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Total synthesis of *cis*-solamin A, a mono-tetrahydrofuran acetogenin isolated from *Annona muricata*

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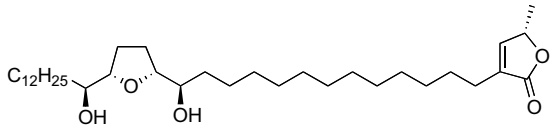
Abstract

Total synthesis of *cis*-solamin A was accomplished without using protecting groups starting from (−)-muricatacin in 11 steps with an overall yield of 4.5%. The backbone of *cis*-solamin A was constructed by olefin cross-metathesis between the tetrahydrofuran moiety and γ-lactone moiety. An enzymatic kinetic transesterification procedure was successfully applied to the synthesis of an optically pure γ-lactone moiety.

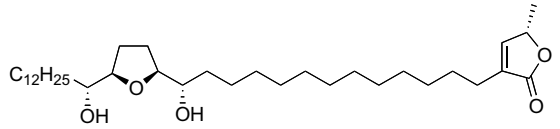
Keywords: Annonaceous acetogenin; Cross-metathesis; Enzymatic transesterification; Solamin; Mitochondrial complex I inhibitor

Annonaceous acetogenins[1,2] are a series of polyethers with antitumor, cytotoxic, antimalarial and antifeedant properties, containing either adjacent or nonadjacent tetrahydrofuran (THF) or tetrahydropyran (THP) ring and an α,β-unsaturated γ-lactone ring. Acetogenins are thought to interact with NADH–ubiquinone oxidoreductase (complex I) in mammalian and insect mitochondrial electron transport systems and/or with ubiquinone-linked NAD(P)H oxidase in cytoplasmic membranes of cancer cells.[3,4] *cis*-Solamin was isolated from the roots of *Annnona muricata* by Gleye et al.[5] (Fig. 1). The relative stereochemistry of the THF–diol part was determined to be *threo–cis–threo*, and the absolute structure of *cis*-solamin was expected to be either *cis*-solamin A (**1**) or *cis*-solamin B (**2**). Because of diverse biological activities and a unique biosynthetic mechanism, the total synthesis of *cis*-solamin was conducted by four groups, Stark's,[6] Donohoe's,[7] Brown's,[8] and Makabe's groups.[9]

Synthetic *cis*-solamin A (**1**) and *cis*-solamin B (**2**) both showed remarkable inhibitory effects against mitochondrial complex I with an IC_{50} value of 2.2 and 2.1 nM, respectively.[9] In 2006, Hu et al. reported that natural *cis*-solamin is a mixture of two tetra-epimeric diastereoisomers consisting of *cis*-solamin A (**1**) and *cis*-solamin B (**2**).[10] In the course of our recent research regarding mitochondrial complex I



cis-solamin A (**1**)



cis-solamin B (**2**)

Fig. 1. *cis*-Solamin A (**1**) and *cis*-solamin B (**2**).

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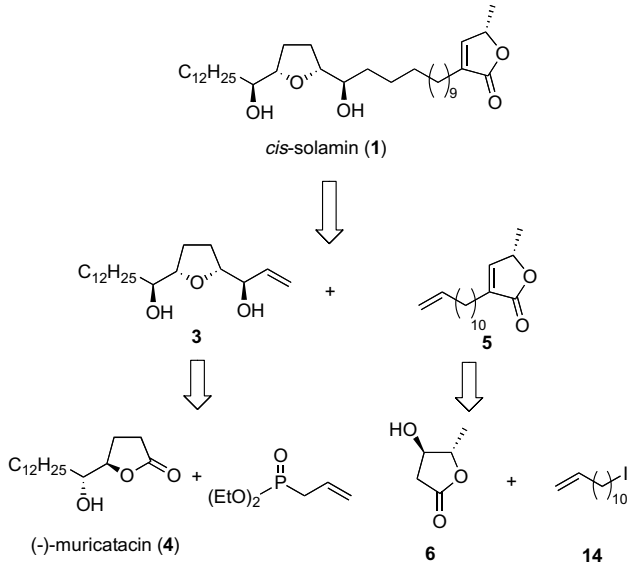
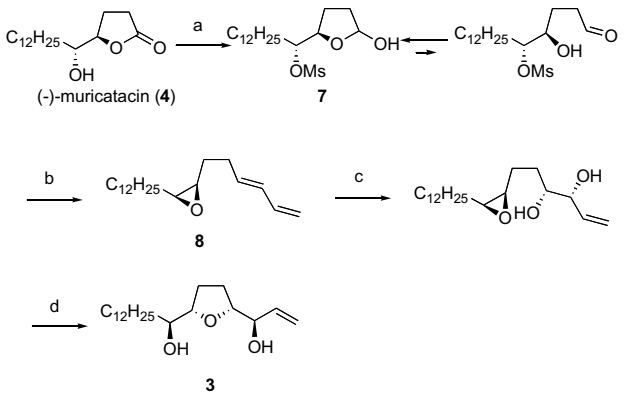
inhibitors based on the acetogenin structures, we have developed a simple route for the synthesis of mono-THF acetogenins. We herein report a concise total synthesis of *cis*-solamin A (**1**), which contains no protection/deprotection steps.

Our plan is shown in Scheme 1. The backbone of *cis*-solamin A (**1**) is constructed via an olefin cross-metathesis[11,12] of the THF–allylic alcohol (**3**) and the γ-lactone moiety with the terminal double bond (**5**). For the metathesis reaction, an allylic alcohol (**3**) containing unprotected hydroxy groups is employed, and thus alcohol (**3**) is prepared from a known compound, (−)-muricatacin (**4**),[14] via Horner Emmons type olefination followed by an asymmetric dihydroxylation without protecting the specific hydroxy groups. The metathesis counterpart γ-lactone (**5**) is synthesized by the alkylation of an enantiopure hydroxy lactone (**6**), which is prepared by an enzymatic kinetic transesterification[15] of the racemic lactone {(±)-**6**}. Since the racemic lactone {(±)-**6**} can be easily obtained by two-step reactions from commercially available *trans*-3-pentenenitrile, the enzymatic route can provide an optically pure lactone[15,16] with practical procedures. Thus, no protection/deprotection procedures are necessary throughout the synthesis, which makes the present synthesis concise.[13]

The synthesis of THF–allylic alcohol (**3**) is shown in Scheme 2. (−)-Muricatacin (**4**) was converted to a mesyl compound using MsCl/Et_3N and the subsequent reduction with DIBAL-H in THF gave hemiacetal (**7**) in 57% yield over two steps. Horner Emmons type olefination and epoxidation of hemiacetal (**7**) using an excess of the lithium salt of diethyl allylphosphate gave an epoxy-*E*-diene (**8**) with a ratio of more than 20:1 (*E*:*Z*) in 64% overall yield as an inseparable mixture. Asymmetric dihydroxylation (AD-mix β)[16] of epoxy-*E*-diene (**8**) and subsequent treatment with a catalytic amount of *p*-TsOH in CH_2Cl_2 afforded the desired THF–allylic alcohol (**3**) as a major product in



Scheme 1. Synthetic plan for *cis*-solamin A (**1**).



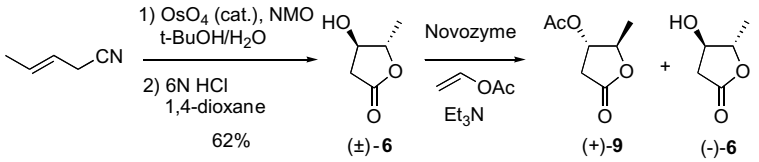
Scheme 2. Synthesis of **3**. Reagents and conditions: (a) (i) MsCl, Et_3N, CH_2Cl_2; (ii) DIBAL-H, THF, −40 °C, 57%; (b) $(EtO)_2P(O)CH_2CHCH_2$, *n*-BuLi, HMPA, THF, −40 °C–0 °C, 64%; (c) AD-mix β, $MeSO_2NH_2$, *t*-BuOH/H_2O, 0 °C. (d) *p*-TsOH (cat.), CH_2Cl_2, 52% (2 steps).

52% yield with a minor regioisomer (26% yield). The diastereomeric excess of **3** was determined to be >98% de. Using this route, THF–allylic alcohol analogues diverse in stereostructures could be similarly prepared by the specific combination of muricatacin analogues and asymmetric dihydroxylation reagents.

Optically active γ-lactone {(−)-**6**} was prepared by employing a lipase-mediated kinetic transesterification.[15] The necessary racemic substrate {(±)-**6**} was synthesized by the OsO_4-catalyzed dihydroxylation of commercially available *trans*-3-pentenenitrile and subsequent hydrolysis–lactonization (6 N HCl at 80 °C) in 62% overall yield. After extensive investigation of a variety of lipases under different conditions, we found Novozyme (*Candida antarctica*, Novo) provided the best results concerning both conversion yield and enantioselectivity. With 4 h of treatment with Novozyme in the presence of vinyl acetate in toluene containing 5% Et_3N,[17] hydroxy lactone {(±)-**6**} gave acetoxy lactone {(+)-**9**} and hydroxy lactone {(−)-**6**} in nearly quantitative yields with high enantiomeric excess[18,19] (Table 1, entry 7).

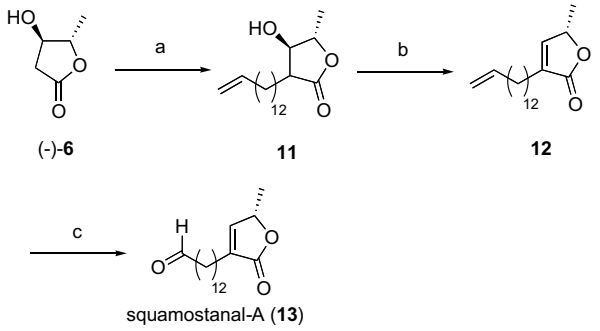
To determine the absolute configuration of the resolution products, hydroxy lactone {(−)-**6**} was converted to squamostanal-A (**13**),[20] an oxidative degradation product of acetogenins isolated from *Annona squamosa* L. (Scheme 3). Alkylation of the sodium enolate of the hydroxy lactone {(−)-**6**} with 13-tetradecenyl iodide (**10**) gave **11** in 80% yield as a diastereomeric mixture (10:1). Treatment of **11** with MsCl/Et_3N in CH_2Cl_2 and the addition of DBU in situ at room temperature afforded unsaturated γ-lactone (**12**) in 94% yield as a single product. Oxidative cleavage of the terminal double bond of **12** by treatment with catalytic OsO_4/co-oxidant NMO and the addition of $NaIO_4$ afforded squamostanal-A (**13**) in 76% yield. The specific rotation of synthetic **13** ($[\alpha]_D^{28}$ +24) is nearly identical to the authentic value ($[\alpha]_D^{28}$ +21). Spectroscopic data for the synthetic squamostanal-A (**13**) were also identical to those for the authentic sample.[21] Thus, the absolute configuration of the hydroxy lactone obtained by the kinetic transesterification was confirmed undoubtedly to be {(−)-**6**}.

Table 1
Kinetic transesterification of racemic-**6**

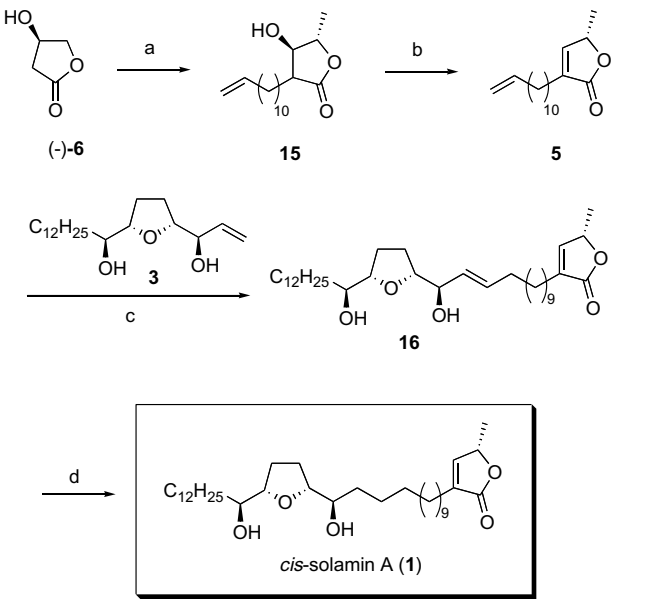


Entry	Solvent	Time (h)	Acetate (+)-9		Alcohol (−)-6	
			Yield[a] (%)	ee[b] (%)	Yield[a] (%)	ee[b] (%)
1	None	4	46	77	52	82
2	THF	4	34	90	45	82
3	MeCN	4	24	83	68	32
4	CH_2Cl_2	4	28	95	43	95
5	*t*-BuOMe	4	44	95	48	98
6	AcOEt	4	49	98	50	98
7	Toluene	4	48	98	50	99

[a] Isolation yield after silica gel chromatography.
[b] Determined by HPLC using CHIRALCEL OD-H column (hexane–*i*-PrOH, 90:10) after transformation to the corresponding benzoate.



Scheme 3. Synthesis of squamostanal-A (**13**). Reagents and conditions: (a) $CH_2CH(CH_2)_{12}I$ (**10**), NaHMDS, THF, −78 °C–rt, 80%; (b) MsCl, Et_3N, CH_2Cl_2, 0 °C–rt then DBU, rt, 94%; (c) OsO_4 (cat.), NMO, THF/H_2O, 0 °C–rt, then $NaIO_4$, rt, 76%.



Scheme 4. Total synthesis of *cis*-solamin A (**1**). Reagents and conditions: (a) $CH_2CH(CH_2)_{10}I$ (**14**), NaHMDS, THF, −78 °C–rt, 84%; (b) MsCl, Et_3N, CH_2Cl_2, 0 °C–rt then DBU, rt, 92%; (c) **3**, Grubbs' catalyst (2nd generation), CH_2Cl_2, 40 °C, 12 h, 52%; (d) *p*-$TsNHNH_2$, NaOAc, ethylene glycol dimethyl ether, reflux, 95%.

cis-Solamin A (**1**) was synthesized according to the route shown in Scheme 4. The coupling of hydroxy lactone {(−)-**6**} and iodide (**14**), and subsequent conversion to unsaturated lactone (**5**) was conducted in a similar manner as in Scheme 3. A cross metathesis reaction of THF–allylic alcohol (**3**) and unsaturated lactone (**5**) with Grubbs' catalyst (second generation) in CH_2Cl_2 proceeded at 40 °C to give the desired **16** as a single *E*-isomer in 52% yield (78% yield based on the starting material **3** consumed) as well as the lactone homo-dimer (ca. 20% yield). Finally, selective hydrogenation of the double bond with *p*$TsNHNH_2$[22] gave *cis*-solamin A (**1**) in 95% yield. Spectroscopic data for the product were identical with those reported by Makabe and co-workers.[9]

In conclusion, we have achieved the total synthesis of *cis*-solamin A (**1**), using a practical route containing no protection/deprotection steps. The route should be effective for the construction of acetogenin libraries diverse in stereochemistry around hydroxylated THF rings as well as alkyl chain lengths. Extensions to structure–activity relationship studies on inhibitory activities of acetogenins against mitochondrial complex I will be reported in due course.

Acknowledgements

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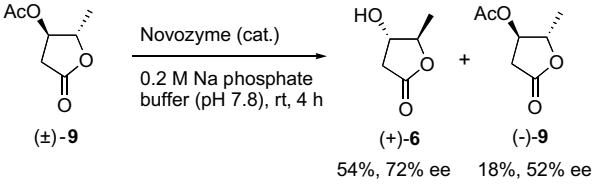

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