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Stereoselectivity in the Birch Reduction of 2-Furoic Acid Derivatives

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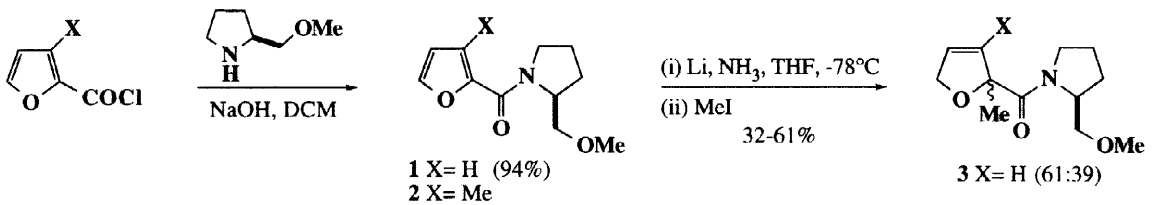
Abstract: The preparation and Birch reduction of chiral 3-methyl-2-furoic acid derivatives is described. Using a C_2 symmetrical amine as a chiral auxiliary, very high levels of sterochemical control could be obtained. Moreover, the auxiliary could be removed conveniently by heating in 6M HCl to liberate a carboxylic acid of high enantiomeric purity. The relative stereochemistry of the Birch reduced amides (and therefore the absolute stereochemistry of the corresponding acids) was determined unambiguously from an X-ray crystal structure. © 1998 Elsevier Science Ltd. All rights reserved.

The Birch reduction is a powerful synthetic reaction which can bridge the gap between aromatic and aliphatic chemistry.[1-3] While this reaction has been applied to many carbocyclic aromatic compounds, its application to heterocyclic systems is more modest.[4-7]

As part of a programme designed to investigate the Birch reduction of heterocycles, we examined the reduction of amides derived from 2-furoic acid. Initial studies on reduction of 2-furoic acid were performed some years ago and showed that reaction with a dissolving metal gave the 2,5-dihydrofuran skeleton.[8-13] Our original remit was concerned with an extension of this work to allow the formation of enantiopure dihydrofuran derivatives: in this regard we drew inspiration from the pioneering work of A. Schultz and constructed the chiral amide **1** (**Scheme 1**).[14,15] Unfortunately, all attempts by ourselves[16] and others[17] to reduce this substrate gave a mixture of diastereoisomers; the highest ratio that we obtained came from a reaction which utilised lithium metal in liquid ammonia (with a quench of methyl iodide) and gave a 61:39 mixture of diastereoisomers (the relative stereochemistry within the major isomer was not determined).[16]



1 X= H (94%)
2 X= Me

3 X= H (61:39)

Scheme 1

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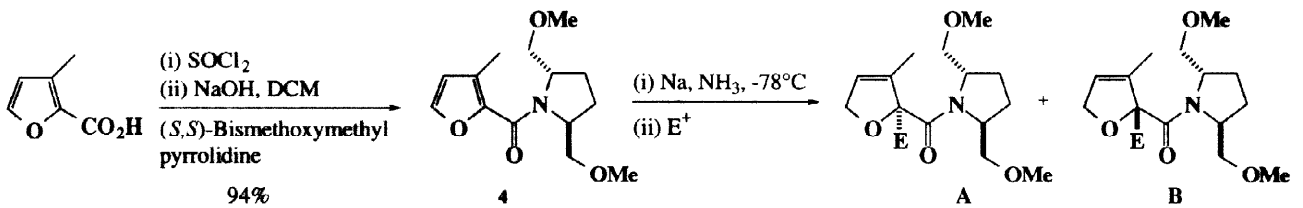
It is interesting to note that, in our hands reductive alkylation proceeded more efficiently *without* the presence of an alcohol (typical procedures in the literature utilise one equivalent of *t*-butyl alcohol as a proton source). We suspect that **1** is sufficiently electron deficient to sustain a dianion, formed by the addition of two electrons. The dianion would then be protonated by ammonia (at C-5) thus leaving an enolate which is quenched by the addition of an external electrophile. We reasoned that the lack of significant stereocontrol had its origins in the formation of two geometric enolate isomers after protonation of the dianion by ammonia. One simple solution to this problem was to introduce an alkyl substituent at the C-3 position: a methyl group has been shown to influence completely the enolate geometry in related benzenoid systems.[18] To this end, commercially available 3-methyl-2-furoic acid was coupled to various chiral amines. Unfortunately, reduction of **2** (X=Me) proved to be non-stereoselective even though we suspected that a single enolate isomer was formed in this reaction.[19] However, we did find that use of a C_2 symmetrical amine and subsequent formation of **4** gave a substrate which could be reduced stereoselectively (**Scheme 2**). Indeed, reductive alkylation of **4** using sodium in liquid ammonia/THF at -78°C (quenching with an electrophile after 30 mins) gave a highly stereoselective outcome (≥30:1 ds) with a variety of different electrophiles (**Table 1**).



Scheme 2

Entry	E^+	E	Ratio A/B[a]	Yield (%)	Product
1	MeI	Me	30:1	88	(-)-**5**
2	EtI	Et	>30:1	74	(-)-**6**
3	^{t}BuI	^{t}Bu	>30:1	68	(-)-**7**
4	CH_2=$CHCH_2Br$	CH_2=$CHCH_2$	≥30:1	62	(-)-**8**
5	NH_4Cl	H	10:1	65	(-)-**9**

Table 1: [a] In each case, the ratio of **A/B** was difficult to assess accurately by nmr spectroscopy and was determined by G.C. on the crude reaction mixture (in comparison with an authentic 1:1 sample).

Although the ratio of diastereoisomers from entry 5, (quenching with ammonium chloride solution) was 10:1, the two compounds could be separated easily on a silica gel column.

Compound **5** was cleaved with aqueous acid (*vide infra*) and the resulting acid coupled (BOPCl) to enantiomerically pure (*R*)-(+)-α-methylbenzylamine to yield a crystalline amide (**10**). An X-ray crystal structure of this compound was obtained (**Figure 1**) and this enabled us to assign the relative stereochemistry within compounds **5-9** (**Table 1**) and the absolute stereochemistry of compounds **11-14** (**Scheme 3**).

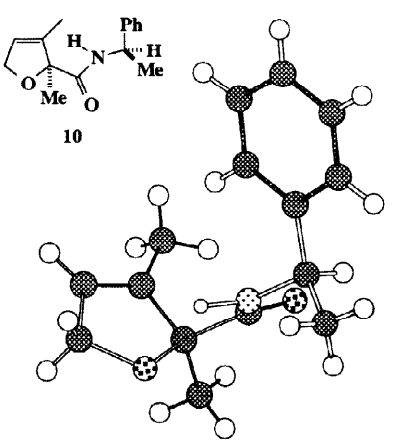
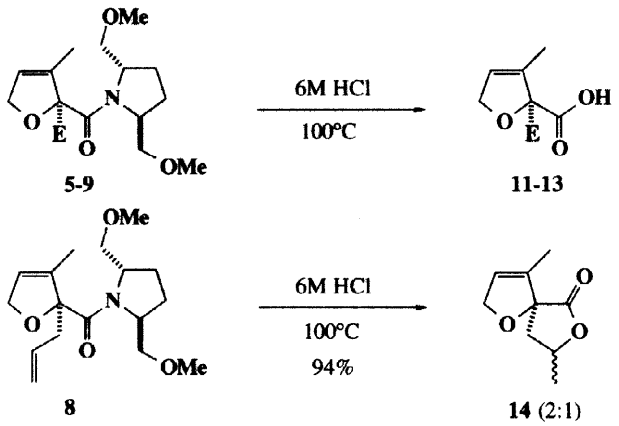


Figure 1: X-ray structure of **10**.

For this methodology to become useful, a method was required for removing the auxiliary and forming the corresponding carboxylic acid. We were delighted to find that this transformation could be accomplished by heating the dihydrofuran-amides **5-9** in 6M HCl at 100°C for 4-6 hours. In most cases, the requisite acid was formed in high yields and the chiral amine could also be recovered (**Scheme 3**). Analysis of the acids formed *via* this reaction showed a very high level of enantiomeric purity. Since the relative stereochemistry of the amides **5-9** is known, the absolute configuration of the corresponding acids can be assigned with confidence.



E	ee of acid (%)[a]	Yield (%)	Compound
Me	≥94	86	(-)-11
Et	≥94	74	(-)-12
^{i}Bu	≥94	68	(-)-13
H	-	b	
Allyl	-	c	14

Scheme 3: [a] In each case the ee of the acid was determined by comparison with a racemic sample using G.C. (chiral column) and checked by ^{1}H nmr spectroscopy in the presence of (*R*)-(+)-α-methyl benzylamine (1-3 equivalents).
[b] Surprisingly, amide **9** was very resistant to hydrolysis under acidic conditions; prolonged exposure led to decomposition.
[c] Reaction of amide **8** with (aq.) HCl gave low and irreproducible yields of the corresponding acid. However, as a result of cleavage under acidic conditions, the corresponding lactones **14** could be obtained in excellent yield as a 2:1 mixture of diastereoisomers.

At the present time, it is difficult to rationalise fully the high levels of stereocontrol that are observed upon reductive alkylation of **4**. We presume that the reduction reaction produces a single enolate isomer and that one face of this enolate is shielded by the chiral auxiliary. The sense of induction is consistent with addition of an electrophile to the *Re* face of either an *E* enolate or a *Z* enolate isomer (**Figure 2**). The situation is complicated because the auxiliary has two CH_2OMe arms, and either could conceivably be expected to block a face of the enolate. If one assumes that the amide unit is planar to maximise conjugation, then this result is consistent with the formation of a *E* enolate and subsequent electrophilic attack from the less hindered face of the enolate. The *Z* enolate would appear to be rather sterically encumbered as a consequence of [$A^{1,3}$] strain. However, the issue of pyramidalisation about the enolate nitrogen and the degree of rotation about the C-N bond is important (and unanswered) as it does have an influence in determining which arm is capable of shielding the enolate. For example, C-N rotation in the *Z* enolate could also provide an enolate conformation which would explain the observed stereochemical outcome.

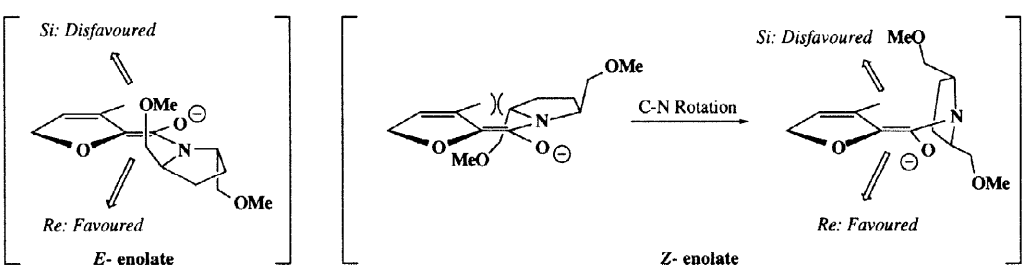


Figure 2

Although we favour the former hypothesis (formation of the *E* enolate for steric reasons) currently we have no experimental evidence that can distinguish between the two and intend the transition state outlined in **Figure 2** as a working model only.

Conclusions: We have developed a stereoselective variant of the Birch reduction of 3-methyl-2-furoic acids using *bis* (methoxymethyl) pyrrolidine as a chiral auxiliary: this unit is capable of lending high levels of stereocontrol to the reductive alkylation process. Moreover, this auxiliary can be cleaved under standard conditions to yield a series of enantiomerically pure acids. Further work is continuing to investigate the sense and level of diasteroselectivity and to utilise this sequence in natural product synthesis.

All new compounds displayed satisfactory spectroscopic data. Representative experimental procedure for the Birch reduction is as follows: Amide **4** (1.0 g, 3.74 mmol, 1.0 eq.) was stirred in THF (15 ml) at -78°C under an atmosphere of nitrogen. Ammonia (200ml) was distilled into the flask, then sodium (258 mg, 3.0 eq.) was added and the deep blue mixture stirred for 30 mins at -78°C. Isoprene (200µl) was then added followed immediately by methyl iodide (700 µl, 3.0 eq). The pale yellow solution was then stirred for 40 mins at -78°C, after which time saturated ammonium chloride solution (4 mls) was added. The ammonia was then allowed to evaporate by removing the cooling bath, and the product was extracted into ethyl acetate (4 x 50 ml). The organic layers were dried over sodium sulfate, and evaporated to dryness under reduced pressure, to yield the crude product as a brown oil (1.1g, 100%). Purification by chromatography on a silica column, eluting with petroleum ether/ethyl acetate (3:1), afforded the title compound **5** as a yellow oil (0.94g, 88%). δ_H (300 MHz, $CDCl_3$) 5.48-5.45 (1H, m, C=C<u>H</u>), 4.70-4.64 (1H, m, CONC<u>H</u>), 4.57-4.53 (2H, m, O<u>CH</u>$_2$CH=C), 4.27-4.18 (1H, m, CONC<u>H</u>), 3.45 (1H, dd, J=9.2, 3.1 Hz, C<u>H</u>$_2$OCH$_3$), 3.30-3.09 (2H, m, C<u>H</u>$_2$OCH$_3$), 3.27 (3H, s, OC<u>H</u>$_3$), 3.21 (3H, s, OC<u>H</u>$_3$), 2.97 (1H, t, =9.1Hz, C<u>H</u>$_2$OCH$_3$), 2.12-1.83 (7H, m, C=CC<u>H</u>$_3$, C<u>H</u>$_2$C<u>H</u>$_2$), 1.44 (3H, s, OCC<u>H</u>$_3$) ppm.

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