Novel Stereoselective Synthesis of (*R*)-3-Aminotetradecanoic Acid (Iturinic Acid)

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Abstract: (*R*)-3-Aminotetradecanoic acid (iturinic acid) has been synthesized starting from dodecanoyl chloride. This new synthetic approach involved the enantioselective reduction of an ynone to the corresponding propargylic alcohol and then into a protected propargylic amine. The iturinic acid was obtained by the transformation of a (phenylseleno)acetylene intermediate into a carboxylic group followed by N-deprotection.

Keywords: β-amino acids, stereoselective synthesis, natural products, selenium, copper catalysis.

INTRODUCTION

Bioactive cyclic lipopeptides, such as the cytotoxic mixirins A-C [1], epichlicin [2], mycosubtilin [3], iturins A-E [4] and bacillomycins D, E and L [5], have been isolated from terrestrial or marine microorganisms. All members are cyclic octapeptides with seven α-amino acids and one β^3-amino acid. Iturins are produced by *Bacillus subtilis* and in iturin-A (**1**, Fig. **1**) the nature of side chain (R in Fig. **1**) in the β^3-amino acid (named iturinic acid) is the essential requisite for the antifungal activity of the lypopeptide [6]. Iturin-A is naturally produced as a mixture of up to eight isomers which differ from each other in the length and isomerism of the β^3-amino acid side chain R. Thus the iturinic acids in iturin A have been determined to have from 13 to 17 carbon atoms and the (*R*)-configuration at the β-carbon [7]. The predominant iturin-A isomer (iturin-A2), contains the *n*-C14 isomer **2** of iturinic acid Fig. (**1**) [6]. Because of the pharmaceutical importance of the long-chain β^3-amino fatty acids, their synthesis has attracted increasing interest.

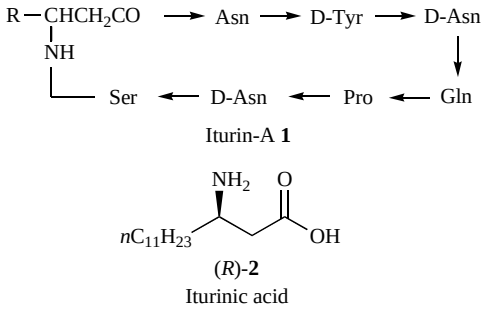

Fig. (1). Structure of iturin-A (R= C_{13}-C_{17} alkyl chain) and iturinic acid.

Few methods have been reported for the asymmetric synthesis of iturinic acid. Some are based on the stereoselective formation of the C-N bond and other on the transformation of an α-amino acid or on the regio- and stereoselective functionalization of linear dicarboxylic acid derivatives. The diastereoselective Michael addition of chiral nitrogen nucleophiles to enoates has been applied by Ohta [8] who obtained the pure enantiomer (*R*)-**2** as the methyl ester in low yield after chromatographic separation and N-debenzylation of the desired isomer. In a similar way, Enders [9] reported the synthesis of (*S*)-**2** (93% ee) by conjugate addition of lithiated TMS-SAMP to an α,β-unsaturated ester. In a different approach, Bland [10] transformed the carboxylic group at C-1 of *L*-aspartic acid into the desired alkyl substituent to obtain, after several steps, (*R*)-**2** as Boc derivative and in 99% ee. Moreover Sibi [11] prepared the same compound in 97% ee through a regio- and stereoselective alkylation of a succinate unit attached to a chiral auxiliary (oxazolidinone) and further selective conversion of one of the carboxy groups into an amino group by Curtius rearrangement. We report here a simple and enantioselective procedure to prepare (*R*)-3-aminotetradecanoic acid (**2**) hydrochloride starting from dodecanoyl chloride.

RESULTS AND DISCUSSION

The application of our recent studies [12] on the transformation of terminal alkynes into Se-phenyl selenocarboxylates led us to develop a simple and stereospecific synthesis of (*R*)-3-aminooctanoic acid starting from commercial (*S*)-1-octyn-3-ol by conversion into the corresponding (*R*)-N-phthalimido propargylic amine [13]. The availability of the optically active propargylic alcohols is the limiting factor for a wide application of our methodology to the synthesis of other naturally occurring β^3-amino acids as, for instance, iturinic acids. However, optically active propargylic alcohols can become available by asymmetric reduction of ynones. Thus (*R*)-**5** was synthesized according to the reaction sequence depicted in Scheme **1**. The ynone (**4**), easily obtained from the dodecanoyl chloride (**3**) by reaction with *bis*-trimethylsilylacetylene in the presence of $AlCl_3$ [14] was enantioselectively reduced with *S*-Alpine-Borane, as reported in the literature for the (*R*) isomer [15], to the (*S*) propargylic alcohol (**5**) [16].

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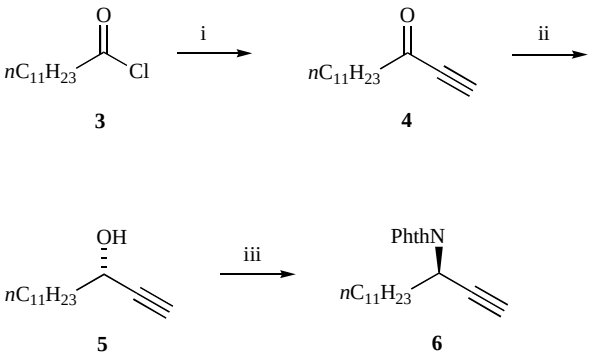
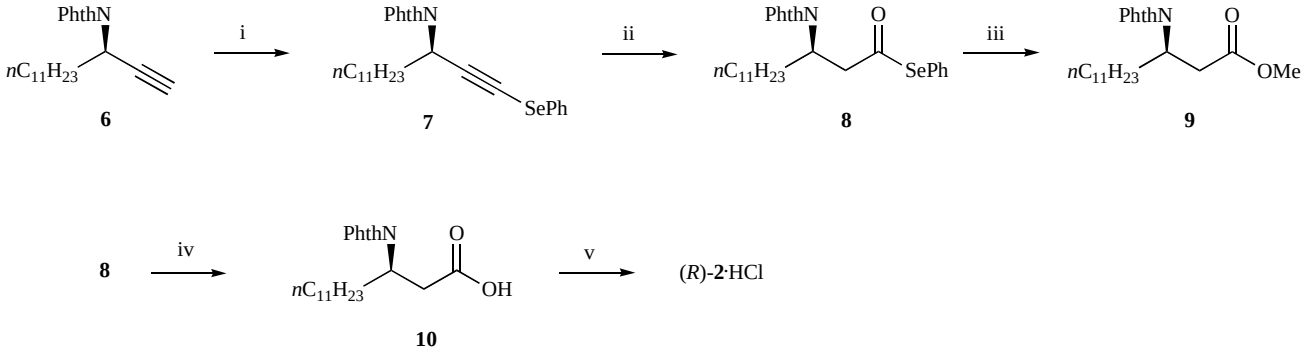


Scheme 1. i) $Me_3Si\text{-}C{\equiv}CSiMe_3$ (1.1 equiv.), $AlCl_3$(1 equiv.), CH_2Cl_2, 0 °C, 4 h then K_2CO_3, 81%; ii) (S)-Alpine-Borane (1.4 equiv.), 0 °C to rt, neat, 16 h then MeCHO (1.4 equiv.), H_2O_2 (3 equiv.), NaOH, 79%; iii) DIAD (1.8 equiv.), PhthNH (1.4 equiv.), Ph_3P (1.4 equiv.), THF, 0 °C to rt, 9 h, 70%.

By reaction with phthalimide under Mitsunobu conditions, compound (**5**) was easily converted into (*R*)-N-phthalimido propargylic amine (**6**) [17] with the expected complete inversion of configuration at the stereogenic carbon atom (Scheme **1**). The enantiomeric purity of (*R*)-**6** was estimated by HPLC analysis on chiral stationary phase. Compound (**6**) presented an enantiomeric ratio of 92:8 which is identical to that of the alkynol (*R*)-**5** reported in the literature [15]. The N-protected propargylic amine (**6**) (Scheme **2**) was then converted, in nearly quantitative yield, into the corresponding alkynyl phenyl selenide (**7**) which was directly employed in the reaction with *p*-toluenesulfonic acid monohydrate [12] to give the Se-phenyl selenocarboxylate (**8**). No racemization occurred during this conversion as demonstrated by HPLC analysis of the corresponding methyl ester derivative (**9**) [18] prepared by reaction of **8** with methanol in acetonitrile and in the presence of anhydrous cupric chloride [12].

When the crude **8** was treated with cupric chloride hydrate in acetonitrile at room temperature the corresponding (*R*)-N-phthalimido-3-aminotetradecanoic acid (**10**) [19] was obtained in good yield (Scheme **2**). The use of cupric chloride hydrate described here represents a new and very simple procedure to obtain carboxylic acids from the Se-phenyl selenocarboxylates. This procedure is more convenient than that which uses hydrogen peroxide [13]. Moreover, by the use of cupric chloride the selenium was recovered as diphenyl diselenide. Finally, the phthalimido group was removed by treating **10** with hydrazine hydrate in refluxing ethanol. Compound (*R*)-**2** was isolated as the hydrochloride in 68% yield [20]. Because under these reaction conditions the stereogenic carbon atom is not involved, it is suggested that the enantiomeric ratio of (*R*)-**2** hydrochloride was 92:8 as in the case of compound (**6**). This was established by treating the (*R*)-**2** hydrochloride with N-ethoxycarbonyl-phthalimide in tetrahydrofuran [21] to obtain the acid (*R*)-**10** which was esterified with methyl iodide in DMF and in the presence of potassium carbonate [22] to afford (*R*)-**9** which showed the same enantiomeric ratio of the compound prepared from **8**, as described above.

In order to confidently determine the enantiomeric excesses by HPLC it was necessary to dispose of the enantiomers *ent*-**6** and *ent*-**9**. These two compounds were obtained following the same procedure and using the *R*-Alpine-Borane as reducing agent of the ynone (**4**)**.** The HPLC analysis on chiral stationary phase of *ent*-**6** and *ent*-**9** was effected as described above for the (*R*) enantiomers and the measured ratio was 93:7. Compound *ent*-**10** could then be transformed into the (*S*) enantiomeric form of **2**.



Scheme 2. i) PhSeBr (1.1 equiv.), CuI (2 equiv.), DMF, rt, 36 h; ii) *p*-TsOH (2 equiv.), CH_2Cl_2, reflux, 6 h; iii) $CuCl_2$ dry (1.1 equiv.), MeOH/ MeCN, rt, 6 h, 40% (three steps); iv) $CuCl_2{\cdot}H_2O$ (1.1 equiv.), MeCN, rt, 14 h, 68% (three steps); v) $H_2N\text{-}NH_2$ (2.2 equiv.), EtOH, 100 °C, 5 h then HCl, 68%.

In summary, the present paper describes a new enantioselective synthesis of iturinic acid (**2**) hydrochloride and we can envision that the present procedure with the use of the appropriate acid chloride will allow the synthesis of the different iturinic acid side chains to be easily effected.

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[17] Selected data for compound (**6**): colorless wax mp 30-32 °C; $[\alpha]_D^{27}$ = + 3.51 (c = 1.69 in Et_2O); HPLC analysis: Chiracel OD-H column (250x4 mm, Daicel), eluent: *i*-PrOH/hexane (0.4:99.6) flow rate: 0.5 mL/min, UV detection at 230 nm; t_R 27.3 min: er = 92:8; ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ= 0.94 (t, *J* = 6.9 Hz, 3H, CH_3), 1.27-1.49 (m, 18H, CH_2), 2.09-2.30 (m, 2H, CH_2), 2.43 (d, *J* = 2.5 Hz, 1H, CH), 5.11 (td, *J* = 8.0, 2.5 Hz, 1 H; CHN), 7.73-7.95 (m, 4H, CH); ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ = 14.0, 22.6, 26.1, 28.7, 29.2, 29.3, 29.4, 29.5 (2C), 31.8, 33.3, 41.4, 71.7, 80.3, 123.3 (2C), 131.7 (2C), 134.0 (2C), 167.0 (2C); GC-MS (EI, 70 eV): *m/z* (%) = 296 (17)[M-41]$^+$, 212 (10), 199 (16), 184 (100), 130 (21), 94 (12); FT-IR (diffuse reflectance): 2922, 2115, 1766, 1713, 1385, 1077 cm^{-1}; Anal. Calcd for $C_{22}H_{29}NO_2$ (339.4): C, 77.84; H, 8.61; N, 4.13. Found: C, 77.41; H, 8.90; N, 3.85.
[18] Selected data for compound (**9**): pale yellow oil; $[\alpha]_D^{29}$ = 2.48 (c= 1.43 in $CHCl_3$); HPLC analysis: Chiracel OD-H column (250x4 mm, Daicel), eluent: *i*-PrOH/hexane (1:99) flow rate: 0.5 mL/min, UV detection at 230 nm; t_R 33.6 min: er = 92:8; ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ = 0.68-0.92 (m, 3H, CH_3), 1.05-1.31 (m, 18H, CH_2), 1.55-1.76 (m, 2H, CH_2), 2.61 (dd, *J*= 16.1 , 5.3 Hz, 1H, CH_2), 3.11 (dd, *J*= 16.1, 9.5 Hz, 1H, CH_2), 3.55 (s, 3H, CH_3) 4.58 (m, 1H, CHN), 7.65-7.90 (m, 4H, CH); ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ = 14.0, 22.5, 26.2, 28.7, 29.4 (4C), 31.0, 31.7, 32.2, 36.6, 47.9, 51.6, 123.1 (2C), 131.6 (2C), 133.8 (2C), 168.2 (2C), 171.3; GC-MS (EI, 70 eV): *m/z* (%) = 387 (61) [M]$^+$, 314 (53), 232 (52), 200 (100), 160 (54), 130 (35); FT-IR (diffuse reflectance): 2915, 1733, 1702, 1370, 976 cm^{-1}; Anal. Calcd for $C_{23}H_{33}NO_4$ (387.5): C, 71.29; H, 8.58; N, 3.61; Found: C, 71.66; H, 8.21; N, 3.19.
[19] Conversion of selenocarboxylic acid Se-phenyl esters (**8**) into acid (**10**): A mixture of selenocarboxylic acid Se-phenyl ester (**8**) (1 mmol) and copper (II) chloride hydrated (1.1 mmol) in acetonitrile (8 mL) was stirred at room temperature. The progress of the reaction was monitored by TLC. After 14 h the selenolester was completely consumed. Tartaric acid (1.2 mmol) was then added. The reaction mixture was stirred for few minutes, then filtered through a celite path and the filtrate concentrated. The crude product was purified by column chromatography on silica gel using a 98:2 mixture of dichloromethane and methanol as eluant. Compound (**10**) was obtained as colorless oil in 68% global yield. Selected data for compound (**10**): $[\alpha]_D^{31}$ = -29.57 (c= 0.45 in DMSO); ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ = 0.85 (t, *J* = 6.5 Hz, 3H, CH_3), 1.10-1.31 (m, 18H, CH_2), 1.58-1.81 (m, 1H, CH_2), 1.96-2.21 (m, 1H, CH_2), 2.82 (dd, *J*= 16.6, 5.4 Hz, 1H, CH_2), 3.21 (dd, *J*= 16.6, 9.5 Hz, 1H, CH_2), 4.65 (m, 1H, CHN), 7.76-7.90 (m, 4H, CH), 8.56 (brs, 1H, OH); ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ = 13.9, 22.5, 26.1, 28.9, 29.1, 29.2, 29.3, 29.4 (2C), 31.7, 32.2, 36.6, 47.6, 123.1 (2C), 129.2 (2C), 135.3 (2C), 168.2 (2C), 176.7; FT-IR (diffuse reflectance): 2921, 2853, 1704.7, 1712.5, 1375.4 cm^{-1}; Anal. Calcd for $C_{22}H_{31}NO_4$ (373.4): C, 70.75; H, 8.37; N, 3.75: Found: C, 70.30; H, 8.99; N, 4.08.
[20] Formation of (*R*)-**2** hydrochloride by deprotection of **10**: Hydrazine hydrate (0.11 mL, 2.2 mmol) was added to a stirred solution of **10** (0.37 g, 1 mmol) in EtOH (3 mL). After stirring for 5 h at 100 °C, the reaction mixture was allowed to slowly reach room temperature and concentrated. The residue was treated with 6 mL of 2N hydrochloric acid, the solid was allowed to settle down and then filtered. Evaporation of the filtrate gave a residue which was dried under reduced pressure to afford (*R*)-**2** hydrochloride in 68% yield. Selected data for compound **2**: White solid mp 131-135 °C; $[\alpha]_D^{25}$ = -17.80 (c= 0.59 in H_2O). ^{1}H NMR (200 MHz, D_2O): δ = 0.65-0.81 (m, 3H, CH_3), 0.97-1.35 (m, 18H, CH_2), 1.42-1.78 (m, 2H, CH_2), 2.62 (d, *J*= 6.3 Hz, 2H, CH_2), 3.38-3.57 (m, 1H, CHN); ^{13}C NMR (50 MHz, D_2O): δ = 14.4, 23.3, 26.0, 28.9, 29.9, 30.2, 30.3, 30.5 (2C), 32.6, 32.8, 48.9, 67.2, 174.2; FT-IR (diffuse reflectance): 2923, 1946.7, 1711.5, 1482.9 cm^{-1}; Anal. Calcd for $C_{14}H_{30}ClNO_2$ (279.8): C, 60.09; H, 10.81; N, 5.01. Found: C, 59.80; H, 11.27; N, 4.78.
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