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Synthesis of Hexahydropyrrolo[2,3-*b*]indole Alkaloids Based on the Aza-Pauson−Khand-Type Reaction of Alkynecarbodiimides

Daisuke Aburano, Tatsunori Yoshida, Naoki Miyakoshi, 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

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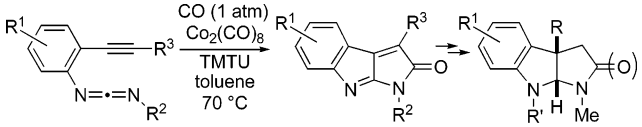
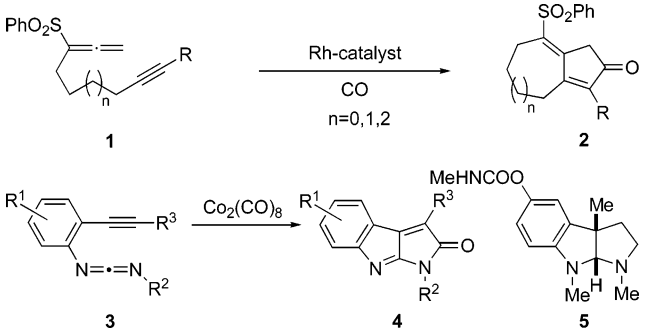


Upon treatment with 30 mol % of $Co_2(CO)_8$ and 30 mol % of TMTU in toluene at 70 °C, benzene-bridged alkynecarbodiimides efficiently underwent a ring-closing reaction to give the pyrrolo[2,3-*b*]-indol-2-ones in good yields. These conditions could nearly suppress the formation of the urea derivatives, which were consistently observed when 10 mol % of $Co_2(CO)_8$ and 60 mol % of TMTU in benzene were used. The synthesis of the eight hexahydropyrrolo[2,3-*b*]indole alkaloids was accomplished from the resulting pyrrolo[2,3-*b*]indol-2-ones via the introduction of an angular substituent at the C_{3a}-position by treatment with $NaBH_4$/alkyl bromide as the crucial step.

Introduction

We have recently been investigating the intramolecular Pauson−Khand-type reaction (PKTR) of phenylsulfonyl-allenynes **1** resulting in the development of an efficient method[1] for the construction of the 2-phenylsulfonylbicyclo[5.3.0]deca-1,7-dien-9-one **2** ($n = 1$) as well as the 2-phenylsulfonylbicyclo-[4.3.0]nona-1,6-dien-8-one **2** ($n = 0$) skeletons. This procedure was also shown to be used for the preparation of the larger-sized 2-phenylsulfonylbicyclo[6.3.0]undeca-1,8-dien-10-ones **2** ($n = 2$).[2] As an extension of our work in this area, we found in the previous paper[3] that the carbodiimide group of the benzene-bridged alkynecarbodiimide compounds **3**, an isoelectronic diaza-alternative of the allene functionality, serves as one of the π bond components in the PKTR under $Co_2(CO)_8$-catalyzed conditions[4] to give the corresponding pyrrolo[2,3-*b*]indol-2-ones **4** in low to moderate yields (Scheme 1). The resulting pyrrolo-

SCHEME 1



[2,3-*b*]indol-2-one derivative could successfully be converted into the calabar bean alkaloid, (±)-physostigmine (**5**), a representative hexahydropyrrolo[2,3-*b*]indole alkaloid. We now describe in detail the further investigation of the $Co_2(CO)_8$-catalyzed aza-PKTR of alkynecarbodiimides and its application to the total synthesis of several hexahydropyrrolo[2,3-*b*]indole alkaloids.

Results and Discussion

Yang and co-workers[4] developed a novel intramolecular $Co_2(CO)_8$-catalyzed Pauson−Khand reaction (PKR) of enynes

* To whom correspondence should be addressed. Phone: +81-76-234-4411. Fax: +81-76-234-4410.

(1) (a) Mukai, C.; Nomura, I.; Yamanishi, K.; Hanaoka, M. *Org. Lett.* **2002**, *4*, 1755−1758. (b) Mukai, C.; Nomura, I.; Kitagaki, S. *J. Org. Chem.* **2003**, *68*, 1376−1385. (c) Mukai, C.; Inagaki, F.; Yoshida, T.; Kitagaki, S. *Tetrahedron Lett.* **2004**, *45*, 4117−4121. (d) Mukai, C.; Inagaki, F.; Yoshida, T.; Yoshitani, K.; Hara, Y.; Kitagaki, S. *J. Org. Chem.* **2005**, *70*, 7159−7171. (e) Inagaki, F.; Mukai, C. *Org. Lett.* **2006**, *8*, 1217−1220. (f) Inagaki, F.; Kawamura, T.; Mukai, C. *Tetrahedron* **2007**, *63*, 5154−5160.

(2) Mukai, C.; Hirose, T.; Teramoto, S.; Kitagaki, S. *Tetrahedron* **2005**, *61*, 10983−10994.

(3) Mukai, C.; Yoshida, T.; Sorimachi, M.; Odani, A. *Org. Lett.* **2006**, *8*, 83−86.

(4) Tang, Y.; Deng, L.; Zhang, Y.; Dong, G.; Chen, J.; Yang, Z. *Org. Lett.* **2005**, *7*, 593−595.

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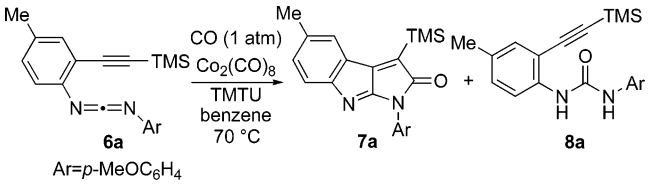
TABLE 1. $Co_2(CO)_8$-Catalyzed Aza-PKTR of 6a

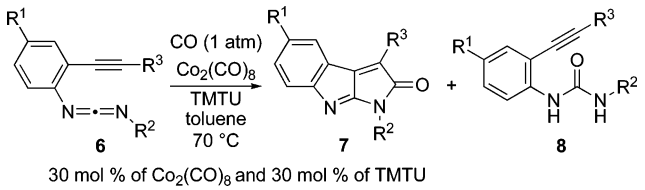


entry	$Co_2(CO)_8$ (mol %)	TMTU (mol %)	$Co_2(CO)_8$/TMTU	**7a** (%)	**8a** (%)
1	10	60	1/6	54	19
2	20	120	1/6	71	7
3	30	180	1/6	69	6
4	40	240	1/6	66	7
5	20	80	1/4	69	9
6	20	60	1/3	72	6
7	30	90	1/3	84	6
8	30	60	1/2	82	5
9	30	30	1/1	77	*a*
10[b]	30	30	1/1	84	*a*

[a] A trace amount of **8** was detected by TLC. [b] Toluene was used under the same conditions.

in benzene at 70 °C in the presence of tetramethylthiourea (TMTU) in an atmosphere of CO, in which the combination of 5 mol % of $Co_2(CO)_8$ with 30 mol % of TMTU ($Co_2(CO)_8$/TMTU = 1/6) was found to be the most effective. In our previous paper,[3] we applied Yang's conditions[4] (10 mol % of $Co_2(CO)_8$/60 mol % of TMTU = 1/6) to the alkynecarbodiimides **6a**, for example, to produce the pyrrolo[2,3-*b*]indol-2-one **7a**[5,6] in 54% yield along with the urea derivative **8a** in 19% yield, which must have been formed by hydrolysis of the starting material **6a**. Thus, the first $Co_2(CO)_8$-catalyzed aza-PKTR of the alkynecarbodiimides could be developed, but the formation of some amounts of the urea derivatives such as **8a** seemed to be the drawback of this transformation. To suppress the formation of the byproduct as well as improve the chemical yield of the desired pyrrolo[2,3-*b*]indol-2-one derivative, our initial effort was directed toward the evaluation of the loading amount of $Co_2(CO)_8$ and the ratio between $Co_2(CO)_8$ and TMTU. These results are summarized in Table 1. Entry 1 shows the previous result[3] for comparison. A significant improvement in the chemical yield of **7a** as well as suppression of **8a** was attained when the loading amount of catalysts was doubled while retaining the ratio between $Co_2(CO)_8$ and TMTU (1/6) (entry 2). Two other conditions, with increasing loading amounts of the catalysts with the same ratio between $Co_2(CO)_8$ and TMTU (1/6), provided results similar to that of entry 2 (entries 3 and 4). Entries 5 and 6 with 20 mol % of $Co_2(CO)_8$ indicated that decreasing the ratio of TMTU to $Co_2(CO)_8$ from 1/6 to 1/4 or 1/3 did not produce any specific changes compared to entry 2. The conditions with 30 mol % of $Co_2(CO)_8$ and 90 or 60 mol % of TMTU, however, effected the ring-closing reaction, resulting in the second improvement regarding the yield of **7a** (entries 7 and 8). In addition, it was found that an equal amount of $Co_2(CO)_8$ and TMTU was effective for the byproduct suppression. In fact, compound **7a** was obtained in a slightly

TABLE 2. $Co_2(CO)_8$-Catalyzed Aza-PKTR of 6



					product (%)[a]	
entry	sub.	R^1	R^2	R^3	**7**	**8**
1[b]	**6a**	Me	*p*-$MeOC_6H_4$	TMS	**7a**: 84 (54)	**8a**: —[c] (19)
2	**6b**	H	*p*-$PhOC_6H_4$	TMS	**7b**: 77 (57)	**8b**: —[c] (6)
3	**6c**	H	PMB	TMS	**7c**: 92 (37[d])	**8c**: —[c] (6)
4	**6d**	H	Me	TMS	**7d**: 65 (41[d])	**8d**: —[c] (15)
5	**6e**	H	*p*-$MeOC_6H_4$	Pr	**7e**: 65 (66)	**8e**: —[c] (10)
6	**6f**	H	*p*-$MeOC_6H_4$	$(CH_2)_2CHCMe_2$	**7f**: 49 (44)	**8f**: 5 (13)
7	**6g**	H	*p*-$MeOC_6H_4$	$(CH_2)_2OTBS$	**7g**: 64 (48)	**8g**: —[c] (8)
8	**6h**	H	*p*-$MeOC_6H_4$	CH_2OTHP	**7h**: 35 (5)	**8h**: —[c] (—[c])
9	**6i**	MeO	*p*-$MeOC_6H_4$	TMS	**7i**: 64 (54)	**8i**: —[c] (18)
10	**6j**	MeO	Me	TMS	**7j**: 74 (55[d])	**8j**: —[c] (10)
11	**6k**	Cl	*p*-$MeOC_6H_4$	TMS	**7i**: 71 (52)	**8i**: —[c] (7)

[a] Number in parentheses indicates the chemical yield (%) of the product obtained under the previous conditions (10 mol % of $Co_2(CO)_8$ and 60 mol % of TMTU in benzene at 70 °C). [b] The result obtained in Table 1, entry 1 is cited from Table 1. [c] A trace amount of **8** was detected by TLC. [d] 20 mol % of $Co_2(CO)_8$ and 120 mol % of TMTU were used.

lower yield (77%) with a trace amount of **8a** (entry 9). Finally, the PKTR of **6a** proceeded in toluene under the same conditions as entry 9 to give **7a** in 84% yield together with a trace amount of **8a**. Thus, the improved reaction conditions (30 mol % of $Co_2(CO)_8$ and 30 mol % of TMTU in toluene) provided **7a** in a satisfactory yield accompanied by a very small amount of the urea derivative **8a**.

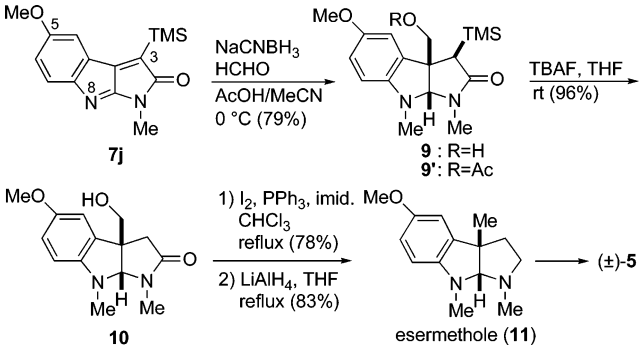
We next investigated the generality of the optimized conditions (30 mol % of $Co_2(CO)_8$ and 30 mol % of TMTU in toluene) using the same ten substrates **6b**−**k** as examined in a previous report.[3] These results are summarized in Table 2 accompanied by the previous results. As can be seen, the chemical yields of **7** were vastly improved in most cases. In particular, compounds **6** having a TMS group at the alkyne terminus consistently produced the corresponding ring-closed products **7** in high yields. For compounds **6e**−**g** with a terminal alkyl tether, the chemical yield of the products **7e**−**g** was somewhat lower compared to those of the TMS derivatives **7a**−**d**,**i**−**k**. The propargyl ether derivative **6h** gave the corresponding ring-closed product **7h** in 35% yield (entry 8), which was previously obtained in only 5% yield when the former was treated with two catalysts in the ratio of 1 to 6. The other point that needs to be mentioned is that the formation of **8** could be nearly suppressed except for compound **6f** that produced the urea **8f** in 5% yield (entry 6). On the basis of the results in Table 2, it might be concluded that the $Co_2(CO)_8$-catalyzed aza-PKTR of the *N*-[2-(1-alkynyl)phenyl]-*N*′-substitutedcarbodiimides **6** smoothly proceeds in the presence of 30 mol % of $Co_2(CO)_8$ and 30 mol % of TMTU in toluene at 70 °C to produce the pyrrolo[2,3-*b*]indol-2-one derivatives **7** in acceptable yields.

The next phase of this investigation was to accomplish the total synthesis of the hexahydropyrrolo[2,3-*b*]indole alkaloids based on the newly developed $Co_2(CO)_8$-catalyzed aza-PKTR of the alkynecarbodiimide derivatives. As shown in Scheme 2, we have already succeeded in the efficient transformation[3] of the pyrrolo[2,3-*b*]indol-2-one **7j** into esermethole (**11**),[7] a precursor of physostigmine (**5**),[8] via compounds **9** and **10**. The

(5) Saito reported the stoichiometric aza-PKTR, which involves the cyclocarbonylation of the alkynecarbodiimide substrates to provide the corresponding diazabicyclic compounds under the $Mo(CO)_6$-mediated conditions: Saito, T.; Shiotani, M.; Otani, T.; Hasaba, S. *Heterocycles* **2003**, *60*, 1045−1048.

(6) Recently, the Rh(I)-catalyzed PKTR of alkynecarbodiimide derivatives was reported by Saito: Saito, T.; Sugizaki, K.; Otani, T.; Suyama, T. *Org. Lett.* **2007**, *9*, 1239−1241.

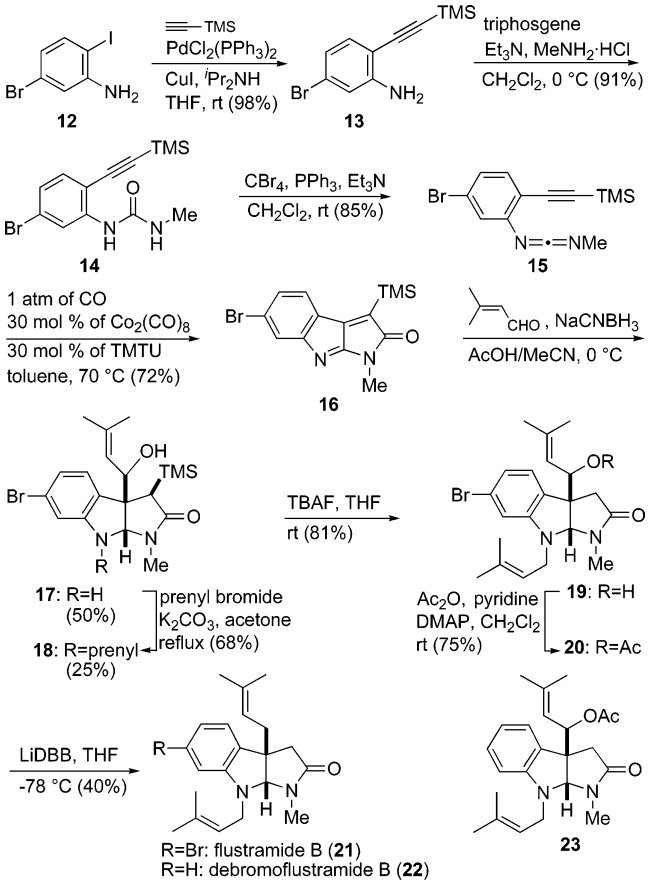
SCHEME 2



crucial operation for the conversion of **7j** into **9** could be interpreted by the initial hydride attack at the C_3-position (1,4-reduction) of **9** resulting in the formation of the indole intermediate, which subsequently reacted with HCHO at the C_{3a}-position to produce the indolenine derivative. The formed imine moiety (N_8-C_{8a}) would be susceptible to the hydride reduction, followed by reductive *N*-methylation to furnish **9**. The relative stereochemistry of **9**, in particular, the relationship between the C_3-TMS group and the angular hydroxymethyl moiety,[9] was determined to be cis by an NOE experiment.

By taking advantage of the procedures described in Scheme 2, we first examined the synthesis of (±)-flustramide B (**21**).[10] The 6-bromopyrrolo[2,3-*b*]indol-2-one derivative **16**, a key intermediate for the natural product target, was prepared via the aza-PKTR as follows (Scheme 3). 5-Bromo-2-iodoaniline (**12**) was converted into the alkynylaniline **13** in 98% yield by the Sonogashira coupling reaction,[11] which was subsequently treated with triphosgene[12] to give the urea **14** in 91% yield. The alkynecarbodiimide **15**, a substrate for the aza-PKTR, was obtained in 85% yield by the dehydration reaction of **14** with carbon tetrabromide and triphenylphosphine.[13] Upon exposure

SCHEME 3



to 30 mol % of $Co_2(CO)_8$ and 30 mol % of TMTU in toluene, compound **15** underwent the ring-closing reaction as expected to give the desired pyrrolo[2,3-*b*]indol-2-one **16** in 72% yield. Treatment of **16** with $NaCNBH_3$ under acidic conditions in the presence of 3-methyl-2-butenal provided the N_8-prenylpyrrolo-[2,3-*b*]indol-2-one **18** in 25% yield and the corresponding N_8-H derivative **17** in 50% yield, the latter of which could be easily converted into the former in 68% yield by the standard *N*-prenylation. In sharp contrast to the reaction of **7j** with HCHO (Scheme 2),[3] the reductive alkylation step with 3-methyl-2-butenal was markedly retarded presumably due to the bulkiness of 3-methyl-2-butenal compared to HCHO and/or deactivation by the C_6-bromo functionality on the benzene ring. Removal of a hydroxyl group at an allylic position was essential to complete the transformation of **18** into **21**. The hydroxyl group of compound **19**, derived from **18**, was activated by acylation to give the acetoxy derivative **20**, which was subsequently exposed to lithium di-*tert*-butylbiphenylide (LiDBB)[14] at −78 °C to give (±)-debromoflustramide B (**22**)[10b,15] in 40% yield instead of (±)-flustramide B (**21**). A small amount of **23** was detected and then characterized by ^{1}H NMR. The isolation of **23** suggested that the debromination of **20** would be faster than

(7) Esermethole (**11**) has already been converted into (±)-physostigmine (**5**): Yu, Q.-S.; Brossi, A. *Heterocycles* **1988**, *27*, 745−750.

(8) For the recent total synthesis of physostigmine, see: (a) Node, M.; Hao, X.; Nishide, K. *Chem. Pharm. Bull*. **1996**, *44*, 715−719. (b) Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc*. **1998**, *120*, 6500−6503. (c) Kawahara, M.; Nishida, A.; Nakagawa, M. *Org. Lett*. **2000**, *2*, 675−678. (d) Tanaka, K.; Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett*. **2001**, *42*, 1049−1052. (e) Mekhael, M. K. G.; Heimgarther, H. *Helv. Chim. Acta* **2003**, *86*, 2805−2813. (f) Haung, A.; Kodanko, J. J.; Overman, L. E. *J. Am. Chem. Soc*. **2004**, *126*, 14043−14053. (g) Santros, P. E.; Srinivasan, N.; Almeida, P. S.; Lob, A. M.; Prabhakar, S. *Tetrahedron* **2005**, *61*, 9147−9156. (h) Rigby, J. H.; Sidique, S. *Org. Lett*. **2007**, *9*, 1219−1221.

(9) Compound **9** was converted into the acetoxy derivative **9′** in 74% yield by a conventional procedure. An NOE experiment of **9′** revealed a 14.7% enhancement between the C_3-TMS group and the methylene protons of the acetoxymethyl functionality indicating that compounds **9** and **9′** should have the relative stereochemistry depicted in Scheme 2. The opposite stereochemical relationship between the TMS group and the hydroxymethyl moiety (trans-relationship) might be reasonable on the basis of the proposed mechanism. Presumably isomerization of the bulky TMS group from the concave face to the convex face would occur during the reaction.

(10) For the recent total synthesis of flustramide B and flustramine B, see: (a) Hino, T.; Tanaka, T.; Matsuki, K.; Nakagawa, M. *Chem. Pharm. Bull*. **1983**, *31*, 1806−1808. (b) M.-Rois, M. S.; S-Castillo, O. R.; T.-Serrato, J. J.; J.-Nathan, P. *J. Org. Chem.* **2001**, *6*, 1186−1192. (c) Austin, J. F.; Kim, S.-G.; Sinz, C. J.; Xiao, W.-J.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5482−5487. (d) Kawasaki, T.; Shinada, M.; Kamimura, D.; Ohzono, M.; Ogawa, A. *Chem. Commun.* **2006**, 420−422.

(11) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467−4470.

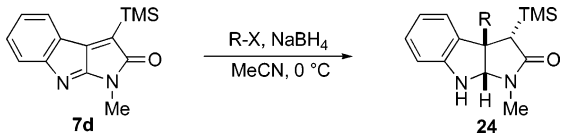
(12) (a) Majer, P.; Randad, R. S. *J. Org. Chem.* **1994**, *59*, 1937−1938. (b) Weiberth, F. J. *Tetrahedron Lett.* **1999**, *40*, 2895−2898.

(13) Nishikawa, T.; Ohyabu, N.; Yamamoto, N.; Isobe, M. *Tetrahedron* **1999**, *55*, 4325−4340.

(14) Krief, A.; Laval, A.-M.; Shastri, M. *Acros Org. Acta* **1995**, *1*, 32−33.

(15) For the recent total synthesis of debromoflustramide B and debromoflustramine B, see: (a) Jensen, J.; Anthoni, U.; Christphersen, C.; Nielson, P. *Acta Chem. Scand*. **1995**, *49*, 68−71. (b) Cardoso, A. S.; Srinivasan, N.; Lobo, A. M.; Prabhankar, S. *Tetrahedron Lett.* **2001**, *42*, 6663−6666. (c) M.-Rios, M. S.; R.-Becerril, E.; J.-Nathan, P. *Tetrahedron*: *Asymmetry* **2005**, *16*, 2493−2499. (d) Miyamoto, H.; Okawa, Y.; Nakazawa, A.; Kobayashi, S. *Tetrahedron Lett.* **2007**, *48*, 1805−1808, and ref 10b.

TABLE 3. Alkylation at the C_3-Position of 7d under Reductive Conditions



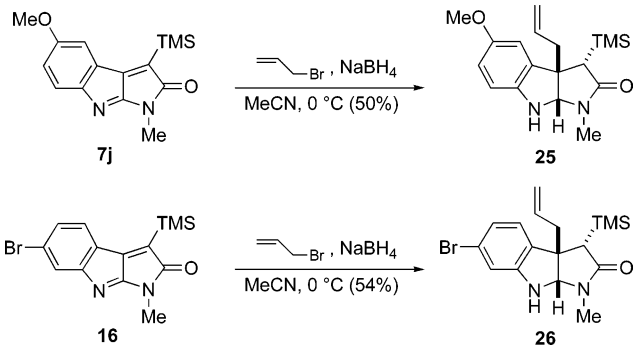
entry	R−X	product	R	yield (%)
1	BnBr	**24a**	Bn−	54
2	H_2CCHCH_2Br	**24b**	H_2CCHCH_2−	51
3	$HCCCH_2Br$	**24c**	$HCCCH_2$−	45
4	$(Me)_2CCHCH_2Br$	**24d**	$(Me)_2CCHCH_2$−	64
5	H_2CCHCO_2Me	**24e**	$MeO_2CCH_2CH_2$−	25
6	BuI	**24f**	Bu−	

the deacetoxylation under the stated conditions. In addition, we examined some typical radical conditions[16] to remove the hydroxyl group from the 1-hydroxyl-3-methyl-2-butenyl moiety. However, it turned out that the dehydroxylation was accompanied by migration of the double bond resulting in the formation of both the 3-methyl-1-butenyl as well as 3-methyl-2-butenyl functionalities.

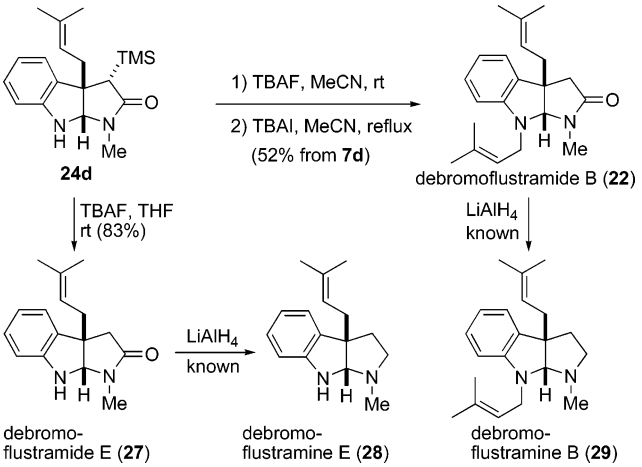
To overcome the difficulty encountered in the dehydroxylation step (undesired debromination and/or double bond migration), an alternative procedure, which would enable the introduction of the angular alkyl appendage at the C_{3a}-position of the pyrrolo[2,3-*b*]indol-2-one skeleton without the dehydroxylation step, had to be mandatory. Thus, alkyl halides were employed as alkylating agents instead of the aldehyde counterparts in the above transformation. Furthermore, we envisaged that $NaBH_4$ would be better than $NaCNBH_3$ because $NaCNBH_3$ requires an acidic condition that must partially retard the N_8-alkylation during the final step.[17] Upon exposure to $NaBH_4$ in acetonitrile at 0 °C in the presence of benzyl bromide, the pyrrolo[2,3-*b*]indol-2-one **7d** underwent a successive 1,4-reduction, benzylation at the C_{3a}-position, and reduction of the formed imine moiety to provide **24a** in 54% yield (Table 3, entry 1). The expected N_8-benzyl derivative of **24a** was not detected in the reaction mixture. When the reaction mixture was allowed to stand at room temperature for a prolonged time, the gradual conversion of **24a** into the corresponding N_8-benzyl derivative could be monitored by TLC. Both allyl bromide and propargyl bromide gave the corresponding pyrrolo[2,3-*b*]indol-2-ones **24b** and **24c** in moderate yields (entries 2,3), and compound **24d** was obtained in a higher yield (64%) when prenyl bromide was used (entry 4). Although a variety of activated alkyl halides could be used for this transformation, a simple alkyl halide was found to be inefficient. In fact, no formation of **24f** could be detected in the reaction with butyl iodide (entry 6). Interestingly, methyl acrylate acted as a Michael acceptor in this reaction to produce **24e** in a lower yield (entry 5).

The two additional examples similar to the preparation of **24** from **7d** are shown in Scheme 4. The experiments with **7j** and **16** indicated that the electronic property of the substituent on the benzene ring did not affect the reactivity of the starting pyrrolo[2,3-*b*]indol-2-ones. The stereochemistry of compounds

SCHEME 4



SCHEME 5



24 (and **25** and **26**) was determined on the basis of NOE experiments. The NOE experiment of **24a**, for instance, revealed an 8.9% enhancement between the C_3-H and benzyl protons, strongly suggesting that the TMS group of **24a** should be located on the concave face of the diazabicyclo[3.3.0] ring as depicted in Table 3. This is in sharp contrast to the stereochemistry of the TMS group of **9**, obtained from **7j** under the reductive conditions with $NaCNBH_3$, being on the convex face.

The final phase of this program involved the transformation of **24d** and its 6-bromo congener into the target natural products (Schemes 5 and 6). Compound **24d** was converted into (±)-debromoflustramide E (**27**)[15d,18] in 83% yield by TBAF treatment. On the other hand, **24d** was consecutively treated with TBAF at room temperature and then with TBAI in refluxing acetonitrile (one pot) to produce (±)-debromoflustramide B (**22**)[15] in 52% overall yield from **7d**. Since both **27** and **22** have already been converted into (±)-debromoflustramine E (**28**)[18] and (±)-debromoflustramine B (**29**),[15c,19] respectively, the present syntheses also amount to the total synthesis of these alkaloids in a racemic form.

Similarly, compound **30** could be prepared from **16** in 65% yield by prenylation under reductive conditions, which was

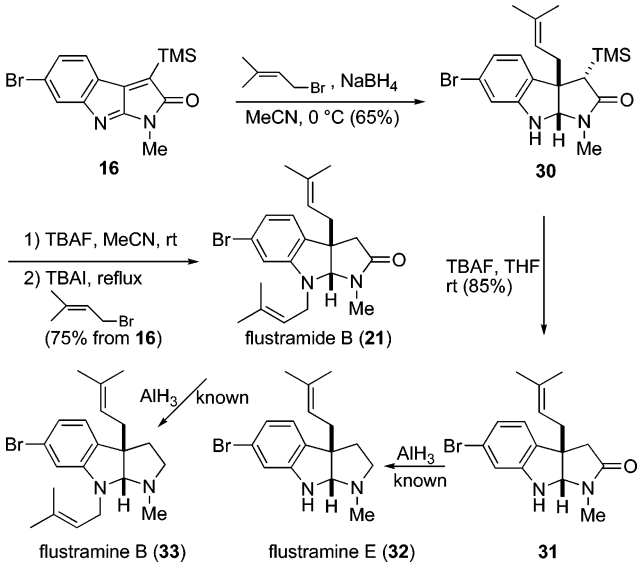
(16) (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans.* **1975**, *1*, 1574−1585. (b) Yamamoto, Y.; Hori, A.; Hutchinson, C. R. *J. Am. Chem. Soc.* **1985**, *107*, 2474−2484. (c) Marukawa, K.; Mori, K. *Eur. J. Org. Chem.* **2002**, 3974−3978 and references cited therein.

(17) Neither compound **24a** nor its N_8-benzyl derivative could be detected when compound **7d** was treated with benzyl bromide in AcOH/MeCN at 0 °C in the presence of $NaCNBH_3$.

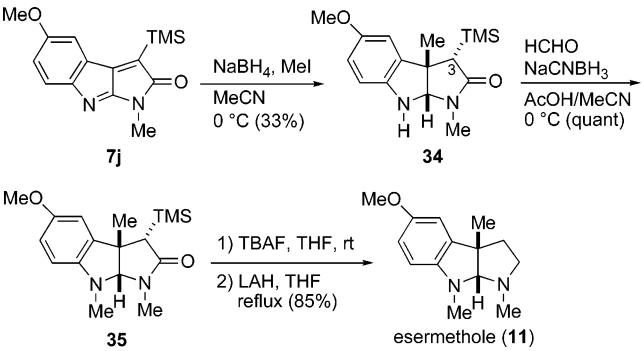
(18) For the recent total synthesis of debromoflustramide E and debromoflustramine E, see: (a) Mitchell, M. O.; Dorroh, P. *Tetrahedron Lett.* **1991**, *32*, 7641−7642. (b) M.-Rios, M. S.; S.-Castillo, O. R.; J.-Nathan, P. *Tetrahedron* **2002**, *58*, 1479−1484 and ref 15d.

(19) Debromoflustramine B was also synthesized by alternative procedures, which did not involve debromoflustramide B, see: (a) Somei, M.; Yamada, F.; Izumi, T.; Nakajou, M. *Heterocycles* **1997**, *45*, 2327−2330. (b) Tang, G. H.; Zhu, X.; Ganesan, A. *Org. Lett.* **2003**, *5*, 1801−1803. L.-Alvarrado, P.; Caballero, E.; Avendano, C.; Menendez, J. C. *Org. Lett.* **2006**, *8*, 4303−4306.

SCHEME 6



SCHEME 7



subsequently desilylated to afford **31** in 85% yield (Scheme 6). The three-step conversion of **16** into (±)-flustramide B (**21**)[10] was also achieved in a satisfactory overall yield. Thus, the formal total syntheses of (±)-flustramine E (**32**)[18] from **31** and (±)-flustraime B (**33**)[10b] from flustramide B (**21**) were also accomplished.

Furthermore, we examined an alternative synthesis of esermethole (**11**) using the newly developed procedure with $NaBH_4$, although we had recognized that the reaction of **7d** with butyl iodide did not produce the desired product at all (see Table 3, entry 6). Treatment of **7j** with $NaBH_4$ in the presence of methyl iodide, however, gave the desired product **34** in a rather low yield (33%) (Scheme 7). Compound **34** has the same stereochemistry[20] as compounds **24**, **25**, and **26**, and opposite that of compound **9** regarding the C_3-stereogenic center. Reductive methylation of **34** gave **35** in a quantitative yield, which was subsequently exposed to TBAF and $LiAlH_4$ to provide esermethole (**11**) in 85% overall yield. Thus, we could succeed in the alternative synthesis of **11**, but it is obvious that the previous method[3] is much superior to the present one as far as the synthesis of **11** is concerned.

In summary, we have described the efficient $Co_2(CO)_8$-catalyzed PKTR of the benzene-bridged alkynecarbodiimides under improved conditions (30 mol % of both $Co_2(CO)_8$ and TMTU in toluene at 70 °C) producing the pyrrolo[2,3-*b*]indol-2-ones in good yields. These conditions could nearly suppress the formation of the urea derivatives, which were consistently observed under the previous conditions. The resulting pyrrolo-[2,3-*b*]indol-2-ones were successfully transformed into seven hexahydropyrrolo[2,3-*b*]indole alkaloids, (±)-flustramide B, (±)-flustramines B and E, (±)-debromoflustramides B and E, and (±)-debromoflustramines B and E via the crucial prenylation at the C_{3a}-position by treatment with $NaBH_4$/prenyl bromide. An alternative synthesis of (±)-physostigmine was accomplished as well. Thus, we developed a simple and general procedure for the preparation of pyrrolo[2,3-*b*]indol-2-ones based on the $Co_2(CO)_8$-catalyzed aza-PKTR of alkynecarbodiimides, and their conversion to the corresponding hexahydropyrrolo[2,3-*b*]indole alkaloids.

Experimental Section

General Procedure for the Ring-Closing Reaction of Carbodiimides with $Co_2(CO)_8$ and TMTU under an Atmosphere of CO. To a solution of carbodiimide **6** (0.15 mmol) in toluene (1.5 mL) were added 30 mol % of $Co_2(CO)_8$ and 30 mol % of TMTU. The reaction mixture was heated at 70 °C (oil bath temperature) under a CO atmosphere until the complete disappearance of the starting material (monitored by TLC). The reactiom mixture was concentrated and chromatographed with hexane−AcOEt to afford pyrrolo[2,3-*b*]indol-2-one **7**.[21] Chemical yields of **7** are summarized in Table 2.

5-Bromo-2-[2-(trimethysilyl)ethynyl]aniline (13). To a solution of 5-bromo-2-iodoaniline[22] (2.58 g, 8.59 mmol), $PdCl_2(PPh_3)_2$ (60.2 mg, 0.0860 mmol), and CuI (33.0 mg, 0.174 mmol) in THF (50 mL) were added trimethylsilylacethylene (1.34 mL, 9.57 mmol) and $^iPr_2NH$ (9.0 mL) at room temperature. The reaction mixture was stirred for 2 h, quenched by addition of saturated aqueous NH_4Cl, and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane−AcOEt (15:1) to afford **13** (2.26 g, 98%) as a pale yellow oil: IR 3497, 3394, 2147 cm^{-1}; ^1H NMR δ 7.12 (d, 1H, J = 8.3 Hz), 6.84 (d, 1H, J = 2.0 Hz), 6.77 (dd, 1H, J = 8.3, 2.0 Hz), 4.27 (s, 2H), 0.25 (s, 9H); ^{13}C NMR δ 149.2, 133.3, 123.7, 120.7, 116.7, 106.7, 100.9, 100.7, 0.0; MS *m*/*z* 267 (M^+, 88.8); HRMS calcd for $C_{11}H_{14}BrNSi$ 267.0079, found 267.0072.

1-[5-Bromo-2-[2-(trimethylsilyl)ethynyl]phenyl]-3-methylurea (14). To a solution of **13** (862 mg, 3.21 mmol) and Et_3N (4.9 mL, 35 mmol) in CH_2Cl_2 (30 mL) was added triphosgene (1.00 g, 3.37 mmol) at 0 °C. After the solution was stirred for 30 min at room temperature, $MeNH_2$·HCl (1.10 g, 16.3 mmol) was added to the reaction mixture, which was then stirred for 1 h, quenched by addition of water, and extracted with CH_2Cl_2. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane−AcOEt (3:1) to afford **14** (950 mg, 91%) as colorless needles: mp 175−176 °C (hexane−AcOEt); IR 3456, 3393, 2149, 1697 cm^{-1}; ^1H NMR δ 8.45 (d, 1H, J = 2.0 Hz), 7.22 (d, 1H, J = 8.2 Hz), 7.08−7.05 (m, 2H), 4.80 (s, 1H), 2.91 (d, 3H, J = 4.9 Hz), 0.28 (s, 9H); ^{13}C NMR δ 154.9, 141.4, 132.7, 124.9, 124.1, 121.2, 109.8, 102.8, 99.9, 27.3, −0.1; MS *m*/*z* 324 (M^+, 41.1); HRMS calcd for $C_{13}H_{17}BrN_2OSi$ 324.0294, found 324.0303.

***N*-[5-Bromo-2-[2-(trimethylsilyl)ethynyl]phenyl]-*N*′-methylcarbodiimide (15).** To a solution of **14** (1.23 g, 3.78 mmol) and Et_3N (2.2 mL, 15 mmol) in CH_2Cl_2 (25 mL) were added CBr_4 (2.51 g, 7.56 mmol) and PPh_3 (1.98 g, 7.56 mmol) at room temperature. The reaction mixture was stirred for 30 min and concentrated to

(20) An 18.3% enhancement between the C_3-H and the angular methyl group was observed in its NOE experiment.

(21) The full characterization data for compounds **6**, **7**, and **8** have already been reported in the Supporting Information of ref 3.

(22) Sakamoto, T.; Kondo, Y.; Iwashita, S.; Yamanaka, H. *Chem. Pharm. Bull.* **1987**, *35*, 1823−1828.

dryness. The residue was chromatographed with hexane−AcOEt (20:1) to afford **15** (980 mg, 85%) as a colorless oil: IR 2154 cm^{-1}; ^1H NMR δ 7.27 (d, 1H, J = 8.3 Hz), 7.18 (d, 1H, J = 1.9 Hz), 7.14 (dd, 1H, J = 8.3, 1.9 Hz), 3.17 (s, 3H), 0.27 (s, 9H); ^{13}C NMR δ 143.0, 134.8, 132.4, 127.1, 126.9, 122.9, 117.5, 101.7, 101.0, 32.3, −0.02; MS *m*/*z* 306 (M^+, 29.9); HRMS calcd for $C_{13}H_{15}BrN_2Si$ 306.0188, found 306.0181.

6-Bromo-1-methyl-3-(trimethylsilyl)pyrrolo[2,3-*b*]indol-2-one (16). According to the standard ring-closing procedure, **15** (305 mg, 0.993 mmol) was treated with $Co_2(CO)_8$ (102 mg, 0.298 mmol) and TMTU (39.3 mg, 0.298 mmol) under a CO atmosphere to afford **16** (238 mg, 72%) as purple needles: mp 130−131 °C (hexane); IR 1740, 1649, 1591 cm^{-1}; ^1H NMR δ 7.23 (d, 1H, J = 1.7 Hz), 7.20 (d, 1H, J = 7.8 Hz), 7.04 (dd, 1H, J = 7.8, 1.7 Hz), 3.10 (s, 3H), 0.37 (s, 9H); ^{13}C NMR δ 177.2, 173.1, 163.7, 153.6, 134.6, 127.5, 127.1, 126.6, 124.1, 123.5, 25.5, −1.0; MS *m*/*z* 334 (M^+, 44.3). Anal. Calcd for $C_{14}H_{15}BrN_2OSi$: C, 50.15; H, 4.51; N, 8.36. Found: C, 50.00; H, 4.50; N, 8.29.

(3*R,3a*S**,8a*S**)-6-Bromo-3a-(1-hydroxy-3-methyl-2-butenyl)-1-methyl-3-(trimethylsilyl)-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indol-2-one (17) and (3*R**,3a*S**,8a*S**)-6-Bromo-3a-(1-hydroxy-3-methyl-2-butenyl)-1-methyl-8-(3-methyl-2-butenyl)-3-(trimethylsilyl)-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indol-2-one (18).** To a solution of **16** (33.5 mg, 0.100 mmol), 3-methyl-2-butenal (0.168 mL, 2.00 mmol), and AcOH (0.10 mL, 1.5 mmol) in MeCN (0.5 mL) was added $NaCNBH_3$ (62.8 mg, 1.00 mmol) at 0 °C. The reaction mixture was stirred for 10 min, quenched by addition of saturated aqueous $NaHCO_3$, and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane−AcOEt (2:1 to 1:3) to afford **17** (20.6 mg, 50%) and **18** (11.0 mg, 25%). Both **17** and **18** were obtained as a mixture of two diastereoisomers (10:1) due to the stereogenic center of allyl alcohol moiety. The major isomer of **17**: colorless needles; mp 238−239 °C (hexane−AcOEt); IR 3605, 3404, 1664 cm^{-1}; ^1H NMR δ 7.13 (d, 1H, J = 7.8 Hz), 6.88 (d, 1H, J = 7.8 Hz), 6.74 (s, 1H), 5.24 (d, 1H, J = 4.2 Hz), 5.07 (d, 1H, J = 9.3 Hz), 4.54−4.51 (m, 2H), 2.91 (s, 3H), 2.28 (s, 1H), 1.74 (d, 6H, J = 10.0 Hz), −0.06 (s, 9H); ^{13}C NMR δ 175.6, 152.3, 140.3, 127.7, 127.5, 122.7, 121.6, 121.5, 112.9, 81.3, 72.5, 57.6, 41.9, 28.1, 26.2, 18.7, −0.7; MS *m*/*z* 422 (M^+, 12.1); HRMS calcd for $C_{19}H_{27}BrN_2O_2Si$ 422.1025, found 422.1025. The major isomer of **18**: colorless oil; IR 3609, 3404, 1663, 1595 cm^{-1}; ^1H NMR δ 7.06 (d, 1H, J = 7.8 Hz), 6.79 (dd, 1H, J = 7.8, 1.6 Hz), 6.51 (d, 1H, J = 1.6 Hz), 5.08 (t, 1H, J = 6.1 Hz), 5.03 (d, 1H, J = 9.3 Hz), 4.95 (s, 1H), 4.47 (d, 1H, J = 9.3 Hz), 3.85 (d, 2H, J = 6.1 Hz), 2.98 (s, 3H), 2.27 (s, 1H), 1.74−1.71 (m, 12H), −0.10 (s, 9H); ^{13}C NMR δ 176.9, 153.6, 139.7, 135.7, 127.4, 127.2, 123.0, 121.8, 119.9, 119.5, 110.4, 86.8, 72.4, 56.9, 46.3, 42.0, 29.7, 26.1, 25.7, 18.7, 18.1, −0.7; MS *m*/*z* 490 (M^+, 75.6); HRMS calcd for $C_{24}H_{35}BrN_2O_2Si$ 490.1651, found 490.1653.

Conversion of 17 into 18. Prenyl bromide (46.9 mg, 0.315 mmol) was added to a suspension of **17** (40.0 mg, 0.0945 mmol) and K_2CO_3 (72.5 mg, 0.525 mmol) in acetone (3.0 mL) at room temperature. The reaction mixture was refluxed for 6 h, quenched by addition of water. Acetone was evaporated off, and the residue was extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane−AcOEt (2:1) to afford **18** (31.6 mg, 68%).

(3a*R,8aS*)-6-Bromo-3a-(1-hydroxy-3-methyl-2-butenyl)-1-methyl-8-(3-methyl-2-butenyl)-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indol-2-one (19).** To a solution of **18** (29.1 mg, 0.0592 mmol) in THF (1.0 mL) was added TBAF (1.0 M solution in THF, 0.09 mL, 0.09 mmol) at room temperature. The reaction mixture was stirred for 10 min, concentrated to dryness, and chromatographed with hexane−AcOEt (1:2) to afford **19** (20.0 mg, 81%) as a mixture of two diastereoisomer (10:1) due to the stereogenic center of the allyl alcohol moiety: the major isomer of **19**: colorless oil; IR 3601, 1682, 1595 cm^{-1}; ^1H NMR δ 6.88 (d, 1H, J = 7.8 Hz), 6.82 (dd, 1H, J = 7.8, 1.6 Hz), 6.62 (d, 1H, J = 1.6 Hz), 5.22 (t, 1H, J = 6.7 Hz), 5.06 (d, 1H, J = 9.4 Hz), 4.97 (s, 1H), 4.35 (d, 1H, J = 9.4 Hz), 3.95 (dd, 1H, J = 15.6, 6.6 Hz), 3.88 (dd, 1H, J = 15.6, 6.8 Hz), 2.86−2.83 (m, 4H), 2.53 (d, 1H, J = 17.3 Hz), 1.74−1.73 (m, 9H), 1.54 (s, 3H); ^{13}C NMR δ 172.6, 151.6, 139.8, 136.0, 131.0, 125.6, 122.8, 122.0, 120.3, 112.0, 85.3, 70.8, 54.2, 47.0, 38.3, 27.8, 26.0, 25.7, 18.6, 18.1; MS *m*/*z* 418 (M^+, 95.5); HRMS calcd for $C_{21}H_{27}BrN_2O_2$ 418.1256, found 418.1252.

(3*R,8a*S**)-3a-(1-Acetoxy-3-methyl-2-butenyl)-6-bromo-8-(3-methyl-2-butenyl)-1-methyl-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]-indol-2-one (20).** To a solution of **19** (20.0 mg, 0.0477 mmol), pyridine (0.07 mL, 0.2 mmol), and DMAP (0.6 mg, 5×10^{-3}mmol) in CH_2Cl_2 (1.0 mL) was added Ac_2O (7.3 mg, 0.072 mmol) at room temperature. The reaction mixture was stirred for 20 min, quenched by addition of water, and extracted with CH_2Cl_2. The extract was washed with 5% aqueous HCl and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane−AcOEt (1:1) to afford **20** (16.6 mg, 75%) as a mixture of two diastereoisomers (10:1) due to the stereogenic center of the allyl alcohol moiety: the major isomer of **20**: colorless oil; IR 1732, 1686, 1597 cm^{-1}; ^1H NMR δ 6.88 (d, 1H, J = 7.8 Hz), 6.83 (dd, 1H, J = 7.8, 1.6 Hz), 6.63 (d, 1H, J = 1.6 Hz), 5.54 (d, 1H, J = 10.0 Hz), 5.21 (tt, 1H, J = 6.8, 1.4 Hz), 4.94 (dt, 1H, J = 10.0, 1.4 Hz), 4.79 (s, 1H), 3.96 (dd, 1H, J = 15.7, 6.5 Hz), 3.87 (dd, 1H, J = 15.7, 6.8 Hz), 2.86 (s, 3H), 2.80 (d, 1H, J = 17.1 Hz), 2.58 (d, 1H, J = 17.1 Hz), 1.97 (s, 3H), 1.75−1.73 (m, 9H), 1.59 (d, 3H, J = 1.2 Hz); ^{13}C NMR δ 172.0, 169.6, 151.4, 141.8, 136.3, 130.4, 125.8, 123.0, 121.7, 119.9, 118.2, 112.2, 85.2, 72.7, 53.1, 47.0, 38.6, 27.7, 26.0, 25.7, 21.0, 18.7, 18.1; MS *m*/*z* 460 (M^+, 100); HRMS calcd for $C_{23}H_{29}BrN_2O_3$ 460.1362, found 460.1363.

(3a*R,8a*S**)-3a,8-Bis(3-methyl-2-butenyl)-1-methyl-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indol-2-one (22) (Debromoflustramide B).** A solution of lithium di-*tert*-butylbiphenylide (LiDBB) in THF was prepared as follows: Lithium (10.0 mg, 1.42 mmol) was added to a solution of *p*,*p*′-di-*tert*-butylbiphenyl (310 mg, 1.19 mmol) in THF (7 mL) at room temperature. The mixture was vigorously stirred at room temperature until dark green radical anion was developed, at which time the reaction mixture was cooled in an ice bath. After being stirred at 0 °C for 3 h, a solution of LiDBB in THF, thus prepared, was added to a solution of **20** (7.5 mg, 0.016 mmol) in THF (2 mL) at −78 °C until the reaction mixture turned deep green. The reaction mixture was stirred for 10 min, quenched by addition of water, and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane−AcOEt (2:1) to afford **22** (2.1 mg, 40%) as a colorless oil: IR 1678, 1605 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.07−7.03 (m, 2H), 6.66 (t, 1H, J = 7.3 Hz), 6.51 (d, 1H, J = 7.8 Hz), 5.18 (t, 1H, J = 6.6 Hz), 4.96 (t, 1H, J = 7.3 Hz), 4.78 (s, 1H), 4.02 (dd, 1H, J = 15.7, 6.6 Hz), 3.88 (dd, 1H, J = 15.7, 6.6 Hz), 2.73 (s, 3H), 2.56 (d, 1H, J = 16.9 Hz), 2.46 (d, 1H, J = 16.9 Hz), 2.36 (dd, 1H, J = 14.4, 8.1 Hz), 2.29 (dd, 1H, J = 14.4, 6.3 Hz), 1.69 (d, 6H, J = 11.5 Hz), 1.63 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 171.1, 149.0, 135.3, 134.5, 134.4, 128.4, 123.3, 121.1, 119.1, 118.4, 108.6, 86.3, 49.4, 46.0, 41.4, 36.9, 27.3, 25.7, 25.5, 17.88, 17.86; MS *m*/*z* 324 (M^+, 47.6); HRMS calcd for $C_{21}H_{28}N_2O$ 324.2202, found 324.2205.

Reaction of Pyrrolo[2,3-*b*]indol-2-ones with Alkyl Halides in the Presence of $NaBH_4$. $NaBH_4$ (0.200 mmol) was added to a solution of pyrrolo[2,3-*b*]indol-2-ones, **7d**, **7j**, and **16** (0.100 mmol) and alkyl halide (0.500 mmol) in MeCN (1.0 mL) at 0 °C. The reaction mixture was stirred at 0 °C until complete disappearance of the starting material (monitored by TLC). The reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$, and extracted with AcOEt, then the extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane−AcOEt to afford the C_{3a}-alkylated

products **24**, **25**, and **26**, respectively. Chemical yields are summarized in Table 3 and Scheme 4.

(3*R,3a*R**,8a*R**)-3a-Benzyl-1-methyl-3-(trimethylsilyl)-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indol-2-one (24a):** colorless plates: mp 215−216 °C (hexane−AcOEt); IR 3398, 1663, 1609 cm^{-1}; ^1H NMR δ 7.34−7.27 (m, 4H), 7.15 (t, 1H, J = 7.4 Hz), 7.08−7.07 (m, 2H), 6.88 (t, 1H, J = 7.3 Hz), 6.60 (t, 1H, J = 7.8 Hz), 5.16 (s, 1H), 4.31 (s, 1H), 3.32 (d, 1H, J = 13.9 Hz), 3.05 (d, 1H, J = 13.9 Hz), 2.81 (s, 3H), 2.37 (s, 1H), 0.06 (s, 9H); ^{13}C NMR δ 175.5, 149.7, 136.5, 131.0, 130.2, 128.8, 128.2, 126.8, 126.3, 118.9, 110.3, 82.4, 54.9, 46.4, 45.7, 27.7, −0.5; MS *m*/*z* 350 (M^+, 52.5). Anal. Calcd for $C_{21}H_{26}N_2OSi$: C, 71.96; H, 7.48; N, 7.99. Found: C, 71.75; H, 7.52; N, 7.97.

(3*R,3a*R**,8a*R**)-1-Methyl-3-(trimethylsilyl)-3a-(2-propenyl)-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indol-2-one (24b):** colorless oil: IR 3400, 2399, 1663 cm^{-1}; ^1H NMR δ 7.12−7.07 (m, 2H), 6.75 (t, 1H, J = 7.4 Hz), 6.59 (d, 1H, J = 7.8 Hz), 5.64−5.58 (m, 1H), 5.13−5.06 (m, 3H), 4.44 (s, 1H), 2.89 (s, 3H), 2.62 (dd, 1H, J = 14.0, 6.3 Hz), 2.53 (dd, 1H, J =14.0, 8.1 Hz), 2.14 (s, 1H), −0.08 (s, 9H); ^{13}C NMR δ 175.9, 149.9, 133.0, 130.8, 128.7, 126.0, 119.2, 118.8, 109.9, 83.6, 53.0, 45.6, 45.5, 28.0, −0.7; MS *m*/*z* 300 (M^+, 62.9); HRMS calcd for $C_{17}H_{24}N_2OSi$ 300.1658, found 300.1646.

(3*R,3a*R**,8a*R**)-1-Methyl-3-(trimethylsilyl)-3a-(2-propynyl)-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indol-2-one (24c):** colorless oil; IR 3398, 3308, 1664, 1609 cm^{-1}; ^1H NMR δ 7.27−7.25 (m, 1H), 7.11 (td, 1H, J = 7.6, 1.2 Hz), 6.76 (td, 1H, J = 7.5, 0.9 Hz), 6.61 (d, 1H, J = 7.8 Hz), 5.14 (d, 1H, J = 2.9 Hz), 4.50 (s, 1H), 2.92 (s, 3H), 2.70 (dd, 1H, J = 16.8, 2.7 Hz), 2.63 (dd, 1H, J = 16.8, 2.7 Hz), 2.38 (s, 1H), 2.01 (t, 1H, J = 2.7 Hz), −0.04 (s, 9H); ^{13}C NMR δ 175.6, 149.5, 130.2, 129.1, 125.9, 118.9, 110.0, 84.3, 80.0, 71.2, 52.5, 44.2, 31.1, 27.9, −0.8; MS *m*/*z* 298 (M^+, 98.2); HRMS calcd for $C_{17}H_{22}N_2OSi$ 298.1502, found 298.1499.

(3*R,3a*R**,8a*R**)-1-Methyl-3a-(3-methyl-2-butenyl)-3-(trimethylsilyl)-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indol-2-one (24d):** colorless plates: mp 92−93 °C (hexane); IR 3398, 1661, 1609 cm^{-1}; ^1H NMR δ 7.12−7.06 (m, 2H), 6.76−6.73 (m, 1H), 6.58 (d, 1H, J = 7.8 Hz), 5.00−4.98 (m, 2H), 4.42 (s, 1H), 2.90 (s, 3H), 2.55−2.47 (m, 2H), 2.14 (s, 1H), 1.66 (s, 3H), 1.60 (s, 3H), −0.08 (s, 9H); ^{13}C NMR δ 176.1, 149.9, 135.4, 131.2, 128.5, 125.9, 118.71, 118.68, 109.8, 83.8, 53.6, 45.6, 39.4, 28.0, 25.9, 18.2, −0.7; MS *m*/*z* 328 (M^+, 65.5). Anal. Calcd for $C_{19}H_{28}N_2OSi$: C, 69.46; H, 8.59; N, 8.53. Found: C, 69.17; H, 8.65; N, 8.54.

(3*R,3a*R**,8a*R**)-3a-(2-Methoxycarbonylethyl)-1-methyl-3-(trimethylsilyl)-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indol-2-one (24e):** colorless oil: IR 3400, 1732, 1664 cm^{-1}; ^1H NMR δ 7.10−7.07 (m, 2H), 6.76 (t, 1H, J = 7.4 Hz), 6.59 (d, 1H, J = 8.1 Hz), 5.05 (s, 1H), 4.44 (s, 1H), 3.63 (s, 3H), 2.90 (s, 3H), 2.31−2.24 (m, 2H), 2.19−2.11 (m, 2H), 2.08 (s, 1H), −0.08 (s, 9H); ^{13}C NMR δ 175.6, 173.4, 149.8, 129.6, 129.0, 126.0, 119.0, 109.9, 83.4, 53.1, 51.8, 46.0, 35.7, 29.3, 27.9, −0.7; MS *m*/*z* 346 (M^+, 100); HRMS calcd for $C_{18}H_{26}N_2O_3Si$ 346.1713, found 346.1715.

(3*R,3a*R**,8a*R**)-6-Bromo-1-methyl-3a-(3-methyl-2-butenyl)-3-(trimethylsilyl)-3,3a,8,8-tetrahydropyrrolo[2,3-*b*]indol-2-one (30).** According to the C_{3a}-alkylation procedure, **30** (56.4 mg, 69%) was obtained from **16** (67.0 mg, 0.200 mmol), prenyl bromide (149 mg, 1.00 mmol), and $NaBH_4$ (15.2 mg, 0.400 mmol) as colorless plates: mp 160−161 °C (hexane−AcOEt); IR 3462, 3321, 1663, 1601 cm^{-1}; ^1H NMR δ 6.94 (d, 1H, J = 8.0 Hz), 6.86 (dd, 1H, J = 8.0, 1.6 Hz), 6.71 (d, 1H, J = 1.6 Hz), 4.99 (d, 1H, J = 3.8 Hz), 4.94 (d, 1H, J = 7.7 Hz), 4.53 (d, 1H, J = 3.8 Hz), 2.88 (s, 3H), 2.47 (d, 2H, J = 8.1 Hz), 2.12 (s, 1H), 1.67 (s, 3H), 1.59 (s, 3H), −0.06 (s, 9H); ^{13}C NMR δ 175.9, 151.3, 135.8, 130.3, 127.1, 122.0, 121.4, 118.4, 112.7, 83.9, 53.1, 45.5, 39.3, 28.1, 26.0, 18.2, −0.7; MS *m*/*z* 406 (M^+, 18.8). Anal. Calcd for $C_{19}H_{27}BrN_2OSi$: C, 56.01; H, 6.68; N, 6.88. Found: C, 55.75; H, 6.65; N, 6.84.

(3a*R,8a*R**)-6-Bromo-3,3a-bis(3-methyl-2-butenyl)-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indol-2-one (21) (Flustramide B).** $NaBH_4$ (7.3 mg, 0.20 mmol) was added to a solution of **16** (33.5 mg, 0.100 mmol) and prenyl bromide (149 mg, 1.00 mmol) in MeCN (1.0 mL) at 0 °C. After the solution was stirred for 30 min, TBAF (1.0 M solution in THF, 0.60 mL, 0.60 mmol) was added to the reaction mixture and stirring was continued for 10 min at room temperature. TBAI (11.1 mg, 0.0300 mmol) was then added to the reaction mixture and the mixture was refluxed for 4 h. The reaction mixture was quenched by addition of water and extracted with AcOEt, and the extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane−AcOEt (1:1) to afford **21** (30.6 mg, 75%) as a colorless oil: IR 1682, 1597 cm^{-1}; ^1H NMR δ 6.85−6.84 (m, 2H), 6.60 (s, 1H), 5.19 (t, 1H, J = 6.7 Hz), 4.96 (dd, 1H, J = 8.1, 6.6 Hz), 4.73 (s, 1H), 3.96 (dd, 1H, J = 15.9, 6.1 Hz), 3.89 (dd, 1H, J = 15.9, 7.1 Hz), 2.87 (s, 3H), 2.64 (s, 2H), 2.37 (dd, 1H, J = 14.6, 8.1 Hz), 2.31 (dd, 1H, J = 14.6, 6.6 Hz), 1.76−1.70 (m, 9H), 1.56 (s, 3H); ^{13}C NMR δ 172.8, 150.5, 136.00, 135.96, 134.3, 124.3, 122.2, 121.5, 120.1, 118.2, 111.6, 87.4, 49.5, 46.5, 41.7, 37.4, 27.9, 25.9, 25.7, 18.08, 18.07; MS *m*/*z* 402 (M^+, 13.5); HRMS calcd for $C_{21}H_{27}BrN_2O$ 402.1307, found 402.1311.

(3a*R,8a*R**)-6-Bromo-1-methyl-3a-(3-methyl-2-butenyl)-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indol-2-one (31).** To a solution of **30** (37.6 mg, 0.0923 mmol) in THF (1.0 mL) was added TBAF (1.0 M solution in THF, 0.11 mL, 0.11 mmol) at room temperature. The reaction mixture was stirred for 10 min, quenched by addition of water, and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane−AcOEt (1:2) to afford **31** (26.4 mg, 85%) as colorless needles: mp 170−171 °C (Et_2O); IR 3433, 1684, 1601 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.02−7.01 (m, 2H), 6.74 (dd, 1H, J = 7.9, 1.6 Hz), 6.65 (d, 1H, J = 1.5 Hz), 5.06 (t, 1H, J = 7.1 Hz), 4.92 (d, 1H, J = 1.5 Hz), 2.66 (s, 3H), 2.56 (d, 1H, J = 16.8 Hz), 2.45 (d, 1H, J = 16.8 Hz), 2.36−2.27 (m, 2H), 1.64 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 171.3, 150.4, 134.4, 133.7, 125.2, 120.9, 120.1, 118.9, 111.3, 81.2, 49.6, 41.1, 35.8, 26.2, 25.7, 17.8; MS *m*/*z* 334 (M^+, 51.0). Anal. Calcd for $C_{16}H_{19}BrN_2O$: C, 57.32; H, 5.71; N, 8.36. Found: C, 57.15, H, 5.79, N, 8.27.

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Supporting Information Available: ^1H NMR spectra for compounds **9′**, **16**, **24a**,**d**, **25**, **30**, **31**, and **34**, ^1H and ^{13}C NMR spectra for compounds **11**, **13**−**15**, **17**−**22**, **24b**,**c**,**e**, **26**, **27**, and **35**, characterization data for compounds **25** and **26**, and preparation and characterization data for compounds **9′**, **11**, **21**, **30**, **31**, **34**, and **35**. This material is available free of charge via the Internet at http://pubs.acs.org.

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