Total Synthesis of Naturally Occurring Furan Compounds 5-{[(4-Hydroxybenzyl)oxy]methyl}-2-furaldehyde and Pichiafuran C

Héctor Quiroz-Florentino,[a] R. Israel Hernández-Benitez,[a] Judit A. Aviña,[a,b] Eleuterio Burgueño-Tapia,[a] Joaquín Tamariz*[a]

[a] Departamento de Química Orgánica, Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional. Prol. Carpio y Plan de Ayala, 11340 México, D.F., Mexico
Fax +52(55)57296300/46211; E-mail: jtamariz@woodward.encb.ipn.mx

[b] Instituto de Investigaciones Quimicobiológicas, Universidad Michoacana de San Nicolas de Hidalgo, Edif. B-1, Ciudad Universitaria, Francisco J. Mujica s/n, 58066 Morelia, Mich., Mexico

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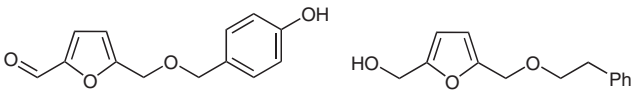
Abstract: The synthesis of the natural furan derivatives 5-{[(4-hydroxybenzyl)oxy]methyl}-2-furaldehyde and pichiafuran C is described. Diverse alternative synthetic approaches were developed for the preparation of these natural products. They were prepared through an etherification reaction of the key furan precursor 5-(hydroxymethyl)-2-furaldehyde (HMF), which can be readily obtained from D-fructose, D-glucose, or sucrose, with the corresponding alcohols. 5-{[(4-Hydroxybenzyl)oxy]methyl}-2-furaldehyde was not only obtained in a two-step methodology but also by a biomimetic single-step synthesis. Similarly, pichiafuran C was prepared by three different syntheses, each one by a two-step procedure, also including a biomimetic approach.

Key words: 5-{[(4-hydroxybenzyl)oxy]methyl}-2-furaldehyde, pichiafuran C, 5-(hydroxymethyl)-2-furaldehyde, *Gastrodia elata* Blume, *Pichia membranifaciens*

The naturally occurring furan compound, 5-{[(4-hydroxybenzyl)oxy]methyl}-2-furaldehyde (**1**) (Figure 1), was recently isolated from the rhizome of *Gastrodia elata* Blume (Orchidaceae), and exhibited weak cytotoxicity against the HT-29 cell line.[1] This rhizome has been traditionally used in Korean and Chinese traditional medicine for the treatment of headaches, migraines, dizziness, epilepsy, and infantile convulsion tetanus,[2] and has many biomedical properties such as enhancing strength and virility, improving circulation, and facilitating memory consolidation and retrieval.[3]



1 2

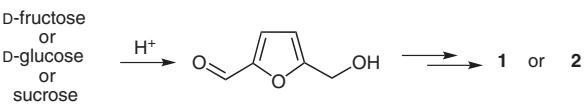
Figure 1 5-{[(4-Hydroxybenzyl)oxy]methyl}-2-furaldehyde (**1**) and pichiafuran C (**2**)

Pichiafuran C (**2**) (Figure 1) is a rare example of a monofuran metabolite that was recently isolated from the yeast *Pichia membranifaciens*, derived from the marine sponge *Petrosia* sp.[4] Sumiki's acid and its acetyl derivative, two natural furan derivatives structurally related to **2**, were isolated from the fungus *Cladosporium herbarum*, which is in turn extracted from the marine sponge *Callyspongia aerizusa*. These two furan derivatives exhibit antimicrobial activity against *Bacillus subtilis* and *Staphylococcus aureus*.[5] Triketides such as dimethyl β-ketoadipate and the monomethyl ester of the *cis*,*cis*-muconic acid, which were isolated from the marine sponge *Plakortis simplex*, seem to be the bioprecursors of the C_6 monofuran moiety of **2** and pichiafurans A and B.[4,6]

The potential pharmacological profile of these compounds, and the interest in continuing with our research program of carrying out the transformation of biomass products into furan fine chemicals, as well as the total synthesis of naturally occurring furan derivatives,[7] prompted us to synthesize compounds **1** and **2** through diverse approaches involving mono- and disaccharides as the starting materials.

5-(Hydroxymethyl)-2-furaldehyde (**3**, HMF) is considered to be one of the key products in the transformation of biomass towards the production of biofuels and fine chemicals for the post-oil era of the near future.[8] Therefore, an intense effort has been made for its preparation from diverse biomass sources.[9] Among other procedures,[10] this seminal compound can be obtained by acid treatment of mono-, di-, and polysaccharides.[11] Due to its strategic significance for the energetic future of the industrial world, as well as its easy preparation and synthetic potential, **3** was chosen as the precursor in the synthesis design of the natural products **1** and **2** (Scheme 1). We have used it before in the synthesis of some other natural furan compounds.[7] Inspired by a previous report,[12] **3** was prepared by a H_2SO_4-catalyzed transformation of D-fructose (**4a**), albeit in a modest yield (68%).

Optimization of the preparation of **3** gave rise to five related methods, differing in the starting saccharide and the heating source (Table 1): (a) following the same proce-



3

Scheme 1

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dure as reported with D-fructose (**4a**) as the starting material,[7] but increasing the temperature to 115 °C, the yield was improved up to 80%; (b) using method **a** but taking D-glucose (**4b**) as the starting material, **3** was obtained in 70% yield; (c) using method **a** but taking sucrose (**4c**) as the starting material, **3** was obtained in 70% yield;[13] (d) conducting microwave (MW) irradiation of a mixture of **4a** and H_2SO_4 (10 mol%) at 125 °C for 15 minutes afforded **3** in 36%; (e) using method **d** but taking **4c** as the starting material, **3** was obtained in 35–64% yield. The yields of the latter method varied depending on the quality of the chosen sugar, with muscovado sugar resulting in the best yield, probably due to the fact that the content of water is higher, since the produced tarry material was lower (Table 1, entries 5–7). In these assays, a side-product was also isolated that corresponded to the key fine chemical and widely industrial used compound 2,5-bisformylfuran (**5**).[12] The latter is probably formed by oxidation of **3**.[14] Although the yields were lower when MW irradiation was applied, several advantages can be taken into account, such as an almost solvent-free procedure (the amount of DMSO used was just enough to moisten the sugar), short reaction times, and the low prices of the unrefined commercial sugars.

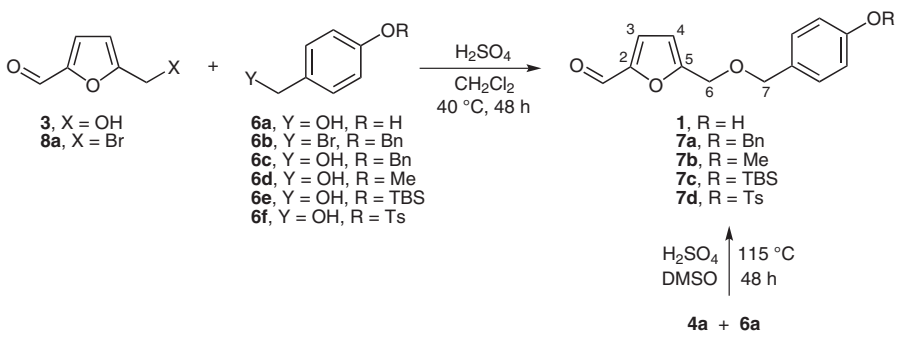
Table 1 Methods for the Preparation of **3**[a]

Entry	Saccharide	Solvent	MW (W)[b]	Temp (°C)	Time (h)	Yield **3/5** (%)[c]
1	**4a**	DMSO	–	115	48	**3** (80)
2	**4b**	DMSO	–	115	48	**3** (70)
3	**4c**[d]	DMSO	–	115	48	**3** (70)
4	**4a**	DMSO	180	125	0.25	**3** (42)
5	**4c**[d]	DMSO	180	125	0.25	**3** (32)/**5** (14)[e]
6	**4c**[f]	DMSO	180	125	0.25	**3** (34)/**5** (10)[e]
7	**4c**[g]	DMSO	180	125	0.25	**3** (64)/**5** (3)[e]

[a] Reaction conditions: **4** (1 equiv), H_2SO_4 (10 mol%).
[b] Pressure of the vessel: 100 psi.
[c] After purification by column chromatography.
[d] As refined sugar.
[e] Calculated per mole of the fructose moiety of sucrose (see ref. 13).
[f] As standard brown sugar.
[g] As muscovado sugar.

The synthesis of natural furan compound **1** was designed through several approaches, which differ in the use of the protected or the unprotected 4-(hydroxymethyl)phenols **6a–f**. Although the most common method to prepare ethers is through the Williamson reaction between an alcohol and an alkyl halide under basic conditions, all attempts failed to achieve the reaction by starting from 1-(benzyloxy)-4-(bromomethyl)benzene (**6b**) and alcohol **3**, either when using potassium or cesium carbonates or sodium hydride as the base (Scheme 2). With the former bases the reaction did not take place, and with the latter the aldehyde group of **3** was reduced. Also the reaction failed when the etherification was carried out between 5-(bromomethyl)-2-furaldehyde (**8a**) and alcohol **6c** under similar conditions, due to the decomposition of the former. Therefore, we investigated the formation of the ether functionality by an acid-catalyzed dehydration reaction between the two alcohols. The direct reaction between alcohol **3** and the unprotected phenol **6a**, under Brønsted acid catalysis (H_2SO_4) and a polar solvent (DMF), furnished only the symmetrical ether from **6a**, instead of the mixed ether. In contrast, when the benzyl protected alcohol **6c** was used in dichloromethane as the solvent, the expected ether **7a** was obtained in high yield (82%). However, the deprotection of the benzyl group by hydrogenolysis led to the cleavage of all benzylic bonds, resulting in the formation of a mixture of alcohols **3**, **6a**, and **6c**, along with other by-products. In order to avoid this undesired effect, we used the methyl protected derivative **6d**, to attain the wanted ether **7b** in good yield (76%) (Scheme 2). Although it is well known that sodium ethanethiolate is a deprotection reagent under basic conditions and is rather selective for the cleavage of aryl methyl ethers,[15] in the case of **7b**, the reaction took place cleaving also the remaining benzylic positions of the molecule.

Owing to the previous unsuccessful attempts of deprotection of **7a** and **7b**, derivatives **6e** and **6f** were prepared, which were protected with the more labile silyl and tosyl groups, respectively. Then, the reaction of 1.2 mol equivalents of these analogues with **3**, in the presence of a catalytic amount of sulfuric acid, led not to the formation of the corresponding ethers **7c** and **7d**, but to the desired natural product **1** in modest yields, with large amounts of starting alcohol **3** and unprotected alcohol **6a** remaining. Since these results indicated that the starting material **6e**



Scheme 2

or **6f**, and the resulting ether **7c** or **7d**, respectively, underwent deprotection during the acid-catalyzed reaction, an excess (2 mol equiv) of the former was used. Thus, natural product **1** was efficiently obtained in 81% and 70% yields from **6e** and **6f**, respectively, in just two steps starting from the carbohydrates.

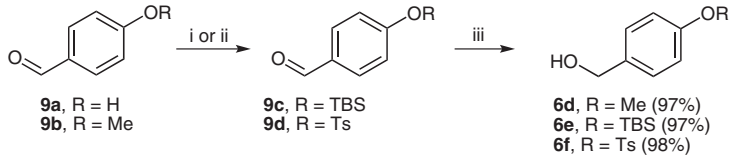
The protected alcohol **6c** was prepared in high yield (93%) by direct reaction between the phenolic alcohol **6a** and BnBr with NaH as the base. By treatment of the former with PBr_3, the benzylic bromide **6b** was obtained in almost quantitative yield (97%). The methyl protected alcohol **6d** was obtained in identical high yield by reduction of the formyl group of commercially available 4-methoxybenzaldehyde (**9b**) with sodium borohydride in wet silica gel.[16] In the case of protected benzylic alcohols **6e** and **6f**, their preparation included protection of 4-hydroxybenzaldehyde (**9a**) with *tert*-butyldimethylsilyl chloride and *p*-TsCl, respectively, followed by reduction of the aldehyde under analogous conditions as for **6d** (Scheme 3). This procedure provided **6e** and **6f** in 93% and 83% overall yield, respectively.

Considering that natural product **1** was isolated from *Gastrodia elata* along with alcohols **3** and **6a**,[1,17] it is likely that **1** is biosynthetically generated from the latter alcohols. Although **1** was unavailable by direct etherification of these alcohols, the procedure that we carried out in a single step by the use of protected derivatives **6e** and **6f** can be considered as a formal biomimetic synthesis of **1**. Moreover, we investigated the development of an alternative biomimetic synthesis of **1**, which may entail a cascade process starting from the originally occurring conversion of a saccharide into the furan intermediate (probably in situ formation of **3**), and subsequent reaction with alcohol **6a**, to give **1** in just one step. Consequently, a mixture of D-fructose (**4a**) and **6a** was treated with a catalytic amount of concentrated sulfuric acid in DMSO and heated at 115 °C for 48 hours to afford the expected product **1** (Scheme 2). Even though a low yield was found (30%), this result would support the idea that the furan product **1** may be eventually formed in nature by combination of analogous starting materials, of course not under our conditions but by an enzymatic pathway.

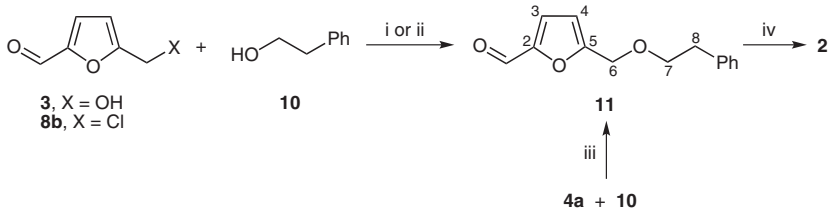
Since pichiafuran (**2**) also possesses an ether functional group, we designed several synthetic approaches taking advantage of the acquired knowledge in the case of **1**. However, in contrast with the latter case, the sulfuric acid catalyzed etherification reaction between alcohols **3** and 2-phenylethanol (**10**) yielded a complex mixture of products, a situation which could be overcome by using catalytic $Yb(OTf)_3$ as the Lewis acid[18] in acetonitrile to give furfural ether **11** in 88% yield (Scheme 4). The carbonyl group of the latter was reduced by treatment with sodium borohydride embedded in silica gel with methanol, providing the desired natural product **2** in high yield (95%), and in 84% overall yield by two steps.

Unlike the Williamson reaction between the bromo derivative **8a** and alcohol **6c**, which failed to produce the ether compound **7a**, the cesium carbonate promoted reaction between the chloro derivative **8b** and alcohol **10** led to **11**, albeit in a modest yield (Scheme 4). Interestingly, thermally treating (75 °C) D-fructose (**4a**) in the presence of $HCl/MgCl_2 \cdot H_2O$ directly gave **8b** in 88% yield.[19]

Pursuing a shorter approach to the synthesis of pichiafuran C (**2**), probably also biomimetic, D-fructose (**4a**) and **10** were used as starting materials (Scheme 4). By treating this mixture with H_2SO_4 in DMSO, and heating it to 125 °C for 15 minutes by MW irradiation (180 W), compound **11** was obtained. Because of the presence of an excess of **10** in the reaction mixture, the purification of **11** by column chromatography was inefficient. Then, the enriched chromatographic fractions with **11** were submitted to the next reduction process without further purification. Thus, the treatment of the partially separated residue of **11** with an excess of sodium borohydride embedded in silica gel[16] with methanol provided, after purification of the crude by a more efficient column chromatography, the desired natural product **2** in 30% overall yield by a two-step process starting from the monosaccharide.



Scheme 3 *Reagents and conditions*: i) TBDMS, imidazole, 20 °C, 12 h, 96% of **9c**; ii) *p*-TsCl, Et_3N, CH_2Cl_2, r.t., 7 h, 85% of **9d**; iii) $NaBH_4$, MeOH, SiO_2/H_2O, CH_2Cl_2, r.t., 30 min.



Scheme 4 *Reagents and conditions*: i) **3**, $Yb(OTf)_3$, MeCN, 80 °C, 5 h, 88% of **11**; ii) **8b**, Cs_2CO_3, THF, r.t., 24 h, 58% of **11**; iii) H_2SO_4, MW (180 W), 125 °C, 15 min; iv) $NaBH_4$, MeOH, SiO_2, CH_2Cl_2, r.t., 30 min, 95% of **2**.

Spectral data of the final products were in agreement with those reported for the natural compounds.[1,4] 2D NMR experiments (HMQC and HMBC) were performed to assign the signals of the ^1H and ^{13}C NMR spectra of **1** and **2**, and of their synthetic precursors (see experimental section).

In summary, we have described the first total syntheses of natural products **1** and **2** through diverse routes. Most of these involved the previous preparation of the furan precursor **3** and subsequent transformation to the desired natural products by formation of the key ether functional group in a formal biomimetic total synthesis. Moreover, when looking for a shorter and also a biomimetic approach, the synthesis of these molecules was also accomplished by direct conversion of the monosaccharide **4a** in the presence of the corresponding alcohols **6a** and **10**, by acid-catalyzed etherification promoted by thermal or MW irradiation.

Melting points (uncorrected) were determined with an Electrothermal capillary melting point apparatus. IR spectra were recorded on a Perkin-Elmer 2000 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury (300 MHz) or a Varian VNMR (500 MHz) instrument, with $CDCl_3$ as the solvent and TMS as internal standard. Mass spectra (MS) were taken, in electron impact mode (70 eV), on a Thermo-Finnigan Polaris Q spectrometer. High-resolution mass spectra (HRMS), in electron impact and FAB^+ modes, were obtained on Jeol JSM-GCMateII and Jeol JMS-SX 102 spectrometers, respectively. Microwave (MW) irradiation was performed on SEV/MIC-1 (Mexico)[20] and CEM MW reactors. Analytical TLC was carried out using E. Merck silica gel 60 F_{254} coated 0.25 plates, visualized by a long and short wavelength UV lamp. Flash column chromatography was performed over Natland International Co. silica gel (230–400 mesh). All air moisture sensitive reactions were carried out under N_2 using oven-dried glassware. THF was freshly distilled over Na; DMF, CH_2Cl_2, and EtOAc were distilled over CaH_2, prior to use. DMSO and acetone were dried by distillation after treatment with 4Å molecular sieves. Et_3N was freshly distilled from NaOH. All other reagents were used without further purification. Concd H_2SO_4 used was 98% and concd HCl 35%.

5-(Hydroxymethyl)-2-furaldehyde (3)

Method A: A solution of **4a** (1.0 g, 5.55 mmol) in DMSO (5 mL) and concd H_2SO_4 (0.055 g, 0.56 mmol) contained in a flask fitted with a Dean–Stark trap and condenser was stirred at 20 °C for 30 min, then heated to 115 °C for 48 h. The mixture was diluted with EtOAc (20 mL), stirred at 20 °C for 20 min, filtered over Celite, and the solvent was removed under high vacuum. The residue was purified by column chromatography over silica gel (30 g, hexane–EtOAc, 7:3) to give **3** (0.56 g, 80%).

Method B: Following Method A, with **4b** (1.0 g, 5.6 mmol) in DMSO (5 mL) and concd H_2SO_4 (0.055 g, 0.56 mmol), to give **3** (0.49 g, 70%).

Method C: Following Method A, with **4c** (refined sugar) (1.0 g, 2.92 mmol) in DMSO (5 mL) and concd H_2SO_4 (0.028 g, 0.286 mmol), to give **3** (0.26 g, 70%).

Method D: A suspension of **4a** (1.0 g, 5.6 mmol) in DMSO (1 mL) and concd H_2SO_4 (0.055 g, 0.56 mmol) was subjected to microwave irradiation (180 W) at 125 °C for 15 min. The mixture was diluted with CH_2Cl_2 (10 mL) and filtered through a short column chromatography over silica gel (10 g, CH_2Cl_2). The residue was purified by column chromatography over silica gel (20 g, hexane–EtOAc, 7:3) to give **3** (0.29 g, 42%).

Method E: Following Method D, with **4c** (muscovado sugar) (1.0 g, 2.92 mmol) in DMSO (1 mL) and concd H_2SO_4 (0.028 g, 0.286 mmol), to give **3** (0.26 g, 64%) as a pale yellow oil.[7a]

[4-(Benzyloxy)phenyl]methanol (6c)

To a solution of **6a** (1.0 g, 8.06 mmol) in anhyd DMF (22 mL) at 0 °C and under N_2 was added NaH (0.35 g, 8.0 mmol). At r.t., BnBr (1.37 g, 8.01 mmol) was added, and the mixture was stirred for 6 h. The solvent was removed under vacuum, the residue dissolved in CH_2Cl_2 (30 mL), and washed with H_2O (2 × 30 mL). The combined organic layers were dried (Na_2SO_4), filtered, the solvent removed under vacuum, and the residue was purified by column chromatography (silica gel, 30 g, hexane–EtOAc, 7:3) to give **6c** (1.6 g, 93%) as a white solid; R_f = 0.26 (hexane–EtOAc, 7:3); mp 85–86.5 °C (hexane–EtOAc, 8:2) (Lit.[21] mp 84.5–85 °C).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.89 (br s, 1 H, OH), 4.58 (s, 2 H, CH_2OH), 5.05 (s, 2 H, CH_2OPh), 6.92–6.98 (m, 2 H, ArH), 7.24–7.31 (m, 2 H, ArH), 7.31–7.45 (m, 5 H, PhH).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 64.8 (CH_2OH), 69.9 (CH_2OPh), 114.8 (ArH), 127.4 (PhH), 127.9 (PhH), 128.5 (ArH), 128.6 (PhH), 133.3 (Ar), 136.8 (Ph), 158.2 (Ar).

1-(Benzyloxy)-4-(bromomethyl)benzene (6b)

To a solution of **6c** (0.20 g, 1.03 mmol) in anhyd CH_2Cl_2 (5 mL) at 0 °C and under N_2 was added dropwise PBr_3 (0.28 g, 1.03 mmol) in anhyd CH_2Cl_2 (5 mL). After stirring at the same temperature and in the dark for 2 h, the mixture was warmed to r.t., stirred for 1 h, poured into ice, and extracted with Et_2O (2 × 10 mL). The combined organic layers were dried (Na_2SO_4), and the solvent removed under vacuum to give 0.25 g (97%) of **6b** as a dark solid, which rapidly decomposed when exposed to light; R_f = 0.75 (hexane–EtOAc, 8:2); mp 85–85.5 °C (cold hexane–Et_2O, 9:1) (Lit.[21]mp 85–86 °C).

^1H NMR (300 MHz, $CDCl_3$): δ = 4.50 (s, 2 H, CH_2Br), 5.05 (s, 2 H, CH_2OPh), 6.90–6.96 (m, 2 H, ArH), 7.28–7.45 (m, 7 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.9 (CH_2Br), 70.0 (CH_2OPh), 115.1 (C-3), 127.4 (ArH), 128.0 (ArH), 128.6 (C-2), 130.2 (ArH), 130.4 (C-1), 136.7 (Ar), 158.8 (C-4).

4-(*tert*-Butyldimethylsilyloxy)benzaldehyde (9c)

To a solution of **9a** (0.25 g, 2.05 mmol) in anhyd CH_2Cl_2 (5 mL) at 0 °C were added *tert*-butyldimethylsilyl chloride (0.25 g, 1.66 mmol) and imidazole (0.25 g, 3.68 mmol), and the mixture was stirred at r.t. overnight. H_2O (5 mL) was added and the mixture extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried (Na_2SO_4), and the solvent removed under vacuum to give **9c** (0.46 g, 96%) as a pale yellow oil, which was used without further purification;[22] R_f = 0.80 (hexane–EtOAc, 8:2).

[4-(*tert*-Butyldimethylsilyloxy)phenyl]methanol (6e)

To a suspension of **9c** (0.5 g, 2.1 mmol) in anhyd CH_2Cl_2 (5 mL) and silica gel (0.64 g, 10.7 mmol) at 0 °C was added $NaBH_4$ (0.08 g, 2.1 mmol) and the mixture was stirred for 5 min. MeOH (1 mL) was added and the mixture stirred at r.t. for 30 min, then filtered by column chromatography over silica gel (5 g, CH_2Cl_2) to give **6e** (0.49 g, 97%) as a colorless oil,[23] which was used without further purification; R_f = 0.40 (hexane–EtOAc, 8:2).

4-(Formyl)phenyl 4-Methylbenzenesulfonate (9d)

To a mixture of **9a** (1.0 g, 8.2 mmol) in anhyd CH_2Cl_2 (50 mL) and Et_3N (0.84 g, 8.3 mmol) at 0 °C and under N_2 was added dropwise a solution of *p*-TsCl (2.7 g, 14.2 mmol) in CH_2Cl_2 (30 mL), and the mixture was stirred at r.t. for 7 h. The mixture was washed with H_2O (2 × 50 mL), the combined organic layers were dried (Na_2SO_4), and the solvent removed under vacuum to give **9d** (1.92 g, 85%) as a pale purple solid; mp 72–74 °C (hexane) (Lit.[24b] mp 72–73 °C); R_f = 0.40 (hexane–EtOAc, 7:3).

IR (film): 1703, 1597, 1497, 1374, 1297, 1200, 1173, 1150, 1092, 864, 709 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.46 (s, 3 H, ArCH_3), 7.16–7.22 (m, 2 H, ArH), 7.26–7.38 (m, 2 H, ArH), 7.66–7.74 (m, 2 H, ArH), 7.80–7.88 (m, 2 H, ArH), 9.98 (s, 1 H, CHO).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.8 (ArCH_3), 123.1 (ArH), 128.4 (ArH), 129.9 (ArH), 131.3 (ArH), 131.8 (Ar), 134.7 (Ar), 145.9 (Ar), 153.8 (Ar), 190.7 (CHO).

MS: *m/z* (%) = 276 ([M]$^+$, 14), 155 (93), 91 (100), 65 (32).

4-(Hydroxymethyl)phenyl 4-Methylbenzenesulfonate (6f)

Following the procedure for **6e**, a mixture of **9d** (5.0 g, 1.81 mmol), silica gel (1.1 g, 18.3 mmol), and $NaBH_4$ (0.07 g, 1.84 mmol) in anyhd CH_2Cl_2 (5 mL) gave, after purification of the crude by column chromatography over silica gel (15 g, hexane–EtOAc, 7:3), **6f** (0.49 g, 98%) as a brown yellow oil;[24c] R_f = 0.20 (hexane–EtOAc, 7:3).

IR (film): 3367, 1597, 1503, 1369, 1197, 1174, 1151, 1092, 1015, 866, 814 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.20 (br s, 1 H, OH), 2.44 (s, 3 H, ArCH_3), 4.62 (s, 2 H, CH_2OH), 6.92–6.96 (m, 2 H, ArH), 7.23–7.27 (m, 2 H, ArH), 7.28–7.32 (m, 2 H, ArH), 7.66–7.70 (m, 2 H, ArH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.6 (ArCH_3), 64.2 (CH_2OH), 122.3 (ArH), 127.9 (ArH), 128.4 (ArH), 129.7 (ArH), 132.2 (Ar), 139.8 (Ar), 145.4 (Ar), 148.8 (Ar).

MS: *m/z* (%) = 278 ([M]$^+$, 47), 261 (11), 249 (5), 155 (51), 123 (37), 107 (53), 91 (100), 77 (13), 65 (33).

(4-Methoxyphenyl)methanol (6d)

Following the procedure for **6f**, a mixture of **9b** (0.50 g, 3.68 mmol), silica gel (2.2 g, 36.7 mmol), and $NaBH_4$ (0.14 g, 3.68 mmol) in anhyd CH_2Cl_2 (5 mL) gave, after purification of the crude by column chromatography over silica gel (15 g, hexane–EtOAc, 7:3), **6d** (0.49 g, 97%) as a colorless oil;[25] R_f = 0.44 (hexane–EtOAc, 7:3).

IR (CH_2Cl_2): 3365, 2058, 1996, 1885, 1770, 1612, 1586, 1513, 1462, 1442, 1421, 1369, 1301, 1247, 1175, 1110, 1033, 933, 817, 753, 708, 637, 572, 515 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.73 (s, 3 H, CH_3O), 4.48 (s, 2 H, CH_2OH), 6.78–6.85 (m, 2 H, H-3), 7.15–7.24 (m, 2 H, H-2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 55.0 (CH_3O), 64.2 (CH_2OH), 113.6 (C-3), 128.4 (C-2), 133.0 (C-1), 158.7 (C-4).

MS: *m/z* (%) = 138 ([M]$^+$, 36), 122 (9), 121 (100), 109 (7), 91 (4), 77 (4).

5-({[(4-Benzyloxy)benzyl]oxy}methyl)-2-furaldehyde (7a)

To a mixture of **6c** (0.20 g, 0.93 mmol) and **3** (0.12 g, 0.95 mmol) in anhyd CH_2Cl_2 (15 mL) at 20 °C and under N_2 was added concd H_2SO_4 (0.01 g, 0.10 mmol) in anhyd CH_2Cl_2 (5 mL). The mixture was stirred at 40 °C for 48 h, washed with H_2O (2 × 10 mL), and the organic layer was dried (Na_2SO_4). The solvent was removed under vacuum, and the residue purified by column chromatography (silica gel, 10 g, hexane–EtOAc, 9:1) to give **7a** (0.38 g, 82%) as a pale yellow oil; R_f = 0.44 (hexane–EtOAc, 7:3).

IR (CH_2Cl_2): 2929, 1697, 1610, 1511, 1454, 1361, 1242, 1173, 1078, 1021, 816, 738, 697 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.53 (s, 2 H, H-6), 4.54 (s, 2 H, H-7), 5.06 (s, 2 H, CH_2OPh), 6.51 (d, *J* = 3.6 Hz, 1 H, H-4), 6.90–7.02 (m, 2 H, ArH), 7.20 (d, *J* = 3.6 Hz, 1 H, H-3), 7.22–7.46 (m, 7 H, ArH), 9.61 (s, 1 H, CHO).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 63.7 (C-6), 69.9 (CH_2OPh), 72.5 (C-7), 111.2 (C-4), 114.8 (ArH), 122.2 (C-3), 127.4 (PhH), 127.9 (PhH), 128.6 (PhH), 129.4 (Ar), 129.6 (ArH), 136.8 (Ar), 152.5 (C-2), 158.4 (C-5), 158.6 (Ar), 177.7 (CHO).

HRMS (EI): *m/z* [M + H]$^+$ calcd for $C_{20}H_{18}O_4$: 323.1283; found: 323.1278.

5-{[(4-Methoxybenzyl)oxy]methyl}-2-furaldehyde (7b)

Following the procedure for **7a**, a mixture of **6d** (0.25 g, 1.81 mmol), **3** (0.23 g, 1.83 mmol), and concd H_2SO_4 (0.02 g, 0.20 mmol) in anhyd CH_2Cl_2 (10 mL) gave, after purification of the crude by column chromatography (silica gel, 10 g, hexane–EtOAc, 9:1), **7b** (0.34 g, 76%) as a pale yellow oil; R_f = 0.67 (hexane–EtOAc, 7:3).

IR (film): 1677, 1611, 1512, 1246, 1174, 1070, 1030, 815, 754 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.77 (s, 3 H, CH_3O), 4.51 (s, 2 H, H-6), 4.52 (s, 2 H, H-7), 6.51 (d, *J* = 3.6 Hz, 1 H, H-4), 6.82–6.91 (m, 2 H, ArH), 7.20 (d, *J* = 3.6 Hz, 1 H, H-3), 7.22–7.30 (m, 2 H, ArH), 9.57 (s, 1 H, CHO).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 54.9 (CH_3O), 63.4 (C-6), 72.2 (C-7), 111.1 (C-4), 113.6 (ArH), 122.0 (C-3), 129.0 (Ar), 129.3 (ArH), 152.2 (C-2), 158.2 (C-5), 159.1 (Ar), 177.4 (CHO).

HRMS (EI): *m/z* [M + H]$^+$ calcd for $C_{14}H_{15}O_4$: 247.0970; found: 247.0970.

5-{[(4-Hydroxybenzyl)oxy]methyl}-2-furaldehyde (1)

Method A: To a mixture of **3** (0.25 g, 1.98 mmol) and **6e** (0.47 g, 1.97 mmol) in CH_2Cl_2 (15 mL) at 20 °C and under N_2 was added concd H_2SO_4 (0.02 g, 0.20 mmol) in anhyd CH_2Cl_2 (5 mL). The mixture was stirred at 40 °C for 24 h. Then, an additional amount of **6e** (0.47 g, 1.97 mmol) in CH_2Cl_2 (5 mL) was added, and the mixture was again stirred at 40 °C for 24 h. The mixture was washed with H_2O (2 × 10 mL), the organic layer dried (Na_2SO_4), the solvent removed under vacuum, and the residue was purified by column chromatography (silica gel, 10 g, hexane–EtOAc 95:5) to give **1** (0.37 g, 81%) as a pale yellow solid.

Method B: Following Method A, to a mixture of **3** (0.25 g, 1.98 mmol) and **6f** (0.55 g, 1.98 mmol) was added concd H_2SO_4 (0.02 g, 0.20 mmol) in anhyd CH_2Cl_2 (20 mL). After adding the second portion of **6f** (0.55 g, 1.98 mmol), the mixture was stirred at 40 °C for 48 h to give **1** (0.32 g, 70%) as a pale yellow solid.

Method C: In a flask fitted with a Dean–Stark trap and condenser, a mixture of **4a** (1.0 g, 5.56 mmol) and concd H_2SO_4 (0.055 g, 0.56 mmol) in DMSO (5 mL) was stirred at 20 °C for 30 min; then **6a** (0.55 g, 4.44 mmol) was added and the mixture was stirred at 115 °C for 48 h. The mixture was diluted with EtOAc (20 mL), stirred at 20 °C for 20 min, and filtered over Celite. The solvent was removed under vacuum and the residue purified by column chromatography (silica gel, 30 g, hexane–EtOAc, 7:3) to give **1** (0.30 g, 30%) as a pale yellow solid;[1] mp 84–85 °C; R_f = 0.22 (hexane–EtOAc, 7:3).

IR (KBr): 3341, 3108, 2933, 1677, 1610, 1517, 1439, 1401, 1371, 1264, 1199, 1050, 1033, 949, 839, 819, 794 cm^{-1}.

^1H NMR (500 MHz, CD_3OD): δ = 4.47 (s, 2 H, H-7), 4.53 (s, 2 H, H-6), 6.61 (d, *J* = 3.5 Hz, 1 H, H-4), 6.73–6.78 (m, 2 H, ArH), 7.14–7.19 (m, 2 H, ArH), 7.36 (d, *J* = 3.5 Hz, 1 H, H-3), 9.54 (s, CHO),

^{13}C NMR (125 MHz, CD_3OD): δ = 64.5 (C-6), 73.6 (C-7), 112.7 (C-4), 116.2 (C-3′), 124.4 (C-3), 129.7 (C-1′), 131.0 (C-2′), 154.2 (C-2), 158.6 (C-4′), 160.3 (C-5), 179.6 (CHO).

HRMS (FAB): *m/z* [M]$^+$ calcd for $C_{13}H_{12}O_4$: 232.0736; found: 232.0732.

5-(Chloromethyl)-2-furaldehyde (8b)

Method A: A solution of **4b** (1.0 g, 5.55 mmol) in toluene (10 mL) contained in a flask fitted with a Dean-Stark trap and condenser was stirred at 0 °C. To this was added a 5% solution of $MgCl_2·6H_2O$ in concd HCl, and then the mixture was heated to 75 °C for 2.5 h. Sat. aq $NaHCO_3$ (20 mL) was added, the organic layer was separated, and dried (Na_2SO_4). The solvent was removed under vacuum and the residue was purified by column chromatography over silica gel (30 g, hexane–EtOAc, 95:5) to give **8b** (0.65 g, 81%) as a brown oil.

Method B: Compound **4a** (1.8 g, 0.1 mol) was mixed with toluene (15 mL), H_2O (0.22 mL), and $MgCl_2·6H_2O$ (2.04 g, 1.0 mol), and the mixture was heated to 75 °C for 30 min. Concd HCl (3.14 g) was added, and the mixture was heated to 75 °C for 1 h. The solid residue was filtered and washed with toluene (50 mL), and the organic layer was washed with brine (2 × 100 mL) and dried (Na_2SO_4). The solvent was removed under vacuum and the residue was purified by column chromatography over silica gel (30 g, CH_2Cl_2) to give **8b** (1.16 g, 88%) as a pale brown oil;[19a] R_f = 0.51 (hexane–EtOAc, 7:3).

IR (CH_2Cl_2): 1676, 1519, 1398, 1261, 1197, 1021, 970, 807, 771, 754, 721 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.45 (s, 2 H, CH_2Cl), 6.53 (d, *J* = 3.6 Hz, 1 H, H-4), 7.15 (d, *J* = 3.6 Hz, 1 H, H-3), 9.55 (s, CHO),

^{13}C NMR (125 MHz, $CDCl_3$): δ = 36.4 (CH_2Cl), 111.9 (C-4), 121.9 (C-3), 152.6 (C-2), 155.9 (C-5), 177.6 (CHO).

5-{[1-(2-Phenyl)ethoxy]methyl}-2-furaldehyde (11)

Method A: To a mixture of **3** (0.25 g, 1.98 mmol) and **10** (1.21 g, 9.92 mmol) in MeCN (2 mL) at 20 °C and under N_2 was added $Yb(OTf)_3$ (99.9%) (0.012 g, 0.02 mmol). The mixture was stirred at 80 °C for 5 h and filtered over Celite. The solvent was removed under vacuum, and the residue purified by column chromatography over silica gel (30 g, hexane–EtOAc, 99:1) to give **11** (0.4 g, 88%) as a pale yellow oil.

Method B: To a mixture of **8b** (0.236 g, 1.64 mmol) and **10** (0.2 g, 1.64 mmol) in anhyd THF (2 mL) at 20 °C and under N_2 was added Cs_2CO_3 (0.534 g, 1.64 mmol). The mixture was stirred at 20 °C for 24 h, filtered, and diluted with EtOAc (20 mL) and H_2O (10 mL). The aqueous layer was washed with EtOAc (2 × 10 mL), the combined organic layers dried (Na_2SO_4), and the solvent removed under vacuum. The residue purified by column chromatography over silica gel (10 g, hexane–EtOAc, 8:2) to give **11** (0.22 g, 58%) as a pale yellow oil;[26] R_f = 0.66 (hexane–EtOAc, 7:3).

IR (film): 1679, 1521, 1453, 1353, 1276, 1191, 1019, 808, 751, 699 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.92 (t, *J* = 7.0 Hz, 2 H, H-8), 3.74 (t, *J* = 7.0 Hz, 2 H, H-7), 4.54 (s, 2 H, H-6), 6.44 (d, *J* = 3.5 Hz, 1 H, H-4), 7.19 (d, *J* = 3.5 Hz, 1 H, H-3), 7.21–7.34 (m, 5 H, PhH), 9.60 (s, 1 H, CHO).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 36.2 (C-8), 65.1 (C-6), 71.6 (C-7), 111.0 (C-4), 121.9 (C-3), 126.3 (C-4′), 128.4 (C-2′), 128.9 (C-3′), 138.5 (C-1′), 152.5 (C-2), 158.5 (C-5), 177.7 (CHO).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{14}O_3$: 230.0943; found: 230.0947.

5-{[(Phenethoxy)methyl]furan-2-yl}methanol (Pichiafuran C, 2)

Method A: A mixture of **4a** (1.0 g, 5.56 mmol), concd H_2SO_4 (0.055 g, 0.56 mmol), and **10** (1.02 g, 8.36 mmol) was irradiated with MW (180 W) at 125 °C for 15 min. The mixture was diluted with CH_2Cl_2 (10 mL) and filtered by short column chromatography (silica gel, 10 g, CH_2Cl_2) to give a mixture of **10/11** (1:1) (0.90 g) as a pale yellow oil. This mixture was dissolved with CH_2Cl_2 (5 mL) and silica gel (1.0 g, 16.7 mmol), then $NaBH_4$ (0.074 g, 1.95 mmol) in CH_2Cl_2 (5 mL) was added at r.t. and under N_2. The mixture stirred at r.t. for 10 min and MeOH (1 mL) was added. The mixture was stirred at r.t. for 30 min, diluted with CH_2Cl_2 (20 mL), and stirred at r.t. for 20 min. The mixture was then filtered over Celite, the solvent removed under vacuum, and the residue purified by column chromatography (silica gel, 30 g, hexane–EtOAc, 99:1) to give **2** (0.39 g, 30%) as a pale yellow oil.

Method B: A suspension of **11** (0.45 g, 1.96 mmol), silica gel (1.0 g, 16.7 mmol), and $NaBH_4$ (0.074 g, 1.95 mmol) in CH_2Cl_2 (5 mL) was stirred at r.t. and under N_2. The mixture was stirred at r.t. for 10 min, then MeOH (1 mL) was added. The mixture was stirred at r.t. for 30 min, diluted with CH_2Cl_2 (20 mL), stirred at r.t. for 20 min, and then filtered over Celite. The solvent was removed under vacuum, and the residue purified by column chromatography (silica gel, 30 g, hexane–EtOAc, 99:1) to give **2** (0.43 g, 95%) as a pale yellow oil;[4] R_f = 0.29 (hexane–EtOAc, 7:3).

IR (film): 3391, 2924, 2855, 1731, 1454, 1376, 1274, 1082, 935, 822, 749, 700 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.91 (t, *J* = 7.3 Hz, 2 H, H-8), 3.69 (t, *J* = 7.3 Hz, 2 H, H-7), 4.44 (s, 2 H, H-6), 4.58 (br s, 2 H, C*H*$_2$OH), 6.24 (s, 2 H, H-3, H-4), 7.19–7.23 (m, 2 H, H-2′, H-4′), 7.26–7.31 (m, 2 H, H-3′).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 36.2 (C-8), 57.6 (CH_2OH), 64.9 (C-6), 71.2 (C-7), 108.4 (C-3), 110.0 (C-4), 126.2 (C-4′), 128.3 (C-2′), 128.9 (C-3′), 138.7 (C-1′), 151.8 (C-5), 154.3 (C-2).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{16}O_3$: 232.1099; found: 232.1100.

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References

(1) Lee, Y.-K.; Woo, M.-H.; Kim, C.-H.; Kim, Y.; Lee, S.-H.; Jeong, B.-S.; Chang, H.-W.; Son, J.-K. *Planta Med.* **2007**, *73*, 1287.

(2) (a) Hus, H. Y.; Chen, Y. P.; Hsu, S. J.; Hsu, C. S.; Chen, C. C.; Chang, H. C. *Oriental Materia Medica: A Concise Guide*; Oriental Health Art Institute: California, **1986**, 662. (b) Tang, W.; Eisenbrand, G. *Chinese Drugs of Plant Origin, Chemistry, Pharmacology, and Use in Traditional and Modern Medicine*; Springer Verlag: Berlin, **1992**, 545–548. (c) Hayashi, J.; Sekine, T.; Deguchi, S.; Lin, Q.; Horie, S.; Tsuchiya, S.; Yano, S.; Watanabe, K.; Ikegami, F. *Phytochemistry* **2002**, *59*, 513.

(3) (a) Hsieh, M.-T.; Wu, C.-R.; Chen, C.-F. *J. Ethnopharmacol.* **1997**, *56*, 45. (b) Wu, C.-R.; Hsieh, M. T.; Huang, S.-C.; Peng, W.-H.; Chang, Y.-S.; Chen, C.-F. *Planta Med.* **1996**, *62*, 317.

(4) Elbandy, M.; Shinde, P. B.; Dang, H. T.; Hong, J.; Bae, K. S.; Jung, J. H. *J. Nat. Prod.* **2008**, *71*, 869.

(5) Jadulco, R.; Proksch, P.; Wray, V.; Sudarsono; Berg, A.; Gräfe, U. *J. Nat. Prod.* **2001**, *64*, 527.

(6) Shen, Y.-C.; Prakash, C. V. S.; Kuo, Y.-H. *J. Nat. Prod.* **2001**, *64*, 324.

(7) (a) Quiroz-Florentino, H.; Aguilar, R.; Santoyo, B. M.; Díaz, F.; Tamariz, J. *Synthesis* **2008**, 1023. (b) Quiroz-Florentino, H.; García, A.; Burgueño-Tapia, E.; Tamariz, J. *Nat. Prod. Res.* **2009**, *23*, 1355.
(8) (a) Kamm, B. *Angew. Chem. Int. Ed.* **2007**, *46*, 5056. (b) Metzger, J. O. *Angew. Chem. Int. Ed.* **2006**, *45*, 696. (c) Kröger, M.; Prüße, U.; Vorlop, K.-D. *Top. Catal.* **2000**, *13*, 237. (d) Marshall, A.-L.; Alaimo, P. J. *Chem. Eur. J.* **2010**, *16*, 4970.
(9) (a) Mascal, M.; Nikitin, E. B. *Angew. Chem. Int. Ed.* **2008**, *47*, 7924. (b) Li, C.; Zhang, Z.; Zhao, Z. K. *Tetrahedron Lett.* **2009**, *50*, 5403.
(10) (a) Binder, J. B.; Raines, R. T. *J. Am. Chem. Soc.* **2009**, *131*, 1979. (b) Yoon, H.-J.; Choi, J.-W.; Cho, J. K.; Lee, Y.-S. *Appl. Chem.* **2010**, *14*, 41.
(11) (a) Román-Leshkov, Y.; Barrett, C. J.; Liu, Z. Y.; Dumesic, J. A. *Nature* **2007**, *447*, 982. (b) Zhao, H.; Holladay, J. E.; Brown, H.; Zhang, Z. C. *Science* **2007**, *316*, 1597. (c) Yong, G.; Zhang, Y.; Ying, J. Y. *Angew. Chem. Int. Ed.* **2008**, *47*, 9345.
(12) Halliday, G. A.; Young, R. J. Jr.; Grushin, V. V. *Org. Lett.* **2003**, *5*, 2003.
(13) Perez-Locas, C.; Yaylayan, V. A. *J. Agric. Food Chem.* **2008**, *56*, 6717.
(14) Lilga, M. A.; Hallen, R. T.; Gray, M. *Top. Catal.* **2010**, *53*, 1264.
(15) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley: New York, **1999**, 250–251.
(16) Zeynizadeh, B.; Behyar, T. *J. Braz. Chem. Soc.* **2005**, *16*, 1200.
(17) Pyo, M. K.; Jin, J. L.; Koo, Y. K.; Yun-Choi, H. S. *Arch. Pharm. Res.* **2004**, *27*, 381.
(18) Kawada, A.; Yasuda, K.; Abe, H.; Harayama, T. *Chem. Pharm. Bull.* **2002**, *50*, 380.
(19) (a) Hamada, K.; Yoshihara, H.; Suzukamo, G. *Chem. Lett.* **1982**, 617. (b) Chakraborty, T. K.; Tapadar, S.; Kumar, S. K. *Tetrahedron Lett.* **2002**, *43*, 1317. (c) Hamada, K.; Yoshihara, H.; Suzukamo, G. *J. Oleo Sci.* **2001**, *50*, 533.
(20) Web page: www.sevmexico.com.
(21) Brun, K. A.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **2002**, *85*, 3422.
(22) Faler, C. A.; Joullié, M. M. *Org. Lett.* **2007**, *9*, 1987.
(23) Kopka, K.; Faust, A.; Keul, P.; Wagner, S.; Breyholz, H.-J.; Höltke, C.; Schober, O.; Schäfers, M.; Levkau, B. *J. Med. Chem.* **2006**, *49*, 6704.
(24) (a) Collado, D.; Perez-Inestrosa, E.; Suau, R.; Lopez-Navarrete, J. T. *Tetrahedron* **2006**, *62*, 2927; and references cited therein. (b) Dale, W. J.; Hennis, H. E. *J. Am. Chem. Soc.* **1956**, *78*, 2543. (c) Levacher, V.; Moberg, C. *React. Polym.* **1995**, *24*, 183.
(25) Rahman, A.; Jonnalagadda, S. B. *J. Mol. Catal. A: Chem.* **2009**, *299*, 98.
(26) Papanov, G.; Malakov, P.; Tomova, K. *Nauchni Tr.-Plovdivski Univ. Paisii Khilendarski* **1990**, *28*, 65; *Chem. Abstr.* **1995**, *122,* 265153.