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Directed Heterodimerization: Stereocontrolled Assembly via Solvent-Caged Unsymmetrical Diazene Fragmentation

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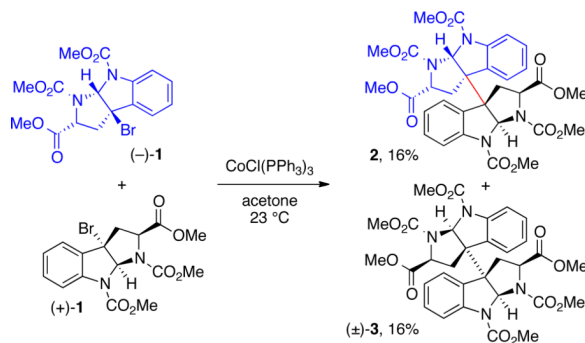
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Abstract

A general strategy for the directed and stereocontrolled assembly of carbon–carbon linked heterodimeric hexahydropyrroloindoles is described. The stepwise union of complex amines in the form of mixed diazenes followed by photoexpulsion of dinitrogen in a solvent–cage provides completely guided assembly at challenging C_{sp^3} – C_{sp^3} and C_{sp^3} – C_{sp^2} connections.

Dimeric and oligomeric cyclotryptamine and cyclotryptophan alkaloids constitute a large family of natural products with diverse molecular architectures that possess a wide range of biological activities.¹ Nature is able to access an array of these alkaloids containing quaternary stereocenters at C3a through the amalgamation of various monomers. In 2007, we reported a versatile strategy for the concise and enantioselective synthesis of homodimeric cyclotryptamine substructures.² However, to date, there are no reported methods for the selective carbon–carbon³ bond construction at the C3a quaternary stereocenter of two dissimilar cyclotryptamine subunits, a synthetically challenging structural motif found in many heterodimeric alkaloids (Figure 1).⁴ Herein we report a strategy for the completely stereoselective and directed union of complex fragments at these sterically crowded linkages. We demonstrate the utility of this chemistry in adjoining differing monomers at carbon–carbon fusions common to this family of natural products.



(1)

Our laboratory seeks effective methodology for controlled union of complex fragments for application in natural product synthesis. While our cobalt(I) promoted homodimerization of

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Supporting Information. Experimental procedures, spectroscopic data, copies of ^1H and ^{13}C NMR spectra, and related mechanistic studies. This material is free of charge via the Internet at <http://pubs.acs.org>.

cyclotryptamine derivatives has enabled concise total syntheses,^{2,5} we found its extension to heterodimerization problematic. For example, uncontrolled dimerization of tricyclic bromide (+)-**1** and (-)-**1** using our cobalt promoted strategy provides the desired heterodimeric *meso*-**2** in only 16% isolated yield (eq 1). The near-statistical product mixture of **2** and **3** also contains the corresponding disproportionation and related byproducts which hampers the isolation of pure heterodimer **2**.⁶ The low yield of the desired product along with complications associated with side product formation restricts the use of this chemistry in preparative heterodimeric assembly. A maximally convergent solution to heterodimeric molecules requires a method that provides a single product with minimal influence of substrate bias in the planned union.

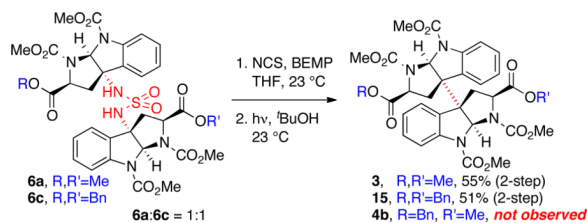
Inspired by the work of Bartlett, Engel, and Naumann,⁷ we considered the possibility of using diazenes as traceless linkers⁸ and radical precursors for our desired heterodimerization chemistry. Dialkyl diazenes are known to undergo expulsion of dinitrogen upon photoexcitation to generate two radical species. However, in these cases^{7b} radical combination is accompanied by varying amounts of disproportionation. Furthermore, photoexcitation of unsymmetrical diazenes are often complicated by crossover products due to out-of-cage coupling,^{7f,l,m} thus limiting their utility in fragment assembly and complex molecule synthesis.

We envisioned the expulsion of dinitrogen from an unsymmetrical diazene **5** (Scheme 1) to form a pair of carbon centered radicals whose directed union in a solvent-cage⁹ would result in selective formation of the desired heterodimer **4**. The use of the mixed sulfamide **6** as the precursor¹⁰ to the unsymmetrical diazene **5** would provide a platform for the directed assembly of the two differing monomeric amines **7** and **7'** (Scheme 1). Implementation of this strategy in complex synthesis would require: a) synthesis of cyclotryptamine based mixed sulfamides,¹¹ b) mild conditions for their conversion to the corresponding unsymmetrical diazenes followed by fragmentation,¹² c) solvent-cage controlled radical pair combination,⁹ and d) minimization of out-of-cage coupling (homodimerization) and disproportionation.⁷

Our initial studies focused on the evaluation of the use of dialkyl diazenes in the context of homodimerization. In this regard, we began with the development of a diazene based synthetic route to homodimer (+)-**3** (Scheme 2). We developed a versatile entry to the necessary amines **7** (Scheme 1) by derivatization of the corresponding benzylic bromides that had been utilized in our cobalt promoted dimerization studies. As illustrated in Scheme 2, exposure of the bromide (+)-**1**⁶ to tin tetrachloride and trimethylsilyl azide followed by reduction of the corresponding azide¹³ provided the desired hexahydropyrroloindolyl amine¹⁴ (+)-**7a** (71%). Exposure of amine (+)-**7a** to sulfonyl chloride provided the sulfamide (+)-**6a** in 81% yield. Under optimal conditions, subsequent oxidation of sulfamide (+)-**6a** with *N*-chlorosuccinimide in the presence of 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine on polystyrene resin (BEMP) generated the desired diazene (+)-**5a** in 61% isolated yield.¹⁵ Detailed structural analysis of this symmetrical diazene was consistent with prior reports of simpler dialkyl diazenes. Specifically, the UV absorption at 355 nm and the ¹³C NMR resonance of the C3a of diazene (+)-**5a** were in accord with previously reported data for dialkyl diazenes.¹⁶ Gratifyingly, photoexcitation¹⁷ of diazene (+)-**5a** led to expulsion of dinitrogen and formation of the desired dimeric hexacycle (+)-**3** in 60% yield. It should be noted that the overall efficiency of the process is increased (48% over two steps) when the freshly prepared crude diazene (~99%, based on ¹H NMR with internal standard) is used in the following step without chromatographic purification.

Having established the viability of using the sulfamide (+)-**6a** as a precursor to homodimer (+)-**3**, we turned our attention to the development of a general method for directed heterodimerization. Stepwise sulfonylation of different hexahydropyrroloindolyl amines was expected to provide a means for assembly of a heterodimeric structure as the prelude to the construction of the desired linkage. The selective synthesis of mixed sulfamide (+)-**6b** is illustrated in Scheme 3. Treatment of amine (+)-**7a** with chlorosulfonic acid followed by addition of sodium carbonate afforded the corresponding sodium sulfamate salt (+)-**12**.^{11a} Sequential in situ activation of **12** to form the sulfamoyl chloride **13**, followed by direct union with complex amine **7b** provided the unsymmetrical sulfamide (+)-**6b** (86%, based on **7b**, Scheme 3). Exposure of the sulfamide (+)-**6b** to *N*-chlorosuccinimide provided the corresponding unsymmetrical diazene **5b**, likely via the transient thiadiaziridine dioxide **14b**. The crude diazene **5b** was subjected to photo-induced expulsion of dinitrogen to *exclusively* afford the desired heterodimer (+)-**4b** in 68% yield from the sulfamide (+)-**6b**. The optimal conditions involved irradiation using a medium pressure mercury vapor lamp in *tert*-butanol¹⁸ as solvent in a Pyrex® reaction vessel. Importantly, neither of the two possible homodimeric products was observed by HPLC analysis of the crude product mixture.¹⁹ Notably, the formation of heterodimer (+)-**4b** (Scheme 3) constitutes the first example of *directed and stereoselective carbon–carbon bond construction fusing two different cyclotryptamine fragments at vicinal quaternary stereocenters*.

The exclusive formation of heterodimeric product (+)-**4b** suggests exquisite control in the solvent-caged coupling of the radical pair formed upon dinitrogen expulsion from the dialkyl diazene **5b**. We sought opportunities to probe the level of control exerted by this strategy in the guided unification of complex monomers. Exposure of an equal mixture of symmetrical sulfamides **6a** and **6c** to the two-step sequence for oxidation and fragmentation afforded only an equal mixture of the respective homodimeric products **3** and **15** (55% and 51% yield, respectively). Notably, HPLC analysis of the crude product mixture against authentic samples of **3**, **4b**, and **15** did not reveal any of the heterodimeric product **4b**.⁶



(2)

Furthermore, photoexpulsion of dinitrogen from (+)-**5a** in the presence of 1,4-cyclohexadiene (5.0 equiv), a hydrogenatom donor, resulted in an almost equal mixture of the desired dimeric product (+)-**3** (45% yield) and the corresponding monomeric C3a-H reduction product (21% yield, ~1:1 molar ratio).⁶ An increase in the amount of hydrogenatom donor (1,4-cyclohexadiene, 20 equiv) afforded a similar molar ratio of product (+)-**3** (41% yield) to monomeric C3a-H reduction product (20% yield). For comparison, under our reported cobalt-mediated dimerization conditions,² bromide (+)-**1** exclusively provided the monomeric C3a-H reduction product in the presence of 1,4-cyclohexadiene (5.0 equiv, 54%; 20 equiv, 82%).⁶ The formation of the dimer as the major product even in the presence of excess hydrogen-atom donor and at higher dilution under our photochemical conditions is consistent with solvent-cage directed radical-pair combination.

Having found conditions for the synthesis of the desired heterodimeric product we sought to further examine the scope of this process. Gratifyingly, mixed sulfamides **6d–6i** (Table 1)

were readily prepared using the optimal conditions described above (Scheme 3). In each case the more readily available amine was converted to the corresponding sulfamoyl chloride, allowing for the directed assembly of the heterodimeric sulfamides. Exposure of mixed sulfamides **6d–6i** to the optimized oxidative diazene synthesis afforded the heterodimeric diazenes **5d–5i** (Table 1). The crude diazenes were subject to photochemical expulsion of dinitrogen and gave the desired dimeric products (+)-**4d–4i** and *meso*-**2**.

Notably, this strategy allows access to complex heterodimers such as products (+)-**4e** and (+)-**4f**. Specifically, heterodimer (+)-**4f** results from the fusion of a tetracyclic diketopiperazine with a cyclotryptamine moiety. Thus, the chemistry described here offers the first solution for directed and exclusive heterodimeric union of requisite dissimilar cyclotryptamine precursors. Coupling the enantiomeric amines (+)-**7a** and (–)-**7a** afforded the *meso*-sulfamide **6g** (Table 1, entry 5), which upon oxidation and photolysis provided cleanly and exclusively the corresponding *meso*-dimer **2** (56% over two steps), a structural core found in *meso*-chimonanthine,^{4e} (+)-leptosin K,^{4d} and many other cyclotryptamine natural products.²⁰ The exclusive formation of *meso*-**2** in 28% overall yield from tricyclic bromides (+)-**1** and (–)-**1** can be directly compared to the example described in equation 1.

Furthermore, we wanted to explore the applicability of this methodology to the synthesis of C3a-aryl substituted quaternary stereocenters. The C_{sp3}-C_{sp2} connectivity between cyclotryptamine substructures is found in many natural alkaloids (Figure 1).¹ Notably, our cobalt promoted dimerization chemistry is not applicable to such unions. We were delighted to find that replacement of one of the amine components with an aniline derivative provided access to mixed aryl–cyclotryptamine sulfamides (Table 1, entries 5–6).^{6,21} Oxidation and photolysis provided the corresponding arylated hexahydropyrroloindoles (+)-**4h** and (+)-**4i**. The efficiency of the dinitrogen expulsion from *N*-aryl *N'*-cyclotryptaminyll diazenes **5h**²² and **5i** were on par with mixed diazenes **5d–5g**. Current efforts are directed at broadening the scope of this methodology by developing milder methods for converting complex mixed aryl-alkyl sulfamides to the corresponding diazenes.²³

We have developed a general strategy for the stereoselective directed synthesis of dimeric substructures found in hexahydropyrroloindole alkaloids. Our findings constitute the first controlled coupling of different cyclotryptamine monomers at quaternary carbons, and is distinct from prior strategies based on desymmetrization chemistry.²⁴ The adjoining of readily available monomers in the form of mixed sulfamides enables access to unsymmetrical diazenes. Photochemically induced expulsion of dinitrogen from diazenes **5** followed by solvent-cage controlled union of the corresponding radical pair delivers the desired heterodimeric products **4** with exquisite selectivity. The described protocol allows for the selective synthesis of heterodimeric products in four operations from the corresponding amines while only requiring purification of the mixed sulfamides and final products after photolysis. This chemistry allows directed heterodimerization at important substructure linkages, particularly the challenging C_{sp3}-C_{sp3} connections, found in this family of heterodimeric complex alkaloids. This completely stereocontrolled and directed fragment coupling draws on the versatility of diazene chemistry^{7,25} and holds great potential for complex molecule assembly.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

- (a) Cordell, GA.; Saxton, JE. *The Alkaloids: Chemistry and Physiology*. Manske, RHF.; Rodrigo, RGA., editors. Vol. 20. New York: Academic Press; 1981. p. 3-294.(b) Hino, T.; Nakagawa, M. *The Alkaloids: Chemistry and Pharmacology*. Brossi, A., editor. Vol. 34. New York: Academic Press; 1989. p. 1-75.(c) Crich D, Banerjee A. *Acc. Chem. Res.* 2007; 40:151. [PubMed: 17309195] (d) Steven A, Overman LE. *Angew. Chem., Int. Ed.* 2007; 46:5488.
- (a) Movassaghi M, Schmidt MA. *Angew. Chem. Int. Ed.* 2007; 46:3725.(b) Movassaghi M, Schmidt MA, Ashenhurst JA. *Angew. Chem., Int. Ed.* 2008; 47:1485.(c) Kim J, Ashenhurst JA, Movassaghi M. *Science.* 2009; 324:238. [PubMed: 19359584] (d) Kim J, Movassaghi M. *J. Am. Chem. Soc.* 2010; 132:14376. [PubMed: 20866039]
- For inventive total syntheses of natural products employing a key carbon(3a)–nitrogen bond construction, see: (a) Newhouse T, Baran PS. *J. Am. Chem. Soc.* 2008; 130:10886. [PubMed: 18656919] (b) Newhouse T, Lewis CA, Eastman KJ, Baran PS. *J. Am. Chem. Soc.* 2010; 132:7119. [PubMed: 20426477] (c) Espejo VR, Rainier JD. *Org. Lett.* 2010; 12:2154. [PubMed: 20345161] (d) Pérez-Balado C, de Lera ÁR. *Org. Biomol. Chem.* 2010; 8:5179. [PubMed: 20848034]
- (a) Eccles RG. *Proc. Am. Pharm. Assoc.* 1888; 84:382.(b) Anet EFLJ, Hughes GK, Ritchie E. *Aust. J. Chem.* 1961; 14:173.(c) Barrow CJ, Sedlock DM. *J. Nat. Prod.* 1994; 57:1239. [PubMed: 7528269] (d) Takahashi C, Minoura K, Takeshi T, Numata A, Kushida K, Shingu T, Hagishita S, Nakai H, Sato T, Harada H. *Tetrahedron.* 1995; 51:3483.(e) Varoglu M, Corbett TH, Valeriotte FA, Crews P. *J. Org. Chem.* 1997; 62:7078. [PubMed: 11671801]
- For other recent applications, see: (a) Pérez-Balado C, de Lera AR. *Org. Lett.* 2008; 10:3701. [PubMed: 18680309] (b) Pérez-Balado C, Rodríguez-Graña P, de Lera AR. *Chem. Eur. J.* 2009; 15:9928. (c) Iwasa E, Hamashima Y, Fujishiro S, Higuchi E, Ito A, Yoshida M, Sodeoka M. *J. Am. Chem. Soc.* 2010; 132:4078. [PubMed: 20210309] (d) Foo K, Newhouse T, Mori I, Takayama H, Baran PS. *Angew. Chem., Int. Ed.* 2011; 50:2716.
- See Supporting Information for details.
- (a) Horner L, Naumann W. *Liebigs Ann. Chem.* 1954; 587:93. (b) Nelsen SF, Bartlett PD. *J. Am. Chem. Soc.* 1966; 88:137. (c) Nelsen SF, Bartlett PD. *J. Am. Chem. Soc.* 1966; 88:143. (d) Timberlake JW, Alender J, Garner AW, Hodges ML, Özmeral C, Szilagy S. *J. Org. Chem.* 1981; 46:2082. (e) Hossain MT, Timberlake JW. *J. Org. Chem.* 2001; 66:6282. [PubMed: 11559175] For other pioneering work in the area of diazene chemistry see: (f) Porter NA, Marnett LJ. *J. Am. Chem. Soc.* 1972; 95:4361. (g) Göllitz P, de Meijere A. *Angew. Chem. Int. Ed.* 1977; 16:854. (h) Porter NA, Dubay GR, Green JG. *J. Am. Chem. Soc.* 1978; 100:920. (i) Baldwin JE, Adlington RM, Bottaro JC, Kolhe JN, Newington IM, Perry MWD. *Tetrahedron.* 1986; 42:4235. (j) Sumiyoshi T, Kamachi M, Kuwae Y, Schnabel W. *Bull. Chem. Soc. Jpn.* 1987; 60:77. (k) Neuman RC Jr, Grow RH, Binegar GA, Gunderson HJ. *J. Org. Chem.* 1990; 55:2682. (l) Engel PS, Pan L, Ying Y, Alemany LB. *J. Am. Chem. Soc.* 2001; 123:3706. [PubMed: 11457102] (m) Hoijemberg PA, Karlen SD, Snaramé CN, Aramendía PF, García-Garibay MA. *Photochemical & Photobiological Sci.* 2009; 8:961. For relevant reviews see: (n) Engel PS, Steel C. *Acc. Chem. Res.* 1973; 6:275. (o) Engel PS. *Chem. Rev.* 1980; 80:99.
- We also explored the use of diacyl peroxides and diacyl diazenes. For diacyl peroxides, see: (a) Bartlett PD, Leffler JE. *J. Am. Chem. Soc.* 1950; 72:3030. (b) Feldhues M, Schäfer HJ. *Tetrahedron.* 1985; 41:4213. (c) Spantulescu MD, Jain RP, Derksen DJ, Vederas JC. *Org. Lett.* 2003; 5:2963. [PubMed: 12889919] (d) Jain RP, Vederas JC. *Org. Lett.* 2003; 5:4669. [PubMed: 14627411] For diacyl diazenes, see: (e) Leffler JE, Bond WB. *J. Am. Chem. Soc.* 1956; 78:335. (f) Cramer R. *J. Am. Chem. Soc.* 1957; 79:6215. (g) Mackay D, Marx UF, Waters WA. *J. Chem. Soc.* 1964:4793.
- (a) Nodelman N, Martin JC. *J. Am. Chem. Soc.* 1976; 98:6597.(b) Braden DA, Parrack EE, Tyler DR. *Coordin. Chem. Rev.* 2001; 211:279.

10. We also examined the oxidation of dialkyl ureas. For pioneering work on diaziridinones, see: (a) Greene FD, Stowell JC. *J. Am. Chem. Soc.* 1964; 86:3569. and. (b) Greene FD, Stowell JC, Bergmark WR. *J. Org. Chem.* 1969; 34:2254.
11. (a) Audrieth LF, Sveda M. *J. Org. Chem.* 1944; 9:89.(b) Hansen NC. *Acta. Chem. Scand.* 1963; 17:2141.(c) Weiss G, Schulze G. *Liebigs Ann. Chem.* 1969; 729:40.(d) Kloek JA, Leschinsky KL. *J. Org. Chem.* 1976; 41:4028.(e) Timberlake JW, Ray WJ Jr, Stevens ED, Cheryl KL. *J. Org. Chem.* 1989; 54:5824.
12. (a) Ohme R, Schmitz E. *Angew. Chem. Int. Ed.* 1965; 4:433.(b) Golzke F, Oberlinner GA, Rüchardt C. *Nouv. J. Chim.* 1977; 1:169.(c) Chang H-H, Weinstein B. *J. Chem. Soc., Perkin Trans. 1.* 1977:1601.(d) Ikeda H, Hoshi Y, Namai H, Tanaka F, Goodman JL, Mizuno K. *Chem. Eur. J.* 2007; 13:9207.
13. For a base promoted introduction of azide and *p*-MeC₆H₄ at C3a of a related cyclotryptophan, see Espejo VR, Li X-B, Rainier JD. *J. Am. Chem. Soc.* 2010; 132:8282. [PubMed: 20518467]
14. For a recent synthesis of C3a-amino cyclotryptamines, see Benkovics T, Guzei IA, Yoon TP. *Angew. Chem., Int. Ed.* 2010; 49:9153.
15. Application of previously reported conditions was found to suffer from incomplete conversion or low yield of the diazene.
16. Key spectroscopic data for representative diazenes: α , α' -azocumene, $\lambda_{\max} = 367$ nm (ref. 7b), ¹³C NMR (CDCl₃) δ 71.32 (α -carbon, ref. 12d); *trans*-*N,N'*-di(1-adamanty)diazene, $\lambda_{\max} =$ (octane) 368 nm (ref. 7k).
17. Photoexcitation at 23 °C was found to be superior to thermal diazene fragmentation for our substrates. For example, diazene (+)-**5a** was stable at 120 °C in DMSO-*d*₆ while resulting in unproductive decomposition at 150 °C.
18. The use of methanol, a lower viscosity solvent, resulted in a drastic decrease in the isolated yield of the desired product.
19. Samples of the homodimeric products were readily available by our cobalt chemistry.
20. (a) Hart NK, Johns SR, Lamberton JA, Summons RE. *J. Aust. Chem.* 1974; 27:639.(b) Libot F, Miet C, Kunesch N, Poisson JE, Pusset J, Sévenet T. *J. Nat. Prod.* 1987; 50:468.(c) Verotta L, Pilati T, Tatø M, Eilsabetsky E, Amador TA, Nunes DS. *J. Nat. Prod.* 1998; 61:392. [PubMed: 9548883] (d) Jannic V, Guéritte F, Laprévotte O, Serani L, Martin M-T, Sévenet T, Potier P. *J. Nat. Prod.* 1999; 62:838. [PubMed: 10395499]
21. Sulfamides **6h** and **6i** were prepared from the corresponding aniline derived sulfamate salts and amine **7a**.
22. Diazene **5h** was found to undergo facile *trans* to *cis* isomerization in solution (CD₃CN) upon exposure to ambient light. Interestingly, a majority of *cis* diazenes have been shown to be unstable above 0 °C in solution (see ref 7f and 7o).
23. Complications during the sulfamide to diazene conversion using our current conditions prevent the use of electron rich anilines; see Forster DL, Gilchrist TL, Rees CW. *J. Chem. Soc., Perkin Trans. 1.* 1971:993. in addition to refs. 7f and 7h.
24. For an elegant example of desymmetrization chemistry in a related system, see Kodanko JJ, Overman LE. *Angew. Chem. Int. Ed.* 2003; 42:2528. Also, see refs. 2b, 5a, and 5d.
25. For representative examples of intramolecular carbon-carbon bond formation using dialkyl diazene intermediates in natural product synthesis, see: (a) Little RD, Carroll GL, Pettersen JL. *J. Am. Chem. Soc.* 1983; 105:928. (b) Little RD. *Chem. Rev.* 1996; 96:93. [PubMed: 11848745] (c) Mascitti V, Corey EJ. *J. Am. Chem. Soc.* 2004; 126:15664. [PubMed: 15571387] (d) Wender PA, Kee J-M, Warrington JM. *Science.* 2008; 320:649. [PubMed: 18451298]

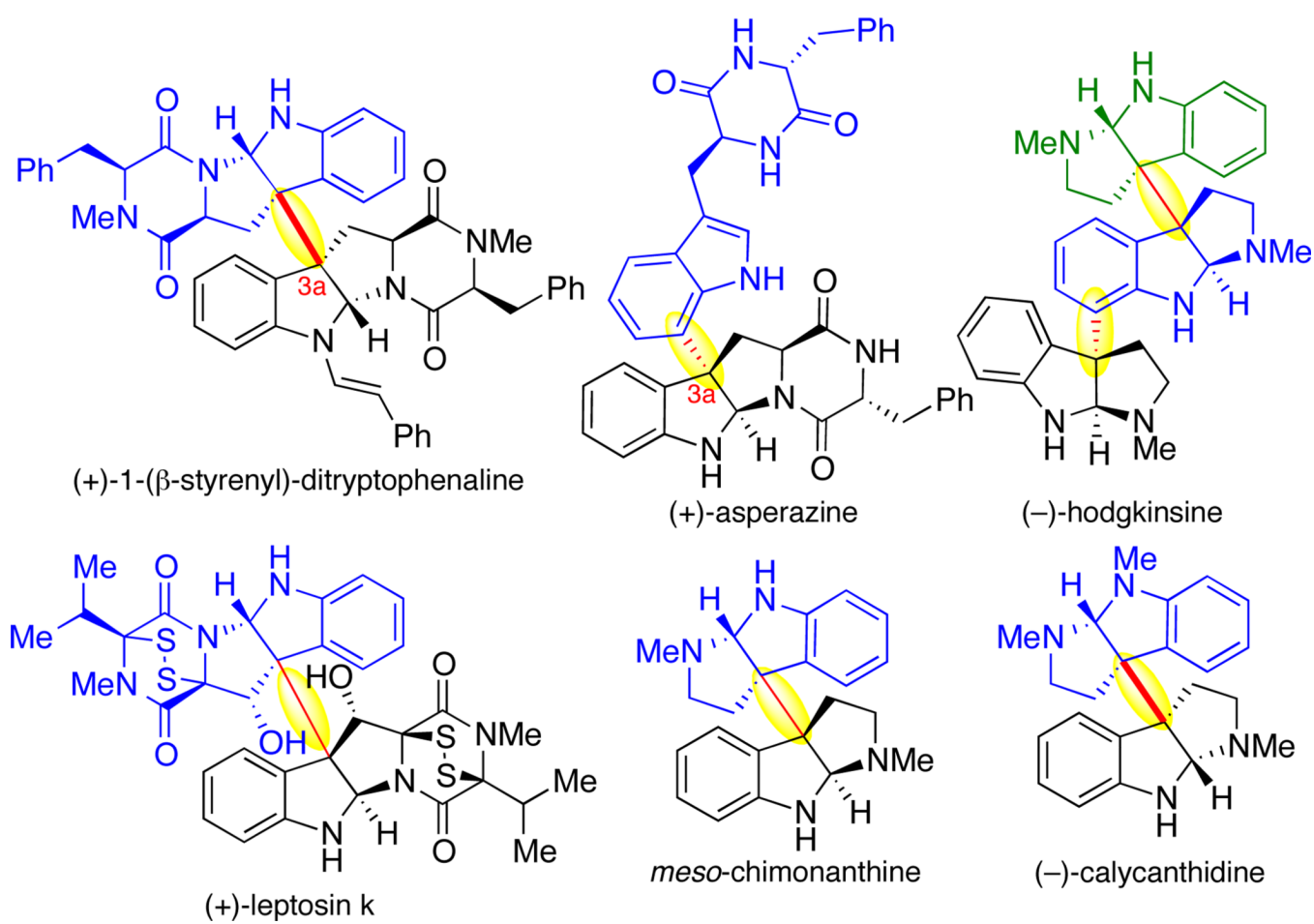
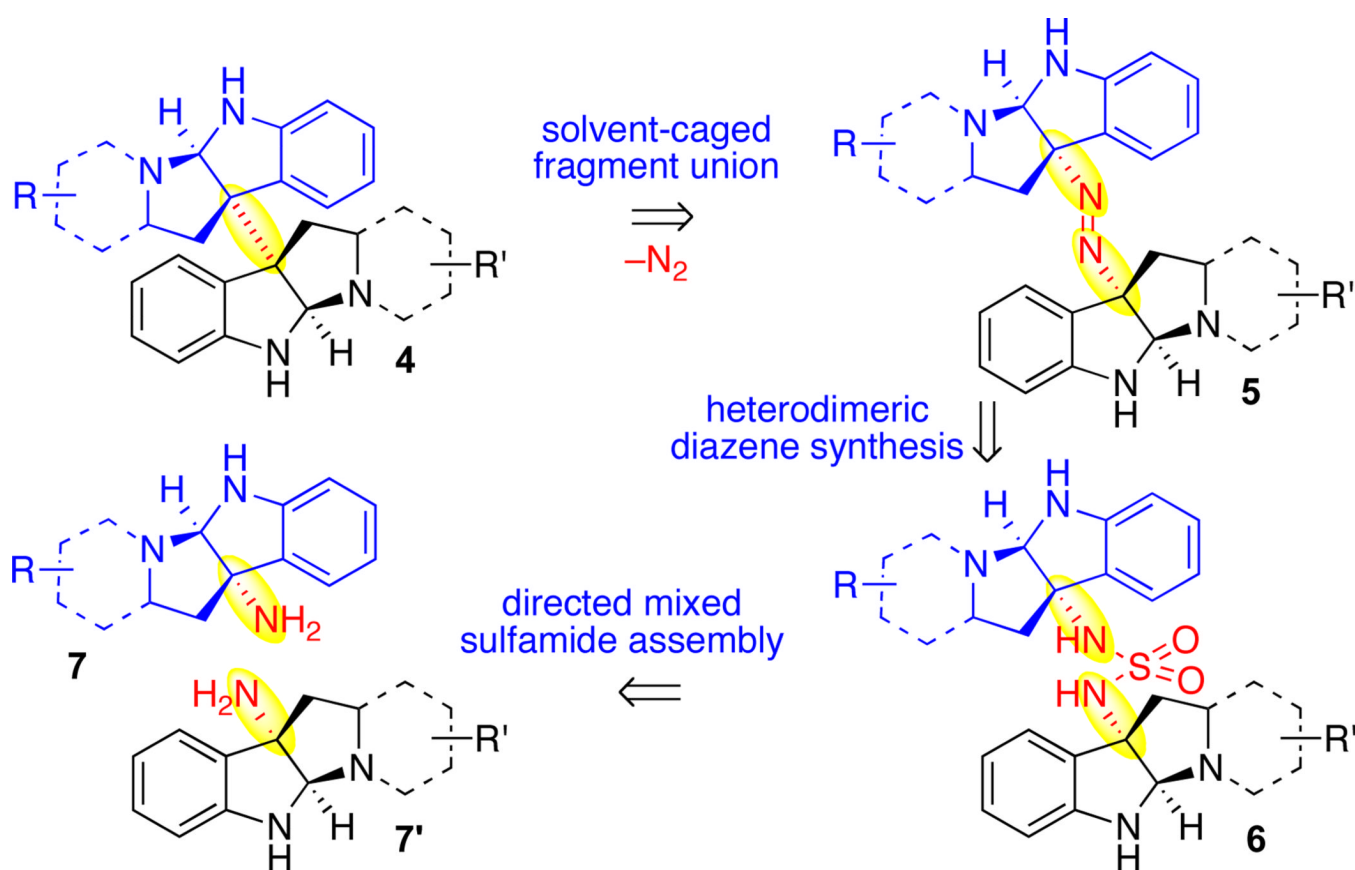
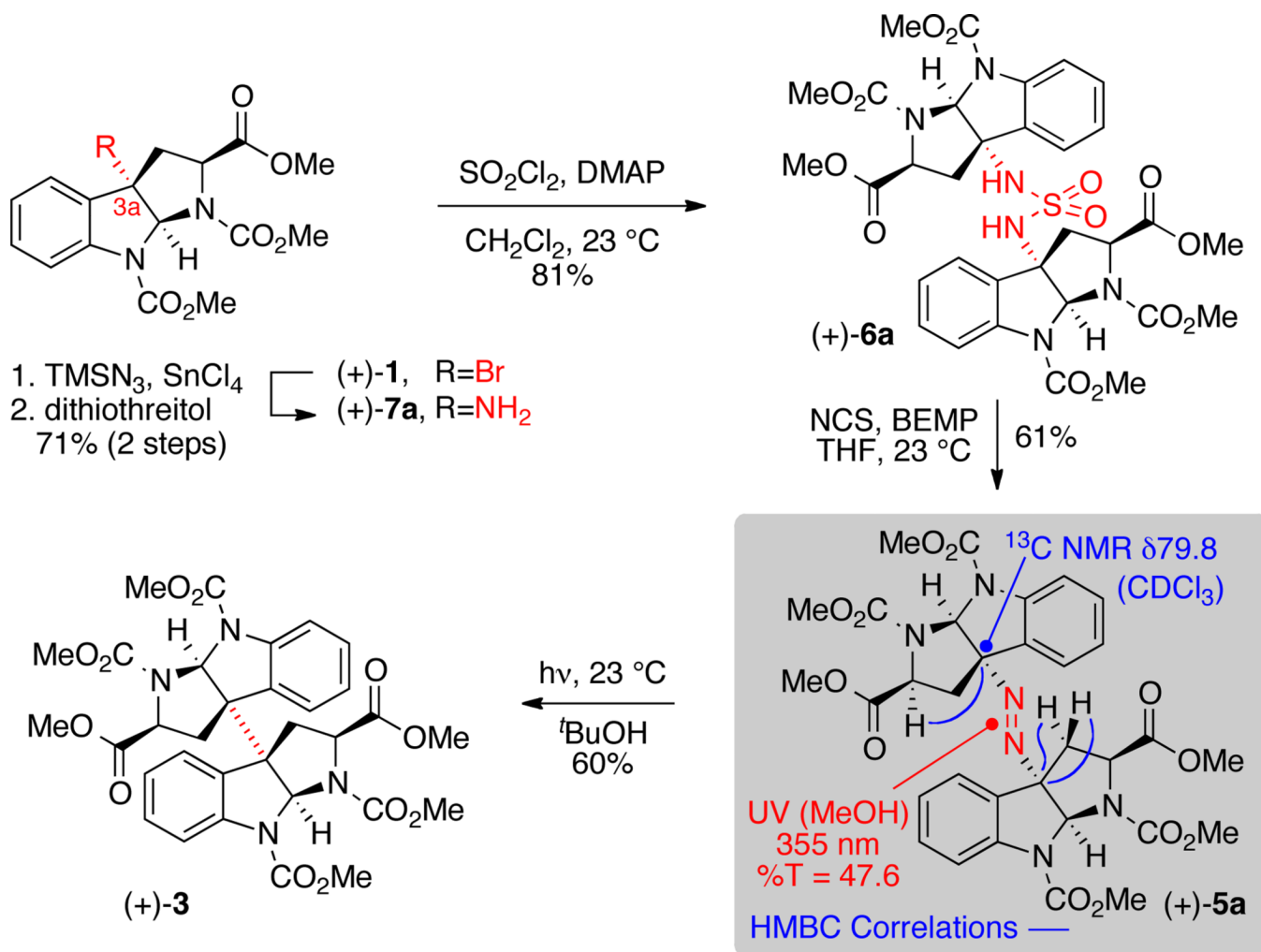


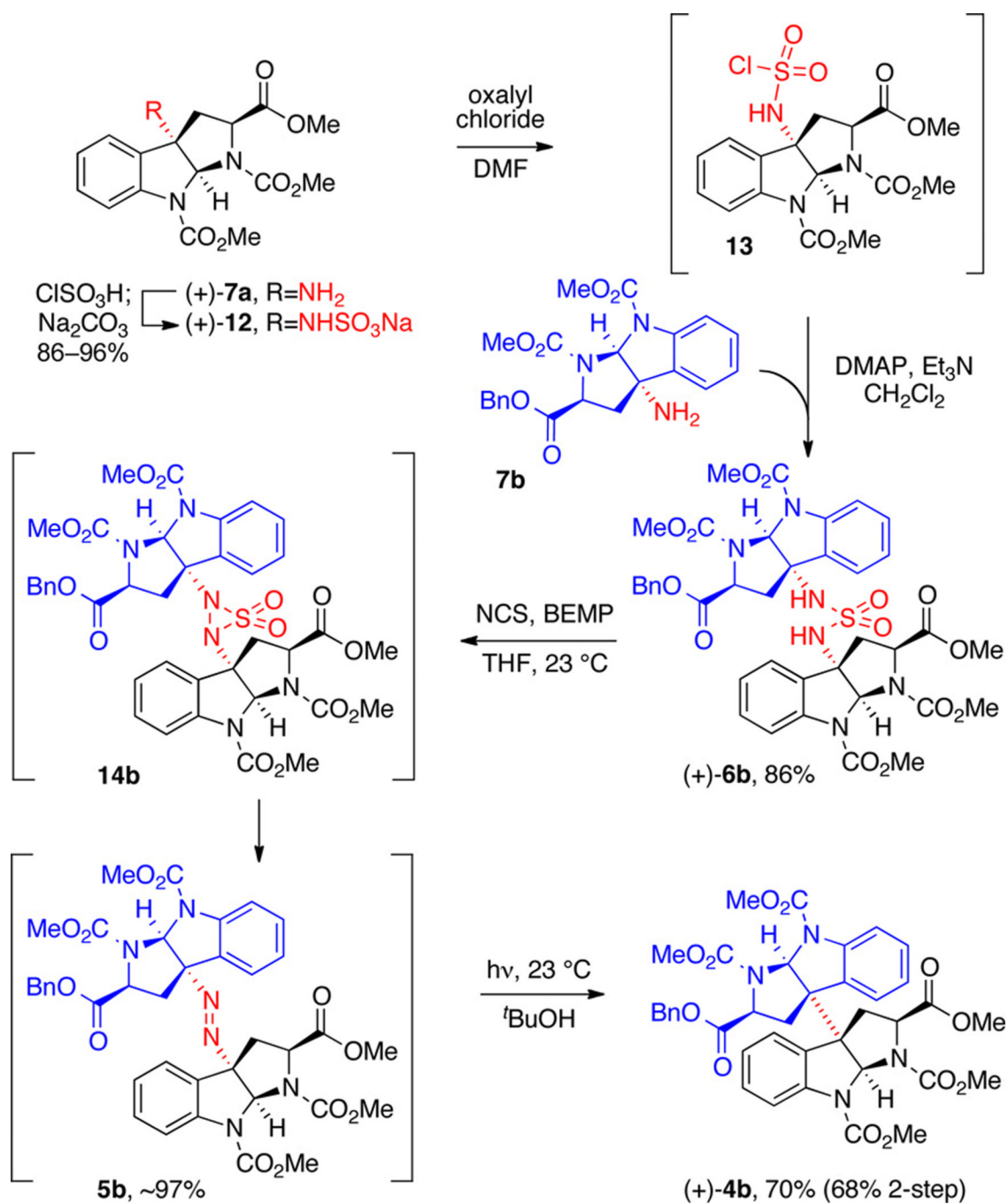
Figure 1.
Representative heterodimeric cyclotryptamine alkaloids.



Scheme 1.
A general strategy for directed heterodimerization.



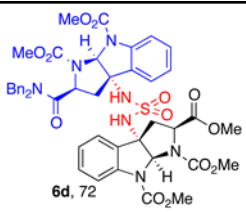
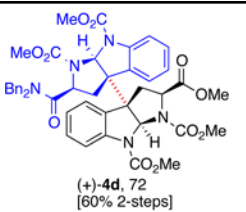
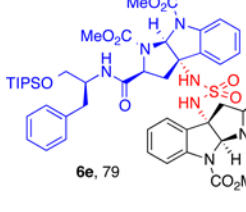
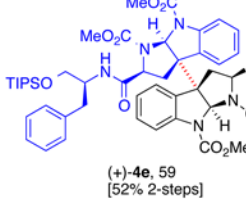
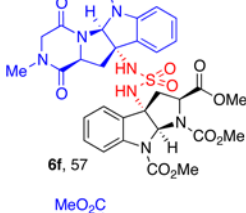
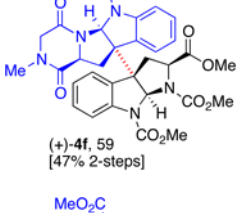
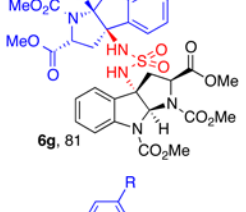
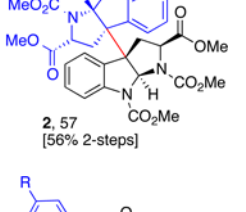
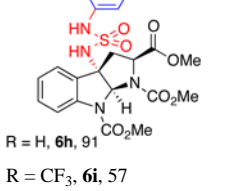
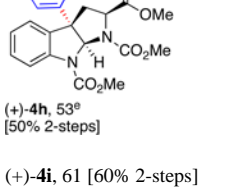
Scheme 2.
 Homodimer Synthesis via Diazene Fragmentation.



Scheme 3.
Directed assembly and heterodimer synthesis.

Table 1

Directed heterodimer synthesis.

Entry	Unsymmetrical Sulfamide ^a	Diazene ^b	Heterodimeric Product ^c
1		5d , (80)	 (+)- 4d , 72 [60% 2-steps]
2		5e , (88)	 (+)- 4e , 59 [52% 2-steps]
3		5f , (83)	 (+)- 4f , 59 [47% 2-steps]
4		5g , (99)	 2 , 57 [56% 2-steps]
5		5h , (91) ^d	 (+)- 4h , 53 ^e [50% 2-steps]
6		5i , (99)	(+)- 4i , 61 [60% 2-steps]

^aMixed sulfamide synthesis: **7**, **13**, DMAP, Et₃N, CH₂Cl₂, 0 → 23 °C. Isolated % yield of **6** after chromatography.^bDiazene synthesis: BEMP, NCS, THF, 23 °C. Crude % yield of sensitive diazene **5** in parentheses.^cHeterodimer synthesis: *t*-BuOH, hv >280 nm, 23 °C, 5 h. Isolated % yield of **4** after chromatography. Yield of **4** from **6** in brackets.^dDBU, NCS, MeOH, 0 → 23 °C.^ehv 300 nm, 12 h.