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Asymmetric carboxylation in the synthesis of L-methionine : a new tool for ^{11}C chemistry

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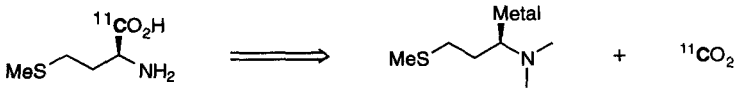
Abstract : L-methionine is obtained in good yield and high e.e. by using the carboxylation of an enantiopure α-lithio oxazolidinone prepared by tin-lithium exchange. The entire process from α-stannyl oxazolidinone takes 35-40mn, time which is compatible with the use of $^{11}CO_2$ in radioactive chemistry directed to PET imaging. © 1997 Published by Elsevier Science Ltd.

Positron emission tomography (PET) has been developed in the last decade as a useful imaging technique to reveal *in vivo* functional processes[1]. The necessity of preparing " tracers " labeled by isotopes with a short half-life introduces a new challenge in organic synthesis since the preparation of these tracers has to be carried out in a limited time after the introduction of the radioactive isotope. This challenge is particularly crucial when it is necessary to label a compound with ^{11}C, which has a half-life of 20.4 mn.

In the course of a program devoted to the study of the protein synthesis in the human brain, we had to develop an approach to enantiomerically pure L-[1-^{11}C] methionine using $^{11}CO_2$ as the labelling reagent . As the reasonable time for producing ^{11}C-labelled compounds is only two half-lives, this isotope has to be introduced in one of the ultimate steps of the synthesis. The only appropriate solution was the carboxylation of a chiral non-racemic α-amino organometallic species :



1

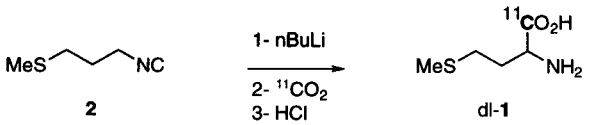
- Scheme 1 -

It is noteworthy that L-[S-methyl ^{11}C] methionine is presently used in PET [2] but that *in vivo* trans-methylations decrease the signal/noise ratio. Better images would be produced with **1**, allowing easier interpretation of the data.

Among the numerous known asymmetric syntheses of α-amino acids,[3] only a few use the carboxylation depicted in scheme 1 and they involve α-aminolithio derivatives produced either by direct metallation of

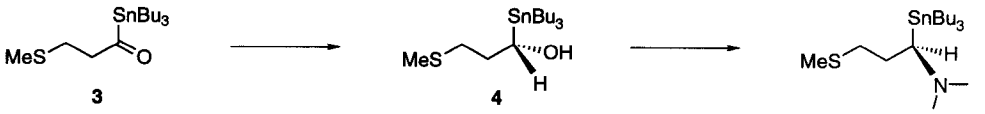
substituted amines, or by tin-lithium exchange carried out on enantio-enriched α-amino stannanes. Using this last method, Chong *et al.* obtained *N-methyl* α-amino acids with ~95 % e.e[4]. Very recently, the enantioselective metallation of N-Boc N-aryl benzyl amines followed by carboxylation was described as a possible way to aryl α-amino acids such as phenylglycine[5] but i) the method seems to be limited to benzylic amines and ii) it would require two steps after carboxylation for the deprotection of the primary amino group.

As racemic **1** was obtained[6] by α-hydrogen abstraction of isocyanide **2** by n-BuLi followed by carboxylation with $^{11}CO_2$ and acidic hydrolysis (scheme 2), we first tried to deprotonate enantioselectively **2** by s-BuLi/sparteine[7]. This was unsuccessful.



- Scheme 2 -

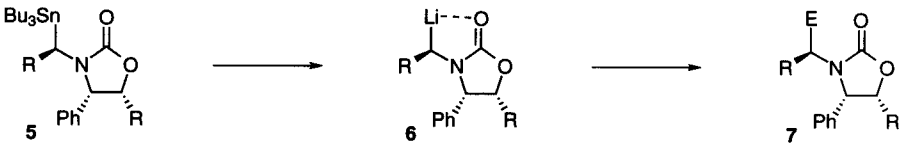
Consequently, we turned our attention to the preparation of enantio-enriched α-aminostannanes, following a sequence described by Chong *et al*[4]. where acylstannane **3** would be enantioselectively reduced, the resulting α-hydroxystannane **4** being submitted to a Mitsunobu reaction using nitrogen nucleophiles.



- Scheme 3 -

Unfortunately, the Mitsunobu reaction on racemic **4** was completely unsuccessful in spite of numerous attempts using various amines, amides or azides. Only the use of phthalimide gave the desired product, but with a yield of 5%.

Consequently, we took advantage of the results of Pearson *et al*[8]. who obtained diastereoselectively diverse amino derivatives using " dipole-stabilized "[9] organolithium species obtained by tin-lithium exchange of oxazolidinones **5** (scheme 4).

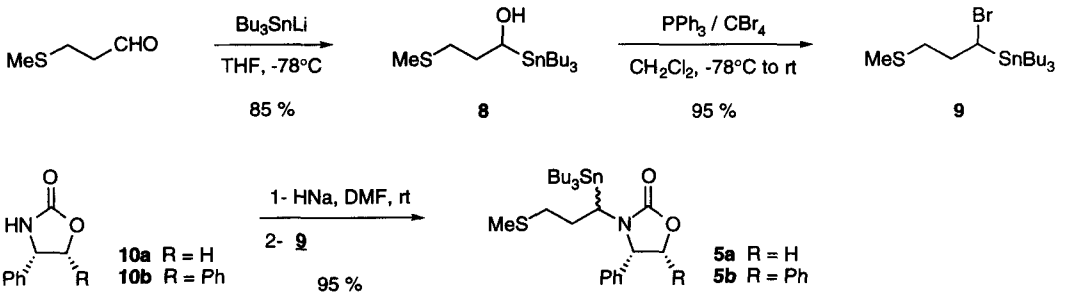


- Scheme 4 -

This strategy was attractive for two reasons: the diastereoselectivity is good due to the high rigidity of the chelated lithio intermediate **6** and the diastereomers of **5** can be separated in many cases. Nevertheless, when

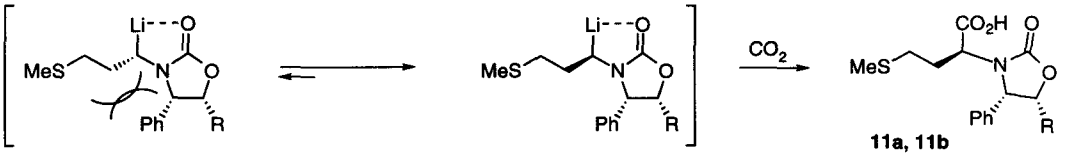
applied to methionine two questions remained: the carboxylation of **6** was not described and, to quote authors " the synthetic utility of these anions will depend on the ease of deprotection of the products ", namely the transformation of the oxazolidinone group to the primary amine. However, this deprotection may be reasonably undertaken by a Birch-type reduction[10] or a palladium-mediated hydrogenolysis[11] but, in our case, this deprotection has to be done *rapidly*.

To answer these two questions, enantio-pure oxazolidinones **5a** (R=H) and **5b** (R=Ph) were prepared (scheme 5). The α-alcoxy stannane **8** obtained by the addition of tri-n-butylstannyl lithium[12] on 3-methylthiopropanal was converted to the bromostannane **9** using PPh_3/CBr_4 [13]. The sodium salts of the oxazolidinones **10a,b** were then alkylated with **9**, giving the expected products **5a,b** in high yield as a 1/1 mixture of diastereomers.



- Scheme 5 -

Transmetallation of **5a** by one equivalent of nBuLi in THF at -70°C followed by carboxylation by gaseous CO_2 produces, *in less than 15 mn* (from CO_2 introduction, including work-up), the oxazolidino acid **11a** as a single diastereomer as proved by ^1H and ^{13}C NMR with a yield of 85 %. The same reaction performed with **5b** is comparable but gives a lower yield (60 %). The high diastereoselectivity observed, in spite of the fact that **5a,b** were mixtures of diastereomers, is in favour of a fast equilibrium between the two diastereomers of the lithio species **6** as anticipated by Pearson *et al* [8]. According to this hypothesis, the configuration of the methionine thus obtained (see below) is evidence that the carboxylation occured with retention of configuration.



- Scheme 6 -

We first tried to transform the oxazolidino group to the primary amine by palladium-ammonium formate hydrogenolysis[11]. As could be anticipated, this reaction was unsuccessful with **11a**, but **11b** was deprotected in less than 15 mn by running the reaction in refluxing methanol. Unfortunately, the separation of methionine from

excess formate proved to be difficult and too long for our purpose. On the contrary, the expected transformation was accomplished by dissolving metal reduction according to a Birch-Evans protocol[10] using Li in liq. NH_3 in the presence of tBuOH/THF at -78°. This reaction, performed *in 5 mn* is followed by a fast ion-exchange chromatography on a Dowex 50WX8 column eluted with 2% aqueous ammonia. (L)-methionine was then obtained with a yield of 85 % and an e.e. ≥ 95 % determined by HPLC on a chiral column[14]. As the yield observed in the preparation of **11a** was better than that of **11b**, we did not try to deprotect the latter compound using the same procedure.

These results show that the highly enantioselective synthesis of α-amino acids using the carboxylation of an enantiopure α-lithio oxazolidinone can be carried out. For our purpose, the fact that the entire process of transforming **5** to (L)-methionine is done in *35-40mn* authorizes its use in the synthesis of this amino acid ^{11}C-labelled on the carboxyl group. This aspect is being pursued as well as the extension of the method to other natural and unnatural amino-acids.

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14. Only L enantiomer was detected. Chiral stationary phase : Astec Chirobiotic T, 250x4.6mm, 5 µm, mobile phase : EtOH : H_2O = 60:40 at 1 $ml.mm^{-1}$. det : UV 220 nm; (L)Met = 5.2 mn (D) Met = 8.0 mn. measured $[\alpha]^{20}_D$ = +20 (*c*2, HCl 2M).

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