ORGANIC LETTERS

2011
Vol. 13, No. 7
1796–1799

Total Syntheses of (−)- and (+)-Goniomitine

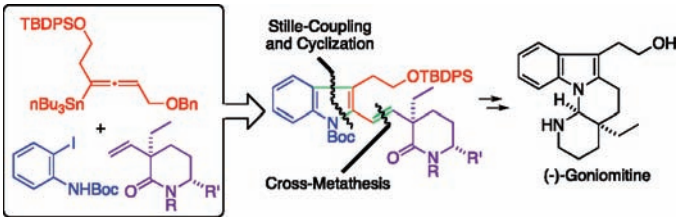
Masaya Mizutani, Fuyuhiko Inagaki, Takeo Nakanishi, Chihiro Yanagihara, Ikumi Tamai, and Chisato Mukai*

Division of Pharmaceutical Sciences, Graduate School of Natural Science and Technology, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan

cmukai@kenroku.kanazawa-u.ac.jp

Received February 2, 2011

ABSTRACT



The Stille coupling reaction of 3-(benzyloxymethyl)-1-(*tert*-butyldiphenylsiloxy)ethyl-1-(tributylstannyl)allene with *N*-(*tert*-butoxycarbonyl)-2-iodoaniline directly produced the corresponding 2-vinylindole derivative, which was independently transformed into natural (−)-goniomitine and unnatural (+)-goniomitine via the cross-metathesis with chiral oxazolopiperidone lactams. The antiproliferative activity of the synthesized natural (−)-goniomitine in Mock and MDCK/MDR1 cells showed them to be more potent to retard cell growth than unnatural (+)-goniomitine.

(−)-Goniomitine (**1**), isolated from the root bark of *Gonioma malagasy*[1] in 1987, is a significantly unique member of the Aspidosperma indole alkaloid family. In 1991, Takano and Ogasawara[2] reported the first total synthesis of this intriguing alkaloid in an optically active form from dicyclopentadiene in 28 steps. The recent independent records from Pagenkopf's[3] and Waser's[4] laboratories showed two additional efficient total syntheses of goniomitine in a racemic form: Pagenkopf's synthesis[3] involved the formal [3 + 2] cycloaddition between the nitrile and cyclopropane derivatives as the crucial step, whereas Waser and co-workers[4] successfully took advantage of the selective cyclization of aminocyclopropane.

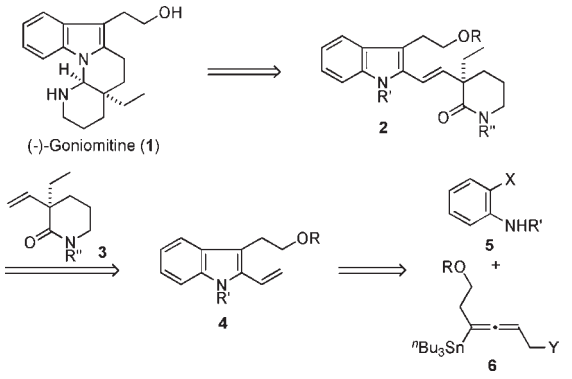
Of particular interest is the first investigation on the bioactivity of goniomitine reported by Waser and co-workers.[4] The preliminary biological assessment indicated that racemic goniomitine displays nanomolar antiproliferative effects on several tumor cell lines. Among them, it should be emphasized that the racemic goniomitine does not lose its effect in the resistant MDR-1-MDCK cell line unlike the well-known taxol and vinblastine. These biological studies regarding the cytotoxicity of racemic goniomitine strongly attracted and inspired us to develop an efficient alternative method for the preparation of the optically active goniomitine for its further biological evaluations. We now describe (i) the novel and efficient total synthesis of (−)-goniomitine (**1**) and its enantiomer by a convergent strategy, which is completely different from the three previous total syntheses, and (ii) comparison of biological activity between (−)- and (+)-goniomitine. The significant feature of this new synthesis consists of (i) a novel method for the construction of the 3-alkyl-2-vinylindole skeleton **4** from the reaction of the stannylallene **6** with the aniline derivative **5**, and (ii) the consecutive cross-metathesis of **4** with the 3-vinylpiperidinone derivative **3** leading to the indole-piperidone derivative **2**, possessing an all-carbon framework of the target natural product (Scheme 1).

3-(Benzyloxymethyl)-1-(*tert*-butyldiphenylsiloxy)ethyl-1-(tributylstannyl)allene (**9**), which is required for the preparation of 2-vinylindole, was synthesized from the

(1) Randriambola, L.; Quirion, J.-C.; Kan-Fan, C.; Husson, H.-P. *Tetrahedron Lett.* **1987**, *28*, 2123–2126.
(2) Takano, S.; Sato, T.; Inomata, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1991**, 462–464.
(3) Morales, C. L.; Pagenkopf, B. L. *Org. Lett.* **2008**, *10*, 157–159.
(4) Simone, F. D.; Gertsch, J.; Waser, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 5767–5770.
(5) Nacro, K.; Baltas, M.; Gorrichon, L. *Tetrahedron* **1999**, *55*, 14013–14030.

10.1021/ol200320z
Published on Web 03/04/2011

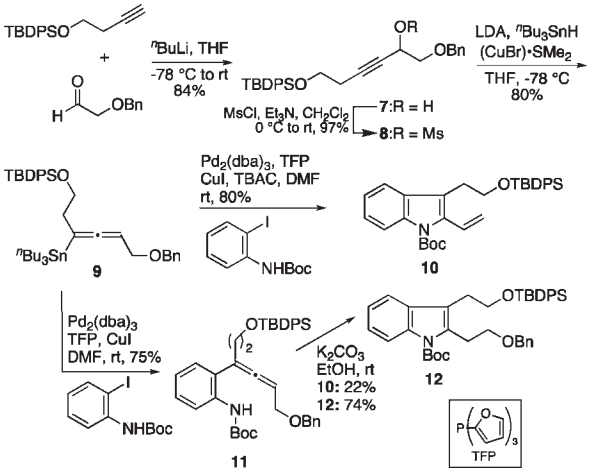
Scheme 1. Retrosynthesis of (−)-Goniomitine



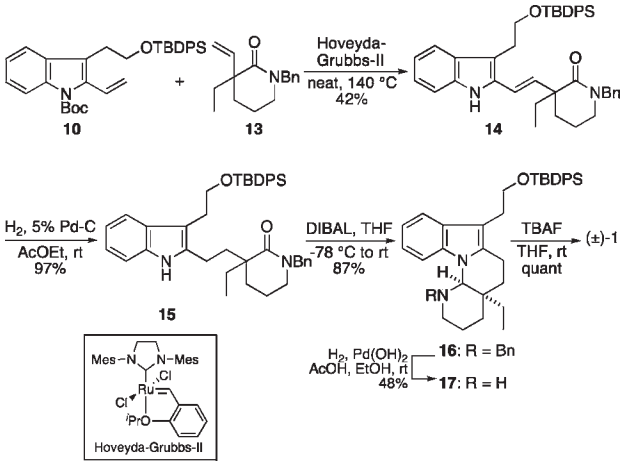
following three-step procedure in high yields. The reaction of 1-(*tert*-butyldiphenylsiloxy)but-3-yne[5] with commercialy available benzyloxyacetaldehyde under basic conditions gave the condensed product **7** in 84% yield. The activation of the resulting secondary hydroxyl group of **7** was performed by treatment with mesyl chloride to afford **8** in 97% yield, which was subsequently exposed to tributyltin hydride under Marshall's conditions[6] to produce the (tributylstannyl)allene **9** in 80% yield. We next examined the preparation of the indole skeleton using our own recently developed procedure.[7] Thus, the Stille coupling reaction of *N*-(*tert*-butoxycarbonyl)-2-iodoaniline with the (tributylstannyl)allene **9** was carried out in the presence of tetrabutylammonium chloride (TBAC) to afford the 3-(2-siloxyethyl)-2-vinylindole **10** directly instead of the expected **12** in 80% yield in one operation. This transformation should involve the initial formation of the allenylaniline derivative **11**, followed by the intramolecular S_N2'-type ring-closing reaction accompanied by the elimination of a benzyloxy group. When this ring-closing reaction was carried out in the absence of TBAC, the formation of the allenylaniline derivative **11** was obtained in 75% yield as the sole product, which was subsequently converted into **10** and **12** by base treatment (Scheme 2).

Prior to the complete total synthesis of natural (−)-goniomitine (**1**), our effort focused on the total synthesis of (±)-goniomitine as a preliminary study. The racemic 3-vinylpiperidin-2-one derivative **13**, a counterpart of the cross-metathesis with **10**, was easily accessible from the known 1-benzyl-3-ethyl-3-hydroxyethylpiperidin-2-one[3] by a dehydration reaction under Grieco's conditions[8] (Scheme 3). After screening several conditions, the neat Hoveyda−Grubbs-II catalyst[9] (30 mol %) at 140 °C was

Scheme 2. Synthesis of 2-Vinylindole Derivative **10**



Scheme 3. Completion of Total Synthesis of (±)-Goniomitine (**1**)



found to effect the cross-metathesis accompanied by the concomitant removal of the *tert*-butoxycarbonyl group producing **14** in 42% yield.[10] Then hydrogenation of **14** under the standard conditions afforded **15** in 97% yield. The construction of the diazabicyclo[4.4.0] framework was the next task for completion of the total synthesis of racemic **1**. The treatment of **15** with diisobutylaluminum hydride (DIBAL)[11] effected the conversion of the lactam functional group to the cyclic imminium group, which was immediately captured by the nitrogen atom of the indole from the opposite face of the angular ethyl group to avoid any serious nonbonding interaction, resulting in the exclusive formation of the tetracyclic compound **16** with

(6) (a) Marshall, J. A.; Wang, X.-j. *J. Org. Chem.* **1990**, *55*, 6246–6248. (b) Marshall, J. A.; Wang, X.-j. *J. Org. Chem.* **1992**, *57*, 1242–1252. (c) Marshall, J. A.; Grant, C. M. *J. Org. Chem.* **1999**, *64*, 8214–8219.

(7) Mukai, C.; Takahashi, Y. *Org. Lett.* **2005**, *7*, 5793–5796.

(8) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485–1486.

(9) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.

(10) The unreacted **13** was recovered and reusable.

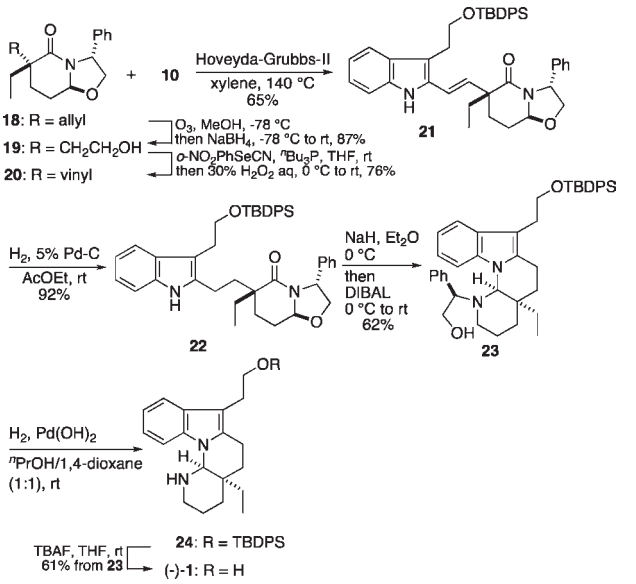
(11) Forns, P.; Diez, A.; Rubiralta, M. *J. Org. Chem.* **1996**, *61*, 7882–7888.

the desired stereochemistry in 87% yield. Debenzylation of **16** under hydrogenolysis conditions afforded **17** in a rather lower yield (48%), which was then transformed into (±)-goniomitine in a quantitative yield as shown in Scheme 3. Thus the new total synthesis of (±)-**1** was achieved, although it is obvious that optimization of the chemical yields, in particular, the conversion of **16** into **17**, still remains.

Our next phase was to complete the convergent total synthesis of the natural (−)-goniomitine (**1**) using the chiral lactam species instead of **13** for the reaction with the 2-vinylindole derivative **10** (Scheme 4). Amat[12] reported a reliable procedure for the preparation of some chiral oxazolopiperidone lactams from phenylglycinol and δ-valerolactone. Thus, the known oxazolopiperidone lactam **18**,[12] prepared by Amat's procedure, was successively treated with ozone and $NaBH_4$ to give the one-carbon shortened **19** in 87% yield, which was then dehydrated under Grieco's conditions, providing the desired vinyllactam **20** in 76% yield. The aforementioned cross-metathesis condition that was effective for the reaction between the indole **10** and the 3-vinylpiperidin-2-one derivative **13** was unfortunately found to be fruitless, but reexamination of the conditions successfully provided a better chemical yield. Namely, a solution of **10** and the vinyllactam **20** in xylene was heated at 140 °C in the presence of 30 mol % of the Hoveyda−Grubbs-II catalyst[9] to furnish **21** in 65% yield.[13] Compound **21** was subsequently hydrogenated to afford **22** in 92% yield. The DIBAL-mediated one-step construction of the tetracyclic framework described in the transformation of **15** to **16** did not work in the case of **22**, and no reaction took place, presumably due to the serious steric congestion around the lactam. We tentatively assumed that the nitrogen anion derived from **22** by base treatment might coordinate with DIBAL, leading to the formation of certain ate-complexes, which should be more powerful hydride sources than DIBAL itself. On the basis of this assumption, several bases were added to **22** before treating with DIBAL. As a result, sodium hydride gave the best result in which the tetracyclic compound **23** was exclusively obtained in 62% yield accompanied by cleavage of the oxazolidine ring. The highly stereoselective construction of the diazabicyclo[4.4.0] framework was again achieved similar to the case of **16**. Removal of the protecting groups on both the nitrogen and oxygen atoms of **23** produced (−)-goniomitine (**1**) in 61% yield. Furthermore, the synthetic route in Scheme 4 with use of *ent*-**20** instead of **20** also afforded the unnatural (+)-goniomitine.

With natural, unnatural, and racemic goniomitine now in hand, we executed their preliminary bioactive assay as follows. To determine whether goniomitine is effluxed by human P-glycoprotein (P-gp, a gene product of MDR1), antiproliferative activity of goniomitine was studied in canine kidney MDCK II with enforced expression of P-gp (MDCK/MDR1) and Mock-transfected MDCK II (Mock) cells. As

Scheme 4. Completion of Total Synthesis of (−)-Goniomitine (**1**)



shown in Table 1 and in Figure 1 in the Supporting Information, no significant increase in 50% growth inhibitory concentration (IC_{50}) of (+)-, (−)-, and (±)-goniomitine was observed in MDCK/MDR1 as compared with those in Mock cells. However, it is noteworthy that a significant difference between the stereoisomers was found in the antiproliferative activity. The IC_{50} of (−)-goniomitine was 2.40- and 3.18-fold lower than those in Mock and MDCK/MDR1 cells, respectively, whereas the values were very close to those of (±)-goniomitine. This observation suggested that (−)-goniomitine is more potent to retard cell growth than (+)-goniomitine. Although the detailed mechanism of greater antiproliferative activity of (−)-goniomitine needs to be investigated, our establishment of the synthesis of (−)-goniomitine may provide us with a clue to develop novel anticancer agents.

Table 1. Antiproliferative Activity of (+)-, (−)-, and (±)-Goniomitine (**1**)

substrate	cell lines	IC_{50} [μM][a]
(+)-goniomitine	Mock	160.7 ± 28.2
	MDR-1-MDCK	174.8 ± 22.1
(−)-goniomitine	Mock	66.8 ± 8.8
	MDR-1-MDCK	55.3 ± 6.0
(±)-goniomitine	Mock	36.8 ± 7.2
	MDR-1-MDCK	55.7 ± 9.1

[a] IC_{50} values were estimated by fitting proliferation assay data to Hill plot as described in the Supporting Information. Experiments were repeated at least twice with $n = 6$.

In summary, the total syntheses of the natural (−)-goniomitine and unnatural (+)-goniomitine were attained (in 10 steps from the commercially available 3-butyn-1-ol or 13 steps from the commercially available δ-valerolactone)

(12) (a) Amat, M.; Bosch, J.; Hidalgo, J.; Cantó, M.; Pérez, M.; Llor, N.; Molins, E.; Miravitlles, C.; Orozco, M.; Luque, J. *J. Org. Chem.* **2000**, *65*, 3074–3084. (b) Amat, M.; Lozano, O.; Escolano, C.; Molins, E.; Bosch, J. *J. Org. Chem.* **2007**, *72*, 4431–4439.

(13) The unreacted **20** was recovered and reusable.

in a highly stereoselective manner by taking advantage of our procedure for the preparation of 2-vinylindole, followed by its cross-metathesis with the chiral oxazolopiperidone derivative. Furthermore, natural (−)-goniomitine was found to have stronger antiproliferative activity in Mock and MDCK/MDR1 cells than its enantiomer.

Acknowledgment. This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan, for which we are thankful.

Supporting Information Available. Full experimental details, compound characterization data, ^{1}H NMR and ^{13}C NMR spectra for all new compounds described. This material is available free of charge via the Internet at http://pubs.acs.org.