Synthesis Y. Ichikawa et al. Paper

Chirality Transfer from a Chiral Primary Alcohol Equivalent Through Allyl Cyanate-to-Isocyanate Rearrangement: Synthesis of (+)-Geranyllinaloisocyanide

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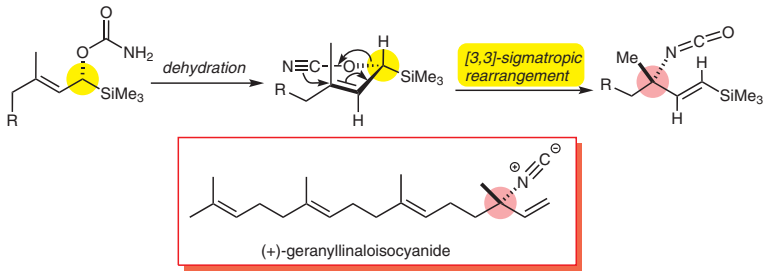


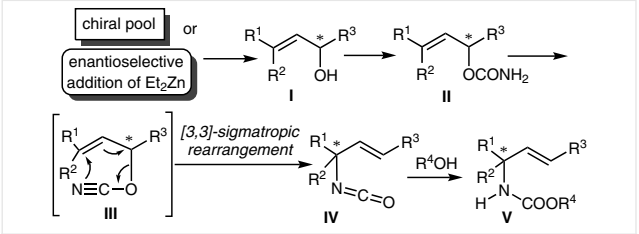
Received: 20.02.2019
Accepted after revision: 06.03.2019
Published online: 03.04.2019
DOI: 10.1055/s-0037-1612422; Art ID: ss-2019-f0110-op

Abstract A new approach was developed to construct quaternary stereogenic centers bearing nitrogen substituents in an enantioselective manner. The strategy takes advantage of [1,3]-chirality transfer from a chiral primary alcohol equivalent through an allyl cyanate-to-isocyanate rearrangement. This approach was employed in an efficient eight-step synthesis of the marine natural product, (+)-geranyllinaloisocyanide, in 43% overall yield.

Key words Hoppe reaction, α-silyl allyl alcohol, allyl cyanate-to-isocyanate rearrangement, chirality transfer, marine natural products

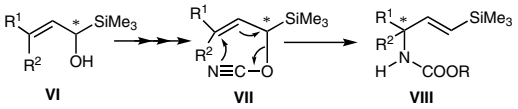
Stereoselective construction of quaternary stereogenic centers poses one of the most difficult challenges in modern organic synthesis.[1] In particular, synthetic methods to generate nitrogen-substituted quaternary chiral stereogenic centers have attracted our continuing interest due to their ubiquity in nitrogen-containing natural products and pharmaceuticals.[2] In order to address problems associated with installation of stereogenic centers of this type, we have developed methods focusing on allyl cyanate-to-isocyanate rearrangement reaction,[3] which is a highly stereoselective carbon–nitrogen bond forming process at sterically encumbered positions (Scheme 1).[4]

In the first step of sequences, a chiral allyl alcohol **I** is prepared from a chiral starting material or by enantioselective addition of diethylzinc to an α,β-unsaturated aldehyde (Scheme 1). The allyl alcohol **I** is then transformed to the corresponding allyl carbamate **II**. Dehydration of **II** generates the allyl cyanate **III**, which undergoes concerted [3,3]-sigmatropic rearrangement to produce allyl isocyanate **IV** with high degree of [1,3]-chirality transfer.[5] Treatment of the resulting allyl isocyanate **IV** with an alcohol (R^4OH) gives rise to the corresponding carbamate **V**, which is the protected form of the corresponding allyl amine. The strategy presented in Scheme 1 has been utilized by us and others in the synthesis of natural products and biologically important compounds.[6]



Scheme 1 Synthesis of chiral quaternary stereogenic centers bearing nitrogen substituents through allyl cyanate-to-isocyanate rearrangement

Our continuing efforts in this area led to the development of a new strategy for stereoselective construction of quaternary stereogenic centers bearing nitrogen substituents (Scheme 2). In the approach, the chiral primary alcohol equivalent **VI**, described earlier by Ireland,[7] serves as the starting material. Rearrangement of the allyl cyanate **VII** derived from **VI** produces the chiral allyl carbamate **VIII**. Protodesilylation of the vinylsilane moiety in **VIII** generates terminal vinyl compound that would have been formed from the corresponding achiral primary alcohol. Moreover, the vinylsilane produced as an intermediate in this sequence can be used advantageously in other processes such as palladium-catalyzed cross-coupling[8] and transformations leading to vinyl halides, α,β-unsaturated ketones, and vinyl boronic esters,[9] which would expand the synthetic utility of this approach. Although chirality transfer of α-silyl allyl alcohol utilizing Ireland–Claisen rearrangement is a well-known process,[10] no reports exist describing its application to the allyl cyanate-to-isocyanate rearrangement.



Scheme 2 A new approach to synthesize chiral nitrogen-substituted quaternary stereocenters

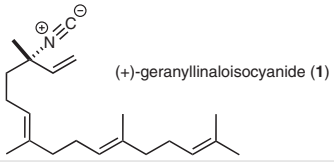
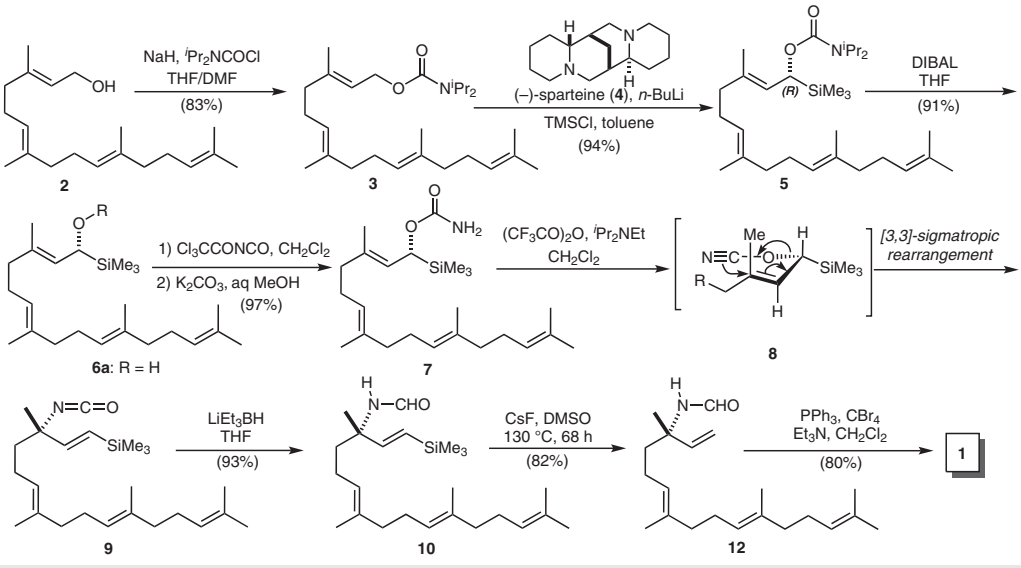


Figure 1 Structure of marine natural product (+)-geranyllinaloisocyanide

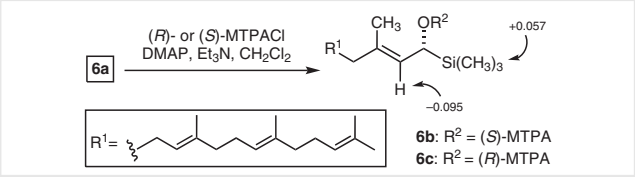
In order to explore the use of α-silyl allyl alcohol in allyl cyanate-to-isocyanate rearrangement (Scheme 2), we set up an asymmetric synthesis of (+)-geranyllinaloisocyanide (**1**) (Figure 1). This substance was isolated from the marine sponge *Halichondria sp*. by Scheuer and Burreson.[11] Spectroscopic analysis and degradation studies led to elucidation of this marine natural product as an isocyanide analogue of the jasmine constituent, geranyllinalool. The first racemic synthesis of **1**, reported in 1993,[12] and the first asymmetric synthesis, described in 2011,[13] were both accomplished using routes in which the allyl cyanate-to-isocyanate rearrangement serves as a key step. Although the first asymmetric synthesis of **1** starting with (–)-lactic acid methyl ester determined the absolute stereochemistry of the quaternary stereogenic carbon possessing the isocyano group as *S*-configuration, the synthetic route is considerably long (25 steps) and inefficient (5.3% overall yield). As a result, we were stimulated to explore a new, potentially more efficient synthetic route to **1** that is based on the strategy outlined in Scheme 2.

The synthesis began with the (–)-sparteine-mediated enantioselective deprotonation and silylation protocol reported by Hoppe (Scheme 3).[14] *N*,*N*-Diisopropylcarbamate **3** was prepared by the reaction of geranylgeraniol (**2**)[15] with diisopropylcarbamoyl chloride and sodium hydride. Enantioselective lithiation of **3** using *n*-butyllithium/(–)-sparteine in toluene at –78 °C in the presence of chlorotrimethylsilane produced the α-silyl geranylgeranyl carbamate **5** along with its enantiomer in 94% yield. The stereochemistry of the major enantiomer **5** with *R*-configuration was initially assigned based on the analogy to that observed in the product of Hoppe's reaction using geranyl *N*,*N*-diisopropylcarbamate. Treatment of carbamate **5** with excess DIBAL in THF furnished allyl alcohol **6a** in 91% yield.

In order to obtain evidence for the assigned stereochemistry and to determine the enantiomeric purity of **6a**, we prepared the corresponding (*S*)- and (*R*)-2-methoxy-2-phenyl-2-(trifluoromethyl)acetic acid (MTPA) esters **6b** and **6c** (Scheme 4). Stereochemical assignment according to the modified Mosher–Kusumi MTPA ester analysis method was made by calculation of the ^{1}H NMR chemical shift differences ($\Delta\delta$ values: $\Delta\delta = \delta_S - \delta_R$).[16] This led to assignment of the *R*-configuration to the stereogenic center in **6a**, which is the same as that predicted for **5** based on Hoppe's observation. The enantiomeric ratio of (*R*)/(*S*)-**6a** was determined to be 93:7 (86% ee) by ^{1}H NMR analysis of Mosher esters **6b** and **6c**.[17]



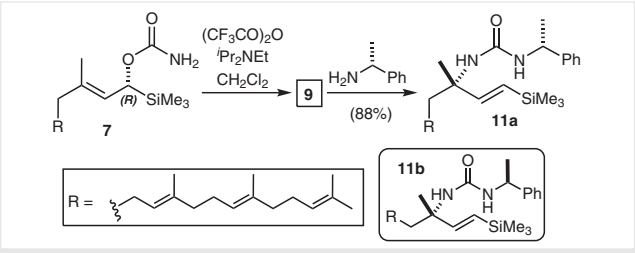
Scheme 3 Synthesis of (+)-geranyllinaloisocyanide starting from a chiral primary alcohol equivalent



Scheme 4 Absolute stereochemistry determination by Δδ values for the Mosher ester derivatives

With chiral α-silyl alcohol **6a** in hand, we next explored the [1,3]-chirality transfer to install the nitrogen-substituted quaternary stereogenic center by using allyl cyanate-to-isocyanate rearrangement (Scheme 3). Treatment of **6a** with trichloroacetyl isocyanate in dichloromethane and subsequent hydrolysis of the resultant *N*-trichloroacetyl carbamate with potassium carbonate in aqueous methanol afforded allyl carbamate **7** in 97% yield. Dehydration of **7** employing trifluoroacetic anhydride and *N*,*N*-diisopropylethylamine generated allyl cyanate **8**,[18] which underwent spontaneous [3,3]-sigmatropic rearrangement. After careful workup, the formed isocyanate **9** was immediately dissolved in THF and treated with lithium triethylborohydride ($LiEt_3BH$) to produce formamide **10** in 93% overall yield from **7**.[19]

In order to check the level of [1,3]-chirality transfer in the rearrangement reaction, allyl isocyanate **9**, generated from **7**, was treated with (*R*)-α-methylbenzylamine to afford urea **11a** and the corresponding diastereomer in a 93:7 ratio (Scheme 5). In a control experiment, **9** was treated with (±)-α-methylbenzylamine to afford a 1:1 mixture of **11a** and **11b**,[20] which clearly demonstrates that kinetic resolution does not occur in the urea forming process. Considering the optical purity of **6a**, the results of these experiments show that the level of [1,3]-chirality transfer using α-silyl allyl alcohol is quantitative, which may be a consequence of the involvement of a well-defined cyclic transition state in the [3,3]-sigmatropic rearrangement of **8** in which the trimethylsilyl group adopts a pseudo-equatorial position.



Scheme 5 Determination of selectivity for allyl cyanate-to-isocyanate rearrangement

Protodesilylation of **10** was more difficult than we initially anticipated (Scheme 3). When the conditions using aqueous tetrafluoroboric acid (HBF_4) in acetonitrile reported by Ireland were used, no reaction occurred. After screening a number of conditions [*n*-Bu_4NF or *n*-$Bu_4NF(^tBuOH)_4$ in various solvents,[21] CuI/TBAF,[22] HF·Et_3N], we found that the use of a large excess of cesium fluoride (10 equiv) in DMSO at 130 °C for 68 hours led to formation of formamide **12** in 82% yield. Finally, dehydration of **12** employing a modification of Appel's conditions completed the synthesis of (+)-geranyllinaloisocyanide (**1**). The spectroscopic properties (optical rotation, IR, ^1H and ^{13}C NMR) of the synthetic material **1** match those reported for the natural product and the previously reported synthetic material (see Supporting Information).

In summary, we have uncovered the first example of allyl cyanate-to-isocyanate rearrangement starting with enantiomerically enriched α-silyl allyl alcohol. In addition, we demonstrated that the rearrangement reaction occurs with a high degree of [1,3]-chirality transfer. This process is highlighted by its use in an eight-step route for synthesis of the marine natural product, (+)-geranyllinaloisocyanide (**1**) in 43% overall yield. Further applications of this method to the synthesis of nitrogen-containing natural products are underway in our laboratory.

Melting points were recorded on a micro melting point apparatus and are not corrected. Optical rotations were measured at the sodium D line with a 100 mm path length cell, and are reported as follows: $[\alpha]_D^T$, concentration (g/100 mL), and solvent. IR spectra are reported in wave numbers (cm^{-1}). ^1H NMR data are reported with the solvent resonance as the internal standard relative to $CHCl_3$ (δ 7.26) as follows; chemical shift (δ), multiplicity (standard abbreviations), coupling constants (*J*, given in Hz) and integration. ^{13}C NMR chemical shifts (δ) are recorded in parts per million (ppm) relative to $CDCl_3$ (δ = 77.0) as an internal standard. Because formamides **10** and **12** exist as mixtures of rotamers on the NMR time sale, the ^1H and ^{13}C NMR signals for the minor rotamers are listed in curly brackets and parentheses, respectively. High-resolution mass spectra (HRMS) are reported in *m*/*z*. Reactions were run under an atmosphere of argon when the reactions were sensitive to moisture or O_2. CH_2Cl_2 was dried over molecular sieves 3 Å. Pyridine and Et_3N were stocked over anhydrous KOH. All other commercially available reagents were used as received.

(2*E*,6*E*,10*E*)-3,7,11,15-Tetramethylhexadeca-2,6,10,14-tetraenyl Diisopropylcarbamate (3)

To a suspension of NaH (510 mg, 60% dispersion in mineral oil, washed with hexane before use, 13.2 mmol) in THF (10.0 mL) was added geranylgeraniol (**2**; 2.40 g, 8.26 mmol). After stirring at r.t. for 30 min, a solution of *N*,*N*-diisopropylcarbamoyl chloride (1.62 g, 9.92 mmol) in THF (6.0 mL) and DMF (4.0 mL) were added successively. The reaction mixture was stirred at r.t. for 2.5 h and then treated cautiously with MeOH and H_2O. The separated aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine, dried (anhyd Na_2SO_4), and then concentrated under reduced pressure to afford the residue (3.24 g), which was subjected to silica gel chromatography (1:10 EtOAc/hexane) to afford carbamate **3**; as a colorless oil yield: 2.87 g (83%).

IR (KBr): 2967, 2928, 1695, 1438, 1302, 1287, 1050 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 5.38 (t, *J* = 6.9 Hz, 1 H), 5.14–5.07 (m, 3 H), 4.60 (d, *J* = 6.9 Hz, 2 H), 2.12–2.06 (m, 8 H), 1.98–1.95 (m, 4 H), 1.70 (s, 3 H), 1.68 (s, 3 H), 1.61–1.57 (m, 11 H), 1.20 (d, *J* = 6.9 Hz, 12 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.8, 140.7, 135.3, 134.9, 131.2, 124.3, 124.1, 123.7, 119.5, 61.4, 45.9, 45.5, 39.7, 39.5, 26.7, 26.6, 26.2, 25.6, 21.1, 21.0, 17.6, 16.4, 16.0, 15.9.

HRMS (ESI): *m*/*z* calcd for $C_{27}H_{48}NO_2$ [M + H]$^+$: 418.3680; found: 418.3679.

(*R*,2*E*,6*E*,10*E*)-3,7,11,15-Tetramethyl-1-(trimethylsilyl)hexadeca-2,6,10,14-tetraenyl Diisopropylcarbamate (5)

N,*N*-Diisopropylcarbamate **3** (2.30 g, 5.58 mmol) was dissolved in toluene (ca. 2 mL) in a 50 mL round-bottomed flask and the solvent was removed azeotropically by rotary evaporation. After drying under vacuum, the flask was charged with toluene (15.0 mL), (–)-sparteine (**4**; 2.18 mL, 9.48 mmol), and chlorotrimethylsilane (1.27 mL, 10.0 mmol, distilled from CaH_2 before use). To this solution cooled to –78 °C with a MeOH/dry ice bath was added *n*-BuLi (1.64 M solution in hexane, 5.50 mL, 8.92 mmol) dropwise over 5 min. After stirring at –78 °C for 2 h, a few drops of MeOH were added to quench the reaction and the cooling bath was removed. Sat. aq NH_4Cl and H_2O were added and the separated aqueous layer was extracted with Et_2O (3 ×). The combined organic layers were washed with brine, dried (anhyd Na_2SO_4), filtered through a cotton plug, and then concentrated to afford the crude product **5** (3.05 g). Purification by silica gel chromatography (1:10 EtOAc/hexane) afforded **5** as colorless liquid; yield: 2.57 g (94%); $[\alpha]_D^{24}$ +6.7 (*c* 1.00, $CHCl_3$).

IR (KBr): 2965, 2928, 1691, 1435 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 5.35 (d, *J* = 10.3 Hz, 1 H), 5.18 (d, *J* = 10.3 Hz, 1 H), 5.11–5.09 (m, 3 H), 2.16–1.93 (m, 12 H), 1.69 (s, 3 H), 1.68 (s, 3 H), 1.58–1.61 (m, 9 H), 1.27–1.09 (m, 12 H), 0.05 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.3, 135.8, 135.0, 134.8, 131.2, 124.3, 124.2, 124.0, 122.5, 67.4, 46.4, 44.8, 39.9, 39.7, 39.7, 26.7, 26.6, 25.6, 21.5, 20.8, 17.6, 16.9, 16.0, 15.9, –3.5.

HRMS (ESI): *m*/*z* calcd for $C_{30}H_{56}NO_2Si$ [M + H]$^+$: 490.4075; found: 490.407118.

HRMS (ESI): *m*/*z* calcd for $C_{30}H_{55}NO_2SiNa$ [M + Na]$^+$: 512.3894; found: 512.3895.

(*R*,2*E*,6*E*,10*E*)-3,7,11,15-Tetramethyl-1-(trimethylsilyl)hexadeca-2,6,10,14-tetraen-1-ol (6a)

To a solution of *N*,*N*-diisopropylcarbamate **5** (2.41 g, 4.92 mmol) in THF (25.0 mL) cooled to 0 °C was added DIBAL (1 M solution in hexane, 50.0 mL, 50.0 mmol). After stirring at r.t. for 4 h, the reaction mixture was cooled to 0 °C, and cautiously treated with MeOH (ca. 3 mL) and sodium potassium tartrate (30.0 g, 106 mmol) in H_2O (50 mL). After vigorous stirring at r.t. for 30 min, the separated aqueous layer was extracted with Et_2O (3 ×). The combined organic layers were washed with brine and dried (anhyd Na_2SO_4). Concentration under reduced pressure gave a residue (1.91 g), which was purified by silica gel chromatography (1: 10 EtOAc/hexane) to afford allyl alcohol **6a** as a colorless oil; yield: 1.62 g (91%); $[\alpha]_D^{26}$ +39.0 (*c* 1.00, $CHCl_3$).

IR (KBr): 3393, 2962, 2923, 2854, 1245 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 5.28 (d, *J* = 10.3 Hz, 1 H), 5.12–5.09 (m, 3 H), 4.19 (d, *J* = 10.3 Hz, 1 H), 2.17–2.03 (m, 8 H), 2.00–1.97 (m, 4 H), 1.68 (s, 3 H), 1.63–1.58 (m, 9 H), 0.04 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 135.2, 135.1, 134.9, 131.2, 125.9, 124.3, 124.2, 123.9, 64.4, 39.9, 39.7, 39.7, 26.7, 26.6, 25.7, 17.6, 16.7, 16.0, 16.0, –4.1.

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{42}OSiNa$ [M + Na]$^+$: 385.2897; found: 385.28955.

(*R*,2*E*,6*E*,10*E*)-3,7,11,15-Tetramethyl-1-(trimethylsilyl)hexadeca-2,6,10,14-tetraenyl Carbamate (7)

To a solution of **6a** (1.58 g, 4.36 mmol) in CH_2Cl_2 (8.0 mL) cooled to –20 °C was added trichloroacetyl isocyanate (0.56 mL, 4.75 mmol). After stirring at –20 °C for 30 min, the solution was treated with a few drops of MeOH and concentrated under reduced pressure. The resulting residue was dissolved in a mixture of MeOH (8.0 mL) and 2 M aq K_2CO_3 (8.6 mL). After stirring at r.t. for 90 min, MeOH was evaporated under reduced pressure. The aqueous layer was extracted with EtOAc (3 ×), and the combined organic layers were washed with brine, dried (anhyd Na_2SO_4), and then concentrated under reduced pressure. Purification by silica gel chromatography (1:5 EtOAc/hexane) afforded carbamate **7** as a clear oil; yield: 1.72 g (97%); $[\alpha]_D^{25}$ +24.7 (*c* 1.00, $CHCl_3$).

IR (KBr): 3337, 2962, 2923, 2854, 1717, 1367, 1247 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 5.26 (d, *J* = 10.3 Hz, 1 H), 5.17 (d, *J* = 10.3 Hz, 1 H), 5.12–5.08 (m, 3 H), 4.52–4.47 (br, 2 H), 2.17–1.94 (m, 12 H), 1.69 (br s, 3 H), 1.68 (br s, 3 H), 1.61–1.58 (m, 9 H), 0.04 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.5, 137.0, 135.2, 134.9, 131.2, 124.3, 124.2, 123.9, 121.7, 68.0, 39.9, 39.7, 39.7, 26.7, 26.6, 26.5, 25.7, 17.6, 16.9, 16.0, 15.9, –3.9.

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{44}NO_2Si$ [M + H]$^+$: 406.3136; found: 406.3137.

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{43}NO_2SiNa$ [M + Na]$^+$: 428.2955; found: 428.2956.

N-[(*S*,1*E*,6*E*,10*E*)-3,7,11,15-Tetramethyl-1-(trimethylsilyl)hexadeca-1,6,10,14-tetraen-3-yl]formamide (10)

Allyl carbamate **7** (550 mg, 1.36 mmol) was dissolved in toluene (ca. 2 mL) in a 100 mL round-bottomed flask and the solvent was removed azeotropically by rotary evaporation. After drying under vacuum, the flask was charged with *N*,*N*-diisopropylethylamine (1.42 mL, 8.14 mmol) and CH_2Cl_2 (10.0 mL). After cooling to –78 °C under argon atmosphere, a solution of trifluoroacetic anhydride (1 M solution in CH_2Cl_2, 2.70 mL, 2.70 mmol) was added. After stirring for 10 min at –78 °C, the reaction mixture was warmed to 0 °C. After stirring at 0 °C for 50 min, the resulting mixture was diluted with hexane and poured into aq pH 7 phosphate buffer (50 mL). The separated organic layer was washed with H_2O and brine, and dried (anhyd Na_2SO_4). Concentration under reduced pressure afforded the crude isocyanate **9**, which was immediately dissolved in THF (10.0 mL). The solution was cooled to 0 °C and then treated with $LiEt_3BH$ (1.0 M solution in THF, 4.10 mL, 4.10 mmol). After stirring at 0 °C for 60 min, the reaction mixture was diluted with Et_2O and the Et_2O layer was washed with sat. aq $NaHCO_3$, H_2O, and brine. After drying (anhyd Na_2SO_4), concentration under reduced pressure gave a residue (1.4 g), which was purified by silica gel chromatography (1:5 EtOAc/hexane) to furnish formamide **10** as a colorless oil; yield: 495 mg (93%); $[\alpha]_D^{22}$ +0.91 (*c* 1.00, $CHCl_3$).

IR (KBr): 3239, 2966, 2929, 1682, 1405, 1336 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = {8.14 (d, *J* = 2.3 Hz)}, 8.09 (d, *J* = 12.0 Hz, 1 H), {6.01 (d, *J* = 19.5 Hz)}, 5.97 (d, *J* = 18.9 Hz, 1 H), 5.82 (d, *J* = 18.9 Hz, 1 H), {5.63 (d, *J* = 19.5 Hz)}, 5.13–5.05 (m, 3 H), 2.12–1.90 (m, 10 H), 1.68 (s, 3 H), 1.60 (s, 3 H), 1.59 (s, 3 H), 1.58 (s, 3 H), {1.48 (s)}, 1.38 (s, 3 H), 0.079 (s, 9 H), {0.084 (s)}.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.3 (160.4), 149.5 (149.5), 136.1 (135.5), 135.0 (134.9), 131.1, 128.9, 126.6, 124.3 (124.0), 123.9 (123.6), 122.9, 57.6 (58.7), 41.5, 39.6 (39.6), 39.6 (39.2), 26.7, 26.4 (26.5), 26.2, 25.6 (24.9), 22.2 (22.5), 17.6, 15.9 (15.9), 9.9, –1.4 (–1.3).

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{44}NOSi$ [M + H]$^+$: 390.31874; found: 390.3187.

_N_-[(_S_,6_E_,10_E_)-3,7,11,15-Tetramethylhexadeca-1,6,10,14-tetraen-3-yl]formamide (12)

A solution of **10** (100 mg, 0.26 mmol) and CsF (390 mg, 2.57 mmol) in DMSO (8.0 mL) was heated at 130 °C for 68 h. The solution was diluted with Et_2O, the Et_2O layer was washed with H_2O and brine, and dried (anhyd Na_2SO_4). Concentration under reduced pressure gave a residue (101 mg), which was purified by silica gel chromatography (1:5 EtOAc/hexane) to afford **12** as a colorless oil; yield: 68 mg (82%); $[\alpha]_D^{26}$ +4.42 (*c* 2.05, $CHCl_3$).

IR (KBr): 3296, 2967, 2923, 2855, 1687, 1532, 1449 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.18 (d, *J* = 12.0 Hz, 1 H), {8.12 (d, *J* = 1.7 Hz)}, {5.94 (dd, *J* = 16.9, 10.9 Hz)}, 5.89 (d, *J* = 16.9, 10.3 Hz, 1 H), 5.22–5.06 (m, 5 H), 2.10–1.93 (m, 10 H), 1.68 (s, 3 H), 1.60 (s, 9 H), {1.48 (s)}, 1.40 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.1 (160.3), 142.9 (142.3), 136.1 (135.7), 135.0, 131.1, 124.3, 123.9 (124.0), 122.9 (123.5), 114.1 (112.5), 56.4 (57.5), 41.6, 39.6 (39.6), 39.5 (39.5), 26.7, 26.4 (26.4), 25.6 (26.2), 24.5, 22.1 (22.4), 17.6, 15.9 (15.9).

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{36}NO$ [M + H]$^+$ 318.2791; found: 318.2792.

Geranyllinaloisocyanide (1)

Formamide **12** (33 mg, 0.104 mmol) was dissolved in toluene (ca. 1 mL) in a 30 mL round-bottomed flask and the solvent was removed azeotropically by rotary evaporation. After drying under vacuum, the flask was charged with PPh_3 (82 mg, 0.31 mmol), Et_3N (0.10 mL, 0.73 mmol), and CH_2Cl_2 (1.0 mL). The flask was cooled in a NaCl/ice bath at –20 °C. CBr_4 (120 mg, 0.36 mmol) in CH_2Cl_2 (0.50 mL) was added. After stirring at –20 °C for 20 min, the reaction mixture was diluted with Et_2O. The resulting mixture was washed with 1N $KHSO_4$, water, sat aq $NaHCO_3$ and brine. After drying (anhyd Na_2SO_4), concentration under reduced pressure gave a residue (208 mg), which was purified by silica gel chromatography (1:30 EtOAc/hexane) to afford **1**; yield: 25 mg (80%); $[\alpha]_D^{22}$ +24.6 (*c* 2.25, CCl_4).

IR (KBr): 2966, 2923, 2855, 2131, 1452 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 5.65 (ddt, *J* = 16.6, 10.3, 2.6 Hz, 1 H), 5.44 (d, *J* = 16.6 Hz, 1 H), 5.21 (d, *J* = 10.3 Hz, 1 H), 5.11–5.08 (m, 3 H), 2.17–1.96 (m, 10 H), 1.68 (br s, 3 H), 1.608 (s, 3 H), 1.602 (s, 3 H), 1.594 (s, 3 H), 1.48 (t, *J* = 2.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.6, 138.1, 136.4, 135.0, 131.2, 124.3, 124.0, 122.3, 114.1, 62.6, 41.4, 39.7, 39.6, 28.4, 26.7, 26.4, 25.7, 22.7, 17.6, 16.0.

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{34}N$ [M + H]$^+$: 300.2686; found: 300.2686.

Acknowledgment

We sincerely thank Professor Hiyoshizo Kotsuki for giving us a 100-mL bottle of (–)-sparteine.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1612421.

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