JOC Article

One-Pot Synthesis of Pentacyclic Diamines from Quinolines by a New Zn/AcOH-Promoted Cascade Reaction

Jean-Christophe Gauffre,[†] Micheline Grignon-Dubois,*[,†] Bernadette Rezzonico,[†] and Jean-Michel Léger[‡]

Laboratoire de Chimie des Substances Végétales, LCSV - Institut du Pin, Université Bordeaux I, 351, Cours de la Libération, 33405 Talence-Cedex, France, and Laboratoire de Chimie Physique, Université Bordeaux 2, 3 place de la Victoire, 33076 Bordeaux Cedex, France

m.grignon@ipin.u-bordeaux.fr

Received October 1, 2001

A simple and efficient method for the one-pot synthesis of pentacyclic diamines from quinolines is described. It involves a new Zn/AcOH-promoted cascade reaction, in which two C−C bonds and four to five stereogenic centers are established under mild conditions. The regiochemistry of the dimerization and cyclization step is governed by substituent effects, allowing access to a head-to-head (**2, 3**) or head-to-tail skeleton (**4**, **5**).

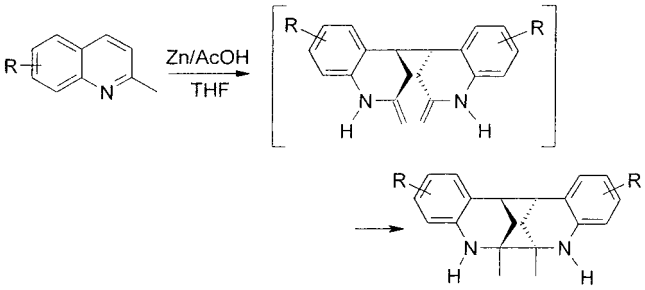
Introduction

The zinc−acetic acid couple is a well-known reducing reagent, capable of a wide range of reactions,[1] of which the reduction of carbonyl or activated alkenes is the most common. In contrast, it has been rarely used in the heteroaromatic series, except for the reduction of potentially labile functionalities such as halogen−carbon bonds at the 2-position.[2] We have recently shown[3] that it reacts with quinaldine to yield 5,6,7,8,13,14-hexahydro-6,7-dimethyl-6,14:7,13-dimethanodibenzo[*e*,*i*][1,4]diazecine, through a two-step domino reaction involving the reductive dimerization of the heterocycle followed by a spontaneous intramolecular cyclization (Scheme 1). An exomethylene intermediate was postulated to be the reactive species of this second step. There is therefore a question of what the regiochemistry of the cyclization might be without the methyl group at the 2-position. Obtaining complex targets from inexpensive and industrially available starting materials through a cascade one-pot process is of increasing importance in synthetic organic chemistry. In this context, it appeared important to study the versatility of this reaction. In this paper, we describe the obtention of new pentacyclic skeletons by reacting the zinc−acetic acid couple with a series of substituted quinolines.

Results and Discussion

We focused on the commercially available quinolines **1a**−**f**. All the reactions were conducted with zinc dust

SCHEME 1



and acetic acid at reflux of THF. Our results are summarized in Scheme 2 and Table 1. As expected, we never obtained dibenzodiazecines, which is in good agreement with our hypothesis concerning the role of the C-2 methyl group in their formation.[3] Instead, original quino-benzazepines **2**−**5** were isolated as the result of a dimerization−cyclization cascade. In this process, two C−C bonds and four to five stereogenic centers are created. Examination of Table 1 shows that the reaction is sensitive to the substitution on the nitrogen ring. When R = H, the 5,6,6a,7,13,13a-hexahydro-6a,14α-dimethyl-7,13-methanoquino[3,4-*c*][1]benzazepine is obtained as a *syn*/*anti* mixture[4] (**2a/3a**; 83% global yield, entry 1). In the same condition, 6-methylquinoline, **1d**, led to very similar results (**2d**/**3d**; 80% global yield, entry 6). The structure of these cyclized products shows that they all come from a 4,4′-dimer. Introduction of a methyl group at the 3- or

[†] Université Bordeaux I.
[‡] Université Bordeaux 2.

(1) See as examples Ham, P. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L., Ed.; John Wiley & Sons: New York, 1995; Vol. 8, pp 5531 5534 and references therein.

(2) (a) Solomon, W. *J. Chem. Soc.* **1946**, 934. (b) Schmidt, U.; Giesselmann, G. *Chem. Ber.* **1960**, *93*, 1590.

(3) (a) Podevin, C.; Grignon-Dubois, M.; Nuissier, G.; Gauffre, J.-C.; Rezzonico, B. *Tetrahedron* **1999**, *55*, 9233. (b) Gauffre, J.-C.; Grignon-Dubois, M. *J. Chem. Res.* **1995**, 242.

(4) Atoming numbering is depicted in Figure 1. The following stereochemical conventions have been adopted. The pentacyclic derivatives isomers have been respectively designated as *syn* or *anti* when the bridgehead protons 6a,13a (compounds **2**, **3**) or 5a,12a (compounds **4**, **5**) were *cis* or *trans* with respect to C-14. The stereochemistry at C-14 has been designated as α or *β*, according to ref 7b, as well as the A/B/C nomenclature for the central tricyclic system. To designate the stereochemistry at C-13 in **4c** and **5c**, we have preferred the *cis* notation, which refers to the methyl group *cis* with respect to C-14, instead of the α/*β* symbolism generally used in the case of fused rings which could have been confusing here.

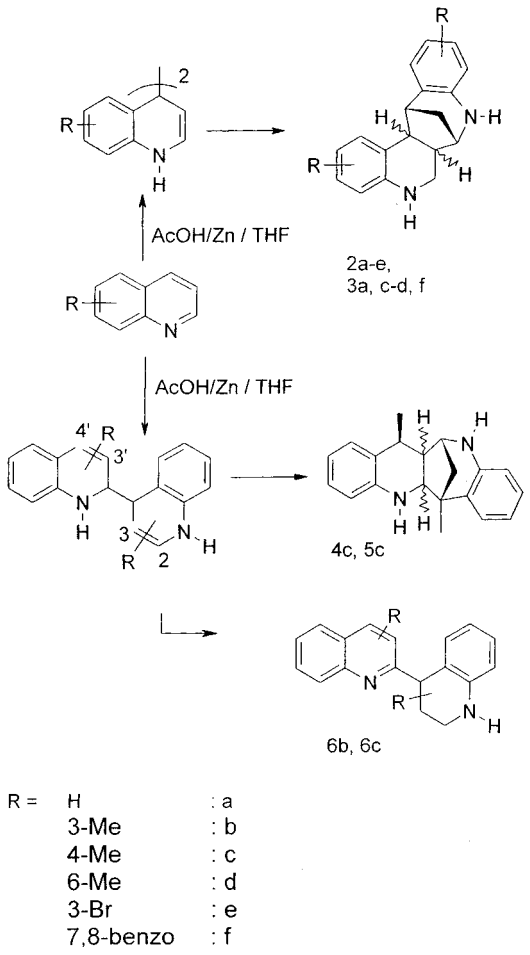
10.1021/jo010961b CCC: $22.00
Published on Web 06/19/2002

TABLE 1. Isolated Yields of Products from Cyclization of Quinolines with Zn/AcOH/THF Reagent (1.5 equiv of Zn and 2.5 equiv of AcOH per mol of quinoline)

				quino[3,4-*c*][1]benzazepine		quino[3,4-*b*][1]benzazepine		
entry	R	**1**	time (h)	**2** (*syn*)	**3** (*anti*)	**4** (*syn*)	**5** (*anti*)	other
1	a	H	17	45	38	–	–	–
2	b	3-CH_3	21	45	–	–	–	**6b**: 15
3	c	4-CH_3	10	10	–			**6c**: 60
4	c	4-CH_3	21	10	2	14	16	16
5[a]	c	4-CH_3	21	7	10	23	25	4
6	d	6-CH_3	18	42	38			
7	e	3-Br	5	20	20	15		**2a**: 15; **2b**: 20
8	f	7,8-benzo		–	43			

[a] AcOH was replaced by TFA.

SCHEME 2



R = H : a
3-Me : b
4-Me : c
6-Me : d
3-Br : e
7,8-benzo : f

4-position results in a loss of selectivity in the dimerization process, as shown by isolation of compounds **6b**, **6c**, from **1b**, **1c**. These products result from a dismutation of uncyclized 2,4′-dimers, whereas 4,4′-dimers were never recovered in the reaction mixture, whatever the substrate. In the case of the 3-methylquinoline (entry 2), dimerization at 4,4′ remains predominant. The *syn* pentacyclic diamine **2b** was isolated as the only cyclized product (45% yield), along with **6b** (15%).[5] In contrast, 2,4′-dimerization was favored with 4-methylquinoline (**2c**), but the cyclization appeared to be difficult as shown by obtention of **6c** in 60% yield (entry 3). In this case, increasing reaction time as well as replacing acetic acid by TFA (entries 4, 5) allowed obtention of quino[3,4-*b*]-[1]benzazepines as a *syn*/*anti* mixture (**4c**/**5c**; 30−48% global yield), along with their regioisomers **2c** and **3c** resulting from the 4,4′-dimers (12%). The 3-bromoquinoline, **1e**, led to the *syn* monobromo pentacyclic diamine **2e**, in a mixture with **2a/3a** resulting from the reduction of the C−Br bond (entry 7). This reduction took place on the substrate itself, as shown by the recovery of quinoline (30% yield), but could also occur during any step of the sequential process. Attempts to isolate pentacyclic dibromo derivatives were unsuccessful. This could be due to the steric congestion associated with an angular bromine on C-6a, which would disfavor its formation and/or make it easily reducible. Isolation of the *syn* diastereoisomers **2b**, **2e** as the only cyclized products from the above reactions, respectively, is not related to a greater stability of the 4,4′ *meso* dimer compared to the *threo*, but to the conformational preference as shown by the study of the available conformational space.[6] On the other hand, the anti isomer **3f** was isolated from the 7,8-benzoquinoline (entry 8). It is worth noting that substituents at C-3 or C-4 of quinoline create a fifth stereogenic center in the cyclized products, respectively, located at C-14 for **2b**, **2e** and at C-13 for **4c**, **5c**. Interestingly, they are all constituted of a single epimer, namely *syn* 14-α for **2b**, **2e** and 13-*cis* for **4c** and **5c** (Figures 1 and 2).[4] This diastereoselection will be discussed below in relation with the mechanism.

The global yield in cyclized products varies in the range of 43−83%. Starting material was never recovered, but tetrahydroquinolines are generally isolated from the reaction mixture (2−10% yield). Replacement of zinc by magnesium did not increase the cyclization-yield, but instead favored the formation of tetrahydroquinolines. Increasing the reaction time did not improve these results, but led to formation of tars. The only exception is the 4-methylquinoline, **1c**, for which the cyclization of the 2,4′-dimers is only significant after 21 h of heating.

(5) A *trans* stereochemistry was assigned to **6b** on the basis of the comparison of the measured and calculated ^3J (^{1}H,^{1}H) coupling constants for H-3 in the two isomers (measured: 10.2, 10.3, 3.9; calculated: 10.3, 10.1, 4.1 Hz for the *trans* and 11.5, 4.9, 4.6 Hz for the *cis* (see Experimental Section).

(6) All the plausible regio- and stereoisomers for both the dimers and the cyclized products were rebuilt and fully analyzed by molecular mechanics. In the case of the dimers, the available conformational space was systematically examined and the "cyclization" distance C-2′···C-3′ and C-2′···C-3 (d) were checked. With R = H or 6-Me, both the *threo* and *meso* dimers have their lowest energy conformer in an ideal geometry for the cyclization (d = 3.6 Å). In contrast, with R = 3-Me or 3-Br, this is only true for the meso dimer, which is in good agreement with the obtention of the *syn* isomer as the only cyclized product. Grignon-Dubois, M. et al., results to be published.

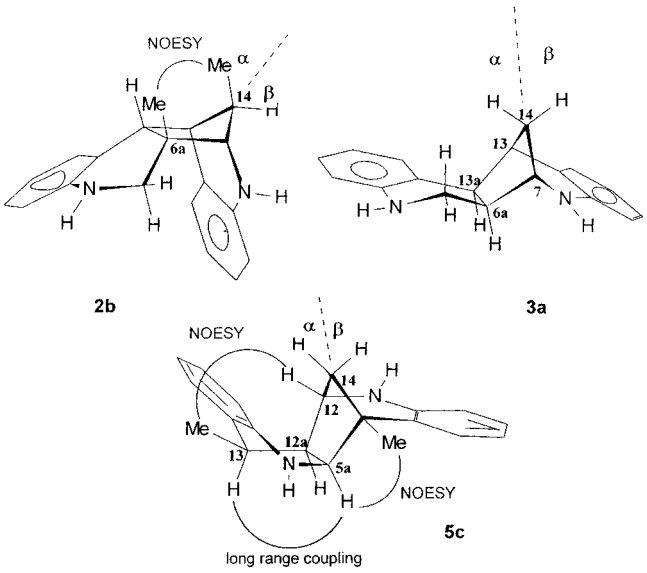


FIGURE 1. Computed structures (Molecular Mechanics[8a]) for **2b**, **3a, 5c** showing atom numbering and NMR connectivities.

The two types of pentacyclic framework mainly differ according to the relative position of the nitrogen atoms, which are head-to-head in **2**, **3** and head-to-tail in **4**, **5**. They are both related to B-norbenzomorphans, which are of interest in medicinal chemistry.[7]

The crude reaction mixtures were purified by chromatography on silica gel. With *syn*/*anti* mixtures, the *anti* isomer was systematically eluted first in the case of head-to-head skeleton, and the *syn* in the case of head-to-tail. The structure assignments are based on satisfactory elemental analysis and physicochemical data (see Experimental Section). In particular, the number and chemical shift of aliphatic methine and methylene carbons allows an easy assignment of head-to-head (**2** and **3**) and head-to-tail (**4** and **5**) ring system. Results were confirmed by recording HMQC and HMBC spectra. 1D and 2D ^{1}H NMR spectra gave a clear understanding of both the structure of the framework and the stereochemistry of the stereogenic centers. All the possible stereoisomers for the two pentacyclic skeletons were rebuilt with PCModel and the ^3J (^{1}H, ^{1}H) coupling constants were calculated according to the work of Altona et al. as implemented in the program.[8] The 6a,13a (compounds **2** and **3**) or 5a,12a (compounds **4** and **5**) coupling constant values clearly show that these protons are always in a *cis* position. The decisive pairs of protons that were used to assign the *syn*/*anti* stereochemistry of the A/B ring junction, namely 6a,7 and 13,13a for **2** and **3** and 12,12a for **4** and **5**, had spin couplings that varied in the range 4.0−5.7 Hz for a *syn* isomer and always remained close to 1 Hz for an *anti*. The α/*β* nomenclature defining the two faces of the C-14 methylene bridge is depicted in Figure 1.[4] The stereochemistry at C-14 is assigned on the basis of the 7, 14 and 13, 14 coupling constants. In the absence of substituents, these four protons give rise to an ABXX′ system in which the coupling constant AB is close to 10−11 Hz, AX and AX′ are close to 1−1.5 Hz, while BX and BX′ vary from 3.0 to 4.4 Hz, whatever the *syn*/*anti* stereochemistry at the A/B ring junction. This led to a ddd and bd pattern for the protons attached at C-14. Modeling with PCModel,[8] as described above, allowed assignment of the ddd to H-14α and the bd to H-14*β*. This conclusion was confirmed by a NOESY experiment on **2b** and **4c** (Figure 1). For **2b**, the most significant NOESY correlation appears between the two methyl groups, which is consistent with the *syn*-14α stereochemistry assigned on the basis of (^{1}H,^{1}H) coupling constant analysis. In **4c**, the correlation between H-5a and the dd at 1.79 ppm allows its assigment to H-14α. In both **4c** and **5c**, NOESY correlations 13-Me,H-12 and 6-Me,H-5a are observed. In addition, the *(syn)*-quino[3,4-*b*][1]benzazepine skeleton for **4c** was confirmed by an X-ray crystallographic study (Figure 2; Tables 2 and 3, in Supporting Information). Noteworthy is the boat conformation of ring A and the *cis-equatorial* position of the 13-Me with respect to the C-14 methylene bridge[4] (respectively, C-22 and C-16 in the crystallographic numbering). The stereochemistry at C-13 is the same in the *anti* isomer **5c** as shown by a ^4J coupling constant between H-13 and H-5a (1.6 Hz).

From a mechanistic point of view, the cascade is initiated by the protonation of the nitrogen and an electron transfer leading to a radical, the coupling of which is followed by an intramolecular cyclization (Scheme 2). The ease of this step is demonstrated by the absence of uncyclized product in the reaction mixture obtained from **1a** and **1d**−**f.** Compounds **2** and **3** contain the same 4,4′-linkage, demonstrating that they both come from a 1,4-dihydro-4,4′-biquinoline derivative or its dianion. In contrast, steric hindrance introduced by methyl substituent at 3- or 4-position led to a competition between 2,2′- and 2,4′-dimerization. Cyclization from the 2,4′-dimers appears to be more difficult than from the 4,4′-dimers, as shown by isolation of uncyclized products **6b**, **6c**, respectively, from 3-methyl- and 4-methylquinoline.

The cyclization step leading to **2** and **3** can be summarized as an intramolecular nucleophilic addition initiated by the protonation of one of the enamine moieties (Scheme 3). This leads to a new C−C bond between the 2- and 3′-positions with "an apparent" proton migration from N-1 to C-3′. The resulting imine was never isolated.[9] Its spontaneous reduction led to compounds **2** and **3,** which are respectively issued from a *meso* (**2**) and *threo* dimer (**3**). Obtention of **2b** and **2e** as a single epimer (C-14α) support an *anti* concerted mechanism for the cyclization step of the cascade, with a proton attacking at C-3 by the outside face of the dimer (which became the *β*-face of the cyclized imine), while the C_6−C_7 bond of the imine is created from an electron displacement between C-2 and C-3′.[10]

To better understand the regio- and stereoselection of the cyclization step, the reaction was also conducted with acetic acid-*d* in the case of **1a**. Deuterated aza-B-

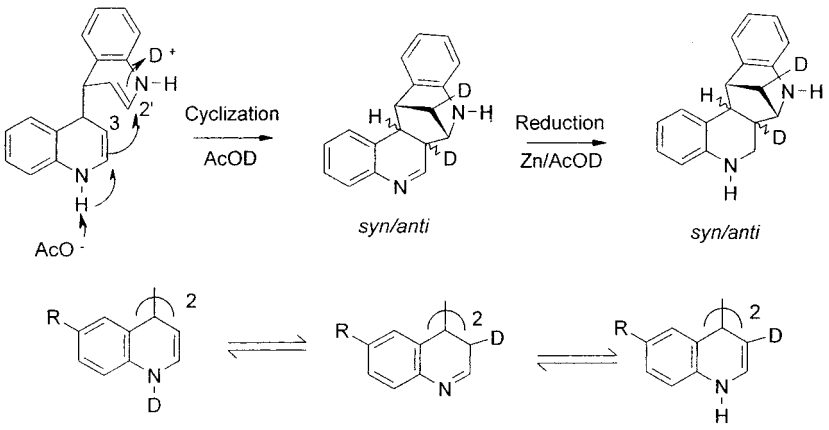
(7) (a) Jacobson, A. E.. Mokotoff, M. *J. Med. Chem*. **1970**, *13*, 7. (b) Palmer, D. C.; Strauss, M. J. *Chem. Rev*. **1977**, 1.

(8) (a) Program PCMODEL V 7.0 (MMX force field), available from Serena Software, P.O. Box 3076, Bloomington, IN 47402-3076. (b) Haasnoot, C. A. G.; De Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783.

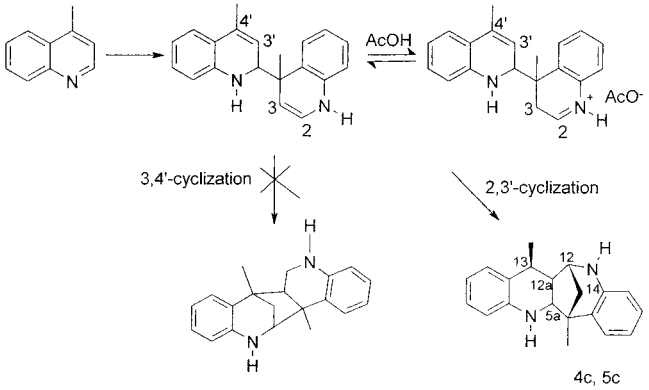
(9) In the case of fluoroquinaldine, the imine was isolated and fully characterized by NMR and MS.[3]

(10) Reductive dimerization of quinolines with sodium naphthalenide or mercury cathode have been previously reported: Banerji, A.; Maiti, S. *Tetrahedron* **1994**, *50*, 9079. Bordner, J.; Elliott, I. W. *Cryst. Struct. Commun*. **1974**, *3*, 689.

SCHEME 3



SCHEME 4



norbenzomorphanes were isolated as a *syn*/*anti* mixture. ^{1}H and ^{2}H NMR spectra were recorded showing as expected the incorporation of a deuterium atom at C-14, but also at C-6a (Scheme 3). This result implies that an imine−enamine equilibrium takes place in the pentacyclic enamine. In both isomers, H-14 appears as a dd (*syn*: 1.57 ppm, $J_{14,13} = 4.1$, $J_{14,7} = 4.2$ Hz; *anti*: 1.95 ppm, $J_{14,13} = 4.1$, $J_{14,7} = 4.2$), in agreement with its α-position. This conclusion is confirmed by the disappearance of the signal of H-14β in the ^{1}H NMR spectra. This shows that the stereochemistry of the cyclization step is the same for the two isomers of the 4,4′-dimer and confirms the *anti* concerted mechanism.

This mechanism seems to be possible only for a bis-enamine structure. Indeed, from the 2,4′-dimers, it should have led through a 3,4′-cyclization to the pentacyclic skeleton I, which was not found in the reaction mixture (Scheme 4). Instead, compounds **4c**, **5c**, respectively, issued from the *erythro* and *threo* 2,4′-dimers, were isolated. The cyclization step could start from the enamine itself or its imine and globally leads to a new C−C bond between the 2- and 3′-positions, while addition of a hydrogen occurs at both the 3- and 4′-positions. Noticeable is the stereospecificity of this step. Indeed, both **4c** and **5c** are composed of a single C-13 epimer with the 13-Me on the same side as the methylene group. This implies that the attack by the hydrogen occurs at the *endo* side in the *erythro* dimer, and at the *exo* side in the *threo* one.

Conclusion

This new and very simple process constitutes a synthetically attractive and versatile approach for the rapid construction of quinobenzazepines. Indeed, two C−C bonds are formed and four to five stereogenic centers are established under mild conditions in a one-pot process. The regiochemistry of the dimerization−cyclization cascade is governed by substituent effects, allowing access to head-to-head or head-to-tail skeleton. The reactions are easy to setup, to perform, and to workup, and only inexpensive reagents are required. All these compounds exhibit interesting features which could lead to pharmacological properties.[11] Synthetic exploitation of these results and biological screening are now in progress.

Experimental Section

Quinaldine, zinc dust, and acetic acid were purchased and used without further purification. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Melting points were determined on a capillary apparatus and are uncorrected. The ^{1}H NMR spectra were recorded at 250 MHz (δ values in ppm, J values in hertz, TMS as internal standard), and the ^{13}C NMR spectra were recorded at 62.88 MHz. Elemental analyses were performed by the Service Central d'Analyse du CNRS (F-69390 Vernaison). All reactions were monitored by thin-layer chromatography (SiO_2, CH_2Cl_2, and UV light detection).

Typical Procedure for the Reduction of Quinolines by Zn−AcOH−THF Reagent. A mixture of zinc dust (2.9 g, 44 mmol) and quinoline (4 g, 30 mmol) in dry THF (15 mL) was stirred at reflux for 0.5 h, and then acetic acid (4.1 mL, 72 mmol) was added. The resulting mixture was heated at reflux for 15 h and vigorously stirred until total conversion of the starting material was achieved as monitored by TLC (SiO_2, CH_2Cl_2). The THF was then removed in vacuo, the residue was dissolved in dichloromethane (30 mL) and filtered through Celite to remove zinc acetate, and water (20 mL) was added. The layers were separated, and the organic layer washed until neutrality with a solution of sodium hydrogenocarbonate, dried over anhydrous $MgSO_4$ and concentrated. The crude product was chromatographed on silica gel (CH_2Cl_2 / acetone 9:1). With *syn*/*anti* mixtures, the *anti* isomer (**3**) was systematically eluted first in the case of head-to-head skeleton, and the *syn* (**4c**) in the case of head-to-tail.

***syn*-5,6,6a,7,13,13a-Hexahydro-7,13-methano-quino[3,4-*c*][1]benzazepine (2a).** White solid; mp 145 °C (C_6H_6); R_f 0.35 (SiO_2, acetone/$CHCl_3$ 10:90); IR (neat) ν_{max}/cm^{-1} (KBr) 3400,

(11) In particular, this skeleton contains the CNS pharmacophore as defined in: Lloyd, E. J.; Andrews, P. R. *J. Med. Chem.* **1986**, *29*, 453.

3020, 2960, 2925, 1630, 1590, 1480, 1370, 1290, 1220, 1160, 1120; δ_H (C_6D_6) 1.59 (1H, ddd, J = 10.9, 4.2, 3.6, H-14α), 1.85 (1H, d, J = 10.9, H-14β), 2.23 (1H, dddd, J = 10.8, 9.7, 6.4, 5.4, H-6a), 2.51 (1H, dd, J = 10.8, 6.4, H_a-6), 2.76 (1H, dd, J = 10.8, 9.7, H_b-6), 3.0 (1H, dd, J = 10.8, 5.1, H-13a), 3.05 (1H, dd, J = 5.1, 3.6, H-13), 3.24 (1H, dd, J = 5.4, 4.2, H-7), 3.90 (2H, NH), 6.16−6.23 (2H, m), 6.37−6.44 (1H, m), 6.73−6.85 (4H, m), 7.19 (1H, m); δ_C ($CDCl_3$) 32.6, 43.4 (CH_2), 44.5, 44.7, 47.3, 55.4, 113.6, 115.3, 116.7, 118.7, 125.9, 127.2, 130.1, 130.2 (CH), 125.1, 127.0, 143.3, 146.9 (C); MS m/z 262 (M^+, 23), 130 (100). Anal. Calcd for $C_{18}H_{18}N_2$ C, 82.40; H, 6.92; N, 10.68. Found C, 82.26; H, 6.86; N, 10.61.

***syn*-5,6,6a,7,13,13a-Hexahydro-6a,14α-dimethyl-7,13-methano-quino[3,4-*c*][1]benzazepine (2b).** White solid; mp 157 °C ($CHCl_3$); R_f 0.45 (SiO_2, acetone/$CHCl_3$ 10:90); IR (neat) ν_{max}/cm^{-1} (KBr) 3400, 3020, 2960, 2920, 1660, 1590, 1490, 1370, 1300, 1220, 1155, 1120; δ_H (CD_2Cl_2) 1.34 (3H, s), 1.52 (3H, d, J = 7.5, Me-14), 2.65 (1H, q, J = 7.5, H-14β), 2.89 (2H, AB, J = 10.8, H-6), 3.26 (1H, d, J = 5.7, H-13), 3.29 (1H, d, J = 5.7, H-13a), 3.38 (1H, d, J = 1.1, H-7), 3.8 (2H, NH), 6.4−6.46 (2H, m), 6.60 (1H, dd, J = 7.9, 1.2), 6.71−7.0 (4H, m), 7.32 (1H, d, J = 7.6); δ_C (MHz, CD_2Cl_2) 17.6, 28.8 (CH_3), 51.0 (CH_2), 40.2, 51.6, 52.2, 67.8, 113.8, 115.3, 116.8, 118.4, 126.2, 127.8, 130.4, 130.4 (CH), 46.1, 124.8, 129.2, 144.2, 146.9 (C); MS m/z 290 (M^+, 38), 130 (100). Anal. Calcd for $C_{20}H_{22}N_2$ C, 82.71; H, 7.64; N, 9.65. Found C, 82.42; H, 7.36; N, 9.56.

***syn*-5,6,6a,7,13,13a-Hexahydro-13,13a-dimethyl-7,13-methano-quino[3,4-*c*][1]benzazepine (2c).** White solid; mp 170 °C (CH_2Cl_2); IR (neat) ν_{max}/cm^{-1} 3400, 3280, 3020, 2960, 2920, 2830, 1660, 1590, 1490, 1370, 1320, 1220, 1155, 1120; δ_H (C_6D_6) 1.17 (3H, s), 1.37 (3H, s), 1.69 (1H, m, H-6a), 1.85 (1H, dd, J = 11.4, 4.1, H-14α), 1.98 (1H, d, J = 11.4, H-14β), 2.69 (1H, dd, J = 11.7, 2.8, H_a-6), 2.80 (1H, dd, J = 11.7, 5.6, H_b-6), 3.08 (1H, dd, J = 10.8, 2.5, H-7), 3.84 (2H, NH), 6.05 (1H, dd, J = 7.8, 1.4), 6.35−6.41 (2H, m), 6.54 (1H, dd, J = 8.1, 1.3), 6.64−6.84 (3H, m), 7.10 (1H, dd, J = 7.5, 1.6); δ_C ($CDCl_3$) 19.6, 28.9 (CH_3), 40.5, 42.0 (CH_2), 55.6, 55.9, 114.2, 114.8, 116.6, 118.1, 125.6, 125.7, 126.0, 126.7 (CH), 48.6, 48.8, 130.4, 131.5, 143.2, 145.8 (C); MS m/z 290 (M^+, 9), 144 (100). Anal. Calcd for $C_{20}H_{22}N_2$ C, 82.71; H, 7.64; N, 9.65. Found C, 82.44; H, 7.54; N, 9.53.

***(syn)*-5,6,6a,7,13,13a-Hexahydro-2,11-dimethyl-7,13-methano-quino[3,4-*c*][1]benzazepine (2d).** White solid; mp 85 °C (C_6H_6); R_f 0.33 (acetone/CH_2Cl_2 10:90); IR (neat) ν_{max}/cm^{-1} 3400, 3025, 2965, 2920, 2830, 1660, 1590, 1470, 1380, 1290, 1220, 1160, 1120; δ_H (CD_2Cl_2) 1.69 (1H, ddd, J = 10.6, 3.7, 4.0, H-14α), 1.94 (1H, d, J = 10.6, H-14β), 2.09 (3H, s), 2.28 (3H, s), 2.55 (1H, dddd, J = 10.8, 10.3, 6.3, 5.3, H-6a), 2.67 (1H, dd, J = 10.7, 10.3, H_a-6), 3.26 (1H, dd, J = 10.7, 6.3, H_b-6), 3.38 (1H, dd, J = 10.8, 5.5, H-13a), 3.66 (1H, dd, J = 3.7, 5.5, H-13), 3.80 (2H, NH), 3.89 (1H, dd, J = 5.3, 4.0, H-7), 6.28 (1H, d, J = 7.7), 6.48 (1H, d, J = 8.0), 6.65 (1H, bs), 6.73 (2H, m), 7.12 (1H, bs); δ_C ($CDCl_3$) 20.1, 20.5 (CH_3), 32.3, 43.2 (CH_2), 43.8, 44.0, 46.8, 54.8, 113.2, 114.9, 126.0, 127.3, 130.2, 130.6 (CH), 124.7, 125.1, 126.8, 127.1, 140.4, 144.1 (C); MS m/z: 290 (M^+, 3), 144 (100). Anal. Calcd for $C_{20}H_{22}N_2$ C, 82.71; H, 7.64; N, 9.65. Found C, 82.57; H, 7.56; N, 9.72.

***syn*-5,6,6a,7,13,13a-Hexahydro-14α-bromo-7,13-methano-quino[3,4-*c*][1]benzazepine (2e).** White solid; mp 171 °C ($CHCl_3$); R_f = 0.58 (SiO_2, acetone/$CHCl_3$ 10:90); IR (neat) ν_{max}/cm^{-1} 3280, 3020, 2960, 2920, 1610, 1560, 1480, 1370, 1290, 1220, 1160, 1120, 780; δ_H (CD_2Cl_2) 2.92 (1H, dd, J = 10.6, 8.8, H_a-6), 3.13 (1H, dddd, J = 11.3, 8.8, 6.2, 5.5, H-6a), 3.34 (1H, dd, J = 10.6, 6.2, H_b-6), 3.52 (1H, d, J = 5.6, H-13), 3.60 (2H, NH), 3.98 (1H, d, J = 5.5, H-7), 4.30 (1H, dd, J = 11.3, 5.6, H-13a), 4.98 (1H, bs, H-14β), 6.28−6.35 (2H, m), 6.42 (1H, dd, J = 7.8, 1.0), 6.56 (1H, dd, J = 7.4, 1.3), 6.67 (1H, ddd, J = 7.4, 7.4, 1.2), 6.75−6.86 (2H, m), 7.11 (1H, d, J = 7.4); δ_C (CD_2Cl_2) 42.7 (CH_2), 41.4, 44.3, 52.6, 57.5, 62.5, 113.8, 115.0, 117.2, 118.5, 125.9, 127.9, 129.6, 130.0 (CH), 123.9, 125.2, 142.1, 147.0 (C); MS m/z 340/342 (M^+, 8/8), 130 (100). Anal. Calcd for $C_{18}H_{17}N_2Br$ C, 63.35; H, 5.02; N, 8.21. Found C, 63.58; H, 4.94; N, 7.87.

***anti*-5,6,6a,7,13,13a-Hexahydro-7,13-methano-quino-[3,4-*c*][1]benzazepine (3a).** White solid; mp 134 °C (C_6H_{12}/CH_2Cl_2 95:5). R_f 0.35 (SiO_2, acetone/$CHCl_3$ 10:90); IR (neat): ν_{max}/cm^{-1} 3400, 1630. δ_H ($CDCl_3$) 1.78 (d, J = 11.0, H-14β); 1.98 (ddd, J = 11.0, 3.9, 2.9, H-14α); 2.78 (ddd, J = 8.3, 4.2, 3.5, H-6a); 3.06 (d, J = 2.9, H-13); 3.12 (dd, J = 10.9, 4.2, H_a-6); 3.26 (dd, J = 10.9, 3.5, H_b-6); 3.64 (d, J = 8.3, H-13a); 3.68 (d, J = 3,9, H-7); 3.80 (2H, NH); 6.60 (d, J = 7.9, 2H); 6.75 (ddd, J = 7.3, 7.4, 1.2, 1H); 6.87 (ddd, J = 7.3, 7.4, 1.2, 1H); 7.12 (m, 3H); 7.39 (d, J = 7.4, 1H); δ_C ($CDCl_3$) 30.1, 45.3 (CH_2); 48.9, 50.05, 51.4, 59.6, 115.1, 115.1, 117.7, 119.1, 126.2, 127.3, 127.6, 129.7 (CH); 126.7, 130.1; 142.3; 147.1 (C). MS m/z 262 (M^+, 17), 130 (100). Anal. Calcd for $C_{18}H_{18}N_2$ C, 82.40; H, 6.92; N, 10.68. Found C, 82.31; H, 6.79; N, 10.70.

***anti*-5,6,6a,7,13,13a-Hexahydro-13,13a-dimethyl-7,13-methano-quino[3,4-*c*][1]benzazepine (3c).** Pale yellow oil**;** R_f 0.36 (SiO_2, acetone/CH_2Cl_2 10:90); IR (neat) ν_{max}/cm^{-1} 3400, 3280, 3020, 2960, 2920, 2830, 1660, 1590, 1490, 1370, 1320, 1220, 1155, 1120; δ_H ($CDCl_3$) 1.12 (6H, s), 1.55 (1H, d, J = 11.4, H-14β), 1.66 (1H, dd, J = 11.4, 4.9, H-14α), 2.11 (1H, bs, H-6a), 2.88 (1H, dd, J = 10.9, 2.5, H_a-6), 3.21 (1H, dd, J = 10.9, 2.5, H_b-6), 3.51 (1H, d, J = 4.8, H-7), 3.60(2H, NH), 6.5 (2H, dd, J = 7.8, 1.5), 6.66 (2H, m), 6.72 (2H, m), 7.18 (2H, m); δ_C ($CDCl_3$) 21.6, 25.5 (CH_3), 40.6, 44.7 (CH_2), 57.9, 59.0, 115.3, 116.0, 117.7, 126.3, 127.0, 127.6, 130.4 (CH), 50.0, 52.6, 129.1, 132.2, 143.0, 148.1 (C); MS m/z 290 (M^+, 9), 144 (100). Anal. Calcd for $C_{20}H_{22}N_2$ C, 82.71; H, 7.64; N, 9.65%. Found C, 82.65; H, 7.47; N, 9.54.

***anti*-5,6,6a,7,13,13a-Hexahydro-2,11-dimethyl-7,13-methano-quino[3,4-*c*][1]benzazepine (3d).** White solid; mp 95 °C (C_6H_{12}/CH_2Cl_2 90:10); R_f 0.45 (acetone/CH_2Cl_2 10:90); IR (neat) ν_{max}/cm^{-1} 3400, 3025, 2965, 2920, 2830, 1660, 1590, 1470, 1380, 1290, 1220, 1160, 1120; δ_H ($CDCl_3$) 1.79 (1H, d, J = 11.2, H-14β), 1.99 (1H, ddd, J = 11.2, 5.4, 4.0, H-14α), 2.37 (3H, s), 2.40 (3H, s), 2.69 (1H, ddd, J = 8.4, 4.1, 3.0, H-6a), 3.06 (1H, d, J = 4.0, H-13), 3.08 (1H, dd, J = 11.0, 4.1, H_a-6), 3.28 (1H, dd, J = 11.0, 2.9, H_b-6), 3.65 (1H, d, J = 8.4, H-13a), 3.67 (1H, d, J = 5.4, H-7), 3.81 (2H, NH), 6.56 (1H, d, 8.0), 6.60(1H, d, 7.9), 6.93 (2H, dd, 8.1, 1.5), 7.0 (1H, bs), 7.16 (1H, bs); δ_C ($CDCl_3$) 20.4, 20.5 (CH_3), 30.4, 45.6 (CH_2), 48.7, 51.1, 51.3, 59.7, 115.0, 115.4, 126.8, 127.8, 128.6, 130.0 (CH), 126.7, 127.9, 128.1, 130.3, 140.0, 144.7 (C); MS m/z 290 (M^+, 4.4), 144 (100). Anal. Calcd for $C_{20}H_{22}N_2$ C, 82.71; H, 7.64; N, 9.65. Found C, 82.62; H, 7.41; N, 9.45.

***anti*-5,6,6a,7,13,13a-Hexahydro-dibenzo[3,4][9,10]-7,13-methano-quino[3,4-*c*][1]benzazepine (3f).** White solid; mp 210 °C (C_6H_{12}/acetone 95:5); R_f = 0.48 (SiO_2 acetone/CH_2Cl_2 10:90); IR (neat) ν_{max}/cm^{-1} 3400, 3025, 2965, 2920, 1630, 1590, 1480, 1370, 1290, 1220, 1160, 1120; δ_H (CD_2Cl_2) 1.66(1H, d, J = 11.1, H-14β), 1.88 (1H, ddd, J = 11.0, 3.7, 3.4, H-14α), 2.73 (1H, ddd, J = 8.4, 4.1, 2.7, H-6a), 3.05 (1H, dd, J = 11.3, 4.1, H_a-6), 3.07 (1H, d, J = 3.3, H-13), 3.4 (1H, dd, J = 11.3, 2.7, H_b-6), 3.77 (1H, d, J = 8.4, H-13a), 3.84 (1H, d, J = 3.7, H-7), 4.4 (2H, NH), 7.2−7.44 (8H, m), 7.64−7.80 (4H, m); δ_C ($CDCl_3$) 30.1, 45.7 (CH_2), 48.5, 51.1, 52.20, 60.1, 118.3, 118.9, 119.9, 120.7, 125.2, 125.4, 125.5, 125.6, 125.7, 127.6, 128.8, 128.9 (CH), 121.2, 123.5, 124.5, 125.3, 133.0, 134.0, 137.5, 142.7 (C); MS m/z: 362 (M^+, 18), 180 (100). Anal. Calcd for $C_{26}H_{22}N_2$ C, 86.15; H, 6.12; N, 7.73. Found C, 86.0; H, 6.02; N, 7.93.

***syn-13-cis*-5,5a,6,12,12a,13-Hexahydro-6,13-dimethyl-6,-12-methano-quino[3,4-*b*][1]benzazepine (4c).** White solid; mp 176 °C (CH_2Cl_2); R_f = 0,70 (SiO_2 acetone/CH_2Cl_2 10:90); IR (neat) ν_{max}/cm^{-1} 3280, 3020, 2960, 2920, 2830, 1600, 1560, 1490, 1370, 1300, 1220, 1155, 1120; δ_H ($CDCl_3$) 1.27 (3H, d, J = 6.7), 1.44 (3H, s), 1.79 (1H, dd, J = 11.6, 4.0, H-14), 1.95 (1H, ddd, J = 11.0, 10.1, 5.1, H-12a), 2.06 (1H, d, J = 11.6, H-14), 2.38 (1H, dq, J = 10.1, 6.7, H-13), 3.31 (1H, d, J = 11.0, H-5a), 3.70 (1H, dd, J = 5.1, 4.0, H-12), 3.8 (2H, NH), 6.27 (1H, dd, J = 7.9, 0.9), 6.41 (1H, d, J = 7.6), 6.53 (1H, ddd, J = 7.6, 7.3, 1.2), 6.64 (1H, ddd, J = 7.3, 7.6, 1.2), 6.78−7.03 (4H,

m); δ_C ($CDCl_3$) 16.7, 22.1 (CH_3), 38.8 (CH_2), 30.5, 54.0, 54.2, 68.3, 113.1, 114.6, 116.6, 118.5, 124.3, 126.0, 126.1, 127.4 (CH), 128 (CH), 46.3, 129.0, 131.4, 142.9, 146.1 (C); MS *m*/*z* 290 (M^+, 13), 144 (100). Anal. Calcd For $C_{20}H_{20}N_2$ C, 82.71; H, 7.64; N, 9.65%. Found C, 82.60; H, 7.63; N, 9.57.

***anti-13-cis*-5,5a,6,12,12a,13-Hexahydro-6,13-dimethyl-6,12-methano-quino[3,4-*b*][1]benzazepine (5c).** White solid; mp 146 °C (CH_2Cl_2); R_f = 0,65 (SiO_2 acetone/CH_2Cl_2 10:90); δ_H (C_6D_6) 1.0 (1H, dd, *J* = 5.0, 11.6, H-14), 1.14 (3H, s), 1.24 (3H, d, *J* = 7.0), 1.35 (1H, d, *J* = 11.6, H-14), 2.55 (1H, dd, *J* = 8.5, 5.3, H-12a), 2.7 (1H, ddq, *J* = 5.3, 1.6, 7.0, H-13), 2.99 (1H, d, *J* = 4.9, H-12), 3.51 (1H, dd, *J* = 8.4, 1.6, H-5a), 4.0 (2H, NH), 6.34−6.40 (2H, m), 6.70−6.91 (2H, m), 7.07−7.13 (4H, m); δ_C (C_6D_6) 15.1, 17.8 (CH_3), 38.06 (CH_2), 31.2, 53.2, 56.9, 69.1, 113.4, 115.2, 117.4, 118.1, 124.4, 124.8, 127.0, 127.2 (CH), 48.4, 129.2, 131.8, 143.5, 146.4 (C). Anal. Calcd For $C_{20}H_{20}N_2$ C, 82.71; H, 7.64; N, 9.65%. Found C, 82.59; H, 7.49; N, 9.55.

***trans*-3,3′-Dimethyl-1,2,3,4-tetrahydro-4:2′-biquinoline (6b).** White solid; mp 179 C ($CHCl_3$); R_f 0.66 (SiO_2, acetone/CH_2Cl_2 10:90); IR (neat) ν_{max}/cm^{-1} (KBr) 3280, 3020, 2960, 2920, 2830, 1600, 1560, 1490, 1370, 1300, 1220, 1155, 1120; δ_H ($CDCl_3$) 0.98 (3H, d, *J* = 6.5), 2.42 (3H, s), 2.77 (1H, qddd, *J* = 6.5, 10.3, 10.2, 3.9, H-3), 3.17 (1H, dd, *J* = 11.2, 10.3), 3.43 (1H, dd, *J* = 11.1, 3.9), 4.2 (1H, NH), 4.40 (1H, d, *J* = 10.2), 6.48−6.56 (2H, m), 6.6 (1H, d, *J* = 7.6), 7.02 (1H, m), 7.51 (1H, ddd, *J* = 8.0, 6.9, 1.4), 7.66 (1H, ddd, *J* = 8.4, 6.9, 1.4), 7.77 (1H, d, *J* = 6.9), 7.94 (1H, s), 8.12 (1H, d, *J* = 8.4); δ_C ($CDCl_3$) 17.6, 19.3 (CH_3), 48.2 (CH_2), 32.0, 51.3, 114.0, 117.0, 125.6, 126.4, 126.6, 128.1, 128.6, 128.6, 136.6 (CH), 123.2, 127.0, 130.2, 144.5, 146.4, 163.5 (C); MS *m*/*z* 288 (M^+, 100), 173 (90), 130 (15). Anal. Calcd for $C_{20}H_{20}N_2$ C, 83.30; H, 6.99; N, 9.71. Found C, 83.09; H, 7.15; N, 9.66.

4,4′-Dimethyl-1,2,3,4-tetrahydro-4:2′-biquinoline (6c). White solid; mp 123 °C (C_6H_{12}/CH_2Cl_2 90:10); R_f 0.57 (acetone/$CHCl_3$ 15:85); ν_{max}/cm^{-1} (KBr) 3280, 3020, 2960, 2920, 2830, 1600, 1560, 1490, 1370, 1300, 1220, 1155, 1120; δ_H ($CDCl_3$) 1.90 (3H, s), 1.94 (1H, ddd, *J* = 11.3, 7.6, 4), 2.50 (3H, s), 2.60 (1H, ddd, *J* = 11.3, 7.9, 3.7), 3.22 (1H, ddd, *J* = 11.6, 7.6, 3.7), 3.40 (1H, ddd, *J* = 11.6, 7.9, 4.0), 4.10 (1H, NH), 6.53 (1H, d, *J* = 7.0), 6.63 (1H, ddd, *J* = 7.3, 7.6, 1.1), 6.94 (1H, d, *J* = 6.8), 6.95 (1H, s), 7.03 (1H, ddd, *J* = 8.5, 8.2, 1.4), 7.47 (1H, ddd, *J* = 8.2, 7.0, 1.1), 7.65 (1H, ddd, *J* = 8.3, 6.9, 1.4), 7.86 (1H, d, *J* = 8.3), 8.13 (1H, d, *J* = 8.4); δ_C ($CDCl_3$) 18.6, 28.7 (CH_3), 36.8, 38.6 (CH_2), 114.3, 116.9, 121.7, 123.3, 125.5, 127.1 128.6, 128.9, 129.7 (CH), 43.7, 126.5, 130.2, 143.3, 144.4, 147.1, 167.9 (C); MS *m*/*z*: 288 (M^+, 92), 144 (100). Anal. Calcd for $C_{20}H_{20}N_2$ C, 83.30; H, 6.99; N, 9.71. Found C, 83.01; H, 7.12; N, 9.63.

Cyclization with Zn/AcOD. Following the typical procedure described above, reaction of quinoline and Zn/AcOD led to a *syn*/*anti* mixture of **2a**-C_{6a},$C_{14\beta}$-d_2 /**3a**-C_{6a},$C_{14\beta}$-d_2 (83% yield, **2a**/**3a** 50:50), which were chromatographed on silica gel.

***syn*-6a,14β-Dideutero-5,6,6a,7,13,13a-hexahydro-7,13-methano-quino[3,4-*c*][1]benzazepine (2a-C_{6a},$C_{14\beta}$-d_2).** White solid; mp 145 °C (C_6H_6); R_f = 0.35 (SiO_2, acetone/$CHCl_3$ 10:90); yield 41%; IR (neat) ν_{max}/cm^{-1} 3400, 1630; δ_H ($CDCl_3$) 1.57 (1H, dd, *J* = 4.0, 4.2, H-14α), 2.51 (1H, d, *J* = 11.0, H_a-6), 2.76 (1H, d, *J* = 11.0, H_b-6), 2.98 (1H, d, *J* = 5.3, H-13a), 3.05 (1H, dd, *J* = 3.8, 5.3, H-13), 3.24 (1H, d, *J* = 4.2, H-7), 3.90 (2H, NH), 7.25 (2H, m), 7.48 (2H, ddd, *J* = 7.4, 7.4, 1.2), 7.87 (3H, m), 8.20 1H, m); δ_C ($CDCl_3$) 32.6 (CHD), 43.4 (CH_2), 44.5 (CD), 44.7, 47.3, 55.4, 113.6, 115.3, 116.7, 118.7, 125.9, 127.3, 130.1, 130.2 (CH), 125.1, 127.0, 143.4, 146.9 (C); δ_D ($CDCl_3$) 1.80 (D-14*β*), 2.25 (D-6a); MS *m*/*z*: 265 (7), 264 (18,1), 131 (100), 130 (54,3).

***anti*-6a,14β-Dideutero-5,6,6a,7,13,13a-hexahydro-7,13-méthano-quino[3,4-*c*][1]benzazepine (3a-C_{6a},$C_{14\beta}$-d_2).** Oil; R_f = 0.44 (SiO_2, acetone/$CHCl_3$ 10:90); yield 42%; IR (neat) ν_{max}/cm^{-1} 3400, 1630; δ_H ($CDCl_3$) 1.95 (1H, dd, *J* = 4.1, 4.2, H-14α), 3.05 (1H, d, *J* = 4.1, H-13), 3.11 (1H, d, *J* = 11.1, H_a-6), 3.24 (1 H, d, *J* = 11.1, H_b-6), 3.62 (1H, s, H-13a), 3.67 (1H, d, *J* = 4.2, H-7), 3.80 (2H, NH), 6.62 (2H, d, *J* = 7.9), 6.80 (1H, ddd, *J* = 7.3, 7.4, 1.2), 6.86 (1H, ddd, *J* = 7.5, 7.3, 1.2), 7.14 (3H, m), 7.40 (1H, d, *J* = 7.4); δ_C ($CDCl_3$) 30.3 (CHD), 45.7 (CH_2), 48.9 (CD), 51.6, 51.8, 59.7, 115.4, 115.7, 118.2, 119.4, 126.5, 127.5, 127.9, 129.8 (CH), 127.0, 130.6, 142.6, 147.3 (C); δ_D ($CDCl_3$) 1.68 (D-14*β*), 2.78 (D-6a); MS *m*/*z*: 265 (3.8), 264 (13.3), 263 (10.4), 262 (2.8),131 (100).

X-ray Structural Determination of 4c. The colorless crystals used had approximate dimensions of 0.10 × 0.15 × 0.35 mm. Data were collected on an Enraf-Nonius CAD-4 diffractometer using graphite monochromated Cu Kα radiation up to a Bragg angle of 55°. Cell constants were determined by least-squares refinement of diffractometer angles for reflections collected in the range 25° < θ < 30°. Crystal and relevant X-ray data are summarized in Tables 2 and 3 (Supporting Information). The structures were solved using the MITHRIL program,[12] and refined by the block-diagonal least-squares method. The non-hydrogen atoms were located from difference Fourier syntheses. Lorentz and polarization corrections as well as an empirical (ψ scans) absorption correction were applied. The projection of the molecule showing the numbering adopted is shown in Figure 2 (Supporting Information).

Supporting Information Available: X-ray data for **4c**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO010961B

(12) Gilmore, C. J. *J. Appl. Crystallogr.* **1984**, *17*, 42.