The Oxa-Pictet–Spengler Reaction of 1-(3-Furyl)alkan-2-ols

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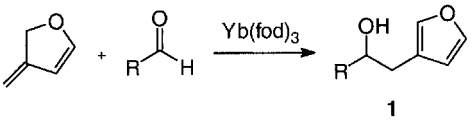
Abstract: The oxa-Pictet–Spengler reaction of 1-(3-furyl)alkan-2-ols with aldehydes catalyzed by *p*-toluenesulfonic acid gives good yields of the corresponding *cis*-5,7-disubstituted 4,5-dihydro-7*H*-furano[2,3-*c*]pyrans.

Key words: oxa-Pictet–Spengler reaction, furans, cyclizations, Lewis acids, ene reactions

The Pictet–Spengler reaction[1] is an excellent and extensively exploited method for the synthesis of isoquinolines. The oxygen version of the Pictet–Spengler reaction, the oxa-Pictet–Spengler reaction,[2–5] has received less attention but holds promise for the synthesis of isochromans.[6] The reaction of phenethyl alcohols with aldehydes or ketones is the simplest version of the oxa-Pictet–Spengler reaction but appears to be limited to electron rich aromatic compounds or requires highly acidic conditions.[2,3] In some studies, acetals of aldehydes have been successfully employed in Lewis acid catalyzed reactions with phenethyl alcohols to give isochromans.[4] The conversion of the phenethyl alcohol into a mixed acetal, which then either spontaneously cyclizes under the reaction conditions or is treated with a Lewis acid in a separate chemical step, also is an attractive variation of the oxa-Pictet–Spengler reaction.[5]

There is little precedent for the oxa-Pictet–Spengler reaction involving furans,[3] although these electron-rich aromatic compounds are ideally suited for the oxa-Pictet–Spengler reaction. In our studies related to 3-methylene-2,3-dihydrofuran,[7] the alicyclic isomer of 3-methylfuran, we developed a general synthesis of 1-(3-furyl)alkan-2-ols, **1** (Scheme 1),[7b] which we envisaged as possible substrates for the oxa-Pictet–Spengler reaction. 5,7-Disubstituted-4,5-dihydro-7*H*-furano[2,3-*c*]pyrans, the products of the oxa-Pictet–Spengler reaction of **1**, are potential intermediates for the synthesis of pyran natural products.[8] This paper describes the conditions and limitations for the oxa-Pictet–Spengler reaction of **1** with aldehydes and acetone.

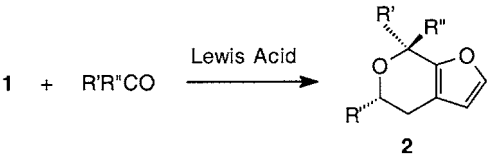
Racemic furanyl alcohols **1** [**1a**, R = $CH(CH_3)_2$; **1b**, R = $(CH_2)_8CH_3$; **1c**, R = 4-$CH_3C_6H_4$] were prepared by the carbonyl-ene reaction of 3-methylene-2,3-dihydrofuran with the corresponding aldehydes using $Yb(fod)_3$ as the catalyst. The oxa-Pictet–Spengler reactions of **1** were



1

Scheme 1

catalyzed by several different Lewis acids (see Scheme 2 and Table). *p*-Toluenesulfonic acid was found to give the best yields of **2** (entries 1, 4–6, 9–13). Scandium triflate also was a very active catalyst for the reaction of **1** with aldehydes (entries 2 and 7) but gave lower yields due to further reactions of the product **2** in the presence of the $Sc(OTf)_3$. Ytterbium triflate (entry 3) and trifluoroacetic acid (entry 8) catalyzed the reaction of **1** with aldehydes, but *p*-toluenesulfonic acid was clearly superior as a catalyst in the reactions attempted. For trimethylacetaldehyde (entry 10), the most sterically hindered aldehyde in the series, and acetone (entry 11), a higher load of *p*-toluenesulfonic acid was necessary for reasonable reaction rates and yields. The reaction of alcohol **1c** with aldehydes (entries 12 and 13) also proceeded best with a higher catalyst load. Although the reaction of **1** with aliphatic aldehydes gave good yields of **2**, the reaction of **1** with aromatic aldehydes (entry 5) gave low yields of **2**.



2

Scheme 2

Prolonged exposure of **2** to Lewis acids resulted in decomposition to unidentified products. The sensitivity of **2** is not unexpected, given the very stable carbocation that forms when the ether oxygen of the pyran ring interacts with the Lewis acid. With careful control of the reaction conditions, the acid sensitivity of most of the products led to only small decreases in yield. The reaction of **1a** with *p*-tolualdehyde to give **2c**, however, was especially troublesome; **2c** was very acid-sensitive and also very air-sensitive. Under many different conditions, we were not able to obtain reasonable yields of **2** in the reactions of **1** with aromatic aldehydes.

The oxa-Pictet–Spengler reaction of **1** with aliphatic aldehydes was remarkably stereoselective, giving only one stereoisomer in most cases. For the reactions of **1b** with

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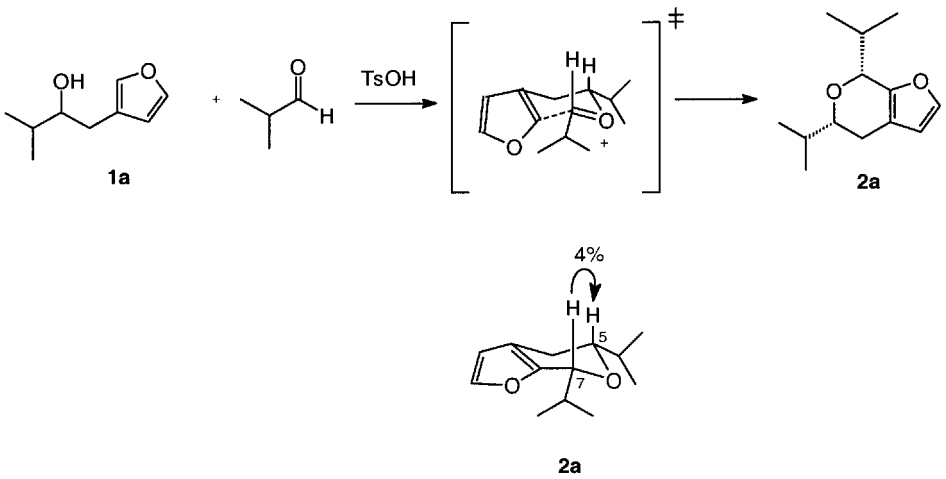
Table Reaction of Furanyl Alcohols **1** with Carbonyl Compounds (Scheme 2)

Entry	Furan: R	Carbonyl: R′; R″	Lewis Acid; Time (h)	Product	Yield (%)[a]
1	$CH(CH_3)_2$ (**1a**)	$CH(CH_3)_2$; H	TsOH, 1 mol%; 2	**2a**	76
2		$CH(CH_3)_2$; H	$Sc(OTf)_3$, 1 mol%; 1 (0 °C)	**2a**	45
3		$CH(CH_3)_2$; H	$Yb(OTf)_3$, 10 mol%; 20	**2a**	56
4		$(CH_2)_3CH_3$; H	TsOH, 1 mol%; 1.25	**2b**	78
5		4-$CH_3C_6H_4$; H	TsOH, 10 mol%; 0.5	**2c**	14
6	$(CH_2)_8CH_3$ (**1b**)	$CH(CH_3)_2$; H	TsOH, 1 mol%; 2	**2d**	78[b]
7		$CH(CH_3)_2$; H	$Sc(OTf)_3$, 0.5 mol%; 0.5 (0 °C)	**2d**	58
8		$CH(CH_3)_2$; H	CF_3CO_2H, 73 mol%; 1	**2d**	48
9		$(CH_2)_3CH_3$; H	TsOH, 1 mol%; 1.25	**2e**	63[c]
10		$C(CH_3)_3$; H	TsOH, 10 mol%; 0.5	**2f**	95
11		CH_3; CH_3[d]	TsOH, 10 mol%; 0.5	**2g**	92
12	4-$CH_3C_6H_4$ (**1c**)	$CH(CH_3)_2$; H	TsOH, 10 mol%; 1	**2h**	82
13		$(CH_2)_3CH_3$; H	TsOH, 3 mol%; 5	**2i**	66

[a] Isolated yield based on **1**.
[b] The *cis*/*trans* ratio of the crude product was ca. 14:1.
[c] The *cis*/*trans* ratio of the crude product was ca. 15:1.
[d] Ten equivalents of acetone were used.

isobutyraldehyde and valeraldehyde, we were able to isolate the other stereoisomer in small amounts. The definitive assignment of the *cis*-stereochemical relationship between the substituents at C-5 and C-7 was made by NOE enhancement experiments. For example, irradiation of the C-7 methine proton of **2a** gave a 4% enhancement of the C-5 methine proton. NOE experiments with **2b**, **2c**, **2d**, **2i**, and the major stereoisomers in the reactions leading to **2e** and **2f** gave similar results. Since the chemical shifts of the C-5 and C-7 protons of **2h** were similar, the NOE studies were more equivocal, although we did observe evidence for a small NOE enhancement. The *cis*-selectivity appears to be kinetic in origin; when a 1:1 mixture of **2d** and *trans*-isomer of **2d** was subjected to standard reaction conditions (TsOH, $MgSO_4$, MeCN), the isomeric mixture was recovered unchanged. The selectivity appears to arise in the cyclization of oxocarbenium ion intermediate (Scheme 3), in which the R and R′ groups assume equatorial positions in the chair-like transition state. High *cis*-selectivity for isochromans has been observed in a few previous studies of the oxa-Pictet–Spengler reaction.[4a,b,e] For the mechanistically similar Prins reaction,[9]



Scheme 3

in which the intermediate oxocarbenium ion is attacked by an alkene rather than an aromatic ring, there are many examples of *cis*-selectivity.

The oxa-Pictet–Spengler reaction of **1** represents another important example of a carbenium cyclization process in furan chemistry.[10] Manipulation of the furan ring is a valuable approach in many organic syntheses,[11] and we feel that furanopyrans offer an exciting access to the synthesis of pyran natural products. The reactions and applications of these furanopyrans will be reported in due course.

All reactions were carried out under Ar or N_2. IR spectra were obtained on a Perkin Elmer 1600 Series FT-IR spectrometer. The ^1H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively, on a JEOL Eclipse+400 spectrometer; all chemical shifts are reported in ppm relative to TMS (δ = 0.00) in the ^1H NMR and relative to $CDCl_3$ (δ = 77.0) in the carbon NMR spectra. Flash chromatography was performed on Merck silica gel 60 (230–400 mesh). Elemental analyses were performed by Galbraith Laboratories, Inc. $Yb(OTf)_3$, $Sc(OTf)_3$, and *tris*-(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)ytterbium [$Yb(fod)_3$] were purchased from Aldrich.

1-(3-Furyl)-3-methylbutan-2-ol (1a)

To a solution of isobutyraldehyde (6.0 mL, 66 mmol) and 3-methylene-2,3-dihydrofuran[7a,c] (10 mL of a 3.5:1 mixture of 3-methylene-2,3-dihydrofuran:3-methylfuran, 95 mmol) in CH_2Cl_2 (75 mL) was added $Yb(fod)_3$ (2.1 g, 2.0 mmol). After stirring for 24 h at r.t., the solvent was removed under reduced pressure. The crude product was purified by column chromatography (2%→10% EtOAc–hexanes) followed by a short path distillation (65–68 °C/0.1 mm) to give **1a** (7.38 g, 72%) as an oil.

IR (film): 3425, 2960, 1502, 1469, 1385, 1158, 1024, 873, 779 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.39 (t, 1 H, *J* = 1.7 Hz), 7.31 (br s, 1 H), 6.32 (br s, 1 H), 3.49 (ddd, 1 H, *J* = 3.4, 5.6, 9.1 Hz), 2.63 (dd, 1 H, *J* = 3.4, 14.6 Hz), 2.48 (dd, 1 H, *J* = 9.0, 14.4 Hz), 1.72 (m, 1 H), 1.61 (br s, 1 H), 0.97 (d, 6 H, *J* = 7.3 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.9, 140.0, 121.5, 111.3, 76.1, 32.9, 29.7, 18.7, 17.3.

Anal. Calcd for $C_9H_{14}O_2$ (154.2): C, 70.10; H, 9.15. Found: C, 69.95; H, 9.30.

1-(3-Furyl)undecan-2-ol (1b)

To a solution of decanal (7.5 mL, 40 mmol) and 3-methylene-2,3-dihydrofuran (7.0 mL of a 3.5:1 mixture of 3-methylene-2,3-dihydrofuran:3-methylfuran, 66 mmol) in CH_2Cl_2 (40 mL) was added $Yb(fod)_3$ (0.85 g, 0.80 mmol). After stirring for 44 h at r.t., the solvent was removed under reduced pressure. The crude product was purified by column chromatography (2%→10% EtOAc–hexanes) followed by a short path distillation (135–140 °C/0.1 mm) to give **1b** (7.74 g, 81%) as an oil that slowly solidified; mp 24–25 °C.

IR (film): 3375, 2926, 1502, 1466, 1025, 873, 781 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.38 (t, 1 H, *J* = 1.6 Hz), 7.30 (br s, 1 H), 6.31 (br s, 1 H), 3.73 (m, 1 H), 2.62 (dd, 1 H, *J* = 3.8, 14.4 Hz), 2.49 (dd, 1 H, *J* = 8.8, 14.3 Hz), 1.60 (br s, 1 H), 1.48 (m, 2 H), 1.26 (m, 14 H), 0.87 (t, 3 H, *J* = 6.6 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.1, 140.2, 121.1, 111.4, 71.4, 36.7, 32.9, 31.9, 29.6 (2 C), 29.5, 29.3, 25.7, 22.7, 14.1.

Anal. Calcd for $C_{15}H_{26}O_2$ (230.4): C, 75.58; H, 10.99. Found: C, 75.65; H, 11.26.

2-(3-Furyl)-1-(4-methylphenyl)ethan-1-ol (1c)

To a solution of *p*-tolualdehyde (4.7 mL, 40 mmol) and 3-methylene-2,3-dihydrofuran (7.0 mL of a 3.5:1 mixture of 3-methylene-2,3-dihydrofuran:3-methylfuran, 66 mmol) in CH_2Cl_2 (40 mL) was added $Yb(fod)_3$ (0.42 g, 0.40 mmol). After stirring for 20 h at r.t., the solvent was removed under reduced pressure. The crude product was purified by column chromatography (hexanes→10% EtOAc–hexanes) to give **1c** (7.86 g, 97%) as an oil.

IR (film): 3400, 2920, 1573, 1514, 1502, 1442, 1383, 1171, 1023, 873, 788 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.32 (br s, 1 H), 7.26 (d, 2 H, *J* = 8.0 Hz), 7.25 (br s, 1 H), 7.16 (d, 2 H, *J* = 7.7 Hz), 6.31 (br s, 1 H), 4.73 (m, 1 H), 2.86 (dd, 1 H, *J* = 7.4, 14.4 Hz), 2.84 (dd, 1 H, *J* = 5.4, 14.3 Hz), 2.33 (s, 3 H), 2.04 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.9, 140.7, 140.4, 137.3, 129.1, 125.8, 120.9, 111.4, 73.9, 34.8, 21.1.

Anal. Calcd for $C_{13}H_{14}O_2$ (202.3): C, 77.20; H, 6.98. Found: C, 77.53; H, 7.28.

***cis*-5,7-Bis(methylethyl)-4,5-dihydro-7*H*-furano[2,3-*c*]pyran (2a) Using *p*-Toluenesulfonic Acid as Catalyst; General Procedure (Table)**

Isobutyraldehyde (0.28 mL, 3.0 mmol) was added to a stirred solution of the alcohol **1a** (0.310 g, 2.01 mmol) in MeCN (20 mL) containing $MgSO_4$ (1 g). When the addition was complete, *p*-toluenesulfonic acid hydrate (0.0041 g, 0.022 mmol) dissolved in MeCN (1 mL) was added, and the reaction mixture was stirred at r.t. for 2 h. The mixture was quenched with aq 10% NaCl solution (50 mL) containing $NaHCO_3$ (0.50 g). The contents of the reaction flask were transferred to a separatory funnel with EtOAc (50 mL). The organic phase was separated and the aqueous phase was further extracted with EtOAc (2 × 50 mL). The combined organic phases were dried (Na_2SO_4) and evaporated on the rotary evaporator. The crude product was purified by flash column chromatography (hexanes→1% EtOAc–hexanes) to give **2a** (0.3196 g, 76%) as an oil.

IR (film): 2932, 2842, 1502, 1469, 1386, 1063, 724 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.26 (dd, 1 H, *J* = 0.7, 1.4 Hz), 6.22 (d, 1 H, *J* = 1.4 Hz), 4.41 (m, 1 H), 3.23 (q, 1 H, *J* = 7.0 Hz), 2.39 (dd, 2 H, *J* = 2.4, 6.8 Hz), 2.13 (d sept, 1 H, *J* = 3.8, 6.8 Hz), 1.79 (app. octet, 1 H, *J* = 6.8 Hz), 1.04 (d, 3 H, *J* = 7.0 Hz), 1.01 (d, 3 H, *J* = 6.6 Hz), 0.95 (d, 3 H, *J* = 6.9 Hz), 0.87 (d, 3 H, *J* = 6.6 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.2, 140.8, 116.2, 109.9, 79.9, 78.0, 33.0, 31.7, 26.4, 18.9, 18.4, 18.3, 16.8.

Anal. Calcd for $C_{13}H_{20}O_2$ (208.3): C, 74.94; H, 9.68. Found: C, 75.32; H, 9.83.

***cis*-7-Butyl-5-(methylethyl)-4,5-dihydro-7*H*-furano[2,3-*c*]pyran (2b)**

IR (film): 2958, 2872, 1503, 1468, 1367, 1128, 1078, 724 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.25 (m, 1 H), 6.22 (d, 1 H, *J* = 1.8 Hz), 4.54 (m, 1 H), 3.24 (ddd, 1 H, *J* = 4.9, 7.3, 9.0 Hz), 2.42 (m, 2 H), 1.91 (m, 1 H), 1.80 (app. octet, 1 H, *J* = 6.8 Hz), 1.65 (m, 1 H), 1.45 (m, 2 H), 1.36 (m, 2 H), 1.03 (d, 3 H, *J* = 7.0 Hz), 0.95 (d, 3 H, *J* = 6.6 Hz), 0.91 (t, 3 H, *J* = 7.1 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.6, 140.8, 115.1, 110.1, 80.6, 73.9, 33.0 (2 C), 27.1, 26.6, 22.7, 19.2, 18.4, 14.1.

Anal. Calcd for $C_{14}H_{22}O_2$ (222.3): C, 75.62; H, 9.98. Found: C, 75.43; H, 10.05.

***cis*-5-(Methylethyl)-7-(4-methylphenyl)-4,5-dihydro-7*H*-furano[2,3,-*c*]pyran (2c)**
IR (film): 2960, 2872, 1606, 1515, 1469, 1370, 1133, 1058, 884, 730 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.27 (d, 2 H, *J* = 8.0 Hz), 7.22 (dd, 1 H, *J* = 0.7, 1.8 Hz), 7.16 (d, 2 H, *J* = 7.7 Hz), 6.26 (d, 1 H, *J* = 1.8 Hz), 5.56 (br s, 1 H), 3.49 (m, 1 H), 2.60 (ddd, 1 H, *J* = 2.8, 10.4, 15.4 Hz), 2.51 (ddd, 1 H, *J* = 2.2, 3.3, 15.4 Hz), 2.34 (s, 3 H), 1.89 (app. octet, 1 H, *J* = 6.7 Hz), 1.03 (d, 3 H, *J* = 6.6 Hz), 0.98 (d, 3 H, *J* = 6.6 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.3, 141.5, 138.0, 136.2, 129.1, 127.7, 115.9, 110.0, 81.0, 76.3, 32.7, 26.2, 21.2, 19.1, 18.2.

Anal. Calcd for $C_{17}H_{20}O_2$ (256.4): C, 79.65; H, 7.86. Found: C, 79.46; H, 7.98.

***cis*-7-(Methylethyl)-5-nonyl-4,5-dihydro-7*H*-furano[2,3-*c*]pyran (2d)**
Flash chromatography of the crude product gave pure **2d** (78%) and a mixture of **2d** and the *trans*-isomer of **2d** (7%). Pure *trans*-isomer of **2d** was isolated by flash chromatography of the enriched fraction.

IR (film): 2922, 2855, 1502, 1466, 1385, 1142, 1068, 722 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.26 (dd, 1 H, *J* = 0.7, 1.8 Hz), 6.21 (d, 1 H, *J* = 1.8 Hz), 4.43 (m, 1 H), 3.52 (m, 1 H), 2.31–2.42 (m, 2 H), 2.12 (d sept, 1 H, *J* = 3.9, 6.9 Hz), 1.20–1.70 (m, 16 H), 1.01 (d, 3 H, *J* = 7.0 Hz), 0.89 (d, 3 H, *J* = 7.0 Hz), 0.88 (t, 3 H, *J* = 7.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.1, 140.8, 116.2, 109.8, 78.0, 75.1, 35.7, 31.9, 31.7, 29.7 (2 C), 29.6, 29.5, 29.4, 25.8, 22.7, 18.1, 17.0, 14.1.

Anal. Calcd for $C_{19}H_{32}O_2$ (292.5): C, 78.02; H, 11.03. Found: C, 78.00; H, 11.25.

***trans*-7-(Methylethyl)-5-nonyl-4,5-dihydro-7*H*-furano[2,3-*c*]pyran (*trans*-Isomer of 2d)**
IR (film): 2920, 2855, 1502, 1467, 1385, 1141, 1059, 723 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, 1 H, *J* = 1.5 Hz), 6.22 (d, 1 H, *J* = 1.2 Hz), 4.23 (d, 1 H, *J* = 8.1 Hz), 3.82 (m, 1 H), 2.50 (dd, 1 H, *J* = 3.7, 14.7 Hz), 2.32 (dd, 1 H, *J* = 8.7, 14.7 Hz), 2.12 (app. octet, 1 H, *J* = 7.0 Hz),), 1.20–1.70 (m, 16 H), 1.05 (d, 3 H, *J* = 6.6 Hz), 1.03 (d, 3 H, *J* = 6.6 Hz), 0.88 (t, 3 H, *J* = 6.8 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.9, 141.0, 114.8, 109.7, 76.6, 69.9, 35.2, 31.9, 31.8, 29.7 (2 C), 29.6, 29.5 (2 C), 26.2, 22.7, 19.2, 18.6, 14.1.

***cis*-7-Butyl-5-nonyl-4,5-dihydro-7*H*-furano[2,3-*c*]pyran (2e)**
Flash chromatography of the crude product gave pure **2e** (63%) and a mixture of **2e** and the *trans*-isomer of **2e** (24%). The *trans*-isomer of **2e** uncontaminated with **2e** could not be obtained.

IR (film): 2954, 2927, 1503, 1466, 1378, 1082, 722 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.25 (m, 1 H), 6.21 (d, 1 H, *J* = 1.4 Hz), 4.56 (d, 1 H, *J* = 2.9 Hz), 3.55 (m, 1 H), 2.39 (m, 2 H), 1.70–1.20 (m, 22 H), 0.91 (t, 3 H, *J* = 7.3 Hz), 0.87 (t, 3 H, *J* = 6.9 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.6, 140.9, 115.2, 110.0, 75.6, 73.9, 35.7, 33.1, 31.9, 29.6 (3 C), 29.5, 29.4, 27.1, 25.9, 22.7, 22.6, 14.2, 14.1.

Anal. Calcd for $C_{20}H_{34}O_2$ (306.5): C, 78.37; H, 11.18. Found: C, 78.24; H, 11.37.

***trans*-7-Butyl-5-nonyl-4,5-dihydro-7*H*-furano[2,3-*c*]pyran (*trans*-Isomer of 2e)**
^1H NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, 1 H, *J* = 1.5 Hz), 6.21 (d, 1 H, *J* = 1.4 Hz), 4.56 (dd, 1 H, *J* = 5.5, 7.7 Hz), 3.76 (m, 1 H), 2.45 (dd, 1 H, *J* = 3.7, 15.4 Hz), 2.34 (ddd, 1 H, *J* = 1.5, 9.2, 15.4 Hz), 1.2–1.8 (m, 22 H), 0.92 (t, 3 H, *J* = 7.1 Hz), 0.87 (t, 3 H, *J* = 6.6 Hz).

***cis*-7-(*tert*-Butyl)-5-nonyl-4,5-dihydro-7*H*-furano[2,3-*c*]pyran (2f)**
IR (film): 2926, 2855, 1502, 1465, 1365, 1138, 1074, 723 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.26 (m, 1 H), 6.21 (d, 1 H, *J* = 1.8 Hz), 4.19 (m, 1 H), 3.47 (m, 1 H), 2.30–2.39 (m, 2 H), 1.25–1.70 (m, 16 H), 0.99 (s, 9 H), 0.88 (t, 3 H, *J* = 6.8 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.2, 140.6, 117.1, 109.8, 81.4, 75.0, 35.7, 35.4, 31.9, 29.7, 29.6 (3 C), 29.3, 25.8, 22.7, 14.1.

Anal. Calcd for $C_{20}H_{34}O_2$ (306.5): C, 78.38; H, 11.18. Found: C, 78.41; H, 11.13.

7,7-Dimethyl-5-nonyl-4,5-dihydro-7*H*-furano[2,3-*c*]pyran (2g)
IR (film): 2921, 2857, 1504, 1466, 1377, 1287, 1156, 1095, 726 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, 1 H, *J* = 1.8 Hz), 6.17 (d, 1 H, *J* = 1.8 Hz), 3.73 (m, 1 H), 2.37 (dd, 1 H, *J* = 3.8, 15.3 Hz), 2.34 (d, 1 H, *J* = 9.9, 15.4 Hz), 1.25–1.70 (m, 16 H), 1.46 (s, 3 H), 1.43 (s, 3 H), 0.87 (t, 3 H, *J* = 6.8 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.8, 140.6, 113.3, 109.8, 72.7, 70.1, 35.7, 31.9, 29.8, 29.6 (3 C), 29.3, 28.0, 25.8, 25.1, 22.7, 14.1.

Anal. Calcd for $C_{18}H_{30}O_2$ (278.4): C, 77.65; H, 10.86. Found: C, 77.69; H, 11.06.

***cis*-7-(Methylethyl)-5-(4-methylphenyl)-4,5-dihydro-7*H*-furano[2,3-*c*]pyran (2h)**
IR (film): 2963, 2923, 1516, 1502, 1460, 1367, 1134, 1067, 815, 725 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.32 (m, 3 H), 7.17 (d, 2 H, *J* = 7.7 Hz), 6.26 (d, 1 H, *J* = 1.5 Hz), 4.68 (m, 1 H), 4.62 (dd, 1 H, *J* = 5.7, 8.2 Hz), 2.62–2.72 (m, 2 H), 2.35 (s, 3 H), 2.23 (d sept, 1 H, *J* = 3.4, 7.0 Hz), 1.07 (d, 3 H, *J* = 7.0 Hz), 0.95 (d, 3 H, *J* = 7.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.7, 141.1, 139.6, 137.0, 128.9, 125.7, 116.4, 109.7, 78.3, 76.3, 31.9, 31.7, 21.2, 18.2, 16.8.

Anal. Calcd for $C_{17}H_{20}O_2$ (256.4): C, 79.65; H, 7.86. Found: C, 79.73; H, 7.96.

***cis*-7-Butyl-5-(4-methylphenyl)-4,5-dihydro-7*H*-furano[2,3-*c*]pyran (2i)**
IR (film): 2929, 2860, 1517, 1503, 1458, 1136, 1078, 726 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.37 (d, 2 H, *J* = 8.0 Hz), 7.34 (d, 1 H, *J* = 1.1 Hz), 7.21 (d, 2 H, *J* = 8.0 Hz), 6.30 (d, 1 H, *J* = 1.5 Hz), 4.85 (m, 1 H), 4.68 (dd, 1 H, *J* = 4.6, 9.4 Hz), 2.68–2.82 (m, 2 H), 2.39 (s, 3 H), 2.01 (m, 1 H), 1.83 (m, 1 H), 1.27–1.62 (m, 4 H), 0.96 (t, 3 H, *J* = 7.3 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.2, 141.0, 139.3, 137.1, 129.0, 125.8, 115.3, 109.9, 76.8, 74.2, 33.1, 31.5, 26.8, 22.8, 21.1, 14.1.

Anal. Calcd for $C_{18}H_{22}O_2$ (270.4): C, 79.96; H, 8.20. Found: C, 80.17; H, 8.26.

***cis*-5,7-Bis(methylethyl)-4,5-dihydro-7*H*-furano[2,3-*c*]pyran (2a) Using Scandium Triflate as Catalyst (Table)**
$Sc(OTf)_3$ (0.115 g, 0.0234 mmol) was added to a stirred solution of the alcohol **1a** (0.310 g, 2.01 mmol) in nitromethane (10 mL) and CH_2Cl_2 (10 mL) containing $MgSO_4$ (1 g) at 0 °C. After the addition was complete, isobutyraldehyde (0.19 mL, 2.1 mmol) was added dropwise over 10 min at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, quenched with H_2O (40 mL) and transferred to a separatory funnel with EtOAc (40 mL). The organic phase was separated and washed with H_2O (4 × 20 mL). The combined organic phases were dried (Na_2SO_4) and evaporated on the rotary evapora-

tor. The crude product was purified by flash chromatography (hexanes→1% EtOAc–hexanes) to give **2a** (0.1893 g, 45%) as an oil.

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