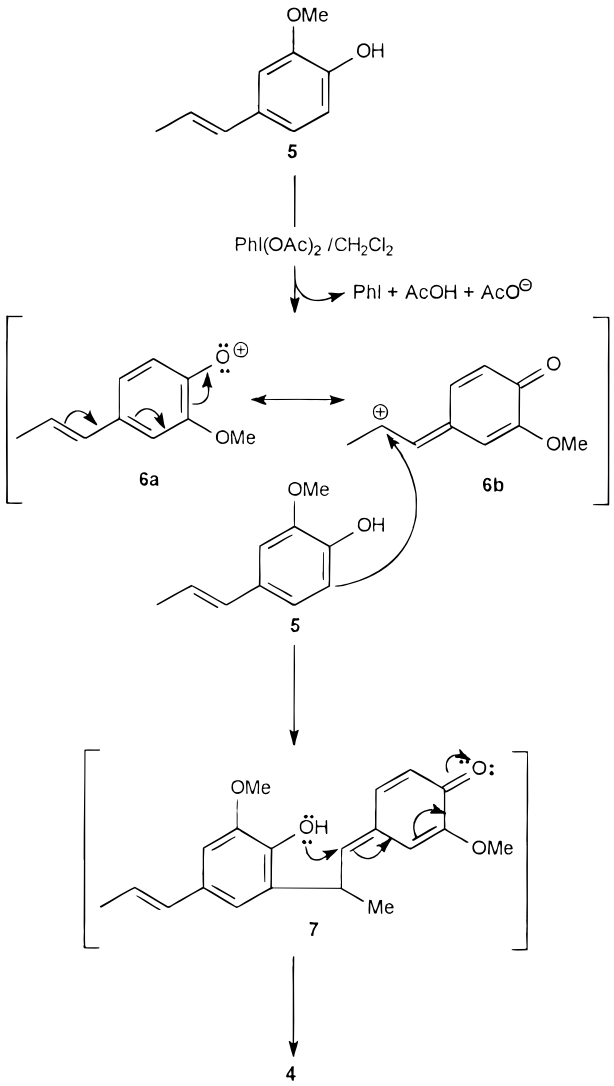
Neolignans possessing a 2,3-dihydrobenzo[*b*]furan skeleton are a prominent subgroup of the naturally occurring *O*-heterocycles owing to their complex biological activities.[1−5] The mace of *Myristica fragrans* Houtt. (Myristicaceae) is a commonly used spice and has been applied as a remedy for strengthening 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.



	R^1	R^2
1	*erythro*-CH(OMe)CH(OH)-Me	H
2	-CH_2-CH_2-OH	H
3	(*E*)-CH=CH-CH_2-OH	Me
4	(*E*)-CH=CH-Me	H

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 paper[13] 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 controlled addition of its phenolic hydroxyl group at the quinone−methide moiety.

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

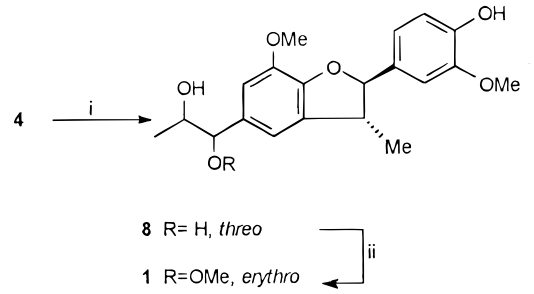


In full accordance with the above-mentioned assumption, transformation of isoeugenol (**5**) with IDA in dry dichloromethane at room temperature resulted only in one product, accompanied by some polymerization based on TLC monitoring of the reaction mixture. Isolation of this product in crystalline form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

* To whom correspondence should be addressed. Tel.: 0036-52-512-900/2471. Fax: 0036-52-453-836. E-mail: antuss@tigris.klte.hu.

10.1021/np990327h CCC: $19.00
Published on Web 04/19/2000

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



i) OsO_4,dioxane,rt.; ii) BF_3•OEt_2, MeOH, rt.

(35%) and its structure was proved to be identical with that of dehydrodiisoeugenol (**4**) by means of ^1H and ^{13}C 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 kachirachiari*,[14] and prepared[15] from **5** via the corresponding quinone−methide radical intermediate generated by $FeCl_3$.

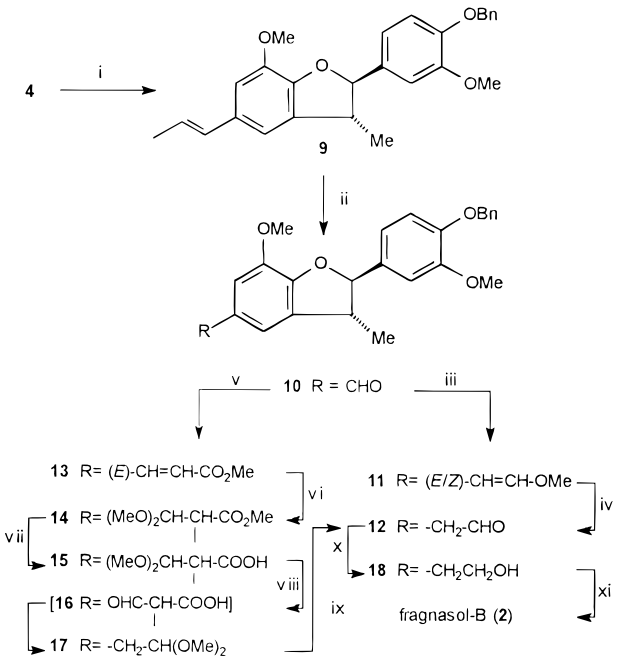
The synthesis of fragnasol A (**1**) could be achieved in two steps starting from dehydrodiisoeugenol (**4**) (Scheme 2). In the first step its unsaturated side-chain of *E*-geometry was hydroxylated with OsO_4 in dioxane at room temperature to give the corresponding *threo*-diol derivative **8** in a satisfactory yield (49%), due to the well-known stereospecific *syn* addition of this reagent[16] 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 ^{13}C 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 OsO_4. 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 chloride[18] 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-triphenylphosphorane[19] 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 group (**15** → **16**) under mild acidic condition in methanol did not result in **12** directly. Spontaneous decarboxylation of the β-oxocarboxylic acid derivative **16** furnished the dimethyl acetal (**17**). Hydrolysis of **17** in the absence of methanol under mild conditions (10% HCl−CH_2Cl_2, 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**.

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



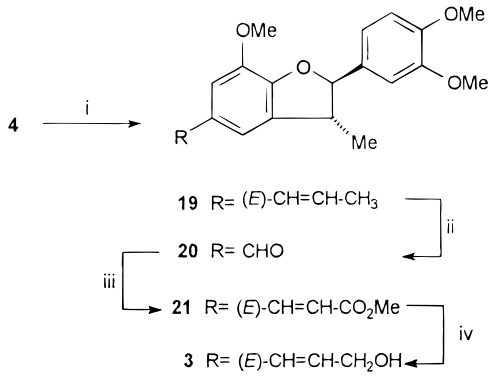
i) BnCl, K_2CO_3, DMF; ii) OsO_4, $NaIO_4$, dioxane; iii) MeO-CH_2-$^{\oplus}PPh_3Cl^{\ominus}$ KtOBu, THF; iv) 10% HCl, CH_2Cl_2; v) $MeCO_2CH{=}PPh_3$, toluene; vi) TTN, MeOH; vii) KOH, MeOH; viii) 10% HCl, MeOH; ix) 10% HCl, CH_2Cl_2; x) $NaBH_4$, MeOH; xi) H_2/Pd, MeOH;

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 $NaIO_4$−OsO_4 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**)



i) Me_2SO_4, K_2CO_3, acetone; ii) OsO_4, $NaIO_4$, dioxane; iii) $MeO_2CCH=PPh_3$,benzene; iv) $LiAlH_4$, ether, rt.

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 F_{254} (Merck). Isoeugenol and the reagents were purchased from Sigma-Aldrich. For workup the solutions were dried ($MgSO_4$) and concentrated in vacuo. The ^1H and ^{13}C NMR spectra were recorded on Bruker WP-200 and Bruker WP-360 (marked by an asterisk*) spectrometers with TMS as internal standard in $CDCl_3$. 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 $NaHCO_3$ was added, and stirring was continued for 5 h. Subsequently, $NaHCO_3$ 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); ^{13}C 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 $C_{20}H_{22}O_4$, 326,1518).

(±)-*threo*-1-[2-(4-Hydroxy-3-methoxyphenyl)-3-methyl-7-methoxy-2,3-dihydrobenzo[*b*]furan-5-yl]-1,2-propandiol (8). A solution of **4** (240 mg, 0.9 mmol) and OsO_4 (230 mg, 0.9 mmol) in dry dioxane (10 mL) was stirred at room temperature. After 2 h, a solution of $NaHSO_3$ 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), ^{13}C NMR* δ 16.83 (Me), 18.22 (C-3″), 44.85 (C-3), 55.28 (OCH_3), 55.38 (OCH_3), 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 $C_{20}H_{24}O_6$, 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 $BF_3{\cdot}OEt_2$ 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); ^{13}C 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 $C_{21}H_{26}O_6$, 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, OCH_2−), 6.10 (1H, m, $J_{1'',2''}$ = 15.69, $J_{2'',3''}$ = 6.55, H-2″), 6.36 (1H, dd, $J_{1'',3''}$ = 1.37, $J_{1'',2''}$ = 15.69, H-1″), 6.57−7.10 (5H, s, Ar−H), 7.20−7.50 (5H, s, OCH_2-Ph); ^{13}C 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 (OCH_2−), 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 (OCH_2Ph), 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 $C_{27}H_{28}O_4$, 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 OsO_4 (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 $NaHSO_3$. 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, $J_{3,Me}$, H-3), 3.88 (3H, s, OMe), 3.94 (3H, s, OMe), 5.17 (2H, s, OCH_2−), 5.25 (1H, d, $J_{2,3}$ = 9.51, H_2), 6.80−7.10 (5H, m, Ar−H), 7.20−7.50 (5H, m, OCH_2-Ph), 9.85 (1H, s, CHO); ^{13}C NMR δ 17.89 (C-3−Me), 44.86 (C-3), 56.10 (OMe), 71.06 (OCH_2), 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 (CH_2Ph), 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 $C_{25}H_{24}O_5$, 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 chloride[18] (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: ^{1}H 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, OCH_2−), 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, OCH_2Ph); ^{13}C NMR* δ 17.68 (C-3−Me), 45.60 (C-3), 55.07 (Ar−OMe), 56.54 (vinyl−OMe), 71.12 (OCH_2), 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 (OCH_2Ph), 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 $C_{27}H_{28}O_5$, 432.1936).

(±)-2-[2-(4-Benzyloxy-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 $NaHCO_3$ 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 $NaHCO_3$ and dried. Evaporation of the solvent gave **12** (10 mg, 74%) as a colorless oil: ^{1}H 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, OCH_2), 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 $C_{26}H_{26}O_5$, 418.1780).

(±)-Methyl-(*E*)-3-[2-(4-benzyloxy-3-methoxyphenyl)-3-methyl-7-methoxy-2,3-dihydrobenzo[*b*]furan-5-yl]propenoate (13). The stirred solution of **10** (340 mg, 0.81 mmol) and methyl carboxymethyltriphenylphosphorane[20] (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: ^{1}H 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, CH_2), 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, OCH_2Ph), 7.65 (1H, d, $J_{1″,2″}$ = 15.88, H-1″); ^{13}C NMR* δ 17.75 (C-3−Me), 45.12 (C-3), 51.52 (ester−OMe), 56.05 (OMe), 71.03 (OCH_2), 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 (CH_2Ph), 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 $C_{28}H_{28}O_6$, 460.1885).

(±)-Methyl-2-[2-(4-benzyloxy-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 onto water (100 mL). The product was extracted with dichloromethane (2 × 20 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ 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: ^{1}H 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, CH_2), 6.76−6.9 (5H, m, Ar−H), 7.22−7.48 (5H, m, CH_2Ph); ^{13}C 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 (CH_2), 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 (CH_2Ph), 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 $C_{31}H_{38}O_8$, 538.2566).

(±)-2-[2-(4-Benzyloxy-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: ^{1}H 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, OCH_2), 6.7−7.6 (10H, m, Ar−H); ^{13}C 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 (CH_2), 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 (CH_2Ph), 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 $C_{30}H_{36}O_8$, 524.2410).

(±)-2-(4-Benzyloxy-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 $NaHCO_3$ (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: ^{1}H 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, OCH_2), 6.6−7.9 (10H, m, Ar−H); HRMS *m*/*z* 480.2510 (calcd for $C_{29}H_{36}O_6$, 480.2511).

(±)-2-[2-(4-Benzyloxy-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 $NaBH_4$ (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: ^{1}H 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, OCH_2), 6.6−7.7 (10H, m, Ar−H); HRMS *m*/*z* 436.2251 (calcd for $C_{27}H_{32}O_5$, 436.2249).

(±)-2-[2-(4-Hydroxy-3-methoxyphenyl)-3-methyl-7-methoxy-2,3-dihydrobenzo[*b*]furan-5-yl]ethanol, *rac*-Fragnasol 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: ^{1}H 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); ^{13}C 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}H 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 (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}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}H NMR δ 1.45 (3H, d, $J_{3,3Me}$ = 6.76, C-3−Me), 3.62 (1H, m, $J_{2,3}$ = 9.45, $J_{3,Me}$, 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}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-triphenylphosphorane[19] (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}H NMR δ 1.41 (3H, d, $J_{3,Me}$ = 6.76, C-3−Me), 3.50 (1H, m, $J_{2,3}$ = 9.33, $J_{3,Me}$, 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}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*-fragnasol 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 $Na_2SO_4 \times 10H_2O$ was added to the reaction mixture. After filtration, the solvent was evaporated to give **3** (74 mg, 80%) as a colorless oil: ^{1}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}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).

Acknowledgment. The authors thank the National Science Foundation (OTKA, T-23687) and the Ministry of Education (grant no. 460/1997) for financial support.

References and Notes

(1) Nagai, M.; Noguchi, M.; Iizuka, T.; Otani, K.; Kamata, K. *Biol. Pharm. Bull.* **1996**, *19*, 228−232.
(2) Fukuyama, Y.; Mizuta, K.; Nakagawa, K.; Qin, W.; Wa, X. *Planta Med.* **1986**, 502−504.
(3) Sih, C. J.; Ravikumar, P. R.; Huang, F.; Buckner, C. Whitlock, H. *J. Am. Chem. Soc.* **1976**, *98*, 5412−5413.
(4) Nikaido, T.; Ohmoto, T.; Kinoshita, T.; Sankawa, H.; Nishibe, S.; Hisada, S. *Chem. Pharm. Bull.* **1981**, *29*, 3586−3592.
(5) Kamata, K.; Itzuka, T.; Nagai, M.; Kasuya, Y. *Gen. Pharmacol.* **1993**, *24*, 977−981.
(6) Hattori, M.; Hada, S.; Watahiki, A.; Ihara, H.; Shu, Y.-Z.; Kakiuchi, N.; Mizuno, T.; Namba, T. *Chem. Pharm. Bull.* **1986**, *34*, 3885−3893.
(7) Hada, S.; Hattori, M.; Tezuka, Y.; Kikuchi, T.; Namba, T. *Phytochemistry* **1988**, *27*, 563−568.
(8) Hattori, M.; Yang, X.-W.; Shu, Y.-Z.; Kakiuchi, N.; Tezuka, Y.; Kikuchi, T.; Namba, T. *Chem. Pharm. Bull.* **1988**, *36*, 648−653.
(9) Antus, S.; Bauer, R.; Gottsegen, Á.; Seligmann, O.; Wagner, H. *Liebigs. Ann. Chem.* **1987**, 357−360.
(10) Antus, S.; Gottsegen, Á.; Kolonits, P.; Wagner, H. *Liebigs. Ann. Chem.* **1989**, 593−594.
(11) Antus, S.; Baitz-Gács, E.; Gottsegen, Á.; Seligman, O.; Wagner, H. *Liebigs Ann. Chem.* **1990**, 495−497.
(12) Leffler, J. E.; Story, L. J. *J. Am. Chem. Soc.* **1967**, *89*, 2333−2338.
(13) Kürti, L.; Herczegh, P.; Simonyi, M.; Antus, S.; Pelter, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 379−380.
(14) Li, W. S.; El-Feraly, F. S. *Proc. Nat. Sci. Counc. Repub. China* **1981**, 145−149.
(15) Leopold, B. *Acta Chem. Scand.* **1950**, *4*, 1523−1537.
(16) Baran, J. S. *J. Org. Chem.* **1960**, *25*, 257−258.
(17) Tõkés, A. L.; Litkei, Gy.; Gulácsi, K.; Antus, S.; Baitz-Gács, E.; Szántay, Cs.; Darkó, L. L. *Tetrahedron* **1999**, *55*, 9283−9296.
(18) Schow, S. R.; McMorris, T. C. *J. Org. Chem.* **1979**, *44*, 3760−3769.
(19) Hercouet, A.; Le Corre, M. *Tetrahedron Lett.* **1979**, 2995−2998.
(20) 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.
(21) Antus, S.; Boross, F.; Nógrádi, M. *Liebigs Ann. Chem.* **1978**, 107−117.

NP990327H