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Tetrahedron Letters 49 (2008) 1601–1604
Tetrahedron Letters

A formal convergent synthesis of (+)-*trans*-solamin

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Received 23 November 2007; revised 1 January 2008; accepted 10 January 2008
Available online 15 January 2008

Abstract

A formal convergent synthesis of solamin is disclosed. The synthetic strategy exploits the potential of the sulfinyl group as an auxiliary, nucleophile and in C–C bond formation. The synthetic route can be adapted to the synthesis of stereoisomers of solamin, analogs with variable carbon side chains, and other members of mono-THF acetogenins.

Keywords: *trans*-Solamin; Sulfoxide; NBS; Bromohydrin; Pummerer ene reaction

Annonaceous acetogenins,[1] isolated from 37 different species of Annonaceae family, are metabolites that possess a wide range of bioactivity including antitumor, antimalarial, pesticidal, immunosuppressive properties and inhibit multi-drug resistant cancer cells.[2] They are characterized by the presence of one to three tetrahydrofuran (THF) ring(s) with varying stereochemistries along a lengthy hydrocarbon chain having terminal α,β-unsaturated γ-lactone moiety. *trans*-Solamin,[3] **1**, is a representative of the mono-THF class of acetogenins (Fig. 1).

The bioactivity, architecture, and the potential use of a synthetic route to prepare other members have been the major stimulants for synthetic activity toward acetogenins. The synthesis of solamin reported to date utilizes Sharpless asymmetric dihydroxylation,[4] Sharpless asymmetric epoxidation,[5,6] chiral pool starting material,[7] or start from muricatacin,[8] a natural product. We report herein a modular formal synthesis of solamin, taking advantage of the nucleophilicity of the sulfinyl moiety to oxidatively functionalize an alkene regio- and stereoselectively.[9]

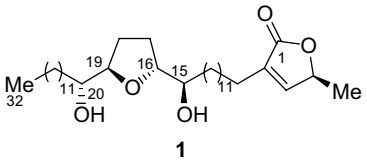

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Fig. 1.

The retrosynthetic analysis is depicted in Scheme 1. Disconnection at C2–C3, C17–C18, and C16–O bonds would afford subunits **2** and **3**. The latter was planned to be obtained by C17–C18 bond formation using Horner–Emmons–Wadsworth reaction employing aldehyde **4** and keto-phosphonate **5**. The aldehyde can be traced to bromoacetonide **6** and keto-phosphonate to oxazolidinone **7**.

The synthesis of aldehyde **4** commenced with bromoacetonide[10] **6** that was readily obtained from acryloyl imidazole **8** in 4 steps. Acetonide **6** was subjected to Pummerer reaction using trifluoroacetic anhydride, and the resulting intermediate without isolation was reacted with 1-undecene and anhydrous $SnCl_4$[11] to afford the ene reaction product[12] **9** (60% yield). Proceeding ahead, the bromine was replaced by a hydroxy group by reaction with sodium nitrite[13] in DMF to furnish **10** (80% yield). Swern oxidation[14] furnished aldehyde **4** (90% yield) which corresponds to the C18–C32 subunit, Scheme 2.

The synthesis of **5** began with the coupling of the known tetradecanoic acid derivative[15] **11** with oxazolidinone[16] **12** following Ho's protocol[17] to afford imide **7** (90% yield,

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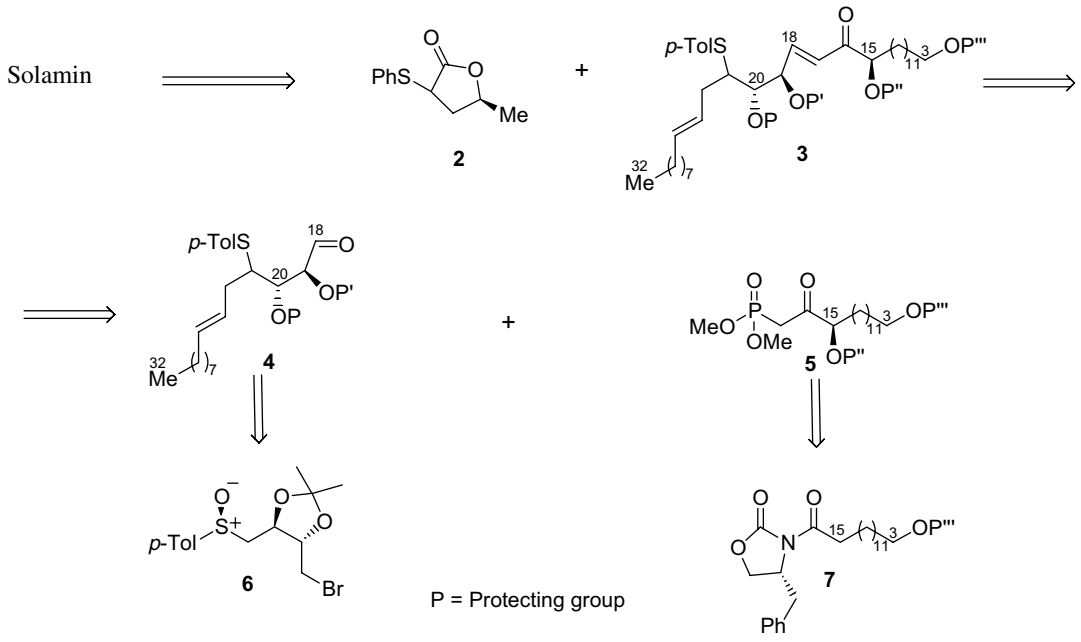
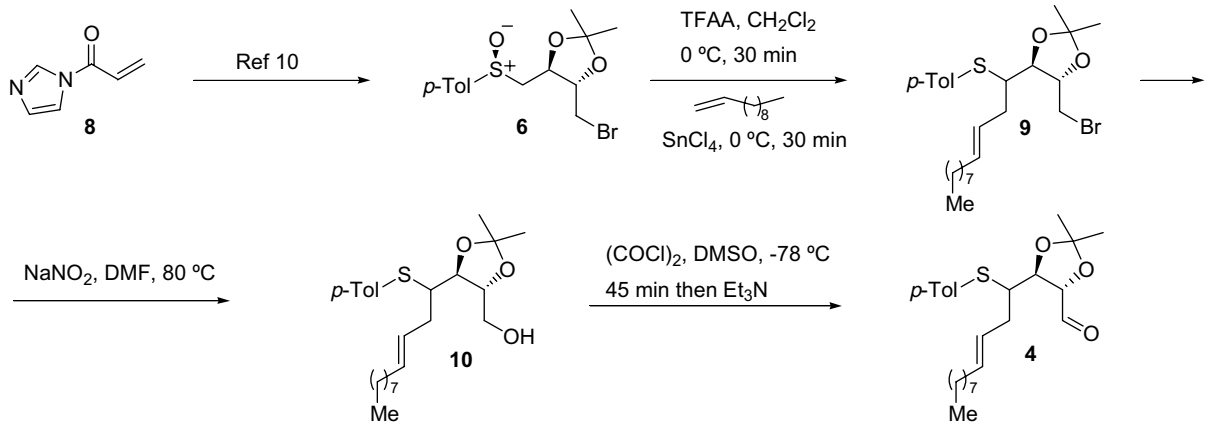
0040-4039/$ - see front matter © 2008 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2008.01.046



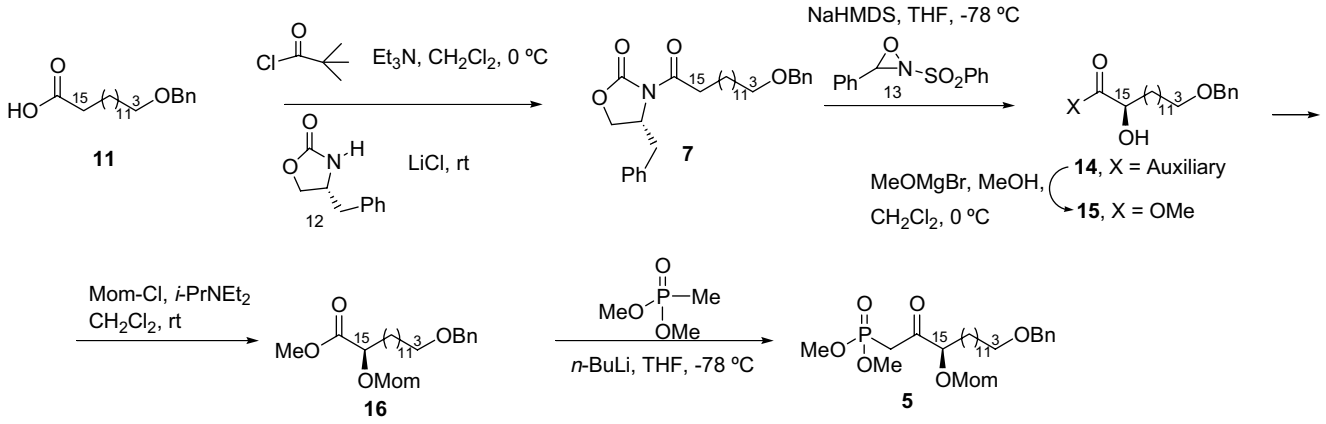
Scheme 1.



Scheme 2.

$[\alpha]_D^{25}$ −51.0 (*c* 0.50, $CHCl_3$)). The hydroxylation reaction using Davis reagent[18] **13** proved tricky and it was essential to follow the reported conditions meticulously.[19] Thus dropwise addition of a precooled (−78 °C) solution of **13** to the sodium anion of **7** generated and maintained at −78 °C and quenching the reaction soon after the addition followed by work up gave **14** as the sole product in 82% yield, $[\alpha]_D^{25}$ −28.0 (*c* 1.0, $CHCl_3$). The auxiliary was removed using methoxymagnesium bromide[20] to afford methyl ester **15** (80% yield, $[\alpha]_D^{25}$ −1.65 (*c* 2.70, $CHCl_3$)). The hydroxy group was protected as its Mom ether **16** (90% yield, $[\alpha]_D^{25}$ +31.27 (*c* 1.3, $CHCl_3$)) and was subsequently reacted with the anion of dimethyl methylphosphonate[21] to furnish keto-phosphonate **5** (75% yield, $[\alpha]_D^{25}$ +12.5 (*c* 1.05, $CHCl_3$)) which corresponds to the C3–C17 fragment of solamin, Scheme 3.

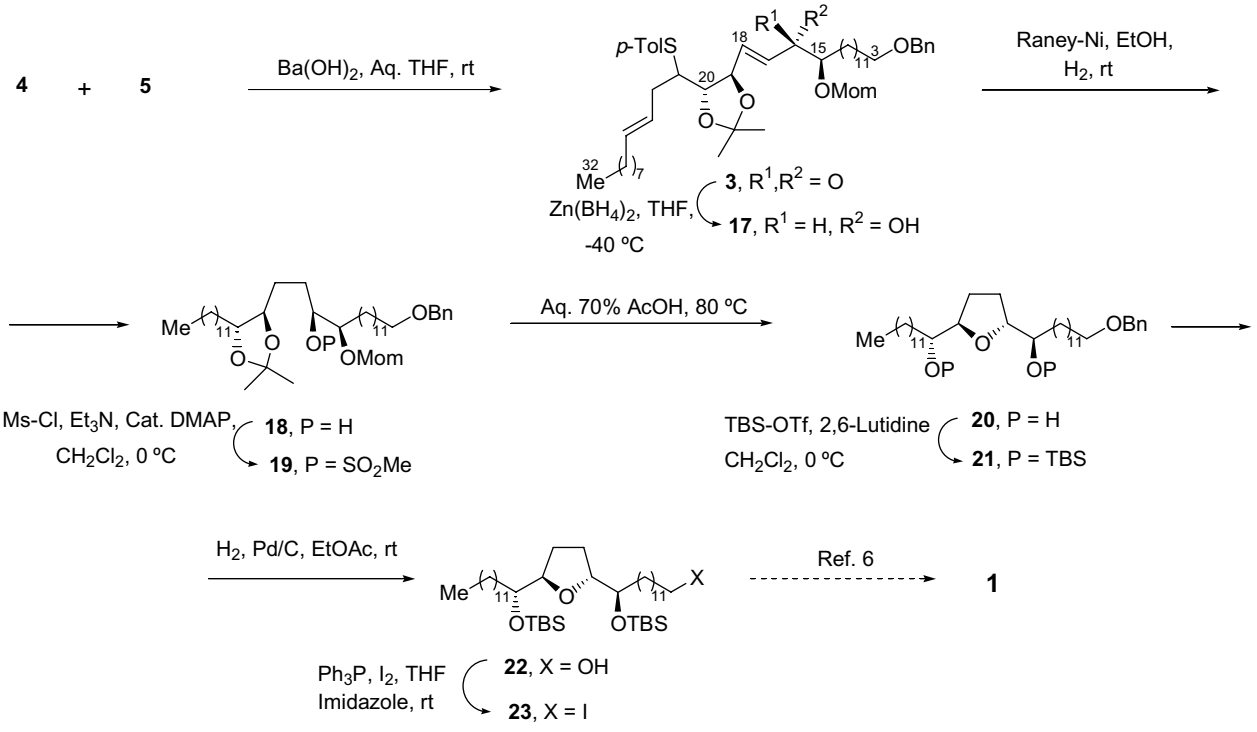
Aldehyde **4** and keto-phosphonate **5** were subjected to Horner–Emmons–Wadsworth olefination using $Ba(OH)_2$[22] to afford unsaturated ketone **3** stereoselectively (70% yield, $[\alpha]_D^{25}$ +16.0 (*c* 2.1, $CHCl_3$)). The carbonyl group was selectively reduced using $Zn(BH_4)_2$[23] in anhydrous THF to afford allyl alcohol **17** (85% yield, $[\alpha]_D^{25}$ +4.22 (*c* 1.85, $CHCl_3$)), essentially as a single isomer.[24] The alcohol upon treatment with Raney-Ni under an atmosphere of hydrogen suffered hydrogenation and selective hydrogenolysis to afford alcohol **18** (65% yield, $[\alpha]_D^{25}$ +7.5 (*c* 1.0, $CHCl_3$)). Having introduced the oxygen functionalities, the THF ring needed to be constructed. It was planned to convert the hydroxyl into a good nucleofuge, deprotect the acetonide selectively in the presence of Mom ether, and subject the resulting diol to treatment with a mild base to form the THF ring. Toward this end, **18** was converted to mesylate



Scheme 3.

19 cleanly (100% yield, $[\alpha]_D^{25}$ +10.0 (*c* 0.25, $CHCl_3$)), and selective deprotection of the acetonide using 70% aq AcOH[25] directly yielded diol **20** (65% yield, $[\alpha]_D^{25}$ +6.00 (*c* 0.65, $CHCl_3$)). The diol is probably formed by the sequential deprotection of the acetonide, cyclization, promoted by the high temperature, and Mom deprotection. The methine protons at C16 and C19 resonated at δ 3.8–3.7 and the methylene protons at C17 and C18 resonated at δ 1.95–1.5 confirming the trans di-substitution of the THF ring.[26] The diol was protected as the di-TBS ether **21** (95% yield, $[\alpha]_D^{25}$ +14.4 (*c* 0.75, $CHCl_3$)). Deprotection of the benzyl ether by hydrogenolysis using Pd/C furnished the primary alcohol **22** (95% yield, $[\alpha]_D^{25}$ +11.2 (*c* 0.85, CH_2Cl_2)). Alcohol **22** was converted to iodo derivative **23** (71% yield, $[\alpha]_D^{25}$ +15.0 (*c* 0.75, $CHCl_3$)) using iodine and triphenylphosphine in the presence of imidazole, Scheme 4.[27] Iodide **23**, an intermediate in the synthesis of **1** reported by Mioskowski and co-workers,[6] had spectral characteristics in full agreement to that reported by them, thus completing the formal synthesis of *trans*-solamin.

In conclusion, we have devised a formal modular synthesis of *trans*-solamin, 15 steps by the longest linear sequence (0.038% overall yield), which demonstrates the potential of the sulfinyl moiety as an auxiliary, potent intramolecular nucleophile and in C–C bond forming reactions. It is noteworthy that the reduction of the keto group in **3** with L-selectride[28] would yield the *threo* alcohol (epimer of **17**) which can be transformed into *cis*-solamin



Scheme 4.

by following the same sequence of reactions delineated for the transformation of **17** into *trans*-solamin. Also other stereoisomers of solamin can be prepared starting from the diastereoisomer of **6** that can be obtained by DIBAL-H/$ZnCl_2$[29] reduction of keto sulfoxide. The methodology should also be useful for the synthesis of analogs possessing longer or shorter chain lengths (possessing functional groups and corresponding to C21–C32 chain) by varying the alkene used in the Pummerer ene reaction.

Acknowledgments

S.R. is thankful to Dr. J. M. Rao, Head, Org. Div. I, Dr. J. S. Yadav, Director, IICT for constant support and encouragement. S.G.S. and K.A.T are thankful to CSIR, New Delhi for a fellowship. Financial assistance from DST (New Delhi) is gratefully acknowledged. We thank Dr. A. C. Kunwar for the NMR spectra and Dr. M. Vairamani for the mass spectra.

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