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Total Synthesis of (±)-Murrayazoline

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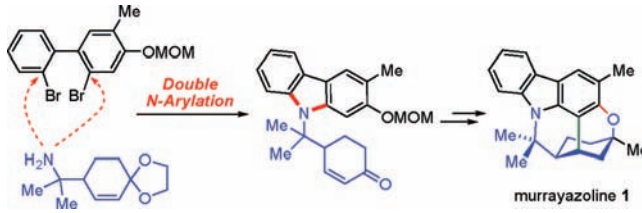
ABSTRACT



The total synthesis of (±)-murrayazoline (1) is described. The characteristic hexa-heterocyclic structure of 1 was constructed by a combination of the intramolecular Friedel−Crafts-type Michael addition and Pd-catalyzed C−O coupling reactions. The N-substituted carbazole component was synthesized in one pot by the double N-arylation of a sterically hindered amine with a dibromobiphenyl derivative.

Murrayazoline (**1**, also known as curryangin and mahanimbidine) is a carbazole alkaloid isolated as a racemic or an optically active compound from the genus *Murraya*.[1] The plants of the genus *Murraya* are shrubs belonging to Rutaceae that have been used as a source of folk medicine for the treatment of analgesia, local anesthesia, eczema, rheumatism, and dropsy in Southern Asia,[1c,d] and murrayazoline and its related carbazole alkaloids have been reported to show a potent antiplatelet aggregation activity.[1e] A structural elucidation study by spectral analyses revealed that murrayazoline is a novel hexa-heterocyclic alkaloid composed of N-substituted carbazole, dihydropyran, and cyclohexane components.[1] The unique structure of **1** was later confirmed by a single-crystal X-ray analysis.[2] Murrayazoline is believed to be biologically synthesized from 2-hydroxy-3-methylcarbazole and a monoterpene (C_{10}) fragment via mahanimbin (**2**), also isolated from the same plant, by the action of the acid. Indeed, Dutta, Quasim, and Wadia reported that when 2-hydroxy-3-methylcarbazole and citral were treated with $SnCl_2$, $FeCl_3$,[1b,3] or polyphosphoric acid, a mixture containing some amount of **1** and **2** was obtained.[3] In spite of its intriguing hexa-heterocyclic structure, which is synthetically fascinating and challenging, no other synthetic approaches to murrayazoline have appeared. In this paper, we report the nonbiomimetic total synthesis of **1**.

Recently, we reported the one-step construction of N-substituted carbazoles by way of the palladium-catalyzed double N-arylation reaction of various primary amines with

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2,2′-dibromobiphenyl derivatives.[4] The double N-arylation, first developed by Nozaki and co-workers,[5] is an important extension of the Buchwald−Hartwig N-arylation reaction[6] and proved to be an excellent protocol for the regioselective construction of unsymmetrical multisubstituted carbazoles in one step.[4,5,7] The usefulness of the reaction has been clearly shown by the efficient total syntheses of the carbazole alkaloids mukonine[5b] and murrastifoline A,[4] and the preparation of aza[7]helicene derivatives,[5c] π-conjugated heteroacenes,[5d] and dithieno[3,2-*b*:2′,3′-*d*]pyrroles.[8]

Our retrosynthetic analysis of **1**, taking into account the utilization of the double N-arylation, suggested that the pentacyclic carbazole−cyclohexanone **3** would be a promising precursor (Figure 1). Compound **3** was expected to be

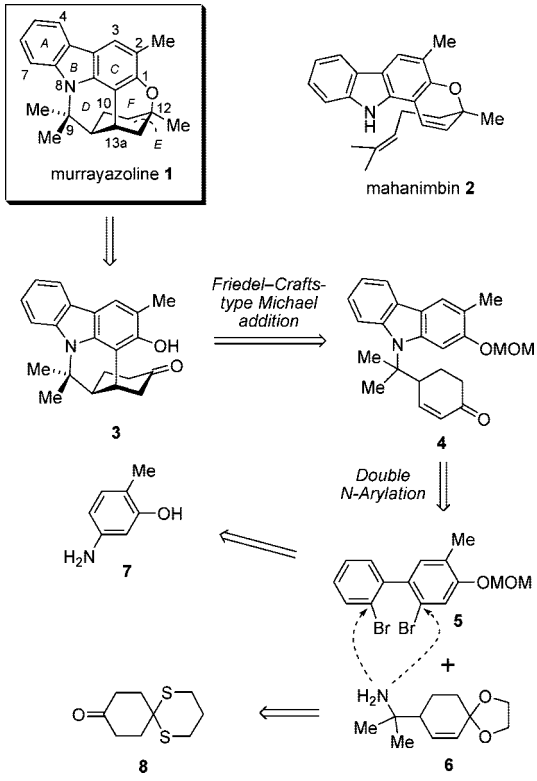
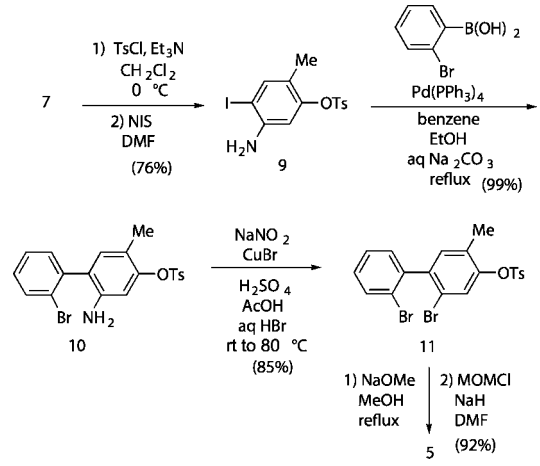


Figure 1. Structures of murrayazoline (**1**) and mahanimbin (**2**) and retrosynthetic analysis of **1**. MOM = $-CH_2OMe$.

prepared by the intramolecular Friedel−Crafts-type Michael addition of N-substituted carbazole **4**. For the preparation of **4**, the double N-arylation reaction of amine **6** with dibromobiphenyl derivative **5** was planned. The two requisite fragments **5** and **6** were envisioned to be derived from 5-amino-2-methylphenol (**7**) and the known 1,5-dithiaspiro-[5,5]unedecane-9-one[9](**8**), respectively.

The synthesis of dibromobiphenyl **5** commenced from commercially available **7** (Scheme 1). The O-tosylation of

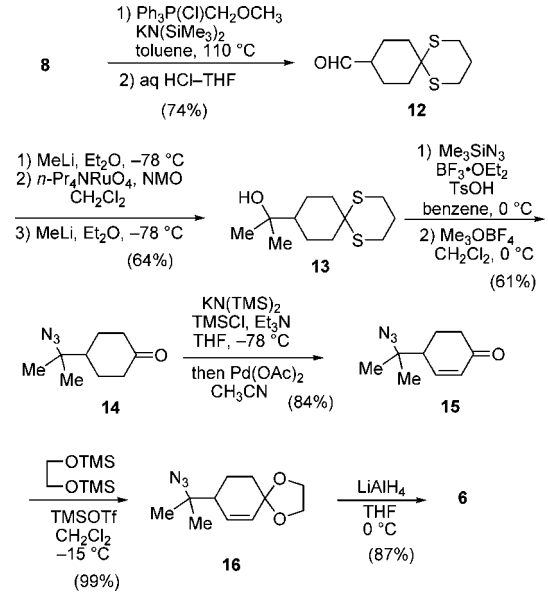
Scheme 1. Preparation of Dibromobiphenyl **5**



7, followed by the conventional iodination with *N*-iodosuccinimide (NIS) gave **9** in 76% yield. The Suzuki−Miyaura cross-coupling[10] of **9** with 2-bromophenylboronic acid cleanly afforded biphenyl **10** in 99% yield. Sandmeyer reaction of **10** under standard conditions provided dibromobiphenyl **11** (85% yield). The *O*-Ts protecting group in **11** was removed by basic methanolysis to give a phenol whose *O*-methoxymethylation furnished **5** in 92% yield from **11**.

The counterpart, the E-ring possessing a primary amine function **6**, was synthesized as shown in Scheme 2. Wittig reaction of the known monothioacetal[9] **8**, prepared from cyclohexane 1,4-dione, with $Ph_3P=CHOMe$, followed by

Scheme 2. Preparation of E-Ring **6**



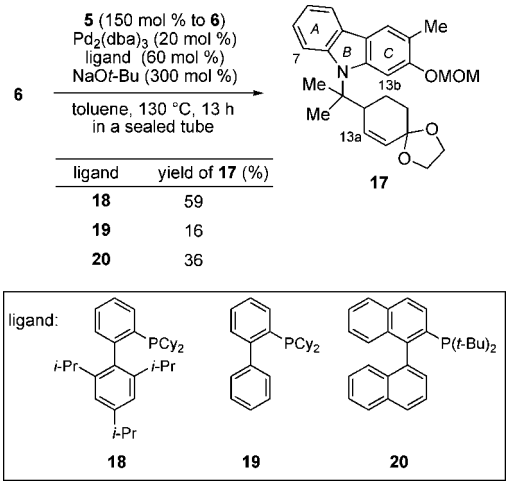
(7) For other approaches for the Pd-catalyzed one-step construction of carbazoles, see: (a) Bedford, R. B.; Betham, M. *J. Org. Chem.* **2006**, *71*, 9403. (b) Watanabe, T.; Ueda, S.; Inuki, S.; Oishi, S.; Fujii, N.; Ohno, H. *Chem. Commun.* **2007**, 4516. (c) Ackermann, L.; Althammer, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 1627. (d) Kitamura, Y.; Yoshikawa, S.; Furuta, T.; Kan, T. *Synlett* **2008**, 377.

(8) Koeckelberghs, G.; De Cremer, L.; Vanormelingen, W.; Dehaen, W.; Verbiest, T.; Persoons, A.; Samyn, C. *Tetrahedron* **2005**, *61*, 687.

acid hydrolysis afforded aldehyde **12** in 74% yield from **8**. The treatment of **12** with MeLi, followed by oxidation afforded a methyl ketone, which was then reacted with MeLi to give tertiary alcohol **13** in 64% yield. The reaction of **13** with $TMSN_3$ in the presence of $BF_3{\cdot}OEt_2$[11] and subsequent deprotection of the thioacetal group afforded azide **14** (61% for two steps). Ito−Saegusa oxidation of **14** cleanly provided racemic cyclohexenone **15** in 84% yield. Protection of the ketone carbonyl group as an ethylene ketal followed by reduction of the azide function afforded amine **6** in 86% yield from **15**.

With both desired segments **5** and **6** in hand, the crucial double N-arylation reaction was explored (Scheme 3). In our earlier study of the palladium-catalyzed double-N-arylation of simple amines with 2,2′-dibromobiphenyl, it was revealed that the use of $Pd_2(dba)_3$ as a palladium source, phosphine **18**[6d] as a ligand and NaO-*t*-Bu as a base gave acceptable results when the sterically hindered aliphatic amine (*tert*-butylamine) was employed.[4] Actually, when a mixture of amine **6** and biphenyl **5** in toluene was heated at 130 °C in the presence of $Pd_2(dba)_3$, NaO-*t*-Bu, and ligand **18**, the double N-arylation successfully took place to provide the desired N-substituted carbazole **17** in 59% yield. The use of other ligands, **19** and **20**,[6c,e] as anticipated, resulted in the lower yields of **17**.

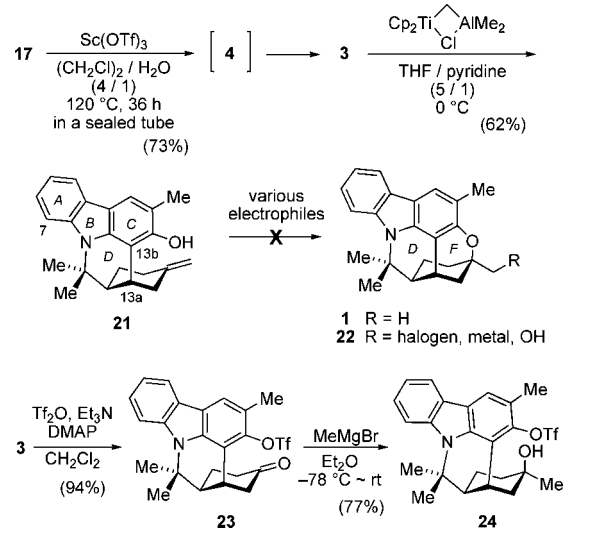
Scheme 3. Construction of a Carbazole by the Double N-Arylation of **6** with **5**



ligand	yield of **17** (%)
18	59
19	16
20	36

The treatment of **17** with $Sc(OTf)_3$ in dichloroethane and H_2O at 120 °C induced the deprotection of the ethylene ketal group as well as the intramolecular Friedel−Crafts-type Michael addition and the deprotection of the *O*-MOM group to construct the D-ring, thus providing pentacyclic ketone **3** in 73% yield (Scheme 4).[12]In this reaction, the electrophilic aromatic substitution exclusively occurred on the C-ring and no formation of other isomers was observed; the electron-donating substituents (*O*-MOM and methyl groups) increased the reactivity of the C-ring to make the new C−C bond between C-13b and C-13a, but not between C-7 and C-13a (murrayazoline numbering).

Scheme 4. Construction of the ABCDE Pentacyclic Structure



Having completed the synthesis of the pentacyclic structure, we next turned our attention to the transformation of **3** into murrayazoline. Tebbe olefination of **3** gave *exo*-olefin **21** in 62% yield. For the construction of the dihydropyranyl F-ring, compound **21** was treated with some Brønsted and Lewis acids (H_2SO_4, CF_3CO_2H, and $Sc(OTf)_3$); however, under these acidic conditions, only decomposition of the substrate was observed. The attempted halo-etherification with NBS or I_2 also resulted in a decomposition.[13] The treatment of **21** with other various electrophiles, such as Hg(II) salts,[14] Pd(II) salts,[15] *N*-(phenylseleno)phthalimide,[16] *m*-CPBA, and oxone−acetone,[17] gave a complex mixture of unidentified products, and the formation of the desired compound **22** was not detected.

(9) Rupp, H.; Schwarz, W.; Musso, H. *Chem. Ber.* **1983**, *116*, 2554.
(10) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147.
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(12) For recent reports of Lewis acid-catalyzed Friedel−Crafts-type Michael addition. See: (a) Zhuang, W.; Hansen, T.; Jørgensen; K, A. *Chem. Commun.* **2001**, 347. (b) Zhou, J.; Tang, Y. *J. Am. Chem. Soc.* **2002**, *124*, 9030. (c) Yamazaki, S.; Morikawa, S.; Iwata, Y.; Yamamoto, M.; Kuramoto, K. *Org. Biomol. Chem.* **2004**, *2*, 3134. (d) Yamazaki, S.; Iwata, Y. *J. Org. Chem.* **2006**, *71*, 739. (e) Kawatsura, M.; Aburatani, S.; Uenishi, J. *Tetrahedron* **2007**, *63*, 4172. For the use of $Sc(OTf)_3$ in Friedel−Crafts alkylation, see: (f) Tsuchimoto, T.; Tobita, K.; Hiyama, T.; Fukuzawa, S.-I. *J. Org. Chem.* **1997**, *62*, 6997.
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(16) (a) Germay, O.; Kumar, N.; Thomas, E. J. *Tetrahedron Lett.* **2001**, *42*, 4969. (b) Iwasaki, K.; Nakatani, M.; Katoh, T. *Tetrahedron Lett.* **2002**, *43*, 7937. (c) Nicolaou, K. C.; Petasis, N. A.; Claremon, D. A. *Tetrahedron* **1985**, *41*, 4835.
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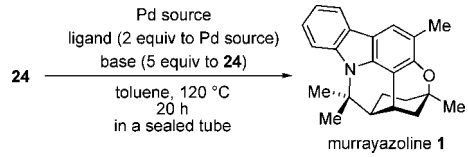
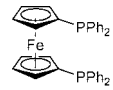
These unsuccessful results led us to examine the intramolecular C−O coupling of a tertiary alcohol function with an aryl *O*-triflate moiety (Scheme 4 and Table 1). Thus, compound **3** was converted into its *O*-triflate derivative **23** in 94% yield by the action of Tf_2O, Et_3N, and DMAP. The reaction of **23** with MeMgBr in Et_2O afforded tertiary alcohol **24** as a single diastereomer in 72% yield from **3**. Although the Ullmann-type etherification of **24** (CuI, 1,10-phenanthroline, Cs_2CO_3 in toluene)[18] resulted in the decomposition of the substrate, the palladium-catalyzed Buchwald−Hartwig conditions[5c,d,6a,c,i,19] were successful. Among the conditions examined (Table 1) when **24** was treated with a stoichiometric amount of $Pd(OAc)_2$, ligand **26**,[19e] and $CsCO_3$ in toluene at 120 °C in a sealed tube for 20 h, (±)-murrayazoline (**1**) was obtained in 80% yield.[20] The ^1H and ^{13}C NMR, and MS data of the synthetic **1** were totally identical to those of natural murrayazoline, kindly provided by Professor Furukawa, and the melting point of the synthetic **1** (263−264 °C) showed good agreement with that reported for the natural (±)-murrayazoline (266 °C).[1b]

Table 1. Intramolecular C−O coupling of **24**



murrayazoline **1**

Pd source (mol %)	ligand[a]	base	yield (%)[b]
$Pd(OAc)_2$ (100)	**25**	Cs_2CO_3	NR[c]
$Pd(OAc)_2$ (100)	**20**	Cs_2CO_3	24
$Pd(OAc)_2$ (100)	**26**	Cs_2CO_3	80
$Pd(OAc)_2$ (20)	**26**	Cs_2CO_3	22
$Pd(OAc)_2$ (100)	**26**	K_3PO_4	NR
$Pd_2(dba)_3$ (100)	**26**	Cs_2CO_3	29

[a]


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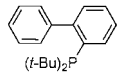

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[b] Isolated yields after chromatographic purification. [c] No reaction.

In summary, the total synthesis of (±)-murrayazoline A (**1**) has been accomplished. This nonbiomimetic synthesis revealed that the double N-arylation is a powerful method for the construction of structurally complex carbazoles. The effective preparation of the hexa-heterocyclic structure in **1** by exploiting the intramolecular Friedel−Crafts-type Michael addition and Bachwald−Hartwig C−O coupling reactions would be applicable for the synthesis of natural products possessing complex multicyclic structures.[21]

Acknowledgment. We thank Professor Hiroshi Furukawa (Meijo University, Nagoya, Japan) for providing us with the spectral data and a sample of the natural murrayazoline.

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

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(20) The severe steric hindrance due to the pentacyclic structure as well as the electron-rich nature of the aryl moiety (C-ring) in **24** would be responsible for the lower efficiency of the catalytic cycle in the C−O coupling. Further screening of ligands might make this process catalytic. For the development of a tunable ligand system in the Pd-catalyzed C−O coupling reaction, see ref 19f.

(21) Chiral synthesis of **1** would be possible if cyclohexenone **15** could be prepared in an optically active form. A study of an enantioselective desymmetrization of **14** utilizing chiral lithium bases is underway. For recent reports of enantioselective deprototation of ketones, see: (a) Rodeschini, V.; Simpkins, N. S.; Wilson, C *J. Org. Chem.* **2007**, *72*, 4265. (b) Inoue, M.; Lee, N.; Kasuya, S.; Sato, T.; Hirama, M.; Moriyama, M.; Fukuyama, Y. *J. Org. Chem.* **2007**, *72*, 3065. (c) Toriyama, M.; Sugasawa, K.; Motohashi, S.; Tokutake, N.; Koga, K. *Chem. Pharm. Bull.* **2001**, *49*, 468.