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Convergent Synthesis of (+)-Muconin

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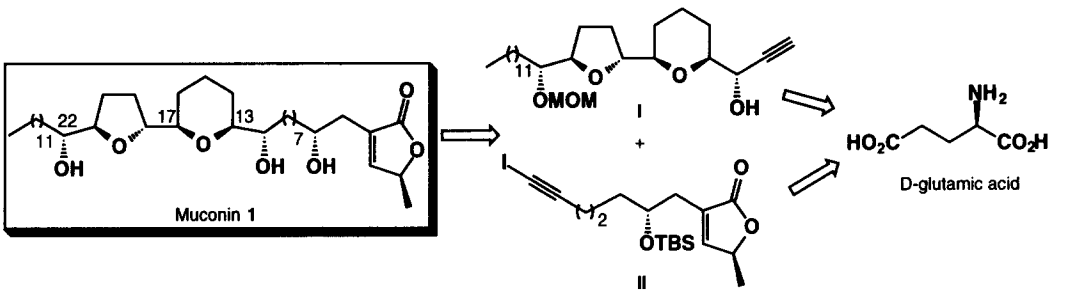
Abstract: *An efficient total synthesis of the tetrahydropyran-bearing acetogenin muconin* ***1*** *is described. Palladium(0)-mediated crossed diyne coupling and the use of only D-glutamic acid as the origin of all absolute stereochemistry highlight this flexible approach that sets the stage for access to structural analogs for further study.*

Annonaceous acetogenins are a rapidly growing class of natural products that have attracted much attention; many members possess a variety of biological activities such as cytotoxic, insecticidal, antitumor, antimicrobial, fungicidal and immunosuppressive effects.[1] Muconin (**1**), a novel tetrahydropyran-bearing acetogenin, was isolated by McLaughlin's group from the leaves of *Rollinia mucosa* and showed potent and selective *in vitro* cytotoxicity against pancreatic and breast tumor cell lines.[2] The remarkable antitumor activity and the unique structure of **1** have consequently stimulated synthetic efforts toward **1**.[3] Herein we wish to report our stereocontrolled synthesis of muconin.

As illustrated in our retrosynthetic analysis (Scheme 1), **1** may be constructed from two key building blocks, **I** and **II**. Both of them must be readily accessed from D-glutamic acid.

Scheme 1



We used and modified Koert's procedure to synthesize the aldehyde **2** via 8 steps in 12% yield.[4] Subsequent 4-step transformations developed by our group in the synthesis of solamin were adopted to elongate the side chain furnishing the aldehyde **3** in 62% yield.[5] Chelation-controlled addition of a Grignard reagent derived from **4**[6] in Et_2O at -78 ° C resulted in the coupled products **5**[7] as an inseparable mixture with a 3:1 diastereoselectivity at C-17 favoring the desired α-epimer.[8] It is surprising that addition of $CuBr \cdot SMe_2$ to the solution of the Grignard reagent prior to addition of **3** did not lead to isolation of any product. Deprotection of the acetonide group of **5** with AcOH in THF-H_2O gave a triol, which was converted to **6** via successive treatment with triisopropylbenzenesulfonyl chloride and NaOMe. Simple treatment of **6** with CSA in CH_2Cl_2 afforded a mixture of **7** (60%) and **8** (20%),[9] which was readily separated by column chromatography on silical gel. Dess-

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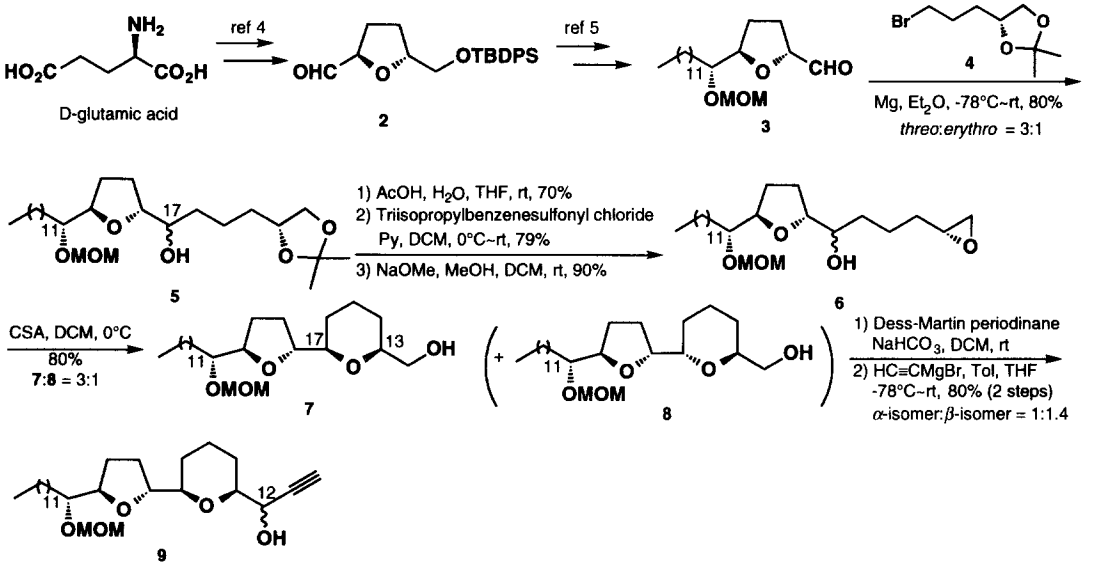
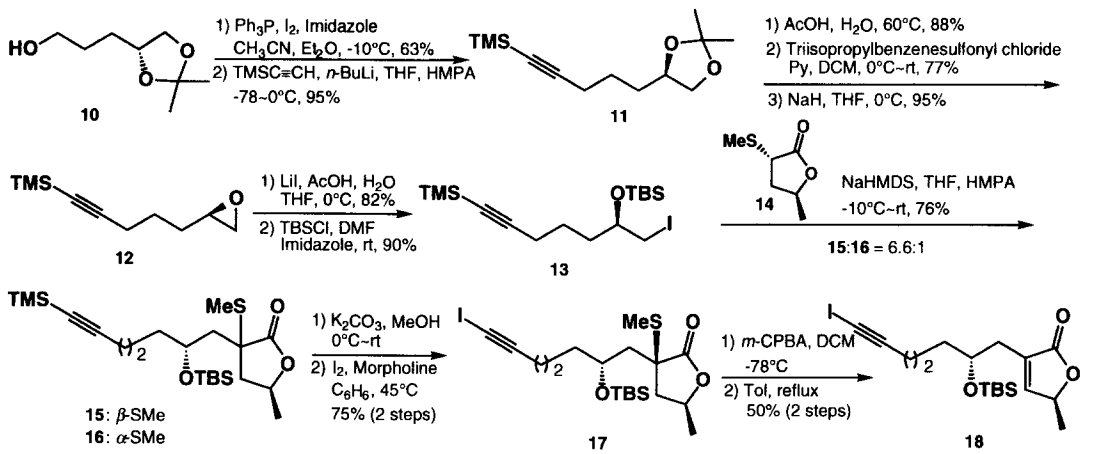
Martin oxidation[10] of **7** furnished an aldehyde which was allowed to react with ethynylmagnesium bromide in toluene-THF[11] to give **9** as a 1:1.4 inseparable mixture of the desired α-alcohol and its epimer[12] in 80% overall yield. Exploration of a variety of reaction conditions failed to uncover any effective method for the chelation-controlled alkylation of the aldehyde.

Scheme 2



Scheme 3

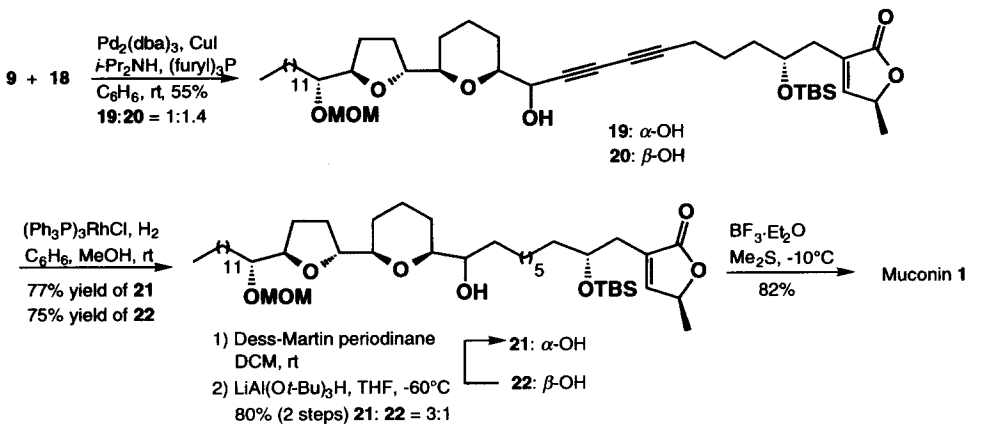


As shown in Scheme 3, the lactone fragment was constructed as follows. Successive iodination and alkylation of the alcohol **10**[13] gave **11** in good yield. This was then converted to **12** via a convenient 3-step sequence: 1) deprotection, 2) sulfonylation and 3) base-promoted epoxide formation. Treatment of **12** with LiI/AcOH/THF and followed by protection of the newly-generated hydroxyl group with TBS ether afforded the iodide **13**. Alkylation of the enolate derived from **14**[14] with iodoether **13** furnished **15** (66%) and **16** (10%)[15] which were separable on silical gel. Of course, both isomers must be useful for the synthesis of muconin because

sulfide would be removed to yield olefin. But, at the moment, we only used the major isomer **15**. Thus, selective removal of the TMS group in **15** liberated the terminal alkyne, which was then iodinated[16] to give **17**. Oxidation of the methyl sulfide with *m*-CPBA, followed by thermal elimination, provided the butenolide **18**.

Palladium(0)-mediated coupling[17] of the alkyne **9** with the iodoalkyne **18** afforded a separable mixture of diynes **19** (23%) and **20** (32%). Hydrogenations of **19** and **20** using Wilkinson's catalyst gave the corresponding reduced products **21** and **22** respectively, and the undesired β-alcohol **22** was inverted to α-alcohol **21** by means of a Dess-Martin oxidation/LiAl(O*t*-Bu)$_3$H reduction sequence. Finally, deprotection of the MOM and TBS group with $BF_3 \cdot Et_2O$ in the presence of dimethyl sulfide provided muconin **1**[18] with spectral properties identical to those of the natural product.

Scheme 4



In conclusion, we have developed an efficient procedure for the stereocontrolled synthesis of muconin. In order to disclose the relationship between structure and biological activity, syntheses of stereochemical and structural analogues are in progress.

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References and Notes

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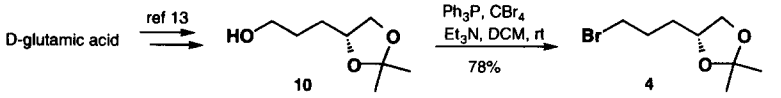
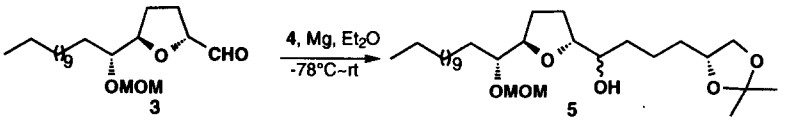
6. Bromide **4** was prepared as follows.



7. Grignard reaction of **3** under various conditions is shown below.



Entry	Additive	Compound **4** (equiv.)	Yield(%)	Recovered aldehyde(%)	Ratio (*threo* : *erythro*)
1	$CuBr{\cdot}SMe_2$	5	0	0	-
2	-	5	36	32	3:1
3	-	7	38	28	3:1
4	-	11	67	8	3:1
5	-	14	80	0	3:1

8. a) The ^{1}HNMR spectra of **5** showed the chemical shift of the proton at C-17 of the major isomer was 3.37 ppm, which indicated the ring was flanked by the hydroxyl in *threo* fashion according to Born's rule.[8b]
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14. a) Mori, K. *Tetrahedron* **1975**, *31*, 3011.
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15. Chemical shifts of thiomethyl protons in **15** were 1.50 ppm, at lower field compared with those of **16** at 1.40 ppm.[14b]
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18. **1**: mp 75-77 ℃; $[\alpha]_D^{27}$ +13.5° (*c* 0.28, $CHCl_3$); IR (film) ν_{max} 3440, 2922, 2850, 1756, 1078 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.87 (3H, t, J = 7.0 Hz), 1.20-2.20 (49H, m), 1.43 (3H, d, J = 6.5 Hz), 2.37 (1H, m), 2.52 (1H, m), 3.16 (1H, m), 3.31 (1H, m), 3.38 (1H, m), 3.43 (1H, m), 3.77-3.90 (3H, m), 5.06 (1H, m), 7.18 (1H, d, J = 0.5 Hz).