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# Enantioselective Total Synthesis of Convolutamydines B and E

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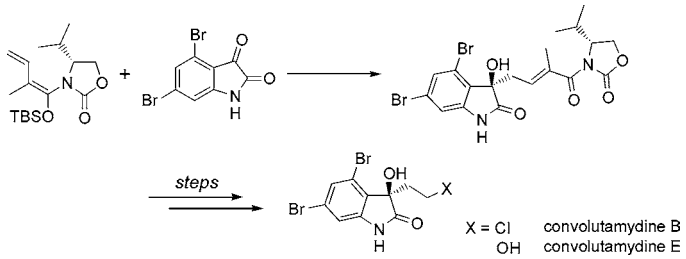
## ABSTRACT




**The first enantioselective total synthesis of convolutamydines B and E has been achieved using our vinylogous Mukaiyama aldol reaction. The synthesis features highly diastereoselective vinylogous Mukaiyama aldol reaction with isatin instead of aldehydes to construct a chiral center of convolutamydines. Additionally, the absolute configuration of natural convolutamydine B has been determined as *R* by its CD spectrum.**

Convolutamydines A−E (**1**−**5**) isolated from the Floridian marine bryozoan *Amathia convoluta* by Kamano et al. are members of a family of oxindole alkaloids having a 4,6-dibromo-3-hydroxyoxindole as a common skeleton (Figure 1).[1] Each convolutamydine differs in a side chain moiety at C-3. Convolutamydines A and B (**1**, **2**) induce the appearance of characteristic features, associated with normally differentiated cells, in the tumor cell line HL-60. The possible biological effects of the other convolutamydines (C−E, **3**−**5**) have not been evaluated due to the scarcity of these derivatives. Furthermore, the stereochemistry of the chiral center at C-3 has not yet been established. The 3*R* configuration was assumed on the basis of the empirical rule for the correlation of CD spectra and absolute configuration proposed by Aimi et al.[2] Although syntheses of convolutamydines (A, C, and E) have already been reported by several groups, these have all been of racemic compounds.[3]

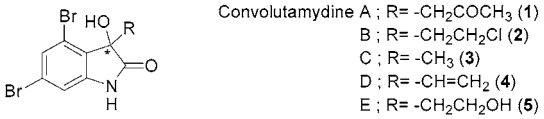



**Figure 1.** Structures of convolutamydines A−E (**1**−**5**).

These facts prompted us to attempt an enantioselective synthesis of convolutamydines in order to determine the absolute stereochemistry as well as to provide these compounds for biological study. The most straightforward approach to this class of compounds is apparently a nucleo-

(1) (a) Kamano, Y.; Zhang, H.-P.; Ichihara, Y.; Kizu, H.; Komiyama, K.; Pettit, G. R. *Tetrahedron Lett.* **1995**, *36*, 2783−2784. (b) Zhang, H.-P.; Kamano, Y.; Ichihara, Y.; Kizu, H.; Komiyama, K.; Itokawa, H.; Pettit, G. R. *Tetrahedron* **1995**, *51*, 5523−5528. (c) Kamano, Y.; Kotake, A.; Hashima, H.; Hayakawa, I.; Hiraide, H.; Zhang, H.-P.; Kizu, H.; Komiyama, K.; Hayashi, M.; Pettit, G. R. *Collect. Czech. Chem. Commun.* **1999**, *64*, 1147−1153.

(2) Takayama, H.; Shimizu, T.; Sada, H.; Harada, Y.; Kitajima, M.; Aimi, N. *Tetrahedron* **1999**, *55*, 6841−6846.

(3) (a) Garden, S. J.; Torres, J. C.; Ferreira, A. A.; Silva, R. B.; Pinto, A. C. *Tetrahedron Lett.* **1997**, *38*, 1501−1504. (b) Miah, S.; Moody, C. J.; Richards, I.; Slawin, A. M. Z. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2405−2412. (c) Jnaneshwara, G. K.; Bedekar, A. V.; Deshpande, V. H. *Synth. Commun.* **1999**, *29*, 3627−3633. (d) Jnaneshwara, G. K.; Deshpande, V. H. *J. Chem. Res., Synop.* **1999**, 632−633. (e) Kawasaki, T.; Nagaoka, M.; Satoh, T.; Okamoto, A.; Ukon, R.; Ogawa, A. *Tetrahedron* **2004**, *60*, 3493−3503.

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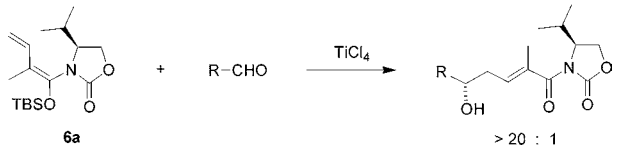
philic addition of an appropriate nucleophile to 4,6-dibromoisatin; however, such a strategy was employed only for the synthesis of convolutamydine A by base-mediated aldol reaction racemic with acetone. To the best of our knowledge, the first example of enantioselective addition (up to 77% ee) to isatin was very recently reported by Tomasini et al. using organocatalysis.[4] We recently developed a highly stereoselective vinylogous Mukaiyama aldol reaction using vinylketene silyl *N*,*O*-acetal **6a** (Scheme 1).[5] Substrates for

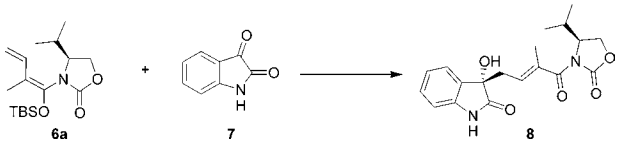
**Scheme 1.** Vinylogous Mukaiyama Aldol Reaction




vinylogous Mukaiyama aldol reaction were limited to aldehydes, and we were also interested in the reaction with isatin derivatives.

Prior to the reaction with 4,6-dibromoisatin, we used isatin **7** as a model substrate in order to establish the optimal conditions (Table 1). As per the previous protocol, titanium

**Table 1.** Optimization of Vinylogous Mukaiyama Aldol Reaction with Isatin (**7**)




| entry | method | isatin (equiv) | $TiCl_4$ (equiv) | concn (mM) | *T* (°C) | yield (%) | dr[a] |
|---|---|---|---|---|---|---|---|
| 1 | A | 2.0 | 2.0 | 10 | −78 to −20 | 32 | 9:1 |
| 2 | A | 4.0 | 2.0 | 5 | −78 to −20 | 60 | 30:1 |
| 3 | A | 6.0 | 2.0 | 5 | −78 to −20 | 90 | 31:1 |
| 4 | A | 6.0 | 3.0 | 5 | −78 to −20 | 50 | 23:1 |
| 5 | B | 6.0 | 2.0 | 5 | −78 | 69 | 60:1 |

[a] Determined by $^1H$ NMR analysis.

tetrachloride (2 equiv) was added to the dichloromethane solution of isatin **7** at −78 °C, followed by the dropwise addition of **6a** (method A). Then the reaction mixture was stirred at −20 °C to obtain **8** in 32% yield. It was quite interesting to find that the reaction proceeded in a stereoselective manner (9:1 ratio).[6]

High yield with excellent selectivity was observed by using an excess of isatin **7** (6 equiv) in 5 mM concentration (entry 3). A large excess of $TiCl_4$ decreased both chemical yield and selectivity (entry 4). However, method A did not afford **8** in a reproducible manner. During these experiments, we observed that the reaction mixture becomes homogeneous when $TiCl_4$ was added. Therefore, we attempted to change the order of addition. Thus, the mixture of isatin **7** and $TiCl_4$ in dichloromethane was stirred at 0 °C for 30 min before addition of **6a** at −78 °C (Method B). This procedure afforded **8** in good yield with excellent selectivity and reproducibility (entry 5). The observed stereoselectivity is noteworthy considering (1) the high degree of remote asymmetric induction and (2) the electrophile is a ketone, albeit it is a part of ketoamide.

$TiCl_4$-mediated reaction of *Z*-vinylketene *N*,*O*-acetal **6b** and isatin **7** was also attempted, producing the corresponding adduct in relatively low yield with a 1.7:1 diastereomeric ratio. These differences in chemical yield and selectivity are in good agreement with the previous results using aldehydes.[5] For the introduction of a C2 unit as the side chain of a convolutamydine, it may be more suitable to introduce an acetate unit rather than crotonate unit. Consequently, isatin **7** was also subjected to an aldol reaction with **6c** and **6d** under typical Evans and Mukaiyama conditions, respectively. In both cases, the corresponding aldol adduct was isolated in relatively low yield with low selectivity as shown in Figure 2. Therefore, only the vinylogous Mukaiyama aldol reaction

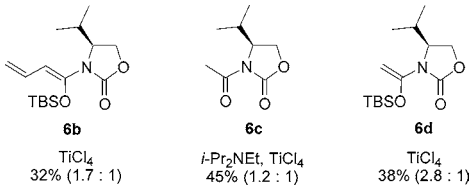



**Figure 2.** Typical nucleophiles for aldol reaction.

using **6a** proceeded in a stereoselective manner.

We reported that vinylketene *N*,*O*-acetal **6a** had a conformation such that the dienolate was orthogonal to the oxazolidin-2-one.[5] Approach of isatin **7** from the upper face of the dienolate plane should be hindered by steric interaction with the isopropyl group of the chiral auxiliary (Figure 3,

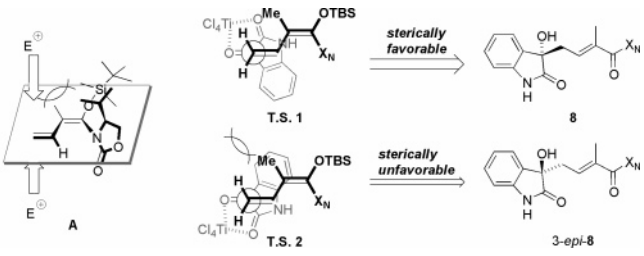



**Figure 3.** Transition states of vinylogous Mukaiyama aldol reaction ($X_N$ = oxazolidinone.)

(4) Luppi, G.; Cozzi, P. G.; Monari, M.; Kaptein, B.; Broxterman, Q. B.; Tomasini, C. *J. Org. Chem.* **2005**, *70*, 7418−7421.

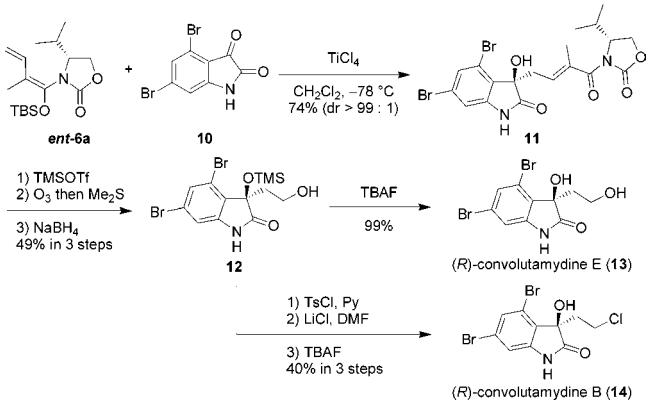
(5) Shirokawa, S.-i.; Kamiyama, M.; Nakamura, T.; Okada, M.; Nakazaki, A.; Hosokawa, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 13604−13605.

(6) See the Supporting Information for determination of the stereochemistry.

**A**). In addition, transition state 1 (**T.S.1**) is sterically more favorable than transition state 2 (**T.S.2**) because in **T.S.2** the methyl group at the α-position of vinylketene *N*,*O*-acetal **6a** can sterically interact with the aromatic ring of isatin **7** (Figure 3).

With optimal conditions established, we next applied the present protocol to the total syntheses of both enantiomers of convolutamydines E and B and to the determination of their absolute configurations. According to Aimi's estimation,[2] we first attempted the synthesis of (*R*)-convolutamydines which would be synthesized from 4,6-dibromoisatin **9**[7] and vinylketene *N*,*O*-acetal *ent*-**6a** derived from D-valine (Scheme 2).

**Scheme 2.** Total Synthesis of Convolutamydines B and E




The vinylogous Mukaiyama aldol reaction of 4,6-dibromoisatin **9** and *ent*-**6a** proceeded smoothly to afford aldol adduct **10** quantitatively almost as a single isomer. Aldol adduct **10** was then converted into a common intermediate **11** in three steps. (*R*)-Convolutamydine E (**12**) was obtained from **11** by removal (99%) of the TMS group in **11**.[6] The synthesis of (*R*)-convolutamydine B (**13**) was also achieved by the simple transformations from **11** [tosylation, chlorination, followed by desilylation (40% yield in three steps)]. In the same manner, (*S*)-convolutamydines B (*ent*-**13**) and E (*ent*-**12**) were also synthesized from vinylketene *N*,*O*-acetal **6a** derived from L-valine. In all cases, the synthetic convolutamydines were in high enantiomeric excess (>97% ee) as determined by chiral HPLC analyses, and spectral data ($^1$H and $^{13}$C NMR) and HRMS data were identical with those of natural products.

(7) (a) Shepherd, R. G. *J. Org. Chem.* **1947**, *12*, 275−283. (b) Carlin, R. B.; Forshey, W. O., Jr. *J. Am. Chem. Soc.* **1950**, *72*, 793−801. (c) Sandmeyer, T. *Helv. Chim. Acta* **1919**, *2*, 234−242.

With both enantiomers in hand, we next attempted to determine the absolute configurations of convolutamydines B and E by the comparison of the optical rotations.[1b,c] However, the $[\alpha]_D$ value of **13** and *ent*-**13** ($[\alpha]^{28}_D$ <1 for both **13** and *ent*-**13**) were much lower than the reported data ($[\alpha]^{25}_D$ +18) for natural convolutamydine B.[1b] Despite the disagreement of these optical rotations, the CD spectrum of *R*-isomer **13** was perfectly matched with that of the natural product; **13** exhibits a negative Cotton effect in the long-wave region (285−245 nm) and a positive effect in the short-wave region (245−210 nm), while *ent*-**13** exhibits exactly the opposite behavior (Figure 4). Accordingly, convolutamydine B was unambiguously established as *3R*. Unfortunately, neither the $[\alpha]_D$ value nor the CD spectrum of convolutamydine E have been reported, so we have been unable to determine the absolute configuration of convolutamydine E.

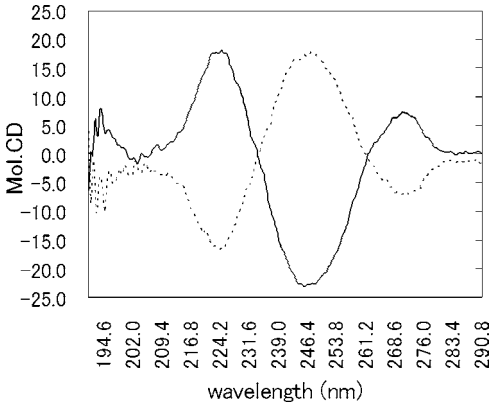



**Figure 4.** CD spectra of **13** (*R*-isomer, solid curve) and *ent*-**13** (*S*-isomer, dashed curve).

In summary, we have developed a highly stereoselective addition to a isatin derivative for the first time by vinylogous Mukaiyama aldol reaction. We also achieved the enantioselective synthesis of convolutamydines B and E and determined the absolute configuration of convolutamydine B.

**Acknowledgment.** We thank Prof. Kenso Soai and Dr. Itaru Sato (Tokyo University of Science) for the measurement of circular dichroism spectra.

**Supporting Information Available:** Detail experimental procedure and characterization data for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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