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Diastereoselective Intramolecular Carbamoylketene/Alkene [2 + 2] Cycloaddition: Enantioselective Access to Pyrrolidinoindoline Alkaloids

Takaaki Araki, Tsukasa Ozawa, Hiromasa Yokoe, Makoto Kanematsu, Masahiro Yoshida, and Kozo Shishido*

Graduate School of Pharmaceutical Sciences, The University of Tokushima, 1-78-1 Sho-machi, Tokushima 770-8505, Japan

shishido@ph.tokushima-u.ac.jp

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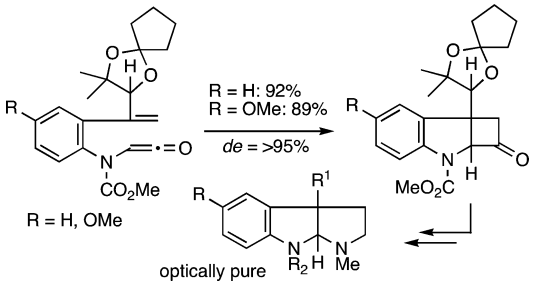
ABSTRACT

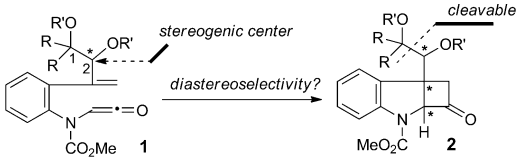


A novel and highly diastereoselective intramolecular carbamoylketene/alkene [2 + 2] cycloaddition has been developed, and the methodology was successfully applied to the enantioselective syntheses of (−)-esermethole and Takayama's intermediate for (+)-psychotrimine.

In previous papers, we have described the syntheses of alkaloids with tetrahydrofuro[2,3-*b*]indole and hexahydropyrrolo[2,3-*b*]indole skeletons employing an intramolecular carbamoylketene/alkene [2 + 2] cycloaddition reaction as the key step.[1] The chemical yield obtained in the cycloaddition is uniformly high, and the subsequent transformations proceed smoothly and selectively to give the alkaloids or the key intermediates.

We thought it important to make the reaction asymmetric. Accordingly we designed a substrate-controlled diastereoselective process.[2] We chose the optically active substrate **1**, which contains the but-3-ene-1,2-diol moiety with a tertiary stereogenic center at the allylic position (C2). The chiral auxiliary would serve to induce chirality at the newly generated benzylic quaternary stereogenic center, and we anticipated that the substituent (R at C1 in **1**) would play an important role in obtaining higher diastereoselectivity in **2**. In addition, the 1,2-diol functionality would facilitate the transformation to a variety of functional groups, e.g., via an oxidative cleavage of the diol moiety (Scheme 1).

Scheme 1. Substrate for Diastereoselective Cycloaddition



In this report, we describe a highly diastereoselective intramolecular carbamoylketene-alkene [2 + 2] cycloaddition of

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(2) For related reports on the diastereoselective intramolecular [2 + 2] cycloadditions of the substrates with a tertiary stereogenic center on the alkenyl part, see: (a) Corey, E. J.; Kang, M.; Desai, M. C.; Ghosh, A. K.; Houpis, I. N. *J. Am. Chem. Soc.* **1988**, *110*, 645–651. (b) Cholerton, T. J.; Collington, E. W.; Finch, H.; Williams, D. *Tetrahedron Lett.* **1988**, *29*, 3369–3372. (c) Corey, E. J.; Rao, K. S. *Tetrahedron Lett.* **1991**, *32*, 4623–4626. (d) Monache, G. D.; Misiti, D.; Salvatore, P.; Zappia, G.; Pierini, M. *Tetrahedron: Asymmetry* **2000**, *11*, 2653–2659.

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the substrate with a chiral auxiliary on the alkenyl unit and application of the methodology to the enantioselective syntheses of (−)-esermethole[1c,3] and the key intermediate for the trimeric indole alkaloid (+)-psychotrimine.[4] Our retrosynthetic analysis of the ketene precursors **3a**−**d** chosen to evaluate the diastereoselection during the cycloaddition is outlined in Figure 1. The aniline derivatives **4a**−**d**, which can be converted to **3a**−**d** in the usual manner,[1] would be prepared by the Suzuki−Miyaura coupling[5] of the aminophenylboronates **5a**,**b**[6] and the corresponding optically active vinyl bromides **6a**−**d**, among which **6a**,**c** are known in the literature.[7]

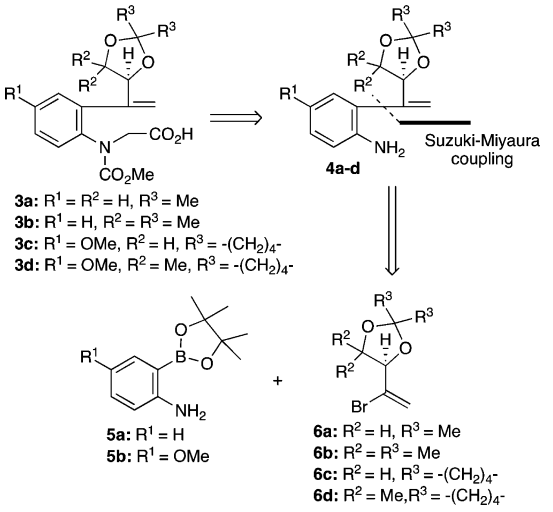
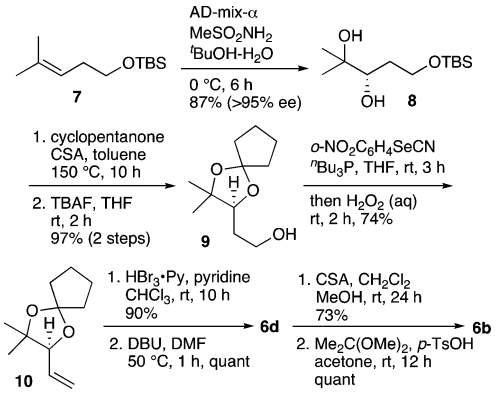


Figure 1. Retrosynthesis of the ketene precursors (**3a**−**d**).

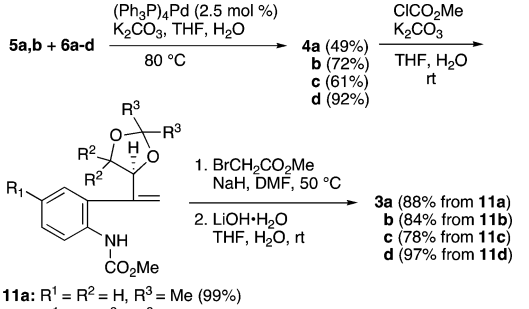
The optically active dimethylated dioxolanes **6b**,**d** were prepared as shown in Scheme 2. Asymmetric dihydroxylation of **7**[8] provided the enantiomerically pure diol **8**,[9] which was treated with cyclopentanone under acidic conditions, followed by desilylation to give the alcohol **9**. On exposure to Nishizawa−Grieco conditions, it afforded **10** which was converted to the vinyl bromide (*R*)-**6d** by bromination and then dehydrobromination.[10] The (*R*)-**6b** was derived from **6d** by sequential deacetalization and acetonide formation (Scheme 2).

Scheme 2. Preparation of Optically Pure Dioxolanes (**6b,d**)



Preparation of the carboxylic acids **3a**−**d** is shown in Scheme 3. Thus, treatment of **5a** with **6a**,**b** in the presence of $(Ph_3P)_4Pd$ and K_2CO_3 in aqueous THF provided **4a,b**. These were sequentially subjected to carbomethoxylation, alkylation, and alkaline hydrolysis[1] to produce (*S*)-**3a**,**b**. The dimethylated analogs (*S*)-**3c**,**d** were prepared efficiently via a similar sequence of reactions as that for the preparation of **3a**,**b** (Scheme 3).

Scheme 3. Syntheses of Carboxylic Acids **3a**−**d**



(3) For asymmetric syntheses, see: (a) Takano, S.; Goto, E.; Hirama, M.; Ogasawara, K. *Chem. Pharm. Bull.* **1982**, *30*, 2641–2643. (b) Takano, S.; Moriya, M.; Iwabuchi, Y.; Ogasawara, K. *Chem. Lett.* **1990**, 109–112. (c) Takano, S.; Sato, T.; Inomata, K.; Ogasawara, K. *Heterocycles* **1990**, *31*, 411–414. (d) Takano, S.; Moriya, M.; Ogasawara, K. *J. Org. Chem.* **1991**, *56*, 5982–5984. (e) Lee, T. B. K.; Wong, G. S. K. *J. Org. Chem.* **1991**, *56*, 872–875. (f) Node, M.; Itoh, A.; Masaki, Y.; Fuji, K. *Heterocycles* **1991**, *32*, 1705–1707. (g) Yu, Q.; Luo, W.; Li, Y.; Brossi, A. *Heterocycles* **1993**, *36*, 1279–1285. (h) Ashimoto, A.; Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Org. Chem.* **1993**, *58*, 6949–6951. (i) Pallavicini, M.; Valoti, E.; Villa, L.; Lianza, F. *Tetrahedron: Asymmetry* **1994**, *5*, 111–116. (j) Pallavicini, M.; Valoti, E.; Villa, L.; Resta, I. *Tetrahedron: Asymmetry* **1994**, *5*, 363–370. (k) Fuji, K.; Kawabata, T.; Ohmori, T.; Shang, M.; Node, M. *Heterocycles* **1998**, *47*, 951–964. (l) Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6500–6503. (m) Ashimoto, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488–6499. (n) Kawabata, M.; Nishida, A.; Nakagawa, M. *Org. Lett.* **2000**, *2*, 675–678. (o) Tanaka, K.; Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **2001**, *42*, 1049–1052. (p) Huang, A.; Kodanko, J. J.; Overman, L. E. *J. Am. Chem. Soc.* **2004**, *126*, 14043–14053. (q) Nishida, A.; Ushigome, S.; Sugimoto, A.; Arai, S. *Heterocycles* **2005**, *66*, 181–185. (r) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2006**, *128*, 4590–4591. (s) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314–6315. (t) Nakao, Y.; Ebata, S.; Yada, A.; Hiyama, T.; Ikawa, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2008**, *130*, 12874–12875. (u) Bui, T.; Syed, S.; Barbas, C. S., III. *J. Am. Chem. Soc.* **2009**, *131*, 8758–8759. (v) Trost, B. M.; Zhang, Y. *Chem.—Eur. J.* **2011**, *17*, 2916–2922. (w) Schammel, A. W.; Chiou, G.; Garg, N. K. *J. Org. Chem.* **2012**, *77*, 725–728.

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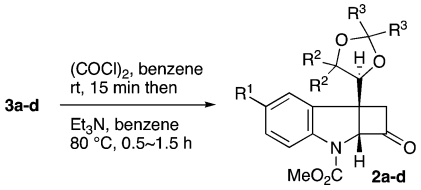
(5) For a review, see: Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.

With the ketene precursors **3a**−**d** in hand, we advanced to the key [2 + 2] cycloaddition. Treatment of **3a** with oxalyl chloride in benzene followed by triethylamine provided the cycloadduct **2a** as an inseparable mixture of diastereoisomers in a ratio of 9:1 in 45% yield (entry 1). However, we anticipated, and indeed found, that the cycloaddition of the alkenyl ketene generated from **3b** resulted in **2b** as a single product in 71% yield (entry 2). In the case of **3c**,**d**, which possess a cyclic acetal moiety, similar diastereoselections were observed and the cycloadducts **2c**,**d** were obtained in higher yields of 81% and 89%, respectively (entries 3 and 4). Thus, we were able to establish a novel diastereoselective process for obtaining the optically pure tricyclic compound (Table 1).

Table 1. [2 + 2] Cycloaddition



entry	carboxylic acid	product	R^1	R^2	R^3	yield (%)	dr[a]
1	**3a**	**2a**	H	H	Me	45	9:1
2	**3b**	**2b**	H	Me	Me	71	1:0
3	**3c**	**2c**	OMe	H	-$(CH_2)_4$-	81	5:1
4	**3d**	**2d**	OMe	Me	-$(CH_2)_4$-	89	1:0

[a] Determined by ^{1}H NMR

The mechanism for the exclusive formation of the cycloadducts **2b**,**d** could be explained by considering the transition states $\mathbf{T_1}$ and $\mathbf{T_2}$, in which the alkenyl moiety with a chiral auxiliary would take the conformation (Ha−C_3−C_2−C_1 is in the same plane) minimizing the allylic strain. As we expected, the bulkiness of the substituent R on the dioxolane ring played an important role in the transition state $\mathbf{T_2}$, in which the R group significantly interacts with the ketene moiety. Therefore, the cycloadditions of the alkenyl ketenes generated from (*S*)-**3b**,**d** resulted in the predominant formation of **2b**,**d** with the (*R*,*R*,*S*) configuration (Figure 2). The absolute configurations of the cycloadducts were confirmed by the following transformation of **2d** to (−)-esermethole (**16**) as shown in Scheme 4.

To test the applicability of this methodology and to confirm the absolute configuration of the cycloadduct, we

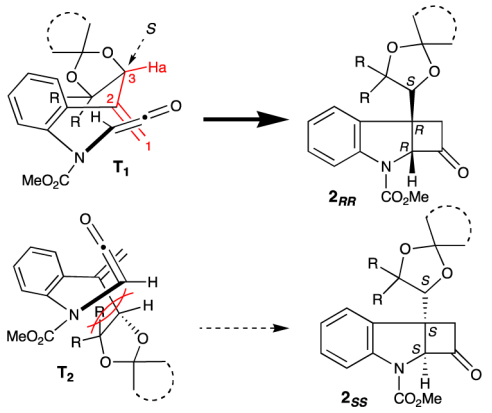
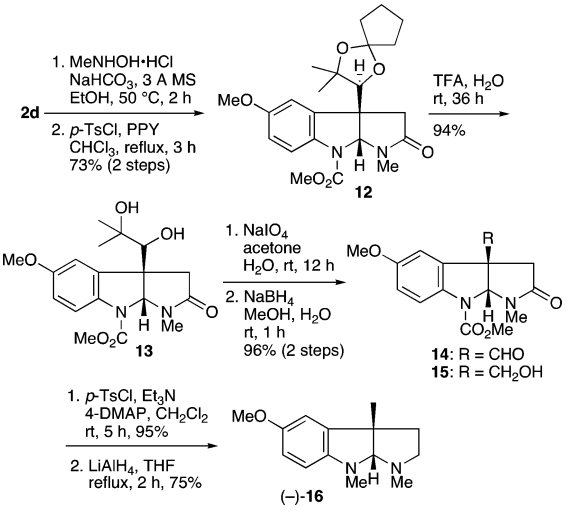


Figure 2. Presumed mechanism for diastereoselection.

examined the conversion of **2d** to (−)-esermethole (**16**). Treatment of **2d** with *N*-methylhydroxylamine hydrochloride, $NaHCO_3$, and 3 A molecular sieves in ethanol at 50 °C provided the nitrone,[11] which, without purification, was immediately reacted with *p*-TsCl and 4-pyrrolidinopyridine (PPY) in refluxing chloroform to give **12**. After acidic hydrolysis, the resulting diol **13** was exposed to oxidative cleavage conditions to produce the aldehyde **14**, which was reduced with $NaBH_4$ to give the alcohol **15**. Tosylation followed by reduction with $LiAlH_4$ provided (−)-esermethole (**16**), whose spectral properties and optical rotation were identical with those reported in the literature.[3b] Thus, the absolute configuration of the cycloadduct obtained diastereoselectively was firmly established to be (*R*,*R*,*S*) as we had expected (Scheme 4).

Scheme 4. Synthesis of (−)-Esermethole (**16**)



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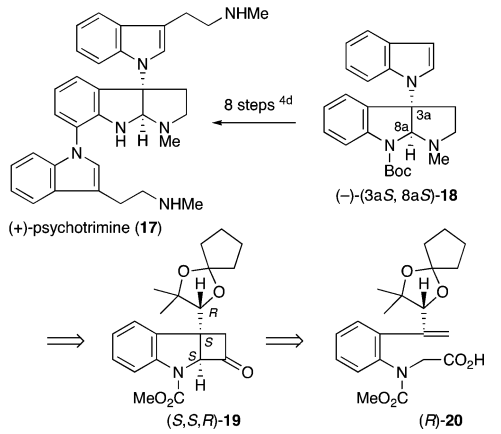


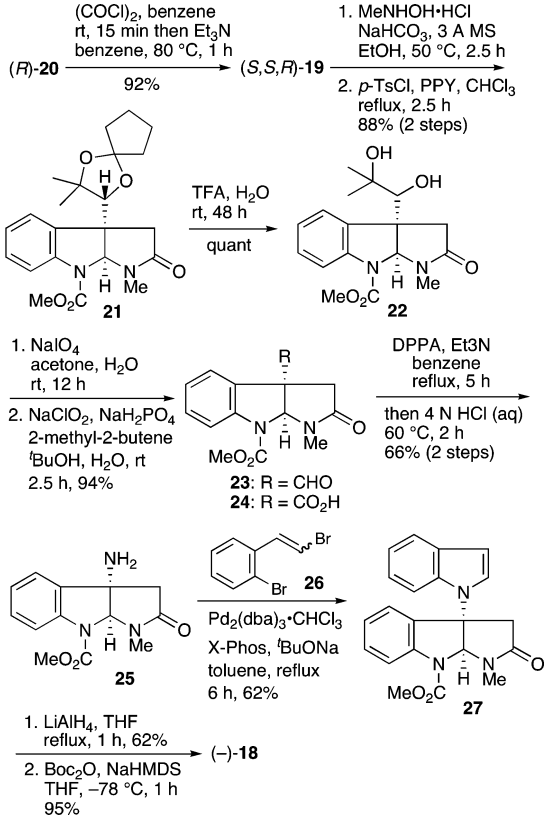
Figure 3. Retrosynthesis of the Takayama's intermediate **18**.

We also applied this method to the synthesis of the alkaloid (+)-psychotrimine (**17**), which was isolated from *Psychotria rostrata* by Takayama et al. in 2004,[4a] and which exhibits antibacterial activity against Gram-positive bacteria and acts via membrane disruption.[12] Several synthetic reports have been published so far,[4b–e] including the first enantioselective total synthesis by Takayama et al.[4d] that established the absolute structure. In the Takayama's enantioselective synthesis, the 3a-indole-substituted pyrrolidinoindoline (**18**) was shown to be a key intermediate, which was converted via an eight-step sequence to (+)-psychotrimine (**17**) uneventfully. Therefore, we attempted the transformation of (*S*,*S*,*R*)-**19**, which can be derived from (*R*)-**20**, to (−)-(3a*S*, 8a*S*)-**18** (Figure 3).

The carboxylic acid (*R*)-**20** was subjected to ketene-forming conditions to provide exclusively the (*S*,*S*,*R*)-**19**. This was then converted to the aldehyde **23** *via* **21** and **22** through the same sequence of reactions described in Scheme 4. Oxidation followed by the Shioiri–Curtius rearrangement of **24** gave the amine **25**, which was exposed to the indole-forming conditions[13] with 1-bromo-2-(2-bromovinyl)benzene (**26**)[14] to furnish the indole **27**. Finally, reduction followed by Boc-protection produced (−)-**18**, whose spectral properties and optical rotation were identical with those reported[4d] (Scheme 5).

In summary, a novel and highly diastereoselective intramolecular carbamoylketene/alkene [2 + 2] cycloaddition

Scheme 5. Synthesis of Takayama's Intermediate **18**



has been developed and the methodology was successfully applied to the enantioselective syntheses of (−)-esermethole and Takayama's intermediate of (+)-psychotrimine. The diastereoselective cycloaddition methodology developed here permitted access to both enantiomeric products, in which the chiral dioxolane moiety can efficiently serve for further transformations and functionalization, and it could also be applied to the enantioselective synthesis of other related alkaloids with more complicated molecular structures.

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Supporting Information Available. Experimental procedures and characterization data for the new compounds are included. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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