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Aminomethylation of chiral silyl enol ethers: access to β²-homotryptophane and β²-homolysine derivatives

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ABSTRACT

We describe here the aminomethylation of chiral silyl enol ether derivatives using iminium ion. The choice of judicious precursors with adequate protecting groups for the silylation/aminomethylation step was required to achieve the synthesis of β²-homotryptophane in few steps. The same methodology was used to prepare a β²-homolysine derivative.

1. Introduction

The development of scalable syntheses of β-amino acids derivatives is an important challenge since these homologues of α-amino acids have relevant roles in medicinal chemistry.[1] Moreover, pioneering work by Seebach et al.[2] and Gellman et al.[3] has demonstrated the folding propensity of oligomers of these compounds, leading to secondary and tertiary structures very similar to that of α-peptides, hence these are considered as excellent peptidomimetics.[4] One will distinguish between β²- and β³-amino acids regarding the position of the side chain on the β-amino acid skeleton. β³-Amino acids are readily available in enantiomerically pure form by homologation strategies of α-amino acids. For instance, a recent catalytic homologation of α-amino acids via the carbonylation of enantiopure oxazolines using a silylcobalt precatalyst has been reported by Coates et al.[5] However the methodology describes only the synthesis of non-functionalized β³-amino acids, that is, bearing alkyl or phenyl chains. Noticeably, the Arndt–Eistert homologation of α-amino acids allows in few steps the preparation of β³-amino acids bearing functional groups on their side chains.[6] The preparation of β²-amino acids is much more challenging and many useful strategies are reported for the synthesis of these compounds, allowing access to β²-amino acids bearing trivial[7] or functionalized[8] side chains. Traditionally, these syntheses involve low temperature reaction (−30 °C to −78 °C), which can make them difficult to scale-up. Anyway, there is still a need for methodologies allowing access to functionalized compounds and easy to scale up.

We recently reported our preliminary results on the homologation of α-amino acids to β²-amino acids via a Reformatsky type reaction using highly reactive preformed iminium ions[9] as aminomethylating agents[10] (Scheme 1).

We have shown that the mild conditions required for this reaction allow its application to the preparation of some orthogonally protected functionalized β²-amino acids. Though, if this methodology is efficient for the preparation of racemic compounds, the application to asymmetric synthesis by use of chiral auxiliaries is very limited as only amino acids bearing high steric hindrance on their side chains gave good diastereoselectivities. The best de were observed with Oppolzer's sultam as chiral auxiliary in this reaction. Anyway the replacement of zinc enolates by silyl enol ethers in the aminomethylation step[11] allowed the preparation of various enantiomerically pure β²-amino acids by this method[12] (Scheme 2).

Herein, we report the application of this methodology to substrates bearing functional group on their side chains through the synthesis of optically pure β²-homotryptophane and β²-homolysine derivatives, representing two examples of various functional substitutions.

2. Synthesis of β²-homotryptophane derivative

The synthesis of β²-homotryptophane was first reported by Seebach et al. in 2002.[13] Initially, a route involving a *Curtius*-degradation step was described, allowing the preparation of the compound

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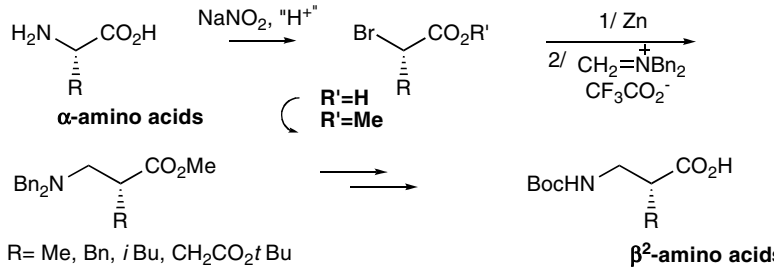
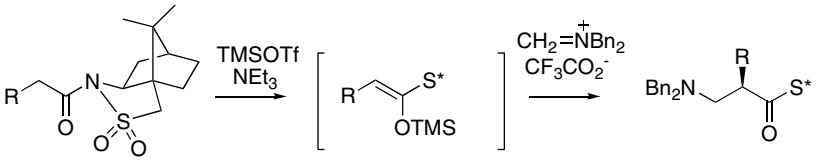


Scheme 1. Synthesis of β^2-amino acids by Reformatsky reaction using iminium trifluoroacetate salt.



Scheme 2. Addition of chiral silyl ketene N,O-acetals on in situ generated iminium salt.

optically active in eleven steps. More recently, the failure of strategies involving aminomethylation reaction for the synthesis of β^2-homotryptophane led the group of Seebach to propose an alternative route consisting of an aldol addition (with a 90/10 de) followed by a deoxygenation step.[8] The title compound was obtained in nine steps.

In a first attempt to apply our strategy to the synthesis of β^2-homotryptophane, the camphorsultam was introduced on the commercially available 3-indolylpropanoic acid **1**. The obtained compound **2** bearing no protection on the indole moiety was tested toward aminomethylation conditions (Scheme 3).

However, compound **2** failed to react with the iminium salt and only the starting material was isolated from the reaction mixture. Noticeably, we previously observed that a red coloration appears through the formation of silyl enol ether derivatives. This red coloration was not observed in silylation attempts involving compound **2**, suggesting that silylation did not occurred. As it seemed necessary to protect the indole ring, we firstly investigated the use of formate as protecting group and compound **3** was prepared from alkanoylsultam **2**. But again, the red coloration was not observed during silylation attempts and as expected, the aminomethylation failed. The protection of the indole moiety was yet considered using a benzyl group on the nitrogen of 3-indolylpropanoic acid **1** leading to compound **4**. After introduction of Oppolzer's Sultam, compound **5** was obtained and engaged in the silylation/aminomethylation reaction. In that case, although the red coloration was observed, only partial conversion occurred, giving the β^2-homotryptophane derivative **6** in a poor yield of 26%, the major product being the starting material. Fortunately, increasing the amount of TMSTf to 2 equiv allowed to rise up the conversion and compound **6** was obtained in a good yield of 88% as a single diastereoisomer (NMR analysis) (Scheme 3).

Finally, deprotection of the dibenzylamine moiety was carried out by hydrogenolysis catalysed by $Pd(OH)_2$ on charcoal. After removal of the Sultam by saponification and Boc-protection, the indole's nitrogen of compound **7** was deprotected under Birch conditions. Thus, *N*-Boc-β^2-homotryptophane **8** was obtained in seven steps in 24% overall yield.[14]

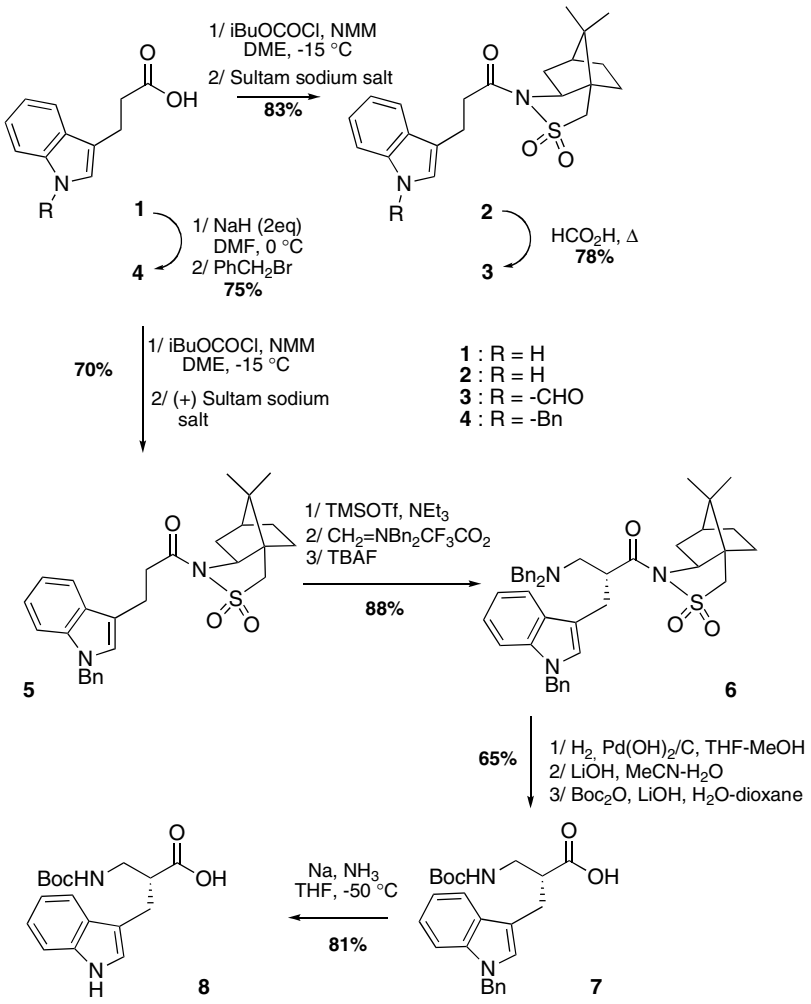
3. Synthesis of β^2-homolysine derivative

The synthesis of β^2-homolysine was reported for the first time by Seebach et al. in 2001.[15] The reported methodology is based on aminomethylation of a chiral compound that bears the side chain of the amino acid, leading to good yields and diastereoselectivities for the aminomethylation key step. In this synthesis, strong Lewis acids were required to activate the poorly reactive aminomethylating reagent, implying the use of robust protective group, which needs to be removed and replaced by a more suitable protecting group for solid phase peptide synthesis. This highly lengthens the synthesis, and 11 linear steps were required for the preparation of β^2-homolysine. Gellman et al. reported the synthesis of the β^2-homolysine by Michael addition of a chiral amine on an acrylate, providing a mixture of diastereoisomers that need to be separated by chromatography.[16] Recently, the same group reported an organocatalytic aminomethylation reaction as a new route to β^2-amino acids.[17] In the reported methodology, good yields and selectivities are obtained when amino acids with hydrocarbonic side chains are involved. However, if the selectivity remains high in the case of functionalized β^2-amino acids, such as β^2-homolysine, a drop of the yield is observed. Consequently, none of these strategies appears to be efficient for the multi gram synthesis of the target compounds.

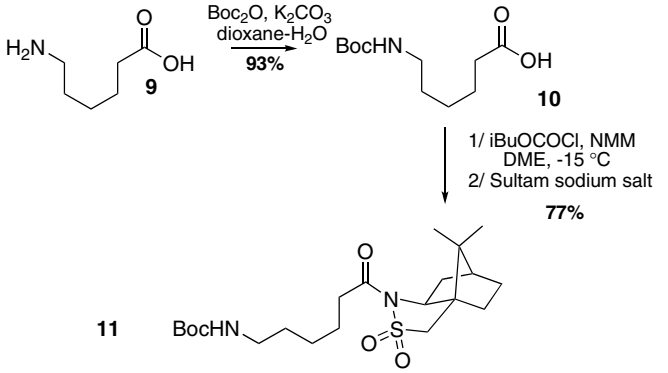
Different precursors that might give a straightforward access to the targeted compound **16** were tested under our aminomethylation conditions. The simplest way would be in principle to start from a compound that already contains the suitably protected amine, in the aim of avoiding any replacement of protective group. Thus, we investigated the synthesis starting from the commercially available 6-amino hexanoic acid **9**. The crucial choice of the protecting group on the ε-amino function appears to be quite tricky as this one has to be stable toward the Lewis acid conditions required for the aminomethylation step and orthogonal to the removal of both the chiral auxiliary and the dibenzyl moiety. Thus, the amine function of compound **9** was protected as Boc-carbamate **10** and after introduction of the chiral auxiliary, compound **11** was engaged in the aminomethylation process. However, the reaction was unsuccessful as only deprotection of the amine moiety was observed (Scheme 4).

We thereof decided to use for the aminomethylation step a precursor of amine function that can be transformed later in the synthesis (Scheme 5).

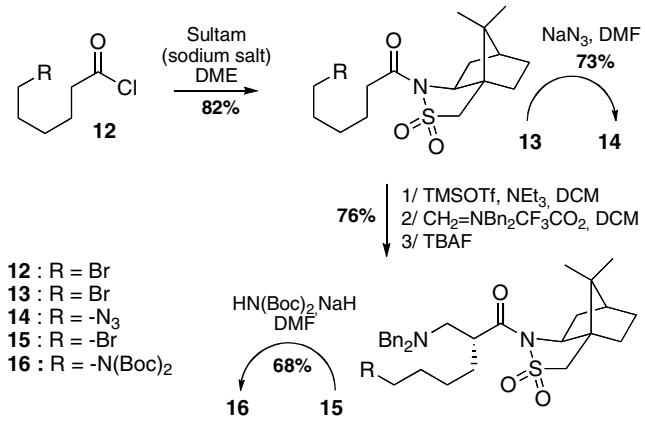
The synthesis was thus considered by aminomethylation of derivative **14** bearing an amine masked as an azido group. This compound was prepared starting from the commercially available 6-bromohexanoic acyl chloride **12**, after introduction of the chiral auxiliary and nucleophilic substitution of the halogeno compound **13**. However, no reaction occurred in that case and the starting



Scheme 3. Synthesis of *N*-Boc-β^2-homotryptophane.



Scheme 4. Attempt to prepare β^2-homolysine from 6-amino hexanoic acid.



Scheme 5. Synthesis of β^2-homolysine derivative **16**.

material was recovered. Again, this was expected since the red coloration of the reaction mixture was not observed. Fortunately, when the reaction was carried out with the bromo derivative **13**, the corresponding aminomethylated compound **15** was obtained in a good yield of 76% as a single diastereoisomer. Substitution of the brome by the commercially available di-*tert*-butyl iminodicarboxylate gives access in three steps to the expected β^2-homolysine skeleton **16**.[18]

In conclusion, the aminomethylation of chiral silyl enol ethers with the very reactive dibenzylidene iminium ion appeared to be a versatile methodology for the preparation of β^2-amino acids derivatives. Noticeably, low temperatures are avoided and multigram scale syntheses are easily feasible.

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14. *(N-benzylindoyl) propanoic acid* **4**: R_f (Cy/AE: 8/2) 0.25; mp 117 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, J = 7.6 Hz, 1H); 7.22–7.29 (m, 5H); 7.17 (t, J = 7.1 Hz, 1H); 7.11 (t, J = 7.6 Hz, 1H); 7.07 (d, J = 7.1 Hz, 1H); 6.93 (s, J = 1H); 5.24 (s, 2H); 3.71 (t, J = 7.6 Hz, 2H); 2.76 (t, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.5; 137.6; 136.7; 128.7; 127.7; 127.5; 126.7; 125.6; 121.9; 119.1; 118.8; 113.8; 109.7; 49.9; 34.8; 20.4. Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.12; H, 6.37; N, 4.89. *(1R)N-3-(N-benzylindoylpropanoyl) camphorsultam* **5**: R_f (Cy/AE/NEt_3: 8/2/0.1) 0.42; mp 123 °C; $[\alpha]_D^{20}$ 57 (*c* 1. $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63–7.65 (m, 1H); 7.20–7.28 (m, 4H); 7.07–7.16 (m, 4H); 6.97 (s, 1H); 5.23 (s, 2H); 3.85 (t, J = 6.3 Hz, 1H); 3.45 (d, J = 13.9 Hz, 1H); 3.42 (d, J = 13.9 Hz, 1H); 3.06–3.19 (m, 4H); 2.03–2.05 (m, 2H); 1.81–1.87 (m, 3H); 1.29–1.39 (m, 2H); 1.05 (s, 3H); 0.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5; 137.7; 136.6; 128.7; 127.9; 127.4; 126.7; 125.8; 121.7; 119.1; 119.0; 113.8; 109.5; 65.2; 52.9; 49.8; 48.4; 47.7; 44.6; 38.5; 36.1; 32.8; 26.4; 20.7; 20.2; 19.8. Anal. Calcd for $C_{28}H_{32}N_2O_3S$: C, 70.56; H, 6.77; N, 5.88. Found: C, 70.31; H, 6.98; N, 5.67. *(1R)-N-(2-Dibenzylaminomethyl-3-N-benzylindoyl propanoyl) camphorsultam* **6**: R_f (Cy/AE, 8/2) 0.35; mp 80–81 °C; $[\alpha]_D^{20}$ 25 (*c* 1. $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78–7.80 (m, 1H); 7.09–7.34 (m, 16H); 6.99–7.01 (m, 2H); 6.85 (s, 1H); 5.20 (s, 2H); 3.88 (m, 2H); 3.42–3.52 (m, 6H); 3.21 (dd, J = 14.4 Hz, 3.8 Hz, 1H); 2.94 (dd, J = 12.4 Hz, 10.3 Hz, 1H); 2.86 (dd, J = 14.4 Hz, 9.1 Hz, 1H); 2.56 (dd, J = 12.6 Hz, 4.5 Hz, 1H); 2.06–2.15 (m, 2H); 1.85–1.87 (m, 3H); 1.30–1.37 (m, 2H); 1.23 (s, 3H); 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.7; 138.7; 137.9; 136.6; 129.1; 128.6; 128.4; 127.9; 127.0; 126.7; 126.6; 121.6; 119.6; 112.4; 109.4; 65.4; 57.5; 55.8; 53.2; 49.8; 48.3; 47.7; 44.7; 38.6; 32.8; 26.5; 25.8; 21.0; 19.9. Anal. Calcd for $C_{43}H_{47}N_3O_3S$: C, 75.29; H, 6.91; N, 6.13. Found: C, 75.45; H, 7.20; N, 5.81. *(R)-(N-tert-butyloxycarbonylaminomethyl)-3-N-benzylindolylpropanoic acid* **7**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62–6.98 (m, 10H); 6.62 (br, 0.5H); 5.27 (s, 2H); 4.96 (br, 0.5H); 3.43–3.30 (m, 2H); 3.21–2.84 (m, 3H); 1.43 and 1.25 (2s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.95; 178.65; 158.16; 156.08; 137.73; 136.85; 136.66; 129.17; 128.85; 128.36; 128.14; 127.99; 127.64; 127.07; 126.76; 126.61; 125.43; 121.99; 119.34; 118.96; 111.69; 111.42; 109.92; 81.10; 79.70; 50.00; 46.81; 46.56; 42.67; 41.35; 28.49; 28.16; 25.78; 25.21. MS: calcd for $C_{24}H_{29}N_2O_4$ [M+H] 409, found 409. (R)-(N-tert-Butyl oxycarbonylaminomethyl)-3-indoyl-propanoic acid **8**: mp 56 °C; $[\alpha]_D^{20}$ 8.5 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (br, 1H); 7.61–7.04 (m, 5H); 6.47 (br, 0.5H); 4.99 (br, 0.5H); 3.43–3.34 (m, 2H); 3.21–2.86 (m, 3H); 1.44 and 1.28 (2s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.91; 178.86; 158.06; 156.26; 136.43; 136.28; 129.17; 128.36; 127.40; 125.43; 122.97; 122.55; 122.08; 119.50; 118.64; 112.32; 112.03; 111.38; 81.21; 79.88; 46.76; 46.43; 42.70; 41.29; 28.51; 28.20; 25.65; 25.15. MS: calcd for $C_{17}H_{23}N_2O_4$ [M+H] 319, found 319.
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18. *(1R)N-(6-Bromohexanoyl) camphorsultam* **13**: R_f (Cy/AE: 8/2) 0.49; mp 54–55 °C; $[\alpha]_D^{20}$ 88 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.86 (dd, 1H, J = 7.4 Hz, 5.3 Hz); 3.50 (d, J = 13.6 Hz, 1H); 3.43 (d, J = 13.6 Hz, 1H); 3.40 (*t*, 2H, J = 6.8 Hz); 2.71–2.75 (m, 2H); 2.04–2.12 (m, 2H); 1.85–1.92 (m, 5H); 1.65–1.74 (m, 2H); 1.33–1.53 (m, 4H); 1.15 (s, 3H); 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6; 65.2; 52.9; 48.4; 47.7; 44.6; 38.5; 35.1; 33.5; 32.8; 32.4; 27.5; 26.4; 23.5; 20.8; 19.9; Anal. Calcd for $C_{16}H_{26}NO_4SBr$: C, 48.98; H, 6.68; N, 3.57. Found: C, 48.93; H, 6.75; N, 3.57. *(1R)N-(2-dibenzyl amino methyl 6-bromo hexanoyl) camphorsultam 15*: R_f (Cy/AE, 8/2) 0.47; mp 90 °C; $[\alpha]_D^{20}$ 57 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20–7.40 (m, 10H); 3.87 (dd, J = 7.3 Hz, J = 5.3 Hz, 1H); 3.68 (d, J = 13.6 Hz, 2H); 3.51 (d, J = 13.9 Hz, 1H); 3.47 (d, J = 13.6 Hz, 2H); 3.43 (d, J = 13.9 Hz, 1H); 3.31–3.37 (m, 3H); 2.77 (dd, J = 12.6 Hz, 6.6 Hz 1H); 2.52 (dd, J = 12.6 Hz, 7.3 Hz, 1H); 2.03–2.07 (m, 2H); 1.86–1.90 (m, 3H); 1.77–1.81 (m, 2H); 1.56–1.60 (m, 2H); 1.33–1.42 (m, 4H); 1.21 (s, 3H); 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.4; 139.0; 129.0; 128.1; 126.9; 65.4; 58.2; 56.3; 53.2; 48.2; 47.7; 44.6; 44.0; 38.5; 33.5; 32.9; 32.8; 28.9; 26.4; 25.7; 21.0; 19.9; ESI$^+$: $[MH^+]$ = 603. *(1R)N-[2-dibenzyl aminomethyl-6-N,N-di-(tert-Butyloxycarbonyl) amino hexanoyl] camphorsultam* **16**: R_f (Cy/AE, 8/2) 0.44; $[\alpha]_D^{20}$ 40 (*c* 1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.18–7.32 (m, 10H); 3.86 (dd, J = 7.5 Hz, 5.0 Hz, 1H); 3.36–3.65 (m, 8H); 2.79 (dd, J = 12.5 Hz, 7.5 Hz, 1H); 2.52 (dd, J = 12.5 Hz, 5.0 Hz, 1H); 2.03–2.06 (m, 2H); 1.86–1.89 (m, 3H); 1.25–1.63 (m, 22H); 1.22 (m, 5H); 0.96 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 174.5; 152.6; 129.1; 128.1; 126.9; 82; 65.4; 58.1; 56.5; 53.3; 48.2; 47.8; 46.4; 44.7; 38.6; 33; 29.9; 29.3; 28.1; 26.5; 24.6; 21.1; 20. Anal. Calcd for $C_{41}H_{59}N_3O_7S$: C, 66.73; H, 8.06; N, 5.69. Found: C, 67.10; H, 8.16; N, 5.59.