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Stereocontrol in the Synthesis of Kainoids

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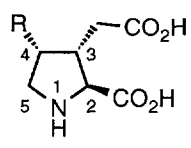
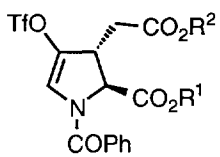
Abstract: *A stereoselective synthesis of acromelic acid analogues is described in which the C-3 / C-4 cis-relative stereochemistry is established by a hydroxyl directed heterogeneous catalytic hydrogenation of an enamide.* Copyright © 1996 Elsevier Science Ltd

There have been many reported syntheses of members of the kainoid class of non-proteinogenic amino acid[1] with general structure **1**. These compounds have proved important in the study of neuronal function[2] and as such, it would be desirable to prepare both naturally occurring and modified structures on a large scale from readily available and cheap starting materials.



1



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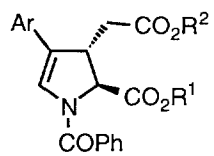
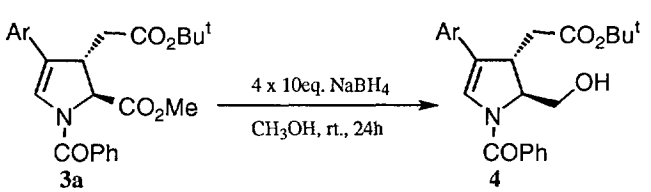


3

We have previously reported a preparation of some acromelic acid analogues **1** (R = various aryl groups) and their C-4 epimers[3], involving as a key step, a palladium (0) catalysed cross-coupling of various arylboronic acids to vinyl triflates of type **2**, themselves being derived from *trans*-4-hydroxy-L-proline in 6 steps. Reduction of the enamide functionality of the coupled products of type **3** by catalytic hydrogenation (Pd black catalyst) gave predominantly the C-4 epimers of the protected acromelic acid analogues and "ionic reduction" with triethylsilane in trifluoroacetic acid gave equal proportions of both C-4 epimers. We have now modified this procedure to produce stereoselectively, the required epimers with C-3 / C-4 *cis*- relative stereochemistry.

Chemoselective reduction of the C-2 methyl ester of enamides **3a** with excess sodium borohydride yielded primary carbinols **4** in good yields (Scheme 1).

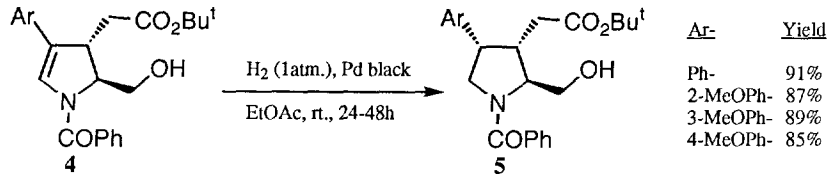


3a → **4**

Ar-	Yield
Ph-	91%
2-MeOPh-	80%
3-MeOPh-	80%
4-MeOPh-	71%

Scheme 1

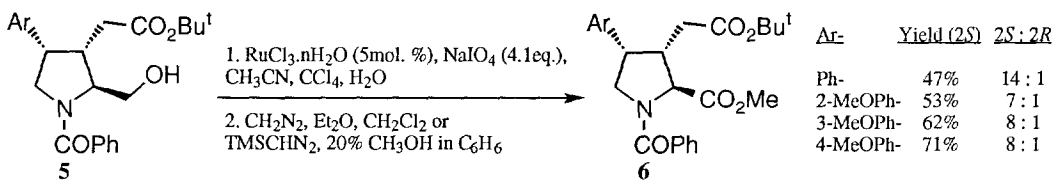
Hydroxyl directed heterogeneous catalytic hydrogenation[4] of these carbinols over palladium black gave the required C-3 / C-4 *cis*- relative stereochemistry in the products **5** (Scheme 2)[5].



Ar-	Yield
Ph-	91%
2-MeOPh-	87%
3-MeOPh-	89%
4-MeOPh-	85%

Scheme 2

Ruthenium tetraoxide oxidation of the primary carbinols[6] followed by re-esterification with diazomethane or trimethylsilyldiazomethane[7] gave methyl esters **6** in reasonable overall yields (Scheme 3), unfortunately with some loss of stereochemical integrity at C-2 (The diastereoisomers were readily separable by silica gel chromatography). Deprotection to the free amino acids was efficiently accomplished using 6M hydrochloric acid under reflux[3,8].



Ar-	Yield (2*S*)	2*S* : 2*R*
Ph-	47%	14 : 1
2-MeOPh-	53%	7 : 1
3-MeOPh-	62%	8 : 1
4-MeOPh-	71%	8 : 1

Scheme 3

In summary, we have developed a short, stereoselective synthesis of acromelic acid analogues which can be readily applied to large-scale work. We are currently investigating the application of this methodology to the preparation of other kainoids.

Acknowledgements

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References and notes

1. For a recent review, see: Parsons, A. F. *Tetrahedron*, **1996**, *52*, 4149-4174.
2. For example, see: McGeer, E. G.; Olney, J. W.; McGeer, P. L. Eds., *Kainic Acid as a Tool in Neurobiology*; Raven Press: New York, 1978.
3. Baldwin, J. E.; Bamford, S. J.; Fryer, A. M.; Wood, M. E. *Tetrahedron Lett.*, **1995**, *36*, 4869-4872.
4. For example, see: Kunzer, H; Sauer, G.; Wiechert, R. *Tetrahedron Lett.*, **1991**, *32*, 743-746.
5. Only a single diastereoisomer of all four carbinols **5** could be detected in the 300MHz ^{1}H nmr spectrum of each crude hydrogenation product.
6. Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.*, **1981**, *46*, 3936-3938.
7. Shioiri, T.; Aoyama, T. *Chem. Pharm. Bull.*, **1981**, *29*, 3249-3255.
8. Final confirmation of stereochemistry was carried out by comparison of spectral data with that of compounds prepared previously[3].

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