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First total synthesis of murisolin†

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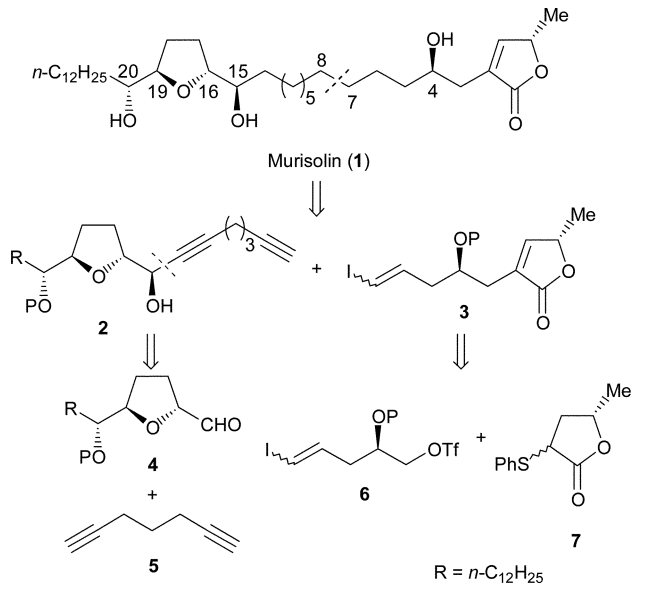
The first and concise total synthesis of murisolin (1) was accomplished using asymmetric alkynylation and Sonogashira coupling as the key steps. The *threo*/*trans*/*threo*-type THF ring moiety was constructed with excellent stereoselectivity by asymmetric alkynylation of 1,6-heptadiyne to α-tetrahydrofuranic aldehyde, which was also prepared *via* the asymmetric alkynylation.

Annonaceous acetogenins are polyketides having one to three tetrahydrofuran (THF) ring(s) with various stereochemistries connected with a butenolide moiety by a long hydrocarbon chain, which often contains oxygenated moieties. Acetogenins have attracted considerable attention since they show various biological activities (antitumor, pesticidal, antimalarial, immunosuppressive, and antifeedant).[1]

Murisolin **1** is a mono-THF acetogenin isolated from the seed of *Annona muricata* by Cortes' group, and shows selective cytotoxic activities against human lung carcinoma (A-549), human colon adenocarcinoma (HT-29), and human kidney carcinoma (A-498) with potency from 10^5 to 10^6 times that of adriamycin.[2,3]

Its potent cytotoxicity and the relatively simple structure among acetogenins make murisolin of great interest as a lead compound of anti-cancer drugs. However, a total synthesis of this compound has never been achieved.

Our synthetic plan is outlined in Scheme 1. Murisolin (**1**) is bisected at the C_7 and C_8 carbons into THF ring segment **2** and γ-lactone segment **3**. The segment **2** is further divided into THF ring segment **4** and polymethylene linker segment **5**. Segment **4** can be synthesized stereoselectively by asymmetric alkynylation of α-oxyaldehyde and stereodivergent THF ring formation.[4] On the other hand, the γ-lactone segment **3** is synthesized by alkylation of α-sulfenyl γ-lactone **7** with triflate **6**.[5,6] In the synthesis of murisolin, we planned an asymmetric alkynylation of **4** with the unprotected diyne **5** to eliminate steps of protection and deprotection, and such asymmetric alkynylation with unprotected diynes has not been reported so far.



Scheme 1

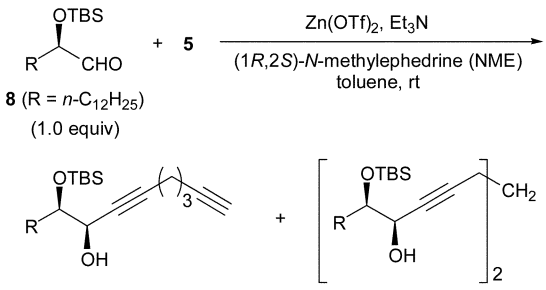
Herein, we report a first total synthesis of murisolin by asymmetric alkynylation with the unprotected diyne and Sonogashira coupling as key steps.

Initially, we examined the selective mono-alkylation of commercially available 1,6-heptadiyne **5** under Carreira's conditions.[7] Table 1 summarizes a model study of asymmetric alkynylation using (*R*)-2-hydroxytetradecanal TBS ether **8**[4] and diyne **5**.

Carreira's protocol afforded alcohol **9** in 58% yield along with diol **10** in 27% yield (entry 1, condition A).[8] When about twice the amounts of the diyne and the reagents were used, the yield of the desired **9** was improved to 71% (entry 2, condition B). The yield was not changed when the amounts of the reagents were reduced (entry 3, condition C). Finally, we found that the use of four equivalents of diyne **5** was the best condition, giving 84% of **9** accompanied by 12% of **10** (entry 4, condition D). The diastereoselectivity of the alkynylation was very high to give in each case each **9** and **10** as the sole products.

Next, we conducted the asymmetric alkynylation of the α-tetrahydrofuranic aldehyde **11** with diyne **5** under the optimized conditions (Scheme 2). Thus, upon treatment of α-tetrahydrofuranic aldehyde **11** with diyne **5** (4 equiv), the alcohol **12** was obtained in 84% yield along with 12% of the diol **13**. The alkynylation of the functionalized aldehyde **11** proceeded with very high diastereoselectivity (> 97 : 3 dr). The absolute configuration

Table 1 Asymmetric alkynylation of α-oxyaldehyde **8** with unprotected diyne **5**



Entry	Conditions[a]	Yield (%) 9	Yield (%) 10
1	A	58	27
2	B	71	24
3	C	72	20
4	D	84	12

[a] Conditions (values in parentheses are equivalents of reagents.) A: **5** (1.2), $Zn(OTf)_2$ (1.3), NME (1.4), Et_3N (1.4). B: **5** (2.0), $Zn(OTf)_2$ (2.2), NME (2.4), Et_3N (2.4). C: **5** (2.0), $Zn(OTf)_2$ (1.3), NME (1.4), Et_3N (1.4). D: **5** (4.0), $Zn(OTf)_2$ (1.3), NME (1.4), Et_3N (1.4).

† Electronic Supplementary Information (ESI) available: characterization data of synthetic murisolin (**1**), and ^1H and ^{13}C NMR spectra of compounds **9**, **12** and **1**. See http://www.rsc.org/suppdata/cc/b3/b312362f/

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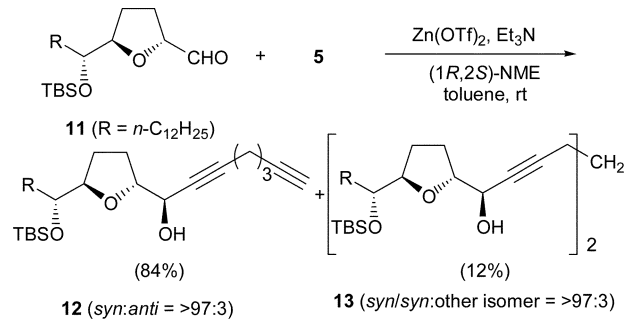
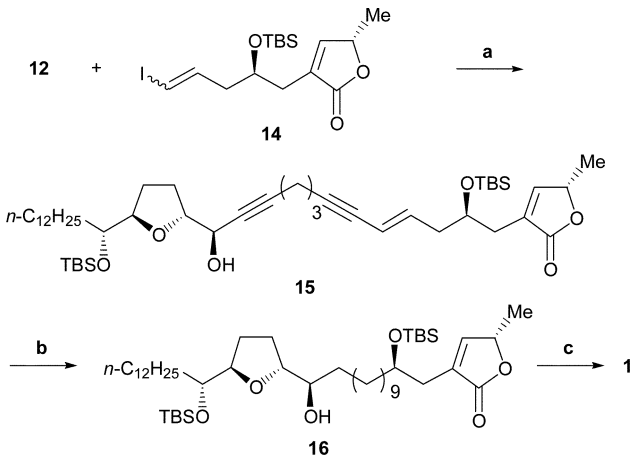
of adduct **12** was confirmed as the desired (*R*)-configuration by the modified Mosher method.[9] Interestingly, the by-product **13** was also a single isomer and is assumed to be a *syn*/*syn*-adduct since the compound has C_2-symmetry.

Completion of the total synthesis of **1** is depicted in Scheme 3. Sonogashira coupling ($Pd(PPh_3)_2Cl_2$, CuI, Et_3N)[10] of **12** and the iodide **14**[5] gave the enediyne **15** in 72% yield. Hydrogenation of **15** with Wilkinson's catalyst afforded the alcohol **16** in 47% yield.[11] Finally, deprotection with HF provided murisolin (**1**) in 91% yield. The spectroscopic data of synthetic **1** (^{1}H NMR, ^{13}C NMR, IR, MS, m.p.) were in good agreement with those reported. On the other hand, the specific rotation of synthetic **1** {$[\alpha]^{23}_D$ +20.7 (*c* 0.39, MeOH), $[\alpha]^{22}_D$ +21.5 (*c* 0.36, $CHCl_3$)} was consistent with the highest value of those reported in the literature {$[\alpha]_D$ +14.8 (*c* 0.1, MeOH), $[\alpha]_D$ +16.0 (*c* 0.1, $CHCl_3$), $[\alpha]^{14.5}_D$ +19.05 (*c* 0.84, $CHCl_3$), $[\alpha]^{18.5}_D$ +20.44 (*c* 5.92, $CHCl_3$)}.[2,3,12]

In conclusion, the first total synthesis of **1** was accomplished using asymmetric alkynylation with the diyne and Sonogashira coupling as the key steps. Our method can be used for the synthesis of various mono-THF acetogenins by changing the combination of the THF core, γ-lactone segment, and the linker segment. Application to the other acetogenins is under investigation and will be reported elsewhere.



Scheme 2



Scheme 3 *Reagents and conditions*: (a) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, room temperature, 72%; (b) H_2, $Rh(PPh_3)_3Cl$, MeOH–benzene, room temperature, 47%; (c) HF (aq.), MeCN–THF, room temperature, 91%.

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