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An Efficient, One-Pot Synthesis of Isomeric Ellipticine Derivatives through Intramolecular Imino-Diels−Alder Reaction

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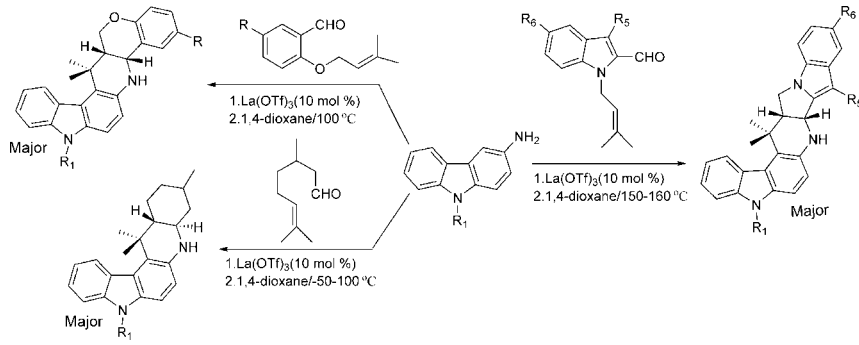
ABSTRACT



New analogues of isomeric ellipticine derivatives fused with biologically important pyrroloindole or chromene moiety have been synthesized by utilizing an intramolecular imino Diels−Alder reaction in a single step.

Polycyclic nitrogen-containing heterocycles form the basic skeleton of numerous alkaloids and physiologically active compounds.[1] Ellipticine is a naturally occurring alkaloid of the 6*H*-pyridocarbazole family; this compound and its derivatives are endowed with antitumor and anticancer properties. They are DNA intercalating molecules, and their high DNA binding affinity is thought to be responsible in part for these pharmacological properties.[2,3] The main reason for the interest in ellipticine and its derivatives for clinical purposes is their high efficiency against several types of cancer, limited toxic side effects, and complete lack of hematological toxicity.[4] Ellipticine has proven to be a popular target for synthesis, and a wide variety of strategies have been reported.[5−7] Similarly, the structurally related aryl- and heteroarylannulated carbazoles have also received considerable synthetic attention.[5−8] Despite the great interest that has given rise to much synthetic work on ellipticine and its derivatives, very little attention has been focused on the synthesis of its isomers and fused with other biologically important molecules.[9] Most of these methods provide access to a variety of derivatives. Still, general and facile synthetic approaches are required to obtain analogues for pharmacological evaluation. In this paper, we present our recent results demonstrating that imines derived from *N*-prenylated indole-

(1) Southon, I. W., Buckingham, J., Eds. *Dictionary of Alkaloids*; Chapman & Hall: New York, 1989.

(2) Wang, J. C. *Annu. Rev. Biochem.* **1996**, *65*, 635–692.

(3) (a) Monks, N. R.; Blankey, D. C.; East, S. J.; Dowell, R. I.; Caluete, J. A.; Curtin, N. J.; Arris, C. E.; Newell, D. R. *Eur. J. Cancer* **2002**, *11*, 1543–1552. (b) LePez, J. B.; DzXuong, N.; Gosse, C.; Paolett, C. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 5078–5082.

(4) Auclair, C. *Arch. Biochem. Biophys.* **1987**, *259*, 1–14.

(5) (a) Gribble, G. W. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, CA, 1990, p 239–352. (b) Knölker, H.-J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303–4427. (c) Marsais, F.; Pineau, P.; Nivolliers, F.; Mallat, M.; Turck, A.; Godard, A.; Queguiner, G. *J. Org. Chem.* **1992**, *57*, 565–573. (d) Gribble, G. W. *Synlett* **1991**, *28*, 289–300. (e) Gribble, G. W.; Saulnier, M. G.; Sibi, M. P.; Obaza-Nutaitis, J. A. *J. Org. Chem.* **1984**, *49*, 4518–4523.

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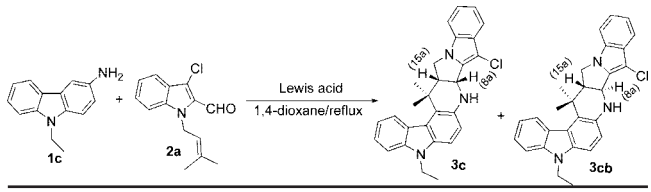
Table 1. Effects of Various Lewis Acids or Brønsted Acids

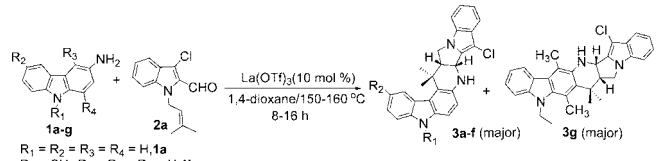


entry	catalyst	time (h)	yield[a] (%)	dr ratio
1	Amberlite-120 (0.1 g)	24	30	60:40
2	Montmorillonite K10 (0.1 g)	24	33	55:45
3	*N*-Boc L-proline (20 mol %)	96	40	90:10
4	Dowex 20-50 mesh (0.1 g)	24	47	54:46
5	$LiClO_4$ (20 mol %)	24	48	71:29
6	Salen $(Mn)H_2$ (20 mol %)	24	49	89:11
7	$BF_3{-}OEt_2$ (20 mol %)	24	51	68:32
8	$CF_3{-}COOH$ (20 mol %)	24	60	62:38
9	CAN (20 mol %)	24	65	74:26
10	$BiCl_3$ (20 mol %)	24	70	77:23
11	molecular iodine (20 mol %)	48	71	71:29
12	$InCl_3$ (20 mol %)[b]	24	82	84:16
13	[Emim]-$[BF_4]$[c]	24	80	70:30
14	[Emim]-$[PF_6]$[c]	24	85	75:25
15	$PPh_3.HClO_4$ (20 mol %)	24	70	77:23
16	PPh_3 triflate (20 mol %)	24	75	73:27
17	$In(OTf)_3$ (10 mol %)	20	83	87:13
18	$Sc(OTf)_3$ (10 mol %)	12	85	87:13
19	$Yb(OTf)_3$ (10 mol %)	12	85	88:12
20	$La(OTf)_3$ (10 mol %)	12	87	91:09
21	$La(OTf)_3$ (10 mol %)[d]	12	85	94:06
22	**$La(OTf)_3$(10 mol %)[e]**	**10**	**88**	**97:03**

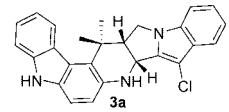
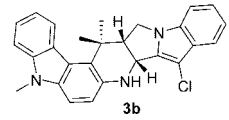
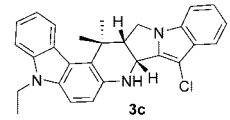
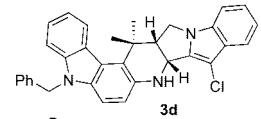
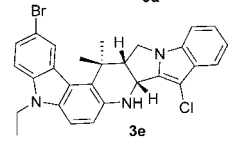
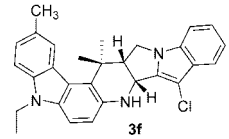
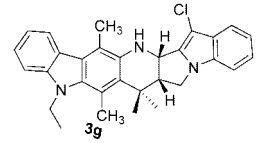
[a] Reactions were carried out at 100 °C, and isolated yields are reported. [b] The temperature was 50 °C; above this temperature, side products were formed. [c] 0.5 g of ionic liquid was used as solvent as well as catalyst. [d] The temperature of the reaction was 130−140 °C. [e] The temperature of the reaction was 150−160 °C.

2-carboxaldehydes and aminocarbazoles are excellent substrates for an intramolecular imino Diels−Alder reaction catalyzed by $La(OTf)_3$ to provide a highly functionalized products with high diastereoselectivity.

Table 2. Imino Diels−Alder Reaction of Various Amines with **2a** in the Presence of $La(OTf)_3$ (10 mol %)



$R_1 = R_2 = R_3 = R_4 = H$,**1a**
$R_1 = CH_3, R_2 = R_3 = R_4 = H$,**1b**
$R_1 = C_2H_5, R_2 = R_3 = R_4 = H$,**1c**
$R_1 = C_7H_7, R_2 = R_3 = R_4 = H$,**1d**
$R_1 = C_2H_5, R_2 = Br, R_3 = R_4 = H$,**1e**
$R_1 = C_2H_5, R_2 = CH_3, R_3 = R_4 = H$,**1f**
$R_1 = C_2H_5, R_2 = H, R_3 = R_4 = CH_3$,**1g**

Entry	Reactant	Product	Time (h)	Yield (%)	dr ratio
1	1a	 **3a**	12	86	97:03
2	1b	 **3b**	10	89	99:01
3	1c	 **3c**	10	88	97:03
4	1d	 **3d**	8	90	96:04
5	1e	 **3e**	12	85	94:06
6	1f	 **3f**	10	92	96:04
7	1g	 **3g**	16	51	90:10

Hetero-Diels−Alder reactions constitute a powerful method for the preparation of biologically interesting heterocycles and natural products.[10] For instance, the imino Diels−Alder reaction (IDA) provides a rapid means for the construction of functionalized rings containing nitrogen with control of regio-, diastereo-, and enantioselectivity.[11] The reaction of imines with electron-rich dienophiles has been reported to be catalyzed by Lewis acids.[12] However, most of the Lewis acids are either decomposed or deactivated due to the formation of water during imine formation. But lanthanum(III) triflate has been used to catalyze a variety of reactions.[13] It is stable under

(6) (a) Sainsbury, M. *Synthesis* **1977**, 437–448. (b) Alvarez, M.; Joule, J. A. In *The Chemistry of Heterocyclic Compounds*; Saxton, J. E., Ed.; Wiley: Chichester, 1994, pp 261–278. (c) Kansal, V. K.; Potier, P. *Tetrahedron* **1986**, *42*, 2389–2408. (d) Hewlins, M. J. E.; Oliveira-Campos, A.-M.; Shannon, P. V. R. *Synthesis* **1984**, 289–302.

(7) (a) Ishikura, M.; Hino, A.; Yaginuma, T.; Agata, I.; Katagiri, N. *Tetrahedron* **2000**, *56*, 193–207. (b) Mal, D.; Senapati, B. K.; Pahari, P. *Synlett* **2005**, 994–996. (c) Miki, Y.; Hachiken, H.; Yanase, N. *Org. Biomol. Chem.* **2001**, 2213–2216.

(8) (a) Tsuchimoto, T.; Matsubayashi, H.; Kaneko, M.; Shirakawa, E.; Kawakami, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 1336–1340. (b) Martı´nez-Esperón, M. F.; Rodrı´guez, D.; Castedo, L.; Saá, C. *Org. Lett.* **2005**, *7*, 2213–2216.

(9) (a) Fujiwara, A. N.; Acton, E. M.; Goodman, L. *J. Med. Chem.* **1967**, *10*, 126–127. (b) May, C.; Moody, C. J. *Chem. Commun.* **1984**, 926. (c) Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.* **1983**, *48*, 2690–2695. (d) Perche, J.-C.; Ruf, S. G.; Buu-Hoï, N. P. *J. Chem. Soc., Perkin Trans. 1* **1972**, 260–262. (e) Elmes, B. C.; Swan, J. M. *Aust. J. Chem.* **1969**, *22*, 1963–1974. (f) Bergman, J.; Carlsson, R. *Tetrahedron Lett.* **1978**, *42*, 4051–4054. (g) Gribble, G. W.; Fletcher, G. L.; Ketcha, D. M.; Rojopadhya, M. *J. Org. Chem.* **1989**, *54*, 3264–3269. (h) Kano, S.; Sugino, E.; Shibuya, S.; Hibino, S. *J. Org. Chem.* **1981**, *46*, 2979–2981. (i) Bistocchi, G. A.; Orvietani, P.; Mauffret, O.; Antri, S. E.; Deroussent, A.; Jacquignon, P. C.; Fermandjian, S.; Ricci, A.; Lescot, E. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2935–2942.

(10) Haug, H.-S.; Chiou, J.-F.; Fong, Y.; Hou, C.-C.; Lu, Y.-C.; Wang, J.-Y.; Shih, J.-W.; Pan, Y.-R.; Lin, J.-J. *J. Med. Chem.* **2003**, *46*, 3300–3307.

aqueous conditions and catalyzes aldol and allylation reactions in aqueous media.[14]

Construction of the polycyclic isomeric ellipticine ring systems employing the cycloaddition of imine derived from *N*-prenylated-2-formyl-3-chloroindole **2a** with 9-ethyl-3-aminocarbazole in 1,4-dioxane at reflux temperature underwent intramolecular [4 + 2] cycloaddition in the presence of a Lewis acid to yield 9-chloro-5-ethyl-16,16-dimethyl-5,8,8a,15,15a,16-hexahydrobenzo[5′,6′]pyrrolizino[2′,1′:5,6]pyrido[2,3-*c*] carbazoles **3c** and **3cb** as a mixture of diastereomers, where the cis isomer is the major product (Table 1).

The reactions proceed smoothly in the presence of Lewis acids or Brønsted acids, but diastereoselectivity depends on the nature of the catalyst (Table 1). However, the cis diastereomer is always the major product. Several catalysts were screened, and among them, $Sc(OTf)_3$, $Yb(OTf)_3$, and $La(OTf)_3$ were found to be better since they provided excellent diastereoselectivity and also have similar reactivity in terms of reaction yield, diastereomer ratio and reaction time. The diastereoselectivity was further improved by maintaining the reaction at 130−140 or 150−160 °C with $La(OTf)_3$ (10 mol %) as catalyst. Further increase in the temperature did not improve the diastereomer ratio with the other catalysts listed in Table 1, except for $Sc(OTf)_3$ and $Yb(OTf)_3$. After several experiments, we found that good yield and excellent diastereoselectivity were obtained when the reaction was carried out in 1,4-dioxane at 150−160 °C. The reaction was faster in 1,4-dioxane than in CH_3CN and THF. Moderate yields were obtained in DMSO or toluene.

The stereochemistry was assigned on the basis of the coupling constant values and also by NOE studies.The five-membered pyrrolidine and six-membered piperidine rings were cis fused, as indicated by the coupling constant J_{8a-15a} = 7.2 Hz between H_{8a} (δ 5.05) and H_{15a} (δ 3.22) in product **3c** and also the strong NOE (34%) enhancement of H_{15a} upon irradiation of H_{8a}. The high coupling constant, J_{8a-15a} = 10.6 Hz between H_{8a} (δ 4.68) and H_{15a} (δ 2.93), supported the trans configuration of the structure of product **3cb**, and there was no considerable NOE between these two protons. Isomers **3cb** and **3a** were also confirmed by single-crystal X-ray diffraction analysis.[15]

Extending this methodology further, we have carried out the imino Diels−Alder reaction of 2**a** with various substituted amines in the presence of $La(OTf)_3$ (10 mol %) under the optimized conditions. The results are summarized in Table 2. In most cases, the corresponding imino Diels−Alder products **3a**−**f** were obtained in excellent yields (Table 2, entries 1−6). The fact that the amine **2g**, having substituents on the first and fourth positions ($R_3 = R_4 = CH_3$), has the slower rate of reaction and that the corresponding product **3g** was obtained in only 51% yield may be due to the steric hindrance of two methyl substituents (Table 2, entry 7). The X-ray crystal structure of **3a** was elucidated in Figure 1.[15]

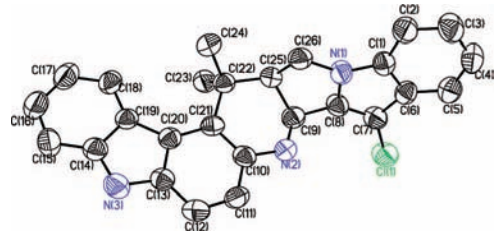
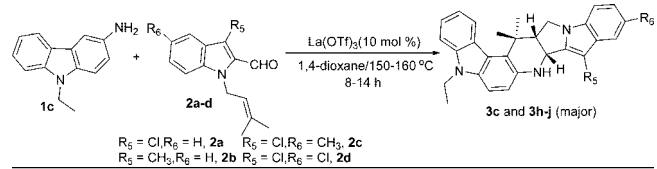
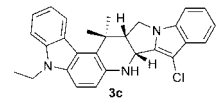
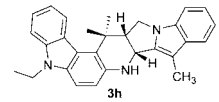
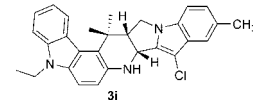
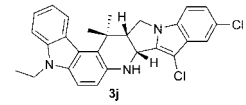


Figure 1. X-ray crystal structure of **3a**.

We, next carried out the imino Diels−Alder reaction of **1c** with prenylated indole-2-aldehydes (**2a**−**d**) in the presence of $La(OTf)_3$ (10 mol %) under the optimized conditions.

Table 3. Synthesis of 16,16-Trimethyl-5,8,8a,15,15a,16-hexahydrobenzo[5′,6′]pyrrolizino[2′,1′:5,6]pyrido[2,3-*c*]carbazole Derivatives



Entry	R_5	R_6	Product	Time (h)	Yield (%)	dr ratio
1	Cl	H	 **3c**	10	88	97:03
2	CH_3	H	 **3h**	8	92	95:05
3	Cl	CH_3	 **3i**	8	93	97:03
4	Cl	Cl	 **3j**	14	85	98:02

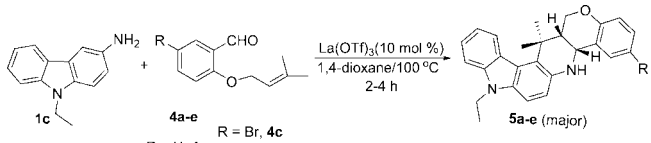
The results are summarized in Table 3. In all cases, the corresponding cycloaddition products (**3c** and **3h**−**j**) were obtained in excellent yields (Table 3). The electron donating or electron-withdrawing substituents (R_5 and R_6) did not significantly affect the reaction rate. The X-ray crystal structures of **3h**−**j** were obtained to confirm their structures.[15]

To prove the generality of this reaction, we have also examined the reactions of O-prenylated salicylaldehydes with aminocarbazole (**3c**) under the same reaction conditions.

The cycloaddition of **1c** with **4a** at 100 °C proceeded efficiently in 1,4-dioxane to afford **5a** in excellent yield (88%,

(11) (a) Waldmann, H. *Synlett* **1995**, 133–141. (b) Barluenga, J.; Joglar, J.; Gonzalez, F. J.; Fustero, S. *Synlett* **1990**, 129–138. (c) Kobayashi, S. *Eur. J. Org. Chem.* **1999**, 15–27. (d) Stevenson, P. J.; Nieuwenhuyzen, M.; Osborne, D. *Chem. Commun.* **2002**, 444–445. (e) Babu, G.; Perumal, P. T. *Aldrichimica Acta* **2000**, *33*, 16–22. (f) Waldmann, H. *Synthesis* **1994**, 535–551. (g) Behforouz, M.; Ahmadian, M. *Tetrahedron* **2000**, *56*, 5259–88. (h) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1–120. (i) Vogt, P. F.; Miller, M. J. *Tetrahedron* **1998**, *54*, 1317–48.

Table 4. Imino Diels−Alder Reaction of **3c** with Various Substituted O-Prenylated Salicylaldehydes



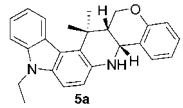
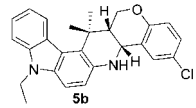
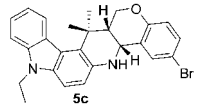
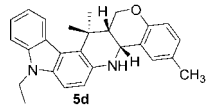
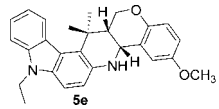
Entry	R	Product	Time (h)	Yield (%)	dr ratio
1	H	 **5a**	3	88	97:03
2	Cl	 **5b**	2	92	95:05
3	Br	 **5c**	2	93	97:03
4	CH_3	 **5d**	4	85	98:02
5	OCH_3	 **5e**	4	85	98:02

Table 4) with higher diastereoselectivity ration; the cis isomer is the major product. Increase in temperature further decreases the reaction yield. In the case of products derived from **4c**, both cis (**5c**) and trans (**5cb**) isomers were separated; their structures were also confirmed by single-crystal X-ray analysis (Figure 2).[15] The results are summarized in Table 4.

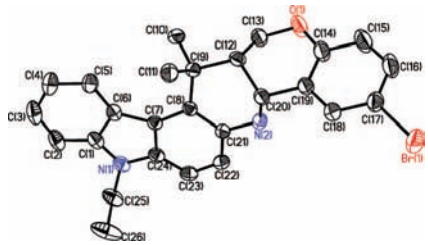
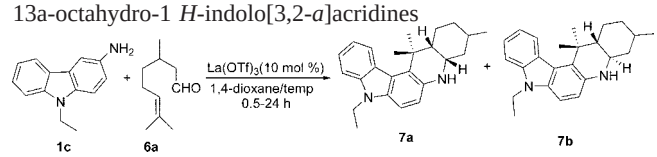


Figure 2. X-ray crystal strucure of **5c**.

We have also examined the imine derived from aliphatic aldehyde **6a** as a dienophile, and the reaction proceeded very smoothly with good yield. Interestingly, the trans isomer is the major product. The diastereoselectivity dramatically changes with respect to the temperature. Better diastereoselectivities were obtained at lower temperature (Table 5).

Table 5. Synthesis of 8-Ethyl-3,13,13-trimethyl-2,3,4,4a,5,8,13,-13a-octahydro-1 *H*-indolo[3,2-*a*]acridines



entry	T (°C)	time (h)	yield (%)	dr ratio[a]
1	150−160	0.5	97	47:53
2	100	1.0	95	40:60
3	RT	6.0	91	21:79
4	0	12.0	90	15:85
5[b]	−50	24.0	95	10:90

[a] Isolated yieds. [b] THF solvent used.

The single-crystal X-ray analysis of compounds **7a** (Figure 3) and **7b** were also achieved in order to confirm their molecular structures.[15]

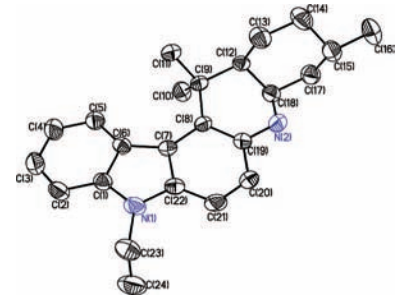


Figure 3. X-ray crystal strucure of **7a**.

In this paper, we described a useful method for the preparation of various isomeric Ellipticine derivatives fused with biologically important pyrroloindole or chromene moiety, utilizing a novel [4 + 2] cycloaddition reaction.

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

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