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CONVERGENT SYNTHESIS OF FLUORESCENCE LABELED SOLAMIN†

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Abstract – The convergent synthesis of dansyl-labeled solamin, an antitumor *Annonaceous* acetogenin, has been achieved. The carbon skeleton was assembled from three fragments: the THF ring fragment, the fluorescent fragment, and the γ-lactone fragment, by asymmetric alkynylation.

Annonaceous acetogenins are waxy derivatives of long-chain fatty acids (C32 or C34) that are linked by a 2-propanol unit at C-2 position to form a γ-methyl-α,β-unsaturated-γ-lactone.[1] Most acetogenins are characterized by one to three 2,5-disubstituted tetrahydrofuran(s) (THFs) with one or two flanking hydroxyl group(s) at the center of a long carbon chain. Many researchers are engaged in the synthesis of acetogenins[2] and their analogues[3] due to their unique structures and potent antitumor activities. The mechanism of action is considered to involve the inhibition of mitochondrial NADH ubiquinone oxidoreductase (complex I). The inhibition suppresses ATP production, leading to apoptosis of cancer cells.[4] However, the structure–activity relationship for complex I inhibition is not completely related to its cytotoxicity. McLaughlin and co-workers suggested that as the mitochondrial assay is cell-free, it does not take into consideration factors such as membrane transport, intracellular transport, and metabolic inactivation.[5] In order to visualize cell distribution, Poupon and co-workers synthesized a γ-lactone-free dansyl-labeled squamocin analogue.[6] Moreover, Yao and co-workers reported the synthesis of a new fluorescent acetogenin analogue whose THF rings were replaced with acyclic ethers for simplification.[7] In living cells, it was suggested that the hydrophilic THF moiety in natural acetogenins is located at the

† Dedicated to the late Professor John W. Daly for his outstanding contributions to natural products chemistry.

surface of the mitochondrial inner membrane and that the γ-lactone moiety interacts with the active site of the membrane.[8] Therefore, we synthesized 7-nitrobenzo[*c*][1,2,5]oxadiazol-4-yl-amino (NBD-NH-) solamin (**2**) that retains all functionalities.[9] However, the total yield of our synthesis was low and the preparation of other derivatives was inconvenient because the synthetic route was linear. Herein, we report a novel approach to labeled solamins and its application to 5-dimethylaminonaphthalen-1-yl-sulfonamide (dansyl-NH-) solamin (**3**), a fluorescent mono-THF annonaceous acetogenin, bearing all functionalities.

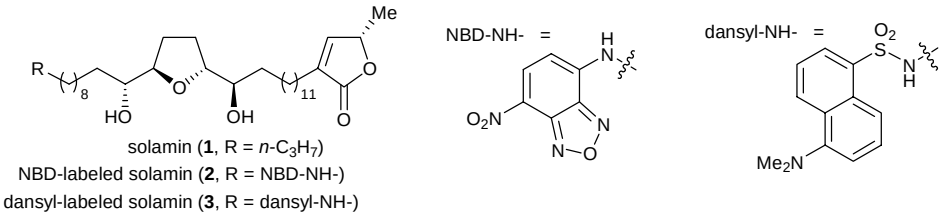
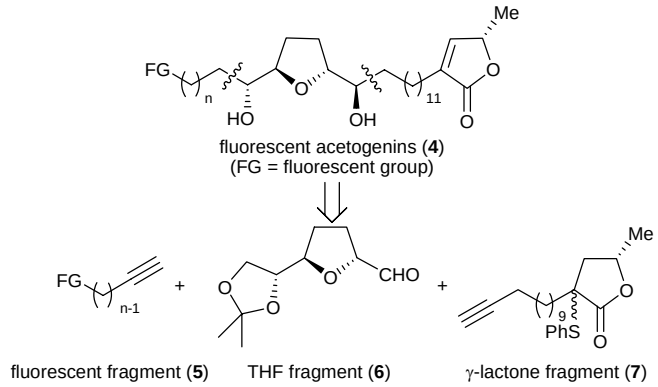


Figure 1. Structure of solamin and fluorescent derivatives

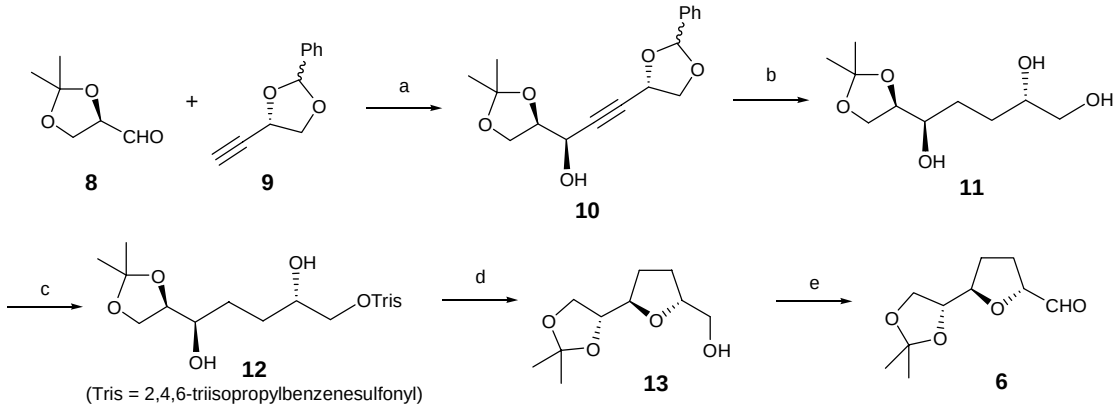
The retrosynthesis of fluorescent acetogenins is summarized in Scheme 1. Fluorescent acetogenins (**4**) are divided into three fragments: fluorescent fragment (**5**), THF fragment (**6**), and γ-lactone fragment (**7**). The fragments could be connected by reagent-controlled asymmetric alkynylation. This synthetic plan should provide ready access to diverse fluorescent derivatives that have other fluorescent groups or long hydrocarbon chains as linker.



Scheme 1. Retrosynthesis of fluorescent acetogenins

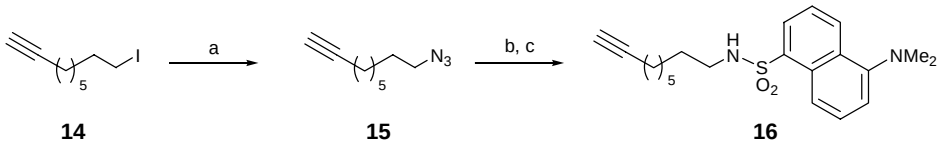
Synthesis of THF fragment (**6**) started from known aldehyde (**8**) and 3-butyne-1,2-diol derivative (**9**)[10] prepared from **8** (Scheme 2). Asymmetric alkynylation of aldehyde (**8**) with alkyne (**9**) was carried out under Carreira's conditions[11] with (*1R,2S*)-*N*-methylephedrine as chiral ligand to give *syn*-adduct[12] (**10**) in 93% yield with high diastereoselectivity (>97:3 dr). Hydrogenation of the triple bond and deprotection of the benzylidene acetal gave triol (**11**) in 84% yield. Selective sulfonylation of primary alcohol followed

by base treatment of resulting **12** afforded *trans/threo* THF-ring (**13**). DMSO oxidation of **13** with SO_3·pyridine complex gave α-tetrahyrofuranyl aldehyde (**6**) in good yield.



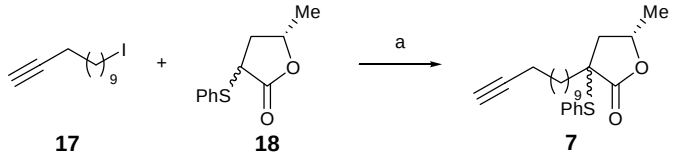
Scheme 2. *Reagents and Conditions*: (a) $Zn(OTf)_2$, Et_3N, (1*R*,2*S*)-*N*-methylephedrine, toluene, rt, 93% (>97:3 dr); (b) H_2 (3 atm), 10% Pd–C, EtOAc, rt, 84%; (c) TrisCl, pyridine, CH_2Cl_2, 0 °C to rt, 79%; (d) K_2CO_3, MeOH, 0 °C to rt, 98%; (e) SO_3·pyridine, DMSO, *i*-Pr_2NEt, CH_2Cl_2, 0 °C to rt, 89%.

Fluorescent fragment (**16**) was prepared from known iodoalkyne (**14**)[13] (Scheme 3). Azidation of **14** was carried out to give azide (**15**) in high yield. The reduction of **15** under Staudinger conditions followed by coupling with dansyl chloride afforded fluorescent fragment (**16**).



Scheme 3. *Reagents and Conditions*: (a) NaN_3, DMSO, rt, 97%; (b) PPh_3, Et_2O–H_2O (17:1), 0 °C; (c) dansyl chloride, *i*-Pr_2NEt, CH_2Cl_2, 0 °C to rt, 96% in two steps.

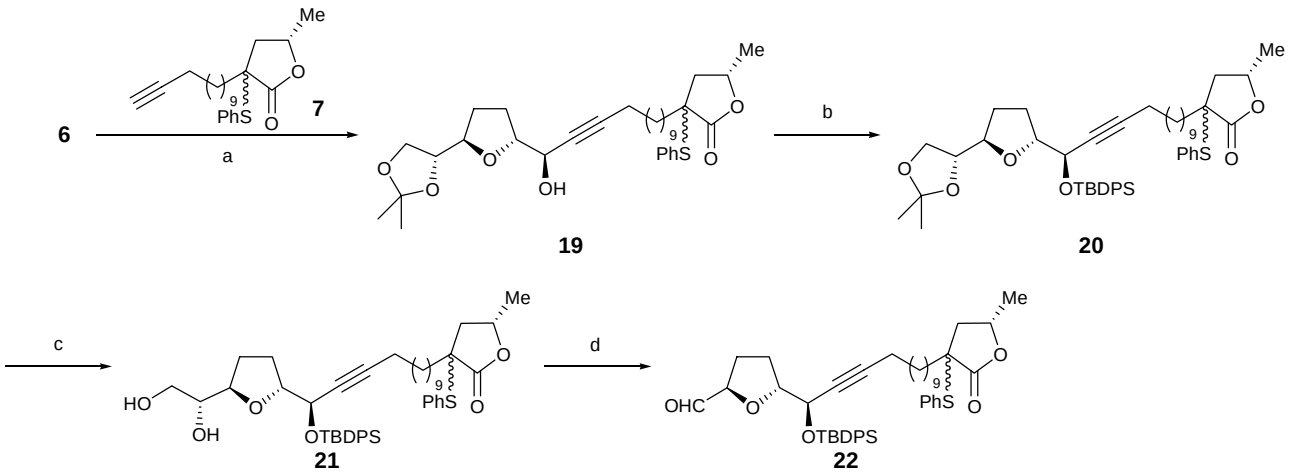
γ-Lactone fragment (**7**) was easily prepared by alkylation of known α-sulfenyl-γ-lactone (**18**)[14] with 12-iodo-1-dodecyne (**17**) [15] under basic conditions in high yield (Scheme 4).



Scheme 4. *Reagents and Conditions*: (a) LDA, THF–HMPA (2:1), –78 °C to rt, 97%.

With all the fragments in hand, we examined the assembly of THF fragment (**6**) and γ-lactone fragment (**7**) because we thought it best that the expensive fluorescent fragment (**16**) be introduced at the late stage

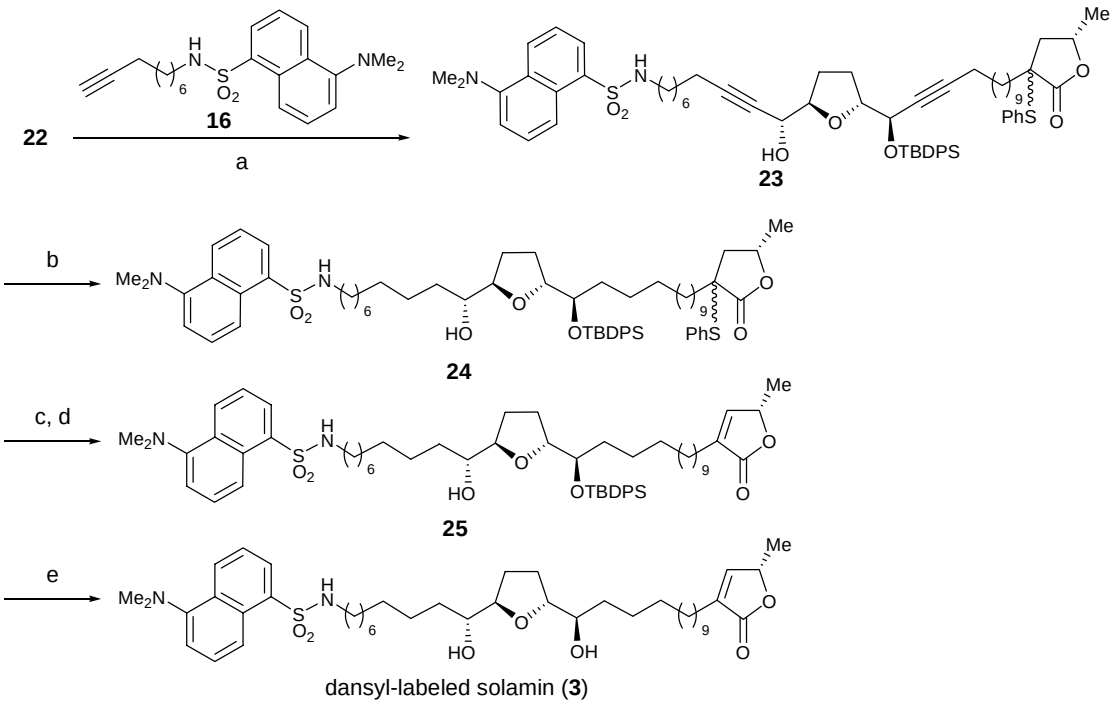
of the synthesis (Scheme 5). Coupling reaction of the two fragments (**6** and **7**) was accomplished by asymmetric alkynylation with high stereoselectivity (95:5 dr).[16] After the secondary alcohol of adduct (**19**) was protected as a TBDPS ether, the hydrolysis of acetonide gave diol (**21**). Oxidative cleavage of 1,2-diol moiety gave α-tetrahydrofuranyl aldehyde (**22**) in 98% yield.



Scheme 5. *Reagents and Conditions*: (a) **7**, $Zn(OTf)_2$, *i*-Pr_2NEt, (1*R*,2*S*)-*N*-methylephedrine, toluene, rt, 74% (95:5 dr); (b) TBDPSCl, imidazole, DMF, 0 °C to rt, quant; (c) Dowex 50 W, THF–MeOH (1:1), rt to 55 ˚C, 82%; (d) $NaIO_4$, THF–H_2O (4:1), rt, 98%.

The introduction of fluorescent fragment (**16**) into α-tetrahydrofuranyl aldehyde (**22**) proceeded successfully, giving desired propargyl alcohol (**23**) in 66% yield with high stereoselectivity (91:9 dr).[16] Resulting diyne (**23**) was hydrogenated on Wilkinson's catalyst to give alcohol (**24**) in 73% yield. Oxidation of the sulfide followed by thermal elimination of the resulting sulfoxide afforded α,β-unsaturated-γ-lactone (**25**). Synthesis of dansyl-labeled solamin (**3**) was completed via deprotection of TBDPS ether under acidic conditions.[17]

In conclusion, we have accomplished the convergent synthesis of fluorescent solamin bearing all functionalities from **8** in 7.5% yield over 14 steps. Our synthesis should provide ready access to diverse derivatives labeled by other fluorescent groups. Further synthesis of other fluorescence labeled acetogenins and visualization of cell distribution are under way.



Scheme 6. *Reagents and Conditions*: (a) **16**, $Zn(OTf)_2$, *i*-Pr_2NEt, (1*R*,2*S*)-*N*-methylephedrine, toluene, rt, 66% (91:9 dr); (b) H_2 (3 atm), $(Ph_3P)_3RhCl$, benzene, rt, 73%; (c) *m*CPBA, CH_2Cl_2, 0 °C; (d) toluene, reflux, 68% in two steps; (e) 48% HF aq., MeCN, rt, 71%.

ACKNOWLEDGEMENT

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