Pergamon

Tetrahedron Letters 42 (2001) 153–154

TETRAHEDRON LETTERS

Synthesis of cyclopropanes via organoiron methodology: preparation of 2-(2′-carboxy-3′-ethylcyclopropyl)glycine

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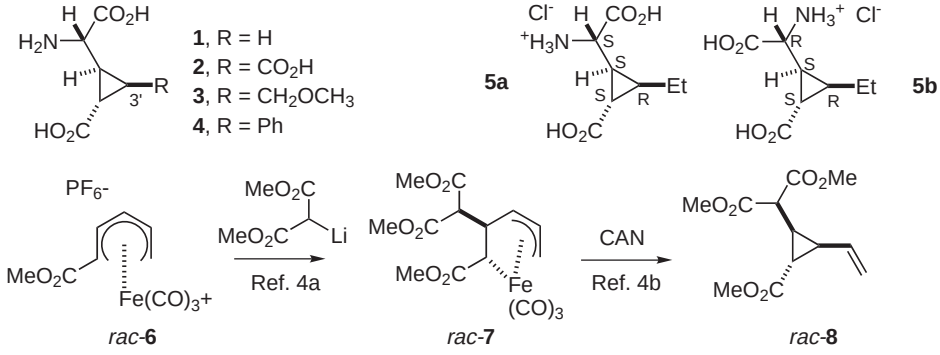
Received 5 October 2000; revised 20 October 2000; accepted 24 October 2000

Abstract—A route to 1,2,3-trisubstituted cyclopropanes has been developed. The relative stereochemistry at the three cyclopropane centers is established by nucleophilic attack on the pentadienyl ligand on the face opposite to iron and subsequent oxidatively induced reductive elimination with retention of configuration. This methodology was applied to the synthesis of 2-(2′-carboxy-3′-ethylcyclopropyl)glycines. The diastereomeric glycine dimethyl esters are separable as their diphenylmethylene imines. © 2000 Elsevier Science Ltd. All rights reserved.

L-Glutamic acid is the major excitatory neurotransmitter for a wide variety of receptors in mammalian systems.[1] The selective activation of different glutamate receptors may depend on recognition of a particular conformer of this flexible molecule. For this reason, the synthesis and evaluation of conformationally restricted 2-(2′-carboxycyclopropyl)glycines has led to the discovery of ligands with mGluR specificity.[2] In particular the extended conformation, as exemplified by compounds **1**–**4**, is believed to be a requirement for binding to the mGluR1 and mGluR2 receptors, while the presence and electronic nature of the 3′-substituent may distinguish between agonist and antagonist activity.[3] As part of our overall program on the development of a novel iron-mediated formation of substituted cyclopropanes, we herein report on the preparation of 2-(2′-carboxy-3′-ethylcyclopropyl)glycines, (2*S*,1′*S*,2′*S*,3′*R*)-**5a** and (2*R*,1′*S*,2′*S*,3′*R*)-**5b**.

We have previously reported that the nucleophilic attack of malonate anions to (1-methoxy-carbonylpentadienyl)$Fe(CO)_3^+$ (*rac*-**6**) proceeds predominantly at an internal carbon, on the face of the pentadienyl ligand opposite to iron, to afford (pentenediyl)iron complexes (*rac*-**7**) (Scheme 1).[4a] Furthermore, oxidatively induced-reductive elimination of *rac*-**7** gives the vinylcyclopropanecarboxylate *rac*-**8**.[4b] It was envisioned that this sequence of reactions might be applicable to the synthesis of 2-(3′-substituted-2′-carboxycyclopropyl)glycines.

Reaction of *rac*-**6** with the anion derived from methyl nitroacetate gave the (pentenediyl)iron complex *rac*-



Scheme 1.

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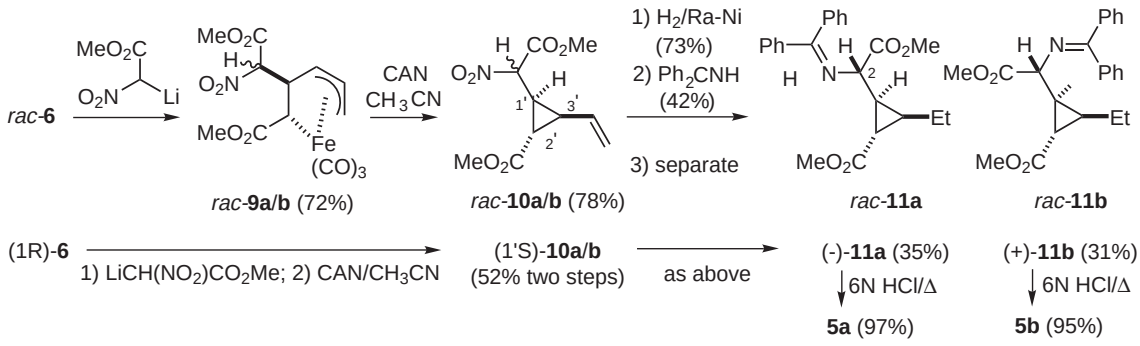
PII: S0040-4039(00)01915-8



Scheme 2.

9a/**b** as a mixture of diastereomers (Scheme 2). Treatment of *rac*-**9a**/**b** with CAN gave *rac*-**10a**/**b**. The relative stereochemistry about the cyclopropane ring in **10a**/**b** was assigned as indicated on the basis of the magnitude of the vicinal couplings ($J_{1'\text{-}2'} = J_{2'\text{-}3'} = 5.3$ Hz).[5] Reduction of **10a**/**b**, followed by reaction with benzophenone imine[6] gave a mixture of *rac*-**11a** and *rac*-**11b**, which were separable by column chromatography. The structure of *rac*-**11a** was confirmed by single-crystal X-ray analysis.[7] Beginning with (1*R*)-**6**,[8] this sequence of reactions gave (−)-**11a** and (+)-**11b**. The 2*S* configuration (−)-**11a** was assigned by comparison of the sign of its specific rotation with that of a series of 13 *N*-diphenylmethylene imines of L-amino esters.[6b–e] Both (−)-**11a** and (+)-**11b** were assessed to be >80% ee by ^{1}H NMR spectroscopy in the presence of Eu(hfc)$_3$ ($CDCl_3$). Separate hydrolysis of (−)-**11a** or of (+)-**11b** gave the cyclopropylglycine hydrochloride salts **5a** or **5b** in excellent yield.

In summary, a route to 2-(2′-carboxy-3′-ethylcyclopropyl)glycines has been developed. Attempts to prepare other conformationally restricted glutamate analogs from **10a**/**b** will be reported in due course.

Acknowledgements

Financial support for this work was provided by the National Institutes of Health (GM-42641) and the Petroleum Research Fund (34297-AC1). The authors are grateful to Professor Robin Polt, University of Arizona, for stimulating discussions.

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