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LETTERS

The Stereoselective Birch Reduction of Pyrroles

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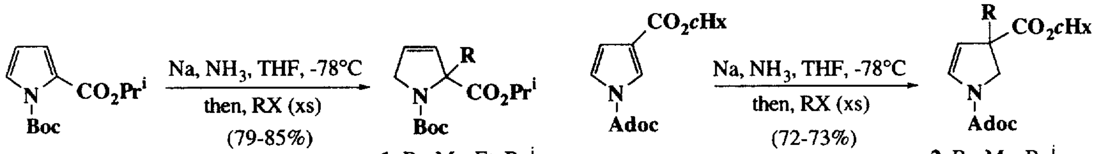
Abstract: The Birch reduction has been applied to electron-deficient pyrroles substituted with a chiral auxiliary at the C-2 position. Using either 8-phenylmenthol or *trans*-2-(α-cumyl)cyclohexanol (TCC) as auxiliaries, high levels of stereoselectivity were obtained. Moreover, the auxiliary could be removed using a high-yielding three-step sequence to furnish substituted dehydroproline derivatives with high enantiomeric purity. By choosing either (-)-8-phenylmenthol or (+)-TCC as an auxiliary either enantiomer of the dehydroproline product could be obtained. © 1998 Elsevier Science Ltd. All rights reserved.

We have recently extended the scope of the Birch reduction to encompass electron deficient pyrroles and in so doing produced pyrroline derivatives.[1,2] The substitution pattern of the pyrrole, prior to reduction, is crucial in determining the regioselectivity of the product: posting an electron-withdrawing group at C-2 of the pyrrole enabled the synthesis of functionalised dehydroproline derivatives (**1**, **Scheme 1**).[3,4] However, changing the position of the electron-withdrawing group to the C-3 of pyrrole allowed us to access the corresponding β-dehydroproline derivatives (**2**, **Scheme 1**).[5]

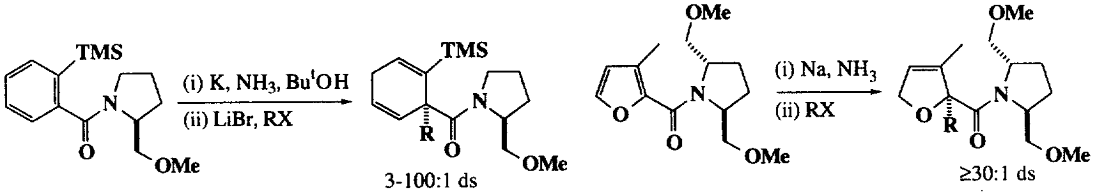


1 R= Me, Et, Bu^i

2 R= Me, Bu^i

Scheme 1

The reactions shown in **Scheme 1** give rise to racemic material and a natural extension of this chemistry would be one which allowed the preparation of enantiopure compounds. An attractive approach would involve attaching a chiral auxiliary to pyrrole, prior to reduction, and performing stereoselective Birch reductions. This idea stems from work reported by A. G. Schultz who developed the area using benzenoid aromatics;[6] moreover, we have recently performed stereoselective Birch reductions on furans (see **3**, **Scheme 2**).[7]



3-100:1 ds
R= Me, Et, Bn (ref 6)

≥30:1 ds
3 R= Me, Et, Bu^i, Bn (ref 7)

Scheme 2

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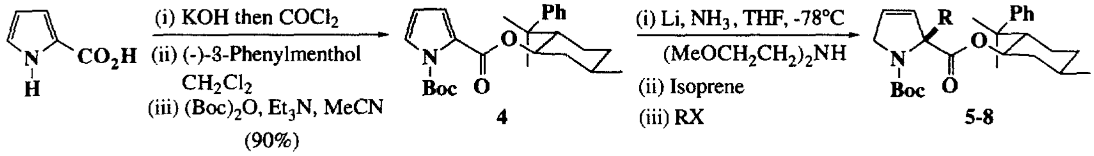
We expected that several chiral auxiliaries would be effective for the Birch reduction of pyrrole; after initial screening experiments decided to utilise (-)-8-phenylmenthol derived esters as chiral controllers.[8] Therefore, pyrrole carboxylic acid was treated sequentially with oxalyl chloride, (-)-8-phenylmenthol and $(Boc)_2O$ to make ester **4** in 90% overall yield (**Scheme 3**). With this ester in hand, we proceeded to reduce it under modified Birch conditions (**Scheme 3**). The best conditions involved lithium metal (3 equiv), liquid ammonia and THF at -78°C; in addition, we found that addition of $(MeOCH_2CH_2)_2NH$ (10 equiv) helped to reduce side reactions caused by the lithium amide formed in the reduction.[5] After 15 minutes, the Birch reductions were quenched with a range of electrophiles and in each case dehydroproline derivatives were formed in excellent yields and with good diastereoselectivities (**5-8**, **Table 1**).[9] The mechanism of similar reductions (see **Scheme 1**) has been discussed previously and seems to involve addition of two electrons to the pyrrole, followed by protonation of the dianion by ammonia.[3-5] This process forms an extended enolate in solution; it is this enolate that reacts with electrophiles at the α-position and forms the observed products.



Scheme 3

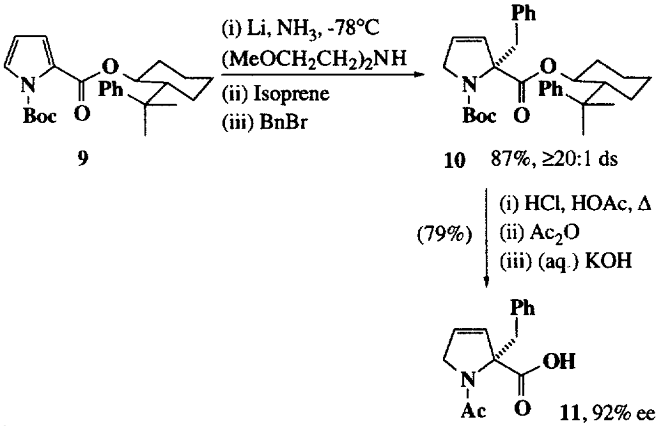
Table 1

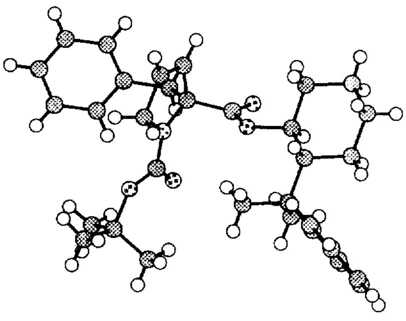
Entry	RX	E	ds[a]	Yield (%)	Product
1	MeI	Me	8:1	97	**5**
2	EtI	Et	13:1	97	**6**
3	Bu'I	Bu'	20:1	91	**7**
4	BnBr	Bn	**b**	96	**8**

a The diastereoisomeric selectivity was assessed by ^1H NMR spectroscopy. **b** Selectivity was high, but difficult to assess accurately.

The results shown in **Table 1** illustrate that 8-phenylmenthol is indeed an effective auxiliary for this process. Performing the reductions shown above with sodium metal altered neither the diastereoisomeric selectivities nor yields and lithium was used mainly for convenience. In addition, a clear trend is evident which shows that the diastereoselectivity is dependent upon the steric bulk of the electrophile: i.e. larger electrophiles show more discrimination in reaction between the unequally shielded faces of the enolate.

One drawback with the use of (-)-8-phenylmenthol is the relative inaccessibility of the (+)-enantiomer. Therefore, we decided to utilise *trans*-2-(α-cumyl)cyclohexanol (TCC) which is commercially available in either enantiomeric form and has been shown by Whitesell to be an effective replacement for 8-phenylmenthol.[10] Compound **9** was prepared from pyrrole carboxylic acid under the same sequence of reactions outlined in **Scheme 3**, with an overall yield of 90% - however, we utilised (+)-TCC as the auxiliary so that we could achieve the opposite facial selectivity to that shown with (-)-8-phenylmenthol (**Scheme 4**). As expected, the TCC auxiliary showed good diastereoselectivity in its reaction with benzyl bromide, although this was difficult to determine accurately by ^1H NMR. However, the TCC auxiliary was conveniently removed (HCl) and the resulting amino acid peracetylated (Ac_2O) and cleaved (KOH) to yield **11** in 79% overall yield and with 92% ee (GC, chiral column). In addition, we were able to prove the relative stereochemistry of **10** *via* an X-ray crystal structure (see **Scheme 4**).



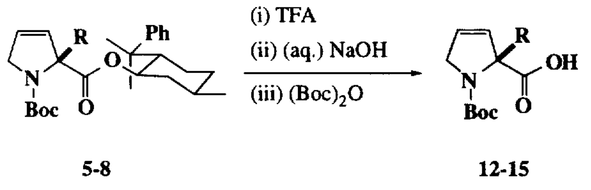


X-ray structure of 10

Scheme 4

Knowing the relative stereochemistry of **10** allows us to assign that of **5-8**, assuming that: (1) (-)-8-phenylmenthol derived esters give the opposite facial selectivity to (+)-TCC derived esters (we have proof of this, see **Scheme 5**); (2) the sense of selectivity with benzyl bromide is the same as that with other electrophiles; this is a reasonable chemical hypothesis.

Our attention was then directed towards developing a method of removing the auxiliary that avoided strong acid. Early work showed that the ester group in compounds **5-8** was resistant to attack by a basic nucleophile. However, we did find that removal of the Boc group under standard conditions gave secondary amines which could be successfully saponified (**Scheme 5**). Subsequent protection under standard conditions gave the corresponding *N*-Boc amino acids **12-15** in excellent overall yield. In each case, the ee of the acid product was found to correspond to the de of the starting auxiliary-derived ester. It is also worthwhile noting that the chiral auxiliary could be easily recovered at the end of the sequence.



R	ee (%)[a]	yield (%)	Compound
Me	78	79	12
Et	86	71	13
Bu^i	90	70	14
Bn	90[b]	67	15

[a] The ee was measured by GC (chiral column) in comparison with a racemic standard.
[b] The ee was measured on the *N*-acetyl amino acid

Scheme 5

Reassuringly, the *N*-acetyl amino acid **11** produced by the cleavage of **8** (under the conditions outlined in **Scheme 4**) was judged to have an ee of 92% in favour of the opposite enantiomer to that formed from **10**.

This is completely expected, and proves that (+)-TCC behaves as a pseudo-enantiomer of (-)-8-phenylmenthol in this chemistry.

The enantiomeric excesses of the compounds described in **Scheme 5** are those obtained when material is brought through the Birch reduction/ cleavage sequence without rigorous purification of the intermediates and, as such, represent the intrinsic facial bias of the 8-phenylmenthol auxiliary. However, when silica-gel chromatography of the intermediates was employed we frequently obtained acids **12-15** with enantiomeric excesses higher than that indicated (e.g **12** 87% ee; **14** 92% ee, **15** 94% ee): this bodes well for the use of our methodology in synthesis.

To conclude, we have shown that both 8-phenylmenthol and TCC are effective chiral auxiliaries for the Birch reduction. Attachment of these compounds to pyrrole carboxylic acid gave derivatives which showed a high level of diastereoselectivity in the Birch reduction. The auxiliary was easily removed *via* a standard three-step sequence and the corresponding α-alkylated dehydroproline compounds were produced with good levels of enantiomeric purity; either enantiomer of product can be obtained by the choice of auxiliary. Dehydroproline derivatives will have uses in both natural products synthesis and medicinal chemistry and further studies are continuing in these directions.

Representative Experimental Procedure: A solution of **4** (210 mg, 0.5 mmol), pre-mixed with bis(2-methoxyethyl)amine (0.7 mL) in THF (20 mL) was added dropwise to a deep-blue solution of ammonia (50 mL), THF (5 mL) and lithium (10.5 mg, 1.5 mmol) at -78°C under an atmosphere of nitrogen. After 15 minutes, isoprene (3 drops) was added followed by methyl iodide (0.75 mL) and the reaction stirred at -78°C for 2 h. A saturated solution of ammonium chloride (10 mL) was then added and the mixture slowly warmed to room temperature, under a stream of nitrogen, to remove the ammonia. The mixture was extracted with ethyl acetate (4 x 50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Chromatography on silica (eluting with acetone/ petrol, 1:10) gave **5** as a colourless oil (214 mg, 97%).

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