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Diene(tricarbonyl)iron complexes linked to spirooxazolones for the synthesis of cyclopropyldihydroxyphenylalanine

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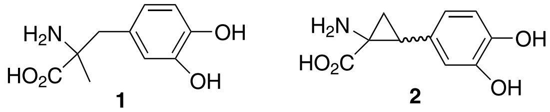
Abstract—Complexed cyclopropyl-3,4-dihydroxyphenylalanine (∇ DOPA) were synthesized by diazomethane cyclopropanation of the appropriate diene(tricarbonyl)iron complexes linked to azlactones. Opening of the oxazolone ring by treatment with MeOH and DMAP gave the corresponding methyl esters. Introduction of the Boc group, cleavage of the carbamate with hydrazine provided Boc-protected cyclopropylogs of DL-dihydroxyphenylalanine. © 2003 Elsevier Science Ltd. All rights reserved.

Cyclopropane amino acids or α-amino acids with a bridging methylene group forming a cyclopropyl ring are of interest as natural products, and also as conformationally restricted analogs of the proteinogenic amino acids.[1] Since α-methyl-3,4-dihydroxyphenylalanine **1** is a clinically efficient drug useful against hypertension, the corresponding cyclopropyl compounds **2**, cyclopropyl-3,4-dihydroxyphenylalanine (∇ DOPA), of either *E* or *Z* configuration, are of considerable interest as possible antihypertensive drugs (Scheme 1).

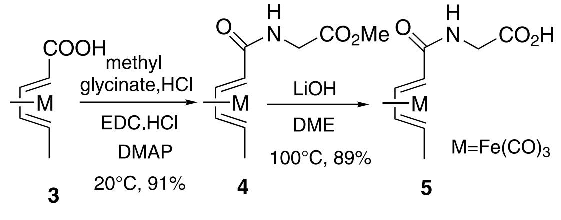
Among the possibilities to prepare cyclopropane-containing amino acids, the addition of diazomethane to 4-arylidene-5(4*H*)-oxazolones remains one of the most powerful methodologies.[2] Moreover attempts to hydrolyse spirooxazolone precursors of DOPA derivatives to the free 2,3-methanoamino acid failed. This could be circumvented by the use of sulfur-containing heterocycles, 4-arylidene-2 benzylthio-5(4*H*)-thiazolones, which can be cleaved by strong aqueous base to form amino acids.[3]



Scheme 1.

Thus we investigated an approach to the synthesis of 'cyclopropyl' DOPA using unsaturated azlactones linked to an iron tricarbonyl complexed diene fragment. We first synthesized the dienyl iron tricarbonyl analog of hippuric acid **5** in two steps. The first step was a coupling reaction between complexed sorbic acid **3** and ethyl glycinate hydrochloride in the presence of the water-soluble *N*-ethyl-*N*′-3-dimethylaminopropylcarbodiimide (EDC).[4] This reaction gave the amide **4** isolated in 91% yield. Hydrolysis of the latter with LiOH in DME afforded the oxazolone precursor **5** in 89% yield (Scheme 2).

In our case, the Erlenmeyer–Plöchl azlactone synthesis[5] modified by Buck and Ide[6] led mainly to the *Z* unsaturated oxazolone **6** (51%), (1% *E*; separated by SiO_2 column chromatography). Indeed the stable isomer has the *Z* configuration in which the aryl group and the carbonyl function have the trans orientation (Scheme 3).[7]



Scheme 2.

Keywords: diene(tricarbonyl)iron complexes; cyclopropyldihydroxyphenylalanine; oxazolones; spiroazlactones; diazomethane; hydrazine.

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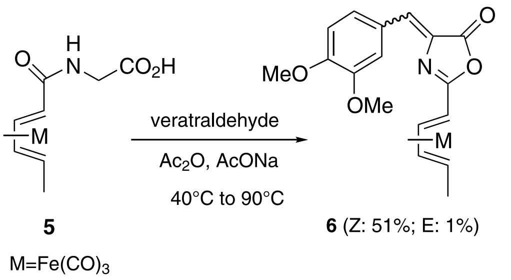


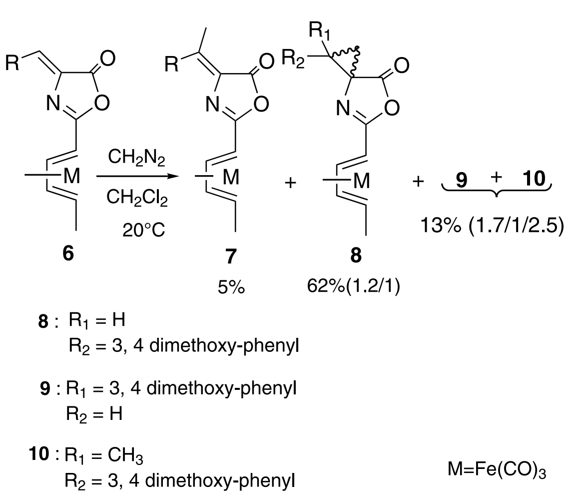
Scheme 3.

The *Z* unsaturated azlactone **6** was then treated with diazomethane giving olefin **7** (42%) along with 29% of spiroazlactone **8** (two diastereomers). Optimized conditions (cyclopropanation at 25°C with gradual addition of DAM) afforded 5% of the olefin **7**, 62% of the *Z* spiroazlactone **8** (two diastereomers:1.2/1) along with a mixture of the *E* spiroazlactone **9** (two diastereomers: 1.7/1) unseparated from the methylated spiroazlactone **10**.[8] At this stage, it is interesting that both the unsaturated azlactones and the spiroazlactones could be purified by chromatography on silica gel without notable degradation.

The formation of olefin **7** could be explained by a concerted H-migration that is favored by a possible *trans* antiparallel position of the H atom and the CN bond.[9]

Although it is known that a 1,3-dipolar cycloaddition of diazoalcanes with an electrophilic olefin is concerted and follows the Michaël reaction pathway,[10] it should be noted that after the loss of N_2, a bond rotation occurs followed by a ring closure to afford also the oxazolone **9** (Scheme 4).

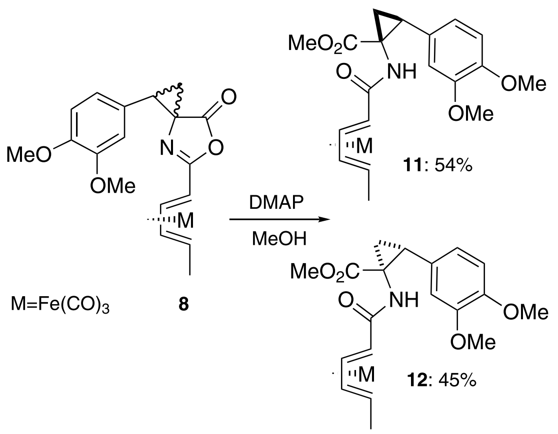
Methanolysis of complexed *Z* spiroazlactones **8** afforded carboxylates **11** (54%)and **12** (45%). Fortunately, thanks to the tricarbonyl iron appendage, at this stage, the two diastereomers of cyclopropyl derivatives could be separated by chromatography on silica gel. (only one enantiomeric series is depicted in the figures) (Scheme 5).



Scheme 4.

An X-ray crystallographic analysis of the cyclopropyl derivative **11** (Fig. 1) confirmed the structure of these products (Fig. 1).

It is well known that amides can be activated towards hydrolysis by prior conversion to their *N*-Boc imide derivatives.[11] Thus amides **11** and **12** were respectively acylated with di-*tert*-butyl dicarbonate (Boc_2O) in the presence of DMAP. Hydrazine allowed the cleavage of the Boc-derivatives and lead to multiprotected cyclopropyldihydroxyphenylalanine **13** (73–86%) along with



Scheme 5.

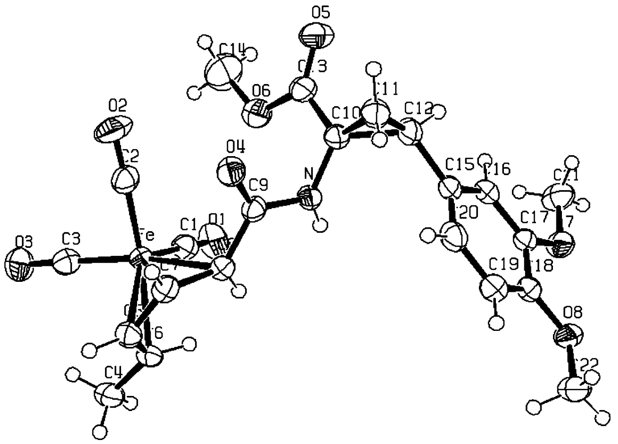
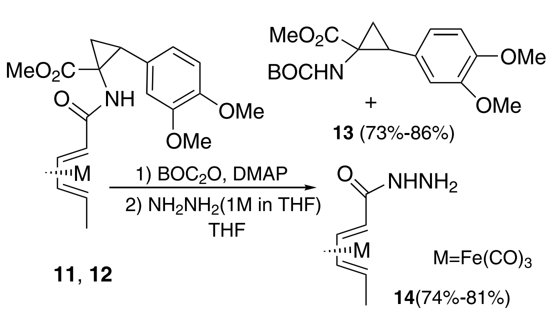
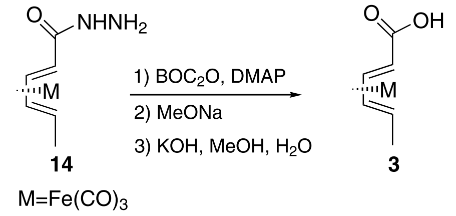


Figure 1. X-Ray structure of **11**.



Scheme 6.



Scheme 7.

the iron tricarbonyl amide complex **14** (74–81%) which could be recycled (Scheme 6).

In fact, it was possible to regenerate the complexed sorbic acid by multiprotection of the amide **14**[12] (tri-Boc derivative) followed by treatment with sodium methoxide. This afforded the complexed methyl ester of sorbic acid in 75% yield. Saponification of the latter then provided the starting iron tricarbonyl complex of sorbic acid **3** quantitatively (Scheme 7).

The same reactions were performed in the *E* series, with approximatively the same yields as in the *Z* series.

In summary, we have succeeded in developing a synthesis of cyclopropane amino acids as separated diastereomers. Indeed the use of the organometallic appendage not only allows the separation of the amides but also facilitate their hydrolysis at the end. This synthesis is currently being extended to the preparation of optically pure amino acids and other conformationally restricted analogs of the proteinogenic amino acids.

Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 209062. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@cccdc.cam.ac.uk].

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12. *Selected spectroscopic data*: Unsaturated azlactone **6** (*Z*): orange solid; mp 160°C; IR (CCl_4): 2060, 2002, 1998, 1797, 1647 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.35 (wide d, $J=8.3$ Hz, 1H), 1.52 (d, $J=6.1$ Hz, 3H), 1.59–1.71 (m, 1H), 3.93 (s, 3H), 3.94 (s, 3H), 5.30 (dd, $J=8.7$ Hz, 4.9 Hz, 1H), 5.96 (dd, $J=8.2$ Hz, 4.9 Hz, 1H), 6.88 (d, $J=8.5$ Hz, 1H), 7.03 (s, 1H), 7.45 (dd, $J=8.3$ Hz, 1.6 Hz, 1H), 7.95 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.2, 42.7, 56.0, 56.1, 59.4, 80.2, 88.4, 111.0, 113.8, 127.2, 127.3, 129.9, 131.2, 149.2, 151.8, 167.6, 167.7, 209.9.

   Amide **12**: yellow solid; mp 170°C; IR (CCl_4): 2056, 1988, 1981, 1728, 1673 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.61 (d, $J=7.7$ Hz, 1H), 1.38 (d, $J=6.1$ Hz, 3H), 1.25–1.35 (m, 1H), 1.65 (dd, $J=7.4$ Hz, 6.3 Hz, 1H), 2.14 (dd, $J=9.4$ Hz, 6.0 Hz, 1H), 2.83 (t, $J=8.8$ Hz, 1H), 3.74 (s, 3H), 3.80 (s, 3H), 3.83 (s, 3H), 5.13 (dd, $J=8.5$ Hz, 5.0 Hz, 1H), 5.33 (wide s, 1H), 5.75 (dd, $J=7.0$ Hz, 5.0 Hz, 1H), 6.65 (s, 1H), 6.66 (d, $J=7.7$ Hz, 1H) 6.79 (d, $J=8.1$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.1, 21.7, 32.0, 39.2, 48.7, 52.6, 55.8, 58.2, 81.9, 87.8, 111.1, 111.9, 120.5, 126.7, 148.3, 172.0, 172.3, 210.1.

   DL-Multiprotected amino acid **13**: colorless oil; IR (CCl_4): 2954, 1732 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.23 (s, 9H), 1.65 (wide s, 1H), 2.04 (wide s, 1H), 2.87 (t, $J=8.8$ Hz, 1H), 3.73 (s, 3H), 3.84 (s, 3H), 3.84 (s, 3H), 4.59 (wide s, 1H), 6.68 (s, 1H), 6.69 (d, $J=6.5$ Hz, 1H), 6.79 (d, $J=8.7$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.5, 28.2, 32.5, 39.5, 52.6, 55.9, 55.9, 79.9, 111.0, 112.1, 121.0, 126.9, 148.4, 148.7, 155.9, 172.9.

   Tricarbonyl amide complex **14**: yellow solid; mp 75°C; IR (CCl_4): 2058, 1998, 1981 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.85 (d, $J=7.4$ Hz, 1H), 1.16–1.37 (m, 1H), 1.44 (d, $J=6.1$ Hz, 3H), 3.94 (wide s, 2H), 5.20 (dd, $J=8.4$ Hz, 5.0 Hz, 1H), 5.80 (dd, $J=6.5$ Hz, 5.7 Hz, 1H), 7.20 (wide s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.1, 58.7, 58.7, 82.0, 87.8, 172.1, 210.4.