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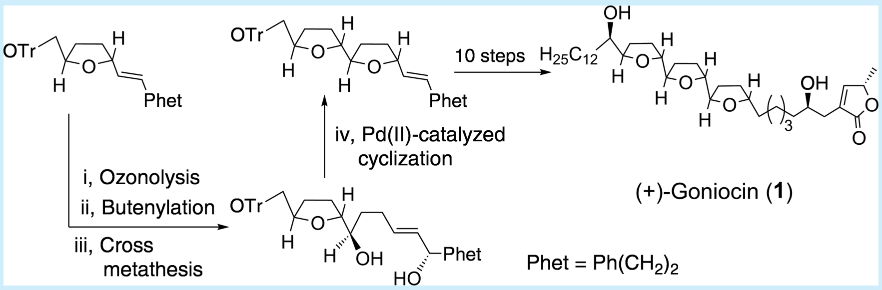
Construction of Iterative Tetrahydrofuran Ring Units and Total Synthesis of (+)-Goniocin

Ai Suzuki, Mai Sasaki, Tetsuya Nakagishi, Tsuyoshi Ueda, Naoyuki Hoshiya, and Jun'ichi Uenishi*

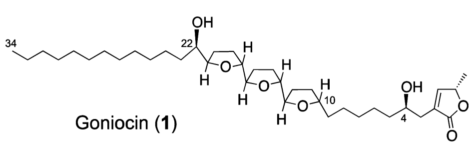
Kyoto Pharmaceutical University, Yamashina, Kyoto 607-8412, Japan

Supporting Information



ABSTRACT: Cytotoxic acetogenin (+)-goniocin has been synthesized in 17 steps from (*R*)-*O*-tritylglycidol. The core structure of the contiguous C_{22}−C_{10} *threo-trans-threo-trans-threo-trans*-tris-tetrahydrofuran (THF) ring involving an iterative THF-ring unit was synthesized. An iterative THF ring unit was constructed from an alkenyl-substituted THF ring in four steps including a Pd(II)-catalyzed ring-closing reaction and cross-metathesis. This method is general and allows the preparation of both *trans-threo-trans-* and *trans-threo-cis*-THF ring units flexibly.

Annonaceae acetogenins are a class of natural lipophilic polyketides with C_{32} or C_{34} unbranched fatty acid chains, and they are isolated from the *Annonaceous* plant family.[1] They display a wide array of biological activities including anticancer, anti-inflammatory, pesticidal, antimalarial, immunosuppressive, and neurotoxic. Goniocin (**1**) was isolated from the bark of *Goniothalamus giganteus* in Thailand by the McLaughlin group in 1994.[2] They discovered the unique structure and potent cytotoxic activity of **1**. The structure of **1** consists of a core contiguous tris-*trans*-tetrahydrofuran (THF) ring unit, a left linear hydrocarbon chain unit, and a methyl-substituted γ-butenolactone unit on the right.



Goniocin (**1**)

The chiral γ-butenolactone moiety is a common pharmacophore of acetogenins. Bioenergetic production has been reported to be hindered by the inhibition of mitochondrial complex I.[3,1b,k] In fact, **1** displays remarkable profiles of potent growth inhibition of cancer cells.[1,4] Goniocin is the only acetogenin that has an all-*trans* tris-THF ring unit in the C_{10}−C_{21} chain. Although the intriguing structure and potent cytotoxic activity of **1** against cancer cell lines at very low concentrations are attractive, this compound has not been fully investigated. Only one landmark total synthesis has been reported by Sinha and Keinan et al. in 1998.[5,6] However, no additional report for the synthesis of **1** has appeared since then. We are interested in the total synthesis of **1** and its biological activity. Herein, we present a short synthetic route to (+)-goniocin along with a new method for the stereocontrolled construction of the bis- and tris-THF ring units.

The contiguous bis-THF ring unit has often been observed in the structure of many acetogenins,[1g−j] and in fact, numerous syntheses have been reported for acetogenins possessing a bis-THF ring unit.[7,8] Nonetheless, flexible and efficient stereocontrolled synthesis of the bis-THF ring unit is desired not only for the synthesis of **1** but also for the synthesis of other members of bis-THF acetogenins. Our synthetic plans for the *trans-threo-trans*-bis-THF (**IA**) and *trans-threo-cis*-bis-THF (**IB**) rings are depicted in Scheme 1. The alkene-substituted bis-THF ring of **IA** could, in principle, be constructed by Pd(II)-catalyzed stereospecific ring formation from chiral ε-hydroxy allylic alcohol **IIA**.[9] This precursor **IIA** could be derived by cross-metathesis of chiral 1-tetrahydrofurylpentenol **III** with chiral allylic alcohol possessing an (*S*)-chiral center. Meanwhile, the *trans-cis*-bis-THF ring isomer **IB** could be derived from **III** via the same two steps, except that (*R*)-allylic alcohol is used instead of (*S*)-allylic alcohol. The common intermediate **III** is provided from the 1-alkenyl THF compound **V** in two steps (ozonolysis followed by stereoselective butenylation). This method would provide an additional stereodefined THF ring unit from a simple alkene **V** or an aldehyde **IV**. Thus, the stereodivergent synthesis of the 2-alkenyl-5,2′-bis-THF ring from the 2-alkenyl-mono-THF ring could be achieved in four steps.

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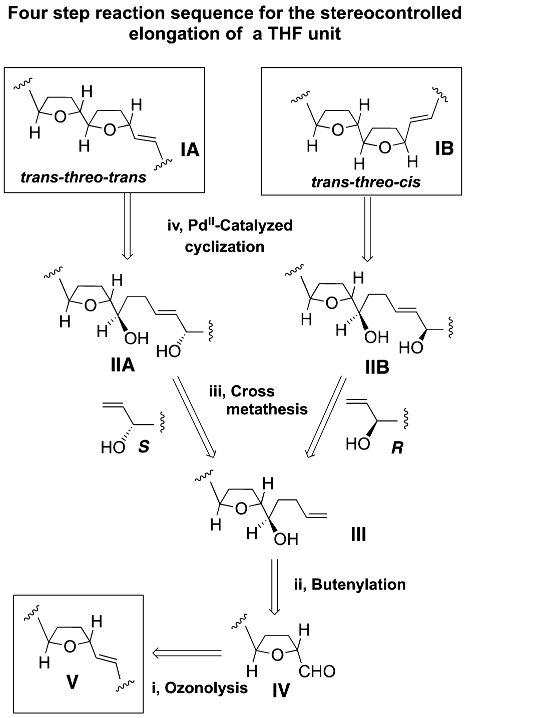
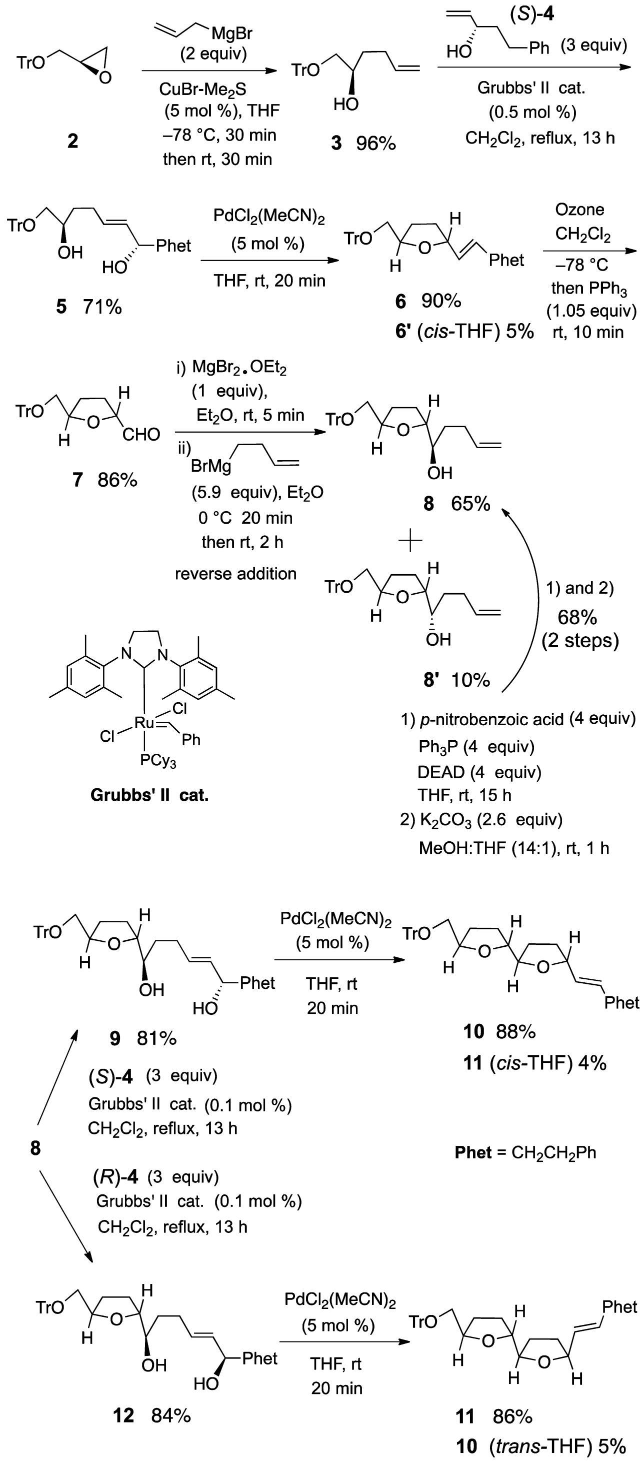
Scheme 1. Synthetic Strategy for *trans-trans-* and *trans-cis-*Bis-THF Ring Units IA and IB



Scheme 2. Stereocontrolled Synthesis of *trans-threo-trans-* and *trans-threo-cis-*Bis-THF Rings



On the basis of this idea, we began the synthesis with (*R*)-*O*-tritylglycidol **2**[10] (Scheme 2). Ring opening of **2** with allylmagnesium bromide gave **3** in 96% yield, which was subjected to cross-metathesis with (*S*)-5-phenylpent-1-en-3-ol (*S*)-**4**[11] in the presence of Grubbs' II catalyst (0.5 mol %) to obtain **5** in 71% yield. Catalytic cyclization of **5** with $PdCl_2(MeCN)_2$ (5 mol %)[9] gave the desired *trans*-THF product **6** in 90% yield along with *cis*-THF ring isomer **6′** in 5% yield. The second THF ring for *trans* isomer **10** was constructed via the following four steps: (i) ozonolysis of **6** afforded THF−aldehyde **7** in 86% yield; (ii) addition of butenylmagnesium bromide to **7** in THF gave the chelation-controlled product **8** in 51% yield and its diastereomer **8′** in 24% yield;[12] (iii) cross-metathesis of **8** with (*S*)-**4** in the presence of Grubbs' II catalyst (0.1 mol %) gave diol **9** in 81% yield; and (iv) Pd(II)-catalyzed cyclization of **9** furnished the *trans-threo-trans*-bis-THF ring product **10** in 88% yield and the *trans-threo-cis* ring isomer **11** in 4% yield. However, cross-metathesis of **8** with (*R*)-**4** under the same conditions gave diol the **12** in 84% yield. Pd(II)-catalyzed cyclization of **12** afforded **11** in 86% yield and **10** in 5% yield.

The facial selectivity in the butenylation of **7** was improved through the addition of a chelate complex of **7** with $MgBr_2$−etherate complex[13] into an excess of the butenylmagnesium bromide in ether. The ratio of isomers became 6.5:1 favoring of the chelation product **8** (65%) over its isomer **8′** (10%). Additionally, the diastereomeric isomer **8′** was converted into the (*R*)-isomer **8** in 68% yield by Mitsunobu inversion followed by hydrolysis of the resulting *p*-nitrobenzoate ester. In the four-step reaction sequence starting from **7** and resulting in either **10** or **11**, we efficiently constructed a bis-THF ring system in a stereocontrolled manner. This methodology was then used for the total syntheses of goniocin.

Scheme 3 summarizes our retrosynthetic plan for goniocin. The C_9−C_{34} unit **13** could be assembled from a right *γ*-butenolide unit (*R*)-**14**[14] by alkene cross-metathesis at the C_8−C_9 bond. The C_{22}-hydroxy group could be created by the addition of a dodecyl unit to the C_{22}-formyl group derived from **15**. The consecutive tris-*trans*-THF ring unit in **15** could be installed following the same strategy described for the formation of the bis-THF intermediate **10**. The preparation of **10** via the mono-THF intermediate **6** is shown in Scheme 2.

Scheme 4 shows the synthesis of **1** from **10**. First, oxidative cleavage of alkenyl bond of **10** by ozonolysis gave aldehyde **16** in 86% yield. Addition of butenylmagnesium bromide to **16** in THF

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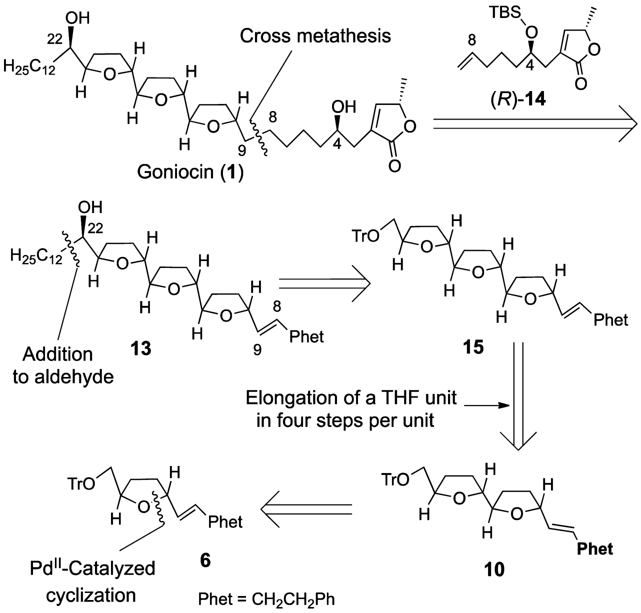
Scheme 3. Retrosynthetic Plan for (+)-Goniocin

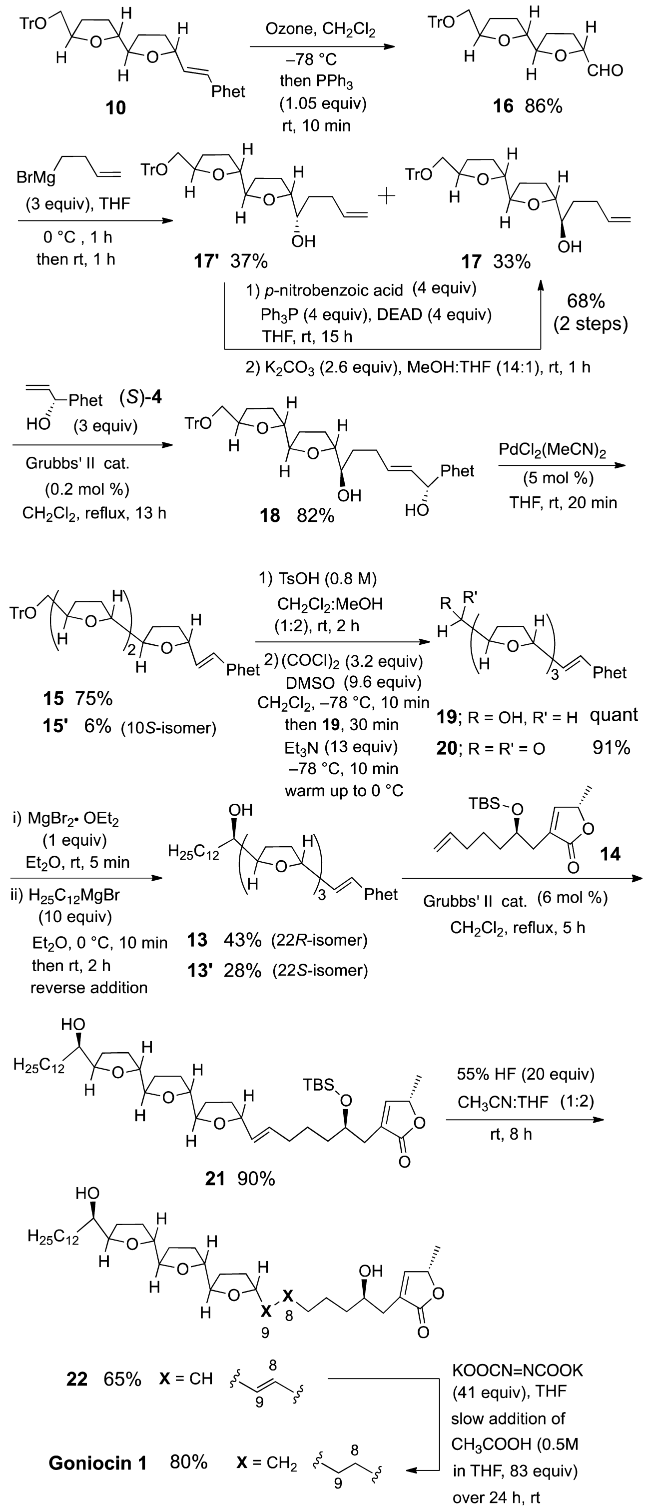


gave the desired product **17** and the undesired isomer **17′** in a 1:1.2 ratio and in 33% and 37% yields, respectively. However, the formation of a $MgBr_2$ complex of bis-THF aldehyde **16** and the addition by butenylmagnesium bromide resulted in a worse ratio of 1:1.7, with **17** and **17′** in 28% and 47% yields, respectively. This result suggests that chelation control in the addition to the aldehyde was not exerted because of the formation of the $MgBr_2$ complex with the bis-THF ring of **16** and, instead, control opposite to that expected occurred through the Felkin−Anh model. The influence of the unexpected stereoselectivity by the existence of a neighboring THF group was reported.[15] The undesired (*S*)-isomer **17′** was transformed into the (*R*)-isomer **17** in 68% overall yield via the Mitsunobu method. Cross-metathesis of **17** with (*S*)-**4** gave **18** in 82% yield. Compound **18** underwent Pd(II)-catalyzed tris-THF ring formation in THF for 20 min at rt, producing **15** in 75% yield along with the *cis* product **15′** in 6% yield. Deprotection of the *O*-Tr group of **15** followed by Swern oxidation provided the aldehyde **20** via alcohol **19** in 91% overall yield. Addition of the $MgBr_2$ complex of aldehyde **20** to a large excess of dodecylmagnesium bromide in ether gave the desired isomer **13** in 43% yield and its isomer **13′** in 28% yield.[16] Coupling of **13** with an excess of **14** via cross-metathesis gave **21** in 90% yield. HF-promoted deprotection of the *O*-silyl group and reduction of the alkene with diimide furnished the total synthesis of **1** in 52% yield in two steps. The spectroscopic data for synthetic **1** (i.e., ^{1}H and ^{13}C NMR and mass spectra) are identical to those previously reported in the literature.[2] In particular, the specific degree of optical rotation was $[\alpha]^{24}_{D}$ +8.2 (*c* 0.42, $CHCl_3$).[17]

Subsequently, the effect of the synthetic goniocin **1** was measured on the proliferation of four cancer cell lines. The IC50 values of cytotoxicity against HL-60, Paca 2, MCF-7, and A 549 were 2.3, 9.4, 21.8, and 6.6 μM/mL, respectively.

In conclusion, we have accomplished the total synthesis of (+)-goniocin. The synthesis comprises 17 linear steps from (*R*)-*O*-tritylglycidol. The four-step reaction sequence from an alkenyl unit provides short access to the installation of an additional THF unit. The synthetic strategy and technologies developed in this paper can be applied for the synthesis of acetogenins and their analogues possessing a multi-THF ring unit.

Scheme 4. Synthesis of (+)-Goniocin



■ ASSOCIATED CONTENT

Supporting Information

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Synthesis protocols and characterization of all new compounds including ^{1}H and ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: juenishi@mb.kyoto-phu.ac.jp.

Notes

The authors declare no competing financial interest.

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(16) Normal addition of dodecylmagnesium bromide to tris-THF aldehyde **20** gave a mixture of **13** and **13′** in poor yield (∼15%) with recovery of the starting material.

(17) The degree of **1** has not been reported in the literature (refs 2 and 5).

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