Stereoselective Synthesis of 3-Hydroxy-2-aryltetrahydrofurans from β-(Triethylsilyl)oxyaldehydes and Aryldiazomethanes

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The biological importance of *C*-aryl glycosides has led to the development of a large number of synthetic methods for their construction.[1,2] We have recently reported a new stereoselective synthesis of 2-furanoic acids from β-(triethylsilyl)oxyaldehydes and α-diazoester,[3] and hoped to apply this same strategy to the synthesis of deoxy *C*-aryl glycosides. Our progress toward this goal is presented here with the report of a new method for the synthesis of 2-aryltetrahydrofurans.

The addition of aryldiazo compounds to aldehydes in the presence of Lewis acids and lithium salts is a well-known process that normally affords benzyl ketones.[4] This reaction is thought to proceed by addition of the diazo compound to the aldehyde carbonyl followed by pinacol- type migration of hydride and loss of nitrogen to afford ketone **4** (Scheme 1, path b).[4a] The synthesis of tetrahydrofurans might by possible via a related pathway involving activation of a β-(triethylsilyl)oxyaldehyde with a Lewis acid followed by addition of an aryldiazomethane to initially give **2**, which could then react with the ether oxygen to afford THF **3** (Scheme 1, pathway a).

In an attempt to test the viability of the THF synthesis, several Lewis acids ($BF_3{\cdot}OEt_2$, $TiCl_4$, $ZrCl_4$, $SnCl_4$, $SnCl_2$) were screened for effectiveness in the reaction of aldehyde **1c** (Table 1) and phenyldiazomethane.[5] The best results were obtained with $BF_3{\cdot}OEt_2$ and $TiCl_4$. Despite the fact the yields were virtually identical, the $TiCl_4$-mediated reaction was difficult to purify due to the presence of myriad byproducts derived from phenyldiazomethane. Thus, $BF_3{\cdot}OEt_2$ was the Lewis acid of choice. A brief survey of the reaction conditions showed 0.4 equiv of $BF_3{\cdot}OEt_2$ at −78 °C with 2.2 equiv of phenyldiazomethane to afford optimal yields of THF **3c**.

Scheme 1

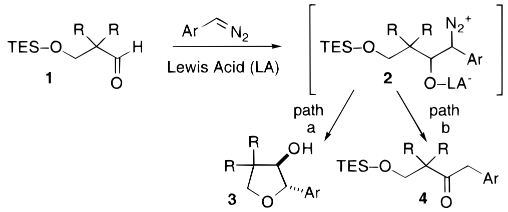
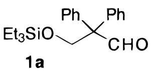
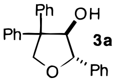
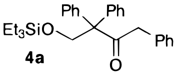
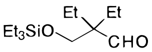
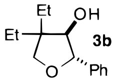
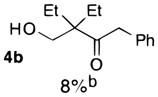
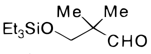
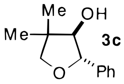
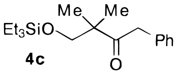
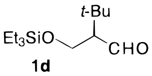
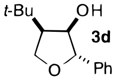
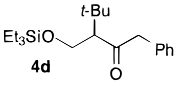
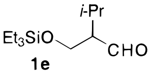
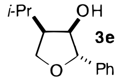
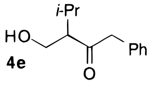
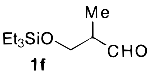
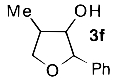
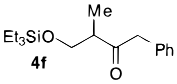


Table 1. Synthesis of 2-Phenyltetrahydrofurans

Entry	Aldehyde	THF	Benzyl Ketone
1	 **1a**	 **3a** 81%	 **4a** [a]
2	 **1b**	 **3b** 73%	 **4b** 8%[b]
3	 **1c**	 **3c** 62% (4:1)[c]	 **4c** 15%
4	 **1d**	 **3d** 59%	 **4d** 30%[a]
5	 **1e**	 **3e** 38% (17:3:1)[c]	 **4e** 38%[b]
6	 **1f**	 **3f** 26% (11:5:2:1)[c,d]	 **4f** 60%

[a] The benzyl ketone was not isolated or detected (^1H NMR) in this case. [b] Desilylation was necessary for isolation of the ketone. [c] Major diastereomer shown. [d] Inseparable mixture of diastereomers, see text.

Table 1 summarizes the results of our study with phenyldiazomethane and a series of readily available aldehydes using the optimized reaction conditions. Steric bulk α to the aldehyde maximized formation of THF products **3** over benzyl ketones **4**. Reaction of **1a** with phenyldiazomethane[5] in the presence of $BF_3{\cdot}OEt_2$ afforded THF **3a** in 81% yield. Benzyl ketone **4a** was not isolated. α,α-Diethylaldehyde **1b** with phenyldiazomethane afforded THF **3b** and benzyl ketone **4b** in 73% and 8% yields, respectively. THF's **3a** and **3b** were obtained as single diastereomers (^1H NMR and GC−MS analysis). The less sterically bulky α,α-dimethyl aldehyde **1c** afforded THF **3c** in 62% yield as a 4:1 mixture of diastereomers and benzyl ketone **4c** in 15% yield. The major diastereomer of **3c** possessed the *trans*-orientation between the hydroxy and phenyl groups, and the minor diastereomer had these two groups in a cis orientation.

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(1) (a) Townsend, L. B. *Chemistry of Nucleosides and Nucleotides*; Plenum Press: New York, 1988. (b) Hacksell, U.; Daves, G. D. *The Chemistry and Biochemistry of C-Nucleosides and C-Arylglycosides*; Ellis, G. P., West, G. B., Ed.; Elsevier Science Publishers: London, 1985; Vol. 22, pp 1−65. (c) Jaramillo, C.; Knapp, S. *Synthesis* **1994**, 1−20.

(2) For leading references to the synthesis of *C*-Glycosides see: (a) Du, Y. G.; Linhardt, R. J.; Vlahov, I. R. *Tetrahedron* **1998**, *54*, 9913−9959. (b) Postema, M. H. D. *C-Glycoside Synthesis*; CRC Press: Boca Raton, 1995. (c) Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545−8599. (d) Calter, M. A.; Zhu, C. *J. Org. Chem.* **1999**, *64*, 1415−1419. (e) Urban, D.; Skrydstrup, T.; Beau, J. M. *Chem. Commun.* **1998**, 955−956. (f) Kim, G.; Kang, S.; Kim, S. N. *Tetrahedron Lett.* **1993**, *34*, 7627−7628. (g) Maeba, I.; Ito, Y.; Wakimura, M.; Ito, C. *Heterocycles* **1993**, *36*, 1617−1623

(3) (a) Angle, S. R.; Bernier, D. S.; Chann, K.; Jones, D. E.; Kim, M. S.; Neitzel, M. L.; White, S. L. *Tetrahedron Lett.* **1998**, *39*, 8195−8198. (b) Angle, S. R.; Wei, G. P.; Ko, Y. K.; Kubo, K. *J. Am. Chem. Soc.* **1995**, *117*, 8041−8042. (c) Angle, S. R.; Bernier, D. S.; El-Said, N. A.; Jones, D. E.; Shaw, S. Z. *Tetrahedron Lett.* **1998**, *39*, 3919−3922.

(4) (a) Mahmood, S. J.; Saha, A. K.; Hossain, M. M. *Tetrahedron* **1998**, *54*, 349−358. (b) Loechorn, C. A.; Nakajima, M.; McCloskey, P. J.; Anselme, J. P. *J. Org. Chem.* **1983**, *48*, 4407−4410.

(5) (a) Creary, X. *J. Am. Chem. Soc.* **1980**, *102*, 1611−1618. (b) Creary, X. *Organic Synthesis* **1985**, *64*, 207−216. (c) Davies, H. W.; Schwarz, M. *J. Org. Chem.* **1965**, *30*, 1242−1244.

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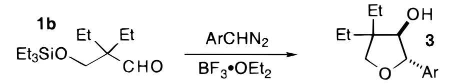
Table 2. Synthesis of 2-Aryltetrahydrofurans



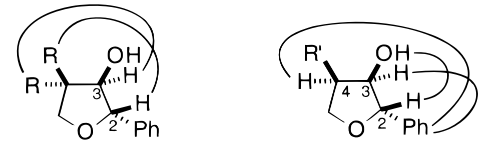
Entry	Ar	THF (yield)
1	$C_6H_4(p\text{-}CH_3)$	**3g** (52%)
2	$C_6H_4(p\text{-}Cl)$	**3h** (66%)
3	$C_6H_4(p\text{-}NO_2)$	**3i** (44%)

A study of aldehydes **1d**−**f** (Table 1, entries 4−6) showed that as the size of the α-substituent decreased, the yield of THF's **3** decreased as did the diastereoselectivity. For example, the α-*tert*-butyl aldehyde **1d** gave THF **3d** in 59% yield as a single diastereomer (GC−MS), and the α-isopropyl aldehyde **1e** afforded **3e** in 38% yield as a 17:3:1 mixture (GC analysis) of three diastereomers. In both cases, the major phenyl THF diastereomer possessed the 2,3-trans-3,4-cis orientation of substituents about the tetrahydrofuran. The stereochemistry of the minor diastereomers of **3e** was not determined. In addition to the THF products, the benzyl ketones **4d** and **4e** were isolated in 30% and 38% yields, respectively. Treatment of α-methylaldehyde **1f** afforded 2-phenyl THF **3f** in 26% yield (11:5:2:1 inseparable mixture of four diastereomers, GC−MS) and benzyl ketone **4f** in 60% yield. The relative stereochemistry of the four diastereomers was not assigned.

The higher yields of THFs derived from aldehydes possessing bulky α-substituents, and decreased yield for those with smaller α-substituents, coupled with the reverse trend for yield of benzyl ketones **4** is consistent with the bifurcated reaction pathway shown in Scheme 1, where a Thorpe−Ingold[6] effect might divert the reaction manifold toward C−O bond formation (THF products **3**) by facilitating cyclization and/or hindering hydrogen migration. In the absence of bulky substituents (Thorpe−Ingold effect), the hydride migration is the dominant reaction pathway (b, Scheme 1) and the benzyl ketones **4** are formed.

The stereoselectivity is consistent with that seen in the reaction of diazoesters with these same substrates.[3] Particularly intriguing is the selectivity for a trans orientation between the phenyl and alcohol functionalities. This relationship appears to be kinetic in origin since resubmission of each purified diastereomer of THF **3c** to the reaction conditions resulted in recovered THF with no epimerization evident by ^{1}H NMR or capillary GC analysis.

Substituted phenyldiazomethanes can also be employed in the reaction as shown in Table 2. Three representative aryldiazomethanes (p-CH$_3$, p-Cl, p-NO$_2$)[5] were screened with aldehyde **1b**. All three substituted phenyldiazo compounds afforded THF products. The decreased yield of **3g** (p-CH$_3$) relative to the parent (R = H) may be due to the instability of the tolyldiazomethane relative to phenyldiazomethane. In the case of the *p*-nitrophenyldiazomethane, the corresponding benzyl ketone was isolated in 7% yield. It is worth noting that the *p*-nitrophenyldiazomethane was still nucleophilic enough to participate in the initial step of reaction, add to the aldehyde carbonyl, and afford THF **3i** in 44% yield.



3b, R = CH$_2$CH$_3$
3c, R = CH$_3$

3d, R' = C(CH$_3$)$_3$
3e, R' = CH(CH$_3$)$_2$

Figure 1. Key NOEs.

The stereochemical assignments for THF's **3b**−**e** are based on H−H NOESY spectra and that for **3i** on an X-ray crystal structure.[7] The stereochemical assignments for the remaining THFs (**3a**,**g**,**h**) are based on comparison of H−H coupling constants to THF's **3b**−**e** and **3i**. The trans orientation of the hydroxyl and phenyl substituents in **3b** and **3c** is based on the key NOE enhancements (from NOESY spectra) depicted in Figure 1. The H(2)−H(3) coupling constant for **3b** and the major diastereomer of **3c** are nearly identical (6.2 and 6.7 Hz) as are the chemical shifts for the resonances of these two key hydrogens. The stereochemistry of the trisubstituted THFs **3d** and **3e** was based on the NOE enhancements (from NOESY spectra) shown in Figure 1. In particular, the NOE between the hydrogens of the phenyl group and both H(3) and H(4) show these groups to be in a cis orientation relative to each other. As expected, the two compounds, **3d** and **3e**, show nearly identical chemical shifts and H−H coupling constants for the analogous hydrogens.

In conclusion, we have developed a novel, one-step method for the stereoselective synthesis of 4-alkyl-2-aryl-3-hydroxytetrahydrofurans from α-alkyl-*β*-(triethylsilyl)oxyaldehydes and aryldiazomethanes. With the ready availability of substituted phenyldiazomethanes, this method should be adaptable to the synthesis of a wide variety of deoxy-*C*-arylglycoside derivatives. Studies to further examine the origin of the stereoselectivity, scope, and limitations of the methodology are currently under investigation.

Experimental Section[8]

General Procedure for Preparation of α-Alkyl(triethylsilyl)oxyaldehydes (1a−f) from the Corresponding 2-Alkyl-1,3-propanediols. To each respective 2-alkyl-1,3-propanediol (1.0 equiv) in CH$_2$Cl$_2$ (0.2 M) were added triethylamine (1.1 equiv) and triethylsilyl chloride (0.9 equiv). After 1 h at room temperature, the CH$_2$Cl$_2$ was removed in vaccuo, diethyl ether (100 mL) was added, and the resulting suspension was filtered to remove the amine hydrochloride. The ether solution was washed with water (3 × 50 mL) to remove unreacted diol, dried (MgSO$_4$), and concentrated to afford the crude monosilylated 2-alkyl-1,3-propanediols. Dess−Martin (1.4 equiv of oxidant) oxidation of the monosilylated 2-alkyl-1,3-propanediols in CH$_2$Cl$_2$ (0.2 M) for 2−3 h, followed by removal of the solvent and flash chromatography (silica gel, hexanes/ethyl acetate, 3% triethylamine) afforded aldehydes **1a**−**f** as clear oils in the yields indicated.

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(6) (a) Curtin, M. L.; Okamura, W. H. *J. Org. Chem.* **1990**, *55*, 5278−5287. (b) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224−232. (c) Jung, M. E.; Marquez, R. *Tetrahedron Lett.* **1997**, *38*, 6521−6524.

(7) THF **3a** showed a cross-peak in the NOESY spectrum for the resonances corresponding to the hydroxyl hydrogen and the C(2)-hydrogen, supportive of the assigned cis orientation between the OH and the C(2)-hydrogen. See the Supporting Information for details.

(8) **General Information**. Capillary GC was carried out using an FID detector on a 25 m HP-102 (methyl silicone) column. The following standard GC parameters were used: flow rate = 60 mL/min; injector temperature = 235 °C; detector temperature = 275 °C; temperature program = 40−280 °C at 5 °C/min, initial time = 1 min.

2,2-Diphenyl-3-[(triethlysilyl)oxy]propanaldehyde (1a): clear oil (78%); ^{1}H NMR (300 MHz, benzene-d_6)δ 9.84 (s, 1H), 7.21−7.03 (m, 10H), 4.46 (s, 2H), 0.83 (t, J = 8.0 Hz, 9H), 0.41 (q, J = 7.9 Hz, 6H); ^{13}C NMR (75 MHz, benzene-d_6)δ 198.5, 139.7, 129.8, 128.6, 127.4, 66.1, 65.4, 6.8, 4.5; IR (neat) 2955, 1721, 1111, 1012, 752 cm^{-1}; MS (EI, 50 eV) m/z 340 (7, M$^+$), 311 (81), 281 (35), 180 (73), 167 (100); HRMS calcd for $C_{21}H_{28}O_2Si$ 340.1859, found 340.1854.

2,2-Diethyl-3-[(triethlysilyl)oxy]propanaldehyde (1b): clear oil (86%); ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.52 (s, 1H), 3.66 (s, 2H), 1.66−1.48 (m, 4H), 0.94 (t, J = 8.0 Hz, 9H), 0.81 (t, J = 7.4 Hz, 6H), 0.57 (q, J = 8.0 Hz, 6H); ^{13}C NMR (75 MHz, benzene-d_6) δ 205.1, 63.2, 54.5, 22.0, 7.8, 7.0, 4.6 cm^{-1} IR (neat) 2959, 1729, 1459, 1101, 728; MS (CI, NH$_3$) m/z 245 (25, MH$^+$), 227 (52), 215 (100), 117 (57); HRMS calcd for $C_{13}H_{29}O_2Si$ (M + H) 245.1937, found 245.1948.

2,2-Dimethyl-3-[(triethlysilyl)oxy]propanaldehyde (1c): clear oil (84%); ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.57 (s, 1H), 3.60 (s, 2H), 1.04 (s, 6H), 0.93 (t, J = 8.0 Hz, 9H), 0.57 (q, J = 7.9 Hz, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 206.1, 68.2, 48.1, 18.5, 6.6, 4.3; IR (neat) 2957, 1733, 1460, 1102, 811, 743 cm^{-1}.

2-(Dimethyl)ethyl-3-[(triethlysilyl)oxy]propanaldehyde (1d): yellow oil (89%); ^{1}H NMR (300 MHz, benzene-d_6) δ 9.71 (d, J = 3.6 Hz, 1H), 3.99 (dd, J = 10.0, 9.0 Hz, 1H), 3.71 (dd, J = 10.3, 4.1 Hz, 1H), 2.19−2.13 (m, 1H), 0.94 (t, J = 8.0 Hz, 9H), 0.80 (s, 9H), 0.53 (q, J = 8.0 Hz, 6H); ^{13}C NMR (75 MHz, benzene-d_6) δ 203.6, 63.5, 59.8, 32.5, 28.2, 6.9, 4.7 cm^{-1}; IR (neat) 2959, 1726, 1093, 744; MS (CI, NH$_3$) m/z 245 (100, MH$^+$), 159 (11), 132 (30), 120 (21); HRMS calcd for $C_{13}H_{29}O_2Si$ (M + H) 245.1937, found 245.1945.

2-(Methyl)ethyl-3-[(triethlysilyl)oxy]propanaldehyde (1e): clear oil (67%); ^{1}H NMR (300 MHz, CDCl$_3$)δ 9.72 (s, 1H), 3.96 (dd, J = 10.2, 7.3 Hz, 1H), 3.83 (dd, J = 10.3, 4.8 Hz, 1H), 2.26−2.18 (m, 1H), 2.16−2.05 (m, 1H), 1.00−0.91 (m, 15H), 0.58 (q, J = 8.0 Hz, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 205.2, 60.5, 60.4, 25.7, 20.4, 20.1, 6.7, 4.3; IR (neat) 2958, 2877, 1726, 1107, 1016, 745 cm^{-1}; MS (CI, NH$_3$) m/z 248 (80, M + NH$_4^+$), 231 (100, MH$^+$), 201 (15), 132 (54), 120 (7); HRMS calcd for $C_{12}H_{27}O_2Si$ (M + H) 231.1780, found 231.1781.

2-Methyl-3-[(triethlysilyl)oxy]propanaldehyde (1f): clear oil (62%); ^{1}H NMR (300 MHz, benzene-d_6) δ 9.50 (s, 1H), 3.50 (m, 2H), 2.14−2.03 (m, 1H), 0.92 (t, J = 8.0 Hz, 9H), 0.85 (d, J = 6.7 Hz, 3H), 0.50 (q, J = 7.9 Hz, 6H); ^{13}C NMR (75 MHz, benzene-d_6) δ 202.6, 63.2, 48.9, 10.3, 6.9, 4.6; IR (neat) 2956, 1736, 1458, 1097, 744 cm^{-1}.

General Procedure for the Reaction of Aryldiazomethane with Aldehydes 1. Freshly distilled BF$_3$·Et$_2$O (0.80 mmol) was added dropwise over 1 h to a −78 °C solution of aldehyde **1** (2.0 mmol), aryldiazomethane (4.4 mmol; CAUTION: diazo compounds are potentially explosive and toxic), and CH$_2$Cl$_2$ (40 mL). After the solution was stirred for an additional 30−180 min, the disappearance of the red color of the aryldiazomethanes signaled completion of the reaction. This was verified by TLC. The reaction mixture was poured into a stirring solution of saturated aqueous NaHCO$_3$ (50 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 100 mL), and the combined organic extracts were dried (MgSO$_4$) and concentrated to afford crude products. Flash chromatography (silica gel, gradient 40:1, 7:1, 3:1 hexanes/ethyl acetate) afforded furans **3** and benzyl ketones **4**. Chromatography fractions of impure THFs **3** were treated with pyridine·HF (1:1 w/v) in CH$_3$CN. Aqueous workup followed by flash chromatography afforded additional THF product (3−15%). In the case of ketones **4b** and **4e**, impurities were present after the initial chromatography, and the impure ketone was treated with pyridine·HF (1:1 w/v) in CH$_3$CN. Aqueous workup followed by flash chromatography afforded the ketones in the yields indicated in Table 1.

(2*S,3*R**)-4,4-Diphenyl-3-hydroxy-2-phenyltetrahydrofuran (3a):** white solid; mp 132−133 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.43−7.32 (m, 15H), 5.03 (d, J = 9.2 Hz, 1H), 4.74 (dd, J = 10.8, 8.2 Hz, 1H), 4.56 (d, J = 8.2 Hz, 1H), 4.44 (d, J = 9.2 Hz, 1H), 1.56 (d, J = 10.8 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 143.8, 140.9, 140.4, 129.2, 128.6, 128.5, 128.5, 127.8, 127.3, 126.9, 125.7, 83.5, 81.8, 77.2, 57.3; IR (KBr) 3515, 3481, 3030, 2938, 2861, 2355, 1494, 1118 cm^{-1}; MS (CI, NH$_3$) m/z 334 (74, M + NH$_4^+$), 299 (24), 180 (100), 105 (37), 91 (33); HRMS calcd for $C_{22}H_{24}O_2N$ (M + NH$_4$) 334.1807, found 334.1804.

(2*S,3*R**)-4,4-Diethyl-3-hydroxy-2-phenyltetrahydrofuran (3b):** clear oil; ^{1}H NMR (300 MHz, benzene-d_6) δ 7.51 (d, J = 7.7 Hz, 2H), 7.23 (t, J = 7.4 Hz, 2H) 7.13 (partially obscured t, J = 7.2 Hz, 1H), 4.60 (d, J = 6.2 Hz, 1H), 3.68 (ABq, J = 9.2 Hz, $\Delta\nu$ = 8.9 Hz, 2H), 3.47 (t, J = 6.2 Hz, 1H), 1.48 (dq, J = 14.9, 7.7 Hz, 1H), 1.39−1.25 (m, 2H), 1.15 (dq, J = 14.9, 7.7 Hz, 1H), 0.92 (d, J = 6.2 Hz, 1H), 0.74 (t, J = 7.4 Hz, 3H), 0.67 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, benzene-d_6) δ 142.9, 128.9, 127.9, 126.2, 87.3, 85.7, 77.2, 48.5, 28.0, 22.3, 8.9, 8.8; IR (neat) 3428, 2965, 1455, 1062, 699 cm^{-1}; MS (EI, 20 eV) m/z 220 (3, M$^+$), 114 (72), 107 (61), 91 (20), 85(100); HRMS calcd for $C_{14}H_{20}O_2$ 220.1463, found 220.1470.

(2*S,3*R**)- and (2*R**,3*R**)-4,4-Dimethyl-3-hydroxy-2-phenyltetrahydrofuran (3c).** The diastereomers were separated by flash chromatography (4:1 mixture based on isolated yields). Major diastereomer (2*S**,3*R**): clear oil; ^{1}H NMR (300 MHz, CDCl$_3$)δ 7.29−7.13 (m, 5H), 4.50 (d, J = 6.7 Hz, 1H), 3.69 (ABq, J = 8.7 Hz, $\Delta\nu$ = 12.7 Hz, 2H), 3.54 (d, J = 5.7 Hz, 1H), 1.75 (br. s, 1H), 1.00 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$)δ 141.5, 128.4, 127.5, 125.5, 86.0, 85.5, 79.5, 42.0, 24.6, 19.6; IR (Neat) 3412, 2931, 1452, 1050, 700 cm^{-1}; MS (EI 20 eV) m/z 192 (13, M$^+$), 107 (100); HRMS calcd for $C_{12}H_{16}O_2$ 192.1150, found 192.1149. Minor diastereomer (2*R**,3*R**): white solid; mp 68−74 °C; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.31−7.16 (m, 5H), 5.19 (d, J = 3.6 Hz, 1H), 3.85 (d, J = 7.7 Hz, 1H), 3.68 (d, J = 3.6 Hz, 1H), 3.61 (d, J = 7.7 Hz, 1H), 1.07 (d, J = 18.5 Hz, 6H), 1.00 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 137.7, 128.5, 127.7, 126.6, 84.4, 80.5, 78.9, 44.1, 25.7, 19.3; IR (KBr) 3436, 2961, 1055, 737, 699 cm^{-1}; MS (EI) m/z 192 (5, M$^+$), 107 (100), 86 (54), 71 (96); HRMS calcd for $C_{12}H_{16}O_2$ 192.1150, found 192.1151.

(2*S,3*R**,4*R**)-4-(Dimethyl)ethyl-3-hydroxy-2-phenyltetrahydrofuran (3d):** white solid; mp 117−118 °C; ^{1}H NMR (300 MHz, benzene-d_6)δ 7.31 (d, J = 7.2 Hz, 2H), 7.18 (partially obscured t, J = 7.2 Hz, 2H), 7.07 (t, J = 7.2 Hz, 1H), 4.84 (s, 1H), 4.13 (d, J = 7.7 Hz), 4.05 (dd, J = 11.0, 7.5 Hz), 3.99 (t, J = 4.6 Hz, 1H), 1.76 (ddd, J = 12.1, 8.2, 4.6 Hz, 1H), 1.14 (d J = 5.6 Hz, 1H), 0.88 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$)δ 141.3, 128.3, 127.2, 125.0, 89.7, 80.5, 68.2, 51.4, 30.8, 29.5; IR (KBr) 3409, 3287, 2950, 1448, 1364, 1060, 740 cm^{-1}; MS (EI 20 eV) m/z 220 (2, M$^+$), 163 (42), 107 (100); HRMS calcd for $C_{14}H_{20}O_2$ 220.1463, found 220.1468.

(2*S,3*R**,4*R**)-3-Hydroxy-4-(methyl)ethyl-2-phenyltetrahydrofuran (3e).** Obtained as a 17:3:1 mixture of diastereomers. Flash chromatography afforded the major diastereomer and a mixture of two minor diastereomers in a 1:3 ratio (GC, t_R = 33.7 and 34.0 min, respectively). Major diastereomer (2*S**,3*R**,4*R**): white solid; mp 87−89 °C; ^{1}H NMR (300 MHz, benzene-d_6) δ 7.44 (d, J = 7.7 Hz, 2H), 7.33−7.27 (m, 2H), 7.19 (t, J = 7.2 Hz, 1H), 5.20 (s, 1H), 4.30 (t, J = 8.0 Hz, 1H), 4.11 (d, J = 4.1 Hz, 1H), 3.97 (dd, J = 10.8, 7.7 Hz, 1H), 2.11 (s, 1H), 1.97−1.85 (m, 1H), 1.83−1.72 (m, 1H), 0.87 (d, J = 6.7 Hz, 3H), 0.76 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, benzene-d_6) δ 142.3, 128.5, 127.3, 125.5, 89.8, 79.2, 71.9, 50.2, 25.6, 21.7, 21.5; IR (KBr) 3424, 3287, 2963, 1078, 1043, 919, 744 cm^{-1}; MS (EI, 20 eV) m/z 207 (3, MH$^+$), 162 (18), 107 (100), 100 (19), 91 (11); HRMS calcd for $C_{13}H_{19}O_2$ (M + H) 207.1385, found 207.1387. Inseparable mixture of minor diastereomers (3:1): white solid; mp 49−54 °C. Major component (GC t_R = 34.0 min): ^{1}H NMR (300 MHz, benzene-d_6)δ 7.47 (d, J = 7.2 Hz, 2H), 7.24−7.12 (m, overlaps with diastereomer, 3H), 4.52 (d, J = 7.2 Hz, 1H), 3.98 (t, J = 8.7 Hz, 1H), 3.69 (dd, J = 9.2, 7.2 Hz, 1H), 3.51 (dd, J = 13.1, 7.2 Hz, 1H), 1.76−1.66 (m, 1H), 1.46−1.29 (m, overlaps with diastereomer, 1H), 0.97 (d, J = 6.2 Hz, 1H), 0.81 (d, J = 6.7 Hz, 3H), 0.67 (d, J = 6.7 Hz, overlaps with diastereomer, 3H). Minor component (GC t_R = 33.7 min): ^{1}H NMR (300 MHz, benzene-d_6)δ 7.36 (d, J = 7.7 Hz, 2H), 7.24−7.08 (m, overlaps with diastereomer, 3H), 4.57 (d, J = 4.6 Hz, 1H), 4.20 (t, J = 8.2 Hz, 1H), 3.84 (t, J = 3.1 Hz, 1H), 3.36 (dd, J = 8.7, 7.7 Hz, 1H), 1.91−1.81 (m, 1H), 1.38−1.24 (m, overlaps with diastereomer, 1H), 0.88 (d, J = 6.7 Hz, 3H), 0.67 (d, J = 6.7 Hz, overlaps with diastereomer, 3H); ^{13}C NMR (75 MHz, benzene-d_6, 3:1 mixture of diastereomers)δ 141.8, 137.8, 128.8, 128.6, 128.5, 127.4, 127.1, 126.1, 86.8, 84.8, 82.7, 77.6, 70.9, 70.6, 55.8, 54.1, 30.7, 30.0, 21.3, 20.8, 20.7; IR (KBr) 3418, 2958, 2872, 1453, 1029, 700 cm^{-1}; MS (EI, 20 eV) m/z 206 (4, M$^+$), 162 (17), 107 (100); HRMS calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.1313.

3-Hydroxy-4-methyl-2-phenyltetrahydrofuran (3g). Mixture of diastereomers (11:5:2:1 ratio). Flash chromatography afforded a minor component (the 2 in the 11:5:2:1 mixture) analytically pure and a mixture of three diastereomers in a ratio of 11:5:1 (GC, t_R = 20.5, 20.0, 19.7 min respectively). Three-component mixture (11:5:1): clear oil. Major component (GC, t_R = 20.5 min): ^{1}H NMR (300 MHz, benzene-d_6, mixture of diastereomers) δ 7.33 (d, J = 7.7 Hz, 2H), 7.23−7.07 (m, overlaps with diastereomer, 3H), 4.83 (d, 1H), 3.56 (dd, J = 9.8, 8.2 Hz, 1H), 1.99−1.82 (m, overlaps with diastereomer, 1H), 1.03 (d, J = 4.6 Hz, 1H), 0.73 (d, J = 7.2 Hz, overlaps with diastereomer, 3H). Second component (GC, t_R = 20.0 min, 5 in the 11:5:1 mixture): ^{1}H NMR (300 MHz, benzene-d_6, mixture of diastereomers) δ 7.45 (d, J = 7.2 Hz, 2H), 7.23−7.07 (m, overlaps with diastereomer, 3H), 4.59 (d, J = 6.7 Hz, 1H), 3.98 (t, J = 8.0 Hz, overlaps with diastereomer, 1H), 3.47 (apparent t, J = 8.0 Hz, 1H), 3.30 (q, J = 6.3 Hz, 1H), 1.99−1.82 (m, overlaps with diastereomer, 1H), 1.12 (d, J = 5.1 Hz, 1H), 0.74 (d, J = 6.7 Hz, overlaps with diastereomer, 3H); ^{13}C NMR (75 MHz, benzene-d_6, mixture of 3 diastereomers)δ 142.5, 142.2, 128.5, 128.5, 127.3, 126.0, 125.8, 88.1, 86.4, 85.6, 80.7, 73.6, 73.3, 42.4, 36.9, 15.4, 9.8; IR (KBr) 3417, 2932, 1453, 1048, 700 cm^{-1}; MS (CI, NH$_3$) m/z 196 (100, M + NH$_4^+$), 179 (93, MH$^+$), 134 (42), 107 (30), 91 (54). Minor component (the 2 in the 11:5:2:1 mixture): clear oil; ^{1}H NMR (300 MHz, benzene-d_6) δ 7.32 (d, J = 7.2 Hz, 2H), 7.19−7.05 (m, 3H), 4.78 (d, J = 4.1 Hz, 1H), 4.24 (dd, J = 8.2, 6.7 Hz, 1H), 3.62 (apparent dd, J = 6.2, 3.6 Hz, 1H), 3.33 (dd, J = 8.2, 4.6 Hz, 1H), 2.20−2.08 (m, 1H), 0.77 (d, J = 4.1 Hz, 1H), 0.74 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, benzene-d_6) δ 138.2, 128.8, 128.5, 127.3, 83.4, 80.1, 73.8, 41.9, 16.6; IR (neat) 3425, 2963, 1453, 1045, 700 cm^{-1}; MS (CI, NH$_3$) m/z 196 (34, M + NH$_4^+$), 179 (100, M + H), 107 (37), 91 (62); HRMS calcd for $C_{11}H_{15}O_2$ (M + H) 179.1072, found 179.1070.

(2*S,3*R**)-4,4-Diethyl-3-hydroxy-2-(4-methylphenyl)tetrahydrofuran (3g):** white solid; mp 66 °C; ^{1}H NMR (500 MHz, benzene-d_6) δ 7.45 (d, J = 8.3 Hz, 2H), 7.07 (d, J = 7.8 Hz, 2H), 4.61 (d, J = 6.4 Hz, 1H), 3.69 (ABq, J = 9.1 Hz, $\Delta\nu$ = 21.9 Hz, 2H), 3.51 (t, J = 6.1 Hz, 1H), 2.14 (s, 3H), 1.48 (dq, J = 14.5, 7.3 Hz, 1H), 1.37−1.29 (m, 2H), 1.17 (dq, J = 14.4, 7.2 Hz, 1H), 0.96 (d, J = 5.9 Hz, 1H), 0.73 (t, J = 7.6 Hz, 3H), 0.68 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, benzene-d_6) δ 139.4, 136.8, 129.3, 126.0, 87.0, 85.2, 76.9, 48.1, 27.7, 21.9, 21.1, 8.6, 8.5; IR (KBr) 3404, 2961, 2360, 1456, 1049, 819 cm^{-1}; MS (EI, 20 eV) m/z 234 (4, M$^+$), 121 (100), 119 (14); HRMS calcd for $C_{15}H_{22}O_2$ 234.1620, found 234.1618.

(2*S,3*R**)-2-(4-Chlorophenyl)-4,4-diethyl-3-hydroxytetrahydrofuran (3h):** white solid; mp 86 °C; ^{1}H NMR (300 MHz, benzene-d_6) δ 7.24−7.16 (m, 4H), 4.43 (d, J = 6.7 Hz, 1H), 3.60 (s, 2H), 3.31 (t, J = 6.2 Hz, 1H), 1.43 (dq, J = 14.6, 7.6 Hz, 1H), 1.33−1.17 (m, 2H), 0.91 (d, J = 6.2 Hz, 1H), 1.08 (dq, J = 14.5, 7.3 Hz, 1H), 0.71 (t, J = 7.4 Hz, 3H), 0.64 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, benzene-d_6) δ 140.9, 133.2, 128.7, 127.2, 86.0, 85.1, 76.8, 48.1, 27.6, 21.8, 8.5, 8.4; IR (KBr) 3408, 2965, 2876, 1492, 1098, 826 cm^{-1}; MS (EI) m/z 255 (13, MH$^+$), 141 (20), 114 (37), 85 (100); HRMS calcd for $C_{14}H_{20}O_2Cl$ (M + H) 255.1153, found 255.1152.

(2*S,3*R**)-4,4-Diethyl-3-hydroxy-2-(4-nitrophenyl)tetrahydrofuran (3i):** white solid; mp 85−87 °C; ^{1}H NMR (300 MHz, benzene-d_6) δ 7.91 (d, J = 8.7 Hz, 2H), 7.19 (partially obscured d, J = 9.8 Hz, 2H), 4.39 (d, J = 6.7 Hz, 1H), 3.56 (s, 2H), 3.21 (t, J = 6.4 Hz, 1H), 1.38 (dq, J = 15.1, 7.7 Hz, 1H), 1.30−1.10 (m, 2H), 1.0 (dq, J = 14.6, 7.2 Hz, 1H), 0.84 (d, J = 6.2 Hz, 1H), 0.70 (t, J = 7.4 Hz, 3H), 0.61 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, benzene-d_6) δ 149.4, 147.6, 125.9, 123.6, 85.6, 84.9, 76.8, 48.3, 27.4, 21.8, 8.5, 8.4; IR (KBr) 3566, 2960, 2874, 1508, 1348 cm^{-1}; MS (EI) m/z 266 (24, MH$^+$), 114 (20), 85 (100); HRMS calcd for $C_{14}H_{20}NO_4$ (M + H) 266.1392, found 266.1398.

3,3-Diethyl-4-hydroxy-1-phenyl-2-butanone (4b): clear oil; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.35−7.17 (m, 5H), 3.79 (s, 2H), 3.74 (d, J = 6.2 Hz, 2H), 1.89 (t, J = 6.4 Hz, 1H), 1.83−1.64 (m, 4H), 0.86 (t, J = 7.7 Hz, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 213.7, 134.2, 129.8, 128.4, 126.8, 63.7, 56.7, 44.3, 25.4, 8.5; IR (neat) 3662, 2963, 1708, 1031, 722 cm^{-1}; MS (CI, NH$_3$) m/z 238 (35, M + NH$_4^+$), 221 (100, MH$^+$), 91 (42); HRMS calcd for $C_{14}H_{21}O_2$ (M + H) 221.1542, found 221.1534.

3,3-Dimethyl-1-phenyl-4-(triethlysilyl)oxy-2-butanone (4c): clear oil; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.36−7.17 (m, 5H), 3.89 (s, 2H), 3.69 (s, 2H), 1.19 (s, 6H), 0.99 (t, J = 8.0 Hz, 9H), 0.64 (q, J = 8.0 Hz, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 212.0, 134.9, 129.7, 128.2, 126.5, 70.1, 49.8, 44.9, 21.6, 6.8, 4.3; IR (neat) 2957, 1715, 1099, 725; cm^{-1}; MS (EI, 20 eV) m/z 306 (5, M$^+$), 277 (100), 219 (39), 187 (48), 159 (50), 115 (46); HRMS calcd for $C_{18}H_{30}O_2Si$ 306.2015, found 306.2018.

3-(Dimethyl)ethyl-4-hydroxy-1-phenyl-2-butanone (4d): white solid; mp 79−81 °C; ^{1}H NMR (300 MHz, benzene-d_6) δ 7.19−7.04 (m, 5H), 3.81 (dt, J = 10.0, 4.4 Hz, 1H), 3.63 (s, 2H), 3.47 (d, J = 9.75 Hz, 1H), 2.62 (dd, J = 10.3, 4.1 Hz, 1H), 1.76 (s, 1H), 0.82 (s, 9H); ^{13}C NMR (75 MHz, benzene-d_6) δ 211.9, 135.0, 130.8, 128.9, 127.3, 62.7, 62.6, 54.6, 33.2, 28.8; IR (neat) 3416, 2959, 1712, 1367, 1039, 700 cm^{-1}; MS (EI, 20 eV) m/z 221 (7, MH$^+$), 129 (100), 91 (41), 83 (75), 57 (99); HRMS calcd for $C_{14}H_{20}O_2$ 220.1463, found 220.14620.

4-Hydroxy-3-(methyl)ethyl-1-phenyl-2-butanone (4e): clear oil; ^{1}H NMR (300 MHz, CDCl$_3$)δ 7.36−7.18 (m, 5H), 3.90−3.81 (m, 1H), 3.79 (s, 2H), 3.74−3.65 (m, 1H), 2.66 (dq, J = 8.0, 4.0 Hz, 1H), 2.17−2.06 (m, 1H), 1.87 (dd, J = 6.7, 5.1 Hz, 1H), 0.93 (d, J = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, benzene-d_6)δ 211.1, 134.5, 130.2, 128.7, 127.0, 62.0, 59.7, 51.5, 27.7, 21.2, 19.9; IR (neat) 3422, 2961, 1708, 1057, 700 cm^{-1}; MS (EI, 20 eV) m/z 206 (8, M$^+$), 115 (90), 91 (31), 85 (35), 69 (100), 57 (36); HRMS calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.1306.

3-Methyl-1-phenyl-4-(triethlysilyl)oxy-2-butanone (4f): clear oil; ^{1}H NMR (300 MHz, benzene-d_6) δ 7.15−7.03 (m, 5H), 3.70 (dd, J = 9.7, 7.7 Hz, 1H), 3.57 (ABq, J = 15.4, $\Delta\nu$ = 27.3, 2H), 3.47 (dd, J = 9.8, 5.6 Hz, 1H), 2.76−2.65 (m, 1H), 0.95 (t, J = 8.0 Hz, 6H), 0.86 (d, J = 6.7 Hz, 3H), 0.53 (q, J = 7.9 Hz, 9H); ^{13}C NMR (75 MHz, benzene-d_6) δ 208.9, 134.9, 129.9, 128.7, 126.9, 65.7, 50.2, 47.8, 13.3, 7.0, 4.6; IR (neat) 2955, 2876, 1714, 1097, 730 cm^{-1}; MS (CI, NH$_3$) m/z 293 (100, MH$^+$), 263 (46), 91 (52); HRMS calcd for $C_{17}H_{29}O_2Si$ (M + H) 293.1937, found 293.1925.

3,3-Diethyl-1-(4-nitrophenyl)-4-(triethylsilyl)oxy-2-butanone (4i): clear oil; 7% yield; ^{1}H NMR (300 MHz, benzene-d_6) δ 7.87(d, J = 9.2 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 3.62 (s, 2H), 3.38 (s, 2H), 1.71−1.58 (m, 2H), 1.49−1.37 (m, 2H), 0.94 (t, J = 8.0 Hz, 9H), 0.66 (t, J = 7.5 Hz, 6H), 0.52 (q, J = 7.9 Hz, 6H); ^{13}C NMR (75 MHz, benzene-d_6) δ 208.9, 147.2, 142.4, 130.8, 123.3, 63.5, 57.1, 44.3, 23.8, 8.2, 7.0, 4.5; IR (neat) 2960, 1521, 1347, 729 cm^{-1}; MS (CI, NH$_3$) m/z 380 (91, MH$^+$), 350 (10), 132 (100); HRMS calcd for $C_{20}H_{34}NO_4Si$ (M + H) 380.2257, found 380.2255.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for all new compounds, NOESY spectra for **3a**−**e**, and X-ray data for **3i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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