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LETTERS

Synthesis of C1–C32 fragment of aza-solamin, an unnatural analogue of the annonaceous acetogenin solamin †

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Abstract

A synthesis of the skeleton of the pyrrolidino analogue of solamin, an annonaceous acetogenin, is presented. The configurations of four out of five stereocenters are controlled by enantioselective aldolization and *C*-glycosylation reactions. © 1999 Elsevier Science Ltd. All rights reserved.

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Annonaceous acetogenins are bioactive natural compounds isolated so far only from the Annonaceae.[2] Their high toxicity towards sensitive and multi drug resistant (MDR) cancerous cell lines[3] have attracted a large amount of interest, and thus tremendous effort towards isolation, total synthesis and biological studies of these compounds have recently appeared in the literature.[2] The study of the mechanism of action has shown that these polyketide derivatives interact with both complex-I and NADH oxidoreductase in the mitochondrias and on the cell membranes, respectively.[4] Both cellular targets may explain the ATP depletion observed in the cell, and consequently their death. This interaction with such proteins may be explained by competitive complexations with cations, as suggested by the theoretical studies performed in our laboratory.[5] In order to modify the chelation properties of the acetogenins and to gain some information on the structure–activity relationships, we decided to synthesize some amino-analogues.[6] In this letter we report the stereoselective preparation of the C1–C32 skeleton of aza-solamin (Scheme 1), the pyrrolidino-analogue of the monotetrahydrofuranic solamin isolated from several species of Annonaceae which has shown interesting cytotoxic activity.[2]

The retrosynthetic approach started from (+)-*N*-Boc-aza-muricatacin **1**[7] and used as a key step the *C*-glycosylation reaction with a cyclic *N*-acyliminium ion and 2-trimethylsilyloxyfurane (TMSOF). We and others have reported that TMSOF can react with cyclic iminium ions affording 2,5-disubstituted pyrrolidines.[8] We have then observed that an alkoxycarbonyl substituent at C-5 on

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[†] Part 83 in the series 'Acetogenins from the Annonaceae'. For Part 82, see Queiroz et al.[1]

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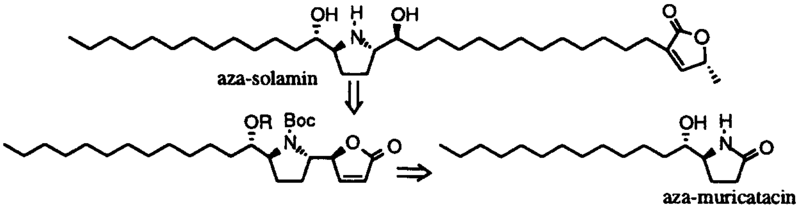
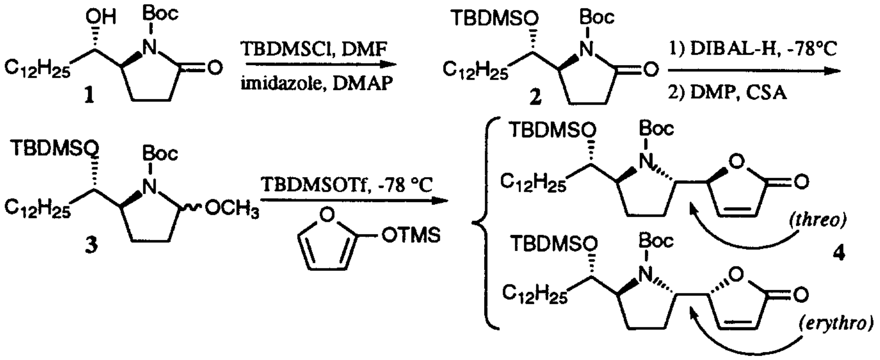


Scheme 1.

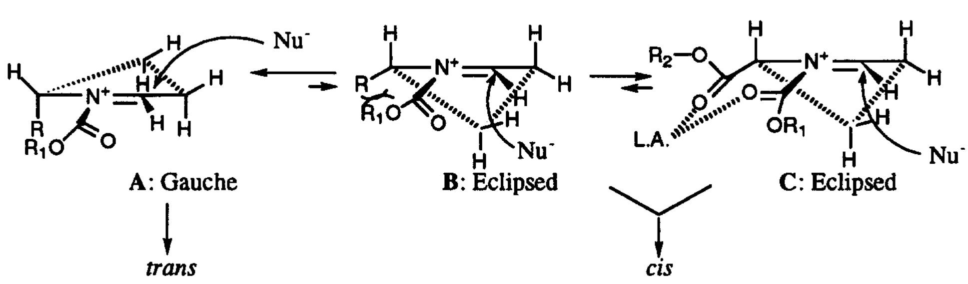
the *N*-Boc-1-methoxypyrrolidine decreased the reactivity of the cyclic *N*-acyliminium ions towards TMSOF.[8a] It was also worth noting that both *cis*- and *trans*-stereomers were obtained. We want now to apply this strategy to the coupling reaction between TMSOF and an *N*-acyliminium ion derived from (+)-*N*-Boc-aza-muricatacin **1** prepared by highly diastereoselective addition of *N*-Boc-2-*tert*-butyldimethylsilyloxypyrrole (TBSOP) on achiral tridecanal in the presence of a chiral Lewis acid.[7b]

After protection of (+)-*N*-Boc-aza-muricatacin **1**, (5*S*,1′*S*)-1-hydroxytridecylpyrrolidin-2-one, as a silyl ether with TBDMSCl in DMF in the presence of imidazole and a catalytic amount of DMAP, the pyrrolidinone **2** so obtained was reduced by 1.6 equivalents of DIBAL-H in toluene at –78°C to afford the corresponding hemiaminals (82%), which were then methylated with dimethoxypropane in the presence of camphor sulfonic acid (CSA)[9] to produce 2-methoxypyrrolidines **3** (95%). Compound **3** was reacted with TMSOF in the presence TBDMSOTf at –78°C and afforded an unseparable mixture of only two products, namely the *erythro–trans–threo* and *threo–trans–threo* desired butenolides **4** in 73% yield and 25:75 diastereomeric ratio (in favor of the *threo* compound).[10] Use of different Lewis acids (BF_3–Et_2O, $TiCl_4$) did not improve this result (Scheme 2). The stereochemical relationships for each butenolide were determined by NMR studies and confirmed by comparison of the spectroscopic data with analogues synthesized by Hanessian[11] and Casiraghi[12] (Scheme 2).



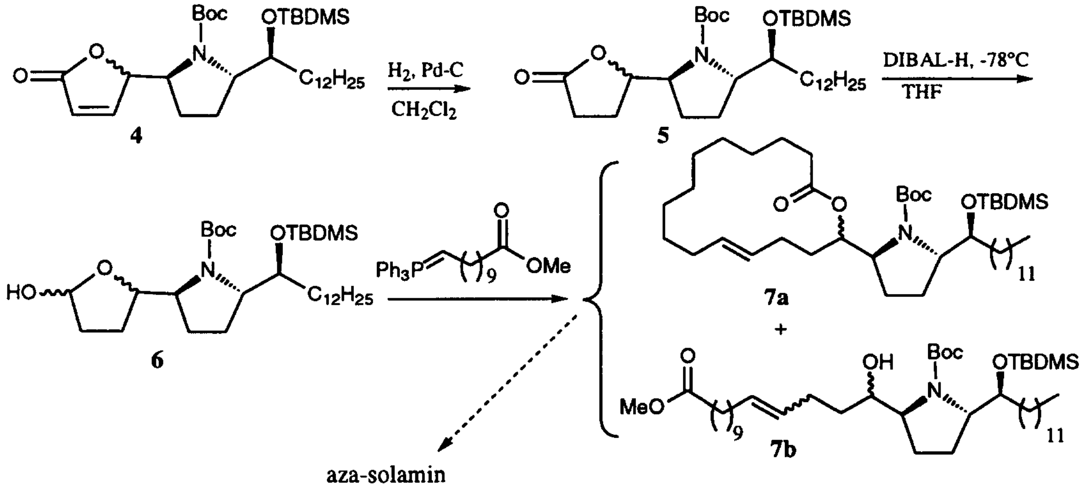
Scheme 2.

The observed *trans* diastereoselectivity in the nucleophilic addition of TMSOF on *N*-Boc-5-hydroxyalkyliminium ions can be rationalized by analysis of the different conformers depicted in Scheme 3. In spite of a *gauche* interaction, the alkyl substituent (R=alkyl) prefers the axial position (conformer **A**) because in equatorial position (conformer **B**) there is a steric hindrance generated by the eclipsed position between alkyl substituent and *N*-acyl group. Equatorial nucleophilic attack of TMSOF on conformer **A** leads to the *trans* stereomers. Whereas in the case of the presence of 5-alkoxycarbonyl group on the iminium ion (e.g. R=$COO\textit{n}C_{12}H_{25}$), the equatorial position is less disfavored due to chelation with Lewis acid (as seen in conformer **C**) which will afford the *cis* diastereomers, after equatorial attack of TMSOF, and thus rationalize the lack of diastereoselectivity observed (*cis*:*trans*=50:50).[8]



Scheme 3.

Then we used **4** as the key building block for the preparation of the C1–C32 fragment of pyrrolidino-solamin. Indeed, mixture of lactones **4** were quantitatively hydrogenated over palladium on charcoal in dichloromethane to afford the unseparable butyrolactones **5** (Scheme 4). Reduction by DIBAL-H at −78°C leads to lactols **6** (80%) which can be treated by 2 equivalents of the required phosphorus ylide in the presence potassium *tert*-butoxide to afford, via a Wittig homologation, the coupled products **7a** and **7b** in 31% yield and 80:20 ratio in favor of the macrocyclic compound **7a**. The latter was formed by macrolactonization of **7b** during the flash chromatography purification, as seen by comparing the ^{1}H NMR data of the crude mixture and the purified products. Then both compounds will lead, through known procedures,[13] to pyrrolidino-solamin, as a 75:25 mixture of epimers at C-15.



Scheme 4.

In conclusion, the very efficient *C*-glycosylation of cyclic *N*-acyliminium ions with TMSOF allows straightforward access to pyrrolidino-acetogenins due to the good stereoselectivity and high yielding reaction.

The mild reaction conditions allow one to prepare a large variety of oligo-pyrrolidine butyrolactones which can be used as building blocks for preparation of more elaborated products.[14]

Acknowledgements

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10. Compounds **4** (mixture of *erythro* and *threo* isomers: 25:75): oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.51 (dd, 0.75H, *J*=1.42, 5.69 Hz), 7.40 (dd, 0.25H, *J*=1.90, 5.89 Hz), 6.17 (dd, 0.25H, *J*=1.95, 5.89 Hz), 6.04 (dd, 0.75H, *J*=1.95, 5.70 Hz), 5.42 (m, 1H), 4.41 (m, 0.75H), 4.33 (m, 0.25H), 4.18 (m, 1H), 3.92 (m, 0.25H), 3.76 (m, 0.75H), 2.14 (m, 1H), 1.89 (m, 2H), 1.65 (m, 1H), 1.45 and 1.48 (2s, 9H), 1.07–1.36 (m, 20H), 0.85 (m, 12H), 0.104 (s, 0.4H), 0.068 (s, 1.2H), 0.039 (s, 2.2H), 0.036 (s, 2.2 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.13, 172.35, 154.03, 154.58, 153.24, 122.88, 120.64, 84.41, 82.60, 80.40, 71.02, 69.63, 62.14, 62.00, 59.24, 58.83, 30.83, 29.57, 29.30, 28.46, 26.87, 26.61, 22.64, 25.74, 24.33, 17.90, 14.06, −3.97, −4.52; MS-CI (NH_4^+) 566, 510, 466, 152.
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