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Total synthesis of muconin

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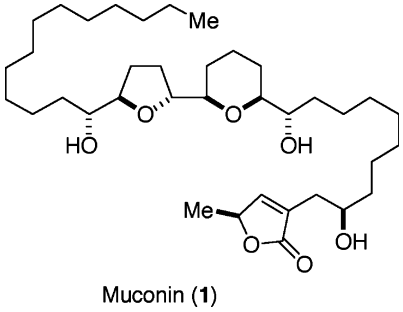
Abstract—An antitumor acetogenin, muconin, was synthesized through a coupling reaction of a THF–THP segment and a terminal butenolide. The key reactions include 6-*exo* cyclization of an epoxy tetraol, regioselective cyclization of hydroxy tosylate, and stereoselective reduction of an acyclic ketone adjacent to the 2,6-*cis* THP ring with $Zn(BH_4)_2$.

Since the discovery of a powerful antitumor agent, mucocin, several annonaceous acetogenins carrying a tetrahydropyran (THP) ring have been isolated from the Annonaceae plant species.[1] These compounds have attracted much attention among synthetic organic chemists because of their structural diversity and strong antitumor activities.[2] Muconin (**1**), which was isolated from the leaves of *Rollinia mucosa* by McLaughlin et al. in 1996, is a rare type of acetogenin bearing a THP ring along with a tetrahydrofuran (THF) ring (Fig. 1).[3] Compound **1** is reported to show potent and selective in vitro cytotoxicity against PACA-2 (pancreatic cancer) and MCF-7 (breast cancer) in a panel of six human solid tumor cell lines. Recently, we have been engaged in the synthetic studies on the THP-acetogenins, resulting in the total synthesis of mucocin and jimenezin.[4] As part of our continuing studies in this field, we describe herein the total synthesis[5] of **1** in a stereocontrolled manner.



Muconin (**1**)

Figure 1.

Our synthetic strategy directed toward **1** was based on a convergent process which involves a Pd-catalyzed cross-coupling reaction of the THF-THP segment **2** and a vinyl iodide **3**, as illustrated in Scheme 1. Disconnection of the acetylene unit and cleavage of the THF ring in **2** lead to a THP derivative **4**, which would be synthesized from an epoxy alcohol **5** through a 6-*exo* cyclization and stereoinversion at the C-8 position. For effective inversion, we planned to utilize a stereoselective reduction of an acyclic ketone adjacent to the 2,6-*cis* THP ring. The usefulness of the method has been already demonstrated in our total synthesis of mucocin and jimenezin.[4a–c]

An unsaturated ester **6**, which was prepared by Keinan and Sinha's procedure,[6] was reduced, and then subjected to tosylation to afford the corresponding tosylate. Treatment of this with sodium cyanide gave a nitrile **7**[7] in 84% overall yield from **6** (Scheme 2). The nitrile **7** was converted into an allyl alcohol **8** by the following sequence: (1) reduction of the nitrile function with DIBAL; (2) Wittig reaction; (3) DIBAL reduction of ester carbonyl (85% overall yield). Installation of the requisite oxygen function into the carbon backbone was accomplished by the Sharpless protocol.[8] Initially, **8** was epoxidized with $Ti(O\textit{i}\text{-}Pr)_4$ and $\textit{t}\text{-}BuO_2H$ in the presence of D-diethyl tartrate to give an epoxide[9] in 91% yield. After silylation with chloro *t*- butyldiphenylsilane and imidazole, the resulting silylether reacted with AD-mix β in the presence of methanesulfonamide (2.0 equiv.) in aq. *t*-BuOH to give the tetraol **5** in almost quantitative yield.[10] Upon treatment of **5** with *d*-camphorsulfonic acid in CH_2Cl_2, 6-*exo* cyclization occurred to produce a THP derivative **9** in 86% yield. From a practical point of view, isolation after the

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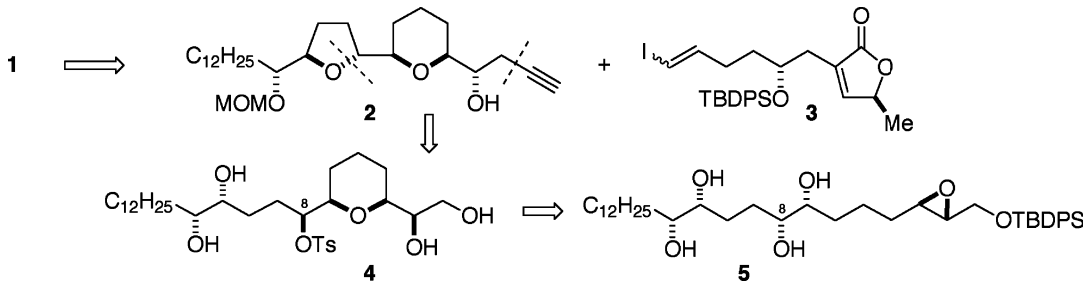
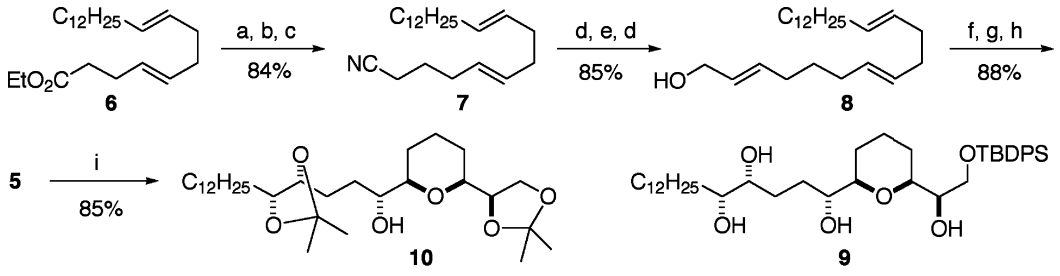


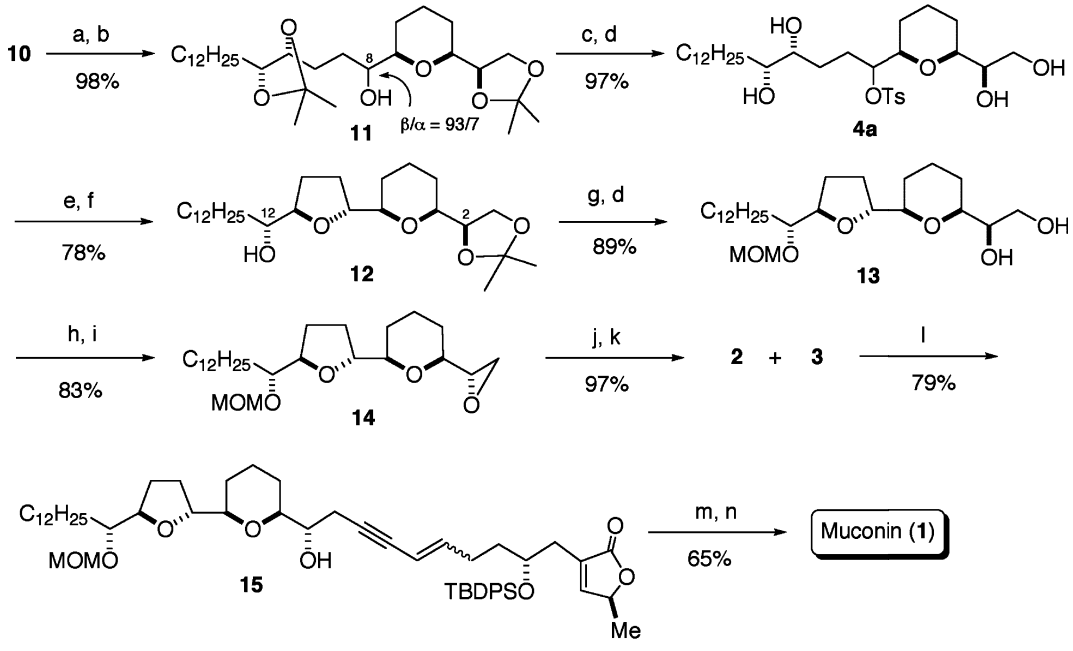
Scheme 1. Retrosynthetic scheme of muconin (**1**).



Scheme 2. (a) $LiAlH_4$, THF, 0°C; (b) *p*-TsCl, pyridine, 0°C; (c) NaCN, DMSO, rt; (d) DIBAL, CH_2Cl_2, −78°C; (e) $(MeO)_2P(O)CH_2CO_2Me$, NaH, THF, 0°C; (f) D-DET, $Ti(Oi\text{-}Pr)_4$, *t*-BuO_2H, MS4A, CH_2Cl_2, −23°C; (g) TBDPSCl, imidazole, DMF, rt; (h) AD-mix β, $MeSO_2NH_2$, aq. *t*-BuOH, 0°C; (i) CSA, CH_2Cl_2, rt, then MeOH, concd., and $(MeO)_2CMe_2$–CH_2Cl_2, rt.

following hydroxy protection was found to be more efficient. Hence, after completion of the cyclization, the reaction mixture was treated with methanol in order to hydrolyze the TBDPS ether, concentrated in vacuo and then reacted with 2,2-dimethoxypropane in CH_2Cl_2 in one pot to give a diacetonide **10** in 85% overall yield. The optical purity of **10** was determined to be >98% e.e. by the ^1H NMR analyses of the corresponding MTPA esters.

The alcohol **10** was oxidized with Dess–Martin periodinane to give a ketone, which was reduced with $Zn(BH_4)_2$[11] in ether at −10°C (Scheme 3). As expected, the reduction proceeded stereoselectively to afford a 93:7 mixture of the desired β-alcohol and its epimer **11** in 98% yield. This high stereoselectivity would be explained by the α-chelation as shown in Fig. 2. As separation of these isomers was found to be difficult at this stage, **11**



Scheme 3. (a) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt; (b) $Zn(BH_4)_2$, Et_2O, −10°C; (c) *p*-TsCl, DMAP, Et_3N, CH_2Cl_2, 0°C; (d) AcOH–H_2O, rt; (e) NaOMe, MeOH, rt–50°C; (f) $(MeO)_2CMe_2$, CSA, CH_2Cl_2, rt; (g) MOMBr, *i*-Pr_2NEt, CH_2Cl_2, rt; (h) BzCl, pyridine, CH_2Cl_2, −20°C, and then MsCl; (i) aq. NaOH, MeOH–THF, −20–5°C; (j) TMS≡Li, $BF_3{\cdot}Et_2O$, THF, −78°C; (k) K_2CO_3, MeOH, rt; (l) $(Ph_3P)_2PdCl_2$, CuI, Et_3N, rt; m) $(Ph_3P)_3RhCl$, H_2, benzene–EtOH, rt; (n) 10% HCl–MeOH, CH_2Cl_2.

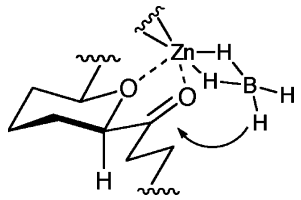


Figure 2.

was transformed into a C-8 epimeric mixture of tetraols **4a** via the corresponding monotosylates (97% yield). Formation of the second ether-ring was achieved by heating **4a** with sodium methoxide (2.0 eq.) in methanol at 50°C to provide the desired cyclic ether **12** in 78% yield after isopropylidenation. The remaining task was introduction of an ethynyl group through a stereoinversion at the C-2 position. Prior to the transformation, the 12-hydroxyl group was protected as a methoxymethyl (MOM) ether, and subsequent hydrolysis gave a diol **13** in 89% yield. Successive treatment of **13** with benzoyl chloride and methanesulfonyl chloride in pyridine provided a mesyl benzoate. Exposure of the benzoate to alkaline conditions led to an oxirane formation to give **14** in 83% yield from **13**. The epoxide **14** reacted with lithium trimethylsilylacetylide in the presence of $BF_3{\cdot}E_2O$ to produce a terminal acetylene **2** in 97% yield after de-silylation (potassium carbonate, MeOH).

The complete carbon skeleton of **1** was assembled by joining **2** and **3**[4d,12] under Hoye's conditions,[13] to give enyne **15** in 79% yield. This underwent regioselective reduction with Wilkinson's catalyst to give a partially protected muconin, in which all protecting groups were subsequently cleaved by hydrogen chloride in methanol–CH_2Cl_2 to give muconin (**1**).[14] The spectroscopic and physical properties of **1** were identical those of natural **1**.

In summary, we have succeeded in a convergent synthesis of **1** via successive ether-ring formation reaction under acidic and basic conditions and stereoselective reduction of acyclic ketone as the key steps.

Acknowledgements

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9. The optical purity was determined to be >94% e.e. by the ^1H NMR analyses of the corresponding MTPA esters.
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14. $[\alpha]_D^{23}$ +12.9° ($c=0.21$, $CHCl_3$); IR (neat) 3421, 2925, 1755, 1464, 1076 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 0.87 (3H, t, $J=6.8$ Hz), 1.20–2.00 (49H, m), 1.43 (3H, d, $J=6.8$ Hz), 2.30–2.62 (3H, m), 2.38 (1H, dd, $J=15.1$, 8.2 Hz), 2.51 (1H, ddd, $J=15.1$, 2.0, 1.5 Hz), 3.16 (1H, m), 3.30 (1H, m), 3.37 (1H, m), 3.42 (1H, m), 3.80 (1H, m), 3.84 (1H, m), 3.88 (1H, m), 5.05 (1H, qd, $J=6.8$, 1.0 Hz), 7.18 (1H, brs); ^{13}C NMR (100MHz, $CDCl_3$) δ 14.1, 19.1, 22.7, 22.9, 25.2, 25.5, 25.6, 27.0, 27.1, 28.3, 29.3, 29.4, 29.6, 29.7, 31.9, 32.4, 33.3, 37.3, 69.9, 74.0, 74.1, 78.0, 80.9, 81.3, 82.9, 131.1, 151.8, 174.6; HRMS (FAB) calcd for $C_{37}H_{66}O_7Na$ 645.4706, found 645.4714.
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