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Synthesis of bridged nicotinates having [*n*](2,5)pyridinophane skeletons (*n* = 8–14)

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Abstract—Synthesis of various bridged nicotinates **6** having [*n*](2,5)pyridinophane skeletons (*n* = 8–14) was accomplished by the unique pyridine-formation reaction of methyl propiolate with a series of formyl-substituted (vinylimino)phosphoranes **5**, which were prepared from the corresponding cycloalkanones **1** via Vilsmeier–Haack formylation giving chloro-substituted cycloalkenals **2**, their thermal and photochemical transformation to formyl azirines **4**, and the following ring-opening reactions with triphenylphosphine. The HPLC analysis of [11](2,5)pyridinophane derivatives, (S_p,*S*)-**14** and (R_p,*S*)-**14**, showed that these diastereomers rapidly epimerize themselves at room temperature and that their planar-chirality was thermodynamically less stable as compared to the corresponding [11](2,5)cyclophane systems.

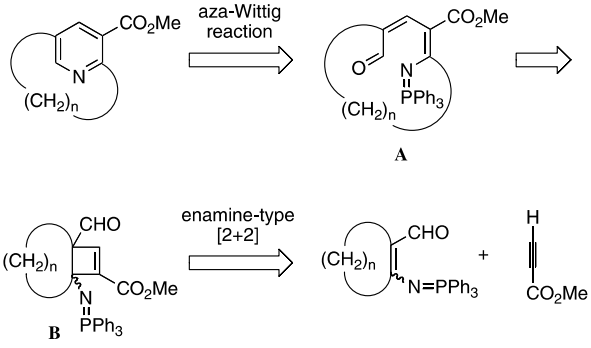
1. Introduction

(Vinylimino)phosphoranes are versatile synthetic synthons of various heteroaromatic compounds,[1] and are particularly useful for the syntheses of pyridine[2–6] and pyridinophane[7–9] derivatives. We have previously reported novel pyridine-formation reactions of formyl-substituted (vinylimino)-phosphoranes with acetylenic esters to give 2- and 2,5-substituted nicotinates,[2] and their synthetic application to a bridged nicotinate having [10](2,5)pyridinophane structure.[7] Our recent studies revealed also that the bridged nicotinate[10] and bridged benzoate[11] are such planar-chiral sources that they are readily accessible by crystallization-induced[11,12] or adsorption-induced[13] asymmetric transformation, and that planar-chiral NADH models, derived from the bridged nicotinate, exhibited one of the highest enantioselectivity in biomimetic asymmetric reduction of pyruvate analogues[7] among a number of NADH-mimicking systems having been reported so far.[14] In the bridged nicoinate systems, the decamethylene chains bridging *para*-positions of the pyridine ring play an extremely important role in shielding either side of two reactive faces and, therefore, the other nicotinates having different sizes of oligomethylene chains became our next target molecules for studying their dynamic motions and the correlation of the bridge lengths with synthetic efficiency. We will report here the detailed results of the synthetic studies on bridged nicotinates having [*n*](2,5)pyridinophane structures (*n* = 8–14) incorporating various lengths of their oligomethylene bridges.

2. Results and discussion

2.1. Synthetic strategy of bridged nicotinates

Scheme 1 illustrates our retrosynthetic route for bridged nicotinates having various lengths of oligomethylene chains,



Scheme 1. Retrosynthetic analysis of bridged nicotinates having various [*n*](2,5)cyclophane skeletons.

Keywords: Planar-chirality; Pyridinophanes; Pyridine-formation reactions; Aza-Wittig reactions; Cycloaddition.
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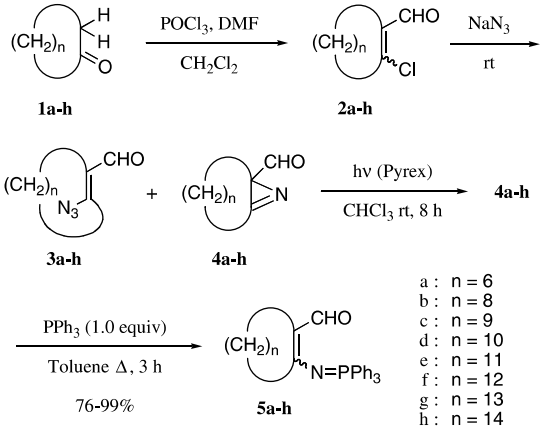
namely methyl [*n*](2,5)pyridinophane-3-carboxylates. The final pyridine-formation is to be accomplished by intramolecular aza-Wittig reactions of intermediates **A** whose diene moieties should be derived from ring-opening isomerizations of cyclobutene intermediates **B**. The enamine-type [2+2] cycloaddition disassembles **B** into methyl propiolate and (vinylimino)phosphorane derivatives, the latter of which are transformed from halo-substituted cycloalkenals being readily available by Vilsmeier–Haack formylation of the corresponding cycloalkanones.

2.2. Preparation of (vinylimino)phosphoranes

The synthetic transformation to formyl-substituted (vinylimino)phosphoranes **5a–h** was achieved by the sequential functionalization from cycloalkanones (**1a–h**) based on our previously reported method giving **5d**[7] (Scheme 2). Vilsmeyer–Haack formylation of cycloalkanones **1a–h** afforded the corresponding (*Z*)- and/or (*E*)-2-chloro-cycloalk-1-enecarbaldehyde (**2a–h**) in good yields (Table 1). At the beginning of our study, we carried out the formylation by using DMF and $POCl_3$ with 1 equiv amount each at a high temperature and, indeed, the reaction of cyclooctanone (**1a**) proceeded smoothly at 70 °C to afford (*Z*)-**2a** exclusively in 84% yield (entry 1). However, significant amounts of by-products (mostly β,γ-unsaturated chloroenals) were co-generated as well as the desired **2b–h** in the similar reaction conditions to those employed for **2a** (entry 2: see footnote). Eventually, we found even milder reaction conditions working very well for the synthesis of **2b–h** where the reactions with excess amounts of DMF and $POCl_3$ at 0 °C effected predominant formation of (*Z*)-**2b–f** in good to moderate isolated yields (entries 2–7). For the reactions giving compounds **2g**,**h**, significant amounts of (*E*)-**2g**,**h** were generated as less reactive isomers in the following steps as well as the desired (*Z*)-**2g**,**h** isolated in moderate yields (entries 8 and 9). In case of compound **2e**, the formylation proceeded with high (*Z*)-selectivity and the product was used for the next step without further purification (entry 6).



Scheme 2. Synthesis of formyl-substituted (vinylimino)phosphoranes **5a–h** from cycloalkanones **1a–h**.

Table 1. Vilsmeier–Haack formylation of **1a–h**

Entry	**1**	Conditions		Yield and ratio of **2**		
		T (°C)	Time (h)	Crude (%)	*E*/*Z*	Isolated (%)
1	**a**	70	6	n/a	0/100	84 (*Z*)
2	**b**	75	6	85[a]	0/100	75 (*Z*)
3	**b**	0	48	Quant	17/83	68 (*Z*)
4	**c**	0	24	99	3/97	90 (*Z*)
5[b]	**d**	0	48	95	18/82	78 (*Z*)
6	**e**	−5	48	91	6/94	n/a[c]
7	**f**	0	48	98	22/78	52 (*Z*)
8	**g**	0	48	92	44/56	53 (*Z*)
9	**h**	0	72	99	48/52	50 (*Z*)

[a] β,γ-Unsaturated chloroenal (15%) was produced as a by-product as well as **2b**.
[b] Previous work. See Ref. 7.
[c] Used in the following steps without further purification.

Then, we initially attempted the conversion of (*Z*)-**2a–h** thus obtained into the corresponding 2-azidocycloalk-1-enecarbaldehyde (**3a–h**), appropriate precursors for the subsequent Staudinger reactions. But the formation of **3a** was not observed in the crude mixture produced by the reaction of **2a** with sodium azide and, instead, formylazirine **4a** was isolated exclusively in 83% yield (entry 1 in Table 2). On the other hand, the reaction of the other chlorocycloalkenals **2b–h** afforded a mixture of (*E*)-**3b–h** and **4b–h**, and none of (*Z*)-**3b–h** was isolated at room temperature. Thus, formation of the azirines **4b–h** was reasonably explained as a result of releasing nitrogen out of less stable (*Z*)-**3b–h**. We have therefore chosen the synthetic route to (vinylimino)-phosphoranes **5a–h** via azirine intermediates as well as the transformation from **2d** to **4d** reported previously.[7] After the reaction of **2b–h** with sodium azide was complete, the crude mixtures containing (*E*)-**3b–h** were irradiated through Pyrex filter (365 nm) to give the compounds **4b–h** in 79–92% isolated yields (entries 2–8). The treatment with triphenylphosphine in refluxing toluene effected the ring-opening reaction of the azirine ring to give the desired formyl-substituted (vinylimino)phosphoranes **5a–h** in 76–99% yields (see Section 3.5). Except for compound **5a**, ^1H NMR spectra of the other iminophosphoranes exhibited two sorts of formyl protons corresponding to (*E*)- and (*Z*)-forms, the chemical shifts of which appeared at δ 9.84–9.93 and 10.57–10.71 ppm, respectively. The former signals were unambiguously assigned to those of (*E*)-**5b–h** whose signals at aliphatic regions were clearly informative of their non-symmetric structures being attributed to highly substituted *trans*-cycloalkenes with planar-chirality.

Table 2. Synthesis of formylazirines **4a–h**

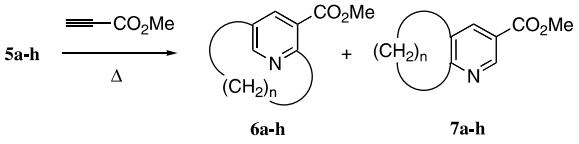
Entry	**2**	Conditions		Isolated yield
		Method[a]	Time (h)	**4** (%)
1	**a**	A	19	83[b]
2	**b**	B	5	79
3	**c**	B	4.5	85
4[c]	**d**	B	5	84
5	**e**	A	3	80
6	**f**	A	3	82
7	**g**	A	3	82
8	**h**	A	3	92

[a] Method A: NaN_3 1.5 equiv, DMF, rt. Method B: NaN_3 1.25 equiv, LiCl 0.1 equiv, wet THF, rt. See Section 3 for details.
[b] Obtained without photolysis.
[c] Previous work. See Ref. 7.

The compounds **5a–c**, having an 11-membered ring or less, exist as (*Z*)-form rich mixtures and, on the other hand, the others exist as (*E*)-form rich mixtures to minimize their ring strain. These compounds were produced as an inseparable mixture and they were used in the following step without further purification (Scheme 3).

2.3. Syntheses of bridged nicotinates

The reactions of the iminophosphoranes **5a–h** with methyl propiolate were thoroughly investigated for synthesizing nicotinates **6a–h** (Scheme 3). Table 3 indicates the reaction conditions and yields of compound **6d**, a representative bridged nicotinates having a [10](2,5)pyridinophane skeleton, as the results of our reinvestigation for seeking more efficient synthetic protocol. Our previous one, where the compound **5d** reacts with 10 equiv amount of methyl propiolate in toluene at 140 °C for 12 h, gave the desired **6d** and its isomer **7d** in 21 and 8% yield, respectively (See entry 4 of Method A in Table 4),[7] and we first examined the solvent effects. After running the reactions of **5d** with 5 equiv amount of methyl propiolate in various solvents at 140 °C, we eventually found that acetonitrile, an aprotic polar solvent, is more suitable for the synthesis of **6d** (entries 1–7). The reactions also work well at 120 °C (entries 8–12), to give **6d** with up to 25% yield (entry 9). The reactions with more or less amount of methyl propiolate did not afford better results for the formation of **6d** (entries 13 and 14). As a result, we were successful in reducing the amount of methyl propiolate to 5 equiv, just a half amount as compared to our original protocol, and in achieving the milder reaction conditions at 120 °C for 10 h (See also Section 3.6).



Scheme 3. Pyridinophane-formation reactions of formyl-substituted (vinylimino)phosphoranes **5a–h** with methyl propiolate.

Table 3. Reaction conditions and the yield of **6d**[a]

Entry	Conditions				Yield[b]
	MP (equiv)[c]	Solvent	*T* (°C)	Time (h)	**6d** (%)
1	5.0	Benzene	140	24	11
2	5.0	Toluene	140	24	17
3	5.0	Xylene	140	24	17
4	5.0	Chlorobenzene	140	24	17
5	5.0	1,1,2-Trichloro-ethane	140	24	19
6	5.0	1,4-Dioxane	140	24	12
7	5.0	Acetonitrile	140	24	22
8	5.0	Acetonitrile	120	12	21[d]
9	5.0	Acetonitrile	120	10	25[d]
10	5.0	Acetonitrile	120	8	24[d]
11	5.0	Acetonitrile	120	6	22[d]
12	5.0	Acetonitrile	120	4	19[d]
13	3.0	Acetonitrile	120	10	17[d]
14	10.0	Acetonitrile	120	8	16[d]

[a] All the reactions were carried out under 0.33 M solution of **5d**.
[b] Isolated yields unless otherwise specified.
[c] Methyl propiolate.
[d] Estimated by ^{1}H NMR spectra.

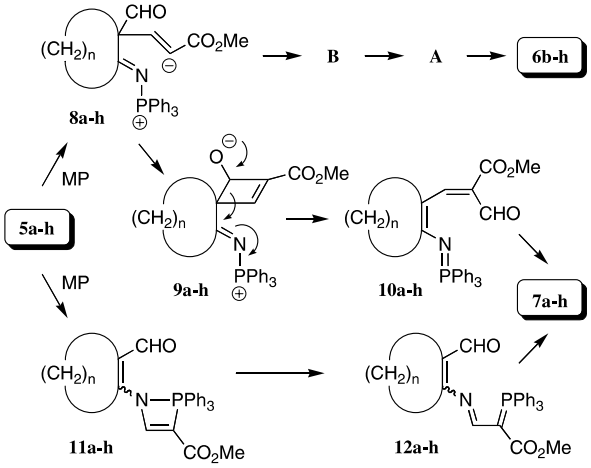
Table 4. Synthesis of bridged nicotinates **6b–h**

Entry	**5**	*n*	Yield (Method A)[a]		Yield (Method B)[b]	
			6 (%)	**7** (%)	**6** (%)	**7** (%)
1	**a**	6	0	5	n/a	n/a
2	**b**	8	4	10	4	25
3	**c**	9	7	4	10	11
4	**d**	10	21[c]	8[c]	25	15
5	**e**	11	26	3	29	8
6	**f**	12	30	3	32	16
7	**g**	13	38	5	41	16
8	**h**	14	40	4	43	16

[a] Method A: reactions were performed with 10 equiv of methyl propiolate in toluene at 140 °C for 12 h in autoclave.
[b] Method B: reactions were performed with 5 equiv of methyl propiolate in acetonitrile at 120 °C for 10 h in autoclave.
[c] Previous work. See Ref. 7.

Table 4 tabulates the yields of bridged nicotinates **6b–h** and their isomers **7a–h** obtained by the reactions of a series of (vinylimino)phosphoranes **5a–h** with methyl propiolate in toluene and acetonitrile as solvent. These reactions also proceeded well to result in the formation of methyl [*n*](2,5)pyridinophane-3-carboxylates **6b–h** having various length of their oligomethylene chains (entries 1–3, 5–8). In each case, the yield of **6b–h** in acetonitrile was better than that in toluene and unidentified by-products formed in these reactions did not seriously disturb the isolation of **6** and **7**. Obviously, the yields of **6b–h** increased as length of the oligomethylene chain becomes longer. Though none of [6](2,5)pyridinophane **6a** was obtained from **5a** (entry 1), the compounds **6b**,**c** were isolated even in relatively low yields due to their higher strain as compared to **6d–h** (entries 2 and 3). The reaction of **5e–h** having a larger ring size reacted with methyl propiolate more smoothly to result in [*n*](2,5)pyridinophane-3-carboxylate **6e–h** (*n*=11–14) in moderate yields (entries 5–8). All the spectral data agree with these proposed structures.

The postulated reaction pathways for the formation of **6b–h** and **7a–h** are shown in Scheme 4. Enamine-type nucleophilic addition[15] of **5a–h** occurs at the β-position of methyl propiolate to form ionic intermediates **8a–h** and the following intramolecular addition onto C=N and C=O produces cyclobutene intermediates **B** and **9**, respectively. The ring-opening reactions of **B** and **9** generate aldehydes **A**



Scheme 4. Postulated reaction pathways for the formation of **6** and **7**.

and **10**, which undergo intramolecular aza-Wittig reactions to give **6b–h** and **7a–h**. The formation of **7a–h** is also explained by the following alternative pathway: [2+2] cycloaddition of methyl propiolate onto N=P double bond of **5a–h** gives intermediates **11** and their subsequent ring-opening to **12** and intramolecular Wittig reaction of **12** afford **7a–h**.[16] Formation of these ionic intermediates shown in Scheme 4 seems to be suitable in an aprotic polar solvent such as acetonitrile, leading to the higher yield of **6** and **7**.

The ^{1}H NMR spectra of parapyridinophanes **6b**,**c** ($n=8$ and 9) showed that some protons at oligomethylene bridges were observed independently with unique chemical shifts and, especially, one of them appeared at δ −0.27 or −0.19 ppm (for **6b** and **6c**, respectively) as a distinctive up-field shift in a shielding region above an aromatic ring. These findings indicate that the compounds **6b**,**c** have a stable planar-chirality as well as [10](2,5)pyridinophane **6d** that we reported previously. As for [11](2,5)pyridinophane **6e**, ^{1}H NMR spectrum exhibited that its rope-skipping mobility of oligomethylene chain is apparently frozen in NMR time scale according to the peak independency of its aliphatic protons appearing at δ 2.62, 2.68, 2.77, and 3.74 ppm (1H each, ArCH_2–) (Fig. 1a).

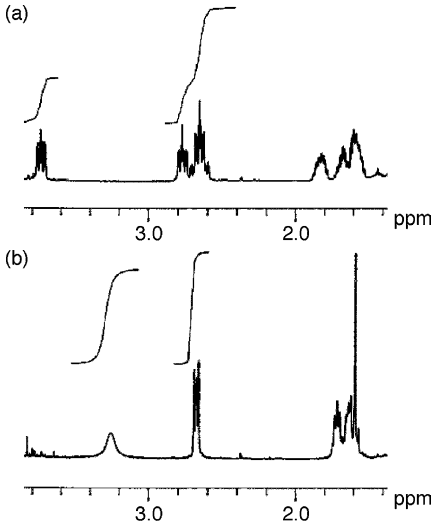
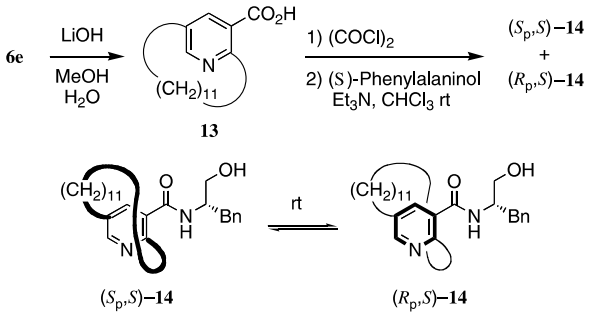


Figure 1. ^{1}H NMR spectra of bridged nicotinates **6e**,**f** at rt: some oligomethylene protons of (a) [11](2,5)pyridinophane **6e** and (b) [12](2,5)pyridinophane **6f**.

On the contrary, HPLC analysis of a diastereomeric mixture of (S_p,*S*)-**14** and (R_p,*S*)-**14**, derived from [11](2,5)pyridinophane-3-carboxylic acid (**13**) (Scheme 5), showed an inseparable single peak at room temperature, which suggests their rapid dynamic interconversion via rope-skipping isomerization in HPLC time scale (Fig. 2).[17] Indeed, at 0 °C, a typical plateau shape was observed in the middle of coalescence peaks of the two diastereoisomers epimerizing themselves.[18] This means that [11](2,5)pyridinophane **6e** also exists as a racemic equilibrium mixture with rapid interconversion and its planar-chirality is not stable enough to be resolved for the synthetic purposes. This is in good contrast to the analogous [11](2,5)cyclophane derivatives, which are reasonably stable against their racemization or epimerization.[11]



Scheme 5. Synthesis of [11](2,5)pyridinophane derivatives, (S_p,*S*)-**14** and (R_p,*S*)-**14**.

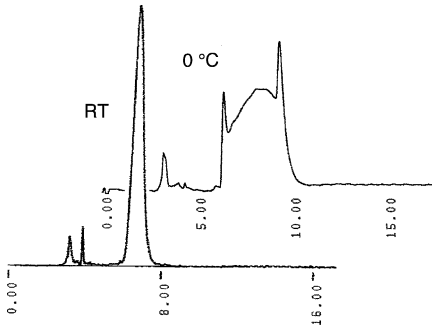


Figure 2. HPLC analyses of a diastereoisomeric mixture of (S_p,*S*)-**14** and (R_p,*S*)-**14** at rt and 0 °C.

On the other hand, ^{1}H NMR spectra of **6f–h** ($n=12$–14) are much simpler than those of **6b–e** and the proton pairs at each methylene unit appear as equivalent signals [see signals appearing at δ 3.26 and 3.93 ppm (2H each, ArCH_2–) for **6f** in Fig. 1b] as well as *Cs*-symmetric isomers of the ortho-bridged **7f–h**. Consequently, undecamethylene or longer bridges ($n\geq 11$) are flexible enough to flip over their pyridine rings and these molecules can hardly retain their planar chirality at room temperature. These findings that we have reported here provide a convenient route for the syntheses of bridged nicotinates having [*n*](2,5)pyridinophane skeletons and unique dynamic behavior of these novel ansa molecules.

3. Experimental

3.1. General

NMR spectra were recorded on Bruker AVANCE600, JEOL JNM-ECA500, JEOL Lambda500, JEOL JNM-A400, JEOL JNM-AL300, or JEOL JNM-EX270 spectrometers. Chemical shifts are reported in parts per million relative to Me_4Si for ^{1}H NMR and to the central line of $CDCl_3$ (77.0 ppm) for ^{13}C NMR as internal standard. Unless otherwise specified, NMR spectra were measured at ambient temperature except for compound **14** (at 50 °C). Mass spectra were recorded on Hitachi M-80, JEOL JMS-SX102, or JEOL-HX110 spectrometers. Thin-layer chromatography was performed using Merck silica gel 60 F_{254} glass plates (Art. 5715, 0.5 mm thick) or Merck aluminum oxide 60 F_{254} glass plates (Art. 5713, 0.25 mm thick). Flash chromatography was performed using Silica gel FL60D

(Fuji Silysia Chemical Ltd) unless otherwise specified. Melting points were recorded on Yanagimoto apparatus and are uncorrected. Cyclooctanone (**1a**), cyclodecanone (**1b**), cylododecanone (**1d**), cyclotridecanone (**1e**), and cyclopentadecanone (**1g**) are commercially available starting materials and were used without further purification. Cycloundecanone (**1c**) was prepared from cyclododecanone according to the literature method.[19]

3.1.1. Cyclotetradecanone (1f). Cyclotetradecanone (**1f**) was prepared from cyclopentadecanone (**1g**) according to the similar method for the preparation of **1c**.[19]

To a solution of cyclopentadecanone (**1g**) (22.4 g, 100 mmol) in toluene (140 ml) and ether (15 ml) was added dropwise bromine (10.0 ml, 200 mmol) and the mixture was stirred with a cooling bath at 20–25 °C for 30 min. After removal of hydrogen bromide generated in vacuo, the residual toluene solution of dibromide was treated with sodium methoxide (18.9 g, 350 mmol) in small portions and the whole mixture was stirred at 20–25 °C for 30 min. After the reaction was complete, the mixture was washed with water (1×50 ml), 5% hydrochloric acid (1×150 ml) and brine (1×50 ml) and the aqueous layer was extracted with ether (3×80 ml). The combined organic layer was dried over sodium sulfate and, after removal of solvent in vacuo, the residue was separated by flash chromatography on silica gel (5% ether in hexane) to give methyl cyclotetradec-1-encarboxylate (24.4 g, 96.7 mmol) in 97% yield: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.23–1.57 (m, 20H), 2.31 (AA′XX′, $J_{AX}+J_{AX'}=11.2$ Hz, 2H), 2.49 (m, 2H), 3.73 (s, 3H), 5.82 (t, $J=7.8$ Hz, 1H). After the product thus obtained was dissolved in sulfuric acid (73 ml) at 5 °C, chloroform (61 ml) was added, sodium azide (9.23 g, 142 mmol) was added in portions at 40 °C, and the reaction mixture was stirred at 35–40 °C for 1 h. The mixture was poured into ice water (200 g each) and was extracted with chloroform (3×100 ml). The combined organic layer was washed with saturated aqueous sodium bicarbonate (2×200 ml) and dried over magnesium sulfate. After removal of solvent in vacuo, the residue was purified by flash chromatography on silica gel (2% ether in hexane) to give cyclotetradecanone (**1f**)[20] (13.7 g, 64.9 mmol) in 69% yield: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.09–1.29 (m, 18H), 1.67 (quint, $J=6.4$ Hz, 4H), 2.44 (t, $J=6.4$ Hz, 4H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 22.8, 24.3, 25.15, 25.20, 25.7, 26.0, 40.7, 212.2.

3.1.2. Cyclohexadecanone (1h). A solution of cyclohexadec-5-enone (11.8 g, 50.0 mmol) (commercially available from Tokyo Kasei Kogyo, TCI Japan) in ethanol (200 ml) was stirred in the presence of Pd/C (5 wt%, 1.18 g) under hydrogen atmosphere at room temperature for 2.5 h. After the reaction was complete, the mixture was filtered through Celite and the filtrate was concentrated in vacuo to give cyclohexadecanone (**1h**)[21] (11.8 g, 49.3 mmol, 99%) as a white solid: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.16–1.38 (m, 22H), 1.64 (quint, $J=6.8$ Hz, 4H), 2.41 (t, $J=6.8$ Hz, 4H).

3.1.3. 2-Chlorocyclooct-1-enecarbaldehyde (2a). To a solution of DMF (1.7 ml, 22.1 mmol) in CH_2Cl_2 (5.0 ml) was added dropwise a solution of phosphorous oxychloride (2.0 ml, 22.0 mmol) in 2.5 ml of CH_2Cl_2 at 0 °C, and the mixture was stirred at room temperature for 30 min. The mixture was cooled down to 0 °C and a solution of cyclooctanone (2.52 g, 20.0 mmol) in CH_2Cl_2 (5.0 ml) was added dropwise at 0 °C. The reaction mixture was heated at 70 °C for 6 h and, then, was poured into ice. The organic layer was separated, the aqueous layer was extracted with CH_2Cl_2, and the combined organic layer was washed with small portions of water, brine and dried over $MgSO_4$. After removal of solvent in vacuo, the residue was distilled (64 °C, 0.3 mmHg) to give chloroaldehyde **2a** (2.92 g, 16.9 mmol) in 84% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44–1.58 (m, 6H), 1.82 (m, 2H), 2.46 (AA′XX′, $J_{AX}+J_{AX'}=12.0$ Hz, 2H), 2.76 (AA′XX′, $J_{AX}+J_{AX'}=12.8$ Hz, 2H), 10.17 (s, 1H). Compound **2a** was reported previously in literature.[22]

3.2. General procedure for the synthesis of 2-chlorocycloalk-1-enecarbaldehyde (2b–h)

To a solution of DMF (4.6 ml, 60.1 mmol) in CH_2Cl_2 (10 ml) was added dropwise a solution of phosphorus oxychloride (9.42 g, 61.4 mmol) in CH_2Cl_2 (10 ml) with ice cooling bath, and the mixture was stirred at room temperature for 30 h. A solution of cycloalkanone **1b–h** (20.1 mmol) in CH_2Cl_2 (10 ml) was added dropwise at 0 °C, and the mixture was stirred at 0 °C for 2 days. Cold water was added and the mixture was extracted with CH_2Cl_2, washed with water and brine, and dried over Na_2SO_4. After removal of solvent in vacuo, the residue gave the crude products of 2-chlorocycloalk-1-enecarbaldehyde (**2b–h**). Compound **2d** was reported previously in literature.[7] Reaction conditions and yields of **2a–h** are summarized in Table 1.

3.2.1. 2-Chlorocyclodec-1-enecarbaldehyde (2b). *Compound* (*Z*)-**2b**. Oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (m, 2H), 1.40–1.52 (m, 6H), 1.62 (m, 2H), 1.90 (br, 2H), 2.53 (t, $J=6.5$ Hz, 2H), 2.83 (br, 2H), 10.29 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.6, 20.8, 24.8, 25.0, 25.2, 25.5, 27.1, 35.7, 135.5, 154.1, 192.4; MS (EI) *m*/*z* (%) 202 (1.1) [M^++2], 200 (3.2) [M^+], 165 (100); HRMS (EI) calcd for $C_{11}H_{17}{}^{35}ClO$ 200.0968, found 200.0971.

3.2.2. 2-Chlorocycloundec-1-enecarbaldehyde (2c). *Compound* (*Z*)-**2c**. Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (m, 2H), 1.27–1.38 (m, 4H), 1.38–1.46 (m, 4H), 1.59 (m, 2H), 1.86 (m, 2H), 2.47 (AA′XX′, $J_{AX}+J_{AX'}=11.9$ Hz, 2H), 2.77 (AA′XX′, $J_{AX}+J_{AX'}=12.2$ Hz, 2H), 10.28 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 23.2, 24.1, 25.2, 25.4, 25.7, 25.8, 32.3, 37.6, 125.5, 154.6, 192.8; MS (EI) *m*/*z* (%) 216 (1.8) [M^++2], 214 (5.3) [M^+], 67 (100). HRMS (EI) calcd for $C_{12}H_{19}{}^{35}ClO$ 214.1124, found 214.1119.

Compound (*E*)-**2c**. Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98–1.18 (m, 3H), 1.18–1.45 (m, 6H), 1.52 (m, 1H), 1.65–1.82 (m, 2H), 1.85–1.99 (m, 2H), 2.40–2.52 (m, 2H), 2.65 (ddd, $J=13.7$, 8.8, 3.9 Hz, 1H), 3.42 (ddd, $J=13.7$, 11.7, 3.4 Hz, 1H), 10.15 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.4, 24.2, 25.07, 25.11, 25.4, 26.4 (2C), 27.0, 35.7, 140.6, 159.2, 188.4. HRMS (EI) calcd for $C_{12}H_{19}{}^{35}ClO$ 214.1124, found 214.1116.

3.2.3. 2-Chlorocyclotridec-1-enecarbaldehyde (2e). *Compound* (*Z*)-**2e**. White solid; mp 38–39 °C (from MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25–1.55 (m, 16H), 1.79 (m, 2H), 2.28 (AA′XX′, $J_{AX}+J_{AX'}=15.4$ Hz, 2H), 2.60 (AA′XX′, $J_{AX}+J_{AX'}=16.1$ Hz, 2H) 10.19 (s, 1H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 24.1, 24.30, 24.34, 24.5, 24.8, 25.0, 25.4, 25.78, 25.84, 26.3, 36.0, 136.2, 154.5, 191.8; MS (EI) *m*/*z* (%) 244 (23) [$M^+ +2$], 242 (73) [M^+], 207 (100); HRMS (EI) calcd for $C_{14}H_{23}{}^{35}ClO$ 242.1437, found 242.1443. Anal. Calcd for $C_{14}H_{23}ClO$: C, 69.26; H, 9.55. Found: C, 69.01; H, 9.56.

Compound (*E*)-**2e**. Obtained as a mixture with (*Z*)-**2e**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 10.03 (s, 1H), and most aliphatic signals are hidden behind those of (*Z*)-**2e** and are unassigned.

3.2.4. 2-Chlorocyclotetradec-1-enecarbaldehyde (2f). *Compound* (*Z*)-**2f**. White solid; mp 42–43 °C (from MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20–1.61 (m, 18H), 1.75 (m, 2H), 2.28 (AA′XX′, $J_{AX}+J_{AX'}=16.6$ Hz, 2H), 2.59 (AA′XX′, $J_{AX}+J_{AX'}=16.6$ Hz, 2H), 10.22 (s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 23.5, 24.0, 24.2, 24.9, 25.1, 25.3, 26.0, 26.4, 26.7, 27.1, 36.1, 136.1, 154.4, 192.1. HRMS (EI) calcd for $C_{15}H_{25}{}^{35}ClO$ 256.1594, found 256.1602. Anal. Calcd for $C_{15}H_{25}ClO$: C, 70.15; H, 9.81. Found: C, 69.78; H, 9.76.

Compound (*E*)-**2f**. Oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.98–1.51 (m, 17H), 1.51–1.75 (m, 2H), 1.85 (m, 1H), 2.43–2.55 (m, 2H), 2.66 (dddd, $J=13.2$, 7.3, 3.4, 1.5 Hz, 1H), 3.47 (ddd, $J=14.4$, 11.7, 3.6 Hz, 1H), 10.04 (d, $J=1.0$ Hz, 1H); MS (EI) *m*/*z* (%) 258 (12) [$M^+ +2$], 256 (39) [M^+] 221 (100). HRMS (EI) calcd for $C_{15}H_{25}{}^{35}ClO$ 256.1594, found 256.1601.

3.2.5. 2-Chlorocyclopentadec-1-enecarbaldehyde (2g). *Compound* (*Z*)-**2g**. Oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25–1.42 (m, 18H), 1.50 (quint, $J=6.8$ Hz, 2H), 1.72 (m, 2H), 2.28 (AA′XX′, $J_{AX}+J_{AX'}=15.8$ Hz, 2H), 2.58 (AA′XX′, $J_{AX}+J_{AX'}=16.7$ Hz, 2H), 10.20 (s, 1H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 25.2, 25.5, 25.9, 25.99, 26.02, 26.2, 26.6, 26.7, 26.9, 27.0, 27.1, 27.4, 37.5, 135.7, 154.3, 191.9; MS (EI) *m*/*z* (%) 272 (15) [$M^+ +2$], 270 (44) [M^+], 235 (100); HRMS (EI) calcd for $C_{16}H_{27}{}^{35}ClO$ 270.1750, found 270.1754.

Compound (*E*)-**2g**. Oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04–1.52 (m, 18H), 1.54–1.69 (m, 3H), 1.81 (m, 1H), 2.44 (ddd, $J=12.4$, 7.5, 3.8 Hz, 1H), 2.49 (ddd, $J=14.5$, 4.7, 4.3 Hz, 1H), 2.66 (ddd, $J=12.4$, 9.4, 3.8 Hz, 1H), 3.44 (ddd, $J=14.5$, 11.3, 3.4 Hz, 1H), 10.03 (s, 1H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 25.6, 26.3, 26.6, 26.7, 26.8, 26.99, 27.04, 27.1, 27.48, 27.53, 27.6, 27.8, 34.6, 140.1, 158.9, 188.2; MS (EI) *m*/*z* (%) 272 (18) [$M^+ +2$], 270 (54) [M^+], 235 (100); HRMS (EI) calcd for $C_{16}H_{27}{}^{35}ClO$ 270.1750, found 270.1755.

3.2.6. 2-Chlorocyclohexadec-1-enecarbaldehyde (2h). *Compound* (*Z*)-**2h**. Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11–1.55 (m, 22H), 1.68 (m, 2H), 2.29 (AA′XX′, $J_{AX}+J_{AX'}=15.1$ Hz, 2H), 2.60 (AA′XX′, $J_{AX}+J_{AX'}=16.1$ Hz, 2H), 10.21 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1, 25.2, 26.07, 26.12, 26.27, 26.34, 26.7, 27.0, 27.3, 27.4, 27.5, 27.6, 28.2, 37.7, 135.8, 154.2, 192.2; MS (EI) *m*/*z* (%) 286 (2.2) [$M^+ +2$], 284 (7.0) [M^+], 55 (100). HRMS (EI) calcd for $C_{17}H_{29}{}^{35}ClO$ 284.1907, found 284.1911.

Compound (*E*)-**2h**. Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15–1.40 (m, 20H), 1.46 (m, 2H), 1.73 (br s, 2H), 2.35–2.60 (br m, 3H), 3.40 (br, 1H), 10.04 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1, 25.2, 26.1, 26.25, 26.31, 26.56, 25.62, 26.93, 26.97, 27.3, 27.4, 27.6, 28.2, 37.7, 135.8, 154.2, 192.1; MS (EI) *m*/*z* (%) 286 (9) [$M^+ +2$], 284 (27) [M^+], 249 (100). HRMS (EI) calcd for $C_{17}H_{29}{}^{35}ClO$ 284.1907, found 284.1902.

3.3. Representative procedure for the synthesis of formylazirine 4a,e–h (Method A)

A solution of (*Z*)-**2a**,**e**–**h** (4.61 mmol) and NaN_3 (412 mg, 6.33 mmol) in 12.5 ml of DMF was stirred at room temperature for 3 h. Water was added and the mixture was extracted with ether. The combined ethereal layer was washed with water and brine and dried over $MgSO_4$. The filtrate was concentrated in vacuo and the residue was dissolved in 25 ml of $CHCl_3$ and was irradiated through Pyrex filter by using ultraviolet lamp ($\lambda_{max}=365$ nm) for 8 h. After removal of solvent in vacuo, the residue was chromatographed on silica gel by using $CHCl_3$–hexane (1/3) to give azirine **4a**,**e**–**h**. See Table 2 for reaction conditions and yields of **4a**,**e**–**h**.

3.3.1. 9-Azabicyclo[6.1.0]non-8-ene-1-carbaldehyde (4a). Oil; bp 95–96 °C (0.3 mmHg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (m, 1H), 1.36–1.50 (m, 3H), 1.53–1.74 (m, 4H), 2.00 (m, 1H), 2.47 (ddd, $J=15.8$, 11.5, 2.1 Hz, 1H), 2.72 (ddd, $J=15.0$, 10.1, 5.1 Hz, 1H), 3.14 (ddd, $J=15.0$, 6.4, 4.3 Hz, 1H), 8.80 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.6, 23.3, 24.9, 26.6, 27.8, 28.1, 48.8, 168.2, 200.8; MS (EI) *m*/*z* (%) 151 (4) [M^+], 150 (19), 81 (100); HRMS (EI) calcd for $C_9H_{13}NO$ 151.0997, found 151.0996.

3.3.2. 14-Azabicyclo[11.1.0]tetradec-13-ene-1-carbaldehyde (4e). White solid; mp 62–63 °C (from hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (m, 1H), 1.19–1.52 (m, 16H), 1.74 (m, 1H), 2.00 (m, 1H), 2.35 (ddd, $J=14.6$, 8.3, 6.3 Hz, 1H), 2.90 (ddd, $J=17.2$, 6.9, 5.0 Hz, 1H), 3.02 (ddd, $J=17.2$, 9.2, 4.5 Hz, 1H), 8.77 (s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 23.5, 23.7, 24.1, 24.4, 24.5, 25.7 (2C), 25.8, 27.0 (2C), 27.7, 49.0, 167.9, 200.9; MS (EI) *m*/*z* (%) 221 (74) [M^+], 192 (100); HRMS (EI) calcd for $C_{14}H_{23}NO$ 221.1780, found 221.1789. Anal. Calcd for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 75.78; H, 10.67; N, 6.17.

3.3.3. 15-Azabicyclo[12.1.0]pentadec-14-ene-1-carbaldehyde (4f). Yellow solid; mp 38–39 °C (from hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20–1.59 (m, 18H), 1.64–1.80 (m, 2H), 1.98 (dtt, $J=12.7$, 8.3, 6.3 Hz, 1H), 2.10 (ddd, $J=15.1$, 8.3, 6.1 Hz, 1H), 2.87 (ddd, $J=17.1$, 8.3, 5.4 Hz, 1H), 2.96 (ddd, $J=17.1$, 7.8, 5.4 Hz, 1H), 8.76 (s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 23.4, 23.9, 25.3, 25.48, 25.54, 25.9, (2C), 26.1, 26.6, 27.19, 27.23, 27.5, 48.9, 168.0, 200.9; MS (EI) m/z (%) 235 (100) [M^+]. HRMS (EI) calcd for $C_{15}H_{25}NO$ 235.1936, found 235.1935. Anal. Calcd for $C_{15}H_{25}NO$: C, 76.55; H, 10.71; N, 5.95. Found: C, 75.98; H, 10.76; N, 5.53.

3.3.4. 16-Azabicyclo[13.1.0]hexadec-15-ene-1-carbaldehyde (4g). Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15–1.42 (m, 19H), 1.51 (m, 1H), 1.66 (ddd, J=15.1, 8.8, 6.3 Hz, 1H), 1.75 (dt, J=15.1, 7.3 Hz, 1H), 1.85 (dtt, J=15.1, 7.8, 6.4 Hz, 1H), 2.03 (ddd, J=14.6, 9.3, 7.3 Hz, 1H), 2.88 (dt, J=16.1, 8.1 Hz, 1H), 2.91 (dt, J=16.1, 8.1 Hz, 1H), 8.75 (s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 23.4, 24.3, 25.77, 25.83, 25.91, 25.93, 26.0, 26.2, 26.5, 27.1, 27.4, 27.7, 27.8, 49.1, 167.8, 200.5; MS (EI) *m/z* (%) 249 (100) [M^+]; HRMS (EI) calcd for $C_{16}H_{27}NO$ 249.2093, found 249.2092.

3.3.5. 17-Azabicyclo[14.1.0]heptadec-16-ene-1-carbaldehyde (4h). Yellow solid; mp 32–33 °C (from hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10–1.43 (m, 20H), 1.43–1.54 (m, 2H), 1.69 (ddd, J=14.6, 9.0, 6.8 Hz, 1H), 1.76 (dt, J=14.6, 6.8 Hz, 1H), 1.91 (d×quint, J=14.0, 7.2 Hz, 1H), 2.05 (ddd, J=14.6, 8.0, 6.8 Hz, 1H), 2.88 (t, J=6.8 Hz, 2H), 8.76 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 24.3, 26.2, 26.3, 26.39, 26.42, 26.5, 26.9 (2C), 27.3, 27.6, 27.69, 27.74, 27.9, 48.9, 168.0, 200.7; MS (EI) *m/z* (%) 263 (100), [M^+]. HRMS (EI) calcd for $C_{17}H_{29}NO$ 263.2249, found 263.2249.

3.4. Representative procedure for the synthesis of formylazirine 4b–d (Method B)

To a solution of (*Z*)-**2b–d** (10.0 mmol) in THF (20 ml) were added NaN_3 (812 mg, 12.5 mmol), LiCl (42.4 mg, 1.00 mmol), and 60 μl of H_2O, and the mixture was stirred at room temperature for 5 h. After white precipitate was filtered off, the filtrate was concentrated in vacuo and the residue was dissolved in ether (30 ml). The white solid was precipitated again, filtered off, and washed several times with ether. The filtrate was concentrated in vacuo to give a crude mixture of the products containing *trans*-2-azidocycloalk-1-enecarbaldehyde **3b–d** and formyl azirine **4b–d**. The mixture was dissolved in $CHCl_3$ (40 ml) and was irradiated through Pyrex filter by using ultraviolet lamp (λ_{max}=365 nm) for 8 h. The conversion of *trans*-azide was monitored successfully with TLC on silica gel by using $CHCl_3$–hexane (2/1) as a developer. After removal of solvent in vacuo, the residue was chromatographed on silica gel by using ether–hexane (1/4) to give azirine **4b–d**. See Table 2 for reaction conditions and yields of **4b–d**. Compound **4d** was reported previously in literature.[7]

3.4.1. 11-Azabicyclo[8.1.0]undec-10-ene-1-carbaldehyde (4b). Oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20–1.68 (m, 10H), 1.71 (ddd, J=15.4, 9.4, 2.1 Hz, 1H), 1.94 (m, 2H), 2.38 (ddd, J=15.4, 8.6, 2.1 Hz, 1H), 2.92 (ddd, J=16.7, 8.1, 4.3 Hz, 1H), 3.08 (ddd, J=16.7, 7.7, 4.3 Hz, 1H), 8.82 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.5, 22.4, 23.2, 23.8, 26.4, 26.5, 27.0, 28.4, 49.0, 169.4, 201.4; MS (EI) *m/z* (%) 179 (49) [M^+], 150 (100); HRMS (EI) calcd for $C_{11}H_{17}NO$ 179.1310, found 139.1312.

3.4.2. 12-Azabicyclo[9.1.0]dodec-11-ene-1-carbaldehyde (4c). White solid; mp 43–44 °C (from hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12–1.52 (m, 12H), 1.57 (m, 1H), 1.87 (m, 2H), 2.48 (dt, J=14.6, 7.3 Hz, 1H), 2.95 (ddd, J=15.6, 6.8, 5.4 Hz, 1H), 3.10 (ddd, J=15.6, 7.3, 5.4 Hz, 1H), 8.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.72, 22.3, 22.9, 23.1, 24.2, 25.3, 25.5, 27.7 (2C), 49.0, 169.2, 201.1; MS (EI) *m/z* (%) 193 (16) [M^+], 164 (100). HRMS (EI) calcd for $C_{12}H_{19}NO$ 193.1467, found 193.1462. Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.31; H, 10.00; N, 7.18.

3.5. General procedure for the synthesis of iminophosphorane 5a–h

A solution of azirine **4a–h** (18.8 mmol) and PPh_3 (5.03 g, 19.2 mmol) in toluene (20 ml) was heated at reflux for 3 h. After the reaction mixture was concentrated in vacuo, yellow solid precipitated in ether was filtered to give iminophosphorane **5a–h**. Compound **5d** was reported previously in literature.[7]

3.5.1. 2-(Triphenylphosphoranylideneamino)cyclooct-1-enecarbaldehyde (5a). Yield 99%; *Z*-form only; mp 175–176 °C (from toluene); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (m, 2H), 1.34–1.43 (m, 4H), 1.53 (m, 2H), 2.23 (t, J=6.7 Hz, 2H), 2.44 (t, J=6.1 Hz, 2H), 7.48 (td, J_{H-H}=7.3 Hz, J_{P-H}=3.1 Hz, 6H), 7.56 (ttd, J_{H-H}=7.3, 1.8 Hz, J_{P-H}=1.2 Hz, 3H), 7.74 (ddd, J_{H-H}=7.3, 1.8 Hz, J_{P-H}=12.8 Hz, 6H), 10.69 (s, 1H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 23.4 (d, J_{P-C}=2.5 Hz), 26.1, 26.8, 28.6, 30.4, 35.5 (d, J_{P-C}=8.7 Hz), 122.1 (d, J_{P-C}=17.4 Hz), 128.6 (d, J_{P-C}=12.5 Hz, 6C), 131.0 (d, J_{P-C}=102.1 Hz, 3C), 132.0 (d, J_{P-C}=3.1 Hz, 3C), 132.2 (d, J_{P-C}=10.0 Hz, 6C), 171.9, 189.7; MS (EI) *m/z* (%) 413 (44) [M^+], 262 (100); HRMS (EI) calcd for $C_{27}H_{28}NOP$ 413.1908, found 413.1908. Anal. Calcd for $C_{27}H_{28}NOP$: C, 78.43; H, 6.82; N, 3.39. Found: C, 78.21; H, 6.86; N, 3.31.

3.5.2. 2-(Triphenylphosphoranylideneamino)cyclodec-1-enecarbaldehyde (5b). Yield 78%; *E*/*Z*=25:75; mp 162–164 °C (from toluene); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.59 (m, 1H, *E*), 0.96 (m, 1H, *E*), 1.01–1.09 (m, 2H, *E*), 1.15 (m, 2H, *Z*), 1.28–1.43 (m, 8H, *Z*), 1.66 (m, 2H, *Z*), 1.80–1.94 (m, 2H, *E*), 2.27 (br, 2H, *Z*), 2.47 (t, J=6.1 Hz, 2H, *Z*), 2.75–2.85 (m, 2H, *E*), 3.20–3.27 (m, 1H, *E*), 7.46 (ddd, J_{H-H}=7.9, 7.3 Hz, J_{P-H}=3.1 Hz, 6H, *Z*), 7.50 (ddd, J_{H-H}=7.9, 7.3 Hz, J_{P-H}=3.1 Hz, 6H, *E*), 7.55 (td, J_{H-H}=7.9 Hz, J_{P-H}=1.2 Hz, 3H, *Z*), 7.58 (td, J_{H-H}=7.9 Hz, J_{P-H}=1.8 Hz, 3H, *E*), 7.71 (dd, J_{H-H}=7.3 Hz, J_{P-H}=12.2 Hz, 6H, *Z*), 7.78 (dd, J_{H-H}=7.3 Hz, J_{P-H}=12.2 Hz, 6H, *E*), 9.84 (s, 1H, *E*), 10.63 (s, 1H, *Z*) and the other signals of *E*-form (7H) are hidden behind those of (*Z*)-form; ^{13}C NMR (76 MHz, $CDCl_3$) δ 21.4 (*E*), 22.0 (*Z*), 22.3 (*Z*), 23.0 (*E*), 23.1 (*E*), 23.4 (*E*), 24.9 (d, J_{P-C}=1.2 Hz, *Z*), 25.5 (*E*), 25.9 (*E*), 26.0 (*Z*), 26.37 (*Z*), 26.42 (*Z*), 26.6 (*E*), 26.8 (*Z*), 33.2 (d, J_{P-C}=6.2 Hz, *Z*), 34.4 (d, J_{P-C}=9.3 Hz, *E*), 122.9 (d, J_{P-C}=15.6 Hz, *Z*), 126.3 (d, J_{P-C}=21.9 Hz, *E*), 128.6 (d, J_{P-C}=12.5 Hz, 6C, *Z*), 128.7 (d, J_{P-C}=10.6 Hz, 6C, *E*), 130.7, (d, J_{P-C}=101.5 Hz, 3C, *E*), 131.4 (d, J_{P-C}=102.8 Hz, 3C, *Z*), 131.9 (d, J_{P-C}=2.5 Hz, 3C, *Z*), 132.2 (d, J_{P-C}=3.1 Hz, 3C, *E*), 132.3 (d, J_{P-C}=10.0 Hz, 6C, *Z*), 132.5 (d, J_{P-C}=10.6 Hz, 6C, *E*), 170.9 (*Z*), 173.1 (*E*), 187.7 (*E*), 191.9 (*Z*); MS (EI) *m/z* (%) 441 (10) [M^+], 262 (100); HRMS (EI) calcd for $C_{29}H_{32}NOP$ 441.2221, found 441.2227. Anal. Calcd for $C_{29}H_{32}NOP$: C, 78.29; H, 7.51; N, 3.26. Found: C, 78.50; H, 7.33; N, 3.12.

3.5.3. 2-(Triphenylphosphoranylideneamino)cycloundec-1-enecarbaldehyde (5c). Yield 80%; *E*/*Z*=94:6; yellow

solid; mp 171.9–172.4 °C (from toluene); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (m, 1H), 1.04 (m, 1H), 1.09–1.36 (m, 8H), 1.46–1.67 (m, 3H), 1.77 (m, 1H), 2.17 (m, 1H), 2.71 (ddd, J=13.2, 9.8, 3.0 Hz, 1H), 2.79 (ddd, J=13.2, 7.5, 3.1 Hz, 1H), 3.13 (td, J=12.4, 0.4 Hz, 1H), 7.49 (dddd, J_{H-H}=7.5, 7.0, 1.5 Hz, J_{P-H}=3.0 Hz, 6H), 7.57 (tq, J_{H-H}=7.5, 1.5 Hz, J_{P-H}=1.5 Hz, 3H), 7.77 (dtd, J_{H-H}=7.0, 1.5 Hz, J_{P-H}=12.4 Hz, 6H), 9.93 (s, 1H) and most signals for (*Z*)-**5c** were overlapped with (*E*)-**5c** except for δ 1.39 (m, 4H), 2.26 (t, J=6.8 Hz, 2H), 7.71 (dtd, J_{H-H}=7.1, 1.5 Hz, J_{P-H}=12.1 Hz, 6H) and 10.57 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.55, 23.64, 24.3, 24.9, 26.55, 26.63 (2C), 26.9, 34.3 (d, J_{P-C}=8.6 Hz), 127.5 (d, J_{P-C}=20.1 Hz) 128.7 (d, J_{P-C}=12.5 Hz, 6C), 131.2 (d, J_{P-C}=102.6 Hz, 3C), 132.1 (d, J_{P-C}=2.9 Hz, 3C), 132.5 (d, J_{P-C}=10.5 Hz, 6C), 173.2, 188.4 (d, J_{P-C}=3.8 Hz); MS (EI) *m*/*z* (%) 455 (15) [M^+], 262 (100). HRMS (EI) calcd for $C_{30}H_{34}NOP$ 455.2378, found 455.2381.

3.5.4. 2-(Triphenylphosphoranylideneamino)cyclododec-1-enecarbaldehyde (5d).[7] Yield 91% (reported as 84% yield in our previous work); *E*/*Z*=75:25.

3.5.5. 2-(Triphenylphosphoranylideneamino)cyclotridec-1-enecarbaldehyde (5e). Yield 88%; *E*/*Z*=67:33; yellow solid; mp 197–199 °C (from ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75–0.93 (m, 1H for *E* and 2H for *Z*), 0.93–1.62 (m, 16H each, *E* and *Z*), 1.62–1.87 (m, 2H, *E*), 1.98 (AA′XX′, $J_{AX}+J_{AX'}$=17.4 Hz, 2H, *Z*), 2.16 (br AA′XX′, $J_{AX}+J_{AX'}$=14.9 Hz, 2H, *Z*), 2.64 (ddd, J=12.5, 10.6, 2.2 Hz, 1H, *E*), 2.79 (ddd, J=12.5, 6.3, 2.6 Hz, 1H, *E*), 3.05 (ddd, J=11.0, 10.7, 2.6 Hz, 1H, *E*), 7.43–7.53 (m, 6H each, *E* and *Z*), 7.53–7.61 (m, 3H each, *E* and *Z*), 7.72 (dddd, J_{H-H}=7.0, 2.0, 1.5 Hz, J_{P-H}=12.1 Hz, 6H, *Z*), 7.77 (dddd, J_{H-H}=6.8, 2.0, 1.5 Hz, J_{P-H}=12.3 Hz, 6H, *E*), 9.85 (s, 1H, *E*), 10.66 (s, 1H, *Z*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 22.0 (*Z*), 22.9 (*E*), 23.6 (*E*), 23.9 (*Z*), 24.0 (3C, *Z*), 24.1 (*Z*), 24.2 (*E*), 24.7 (*E*), 25.2 (*E*), 25.3 (*E*), 25.5 (*Z*), 26.3, (*Z*), 26.7 (*Z*), 26.8 (*E*), 26.9 (*Z*), 27.1 (*E*), 27.4 (*E*), 28.1 (*E*), 32.7 (d, J_{P-C}=8.1 Hz, *E*), 35.4 (d, J_{P-C}=7.3 Hz, *Z*), 122.3 (d, J_{P-C}=16.9 Hz, *Z*), 127.0 (d, J_{P-C}=20.1 Hz, *E*), 128.7 (d, J_{P-C}=12.1 Hz, 6C, *E*), 128.8 (d, J_{P-C}=12.1 Hz, 6C, *Z*), 131.0 (d, J_{P-C}=102.3 Hz, 3C, *E*), 131.2 (d, J_{P-C}=102.3 Hz, 3C, *Z*), 132.10 (d, J_{P-C}=3.2 Hz, 3C, *Z*), 132.13 (d, J_{P-C}=3.2 Hz, 3C, *E*), 132.5 (d, J_{P-C}=10.5 Hz, 6C, *Z*), 132.6 (d, J_{P-C}=10.5 Hz, 6C, *E*), 171.8 (*Z*), 172.3 (*E*), 188.3 (d, J_{P-C}=4.0 Hz, *E*), 190.6 (*Z*); MS (EI) *m*/*z* (%) 483 (13.5) [M^+], 262 (100); HRMS (EI) calcd for $C_{32}H_{38}NOP$ 483.2691, found 483.2689. Anal. Calcd for $C_{32}H_{38}NOP$: C, 79.47; H, 7.92; N, 2.90. Found: C, 79.15; H, 8.05; N, 2.88.

3.5.6. 2-(Triphenylphosphoranylideneamino)cyclotetradec-1-enecarbaldehyde (5f). Yield 76%; *E*/*Z*=68:32; yellow solid; mp 171–173 °C (from toluene); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.77 (m, 2H, *Z*), 0.94–1.51 (m, 18H each, *E* and *Z*), 1.53–1.70 (m, 2H, *E*), 1.79 (m, 1H, *E*), 2.07 (AA′XX′, $J_{AX}+J_{AX'}$=17.4 Hz, 2H, *Z*), 2.21 (AA′XX′, $J_{AX}+J_{AX'}$=15.6 Hz, 2H, *Z*), 2.68 (ddd, J=12.8, 8.1, 3.3 Hz, 1H, *E*), 2.90 (ddd, J=12.8, 8.8, 3.1 Hz, 1H, *E*), 3.08 (m, 1H, *E*), 7.44–7.51 (m, 6H each, *E* and *Z*), 7.53–7.60 (m, 3H each, *E* and *Z*), 7.72 (ddd, J_{H-H}=8.2, 1.1 Hz, J_{P-H}=12.3 Hz, 6H, *Z*), 7.77 (ddd, J_{H-H}=8.3, 1.3 Hz, J_{P-H}=12.5 Hz, 6H, *E*), 9.85 (s, 1H, *E*), 10.71 (s, 1H, *Z*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.7 (*Z*), 23.9 (*E*), 24.13 (*Z*), 24.2 (*E*), 24.3 (*E*), 24.76 (*E*), 24.81 (*Z*), 24.9 (*Z*), 25.0 (*Z*), 25.1 (*Z*), 25.4 (*Z*), 25.5 (*E*), 25.9 (*E*), 26.0 (*Z*), 26.4 (*E*), 26.91 (*Z*), 26.93 (*E*), 27.25 (*Z*), 27.33 (*E*), 27.6 (*Z*), 28.0 (*E*), 28.8 (*E*), 32.3 (d, J_{P-C}=7.2 Hz, *E*), 36.9 (d, J_{P-C}=8.3 Hz, *Z*), 122.8 (d, J_{P-C}=15.5 Hz, *Z*), 126.0 (d, J_{P-C}=19.7 Hz, *E*), 128.68 (d J_{P-C}=12.4 Hz, 6C, *E*), 128.70 (d, J_{P-C}=12.4 Hz, 6C, *Z*), 130.9 (d, J_{P-C}=102.4 Hz, 3C, *E*), 131.2 (d, J_{P-C}=102.4 Hz, 3C, *Z*), 132.0 (d, J_{P-C}=3.1 Hz, 3C, *Z*), 132.1 (d, J_{P-C}=3.1 Hz, 3C, *E*), 132.36 (d, J_{P-C}=9.3 Hz, 6C, *Z*), 132.44 (d, J_{P-C}=10.3 Hz, 6C, *E*), 171.3 (*Z*), 171.8 (*E*), 188.3 (d, J_{P-C}=5.2 Hz, *E*), 191.3 (*Z*); MS (EI) *m*/*z* (%) 497 (9) [M^+] 262 (100). HRMS (EI) calcd for $C_{33}H_{40}NOP$ 497.2848, found 497.2850. Anal. Calcd for $C_{33}H_{40}NOP$: C, 79.64; H, 8.10; N, 2.81. Found: C, 79.83; H, 8.22; N, 2.69.

3.5.7. 2-(Triphenylphosphoranylideneamino)cyclopentadec-1-enecarbaldehyde (5g). Yield 85%; *E*/*Z*=67:33; mp 173–176 °C (from toluene); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.70 (m, 2H, *Z*), 0.87–1.65 (m, 22H for *E* and 19H for *Z*), 1.78 (m, 1H, *E*), 2.06 (AA′XX′, $J_{AX}+J_{AX'}$=17.3 Hz, 2H, *Z*), 2.20 (AA′XX′, $J_{AX}+J_{AX'}$=15.0 Hz, 2H, *Z*), 2.71 (ddd, J=12.8, 9.2, 3.7, 1H, *E*), 2.78 (ddd, J=12.8, 5.9, 4.0 Hz, 1H, *E*), 3.04 (ddd, J=13.4, 10.3, 3.3 Hz, 1H, *E*), 7.43–7.61 (m, 9H each, *E* and *Z*), 7.71 (dtd, J_{H-H}=7.0, 1.5 Hz, J_{P-H}=12.5 Hz, 6H, *Z*), 7.75 (dddd, J_{H-H}=7.0, 1.7, 1.5 Hz, J_{P-H}=12.5 Hz, 6H, *E*), 9.85 (s, 1H, *E*), 10.67 (s, 1H, *Z*); ^{13}C NMR (76 MHz, $CDCl_3$) δ 23.9 (*E*), 24.5 (*Z*), 24.7 (*Z*), 24.8 (d, J_{P-C}=1.2 Hz, *Z*), 24.9 (*E*), 25.7 (*Z*), 25.8 (*Z*), 26.1 (*E*), 26.17 (*Z*), 26.24 (*Z*), 26.46 (*E*), 26.51 (*Z*), 26.7 (*E*), 26.9 (*E*), 27.0 (*E*), 27.1 (*Z*), 27.21 (*E*), 27.25 (*E*), 27.9 (*Z*), 28.0 (*E*), 28.3 (*E*), 28.9 (*E*), 31.9 (d, J_{P-C}=8.1 Hz, *E*), 37.1 (d, J_{P-C}=7.5 Hz, *Z*), 122.5 (d, J_{P-C}=16.8 Hz, *Z*), 125.4 (d, J_{P-C}=20.6 Hz, *E*), 128.5 (d, J_{P-C}=12.5 Hz, 6C each, *E* and *Z*), 130.4 (d, J_{P-C}=102.1 Hz, 3C, *E*), 130.9 (d, J_{P-C}=101.5 Hz, 3C, *Z*), 131.8 (d, J_{P-C}=3.1 Hz, 3C, *Z*), 132.0 (d, J_{P-C}=2.5 Hz, 3C. *E*), 132.1 (d, J_{P-C}=10.0 Hz, 6C, *Z*), 132.2 (d, J_{P-C}=10.6 Hz, 6C, *E*), 171.4 (1C each, *E* and *Z*), 187.9 (d, J_{P-C}=3.7 Hz, *E*), 190.8 (*Z*) and two signals of *Z*-form are overlapped; MS (EI) *m*/*z* (%) 511 (28) [M^+], 262 (100); HRMS (EI) calcd for $C_{34}H_{42}NOP$ 511.3004, found 511.3004. Anal. Calcd for $C_{34}H_{42}NOP$: C, 79.81; H, 8.27; N, 2.74. Found: C, 79.57; H, 8.31; N, 2.73.

3.5.8. 2-(Triphenylphosphoranylideneamino)cyclohexadec-1-enecarbaldehyde (5h). Yield 85%; *E*/*Z*=56:44; white solid; mp 97–98 °C (from toluene); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76 (m, 2H, *Z*), 0.85–0.98 (m, 1H for *E* and 2H for *Z*), 1.12–1.44 (m, 22H for *E* and 18H for *Z*), 1.55–1.76 (m, 2H each, *E* and *Z*), 2.07 (AA′XX′, $J_{AX}+J_{AX'}$=17.1 Hz, 2H, *Z*), 2.21 (br AA′XX′, $J_{AX}+J_{AX'}$=16.6 Hz, 2H, *Z*), 2.65 (ddd, J=12.7, 8.1, 5.1 Hz, 1H, *E*), 2.82 (ddd, J=12.7, 6.7, 5.4 Hz, 1H, *E*), 3.07 (ddd, J=13.0, 9.8, 5.6 Hz, 1H, *E*), 7.43–7.52 (m, 6H each, *E* and *Z*), 7.53–7.61 (m, 3H each, *E* and *Z*), 7.68–7.79 (m, 6H each, *E* and *Z*), 9.85 (s, 1H, *E*), 10.70 (s, 1H, *Z*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.2, 25.2, 25.4, 25.8, 26.1, 26.30, 26.32 (2C), 26.4, 26.6, 26.7, 26.8, 26.98, 27.01, 27.1, 27.4, 27.5 (2C), 27.7, 27.90, 27.93, 28.0, 28.4, 28.6, 29.3, 29.7, 32.9 (d, J_{P-C}=8.3 Hz), 37.7 (d, J_{P-C}=8.3 Hz), 122.8 (d, J_{P-C}=17.6 Hz), 125.8 (d, J_{P-C}=21.2 Hz), 128.7 (d, J_{P-C}=9.9 Hz), 130.9 (d, J_{P-C}=102.6 Hz), 131.3 (d,

J_{P-C}=102.6 Hz), 132.1, 132.2, 132.4 (d, J_{P-C}=9.9 Hz), 132.5 (d, J_{P-C}=9.9 Hz), 171.3, 171.9, 188.1 (d, J_{P-C}=3.3 Hz), 191.4; MS (EI) *m/z* (%) 525 (28) [M^+], 262 (100). HRMS (EI) calcd for $C_{35}H_{44}NOP$ 525.3161, found 525.3154.

3.6. Reaction of 5 with methyl propiolate

Method A. Representative procedure. A solution of iminophosphorane **5g** (4.06 g, 7.93 mmol) and methyl propiolate (6.87 g, 81.7 mmol) in toluene (25 ml) was heated at 140 °C in an autoclave reactor for 12 h. After the mixture was concentrated in vacuo, the residue was separated by flash chromatographed on silica gel (FL60D, Fuji Silysia Chemical Ltd) by using ether–hexane (1/5) to give nicotinates **6g** (741 mg, 2.34 mmol) and **7g** (70.8 mg, 0.223 mmol) in 30 and 3% yields, respectively.

Method B. Representative procedure. A solution of iminophosphorane **5d** (4.70 g, 10.0 mmol) and methyl propiolate (4.21 g, 50.0 mmol) in acetonitrile (30 ml) was heated at 120 °C in an autoclave reactor for 10 h. After removal of solvent and excess methyl propiolate in vacuo, the residue was chromatographed on silica gel (silica gel 60 N spherical, neutral, 40–50 μm, KANTO chemical Co., Inc.) by using acetone–toluene (1/19) to afford a crude mixture of nicotinates **6d** and **7d**. The mixture was further purified by flash chromatography on silica gel (FL60D, Fuji Silysia Chemical Ltd) by using ether–hexane (1/5) to give nicotinates **6d** (688 mg, 2.50 mmol) and **7d** (408 mg, 1.48 mmol) in 25 and 15% yields, respectively.

Compounds **6d** and **7d** were reported previously in literature.[7] See Table 3 for reaction conditions and yields of **6b–h** and **7a–h**.

3.6.1. Methyl [8](2,5)pyridinophane-3-carboxylate (6b). Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.27 (m,1H), 0.14 (m, 1H), 0.41–0.60 (m, 2H), 0.86–1.15 (m, 4H), 1.15–1.39 (m, 2H), 1.58–1.83 (m, 2H), 2.66 (ddd, J=13.0, 8.8, 4.8 Hz, 1H), 2.73 (ddd, J=12.7, 9.9, 4.7 Hz, 1H), 2.75 (ddd, J=13.0, 6.4, 4.8 Hz, 1H), 3.87 (ddd, J=12.7, 6.2, 4.2 Hz, 1H), 3.93 (s,3H), 8.02 (d, J=1.8 Hz, 1H), 8.43 (d, J=1.8 Hz, 1H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 25.3, 25.4, 28.0, 28.7, 29.6, 30.6, 32.3, 36.6, 52.2, 124.8, 133.9, 138.5, 150.6, 163.0, 167.0; MS (EI) *m/z* (%) 247 (100) [M^+]; HRMS (EI) calcd for $C_{15}H_{21}NO_2$ 247.1572, found 247.1579.

3.6.2. Methyl [9](2,5)pyridinophane-3-carboxylate (6c). Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.19 (m, 1H), 0.31 (m, 1H), 0.47 (m, 1H), 0.58–0.85 (m, 3H), 0.85–1.12 (m, 4H), 1.28–1.63 (m, 3H), 1.70 (m, 1H), 2.55 (ddd, J=13.2, 8.2, 4.4 Hz, 1H), 2.76–2.85 (m, 2H), 3.79 (ddd, J=12.2, 7.3, 4.4 Hz, 1H), 3.94 (s, 3H), 7.97 (d, J=2.0 Hz, 1H), 8.50 (d, J=2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 23.7, 25.5, 27.4, 27.6, 28.6, 29.7, 32.3, 35.8, 52.3, 125.1, 134.4, 138.6, 151.9, 161.5, 167.3; MS (EI) *m/z* (%) 261 (100) [M^+]. HRMS (EI) calcd for $C_{16}H_{23}NO_2$ 261.1729, found 261.1728.

3.6.3. Methyl [11](2,5)pyridinophane-3-carboxylate (6e). Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.55–1.01 (m, 10H), 1.14 (m, 1H), 1.19–1.30 (m, 3H), 1.61–1.74 (m, 3H), 1.83 (m, 1H), 2.62 (ddd, J=13.2, 8.4, 3.2 Hz, 1H), 2.68 (ddd, J=13.2, 8.0, 3.6 Hz, 1H), 2.77 (ddd, J=12.5, 9.4, 3.6 Hz, 1H), 3.74 (ddd, J=12.5, 8.6, 3.6 Hz, 1H), 3.93 (s, 3H), 7.97 (d, J=2.3 Hz, 1H), 8.49 (d, J=2.3 Hz, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 25.3, 25.8, 26.4, 26.7, 27.2, 27.77, 27.82, 28.0, 28.5, 32.5, 36.0, 52.3, 125.3, 135.2, 138.6, 151.9, 161.3, 167.3; MS (EI) *m/z* (%) 289 (62) [M^+], 230 (100); HRMS (EI) calcd for $C_{18}H_{27}NO_2$ 289.2042, found 289.2055.

3.6.4. Methyl [12](2,5)pyridinophane-3-carboxylate (6f). Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77–0.90 (m, 6H), 0.96–1.17 (m, 10H), 1.63 (m, 2H), 1.71 (quint, J=6.6 Hz, 2H), 2.68 (AA′XX′, $J_{AX}+J_{AX'}$=12.2 Hz, 2H), 3.26 (br, 2H), 3.93 (s, 3H), 7.94 (d, J=2.2 Hz, 1H), 8.47 (d, J=2.2 Hz, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 24.7, 25.7, 25.9, 26.2, 26.8, 26.9, 27.36, 27.40, 28.6, 29.2, 31.7, 35.4, 52.1, 125.3, 134.7, 138.3, 151.9, 161.4, 167.4; MS (EI) *m/z* (%) 303 (52) [M^+] 244 (100). HRMS (EI) calcd for $C_{19}H_{29}NO_2$ 303.2198, found 303.2190.

3.6.5. Methyl [13](2,5)pyridinophane-3-carboxylate (6g). Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (m, 2H), 0.92–1.19 (m, 16H), 1.67 (m, 2H), 1.75 (m, 2H), 2.66 (AA′XX′, $J_{AX}+J_{AX'}$=12.2 Hz, 2H), 3.24 (AA′XX′, $J_{AX}+J_{AX'}$=12.2 Hz, 2H), 3.93 (s, 3H), 7.94 (d, J=2.4 Hz, 1H), 8.48 (d, J=2.4 Hz, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 25.8, 26.5, 26.6, 27.2, 27.3, 27.4, 27.7 (2C), 27.9, 28.6, 29.2, 31.8, 35.6, 52.2, 125.4, 134.6, 138.4, 153.1, 160.9, 167.6; MS (EI) *m/z* (%) 317 (100) [M^+]; HRMS (EI) calcd for $C_{20}H_{31}NO_2$ 317.2355, found 317.2363.

3.6.6. Methyl [14](2,5)pyridinophane-3-carboxylate (6h). Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88–1.13 (m, 12H), 1.14–1.35 (m, 8H), 1.67 (m, 2H), 1.74 (m, 2H), 2.69 (AA′XX′, $J_{AX}+J_{AX'}$=12.2 Hz, 2H), 3.24 (AA′XX′, $J_{AX}+J_{AX'}$=12.2 Hz, 2H), 3.92 (s, 3H), 7.93 (d, J=2.2 Hz, 1H), 8.47 (d, J=2.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 25.5, 26.3 (2C), 27.0, 27.3, 27.36, 27.44, 28.0 (2C), 28.5, 29.1, 31.4, 35.0, 52.2, 125.5, 134.2, 138.3, 152.0, 160.5, 167.6; MS (EI) m/z (%) 331 (100) [M^+]. HRMS (EI) calcd for $C_{21}H_{33}NO_2$ 331.2511, found 331.2512.

3.6.7. Methyl 5,6,7,8,9,10-hexahydrocycloocta[*b*]pyridine-3-carboxylate (7a). Oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33–1.43 (m 4H), 1.73 (m, 2H), 1.82 (m, 2H), 2.83 (AA′XX′, $J_{AX}+J_{AX'}$=12.8 Hz, 2H), 3.03 (AA′XX′, $J_{AX}+J_{AX'}$=12.5 Hz, 2H), 3.93 (s, 3H), 7.99 (d, J=2.2 Hz, 1H), 8.98 (d, J=2.2 Hz, 1H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 25.8, 25.9, 30.5, 31.8, 32.0, 34.8, 52.2, 123.9, 136.1, 137.4, 148.3, 166.0, 166.3; MS (EI) *m/z* (%) 219 (100) [M^+], 190 (98); HRMS (EI) calcd for $C_{13}H_{17}NO_2$ 219.1259, found 219.1253.

3.6.8. Methyl 5,6,7,8,9,10,11,12-octahydrocyclodeca[*b*]-pyridine-3-carboxylate (7b). White solid; mp 61–63 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.06–1.17 (m, 4H), 1.46–1.54 (m, 4H), 1.85 (tt, J=6.4, 6.0 Hz, 2H), 2.00 (m, 2H), 2.91 (t, J=6.4 Hz, 2H), 3.06 (m, 2H), 3.94 (s, 3H), 8.06 (d, J=1.8 Hz, 1H), 9.02 (d, J=1.8 Hz, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 20.5, 21.1, 26.1, 26.7, 28.3, 28.8, 29.1, 31.9, 52.2, 123.3, 135.5, 137.6, 147.8, 165.1, 166.1; MS (EI) *m/z* (%) 247 (34) [M^+], 204 (100); HRMS (EI)

calcd for $C_{15}H_{21}NO_2$ 247.1572, found 247.1573. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.86; H, 8.56; N, 5.66. Found: C, 72.36; H, 8.56; N, 5.24.

3.6.9. Methyl methyl 6,7,8,9,10,11,12,13-octahydrocycloundeca[*b*]pyridine-3-carboxylate (7c). White solid; mp 97–98 °C (from ethyl acetate–hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09–1.28 (m, 6H), 1.30–1.42 (m, 4H), 1.82 (m, 2H), 1.97 (m, 2H), 2.83 (t, J=6.4 Hz, 2H), 2.97 (t, J=6.0 Hz, 2H), 3.94 (s, 3H), 8.06 (d J=2.3 Hz, 1H), 8.99 (d, J=2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 23.7, 25.4, 26.26, 26.29, 27.5, 28.2, 29.3, 33.0, 52.2, 123.2, 136.3, 137.3, 147.6, 166.1, 166.3; MS (EI) *m*/*z* (%) 261 (29) [M^+], 165 (100). HRMS (EI) calcd for $C_{16}H_{23}NO_2$ 261.1729, found 261.1730.

3.6.10. Methyl 6,7,8,9,10,11,12,13,14,15-decahydrocyclotrideca[*b*]pyridine-3-carboxylate (7e). Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20–1.58 (m, 14H), 1.71 (m, 2H), 1.81 (m, 2H), 2.65 (AA′XX′, $J_{AX}+J_{AX'}$=16.9 Hz, 2H), 2.85 (AA′XX′, $J_{AX}+J_{AX'}$=16.7 Hz, 2H), 3.93 (s, 3H), 8.01 (d, J=2.0 Hz, 1H), 8.95 (d, J=2.0 Hz, 1H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 23.9, 24.0, 24.66, 24.67, 26.2, 26.3, 26.4, 26.5, 27.5, 30.7, 33.9, 52.2, 123.7, 135.7, 138.1, 147.9, 165.5, 166.3; MS (EI) *m*/*z* (%) 289 (46) [M^+], 165 (100); HRMS (EI) calcd for $C_{18}H_{27}NO_2$ 289.2042, found 289.2054.

3.6.11. Methyl 5,6,7,8,9,10,11,12,13,14,15,16-dodecahydrocyclotetradeca[*b*]pyridine-3-carboxylate (7f). White solid; mp 81–83 °C (from ethyl acetate–hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22–1.67 (m, 18H), 1.73 (m, 2H), 2.64 (AA′XX′, $J_{AX}+J_{AX'}$=16.5 Hz, 2H), 2.82 (AA′XX′, $J_{AX}+J_{AX'}$=16.9 Hz, 2H), 3.93 (s, 3H), 8.04 (d, J=2.3 Hz, 1H), 8.96 (d, J=2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 24.0, 24.9, 25.2, 25.35, 25.42, 27.1, 27.5, 27.6, 29.2, 31.8, 34.4, 52.1, 123.5, 135.5, 138.1, 147.9, 165.1, 166.2; MS (EI) *m*/*z* (%) 303 (24) [M^+] 165 (100). HRMS (EI) calcd for $C_{19}H_{29}NO_2$ 303.2198, found 303.2208.

3.6.12. Methyl 6,7,8,9,10,11,12,13,14,15,16,17-dodecahydrocyclopentadeca[*b*]pyridine-3-carboxylate (7g). Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22–1.83 (m, 22H), 2.66 (AA′XX′, $J_{AX}+J_{AX'}$=16.5 Hz, 2H), 2.84 (AA′XX′, $J_{AX}+J_{AX'}$=16.5 Hz, 2H), 3.93 (s, 3H), 8.02 (d, J=2.0 Hz, 1H), 8.96 (d, J=2.0 Hz, 1H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 25.4, 25.5, 25.9, 26.0, 26.6, 26.78, 26.83, 27.3, 27.4, 28.1, 29.3, 32.2, 35.2, 52.1, 123.6, 135.6, 137.9, 147.8, 165.3, 166.2; MS (EI) *m*/*z* (%) 317 (75) [M^+], 165 (100); HRMS (EI) calcd for $C_{20}H_{31}NO_2$ 317.2355, found 317.2359.

3.6.13. Methyl 5,6,7,8,9,10,11,12,13,14,15,16,17,18-tetradecahydrocyclohexadeca[*b*]pyridine-3-carboxylate (7h). White solid; mp 57–58 °C (from ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25–1.39 (m, 12H), 1.39–1.52 (m, 8H), 1.59 (m, 2H), 1.71 (m, 2H), 2.66 (AA′XX′, $J_{AX}+J_{AX'}$=16.0 Hz, 2H), 2.84 (AA′XX′, $J_{AX}+J_{AX'}$=16.5 Hz, 2H), 3.93 (s, 3H), 8.04 (d, J=2.3 Hz, 1H), 8.96 (d, J=2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.7 (2C), 26.30, 26.33, 26.36, 26.44, 27.4 (2C), 27.8, 28.0, 28.9, 30.3, 32.2, 35.1, 52.1, 123.5, 135.5, 137.8, 147.9, 165.2, 166.2; MS (EI) m/z (%) 331 (27) [M^+], 165 (100). HRMS (EI) calcd for $C_{21}H_{33}NO_2$ 331.2511, found 331.2501.

3.7. Hydrolysis of [11](2,5)pyridinophane 6e

A solution of **6e** (170 mg, 0.587 mmol) in methanol–water (9/1, 8.0 ml) was stirred in the presence of lithium hydroxide monohydrate (124 mg, 2.94 mmol) at room temperature overnight. After removal of solvent in vacuo, water was added and the solution was washed with ether. The aqueous layer was acidified to pH 3 with hydrochloric acid and extracted with chloroform. The organic layer was dried over magnesium sulfate and was concentrated in vacuo to give compound **13** (138 mg, 0.502 mmol) in 85% yield.

3.7.1. [11](2,5)Pyridinophane-3-carboxylic acid (13). White solid; mp 200–201 °C (from ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.51–1.04 (m, 10H), 1.10–1.35 (m, 4H), 1.46–1.95 (m, 4H), 2.59–2.77 (m, 2H), 2.83 (ddd, J=12.8, 8.7, 3.2 Hz, 1H), 3.91 (m, 1H), 4.14 (br s, 1H), 8.17 (d, J=2.1 Hz, 1H), 8.55 (d, J=2.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 25.6, 26.2, 26.5, 27.1, 27.7, 27.8, 27.9, 28.3, 32.4, 35.0, 126.8, 136.1, 140.3, 150.5, 161.1, 169.0; MS (EI) *m*/*z* (%) 275 (16) [M^+], 230 (20), 69 (100). HRMS (EI) calcd for $C_{17}H_{25}NO_2$ 275.1885, found 275.1879. Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 73.90; H, 9.19; N, 5.02.

3.8. Synthesis of (S_p,*S*)-14 and (R_p,*S*)-14

The compound **13** (207 mg, 0.754 mmol) was treated with oxalyl chloride (132 μl, 1.51 mmol) in chloroform (1.5 ml) and the mixture was stirred at room temperature for 1.5 h. After solvent was removed in vacuo, the acid chloride thus obtained was dissolved in chloroform (1.5 ml) and the solution was added dropwise by syringe to a solution of (*S*)-phenylalaninol (171 mg, 1.13 mmol) and triethylamine (114 mg, 1.13 mmol) in chloroform (2.0 ml) at 0 °C. The reaction mixture was then stirred at room temperature overnight. After the reaction was complete, the mixture was washed with saturated aqueous sodium bicarbonate, was dried over magnesium sulfate, and was concentrated in vacuo. The residue was then chromatographed on silica gel by using ether to give an inseparable mixture of (S_p,*S*)-**14** and (R_p,*S*)-**14** (256 mg, 0.627 mmol) in 83% yield. HPLC analyses, shown in Figure 2, were performed by using SenshuPak PEGASIL Silica 120–5 column (4.6×250 mm) and a UV detector (254 nm) with 20% acetonitrile in ethyl acetate as an eluent (flow rate: 1.0 ml/min).

3.8.1. (*S*)-*N*-(1-Hydroxy-3-phenylpropan-2-yl)-(*S*)-[11](2,5)pyridinophane-3-carboxamide [(S_p,*S*)-14 and (R_p,*S*)-14]. Sticky oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.60 (m, 2H), 0.67–1.10 (m, 18H), 1.10–1.28 (m, 8H), 1.48–1.79 (m, 8H), 2.43–2.55 (m, 2H), 2.59–2.68 (m, 3H), 2.73 (ddd, J=13.2, 8.4, 3.2 Hz, 1H), 2.87 (ddd, J=12.8, 9.2, 3.2 Hz, 1H), 2.90–3.09 (m, 6H), 3.15 (ddd, J=13.2, 9.2, 5.6 Hz, 1H), 3.71–3.75 (m, 2H), 3.80–3.84 (m, 2H), 4.37–4.46 (m, 2H), 6.00 (br, 1H), 6.08 (br, 1H), 7.25–7.38 (m, 12H), 8.39 (d, J=2.4 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$, 50 °C) δ 25.6 (2C), 26.0 (2C), 26.6 (2C), 26.8, 26.9, 27.27, 27.30, 27.47, 27.54, 27.965, 27.973, 27.99 (2C), 28.6 (2C), 32.56,

32.58, 34.9, 35.1, 37.0, 37.1, 53.1, 53.3, 63.8, 64.3, 126.7, 126.8, 128.7 (2C), 128.8 (2C), 129.2 (4C), 131.7, 131.9, 135.30 (2C), 135.32, 135.6, 137.6, 137.6, 150.49, 150.54, 157.4, 157.8, 169.0, 169.2; MS (FAB+) *m/z* (%) 409 (100 [M+H$^+$]), 391 (21), 258 (34). HRMS (FAB+) calcd for $C_{26}H_{37}N_2O_2$ [M+H$^+$] 409.2855, found 409.2856. Anal. Calcd for $C_{26}H_{36}N_2O_2$: C, 76.43; H, 8.88; N, 6.86. Found: C, 76.56; H, 8.80; N, 6.35.

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