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Highly efficient methods for metacyclophane synthesis

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Abstract—Highly efficient methods for synthesizing metacyclophanes such as 2,6-bridged pyrones and pyridines are described. 4-Hydroxy-2-pyrone derivative **3** bridged at the 3 and 6-positions is readily available. This compound was transformed into 2,6-bridged 4-pyrone **4** on heating in ethanol or in hydrochloric acid. Heating **4** with ammonia or methylamine afforded the corresponding 2,6-bridged 4-pyrone **7** or **8**. These pyridones were synthesized directly from **3** by treatment with ammonia or methylamine. These methods have a wide applicability to the bridge length of metacyclophane; compounds with a short bridge (n=8) as well as long bridge (n=18) are synthesized in satisfactory yields.

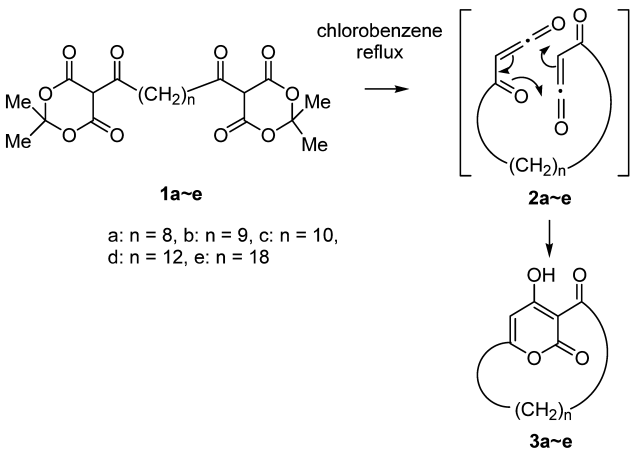
1. Introduction

The design and synthesis of cyclophanes, macrocycles containing aromatic groups, is a fascinating branch of organic and supramolecular chemistry.[1,2] It is well recognized that cyclophanes have a wide range of applicability in emerging technology as synthetic receptors in molecular recognition, sensors, and components of molecular motors.[2] Recently, ring-closing metathesis (RCM)[3] has emerged as a powerful method for generating diverse ring systems including macrocycles.[4] However, the overall product yields in the wide variety of synthetic methods so far developed generally suffer from the multistep sequences involved.[5] Even in the methods of short sequences, the products yield result poor.[6] We report here a highly efficient method for preparing metacyclophanes by ring transformation of paracyclophane **3** readily obtained from commercially available compounds in a few steps.[7]

2. Result and discussion

2.1. Preparation of cyclophane 3

Compounds **3a–e** (n=8, 9, 10, 12, 18) were prepared according to the literature.[7] Bis(4,6-dioxo-1,3-dioxane)s **1a–e** obtained by condensation of dicarboxylic acid dichlorides with two molecules of Meldrum's acid were heated in refluxing chlorobenzene to generate bisketenes **2a–e**, which in situ underwent intramolecular cyclization to give **3a–e** generally in high yields. The synthesis of **3a–e** was carried out on a 10–30 mmol scales, and the cyclophanes **3a–e** were readily purified either by distillation or by chromatography on silica gel short column (Scheme 1).



Scheme 1.

2.2. Synthesis of 2,6-bridged 4-pyrone 4

On heating with conc. HCl, dehydroacetic acid is transformed into 2,6-dimethyl-4-pyrone.[8,9] We applied this ring transformation to the synthesis of 2,6-bridged 4-pyrone **4** from **3**. On heating with conc. HCl, compounds **3c–e** (n=10, 12, 18) were transformed into 4-pyrones **4c–e** in satisfactory yields. Compounds **3a** (n=8) and **3b** (n=9) were rapidly decomposed under the acidic conditions producing the corresponding **4a** and **4b** in low yields, respectively. Thus, we examined the ring transformation of **3a** and **3b** under mild conditions and we found that these compounds are transformed into **4a** and **4b** in good yields on

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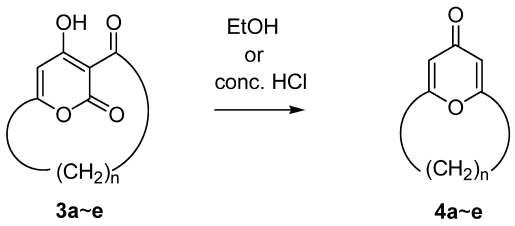


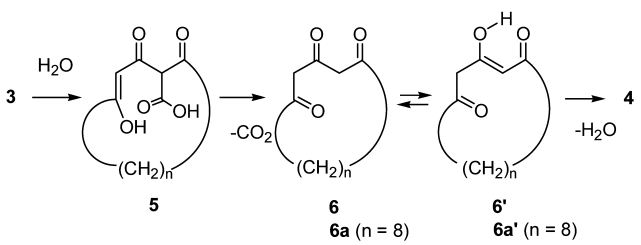
Scheme 2.

Table 1. Synthesis of heterophane **4** from **3**

No.	*n*	Conditions	Yield (%) of **4**
3a	8	EtOH, reflux, 40 h	82
3b	9	EtOH, reflux, 7 days	76
3c	10	Conc. HCl, reflux, 15 h	90
3d	12	Conc. HCl, 100°C, 24 h	83
3e	18	Conc. HCl, 100°C, 24 h	79

heating in ethanol for prolonged period, respectively (Scheme 2 and Table 1).

A possible mechanism for these ring transformations is shown in Scheme 3. The initial step is hydrolysis of **3** to give β-ketocarboxylic acid **5**. Under the reaction conditions, compound **5** is decarboxylated to afford macrocyclic triketone **6**, intramolecular cyclization of which leads to **4**. In the reaction in ethanol (99.5%), the hydrolysis to **5** occurs presumably by small amount of water in the solvent. When **3a** was heated in water under reflux for 2 h, triketone **6a** was obtained in 52% yield along with **4a** (4%), and prolonged refluxing for 40 h resulted in the formation of **6a** (10%) and **4a** (43%). Compound **6a** existed mostly as enol form **6a′** as indicated by ^{1}H NMR analysis.

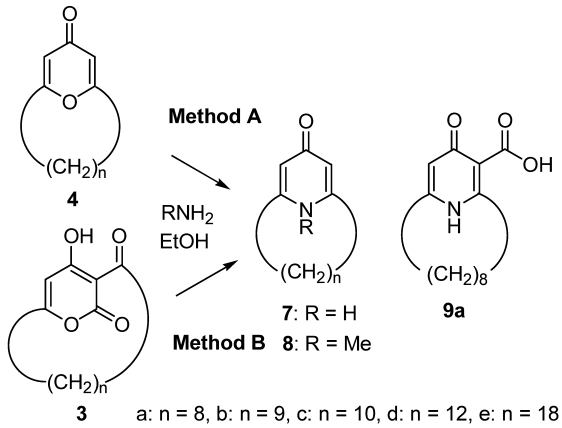


Scheme 3.

2.3. Synthesis of 2,6-bridged 4-pyridones

2,6-Dimethyl-4-pyridones are synthesized from 2,6-dimethyl-4-pyrone[8,10] or from dehydroacetic acid (3-acetyl-4-hydroxy-6-methyl-2-pyrone)[11] by heating with ammonia or primary amines.

First, we examined the reaction of 2,6-bridged 4-pyrone **4** with ammonia or methylamine to synthesize 2,6-bridged 4-pyridone **7** (R=H) or **8** (R=Me) (method A). A solution of **4** in ethanol saturated with ammonia at 0°C was heated in a cylinder at 130°C for 15 h ~6 days to give pyridone **7** in 60–91% yields. It should be noted that compound **4a** having relatively short bridge reacted with ammonia faster than other pyrones. The reaction of **4b–e** with methylamine under heating afforded *N*-methyl derivatives **8b–e** in satisfactory yields (Scheme 4, Table 2).



Scheme 4.

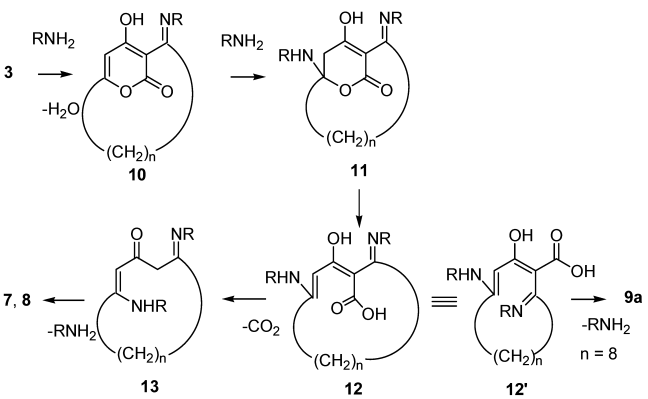
Table 2. Synthesis of 2,6-bridged pyridones **7** and **8**

No.	R	*n*	Yield (%)	
			From **4**	From **3**
7a	H	8	60[a]	56[b]
7b	H	9	84[c]	60[d]
7c	H	10	90[d]	55[d]
7d	H	12	79[d]	82[d]
7e	H	18	66[d]	62[d]
8c	CH_3	10	91[d]	81[e]
8d	CH_3	12	74[d]	52[d]
8e	CH_3	18	84[d]	81[d]

[a] Reaction conditions: 130°C, 10 h.
[b] Reaction conditions: 100°C, 6 h.
[c] Reaction conditions: 130°C, 6 days.
[d] Reaction conditions: 130°C, 2 days.
[e] Reaction conditions: 140°C, 2 days.

Next, we studied one-step synthesis of pyridones **7** and **8** from cyclophane **3** (method B).

Reaction of **3a** with ammonia in the same manner as in method A afforded compound **7a** in 56% yield together with carboxylic acid derivative **9a** (40%). Reaction of compounds **3b–e** with ammonia afforded the corresponding pyridones **7b–e** in 52–82% yields; carboxylic acids of type **9a** were not obtained in these cases. Reaction of compounds **3c–e** with methylamine under heating afforded the corresponding *N*-methylpyridones **8c–e** in 52–81% yields. The most plausible mechanism for the ring transformation of **3** to **7**, **8** and **9a** is shown in Scheme 5.



Scheme 5.

It has been known that ammonia or primary amines readily condenses with dehydroacetic acid at the acetyl carbonyl group to produce imines.[9] The imino compound **10** thus formed from **3** reacts with another molecule of ammonia or methylamine to produce carboxylic acid **12**. Decarboxylation of **12** followed by intramolecular cyclization by elimination of ammonia or methylamine produces **7** or **8**. In the reaction of **3a** with ammonia, considerable amount of carboxylic acid **9a** was obtained as the side product. The formation of **9a** is explained by direct cyclization of **12a** prior to decarboxylation to **13a**, and this exceptional case may be attributable to relatively small ring size of **12a**.

It should be noted that pyridinophane **7** (R=H) favors 4-pyridone form but not 4-hydroxypyridine form as indicated by IR and UV spectra analysis; the IR (KBr) and UV ($CHCl_3$) spectra of **7** were very similar to those of the *N*-methyl derivative **8**.

3. Conclusion

In conclusion, highly efficient methods for synthesizing metacyclophanes **4**, **7** and **8** have been developed using ring transformation of paracyclophane **3** as the key intermediate. One-step synthesis of **7** and **8** from **3** (Method B) is particularly facile. The most characteristic feature of this cyclophane synthesis is a wide applicability to the bridge length; metacyclophanes with a short bridge (n=8) as well as long bridge (n=18) are synthesized in satisfactory yields. We are currently investigating an extension of this ring transformation methodology to the synthesis of crown ether-type metacyclophanes such as 2,6-bridged pyridines and 4-pyrones using oligo(ethylene glycol) unit as the bridge. We are also studying the first synthesis of planar chiral 4-dimethylaminopyridines bridged at the 3,6-positions starting from **3**.

4. Experimental

4.1. General

Melting points were determined with a Yazawa micro melting point apparatus without correction. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL JNM-GSX 270 or JNM-GSX 500 spectrometer with tetramethylsilane as an internal standard. UV spectra were obtained on a HITACHI U-3410 spectrometer. IR spectra were determined on a JASCO FT/IR-8000 spectrometer. High-resolution mass spectra were recorded on a JEOL JMS-700 MStation spectrometer by using *m*-nitrobenzyl alcohol or polyethyleneglycol matrix. Column chromatography was done with Silica Gel 60 N (KANTO CHEMICAL CO., INC.). The ratios of solvent mixtures for chromatography are shown as volume/volume.

4.2. Synthesis of compounds 3a–e

Compounds **3a–e** were prepared by heating **1a–e** in refluxing chlorobenzene, following the reported procedure.[7] Compounds **3a–c** were purified by distillation and compounds **3d**,**e** were purified by chromatography on silica gel short column. Yield **3a**, 60%; **3b**, 70%; **3c**, 87%; **3d**, 89%; **3e**: 72%.

4.2.1. 14-Oxabicyclo[8.3.1]tetradecane-1(13),10-dien-12-one 4a. A solution of compound **3a** (250 mg, 1.0 mmol) in 99.5% ethanol (10 ml) was refluxed for 40 h. After evaporation of the solvent, the residue was purified by silica gel column chromatography using hexane/ethyl acetate (1/1) as an eluent to give **4a** (168 mg, 82%). Colorless needles of mp 101–102°C (pentane-ethyl acetate): IR ($CHCl_3$) ν 1658, 1606 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (4H, m), 1.43 (4H, m), 1.74 (4H, m), 2.63 (4H, t, J=7.0 Hz), 6.11 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.5, 23.7, 24.0, 31.4, 114.3, 168.8, 180.5; MS (FAB) m/z 207 $[M+H]^+$; HRMS (FAB) calcd for $C_{13}H_{19}O_2$ $[M+H]^+$ 207.1385, found 207.1373.

4.2.2. 15-Oxabicyclo[9.3.1]pentadecane-1(14),11-dien-13-one 4b. A solution of compound **3b** (264 mg, 1.0 mmol) in 99.5% ethanol (10 ml) was refluxed for 7 days. After evaporation of the solvent, the residue was purified by silica gel column chromatography using hexane/ethyl acetate (1/1) as an eluent to give **4b** (167 mg, 76%). Colorless needles of mp 108–110°C (pentane–ethyl acetate): IR ($CHCl_3$) ν 1659, 1611 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.21 (4H, m), 1.39 (6H, m), 1.77 (4H, m), 2.59 (4H, t, J=6.0 Hz), 6.12 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.7, 23.4, 24.7, 25.0, 33.4, 114.6, 169.0, 180.3; MS (FAB) m/z 221 $[M+H]^+$; HRMS (FAB) calcd for $C_{14}H_{21}O_2$ $[M+H]^+$ 221.1542, found 221.1539.

4.2.3. 16-Oxabicyclo[10.3.1]hexadecane-1(15),12-dien-13-one 4c. A solution of compound **3c** (139 mg, 0.5 mmol) in concentrated hydrochloric acid (5 ml) was refluxed for 15 h. After evaporation of the acid, the residue was neutralized with sodium hydrogen carbonate solution and then extracted with ether. The organic layer was dried over anhydrous potassium carbonate and concentrated. Recrystallization of the residue from hexane-ether gave **4c** (105 mg, 90%). Colorless needles, mp 87–88°C: IR ($CHCl_3$) ν 1659, 1607 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32 (12H, m), 1.74 (4H, m), 2.56 (4H, t, J=6.0 Hz), 6.10 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.6, 25.8, 26.3 (signals unresolved), 32.6, 114.1, 169.6, 180.4; MS (FAB) m/z 235 $[M+H]^+$; HRMS (FAB) calcd for $C_{15}H_{23}O_2$ $[M+H]^+$ 235.1698, found 235.1678.

4.2.4. 18-Oxabicyclo[12.3.1]octadecane-1(17),14-dien-15-one 4d. A solution of compound **3d** (306 mg, 1.0 mmol) in concentrated hydrochloric acid (5 ml) was heated in a stainless steel cylinder (100 ml) at 100°C for 24 h. The reaction mixture was evaporated to dryness. The residue was neutralized with sodium hydrogen carbonate solution and then extracted with $CHCl_3$. The organic layer was dried over anhydrous potassium carbonate and concentrated. Recrystallization of the residue from hexane–ether gave **4d** (217 mg, 83%). Colorless needles, mp 95–96°C: IR ($CHCl_3$) ν 1659, 1607 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (4H, m), 1.34 (12H, m), 1.68 (4H, m), 2.54 (4H, t, J=6.0 Hz), 6.10 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.2, 26.2, 26.6 (signals unresolved), 27.0, 33.4, 114.0, 169.4, 180.4; MS (FAB) m/z 263

$[M+H]^+$; HRMS (FAB) calcd for $C_{17}H_{27}O_2$ $[M+H]^+$ 263.2011, found 263.2010.

4.2.5. 24-Oxabicyclo[18.3.1]tetracosane-1(23),20-dien-22-one 4e. A solution of compound **3e** (390 mg, 1.0 mmol) in concentrated hydrochloric acid (5 ml) was heated in a stainless steel cylinder at 100°C for 24 h. The reaction mixture was evaporated to dryness. The residue was neutralized with sodium hydrogen carbonate solution and then extracted with ether. The organic layer was dried over anhydrous potassium carbonate and concentrated. Recrystallization of the residue from hexane-ether gave **4d** (273 mg, 79%). Colorless needles, mp 92–93°C: IR ($CHCl_3$) ν 1661, 1609 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.29 (28H, m), 1.64 (4H, m), 2.50 (4H, t, J=7.0 Hz), 6.08 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.1, 27.3, 27.6, 28.0, 28.3, 28.5, 28.6, 28.9, 33.8, 113.3, 169.3, 180.5; MS (FAB) m/z 347 $[M+H]^+$; HRMS (FAB) calcd for $C_{23}H_{39}O_2$ $[M+H]^+$ 347.2950, found 347.2928.

4.2.6. 3-Hydroxycyclotridec-2-ene-1,5-dione 6a′. A solution of compound **3a** (250 mg, 1.0 mmol) in water (10 ml) was refluxed for 2 h. After evaporation of the solvent, the residue was purified by silica gel column chromatography using hexane/ethyl acetate (20/1) as an eluent to give **6a′** (115 mg, 52%). Further elution with hexane/ethyl acetate (1/1) gave **4a** (8 mg, 4%). The reaction of **3a** in refluxing water for 40 h gave **6a′** (10%) and **4a** (43%). **6a′**: colorless needles of mp 73–74°C (recrystallized from pentane): IR ($CHCl_3$) ν 1715, 1605 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.28 (8H, m), 1.66 (4H, m), 2.32 (2H, t, J=6.5 Hz), 2.54 (2H, t, J=7.0 Hz), 3.41 (2H, s), 5.97 (1H, s), 15.1 (1H, broad); ^{13}C NMR (68 MHz, $CDCl_3$) δ 22.9, 24.1, 25.9, 25.9, 26.1, 26.2, 37.2, 42.2, 55.5, 100.6, 187.2, 193.3, 203.9; MS (FAB) m/z: 225 $[M+H]$; HRMS (FAB) calcd for $C_{13}H_{21}O_3$ $[M+H]^+$ 225.1491, found 225.1492.

4.2.7. 14-Azabicyclo[8.3.1]tetradeca-1(13),10-dien-12-one 7a. *General procedure for synthesis of 7 from 4 (Method A).* A solution of **4a** (206 mg, 1.0 mmol) in ethanol (10 ml) was cooled in an ice-bath and then saturated with NH_3. The solution was heated in a stainless steel cylinder (100 ml) at 130°C for 15 h. The reaction mixture was evaporated in vacuo and the residue was purified by silica gel column chromatography using chloroform/methanol (50/1) as an eluent to give first unreacted **4a** (70 mg, 34%) and then **7a** in 60% yield.

General procedure for synthesis of 7 from 3 (Method B). A solution of **3a** (250 mg, 1.0 mmol) in ethanol (10 ml) was cooled in an ice-bath and then saturated with NH_3. The solution was heated in a stainless steel cylinder at 100°C for 6 h. Chromatography as in Method A gave first **9a** and then **7a** in 56% yield. Colorless prisms of mp 189–190°C (ethyl acetate–methanol): UV ($CHCl_3$) λ_{max} (log ε) 265 (4.15) nm; IR (KBr) ν 1626, 1520 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 1.14 (4H, m), 1.25 (4H, m), 1.74 (4H, m), 2.65 (4H, t, J=6.5 Hz), 6.20 (2H, s); ^{13}C NMR (125 MHz, CD_3OD) δ 23.4, 26.6, 28.4, 32.9, 115.2, 154.8, 182.8; MS (FAB) m/z 206 $[M+H]^+$; HRMS (FAB) calcd for $C_{13}H_{20}NO$ $[M+H]^+$ 206.1545, found 206.1569.

4.2.8. 12-Oxo-14-azabicylo[8.3.1]tetradeca-1(13),10-diene-11-carboxylic acid 9a. Yield: 40%. Colorless prisms of mp 253–254°C (ethyl acetate–methanol): IR (KBr) ν 1672, 1512 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 1.10 (2H, m), 1.23 (6H, m), 1.79–1.84 (4H, m), 2.65 (2H, t, J=6.5 Hz), 3.25 (2H, m), 6.31 (1H, s); ^{13}C NMR (125 MHz, CD_3OD) δ 22.2, 24.0, 24.8, 25.9, 27.5, 27.7, 32.0, 32.4, 118.0, 118.2, 152.7, 159.0, 170.0, 180.9; MS (FAB) m/z 249 $[M]^+$; HRMS (FAB) calcd for $C_{14}H_{19}NO_3$ $[M]^+$ 249.1365, found 249.1386.

4.2.9. 15-Azabicyclo[9.3.1]pentadeca-1(14),11-dien-13-one 7b. Reaction of **4b** with ammonia as in method A for 6 days gave **7b** in 84% yield. Reaction of **3b** with ammonia as in method B for 1 day gave **7b** in 84% yield. Colorless prisms of mp 189–190°C (ethyl acetate–methanol): UV ($CHCl_3$) λ_{max} (log ε) 264 (4.20) nm; IR (KBr) ν 1622, 1520 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 1.01 (4H, m), 1.30 (6H, m), 1.80 (4H, m), 2.67 (4H, t, J=6.5 Hz), 6.22 (2H, s); ^{13}C NMR (125 MHz, CD_3OD) δ 25.5, 25.6, 25.7, 25.8, 33.4, 115.9, 154.5, 182.2; MS (FAB) m/z 220 $[M+H]^+$; HRMS (FAB) calcd for $C_{14}H_{22}NO$ $[M+H]^+$ 220.1701, found 220.1689.

4.2.10. 16-Azabicyclo[10.3.1]hexadecane-1(15),12-dien-14-one 7c. Reaction of **4c** with ammonia as in method A at 130°C for 2 days gave **7c** in 90% yield. Reaction of **3c** with ammonia as in method B at 130°C for 2 days gave **7c** in 55% yield. Colorless prisms of mp 203–205°C (ethyl acetate–methanol): UV ($CHCl_3$) λ_{max} (log ε) 263 (4.15) nm; IR (KBr) ν 1620, 1514 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 1.11 (4H, m), 1.25 (4H, m), 1.30 (4H, m), 1.80 (4H, m), 2.67 (4H, t, J=6.0 Hz), 6.25 (2H, s); ^{13}C NMR (125 MHz, CD_3OD) δ 26.7, 27.1, 27.4, 28.2, 33.4, 115.5, 154.9, 182.0; MS (FAB) m/z 234 $[M+H]^+$; HRMS (FAB) calcd for $C_{15}H_{24}NO$ $[M+H]^+$ 234.1858, found 234.1848.

4.2.11. 18-Azabicyclo[12.3.1]octadecane-1(17),14-dien-16-one 7d. Reaction of **4d** with ammonia as in method A at 130°C for 2 days gave **7d** in 79% yield. Reaction of **3d** with ammonia as in method B at 130°C for 2 days gave 7d in 82% yield (purified by silica gel column chromatography using chloroform/ethanol (10/1) as an eluent). Colorless prisms of mp 209–211°C (ethyl acetate–methanol): UV ($CHCl_3$) λ_{max} (log ε) 263 (4.12) nm; IR (KBr) ν 1620, 1528 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 1.18 (4H, m), 1.30 (12H, m), 1.72 (4H, m), 2.65 (4H, t, J=6.0 Hz), 6.22 (2H, s); ^{13}C NMR (125 MHz, CD_3OD) δ 27.0, 27.2, 27.5, 28.1, 29.0, 33.5, 115.5, 154.6, 181.8; MS (FAB) m/z 262 $[M+H]^+$; HRMS (FAB) calcd for $C_{17}H_{28}NO$ $[M+H]^+$ 262.2171, found 262.2169.

4.2.12. 24-Azabicyclo[18.3.1]tetracosan-1(23),20-dien-22-one 7e. Reaction of **4e** with ammonia as in method A at 130°C for 2 days gave **7e** in 66% yield. Reaction of **3e** with ammonia as in method B at 130°C for 2 days gave **7e** in 62% yield (purified by silica gel column chromatography using chloroform/ethanol (10/1) as an eluent). Colorless prisms of mp 224–225°C (ethyl acetate–methanol): UV ($CHCl_3$) λ_{max} (log ε) 263 (4.24) nm; IR (KBr) ν 1620, 1522 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 1.29 (28H, m), 1.66 (4H, m), 2.60 (4H, t, J=7.0 Hz), 6.20 (2H, s); ^{13}C NMR

(125 MHz, CD_3OD) δ 28.2, 28.7, 29.2, 29.4, 29.5, 29.6, 30.2, 30.4, 34.1, 115.0, 154.7, 182.3; MS (FAB) *m/z* 346 $[M+H]^+$; HRMS (FAB) calcd for $C_{23}H_{40}NO$ $[M+H]^+$ 346.3110, found 346.3111.

4.2.13. 16-Methyl-16-azabicyclo[10.3.1]hexadecane-1(15),12-dien-14-one 8c. *General procedure for synthesis of* ***8*** *from* ***4*** *(Method A).* A solution of **4c** (234 mg, 1.0 mmol) and 40% methylamine solution (4 ml) in ethanol (10 ml) was heated in a stainless steel cylinder (100 ml) at 130°C for 2 days. The reaction mixture was evaporated in vacuo and the residue was purified by silica gel column chromatography using chloroform/ethanol (20/1) as an eluent to give **8c** (113 mg, 91%).

General procedure for synthesis of ***8*** *from* ***3*** *(Method B).* A solution of **3c** (278 mg, 1.0 mmol) and 40% methylamine solution (4 ml) in ethanol (10 ml) was heated in a stainless steel cylinder (100 ml) at 140°C for 2 days. Chromatography as in method A gave **8c** in 81% yield. Colorless prisms of mp 203–204°C (ethyl acetate–methanol): UV ($CHCl_3$) λ_{max} (log ε) 273 (4.24) nm; IR (KBr) ν 1630, 1566 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 1.01–1.07 (6H, m), 1.24 (4H, m), 1.40 (2H, m), 1.80 (2H, m), 2.60 (2H, ddd, J=15.0, 10.0, 4.5 Hz), 3.13 (2H, ddd, J=15.0, 7.0, 4.0 Hz), 3.79 (3H, s), 6.35 (2H, s); ^{13}C NMR (125 MHz, CD_3OD) δ 26.5, 27.1, 27.7, 28.2, 34.5, 37.6, 119.4, 157.8, 180.1; MS (FAB) *m/z* 248 $[M+H]^+$; HRMS (FAB) calcd for $C_{16}H_{26}NO$ $[M+H]^+$ 248.2014, found 248.2011.

4.2.14. 18-Methyl-18-azabicyclo[12.3.1]octadecane-1(17),14-dien-16-one 8d. Reaction of **4d** with methylamine as in method A gave **8d** in 74% yield. Reaction of **3d** with methylamine as in method B at 130°C for 2 days gave **8d** in 52% yield (purified by silica gel column chromatography using chloroform/ethanol (40/1) as an eluent). Colorless prisms of mp 183–184°C (ethyl acetate–methanol): UV ($CHCl_3$) λ_{max} (log ε) 270 (4.19) nm; IR (KBr) ν 1628, 1535 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 1.13–1.25 (16H, m), 1.69 (2H, m), 1.76 (2H, m), 2.63 (2H, ddd, J=14.5, 10.0, 4.5 Hz), 3.13 (2H, ddd, J=15.0, 6.5, 4.0 Hz), 3.75 (3H, s), 6.33 (2H, s); ^{13}C NMR (125 MHz, CD_3OD) δ 26.6, 27.2, 27.4, 28.1, 28.4, 34.3, 37.1, 119.2, 157.0, 179.9; MS (FAB) *m/z* 276 $[M+H]^+$; HRMS (FAB) calcd for $C_{18}H_{30}NO$ $[M+H]^+$ 276.2327, found 276.2309.

4.2.15. 24-Methyl-24-azabicyclo[18.3.1]tetracosan-1(23),20-dien-22-one 8e. Reaction of **4e** with methylamine as in method A gave **8e** in 84% yield. Reaction of **3e** with methylamine as in method B at 130°C for 2 days gave **8e** in 81% yield. Colorless prisms of mp 125–126°C (ethyl acetate–methanol): UV ($CHCl_3$) λ_{max} (log ε) 269 (4.21) nm; IR (KBr) ν 1630, 1537 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 1.29–1.37 (28H, m), 1.66 (4H, m), 2.77 (4H, t, J=7.0 Hz), 3.70 (3H, s), 6.31 (2H, s); ^{13}C NMR (125 MHz, CD_3OD) δ 28.8, 28.9, 29.3, 29.4, 29.5, 34.6, 36.2, 118.1, 156.9, 180.2; MS (FAB) *m/z* 360 $[M+H]^+$; HRMS (FAB) calcd for $C_{24}H_{42}NO$ $[M+H]^+$ 360.3266, found 360.3256.

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