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Synthesis of (+)-(*R*)-methyl 2-aminotetraline-2-carboxylate: the hydroxypinanone method versus the bislactim method

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Abstract—The methyl ester of 2-aminotetraline-2-carboxylic acid (Atc-OMe), an important residue for modified peptides, could only be synthesized from the Schöllkopf bislactim method, the hydroxypinanone method leading, during the second step, to elimination instead of alkylation toward the expected *spiro* product. The (+)-(*R*)-Atc-OMe was thus obtained in three steps and 55% overall yield from the (−)-(*R*)-bislactim derived from D-valine.

1. Introduction

As part of our work to investigate the effect of conformationally constrained amino acids at the X_{+1} position of the Grb2-SH2 consensus sequence pTyr-X_{+1}-Asn-X_{+3},[1] we required optically active 2-aminotetraline-2-carboxylic acid (Atc). However, until now, only *racemic* Atc has been prepared and used. We report here a short (three steps) enantioselective synthesis of (+)-(*R*)-Atc-OMe **8** through diastereoselective dialkylation of glycinate derivatives.

2. Alkylating agent 1

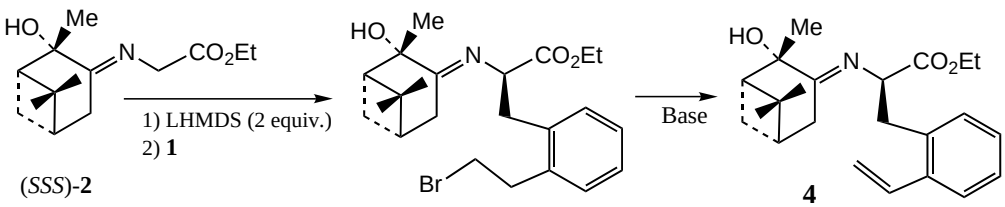
Alkylating agent **1** was obtained in two steps ($LiAlH_4$ reduction followed by CBr_4/PPh_3 bromination) and 65% isolated yield from commercially available homophthalic acid.

3. Alkylation of (*S,S,S*)-(−)-iminoglycinate 2

Alkylation of (*S,S,S*)-(−)-iminoglycinate **2**, derived from (*S,S,S*)-(−)-hydroxypinanone, which usually provides highly diastereoselective alkylations,[2,3] was envisaged first. (*S,S,S*)-Iminoglycinate **2** was prepared in 95% yield from (*S,S,S*)-hydroxypinanone and ethyl glycinate following the usual procedure.[2–4] The lithium enolate was generated at −78°C with LHMDS and alkylation with the dibromide **1** at −78°C afforded the desired adduct **3** as a single diastereoisomer **3I**[5] in 98% yield (Scheme 1).

This first alkylation occurred, as expected, at the benzylic position, as can be seen from the ABX system observed in the ^1H NMR spectrum (200 MHz).

However, whatever the base used for the second alkylation step (LHMDS/THF, LDA/THF, *t*-BuOK/MeCN



(*SSS*)-**2**

(*SSS,R*)-**3I** : 98% $[\alpha]_D$ = +77 (c=1, $CHCl_3$)

Scheme 1.

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or LiBr/NEt_3/THF), the elimination compound **4**[5] was the only new product observed, while **3I** was recovered in ~60% yield; no trace of the desired *spiro* adduct was detected.

4. Alkylation of (*R*)-(−)-bislactim ether 5

We thus switched to Schöllkopf's substrates, which had already been successfully used to prepare quaternary amino acids.[6,7]

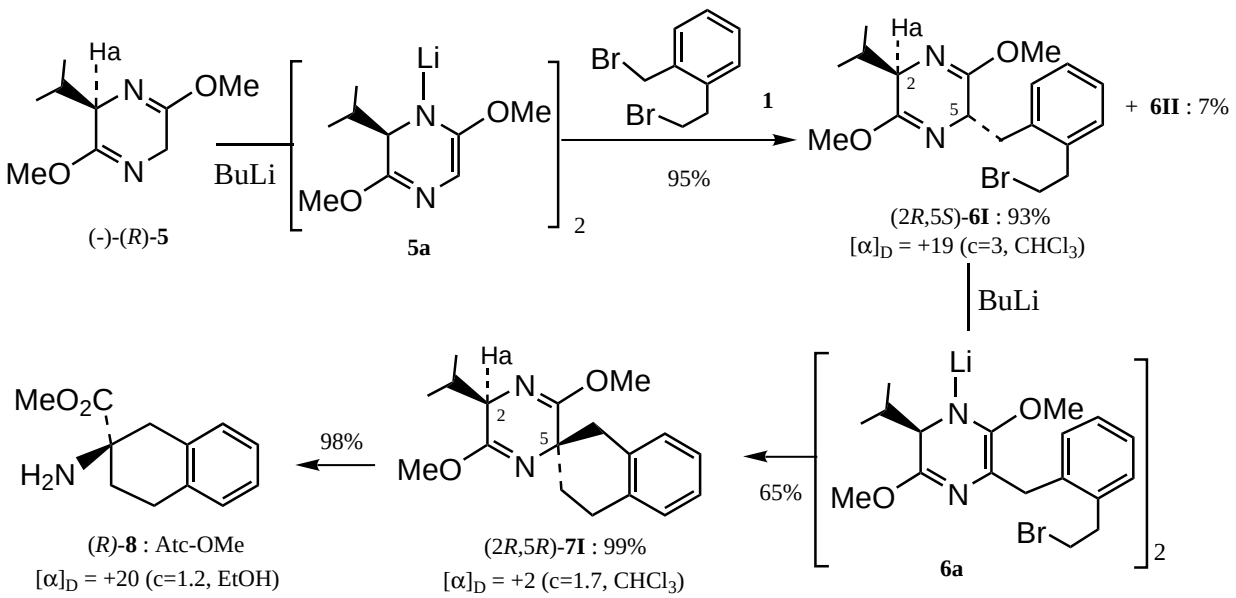
Commercially available (*R*)-(−)-bislactim ether **5** was treated with BuLi at −78°C to provide the lithium derivative **5a** (Scheme 2). Alkylation with the dibromide **1** then afforded the desired adduct **6**[8] as a 93/7 mixture of the two possible diastereomers. Here again, the first alkylation occurred at the benzylic position, as can be seen from the ABX systems observed for both diastereomers in the ^{1}H NMR spectrum of the crude product.

Using the same base (BuLi) and more diluted solutions (0.1 M in THF instead of 0.3 M in THF used for the first step), the desired *spiro* compound **7I**[8] was obtained as a single diastereomer (only one AB system in the ^{1}H NMR spectrum of the crude product).

After hydrolysis and neutralization, the methyl ester of 2-aminotetraline-2-carboxylic acid (Atc-OMe) **8**,[9] having a (+)-rotation in EtOH and MeOH, was isolated in 98% yield (55% overall yield from the starting substrate **5**) with an identical enantiomeric purity to that of **7I**.

5. Determination of the *R*-configuration of 8

On the basis of the *trans*-addition usually observed,[6] the starting (*R*)-bislactim ether used should provide Atc-OMe having the (*R*)-configuration and, as a matter of fact, a NOESY experiment (Bruker AC 400) on adduct **7I** exhibits a correlation spot between an isopropyl methyl group and a hydrogen atom of the AB system (H*equatorial*) corresponding to the isolated benzylic CH_2. This indicates that the configuration of **7I** is (*R*,*R*) (Fig. 1). Moreover, NOESY also exhibits a correlation spot between the second H of the AB system and the *axial* H of the non-benzylic CH_2 (Fig. 1), which is easily identified as non-benzylic by its position ($\delta = 2.23$ ppm) and as *axial* from the pattern, i.e. a double triplet ($^2J = {}^3J_{trans} = 12.5$ Hz, ${}^3J_{gauche} = 5$ Hz). A conformational study of (*R*,*R*)-**7I** using PM3 from MOPAC shows a conformation having the following: a flat heterocycle, ring A in a twisted form, the methyls of the methoxy in a *cis* relationship with the N atoms and a methyl of the



Scheme 2.

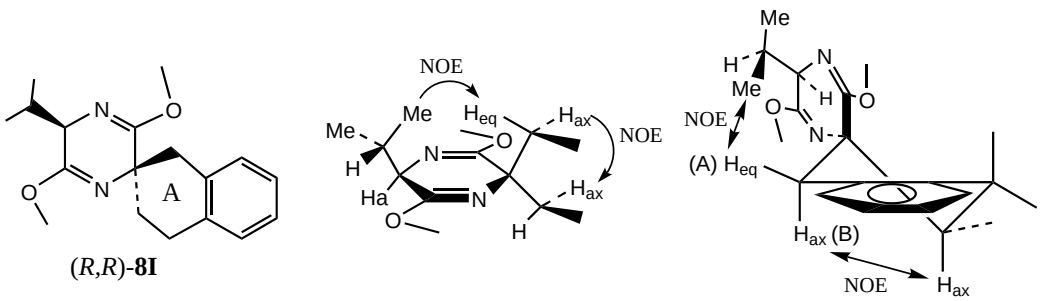


Figure 1.

isopropyl group above the heterocycle is the most stable,[10] consistent with the NOESY observed (Fig. 1). The small value of 3.5 Hz found for $^3J_{HH}$ between Ha and the methine proton of the isopropyl is consistent with a dihedral angle (Ha–C–C–H) of 60–90° and with a methyl positioned 'above' the ring (as elucidated by NOESY and simulation).

It is worth noting that the variation of the chemical shift of proton Ha (Scheme 2) from compound **5** to compounds **6I** and then **7I** indicates that the first intermolecular alkylation step occurred in a *trans* fashion, as expected. In the starting bislactim ether **5** proton Ha appears at 4.0 ppm (overlapped with the CH_2 signal), while in adduct **6I** proton Ha (assigned through decoupling of the isopropyl proton, a double septuplet at 2.2 ppm) is located at 3.4 ppm (0.6 ppm shielding), consistent with the presence of an aromatic ring in a *cis* relationship and also consistent with literature results[11,12] for similar aromatic-substituted compounds. Thus, in compound **7I**, where the aromatic ring is constrained away from Ha, its signal (doublet) moved again to 4.0 ppm. Therefore, it is reasonable to conclude that compound **6I** has a *trans* structure. Compound **7I**, having an (*R*,*R*)-configuration, demonstrates that the second alkylation step also occurred in a *trans* fashion.

In conclusion, (+)-(*R*)-Atc-OMe has been obtained from (−)-(*R*)-bislactim through two consecutive *trans*-alkylation steps.

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5. Compound **31**: $[\alpha]_D^{20}=+77$ (*c* 1, $CHCl_3$). Anal. calcd for $C_{24}H_{32}BrNO_3$: C, 62.35; H, 6.92. Found: C, 62.11; H, 6.85. ^{1}H NMR (200 MHz, $CDCl_3$): 7.1 (bm, 4H), 4.47 (X part of an ABX system, $^3J=3$ and 8 Hz, 1H), 4.20 (q, 2H), 3.60 (m, 2H), 3.35 (AB of the ABX, $^2J=12$ Hz, $^3J=3$ and 8 Hz, 2H overlapped with m, 2H), 2.45 (bm, 1H), 2.20 (m, 1H), 1.90 (m, 3H), 1.45 (d, $^2J=11$ Hz, 1H), 1.32 (s, 3H), 1.28 (t, 3H), 1.20 (s, 3H), 0.35 (s, 3H); ^{13}C NMR ($CDCl_3$): 178.4, 170.7, 137.0, 135.3 (C), 130.3, 129.2, 126.6 (CH arom.), 76.0 (C), 63.3 (CH), 60.7 (CH_2), 49.6, 37.8 (CH), 37.6, 36.1, 34.9, 32.7 (CH_2), 31.8 (C), 27.8 (CH_3), 27.5 (CH_2), 26.8, 22.4, 21.8, 13.8 (CH_3). Compound **4**: ^{1}H NMR (200 MHz, $CDCl_3$): similar to **31** but olefinic signals at 5.70 (dd, $^2J=1.5$ Hz, $^3J=18$ Hz, IH) and 5.30 (dd, $^2J=1.5$ Hz, $^3J=11$ Hz, 1H) and disparition of the CH_2–CH_2 signals at 3.5 and 3.3 ppm.
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8. Compound **6I**: $[\alpha]_D^{20}=+19$ (*c* 3.0, $CHCl_3$). Anal. calcd for $C_{18}H_{25}BrN_2O_2$: C, 56.70; H, 6.61. Found: C, 56.50; H, 6.56. ^{1}H NMR (200 MHz, $CDCl_3$): 7.15 (bs, 4H), 4.28 (m, 1H, X part of an ABX system), 3.74 (s, 3H), 3.63 (s, 3H), 3.51 (*pseudo* t, 2H, XX′ part of an AA′XX′ system), 3.45 (d, 1H, $^3J=3.5$ Hz), 3.25 (m, 3H, AA′ part of the AA′XX′ system superimposed with A part of the ABX system), 2.96 (dd, 1H, B part of the ABX system, $^2J=14$ Hz, $^3J\sim6.5$ Hz), 2.18 (sept.d, 1H, $^3J=6.5$ and 3.5 Hz), 0.97 (d, 3H, $^3J=6.5$ Hz), 0.62 (d, 3H, $^3J=6.5$ Hz); ^{13}C NMR ($CDCl_3$): 163.8 (C), 162.6 (C), 137.8 (C), 136.2 (C), 130.9 (CH), 129.4 (CH), 126.6 (2 CH), 60.2 (CH_3), 57.0 (CH_3), 52.3 (CH), 36.6 (CH_2), 36.2 (CH_2), 32.3 (CH_2), 31.2 (CH), 19.0 (CH_3), 16.4 (CH_3). Compound **7I**: $[\alpha]_D^{20}=+2$ (*c* 1.7, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 7.11 (m, 3H), 7.03 (m, 1H), 4.00 (d, 1H, $^3J=3.5$ Hz, Ha), 3.70 (s, 3H), 3.52 (s, 3H), 3.44 (d, 1H, $^2J=16.5$ Hz), 3.22 (ddd, 1H, $^2J=16.5$ Hz, $^3J\sim12$ and 5 Hz), 2.69 (ddd, 1H, $^2J=16.5$ Hz, $^3J\sim2.5$ and 5.5 Hz), 2.54 (d, 1H, $^2J=16.5$ Hz), 2.29 (d.sept., 1H), 2.23 (td, 1H, $^2J=12.5$ Hz, $^3J\sim12.5$ and 5 Hz), 1.67 (ddd, 1H, $^2J=12.5$ Hz, $^3J\sim2.5$ and 5.5 Hz), 1.11 (d, 3H, $^3J=6.5$ Hz), 0.76 (d, 3H, $^3J=6.5$ Hz); ^{13}C NMR ($CDCl_3$): 165.9 (C), 161.2 (C), 136.3 (C), 134.8 (C), 129.0 (CH), 128.4 (CH), 125.3 (CH), 125.2 (CH), 60.6 (CH_3), 56.4 (C), 52.5 (CH), 52.2 (CH), 40.4 (CH_2), 33.6 (CH_2), 31.1 (CH_3), 25.2 (CH_2), 19.4 (CH_3) and 17.0 (CH_3).
9. Compound (*R*)-**8**: $[\alpha]_D^{20}=+20$ (*c* 1.26, EtOH) and +17 (*c* 1.01, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$): 7.11 (m, 4H), 3.74 (s, 3H), 3.30 (d, 1H, A part of an AB system, $^2J=16.5$ Hz), 2.95 (m, 2H, AB part of an ABXY system), 2.74 (d, 1H, B part of the AB system, $^2J=16.5$ Hz), 2.20 (ddd, 1H, X part of the ABXY system, $^2J=13.5$ Hz, $^3J\sim6$ and 10 Hz), 1.89 (m, 1H, Y part of the ABXY system), 1.65 (s, 2H, NH_2). Anal. calcd for $C_{13}H_{18}ClNO_2$: C, 61.05; H, 7.09; N, 5.47. Found: C, 60.77; H, 6.96; N, 5.32.
10. It is 1.7 and 2.7 kcal/mol lower than for the other two conformations of the isopropyl, and 4 kcal/mol lower than the one having ring A in a boat conformation and the isopropyl group in the best orientation.
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