Regioselective Preparation of 2,4-, 3,4-, and 2,3,4-Substituted Furan Rings. 2.[1] Regioselective Lithiation of 2-Silylated-3-substituted Furan Rings

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A new method for the preparation of 3,4- and 2,5-disubstituted furan rings is described. A variety of 2-silylated-3-(hydroxymethyl)furans and 2-silylated-3-furoic acids lithiate exclusively at C-4 when treated with 2.2 equivs of BuLi. The resulting dianions were quenched with a variety of electrophiles to provide 2-silylated-3-(hydroxymethyl)-4-substituted furans and 2-silylated-4-substituted 3-furoic acids in good to excellent yields. Removal of the silyl group (n-Bu_4NF) provided a variety of 4-substituted-3-(hydroxymethyl)furans and methyl 4-substituted-3-furoates, respectively. The latter esters were prepared due to difficulties encountered in isolating 4-substituted-3-furoic acids. The site of lithiation was altered by protecting the 3-hydroxyl group with a triethylsilane. Lithiation of 2-silylated-3-(((triethylsilyl)oxy)methyl)furan with 1.2 equivs of BuLi followed by the addition of electrophiles provided 2-silylated-3-(((triethylsilyl)oxy)methyl)-5-substituted furan rings. Subsequent removal of both silyl groups provided 2,4-disubstituted furan rings in moderate to good yields. A rationale is provided to explain why protection of the hydroxyl group at C-3 leads to a change in lithiation from the C-4 to the C-5 position of the furan ring. In addition, an explanation for the observed effect of adding HMPA or LiCl to the solution during the lithiation of 2-(*tert*-butyldimethylsilyl)-3-(hydroxymethyl)furan is provided.

In the preceding paper,[1] the difficulty in preparing 3,4- and 2,4-disubstituted furan rings due to the preference for furan rings to lithiate[2] and add electrophiles[3] in the C-2 or C-5 positions was discussed. New synthetic routes toward the preparation of furan rings which contain groups in the 3 and/or 4 positions are useful, since many natural products incorporate furan rings with either a 3,4- or 2,4-disubstituted or 2,3,4-trisubstituted pattern.[4] This paper describes a full account of our work in this area.

Some previous reports on the preparation of 3,4-disubstituted furans have involved using Diels−Alder/retro-Diels−Alder chemistry,[5] chemical modifications of 3,4-furandicarboxylic acid,[6] and the synthetic modification of acyclic precursors.[7] An alternative approach to the preparation of 3,4-disubstituted furans is the direct lithiation of substituted furan rings. The C-4 lithiation of a 3-substituted furan, however, has not been successful

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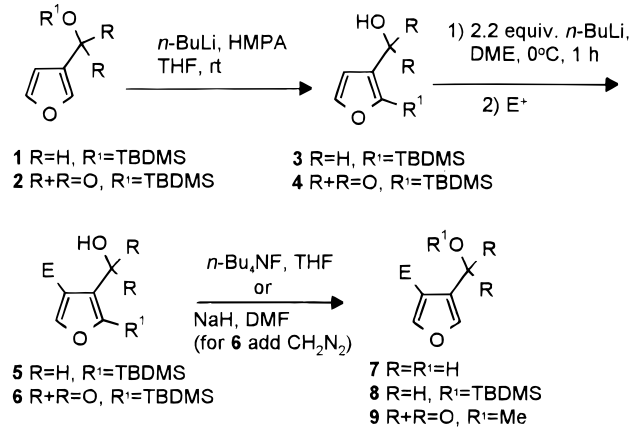
Scheme 1

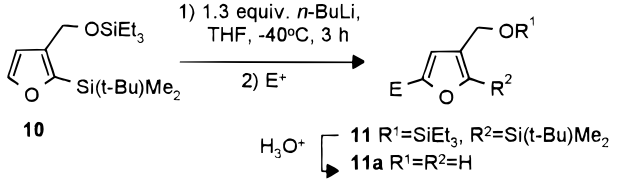


to date; only products resulting from a C-2 and/or C-5 lithiation have been isolated.[8] Recently, Lee and Garst[9] have reported that the *in situ* lithiation of an α-amino alkoxide from 3-furaldehyde provided some 3,4-disubstituted furan (3−13%) in addition to the expected 2,3- (24−36%) and 3,5- (2−8%) disubstituted products. Until recently, the lithiation of a 2,3-disubstituted furan had provided the C-5 lithiated species exclusively.[8g,h,k,10]

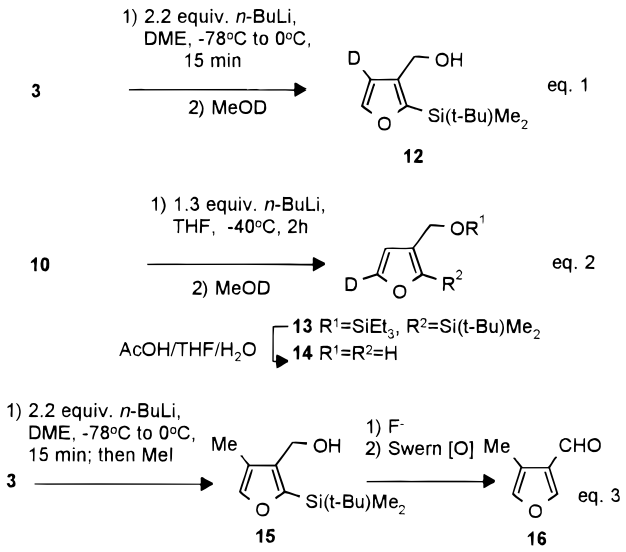
We reported the first successful regiospecific C-4 lithiation of a 2,3-disubstituted furan in 1988.[11] Thus 2-(*tert*-butyldimethylsilyl)-3-(hydroxymethyl)furan (**3**) provided 2,3,4-trisubstituted furans **5** when treated with 2.2 equivs of BuLi in DME at 0 °C for 1 h, and the resulting anion was quenched with an electrophile (Scheme 1). Furan **3** was prepared by a [1,4] O → C silyl migration of **1**.[12] Removal of the C-2 silyl group from **5** with *n*-Bu_4NF or by a [1,4] C → O silyl rearrangement (NaH, DMF) provided the corresponding 3,4-disubstituted furans (**7** or **8**), respectively.[13] These preliminary studies indicated that direct, high-yielding synthesis of 3,4-disubstituted furans via lithiation was possible. We later showed that 2-silylated-3-furoic acids would also undergo a C-4 lithiation, which after the removal of the C-2 silyl group followed by the addition of diazomethane (for ease of workup) provided 4-substituted-3-furoic esters in good to excellent yields (Scheme 1, see **2** → **4** → **6** → **9**).[14,15]

As previously mentioned, 2,4-disubstituted furans are also difficult to prepare. They have been synthesized by (a) the formation of the furan ring from acyclic precursors,[3] (b) a double electrophilic aromatic substitution of a 2-substituted furan (to give a 2,3,5-trisubstituted furan)[16] followed by removal of the initial C-2 group;[17] or (c) the direct C-5 lithiation of a 2,3-disubstituted furan followed by the removal of the initial C-2 group.[8g,h,9,18]

Scheme 2



Scheme 3



Both a bromine atom[16,18] and a phenylthio group[8g,h,17] have been successfully removed from the C-2 position of a 2,3,5-trisubstituted furan (*i.e.*, replaced by a hydrogen atom) thereby producing a 2,4-disubstituted furan.

More recently, we reported that if the hydroxymethyl group of furan **3** was protected with a silane (*i.e.*, furan **10**, Scheme 2), lithiation occurred exclusively at the C-5 position.[19] Trapping the resulting anion with electrophiles provided furans **11**, which upon removal of the silyl groups, gave 2,4-disubstituted furans **11a**.

This paper provides a full account of (a) the regiospecific C-4 lithiation of 2-silyl-3-(hydroxymethyl)furans, (b) the regiospecific C-4 lithiation of 2-silyl-3-furoic acids, and (c) the regiospecific C-5 lithiation of 2-silyl-3-(((triethylsilyl)oxy)methyl)furans as a means of preparing 3,4- and 2,4-disubstituted furan rings. In addition, a rationale for the change in regioselectivity of the lithiation when the hydroxyl group of furan **3** is converted into silyl ether **10** is provided. The previous paper in this issue[1] described in detail the preparation of the precursors for these lithiation studies by [1,4] O → C silyl migrations of 3-substituted furans.

C-4 Lithiation of 2-(*tert*-Butyldimethylsilyl)-3-(hydroxymethyl)furan (3)

Treatment of furan **3** with 2.2 equivs of BuLi in DME at −78 °C, warming the mixture to 0 °C, and stirring for 15 min, followed by the addition of MeOD, provided 4-deuterio-3-hydroxymethyl-2-(*tert*-butyldimethylsilyl)-furan (**12**) in 95% yield (Scheme 3). The ^1H NMR spectrum of furan **12** showed the presence of the α-furan signal at δ 7.6, the hydroxymethyl hydrogens at δ 4.6, and the groups attached to the silane at δ 0.9 (*tert*-butyl)

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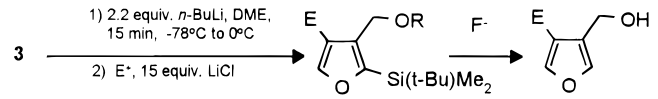
Table 1. Results from the C-4 Lithiation of Furan 3



entry	electrophile	product (% yield)[a]	product (% yield)[a]
1	MeOD	**12**, E = D; R = H (95)	**26** (92)
2	I_2	**17**, E = I; R = H (92)	**27** (91)
3	MeI	**15**, E = Me; R = H (82)	**28** (90)
4	Me_3SiCl	**18**, E = $SiMe_3$; R = H (78)	
5	$Cl(CH_2)_3I$	**19**, E = $(CH_2)_3Cl$; R = H (66)	**29** (94)
6	$ClCO_2Me$	**20**, E = R = CO_2Me (57)	**30**[b] (91)
7	$ClCONEt_2$	**21**, E = R = $CONEt_2$ (75)	**31** (90)
8	Bu_3SnCl	**22**, E = $SnBu_3$; R = H (89)	**32** (92)
9	Me_3SnCl	**23**, E = $SnMe_3$; R = H (88)	
10	DMF	**24**, E = CHO; R = H (91)	
11	allyl bromide	**25**, E = $CH_2CH=CH_2$; R = H (83)	

[a] Isolated yields. [b] Desilylation was performed on methyl 2-(*tert*-butyldimethylsilyl)-3-(hydroxymethyl)-4-furoate which was formed by hydrolysis of the carbonate group (K_2CO_3/MeOH) in **20**.

and 0.01 (2 × CH_3). The absence of a signal at δ 6.5 (present in furan **3**) indicated that the deuterium was at the C-4 position of furan ring in compound **12**.[20] Further confirmation was obtained from the broad band ^{13}C NMR spectrum. The ^{13}C NMR spectrum of compound **12** was similar to that of furan **3** except for a set of three lines in a 1:1:1 ratio centered at δ 110.5 (very weak in intensity). This was indicative of a carbon atom directly attached to one deuterium atom. The signal at δ 110.5 in the ^{13}C NMR spectrum of furan **3** had been previously assigned to the C-4 carbon atom,[21] since the C-5 carbon atom appeared downfield as a singlet at δ 146.7. Lithiation had occurred therefore at C-4 of furan **3** and not at C-5.

To further confirm that lithiation had occurred at the C-4 position, two synthetic sequences were performed. First, treatment of **10** with 1.3 equivs of BuLi in THF (−40 °C, 2 h), followed by a quench with MeOD, provided furan **13** (Scheme 3). Compound **13** was immediately treated with a 8:8:1 mixture of AcOH:THF:H_2O for 1 h to provide 5-deuteriofuran **14** in 77% yield. The furan region of the ^1H NMR spectrum of compound **14** only showed the absence of a peak at δ 7.6 and a signal at δ 6.5, while the broad band ^{13}C NMR spectrum showed a very weak three-line signal (line ratio 1:1:1) at δ 146.7 and a strong signal at δ 110.5. These data indicate that lithiation of **10** had occurred at the C-5 position. The preparation of the two possible deuterium isomers (compounds **12** and **14**) of 3-(hydroxymethyl)furan clearly showed that the lithiation of furans **3** and **10** provided the C-4 and C-5 carbanions, respectively.

The second piece of evidence to support a C-4 lithiation of furan **3** was the preparation of 4-methyl-3-furfural (**16**) (Scheme 3). The dianion of furan **3** was treated with 1 equiv of iodomethane to provide furan **15**. Desilylation of **15** with *n*-Bu_4NF followed by Swern oxidation[22] provided 4-methyl-3-furfural (**16**). The spectral data of synthetic **16** were identical to those reported for the same compound prepared by Reich[7c] from an acyclic acetylenic precursor.

The C-4 lithiation of furan **3** was optimized by treating **3** with 2.2 equivs of BuLi in DME at 0 °C for 15 min. The resultant dianion was quenched with a variety of electrophiles (Table 1), in the presence of 15 equivs of LiCl and stirred at 0 °C overnight to provide 2,3,4-trisubstituted furans in moderate to good yields. Only methyl chloroformate and *N*,*N*-diethylcarbamyl chloride reacted with both the C−Li and O−Li anions (entries 6 and 7, Table 1).

One important point regarding this reaction is noteworthy. If 15 equivs of LiCl was not added to the dianion prior to the electrophile, the yields of compounds **15** and **17**−**25** ranged from approximately 30 to 55% depending on the electrophile. The addition of TMEDA[23] or HMPA[23c,24] did not increase the yield of the products. This was surprising, since it has been reported[2,23,24] that additives such as TMEDA or HMPA usually increase the yield of products due to their ability to dissociate hexamers and tetramers of lithium-containing compounds, thereby making the anionic species more reactive to electrophiles. Only the addition of LiCl increased the yields of the products.

One explanation for the decreased reactivity of the dilithiated intermediate is the formation of a stabilized bridged dilithio species (**33**) (Scheme 4). It is well documented that some dilithiated compounds preferentially form bridged dilithio species rather than existing as two distinct lithium atoms. Supporting evidence for the formation of bridged dilithio species in other systems have been obtained by X-ray crystallography[25] and through semiempirical and *ab initio* level calculations.[26] With our system, *ab initio* calculations at the MP2/6-31+G*//6-21G* level on **33**−**35** indicated that **33** was

(20) We have often found the integration of the proton spectrum of substituted furan rings provides values which do not correspond to the structure if a normal pulse delay of zero seconds is used. T_1 measurements of the hydrogen atoms on substituted furan rings indicated that they fall in the range of 10−15 s. To obtain accurate integrals in the ^1H NMR spectra, we normally use a pulse delay of 60 s.

(21) It is well documented that the α-hydrogen and α-carbon atoms on a furan ring appear downfield relative to the β-hydrogen and β-carbon atoms in the ^1H and ^{13}C NMR spectra, respectively. See: (a) Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*, 5th ed.; John Wiley & Sons, Inc., 1991. (b) Biemann, K. (Translator from German). *Tables of Spectral Data for Structure Determination of Organic Compounds*; Boschke, F. L., Fresenius, W., Huber, J. F. K., Pungor, E., Rechnitz, G. A., Simon W., West, Th. S., Eds.; Springer-Verlag: Berlin, 1983.

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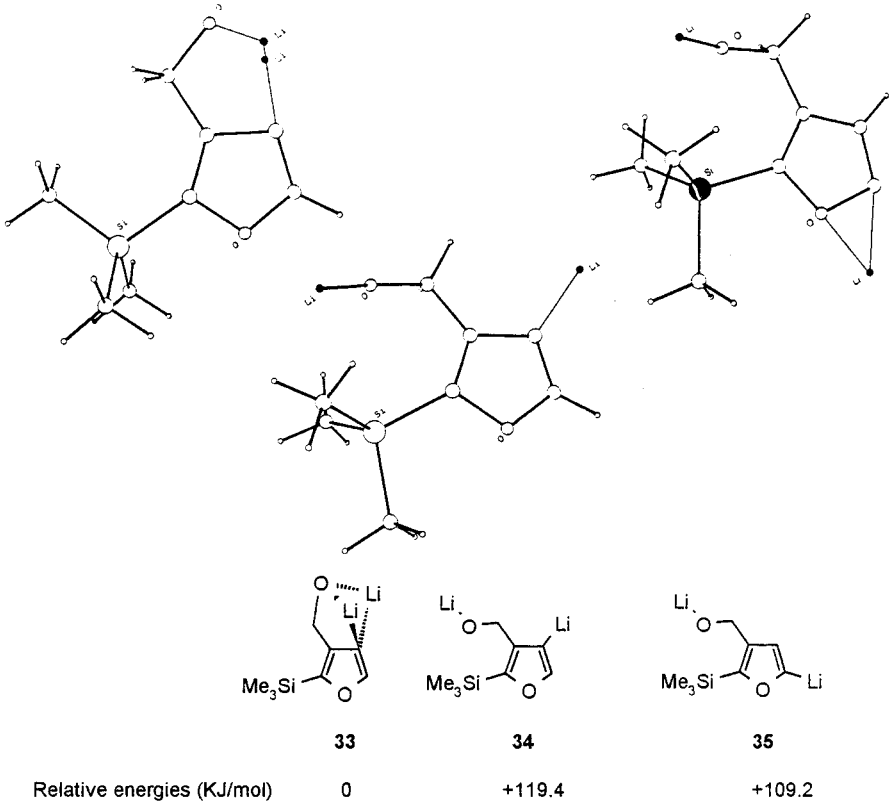
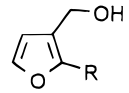
Scheme 4



more stable than **34** and **35** by 119.4 and 109.2 kJ/mol, respectively (Scheme 4). Thus the increased stability of **33** relative to that of **34** may be responsible for the decreased reactivity of the dilithiated species toward nucleophiles (at least in the gas phase). An increase in the rate of reaction with electrophiles, upon the addition of excess LiCl, may be explained by a deaggregation of the bridged dilithio compound **33** by an exchange of Li cations.[27,28]

The effect of substituents at the C-2 position of the furan ring on the regioselectivity of the lithiation was studied (Table 2). All of the substituted silanes prepared resulted in lithiation at the C-4 position of the furan ring (entries 1−5). Only the smaller methyl group resulted in a mixture of C-4 and C-5 (2:1) monolithiated species. These results would indicate that perhaps the size of the C-2 substituent could be in part responsible for the C-4 lithiation. The larger groups at C-2 could be hindering coordination of the BuLi to the furan oxygen atom, thereby allowing the hydroxymethyl group to direct the lithiation. Two pieces of data do not support this notion. First, when the alcohol of the hydroxymethyl group is protected with a silane, lithiation occurs exclusively at the C-5 position (Scheme 3, eq 2). Thus, the C-2 substituent cannot be completely blocking coordination of the BuLi with the furan oxygen atom. Second, we have shown by competitive NMR binding studies[29] and by *ab initio* calculations[30] that dialkyl ethers are much more Lewis basic than furan oxygen atoms. By analogy, the BuLi would be expected to coordinate preferentially with the hydroxymethyl (or $LiOCH_2R$) group than with the furan oxygen atom. Thus, the bulkiness of the C-2 substituent in blocking the coordination of the BuLi with the furan oxygen should play a minor role in effecting the regioselectivity of the lithiation. The presence of a smaller methyl group at C-2, however, results in a 2:1 ratio of C-4:C-5 lithiated furans.[31] An alternative expla-

Table 2. Effect of C-2 Substituents on the C-4:C-5 Anion Ratios[a]



entry	compd (R =)	C-4:C-5 anion ratio[b,c]
1	$SiMe_3$	100:1
2	Si(*i*-Pr)Me_2	100:1
3	Si(*t*-Bu)Me_2	100:1
4	Si(*t*-Bu)Ph_2	100:1
5	Si(*i*-Pr)$_3$	100:1
6	CH_3	64:36

[a] All reactions performed by treating the compound with 2.2 equivs of BuLi in DME at either −20 or 0 °C for 1 h, followed by a MeOD quench. [b] Ratio determined by integration of the ^{1}H NMR spectrum using a pulse delay of 60 s.[20] [c] Ratio was adjusted for the %H content of the MeOD as determined by mass spectrometry.

(26) (a) Saá, J. M.; Morey, J.; Frontera, A.; Deyá, P. M. *J. Am. Chem. Soc.* **1995**, *117*, 1105 and references therein. (b) Bauer, W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1989**, *111*, 7191. (c) Schleyer, P. v. R. *Pure Appl. Chem.* **1984**, *56*, 151. (d) Schleyer, P. v. R. *Pure Appl. Chem.* **1983**, *55*, 355.

(27) For papers related to the effect of adding lithium salts to asymmetric alkylations and aldol reactions, see: (a) Seebach, D.; Beck, A. K.; Studer, A. *Mod. Synth. Methods* **1995**, *7*, 1 and references therein. (b) Juaristi, E.; Beck, A. K.; Hansen, J.; Matt, T.; Mukhopadhyay, T.; Simson, M.; Seebach, D. *Synthesis* **1993**, 1271. (c) Hasegawa, Y.; Kawasaki, H.; Koga, K. *Tetrahedron Lett.* **1993**, *34*, 1963. (d) Loupy, A.; Tchoubar, B.; Astruc, D. *Chem. Rev.* **1992**, *92*, 1141. (e) Hall, P. L.; Gilchrist, J. H.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9571. (f) Thaler, A.; Seebach, D.; Cardinaux, F. *Helv. Chim. Acta* **1991**, *74*, 617. (g) Seebach, D.; Thaler, A.; Beck, A. K. *Helv. Chim. Acta* **1989**, *72*, 857.

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(29) (a) Hunt, I. R.; Rogers, C.; Woo, S.; Rauk, A.; Keay, B. A. *J. Am. Chem. Soc.* **1995**, *117*, 1049. (b) Hunt, I. R; Rauk, A.; Keay, B. A. *J. Org. Chem.* **1996**, *61*, 751.

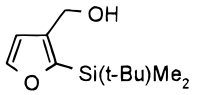
(30) Rauk, A.; Hunt, I. R.; Keay, B. A. *J. Org. Chem.* **1994**, *59*, 6808.

nation is that the size of the C-2 substituent results in an unfavorable steric interaction with the C-3 hydroxymethyl group. This interaction causes the hydroxymethyl or carboxylate group to rotate into a conformation whereby the hydroxyl is in close proximity to the C-4 hydrogen atom.[32,33] Lithiation occurs at C-4 due to preferential coordination of the BuLi with the hydroxymethyl group rather than with the furan oxygen atom. Thus the presence of bulky groups at C-2 enhances the *ortho*-directing effect of the hydroxymethyl group. The smaller methyl group invokes less steric interaction with the adjacent hydroxymethyl group, thereby leading to a diminished directing effect by this group and both C-4 and C-5 lithiation compete.

The observed exclusive C-5 lithiation with silyl-protected hydroxymethyl groups at C-4 (*vide infra*) can be explained simply by (1) a reduced basicity of the oxygen atom due to the attached silicon atom,[34] and (2) by an increased steric bulk around the same oxygen atom due to the attached silyl group. Both factors reduce the tendency for BuLi to coordinate to the ether oxygen atom and thus C-5 lithiation occurs.

The effect of various solvents and the addition of HMPA on the regioselectivity of metalation of furan **3** was determined (Table 3). Lithiation of **3** in hexane (with or without HMPA), ether, and THF (with and without TMEDA) provided C-4:C-5 ratios ranging from 65:35 to 75:25 (entries 1−3, 5, and 6). The addition of HMPA to ether and THF prior to the addition of BuLi resulted in the regiospecific lithiation of **3** at C-4 (entries 4 and 7). Interestingly, DME provided only C-4 lithiation in the presence and absence of HMPA (entries 8 and 9).[35] Stirring the anions prepared in hexane, ether, or THF for 6 h at 0 °C did not result in an "equilibration−disproportionation"[36] of the C-5 anion to the C-4 anion. That equilibration did not take place was initially surprising since the C-5 dianion **35** is less stable than the bridged dilthio species **33** by 109.2 kJ/mol (at least in the gas phase) (Scheme 4). If the lithiation reaction is under thermodynamic control, then the C-5 anion should have equilibrated to the C-4 anion. To test if the addition of HMPA would cause the equilibration, it was added to a mixture of the C-4 and C-5 anions generated in ether. The C-5 anion did not equilibrate to the C-4 position. These results indicated that the presence of HMPA in ether or THF or DME alone enhanced the *ortho*-directing effect of the hydroxymethyl group.

Table 3. Solvent Effects on the C-4:C-5 Anion Ratios of Furan 3[a]



3

entry	solvent	additive	C-4:C-5 ratio[b,c]
1	hexane		70:30
2	hexane	HMPA	66:34
3	ether		68:32
4	ether	HMPA	100:0
5	THF		75:25
6	THF	TMEDA	65:35
7	THF	HMPA	100:0
8	DME		100:0
9	DME	HMPA	100:0

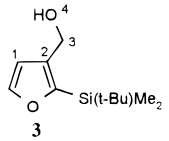
[a] All reactions performed by treating adding 2.2 equivs of BuLi to a mixture of compound **3**, the appropriate solvent, and HMPA or TMEDA (if required) at 0 °C for 1 h, followed by a MeOD quench. [b] Ratio determined by integration of the ^{1}H NMR spectrum using a pulse delay of 60 s.[20] [c] Ratio was adjusted for the %H content of the MeOD as determined by mass spectrometry.

The fact that lithiation of **3**, under a variety of conditions, occurs primarily at C-4 can possibly be explained by invoking a complex induced proximity effect (CIPE).[23e] This CIPE process has been postulated to explain the regiospecific lithiation of other systems containing hydroxymethyl groups,[37] alcohols (some generated *in situ*),[38,39] phenols,[40] aryl anions,[41] and allylic anions.[42] The initially formed lithium species directs the subsequent lithiation to an adjacent site. Closer examination of examples given in the account written by Beak and Meyers[23e] indicate that the addition of HMPA to systems exhibiting a CIPE process usually results in an interference with the CIPE process which results in a decreased directing effect.[43] In our case, however, the addition of HMPA appears to increase the CIPE effect since only C-4 lithiation is observed with HMPA in ether or THF. In the examples cited, in which the addition of HMPA results in a diminished CIPE effect, coordination of BuLi was to a carbonyl oxygen atom[43a] or a thioether;[43b] there were no reports of this effect for systems in which a lithium alkoxide was initially formed. Therefore, the

(31) An alternative explanation is that the acidity of the C-4 hydrogen atom has increased relative to that of the C-5 hydrogen atom due to electronic factors resulting from the presence of a silicon atom at C-2 of the furan ring. Semiempirical calculations (PM3) on 2-(trimethylsilyl)-3-(hydroxymethyl)furan indicated that the electronic density at the furan carbon atoms and the C-4 and C-5 hydrogen atoms were not significantly changed relative to the electronic densities calculated for similar atoms in 3-(hydroxymethyl)furan; therefore we believe stereoelectronic factors are not the driving force for the observed C-4 lithiation.

(32) This explanation is akin to a "gearing" or "cogwheeling" phenomenon, which leads to a "conformational lock". For a discussion on "gearing", etc., see: Eliel, E.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley and Sons: New York, 1994; p 1160 and references therein.

(33) Semiempirical PM3 geometry optimization calculations on compound **3** indicated that any initial geometry that had the hydroxyl group orientated toward the C-2 silyl group (including structures which had the hydroxyl group initially bisecting two of the silyl substituents) resulted in minimum energy structures in which the hydroxyl group was rotated away from the silyl group toward the C-4 hydrogen atom. The local minima structures (nine in total) had the $C_1-C_2-C_3-O_4$ dihedral angle ranging from +36° to +85°.



3

(34) (a) Shambayati, S.; Blake, J. F.; Wierschke, S. G.; Jorgensen, W. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 697. (b) Beak, P.; Kerrick, S. T.; Gallagher, D. J. *J. Am. Chem. Soc.* **1993**, *115*, 10628. (c) Shepherd, B. D. *J. Am. Chem. Soc.* **1991**, *113*, 5581.

(35) We do not understand why compound **3** lithiates exclusively at C-4 in DME in the absence of an additive. The bidendate nature of this solvent may not be the reason since the lithiation of 3 in a THF−TMEDA mixture resulted in a C-4:C-5 mixture.

(36) (a) Ziegler, F. E.; Fowler, K. W. *J. Org. Chem.* **1976**, *41*, 1564. (b) Leonard, N. J.; Bryant, J. D. *J. Org. Chem.* **1979**, *44*, 4612. (c) Ronald, R. C.; Winkle, M. W. *Tetrahedron* **1983**, *39*, 2031. (d) Marsais, F.; Quegwiner, G. *Tetrahedron* **1983**, *39*, 2009.

(37) MacDonald, T. L.; Narayanan, B. A. *J. Org. Chem.* **1983**, *48*, 1131.

(38) Taylor, S. L.; Lee, D. Y.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156.

(39) Commins, D. L.; Brown, J. D.; Mantlo, N. B. *Tetrahedron Lett.* **1982**, *23*, 3979.

(40) Posner, G. H.; Canella, K. A. *J. Am. Chem. Soc.* **1985**, *107*, 2571.

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(42) Bates, R. B.; Gordan, B., III; Highsmith, J. H.; White, J. J. *J. Org. Chem.* **1984**, *49*, 298.

(43) (a) Harris, F. L.; Weiler, L. *J. Chem. Soc., Chem. Commun.* **1985**, 1124. (b) Ekogha, C. B. B.; Ruel, O.; Julia, S. A. *Tetrahedron Lett.* **1983**, *24*, 4825 and 4829.

HMPA must be having an alternative effect on the system in **3** when treated with BuLi.

Jackman and Chen have recently reported[44] that the addition of HMPA to a variety of lithium phenolates can result in an increase or decrease of aggregation as well as the formation of "triple ion species".[45] The observed behavior depends on the basicity of the anion, steric factors, and the polarity of the solvent. Thus, we postulate that the presence of HMPA during the lithiation of **3** might be enhancing the directing ability of the lithium alkoxide group by increasing its ability to complex with another molecule of BuLi (*i.e.*, through increased aggregation).

Although the addition of HMPA enhances the C-4 lithiation of **3** in THF and ether, other factors must be playing an important role in the lithiation, since C-4 lithiation occurs exclusively at C-4 in DME without HMPA. These factors include (1) the presence of a silyl compound at C-2, (2) the presence of a hydroxymethyl group at C-3, (3) the solvent employed, and (4) whether HMPA is added prior to the addition of BuLi. Whatever the reason, 2-silylated-3-(hydroxymethyl)furan systems lithiate at C-4 and provide a short simple entry for the preparation of 2,3,4-trisubstituted furan rings and as the next section describes, a simple entry into 3,4-disubstituted furans rings.

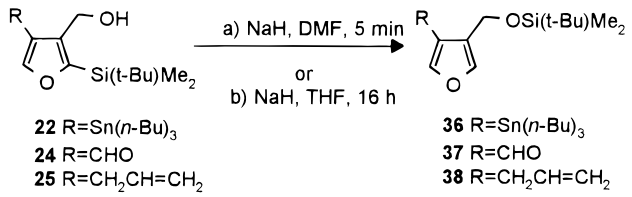
Preparation of 3,4-Disubstituted Furans

3,4-Disubstituted furan rings were easily prepared by the removal of the C-2 silyl group. Treatment of 2-silylated-3,4-disubstituted furans **12**, **17**, **15**, and **19**−**22** with *n*-Bu_4NF in THF (entries 1−3 and 5−8, Table 1) provided 3,4-disubstituted furans **26**−**32**, respectively, in excellent yield. The carbonate and urethane groups of furans **20** and **21** were removed prior to the desilylation by treating them with K_2CO_3/MeOH/1 h/rt and NaOMe/MeOH/12 h/60 °C, respectively. An alternative procedure for the preparation of 3,4-disubstituted furans was to reuse the C-2 silyl group as a protecting group for the hydroxymethyl group at C-3. A [1,4] C → O silyl migration[46] on compounds **22**, **24**, and **25** provided furans **36**−**38**, respectively, in excellent yield (Scheme 5) according to the procedures reported in the previous paper.[1]

C-4 Lithiation of 2-(*tert*-Butyldimethylsilyl)-3-furoic Acid (4) and Preparation of 4-Substituted-3-Furoic Esters

Due to low yields associated with the oxidation of 3-substituted-2-(*tert*-butyldimethylsilyl)-3-furaldehydes to the corresponding 3-furoic acids, we investigated whether 2-(*tert*-butyldimethylsilyl)-3-furoic acid (**4**) could

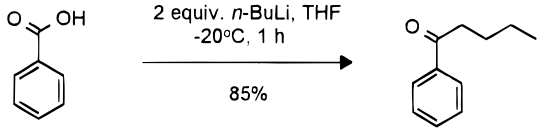
Scheme 5



22 R=Sn(*n*-Bu)$_3$
24 R=CHO
25 R=$CH_2CH{=}CH_2$

36 R=Sn(*n*-Bu)$_3$
37 R=CHO
38 R=$CH_2CH{=}CH_2$

Scheme 6



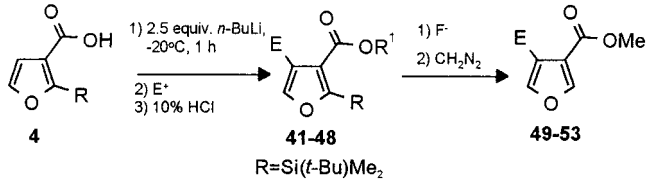
39 **40**

be lithiated at the C-4 position (Scheme 1).[15] Although we[15] and others[47] have reported that the treatment of benzoic acid (**39**) with 2 equivs of BuLi leads to the formation of the butyl ketone **40** (Scheme 6),[15] there have been some reports that carboxylate salts at low temperatures are resistant to addition of alkyllithiums (<−78 °C).[48] This fact, combined with the reports[49] that *ortho*-lithiated lithium benzoates can be formed by halogen−lithium exchange indicated that it may be possible to use carboxylic acids to direct lithiation. In fact, a search of the literature revealed that in 1964 Canton and coworkers[50] lithiated 3-methylisothiazole-4-carboxylic acid in the C-5 position by treating the acid with 2 equivs of BuLi! Since then, a number of heteroaromatic carboxylic acids have been *ortho*-lithiated using either BuLi[48d,51] or LDA.[8e,52] More recently Mortier *et al.* have shown that various benzoic acids will direct lithiation to the *ortho* position when treated with *s*-BuLi/TMEDA at −90 °C in THF.[53] Their work indicated *ortho*-lithiation with carboxylic acids was a general reaction when the lithiation was performed at −90 °C. This section describes the C-4 lithiation of 2-(*tert*-butyldimethylsilyl)-3-furoic acid (**4**).[15]

Treatment of acid **4** with 2.2 equivs of LDA at −78 °C for 1 h in either THF or DME (with or without HMPA) followed by quenching any dianion with MeOD provided only unreacted starting material. Repeating the reaction at −20 °C (1 h) did not result in any C-4 or C-5 deuteration. This failure led us to investigate the use of BuLi as the base for deprotonation. Treatment of acid **4** with 2.5 equivs of BuLi in THF or 1 h at −20 °C followed

(44) Jackman, L. M.; Chen, X. *J. Am. Chem. Soc.* **1992**, *114*, 403.
(45) (a) Jackman, L. M.; Scarmoutzos, L. M.; Porter, W. *J. Am. Chem. Soc.* **1987**, *109*, 6524. (b) Romesberg, F. E.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 5751.
(46) .(a) Woodbury, R. P.; Rathke, M. W. *J. Org. Chem.* **1978**, *43*, 1947. (b) Isobe, M.; Kitamura, M.; Goto, T. *Tetrahedron Lett.* **1979**, *20*, 3465. (c) Matsuda, I.; Murata, S.; Izumi, Y. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2389. (d) Matsuda, I.; Murata, S.; Ishii, Y. *J. Chem. Soc., Perkin Trans. 1* **1979**, 26. (e) Isobe, M.; Kitamura, M.; Goto, T. *Tetrahedron Lett.* **1980**, *21*, 4727. (f) Fleming, I.; Floyd, C. D. *J. Chem. Soc., Perkin Trans. 1* **1981**, 969. (g) Takeda, T.; Naito, S.; Ando, K.; Fujiwara, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 967. (h) Brook, A. G.; Chrusciel, J. J. *Organometallics* **1984**, *3*, 1317. (i) Isobe, M.; Ichikawa, Y.; Funabashi, Y.; Mio, S.; Goto, T. *Tetrahedron* **1986**, *42*, 2863. (j) Tietze, L. F.; Feissler, H.; Gewert, J. A.; Jakobi, U. *Synlett* **1994**, 2863. (k) Lautens, M.; Delanghe, P. H. M.; Goh, J. B.; Zhang, C. H. *J. Org. Chem.* **1995**, *60*, 4213.
(47) See ref 2, p 68.
(48) (a) Harper, R. J., Jr.; Solosky, E. J.; Tamborski, C. *J. Org. Chem.* **1964**, *29*, 2385. (b) Tamborski, C.; Soloski, E. J. *J. Org. Chem.* **1966**, *31*, 743 and 746. (c) Hauser, F. M.; Rhee, R. *J. Am. Chem. Soc.* **1977**, *99*, 4533. (d) Beak, P.; Brown, R. A. *J. Org. Chem.* **1979**, *44*, 4463. (e) Beak, P.; Brown, R. A. *J. Org. Chem.* **1982**, *47*, 34. (f) Winkle, M. R.; Ronald, R. C. *J. Org. Chem.* **1982**, *47*, 2101. (g) Palmer, B. D.; Boyd, M.; Denny, W. A. *J. Org. Chem.* **1990**, *55*, 438. (h) Cantegril, R.; Croisat, D.; Desbordes, P.; Guigues, F.; Mortier, J.; Peignier, R.; Vors, J.-P. Wo. Pat. 932287, 1993.
(49) (a) Gilman, H.; Melstrom, D. S. *J. Am. Chem. Soc.* **1948**, *70*, 4177. (b) Parham, W. E.; Sayed, Y. A.; *J. Org. Chem.* **1974**, *39*, 2051 and 2053. (c) Raynolds, P. W.; Manning M. J.; Swenton, J. S. Tetrahedron Lett. 1977, 2383. (d) Parham, W. E.; Bradsher, C. K.; Edgar, K. J. *J. Org. Chem.* **1981**, *46*, 1057.
(50) Canton, M. P.; Jones, D. H.; Slack, R.; Woolridge, K. R. H. *J. Chem. Soc.* **1964**, 446.
(51) Carpenter, A. J.; Chadwick, D. J. *Tetrahedron Lett.* **1985**, *26*, 1777.
(52) (a) Davies, G. M.; Davies, P. S. *Tetrahedron Lett.* **1972**, 3507. (b) Knight, D. W.; Nott, A. P. *J. Chem. Soc., Perkin Trans. 1* **1983**, 791. (c) Gammill, R. B.; Hyde, B. R. *J. Org. Chem.* **1983**, *48*, 3863. (d) Buttery, C. D.; Jones, R. G.; Knight, D. W. *Synlett* **1991**, 315.
(53) Mortier, J.; Moyroud, J.; Bennetau, B.; Cain, P. A. *J. Org. Chem.* **1994**, *59*, 4042.

Table 4. Preparation of 4-Substituted-3-furoic Esters



entry	E^+	solvent	additive	product (%)[a]	product (%)[a]
1	MeOD	THF		**41** (90) E = D; R^1 = H	**49** (86) E = D
2	MeI	DME	HMPA	**42** (88) E = Me; R^1 = H	**50** (90) E = Me
3	DMF	DME	HMPA	**43** (87) E = CHO; R^1 = H	
4	Me_3SiCl	DME	HMPA	**44** (86) E = $SiMe_3$; R^1 = H	
5	Me_3SnCl	THF	HMPA	**45** (86) E = $SnMe_3$	
6	CO_2	THF	HMPA	**46** (69)[b] E = CO_2Me; R^1 = Me	**51** (40) E = CO_2Me
7	propanal	THF	$MgBr_2$	**47** (52) E = CH(OH)Et; R^1 = H	**52** (31) E = CH(OH)Et
8	I_2	THF	$MgBr_2$	**48** (71) E = I; R^1 = H	**53** (87) E = I

[a]Isolated yields. [b] The diacid was difficult to isolate so the crude mixture was treated with excess diazomethane to provide diester **46**.

by the addition of MeOD provided 4-deuterio-2-(*tert*-butyldimethylsilyl)-3-furoic acid (**41**) (Table 4). The ^{1}H NMR spectrum of **41** indicated that the C-4 proton resonance which was at δ 6.80 in **4**, was absent. The C-5 hydrogen appeared as a broad singlet at δ 7.63. The ^{13}C NMR spectrum of **4** also confirmed the presence of a deuterium atom at C-4 by the presence of a very weak three line signal at δ 111.0 with intensities of 1:1:1. Further confirmation that a deuterium atom had been introduced was found in the mass spectrum of **41**. A base peak at *m/e* 170 ($M^{\bullet+}$ − *t*-Bu) confirmed the presence of a single deuterium atom.

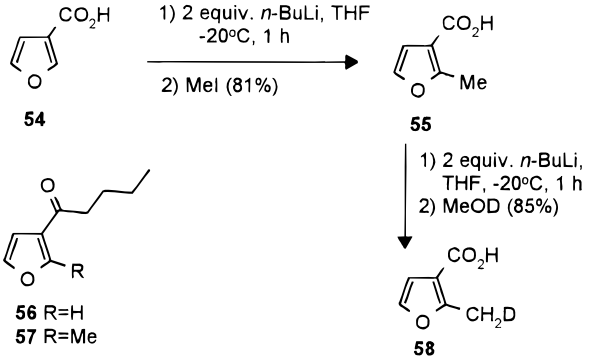
The dianion of **4** could be trapped with a number of electrophiles (Table 4) to provide 2,3,4-substituted furans **42**−**48**. The yields of compounds **42**−**46** were higher in the presence of HMPA, while treatment of the dianion of **4** with either propanal or iodine required an exchange of the lithium counterion to magnesium by the addition of $MgBr_2$ for reasonable yields to be obtained (entries 7 and 8, Table 4).

Compounds **41**, **42**, and **46**−**48** were desilylated by treatment with *n*-Bu_4NF in THF. The corresponding desilylated acids were difficult to purify by either column chromatography or distillation, so the crude materials were immediately treated with diazomethane in ether to provide esters **49**−**53** (Table 4).

We attempted to remove the C-2 silyl group by performing a [1,4] C → O silyl migration.[1] Treatment of furan **42** with catalytic amounts of NaH in DMF provided only 4-methyl-3-furoic acid (by ^{1}H NMR of the crude material) after workup. Either the NaH/DMF mixture was reductively removing the silyl group from the expected silyl ester[54] or the aqueous workup removed the silyl group to provide the acid. Silyl esters are known to be sensitive to hydrolysis by water.[55]

The use of BuLi to direct *ortho*-lithiation with furans was not limited to only furoic acid 4. 3-Furoic acid (**54**), when treated with 2 equivs of BuLi in THF at −20 °C for 1 h followed by the addition of iodomethane, provided 2-methyl-3-furoic acid (55) in 81% yield (Scheme 7). The remainder of material in the crude mixture was unreacted 3-furoic acid. Butyl ketone **56** was not detected by ^{1}H NMR or by GC/MS. Subsequent treatment of acid **55** with 2 equivs of BuLi (THF, −20 °C, 1 h) resulted in lithiation at the methyl group. Deuteration with MeOD afforded furoic acid **58** (85%) and ketone **57** (8%).[56] These results indicate that BuLi can be used directly on some furoic acids to direct lithiation; however, the presence of ketone **57** indicates that some side reactions at higher temperatures may occur (Scheme 7). Lowering the reaction temperature, however, may reduce the ability of BuLi to attack the carboxylate group.[53]

Scheme 7



The regioselectivity of lithiation with acids **54** and **55** can be explained by the increase in acidity of the C-2 furan hydrogen in **54**[57] and γ hydrogen in **55**[58] relative to the C-4 hydrogen atom. The regioselective C-4 lithiation of **4** must be due, in part, to the presence of the C-2

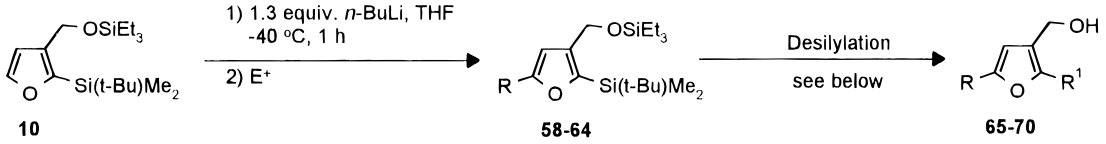
(54) For an example of a reductive desilylation using NaH/HMPA, see: Shekani, M. S.; Kahn, K. M.; Mahmood, K. *Tetrahedron Lett.* **1988**, *29*, 6161.

(55) Greene, T. W.; Wuts, P. G. M. Protective Groups in Organic Synthesis, 2nd ed.; John Wiley & Sons Inc.: New York, 1991.

(56) We have shown that the γ anion can be trapped with a variety of electrophiles in good to excellent yields, see: Yu, S.; Beese, G.; Keay, B. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2729.

(57) (a) Wakefield, B. J. *The Chemistry of Organolithium Compounds*; Pergamon: New York, 1974; p 26 and 44. (b) Paquette, L. A. *Principles of Modern Heterocyclic Chemistry*; W. A. Benjamin Inc.: New York, 1968; p 102 and references therein.

Table 5. Results from the Lithiation of Furan 10 and Subsequent Desilylations



10 **58-64** **65-70**

entry	electrophile	lithiation product (% yield)[a]	desilylation conditions	desilylation product (% yield)[a]
1	MeOD	**13**, R = D[b]	AcOH:THF:H_2O (8:8:1)	**65**, R = D; R^1 = Si(*t*-Bu)Me_2 (77)
2	MeI	**59**, R = Me (66)	AcOH:THF:H_2O (8:8:1)	**66**, R = Me; R^1 = Si(*t*-Bu)Me_2 (70)
3	$ICH_2CH{=}CH_2$	**60**, R = $CH_2CH{=}CH_2$[b]	AcOH:THF:H_2O (8:8:1)	**67**, R = $CH_2CH{=}CH{=}CH_2$; R^1 = Si(*t*-Bu)Me_2 (54)
4	DMF	**61**, R = CHO (61)	(a) AcOH:THF:H_2 (8:8:1)	**68**, R = CHO; R^1 = Si(*t*-Bu)Me_2 (72)
			(b) $Bu_4N^+F^-$/THF	**69**, R = CHO; R^1 = H (83)
5	$ClCONEt_2$	**62**, R = $CONEt_2$ (92)	$Bu_4N^+F^-$/THF	**70**, R = $CONEt_2$; R^1 = H (68)
6	$ClSnBu_3$	**63**, R = $SnBu_3$ (40)	AcOH:THF:H_2O (8:8:1)	decomposed[c]
7	$ClCO_2Me$	**64**, R = CO_2Me (34)[d]	K_2CO_3/MeOH[c]	complex mixture

[a] Isolated yields. [b] The crude reaction mixture was treated directly with a mixture of AcOH:THF:H_2O. [c] 2-Stannylfurans were very unstable to various types of acids and $Bu_4N^+F^-$/THF. [d] The yield is low due to the concomitant formation of methyl 3-(((methoxycarbonyl)oxy)methyl)-2-(*tert*-butyldimethylsilyl)-5-furanoate (35%) and is estimated by integration of the ^{1}H NMR spectrum of the mixture. [e] The above mixture (d) was treated with K_2CO_3/MeOH.

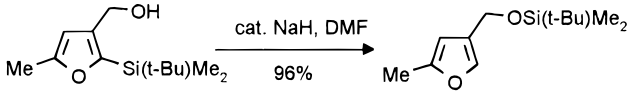
silyl group (*vide supra*). Similar complex induced proximity effects that occur with the hydroxymethyl group in furan **3** may be happening with the carboxylate group in furan **4**. In addition, the adjacent silyl group may be sterically hindering attack of the BuLi at the carbon atom of the carboxylate group. A rigid rotor search at the semiempirical level (PM3)[59] on the lithium salt of furan **4** indicated that structures which constituted >92% of the Boltzman distribution had the carboxylate in the plane of the furan ring. In these conformations, the carbon atom of the carboxylate is sterically blocked to attack by BuLi by the adjacent silyl group. This hindrance must allow the second equivalent of BuLi to coordinate to the carboxylate group, which results in lithiation at C-4, rather than the BuLi adding to the carboxylate group. In addition to this steric argument, the conjugate base of the furoic acid is deactivated by the strong donor/acceptor interaction between the electron-rich furan ring and the electron-deficient carboxylate, thereby slowing nucleophilic attack on the carboxylate.

The above results indicate that 2-silylated-3-furoic acids can be regiospecifically lithiated at the C-4 position and the resulting dianion quenched with electrophiles. Subsequent treatment with diazomethane followed by desilylation provided a simple entry into the preparation of 4-substituted-3-furoic esters.

Preparation of 2,4-Disubstituted Furan Rings

Protection of the hydroxymethyl group in furan **3** with a triethylsilyl group results in a change in the regioselectivity of lithiation (Scheme 2). Lithiation of **10** with 1.3 equivs of BuLi results in lithiation at C-5 exclusively. This was proven by trapping the anion with MeOD. The absence of a signal at δ 7.6 in the ^{1}H NMR spectrum of furan **13** (Scheme 3, eq 2, and Table 5, entry 1) indicated that lithiation had occurred at C-5.

Scheme 8



66 **71**

A variety of 2,4-disubstituted furans were prepared by trapping the C-5 anion with electrophiles followed by removal of the silyl group(s) (Table 5). The reaction was limited to reactive electrophiles since the addition of 1-chloro-3-iodopropane to the anion only provided only a 30% yield of the expected product. Products were generally isolated in moderate to good yields, but furan **60** and stannane **63** were sensitive to the workup procedure. The addition of methyl chloroformate resulted in a low yield of furan **64** and the formation of a product which was the result of a desilylation of the triethylsilyl group in product **64** and subsequent reaction of the resulting alcohol reacting with methyl chloroformate (35%). Workup involved stirring the mixtures with a solution of saturated ammonium chloride; however, stirring longer than 15 min resulted in partial removal of the triethylsilyl group. Although the reaction mixtures could be worked up and the products isolated, we found it convenient to treat some of the crude mixtures directly with a mixture of AcOH:THF:H_2O (8:8:1). This resulted in complete removal of the triethylsilyl group. Thus, alcohols **59** and **61** were isolated and then treated with the acetic acid mixture or the crude mixture containing **13** and **60** was directly treated with the acetic acid mixture to provide furans **65**−**68**, respectively, in moderate to good yields. Both silyl groups could be removed by treatment with *n*-Bu_4NF; compounds **61** and **62** provided furans **69** and **70**, respectively (entries 4b and 5, Table 5). The stannane **63** was found to be very sensitive to acids and bases, and decomposition occurred while removing the silyl groups. Various attempts to remove the silyl groups from ester **64** also failed, resulting in complex mixtures.

The hydroxymethyl group could be protected as a *tert*-butyldimethylsilyl ether by migrating the silyl group at C-2 to the oxygen atom using a [1,4] C → O silyl migration.[1] Thus, treatment of furan **66** with a catalytic amount of NaH in DMF afforded **71** in 96% yield (Scheme 8). This reaction illustrates that the somewhat expensive *tert*-butyldimethylsilyl group can be used as both a blocking group at C-2 in **10**, so lithiation occurs at C-5

(58) (a) Kraus, G. A. *J. Org. Chem.* **1981**, *46*, 201. (b) Vaulz, R. L.; Puterbaugh, W. H.; Hauser, C. R. *J. Org. Chem.* **1964**, *29*, 3514. (c) Braun, M.; Ringer, E. *Tetrahedron Lett.* **1983**, *24*, 1233.

(59) Semiempirical PM3 level calculations were performed on the carboxylate anion of furan **4** using *SPARTAN* version 4.0 (Wavefunction, Inc., 18401 Von Karman Ave., #370, Irvine, CA, 92715). A rigid rotor search was performed in which the Si−C_2 and $C-C_3$ bonds were rotated independently by increments of 36° and a geometry optimization performed on the resulting intermediate structure. A total of 23 structures were obtained, and the Boltzman distribution was calculated at 298 K.

(or C-4 *vide supra*), and then reused as a protecting group for the hydroxymethyl moiety at C-3 in **66**.

Conclusions

2-Silylated-3-(hydroxymethyl)furan and 2-silylated-3-furoic acids lithiate exclusively at C-4 upon treatment with 2.2 equivs of BuLi. 3,4-Disubstituted furan rings were prepared in good to excellent yields by the addition of various electrophiles followed by subsequent removal of the silyl group. The regioselectivity of lithiation could be changed to the C-5 position by protection of the hydroxymethyl group with a silyl ether. Trapping the C-5 anion with electrophiles followed by the removal of both silyl-protecting groups afforded 2,5-disubstituted furans in moderate to good yields. Work is continuing to apply these methods to the synthesis of natural products.[11f]

Experimental Section

^{1}H NMR spectra were run at 200 or 300 MHz and ^{13}C NMR spectra were run at 50 or 75 MHz in $CDCl_3$ as a solvent unless noted otherwise. Elemental analyses were performed by either Guelph Chemical Laboratories, Guelph, Ontario, Canada, or by Ms. Dorothy Fox at the University of Calgary. *tert*-Butyldimethylsilyl chloride was supplied from the Lithium Corporation of America (now FMC), Gastonia, NC. All solvents were dried and distilled prior to use. The oil from the NaH was removed by three successive washes with anhydrous ether. The remaining ether was removed under a high vacuum (4 h, rt). Flash column chromatography was performed using E. Merck silica gel (230−400 mesh A.S.T.M.) by the method developed by Still *et al.*[60] Compounds **1**−**4**, **37**, **38**[1] and **22**, **23**, **32**, **36**[11b] were prepared as previously described.

General Procedure 1: Lithiation of Furan 3. To a solution of furan **3** (0.25 g, 1.2 mmol) in dry DME (5 mL) at −78 °C under argon was added BuLi (1.04 mL of 2.5 M in hexane, 2.6 mmol). The mixture was stirred at 0 °C for 15 min and treated with 15 equivs of anhydrous LiCl (dried under a high vacuum by heating the a flask containing the LiCl with a Bunsen burner). After 15 min of stirring, an electrophile was added and the solution stirred at rt overnight. Saturated ammonium chloride (5 mL) was added and the mixture extracted with ethyl acetate (2 × 5 mL). The solvent was dried (Na_2SO_4) and removed *in vacuo* to leave an oil. If the oil was a mixture, column chromatography using silica gel was performed to separate the mixture. All compounds were purified by distillation.

2-(*tert*-Butyldimethylsilyl)-4-deuterio-3-(hydroxymethyl)furan (12). Using general procedure 1, compound **12** was prepared in 95% yield by adding MeOD (1.1 equivs) to the dianion: bp 76−78 °C/0.02 Torr; IR (KBr) 3319, 1070 cm^{-1}; ^{1}H NMR δ 0.01 (s, 6H), 0.89 (s, 9H), 1.5 (bs, 1H, exchanges with D_2O), 4.57 (s, 2H), 7.57 (s, 1H); ^{13}C NMR δ −5.7, 18.1, 25.7, 57.1, 110.5 (three lines equal intensity), 135.9, 146.7, 155.0; mass spectrum *m/e* 213 (M^+).

General Procedure 2: Desilylation To Prepare Furans 26−32. Furan **12** (1 equiv) was stirred with *n*-Bu_4NF (2 equivs) in dry THF (1 mL per mmol of **12**) under argon until TLC indicated the reaction was complete. Saturated ammonium chloride (1 mL per mmol of **12**) was added and the mixture extracted with ethyl acetate (2 × 3 mL). The solvent was dried (Na_2SO_4) and removed *in vacuo* to leave an oil. If the oil was a mixture column chromatography using silica gel was performed to separate the mixture. All compounds were purified by distillation.

4-Deuterio-3-(hydroxymethyl)furan (26). Using general procedure 2, compound **26** was prepared in 92% from furan **12**: bp 87−90 °C/0.02 Torr; IR (KBr) 3350, 1050 cm^{-1}; ^{1}H NMR δ 3.2 (bs, 1H, exchanges with D_2O), 4.55 (s, 2H), 7.39 (s, 1H), 7.40 (s, 1H); ^{13}C NMR δ 56.4, 109.8 (three lines equal intensity), 125.1, 139.8, 143.3; mass spectrum *m/e* 99 (M^+).

4-Methyl-3-furaldehyde (16). To a solution of oxalyl chloride (0.16 mL, 1.1 equivs) in dry CH_2Cl_2 (5 mL) at −50 °C was added dimethyl sulfoxide (0.25 mL, 2.2 equivs). After 2 min furan **15** (0.18 g) in CH_2Cl_2 (2 mL) was added. After 15 min, Et_3N (1.13 mL, 5.0 equivs) was added and the mixture warmed slowly to rt. Water (10 mL) was added, and the CH_2Cl_2 extracts were washed with saturated NaCl (10 mL), 1% HCl (10 mL), water (10 mL), 5% Na_2CO_3 (10 mL), and water (10 mL). The CH_2Cl_2 was dried (Na_2SO_4) and removed *in vacuo* to provide an oil which was purified by distillation to yield **16** (89%): bp 67−72 °C/20 Torr; IR (neat) 1690 cm^{-1}; ^{1}H NMR δ 2.06 (s, 3H), 7.07 (s, 1H), 7.80 (s, 1H), 9.81 (s, 1H); mass spectrum *m/e* 110 (M^+) [lit.[7c] IR (neat) 1685 cm^{-1}; ^{1}H NMR δ 2.08 (s, 3H), 7.08 (s, 1H), 7.82 (s, 1H), 9.82 (s, 1H)].

1-Phenyl-1-pentanone (40). Benzoic acid (0.14 g, 1.15 mmol) in dry THF (5 mL) at −20 °C under argon was treated with BuLi (2.2 equivs). The mixture was stirred at −20 °C for 1 h. Saturated ammonium chloride was added, followed by an extraction with ethyl acetate (2 × 5 mL). The solvent was dried (Na_2SO_4) and removed *in vacuo* to leave an oil which was purified to provide ketone **40** (85%): bp 128−132 °C/20 Torr [lit.[61] bp 105−107 °C/5 Torr]; IR (neat) 1685 cm^{-1}; ^{1}H NMR δ 0.96 (t, 3H), 1.40 (sextet, J = 7.3 Hz, 2H), 1.72 (quintet, J = 7.3 Hz, 2H), 2.95 (t, J = 7.3 Hz, 2H), 7.4−7.5 (m, 2H), 7.5−7.6 (m, 1H), 7.92−7.96 (m, 2H); ^{13}C NMR δ 13.9, 22.9, 26.7, 38.0, 128.1, 128.6, 132.9, 137.3, 200.3; mass spectrum *m/e* 162 (M^+).

General Procedure 3: Lithiation of Furoic Acid 4. To a solution of furan **4** (1.0 mmol) in dry THF (5 mL) at −78 °C under argon was added BuLi (2.2 equivs). The mixture was stirred at −20 °C for 1 h and treated with HMPA (2.5 mmol) (or $MgBr_2$, 5 mmol). After 1 h an electrophile was added and the mixture stirred at 0 °C for 6 h. The mixture was poured into a separatory funnel, and ethyl acetate (10 mL) was added followed by the addition of water (10 mL). The mixture was acidified by the addition of 10% HCl (10 mL) and shaken vigorously, and the ethyl acetate was immediately separated from the acid layer (this minimizes decomposition of the furan ring by the HCl). The ethyl acetate extract was dried (Na_2SO_4) and removed *in vacuo*. The crude material was purified by column chromatography using silica gel.

2-(*tert*-Butyldimethylsilyl)-4-deuterio-3-furoic Acid (41). Using general procedure 3, compound **41** was prepared in 90% yield by adding MeOD (1.1 equivs) to the dianion. **41**: column chromatography, petroleum ether:EtOAc (20:1); mp 83−88 °C; IR (KBr) 3500−2500 (b), 1685 cm^{-1}; ^{1}H NMR δ 0.01 (s, 6H), 0.96 (s, 9H), 7.93 (s, 1H), 9.5 (bs, 1H, exchanges with D_2O); ^{13}C NMR δ −5.7, 16.0, 26.7, 110.5 (three lines equal intensity), 126.0, 146.4, 166.0, 170.1; mass spectrum *m/e* 170 (M^+ − *t*-Bu); HRMS calcd for $C_7H_8DO_3Si$ 170.0384, found 170.0382.

General Procedure 4: Desilylation and Esterification of Furoic Acids 41, 42, and 46−48. To a solution of a furoic acid (1.3 mmol) in dry THF (5 mL) at 0 °C under argon was added *n*-Bu_4NF (1.5 equivs). The mixture was stirred at 0 °C for 1 h, and the mixture extracted with ethyl acetate (2 × 10 mL). The ethyl acetate was dried (Na_2SO_4) and removed *in vacuo*. The crude material was immediately dissolved in dry ether (20 mL) and cooled to 0 °C. Excess diazomethane was added slowly, and the mixture was warmed to rt. Argon was bubbled through the solution for 1 h, and the ether was removed *in vacuo* to leave an oil.

Methyl 4-Deuterio-3-furoate (49). Using general procedure 4, compound **49** was prepared in 86% yield from furoic acid **41**: IR (KBr) 1734 cm^{-1}; ^{1}H NMR δ 3.85 (s, 3H), 7.43 (s, 1H), 8.02 (s, 1H); mass spectrum *m/e* 127 (M^+), 96 (M^+ − OMe); HRMS calcd for $C_6H_5DO_3$ 127.0378, found 127.0388.

2-Methyl-3-furoic Acid (55). To a solution of furan **54** (0.10 g, 0.89 mmol) in dry THF (7.0 mL) at −78 °C under N_2 was added BuLi (2.0 equivs of 2.5 M in hexanes). The mixture was stirred at −20 °C for 1 h and treated with freshly distilled iodomethane (excess, passed through basic alumina prior to

(60) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(61) *Dictionary of Organic Compounds*, 5th ed.; Vol. 5, p 4653.

distillation). The mixture was stirred at rt overnight. The THF was removed *in vacuo*, and ether (5 mL) and saturated ammonium chloride (5 mL) were added. HCl (5 mL of 10%) was added, and the ether was separated within 5 min, dried (Na_2SO_4), and removed *in vacuo* to leave an oil which was purified by distillation to provide acid **55** (81%) as a solid: mp 102−105 °C [lit.[8f] mp 101−102 °C]; ^{1}H NMR δ 2.55 (s, 3H), 6.43 (d, 1H, J = 1.6 Hz), 7.0 (d, 1H, J = 1.6 Hz); mass spectrum *m/e* 126 (M^+).

2-(Deuteriomethyl)-3-furoic Acid (58). To a solution of furan **55** (0.12 g, 0.95 mmol) in dry THF (7.0 mL) at −78 °C under N_2 was added BuLi (2.0 equivs of 2.5 M in hexanes). The mixture was stirred at −20 °C for 1 h and treated with MeOD. The mixture was stirred at rt for 1 h and the THF removed *in vacuo*. Diethyl ether (5 mL) and saturated ammonium chloride (5 mL) were added. HCl (5 mL of 10%) was added, and the ether was separated within 5 min, dried (Na_2SO_4), and removed *in vacuo* to leave a mixture of acid **58** (85%) and ketone **57** (identified by GC/MS and not purified, 8% by ^{1}H NMR); column chromatography, petroleum ether: EtOAc (1:1) provided acid **58**: ^{1}H NMR δ 2.55 (broadened s, 2H), 6.43 (d, 1H, J = 1.6 Hz), 7.0 (d, 1H, J = 1.6 Hz); mass spectrum *m/e* 127 (M^+).

2-(*tert*-Butyldimethylsilyl)-3-(((triethylsilyl)oxy)methyl)furan (10). To a solution of imidazole (84 mmol) in DMF (20 mL) at 0 °C was added chlorotriethylsilane (40 mmol). After 10 min, alcohol **3** (40 mmol) was added and the mixture stirred 12 h at rt. Saturated sodium chloride (20 mL) and ether (20 mL) were added, and the ether layer was separated, dried (Na_2SO_4), and removed *in vacuo* to leave an oil. Distillation provided furan **10** in 89% yield: bp 76−84 °C/0.05 Torr; IR (KBr) 2911, 1100 cm^{-1}; ^{1}H NMR δ 0.28 (s, 6H), 0.65 (q, 6H), 0.90 (s, 9H), 0.98 (t, 9H), 4.62 (s, 2H), 6.47 (d, 1H, J = 1.4 Hz), 7.58 (d, 1H, J = 1.4 Hz); ^{13}C NMR δ −5.60, 4.5, 6.7, 17.5, 26.4, 57.2, 110.6, 136.7, 146.2, 153.5; mass spectrum *m/e* 269 (M^+ − *t*-Bu); HRMS calcd for $C_{13}H_{25}O_2Si_2$ 269.1383, found 269.1393. Anal. Calcd for $C_{17}H_{34}O_2Si_2$: C, 62.51; H, 10.49. Found: C, 63.08; H, 11.05.

General Procedure 5: C-5 Lithiation of Furan 10. To a solution of furan **10** (0.25 g, 0.76 mmol) in dry THF (9.4 mL) at −78 °C under N_2 was added BuLi (1.3 equivs of 2.5 M in hexanes). The mixture was stirred at −40 °C for 3 h and treated with an electrophile. The mixture was stirred at rt overnight. The THF was removed *in vacuo*, and ether (5 mL) and saturated ammonium chloride (5 mL) were added. The ether was separated within 5 min, dried (Na_2SO_4), and removed *in vacuo* to leave an oil. The compound was either purified by distillation.

2-(*tert*-Butyldimethylsilyl)-5-methyl-3-(((triethylsilyl)oxy)methyl)furan (59). Using general procedure 5, compound **59** was prepared in 66% yield by adding freshly distilled MeI (2 equivs, passed through basic alumina prior to distillation): bp 88−94 °C/0.04 Torr; IR (neat) 1250 cm^{-1}; ^{1}H NMR δ 0.25 (s, 6H), 0.66 (q, J = 6.9 Hz, 6H), 0.91 (s, 9H), 0.95 (t, J = 6.9 Hz, 9H), 2.28 (s, 3H), 4.54 (s, 2H), 6.05 (s, 1H); ^{13}C NMR δ −5.9, 4.5, 6.8, 13.7, 17.4, 26.4, 57.3, 117.0, 137.8, 151.6, 158.1; mass spectrum *m/e* 283 (M^+ − *t*-Bu). Anal. Calcd for $C_{18}H_{36}O_2Si_2$: C, 63.47; H, 10.65. Found: C, 63.84; H, 10.93.

2-(*tert*-Butyldimethylsilyl)-3-(hydroxymethyl)-5-methylfuran (66). Furan **59** (0.1 g, 0.29 mmol) was treated with an AcOH:THF:H_2O (1:1:1) mixture (5 mL total volume) and stirred at rt overnight. Saturated Na_2CO_3 was added slowly to neutralize the AcOH. The THF was removed *in vacuo*, and ether (5 mL) was added. The ether was separated within 5 min, dried (Na_2SO_4), and removed *in vacuo* to leave an oil. The compound was purified by distillation: yield 70%; mp 50−51 °C; IR (neat) 3349, 1253 cm^{-1}; ^{1}H NMR δ 0.28 (s, 6H), 0.91 (s, 9H), 2.30 (s, 3H), 4.52 (s, 2H), 6.07 (s, 1H); ^{13}C NMR δ −5.9, 13.7, 17.1, 26.3, 57.3, 106.7, 137.0, 153.0, 156.6; mass spectrum *m/e* 169 (M^+ − *t*-Bu).

4-(Hydroxymethyl)-2-furaldehyde (69). A solution of furan **61** (0.22 g, 0.62 mmol) in THF (5 mL) at 0 °C was treated with *n*-Bu_4NF (1.5 equivs, 1 M solution in THF). The mixture was warmed to rt and stirred overnight. The THF was removed *in vacuo*, and ether (5 mL) and saturated ammonium chloride (5 mL) was added. The ether was separated, dried (Na_2SO_4), and removed *in vacuo* to leave an oil. The compound was purified by distillation: yield 83%; bp 62−7 °C/0.02 Torr; IR (neat) 3464, 1679 cm^{-1}; ^{1}H NMR δ 3.10 (bs, 1H, exchanges with D_2O), 4.57 (s, 2H), 7.24 (s, 1H), 7.64 (s, 1H), 9.54 (s, 1H); ^{13}C NMR δ 55.8, 120.8, 128.4, 145.3, 153.1, 176.1; mass spectrum *m/e* 126 (M^+), 125 (M^+ − H); HRMS calcd for $C_6H_6O_3$ 126.0317, found 126.0308.

General Procedure 6: C-5 Lithiation of Furan 10 and Immediate Removal of the Triethylsilyl Group. To a solution of furan **10** (0.25 g, 0.76 mmol) in dry THF (9.4 mL) at −78 °C under N_2 was added BuLi (1.3 equivs of 2.5 M in hexanes). The mixture was stirred at −40 °C for 3 h and treated with an electrophile. The mixture was stirred at rt overnight. The THF was removed *in vacuo*, and ether (5 mL) and saturated ammonium chloride (5 mL) were added. The ether was separated within 5 min, dried (Na_2SO_4), and removed *in vacuo* to leave an oil. The oil was immediately treated with an AcOH:THF:H_2O (1:1:1) mixture (10 mL total volume) and stirred at rt overnight. Saturated Na_2CO_3 was added slowly to neutralize the AcOH. The THF was removed *in vacuo* and ether (5 mL) was added. The ether was separated within 5 min, dried (Na_2SO_4), and removed *in vacuo* to leave an oil. The compound was purified by distillation.

2-(*tert*-Butyldimethylsilyl)-5-deuterio-3-(hydroxymethyl)furan (65). Using general procedure 6, compound **65** was prepared in 77% yield by adding MeOD to the anion: bp 72−79 °C/0.04 Torr; IR (KBr) 3560, 1253 cm^{-1}; ^{1}H NMR δ 0.30 (s, 6H), 0.92 (s, 9H), 4.59 (s, 2H), 6.48 (s, 1H); ^{13}C NMR δ −5.7, 17.3, 25.9, 57.1, 110.2, 135.9, 146.8, 155.0 (three lines equal intensity); mass spectrum *m/e* 156 (M^+ − *t*-Bu).

4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-methylfuran (71). A solution of freshly distilled **66** (0.74 g, 3.3 mmol) and HMPA (3.6 mmol, dried over CaH_2, distilled and stored over 4 Å molecular sieves) in dry THF (10 mL) was cooled to −78 °C under argon and treated with BuLi (1.43 mL of 2.5 M in hexanes, 3.6 mmol). The solution was allowed to come to rt over 6 h and stirred at rt overnight. Saturated ammonium chloride was added and the solution extracted with ether. The organic layer was washed three times with saturated copper sulfate and dried (Na_2SO_4), and the solvent was removed *in vacuo* to afford after distillation **71**: yield 71%; bp 88−94 °C/20 Torr; IR (neat) 1259 cm^{-1}; ^{1}H NMR δ 0.10 (s, 6H), 0.92 (s, 9H), 2.26 (s, 3H), 4.54 (s, 2H), 5.96 (s, 1H), 7.19 (s, 1H); ^{13}C NMR δ −5.2, 13.5, 16.4, 25.9, 57.6, 105.7, 126.5, 137.8, 152.7; mass spectrum *m/e* 226 (M^+), 169 (M^+ − *t*-Bu).

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Supporting Information Available: Complete spectral data for **14**, **15**, **17**−**21**, **24**, **25**, **27**−**29**, **30**, **32**, **42**−**48**, **50**−**53**, **61**−**64**, **67**, **68**, and **70** (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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