Synthesis of pyrrolidine analogues of solamin

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Abstract—A convergent synthesis of pyrrolidine analogues of solamin, which possessed a pyrrolidine in place of the tetrahydrofuran ring, was presented in a facile route from 2,5-*trans*-bis(methoxycarbonyl)pyrrolidine. The stereochemistry of pyrrolidine core unit was determined by ^{1}H NMR spectroscopic analysis.
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The annonaceous acetogenins are a rapidly growing class of natural products in the past two decades. They are mostly characterized by one or more tetrahydrofuran rings together with a terminal γ-lactone moiety on a C-35 or C-37 carbon chain. Many of these compounds have very potent and diverse biological effects such as cytotoxic, antitumour and pesticidal activities. Therefore tremendous effort towards the isolation, total synthesis and biological evaluation have appeared in the literature.[1,2] In general, main action of acetogenins is thought to be the inhibition of the complex I (NADH–ubiquinone oxidoreductase),[3] although their mechanism and structure–activity relationship (SAR) still remain ambiguous. On the other hand, their high toxicity to normal cells and their poor solubility would be another obstacle in further studies on developing therapeutic agents. In an attempt to overcome some of their shortcomings and seek for better lead compounds, a diversity of structural analogues of acetogenins such as the hybrid acetogenin analogues[4] and the polyether simplified imitations,[5] have been reported. Some of them have been found exhibiting potential bioactivities or/and selectivities. Therefore, more efforts are encouraged towards the preparation of structural diverse analogues and the investigation of the SAR.

However, the aza-acetogenin, in which the tetrahydrofuran core unit is replaced by pyrrolidine, has rarely been considered except for the attempt of Casiraghi and co-workers[6] and Figadère and co-workers.[7] So far only the synthesis of partial units of hybrid acetogenin has been reported, whereas the preparation of aza-acetogenins in structural integrity has not appeared. Due to these reasons, we made the effort to complete the total synthesis of pyrrolidine analogues of aza-acetogenin, and we selected aza-solamin as the target molecule. Solamin is a monotetrahydrofuran containing natural acetogenin with interesting bioactivities.[8] This report describes a facile method to prepare aza-solamin's four possible relative configurations. It seems also useful for synthesis of other pyrrolidine analogues of acetogenins.

The retrosynthetic strategy is illustrated in Scheme 1. Aza-solamin **1** could be obtained by coupling the 2,5-disubstituted *trans*-pyrrolidine segment **2** with vinyl iodide segment **4**. Thereof segment **2** has four possible relative configurations according to $C_{15–16}$, $C_{16–19}$ and $C_{19–20}$: **2a** (*erythro-trans-erythro*), **2b** (*erythro-trans-threo*), **2c** (*threo-trans-erythro*) and **2d** (*threo-trans-threo*). Segment **2** might be accomplished by successive asymmetric alkylation of precursor **3**, which derived from adipic acid. The vinyl iodide γ-lactone **4** was prepared starting from ethyl (*S*)-lactate and undecylenic acid.

The convergent synthesis route is shown in Scheme 2. The C_2 symmetrical precursor 2,5-*trans*-bis(methoxycarbonyl)pyrrolidine **3** was prepared from adipic acid.[9] Transformation of the diester **3** to monohydroxy compound was achieved by the reduction with $NaBH_4/LiCl$ to afford pyrrolidinol **5** in good yield, which was
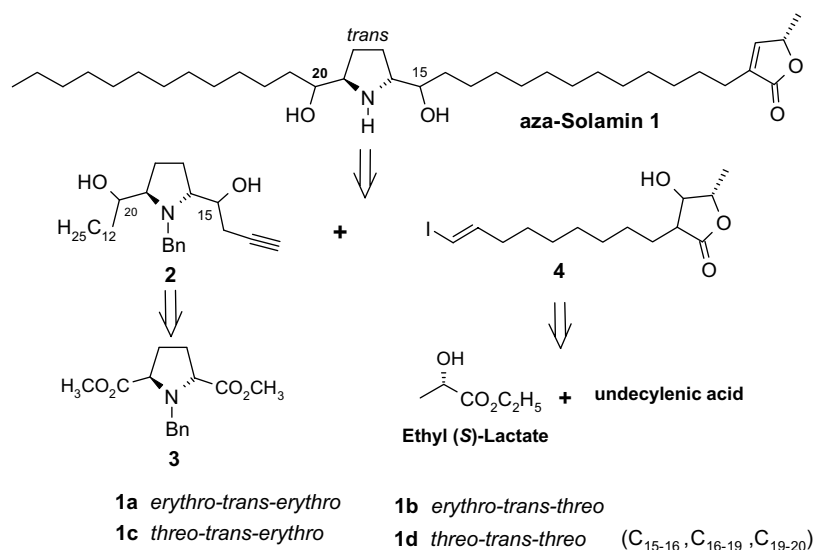
Scheme 1. The retrosynthetic strategy of aza-solamin.
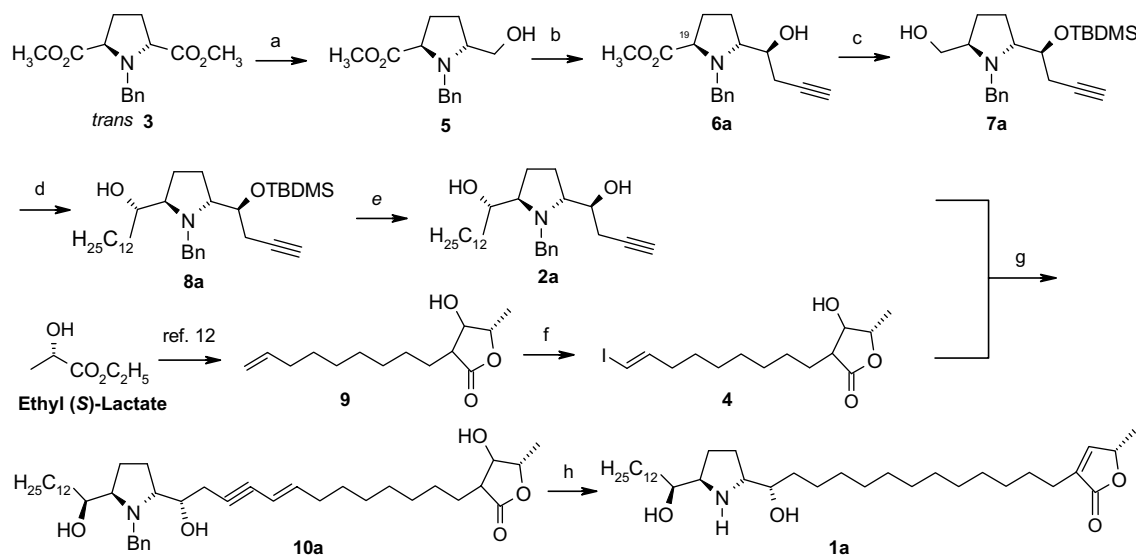
Scheme 2. Reagents and conditions: (a) NaBH$_4$, LiCl·H$_2$O, THF, 84% (based on the recovering substrate); (b) (i) Swern oxidation; (ii) propargyl bromide, Zn, DMF, Et$_2$O, *erythro* isomer **6a**, 41% and *threo* isomer **6b**, 33%; (c) (i) TBDMSOTf, 2,6-lutidine, CH$_2$Cl$_2$, 84%; (ii) LiAlH$_4$, Et$_2$O, 97%; (d) (i) Swern oxidation; (ii) C$_{12}$H$_{25}$MgBr, THF, rt, **8a** and **b** (3:1) 58%; (e) *n*-Bu$_4$NF, THF, 74%; (f) (i) AD-mix, *t*-BuOH, H$_2$O, rt, 85%; (ii) NaIO$_4$, CH$_2$Cl$_2$, rt; (iii) CHI$_3$, CrCl$_2$, THF, 0 °C, 5 h, 72%; (g) Pd(PPh$_3$)$_4$, CuI, Et$_3$N, rt, 6 h, 72%; (h) (i) 10% Pd–C, H$_2$, 1 N HCl (2 equiv), EtOH, 36 h; (ii) (CF$_3$CO)$_2$O, Et$_3$N, rt, 16 h, 40%.

converted to aldehyde via Swern oxidation reaction. Sequential treatment of the aldehyde with zinc reagent[10] furnished alkynol **6** in 74% yield, from which two isomers were readily separated by column chromatography in a ratio of 4:3. The relative configurations of the isomers **6a** and **b** were *erythro* and *threo*, respectively. The determination of the configuration will be discussed below, and the isolated isomer **6a** was employed to the subsequent reactions. Owing to the failure of reaction with TBDMSCl reagent, compound **6a** was treated with TBDMSOTf[11] to give the silyl ether product in 84% yield. Subsequent reduction of the protected monoester with LiAlH$_4$ afforded compound **7a**, which was successively subjected to a Swern oxidation and a Grignard

reaction with C$_{12}$H$_{25}$MgBr in anhydride THF to obtain **8a** and **b** (*erythro*:*threo* = 3:1) in 58% yield. Carefully separated by column chromatography, compound **8a** was desilylated with *n*-Bu$_4$NF to afford the 2,5-disubstituted pyrrolidine **2a** in 74% yield.

Meanwhile, the γ-lactone moiety **4** was prepared from segment **9**, which was constructed according to the reported method from ethyl (*S*)-lactate and undecylenic acid.[12] Therewith, dihydroxylation of olefin **9** with AD-mix gave diol intermediate in 85% yield, which was oxidated by NaIO$_4$ in dichloromethane to afford aldehyde. Subsequent treatment of the aldehyde with CHI$_3$ and CrCl$_2$ produced the vinyl iodide **4** in 72% yield.[13]

Then, segment **2a** coupled with the vinyl iodide **4** using Pd(PPh₃)₄/CuI/Et₃N system[14] to give compound **10a**, which was sequentially subjected to a catalytic hydrogenation of double and triple bonds along with simultaneous debenzylation to give the expected amine. Further treatment of the crude amine with trifluoroacetic anhydride in the presence of triethylamine[15] afforded the target molecule **1a.** It was noticeable that the in situ generated trifluoroacetate ester of β-hydroxyl-γ-lactone was inclined to undergo β-elimination, thus α,β-unsaturated γ-lactone was formed.

Other target molecules **1b–d** were synthesized in a similar manner starting from the appropriate form of precursors **6** and **8**.

Since there was no reaction suffering at C-2 and C-5 of pyrrolidine core, and no significant epimerization was observed, we considered that the corresponding *trans* configuration of C-16 and C-19 retained. To determine the stereo configuration of C-15 and C-20, that were introduced by adductive reactions, the corresponding oxazolidin-2-one derivatives were prepared to restrain the rotation of bonds of C_{15}–C_{16} and C_{19}–C_{20} (Scheme 3). The *N*-benzyl pyrrolidine **6a** underwent the hydrogenolysis followed by a reaction with triphosgene without any purification to furnish the restrained oxazolidin-2-one derivative. In order to obviate the base mediated epimerization at C-19 site, the ester group of **6a** was transformed into acetal group. Compound **6a** was firstly converted into the monohydroxyl form **7a**, then the aldehyde by Swern oxidation. The aldehyde was protected with ethylene glycol to give cyclic acetal

11a in 50% yield. Successive desilylation with *n*-Bu₄NF and debenzylation through catalytic hydrogenolysis of acetal **11a** afforded a crude hydroxylmethylene pyrrolidine, which was further treated with triphosgene and Et₃N to form oxazolidin-2-one **12a**. Another oxazolidin-2-one derivative **13a** was prepared by sequential hydrogenolysis of compound **8a** and reaction with triphosgene. Following similar procedures, the other four configuration restrained oxazolidin-2-one derivatives **12b** and **13b–d** were accomplished.

From ¹H NMR spectra of six configuration restrained oxazolidin-2-one derivatives, the specific ¹H–¹H coupling constants were determined. The ¹H–¹H coupling constants of these derivatives are shown in Figure 1. Futagawa et al. suggested that the coupling constant between C–H and C–H in oxazolidin-2-one derivatives was larger in *erythro* form than in *threo* form.[16] According to this hypothesis, we believed that compounds **12a** and **13a,c** were *anti*-adducts and compound **12b** and **13b,d** were *syn*-adducts. Then, the relative configuration of C-15 and C-20 stereocentres could be determined indirectly.

In conclusion, four aza-solamin isomers,[17] in which the central tetrahydrofuran ring of natural solamin was replaced by *trans*-pyrrolidine, were first synthesized in a facile route, and their stereochemistry was characterized by ¹H NMR spectroscopic analysis of oxazolidin-2-one derivatives. Moreover, some preliminary biological activities of the solamin analogues against several tumour cell lines were observed, and the detailed investigation is ongoing.
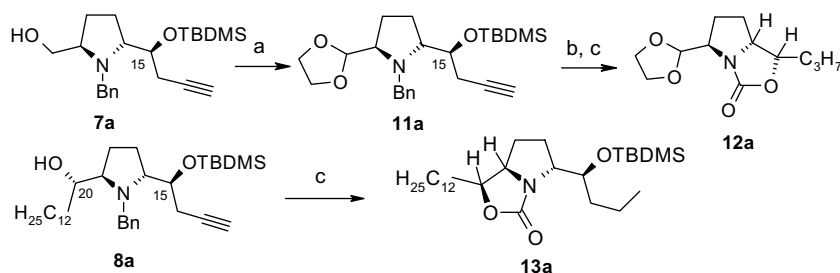
Scheme 3. Reagents and conditions: (a) (i) Swern oxidation; (ii) ethylene glycol, *p*-TsOH, benzene, 50%; (b) *n*-Bu₄NF, THF, 61%; (c) (i) 10% Pd–C, H₂; (ii) triphosgene, Et₃N, CH₂Cl₂, 10–40%.
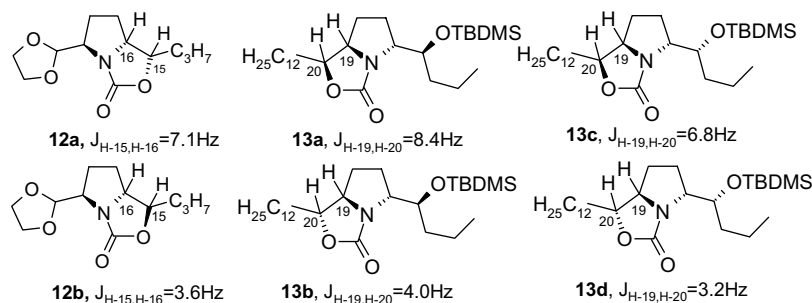
Figure 1. The ¹H–¹H coupling constants of configuration restrained oxazolidin-2-one derivatives.

Acknowledgement

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17. Four aza-solamins were characterized by detailed spectroscopic analysis. Compound **1a** MS (EI, 70 V) m/z: 563 (M^+), 364, 268; IR v_{max} (cm^{-1}, film): 3226, 1751, 1677, 1180, 1135; ^{1}H NMR (400 MHz, CDCl$_3$): 6.99 (1H, d, $J = 1.27$ Hz), 5.04–4.97 (1H, m), 4.06–4.01 (2H, m), 3.69–3.62 (2H, m), 2.28–2.22 (2H, m), 2.06–1.96 (4H, m), 1.60–1.20 (47H, m), 0.90–0.84 (3H, t, $J = 6.86$ Hz); ^{13}C NMR (400 MHz, CDCl$_3$): 173.7, 148.8, 134.0, 77.5, 68.2, 64.1, 33.8, 32.0, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 27.5, 26.0, 25.3, 23.2, 22.8, 19.3, 14.3. Compound **1b** MS (EI, 70 V) m/z: 563 (M^+), 364, 268; IR v_{max} (cm^{-1}, film): 3349, 3120, 1747, 1673, 1201, 1137; ^{1}H NMR (400 MHz, CDCl$_3$): 6.99 (1H, d, $J = 1.42$ Hz), 5.00–4.95 (1H, m), 4.10–4.06 (1H, m), 3.78–3.74 (1H, m), 3.70–3.65 (1H, m), 3.51–3.46 (1H, m), 2.26–2.22 (2H, m), 2.15–1.94 (4H, m), 1.65–1.20 (47H, m), 0.90–0.84 (3H, t, $J = 6.81$ Hz); ^{13}C NMR (400 MHz, CDCl$_3$): 173.7, 148.7, 134.1, 77.4, 71.8, 68.1, 66.2, 63.6, 34.4, 33.8, 32.0, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 28.4, 27.6, 26.0, 25.3, 23.6, 22.9, 19.4, 14.3. Compound **1c** MS (EI, 70 V) m/z: 563 (M^+), 364, 268; IR v_{max}(cm^{-1}, film): 3349, 1751, 1670, 1201, 1137; ^{1}H NMR (400 MHz, CDCl$_3$): 6.99 (1H, d, $J = 1.37$ Hz), 5.05–4.96 (1H, m), 4.05–3.97 (1H, m), 3.70–3.61 (2H, m), 3.52–3.45 (1H, m), 2.28–2.22 (2H, m), 2.14–1.95 (4H, m), 1.60–1.20 (47H, m), 0.85–0.51 (3H, t, $J = 6.80$ Hz); ^{13}C NMR (400 MHz, CDCl$_3$): 173.7, 148.7, 134.0, 77.4, 71.7, 68.1, 67.9, 66.1, 64.2, 63.5, 34.4, 33.8, 32.0, 29.8, 29.7, 29.5, 29.4, 29.3, 28.3, 27.5, 26.0, 25.3, 23.5, 23.2, 22.8, 19.3, 14.3. Compound **1d** MS (EI, 70 V) m/z: 563(M^+), 364, 268; IR v_{max} (cm^{-1}, film): 3388, 1754, 1673, 1203, 1137; ^{1}H NMR (400 MHz, CDCl$_3$): 6.99 (1H, d, $J = 1.37$ Hz), 5.04–4.96 (1H, m), 4.01–3.98 (1H, m), 3.71–3.60 (2H, m), 3.52–3.48 (1H, m), 2.30–2.20 (2H, m), 2.20–1.20 (51H, m), 0.90–0.80 (3H, t, $J = 6.80$ Hz); ^{13}C NMR (400 MHz, CDCl$_3$): 174.0, 149.0, 134.3, 77.4, 71.7, 67.5, 66.0, 65.2, 64.0, 34.2, 33.8, 32.8, 31.9, 29.7, 29.3, 28.3, 27.4, 25.2, 24.4, 22.7, 19.7, 19.2, 14.1.