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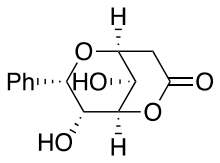
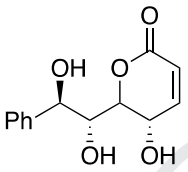


(+)-goniopypyrone



(+)-goniotriol

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Synthesis of (+)-goniopypyrone and (+)-goniotriol using Pd-catalyzed carbonylation

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ABSTRACT

Syntheses of (+)-goniopypyrone and (+)-goniotriol isolated from *Goniothalamus giganteus* were achieved. The key steps involve Pd-catalyzed carbonylation for lactone ring formation and diastereoselective reduction of ynone using the (*R*)-CBS catalyst and borane dimethyl sulfide complex.

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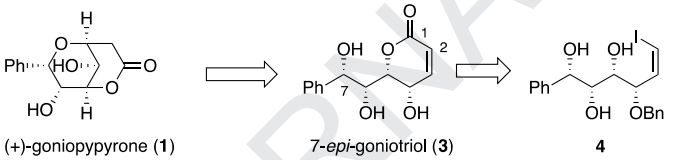
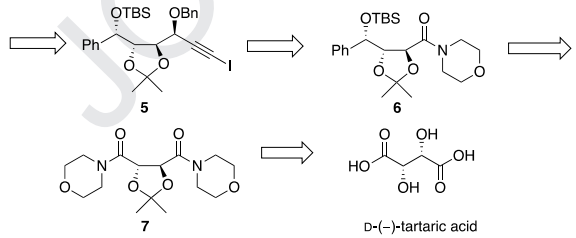
The trees of *Goniothalamus* genus, a group of the *Annonaceae* family in South East Asia, are known as sources of folk medicines. McLaughlin and co-workers isolated a number of styryl lactones from *Goniothalamus giganteus* including (+)-goniopypyrone and (+)-goniotriol.[1,2] These styryl lactones showed significant cytotoxicity against 3PS murine lymphocytic leukemia cells.[3] Because of their unique structure and significant biological activities, much effort toward the synthesis of these compounds has been made.[4-11] Shing and co-workers utilized D-glycero-D-gulo-heptano-γ-lactone as a chiral source. Overall yield of their synthesis was rather low (> 5%).[4,6] Zhou and co-workers accomplished efficient asymmetric total synthesis of (+)-goniopypyrone from methyl cinnamate using asymmetric dihydroxylation and addition of 2-furylcopper in a stereoselective manner.[5] Tsubuki and co-workers employed chiral lactonic aldehydes prepared from D-isopropyldinedioxy glyceraldehyde. Their synthesis needed to separate unnecessary diastereomer.[7] Surivet and Vatele used mandelic acid as the chiral source. Their synthesis required the separation of the mixture of different kind of styryllactones.[8] Prasad synthesized these styryl lactones from a common intermediate. Introduction of the α,β-unsaturated double bond required two steps from saturated lactone via syn elimination of selenoxide.[9, 11] Yadav and co-worker synthesized **1** using stereoselective Grignard reaction and Grubbs' ring-closing metathesis from a common precursor prepared from D-(+)-mannitol.[10]

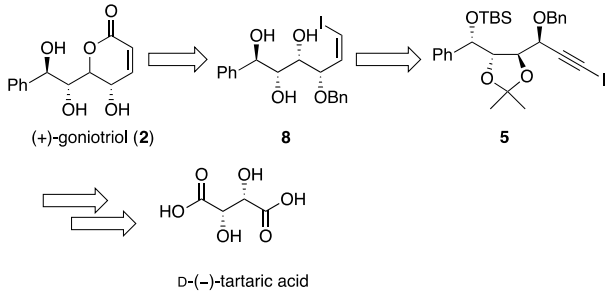
Fig 1. Structures of (+)-goniopypyrone (**1**) and (+)-goniotriol (**2**).

The synthetic strategy was shown in Scheme 1. (+)-Goniopypyrone (**1**) can be synthesized from 7-*epi*-goniotriol (**3**). The α,β-unsaturated δ-lactone ring of **3** would be constructed using palladium-catalyzed carbonylation and cyclization of *Z*-vinyl iodide **4**. The *Z*-vinyl iodide **4** can be synthesized from iodo alkyne **5**. Compound **5** can be prepared from amide **6**. Amide **6** is prepared from D-(−)-tartaric acid (Scheme 1A and Scheme 1B).



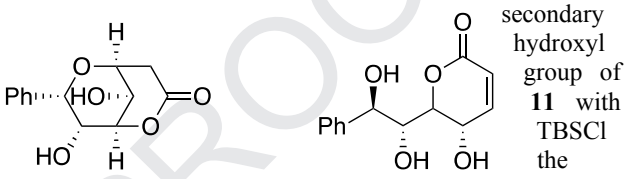


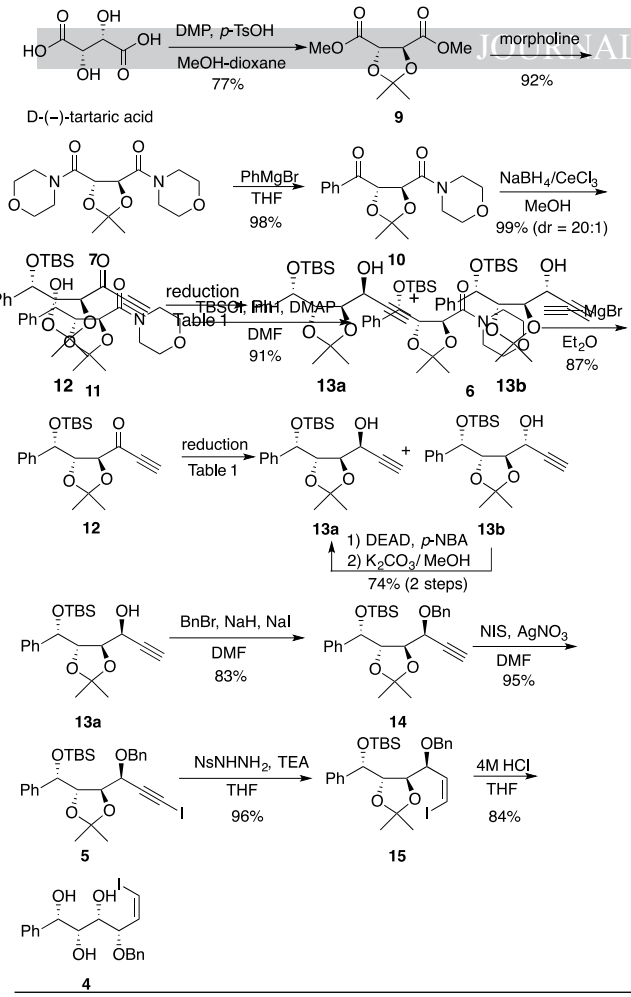
Scheme 1A. Synthetic strategy of (+)-goniopypyrone (**1**).



Scheme 1B. Synthetic strategy of (+)-goniotriol (**2**).

Scheme 2 and 3 show the synthesis of (+)-goniopypyrone (**1**) and 7-*epi*-goniotriol (**3**). At the outset, we focused on the preparation of the key building block **5** from D-(−)-tartaric acid. D-(−)-Tartaric acid was treated with *p*-TsOH and 2,2-dimethoxypropane in a mixture of MeOH and dioxane to give dimethyl ester **9**. Treatment of **9** with morpholine afforded diamide **7**. Addition of 1.5 eq. of phenylmagnesium bromide furnished γ-oxo butylamide **10**. Reduction of the keto group of **10** with $NaBH_4/CeCl_3$ afforded a diastereomeric mixture of alcohols in a 20:1 ratio, which after recrystallization gave diastereomerically pure **11**. The absolute configuration of newly formed chiral center of **11** was confirmed using the advanced Mosher method (Electronic Supporting information (ESI), Fig. S1).[18] Protection of the secondary hydroxyl group of **11** with TBSCl in the presence of imidazole afforded **6**. Addition of ethynylmagnesium bromide to **6** furnished ynone **12**. Reduction of the carbonyl group of **12** with various reagents is shown in Table 1.





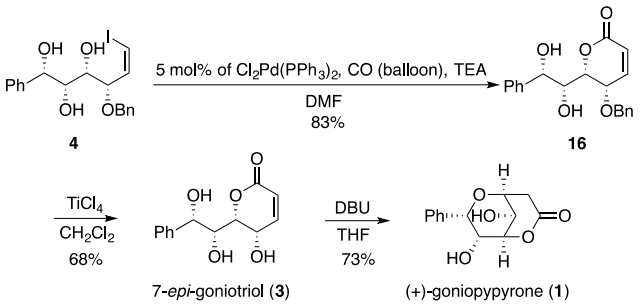
Scheme 2. Synthesis of cyclization precursor **4**.

Table 1. Reduction of the keto group of **12** using various hydride reagents**.**

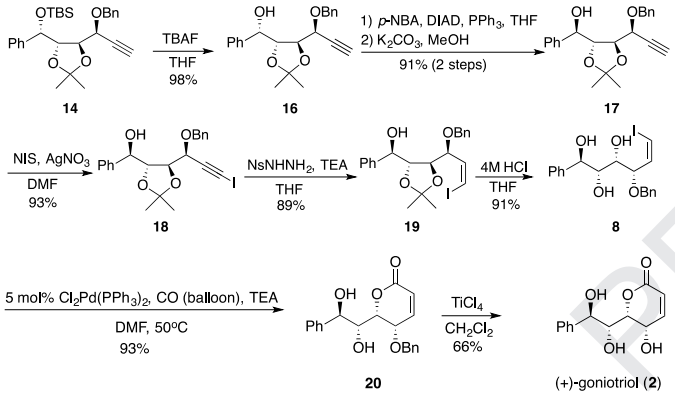
reagent	Conditions	Ratio **13a** : **13b**	Yield %
LS-Selectride	THF, −20 °C, 0.5 h	63 : 37	79
9-BBN, (+)-a-pinene	THF, rt, 13 h	−	decomp.
$LiAlH_4$	THF, 0 °C, 0.5 h	−	decomp.
DIBALH	THF, −40 °C, 1 h	55 : 45	85
$NaBH_4$, $CeCl_3$	MeOH, −78 °C, 2.5 h	32 : 68	88
L-Selectride	THF, −78 °C, 0.5 h	58 : 42	44
$NaBH(OAc)_3$	THF, 0 °C, 24 h	52 : 48	80
(*S*)-CBS (0.2 eq.), BH_3 · DMS (2.0 eq.)	THF, −20 °C, 24 h	31 : 69	88
(*R*)-CBS (0.5 eq.), BH_3 · DMS (1.2 eq.)	THF, −30 to −20 °C, 1.5 h	88 : 12	78

As shown in Table 1, stereoselective reduction of the keto group was rather difficult. However, using the (*S*)-CBS catalyst[19] and borane dimethyl sulfide complex gave some stereoselectivity. Thus, we optimized the reaction conditions to synthesize **13a** in a stereoselective manner (Electronic Supporting information (ESI), Table. S1). Using 0.5 eq. of the (*R*)-CBS catalyst and 1.2 eq. of the borane dimethyl sulfide complex afforded **13a**:**13b** at a ratio of 88:12. The ratio of **13a**:**13b** was determined by isolation yield. Compound **13a** was purified using silica gel column chromatography. The absolute configuration of the newly formed chiral center of **13a** was confirmed using the advanced Mosher method (ESI, Fig. S2).[18] Undesired **13b** was converted to **13a** using the Mitsunobu reaction.[20] The hydroxy group of **13a** was protected as a benzyl ether afforded **14**. Introduction of the iodide group to **14** using NIS in the presence of $AgNO_3$ furnished **5**. The diimide reaction of **5** using $NsNHNH_2$ and subsequent deprotection of the acetonide and TBS group under acidic condition afforded the cyclization precursor **4** (Scheme 2).

With the cyclization precursor **4** to hand, Pd-catalyzed carbonylation of **4** was performed. As shown in Scheme 3, using $Cl_2Pd(PPh_3)_2$ as a catalyst (5 mol%) and Et_3N (1.2 eq.) as a base under a balloon pressure of CO atmosphere at 50°C afforded **16** in 83% yield. Deprotection of the benzyl ether of **16** using $TiCl_4$ afforded 7-*epi*-goniotriol (**3**).[11] Finally, treatment of **3** with DBU furnished (+)-goniopypyrone (**1**) (Scheme 3). The spectral and physicochemical data of synthetic **1** are in good agreement with those of the reported values.[7]



Scheme 3. Synthesis of (+)-goniopypyrone (1).



Scheme 4. Synthesis of (+)-goniotriol (**2**).

Synthesis of (+)-goniotriol (**2**) utilizing similar Pd-catalyzed carbonylation as the key step is as follows (Scheme 4). Treatment of **14** with TBAF afforded alcohol **16**. Mitsunobu reaction of the secondary hydroxyl group of **16** furnished **17** with a yield of 91 % yield. Introduction of the iodide group of **17** using NIS in the presence of $AgNO_3$ furnished **18**. The diimide reaction of **18** using $NsNHNH_2$ and subsequent deprotection of the acetonide group under acidic condition afforded cyclization precursor **8**. Pd-catalyzed carbonylation of **8** afforded **20** in high yield. Deprotection of the benzyl ether of **20** using $TiCl_4$ afforded (+)-goniotriol (**2**) (Scheme 4). The spectral and physicochemical data of synthetic **2** are in good agreement with those of the reported values.[11]

In conclusion, (+)-goniopypyrone (**1**) and (+)-goniotriol (**2**) were synthesized through 14 steps in 8.5% and 16 steps in 11%, respectively. The key reaction was Pd-catalyzed carbonylation to construct lactone ring. This synthetic strategy should be a useful for synthesizing other styryl lactones.

Conflict of interest

The authors declare no conflicts of interest.

Acknowledgments

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Supplementary Material

Supplementary data associated with this article can be found, in the online version at doi:

Synthesis of (+)-goniopypyrone and (+)-goniotriol was accomplished.

The lactone ring was constructed using Pd-catalyzed carbonylation.

Diastereoselective reduction of ynone was accomplished using (*R*)-CBS catalyst.