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Preparation of Polyfunctional Aryl Azides from Aryl Triazenes. A New Synthesis of Ellipticine, 9-Methoxyellipticine, Isoellipticine, and 7-Carbethoxyisoellipticine

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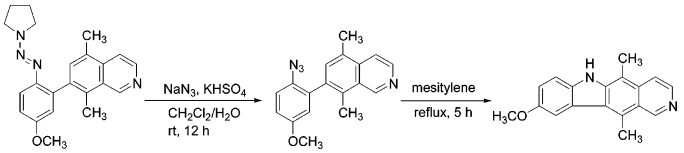
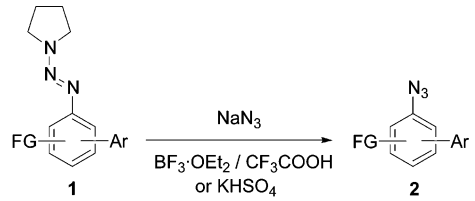


The preparation of polyfunctional aryl azides by the reaction of aryl triazenes with NaN_3 in the presence of $KHSO_4$ or $BF_3{\cdot}OEt_2$/TFA (trifluoroacetic acid) has been described. A variety of functional groups (halides, esters, ketones, nitriles, aldehydes, and boronic esters) are tolerated under the Lewis acidic conditions. By using this methodology, the potent antitumor agents, ellipticine and 9-methoxyellipticine, have been synthesized. In addition, isoellipticine and a related derivative, 7-carbethoxyisoellipticine, were also prepared.

1. Introduction

The use of aryl azides as synthetic intermediates has attracted much attention due to their potential applications in organic synthesis.[1] They have been used for the synthesis of anilines,[2] in cycloaddition reactions,[3] and for the generation of nitrenes.[4] Recently, Bräse has prepared aryl azides starting from polymer-bound triazenes.[5] A variety of triazene resins have proved to be useful intermediates for the solid-phase synthesis of aryl azides. We also reported a halogen−magnesium exchange reaction of halogenated aryl triazenes (X = Br or I) by using the mixed Mg/Li-reagent *i*-PrMgCl·LiCl.[6] This method allowed us to prepare polyfunctional aryl triazenes of type **1** (Scheme 1).[6h] The triazene functionality ($ArN{=}N{-}NR_2$) can be considered as being a synthetic equivalent of a protected diazonium salt. This allows the reactive diazonium salt to carry through several synthetic steps. More noteworthy is the conversion of a triazene moiety to an azide group under mild reaction conditions,

SCHEME 1. Conversion of Triazenes of Type 1 to Azides of Type 2



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(1) (a) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem.* **2005**, *117*, 5320; *Angew. Chem., Int. Ed.* **2005**, *44*, 5188;. (b) Patai, S. The Chemistry of Diazonium and Diazo Groups. In *The Chemistry of Functional Groups*; Patai, S., Ed.; John Wiley: Chichester, UK, 1978.

(2) Kumar, H. M. S.; Reddy, B. V. S.; Anjaneyulu, S.; Jadav, J. S. *Tetrahedron Lett.* **1999**, *40*, 8305.

(3) (a) Huisgen, R. *Angew. Chem.* **1963**, *75*, 604; *Angew. Chem., Int. Ed.* **1963**, *2*, 565. (b) Huisgen, R.; Knorr, R.; Möbius, L.; Szeimies, G. *Chem. Ber.* **1965**, *98*, 4014.

(4) (a) Tiemann, F. *Ber. Dtsch. Chem. Ges.* **1891**, *24*, 4162. (b) Gritsan, N. P.; Pritchina, E. A. *Russ. Chem. Rev.* **1992**, *61*, 500. (c) Budyka, M. F.; Kantor, M. M.; Alfimov, M. V. *Russ. Chem. Rev.* **1992**, *61*, 25. Bucher, G. In *CRC Handbook of Organic Photochemistry and Photobiology*; CRC: Boca Raton, FL, 2004; S. 44/1−44/31.

(5) Bräse, S.; Gil, C.; knepper, K.; Zimmermann, V. *Synlett* **2004**, 1163.

(6) (a) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333. (b) Kopp, F.; Krasovskiy, A.; Knochel, P. *Chem. Commun.* **2004**, 2288. (c) Ren, H.; Krasovskiy, A.; Knochel, P. *Org. Lett.* **2004**, *6*, 4215. (d) Ren, H.; Krasovskiy, A.; Knochel, P. *Chem. Commun.* **2005**, 543. (e) Kopp, F.; Sklute, G.; Polborn, K.; Marek, J.; Knochel, P. *Org. Lett.* **2005**, *7*, 3789. (f) Liu, C. Y.; Ren, H.; Knochel, P. *Org. Lett.* **2006**, *8*, 617. See also: (g) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302. (h) Liu, C. Y.; Knochel, P. *Org. Lett.* **2005**, *7*, 2543.

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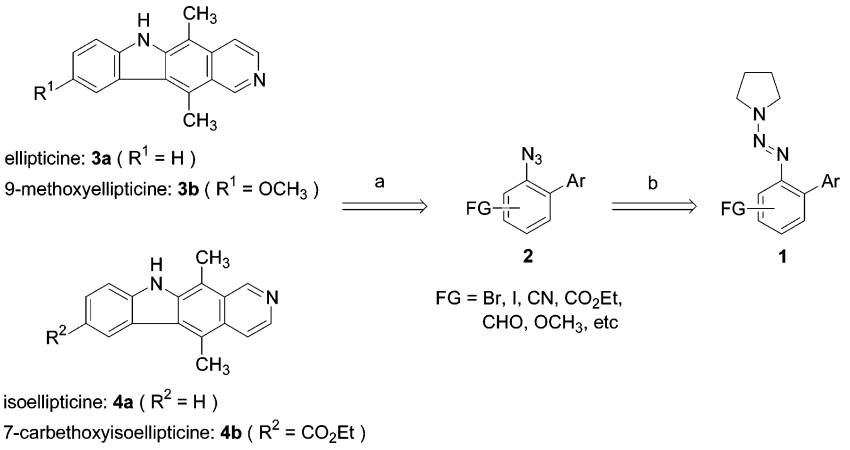
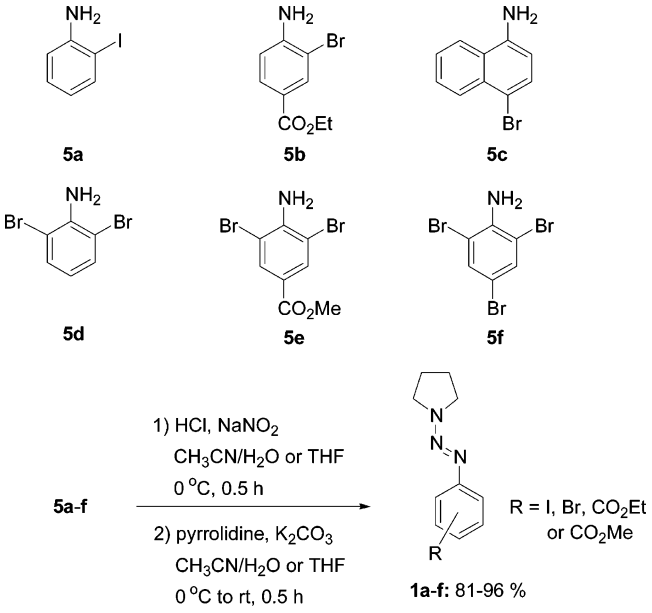
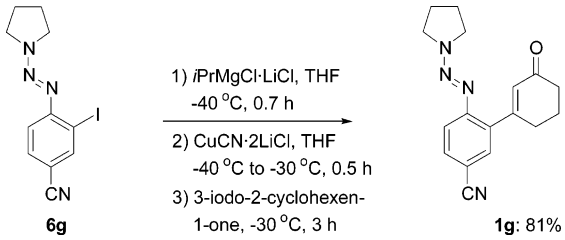
SCHEME 2. Retrosynthetic Analysis of Compounds 3a, 3b, 4a, and 4b: (a) Thermal Decomposition of Azides and (b) Conversion of the Triazene Group to an Azide



SCHEME 3. Synthesis of the Triazenes 1a−f



SCHEME 4. Synthesis of the Polyfunctional Triazene 1g



a transformation that would further extend the scope of this important functionality. Thus, in spite of the importance and usefulness of azides, a practical synthesis of natural products involving a triazene to azide conversion as a key step has not been reported yet. Herein, we wish to develop an efficient method for the conversion of triazenes of type **1** to the polyfunctional aryl azides of type **2** (Scheme 1).

By using this approach, we have envisioned that the biologically active compounds ellipticine (**3a**) and 9-methoxyellipticine (**3b**) could be readily prepared in two steps starting from the corresponding aryl triazenes of type **1** via aryl azides of type **2**. Similarly, the synthesis of isoellipticine (**4a**) and 7-carbethoxyisoellipticine (**4b**) might also be envisaged by using the same strategy (Scheme 2).

2. Results and Discussion

Preparation of Polyfunctional Aryl Triazenes of Type 1. Triazenes **1a−f** were easily prepared from the corresponding anilines **5a−f** (Scheme 3), and the polyfunctional triazenes **1g−o** were prepared from the halo-substituted triazenes **6g−o**, which were further functionalized by using a I/Mg- or Br/Mg-exchange reaction as shown in Schemes 4−8. Thus, 1-(2-iodophenylazo)-pyrrolidine (**1a**) was obtained from 2-iodoaniline **5a** in 92% yield via a diazotation and trapping with pyrrolidine.[6h] Triazenes **1b−f** were also readily prepared from the corresponding anilines **5b−f** under similar reaction conditions (Scheme 3).[6h,7,8] 1-(4-Cyano-2-iodophenylazo)pyrrolidine (**6g**)[6h] reacted with *i*PrMgCl·LiCl affording the expected arylmagnesium derivative, which was transmetalated with CuCN·2LiCl to the corresponding organocopper species.[9] This copper reagent readily underwent an addition−elimination reaction with 3-iodo-2-cyclohexen-1-one[10] giving the triazene **1g** in 81% yield (Scheme 4). The iodoaryltriazenes **6h−j** reacted with *i*PrMgCl·LiCl (−40 °C, 0.7−1 h) giving the magnesiated triazenes, which underwent a copper-catalyzed acylation with furoyl chloride leading to the polyfunctional ketones **1h−j** in 85−88% (Scheme 5). Reaction of the arylmagnesium derivative of 1-(2-carbethoxy-4-iodophenylazo)pyrrolidine (**6k**) with *N*,*N*-dimethylformamide furnished the expected triazene **1k** in 85% yield (Scheme 6). Iron(III)-catalyzed oxidative homocoupling[11] of 1-(4-carbethoxy-2-iodophenylazo)pyrrolidine (**6*l***) afforded the *bis*-triazene **1*l*** in 52% yield with use of Fe(acac)$_3$ (0.5 equiv, −40 °C to rt, 1 h, Scheme 6). The arylmagnesium species of **6m−n** were transmetalated

(7) (a) Wallach, O. *Liebigs Ann. Chem.* **1886**, *235*, 233. (b) Wallach, O.; Heusler, F. *Liebigs Ann. Chem.* **1888**, *243*, 219. (c) Merkushev, E. B. *Synthesis* **1988**, 923. (d) Gross, M. L.; Blank, D. H.; Welch, W. M. *J. Org. Chem.* **1993**, *58*, 2104. (e) Satamurthy, N.; Barrio, J. B.; Bida, G. T.; Phelps, M. E. *Tetrahedron Lett.* **1990**, *31*, 4409. (f) Cohen, T.; Dietz, A. G., Jr.; Miser, J. R. *J. Org. Chem.* **1977**, *42*, 2053.

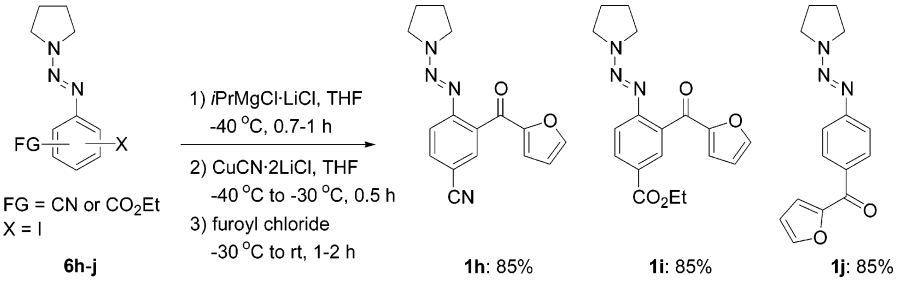
(8) (a) Nicolaou, K. C.; Boddy, C. N. C.; Natarajan, S.; Yue, T. Y.; Li, H.; Bräse, S.; Ramanjulu, J. M. *J. Am. Chem. Soc.* **1997**, *119*, 3421. (b) Nicolaou, K. C.; Li, H.; Boddy, C. N. C.; Ramanjulu, J. M.; Yue, T. Y.; Natarajan, S.; Chu, X. J.; Bräse, S.; Rübsam, F. *Chem. Eur. J.* **1999**, *5*, 2584.

(9) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

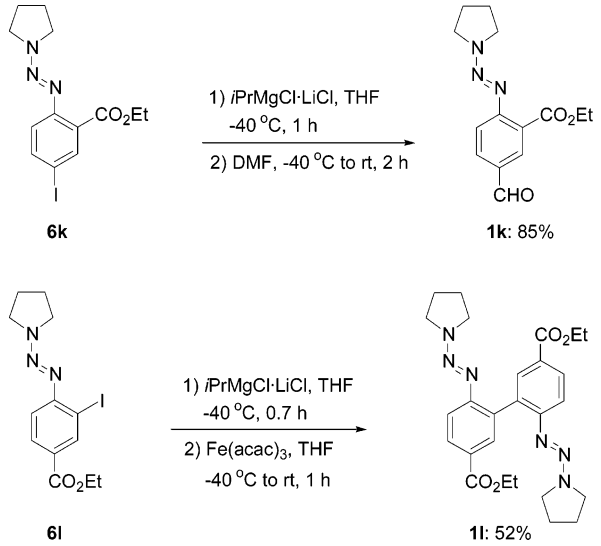
(10) Barnier, J. P.; Blanco, L. *Synth. Commun.* **2003**, *33*, 2487.

(11) Nagono, T.; Hayashi, T. *Org. Lett.* **2005**, *7*, 491.

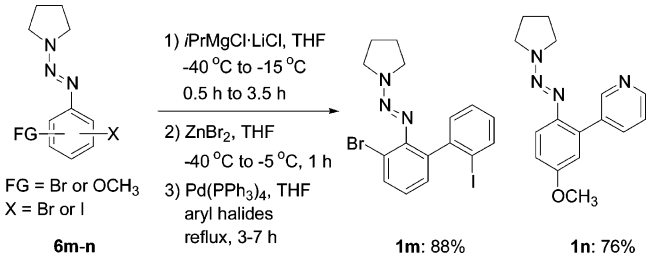
SCHEME 5. Synthesis of the Polyfunctional Triazenes 1h−j



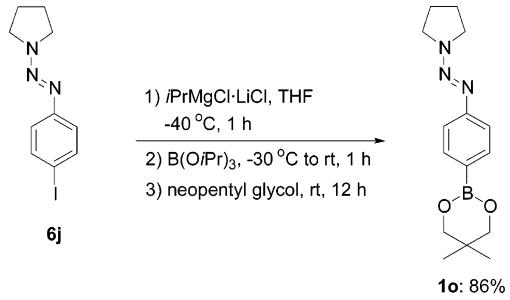
SCHEME 6. Synthesis of the Polyfunctional Triazenes 1k,*l*



SCHEME 7. Synthesis of the Polyfunctional Triazenes 1m,n

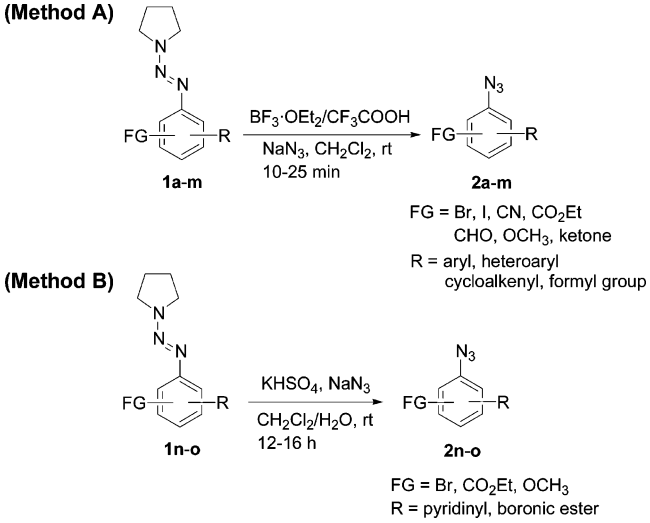


SCHEME 8. Synthesis of the Polyfunctional Triazene 1o



with $ZnBr_2$ to the corresponding arylzinc reagents, then the Negishi cross-coupling reactions[12] were performed respectively with 1,2-diiodobenzene or 3-iodopyridine providing the biphenyl triazenes **1m** (88%) and **1n** (76%) as shown in Scheme 7. Treatment of the arylmagnesium derivative of 1-(4-iodophenylazo)pyrrolidine (**6j**) with triisopropyl borate followed by the addition of neopentyl glycol produced the expected triazene-substituted boronic ester **1o** in 86% yield (Scheme 8).

SCHEME 9. Synthesis of the Polyfunctional Aryl Azides 2a−m (Method A) and 2n,o (Method B)



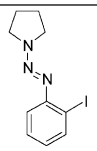
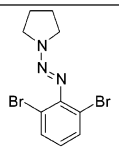
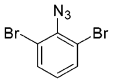
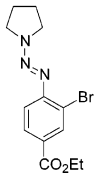
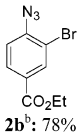
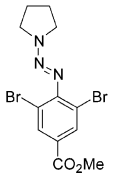
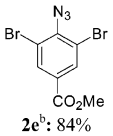
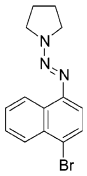
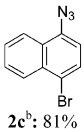
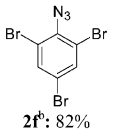
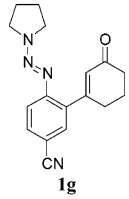
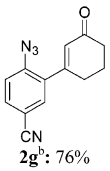
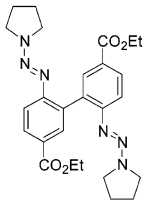
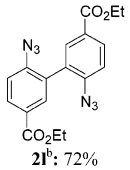
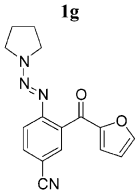
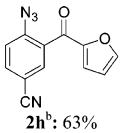
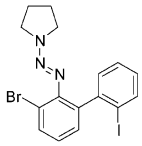
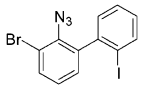
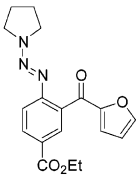
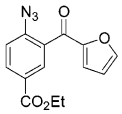
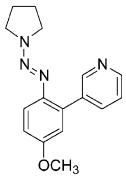
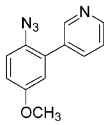
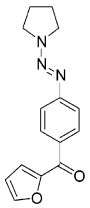
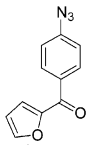
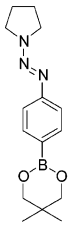
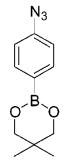
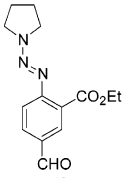
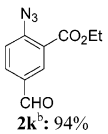
Preparation of Polyfunctional Aryl Azides of Type 2. The aryl triazenes of type **1** can be readily converted to the corresponding azides of type **2** in moderate to excellent yields. The azidation reactions were performed either by using BF_3·OEt_2/TFA (trifluoroacetic acid) in CH_2Cl_2 (Method A)[5] or by using $KHSO_4$ in CH_2Cl_2/H_2O (Method B) at room temperature in the presence of sodium azide (Scheme 9).

Thus, the azidation of 1-(2-iodophenylazo)pyrrolidine (**1a**) was accomplished by using a mixture of BF_3·OEt_2 and TFA (1/1, 2 equiv to the triazene) and sodium azide (2 equiv to the triazene) in CH_2Cl_2 at room temperature (Method A) affording the expected 1-azido-2-iodobenzene (**2a**) in 80% yield (entry 1 of Table 1).

The azidation of aryl triazenes **1b−m** with the same reaction conditions as described above furnished the aryl azides **2b−m** in 72−94% yield (entries 2−13). It is worth noting that the combination of BF_3·OEt_2 and TFA is a more efficient reagent than either reagent alone, BF_3·OEt_2 or TFA. For instance, the reaction of aryl triazenes **1b−m** with either BF_3·OEt_2 (2.0 equiv) or TFA (2.0 equiv) in the presence of sodium azide (2.0 equiv) did not proceed to completion and 30−40% of the starting material was recovered when the reaction mixture was stirred at room temperature for 1 h. The mixture of BF_3·OEt_2 and TFA

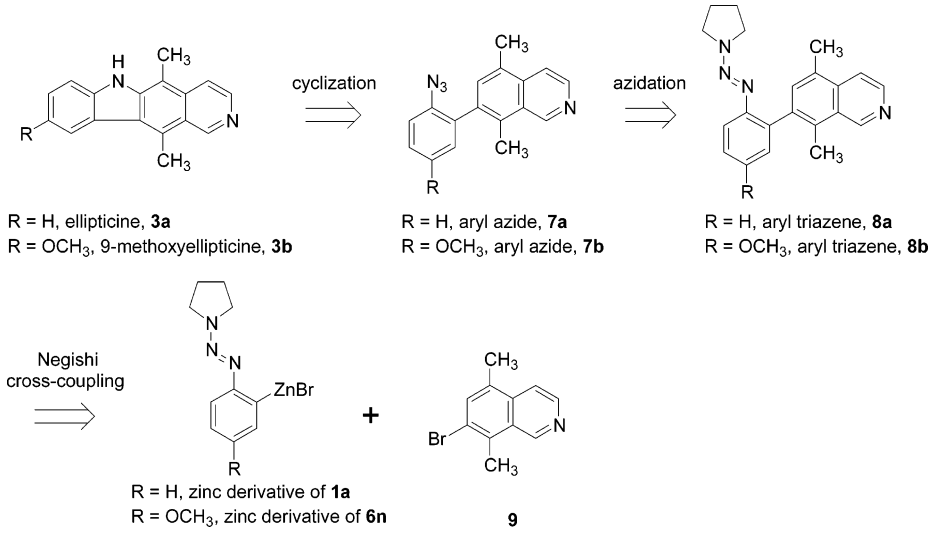
(12) (a) Green, L.; Chauder, B.; Snieckus, V. *J. Heterocycl. Chem.* **1999**, *36*, 1453. (b) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298. (c) Kobayashi, M.; Negishi, E. *J. Org. Chem.* **1980**, *45*, 5223. (d) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340. (e) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Tetrahedron Lett.* **1986**, *27*, 955. (f) Klement, I.; Rottländer, M.; Tucker, C. E.; Majid, T. N.; Knochel, P.; Venegas, P.; Cahiez, G. *Tetrahedron* **1996**, *52*, 7201.

TABLE 1. Preparation of Polyfunctional Aryl Azides of Type 2

Entry	Triazenes of type **1**	Azides of type **2**[a]	Entry	Triazenes of type **1**	Azides of type **2**[a]
1	 **1a**	 **2a**[b]: 80%	4	 **1d**	 **2d**[b]: 88%
2	 **1b**	 **2b**[b]: 78%	5	 **1e**	 **2e**[b]: 84%
3	 **1c**	 **2c**[b]: 81%	6	 **1f**	 **2f**[b]: 82%
7	 **1g**	 **2g**[b]: 76%	12	 **1l**	 **2l**[b]: 72%
8	 **1h**	 **2h**[b]: 63%	13	 **1m**	 **2m**[b]: 78%
9	 **1i**	 **2i**[b]: 86%	14	 **1n**	 **2n**[c]: 78%
10	 **1j**	 **2j**[b]: 93%	15	 **1o**	 **2o**[c]: 96%
11	 **1k**	 **2k**[b]: 94%			

[a] Isolated yield of analytically pure product. [b] Prepared according to Method A: $BF_3{\cdot}OEt_2$/TFA, NaN_3, CH_2Cl_2, rt, 10−25 min. [c] Prepared according to Method B: $KHSO_4$, NaN_3, CH_2Cl_2/H_2O, rt, 12−16 h. TFA = trifluoroacetic acid.

SCHEME 10. Retrosynthetic Analysis of 3a and 3b



can be regarded as a super-Brønsted acid,[13] a more powerful and convenient reagent for the conversion of triazenes to azides. A range of functional groups are also tolerated under these mild reaction conditions giving a practical access to a variety of new functionalized aryl azides. The triazenes **1n** and **1o** were readily converted to the corresponding aryl azides **2n** (78%, entry 14) and **2o** (96%, entry 15) by using $KHSO_4$ (10 equiv) in CH_2Cl_2 at room temperature in the presence of sodium azide (5 equiv). It is interesting to note that heterocycles or reactive functional groups, such as a pyridine ring (compound **2n**) or a boronic ester (compound **2o**), are tolerated. Thus, with $KHSO_4$ as the reagent, a smooth conversion of an aryl triazene to an aryl azide is achieved. However, the reaction time is usually longer (12−16 h; Method B).

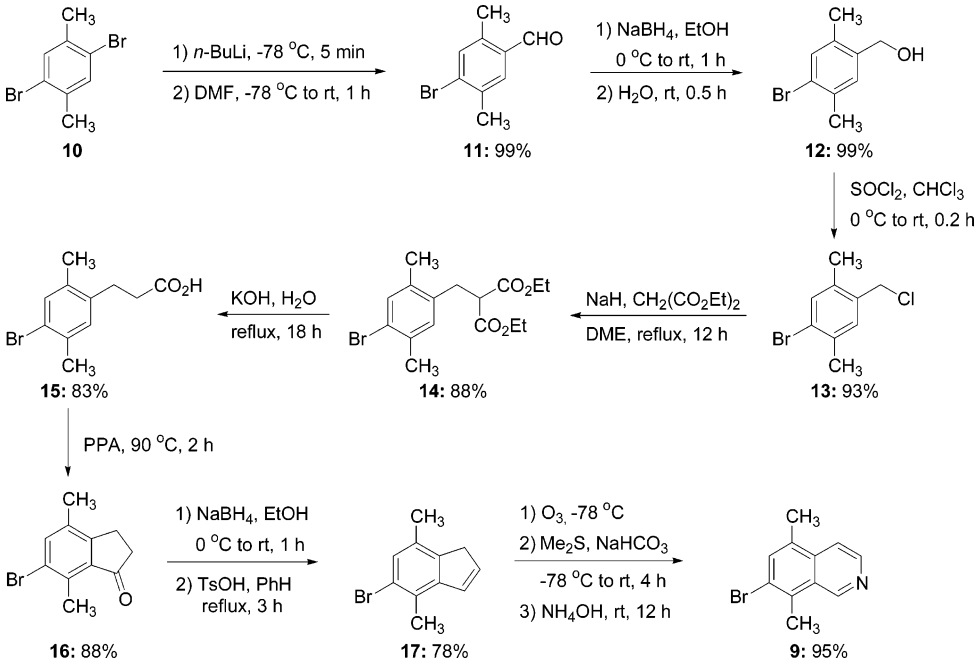
Synthesis of Ellipticine and 9-Methoxyellipticine by the Thermal Decomposition of Azides. The Ochrosia and Aspidosperma plant alkaloid ellipticine (**3a**)[14] and its 9-oxygenated derivatives have been shown to exhibit potential anticancer activities.[15] Particularly, 9-methoxyellipticine (**3b**) was used to treat patients with acute myeloblastic leukemia.[16] Therefore, the preparation of **3a** or **3b** has attracted the interest of synthetic organic chemists for the past half century and numerous total or partial syntheses have been reported.[17−24] We have envisioned a synthesis starting from polyfunctional aryl azides (**7a**, **7b**), which would undergo a thermal decomposition giving the ellipticine derivatives such as ellipticine (**3a**) and 9-methoxyellipticine (**3b**) (Scheme 10).[25]

Herein, we describe a short and practical synthesis of these potent anticancer agents using three key synthetic transformations, namely, a Negishi cross-coupling, azidation, and cyclization. The precursors were prepared by using a Negishi cross-coupling reaction[12] of the zinc species of 1-(2-iodophenylazo)-pyrrolidine (**1a**) or 1-(4-methoxy-2-iodophenylazo)pyrrolidine (**6n**) with 7-bromo-5,8-dimethylisoquinoline (**9**) to give the aryl triazene **8a** or **8b**, which was then converted to the aryl azide **7a** or **7b** followed by a thermal cyclization (Scheme 10).

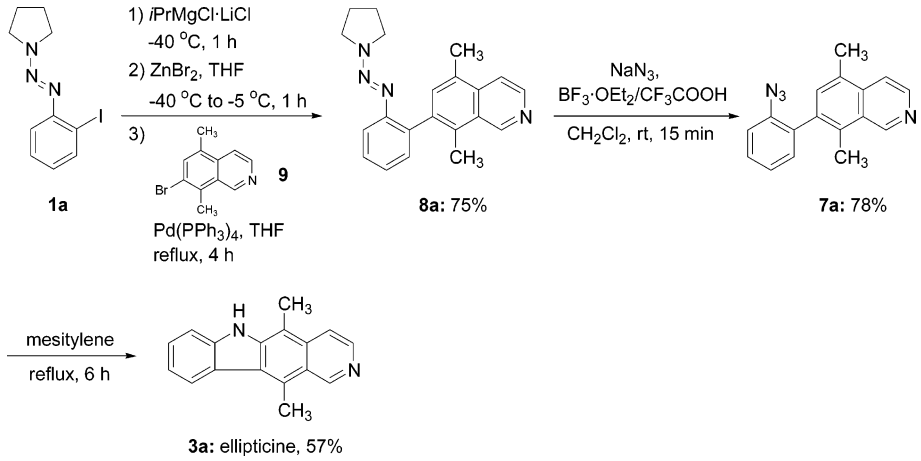
The preparation of 7-bromo-5,8-dimethylisoquinoline (**9**) was achieved starting from the 1,4-dibromo-2,5-dimethylbenzene (**10**). First, we have performed a Br/Li-exchange with *n*-BuLi followed by the addition of DMF affording the aldehyde **11** in 99% yield.[26] The reaction of **11** with $NaBH_4$ provided the benzyl alcohol **12** (99%), which was then converted to the benzyl chloride **13** (93%) by the addition of $SOCl_2$. The malonate **14** was prepared by the reaction of **13** with diethyl malonate in 88% yield.[27] Hydrolysis and decarboxylation gave the corresponding carboxylic acid **15** in 83% overall yield. Polyphosphoric acid (PPA) catalyzed ring closure[28] furnished the indanone **16** (88%), which was then reduced to the corresponding indanol, followed by a dehydration with a catalytic amount of *p*-TsOH in refluxing benzene affording the indene **17** in 78% overall yield. Ozonolysis of **17** in a mixture of $MeOH/CH_2Cl_2$, followed by a reductive workup with Me_2S and treatment with concd NH_4OH provided 7-bromo-5,8-dimethylisoquinoline (**9**) in 95% yield (Scheme 11).[29]

(13) (a) Ishihara, K.; Hasegawa, A.; Yamamoto, H. *Synlett* **2002**, 1296. (b) Ishihara, K.; Hasegawa, A.; Yamamoto, H. *Synlett* **2002**, 1299.
(14) (a) Goodwin, S.; Smith, A. F.; Horning, E. C. *J. Am. Chem. Soc.* **1959**, *81*, 1903. (b) Woodward, R. B.; Iacobucci, G. A.; Hochstein, F. A. *J. Am. Chem. Soc.* **1959**, *81*, 4434.
(15) Van-Bac, N.; Moisand, C.; Gouyette, A.; Muzard, G.; Dat-Xuong, N.; Le Pecq, J. B.; Paoletti, C. *Cancer Treat. Rep.* **1980**, *64*, 879 and references cited therein.
(16) Mathé, G.; Hayat, M.; De Vassal, F.; Schwarzenberg, L.; Schneider, M.; Schlumberger, J. R.; Jasmin, C.; Rosenfeld, C. *Rev. Eur. Etud. Clin. Biol.* **1970**, *15*, 541.
(17) Sainsbury, M. Ellipticines. In *Chemistry of Antitumour Agents*; Wilman, D. E. V., Ed.; Blackie: Glasgow and London, UK, 1990.
(18) Gribble, G. W. Synthesis and Antitumour Activity of Ellipticine Alkaloids and Related Compounds. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, CA, 1990; Vol. 39, p 239.
(19) Gribble, G. W.; Saulnier, M. G. *Heterocycles* **1985**, *23*, 1277.
(20) Gribble, G. W. Synthetic Approaches to the Ellipticine Alkaloids via Metalation and Cycloaddition Chemistry. In: *Advances in Heterocyclic Natural Product Synthesis*; W. H. Pearson, W. H., Ed.; Jai Press: Greenwich, CT, 1990; Vol. 1.
(21) Gribble, G. W. *Synlett* **1991**, 289.
(22) Gribble, G. W.; Saulnier, M. G.; Sibi, M. P.; Obaza-Nutaitis, J. A. *J. Org. Chem.* **1984**, *49*, 4518.
(23) May, C.; Moody, C. J. *J. Chem. Soc., Chem. Commun.* **1984**, 926.
(24) May, C.; Moody, C. J. *J. Chem. Soc., Perkin Trans.* **1988**, *1*, 247.
(25) (a) Smith, P. A. S.; Brown, B. B. *J. Am. Chem. Soc.* **1951**, *73*, 2435. (b) Jian, H.; Tour, J. M. *J. Org. Chem.* **2003**, *68*, 5091.
(26) Jørgensen, M.; Krebs, F. C. *J. Org. Chem.* **2004**, *69*, 6688.
(27) Musso, D. L.; Cochran, F. R.; Kelley, J. L.; McLean, E. W.; Selph, J. L.; Rigdon, G. C.; Orr, G. F.; Davis, R. G.; Cooper, B. R.; Styles, V. L.; Thompson, J. B.; Hall, W. R. *J. Med. Chem.* **2003**, *46*, 399.
(28) Lewis, M. L.; de Meijere, A. *Synlett* **1997**, 261.
(29) Miller, R. B.; Stowell, J. G.; Dugar, S.; Moock, T. E.; Jenks, C. W.; Farmer, S. C.; Phan, B.; Wujcik, C. E.; Olmstead, M. M. *Tetrahedron* **2002**, *58*, 6061.

SCHEME 11. Synthesis of the Isoquinoline 9



SCHEME 12. Synthesis of Ellipticine (3a)



A new ellipticine synthesis[30] was accomplished by starting with the triazene **1a**. After I/Mg exchange with *i*PrMgCl·LiCl (−40 °C, 1 h) and transmetalation with $ZnBr_2$, the resulting zinc intermediate was submitted to a Negishi cross-coupling[12] with 7-bromo-5,8-dimethylisoquinoline (**9**) leading to the polyfunctional aryl triazene **8a** (75%). This compound was readily converted to the corresponding aryl azide **7a** (78%) by the addition of BF_3·OEt_2/TFA in CH_2Cl_2 in the presence of NaN_3 (Method A). Thermal decomposition of azide **7a** in refluxing mesitylene (6 h) gave ellipticine (**3a**) in 57% yield (Scheme 12).

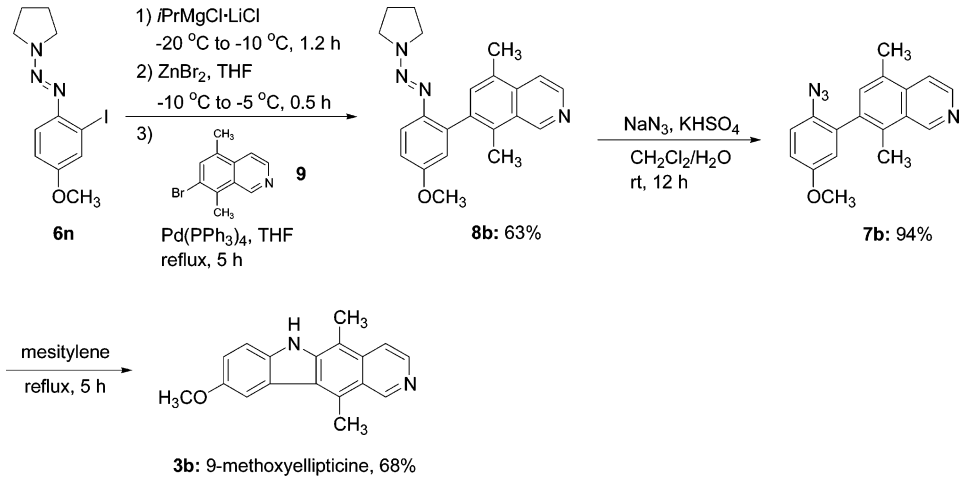
The same approach was used for preparing 9-methoxyellipticine (**3b**). Indeed, starting with the Grignard reagent derived from 1-(4-methoxy-2-iodophenylazo)pyrrolidine (**6n**) (*i*PrMgCl·LiCl, −20 to −10 °C, 1.2 h), we performed after transmetalation with $ZnBr_2$ a Negishi cross-coupling[12] with the isoquinoline **9** leading to the triazene **8b** (63%), which was readily converted to the aryl azide **7b** (94%) by using $KHSO_4$ in CH_2Cl_2/H_2O in the presence of NaN_3 (Method B). A solution of **7b** in mesitylene was heated at reflux for 5 h to give 9-methoxyellipticine (**3b**) in 68% yield (Scheme 13).

Synthesis of Isoellipticine and 7-Carbethoxyisoellipticine by a Thermal Decomposition of Azides. Interestingly, we found that this method was also successfully applied to the preparation of isoellipticine (**4a**) and a related derivative, 7-carbethoxyisoellipticine (**4b**). Thus, the arylmagnesium species generated from **1a** and **18** (*i*PrMgCl·LiCl, −40 °C, 0.7−1 h) were transmetalated with $ZnBr_2$. These arylzinc reagents underwent Negishi cross-coupling reactions[12] with 6-bromo-5,8-dimethylisoquinoline (**19**)[29,31] affording the derived polyfunctional aryl triazenes **20a** (78%) and **20b** (81%). These triazenes **20a**,**b** were readily converted to the aryl azides **21a** (95%) and **21b** (81%) by using Method B and Method A, respectively. Thermal decomposition of the aryl azides **21a**,**b** in refluxing mesitylene (4−6 h) furnished the isoellipticines **4a** (63%) and **4b** (64%) (Scheme 14).

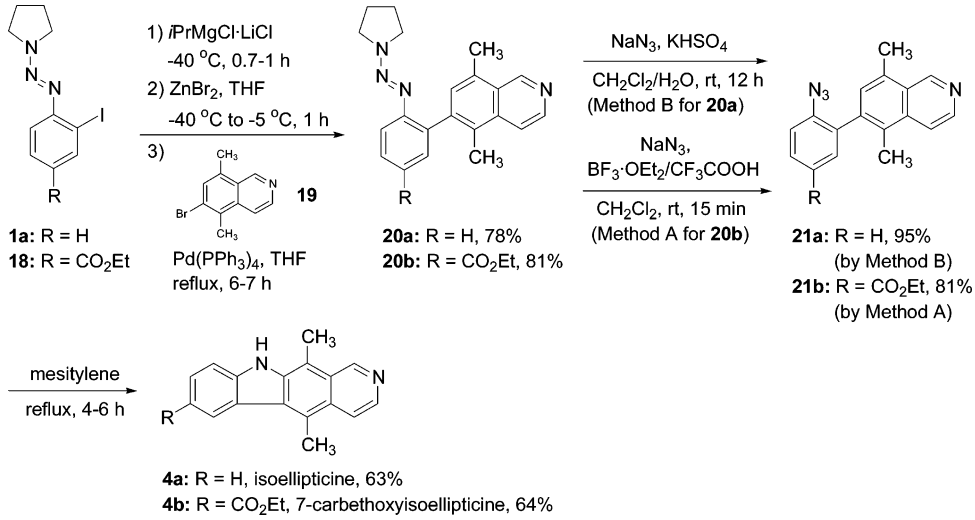
(30) Knölker, H. S.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303.

(31) Miller, R. B.; Moock, T. *Tetrahedron Lett.* **1980**, *21*, 3319.

SCHEME 13. Synthesis of 9-Methoxyellipticine (3b)



SCHEME 14. Synthesis of Isoellipticine (4a) and 7-Carbethoxyisoellipticine (4b)



3. Conclusion

In summary, we have developed an efficient synthetic method for the preparation of polyfunctional aryl azides from the corresponding polyfunctional aryl triazenes, which are readily obtained from the anilines or the iodo- or bromo-substituted aryl triazenes by using a novel exchange protocol.[6] Furthermore, as an application of the versatility of these polyfunctional aryl azides, we have used them for a new synthesis of ellipticine, 9-methoxyellipticine, isoellipticine, and 7-carbethoxyisoellipticine. Extensions of this methodology are currently being investigated in our laboratories.

4. Experimental Section

Caution! Aryl triazenes are known carcinogens, and ellipticine derivatives are potent cytostatics. Proper precautions during the work with these compounds are strongly recommended. Any skin contact or risk of inhalation of dust of these compounds should be avoided.

Starting Materials. 2-Iodoaniline (**5a**), 1-amino-4-bromonaphthaline (**5c**), and 2,6-dibromoaniline (**5d**) are commercially available. The following compounds were prepared according to literature procedures: ethyl 4-amino-3-bromobenzoate (**5b**);[32] methyl 4-amino-3,5-dibromobenzoate (**5e**);[8b] 2,4,6-tribromoaniline (**5f**);[8b] aryl triazenes **6g**−**m**, **1d**, **1h**−**j**, **1m**, **18**[6h] and **1e**−**f**;[8b] and 6-bromo-5,8-dimethyl-isoquinoline (**19**).[29,31] Procedures for the synthesis of compounds **1a**−**o** and **2a**−**o** are given in the Supporting Information.

4-Bromo-2,5-dimethylbenzaldehyde (11). To a solution of 1,4-dibromo-2,5-dimethylbenzene (**10**) (2.64 g, 10 mmol) in THF (5 mL) was slowly added *n*-BuLi (4.4 mL, 10.5 mmol, 2.4 M in hexane) at −78 °C. The reaction mixture was continuously stirred at −78 °C for 10 min. After 10 min, a complete conversion to the corresponding lithium reagent was observed as indicated by GC analysis of hydrolyzed reaction aliquots. *N*,*N*-Dimethylformamide (1.6 mL, 20 mmol) was added and the reaction mixture was warmed to rt and stirred again for 1 h before the addition of aq NH_4Cl (20 mL). The aqueous phase was extracted with ether (2 × 50 mL). The organic layers were washed with brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo to give the pure product **11** (2.1 g, 99%) as a white powder. Mp 58.2−59.8 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.15 (s, 1H), 7.58 (s, 1H), 7.41 (s, 1H), 2.56 (s, 3H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.7, 139.2, 136.1, 135.4, 133.5, 133.0, 131.2; IR (KBr) 2956 (w), 2923

(32) Tobe, Y.; Utsumi, N.; Kawabata, K.; Nagono, A.; Adachi, K.; Araki, S.; Sonoda, M.; Hirose, K.; Naemura, K. *J. Am. Chem. Soc.* **2002**, *124*, 5350.

(w), 2862 (w), 2836 (w), 2760 (w), 2724 (w), 1682 (s), 1595 (m), 1546 (m), 1443 (m), 1382 (m), 1235 (m), 1182 (m), 959 (m) cm^{-1}; MS (EI, 70 eV) 213 (M^+, 100), 183 (32), 104 (35), 77 (31); HRMS (EI) calcd for C_9H_9BrO:211.9837, found 211.9836.

4-Bromo-2,5-dimethylbenzyl Alcohol (12). A solution of **11** (1.02 g, 4.77 mmol) in EtOH (20 mL) was cooled in an ice bath and $NaBH_4$ (181 mg, 4.77 mmol) was added over 5 min with stirring. Then the reaction mixture was gradually warmed to rt. After 0.5 h the solvent was evaporated and H_2O (20 mL) was added. The aqueous mixture was extracted with ether (2 × 20 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give the pure product **12** (1.01 g, 99%) as a white powder. Mp 92.0−92.7 °C; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.32 (s, 1H), 7.19 (s, 1H), 4.58 (s, 2H), 2.34 (s, 3H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 137.8, 135.20, 135.18, 133.7, 129.9, 123.7, 62.8, 22.3, 17.8; IR (KBr) 3100−3400 (broad), 2981 (m), 2918 (m), 2858 (m), 1754 (w), 1557 (w), 1484 (s), 1452 (s), 1387 (m), 1282 (w), 1185 (w), 1134 (w), 1040 (s), 957 (m) cm^{-1}; MS (EI, 70 eV) 214 (M^+, 60), 196 (100), 185 (13), 171 (8), 135 (19), 117 (38), 107 (54), 91 (75), 77 (25); HRMS (EI) calcd for $C_9H_{11}BrO$ 213.9993, found 213.9991.

4-Bromo-2,5-dimethylbenzyl Chloride (13). To a solution of **12** (930 mg, 4.35 mmol) in $CHCl_3$ (3 mL) in an ice bath was added slowly a solution of $SOCl_2$ (0.4 mL) in $CHCl_3$ (0.6 mL). After 10 min, the reaction mixture was warmed to rt and stirred for 0.5 h before the addition of H_2O (5.0 mL). The aqueous phase was extracted with ether (2 × 5 mL). The organic layers were washed with brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo to give the pure product **13** (945 mg, 93%) as a pale yellow liquid. ^1H NMR ($CDCl_3$, 600 MHz) δ 7.36 (s, 1H), 7.15 (s, 1H), 4.50 (s, 2H), 2.34 (s, 3H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 136.3, 135.7, 134.7, 134.2, 132.0, 125.1, 44.1, 22.2, 18.0; IR (neat) 2948 (m), 2921 (m), 2876 (w), 1488 (s), 1449 (s), 1263 (s), 962 (s) cm^{-1}; MS (EI, 70 eV) 234 (M^+, 33), 197 (100), 115 (30), 103 (8), 91 (18), 77 (8); HRMS (EI) calcd for $C_9H_{10}BrCl$ 231.9654, found 231.9644.

2-(4-Bromo-2,5-dimethylbenzyl)malonic Acid Diethyl Ester (14). To a mixture of sodium hydride (720 mg, 18 mmol, 60% dispersion in mineral oil) in 1,2-dimethoxyethane (4.5 mL) under a nitrogen atmosphere was added dropwise a solution of diethyl malonate (3.04 g, 19 mmol) in 1,2-dimethoxyethane (9 mL). After the reaction mixture was stirred at rt for 2 h, a solution of **13** (840 mg, 3.6 mmol) in 1,2-dimethoxyethane (1.8 mL) was added dropwise. The reaction mixture was refluxed for 12 h and then concentrated in vacuo, and the residue was treated with a mixture of water (6 mL) and CH_2Cl_2 (6 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were washed with brine (30 mL), dried (Na_2SO_4), and concentrated in vacuo to give the crude product. Purification by flash chromatography (pentane:ether = 9:1) yielded the pure product **14** (1.13 g, 88%) as a white powder. Mp 47.8−48.7 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.28 (s, 1H), 6.97 (s, 1H), 4.14 (q, J = 7.2 Hz, 4H), 3.56 (t, J = 7.8 Hz, 1H), 3.12 (d, J = 7.8 Hz, 2H), 2.28 (s, 3H), 2.25 (s, 3H), 1.20 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.8, 135.6, 135.4, 135.3, 135.0, 133.8, 131.6, 61.5, 52.2, 31.3, 22.2, 18.5, 14.0; IR (KBr) 2983 (m), 2936 (w), 2874 (w), 1738 (s), 1724 (s), 1489 (w), 1368 (m), 1327 (m), 1288 (m), 1222 (m), 1170 (m), 1149 (m), 1026 (m), 958 (m) cm^{-1}; MS (EI, 70 eV) 356 (M^+, 30), 338 (30), 312 (19), 284 (48), 265 (50), 239 (100), 210 (29), 197 (81), 185 (48), 158 (59), 145 (10), 129 (60), 115 (66), 103 (14), 91 (30), 77 (14); HRMS (EI) calcd for $C_{16}H_{21}BrO_4$ 356.0623, found 356.0619.

3-(4-Bromo-2,5-dimethylphenyl)propionic Acid (15). A mixture of malonic ester **14** (927 mg, 2.6 mmol) and potassium hydroxide (296 mg, 5.2 mmol) in water (4.5 mL) was refluxed for 5 h. The reaction mixture was concentrated in vacuo to remove the ethanol, and then a solution of concd sulfuric acid (0.5 mL) and water (1.5 mL) was added. The mixture was refluxed for 20 h. The reaction mixture was chilled in an ice bath and the resulting solid was filtered and washed with water to give the pure product **15** (555 mg, 83%) as a white powder. Mp 93.2−94.5 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 12.0 (br s, 1H), 7.29 (s, 1H), 7.06 (s, 1H), 2.68 (t, J = 7.8 Hz, 2H), 2.41 (t, J = 7.8 Hz, 2H), 2.21 (s, 3H), 2.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.4, 139.3, 136.4, 134.9, 133.7, 131.8, 121.9, 34.5, 27.8, 22.5, 18.7; IR (KBr) 2900−3400 (broad), 2571 (w), 1692 (s), 1487 (m), 1453 (m), 1416 (m), 1304 (m), 1213 (w), 1166 (w), 1024 (m), 962 (m) cm^{-1}; MS (EI, 70 eV) 256 (M^+, 50), 240 (3), 225 (2), 210 (8), 197 (100), 135 (23), 117 (32), 103 (9), 91 (21); HRMS (EI) calcd for $C_{11}H_{13}BrO_2$ 256.0099, found 256.0087.

6-Bromo-4,7-dimethylindan-1-one (16). The mixture of **15** (475 mg, 1.86 mmol) and polyphosphoric acid (2.2 mL) was heated at 100 °C for 2.5 h. After the mixture was cooled, ice water (7.5 mL) was added and the reaction mixture was stirred for 0.5 h, and then the aqueous phase was extracted with ether (2 × 15 mL). The organic layers were washed with 10% aqueous $NaHCO_3$ (30 mL) and water (2 × 20 mL), dried (Na_2SO_4), and concentrated in vacuo to give the pure product **16** (391 mg, 88%) as a pale yellow solid. Mp 127.8−128.6 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.51 (s, 1H), 2.80−2.90 (m, 2H), 2.60−2.72 (m, 5H), 2.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.1, 154.1, 137.8, 135.6, 135.3, 134.4, 124.9, 36.8, 23.6, 17.1, 16.5; IR (KBr) 3076 (w), 3030 (w), 2920 (w), 2857 (w), 1697 (s), 1568 (w), 1469 (m), 1435 (m), 1367 (w), 1252 (m), 1220 (m), 1102 (w), 989 (w) cm^{-1}; MS (EI, 70 eV) 238 (M^+, 100), 223 (6), 210 (12), 196 (6), 159 (41), 131 (35), 115 (32), 103 (6), 91 (16); HRMS (EI) calcd for $C_{11}H_{11}BrO$ 237.9993, found 237.9984.

6-Bromo-4,7-dimethylindan-1-ol. A solution of **16** (180 mg, 0.76 mmol) in EtOH (3.2 mL) was cooled in an ice bath and $NaBH_4$ (29 mg, 0.76 mmol) was added over 5 min with stirring. Then the reaction mixture was gradually warmed to rt. After 0.5 h the solvent was evaporated and H_2O (5 mL) was added. The aqueous mixture was extracted with ether (2 × 5 mL) and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give the pure product (179 mg, 98%) as a pale yellow solid. Mp 124.0−125.5 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.27 (s, 1H), 5.27 (d, J = 6.0 Hz, 1H), 2.88−3.02 (m, 1H), 2.68 (ddd, J = 17.0, 9.5, 2.6 Hz, 1H), 2.41 (s, 3H), 2.30−2.37 (m, 1H), 2.18 (s, 3H), 1.96−2.12 (m, 1H), 1.64 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.2, 142.1, 133.2, 133.1, 132.0, 123.2, 76.0, 34.8, 28.7, 18.4, 15.2; IR (KBr) 3000−3400 (broad), 2922 (m), 1467 (s), 1378 (m), 1308 (w), 1254 (w), 1180 (m), 1154 (m), 1044 (s), 958 (s) cm^{-1}; MS (EI, 70 eV) 240 (M^+, 72), 222 (100), 209 (4), 197 (8), 183 (10), 161 (30), 143 (86), 128 (48), 115 (40), 103 (8), 91 (16); HRMS (EI) calcd for $C_{11}H_{13}BrO$ 240.0150, found 240.0143.

5-Bromo-4,7-dimethyl-1*H*-indene (17). A solution of 6-bromo-4,7-dimethylindan-1-ol (164 mg, 0.68 mmol) and *p*-TsOH (1.7 mg, 7 μmol) in benzene (17 mL) was heated at reflux. After 2 h, the reaction mixture was allowed to cool and the solvent was evaporated in vacuo (30 °C, 30 mmHg) to give the crude product. Purification by flash chromatography (pentane) yielded the pure product **17** (130 mg, 86%) as a pale yellow liquid. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.53 (s, 1H), 7.27 (dt, J = 5.7, 2.0 Hz, 1H), 6.89 (dt, J = 5.7, 2.0 Hz, 1H), 3.56 (t, J = 2.0 Hz, 2H), 2.78 (s, 3H), 2.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.8, 141.3, 134.5, 131.7, 130.9, 129.3, 127.5, 123.0, 38.3, 18.6, 18.1; IR (neat) 3061 (w), 2974 (w), 2919 (w), 2857 (w), 1666(w), 1583 (w), 1549 (w), 1461 (m), 1372 (m), 1247 (w), 1170 (w), 950 (m) cm^{-1}; MS (EI, 70 eV) 222 (M^+, 34), 207 (4), 143 (100), 128 (52), 115 (20), 102 (8), 89 (8), 77 (8); HRMS (EI) calcd for $C_{11}H_{11}Br$ 222.0044, found 222.0038.

7-Bromo-5,8-dimethylisoquinoline (9). A solution of **17** (100 mg, 0.45 mmol) in MeOH (2.5 mL) and CH_2Cl_2 (2.5 mL) was cooled to −78 °C and treated with ozone until the solution turned blue. Then the solution was purged with nitrogen until the blue color disappeared. Me_2S (0.3 mL) and $NaHCO_3$ (52 mg) were added, and the reaction mixture was stirred for 4 h at rt. Concentrated NH_4OH (2.5 mL) was added and reaction mixture

was stirred overnight. The solvent was mostly evaporated and the remaining aqueous suspension was extracted with $CHCl_3$ and the combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated to afford the crude product. Recrystallization (EtOAc) gave **9** (101 mg, 95%) as bright yellow crystals. Mp 102.5−103.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.39 (s, 1H), 8.54 (d, J = 5.3, 1H), 7.63 (d, J = 5.3 Hz, 1H), 7.56 (s, 1H), 2.75 (s, 3H), 2.53 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.4, 142.8, 134.6, 134.5, 133.0, 132.0, 128.2, 123.2, 117.2, 18.0, 17.6; IR (KBr) 3050 (w), 2945 (w), 2920 (w), 2855 (w), 1588 (m), 1564 (m), 1491 (m), 1433 (m), 1378 (m), 1274 (m), 1212 (w), 1072 (w) cm^{-1}; MS (EI, 70 eV) 235 (M$^+$, 100), 220 (3), 156 (86), 141 (11), 128 (23), 116 (6), 102 (6), 77 (11); HRMS (EI) calcd for $C_{11}H_{10}BrN$ 234.9997, found 235.0007.

Triazene (**8a**) was prepared from 1-(2-iodophenylazo)pyrrolidine (**1a**) (903 mg, 3 mmol) and 7-bromo-5,8-dimethylisoquinoline (**9**) (705 mg, 3 mmol) according to the procedures for the preparation of **1n** and yielding the pure product **8a** (743 mg, 75%) as a pale yellow solid. Mp 121.3−123.6 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 9.53 (s, 1H), 8.57 (d, J = 5.7 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.44 (s, 1H), 7.32−7.37 (m, 1H), 7.17−7.23 (m, 2H), 2.80−4.10 (br s, 4H), 2.62 (s, 3H), 2.49 (s, 3H), 1.83 (br s, 4H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 150.1, 148.9, 142.0, 138.8, 135.9, 134.7, 134.2, 130.8, 130.7, 129.7, 128.3, 127.9, 124.9, 117.3, 117.0, 23.6, 18.3, 15.5; IR (KBr) 2990 (w), 2868 (w), 1597 (w), 1406 (s), 1315 (m), 1268 (m), 1200 (w), 1095 (w) cm^{-1}; MS (EI, 70 eV) 330 (M$^+$, 6), 260 (6), 245 (46), 232 (98), 217 (100), 202 (11), 189 (15), 108 (9); HRMS (EI) calcd for $C_{21}H_{22}N_4$ 330.1844, found 330.1844.

Aryl azide (7a) was prepared from the corresponding triazene (**8a**) (165 mg, 0.5 mmol) according to the general procedure B and yielding the pure product **7a** (107 mg, 78%) as a yellow liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.55 (s, 1H), 8.61 (d, J = 5.7 Hz, 1H), 7.79 (d, J = 5.7 Hz, 1H), 7.42−7.51 (m, 1H), 7.21−7.35 (m, 4H), 2.67 (s, 3H), 2.55 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.0, 142.7, 138.1, 136.0, 135.2, 133.1, 132.8, 131.4, 131.0, 130.9, 129.0, 127.7, 124.7, 118.4, 117.3, 18.3, 15.1; IR (neat) 2923 (w), 2120 (s), 1599 (w), 1570 (w), 1487 (w), 1443 (w), 1386 (w), 1284 (m), 1095 (w), 961 (w) cm^{-1}; MS (EI, 70 eV) 274 (M$^+$, 10), 246 (100), 231 (80), 203 (10), 152 (5), 109 (6), 88 (4); HRMS (EI) calcd for $C_{17}H_{14}N_4$ 274.1218, found 274.1232.

Ellipticine (3a). A solution of the aryl azide **7a** (101 mg, 0.37 mmol) in mesitylene (5 mL) was heated at reflux. After 6 h, the solvent was evaporated in vacuo to give the crude product. Purification by flash chromatography (methanol:ether = 1:9) yielded the pure product **3a** (52 mg, 57%) as a yellow solid. Mp 247.3−249.1 °C (lit.[36] mp 243−250 °C); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 9.71 (s, 1H), 8.49 (d, J = 5.8 Hz, 1H), 8.37 (d, J = 7.8 Hz, 1H), 7.85 (d, J = 5.8 Hz, 1H), 7.46−7.54 (m, 2H), 7.28−7.34 (m, 2H), 3.30 (s, 3H), 2.77 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 150.2, 144.6, 141.8, 141.2, 130.3, 129.5, 129.0, 127.4, 126.1, 124.3, 124.2, 120.2, 116.1, 115.1, 110.6, 14.9, 12.2; IR (KBr) 3480 (s), 1630 (m), 1605 (m), 1440 (w), 1400 (w), 1377 (w), 1303 (m), 1230 (m), 1010 (m) cm^{-1}; MS (EI, 70 eV) 246 (M$^+$, 100), 231 (97), 216 (6), 204 (12), 176 (6), 122 (6), 109 (5), 96 (6), 51 (3); HRMS (EI) calcd for $C_{17}H_{14}N_2$ 246.1157, found 246.1145.

Triazene (**8b**) was prepared from 1-(4-methoxy-2-iodophenylazo)pyrrolidine (**6n**) (993 mg, 3.0 mmol) and 7-bromo-5,8-dimethylisoquinoline (**9**) (705 mg, 3 mmol) according to the procedures for the preparation of **1n**, yielding the pure product **8b** (680 mg, 63%) as a brown solid. Mp 62.1−64.5 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 9.52 (s, 1H), 8.57 (d, J = 6.0 Hz, 1H), 7.76 (d, J = 6.0 Hz, 1H), 7.45 (d, J = 9.0 Hz, 1H), 7.43 (s, 1H), 6.91 (dd, J = 9.0, 2.8 Hz, 1H), 6.76 (d, J = 2.8 Hz, 1H), 3.82 (s, 3H), 2.90−3.75 (br s, 4H), 2.62 (s, 3H), 2.51 (s, 3H), 1.77−1.84 (m, 4H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 157.3, 150.3, 143.1, 142.4, 138.8, 137.2, 135.0, 134.1, 131.1, 130.0, 128.1, 118.2, 117.5, 115.5, 114.4, 55.8, 23.9, 18.5, 15.8; IR (KBr) 2962 (w), 2850 (w), 1596 (m), 1495 (m), 1407 (m), 1319 (m), 1269 (m), 1209 (m), 1109 (w), 1035 (m), 817 (m) cm^{-1}; MS (EI, 70 eV) 360 (M$^+$, 28), 290 (22), 275 (15), 262 (100), 247 (56), 231 (22), 219 (18), 204 (15); HRMS (EI) calcd for $C_{22}H_{24}N_4O$ 360.1950, found 360.1933.

Aryl azide (**7b**) was prepared from the corresponding triazene (**8b**) (281 mg, 0.78 mmol) according to the general procedure C, yielding the pure product **7b** (223 mg, 94%) as a brown liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.53 (s, 1H), 8.60 (d, J = 5.8 Hz, 1H), 7.76 (d, J = 5.8 Hz, 1H), 7.30 (s, 1H), 7.18 (d, J = 8.8 Hz, 1H), 6.98 (dd, J = 8.8, 3.1 Hz, 1H), 6.76 (d, J = 3.1 Hz, 1H), 3.81 (s, 3H), 2.64 (s, 3H), 2.53 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.6, 150.2, 150.1, 143.0, 135.9, 134.3, 133.4, 132.5, 131.0, 130.6, 127.7, 119.5, 117.2, 116.7, 114.6, 55.6, 18.4, 15.1; IR (neat) 2938 (w), 2110 (s), 1596 (m), 1488 (m), 1462 (m), 1420 (m), 1384 (m), 1285 (m), 1225 (m), 1177 (m), 1032 (m) cm^{-1}; MS (EI, 70 eV) 304 (M$^+$, 6), 276 (100), 261 (96), 246 (23), 233 (30), 218 (28), 204 (7), 117 (5), 102 (3); HRMS (EI) calcd for $C_{18}H_{16}N_4O$ 304.1324, found 304.1340.

9-Methoxyellipticine (3b). A solution of the aryl azide **7b** (100 mg, 0.33 mmol) in mesitylene (3.3 mL) was heated at reflux. After 5 h, the solvent was evaporated in vacuo to give the crude product. Purification by flash chromatography (methanol:ether = 1:9) yielded the pure product **3b** (62 mg, 68%) as an amber solid. Mp 276.3−278.5 °C dec (lit.[37] mp 275−278 °C dec); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.14 (s, 1H), 8.69 (d, J = 5.2 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.19 (d, J = 5.2 Hz, 1H), 6.98 (d, J = 2.6 Hz, 1H), 6.87 (dd, J = 8.4, 2.6 Hz, 1H), 6.49 (s, 1H), 3.85 (s, 3H), 2.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.6, 152.4, 148.2, 146.1, 144.1, 143.4, 135.0, 124.2, 122.2, 118.5, 116.5, 115.5, 114.6, 112.7, 108.6, 55.7, 27.6, 18.9; IR (KBr) 3310 (s), 2921 (m), 1722 (w), 1588 (s), 1468 (s), 1367 (w), 1348 (w), 1285 (s), 1207 (m), 1027 (s) cm^{-1}; MS (EI, 70 eV) 276 (M$^+$, 100), 261 (60), 246 (27), 233 (27), 218 (33), 204 (5), 190 (10), 177 (5), 164 (7), 138 (7), 116 (7), 109 (7), 95 (5), 88 (5); HRMS (EI) calcd for $C_{18}H_{16}N_2O$ 276.1263, found 276.1268.

Triazene (**20a**) was prepared from 1-(2-iodophenylazo)pyrrolidine (**1a**) (160 mg, 0.53 mmol) and 6-bromo-5,8-dimethylisoquinoline (**19**) (150 mg, 0.53 mmol) according to the procedure for the preparation of **1n**, yielding the pure product **20a** (136 mg, 78%) as a pale yellow solid. Mp 55.5−56.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.42 (s, 1H), 8.56 (d, J = 6.2 Hz, 1H), 7.80 (d, J = 6.2 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.31−7.38 (m, 1H), 7.30 (s, 1H), 7.18−7.22 (m, 2H), 3.00−4.00 (br s, 4H), 2.73 (s, 3H), 2.36 (s, 3H), 1.77−1.87 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.6, 148.7, 142.9, 141.8, 136.1, 135.7, 131.3, 130.4, 129.1, 128.3, 126.9, 124.9, 117.6, 117.1, 65.8, 23.7, 18.2, 15.6; IR (KBr) 2970 (w), 2867 (w), 1612 (w), 1443 (w), 1408 (m), 1314 (m), 1268 (w), 1209 (w), 1157 (w), 1102 (w) cm^{-1}; MS (EI, 70 eV) 330 (M$^+$, 5), 260 (5), 245 (40), 232 (100), 217 (66), 202 (11), 189 (16), 108 (9); HRMS (EI) calcd for $C_{21}H_{22}N_4$ 330.1844, found 330.1837.

Aryl azide (**21a**) was prepared from the corresponding triazene (**20a**) (122 mg, 0.37 mmol) according to the general procedure C, yielding the pure product **21a** (96 mg, 95%) as a pale yellow liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.46 (s, 1H), 8.60 (d, J = 5.8 Hz, 1H), 7.83 (d, J = 5.8 Hz, 1H), 7.40−7.50 (m, 1H), 7.15−7.30 (m, 4H), 2.77 (s, 3H), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.7, 143.4, 138.9, 138.0, 135.7, 133.3, 132.6, 131.2, 130.1, 129.5, 129.1, 124.8, 118.4, 117.9, 117.7, 18.3, 15.3; IR (neat) 3057 (w), 2961 (w), 2923 (w), 2855 (w), 2123 (s), 2098 (s), 1612 (m), 1482 (m), 1382 (w), 1301 (m), 1277 (m), 1034 (w) cm^{-1}; MS (EI, 70 eV) 274 (M$^+$, 8), 246 (100), 231 (74), 217 (10), 204 (12), 189 (8), 176 (8), 152 (6), 122 (8), 108 (14); HRMS (EI) calcd for $C_{17}H_{14}N_4$ 274.1218, found 274.1221.

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Isoellipticine (4a). A solution of the aryl azide **21a** (22 mg, 0.08 mmol) in mesitylene (1 mL) was heated at reflux. After 5 h, the solvent was evaporated in vacuo to give the crude product. Purification by flash chromatography (methanol:ether = 1:9) yielded the pure product **4a** (12 mg, 63%) as a yellow solid. Mp 309.0−310.0 °C (lit.[36] mp 312−314 °C); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.4 (br s, 1H), 9.54 (s, 1H), 8.08 (d, J = 6.0 Hz, 1H), 7.44−7.58 (m, 2H), 7.20 (t, J = 8.0 Hz, 1H), 3.10 (s, 3H), 2.92 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 149.5, 143.8, 139.2, 139.1, 128.9, 128.3, 126.4, 125.9, 125.5, 124.9, 123.3, 119.6, 117.5, 111.4, 111.3, 15.2, 12.6; IR (KBr) 3420 (s), 3143 (m), 3076 (m), 2977 (w), 2921 (w), 2869 (w), 1613 (m), 1596 (m), 1497 (w), 1461 (w), 1406 (m), 1319 (m), 1273 (m), 1230 (m), 1012 (m) cm^{-1}; MS (EI, 70 eV) 246 (M$^+$, 100), 231 (29), 217 (9), 123 (12), 108 (9), 95 (6); HRMS (EI) calcd for $C_{17}H_{14}N_2$ 246.1157, found 246.1140.

Triazene (**20b**) was prepared from 1-(4-carbethoxy-2-iodophenylazo)pyrrolidine (**18**) (746 mg, 2 mmol) and 6-bromo-5,8-dimethylisoquinoline (**19**) (472 mg, 2 mmol) according to the procedure for the preparation of **1n**, yielding the pure product **20b** (651 mg, 81%) as a white solid. Mp 71.6−72.0 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 9.47 (s, 1H), 8.58 (d, J = 5.9 Hz, 1H), 8.02 (d, J = 8.8 Hz, 1H), 7.91 (s, 1H), 7.82 (d, J = 5.9 Hz, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.29 (s, 1H), 4.35 (q, J = 7.3 Hz, 2H), 3.84 (br s, 2H), 3.14 (br s, 2H), 2.75 (s, 3H), 2.35 (s, 3H), 1.86 (br s, 4H), 1.36 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 166.8, 152.4, 149.8, 142.9, 136.1, 136.0, 132.3, 132.0, 131.3, 130.0, 129.5, 127.2, 126.7, 118.0, 117.0, 116.8, 61.0, 51.2, 46.7, 24.1, 23.5, 18.4, 15.9, 14.6; IR (KBr) 2975 (w), 2870 (w), 1707 (s), 1600 (m), 1401 (m), 1362 (m), 1310 (m), 1283 (m), 1263 (m), 1240 (s), 1100 (s), 1026 (m) cm^{-1}; MS (EI, 70 eV) 402 (M$^+$, 7), 357 (8), 317 (56), 260 (25), 232 (100), 216 (41), 202 (15), 189 (7), 115 (5), 86 (14); HRMS (EI) calcd for $C_{24}H_{26}N_4O_2$ 402.2056, found 402.2042.

Aryl azide (**21b**) was prepared from the corresponding triazene (**20b**) (200 mg, 0.5 mmol) according to the general procedure B, yielding the pure product **21b** (131 mg, 76%) as a pale yellow solid. Mp 122.5−123.9 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 9.46 (s, 1H), 8.62 (d, J = 5.8 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.91 (s, 1H), 7.83 (d, J = 5.8 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.16 (s, 1H), 4.36 (q, J = 7.0 Hz, 2H), 2.77 (s, 3H), 2.38 (s, 3H), 1.37 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 165.6, 149.7, 143.4, 142.5, 138.0, 135.7, 133.2, 132.9, 132.5, 130.5, 129.8, 129.6, 127.2, 127.0, 118.2, 117.6, 61.2, 18.3, 15.3, 14.3; IR (KBr) 2970 (w), 2124 (s), 1712 (s), 1604 (m), 1586 (m), 1494 (w), 1466 (w), 1444 (w), 1385 (w), 1364 (w), 1285 (s), 1228 (s), 1126 (m), 1098 (m), 1026 (m) cm^{-1}; MS (EI, 70 eV) 346 (M$^+$, 18), 318 (100), 303 (43), 289 (77), 275 (54), 245 (70), 230 (20), 216 (12), 189 (8), 145 (7), 108 (11); HRMS (EI) calcd for $C_{20}H_{18}N_4O_2$ 346.1430, found 346.1442.

7-Carbethoxyisoellipticine (4b). A solution of the aryl azide **21b** (464 mg, 1.34 mmol) in a mixture of mesitylene (14 mL) and DMF (1 mL) was heated at reflux. After 6 h, the solvent was evaporated in vacuo to give the crude product. Purification by flash chromatography (methanol:ether = 1:9) yielded the pure product **4b** (273 mg, 64%) as a bright yellow solid. Mp 250 °C dec; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.73 (s, 1H), 9.55 (s, 1H), 8.88 (s, 1H), 8.40 (d, J = 5.9 Hz, 1H), 8.05−8.15 (m, 2H), 7.56 (d, J = 8.6 Hz, 1H), 4.33 (q, J = 7.0 Hz, 2H), 3.09 (s, 3H), 2.90 (s, 3H), 1.34 (t, J = 7.0 Hz, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 166.9, 149.6, 146.8, 139.7, 139.3, 129.5, 129.4, 126.3, 126.2, 125.8, 123.1, 120.9, 117.5, 117.4, 112.3, 111.1, 61.1, 15.2, 15.0, 12.5; IR (KBr) 3200 (s), 2925 (w), 1710 (s), 1612 (m), 1465 (w), 1364 (w), 1277 (m), 1244 (s), 1167 (m), 1098 (m), 1017 (m) cm^{-1}; MS (EI, 70 eV) 318 (M$^+$, 100), 304 (33), 289 (40), 273 (21), 245 (33), 229 (19), 207 (35), 191 (6), 175 (6), 115 (10), 73 (10); HRMS (EI) calcd for $C_{20}H_{18}N_2O_2$ 318.1368, found 318.1349.

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Supporting Information Available: General procedures A−C, synthetic procedures for compounds **1a**−**o** and **2a**−**o**, and ^{1}H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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