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New Strategy for the Construction of a Monotetrahydrofuran Ring in *Annonaceous* Acetogenin Based on a Ruthenium Ring-Closing Metathesis: Application to the Synthesis of Solamin

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Abstract: An original convergent total synthesis of Solamin (type A *annonaceous* acetogenin) was achieved. The central THF core was obtained by means of a ring-closing metathesis (RCM) reaction using a ruthenium imidazolylidene complex. The RCM substrate was prepared from a vinyl-substituted epoxide by reaction with an allyl alcohol, both synthesized from propargylic alcohol. The flexibility of the strategy should be useful in preparing various natural and unnatural *annonaceous* acetogenins.

Annonaceous acetogenins are a class of plant metabolites isolated from a worldwide family of tropical plants called Annonaceae.[1] Since uvaricin,[2] the first acetogenin identified from the roots of *Uvaria accuminata*, more than 350 members of this family have been isolated from 37 different species and have attracted attention due to their excellent antitumor, antimalarial, pesticidal, and immunosuppressive properties.[1,3] Inhibition of mitochondrial complex I (NADH-ubiquinone oxidoreductase) is considered to be one mode of action for acetogenins, leading to a lack of ATP in the tumor cell and subsequent apoptosis.[4] More recently some acetogenins have been shown to inhibit multidrug-resistant cancer cells with an ATP-driven transporter system.[3a,b]

Most of the *annonaceous* acetogenins are characterized by the presence of one to three tetrahydrofuran (THF) ring(s) with various stereochemistries in the center of a long hydrocarbon chain bearing a terminal α,β-unsaturated γ-lactone moiety (Figure 1).

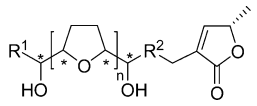

FIGURE 1. Representative general structure of *annonaceous* acetogenins (n = 1−3, R^1, R^2 = hydrocarbon chain with or without hydroxylated moieties and/or double bonds).

Numerous total syntheses have been reported using several key reactions for the central THF ring(s) construction. Type A acetogenins (one THF ring) have been prepared via a multiple-step sequence from glutamic acid,[5] tartaric acid,[6] carbohydrates,[7] or a synthetic chiral intermediate.[8] Other approaches using aldolization and Baeyer−Villiger oxidation,[9] oxidative cyclization reaction of 1,5-diene,[10] Ramberg−Backlund olefination,[11] asymmetric alkynylation,[12] or anomeric oxygen-to-carbon rearrangement[13] have been reported. Very recently, a fluorous mixture synthesis method was employed to synthesize a library of 16 diastereoisomers of Murisolin, a monotetrahydrofuran acetogenin.[14] Oligo-tetrahydrofuran units (type B, C, or D acetogenins) have been prepared by addition of a THF ring to a preexisting THF core[15] by epoxide opening or cyclization cascade,[16] intramolecular Williamson etherification reactions,[17] oxidative polycyclizations,[18] or C-glycosylation.[19] The synthesis of other

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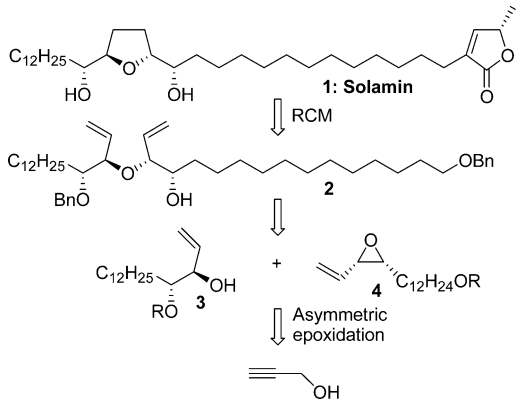
types of *annonaceous* acetogenins possessing tetrahydropyran (THP)[20] and nonadjacent bis-THF[21] have been reported recently.

Very few syntheses of *annonaceous* acetogenins[22] have used a ring-closing metathesis reaction (RCM)[23] to form the THF central core, despite the proven usefulness of RCM for generation of such cyclic ether moieties.[24] To the best of our knowledge, a ruthenium-based RCM strategy has not been reported for the construction of the central THF core of type A acetogenin. Only the synthesis of Muconin, a THF−THP acetogenin prepared by RCM with molybdenum catalyst is known.[22a]

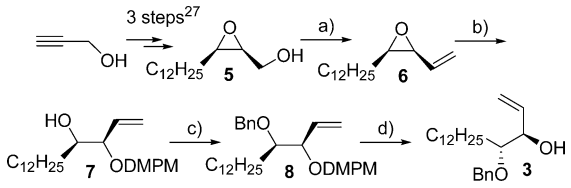
In this note, we report the first application of RCM using ruthenium catalyst for the total synthesis of Solamin **1**[25] demonstrating the efficiency of this reaction for constructing type A acetogenins.

Our synthetic plans are centered on the assembly of the THF core via a RCM reaction of the corresponding suitably elaborated open diene **2**. The RCM substrate **2** was obtained by assembly of two simple building blocks,

SCHEME 1. Retrosynthetic Approach for the Synthesis of Solamin 1



SCHEME 2. Synthesis of Allyl Alcohol 3[a]



[a] Reaction conditions: (a) (i) SO_3-pyridine, NEt_3, DMSO/CH_2Cl_2; (ii) Ph_3PCH_3Br, NaHMDS, THF, 0 °C, 77% (two steps). (b) $BF_3{\cdot}Et_2O$, DMPMOH, CH_2Cl_2, 75%. (c) NaH, BnBr, DMF, 95%. (d) DDQ, CH_2Cl_2/H_2O, 95%.

an allyl alcohol **3** and a vinyl-substituted epoxide **4**, using our regio- and stereospecific ring-opening methodology.[26] This synthesis is therefore convergent and only required the preparation of chiral building blocks, both of which were obtained from propargyl alcohol (Scheme 1).

As both allyl alcohol **3** and vinyl-substituted epoxide **4** were synthesized via alkyne reduction yielding (*E*)- or (*Z*)-allylic alcohol followed by Sharpless asymmetric epoxidation using (+)- or (−)-DET, this synthesis is quite flexible and all stereoisomers of the central THF core of Solamin should be easily obtained.

The synthesis of substrate **3** is outlined in Scheme 2. The precursor (2*S*,3*R*)-2,3-epoxypentadecanol **5** was synthesized from propargyl alcohol in three steps following a known procedure.[27] Parikh−Doering oxidation[28] of **5** with sulfur trioxide pyridine complex, followed by Wittig olefination, gave vinyl-substituted epoxide **6** in 77% yield (two steps). Ring opening of **6** with 3,4-dimethoxybenzyl alcohol (DMPMOH) and $BF_3{\cdot}Et_2O$ catalysis yielded alcohol **7** (75% yield).[26] Standard benzylation conditions of **7** gave benzyl ether **8** (95% yield). Removal of the 3,4-dimethoxybenzyl protecting group using DDQ afforded the allyl alcohol **3** in 95% yield.[29]

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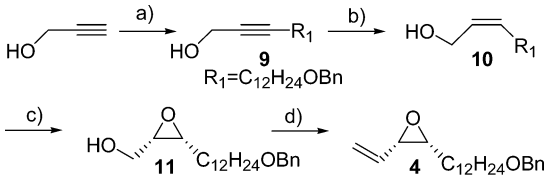
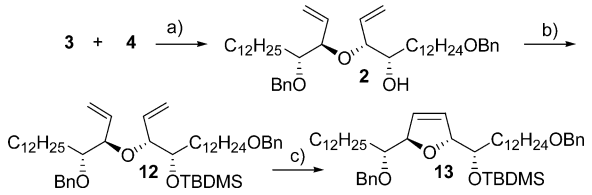
(29) We note that isomers of **3** can easily be obtained from precursors of epoxides **5** or **6** using other reducing and/or asymmetric epoxidation reagents.

SCHEME 3. Synthesis of 4[a]



[a] Reaction conditions: (a) (i) Li, NH_3, −45 °C; (ii) $BnOC_{12}H_{24}Br$, THF, −45 °C → rt, 85%. (b) H_2, P-2 Ni = $Ni(OAc)_2$, $NaBH_4$, $NH_2(CH_2)_2NH_2$, MeOH; 82%. (c) (+)-DET, $Ti(OiPr)_4$, *t*BuOOH, CH_2Cl_2, −25 °C, 82%. (d) (i) SO_3-pyridine, NEt_3, DMSO/CH_2Cl_2, 0 °C; (ii) Ph_3PCH_3Br, NaHMDS, THF, 0 °C, 71% (two steps).

SCHEME 4. Coupling Reaction and RCM[a]



[a] Reaction conditions: (a) $Cu(OTf)_2$, CH_2Cl_2, 35%. (b) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 95%. (c) Catalyst **B**, CH_2Cl_2, 35%, or catalyst **C** refluxed CH_2Cl_2, 80%.

The preparation of epoxide precursor **4** is illustrated in Scheme 3 and used the same strategy used to prepare epoxide **5**. Alkylation of commercially available propargyl alcohol with benzyl-12-bromododecyl ether[30] employing lithium amide in liquid ammonia afforded hydroxy alkyne **9** in 85% yield. Catalytic hydrogenation of **9** over "P-2 Ni" catalyst[31] ($Ni(OAc)_2$, $NaBH_4$, ethylenediamine) gave (*Z*)-allyl alcohol **10** (82% yield). Sharpless asymmetric epoxidation[32] of **10** with (+)-diethyl tartrate afforded (2*S*,3*R*)-epoxy alcohol **11** (82% yield, ee = 86%).[33] SO_3-pyridine oxidation of alcohol **11** to the corresponding epoxy aldehyde and direct Wittig reaction using methyltriphenylphosphonium bromide afforded vinyl-substituted epoxide **4** in an overall yield of 71% for the two steps.[34]

The allyl alcohol **3** and the vinyl epoxide **4** precursors to the Solamin skeleton were then ready to be coupled and further elaborated toward the target molecule. Scheme 4 depicts the chemistry leading to RCM substrate **2** and RCM product **13**. Allyl alcohol **3** was first reacted with vinyl epoxide **4** in the standard epoxide ring-opening conditions using $BF_3{\cdot}Et_2O$ catalysis.[26a] Diene **2** was isolated in 30% yield. Ring-opening reaction of **4** with alcohol **3** using $Cu(OTf)_2$ catalyst gave the best results, affording diene **2** in 35% yield and unreacted recovered alcohol **3** (46%).[35] Then, the RCM reaction was applied

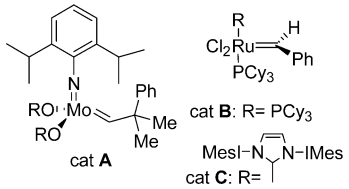


FIGURE 2. Metathesis catalysts.

to diene **2**. Subjecting **2** to Schrock's catalyst[36] (Figure 2, cat **A**) or to the Grubbs complex[37] (Figure 2, cat **B**) did not afford the RCM product but only led to recovery of starting material **2**. The lack of success in this RCM reaction was maybe due to the presence of a free secondary alcohol in **2**. Compound **2** was then protected to furnish the silyl ether **12** in 95% yield. The protected diene **12** was submitted to RCM conditions using several metathesis catalysts. The reactivity of **12** was investigated with Schrock's catalyst (Figure 2, cat **A**), a sensitive catalyst showing a greater reactivity with hindered substrates. Despite prolonged reaction time, no reaction occurred with catalyst **A** and only the starting diene **12** was recovered.[38] With Grubbs catalyst **B**,[37] RCM reaction appeared to be very slow and afforded cyclic substrate **13** in a moderate 35% yield after 12 h in CH_2Cl_2. Use of a prolonged reaction time (1 week) and further catalyst additions (30% mol) afforded dihydrofuran **16**, isolated in 50% yield. In view of the increased thermal stability and higher reactivity displayed by 1,3-dimesitylimidazol-2-ylidene ruthenium benzylidene catalyst ($RuCl_2$(=C(H)-Ph)(PCy_3)($IMes)_2$)[39] (Figure 2, cat **C**), it was employed in the RCM reaction of **12**. Cyclic adduct **13** was obtained in very good yield (80%) after 12 h in refluxing CH_2Cl_2 with only 5% mol catalyst.

With the cyclic compound **13** in hand, the final sequence of the Solamin synthesis was performed as shown in Scheme 5. Hydrogenation of the double bond of dihydrofuran **13** using Pd/C catalyst afforded saturated THF with concomitant removal of the benzyl ether protecting groups, yielding quantitatively THF-diol **14**. Compound **14** was submitted to silylation to give persilylated THF **15** (95% yield), which was then selectively desilylated at the primary position by exposure to CSA to furnish bis-silylated product **16** in 95% yield.

Iodination of the primary alcohol in **16** using triphenylphosphine-iodine gave **17** (73% yield), which was then submitted to alkylation with the sodium enolate of lactone **18**[40] to afford **19** in 79% yield. Oxidation of the sulfide **19** followed by thermal elimination and finally removal of the two silyl protective groups gave Solamin

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(33) ^{19}F NMR of Mosher's esters of **11** showed ee's = 86%. Epoxide **11** was isolated as an oil.

(34) We note that trans isomers of epoxide **4** can be easily obtained using other reducing and other asymmetric epoxidation reagents.

(35) Modest yield of this coupling reaction was presumably due to decomposition and/or polymerization of vinyl epoxide **4**.

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(38) This lack of reactivity could be due to the substrate structure or to the molybdenum catalyst, which was previously reported to be extremely sensitive to air and moisture as well as decomposition upon storage; see: Scholl, M.; Ding, S.; Lee, W. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−953.

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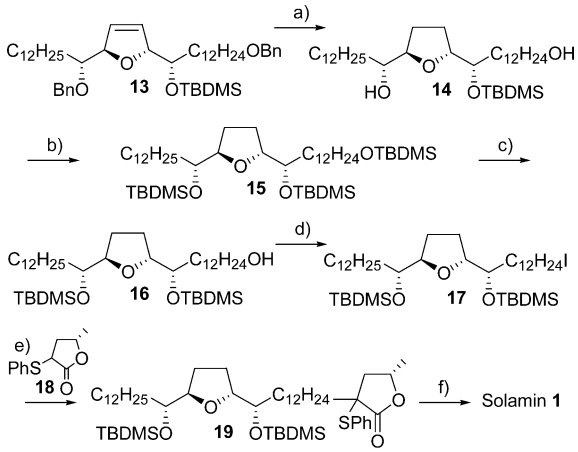
(40) Lactone **18** was prepared in quantitative yield from phenylthioacetic acid and (*S*)-propylene oxide using White's method: White, J. D.; Somers, T. C.; Reddy, G. N. *J. Org. Chem.* **1992**, *57*, 4991−4998.

SCHEME 5. Synthesis of Solamin 1[a]



[a] Reaction conditions: (a) H_2, Pd/C, EtOH, 99%. (b) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 95%. (c) CSA, MeOH/CH_2Cl_2, 95%. (d) I_2, PPh_3, imidazole, CH_2Cl_2, 95%. (e) **18**, NaHMDS, THF, 0 °C, 75%. (f) (i) *m*CPBA, CH_2Cl_2; (ii) refluxed toluene; (iii) CH_3COCl, MeOH, 85% (three steps).

1[41] in 85% yield for the three steps. Synthetic Solamin **1** exhibited spectroscopic features identical to those reported for the natural material.[25a,b]

(41) Solamin **1** was recrystallized from hexane. ^1H and ^{13}C NMR, IR, and MS spectral data and optical rotation (see Supporting Information) are in agreement with those previously reported.[25a,b]

In conclusion, this total synthesis of Solamin **1** demonstrates the power of recently developed synthetic methodology for the construction of cyclic ethers. Specifically, the central THF core of Solamin was efficiently prepared by a RCM reaction using a ruthenium-based imidazolylidene complex **C**, and the ring-opening method of vinyl-substituted epoxide yielding regio- and stereoselective alcohol was applied with success to yield to the RCM substrate. The two chiral buiding blocks (allyl alcohol **3** and vinyl-substituted epoxide **4**) were both prepared from commercially available propargyl alcohol. All the stereoisomers of Solamin **1** can be easily obtained employing this strategy and using (*E*)- or (*Z*)-allyl alcohol and (+)- or (−)-DET for the asymmetric epoxidations. With this method for constructing such a THF core and its flexibility in the preparation of the key substrates, the road toward total synthesis of natural and unnatural *annonaceous* acetogenin is now open.

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Supporting Information Available: Experimental procedures, as well as characterization and copies of ^1H NMR and ^{13}C NMR spectra for compounds **1**−**17** and **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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