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Silyl substituted furans in the stereoselective Birch reduction

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Abstract—Chiral derivatives of 3-silyl-2-furoic acid were prepared and subjected to a Birch reductive alkylation reaction. It was found that the presence of a silicon atom, *ortho* to the chiral auxiliary, enabled the synthesis of dihydrofurans with high levels of stereoselectivity. We believe that the silicon group is essential in order to control the geometry of the enolate formed in the reduction regime. Remarkably, the partial reduction conditions could be tailored so that the silicon is removed in situ, before the furan derived enolate is alkylated.

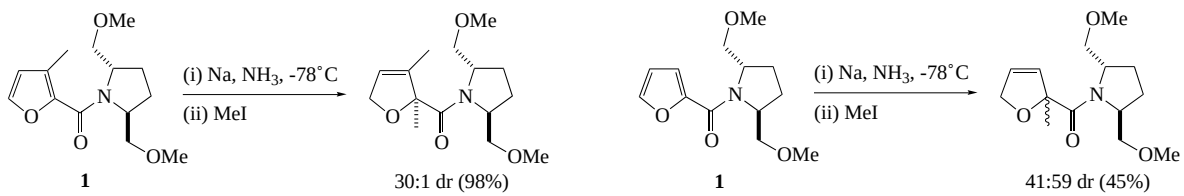
The notion of placing a chiral auxiliary on an acyl group attached to an aromatic ring and then perfoming a stereoselective Birch reduction belongs to A. G. Shultz, who published a series of papers describing the Birch reduction of all manner of benzenoid compounds.[1] More recently, we extended this concept to encompass heterocycles and published the results of the stereoselective Birch reduction of both pyrroles[2] and furans.[3] Initial work concerning the reductive alkylation of furans revealed that it was essential that a methyl group be placed adjacent to the auxiliary bearing acyl group at C-3 (Scheme 1).[3] We suggested that the alkyl group had the effect of fixing enolate geometry for without it little stereoselection was observed.

The C-3 methyl group can be replaced successfully with a larger alkyl derivative but, clearly, this substitution pattern requirement places limitations on the nature of the furans that can be alkylated stereoselectively.

In an attempt to overturn this shortcoming, we decided to replace the C-3 alkyl group with one that might facilitate stereoselectivity during reduction but that could be removed afterwards; a TMS group seemed ideal. The requisite furan **2** was prepared in two high yielding steps from furoyl chloride via (i) amide formation and (ii) amide directed *ortho* lithiation of **1** which was directed exclusively towards C-3 rather than C-5 of the furan[4] (Scheme 2). Preliminary studies showed that the (chelating?) bis-hydroxymethylpyrroline amide was essential to achieve good regioselectivity during *ortho*-lithiation.

Birch reductive alkylation of the amide **2** allowed the introduction of a variety of groups at the C-2 position in good yields and with high levels of stereoselectivity (Table 1).

The relative stereochemistry of the products **3**–**7** was assigned after X-ray crystallography on a derivative of **3**;[7] we assume that the sense of selectivity displayed by reaction with one electrophile is conserved during reaction with the others outlined in Table 1. The relative stereochemistry contained within compounds **3**–**7** is consistent with our previously described mechanistic model which assumes that (after addition of two electrons and a proton to **2**) a *trans* enolate **A** is formed



Scheme 1.

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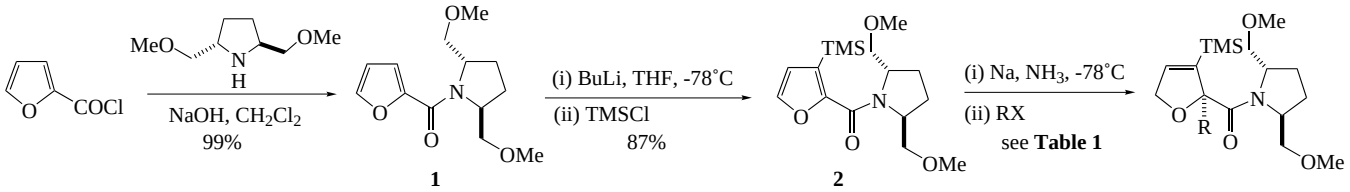


Scheme 2.

Table 1.

RX	R	De[5] (%) (**3**–**7**)	Yield (%)	Compound
MeI	Me	94	90	**3**
^{i}BuI	^{i}Bu	94	70	**4**
BnBr	Bn	94	79	**5**
MOMCl	CH_2OMe	94[6]	92	**6**
$I(CH_2)_3Cl$	$(CH_2)_3Cl$	94[6]	80	**7**

which reacts with a high degree of *Re* face stereoselectivity under the influence of the chiral auxiliary (Fig. 1).[3] We speculate that the *trans* enolate geometry is favoured firstly by steric considerations but also by the possibility of an attractive O–Si interaction.

Removal of the auxiliary was straightforward under the action of aqueous HCl (Scheme 3). Depending upon the conditions used, we were able to hydrolyse the auxiliary with retention of the TMS group or, by reaction under more vigorous conditions, remove the *ortho* silyl group completely by *ipso* protodesilylation.[8] When particularly bulky groups were situated at C-2 of the dihydrofurans (e.g. ^{i}Bu), then it was not possible to remove the amide auxiliary without at least partial replacement of the TMS group; in such cases it proved best to use more vigorous conditions and remove both auxiliaries at the same time. As we already know the relative sterochemistry of **3**–**7**, vide supra, we can readily assign the absolute stereochemistry of the corresponding acids to be as shown.

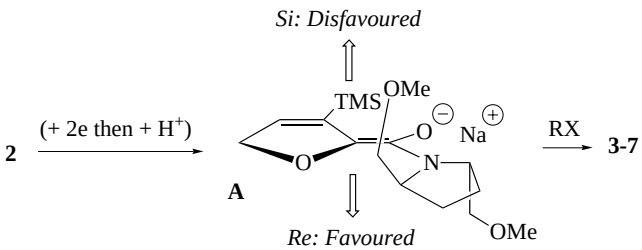
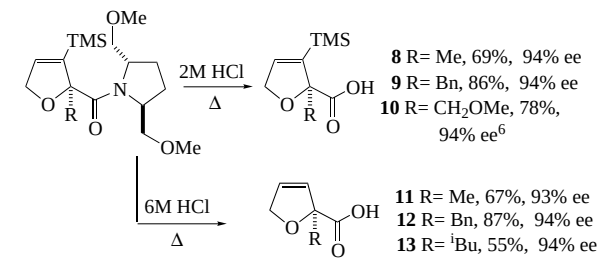


Figure 1.

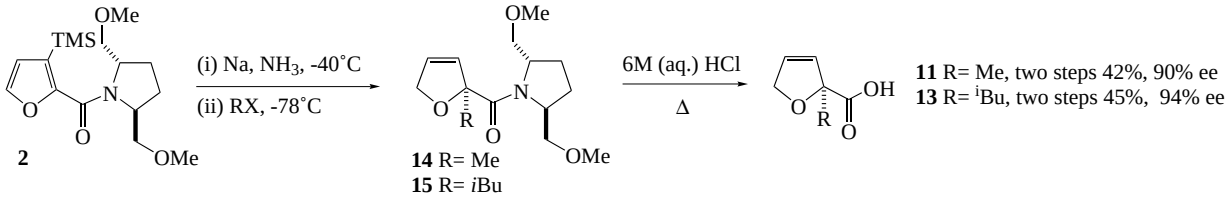


Scheme 3. The ee of the acids **8** and **11**–**13** was measured by GC (chiral column) and in comparison with an authentic racemic standard.

While experimenting with the reducing conditions we made an interesting discovery regarding the behaviour of enolate **A** under sodium/NH_3 conditions (Scheme 4). The reduction reaction of **2** was performed at −40°C rather than the usual −78°C and subsequently re-cooled to −78°C before addition of an alkyl halide.[9] Remarkably, the products that were formed lacked the C-3 TMS group which had obviously been removed at the higher temperatures involved. We know that the TMS group cannot have been dislodged prior to reduction of the furan as the enolate thus formed does not react with high stereoselectivity (Scheme 1). The most likely scenario is that the furan is reduced to give enolate **A**, as before, and the silicon is subsequently replaced by a hydrogen to give another enolate which then reacts stereoselectively (Fig. 2).

We do know that the enolate formed after removal of the TMS group **B** reacted with the same sense of diastereoselectivity as the enolate **A** which preceded it; this was proven by hydrolysis of the amides **14** and **15** and formation of the acids **11** and **13** which had the same absolute stereochemistry as those formed earlier.

We propose that sodamide (formed when ammonia supplies a proton to the dianion derived from **2**) attacks the silicon atom within the enolate **A** and displaces a vinylic anion which itself deprotonates ammonia, and furnishes **B** (Fig. 2). Alternatively, one can postulate a Brook[10] type migration of silicon from carbon to oxygen (the vinylic carbanion becoming protonated by ammonia in the process) and then generation of the enolate **B** in situ by attack of sodamide on the silyl enol ether that is formed via this pathway. The enantiomeric excesses of acids **11** and **13** prepared by this route was not quite as high as those obtained via reduction at −78°C followed by removal of the TMS group under acidic conditions; this may be a consequence of some disruption of the enolate **B** (aggregate?) structure at the higher temperatures it encounters.[11] Despite this observation, the results described in Scheme 4 also dovetail with our mechanistic model which presumes that the C-3 sub-



Scheme 4. The enantioselectivity of the acids **11** and **13** was measured by GC (chiral column) and in comparison with an authentic racemic standard.

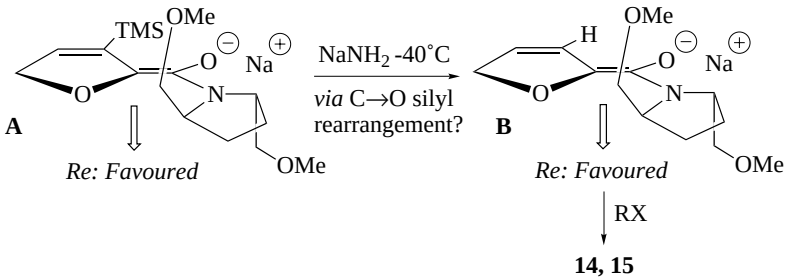


Figure 2.

stituent is needed simply to control enolate geometry and so removal of the silyl group after the enolate geometry has been set does not influence the facial selectivity imposed on the enolate by the auxiliary.

To conclude, we have described a general protocol for the stereoselective Birch reductive alkylation of C-3 silyl substituted furans. During this regime, which proceeds with high levels of stereocontrol, the silicon group can either be retained for further functionalisation or removed in situ. Moreover, removal of the chiral auxiliary, after reduction, allows us to prepare a range of enantiomerically pure dihydrofurans; the flexibility allowed by this process is expected to be useful in natural products synthesis.

Acknowledgements

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References

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4. Carpenter, A. J.; Chadwick, D. J. *J. Org. Chem.* **1985**, *50*, 4362.
5. It was not possible to measure the diasteroisomeric excesses of the products from Birch reduction of **2** directly and the values quoted are extrapolated from the enantiomeric excesses measured from the corresponding acids. These ee values were taken from material that had been subjected to the Birch reduction and then to acid cleavage without any chromatography. Thus, the integrity of the de ratios remains intact. In any case, based on our experience with these compounds, we think that the diastereoisomers of **3**–**7** are inseparable by chromatography.
6. It should be noted that we were unable to measure the enantiomeric excesses of the acids derived from amides **6** and **7**: we have therefore assigned a value of $\geq$94% de to **6** and **7** as it seems rather unlikely that the two electrophiles in question (MOMCl and $Cl(CH_2)_3I$) would react with enolate **A** with less stereoselectivity than that displayed by the other electrophiles indicated in Table 1. By this argument the ee of **10** should also be $\geq$94%.
7. Donohoe, T. J.; Guillermin, J. B.; Frampton, C., unpublished results.
8. For an example, see: Majetich, G.; Zhang, Y.; Liu, S. *Tetrahedron Lett.* **1994**, *34*, 4887.
9. All new compounds were fully characterised (^1H and ^{13}C NMR, mass spec, IR and HRMS). Typical experimental procedure. To a blue solution of sodium (39 mg, 1.7 mmol) in freshly distilled liquid ammonia (30 ml) at −40°C was added a solution of **2** (80 mg, 0.25 mmol) in dry THF (10 ml). The solution was stirred at −40°C for a further 2 h before being cooled to −78°C. Isoprene was then added dropwise (until the blue colour dispersed) followed by addition of iodomethane (1 ml, 16 mmol) to give a yellow solution. After a further 30 minutes, the solution was quenched by addition of a saturated ammonium chloride solution. The ammonia was then allowed to evaporate and the residual solution was extracted with diethyl ether. The combined organics were dried over

magnesium sulphate, filtered and evaporated under reduced pressure. The crude material was purified by column chromatography (60/40 diethyl ether/petrol) to afford **14** as a colourless oil (47 mg, 0.17 mol, 71%); $[\alpha]_D = -82.3$ ($c = 1.23$ in EtOH); ν_{max} (film)/cm^{-1} 2925 (br CH), 1623 (C=O); δ_H (300 MHz, $CDCl_3$): 1.36 (3H, s), 1.72–1.94 (4H, m), 2.95 (1H, t, *J* 9.1), 3.08–3.24 (2H, m), 3.17 (3H, s), 3.18 (3H, s), 3.40 (1H, dd, *J* 9.2 and 2.1), 4.04–4.12 (1H, m), 4.44–4.51 (1H, m), 4.58 (2H, 2dt, *J* 13.2 and 1.7), 5.75 (1H, d, *J* 6.0), 5.97 (1H, td, *J* 2.4 and 6.0); δ_C (75 MHz, $CDCl_3$): 23.73, 27.11, 27.19, 57.68, 57.72, 58.72, 58.79, 71.23, 74.56, 75.46, 93.45, 125.156, 132.91, 173.00; *m*/*z* (CI) 269.1627 (M+H$^+$ $C_{14}H_{23}NO_4$ requires 270.1705, error 0.7 ppm), 270 (100%), 271 (8).

A solution of **14** (58 mg, 0.21 mmol) in a 6 M solution of aqueous HCl (10 ml) was heated at reflux for 3 h before being allowed to cool to rt. The cooled solution was then basified to pH ≈ 14 using a solution of NaOH and extracted with dichloromethane. The resulting aqueous layer was collected and acidified using concentrated HCl solution to pH ≈ 1 and extracted several times with dichloromethane. The organics were dried over magnesium sulphate, filtered and evaporated under reduced pressure to afford **11** as a colourless oil (16 mg, 0.13 mol, 59%); $[\alpha]_D = -141.5$ ($c = 0.54$ in EtOH); ν_{max} (film)/cm^{-1} 3465 (br OH), 2872 (br CH), 1735 (C=O); δ_H (300 MHz, $CDCl_3$): 1.51 (3H, s), 4.68–4.80 (2H, m), 5.94 (1H, td, *J* 1.5 and 6.2), 5.94 (1H, dt, *J* 1.5 and 6.2); δ_C (75 MHz, $CDCl_3$): 23.82, 75.95, 90.58, 127.67 and 129.47 (C*HCH*), 175.17 (*C*=O); *m*/*z* (CI) 128.04734 (M+NH_4^+ $C_6H_8O_3$ requires 146.0817, error 0.5 ppm), 146 (100%), 83 (52).

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11. Shultz, A. G.; Macielag, M.; Sundaraman, P.; Taveras, A. G.; Welch, M. *J. Am. Chem. Soc.* **1988**, *110*, 7828; this paper contains examples of an enolate generated under Birch conditions that changes its reactivity after warming (albeit to rt) and then re-cooling.