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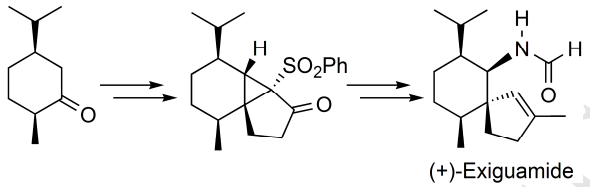

(+)-Exiguamide

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First enantioselective synthesis of exiguamide, a nitrogen-containing spirocyclic sesquiterpene isolated from the marine sponge *Geodia exigua*

Shunsuke Konishi [a, b], Yuki Mitani [a], Naoki Mori [a], Hirosato Takikawa [a, *], Hidenori Watanabe [a]

[a] *Department of Applied Biological Chemistry, Graduate School of Agricultural and Life Sciences, The University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113-8657, Japan*
[b] *Technical Research Institute, R&D Center, T. Hasegawa Co., Ltd., 29-7 Kariyado, Nakahara-ku, Kawasaki, Kanagawa 211-0022, Japan*

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ABSTRACT

(+)-Exiguamide is a nitrogen-containing spirocyclic sesquiterpene isolated from the marine sponge *Geodia exigua*. This study aims to report the first synthesis of both enantiomers of exiguamide, featuring the stereoselective intramolecular cyclopropanation and stereoselective homoconjugate addition of azide to cyclopropyl ketone as the key steps.

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1. Introduction

In 2002, (+)-exiguamide (**1**) was isolated from the marine sponge *Geodia exigua* by Ikegami *et al.* [1a] (Figure 1). This nitrogen-containing spirocyclic sesquiterpene was reported to inhibit the micromere formation of sea urchin embryos and subsequent spicule formation at a quite low concentration. The relative stereochemistry of (+)-**1** was elucidated unambiguously using X-ray crystallographic analysis, and its absolute configuration was determined as 5*S*,6*R*,7*S*,10*S* by applying the modified Mosher's method to the amine derived from (+)-**1** [1b]. There exist a certain number of structurally related marine natural products as follows: (+)-exicarbamate (**2**) and (−)-exigurin (**3**) isolated from *G. exigua* [1b]; (−)-10-*epi*-axisonitrile-3 (**4**) isolated from *Phyllidia pustulosa* [2]; and (−)-axamide-3 (**5**) and (+)-axisonitrile-3 (**6**) isolated from *Axinella cannabina* [3,4]. These compounds possess four contiguous stereogenic centers on the spiro[4.5]decane skeleton. Although the enantioselective synthesis of **5** and **6** has been reported [5], other four compounds (**1**–**4**) with exiguamide-type stereochemistry have not been synthesized yet. Inspired by the unique structure and interesting biological profile of **1**, we initiated our studies toward the enantioselective synthesis of **1**. Herein, we report the first synthesis of both enantiomers of **1**.

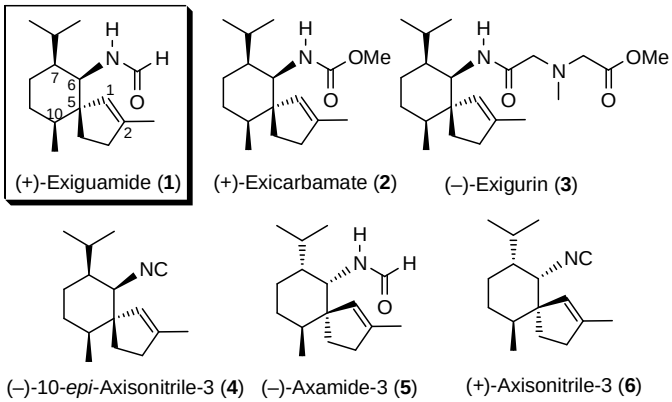

Figure 1. Structures of (+)-exiguamide (**1**) and related marine natural products.

2. Results and Discussion

Our synthetic plan for (+)-**1** is shown in Scheme 1. We anticipated that the synthesis of **1** would be achieved by Negishi coupling of **7** followed by reduction of azide and sulfonyl groups. The enol triflate **7** would be obtained from the tricyclic key intermediate **8** by stereoselective homoconjugate 1,5-addition of

* Corresponding author. Tel.: +81-3-5841-5119; fax: +81-3-5841-8019; e-mail: atakikawa@mail.ecc.u-tokyo.ac.jp

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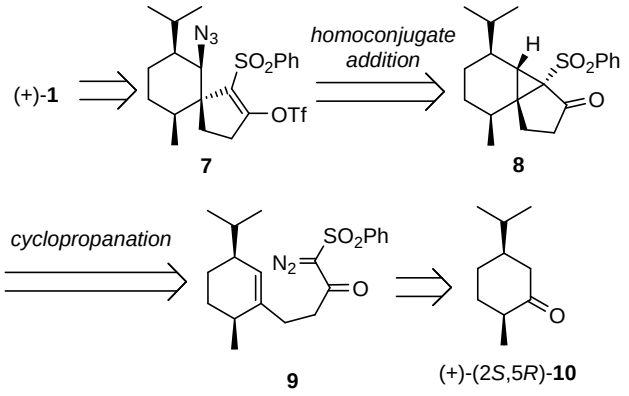
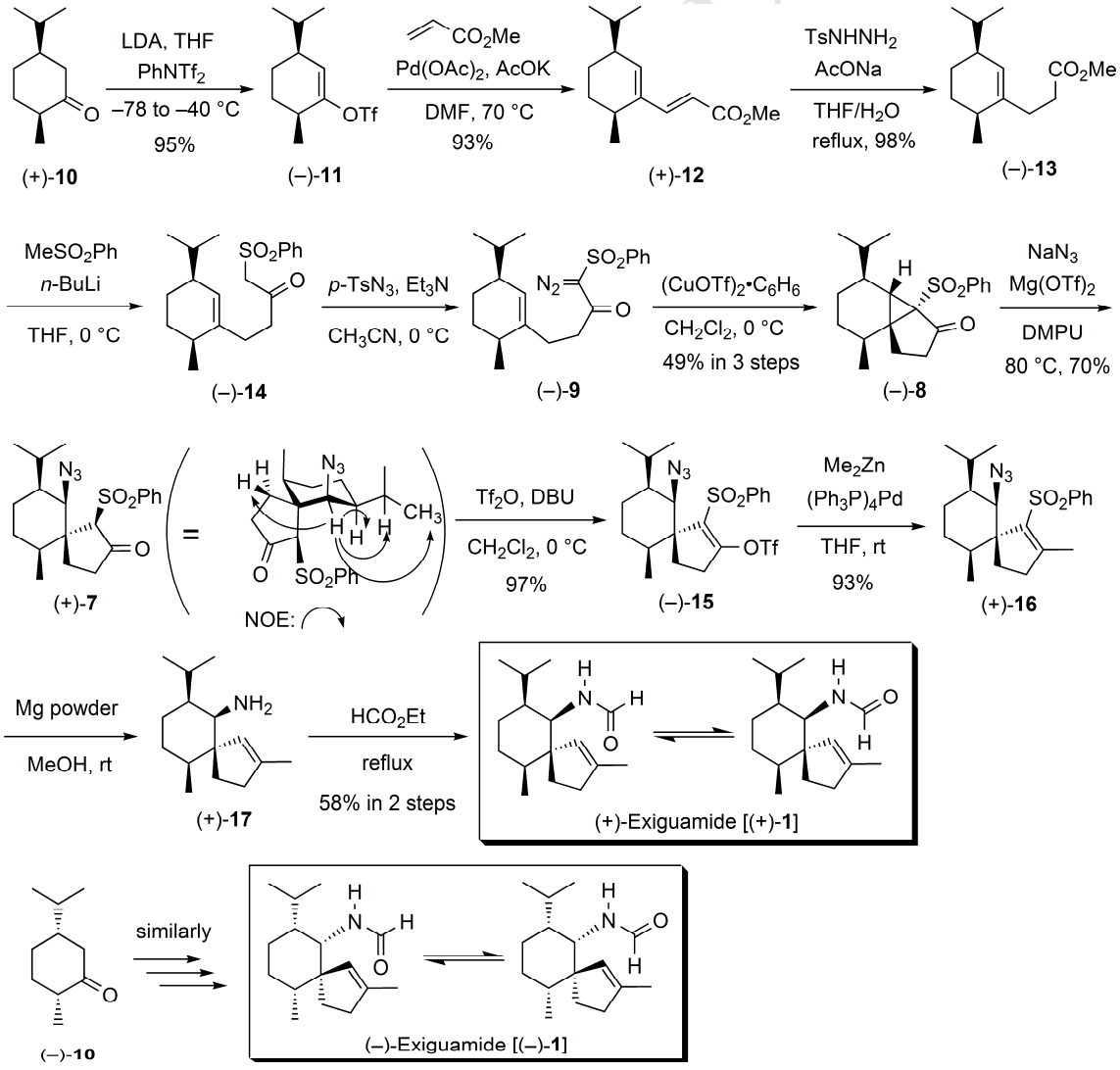
azide group and regioselective enol triflation. In this sequence, the sulfonyl group would play two important roles in accelerating the homoconjugate addition and controlling the regioselectivity in enolization. The cyclopropyl ketone **8** would be accessed by the stereoselective intramolecular cyclopropanation of **9**, which would be efficiently prepared from the known optically active ketone, (2*S*,5*R*)-carvomenthone [(+)-**10**] [6].



Scheme 1. Synthetic plan for (+)-**1**.

As shown in Scheme 2, our synthesis commenced with the enol triflation [7] of (2*S*,5*R*)-carvomenthone [(+)-**10**] that was prepared from (−)-(*R*)-carvone by hydrogenation and chromatographic purification [6]. The enol triflate (−)-**11** was subjected to Heck reaction with methyl acrylate to give (+)-**12** in excellent yield. The diimide reduction of the ester (+)-**12** (98%) followed by condensation with the lithium salt of methyl phenyl sulfone gave the β-ketosulfone (−)-**14**. The diazo-transfer reaction of (−)-**14** with *p*-TsN_3 was executed to afford the corresponding α-diazo-β-ketosulfone (−)-**9**. Subsequent intramolecular cyclopropanation of (−)-**9** was successfully catalyzed by $(CuOTf)_2 \cdot C_6H_6$ to afford the key intermediate (−)-**8** as a single diastereomer (49% in three steps).

With the key intermediate (−)-**8** in hand, attention was turned to the homoconjugate 1,5-addition of azide to (−)-**8**. Cyclopropanes with electron-withdrawing substituent are known to undergo nucleophilic ring-opening in 1,5-addition manner [8]. Especially, doubly activated cyclopropanes with geminal two electron-withdrawing substituents are preferable substrates for homoconjugate addition, and this type of reaction is known to be



Scheme 2. Synthesis of (+)- and (−)-**1**.

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accelerated with Lewis acid [9]. Thus, we chose $Mg(OTf)_2$ as the activator for conversion of **8** into **7**. As a result, the homoconjugate addition of azide to (−)-**8** proceeded in the presence of $Mg(OTf)_2$ in DMPU to afford (+)-**7** as a single diastereomer in 70% yield [10]. The relative stereochemistry of (+)-**7** was confirmed based on NOE experiments as depicted in Scheme 2. It is worth noting that the orientation of SO_2Ph group at C-1 was not clarified by NOE studies, but it was estimated to be β based on thermodynamic stability [11].

After converting (+)-**7** into the corresponding enol triflate (−)-**15** (97%), it was methylated by Negishi coupling under the following conditions, i.e., Me_2Zn, $Pd(PPh_3)_4$ in THF [12], affording (+)-**16** in 93% yield. Various reductive conditions were screened for reductive removal of sulfonyl group and transformation of azide into amine in one-pot. Although many reducing reagents, e.g., Raney-Nickel, Na-Hg and sodium naphthalenide, gave disappointing results, the desired reduction was successfully performed by treatment with Mg powder in MeOH to afford (+)-**17** [13,14]. Finally, the obtained amine (+)-**17** was heated in ethyl formate under reflux to give (+)-exiguamide (**1**) in 58% yield in two steps. The NMR data of synthetic (+)-**1** suggested that it was a mixture of two rotamers due to amide bond. ^{1}H NMR and ^{13}C NMR spectra of synthetic (+)-**1** are in good accordance with those of the natural product [1a]. The specific rotation value of the synthetic (+)-**1**, $[\alpha]_D^{25}$ = +48.4 (*c* 0.08, $CHCl_3$), showed the same sign to that of the natural product, $[\alpha]_D^{25}$ = +31.7 (*c* 0.08, $CHCl_3$) [1a]. Similarly, the synthesis of (−)-**1** was also achieved by starting from (2*R*,5*S*)-carvomenthone [(−)-**10**].

3. Conclusion

In summary, we achieved the first synthesis of (+)-exiguamide (**1**) using (2*S*,5*R*)-carvomenthone (**10**) as a chiral starting material. The overall yield was 15% in 11 steps. For the formation of the spirocyclic carbon framework, the diastereoselective intramolecular cyclopropanation and the following homoconjugate addition of azide were featured as the key steps. The synthesis of (−)-**1** was also achieved by starting from (2*R*,5*S*)-**10**. Biological evaluation of both enantiomers of **1** and the synthesis of exiguamide analogs are currently under investigation.

4. Experimental section

4.1. General

All air- and/or water-sensitive reactions were carried out under Ar atmosphere in dry solvents. Solvents were dried as follows; THF over sodium-benzophenone, CH_2Cl_2 over P_2O_5. All melting points (mps) were uncorrected. Melting points were recorded on a Yanaco Melting Point Apparatus. IR spectra were measured with a Jasco FT/IR-230 spectrophotometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) data were recorded by JEOL ECS400. Chemical shifts (δ) were referenced to the residual solvent peak as the internal standard ($CDCl_3$: δ_H = 7.26, δ_C = 77.0; CD_3OD: δ_H = 3.30, δ_C = 49.0; DMSO-d_6: δ_H = 2.49, δ_C = 39.5). Optical rotations were measured on a Jasco P-1030 polarimeter. The enantiomeric purities of **10** were determined by gas chromatography using a chiral separative column: 50% (w/w) 2,3-MOM-6-TBDMS-β-CD in OV-1701 (30 m, ID 0.25 mm, film 0.25 μm) [15]. The carrier gas was Helium with a flow rate of 0.7 mL/min. Injector and detector temperatures were 230 °C and 250 °C, respectively. The oven temperature was 40–180 °C, raised at 0.7 °C/min. Mass spectra were recorded on JEOL JMS SX102 or JEOL JMS-T100GCV. Column chromatography was performed on Merck silica gel 60 (0.060–0.200 mm), TLC was carried out on Merck glass plates pre-coated with silica gel 60 F_{254} (0.25 mm).

*4.2. (3S,6S)-3-Isopropyl-6-methylcyclohex-1-enyl trifluoromethanesulfonate [(−)-**11**]*

LDA was prepared by adding *n*-BuLi (2.65 M in hexane; 28.8 mL, 76.3 mmol) to a solution of $(i\text{-Pr})_2NH$ (10.7 mL, 76.3 mmol) in THF (150 mL) at −78 °C. The solution was stirred for 30 min at 0 °C and then cooled again to −78 °C. To the LDA solution was added a solution of (2*S*,5*R*)-carvomenthone [(+)-**10**] (9.69 g, 63.6 mmol, 98.0% ee) in THF (20 mL). After stirring for 1 h at −78 °C, $PhNTf_2$ (25.0 g, 70.0 mmol) was added to the mixture at −78 °C, and stirring was continued at −40 °C for 25 h. The reaction mixture was poured into sat. aq. NH_4Cl and extracted with hexane. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed over silica gel. Elution with hexane-EtOAc (50:1) gave (−)-**11** (17.4 g, 60.7 mmol, colorless oil, 95.4%). $[\alpha]_D^{25}$ −38.4 (*c* 1.0, $CHCl_3$); IR (film): 2964, 2941, 2875, 1681, 1416, 1209, 1143, 885 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, d, *J* = 5.2 Hz), 0.92 (3H, d, *J* = 5.2 Hz), 1.14 (3H, d, *J* = 7.2 Hz), 1.39 (1H, m), 1.52–1.70 (3H, m), 1.84 (1H, ddt, *J* = 2.8, 6.0, 13.2 Hz), 2.16 (1H, m), 2.49 (1H, m), 5.64 (1H, d, *J* = 2.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.91, 19.39, 19.56, 20.23, 29.46, 31.69, 31.87, 41.95, 118.46 (q, $^1J_{C-F}$= 318.5 Hz), 121.16, 153.73; HR-FIMS *m/z* calcd for $C_{11}H_{17}F_3O_3S$ $[M]^+$: 286.0851, found 286.0861.

*4.3. (3R,6R)-3-Isopropyl-6-methylcyclohex-1-enyl trifluoromethanesulfonate [(+)-**11**]*

In the same manner as described above, (2*R*,5*S*)-carvomenthone [(−)-**10**] (9.69 g, 63.6 mmol, 96.1% ee) afforded (+)-**11** (16.9 g, 59.1 mmol, 92.9%) as a colorless oil. $[\alpha]_D^{29}$ +35.5 (*c* 1.0, $CHCl_3$); HR-FIMS *m/z* calcd for $C_{11}H_{17}F_3O_3S$ $[M]^+$: 286.0851, found 286.0838. All other data were identical with those of (−)-**11**.

*4.4. Methyl (E)-3-[(3'S,6'S)-3'-isopropyl-6'-methylcyclohex-1'-enyl]prop-2-enoate [(+)-**12**]*

To a solution of (−)-**11** (16.9 g, 58.9 mmol) and KOAc (23.1 g, 235 mmol) in DMF (88 mL) was successively added methyl acrylate (15.9 mL, 177 mmol) and $Pd(OAc)_2$ (661 mg, 2.94 mmol) at room temperature, and stirring was continued at 70 °C for 8 h. The reaction mixture was poured into ice-cooled water and extracted with ether. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed over silica gel. Elution with hexane-EtOAc (20:1) gave (+)-**12** (12.1 g, 54.4 mmol, slightly yellow oil, 92.5%). $[\alpha]_D^{31}$ +3.42 (*c* 1.0, $CHCl_3$); IR (film): 2958, 2871, 1721, 1624, 1285, 1166 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, d, *J* = 6.8 Hz), 0.91 (3H, d, *J* = 6.8 Hz), 1.06 (3H, d, *J* = 7.2 Hz), 1.43 (1H, ddt, *J* = 4.0, 10.4, 12.8 Hz), 1.56 (1H, dt, *J* = 16.0, 3.2 Hz), 1.60–1.72 (3H, m), 2.13 (1H, m), 2.52 (1H, m), 3.74 (3H, s), 5.82 (1H, d, *J* = 16.0 Hz), 5.97 (1H, d, *J* = 2.4 Hz), 7.22 (1H, d, *J* = 16.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.03, 19.54, 19.56, 27.47, 29.34 (×2), 31.94, 43.44, 51.41, 114.27, 140.33, 142.36, 147.96, 168.17; HR-FIMS *m/z* calcd for $C_{14}H_{22}O_2$ $[M]^+$: 222.1620, found 222.1618.

*4.5. Methyl (E)-3-[(3'R,6'R)-3'-isopropyl-6'-methylcyclohex-1'-enyl]prop-2-enoate [(−)-**12**]*

In the same manner as described above, (+)-**11** (16.3 g, 57.0 mmol) afforded (−)-**12** (11.8 g, 52.9 mmol, 92.8%) as a slightly

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yellow oil. $[\alpha]_D^{31}$ −6.54 (*c* 1.0, $CHCl_3$); HR-FIMS *m/z* calcd for $C_{14}H_{22}O_2$ $[M]^+$: 222.1620, found 222.1626. All other data were identical with those of (+)-**12**.

*4.6. Methyl 3-[(3'S,6'S)-3'-isopropyl-6'-methylcyclohex-1'-enyl]propanoate [(−)-**13**]*

To a suspension of (+)-**12** (12.1 g, 54.4 mmol) in THF (50 mL) and water (50 mL) were successively added NaOAc (20.1 g, 245 mmol) and *p*-$TsNHNH_2$ (30.4 g, 163 mmol) at room temperature, and the mixture was heated under reflux for 12 h. The reaction mixture was poured into water and extracted with hexane. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed over silica gel. Elution with hexane-EtOAc (10:1) gave (−)-**13** (12.0 g, 53.3 mmol, colorless oil, 97.9%). $[\alpha]_D^{29}$ −16.4 (*c* 1.0, $CHCl_3$); IR (film): 2957, 2932, 2870, 1743, 1436, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.83 (3H, d, *J* = 6.8 Hz), 0.86 (3H, d, *J* = 6.8 Hz), 1.00 (3H, d, *J* = 7.2 Hz), 1.34 (1H, m), 1.42–1.68 (4H, m), 1.88 (1H, m), 2.06 (1H, m), 2.20–2.50 (4H, m), 3.66 (3H, s), 5.24 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.11, 19.55, 19.65, 20.36, 30.02, 30.40, 31.34, 32.17, 32.95, 42.12, 51.49, 124.93, 140.87, 174.11; HR-FIMS *m/z* calcd for $C_{14}H_{24}O_2$ $[M]^+$: 224.1776, found 224.1788.

*4.7. Methyl 3-[(3'R,6'R)-3'-isopropyl-6'-methylcyclohex-1'-enyl]propanoate [(+)-**13**]*

In the same manner as described above, (−)-**12** (11.1 g, 50.0 mmol) afforded (+)-**13** (11.0 g, 48.9 mmol, 97.8%) as a colorless oil. $[\alpha]_D^{29}$ +19.9 (*c* 1.0, $CHCl_3$); HR-FIMS *m/z* calcd for $C_{14}H_{24}O_2$ $[M]^+$: 224.1776, found 224.1787. All other data were identical with those of (−)-**13**.

*4.8. 4-[(3'S,6'S)-3'-Isopropyl-6'-methylcyclohex-1'-enyl]-1-(phenylsulfonyl)butan-2-one [(−)-**14**]*

To a solution of $MeSO_2Ph$ (8.20 g, 52.5 mmol) in THF (250 mL) was added *n*-BuLi (2.65 M in hexane, 19.3 mL, 51.3 mmol) at 0 °C. After stirring for 30 min, a solution of (−)-**13** (5.61 g, 25.0 mmol) in THF (20 mL) was added at 0 °C and stirring was continued at 0 °C for 2 h. The reaction mixture was poured into a sat. aq. NH_4Cl and extracted with EtOAc. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was used in the next step without purification. A small amount of the crude (−)-**14** was purified by column chromatography on silica gel (hexane-EtOAc = 4:1) to give an analytical sample as a slightly yellow viscous oil. $[\alpha]_D^{27}$ −12.7 (*c* 1.0, $CHCl_3$); IR (film): 3064, 2957, 2931, 2869, 1720, 1585, 1447, 1322, 1154 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.83 (3H, d, *J* = 6.8 Hz), 0.86 (3H, d, *J* = 6.8 Hz), 0.98 (3H, d, *J* = 7.6 Hz), 1.31 (1H, m), 1.43–1.64 (4H, m), 1.87 (1H, m), 2.04 (1H, m), 2.16–2.31 (2H, m), 2.76 (1H, ddd, *J* = 6.4, 8.8 17.6 Hz), 2.84 (1H, ddd, *J* = 6.4, 8.8 17.6 Hz), 4.16 (2H, s), 5.20 (1H, s), 7.58 (2H, t, *J* = 7.6 Hz), 7.68 (1H, t, *J* = 7.6 Hz), 7.89 (2H, d, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.11, 19.54, 19.73, 20.29, 28.77, 29.97, 31.31, 32.14, 42.14, 43.11, 66.79, 125.52, 128.29, 129.31, 134.27, 138.64, 140.36, 198.09; HR-ESIMS *m/z* calcd for $C_{20}H_{28}NaO_3S$ $[M+Na]^+$: 371.1657, found 371.1672.

*4.9. 4-[(3'R,6'R)-3'-Isopropyl-6'-methylcyclohex-1'-enyl]-1-(phenylsulfonyl)butan-2-one [(+)-**14**]*

In the same manner as described above, (+)-**13** (7.85 g, 35.0 mmol) afforded the crude (+)-**14**. $[\alpha]_D^{28}$ +12.2 (*c* 1.0, $CHCl_3$); HR-ESIMS *m/z* calcd for $C_{20}H_{28}NaO_3S$ $[M+Na]^+$: 371.1657, found 371.1648. All other data were identical with those of (−)-**14**.

*4.10. 1-Diazo-4-[(3'S,6'S)-3'-isopropyl-6'-methylcyclohex-1'-enyl]-1-(phenylsulfonyl)butan-2-one [(−)-**9**]*

To a solution of the crude (−)-**14** in CH_3CN (150 mL) were successively added Et_3N (10.5 mL, 75.3 mmol) and a solution of *p*-TsN_3 (7.39 g, 37.5 mmol) in CH_3CN (15 mL) at 0 °C. After stirring at room temperature for 15 h, the reaction mixture was poured into 2 M aq. KOH and extracted with ether. The organic phase was washed with dil. HCl and sat. aq. $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was filtered through silica gel, and the filtrate was concentrated *in vacuo* to afford the crude (−)-**9**. A small amount of the crude (−)-**9** was purified by column chromatography on silica gel (toluene as eluent) to give an analytical sample as a yellow viscous oil. $[\alpha]_D^{26}$ −14.0 (*c* 1.0, $CHCl_3$); IR (film): 3064, 2957, 2932, 2869, 2108, 1667, 1447, 1341, 1155 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.80 (3H, d, *J* = 6.8 Hz), 0.84 (3H, d, *J* = 6.8 Hz), 0.92 (3H, d, *J* = 6.8 Hz), 1.28 (1H, m), 1.40–1.60 (4H, m), 1.82 (1H, m), 1.93 (1H, m), 2.03–2.27 (2H, m), 2.61 (1H, ddd, *J* = 6.8, 8.4, 24.8 Hz), 2.65 (1H, ddd, *J* = 6.8, 8.4, 24.8 Hz), 5.10 (1H, br s), 7.57 (2H, t, *J* = 7.6 Hz), 7.67 (1H, t, *J* = 7.6 Hz), 7.98 (2H, d, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.01, 19.46, 19.64, 20.14, 29.06, 29.89, 31.33, 32.05, 37.97, 42.01, 125.44, 127.33, 129.41, 134.10, 140.32, 141.92, 188.21; HR-ESIMS *m/z* calcd for $C_{20}H_{26}N_2NaO_3S$ $[M+Na]^+$: 397.1562, found 397.1551.

*4.11. 1-Diazo-4-[(3'R,6'R)-3'-isopropyl-6'-methylcyclohex-1'-enyl]-1-(phenylsulfonyl)butan-2-one [(+)-**9**]*

In the same manner as described above, the crude (+)-**14** afforded crude (+)-**9**. $[\alpha]_D^{27}$ +13.6 (*c* 1.0, $CHCl_3$); HR-ESIMS *m/z* calcd for $C_{20}H_{26}N_2NaO_3S$ $[M+Na]^+$: 397.1562, found 397.1570. All other data were identical with those of (−)-**9**.

*4.12. (1R,5S,6S,7S,10S)-7-Isopropyl-10-methyl-5-phenylsulfonyltricyclo[4.4.0.0^{1,5}]decan-4-one [(−)-**8**]*

To a solution of the crude (−)-**9** in CH_2Cl_2 (250 mL) was added $(CuOTf)_2 \cdot C_6H_6$ (315 mg, 0.63 mmol) at 0 °C. After stirring at 0 °C for 6 h, the same amount of $(CuOTf)_2 \cdot C_6H_6$ was added. The reaction mixture was stirred for 15 h at 0 °C and concentrated *in vacuo*. The residue was chromatographed over silica gel. Elution with hexane-EtOAc (5:1) gave (−)-**8** (4.27 g, 12.3 mmol, yellow solid, 49.3% in 3 steps). An analytical sample was obtained by recrystallization from CH_2Cl_2/hexane as colorless crystals. mp 131 °C; $[\alpha]_D^{28}$ −57.1 (*c* 1.0, $CHCl_3$); IR (film): 3067, 3022, 2959, 2873, 1730, 1585, 1466, 1447, 1308, 1149 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, d, *J* = 6.8 Hz), 1.02 (3H, d, *J* = 6.8 Hz), 1.14 (3H, d, *J* = 6.8 Hz), 1.18 (1H, m), 1.35 (1H, m), 1.50 (1H, dq, *J* = 13.6, 6.8 Hz), 1.57 (1H, d, *J* = 8.0 Hz), 1.81–1.96 (3H, m), 2.00–2.20 (3H, m), 2.37 (1H, ddt, *J* = 4.8, 12.8, 7.2 Hz), 2.82 (1H, tt, *J* = 6.8, 11.2 Hz), 7.51 (2H, t, *J* = 7.6 Hz), 7.60 (1H, t, *J* = 7.6 Hz), 8.00 (2H, d, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.30, 19.50, 20.57, 22.37, 24.29, 29.03, 32.42, 33.77, 34.78, 39.41, 46.15, 58.16, 128.51, 128.59, 133.40, 141.40, 205.61; HR-ESIMS *m/z* calcd for $C_{20}H_{26}NaO_3S$ $[M+Na]^+$: 369.1500, found 369.1508.

*4.13. (1S,5R,6R,7R,10R)-7-Isopropyl-10-methyl-5-phenylsulfonyltricyclo[4.4.0.0^{1,5}]decan-4-one [(+)-**8**]*

In the same manner as described above, the crude (+)-**9** afforded (+)-**8** (4.83 g, 13.9 mmol, 39.8% in 3 steps) as colorless crystals. mp 131 °C; $[\alpha]_D^{25}$ +57.1 (*c* 1.0, $CHCl_3$); HR-ESIMS *m/z* calcd for $C_{20}H_{26}NaO_3S$ $[M+Na]^+$: 369.1500, found 369.1504. All other data were identical with those of (−)-**8**.

*4.14. (1R,5R,6R,7S,10S)-6-Azido-7-isopropyl-10-methyl-1-phenylsulfonylspiro[4.5]decan-2-one [(+)-**7**]*

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A mixture of (−)-**8** (4.17 g, 12.0 mmol), NaN_3 (3.91 g, 60 mmol) and $Mg(OTf)_2$ (3.90 g, 12.1 mmol) in *N*,*N*′-dimethylpropyleneurea (120 mL) was heated at 80 °C for 20 h. The reaction mixture was poured into sat. aq. $NaHCO_3$ and extracted with ether. The organic phase was washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed over silica gel. Elution with hexane-EtOAc (8:1) gave (+)-**7** (3.30 g, 8.47 mmol, colorless solid, 70.4%). mp 158–159 °C; $[\alpha]_D^{25}$ +52.8 (*c* 1.0, $CHCl_3$); IR (film): 3066, 2962, 2875, 2102, 1749, 1585, 1448, 1310, 1155 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (3H, d, *J* = 6.4 Hz), 1.13 (3H, d, *J* = 6.4 Hz), 1.17 (3H, s), 1.18 (1H, m), 1.35 (1H, dq, *J* = 4.4, 120 Hz), 1.47–1.62 (3H, m), 1.66–1.77 (2H, m), 2.25 (1H, dt, *J* = 19.2, 9.6 Hz), 2.53 (1H, dd, *J* = 8.4, 12.8 Hz), 2.63 (1H, dd, *J* = 9.6, 19.2 Hz), 2.73 (1H, m), 3.60 (1H, s), 4.80 (1H, s), 7.57 (2H, t, *J* = 7.6 Hz), 7.69 (1H, dt, *J* = 1.2, 7.6 Hz), 7.78 (2H, dd, *J* = 1.2, 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.04, 18.89, 20.08, 20.88, 28.94, 28.98, 30.18, 34.00, 34.13, 45.85, 54.42, 66.36, 78.01, 128.85, 128.99, 134.27, 138.28, 207.51; HR-ESIMS *m*/*z* calcd for $C_{20}H_{27}N_3NaO_3S$ $[M+Na]^+$: 412.1671, found 412.1653.

*4.15. (1S,5S,6S,7R,10R)-6-Azido-7-isopropyl-10-methyl-1-phenylsulfonylspiro[4.5]decan-2-one [(−)-**7**]*

In the same manner as described above, (+)-**8** (3.98 g, 11.5 mmol) afforded (−)-**7** (2.94 g, 7.56 mmol, 65.8%) as a colorless solid. mp 157–158 °C; $[\alpha]_D^{24}$ −51.8 (*c* 1.0, $CHCl_3$); HR-ESIMS *m*/*z* calcd for $C_{20}H_{27}N_3NaO_3S$ $[M+Na]^+$: 412.1671, found 412.1664. All other data were identical with those of (+)-**7**.

*4.16. (5R,6R,7S,10S)-6-Azido-7-isopropyl-10-methyl-1-phenylsulfonylspiro[4.5]dec-1-en-2-yl trifluoromethanesulfonate [(−)-**15**]*

To a solution of (+)-**7** (390 mg, 1.00 mmol) in CH_2Cl_2 (5 mL) were successively added DBU (275 μl, 1.84 mmol) and Tf_2O (252 μl, 1.50 mmol) at 0 °C and stirring was continued for 20 min. The reaction mixture was poured into sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed over silica gel. Elution with hexane-EtOAc (10:1) gave (−)-**15** (505 mg, 0.968 mmol, colorless solid, 96.8%). mp 116–119 °C; $[\alpha]_D^{23}$ −20.8 (*c* 1.0, $CHCl_3$); IR (film): 3069, 2965, 2934, 2872, 2100, 1638, 1585, 1326, 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, d, *J* = 2.8 Hz), 0.93 (3H, d, *J* = 2.8 Hz), 1.19 (1H, m), 1.20 (3H, d, *J* = 6.0 Hz), 1.46 (1H, m), 1.52 (1H, tt, *J* = 3.2, 13.6 Hz), 1.74–1.83 (2H, m), 1.87 (1H, ddd, *J* = 2.4, 9.6, 12.8 Hz), 2.01 (1H, m), 2.10 (1H, ddd, *J* = 8.4, 10.4, 12.8 Hz), 2.47 (1H, ddt, *J* = 4.4, 18.8, 11.2 Hz), 2.62 (1H, ddd, *J* = 2.4, 10.8, 18.0 Hz), 2.70 (1H, dt, *J* = 8.4, 18.0 Hz), 4.79 (1H, d, *J* = 4.4 Hz), 7.58–7.68 (3H, m), 7.99 (2H, dd, *J* = 1.6, 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.86, 22.27, 23.04, 23.40, 25.61, 26.68, 27.47, 31.18, 38.11, 43.71, 60.00, 67.10, 118.16 (q, $^1J_{C-F}$= 319.4 Hz), 127.90, 129.14, 133.94, 133.98, 140.99, 155.18; HR-ESIMS *m*/*z* calcd for $C_{21}H_{26}F_3N_3NaO_5S_2$ $[M+Na]^+$: 544.1164, found 544.1155.

*4.17. (5S,6S,7R,10R)-6-Azido-7-isopropyl-10-methyl-1-phenylsulfonylspiro[4.5]dec-1-en-2-yl trifluoromethanesulfonate [(+)-**15**]*

In the same manner as described above, (−)-**7** (1.81 g, 4.64 mmol) afforded (+)-**15** (2.31 g, 4.43 mmol, 95.4%) as a colorless solid. mp 116–118 °C; $[\alpha]_D^{26}$ +19.4 (*c* 1.0, $CHCl_3$); HR-ESIMS *m*/*z* calcd for $C_{21}H_{26}F_3N_3NaO_5S_2$ $[M+Na]^+$: 544.1164, found 544.1154. All other data were identical with those of (−)-**15**.

*4.18. (5R,6R,7S,10S)-6-Azido-7-isopropyl-2,10-dimethyl-1-phenylsulfonylspiro[4.5]dec-1-ene [(+)-**16**]*

To a solution of (−)-**15** (166 mg, 0.318 mmol) in THF (8 mL) was added $Pd(PPh_3)_4$ (36.7 mg, 0.0318 mmol) at 0 °C. After stirring for 10 min, Me_2Zn (2.0 M in toluene, 477 μl, 0.954 mmol) was added to the solution at 0 °C, and stirring was continued at room temperature for 10 h. The reaction mixture was poured into dil. HCl and extracted with EtOAc. The organic phase was washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed over silica gel. Elution with hexane-EtOAc (10:1) gave (+)-**16** (115 mg, 0.296 mmol, colorless solid, 93.1%). mp 124–125 °C; $[\alpha]_D^{23}$ +29.2 (*c* 1.0, $CHCl_3$); IR (film): 2960, 2930, 2870, 2097, 1616, 1461, 1301, 1143, 1084 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.73 (3H, d, *J* = 6.8 Hz), 0.90 (3H, d, *J* = 6.4 Hz), 1.17 (3H, d, *J* = 6.4 Hz), 1.18 (1H, m), 1.39 (1H, m), 1.48 (1H, tt, *J* = 3.6, 13.6 Hz), 1.72–1.78 (2H, m), 1.82 (1H, m), 1.92–2.00 (2H, m), 2.09 (3H, s), 2.31–2.48 (3H, m), 4.76 (1H, d, *J* = 4.8 Hz), 7.54–7.60 (3H, m), 7.94 (2H, dd, *J* = 1.2, 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.13, 16.88, 22.35, 23.02, 25.10, 26.09, 26.59, 27.59, 38.25, 40.11, 43.88, 64.15, 67.85, 126.85, 128.95, 132.79, 137.57, 143.18, 158.44; HR-ESIMS *m*/*z* calcd for $C_{21}H_{29}N_3NaO_2S$ $[M+Na]^+$: 410.1878, found 410.1870.

*4.19. (5S,6S,7R,10R)-6-Azido-7-isopropyl-2,10-dimethyl-1-phenylsulfonylspiro[4.5]dec-1-ene [(−)-**16**]*

In the same manner as described above, (+)-**15** (1.49 g, 2.85 mmol) afforded (−)-**16** (1.05 g, 2.72 mmol, 95.4%) as a colorless solid. mp 122 °C; $[\alpha]_D^{24}$ −30.9 (*c* 1.0, $CHCl_3$); HR-ESIMS *m*/*z* calcd for $C_{21}H_{29}N_3NaO_2S$ $[M+Na]^+$: 410.1878, found 410.1870. All other data were identical with those of (+)-**16**.

*4.20. (5S,6R,7S,10S)-7-Isopropyl-2,10-dimethylspiro[4.5]dec-1-en-6-ylamine [(+)-**17**]*

To a solution of (+)-**16** (77.9 mg, 0.201 mmol) in MeOH (2 mL) was added Mg powder (243 mg, 10.0 mmol) and the mixture was heated under reflux. After stirring for 1.5 h, the mixture was diluted with EtOAc, and the suspension was filtered through a pad of Celite. The filtrate was concentrated *in vacuo* to afford the crude (+)-**17**, which was used in the next step without further purification. A small amount of the crude (+)-**17** was purified by column chromatography on silica gel (CH_2Cl_2-MeOH = 5:1) to give an analytical sample as a slightly yellow oil. $[\alpha]_D^{27}$ +33.6 (*c* 1.0, $CHCl_3$); IR (film): 3043, 2957, 2928, 2869, 1614, 1456, 1375, 993 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 0.89 (3H, d, *J* = 6.4 Hz), 0.94 (3H, d, *J* = 6.4 Hz), 1.04 (3H, d, *J* = 7.6 Hz), 1.25 (1H, m), 1.41–1.58 (5H, m), 1.69 (3H, s), 1.70–1.85 (2H, m), 2.01 (1H, ddd, *J* = 4.8, 8.0, 12.8 Hz), 2.18 (1H, m), 2.28 (1H, m), 2.79 (1H, d, *J* = 3.2 Hz), 5.49 (1H, br s); ^{13}C NMR (100 MHz, CD_3OD) δ 16.91, 17.54, 21.03, 21.56, 22.05, 29.54, 30.43, 33.54, 36.39, 38.36, 46.76, 57.42, 58.16, 133.71, 140.66; HR-FIMS *m*/*z* calcd for $C_{15}H_{27}N$ $[M]^+$: 221.2144, found 221.2155.

*4.21. (5R,6S,7R,10R)-7-Isopropyl-2,10-dimethylspiro[4.5]dec-1-en-6-ylamine [(−)-**17**]*

In the same manner as described above, (−)-**16** (194 mg, 0.503 mmol) afforded the crude (−)-**17**. $[\alpha]_D^{23}$ −30.7 (*c* 1.0, $CHCl_3$); HR-FIMS *m*/*z* calcd for $C_{15}H_{27}N$ $[M]^+$: 221.2144, found 221.2149. All other data were identical with those of (+)-**17**.

*4.22. (+)-Exiguamide [(+)-**1**]*

A solution of the crude (+)-**17** in HCOOEt (3 mL) was heated under reflux for 6 h. The reaction mixture was chromatographed over silica gel. Elution with hexane-EtOAc (5:1) gave (+)-**1** (29.0 mg, 0.116 mmol, colorless solid, 57.9% in 2 steps). mp 140–141

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°C (recrystallized from MeOH/H_2O); $[\alpha]_D^{25}$ +48.4 (*c* 0.08, $CHCl_3$), $[\alpha]_D^{25}$ +46.4 (*c* 1.0, $CHCl_3$); IR (film): 3310, 3042, 2959, 2928, 2870, 1654, 1530, 1456, 1380, 756 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.66 (3H, d, *J* = 6.4 Hz), 0.85 (3H, d, *J* = 6.4 Hz), 0.93 (3H, d, *J* = 7.6 Hz), 1.09 (1H, ddt, *J* = 9.6, 12.8, 3.2 Hz), 1.25–1.49 (5H, m), 1.55 (1H, dd, *J* = 3.2, 13.2 Hz), 1.67 (3H, s), 1.72 (1H, dt, *J* = 14.0, 4.0 Hz), 1.78 (1H, ddd, *J* = 2.0, 8.0, 12.4 Hz), 1.98 (1H, dd, *J* = 8.0, 15.6 Hz), 2.33 (1H, dt, *J* = 15.6, 8.0 Hz), 3.80 (1H, dd, *J* = 3.2, 10.4 Hz), 5.57 (1H, br s), 7.64 (1H, d, *J* = 10.4 Hz), 8.07 (1H, d, *J* = 1.6 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 15.92, 16.90, 19.47, 20.43, 21.16, 29.09, 29.48, 33.88, 34.73, 36.42, 43.40, 50.35, 56.21, 131.83, 139.39, 161.27; HR-ESIMS *m*/*z* calcd for $C_{16}H_{27}NNaO$ $[M+Na]^+$: 272.1985, found 272.1973.

*4.23. (−)-Exiguamide [(−)-**1**]*

In the same manner as described above, the crude (−)-**17** afforded (−)-**1** (71.0 mg, 0.285 mmol, 57.0% in 2 steps) as a colorless solid. mp 140–141 °C (recrystallized from MeOH/H_2O); $[\alpha]_D^{28}$ −47.9 (*c* 0.08, $CHCl_3$), $[\alpha]_D^{25}$ −45.1 (*c* 1.0, $CHCl_3$); HR-ESIMS *m*/*z* calcd for $C_{16}H_{27}NNaO$ $[M+Na]^+$: 272.1985, found 272.1979. All other data were identical with those of (+)-**1**.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at ~.

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Highlights：

The first synthesis of both enantiomers of exiguamide was achieved.

Exiguamide is a nitrogen-containing spirocyclic sesquiterpene isolated from *Geodia exigua*.

The intramolecular cyclopropanation and homoconjugate addition of azide were the key steps.

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