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Preparation and Electrophilic Cyclization of Multisubstituted Dienamides Leading to Cyclic Iminoethers

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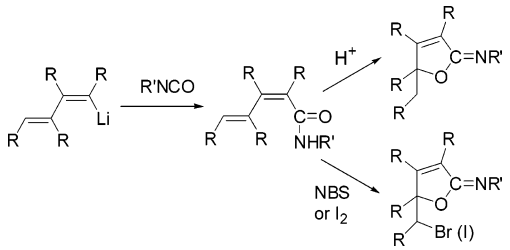


Stereodefined multisubstituted dienamides could be concisely prepared in high yields by direct addition of 1-lithiobutadiene derivatives to both *N*-aryl and *N*-alkyl isocyanates. Electrophilic cyclization of these dienamides was achieved to generate substituted cyclic iminoethers in excellent yields with perfect selectivity. When treated with 12 N aqueous HCl, dienamides underwent efficient and selective electrophilic cyclization to afford cyclic imidate derivatives. When treated with NBS, monobrominated or double-brominated cyclic iminoethers were formed.

Introduction

Nonconjugated unsaturated amides **1** (Figure 1) have been found to be very useful for the preparation of various functionalized lactones, lactams, and oxazolines via electrophilic cyclization (Scheme 1).[1,2] Conjugated α,β-unsaturated amides **2** (Figure 1) have also been applied for the preparation of four-membered heterocycles through *endo* or *exo* cyclization, depending on the reaction conditions, the substitution patterns, and the electrophiles used.[3] Both *O*-attack and *N*-attack pathways have been reported to predominately afford lactones or lactams as the final products.[1−3] Competition between these two pathways from the same substrate was observed in a few cases.[1,4,5]

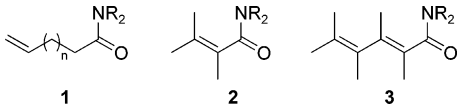
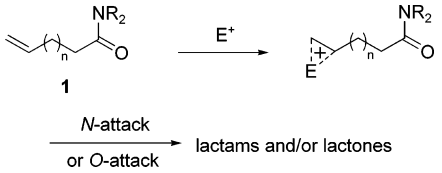


FIGURE 1. Conjugated and nonconjugated unsaturated amides.

SCHEME 1. Electrophilic Cyclization of Nonconjugated Unsaturated Amides



Although a number of preparative methods for dienamides **3** have appeared in the literature[6−11] and useful

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(1) For a review on electrophilic cyclization of unsaturated amides, see: Robin, S.; Rousseau, G. *Tetrahedron* **1998**, *54*, 13681−13736.

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heterocycles can be expected from electrophilic cyclization reaction of dienamides **3** (Figure 1), few examples have been reported on this kind of investigation.[3,12,13]

In this paper, we report an alternative synthesis of these conjugated unsaturated amides **3** and their applications to the preparation of heterocycles via electrophilic cyclization. Surprisingly, our results reveal that these multisubstituted dienamides **3** undergo the electrophilic cyclization exclusively through the *O*-attack pathway to afford cyclic imino ethers, which are seldom obtained via the electrophilic cyclization.[1−5]

Results and Discussion

Reaction of 1-Lithio-1,3-dienes 5 with Isocyanates. Preparation of Multisubstituted Stereodefined Dienamides 3. Multisubstituted stereodefined 1-iodo-1,3-dienes **4** are readily available.[14] Lithiation of **4** with *t*-BuLi affords their corresponding 1-lithio-1,3-diene derivatives **5** quantitatively.[15] Treatment of these in situ formed organolithium reagents **5** with isocyanates produced multisubstituted stereodefined dienamides **3** in high isolation yields after hydrolysis (Scheme 2). As shown in Table 1, a variety of aromatic isocyanates and different types of organolithium reagents **5** could be used to afford stereodefined dienamides **3** with various substituents.

In addition to *N*-aryl isocyanates, *N*-alkyl isocyanates could be also applied for this reaction to prepare their corresponding dienamide derivatives **3** (Figure 2). Reaction of *n*-Hex-NCO and $PhCH_2$-NCO with 1-lithio-1,2,3,4-tetrapropyl-1,3-diene **5b** afforded dienamides **3j** and **3k** as the only product in 80% and 71% isolated yields, respectively (Figure 2). Dienamide derivatives **3l** and **3m** possessing substitution patterns different from those of **3a**−**k** were prepared in 89% and 78% isolated yields, respectively, from 1,2-disubstituted organolithium reagent **5e** and 2,3-disubstituted organolithium reagent **5f** (Figure 2).

SCHEME 2. Reaction of Organolithium Reagents 5 with Isocyanates Leading to Dienamides 3

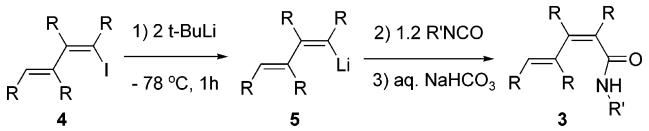
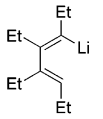
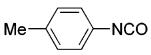
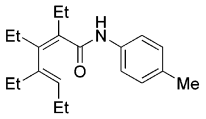
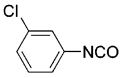
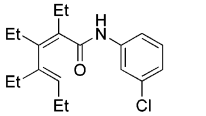
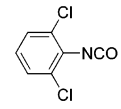
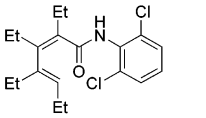
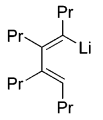
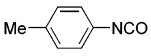
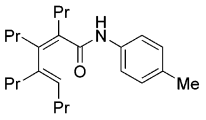
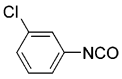
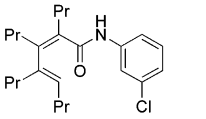
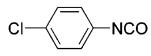
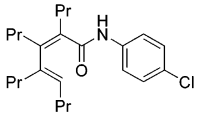
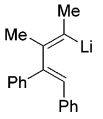
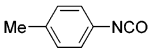
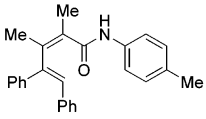
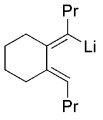
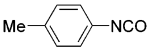
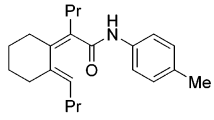
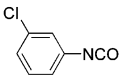
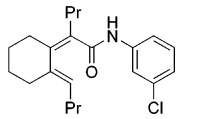


TABLE 1. Efficient Preparation of Multisubstituted Stereodefined Dienamides 3[a]

1-lithio-1,3-diene **5**	Isocyanate	Product **3**	Yield (%)[b]
 **5a**		 **3a**	83
5a		 **3b**	85
5a		 **3c**	84
 **5b**		 **3d**	81
5b		 **3e**	90
5b		 **3f**	86
 **5c**		 **3g**	78
 **5d**		 **3h**	84
5d		 **3i**	82

[a] Reaction conditions are shown in Scheme 2. [b] Isolated yields.

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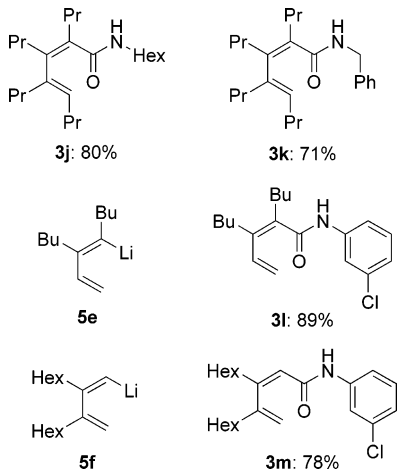
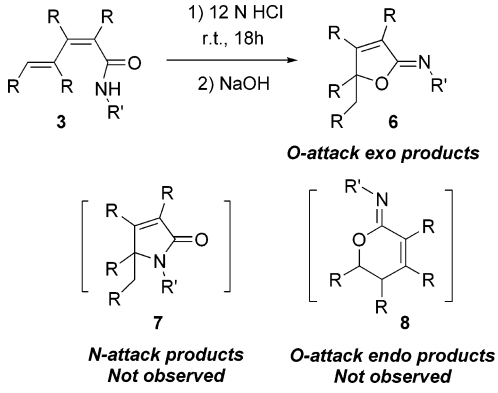


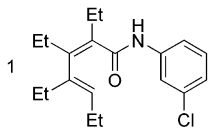
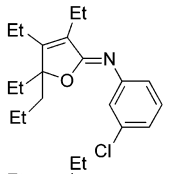
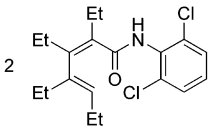
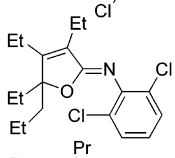
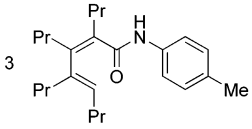
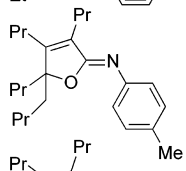
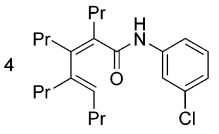
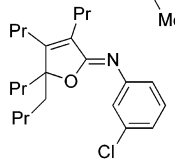
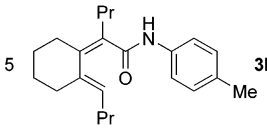
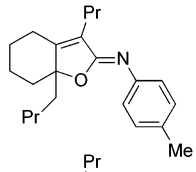
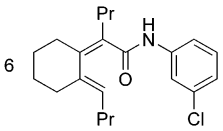
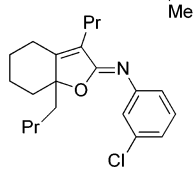
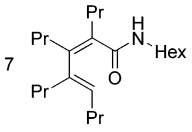
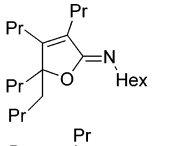
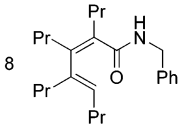
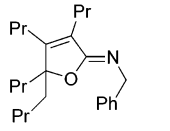
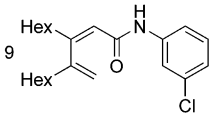
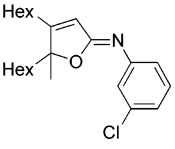
FIGURE 2. Examples of dienamides from alkyl isocyanates (**3j** and **3k**) and examples of dienamides with different substitution patterns on the dienyl skeletons (**3l** and **3m**).

SCHEME 3. Acid-Promoted Cyclization of Multisubstituted Dienamides 3 Affording Exocyclic Imino Ethers 6



Electrophilic Cyclization of Conjugated Unsaturated Amides 3 Leading to Cyclic Imino Ethers. It is known that the electrophilic cyclization reaction patterns of unsaturated amides remarkably depend on the reaction solvents and the electrophiles employed.[1–4] For these cases of dienamides **3a**−**m**, we found that the best conditions for the cyclization reaction were the use of 12 N HCl both as a electrophile and as a solvent at room temperature (Scheme 3). Although the substitution patterns of the dienyl skeletons of **3a**−**k** is different from that of **3l** and **3m**, all these dienamides, except **3l**, underwent the same type of electrophilic cyclization. Two unusual features were observed in this synthetically useful reaction. One is that only O-attack pathway is involved; the other is that exo cyclic imino ethers **6** are obtained as the sole products in excellent isolation yields (Table 2). No formation of either the N-attack products **7** or endo heterocyclic products were observed. The structure of imino ether **6b** has been determined by single-crystal X-ray structural analysis (Figure 3).[16] Only one product was obtained for **6a**−**h**, except that **6i** was obtained as a mixture of two geometric isomers at the N atom in a ratio of 7:3, probably due to the substitution pattern of the dienyl skeleton of **3m**.[17]

TABLE 2. Cyclic Imino Ethers 6 from 12 N HCl-Promoted Cyclization of Multisubstituted Dienamides 3[a]

entry	dienamide 3		product 6		yield of 6/%[b]
1		**3b**		**6a**	92
2		**3c**		**6b**	91
3		**3d**		**6c**	92
4		**3e**		**6d**	95
5		**3h**		**6e**	91
6		**3i**		**6f**	90
7		**3j**		**6g**	90
8		**3k**		**6h**	89
9		**3m**		**6i**[c]	95

[a] Reaction conditions: shown in Scheme 3. [b] Isolated yields. [c] Combined isolated yield. Two isomers in 7:3 ratio.

To further demonstrate the usefulness of these stereodefined multisubstituted dienamides, we used NBS and I_2 as the electrophiles. Abarbri and co-workers reported halocyclization reactions of (2*Z*,4*E*)-dienamides using ICl as the best reagent and CH_2Cl_2 as the best solvent to afford 5-alkylidenepyrrol-2(5*H*)-ones.[12] This reaction must proceed via an *N*-attack pathway. However, in our cases, although the reasons are not clear yet, no *N*-attack

(16) CCDC: 214277.

(17) Nitta, M.; Naya, S. *J. Chem. Res.* **1998**, 522−523.

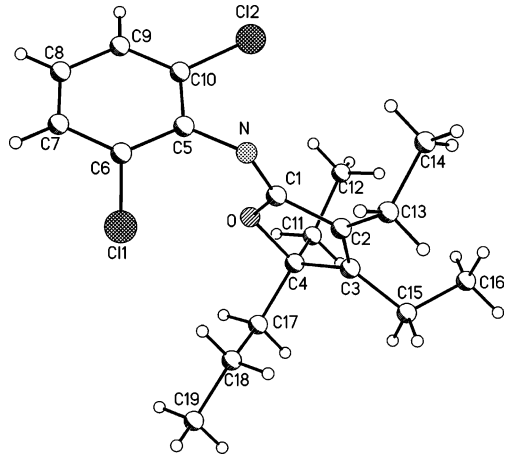


FIGURE 3. X-ray structure of **6b**.

products were obtained; instead, *O*-attack products, multisubstituted halogenated *exo* iminoethers **9**, were obtained as the only products in excellent isolated yields (Table 3). Both CH_2Cl_2 and a 1:1 mixture of THF and H_2O could be used as the solvent to afford similar yields of products (yields listed in Table 3 were obtained from a 1:1 mixture of THF and H_2O as the solvent). When I_2 was used as the electrophile in CH_2Cl_2, monoiodonated imino ethers **9** were also obtained in excellent isolated yields (Table 3).

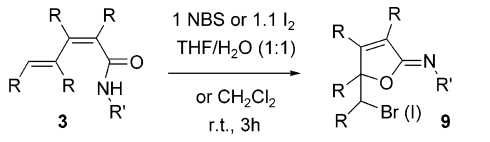
Furthermore, when 3 equiv of NBS was used, formation of double-brominated imino ether **10** was found (Scheme 4). In the presence of an excess amount of NBS, the *N*-phenyl ring, induced by the N atom and the Cl atom, underwent an electrophilic substitution reaction to afford **10** as the only product. This bromination of the *N*-phenyl ring was also observed in other cases, but generally afforded mixtures.

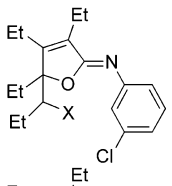
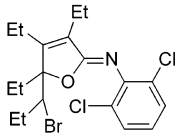
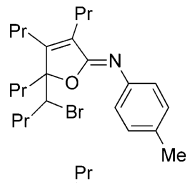
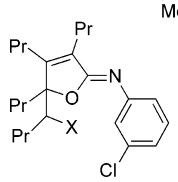
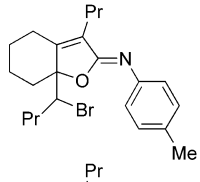
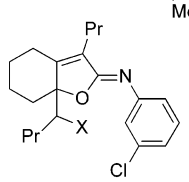
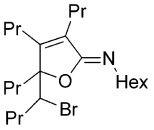
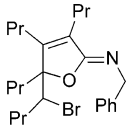
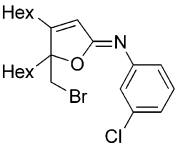
How are the two unusual features realized in this synthetically useful reaction? It is assumed that substitution at the 4 position and the relative stability of the allylic carbocation might be essential for the exo products from O-attack. By comparison of our results (our work: the 4 position is substituted) with those (Abarbri's work: the 4 position is unsubstituted) by Abarbri et al.,[12] it seems that substitution at position 4 is critical for O-attack. Obviously, position 4 is more crowded when it is substituted. On the other hand, the O atom environment of the amide moiety is less bulky than the N atom environment. Thus, if the 4 position is substituted, O-attack will take place. Otherwise, if the 4 position is not substituted, N-attack will occur. For **3l** which does not possess substituent at the 4 position, we have tried several times reactions of **3l** with different electrophiles, but a messy mixture has always been obtained, which indicates that the 4 position substituent is critical for the O-attack path. The relative stability of the allylic carbocation generated in situ in the reaction mixtures is proposed to be essential for the formation of exo products from O-attack.

Conclusions

We have reported a convenient high-yield preparation of stereodefined multisubstituted dienamides and electrophilic cyclization of these dienamides affording substituted cyclic iminoethers in excellent yields with perfect selectivity. Only O-attack exo cyclic imino ethers are

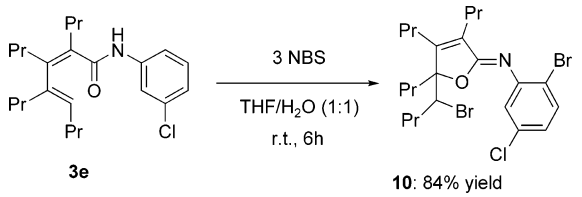
TABLE 3. NBS or I_2-Promoted Cyclization of Multisubstituted Dienamides 3 Affording Halogenated Imino Ethers 9[a]



entry	dienamide **3**	product **9**		yield of **9**/%[b]
1	**3b**		**9a**: X = Br	91
			9b: X = I	95
2	**3c**		**9c**	95
3	**3d**		**9d**	91
4	**3e**		**9e**: X = Br	93
			9f: X = I	93
5	**3h**		**9g**	93
6	**3i**		**9h**: X = Br	91
			9i: X = I	92
7	**3j**		**9j**	96
8	**3k**		**9k**	92
9	**3m**		**9l**[c]	94

[a] In the case of iodocyclization, CH_2Cl_2 was used as the solvent. [b] Isolated yields. [c] Two isomers in 8:2 ratio.

SCHEME 4. Formation of Double-Brominated Imino Ether 10



obtained as the sole products. No formation of the N-attack products and O-attack endo heterocyclic products is found. This methodology should prove quite useful for the synthesis of otherwise unavailable dienamides and functionalized cyclic iminoethers. Further synthetic applications of these dienamides and cyclic iminoethers can be expected.

Experimental Section

Typical Procedure for the Preparation of Stereodefined Dienamides 3a−m from the Corresponding Monoiodo Compounds. To a diethyl ether (5 mL) solution of 1-iodo-1,3-butadiene (1.0 mmol) at −78 °C was added *t*-BuLi (2.0 mmol, 1.5 M in pentane). The above reaction mixture was then stirred at −78 °C for 1 h to generate 1-lithio-1,3-diene, which was monitored by GC analysis or by TLC. After addition of isocyanates (1.2 mmol) at −78 °C, the mixture was stirred at room temperature for 2 h. The above reaction mixture was then quenched with saturated aqueous $NaHCO_3$ and extracted with diethyl ether. The extract was washed with brine and dried over $MgSO_4$. The solvent was evaporated in vacuo to give a red-orange oil, which was purified by column chromatograph (silica, CH_2Cl_2/hexane = 1:1) to afford **3a**−**m**.

3a: colorless liquid, isolated yield 83% (248 mg); ^{1}H NMR ($CDCl_3$, TMS) δ 0.86 (t, J = 7.5 Hz, 3H), 0.96−1.12 (m, 9H), 1.97−2.04 (m, 2H), 2.16−2.25 (m, 4H), 2.30 (s, 3H), 2.38−2.45 (m, 2H), 5.44 (t, J = 7.2 Hz, 1H), 7.09 (d, J = 8.4 Hz, 2H), 7.25 (br, 1H), 7.34 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, TMS) δ 12.8, 13.6, 13.8, 14.3, 20.8, 21.3, 22.8, 23.3, 24.4, 119.3, 129.4, 132.03, 133.4, 135.8, 135.8, 140.4, 145.1, 169.8; HRMS calcd for $C_{20}H_{29}NO$ 299.2249, found 299.2247.

3b: colorless liquid; isolated yield 85% (271 mg); ^{1}H NMR ($CDCl_3$, TMS) δ 0.82−1.10 (m, 12H), 1.97−2.45 (m, 8H), 5.44 (t, J = 7.5 Hz, 1H), 7.02−7.38 (m, 4H), 7.64 (br, 1H); ^{13}C NMR ($CDCl_3$, TMS) δ 12.8, 13.7, 13.8, 14.3, 21.3, 22.8, 23.3, 24.3, 117.1, 119.3, 123.8, 129.9, 132.4, 134.6, 135.4, 139.5, 140.3, 146.0, 170.0; HRMS calcd for $C_{19}H_{26}NOCl$ 319.1703, found 319.1710.

3c: colorless solid; mp 65−66 °C, isolated yield 84% (297 mg); ^{1}H NMR ($CDCl_3$, TMS) δ 0.93−1.18 (m, 12H), 2.03−2.47 (m, 8H), 5.43 (t, J = 7.2 Hz, 1H), 7.07−7.12 (m, 1H), 7.29−7.32 (m, 3H); ^{13}C NMR ($CDCl_3$, TMS) δ 12.6, 13.2, 14.1, 14.2, 21.5, 22.9, 23.7, 24.3, 127.8, 128.5, 132.2, 132.4, 133.0, 133.9, 139.9, 146.8, 168.9; HRMS calcd for $C_{19}H_{25}NOCl_2$ 353.1313, found 353.1308.

3d: colorless solid; mp 74−75 °C, isolated yield 81% (288 mg); ^{1}H NMR ($CDCl_3$, TMS) δ 0.81 (t, J = 7.5 Hz, 3H), 0.90−0.98 (m, 9H), 1.21−1.52 (m, 8H), 1.93−2.01 (m, 2H), 2.10−2.19 (m, 4H), 2.29 (s, 3H), 2.34−2.40 (m, 2H), 5.47 (t, J = 7.5 Hz, 1H), 7.08 (d, J = 8.4 Hz, 2H), 7.17 (br, 1H), 7.33 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, TMS) δ 13.9, 14.1, 14.8, 20.8, 21.4, 22.5, 22.6, 22.9, 30.2, 32.3, 33.2, 119.4, 129.4, 130.8, 133.4, 134.9, 135.8, 139.9, 144.4, 170.0. Anal. Calcd for $C_{24}H_{37}NO$: C, 81.07; H, 10.49; N, 3.94. Found: C, 81.10; H, 10.46; N, 3.80.

3e: colorless solid; mp 59−60 °C, isolated yield 90% (337 mg); ^{1}H NMR ($CDCl_3$, TMS) δ 0.78−0.99 (m, 12H), 1.19−1.53 (m, 8H), 1.93−2.39 (m, 8H), 5.47 (t, J = 7.5 Hz, 1H), 7.01−7.29 (m, 4H), 7.63 (br, 1H); ^{13}C NMR ($CDCl_3$, TMS) δ 13.9, 14.1, 14.8, 21.4, 22.3, 22.7, 22.9, 30.2, 32.2, 32.3, 33.1, 117.2, 119.4, 123.8, 129.9, 131.1, 134.5, 134.6, 139.5, 139.8, 145.3, 170.3; HRMS calcd for $C_{23}H_{34}NOCl$ 375.2329, found 375.2329.

3f: colorless solid; mp 63−64 °C, isolated yield 86% (323 mg); ^{1}H NMR ($CDCl_3$, TMS) δ 0.77−0.98 (m, 12H), 1.18−1.51 (m, 8H), 1.92−1.99 (m, 2H), 2.10−2.19 (m, 4H), 2.34−2.39 (m, 2H), 5.46 (t, J = 7.2 Hz, 1H), 7.22−7.27 (m, 3H), 7.39−7.42 (m, 2H); ^{13}C NMR ($CDCl_3$, TMS) δ 13.9, 14.1, 14.8, 21.4, 22.3, 22.7, 22.9, 30.2, 32.25, 32.3, 33.1, 120.4, 128.7, 128.9, 131.1, 134.6, 136.9, 139.9, 145.1, 170.2; HRMS calcd for $C_{23}H_{34}NOCl$ 375.2329, found 375.2324.

3g: colorless solid; mp 167−168 °C, isolated yield 78% (286 mg); ^{1}H NMR ($CDCl_3$, TMS) δ 1.82 (s, 3H), 2.08 (s, 3H), 2.22 (s, 3H), 6.72 (s, 1H), 6.96−7.24 (m, 14H), 7.53 (br, 1H); ^{13}C NMR ($CDCl_3$, TMS) δ 16.8, 19.0, 20.8, 120.2, 126.9, 127.7, 127.9, 128.6, 129.3, 129.4, 129.6, 131.9, 133.7, 135.2, 136.7, 138.1, 139.9, 143.1, 169.6; HRMS calcd for $C_{26}H_{25}NO$ 367.1936, found 367.1929. Anal. Calcd for $C_{26}H_{25}NO$: C, 84.98; H, 6.86; N, 3.81. Found: C, 84.74; H, 6.91; N, 3.81.

3h: colorless solid; mp 94−95 °C, isolated yield 84% (273 mg); ^{1}H NMR ($CDCl_3$, TMS) δ 0.72 (t, J = 7.5 Hz, 3H), 0.93 (t, J = 7.2 Hz, 3H), 1.10−1.18 (m, 2H), 1.44−1.52 (m, 2H), 1.70 (br, 4H), 1.84−1.92 (m, 2H), 2.27−2.35 (m, 9H), 5.44 (t, J = 7.5 Hz, 1H), 7.03−7.05 (m, 2H), 7.17 (br, 1H), 7.30−7.33 (m, 2H); ^{13}C NMR ($CDCl_3$, TMS) δ 13.8, 14.0, 20.8, 22.2, 22.7, 27.3, 27.6, 29.6, 29.7, 31.2, 31.9, 119.8, 127.4, 129.2, 131.7, 133.2, 135.9, 138.5, 143.6, 170.7; HRMS calcd for $C_{22}H_{31}NO$ 325.2406, found 325.2399.

3i: colorless solid; mp 113−114 °C, isolated yield 82% (283 mg); ^{1}H NMR ($CDCl_3$, TMS) δ 0.72 (t, J = 7.5 Hz, 3H), 0.93 (t, J = 7.2 Hz, 3H), 1.06−1.18 (m, 2H), 1.41−1.53 (m, 2H), 1.71 (br, 4H), 1.84−1.92 (m, 2H), 2.28−2.35 (m, 6H), 5.42 (t, J = 7.5 Hz, 1H), 7.00−7.03 (m, 1H), 7.14−7.27 (m, 3H), 7.58 (br, 1H); ^{13}C NMR ($CDCl_3$, TMS) δ 13.7, 14.0, 22.3, 22.7, 27.2, 27.6, 29.7, 29.7, 31.3, 31.9, 117.5, 119.6, 123.8, 127.9, 129.8, 131.4, 134.5, 138.4, 139.6, 144.6, 170.9; HRMS calcd for $C_{21}H_{28}NOCl$ 345.1859, found 345.1851.

3j: colorless solid; mp 39−40 °C, isolated yield 80% (280 mg); ^{1}H NMR ($CDCl_3$, TMS) δ 0.86−0.98 (m, 15H), 1.28−1.42 (m, 16H), 1.96−2.11 (m, 6H), 2.28 (t, J = 7.5 Hz, 2H), 3.17 (q, J = 6.9 Hz, 2H), 5.35 (t, J = 7.2 Hz, 1H), 5.45 (br, 1H); ^{13}C NMR ($CDCl_3$, TMS) δ 14.0, 14.05, 14.07, 14.1, 14.8, 21.4, 22.1, 22.5, 22.7, 23.0, 26.8, 29.6, 30.2, 31.6, 32.3, 32.8, 39.5, 129.9, 134.7, 139.8, 143.0, 172.1; HRMS calcd for $C_{23}H_{43}NO$ 349.3345, found 349.3347.

3k: colorless liquid; isolated yield 71% (252 mg); ^{1}H NMR ($CDCl_3$, TMS) δ 0.84−0.95 (m, 12H), 1.17−1.50 (m, 8H), 1.86−2.11 (m, 6H), 2.29−2.34 (m, 2H), 4.37 (d, J = 5.7 Hz, 2H), 5.32 (t, J = 7.2 Hz, 1H), 5.75 (br, 1H), 7.23−7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, TMS) δ 14.0, 14.1, 14.7, 21.4, 22.2, 22.3, 22.9, 30.1, 32.3, 32.3, 33.0, 43.8, 127.4, 128.1, 128.6, 130.0, 134.1, 138.3, 139.9, 143.7, 171.8; HRMS calcd for $C_{24}H_{37}NO$ 355.2875, found 355.2872.

3l: colorless liquid; isolated yield 89% (284 mg); ^{1}H NMR ($CDCl_3$, TMS) δ 0.83−0.97 (m, 6H), 1.26−1.49 (m, 8H), 2.25 (t, J = 7.2 Hz, 2H), 2.38 (t, J = 7.8 Hz, 2H), 5.12−5.35 (m, 2H), 6.48−6.58 (m, 1H), 7.04−7.07 (m, 1H), 7.17−7.22 (m, 1H), 7.38−7.41 (m, 1H), 7.70 (t, J = 2.1 Hz, 1H), 7.77 (br, 1H); ^{13}C NMR ($CDCl_3$, TMS) δ 13.9, 22.9, 23.1, 27.2, 30.5, 30.9, 31.1, 115.6, 117.9, 120.0, 124.3, 129.9, 134.6, 134.7, 137.5, 137.6, 139.1, 170.1; HRMS calcd for $C_{19}H_{26}NOCl$ 319.1703, found 319.1704.

3m: colorless liquid; isolated yield 78% (293 mg); ^{1}H NMR ($CDCl_3$, TMS) δ 0.83−0.88 (m, 6H), 1.26−1.47 (m, 16H), 2.18−2.25 (m, 4H), 4.99 (s, 1H), 5.19 (s, 1H), 5.75 (s, 1H), 7.01−7.34 (m, 3H), 7.64 (br, 1H), 8.34 (br, 1H); ^{13}C NMR ($CDCl_3$, TMS) δ 14.1, 14.1, 22.6, 27.3, 27.7, 28.9, 29.2, 31.7, 35.8, 38.5, 112.9, 117.5, 119.6, 120.4, 123.9, 129.9, 134.6, 139.4, 150.0, 156.6, 164.71; HRMS calcd for $C_{23}H_{34}NOCl$ 375.2329, found 375.2325.

A Typical Procedure for the Preparation of Compound 6a−i. To a diethyl ether (5 mL) solution of compound **3** (1.0 mmol) at room temperature was added 12 N HCl (4.0 mL). The above reaction mixture was then stirred at room

temperature for 18 h. After addition of NaOH (48 mmol, 1.92 g) at 0 °C, the mixture was stirred at room temperature for 5 min. The above reaction mixture was then extracted with diethyl ether. The extract was washed with brine and dried over $MgSO_4$. The solvent was evaporated in vacuo to give an orange solid, which was purified by column chromatograph (silica, CH_2Cl_2/hexane = 1:3) to afford **6a**−**i**.

6a: colorless liquid; isolated yield 92% (294 mg); ^{1}H NMR ($CDCl_3$, TMS): δ 0.71 (t, J = 7.5 Hz, 3H), 0.85 (t, J = 7.2 Hz, 3H), 1.02−1.28 (m, 8H), 1.52−1.89 (m, 4H), 2.21 (q, J = 7.8 Hz, 2H), 2.38 (q, J = 7.5 Hz, 2H), 6.96−7.05 (m, 2H), 7.15−7.21 (m, 2H); ^{13}C NMR ($CDCl_3$, TMS): δ 7.3, 12.6, 13.6, 14.1, 16.4, 17.4, 18.9, 30.0, 39.3, 94.6, 121.7, 122.9, 123.6, 129.4, 133.5, 133.8, 149.3, 156.2, 163.5; HRMS calcd for $C_{19}H_{26}NOCl$ 319.1703, found 319.1702.

6b: colorless solid; mp 95−96 °C; isolated yield 91% (321 mg); ^{1}H NMR ($CDCl_3$, TMS) δ 0.70−1.87 (m, 18H), 2.21 (q, J = 7.8 Hz, 2H), 2.45 (q, J = 7.5 Hz, 2H), 6.83−6.88 (m, 1H), 7.24−7.26 (m, 2H); ^{13}C NMR ($CDCl_3$, TMS) δ 7.2, 12.6, 13.6, 14.1, 16.1, 17.6, 19.0, 29.8, 39.3, 95.2, 123.3, 127.3, 127.7, 132.6, 144.2, 157.2, 164.0; HRMS calcd for $C_{19}H_{25}NOCl_2$ 353.1313, found 353.1303. Anal. Calcd for $C_{19}H_{25}NOCl_2$: C, 64.41; H, 7.11; N, 3.95. Found: C, 64.56; H, 7.16; N, 3.89. CCDC: 214277

6c: colorless liquid; isolated yield 92% (327 mg); ^{1}H NMR ($CDCl_3$, TMS) δ 0.81−1.28 (m, 18H), 1.45−1.81 (m, 8H), 2.10−2.15 (m, 2H), 2.30−2.35 (m, 5H), 7.07 (br, 4H); ^{13}C NMR ($CDCl_3$, TMS) δ 14.0, 14.1, 14.3, 15.0, 16.3, 21.0, 21.6, 21.9, 22.7, 25.1, 26.3, 28.5, 37.2, 39.8, 93.8, 123.3, 129.0, 132.2, 132.3, 145.3, 154.7, 162.6; HRMS calcd for $C_{24}H_{37}NO$ 355.2875, found 355.2871.

6d: colorless liquid; isolated yield 95% (356 mg); ^{1}H NMR ($CDCl_3$, TMS) δ 0.82−1.34 (m, 18H), 1.46−1.81 (m, 8H), 2.11−2.16 (m, 2H), 2.29−2.34 (m, 2H), 6.96−7.03 (m, 2H), 7.15−7.20 (m, 2H); ^{13}C NMR ($CDCl_3$, TMS) δ 14.0, 14.1, 14.2, 15.0, 16.3, 21.6, 21.9, 22.7, 25.1, 26.2, 28.5, 37.0, 39.6, 94.4, 121.7, 122.9, 123.6, 129.4, 132.0, 133.8, 149.4, 156.1, 163.6; HRMS calcd for $C_{23}H_{34}NOCl$ 375.2329, found 375.2321.

6e: colorless liquid; isolated yield 91% (296 mg); ^{1}H NMR ($CDCl_3$, TMS) δ 0.85−2.33 (m, 26H), 2.71−2.76 (m, 1H), 7.08 (br, 4H); ^{13}C NMR ($CDCl_3$, TMS) δ 13.9, 14.0, 21.0, 22.0, 22.8, 23.1, 25.0, 25.3, 25.5, 27.3, 34.2, 39.1, 90.2, 123.3, 126.9, 129.0, 132.3, 145.1, 156.3, 162.6; HRMS calcd for $C_{22}H_{31}NO$ 325.2406, found 325.2396.

6f: colorless liquid; isolated yield 90% (311 mg); ^{1}H NMR ($CDCl_3$, TMS) δ 0.86−2.33 (m, 23H), 2.73−2.77 (m, 1H), 6.97−7.25 (m, 4H); ^{13}C NMR ($CDCl_3$, TMS) δ 13.9, 14.0, 21.9, 22.7, 23.1, 25.0, 25.3, 25.4, 27.3, 34.1, 39.0, 90.8, 121.8, 122.9, 123.6, 126.7, 129.4, 133.8, 149.2, 157.5, 163.5; HRMS calcd for $C_{21}H_{28}NOCl$ 345.1859, found 345.1861.

6g: colorless liquid; isolated yield 90% (314 mg); ^{1}H NMR ($CDCl_3$, TMS) δ 0.83−1.79 (m, 37H), 2.04−2.10 (m, 2H), 2.19−2.24 (m, 2H), 3.32 (t, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, TMS) δ 14.0, 14.1, 14.2, 14.2, 15.0, 16.3, 21.7, 21.9, 22.7, 22.8, 25.1, 26.3, 27.4, 28.4, 31.0, 31.9, 37.4, 40.1, 47.2, 92.2, 131.64 152.7, 163.4; HRMS calcd for $C_{23}H_{43}NO$ 349.3345, found 349.3342.

6h: reaction time 3 days; colorless liquid; isolated yield 89% (316 mg); ^{1}H NMR ($CDCl_3$, TMS) δ 0.81−1.77 (m, 26H), 2.06−2.11 (m, 2H), 2.24−2.29 (m, 2H), 4.57 (s, 2H), 7.14−7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, TMS) δ 14.0, 14.2, 14.3, 15.0, 16.3, 21.7, 21.9, 22.8, 25.1, 26.3, 28.4, 37.3, 39.9, 50.7, 92.8, 125.9, 127.6, 128.0, 131.6, 141.8, 153.6, 164.5; HRMS calcd for $C_{24}H_{37}NO$ 355.2875, found 355.2877.

6i: two isomers in 7:3 ratio; colorless liquid; combined isolated yield 95% (357 mg); ^{1}H NMR ($CDCl_3$, TMS) δ 0.84−2.13 (m, 29H), 5.77 (br, 0.3H), 5.90 (br, 0.7H), 6.79−7.23 (m, 4H); ^{13}C NMR ($CDCl_3$, TMS) δ 14.0, 14.1, 22.5, 22.5, 22.6, 22.6, 23.1, 24.3, 24.5, 26.8, 26.8, 27.2, 29.0, 29.1, 29.2, 29.3, 31.5, 31.6, 31.7, 37.5, 37.7, 91.4, 94.1, 110.3, 118.2, 120.7, 122.0, 122.5, 123.0, 123.3, 123.7, 129.4, 129.9, 133.9, 134.3, 148.5, 150.7, 163.2, 166.8, 167.4, 170.6; HRMS calcd for $C_{23}H_{34}NOCl$ 375.2329, found 375.2337.

Typical Procedure for the Preparation of Compounds 9a,c−e,g,h,j−l. To a THF and H_2O (1:1, 10 mL) solution of compound **3b** (1.0 mmol) at room temperature was added NBS (1.0 mmol). The above reaction mixture was then stirred at room temperature for 3 h to generate compound **9a**, which was monitored by GC analysis or by TLC. The above reaction mixture was then extracted with diethyl ether. The extract was washed with brine and dried over $MgSO_4$. The solvent was evaporated in vacuo to give a red-orange oil, which was purified by column chromatograph (silica, CH_2Cl_2/hexane = 1:3) to afford **9a**.

9a: colorless liquid; isolated yield 91% (361 mg); ^{1}H NMR ($CDCl_3$, TMS) δ 0.69 (t, J = 7.2 Hz, 3H), 1.04−1.22 (m, 9H), 1.62−1.84(m, 3H), 2.14−2.44(m, 5H), 4.01 (dd, J_1 = 2.7 Hz, J_2 = 10.8 Hz, 1H), 6.99−7.27 (m, 4H); ^{13}C NMR ($CDCl_3$, TMS) δ 7.3, 12.6, 13.0, 13.4, 17.6, 19.2, 26.6, 28.9, 63.2, 95.2, 122.1, 123.5, 124.0, 129.4, 133.8, 135.9, 148.3, 153.5, 162.0; HRMS calcd for $C_{19}H_{25}NOClBr$ 397.0808, found 397.0792.

9c: colorless solid; mp 124−125 °C; isolated yield 95% (409 mg); ^{1}H NMR ($CDCl_3$, TMS) δ 0.72 (t, J = 7.2 Hz, 3H), 1.04 (t, J = 7.2 Hz, 3H), 1.18 (t, J = 7.5 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H), 1.61−1.85 (m, 3H), 2.13−2.39 (m, 3H), 2.47 (q, J = 7.5 Hz, 2H), 3.90 (dd, J_1 = 3.3 Hz, J_2 = 10.5 Hz, 1H), 6.85−6.90 (m, 1H), 7.24−7.27 (m, 2H); ^{13}C NMR ($CDCl_3$, TMS) δ 7.2, 12.6, 13.0, 13.3, 17.7, 19.3, 26.4, 28.5, 62.6, 95.6, 123.6, 126.8, 127.7, 134.5, 143.5, 155.1, 162.8; HRMS calcd for $C_{19}H_{24}NOCl_2Br$ 431.0418, found 431.0430.

9d: colorless solid; mp 67−68 °C; isolated yield 91% (394 mg); ^{1}H NMR ($CDCl_3$, TMS) δ 0.82−1.77 (m, 22H), 2.08−2.37 (m, 9H), 4.09 (dd, J_1 = 2.4 Hz, J_2 = 10.8 Hz, 1H), 7.08−7.21 (m, 4H); ^{13}C NMR ($CDCl_3$, TMS) δ 13.3, 13.9, 14.4, 15.0, 16.3, 21.0, 21.3, 21.6, 21.8, 26.5, 28.7, 35.0, 38.3, 61.4, 94.4, 123.9, 129.1, 132.9, 134.8, 144.2, 151.9, 161.0; HRMS calcd for $C_{24}H_{36}NOBr$ 433.1980, found 433.1978.

9e: colorless liquid; isolated yield 92% (417 mg); ^{1}H NMR ($CDCl_3$, TMS) δ 0.84−1.75 (m, 23H), 2.12−2.36 (m, 5H), 4.09 (dd, J_1 = 2.7 Hz, J_2 = 10.5 Hz, 1H), 6.99−7.02 (m, 1H), 7.12−7.25 (m, 3H); ^{13}C NMR ($CDCl_3$, TMS) δ 13.3, 13.9, 14.3, 15.0, 16.3, 21.3, 21.5, 21.7, 26.4, 28.8, 35.0, 38.1, 60.9, 94.9, 122.0, 123.4, 124.1, 129.4, 133.8, 134.4, 148.3, 153.3, 162.2; HRMS calcd for $C_{23}H_{33}NOClBr$ 453.1434, found 453.1451.

9g: colorless liquid; isolated yield 93% (375 mg); ^{1}H NMR ($CDCl_3$, TMS) δ 0.86−0.96 (m, 6H), 1.26−2.00 (m, 12H), 2.27−2.36 (m, 5H), 2.75−2.87 (m, 2H), 4.35 (dd, J_1 = 2.1 Hz, J_2 =11.1 Hz, 1H), 7.09−7.11 (m, 2H), 7.24−7.27 (m, 2H); ^{13}C NMR ($CDCl_3$, TMS) δ 13.3, 14.0, 21.0, 21.3, 21.3, 22.3, 25.5, 25.7, 27.3, 33.9, 39.1, 57.1, 90.6, 124.1, 129.1, 129.5, 133.2, 143.8, 153.2, 160.8; HRMS calcd for $C_{22}H_{30}NOBr$ 403.1511, found 403.1506.

9h: colorless liquid; isolated yield 91% (385 mg); ^{1}H NMR ($CDCl_3$, TMS): δ 0.86−0.96 (m, 6H), 1.27−2.01 (m, 12H), 2.30−2.35 (m, 2H), 2.76−2.89 (m, 2H), 4.31−4.36 (m, 1H), 7.00−7.33 (m, 4H); ^{13}C NMR ($CDCl_3$, TMS) δ 13.3, 13.9, 21.3, 21.8, 22.3, 25.55, 25.59, 27.3, 33.9, 39.1, 56.6, 91.1, 122.4, 123.6, 124.4, 129.2, 129.4, 133.9, 148.0, 154.5, 162.0; HRMS calcd for $C_{21}H_{27}NOClBr$ 423.0965, found 423.0963.

9j: colorless liquid; isolated yield 96% (410 mg); ^{1}H NMR ($CDCl_3$, TMS) δ 0.86−1.71 (m, 33H), 2.06−2.37 (m, 6H), 3.35−3.39 (m, 2H), 4.04−4.08 (m, 1H); ^{13}C NMR ($CDCl_3$, TMS) δ 13.3, 14.0, 14.1, 14.3, 15.0, 16.4, 21.2, 21.7, 21.8, 22.7, 26.4, 27.3, 28.6, 30.7, 31.8, 34.8, 38.6, 47.1, 61.9, 93.1, 133.9, 150.6, 162.3; HRMS calcd for $C_{23}H_{42}NOBr$ 427.2450, found 427.2443.

9k: colorless liquid; isolated yield 92% (399 mg); ^{1}H NMR ($CDCl_3$, TMS) δ 0.81−1.64 (m, 23H), 2.01−2.39 (m, 5H), 4.04 (q, J_1 = 9.6 Hz, J_2 = 3.6 Hz, 1H), 4.59 (s, 2H), 7.15−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, TMS) δ 13.3, 14.0, 14.3, 15.0, 16.3, 21.1, 21.6, 21.7, 26.5, 28.6, 34.6, 38.6, 50.9, 61.7, 93.4, 126.0, 127.8, 128.0, 133.9, 141.3, 150.9, 163.1; HRMS calcd for $C_{24}H_{36}NOBr$ 433.1980, found 433.1975.

9l: two isomers in 8:2 ratio; colorless liquid; combined isolated yield 94% (426 mg); ^{1}H NMR ($CDCl_3$, TMS) δ 0.83−2.23 (m, 26H), 3.45−3.76 (m, 2H), 5.94 (br, 0.2H), 6.08 (br,

0.8H), 6.80−7.27 (m, 4H); ^{13}C NMR ($CDCl_3$, TMS) δ 14.0, 14.0, 14.1, 22.5, 22.6, 23.2, 26.5, 26.7, 27.1, 29.0, 29.1, 29.2, 31.5, 31.5, 31.6, 35.0, 35.2, 35.9, 36.0, 91.1, 93.4, 113.4, 120.6, 121.2, 121.8, 122.3, 123.2, 123.5, 123.6, 129.5, 129.9, 133.9, 134.3, 148.2, 150.2, 162.3, 162.7, 165.8, 166.3. HRMS calcd for $C_{23}H_{33}NOClBr$ 453.1434, found 453.1437.

Typical Procedure for the Preparation of Compound 9b,f,i. To a dry dichloromethane (5 mL) solution of compound **3b** (1.0 mmol) at room temperature was added iodine (1.2 mmol). The above reaction mixture was stirred at room temperature for 8 h to generate compound **9b**, which was monitored by TLC. The above reaction mixture was hydrolyzed by addition of a 5% solution of sodium thiosulfate until the solution became clear, then the solution was extracted with diethyl ether. The extract was washed with brine and dried over $MgSO_4$. The solvent was evaporated in vacuo to give an orange oil, which was purified by column chromatograph (silica, CH_2Cl_2/hexane = 1:3) to afford **9b**.

9b: colorless liquid; isolated yield 95% (423 mg); ^{1}H NMR ($CDCl_3$, TMS) δ 0.69 (t, J = 7.5 Hz, 3H), 1.05 (t, J = 7.2 Hz, 3H), 1.16−1.23 (m, 6H), 1.56−1.77 (m, 3H), 2.17−2.44 (m, 5H), 4.16 (dd, J_1 = 3.0 Hz, J_2 = 10.8 Hz, 1H), 7.00−7.04 (m, 1H), 7.15−7.32 (m, 3H); ^{13}C NMR ($CDCl_3$, TMS) δ 7.6, 12.5, 13.3, 15.1, 17.7, 19.2, 28.3, 31.5, 46.2, 95.2, 122.2, 123.5, 124.1, 129.4, 133.8, 135.9, 148.2, 152.9, 161.6; HRMS calcd for $C_{19}H_{25}NOClI$ 445.0669, found 445.0658.

9f: colorless liquid; isolated yield 93% (466 mg); ^{1}H NMR ($CDCl_3$, TMS) δ 0.84−1.77 (m, 22H), 2.13−2.37 (m, 6H), 4.21−4.25 (m, 1H), 7.00−7.03 (m, 1H), 7.14−7.31 (m, 3H); ^{13}C NMR ($CDCl_3$, TMS) δ 13.1, 13.9, 14.4, 15.0, 16.5, 21.4, 21.8, 23.4, 26.5, 28.8, 36.5, 40.6, 43.7, 94.9, 122.2, 123.5, 124.2, 129.4, 133.9, 134.5, 148.2, 152.8, 161.8; HRMS calcd for $C_{23}H_{33}NOClI$ 501.1295, found 501.1287.

9i: colorless liquid; isolated yield 92% (433 mg); ^{1}H NMR ($CDCl_3$, TMS) δ 0.86−0.96 (m, 6H), 1.19−2.02 (m, 12H), 2.25−2.40 (m, 2H), 2.76−2.79 (m, 2H), 4.44 (dd, J_1 = 2.7 Hz, J_2 = 10.8 Hz, 1H), 7.01−7.04 (m, 1H), 7.18−7.25 (m, 2H), 7.39−7.40 (m, 1H); ^{13}C NMR ($CDCl_3$, TMS) δ 13.1, 13.9, 21.8, 22.4, 23.4, 25.6, 25.7, 27.2, 35.5, 39.0, 42.1, 91.4, 122.6, 123.7, 124.5, 129.4, 133.9, 147.8, 153.7, 161.5; HRMS calcd for $C_{21}H_{27}NOClI$ 471.0826, found 471.0818.

Typical Procedure for the Preparation of Compound 10. To a THF and H_2O (1:1, 10 mL) solution of compound **3e** (1.0 mmol) at room temperature was added NBS (3.0 mmol). The above reaction mixture was then stirred at room temperature for 6h to generate compound **10**, which was monitored by TLC. The above reaction mixture was then extracted with diethyl ether. The extract was washed with brine and dried over $MgSO_4$. The solvent was evaporated in vacuo to give a red-orange oil, which was purified by column chromatograph (silica, CH_2Cl_2/hexane = 1:3) to afford **10**.

10: colorless liquid; isolated yield 84% (446 mg); ^{1}H NMR ($CDCl_3$, TMS) δ 0.84−1.73 (m, 23H), 2.15−2.36 (m, 5H), 4.10 (dd, J_1 = 3.0 Hz, J_2 = 10.5 Hz, 1H), 7.02−7.06 (m, 1H), 7.37−7.38 (m, 1H), 7.47−7.50 (m, 1H); ^{13}C NMR ($CDCl_3$, TMS) δ 13.3, 13.9, 14.3, 15.0, 16.3, 21.3, 21.5, 21.7, 26.4, 28.8, 35.0, 38.1, 60.7, 95.2, 116.0, 123.8, 125.9, 133.2, 133.8, 134.4, 147.4, 153.8, 162.6; HRMS calcd for $C_{23}H_{32}NOClBr_2$ 531.0539, found 531.0539.

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Supporting Information Available: Experimental details and spectroscopic characterization of all new compounds; structures and tables of crystallographic data, atomic coordinates, thermal parameters, and bond lengths and angles for **6b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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