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Synthesis of (15*S*,16*S*,21*R*)-4-deoxyrollicosin analog

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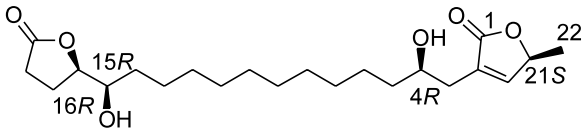
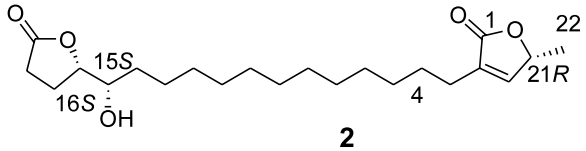
Abstract—Synthesis of 4-deoxy rollicosin analog **2** was completed in nine steps, which was based on palladium-catalyzed coupling of two building blocks **3** and **4**. Lactone **3** was synthesized from 5-hexyn-1-ol, and vinyl iodide **4** was accessed from L-glutamate and 1-hexyne.

Annonaceous acetogenins are a class of rapid growing natural products. More than 350 acetogenins have been isolated from various annonaceae plants because of their unique structure and wide scope of biological activities.[1] Annonaceous acetogenin showed remarkable cytotoxicity against human cancer, acting as a blocker of NADH-ubiquinone oxidoreductase (complex I) of the mitochondrial electron transport system (ETS).[2] Rollicosin **1**,[3] isolated from the unripe fruit of annonaceae plant, *Rollina mucosa* Baill, possesses a partial skeleton of annonaceous acetogenins containing two γ-lactone moieties on both sides of an aliphatic chain. The subtype structure of annonaceous acetogenons may be generated from oxidative cleavage of classical acetogenins resulting in special feature of two lactone moieties. It is considered that the new discovered metabolite of acetogenins will receive a highlight attention with biological activities and chemical probing. Hence, we report herein a general route to prepare the 4-deoxy rollicosin domain **2** with stereochemical construction as 15*S*,16*S*,21*R*.

As illustrated in Scheme 1, the retrosynthetic strategy of **2** was based on a convergent process including palladium-catalyzed coupling reaction of lactone **3** and vinyl iodide **4**. Compound **3** could be synthesized from 5-hexyn-1-ol. Generation of intermediate **4** could be accomplished by using L-glutamic acid and 1-hexyne as starting materials.

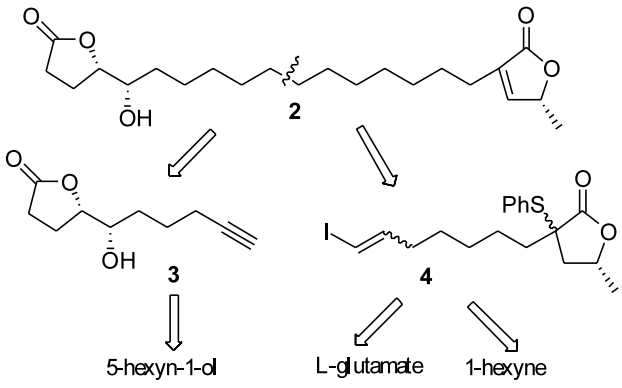


Rollicosin **1**



2

The lactone fragment **3** was constructed as shown in Scheme 2. The synthesis was started from 5-hexyn-1-ol, which was treated with trimethylsilyl chloride to give



Scheme 1.

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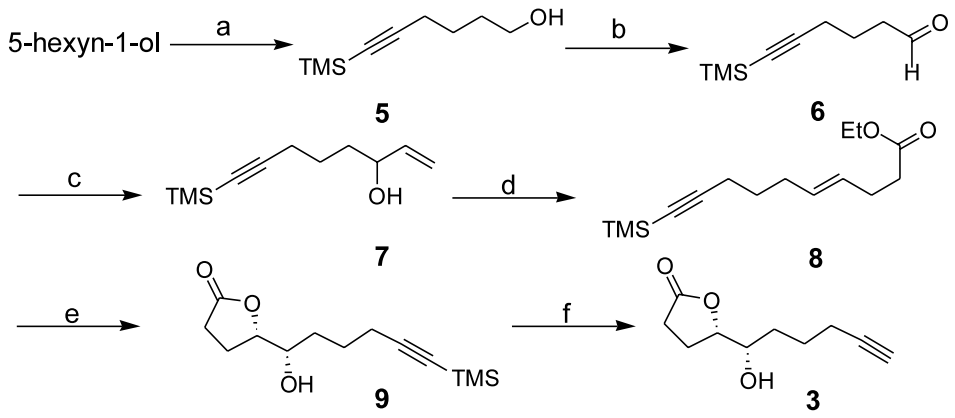


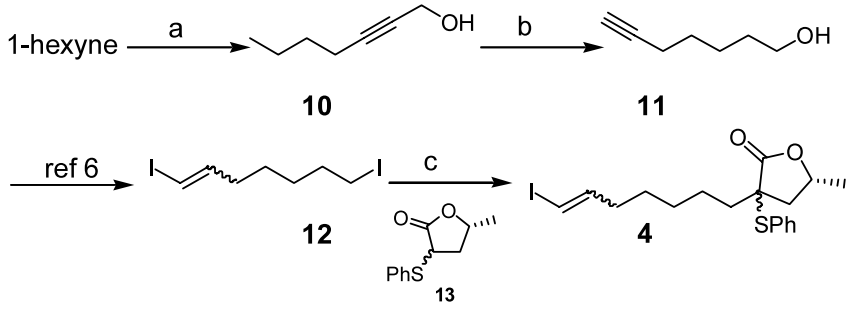
Scheme 2. *Reagents and conditions*: (a) (i) *n*-BuLi, THF, 0°C, 40 min; (ii) TMSCl, 0°C to rt, 2 h, 80%; (b) PCC, CH_2Cl_2, rt, 4 h, 60%; (c) vinylmagnesium bromide, THF, –78°C, 1 h, 71%; (d) CH_3CH_2COOH, $CH_3C(OEt)_3$, 180°C, 2 h, 84%; (e) AD-MIX-α, $CH_3SO_2NH_2$, *t*-BuOH/H_2O, 0°C, 24 h, 62%; (f) TBAF, THF, 0°C, 5 h, 73%.

alcohol **5**. Compound **5** was converted to aldehyde **6** via oxidation with pyridinium chlorochromate. Addition of vinylmagnesium bromide to **6** resulted in the formation of the allylic alcohol **7**. Reaction of **7** with triethyl orthoacetate and propionic acid proceeded through orthoacetate Claisen rearrangement[4] to afford γ,δ-unsaturated ester **8**, followed by Sharpless AD reaction[5] to give lactone **9**. Finally, protecting group was removed by tetra-*n*-butylammonium fluoride to liberate terminal acetylene to give **3**.

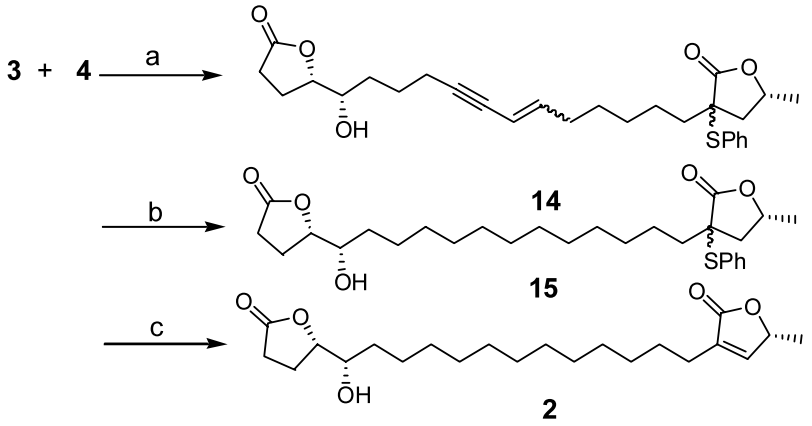
The butanolide portion **4** of the target molecule was prepared according to the process reported by Keinan[6] with slight modification. Applying 1-hexyne with *n*-butylithium in tetrahydrofuran resulted in formation of acetylenic lithium salt, subsequent exposure to paraformaldehyde solution gave internal alkyne **10**. Isomerization[7] of **10** was promoted in the presence of potassium hydride in 1,3-diaminopropane to provide terminal acetylene **11**. Conversion of **11** to diiodide **12** was performed using Keinan's procedure, including protection of the alcohol as a silylether, hydrostannylation of the terminal alkyne, iodolysis, deprotection of the silylether, tosylation of the alcohol, and iodination. The butanolide **4** was obtained by alkylation of the enolate prepared by mixing **13**[8] and LDA with diiodide **12** (Scheme 3).

Palladium-catalyzed coupling[9] of the terminal alkyne **3** with the vinyl iodide **4** afforded eneyne **14**. Hydrogenation of **14** using Wilkinson's catalyst gave the corresponding saturated product **15**. Finally, oxidation of compound **15** with *m*-CPBA provided a sulfoxide intermediate, followed by thermal elimination to afford rollicosin analog **2**[10] (Scheme 4). Compound **2** was obtained as white power and the absolute configuration of **2** demonstrated by X-ray[11] shown in Figure 1.

In conclusion, we have reported a convergent synthesis of deoxy rollicosin analog **2**, which may serve as a building block for the synthesis of a series of 4-deoxy acetogenins. The application of this method to synthesize a variety of deoxy rollicosin analogs with variant main carbon chains is currently under investigation.



Scheme 3. *Reagents and conditions*: (a) (i) *n*-BuLi, THF, –78°C, 1 h, (ii) $(CH_2O)_n$, –78°C to rt, 18 h, 99%; (b) 30% KH, 1,3-diaminopropane, 10–15°C, 1.5 h, 67%; (c) (i) LDA, THF, **13**, 0°C, 30 min; (ii) **12** and HMPA, reflux, 70%.



Scheme 4. *Reagents and conditions*: (a) $PdCl_2(PPh_3)_2$, Et_3N, CuI, 24 h, 67%; (b) $RhCl(PPh_3)_3$, H_2, benzene/MeOH 1:1, 24 h, 87%; (c) (i) *m*-CPBA, CH_2Cl_2, 30 min, (ii) toluene, reflux, 4 h, 46% (two steps).

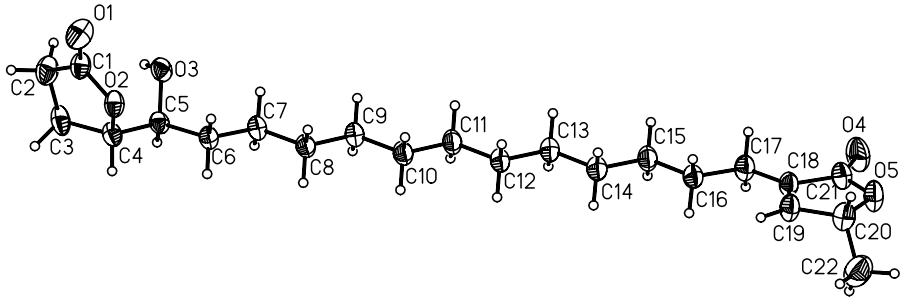


Figure 1. X-Ray structure of compound **2**.

Acknowledgements

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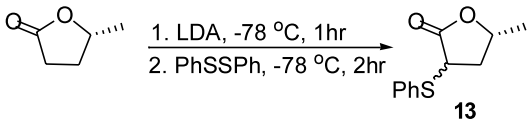
8. (a) Harmange, J.-C.; Figadère, B.; Hocquemiller, R. *Tetrahedron: Asymmetry* **1991**, *2*, 347; (b) Preparation of **13** was completed by following process:



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10. Data for **2**: mp 103–104°C; $[\alpha]_D^{25} = -13.6$ (*c* 0.01, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ: 6.98 (1H, d, $J = 1.6$ Hz), 5.01–4.95 (1H, m), 4.41 (1H, td, $J = 7.6$ Hz, 4.4 Hz), 3.58–3.54 (1H, m), 2.60–2.48 (2H, m) 2.28–2.21 (3H, m), 2.15–2.08 (1H, m), 1.73 (1H, br), 1.57–1.41 (6H, m), 1.39 (3H, d, $J = 6.8$ Hz), 1.37–1.19 (16H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 177.2, 173.9, 148.9, 134.2, 82.9, 77.4, 73.57, 32.9, 29.5 (3C), 29.4 (3C), 29.2, 29.1, 28.6, 27.3, 25.4, 25.1, 24.0, 19.16. HRMS (EI) calcd for $C_{22}H_{36}O_5$: 380.2563. Found: 380.2559.
11. The deposition number provided by CCDC is 216122.