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Total Synthesis and Structural Confirmation of (+)-Longicin

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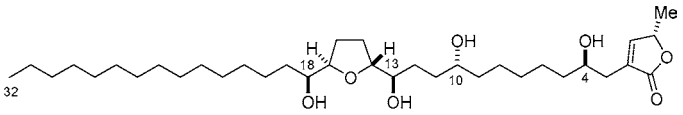
ABSTRACT



Longicin, **1**

A stereocontrolled total synthesis of (+)-longicin, a representative of the class of mono-THF-acetogenins, is described. The strategy involves the utilization of D- and L-glutamic acids as chirons that correspond to two five-carbon segments harboring stereogenic centers at C4 and at C17 of the C_{32} polyketide-derived natural product. The use of Grubbs' RCM reaction as a novel "chain elongation" strategy for the synthesis of acetogenin-type structures and a new protocol for butenolide incorporation are also described.

The acetogenin family of natural products is a class of polyketide-derived metabolites originally isolated from tropical and subtropical plants commonly known as *Annonacea*.[1] They are usually characterized by the presence of one or more tetrahydrofuran units embedded within a long fatty acid chain also bearing noncontiguous secondary hydroxyl groups. This unique class of annonaceous acetogenins, represented by several hundred well-defined structures, has attracted particular attention due to their broad range of physiological effects.[1,2] Tumor cell death by apoptosis due to interference with ATP supply via inhibition of mitochondrial complex I is among the diverse biological modes of action of the acetogenins.[3] Their antitumor activity in particular[4] has instigated intense efforts toward the stereocontrolled total synthesis of several members of this class.[5,6] Indeed, there are a number of reported total syntheses of acetogenins that contain a central tetrahydrofuran ring,[7] as well as those with more than one ring.[8]

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(6) For a summary of synthetic approaches, see: Prestat, G.; Baylon, C.; Heck, M.-P.; Grasa, G. A.; Nolan, S. P.; Mioskowski, C. *J. Org. Chem.* **2004**, *69*, 5770.

(7) For selected syntheses, see Solamin: (a) Trost, B. M.; Shi, Z. *J. Am. Chem. Soc.* **1994**, *116*, 7459. (b) Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1993**, *115*, 4891. (c) Makabe, H.; Tanaka, A. J.; Oritani, T. *J. Chem. Soc. Perkin Trans. 1* **1994**, 1975. Kuriyama, W.; Ishigami, K.; Kitahara, T. *Heterocycles* **1999**, *50*, 981. Corossolone: Yao, Z.-J.; W, Y.-L. *J. Org. Chem.* **1995**, *60*, 1170. Reticulacin: ref 6b,c. Longifolicin: Marshall, J. A.; Jiang, H. *Tetrahedron Lett.* **1998**, *39*, 1497. Murisolin: Zhang, Q.; Lu, H.; Richard, C.; Curran, D. *J. Am. Chem. Soc.* **2004**, *126*, 36.

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In 1995, McLaughlin and co-workers[9] reported the isolation of longicin **1** and the C-18 epimer goniothalamicin from *Asimina longiolia* (annonacea), commonly known as long leaf paw paw (Figure 1). Longicin is reported to exhibit over

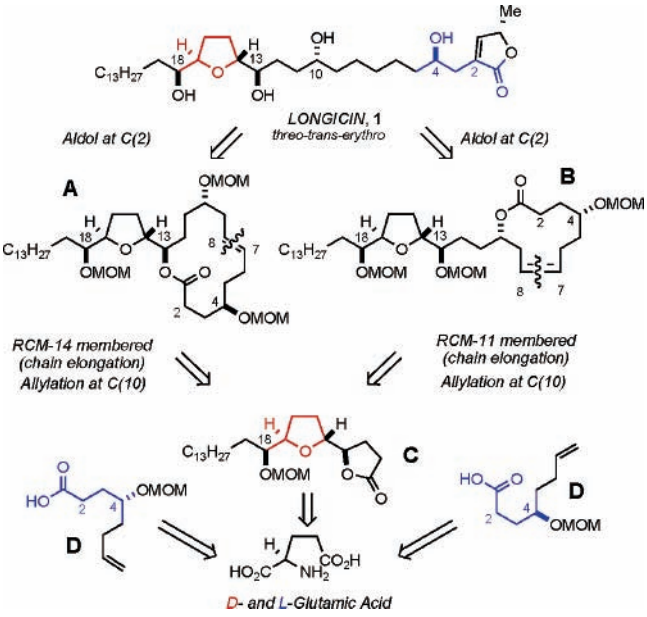


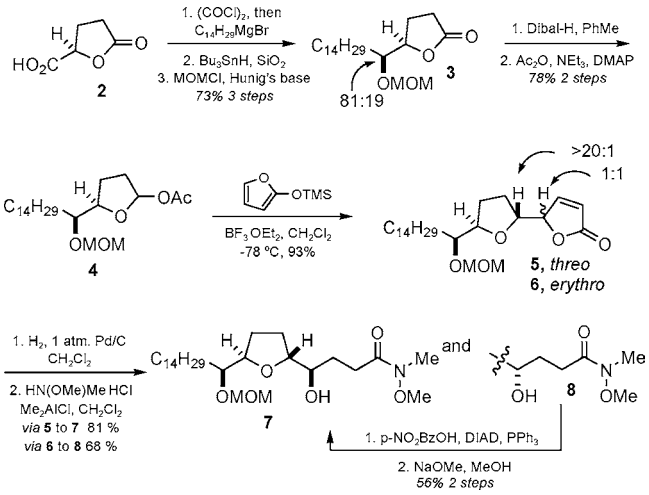
Figure 1. Retrosynthetic analysis.

1 million-fold selective antitumor activity against pancreatic cancer cells compared to adriamycin.[9] This unique potency, as well as an uncommon *threo-trans-erythro* stereochemical pattern and the presence of the hydroxyl substituent specifically at C10, prompted us to investigate its total synthesis.

In this Letter, we wish to report the first total synthesis, stereochemical assignment, and structural confirmation of longicin, **1**. The disconnective analysis (Figure 1) relies on a novel strategy that uses the venerable RCM reaction as a "chain elongating" method to access advanced macrolactone intermediates A and B independently. Thus, a disconnection at C7−C8 in both A and B generates olefinic subunits that can be accessed from the common lactone precursor C, harboring the *threo-trans-threo* pattern. Lactone C can be generated by the well-precedented vinylogous aldol-type reaction[10] on an oxocarbenium ion readily available from D-glutamic acid (red). An eight-carbon carboxylic acid chain elongator D that contains the C4 hydroxyl group and a terminal olefin originates from L-glutamic acid (blue).

The readily available lactone **2**, prepared in one step from D-glutamic acid,[11] was converted to the acyl chloride, and the latter reacted with $C_{14}H_{29}MgBr$ in THF solution to afford the corresponding ketone in 80% yield (Scheme 1).

Scheme 1. Synthesis of Intermediate **7**



After several attempts to achieve anti selectivity in the reduction of the ketone, it was found that *n*-Bu_3SnH in the presence of silica gel in a dichloromethane suspension[12] provided the desired alcohol in an 81:19 diastereomeric ratio that could be easily separated by chromatography.[13] Protection of this alcohol as a MOM ether afforded **3** in excellent overall yield.

The next crucial step involved a four-carbon extension based on previous experience with annoanacin A.[14] Thus, lactone **3** was reduced with Dibal-H in toluene to the corresponding hemiacetal and acetylated to give **4** in 78% yield for the two steps. Addition of 2-trimethylsiloxyfuran in the presence of $BF_3{\cdot}Et_2O$ gave the desired trans junction at C13 in a ratio >20:1 and a ratio of 1:1 at C12 in 93% yield.[10,15] The desired *threo* isomer **5** could be easily separated from its *erythro* isomer **6** by flash column chromatography. Catalytic hydrogenation of **5** and **6** afforded the corresponding reduced lactones, which were treated with HCl·HN(OMe)Me in the presence of dimethylaluminum chloride[16] to afford amides **7** and **8** in excellent yields. The undesired isomer **8** could be recycled through a Mitsunobu inversion[17] to give **7** in 56% yield for the two-step process. Thus, the desired *threo-trans-erythro* isomer **7** could be obtained in a combined overall yield of 55% from **4**.

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(10) For examples of related reactions, see: (a) Zanardi, F.; Battistini, L.; Rassu, G.; Pinna, L.; Mor, M.; Culeddu, N.; Casiraghi, G. *J. Org. Chem.* **1998**, *63*, 1368. (b) Casiraghi, G., Zanardi, F.; Battistini, L.; Rassu, G.; Appendino, G. *Chemtracts* **1998**, *11*, 803 (c) Figadère, B.; Peyrat, J.-F.; Cavé, A. *J. Org. Chem.* **1997**, *62*, 3428. (d) Koert, U.; Stein, M.; Harms, K. *Tetrahedron Lett.* **1993**, *34*, 2299. (e) Rassu G.; Spanu, G.; Casiraghi, G.; Pinn, L. *Tetrahedron* **1991**, *47*, 8025. (f) Jefford, C. W.; Jaggi, D.; Boukouvalas, J. *Tetrahedron Lett.* **1987**, *28*, 4037.

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(13) Stereochemistry at C18 (longicin numbering) was confirmed by X-ray crystallography; see Supporting Information.

(14) Hanessian, S.; Grillo, T. A. *J. Org. Chem.* **1998**, *63*, 1049.

(15) Stereochemistry at C13 and C14 (longicin numbering) was confirmed by X-ray crystallography; see Supporting Information.

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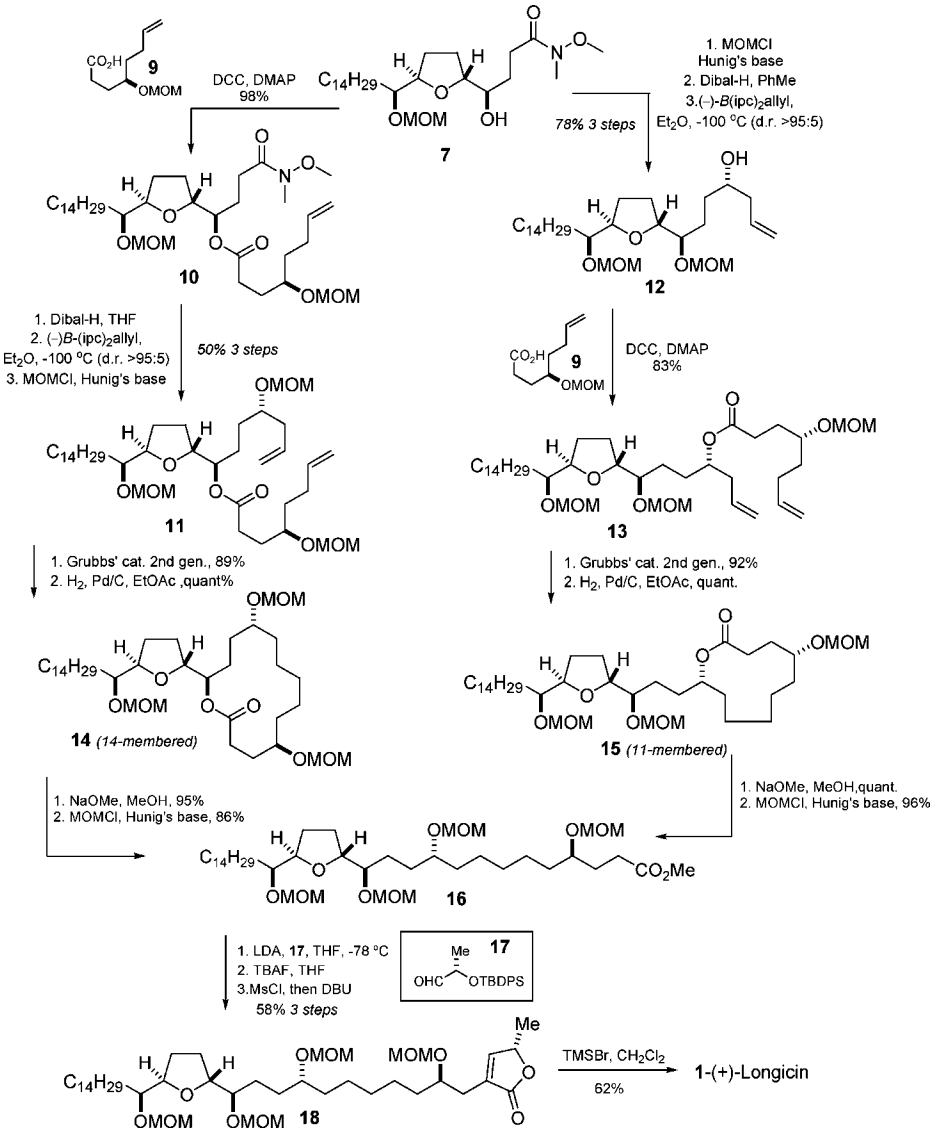
Scheme 2. Total Synthesis of (+)-Longicin **1**



Having secured the requisite *threo-trans-erythro* pattern for the core THF subunit, the stage was set for the installation of the olefinic partners as esters on strategically located hydroxyl groups to carry out the respective "chain-elongating" RCM reactions, eventually leading to a common advanced intermediate. In the first of two approaches, acylation of **7** with acid **9**[18] in the presence of DCC and DMAP gave amide **10** in 98% yield. Direct Mitsunobu inversion of **8** with **9** to give **10** (40% yield) could also be achieved in lieu of the three-step process shown in Schemes 1 and 2 (**8**→**7**→**10**).[19] Amide **10** was selectively reduced to the corresponding aldehyde (Dibal-H, THF, −78 °C) without any detectable reduction of the ester. The aldehyde was then subjected to an asymmetric Racherla−Brown allylation reaction with (−)-*B*-allyl(diisopinocampheyl)borane,[20] and the resulting alcohol (dr > 95:5) was protected as a MOM ether to give diolefin **11** in 50% overall yield for three steps. In the second approach, common precursor **7** was homologated to the allylic alcohol **12** in excellent overall yield. Esterification with the chain-elongating acid **9** gave the diolefin **13** in 83% yield.

With diolefins **11** and **13** in hand, we were ready to apply the ester-tethered RCM macrocyclization[21] to 14- (**14**) and 11-membered (**15**) ring lactones, respectively. Much to our delight, in the presence of 5 mol % Grubbs' second-generation catalyst in refluxing CH_2Cl_2, **11** was smoothly

(18) See Supporting Information for synthesis.

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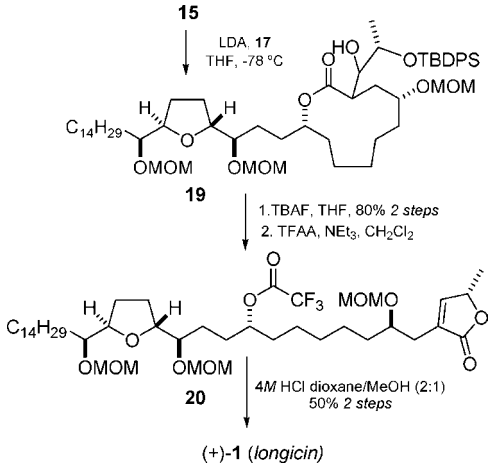
(21) For relevant reviews, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Armstrong, S. K. *J. Chem Soc., Perkin Trans. 1* **1998**, 371. (c) Schuster M., Blechert, S. *Angew. Chem. Int. Ed.* **1997**, *36*, 2037. (d) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **1995**, *34*, 2039. For recent reference to the synthesis of 11-membered rings by RCM, see: Nicolaou, K. C.; Montagnon, T.; Vassilikogiannakis, G.; Mathison, C. J. N. *J. Am. Chem. Soc.* **2005**, *127*, 8872.

transformed to the desired 14-membered lactone (E/Z > 10:1). Reduction with H_2 and 10% Pd/C in EtOAc gave **14** in 83% yield for the two steps. The 11-membered lactone **15** could also be prepared in the same sequence in an astounding 92% overall yield.[21] It should be noted that both cyclizations were also possible using Grubbs' first-generation catalyst (20−30 mol %) but with slightly lower yields (75−80%). Saponification of macrolactones **14** and **15** with NaOMe in refluxing methanol, followed by protection of the two respective hydroxyesters as the MOM ethers, gave the common intermediate **16** with identical physical data independent of the route used. Previous syntheses of acetogenins[7,8] have utilized an intermolecular aldol reaction followed by elimination to install the butenolide moiety. Thus, the lithium enolate formed from **16** with LDA at −78C was treated with **17**,[18] and the resulting aldol product was subjected to de-O-silylation and in situ lactonization with Bu_4NF. Mesylation of the intermediate β-hydroxylactone and elimination with DBU gave **18**. Removal of the MOM groups with TMSBr[22] afforded crude longicin **1**, which was purified by flash chromatography, giving material identical to the natural product on the basis of the reported physical constants.[9]

Having secured the stereochemical identity of longicin by a stereocontrolled route, we opted for an alternative strategy that exploits the inherent features of macrolactone intermediates. Thus, formation of the Li-enolate of **15** and treatment with **17** led to the corresponding mixture of aldol products **19** (Scheme 3). Desilylation with TBAF led, via internal translactonization, to the corresponding γ-lactone. Esterification with TFAA/NEt_3 in the presence of catalytic amount of DBU gave the butenolide **20**. Finally, treatment of **20** with 4 M HCl in dioxane/MeOH (2:1) gave (+)-longicin in 7.5% overall yield from **2** (18 steps for the longest linear sequence).

We have described the first total synthesis of longicin, a new member of annonaceous mono-THF-containing metabolite, relying on a strategy that capitalizes on the efficient utilization of D- and L-glutamic acids as chirons. Subunit coupling was achieved by a novel application of the Grubbs' RCM reaction for "chain-elongation", thus assembling the entire aliphatic chain of longicin. A new strategy was used to construct the butenolide subunit via an aldol reaction with a macrocyclic lactone precursor. The RCM macrocyclization via "chain elongation" with diolefinic ester precursors should find extensive application in the synthesis of biogenetically related acetogenins.[23,24]

Scheme 3. Internal Translactonization Strategy



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Supporting Information Available: Typical exprimental procedures for key reactions, NMR spectra, and X-ray ORTEP structures (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) Bermejo, A.; Figadère, B.; Zafra-Polo, M.-C.; Barrachina, I.; Estornell. E.; Cortes, D. *Nat. Prod. Rep.* **2005**, *22*, 269.