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Intramolecular cyclodehydration of (4*S*)-(+)-4-carboxyethyl-4-(pyrrol-1-yl)butanal as the key step in the formal synthesis of (*S*)-(−)-Myrmicarin 217

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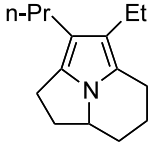
Abstract—(*S*)-(−)-Myrmicarin 217, a tricyclic alkaloid recently discovered in the poison glands of Myrmicaria ants, has been formally synthesized. The intramolecular cyclodehydration of 4-carboxyethyl-4-(pyrrol-1-yl)butanal is the key step in the construction of the required six-membered ring. © 2003 Elsevier Science Ltd. All rights reserved.

Myrmicarin 217 is a tricyclic alkaloid recently discovered in the poison glands of Myrmicaria ants, a genus of african Myrmicinae. The first synthesis of non racemic M217 was reported by Vallée et al.[1] Schröder and Francke described the synthesis of racemic M217[2] and the same authors have previously isolated various natural myrmicarins.



As a pyrrolo[2,1,5-*cd*]indolizidine, Myrmicarin 217 belongs to the 'izidine' type alkaloids, widely present in nature and characterized by a variety of physiological activities.[3] We recently found a new approach to 5,6-dihydroindolizines via an in situ domino hydroformylation/cyclization/dehydration reaction sequence of 1-allylpyrroles.[4] In this pathway an unprecedented intramolecular electrophilic substitution by the carbonyl group of the produced 4-pyrrolylbutanals on the C-2 pyrrole carbon is the key step to construct the six-membered ring of the indolizine moiety. The 4-pyrrolylbutanals are a class of compounds almost unknown in literature, perhaps because they are very reactive or difficult to be prepared via traditional synthetic chemistry. Encouraged by the success of our protocol and attracted by the intriguing structure of the above alkaloid, we tried to synthesize non racemic Myrmicarin 217 via the cyclodehydration of a suitable chiral 4-(pyrrol-1-yl)butanal (Scheme 1)

We chose L-glutamic acid diethyl ester hydrochloride **1** to introduce the appropriate stereogenic center. According to a well known procedure,[5] **1** was condensed with 2,5-dimethoxytetrahydrofuran under non-racemizing conditions, namely, in a stirred mixture of warm water and 1,2-dichloroethane to give the pyrrolyldiester (2*S*)-(−)-diethyl-2-(pyrrol-1-yl)pentanedioate **2** in excellent yield. The reduction of **2** into **3** was successfully accomplished by treatment of **2** with DIBAH in hexane (1.8 equiv.) at −78°C. The pyrrolylbutanal **3** was chemo- and regioselectively obtained, only the distal ester group being reduced to the corresponding carbonyl group. The (4*S*)-(+)-4-carboxyethyl-4-(pyrrol-1-yl)butanal **3** is stable enough to be handled at room temperature and can be stored at 0°C for a few days without any decomposition.[6] Over longer times, **3** spontaneously cyclizes, presumably giving the bicyclic alcohol bearing the hydroxyl group on C-8.[7] A one pot ring closure/dehydration sequence was carried out by heating the butanal **3** at 100°C in anhydrous DMSO, a typical neutral dehydration agent of benzyl alcohols.[8] The 5,6-dihydroindolizine **4** bearing an ester group on position 5 was obtained selectively.[9] The product **4** was isolated by silica chromatography by eluting with hexane/Et_2O 2:1 and was transformed

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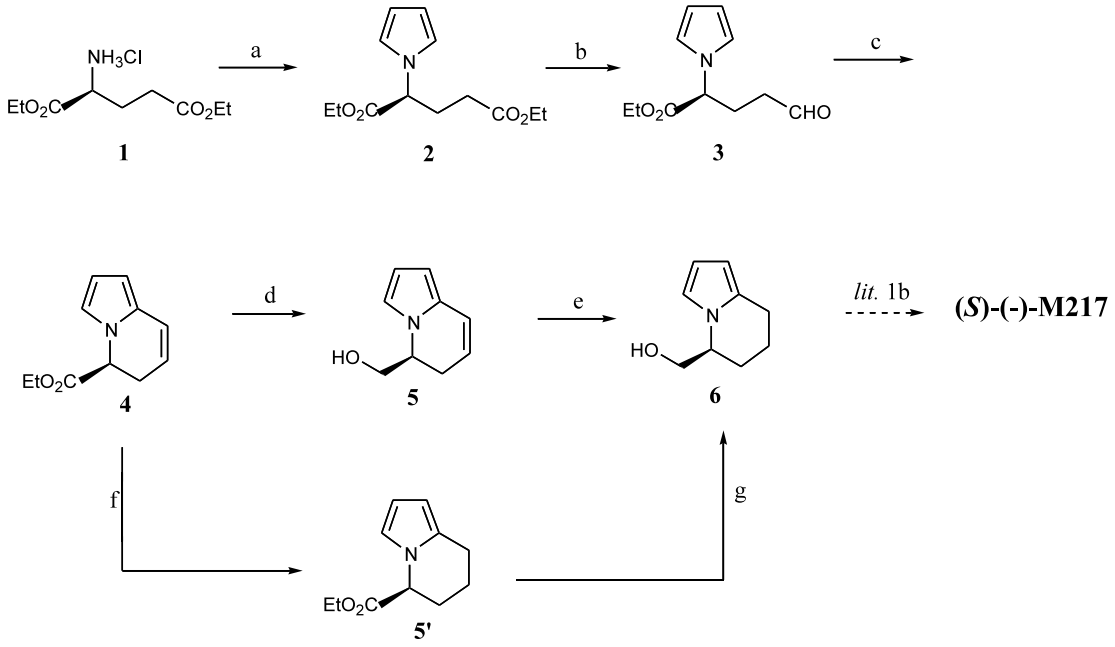

Scheme 1. *Reagents and conditions*: (a) 2,5-dimethoxytetrahydrofuran, 1,2-dicloroethane/H_2O (1:1), 80°C, 50 min, 80%; (b) 1 M DIBAH in hexane (1.8 equiv.), −78°C, 3 h, 65%; (c) DMSO, 100°C, 2 h, 55%; (d) $LiAlH_4$, THF, rt, 2 h, 85%; (e) H_2, 5% Rh, Et_2O, 80%; (f) 5% Rh, Et_2O, 75%; (g) $LiAlH_4$, THF, rt, 2.5 h, 80%.

into (5*S*)-(−)-5-hydroxymethyl-5,6,7,8-tetrahydroindolizine **6** using two different methods. In the first the reduction of the ester group of **4** to the corresponding hydroxymethyl group in **5**[10] was achieved by treatment of **4** with $LiAlH_4$ at room temperature; subsequently the double bond in **5** was reduced with H_2 in the presence of 5% rhodium on carbon catalyst to give **6** (d–e in Scheme 1). In an alternative sequence, the unsaturated ester **4** was submitted to hydrogenation of the double bond under the same experimental conditions adopted in the case of **5** selectively giving **5′** (f in Scheme 1).[11] Then **5′** was transformed into **6** by treatment with $LiAlH_4$ (g in Scheme 1). Spectroscopic data (^1H and ^{13}C NMR, MS) and specific rotation for the resulting alcohol **6** are in full agreement with that reported by Vallée et al.: $[\alpha]_D^{20} = -34.1$ (*c* 1, CH_2Cl_2); lit.[1b] $[\alpha]_D^{20} = -33.7$ (*c* 1, CH_2Cl_2).

The (5*S*)-(−)-5-hydroxymethyl-5,6,7,8-tetrahydroindolizine **6** has previously been converted by Vallée into (*S*)-(−)-M217 having 98% enantiomeric excess.[1b]

In summary, a formal synthesis of (*S*)-M217 has been achieved by intramolecular cyclodehydration of the (4*S*)-4-carboxyethyl-4-(pyrrol-1-yl)butanal **3** promoted by the strong nucleophilic character of the pyrrole carbon atom α to the nitrogen. The synthesis of **3** shows that pyrrolylbutanals[4] can be prepared via traditional organic chemistry and they can be isolated and fully characterized. The new intermediates **4** and **5** were also isolated and characterized; they are two examples of 5,6-dihydroindolizines, a class of compounds almost unknown in literature, recently obtained by us under rhodium catalyzed hydroformylation of 1-allylpyrroles.[4] Synthesis of natural products of similar structure via the above procedure are in progress.

Acknowledgements

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6. Selected data for **3**: yellow liquid; $[\alpha]_D^{20} = +53.2$ (*c* 1, benzene); ^1H NMR ($CDCl_3$, 200 MHz, TMS): δ 9.66 (bs, 1H), 6.73 (t, $J = 2.0$ Hz, 2H), 6.21 (t, $J = 2.0$ Hz, 2H), 4.67 (m, 1H), 4.22 (m, 2H), 2.52–2.20 (m, 4H), 1.28 (t, $J = 7.2$ Hz, 3H).
7. ^1H NMR spectra of pure samples of **3**, carried out at different times, showed a decrease of the CHO signal and the corresponding increase of a structurated signal at 5.15 ppm, compatible with the CHOH proton in the 5-carboxyethyl-8-hydroxyl-5,6,7,8-tetraidroindolizine. However, a GC–MS control of the same samples showed the typical fragmentation of 5-carboxyethyl-5,6-dihydroindolizine **4**.[9]

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9. Selected data for **4**: yellow oil; $[\alpha]_D^{20} = -127.5$ (*c* 0.35, hexane); ^{1}H NMR ($CDCl_3$, 200 MHz, TMS): δ 6.63 (dd, $J = 1.5$; 2.7 Hz, 1H), 6.45 (dt, $J = 9.6$; 1.6 Hz, 1H), 6.17 (dd, $J = 2.7$; 3.6 Hz, 1H), 6.08 (dd, $J = 1.5$; 3.6 Hz, 1H), 5.60 (m, 1H), 4.71 (m, 1H), 4.15 (m, 2H), 2.83 (m, 2H), 1.24 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 14.1, 27.6, 56.5, 61.5, 106.8, 108.9, 116.1, 120.6, 121.6, 129.2, 171.0; MS *m*/*e* 191 (M^+ 13), 118 (100), 90 (10).
10. Selected data for **5**: yellow oil; $[\alpha]_D^{20} = +69.6$ (*c* 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 200 MHz, TMS): δ 6.75 (s, 1H), 6.42 (dd, $J = 2.6$, 9.8 Hz, 1H), 6.15 (t, $J = 3.0$ Hz, 1H), 6.07 (m, 1H), 5.61 (m, 1H), 4.16 (m, 1H), 3.79–3.60 (m, 2H), 2.77 (m, 1H), 2.40 (m, 1H), 1.96 (bs, 1H); ^{13}C NMR ($CDCl_3$): δ 128.5, 121.2, 120.0, 117.4, 108.2, 106.6, 64.5, 56.1, 26.1; MS *m*/*e* 149 (M^+ 37), 118 (100), 117 (79), 91 (14).
11. The spectroscopic parameters (^{1}H and ^{13}C NMR, MS) for **5′** resulted in agreement with that reported in literature for the same compound prepared in an alternative way.[1b]