Highly Efficient Conversion of Alcohols to Isocyanides

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Abstract: Treatment of tertiary alcohols with silver salts ($AgClO_4$, $AgBF_4$, or AgOTf) and trimethylsilyl cyanide (TMSCN), followed by hydrolysis, directly affords excellent yields of corresponding isocyanides. This reaction proceeds selectively with tertiary alcohols in the presence of primary and secondary alcohols.

Key words: alcohols, isocyanides, silver salts, trimethylsilyl cyanide

The versatility of isocyanide is well known because of its various biological active components, the variety of its reactions in organic syntheses, and its ability to function as a bonding partner for metals in complexes.[1,2] Especially, tertiary isocyanide is a versatile compound because biologically active isocyanoterpenes, which have been isolated from marine organisms, have tertiary isocyanide as the main component.[2] Isocyanides are commonly prepared by dehydrating formamides.[3] However, the preparation of tertiary isocyanides presents some difficulties. Harsh conditions are generally required in order to prepare tertiary alkyl amines as precursors of formamides. In addition, product yield is low throughout the process. Therefore, we have been attempting to develop a simple, efficient method for preparing tertiary isocyanides.

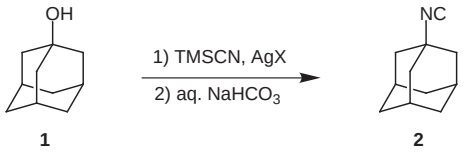
Recently, we reported methods for preparing tertiary isocyanides from alcohols[4] and alkenes[5] with TMSCN as an isocyano source.[6] In the conversion of alcohols to isocyanides with zinc salts and TMSCN, however, product yield was often low because the corresponding alkene and alkyl halide were obtained as byproducts. For this reason, a more efficient method of preparing tertiary isocyanides from tertiary alcohols was needed. After making various efforts to solve this problem, we found that silver salts work more efficiently than zinc salts. We describe herein a highly efficient method for preparing isocyanides from alcohols by using silver salts and TMSCN.

The reactions were carried out in nitromethane with 1.2 equivalents each of silver salts (AgX) and TMSCN unless otherwise noted. Results for the reaction of 1-adamantanol **1** are summarized in Scheme 1 and Table 1. These results show that 1-adamantyl isocyanide **2** was obtained with $AgClO_4$, $AgBF_4$, or AgOTf as a Lewis acid. In all cases, **2** was obtained with no significant byproducts, but the reaction proceeded more effectively with $AgClO_4$ than with $AgBF_4$ or AgOTf. Nitrile was not observed under these conditions.[7] However, other silver salts such as AgF, AgCl, AgBr, AgI, AgO_2CCF_3, $AgNO_3$, and $AgIO_3$ gave the corresponding trimethylsilylethers.[4,8]

Table 1 Reactions of 1-Adamantanol **1** with TMSCN and AgX

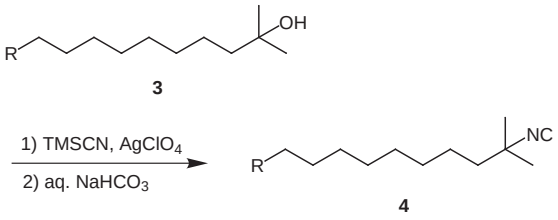
Entry	Reagent	Time (h)	Yield (%)[a]
1	$AgClO_4$	0.5	99 (94)[b]
2[c]	$AgBF_4$	1	99
3	AgOTf	1	98

[a] Determined by GLC analysis.
[b] Isolated yield.
[c] 1.5 equiv of TMSCN and 2.0 equiv of $AgBF_4$ were used.

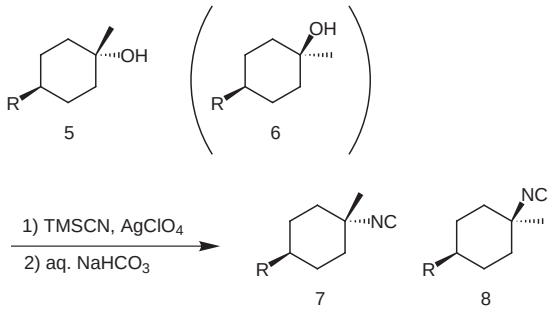


Scheme 1

In this study, we attempted to carry out the reactions of various tertiary alcohols with $AgClO_4$ and TMSCN (Schemes 2, 3 and Tables 2, 3). Each gave high yields of the corresponding isocyanides. Various functional groups, including ester, sulfide, amine, amide, and imide were not affected under these conditions. Moreover, this reaction proceeded selectively with tertiary alcohols in the presence of primary and secondary alcohols. As shown in Scheme 3 and Table 3, stereoselectivity was examined with the substrates when the 1-methyl-1-cyclohexanol derivatives possessed substituents in the 4-position. In all cases, stereoisomeric alcohols gave the same products with approximately the same ratio, and the stereochemistry of the major isomer was the axially oriented isocyano substituent. However, the orientation of the isocyano group at the substituent in the 4-position was controlled by the type of functional group.



Scheme 2



Scheme 3

The reaction mechanism is proposed in Scheme 4. In order to elucidate the reaction mechanism, similar reactions, shown in Scheme 1, were carried out in $CDCl_3$. The ^1H NMR signals of the mixture of **2** and a silver salt appeared downfield relative to those of **2**.[9] However, the ^1H NMR spectra of the intermediate were evidently different from the simple mixture.[10] Moreover, the signal of the TMS group, which does not belong to either trimethylsilane or TMSCN, was observed in ^1H NMR analyses. Although a perfect structure has not been elucidated, these results suggest that the existence of the intermediate **A**, which was bonding to the TMS group, and the counter-anion of intermediate **A** were ligands of silver salt or hydroxyion. The intermediate **A** was then hydrolyzed to isocyanide **2**.

Table 2 Reactions of *tert*-Alcohols with TMSCN and $AgClO_4$

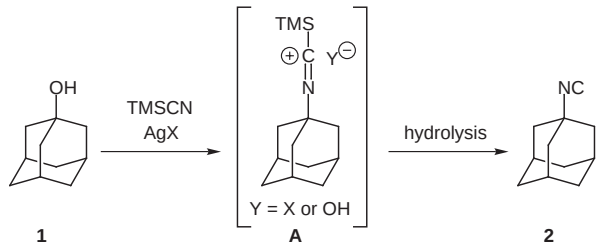
Entry[a]	Substrate	R	Product	Yield (%)[b]
1	**3a**	$HOCH_2$	**4a**	91
2	**3b**	MeO_2C	**4b**	93
3	**3c**	$PhSCH_2$	**4c**	94
4	**3d**	Phthalimide-CH_2	**4d**	96
5	**3e**	H_2NCH_2	**4e**	70
6	**3f**	$AcNHCH_2$	**4f**	91

[a] All reactions were carried out at ambient temperature for 1 h with 1.2 equiv each of TMSCN and $AgClO_4$ under Ar.
[b] Isolated yield.

Table 3 Reactions of *tert*-Alcohols with TMSCN and $AgClO_4$

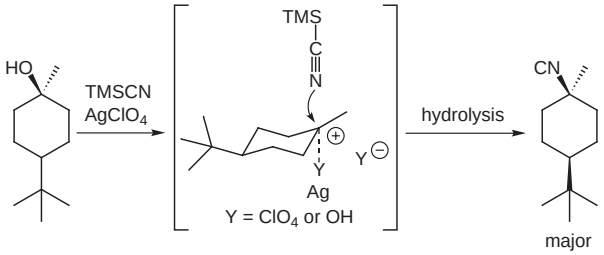
Entry[a]	Substrate	R	Products[b]	Yield (%)[c]
1	**5a**	t-Bu	**7a : 8a**	98[d]
2	**6a**		(4 : 96)[d]	97[d]
3	**5b**	HO	**7b : 8b**	80
4	**6b**		(75 : 25)[e]	80
5	**5c**	AcO	**7c : 8c**	90
6	**6c**		(75 : 25)[e]	89
7	**5d**	$AcOCH_2$	**7d : 8d**	89
8	**6d**		(9 : 91)[e]	90

[a] All reactions were carried out at ambient temperature for 1 h with 1.2 equiv each of TMSCN and $AgClO_4$ under Ar.
[b] The ratio of stereoisomer is represented in parentheses.
[c] Isolated yield, except for entry 1 and 2.
[d] Determined by GLC analysis.
[e] Determined by ^1H NMR analysis.

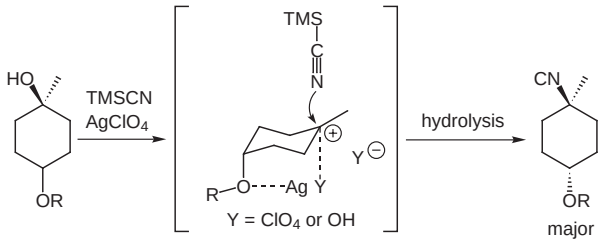


Scheme 4

The stereochemistry of this reaction is represented in Schemes 5 and 6. After the generation of the carbocation, the counter-anion coordinates with the carbocation to from a less-hindered site as the silver salt. Subsequently, the attack of TMSCN tends to occur from the side opposite the silver salt. In the case of Scheme 5, the attack of TMSCN occurs from *cis*-orientation at the tertiary butyl group through a conformation in which the substituent is equatorially oriented. In the case of Scheme 6, the attack of TMSCN tends to occur from *trans*-orientation at the alkoxy group through a conformation in which the substituent is axially oriented by the coordination with silver salt. The above information clearly shows that stereoselectivity is reversed by the type of functional group.



Scheme 5



Scheme 6

In conclusion, we have developed a highly efficient method of converting alcohols to their corresponding isocyanides. We believe this method provides a convenient and useful way to synthesize tertiary isocyanides.

Table 4 Spectral Data of Compound **2**–**7**

Compound	^{1}H NMR[a, b] δ, *J* (Hz)	^{13}C NMR[c, d] δ, *J* (Hz)	IR ν (cm^{-1})
2	2.12–2.07 (m, 3 H), 2.06–2.00 (m, 6 H), 1.70–1.63 (m, 6 H)	151.65 (t, *J* = 5.0), 54.24 (t, *J* = 5.0), 43.58, 35.51, 28.74	(KBr) 2935, 2859, 2123
3a	3.64 (t, 2 H, *J* = 6.6), 1.57 (quintet, 2 H, *J* = 6.9), 1.46 (m, 2 H), 1.38–1.24 (m, 12 H), 1.21 (s, 6 H)	77.08, 63.03, 43.95, 32.77, 30.14, 29.54, 29.54, 29.41, 29.20, 25.72, 24.33	(KBr) 3358 (br), 2966, 2923, 2970, 1184, 1070
3b	3.66 (s, 3 H), 2.30 (t, 2 H, *J* = 7.4), 1.57–1.50 (m, 3 H), 1.49–1.42 (m, 2 H), 1.42–1.37 (m, 10 H), 1.24–1.37 (m, 10 H), 1.20 (s, 6 H)	174.21, 71.04, 51.47, 44.02, 34017, 30.16, 29.47, 29.30, 29.25, 29.19, 25.02, 24.38	(neat) 3348 (br), 2960, 2931, 2856, 1741, 1201, 1170
3c	7.33–7.24 (m, 4 H), 7.15 (m, 1 H), 2.91 (t, 2 H, *J* = 7.4), 1.64 (m, 2 H), 1.48–1.23 (m, 14 H), 1.20 (s, 6 H)	137.00, 128.81, 128.75, 125.59, 71.08, 44.06, 33.68, 30.23, 29.63, 29.52, 29.32, 29.23, 29.23, 28.90, 24.42	(KBr) 3379 (br), 3078, 3057, 2968, 2927, 2854, 1853, 1481, 1153
3d	7.83 (dd, 2 H, *J* = 5.4, 3.1), 7.70 (dd, 2 H, *J* = 5.4, 3.1), 3.67 (t, 2 H, *J* = 7.6), 1.67 (m, 2 H), 1.45 (m, 2 H), 1.37–1.22 (m, 12 H), 1.20 (s, 6 H)	168.37, 133.76, 132.15, 123.10, 71.06, 44.06, 38.13, 30.16, 29.55, 29.44, 29.30, 29.20, 28.64, 26.90, 24.37	(KBr) 3367 (br), 2969, 2931, 2852, 1774, 1716, 1149
3e	2.98 (t, 2 H, *J* = 7.7), 1.77 (quintet, 2 H, *J* = 7.7), 1.46 (m, 2 H), 1.40 (m, 2 H), 1.37–1.26 (m, 10 H), 1.20 (s, 6 H)	71.10, 43.89, 39.93, 29.89, 29.24, 29.24, 29.02, 28.75, 27.53, 26.37, 24.14	(KBr) 3384 (br), 3340 (br), 2937, 2980, 2850, 1633, 1139
3f	5.44 (br s, 1 H), 3.23 (q, 2 H, *J* = 6.7), 1.97 (s, 3 H), 1.63 (br s, 1 H), 1.49 (m, 2 H), 1.46 (m, 2 H), 1.36–1.25 (m, 12 H), 1.21 (s, 6 H)	169.97, 71.03, 43.98, 39.70, 30.13, 29.62, 29.51, 29.43, 29.25, 29.25, 26.89, 24.31, 23.39	(KBr) 3330 (br), 3255 (br), 2971, 2929, 2848, 1656, 1560, 1186
4a	3.64 (t, 2 H, *J* = 6.6), 1.63 (br s, 1 H), 1.60–1.52 (m, 4 H), 1.48–1.41 (m, 2 H), 1.40 (t, 6 H, *J* = 1.8), 1.38–1.27 (m, 10 H)	152.57 (t, *J* = 4.3), 63.04, 57.43 (t, *J* = 5.0), 42.45, 32.76, 29.45, 29.45, 29.36, 29.36, 28.97, 25.69, 24.10	(neat) 3948 (br), 2983, 2929, 2854, 2130, 1070
4b	3.66 (s, 3 H), 2.30 (t, 2 H, *J* = 7.4), 1.67–1.40 (m, 6 H), 1.39 (t, 6 H, *J* = 1.8), 1.35–1.27 (m, 8 H)	174.15, 152.79 (t, *J* = 4.2), 57.43 (t, *J* = 5.0), 51.47, 42.53, 34.15, 29.49, 29.31, 29.21, 29.15, 29.06, 29.98, 24.18	(neat) 2983, 2935, 2856, 2130, 1739, 1201, 1170
4c	7.33–7.24 (m, 4 H), 7.15 (m, 1 H), 2.91 (t, 2 H, *J* = 7.4), 1.65 (m, 2 H), 1.58–1.39 (m, 4 H), 1.39 (t, 6 H, *J* = 1.8), 1.33–1.26 (m, 10 H)	152.76 (t, *J* = 4.2), 136.97, 128.82, 128.75, 125.59, 57.45 (t, *J* = 5.0), 42.55, 33.67, 29.55, 29.46, 29.45, 29.21, 29.19, 29.07, 28.86, 24.21	(neat) 3078, 3057, 2981, 2927, 2854, 2131, 1583, 1481
4d	7.84 (dd, 2 H, *J* = 5.5, 3.1), 7.70 (dd, 2 H, *J* = 5.5, 3.1), 3.68 (t, 2 H, *J* = 7.4), 1.67 (m, 2 H), 1.54 (m, 2 H), 1.39 (t, 6 H, *J* = 1.7), 1.49–1.23 (m, 12 H)	168.48, 152.85 (t, *J* = 5.0), 133.85, 132.22, 123.16, 57.41 (t, *J* = 5.0), 42.50, 38.06, 29.47, 29.38, 29.36, 29.12, 28.99, 28.59, 26.82, 24.12	(neat) 2981, 2933, 2856, 2130, 1772, 1712
4e	2.68 (t, 2 H, *J* = 6.9), 1.58–1.52 (m, 2 H), 1.48–1.40 (m, 4 H), 1.39 (t, 6 H, *J* = 1.8), 1.37–1.26 (m, 8 H)	151.96 (t, *J* = 5.0), 56.69 (t, *J* = 5.0), 41.79, 41.54, 33.15, 28.82, 28.81, 28.77, 28.72, 28.31, 26.18, 23.45	(neat) 3322 (br), 2981, 2927, 2854, 2130, 1579
4f	5.49 (br s, 1 H), 3.23 (q, 2 H, *J* = 6.7), 1.97 (s, 3 H), 1.58–1.40 (m, 6 H), 1.39 (t, 6 H, *J* = 1.8 Hz), 1.35–1.23 (m, 10 H)	169.86, 152.66 (t, *J* = 5.0), 57.46 (t, *J* = 5.0), 42.51, 39.73, 29.66, 29.47, 29.41, 29.37, 29.26, 29.06, 26.93, 24.15, 23.44	(neat) 3295 (br), 2981, 29229, 2854, 2130, 1656, 1562
5a	1.75–1.69 (m, 4 H), 1.41 (m, 2 H), 1.31 (br s, 1 H), 1.21 (s, 3 H), 1.09 (m, 2 H), 1.00 (m, 1 H), 0.86 (s, 9 H)	71.03, 47.76, 40.93, 32.25, 27.67, 25.32, 25.00	(KBr) 3276 (br), 2969, 2933, 2861, 2840, 1139
6a	1.68 (m, 2 H), 1.59 (m, 2 H), 1.38–1.26 (m, 4 H), 1.17 (br s, 1 H), 1.20 (s, 3 H), 0.92 (m, 1 H), 0.87 (s, 9 H)	68.95, 47.68, 39.32, 32.40, 31.36, 27.62, 22.69	(KBr) 3372 (br), 2960, 2930, 2865, 2840, 1126
5b	3.89 (m, 1 H), 1.90 (m, 2 H), 1.75 (m, 2 H), 1.55–1.44 (m, 4 H), 1.28 (br s, 1 H), 1.27 (s, 3 H), 1.14 (br s, 1 H)	67.79, 67.77, 35.15, 30.46, 28.99	(KBr) 3313 (br), 3260 (br), 2956, 2923, 2863, 1135

Table 4 (continued)

Compound	^{1}H NMR[a, b] δ, *J* (Hz)	^{13}C NMR[c, d] δ, *J* (Hz)	IR ν (cm^{-1})
6b	3.61 (m, 1 H), 1.77 (m, 2 H), 1.72−1.60 (m, 4 H), 1.44 (m, 2 H), 1.42 (br s, 1 H), 1.23 (s, 3 H), 1.20 (br s, 1 H)	69.89, 68.54, 36.85, 31.06, 30.22	(KBr) 3261 (br), 2966, 2944, 2863, 1137, 1126
5c	4.93 (m, 1 H), 2.04 (s, 3 H), 1.90 (m, 2 H), 1.73−1.60 (m, 4 H), 1.51 (m, 2 H), 1.27 (s, 3 H), 1.14 (br s, 1 H)	170.65, 70.17, 69.31, 34.81, 29.72, 26.67, 21.41	(neat) 3409 (br), 2953, 2933, 2871, 1725, 1252, 1126
6c	4.71 (m, 1 H), 2.04 (s, 3 H), 1.79−1.74 (m, 4 H), 1.70 (m, 2 H), 1.50 (m, 2 H), 1.24 (s, 3 H), 1.16 (br s, 1 H)	170.72, 72.08, 68.56, 36.62, 30.04, 27.21, 21.43	(KBr) 3330 (br), 2962, 2942, 2869, 1731, 1247, 1126
5d	3.92 (d, 2 H, *J* = 6.2), 2.06 (s, 3 H), 1.67 (m, 2 H), 1.61−1.56 (m, 3 H), 1.52 (br s, 1 H), 1.42−1.33 (m, 4 H), 1.23 (s, 3 H)	171.23, 69.29, 37.98, 36.39, 31.45, 24.87, 24.87, 20.97	(neat) 3421 (br), 2956, 2931, 2858, 1737, 1241, 1130
6d	3.93 (d, 2 H, *J* = 6.6), 2.06 (s, 3 H), 1.76 (m, 2 H), 1.70 (m, 2 H), 1.68 (m, 2 H), 1.46 (ddd, 2 H, *J* = 12.8, 12.8, 4.0), 1.31 (br s, 1 H), 1.23 (s, 3 H), 1.14 (m, 1 H)	171.21, 70.70, 68.49, 38.99, 36.07, 26.66, 26.15, 20.95	(neat) 3363 (br), 2967, 2926, 2856, 1739, 1249, 1164
7a	1.97 (m, 2 H), 1.78 (m, 2 H), 1.69 (m, 2 H), 1.41 (br t, 3 H, *J* = 1.8), 1.08 (m, 2 H), 1.04 (m, 1 H), 0.85 (s, 9 H)	151.53 (t, *J* = 5.0), 56.70 (t, *J* = 5.0), 47.09, 39.39, 32.34, 27.51, 24.29, 23.02	(KBr) 2954, 2925, 2869, 2856, 2134
8a	1.94 (m, 2 H), 1.69 (m, 2 H), 1.42 (m, 2 H), 1.40 (t, 3 H, *J* = 1.7), 1.30 (m, 2 H), 0.93 (m, 1 H), 0.88 (s, 9 H)	153.43 (t, *J* = 5.0), 58.02 (t, *J* = 5.0), 47.06, 38.82, 32.44, 30.08, 27.57, 22.84	(KBr) 2962, 2925, 2869, 2841, 2136
7b	4.08 (m, 1 H), 1.91 (m, 2 H), 1.81 (m, 2 H), 1.72−1.66 (m, 4 H), 1.44 (t, 3 H, *J* = 1.8), 1.28 (br s, 1 H)	153.80 (t, *J* = 5.0), 64.67, 57.85 (t, *J* = 5.0), 32.41, 29.54, 28.77	(KBr) 3300 (br), 2977, 2933, 2858, 2132, 1137
8b	3.57 (m, 1 H), 1.99−1.88 (m, 4 H), 1.70 (m, 2 H), 1.49 (br s, 1 H), 1.43 (t, 3 H, *J* = 1.8), 1.42 (m, 2 H)	154.61 (t, *J* = 5.0), 69.29, 57.01 (t, *J* = 5.0), 36.68, 30.98, 29.25	(KBr) 3432, 2980, 2942, 2888, 2861, 2152, 1132
7c	5.05 (m, 1 H), 2.05 (s, 3 H), 1.92 (m, 2 H), 1.84 (m, 2 H), 1.76 (m, 2 H), 1.67 (m, 2 H), 1.47 (t, 3 H, *J* = 1.8)	170.27, 154.47 (t, *J* = 5.0), 67.72, 57.49 (t, *J* = 5.0), 32.95, 29.64, 25.82, 21.32	(neat) 2970, 2946, 2871, 2127, 1733, 1243
8c	4.65 (m, 1 H), 2.05 (s, 3 H), 1.98 (m, 2 H), 1.92 (m, 2 H), 1.80 (m, 2 H), 1.47 (m, 2 H), 1.45 (t, 3 H, *J* = 1.8)	170.63, 154.93 (t, *J* = 5.0), 71.12, 56.96 (t, *J* = 5.0), 36.41, 29.15, 27.03, 21.31	(neat) 2970, 2952, 2859, 2130, 1737, 1234
8d	3.95 (d, 2 H, *J* = 6.6), 2.06 (s, 3 H), 1.95 (m, 2 H), 1.72 (m, 2 H), 1.60 (m, 1 H), 1.45 (m, 2 H), 1.44 (t, 3 H, *J* = 1.8), 1.35 (m, 2 H)	171.12, 154.17 (t, *J* = 5.0), 68.70, 57.84 (t, *J* = 5.0), 37.53, 35.89, 29.99, 24.86, 20.93	(neat) 2979, 2939, 2859, 2130, 1741, 1247, 1230

[a] **2**, **3a**, **3d**, **3e**, **4a**, **4d**, **5a**, **6a**, **5b**, **6b**, **5c**, **6c**, **5d**, **6d**, **7a**, **7b**, **8b**, **7c**, **8c**, **8d**: 600 MHz, $CDCl_3$.
[b] **3b**, **3c**, **3f**, **4b**, **4c**, **4e**, **4f**, **8a**: 400 MHz, $CDCl_3$.
[c] **2**, **3a**, **3d**, **3e**, **3f**, **4a**, **4d**, **4e**, **4f**, **5a**, **6a**, **5b**, **6b**, **5c**, **6c**, **5d**, **6d**, **7b**, **8b**, **7c**, **8c**, **8d**: 150.8 MHz, $CDCl_3$.
[d] **3b**, **3c**, **4b**, **4c**, **7a**, **8a**: 100.4 MHz, $CDCl_3$.

Mps were determined on a MEL-TEMP (Laboratory Device) and are uncorrected. NMR spectra were obtained in $CDCl_3$ on a JEOL EX-270, AL-400, or alpha-600 spectrometer. All ^{1}H NMR spectra are reported in ppm relative to TMS. All ^{13}C NMR spectra are reported in ppm relative to the central line of the triplet for $CDCl_3$ at 77.03 ppm. IR spectra were recorded on a JEOL WINSPEC-50 spectrometer. Low- and high-resolution mass spectra were recorded on a JEOL SX-102A spectrometer under ionization condition (70 eV). GLC analyses were carried out on a HEWLETT PACKARD HP 4980A fitted with a HP-5 column (10 m × 0.53 mm i.d.). Chromatographic separations were carried out on a silica gel column (Fuji Silysia Chemical BW-127ZH; 100–270 mesh) unless otherwise stated. Nitromethane was purchased from Wako Pure Chemical Industries, Ltd. and used without further purification. The stereochemistry of the compounds in Scheme 3 was established from NOE experiments and coupling constants.

10-Methylundecane-1,10-diol (3a)

Prepared from methyl 10-unedecenoate (5.0 g, 25.2 mmol) as follows. First, the tertiary alcohol, which was the precursor of **3a**, was synthesized according to methylation with methyllithium (2.5 equiv). Then, **3a** was obtained from the precursor according to ozonolysis followed by reduction with $NaBH_4$ (2.0 equiv), yield: 83%.

White solid, mp: 45–46 °C.

LR-EIMS: *m/z* (%) = 187 (M^+–CH_3, 12), 169 (M^+–CH_5O, 10), 151 (M^+–CH_7O_2, 6), 59 (M^+–$C_9H_{19}O$, 100).

HR-EIMS calcd for $C_{11}H_{23}O$ [M^+–CH_3]: 187.1698. Found: 187.1698.

Methyl 10-Hydroxy-10-methylundecanoate (3b)
Prepared from **3a** (500 mg, 2.47 mmol) according to standard Jones oxidation followed by methylation with MeI (5.0 equiv) and K_2CO_3 (3.0 equiv), yield: 83%.

Colorless oil.

LR-EIMS: *m/z* (%) = 215 (M^+–CH_3, 20), 199 (M^+–CH_3O, 9), 183 (M^+– CH_3O_2, 80), 172 (M^+–C_3H_6O, 84), 87 (M^+–$C_9H_{19}O$, 100), 74 (M^+–$C_{10}H_{20}O$, 45), 59 (M^+–$C_{10}H_{19}O_2$ or M^+–$C_{11}H_{23}O$, 68).

HR-EIMS calcd for $C_{12}H_{23}O_3$ [M^+–CH_3]: 215.1647. Found: 215.1645.

2-Methyl-11-phenylthioundecan-2-ol (3c)
Prepared from **3a** (610 mg, 3.01 mmol) according to a standard Mitsunobu reaction with thiophenol (1.7 equiv), Ph_3P (1.3 equiv), and DEAD (1.3 equiv), yield: 34%.

Colorless oil.

LR-EIMS: *m/z* (%) = 294 (M^+, 35), 279 (M^+–CH_3, 15), 276 (M^+–H_2O, 31), 236 (M^+–C_3H_6O, 22), 123 (M^+–$C_{11}H_{23}O$, 41), 110 (M^+–$C_{12}H_{24}O$, 100).

HR-EIMS calcd for $C_{18}H_{30}OS$ [M^+]: 294.2017. Found: 294.2021.

2-(10-Hydroxy-10-methylundecyl)isoindoline-1,3-dione (3d)
Prepared from **3a** (971 mg, 4.80 mmol) according to a standard Mitsunobu reaction with phthalimide (1.5 equiv), Ph_3P (1.2 equiv), and DEAD (1.2 equiv), yield: 94%.

White solid, mp: 33–34 °C.

LR-EIMS: *m/z* (%) = 316 (M^+–CH_3, 24), 313 (M^+–H_2O, 28), 273 (M^+–C_3H_6O, 35), 160 (M^+–$C_{11}H_{23}O$, 100), 59 (M^+–$C_{17}H_{22}NO_2$, 9).

HR-EIMS calcd for $C_{19}H_{26}NO_3$ [M^+–CH_3]: 316.1913. Found: 316.1909. Calcd for $C_{20}H_{27}NO_2$ [M^+–H_2O]: 313.2042. Found: 313.2033.

11-Amino-2-methylundecan-2-ol (3e)
Prepared from **3d** (1.16 g, 3.50 mmol) according to a reaction with hydrazine monohydrate (2.0 equiv), yield: 78%.

White solid, mp: 65–66 °C.

LR-EIMS: *m/z* (%) = 201 (M^+, 1), 186 (M^+–CH_3, 100), 183 (M^+–H_2O, 31), 168 (M^+–CH_5O, 4), 143 (M^+–C_3H_6O, 41), 142 (M^+–C_3H_7O, 26), 59 (M^+–$C_9H_{20}N$, 44).

HR-EIMS calcd for $C_{12}H_{27}NO$ [M^+]: 201.2093. Found: 201.2090. Calcd for $C_{11}H_{24}NO$ [M^+–CH_3]: 186.1858. Found: 186.1854.

***N*-(10-Hydroxy-10-methylundecyl)acetamide (3f)**
Prepared from **3e** (263 mg, 1.31 mmol) according to acetylation with acetic anhydride and pyridine (excess), yield: 84%.

White solid, mp: 43–44 °C.

LR-EIMS: *m/z* (%) = 228 (M^+–CH_3, 88), 225 (M^+–H_2O, 100), 210 (M^+–CH_5O, 6), 186 (M^+–C_2H_3NO, 63), 185 (M^+–C_2H_4NO, 44), 170 (M^+–C_3H_7NO, 33), 59 (M^+–$C_{11}H_{22}NO$, 33).

HR-EIMS calcd for $C_{13}H_{26}NO_2$ [M^+–CH_3]: 228.1964. Found: 228.1971. Calcd for $C_{14}H_{27}NO$ [M^+–H_2O]: 225.2093. Found: 225.2083.

***trans*-4-(*tert*-Butyl)-1-methylcyclohexan-1-ol (5a)**
***cis*-4-(*tert*-Butyl)-1-methylcyclohexan-1-ol (6a)**
Prepared from 4-*tert*-butylcyclohexanone (5.0 g, 32.4 mmol) according to methylation with methyllithium (1.5 equiv), yield: 92% (**5a**:**6a** = 40:60).

5a:
White solid, mp: 92–93 °C.

LR-EIMS: *m/z* (%) = 170 (M^+, 28), 155 (M^+–CH_3, 62), 137 (M^+–CH_5O, 44), 113 (M^+–C_4H_9, 40), 95 (M^+–$C_4H_{11}O$, 60), 71 (M^+–$C_6H_{11}O$, 100), 57 (M^+–$C_7H_{13}O$, 78).

HR-EIMS calcd for $C_{11}H_{22}O$ [M^+]: 170.1671. Found: 170.1668.

6a:
White solid, mp: 67–68 °C.

LR-EIMS: *m/z* (%) = 170 (M^+, 35), 155 (M^+–CH_3, 65), 137 (M^+–CH_5O, 46), 113 (M^+–C_4H_9, 32), 95 (M^+–$C_4H_{11}O$, 80), 71 (M^+–$C_6H_{11}O$, 93), 57 (M^+–$C_7H_{13}O$, 100).

HR-EIMS calcd for $C_{11}H_{22}O$ [M^+]: 170.1671. Found: 170.1671.

***trans*-1-Methylcyclohexane-1,4-diol (5b)**
***cis*-1-Methylcyclohexane-1,4-diol (6b)**
Prepared from 1,4-cyclohexanedione *mono*-ethyleneketal (6.0 g, 38.4 mg) as follows. First, 4-hydroxy-4-methylcyclohexanone, which was the precursor of **5b** and **6b**, was synthesized according to methylation with methyllithium (1.5 equiv) followed by hydrolysis of acetal with aqueous HCl. Then, **5b** and **6b** were obtained from the precursor according to reduction with $NaBH_4$ (1.5 equiv), yield: 48% (**5b**:**6b** = 25:75).

5b:
White solid, mp: 123–124 °C.

LR-EIMS: *m/z* (%) = 130 (M^+, 1.3), 115 (M^+–CH_3, 17), 112 (M^+–H_2O, 14), 97 (M^+–CH_5O, 68), 84 (M^+–C_2H_6O, 17), 72 (M^+–C_3H_7O, 100).

HR-EIMS calcd for $C_7H_{14}O_2$ [M^+]: 130.0994. Found: 130.0990. Calcd for $C_6H_{11}O_2$ [M^+–CH_3]: 115.0759. Found: 115.0776.

6b:
White solid, mp: 121–123 °C.

LR-EIMS: *m/z* (%) = 130 (M^+, 1.3), 115 (M^+–CH_3, 12), 112 (M^+–H_2O, 15), 97 (M^+–CH_5O, 64), 84 (M^+–C_2H_6O, 41), 72 (M^+–C_3H_7O, 100).

HR-EIMS calcd for $C_7H_{14}O_2$ [M^+]: 130.0994. Found: 130.0994. Calcd for $C_6H_{11}O_2$ [M^+–CH_3]: 115.0759. Found: 115.0756.

***trans*-4-Hydroxy-4-methylcyclohexyl Acetate (5c)**
***cis*-4-Hydroxy-4-methylcyclohexyl Acetate (6c)**
Prepared from **5b** (170 mg, 1.30 mmol) and **6b** (170 mg, 1.30 mmol) according to acetylation with acetic anhydride and pyridine (excess), respectively, yield: 96% (**5c**), 95% (**6c**).

5c:
Colorless oil.

LR-EIMS: *m/z* (%) = 157 (M^+–CH_3, 7), 112 (M^+–$C_2H_4O_2$, 100), 97 (M^+–$C_3H_7O_2$, 60).

HR-EIMS calcd for $C_8H_{13}O_3$ [M^+–CH_3]: 157.0865. Found: 157.0859. Calcd for $C_7H_{12}O$ [M^+–$C_2H_4O_2$]: 112.0888. Found: 112.0884.

6c:
White solid, mp: 50–51 °C.

LR-EIMS: *m/z* (%) = 157 (M^+–CH_3, 5), 112 (M^+–$C_2H_4O_2$, 100), 97 (M^+–$C_3H_7O_2$, 52).

HR-EIMS calcd for $C_8H_{13}O_3$ [M^+–CH_3]: 157.0865. Found: 157.0860. Calcd for $C_7H_{12}O$ [M^+–$C_2H_4O_2$]: 112.0888. Found: 112.0886.

***trans*-(4-Hydroxy-4-methylcyclohexyl)methyl Acetate (5d)**
***cis*-(4-Hydroxy-4-methylcyclohexyl)methyl Acetate (6d)**
Prepared from 4-hydroxy-4-methylcyclohexanone[12] (930 mg, 7.14 mmol) as follows. First, the aldehyde, which was the precursor of **5d** and **6d**, was synthesized according to a standard Wittig reaction with (methoxymethyl)triphenylphosphonium chloride (2.1 equiv) and BuLi (2.0 equiv) followed by hydrolysis of enolate with PPTS (cat.). Then, **5d** and **6d** were obtained from the precursor according to reduction with $NaBH_4$ (1.5 equiv) followed by acetylation with acetic anhydride and pyridine (excess), yield; 40% (**5d**:**6d** = 40:60).

5d:
Colorless oil.

LR-EIMS: *m/z* (%) = 171 (M^+–CH_3, 15), 126 (M^+–$C_2H_4O_2$, 100), 111 (M^+–$C_3H_7O_2$, 38), 108 (M^+–$C_2H_6O_3$, 31), 97 (M^+–$C_4H_9O_2$, 71), 93 (M^+–$C_3H_9O_3$, 38).

HR-EIMS calcd for $C_9H_{15}O_3$ [M^+–CH_3]: 171.1021. Found: 171.1019. Calcd for $C_8H_{14}O$ [M^+–$C_2H_4O_2$]: 126.1045. Found: 126.1039.

6d:
White solid, mp: 36–37 °C.

LR-EIMS: *m/z* (%) = 171 (M^+–CH_3, 13), 126 (M^+–$C_2H_4O_2$, 100), 111 (M^+–$C_3H_7O_2$, 44), 108 (M^+–$C_2H_6O_3$, 46), 97 (M^+–$C_4H_9O_2$, 80), 93 (M^+–$C_3H_9O_3$, 36).

HR-EIMS calcd for $C_9H_{15}O_3$ [M^+–CH_3]: 171.1021. Found: 171.1012. Calcd for $C_8H_{14}O$ [M^+–$C_2H_4O_2$]: 126.1045. Found 126.1048.

Tertiary Isocyanide; General Procedure
TMSCN (0.6 mmol) and silver salt (0.6 mmol) under Ar were added to a solution of alcohol (0.5 mmol) in nitromethane (2 mL). The reaction mixture was adequately stirred at ambient temperature. Then sat. $NaHCO_3$ (2 mL) was added. After stirring for an additional 10 min, the mixture was filtered with Celite and washed with Et_2O or EtOAc. The combined organic extracts were washed with H_2O and brine and dried ($MgSO_4$). The crude product was analyzed by GLC or purified by silica-gel column chromatography.

1-Adamantyl Isocyanide (2)[11]
Obtained from 1-adamantanol **1** after purification by silica-gel column chromatography (hexane/EtOAc, 20:1).

White solid, mp: 185–186 °C.

LR-EIMS: *m/z* (%) = 161 (M^+, 41), 135 (M^+–NC, 100).

HR-EIMS calcd for $C_{11}H_{15}N$ [M^+]: 161.1204. Found: 161.1207.

10-Hydroxy-1,1-dimethyldecyl isocyanide (4a)
Obtained from **3a** after purification by silica-gel column chromatography (hexane/EtOAc, 2:1).

Colorless oil.

LR-EIMS: *m/z* (%) = 211 (M^+, 1.3), 196 (M^+–CH_3, 25), 185 (M^+–CN, 16), 69 (M^+–$C_9H_{18}O$, 100).

HR-EIMS calcd for $C_{13}H_{25}NO$ [M^+]: 211.1936. Found: 211.1938. Calcd for $C_{12}H_{22}NO$ [M^+–CH_3]: 196.1701. Found: 196.1687.

Methyl 10-Isocyano-10-methylundecanoate (4b)
Obtained from **3b** after purification by silica-gel column chromatography (hexane/EtOAc, 10:1).

Colorless oil.

LR-EIMS: *m/z* (%) = 224 (M^+–CH_3, 15), 212 (M^+–HCN, 20), 192 (M^+–CH_3O_2, 7), 87 (M^+–$C_{10}H_{18}N$, 43), 83 (M^+–$C_9H_{16}O_2$, 45), 74 (M^+–$C_{11}H_{19}N$, 57), 69 (M^+–$C_{10}H_{18}O_2$, 100).

HR-EIMS calcd for $C_{13}H_{22}NO_2$ [M^+–CH_3]: 224.1651. Found: 224.1644. Calcd for $C_{13}H_{24}O_2$ [M^+–HCN]: 212.1776. Found: 212.1764.

1,1-Dimethyl-11-phenylthioldecyl Isocyanide (4c)
Obtained from **3c** after purification by silica-gel column chromatography (hexane/EtOAc, 15:1).

Colorless oil.

LR-EIMS: *m/z* (%) = 276 (M^+–HCN, 69), 123 (M^+–$C_{12}H_{22}N$, 50), 110 (M^+–$C_{13}H_{23}N$, 100), 69 (M^+–$C_{15}H_{22}S$, 32).

HR-EIMS calcd for $C_{18}H_{28}S$ [M^+–HCN]: 276.1912. Found: 276.1910.

2-(10-Isocyano-10-methylundecyl)isoindoline-1,3-dione (4d)
Obtained from **3d** after purification by silica-gel column chromatography (hexane/EtOAc, 9:1).

Colorless oil.

LR-EIMS: *m/z* (%) = 340 (M^+, 19), 313 (M^+–HCN, 46), 258 (M^+–C_3H_5N, 23), 160 (M^+–$C_{12}H_{22}N$, 100), 69 (M^+–$C_{17}H_{21}NO_2$, 9).

HR-EIMS calcd for $C_{21}H_{28}N_2O_2$ [M^+]: 340.2151. Found: 340.2151.

10-Amino-1,1-dimethyldecyl Isocyanide (4e)
Obtained from **3e** after purification by silica-gel column chromatography (Fuji Silysia Chemical NH DM-1020; 100–200 mesh; EtOAc/MeOH, 10:1).

Colorless oil.

LR-EIMS: *m/z* (%) = 210 (M^+, 15), 195 (M^+–CH_3, 24), 183 (M^+–HCN, 100), 142 (M^+–C_4H_6N, 24), 69 (M^+–$C_9H_{19}N$, 86).

HR-EIMS calcd for $C_{13}H_{26}N_2$ [M^+]: 210.2096. Found: 210.2087. Calcd for $C_{12}H_{23}N_2$ [M^+–CH_3]: 195.1861. Found: 195.1861.

***N*-(10-Isocyano-10-methylundecyl)acetamide (4f)**
Obtained from **3f** after purification by silica-gel column chromatography (hexane/EtOAc, 1:3).

Colorless oil.

LR-EIMS: *m/z* (%) = 252 (M^+, 1), 225 (M^+–HCN, 100), 210 (M^+–C_2H_4N, 9), 182 (M^+–C_3H_4NO, 23), 69 (M^+–$C_{11}H_{21}NO$, 34).

HR-EIMS calcd for $C_{15}H_{28}N_2O$ [M^+]: 252.2202. Found 252.2201. Calcd for $C_{14}H_{27}NO$ [M^+–HCN]: 225.2093. Found: 225.2080.

***trans*-4-(*tert*-Butyl)-1-methylcyclohexyl Isocyanide (7a)**
***cis*-4-(*tert*-Butyl)-1-methylcyclohexyl Isocyanide (8a)**
These compounds were obtained from **5a** or **6a** according to the general procedure. However, authentic samples of these compounds were prepared from the corresponding formamides according to dehydration with *p*-toluenesulfonyl chloride (2.0 equiv) and pyridine (excess) because the stereoisomers were easily separated by silica-gel column chromatography. The corresponding formamides were prepared from **5a** (850 mg, 5.0 mmol) following the modified Ritter reaction,[13] yield: 45% (**7a**:**8a** = 86:14)

7a:
White solid, mp: 39–41 °C.

LR-EIMS: *m/z* (%) = 164 (M^+–CH_3, 12), 153 (M^+–NC, 60), 137 (M^+–C_2H_4N, 19), 122 (M^+–C_4H_9, 12), 109 (M^+–C_5H_{10}, 12), 97 (M^+–C_5H_8N, 100), 96 (M^+–C_5H_9N, 75), 81 (M^+–$C_6H_{12}N$, 76), 57 (M^+–$C_8H_{12}N$, 61).

HR-EIMS calcd for $C_{11}H_{18}N$ [M^+–CH_3]: 164.1439. Found: 164.1437.

8a:
White solid, mp: 40–41 °C.

LR-EIMS: *m/z* (%) = 164 (M^+–CH_3, 18), 152 (M^+–NC, 9), 137 (M^+–C_2H_4N, 20), 122 (M^+–C_4H_9, 9), 109 (M^+–C_5H_{10}, 8), 96 (M^+–C_5H_9N, 100), 81 (M^+–$C_6H_{12}N$, 79), 57 (M^+–$C_8H_{12}N$, 16).

HR-EIMS calcd for $C_{11}H_{18}N$ [M^+–CH_3]: 164.1439. Found: 164.1433.

***trans*-4-Hydroxy-1-methylcyclohexyl Isocyanide (7b)**
***cis*-4-Hydroxy-1-methylcyclohexyl Isocyanide (8b)**
Obtained from **5b** or **6b** after purification by silica-gel column chromatography (hexane/EtOAc, 1:1–1:2).

7b:
White solid, mp: 51–53 °C.

LR-EIMS: *m/z* (%) = 112 (M^+–HCN, 12), 94 (M^+–CH_3NO, 18), 84 (M^+–C_3H_5N, 100).

HR-EIMS calcd for $C_7H_{12}O$ [M^+–HCN]: 112.0888. Found: 112.0889.

8b:
White solid, mp: 53–54 °C.

LR-EIMS: *m/z* (%) = 112 (M^+–HCN, 14), 94 (M^+–CH_3NO, 22), 84 (M^+–C_3H_5N, 100).

HR-EIMS calcd for $C_7H_{12}O$ [M^+–HCN]: 112.0888. Found: 112.0885.

***trans*-4-Isocyano-4-methylcyclohexyl Acetate (7c)**
***cis*-4-Isocyano-4-methylcyclohexyl Acetate (8c)**
Obtained from **5c** or **6c** after purification by silica-gel column chromatography (hexane/EtOAc, 4:1–3:1).

7c:
Colorless oil.

LR-EIMS: *m/z* (%) = 112 (M^+–C_3H_3NO, 23), 94 (M^+–$C_3H_5NO_2$, 100), 79 (M^+–$C_4H_8NO_2$, 52).

HR-EIMS calcd for $C_7H_{12}O$ [M^+–C_3H_3NO]: 112.0888. Found: 112.0891. Calcd for C_7H_{10} [M^+–$C_3H_5NO_2$]: 94.0783. Found: 94.0766.

8c:
Colorless oil.

LR-EIMS: *m/z* (%) = 112 (M^+–C_3H_3NO, 26), 94 (M^+–$C_3H_5NO_2$, 100), 79 (M^+–$C_4H_8NO_2$, 43).

HR-EIMS calcd for $C_7H_{12}O$ [M^+–C_3H_3NO]: 112.0888. Found: 112.0889. Calcd for C_7H_{10} [M^+–$C_3H_5NO_2$]: 94.0783. Found: 94.0766.

***cis*-(4-Isocyano-4-methylcyclohexyl)methyl Acetate (8d)[14]**
Obtained from **5d** or **6d** after purification by silica-gel column chromatography (hexane/EtOAc, 4:1–3:1) as a diastereoisomeric mixture.

Colorless oil.

LR-EIMS: *m/z* (%) = 180 (M^+–CH_3, 1), 169 (M^+–NC, 3), 135 (M^+–$C_2H_4O_2$, 4), 108 (M^+–$C_3H_5NO_2$, 100), 93 (M^+–$C_4H_8NO_2$, 73), 81 (M^+–$C_5H_8NO_2$, 89).

HR-EIMS calcd for $C_{10}H_{14}NO_2$ [M^+–CH_3]: 180.1025. Found: 180.1022. Calcd for $C_{10}H_{17}O_2$ [M^+–NC]: 169.1229. Found: 169.1229.

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