An Effective One-Pot Synthesis of 3-Benzylfurans and Their Potential Utility as Versatile Precursors of 3,4-Dibenzyltetrahydrofuran Lignans. Formal Synthesis of (±)-Burseran

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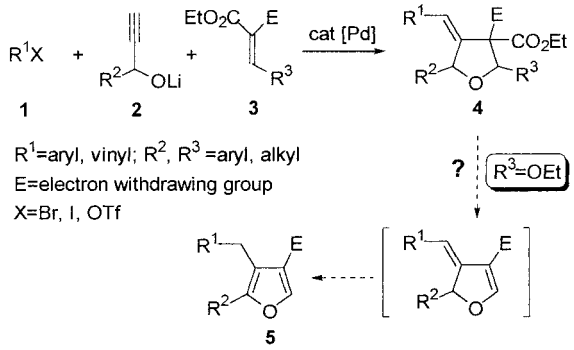
Introduction

Furans are widely diffused among natural substances which exhibit interesting biological activities.[1] Additionally, they can serve as building blocks in natural product synthesis as well as in heterocyclic chemistry.[2] For these reasons, new synthetic methods leading to this class of compounds are of considerable interest. With a view to efficiency, new procedures should be simple to carry out, use readily available starting marterials, and offer a flexible entry to polysubstituted molecules accommodating considerable functionalities.[3] For such purposes, multicomponent sequential reactions are at a premium because they create diversity and allow for the construction of complex molecules by combining several transformations without isolation of intermediates.[4]

As part of a program devoted to the development of new strategies for the synthesis of heterocyclic structures,[5] we recently reported a novel three-component reaction that permitted the preparation of highly functionalized 3-arylidene-(or alkenylidene-)tetrahydrofurans **4**. The proposed one-pot procedure proved very practical and versatile, involving commercially available or easily accessible starting materials. From a mechanistic point of view, the strategy was based on a domino reaction in which the enolate resulting from initial 1,4-addition of a propargylic alkoxide **2** to a conjugate acceptor **3** subsequently underwent a palladium-mediated cyclization involving an unsaturated halide (or triflate) **1** as a coupling partner.[6,7] The effectiveness of the methodology encouraged us to investigate a possible extension of this chemistry to the synthesis of 3-benzyl-(or allyl-)furans **5**. It was indeed hoped that substitution of the benzylidene (or alkylidene) malonates for their ethoxymethylene analogues (**3**, $R^3 = OEt$) as activated olefins would result in the formation of the corresponding 2-ethoxy-4-arylidene-tetrahydrofurans which we anticipated to be particularly prone to decarboxylative elimination. If so, the resulting 3-arylidene 2,3-dihydrofurans would then be expected to undergo isomerization to afford the desired aromatized compounds (Scheme 1).

Scheme 1



In this paper, we report the successful execution of this strategy and its use in the formal synthesis of the lignan antitumor agent, burseran.

Results and Discussion

Two-Step Synthesis: Preliminary Results and Scope. One of the problems that we expected to face when we started this study was a possible premature departure of the nucleofuge ethoxy group during the reversible initial 1,4-addition step which would have resulted in the formation of transetherification products, thereby consuming part of the propargyl alcohol. For initial evaluation of the approach, the commercially available diethyl ethoxymethylene malonate (**3a)** was subjected to our previously reported[6] reaction conditions. **3a** was thus reacted in THF:DMSO (2:1) with equimolar quantities of lithium propargyl alkoxide and phenyl iodide in the presence of a catalytic system issued from the reduction of $PdCl_2(PPh_3)_2$ with *n*-BuLi. Pleasingly, stirring the reaction mixture for 1 h at room temperature led to the exclusive formation of the expected 2-ethoxy-4-benzylidene tetrahydrofuran **4a** in 70% isolated yield. In line with previous synthetic studies reported by our laboratory,[8] it was then found that potassium *tert*-butoxide was highly effective for the decarboethoxylation of diester **4a**. Thus, treatment of the later with a slight excess of this reagent in THF at room temperature

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(3) The synthesis of furans has been recently reviewed: Hou, X. L.; Cheung, H. Y.; Hon, T. Y.; Kwan, P. L.; Lo, T. H.; Tong, S. Y.; Wong, H. N. C. *Tetrahedron* **1998**, *54*, 1955.

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(5) See: Marat, X.; Monteiro, N.; Balme, G. *Synlett* **1997**, 845. Clique, B.; Monteiro, N.; Balme, G. *Tetrahedron Lett.* **1999**, *40*, 1301. Woods, M.; Monteiro, N.; Balme, G. *Eur. J. Org. Chem.* **2000**, 1711. Monteiro, N.; Balme, G. *J. Org. Chem.* **2000**, *65*, 3223.

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(8) Monteiro, N.; Gore, J.; Balme, G. *Tetrahedron* **1992**, *48*, 10103. Monteiro, N.; Balme, G.; Gore, J. *Synlett* **1992**, 227.

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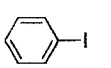
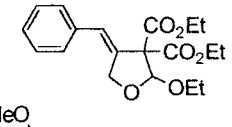
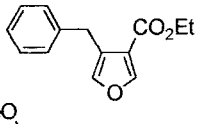
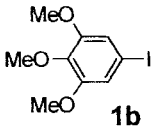
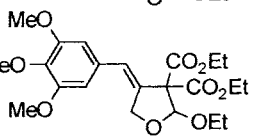
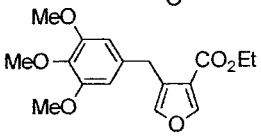
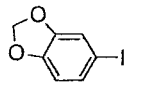
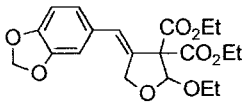
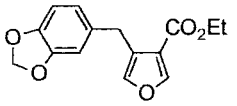
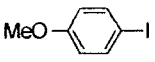
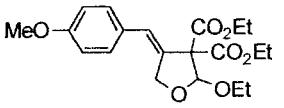
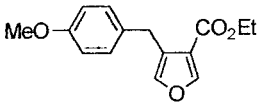
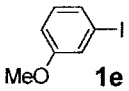
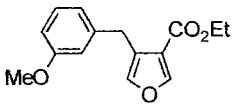
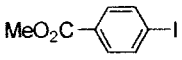
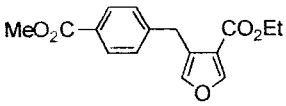
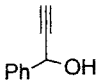
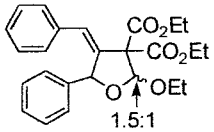
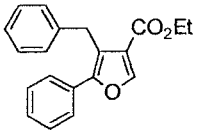
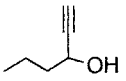
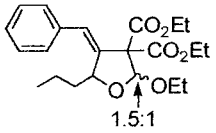
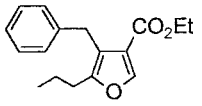
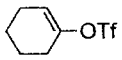
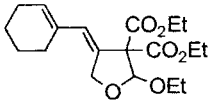
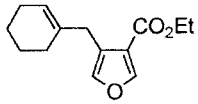
Table 1. Synthesis of 3-Benzylfurans: Stepwise versus One-Pot Procedure

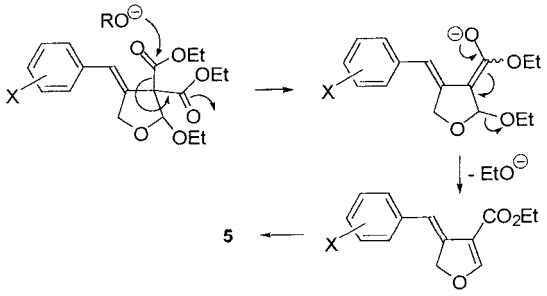
Entry	Halide (or triflate)	Propargyl alcohol	Three-component reaction[b] Product	Yield (%)	Decarboxylative elimination[c] Product	Yield (%)	One-pot procedure Yield (%)[d]
1	 **1a**	 **2a**		**4a** 70		**5a** 85	53 (60)
2	 **1b**	**2a**		**4b** 80		**5b** 78	56 (62)
3	 **1c**	**2a**		**4c** 61		**5c** 74	48 (45)
4	 **1d**	**2a**		**4d** 59		**5d** 75	42 (44)
5	 **1e**	**2a**		**5e** 58			
6	 **1f**	**2a**		**5f** 29[e]			
7	**1a**	 **2b**	 1.5:1	**4g** 58		**5g** 78	51 (45)
8	**1a**	 **2c**	 1.5:1	**4h** 82		**5h** 79	60 (65)
9		**2a**		**6** 63		**7** 79	53 (50)

[a] All reactions were performed at room temperature on a 1 mmol scale. [b] Equimolar amounts of the three partners were used. [c] The reactions were carried out in THF. [d] Yields in brackets refer to overall yields of the two reactions performed independently (stepwise procedure). [e] Not isolated as a pure compound. Contains small amounts of an unidentified product, presumably a 1,4-addition adduct of type $(RO)_2CHCH(CO_2Et)_2$.

afforded within 1 h the desired benzylfuran **5a** in 85% isolated yield.

Once the validity of our approach had been established, we sought to gauge the scope and limitations of this chemistry. In this regard, we have submitted **3a**, several propargylic alkoxides, and organic halides (or triflates) to the two-step protocol. The results are summarized in Table 1. As can be seen, the procedure proved very effective for the preparation of various 3-benzylfurans **5**. For this purpose, *aryl* halides were partners of choice in the three-component reaction (entries 1−8), whereas the corresponding triflates have been found essentially unreactive under identical conditions. On the other hand, *vinyl* triflates should prove useful as versatile starting materials for the preparation of 3-allylfurans as illustrated with the synthesis of the cyclohexenyl derivative **7** (entry 9). Interestingly, the use of potassium *tert*-butoxide was not always needed to induce the decarboxylative elimination. Indeed, in two of the cases that were examined, those involving *m*-methoxyphenyl iodide and *p*-methoxycarbonylphenyl iodide as the unsaturated halide partners, the three-component reaction spontaneously produced the decarboethoxylated aromatized heterocycles (entries 5, 6). In any of those cases could the tetrahydrofuran intermediate be isolated. Such a difference in reactivity is somewhat surprising. From a mechanistic point of view, the present decarboethoxylation presumably occurs via attack of one of the ester groups by the alkoxide[8,9] resulting in the generation of an γ-aryldienolate which then evolves through elimination of the nucleofuge ethoxy group (Scheme 2). Substituents on the aryl ring should therefore exert significant effect on the

Scheme 2

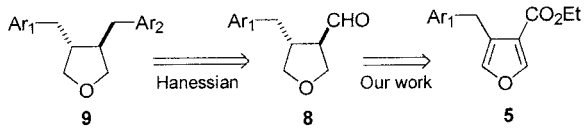


polarization of the carbon−carbon bond to be broken and, thereby, affect the reactivity of the tetrahydrofurans toward decarboethoxylation. It is expected that their stability will increase with the electron density of the aryl ring. According to this, the elimination reaction leading to **5e** should be greatly facilitated by the presence of the electron-withdrawing group at the *para* position. We may therefore suggest that propargyl alkoxide itself is nucleophilic enough to initiate the decarboethoxylative process which may then proceed by action of the continuously generated ethoxide anion. However, the case of **5f** remains unclear especially in view of the fact that **4b** involving more electron-donating substituents could be successfully isolated. Fairly subtle electronic effects seem to govern the outcome of these reactions.

Attempts were also made to involve another electron-deficient olefin that differed from **3a** in the nature of one of the electron-withdrawing groups, i.e., the commercially available ethyl (ethoxymethylene) cyanoacetate (**3b**). Unfortunately, when **3b** was reacted with lithium propargyl alkoxide and phenyl iodide under our standard conditions, complex mixtures were obtained from which we were unable to isolate the desired tetrahydrofuran.

One-Pot Procedure. The similarities between the optimized reaction conditions for both steps led us to next consider the possibility of integrating the stepwise chemical process into a general one-pot reaction for an expedient synthesis of the targeted compounds. The two steps would be conducted sequentially in the same reaction vessel without isolation of the intermediates. Since the use of DMSO as cosolvent could not be avoided in the first step,[7] we conducted a test experiment on tetrahydrofuran **4h** that showed that the decarboxylative elimination reaction was compatible with the presence of such a solvent, although a slightly lower yield (76% compared to 79%) was obtained.[10] The one-pot protocol was as follows: the reaction mixtures obtained by combining the three partners were treated with a solution of potassium *tert*-butoxide in THF once these had reacted (GC; 1−3 h), and stirring was continued until complete decarboxylation was observed (<1 h). As indicated in Table 1, we did not observe significant differences between yields obtained through the stepwise procedure and those obtained by using the one-pot protocol. Avoiding material loss during isolation and purification of the tetrahydrofuran intermediates probably just made up for the lower performance of the decarboxylative elimination that was anticipated in the new solvent system. Even so, the one-pot methodology may be preferred for economical and environmental reasons.

Scheme 3. Plan for the Synthesis of 3,4-Dibenzyltetrahydrofurans



Formal Synthesis of Burseran. In an effort to find a possible application of this methodology to natural product synthesis, we found that furans **5** were potential precursors of 3,4-dibenzyltetrahydrofuran lignans. These compounds have been recognized as important synthetic targets because of their widespread occurrence in nature and the interesting biological properties exhibited by some of them. In addition, 3,4-dibenzyltetrahydrofurans may also be transformed into bicyclic lignans of the phenyltetralin and dibenzocyclooctane series, thus emphasizing the importance of discovering new synthetic routes to this class of lignans.[11] In our plan (Scheme 3), we relied on previous work reported by Hanessian and co-workers which concerned the facile transformation of racemic 4-benzyltetrahydrofuran-3-carboxaldehydes **8** into various 3,4-dibenzyl tetrahydrofurans **9** by a three-step sequence that allowed the production of both the (−)- and (+)-enantiomers.[12] As a formal synthesis of 3,4-dibenzyltetrahydrofurans we envisioned the conversion of the 4-benzylfuran-3-carboxylates **5**, which we are now able to synthesize in a single-step procedure, into the corresponding 4-benzyltetrahydrofuran-3-carboxaldehydes by the following series of steps: reduction of the ester into the corresponding alcohol, hydrogenation, and oxidation.

To illustrate the viability of this concept, we have achieved the formal synthesis of the lignan antitumor burseran. Thus, reaction of furan **5b** with $LiAlH_4$ furnished the corresponding alcohol **10** in essentially quantitative yield. Hydrogenation of the furan ring[13] was then achieved over Raney Ni under 10 bar of H_2 at room temperature to give a mixture of two isomeric tetrahydrofurans **11** (*trans*:*cis*, 1:1). Finally, oxidation of the later under Swern conditions afforded the targeted aldehyde **8b** in 90% isolated yield as a mixture of diastereomers (*trans*:*cis*, 2.5:1). In accordance with Hanessian's findings, equilibration with DBU (CH_2Cl_2, rt) afforded **8b** as a highly enriched *trans* isomer (20:1) (Scheme 4). The desired precursor of burseran has thus been obtained in only four synthetic steps and in 47% overall yield from a combination of three simple building blocks.

(9) Similar alkoxide-induced decarboxylations had been previously reported; see Eglinton, G.; Whiting, M. C. *J. Chem. Soc.* **1953**, 3052. Bottini, A. T.; Maroski, J. G.; Dev, V. *J. Org. Chem.* **1973**, *38*, 1767. See also ref 8.

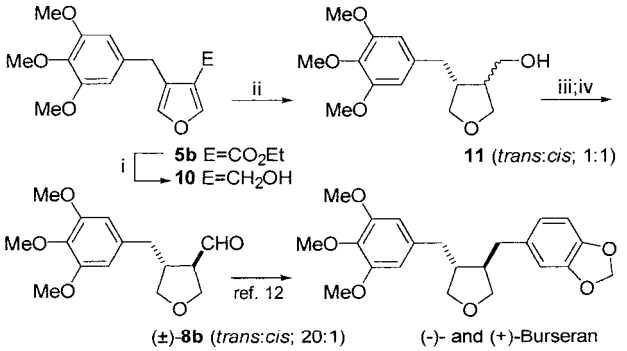
(10) A new concept aimed at designing one-pot processes by the integration of several synthetic steps was recently introduced by Otera and termed "Integrated Chemical Process": See Orita, A.; Yoshioka, N.; Struwe, P.; Braiser, A.; Beckmann, A.; Otera, J. *Chem. Eur. J.* **1999**, *5*, 1355 and references therein.

(11) Reviews: Ayres, D. C.; Loike, J. D. in *Lignans: Chemical, Biological and Clinical Properties*; Cambridge University Press: Cambridge, 1990. Ward, R. S. *Nat. Prod. Rep.* **1999**, *16*, 75−96, and previous reports referred to therein.

(12) Hanessian, S.; Léger, R. *Synlett* **1992**, 402.

(13) It should be noted that carboxylate **5b** proved essentially unreactive toward saturation of the furan ring despite extensive modification of the reaction parameters (hydrogen pressure, temperature, solvent) and the nature of the catalyst (Pd/C.; PtO_2; Raney-Ni). In contrast, the same transformation had been successfully achieved on analogue **5a** (Raney-Ni, MeOH, 1 atm H_2, 50 °C). Prior reduction of the carboxylic ester proved essential in the case of **5b**. Hydrogenation of furan 3,4-dicarboxylates has been reported to work under Pd/C catalysis: Pei, W.; Pei, J.; Li, S.; Ye, X. *Synthesis* **2000**, 2069.

Scheme 4. Formal Total Synthesis of Burseran



Reagents and conditions. i: $LiAlH_4$, THF, rt, quant.; ii: Raney-Ni, H_2 (10 bars), THF, rt, 93%. iii: $(COCl)_2$, DMSO, CH_2Cl_2, -78°C; Et_3N, -78°C to rt, 90%; iv: DBU, CH_2Cl_2, rt, quant.

Conclusion

A novel two-step synthetic entry into functionalized furan derivatives has been devised. It successively involves a conjugate addition, a palladium-catalyzed coupling-cyclization, an alkoxide-induced decarboxylative elimination, and finally, a double bond isomerization. The stepwise chemical process may be integrated into a one-pot reaction that allows for the preparation of various analogues by simply combining three starting materials, most of which are commercially available. As exemplified by a short formal synthesis of burseran, the title compounds should prove useful as versatile precursors of naturally occurring lignans, as well as their unnatural analogues.

Experimental Section

General Methods. Unless otherwise noted, all reactions were carried out under a nitrogen atmosphere using standard syringe, cannula, and septa techniques. Commercially available reagents were used as purchased. 5-Iodo-1,2,3-trimethoxybenzene,[14] 4-iodo-1,2-(methylenedioxy)benzene,[15] and cyclohex-1-enyl triflate[16] were prepared according to known procedures. Tetrahydrofuran and dimethyl sulfoxide were distilled over calcium hydride. Thin-layer chromatography was carried out on Merck silica 60/F-254 aluminum-backed plates. Flash chromatography was performed using Merck silica gel 60 (40−63 μm). NMR spectra were recorded in $CDCl_3$. Chemical shifts (δ) are quoted in parts per million. J values are given in Hz.

Representative Procedure for the Three-Component Reaction. Synthesis of Ethyl 4-Benzylidene-2-ethoxy-tetrahydrofuran-3,3-dicarboxylate (4a). *n*-BuLi (2.0 M in hexanes, 500 μL, 1.0 mmol) was added dropwise to an ice-cooled solution of propargyl alcohol (60 μL, 1.0 mmol) in THF (3 mL), and the solution was allowed to reach room temperature (15 min). In a separate flask, *n*-BuLi (2.0 M in hexanes, 50 μL, 0.1 mmol) was added dropwise to a well-stirred suspension of $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol) in DMSO (2 mL) to give a dark red homogeneous solution. To this palladium complex solution were successively added via cannula a mixture of diethyl ethoxymethylene malonate (216 mg, 1.0 mmol) and phenyl iodide (205 mg, 1.0 mmol) in THF (1 mL), and the propargyl alkoxide solution. The reaction mixture was stirred at room temperature for 1 h and after usual workup with aqueous NH_4Cl solution and diethyl ether, the organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was subjected to column chromatography (silica gel; ethyl acetate/petroleum ether) to afford the tetrahydrofuran **4a** (243 mg, 70%). Oil. IR (neat) 2980, 1770 1740, 1260−1220, 1100−1020 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.35−7.21 (2m, 5H), 6.93 (t, J = 2.6, 1H), 5.67 (s, 1H), 4.87 (dd, J = 13.6 and 2.6, 1H), 4.76 (dd, J = 13.6 and 2.6, 1H), 4.23 (m, 4H), 3.79 (m, 1H), 3.59 (m, 1H), 1.29 (m, 6H), 1.16 (t, J = 7, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 167.3, 166.2, 136.6, 133.8, 128.7, 128.6, 128.5, 127.6, 127.5, 104.4, 69.0, 68.8, 63.8, 62.0, 61.6, 14.9, 14.1, 14.0. HRMS calcd for $C_{19}H_{24}O_6$ (M^+) 348.1573; found 348.1573.

Data for compounds **4b**−**d**, **4g**−**h**, and **6** are provided in the Supporting Information.

Representative Procedure for the Decarboxylative Elimination. Synthesis of Ethyl 4-benzyl-furan-3-carboxylate (5a). A solution of potassium *tert*-butoxide (100 mg, 0.9 mmol) in THF (1 mL) was added dropwise to a solution of **4a** (278 mg, 0.8 mmol) in THF (4 mL). The reaction mixture was stirred at room temperature for 1 h and concentrated in vacuo. The residue was purified by flash chromatography (eluent ethyl acetate/petroleum ether) to afford furan **5a** (156 mg, 85%). Oil. IR (neat) 3180, 3020, 2980, 1740, 1230, 1080. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.01 (d, J = 1.8, 1H), 7.27 (m, 5H), 7.04 (d, J = 1.8, 1H), 4.29 (q, J = 7.0, 2H), 4.03 (s, 2H), 1.31 (t, J = 7.0, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 163.5, 149.1, 142.0, 139.8, 128.8, 128.4, 126.2, 125.0, 118.5, 60.2, 30.4, 14.3. Anal. Calcd for $C_{14}H_{14}O_3$; C, 73.03; H, 6.13. Found C, 73.31; H, 5.93.

General Procedure for the One-Pot Synthesis of Furans. The propargylic alcohol, the unsaturated halide, and diethyl ethoxymethylene carboxylate (1 mmol each) were reacted as described above. After total consumption of the later (GC; 1−3 h) the reaction mixture was treated with a solution of potassium *tert*-butoxide (1.1 mmol) in THF (1.5 mL), and stirring was continued until complete conversion was observed (TLC; 1 h). After usual workup with aqueous NH_4Cl solution and diethyl ether, the organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was subjected to column chromatography (silica gel; ethyl acetate/petroleum ether) to afford the desired furan **5**.

Ethyl 4-(3,4,5-Trimethoxybenzyl)-furan-3-carboxylate (5b). Oil. IR (neat) 3120, 2980, 1730, 1240, 1080 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.97 (d, J = 1.8, 1H.), 7.04 (d, J = 1.8, 1H), 6.46 (s, 2H), 4.24 (q, J = 7.0, 2H), 3.93 (s, 2H), 3.80 (s, 9H), 1.31 (t, J = 7.0, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 163.5, 158.1, 149.0, 141.9, 135.4, 125.1, 117.9, 105.7, 60.1, 60.8, 56.0, 30.7, 14.32. HRMS calcd for $C_{17}H_{20}O_6$ (M^+) 320.1260; found 320.1260.

Ethyl 4-Benzo[1,3]dioxol-5-yl Methyl-furan-3-carboxylate (5c). IR (neat) 3120, 2980, 1730, 1250, 1080 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.97 (d, J = 1.8., 1H), 7.04 (d, J = 1.8, 1H), 6.72 (m, 3H), 5.92 (s, 2H), 4,28 (q, J = 7.0, 2H), 3.91 (s, 2H), 1.31 (t, J = 7.0, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 163.5, 149.1, 147.6, 145.9, 141.9, 133.6, 125.2, 121.6, 118.3, 109.3, 108.2, 100.9, 60.2, 30.0, 14.3. HRMS calcd for $C_{15}H_{14}O_5$ (M^+) 274.0841; found 274.0839.

Ethyl 4-(4-Methoxy-benzyl)-furan-3-carboxylate (5d). Oil. IR (neat) 3120, 2980, 1730, 1250, 1080 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.99 (d, J = 1.8, 1H), 7.15 (d, J = 8.8, 2H), 7.0 (d, J = 1.8, 1H), 6.85 (d, J = 8.8, 2H), 4.28 (q, J = 7.0, 2H), 3.94 (s, 2H), 3.79 (s, 3H), 1.33 (t, J = 7.0, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 163.6, 158.1, 149.1, 141.9, 131.9, 129.8, 125.6, 118.4, 113.8, 60.1, 55.3, 29.5, 14.3. HRMS calcd for $C_{15}H_{16}O_4$ (M^+) 260.1049; found 260.1050.

Ethyl 4-(3-Methoxy-benzyl)-furan-3-carboxylate (5e). Treatment with *t*-BuOK was not needed. Oil. IR (neat) 3120, 2980, 1730, 1250, 1080 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.97 (d, J = 1.8, 1H), 7.18 (m, 2H), 6.98 (d, J = 1.8, 1H), 6.88 (m, 2H), 4.26 (q, J = 7.0, 2H), 3.99 (s, 2H), 3.82 (s, 3H), 1.31 (t, J = 7.0, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 163.7, 157.4, 148.8, 142.1, 130.0, 128,4, 127.5, 124.3, 120.4, 118.6, 110.3, 60.1, 55.3, 24.4, 14,2. HRMS calcd for $C_{15}H_{16}O_4$ (M^+) 260.1049; found 260.1050.

Ethyl 4-(4-Methoxycarbonyl-benzyl)-furan-3-carboxylate (5f). Treatment with *t*-BuOK was not needed. Oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.96 (s, 1H), 7.93 (d, J = 8.0, 2H), 7.28 (d, J = 8.0, 2H), 7.07 (s, 1H), 4.23 (q, J = 7.0, 2H), 4.04 (s, 2H), 3.73 (s, 3H), 1.28 (t, J = 7.0, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 167.1, 166.2, 163.3, 149.2, 145.3, 142.0, 129.7, 128.7, 128.3, 123.9, 118.3, 101.1, 63.3, 61.5, 60.2, 52.0, 30.2, 15.2, 14.3, 14.1. HRMS calcd for $C_{16}H_{16}O_5$ (M^+) 288.0998; found 288.0998.

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Ethyl 4-Benzyl-5-phenyl-furan-3-carboxylate (5g). Oil. IR (neat) 3020, 2980, 1730, 1240, 1080 cm^{-1}.^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.13 (s, 1H), 7.57−7.22 (m, 10H), 4.33 (s, 2H), 4.20 (q, J = 7.0, 2H), 1.22 (t, J = 7.0, 3H).^{13}C NMR ($CDCl_3$, 50 MHz) δ 163.3, 152.4, 147.7, 140.1, 128.8, 128.5, 128.1, 126.2, 126.0, 120.5, 118.3, 60.2, 29.8, 14.2. HRMS calcd for $C_{20}H_{18}O_3$ (M^+) 306.1256; found 306.1256.

Ethyl 4-Benzyl-5-propyl-furan-3-carboxylate (5h). Oil. IR (neat) 3020, 2980, 1730, 1240, 1080 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.92 (s, 1H), 7.17 (m, 5H), 4.19 (q, J = 7.0, 2H), 4.01 (s, 2H), 2.58 (t, J = 7.0, 2H), 1.62 (m, 2H), 1.22 (t, J = 7.0, 3H), 0.9 (t, J = 7.0, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 163.8, 154.8, 146.8, 140.9, 128.2, 128.1, 125.8, 118.9, 117.2, 59.9, 29.2, 28.2, 21.6, 14.2, 13.7. HRMS calcd for $C_{17}H_{20}O_3$ (M^+) 272.1412; found 272.1412.

Ethyl 4-Cyclohex-1-enylmethyl-furan-3-carboxylate (7). Oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.95 (d, J = 1.5, 1H), 7.17 (s, 1H), 5.40 (s, 1H), 4.26 (q, J = 7.0, 2H), 3.27 (s, 2H), 2.05−1.85 (m, 4H), 1.62−1.52 (m, 4H), 1.32 (t, J = 7.0, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 163.6, 148.8, 141.7, 135.9, 123.6, 122.5, 118.8, 60.0, 31.9, 28.4, 25.7, 23.0, 22.5, 14.3. HRMS calcd for $C_{14}H_{19}O_3$ (MH^+) 235.1334; found 235.1334.

Formal Synthesis of Burseran. Preparation of Alcohol 10 from 5b. To an ice-cooled solution of **5b** (250 mg, 0.78 mmol) in dry THF (5.5 mL) was added $LiAlH_4$ (30 mg, 0.78 mmol), and the suspension was stirred at room temperature for 1 h. After the usual workup, the alcohol **10** (210 mg, quant.) was isolated following percolation on silica gel with 3:1 hexanes:ethyl acetate. Solid. mp 92−95 °C. IR (KBr) 3060−3200, 2930, 1250, 1050 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (s,1H), 7.16 (s,1H), 6.43 (s, 2H), 4.38 (s, 2H), 3.80 (s, 9H), 3.72 (s, 2H), 1.90 (brs, 1H, O*H*). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 153.3, 141.3, 141.0, 135.7, 124.8, 123.5, 105.5, 60.9, 56.1, 55.5, 30.1. Anal. Calcd for $C_{15}H_{18}O_5$ C, 64.74; H 6.52. Found C, 64.66; H, 6.57.

Preparation of Alcohol 11. A pressure tube equipped with a magnetic stirbar was charged with the preceding alcohol (**10**) in 3 mL of THF. A catalytic amount of Raney-Ni was then added to the solution. The vessel was flushed with H_2 under stirring and then pressurized to 10 bar and maintained at that pressure for 15 h at room temperature. The pressure was released, and the reaction mixture was filtered through a short pad of Celite. Removal of the solvent in vacuo afforded 200 mg (93% yield) of alcohol **11** as a mixture of diastereomers (*trans*:*cis*=1:1). Solid. IR (KBr) 3060−3200, 2930, 1250, 1050 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (mixture of isomers) 6.43 (s, 2H), 6.41 (s, 2H), 3.99 (m, 2H), 3.92−3.79 (m, 22H), 3.76−3.68 (m, 2H), 3.63−3.58 (m, 2H), 3.56−3.48 (m, 2H), 2.85 (dd, J = 13.6 and 5.46 Hz,1H), 2.75 (dd, J = 13.6 and 7.2 Hz, 1H), 2.71−2.62 (m, 2H), 2.55−2.49 (m, 2H), 2.18 (m, 1H), 1.70 (brs, 2H).^{13}C NMR ($CDCl_3$, 50 MHz) δ 153.2, 136.4, 136.0, 105.6, 105.5, 73.2, 72.4, 70.9, 70.8, 64.4, 61.3, 60.8, 56.1, 47.4, 44.0, 43.3, 42.5, 39.8, 33.8. Anal. Calcd for $C_{15}H_{22}O_5$ C, 63.81; H, 7.85. Found C, 63.74; H, 7.95.

Preparation of Aldehyde 8. A solution of oxalyl chloride (70μL, 0.78 mmol) in CH_2Cl_2 (2.5 mL) was cooled to −78 °C. Dimethyl sulfoxide (100 μL, 1.57 mmol) in 0.5 mL of CH_2Cl_2 was added dropwise over 3 min. Alcohol **11** (100 mg, 0.35 mmol) in 6 mL of CH_2Cl_2 was added, and the reaction mixture was stirred for 30 min at −78 °C. Triethylamine (580 μL, 4.14 mmol) was then added dropwise, and the solution was warmed to room temperature and stirred 30 min. The reaction was quenched by addition of water, and the product was extracted with CH_2Cl_2. Organics were washed with 10% HCl, sodium bicarbonate, and brine and then dried over magnesium sulfate. Flash chromatography on silica gel with 6:4 hexanes:ethyl acetate afforded 90 mg (90% yield) of the corresponding aldehyde as a 2.5:1 mixture of the *trans* and *cis* isomers, respectively. Equilibration with DBU (CH_2Cl_2, rt, overnight) afforded **8** as the highly enriched *trans* isomer (20:1). Oil. IR (neat) 2930, 1725, 1240, 1120 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.53 (d, J = 2.0, 1H), 6.37 (s, 2H), 4.12 (dd, J = 9.5 and 5.1, 1H), 3.95 (m, 2H), 3.85 (s, 6H), 3.84 (s, 3H), 3.55 (dd, J = 8.6 and 5.9, 1H), 2.82 (m, 2H), 2.74 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 200.5, 153.4, 136.8, 134.9, 105.7, 73.2, 67.4, 60.9, 57.2, 56.2, 42.6, 38.9. HRMS calcd for $C_{15}H_{20}O_5$ (M^+) 280.1311; found 280.1311.

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Supporting Information Available: IR and NMR data for 2-ethoxytetrahydrofurans **4b**−**d, 4f**−**h**, and **6** including copies of ^{1}H (or ^{13}C) NMR spectra for **4a**−**d**, **4g**,**h**, **5a**−**e**, **5g,h**, **6**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org

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