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Synthesis of cyclic azobenzene analogues

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ABSTRACT

Reaction of 2,2'-dinitrodibenzyl with lead metal powder in the presence of a basic triethylammonium formate buffer gave a cyclic azoxybenzene, 11,12-dihydrodibenzo[c,g][1,2]diazocine-5-oxide. The latter compound was converted into cyclic azobenzene and analogues (chloro-, bromo-, and cyano-) through subsequent transformations. Hydrolysis of the cyano cyclic azobenzene gave the corresponding carboxylic acid. This carboxylic acid was finally reacted with p-threoninol to give the corresponding amide, which readily undergoes photoisomerization upon illumination with light.

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1. Introduction

Aromatic azo compounds possess a conjugate system that can be readily 'tuned' through structural modifications to adjust their chemical and photochemical properties, and have thus found wide applications as dyes and pigments, food additives, radical initiators, therapeutic agents, as well as functional materials.^{1–4} In addition, some aromatic azo compounds, such as azobenzene **1**, have been shown to undergo photo- and thermoisomerization, where the *E*and *Z*-isomers oscillate back and forth when excited by light of selected wavelength or heat (Fig. 1). This latter phenomenon has been exploited as a useful photoswitch where a signal can be induced by light and harnessed.^{5,6} One such application involves the incorporation of azobenzene into biomolecules, such as proteins and nucleic acids to trigger conformational changes to the biomolecules that impact their functions.^{7–10}



Fig. 1. *E*–*Z* isomerization of azobenzene.

As can be seen from Fig. 2a, the (*E*)-azobenzene isomer displays a strong absorption band at 318 nm and another weak absorption band at 432 nm. The (*Z*)-isomer has two absorption bands, a strong absorption at 260 nm and a weak absorption at 440 nm. There is an obvious overlap in the absorption of the two isomers, and as such, isomerization of this system is not very efficient. Furthermore, although it is possible to derivatize azobenzene to achieve bidirectional switching without UV light,¹¹ the isomerization of the unmodified azobenzene generally necessitates irradiation by light in the UV region, which readily causes damages to biomolecules, particularly nucleic acids through photodamage. In addition, azobenzene has relatively low quantum yields for direct photo-isomerization (*trans* \rightarrow *cis* and *cis* \rightarrow *trans*).¹²

Among the many azobenzene analogues known in the literature, the cyclic (or 'bridged') azobenezene 5,6-dihydrodibenzo[c,g][1,2] diazocine **2** where the benzene rings are constrained with an ethylenic bridge is of particular interest. In this system, the (Z)-isomer is the more stable isomer, instead of the (E)-isomer in azobenzene, and it can be transformed into the (E)-isomer with an efficiency greater than 90% by irradiation with blue light (370–400 nm). The (E)-isomer can be switched back to the (Z)-isomer with virtually quantitative efficiency by illumination with green light (480–550 nm) (Figs. 2b and 3).¹⁴ In addition, this system is likely to be better tolerated in biological systems as irradiation wavelengths are shifted away from the UV region.

Considerable interest has been invested towards understanding this new photoswitch, particularly from the theoretical point of view.^{15–20} What has been challenging with this system is the

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Fig. 2. UV/vis absorption spectra of (a). azobenzene **1** (solid line: (*Z*)-isomer; dash line: (*E*)-isomer) (reprinted with permission from Zimmerman, G.; Chow, L.-Y.; Paik, U.-J. *J. Am. Chem. Soc.* **1958**, *80*, 3528–3531.¹³ Copyright 1958 American Chemical Society); (b). cyclic azobenzene **2** (solid line: (*Z*)-isomer; dash line: (*E*)-isomer) (reprinted with permission from Siewertsen, R.; Neumann, H.; Buchheim-Stehn, B.; Herges, R.; Näther, C.; Renth, F.; Temps, F. *J. Am. Chem. Soc.* **2009**, *131*, 15594.¹⁴ Copyright 2009 American Chemical Society).



Fig. 3. Isomerization of the cyclic azobenzene.

extremely poor efficiency of its synthesis (4%) from 2,2'-dinitrodibenzyl^{14,21,22} and thereafter the lack of effective methods for further modification, which would be of particular concern if this system were to be incorporated into biomolecules as a photoswitch. We report herein the transformation of 2,2'dinitrodibenzyl into cyclic azobenzene and analogues, which would allow for further incorporation of this cyclic azobenzene into other molecules.

2. Results/discussion

Although a number of approaches were reported for the synthesis of azo- from arylnitro-compounds with high efficiency,^{23–27} treatment of 2,2'-dinitrodibenzyl **3** under these conditions has invariably failed to give the cyclic azobenzene **2** in sufficient yields.

When 2,2'-dinitrodibenzyl 3 was treated with zinc powder under neutral pH, cyclic hydrazine **4** (5,6,11,12-tetrahydro-dibenzo[c,g] [1,2]diazocine) was formed in moderate yields (up to 70%); however, this transformation was found to be highly dependent on the surface properties and/or impurity of zinc powder, as use of newer batches of zinc powder only gave **4** in very low yields (<5%). Work is currently underway to investigate the causes of this discrepancy. On the other hand treatment of 2.2'-dinitrodibenzyl **3** with lead metal at pH 9.5 in methanol gave cyclic azoxybenzene 5 (11,12dihydrodibenzo[c,g][1,2]diazocine-5-oxide) in moderate yields (61%) (Scheme 1). It was noted that a rather efficient method to prepare this cyclic azoxybenzene 5 from the N-nitrosohydroxylamine ammonium salt of 2,2'-dinitrodibenzyl was previously documented.²⁸ This literature procedure was not used in the present study as it necessitates an extra step from a commercially available compound.

The azoxybenzene 5 was subsequently transformed into the corresponding bridged azobenzene 2 in 59% yield through catalytic deoxygenation using triphenylphosphine as oxygen acceptor in the presence of a molybdenum catalyst.^{29,30} Structure of the cyclic azobenzene **2** was confirmed by X-ray crystallography, where the ethylene bridge is disordered over two sets of sites with refined occupancies of 0.552 (14) and 0.448 (14) (Fig. 4a). The azoxybenzene 5 also undergoes concomitant deoxygenation and halogenation when treated with aluminium halide (chloride or bromide) in carbon disulfide³¹ to give the corresponding chloro ($\mathbf{6}$) or bromo (7) analogues in poor yields (8 and 9% for the 6 and 7, respectively). It was found, however, that azoxybenzene 5 can be brominated with bromine³² to give the corresponding bromoazoxybenzene 8 (2-bromo-11,12-dihydrodibenzo[c,g][1,2] diazocine-6-oxide) in 70% yield. The identity of bromoazoxybenzene 8 was established by X-ray crystal structure (Fig. 4b), where two independent molecules with slightly different conformations were found in the asymmetric unit. Interestingly, treatment of bromoazoxybenzene 8 with triphenylphosphine and the molybdenum catalyst failed to give cyclic bromoazobenzene 7.

When bromoazoxybenzene $\mathbf{8}$ was treated with copper (I) cyanide,³⁴ the corresponding cyanoazoxybenzene **9** was obtained in 69% yield. Treatment of the latter compound 9 with aluminium and hydrazine hydrate³⁵ gave a mixture of cyclic cyanoazobenzene **11** and the over-reduced hydrazine **10**, with the latter being a major product. The hydrazine **10** can be transformed into corresponding cyclic cyanoazobenzene 11 by treating with titanium (III) chloride, hydrobromic acid and hydrogen peroxide.³⁶ Finally, cyclic cyanoazobenzene 11 was hydrolyzed under basic conditions to give the corresponding carboxylic acid 12 in 78% yield. This carboxylic compound was readily condensed with p-threoninol using dicyclohexylcarbodiimide as activator in the presence of N-hydroxvsuccinimide. Work is currently underway in our laboratory to incorporate cyclic azobenzene into biomolecules using analogue 13. When the amide 13 was subjected to LED irradiation at either 380 or 400 nm (the LED light source spans±5 nm), a clear colour change from yellow (the (Z)-isomer) to red (the (E)-isomer) was observed (Fig. 5).

Extents of photoisomerization can be qualitatively determined by HPLC (Fig. 6). As can be seen in Fig. 6a and b, when the unmodified cyclic azobenzene **2** was subjected to irradiation with LED light at 380 ± 5 nm for 2 h, 90% of the (*Z*)-isomer was converted to the (*E*)-isomer (Fig. 6b). The extent of the isomerization of **2** is consistent with yield reported in the literature.¹⁴ Under the same conditions, approximately 70% of (*Z*)-isomer of amide **13** was converted to the corresponding (*E*)-isomer (Fig. 6c and d).

The UV/vis spectra of (**Z**)-**13** and the isomerization product (with an approximate Z/E ratio of 30:70) are shown in Fig. 7a. Compared with the UV/vis spectra of (**Z**)-**2** and the corresponding isomerization product (with an approximate Z/E ratio of 10:90)



Scheme 1. Reagents and conditions: (i). Pb, pH 9.5, MeOH; (ii). Zn, pH 7.0, EtOH; (iii). TiCl₃, *aq*. HBr, H₂O₂; (iv). Ph₃P, MoCl₂O₂ (dmf) ₂, THF; (v). AlCl₃, CS₂; (vi). AlBr₃, CS₂; (vii). Br₂, CH₃COOH; (viii). CuCN, DMF; (ix). Al, NH₂NH₂; (x). (a). KOH, EtOH, H₂O, reflux; (b). *aq*. HCl; (xi). b-threoninol, DCC, *N*-hydroxysuccinimide, DMF.

(Fig. 7b), the maximal absorption wavelengths for (Z)-2 and (Z)-13 are the same (at 400 nm), whereas that of (E)-13 shifted from 483 nm for (E)-2 to 487 nm.

The time course of $(Z) \rightarrow (E)$ -**13** isomerization was followed by measuring the percentage transmission at 480 nm of the methanol solution exposed to 380 nm LED light over time. After the transmission reached the minimum, the solution is illuminated at 480 nm and the transmission at 480 nm was measured again over time. As can be seen from Fig. 8, under this condition, the $(Z) \rightarrow (E)$ isomerization reached the maximum steady state after approximately 40 min, whereas the $(E) \rightarrow (Z)$ isomerization was slower with a full recovery of transmission after approximately 2 h.

3. Conclusion

In conclusion, bromo-, chloro-, cyano-, carboxyl and unsubstituted cyclic azobenzene were prepared from 2,2'-dinitrodibenzyl. Condensation of the carboxylic analogue with Dthreoninol gave a building block with both a primary and secondary alcohols that can be readily isomerized by illumination with light. Incorporation of this building block into oligonucleotides through the phosphoramidite chemistry⁸ is currently underway in this laboratory.

4. Experimental

4.1. General

¹H NMR spectra were measured at 600 MHz with a Bruker AV600 spectrometer; tetramethylsilane was used as an internal standard; *J* values are given in Hertz. ¹³C NMR spectra were measured at 150.9 MHz with the same spectrometer. Chemical shifts are given in parts per million. Low and high resolution mass spectra were obtained with Kratos Concept 1S high resolution mass spectrometer using electron impact sources interfaced with DART 32 bit acquisition system through a Sun Sparcstation 10 and Mach 3 software. Desican 230–400 mesh silica gel 60 was used for flash column chromatography, respectively. Thin layer chromatography was performed on Silicycle SiliaPlate F-254 TLC plates using dichloromethane–hexane (90:10, v/v) unless stated otherwise.



Fig. 4. The molecular structure of (a) 2 (the dashed lines indicate the bonds of a minor component of disorder) and (b) 8 (two independent molecules with slightly different conformations were found in the asymmetric unit) with 30% probability displacement ellipsoids (prepared with PLATON).³³.

2.00

1.50

1.00

0.50 0.00

200

250

300

350



Fig. 5. Colour change of 13 as a result of photoisomerization.



Fig. 6. HPLC profiles of cyclic azobenzene 2 and 13. (a). (Z)-2; (b). (E)-2; (c). (Z)-13; (d). (*E*)-13. (Profiles a and b: linear gradient of water-acetonitrile (55:45 to 15:85, v/v) over 15 min; profiles c and d: linear gradient of water-acetonitrile (90:10 to 55:45, v/v) over 15 min).

Reverse phase high-performance liquid chromatography (HPLC) was carried out on a 4.6 $\times 150$ mm Acclaim PA C18 3 μ column: the column was eluted with water-acetonitrile mixtures at a flow rate of 0.80 ml/min. UV/vis spectra were recorded with a Biochrom Ultrospec 2100pro UV/visible spectrophotometer. Chemicals were purchased from Aldrich or TCI America and used without further purification unless stated otherwise. Dichloromethane, toluene and dimethylformamide were purified by Pure-Solv Solvent Purification Systems (Innovative Technology), and stored over activated 4 Å molecular sieves.

4.2. 11,12-Dihydrodibenzo[c,g][1,2]diazocine-5-oxide (5)

Triethylamine (22 mL, 0.16 mol) was added to methanol (50 mL) followed by addition of formic acid (1 mL, 0.026 mol) and water



Fig. 7. UV/vis spectra. (a). (Z)- and (Z)/(E)-2 in methanol (0.60 mM); (b). (Z)- and (Z)/ (E)-13 in methanol (1.1 mM).

450

Wavelength (nm)

0.20

0.10

0.00

400

350 400 450

500

500

550

550

600 650

600

650

700



Fig. 8. Isomerization time course of 13 in methanol (0.94 mM) as determined by the percent transmission at 480 nm. \blacklozenge : (*Z*) \rightarrow (*E*) isomerization illuminated at 380 nm; O: $(E) \rightarrow (Z)$ isomerization illuminated at 480 nm.

(14 mL). The final pH of the solution was adjusted to 9.5 with triethylamine (ca. 20 mL). To this solution were added 2,2'-dinitrodibenzyl (1.00 g, 3.67 mmol) and lead metal powder (3.50 g, 16.9 mol, ~200 mesh, 99% metal basis). After the reaction mixture was stirred vigorously at room temperature for 24 h, another portion of lead metal powder (3.50 g, 14.5 mmol) was added, and stirring was continued for another 24 h. The products were filtered and the filtrate was concentrated under reduced pressure. The residue was re-dissolved in dichloromethane (30 mL) and extracted with saturated aqueous sodium hydrogen carbonate (3×10 mL). The organic layer was dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel. The appropriate fractions, which were eluted with dichloromethane-hexane (40:60 v/v), were pooled and concentrated under reduced pressure to give the title compound as a pale yellow solid (500 mg, 61%). Mp 167–169 °C (ethanol). Rf: 0.49. HRMS (EI) found 224.09420, C₁₄H₁₂N₂O required 224.09496. $\delta_{\rm H}$ (CDCl₃): 2.88 (1H, ddd, *J*=5.9, 9.6, and 14.4), 2.98 (1H, ddd, *J*=5.2, 10.0, and 14.9), 3.22 (1H, ddd, *J*=5.1, 10.1, and 14.6), 3.37 (1H, ddd, J=5.9, 10.1, and 15.0), 6.94 (1H, d, J=7.8), 7.02 (2H, d, J=4.0), 7.04 $(1H, d, J=7.6), 7.10-7.20 (4H, m). \delta_{C}(CDCl_{3}): 30.1, 31.2, 121.6, 121.7,$ 127.2, 127.3, 127.8, 129.6, 130.3, 130.4, 131.5, 131.8, 146.0, 148.7.

4.3. 2-Chloro-11,12-dihydrodibenzo[c,g][1,2]diazocine (6)

To a suspension of aluminium chloride (208 mg, 1.56 mmol) in carbon disulfide (3.0 mL), a solution of 11,12-dihydrodibenzo[*c*,g] [1,2]diazocine-5-oxide 5 (350 mg, 1.56 mmol) in carbon disulfide (2.0 mL) was added drop-wise under nitrogen. The reaction mixture was heated under reflux for 5 h and then cooled and concentrated under reduced pressure. To the dark residue was added hydrochloric acid (0.1 M, 6 mL), and the mixture was extracted with diethyl ether $(3 \times 5 \text{ mL})$. The organic layers were washed first with water (2×20 mL) and then with saturated aqueous sodium bicarbonate (2×20 mL), dried (MgSO₄), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel. The appropriate fractions, which were eluted with dichloromethane-hexane (30:70 v/v), were combined and concentrated under reduced pressure to give the title compound as a light yellow solid (30 mg, 8%). Mp 80-82 °C (ethanol). R_f: 0.78. HRMS (EI) found 242.06156, C₁₄H₁₁ClN₂ required 242.06108. δ_H(CDCl₃): 2.76 (2H, m), 2.98 (2H, br, m), 6.79 (1H, d, *J*=8.4), 6.85 (1H, d, *J*=7.8), 6.99 (1H, d, *J*=1.5), 7.01 (1H, d, *J*=7.5), 7.06 (1H, t, J=7.5), 7.11 (1H, dd, J=1.9 and 8.4), 7.17 (1H, t, J=7.7). $\delta_{C}(CDCl_{3})$: 31.4, 31.7, 118.7, 120.4, 126.8, 126.9, 127.4, 127.6, 129.5, 129.7, 130.2, 132.2, 153.7, 155.3.

4.4. 2-Bromo-11,12-dihydrodibenzo[c,g][1,2]diazocine (7)

To a suspension of aluminium bromide (145 mg, 0.544 mmol) in carbon disulfide (3.0 mL) a solution of 11,12-dihydrodibenzo[c,g] [1,2]diazocine-5-oxide 5 (100 mg, 0.446 mmol) in carbon disulfide (2.0 mL) was added drop-wise under nitrogen. The reaction mixture was heated under reflux for 5 h, and then cooled and concentrated under reduced pressure. The dark residue was then treated carefully with hydrochloric acid (0.1 M, 6 mL), and extracted with diethyl ether $(3 \times 5 \text{ mL})$. The ether layers were combined and washed successively with water $(2 \times 20 \text{ mL})$ and saturated aqueous sodium bicarbonate (2×20 ml). The organic layer was separated, dried (MgSO₄) and evaporated to dryness under reduced pressure. The residue was purified by column chromatography on silica gel. The appropriate fractions, which were eluted with dichloromethane–hexane (30:70 v/v), were combined and concentrated under reduced pressure to give the *title compound* as a light yellow solid (12 mg, 9%). Rf: 0.78. HRMS (EI) found 286.01081, C14H11BrN2 required 286.01056. δ_H(CDCl₃): 2.76 (2H, m), 2.99 (2H, br, m), 6.73 (1H, d, J=8.4), 6.85 (1H, d, J=7.8), 7.02 (1H, d, J=7.5), 7.07 (1H, t, *J*=7.4), 7.15 (1H, d, *J*=1.6), 7.18 (1H, t, *J*=7.5), 7.26 (1H, dd, *J*=1.7 and 8.4). δ_C(CDCl₃): 31.4, 31.6, 118.7, 120.3, 120.6, 127.0, 127.4, 127.5, 129.7, 129.8, 130.4, 132.4, 154.2, 155.3.

4.5. 11,12-Dihydrodibenzo[c,g][1,2]diazocine (2)

To a solution of 11,12-dihydrodibenzo[*c*,g][1,2]diazocine-5oxide **5** (100 mg, 0.446 mmol) in dry tetrahydrofuran (5 mL) were added triphenylphosphine (585 mg, 2.23 mmol) and molybdenum dioxo dichloride $(dmf)_2^{29,30}$ (20 mg, 5.6 mmol). The reaction mixture was heated under reflux for 3 h and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel. The appropriate fractions, which were eluted with dichloromethane–hexane (30:70 *v/v*), were combined and concentrated under reduced pressure to give 5,6dihydrodibenzo[*c*,g][1,2]diazocine **2** as a light yellow solid (55 mg, 59%). Mp111–113 °C (ethanol), lit.²¹ 112–113 °C. *R*_f: 0.72. HRMS (EI) found: 208.10023, C₁₄H₁₂N₂ required 208.10005. $\delta_{\rm H}$ (CDCl₃): 2,75–2.83 (2H, m), 2.97–3.05 (2H, m), 6.85 (2H, d, *J*=7.8), 7.00 (2H, t, *J*=7.5), 7.03 (2H, t, *J*=7.3), 7.15 (2H, *J*=7.3). $\delta_{\rm C}$ (CDCl₃): 31.7, 118.7, 126.7, 127.1, 128.1, 129.6, 155.5.

4.6. 2-Bromo-11,12-dihydrodibenzo[c,g][1,2]diazocine-6-oxide (8)

To a solution of azoxybenzene 5 (100 mg, 0.446 mmol) in acetic acid (1.0 mL), bromine (100 µL, 1.95 mmol) was added drop-wise. After the reaction mixture was heated at 50 °C for 4 h, stirring was allowed to continue overnight at room temperature. The products were then diluted with cold water (50 mL). Sodium hydrogen sulfite (40% aqueous solution) was added drop-wise until the colour changed from brown to pale vellow. The mixture was extracted with dichloromethane $(3 \times 30 \text{ mL})$. The organic layers were combined and washed with water (2×25 mL) and saturated bicarbonate solution (2×25 mL). The organic layer was dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel. The desired product was obtained upon evaporation of appropriate fractions, which were eluted with dichloromethane-hexane (40:60 v/v), as a light brown solid (94.5 mg, 70%). Mp 143–146 °C (ethanol). R_f: 0.54. HRMS (EI) found 302.00508, C₁₄H₁₁BrN₂O required 302.00547. δ_H(CDCl₃): 2.84 (1H, ddd, *J*=5.9, 9.6, and 14.8), 2.98 (1H, ddd, J=5.1, 9.9 and 14.8), 3.21 (1H, ddd, J=5.1, 10.1, and 14.8), 3.36 (1H, ddd, *J*=5.9, 9.9, and 15.0), 6.82 (1H, d, *J*=8.4), 7.07 (1H, d, *J*=7.5), 7.16–7.22 (3H, m), 7.24–7.26 (2H, m). δ_C(CDCl₃): 30.1, 30.9, 120.5, 121.7, 123.5, 128.1, 129.6, 130.3, 130.6, 131.1, 133.2, 134.1, 145.0, 148.7.

4.7. 2-Cyano-11,12-dihydrodibenzo[c,g][1,2]diazocine-6-oxide (9)

To a solution of 2-bromo-11,12-dihydrodibenzo[c,g][1,2]diazocine-6-oxide 8 (1.08 g, 3.56 mmol) in dry N,N-dimethyl formamide (8.5 mL), copper (I) cyanide (480 mg, 5.36 mmol) was added. After the reaction mixture was heated under reflux overnight, the products were cooled to room temperature, followed by addition of ethylenediamine (10% aqueous solution, 100 mL) and the mixture was extracted with dichloromethane (3×30 mL). The organic layer was separated and successively washed with sodium cyanide (10% aqueous solution, 50 mL) and water (3×30 mL). The organic layer was dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel. The desired product was obtained upon evaporation of appropriate fractions, which were eluted with dichloromethane-hexane (60:40 v/v) as a pale yellow solid (615 mg, 69%). Mp 178–181 °C (ethanol). Rf: 0.32. HRMS (EI) found 249.08949, C15H11N3O required 249.09021. δ_H(CDCl₃): 2.94 (1H, ddd, *J*=5.3, 10.0, and 14.8), 3.02 (1H, ddd, *J*=4.8, 10.1, and 14.8), 3.26 (1H, ddd, *J*=4.6, 10.3, and 14.7), 3.40 (1H, ddd, *J*=5.2, 10.0, 14.8), 7.05 (1H, d, *J*=8.2), 7.07 (1H, d, *J*=7.5), 7.17 (1H, d, J=7.6), 7.22 (1H, t, J=7.4), 7.25 (1H, d, J=7.4), 7.35 (1H, s),

7.43 (1H, d, *J*=8.1). $\delta_{C}(CDCI_{3})$: 29.9, 30.7, 111.0, 118.1, 121.6, 122.8, 128.3, 129.8, 130.7, 131.0, 131.3, 133.8, 134.2, 148.6, 149.5.

4.8. 5,6,11,12-Tetrahydrodibenzo[c,g][1,2]diazocine-2-carbonitrile (10)

To a solution of 2-cvano-11.12-dihvdrodibenzo[c.g][1.2]diazocine-6-oxide 9 (1.00 g, 4.02 mmol) in methanol (30 mL), hydrazine monohydrate (5.0 mL, 0.10 mol) and aluminium powder (1.40 g, 51.9 mmol) were added. After the reaction mixture was heated under reflux for 24 h, the products were filtered through a thin layer of Celite and washed with dichloromethane (50 mL). The filtrate and washing were combined and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel. The desired product was obtained upon evaporation of appropriate fractions, which were eluted with ethyl acetate-hexane (20:80 v/v), as a pale yellow solid (620 mg, 66%). $R_{\rm f}$: 0.43. HRMS (EI) found 235.11045, C₁₅H₁₃N₃ required 235.11095. δ_H(DMSO-d₆): 2.97–2.99 (2H, m, br), 2.31–2.34 (2H, m, br), 6.84 (1H, dt, J=1.0 and 7.3), 6.86 (1H, d, J=8.2), 6.87 (1H, d, J=7.3), 7.03 (1H, dt, J=1.2 and 7.4), 7.08 (1H, d, J=7.2), 7.26 (1H, d, J=4.3), 7.43 (1H, dd, J=1.9 and 8.3), 7.48 (1H, d, J=1.5), 7.93 (1H, d, J=4.3). $\delta_{C}(DMSO-d_{6})$: 30.2, 31.3, 101.0, 116.3, 118.4, 120.5, 121.9, 126.7, 130.7, 131.2, 132.5, 132.8, 134.6, 147.8, 153.3.

4.9. 11,12-Dihydrodibenzo[c,g][1,2]diazocine-2-carbonitrile(11)

To a solution of 5,6,11,12-tetrahydrodibenzo[c,g][1,2]diazocine-2-carbonitrile 10 (500 mg, 2.13 mmol) in methanol (9 mL), titanium (III) chloride (25 μ L, prepared by diluting 1 mL of ~10 wt.% solution of TiCl₃ in 20-30 wt.% hydrochloric acid with 10 mL of methanol) and hydrobromic acid solution (25 µL, prepared by diluting 1 mL of 33% hydrobromic acid in acetic acid with 10 mL of methanol) were added using a 50 µL Hamilton syringe at room temperature under nitrogen. After a solution of hydrogen peroxide (450 µL, 20% in water, 2.37 mmol) was added drop-wise at room temperature, the reaction mixture was stirred at room temperature for 15 min. The volatiles were removed under reduced pressure and the solid residue was purified by column chromatography on silica gel. The appropriate fractions, which were eluted with dichloromethane-hexane (55:45 v/v), were combined and concentrated under reduced pressure to give the title compound as a light yellow solid (390 mg, 79%). Rf: 0.60. HRMS (EI) found 233.09554, C₁₅H₁₁N₃ required 233.09530. δ_H(CDCl₃): 2.78–2.87 (2H, m), 3.00–3.07 (2H, m), 6.87 (1H, d, J=7.7), 6.92 (1H, d, J=8.1), 7.01 (1H, d, J=7.5), 7.08 (1H, dt, J=1.2 and 7.5), 7.19 (1H, t, J=7.5), 7.32 (1H, d, J=1.2), 7.44 (1H, dd, J=1.4 and 8.0). $\delta_{\rm C}({\rm CDCl}_3)$: 31.9, 110.8, 118.2, 118.6, 119.5, 127.0, 127.2, 127.8, 129.9, 130.1, 130.7, 133.5, 155.3. 158.7.

4.10. 11,12-Dihydrodibenzo[*c*,*g*][1,2]diazocine-2-carboxylic acid (12)

The carbonitrile **11** (350 mg, 1.50 mmol) was placed in a solution of potassium hydroxide (9.3 g) in ethanol (65 mL) and water (20 mL) and heated under reflux for 4 h. Ethanol was removed under reduced pressure and the residue was treated with aqueous hydrochloric acid (6 *N*) until the mixture turned acidic (pH 4). The mixture was extracted with ethyl acetate (3×30 mL). The combined organic layers were washed with brine (2×15 mL), dried (MgSO₄), and concentrated under reduced pressure to give the crude carboxylic acid, which is purified by column chromatography on silica gel. The appropriate fractions, which were eluted with dichloromethane–methanol (95:5 *v*/*v*), were combined and concentrated under reduced pressure to give the *title compound* as a light yellow solid (293 mg, 78%). HRMS (EI) found 252.08979, C₁₅H₁₂N₂O₂ required 252.08988. δ_{H} (CDCl₃): 2.83 (1H, m), 2.89 (1H, m), 3.04 (2H, m), 6.87 (1H, d, *J*=7.8), 6.92 (1H, d, *J*=8.1), 7.00 (1H, d, *J*=7.6), 7.05 (1H, t, *J*=7.7), 7.17 (1H, t, *J*=7.5), 7.76 (1H, d, *J*=1.2), 7.87 (1H, dd, *J*=1.3 and 8.1). δ_{C} (CDCl₃): 31.4, 31.5, 118.6, 118.8, 127.0, 127.4, 127.5, 127.6, 128.9, 129.9, 131.8, 155.4, 159.8, 169.9.

4.11. (*Z*)-*N*-((*2S*,3*S*)-1,3-Dihydroxybutan-2-yl)-11,12-dihydrodibenzo[*c*,g][1,2]diazocine-2-carboxamide (13)

To a solution of 11,12-dihydrodibenzo[c,g][1,2]diazocine-2-carboxylic acid 12 (100 mg, 0.397 mmol) in dry N,N-dimethyl formamide (2.0 ml), D-threoninol (35 mg, 0.33 mmol), N,N'dicyclohexylcarbodiimide (82 mg, 0.40 mmol) and N-hydroxysuccinamide (46 mg, 0.40 mmol) were added. After the reaction mixture was stirred for 5 h at room temperature under a nitrogen atmosphere, the precipitate was removed by filtration and the filtrate was evaporated under reduced pressure. The oily residue was purified by column chromatography on silica gel. Evaporation of appropriate fractions, which were eluted by dicholoromethane–methanol (95:5 v/v), gave the *title compound* as a pale yellow solid (105 mg, 93% based on D-threoninol). Rf: 0.74 (dichloromethane–methanol, 90:10 v/v). $[\alpha]_{D}^{20} = -12.8$ (c=0.10, methanol). HRMS (EI) found 339.1569, C₁₉H₂₁N₃O₃ required 339.15829. δ_H(DMSO-d₆): 1.01 (3H, t, J=6.1), 2.83-2.86 (2H, m), 2.88-2.91 (2H, m), 3.40-3.45 (1H, m), 3.51-3.55 (1H, m), 0.3.81-3.84 (1H, m), 3.85-3.88 (1H, m), 4.56-4.61 (2H, m, br, OH, ex), 6.88 (1H, d, *J*=7.8), 6.92 (1H, d, *J*=8.1), 7.07 (1H, t, *J*=7.3), 7.10 (1H, d, *J*=7.2), 7.19 (1H, dt, *J*=7.19) (1H, t, *J*=7.2), 7.60 (1H, d, *J*=2.9), 7.66 (1H, d, I=8.1), 7.71 (1H, d, I=8.3, NH, ex). $\delta_{C}(DMSO-d_{6})$: 20.6 and 20.7, 31.2 and 31.4, 57.2, 60.7 and 60.9, 65.3, 118.6 and 118.7, 118.8, 126.5 and 126.6, 127.4, 127.8, 128.1, 128.5 and 128.6, 129.5 and 129.6, 130.4, 133.8, 155.6, 157.5, 166.1.

4.12. Crystal growth

Single crystals of **2** and **8** were obtained by slow evaporation of corresponding solutions in absolute ethanol.

4.13. X-ray diffraction experiment

Data were collected on a Nonius Kappa-CCD diffractometer using monochromated Mo-K α radiation and were measured using a combination of ϕ scans and ω scans with κ offsets, to fill the Ewald sphere. The data were processed using the Denzo-SMN package.³⁷ Absorption corrections were carried out using SORTAV.³⁸ The structure was solved and refined using SHELXTL V6.1³⁹ for fullmatrix least-squares refinement that was based on F^2 . All H atoms were included in calculated positions and allowed to refine in riding-motion approximation with U_{iso} tied to the carrier atom.

CCDC 859314 and 859315 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

4.14. Photoisomerization experiments

A home-built LED light source was used for the isomerization experiments. Photoisomerization of **2** and **13** was carried out by illuminating methanol solutions of (*Z*)-**2** and (*Z*)-**13** at 380 (\pm 5) nm with an energy density of 0.45 mW/cm² or (*Z*)/(*E*)-mixture of **13** at 480 (\pm 5) nm with an energy density of 32.3 mW/cm².

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Supplementary data

NMR spectra of the compounds reported in this paper are available online as Supplementary data. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2012.06.007.

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