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Article

Enantioselective Synthesis of (+)-Polyzonimine, Defensive Monoterpene Alkaloid Produced by a Milliped *Polyzonium rosalbum*, and Determination of Its *S* Absolute Configuration by Its Conversion to (4*S*,5*R*,6*S*)-(+)-Nitropolyzonamine+

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A adição de Michael da enamina derivada do 2,2-dimetilciclopentanocarboxaldeído e do éter metílico do (*S*)-prolinol com o nitroetileno, forneceu o aduto correspondente em 75-76% ee, o qual foi convertido na (+)-polizonimina enantiomericamente pura, um espiro composto nitrogenado isolado das glândulas que contêm os compostos de defesa do "milliped" *Polyzonium rosalbum*. Através da conversão da (+)-polizonimina na (4*S*, 5*R*, 6*S*)-(+)-nitropolizonamina, foi possível estabelecer a configuração absoluta desta como sendo *S*.

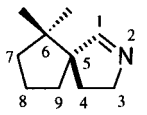
Asymmetric Michael addition of the enamine derived from 2,2-dimethylcyclopentanecarboxaldehyde and (*S*)-prolinol methyl ether to nitroethylene afforded the adduct of 75-76% ee, which finally yielded enantiomerically pure (+)-polyzonimine, a nitrogen-containing spirocyclic compound isolated from the defensive glands of a milliped, *Polyzonium rosalbum*. By converting (+)-polyzonimine into (4*S*,5*R*,6*S*)-(+)-nitropolyzonamine, the hitherto uncertain absolute configuration of the former was established as *S*.

Keywords: alkaloids, asymmetric synthesis, insects, spirocyclic compounds

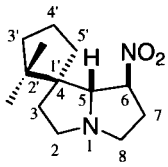
Introduction

Chemical defense against predation by other organisms is an important research subject in chemical ecology as pioneered by Eisner[1]. In 1975, in the course of their studies on compounds from the defensive glands of a milliped *Polyzonium rosalbum*, Meinwald, Eisner and their respective co-workers isolated and identified the following two nitrogen-containing spirocyclic compounds[2,3]. (+)-Polyzonimine {6,6-dimethyl-2-azaspiro[4.4]non-1-ene (**1**)} was isolated as a volatile insect repellent, which acts as a topical irritant to predating insects such as ants and cockroaches[2] (Figure 1).

Its structure as a monoterpene alkaloid **1** (without assigning absolute configuration) was suggested by the X-ray crystallographic analysis of a closely related minor (*ca.* 15% of the content of **1**), less volatile and crystalline component of the secretion, (+)-nitropolyzonamine [2',2'-dimethyl-6-nitrospiro{1-azabicyclo[3.3.0]octane-4,1'-cyclopentane} (**2**)][3,4]. The absolute configuration of **2** was derived from the X-ray anomalous scattering effect of the chlorine atom of the perchlorate salt of **2**, and shown to be 4*S*,5*R*,6*S*[4]. Because (+)-polyzonimine (**1**) co-occurs with (+)-nitropolyzonamine (**2**), it is highly probable that the former shares the same *S* configuration at the spiro center as that of the latter. However, this must be proved. The structures **1** and **2** proposed for these milliped alkaloids were confirmed by the synthesis of their racemates[2,3,5]. Only a single existing asymmetric synthesis of (+)-**1** with 68% ee could not tell us anything about its absolute configuration[6]. In this paper, we report in detail our synthesis of enantiomerically pure (+)-**2** *via* (+)-**1**, which establishes the absolute configuration of (+)-**1** as *S*[7].



Polyzonimine
(*S*)-(+)-**1**



Nitropolyzonamine
(4*S*,5*R*,6*S*)-(+)-**2**

Figure 1. Structures of polyzonimine and nitropolyzonamine.

+Paper XXVIII in the series "Synthesis of Mono- and Sesquiterpenoids": Paper XXVII: Horiuchi, S.; Takikawa, H.; Mori, K.; *Eur. J. Org. Chem.* **1998**, 2851.

Experimental

General

Boiling points and melting points: uncorrected values. – IR: Jasco 410 and Jasco A-102. – ^{1}H NMR: Jeol JNM-LA500 (500 MHz) and Jeol JNM-AL300 (300 MHz) and Jeol JNM-EX 90A (90 MHz) ($CHCl_3$ at δ 7.26 as an internal standard). – Optical rotation: Jasco P-1020. – MS: Jeol JMS-AX505HA and Jeol JMS-SX102A. – M.p.: Yanaco MP-S3. – Column chromatography: Merck Kieselgel 60 Art. 1.07734. – TLC: 0.25-mm Merck silica gel plates (60F-254).

2,2-Dimethylcyclopentylmethanol **(6)**: A solution of **5** (12.1g, 85.2 mmol) in diethyl ether (36 cm^3) was added dropwise to a stirred and cooled suspension of $LiAlH_4$ (6.50g, 171 mmol) in diethyl ether (240 cm^3) at 0°C, and the reaction mixture was stirred for 1.5 h at room temperature. The excess $LiAlH_4$ was destroyed by the careful addition of water (6.5 cm^3), 15% aq. NaOH (6.5 cm^3) and water (20 cm^3) at 0°C. After having been stirred for 10 min, the mixture was filtered through Celite, and the filtrate was concentrated in vacuo. The residue was distilled to give 9.52 g (87%) of **6** as a colorless oil, b.p. 77-80°C/10 Torr, n_D^{24} = 1.4582. Elemental analysis: (Found C, 74.85; H 12.43. Calc. for $C_8H_{16}O$: C, 74.94; H, 12.58%). IR: ν_{max}/cm^{-1} 3335s, 1045m, 1015m, 1000m (film). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (s, 3H, 2-CH_3), 1.06 (s, 3H, 2-CH_3), 1.35–1.46 (m, 4H, 3,4-H), 1.56–1.72 (m, 3H, 1,5-H), 1.87-1.98 (m, 1H, 1-CH_2OH), 3.47 (dd, *J* 10.5 and 8.4, Hz, 1H, 1-C*H*HOH), 3.72 (dd, *J* 10.5 and 5.4 Hz, 1H, 1-CH*H*OH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 22.1, 28.5, 29.1, 40.2, 42.4, 51.6, 64.8.;

2,2-Dimethylcyclopentanecarboxaldehyde **(7)**: To a stirred solution of $(COCl)_2$ (18.3 cm^3, 192 mmol) in CH_2Cl_2 (160 cm^3), a solution of DMSO (27.2 cm^3, 385 mmol) in CH_2Cl_2 (10 cm^3) was added at –60°C. After stirring for 20 min, a solution of **6** (20.0 g, 156 mmol) in CH_2Cl_2 (80 cm^3) was added dropwise. After stirring for 40 min at –40°C, then the reaction mixture was cooled to –60°C, and Et_3N (112 cm^3, 805 mmol) was added. After warming to room temperature, water was added and the aqueous layer was extracted several times with CH_2Cl_2. The combined organic extracts were washed with water and brine, and dried with $MgSO_4$. After concentration under atmospheric pressure, the residue was distilled to give 17.4 g (88%) of **7** as a colorless oil, b.p. 91°C/75 Torr, n_D^{24} = 1.4422. IR: ν_{max}/ cm^{-1} 2630s, 1730s, 1720s, 1650w (film). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (s, 3H, 2-CH_3), 1.20 (s, 3H, 2-CH_3), 1.48–2.16 (m, 6H, 3,4,5-H), 2.34 (ddd, *J* 8.1, 8.1 and 3.0 Hz, 1H, 1-H), 9.71 (d, *J* 3.0 Hz, 1H, 1-C*H*O). This unstable aldehyde was used directly in the next step.

2-Methoxymethyl-N-2",2"-dimethylcyclopentylidene-methylpyrrolidine **(8)** – i) (*S*)-Isomer**:** A mixture of 2,2-dimethylcyclopentanecarboxaldehyde (**7**; 5.00 g, 39.7 mmol), (*S*)-(+)-2-(methoxymethyl)pyrrolidine (5.50 g, 47.8 mmol), and molecular sieves 4A (5 g) in benzene (20 cm^3) was refluxed utilizing a Dean-Stark apparatus. After stirring for 19 h, the reaction mixture was filtered through Celite, and the filtrate was concentrated in vacuo to give 9.94 g (quant.) of crude (*S*)-**8**. This was used immediately in the next reaction without purification. IR:: ν_{max}/ cm^{-1} 1660s (C=C) (film). EIMS: *m/z* 223.10 (M^+). Calc. for $C_{14}H_{25}NO$: 223.19.

ii) (*R*)-Isomer: In the same manner as described above, **7** (4.00 g, 31.7 mmol) and (*R*)-(–)-2-(methoxymethyl) pyrrolidine (4.40 g, 38.3 mmol) were converted to crude (*R*)-**8'** (8.36 g, quant.). IR: ν_{max}/cm^{-1} 1670s (C=C) (film). EIMS: *m/z* 223.10 (M^+). Calc. for $C_{14}H_{25}NO$: 223.19.

1-(2"-Nitroethyl)-2,2-dimethylcyclopentanecarboxal-dehyde **(9)** – i) (*S*)-Isomer: Neat 2-nitroethyl acetate (6.00 g, 45.1 mmol) was added to a solution of the crude enamine (*S*)-**8** (9.94 g) and *N*-ethylmorpholine (3.60 cm^3, 28.3 mmol) in acetonitrile (16 cm^3) at 0 °C under Ar. After stirring for 20 min, this mixture was concentrated in vacuo. The residue was chromatographed on silica gel (200 g, hexane/ ethyl acetate, 50:1) to give 6.18 g of impure (*S*)-**9**. This compound was employed in the next step without further purification. An analytical sample was obtained by deprotection of purified acetal (*S*)-**10**. Properties of (*S*)-**9**: n_D^{25} = 1.4830, $[\alpha]_D^{22}$ = –2.7 (*c* = 0.29, $CHCl_3$). Elemental analysis: (Found: C, 60.35; H, 8.41; N, 7.13. Calc. for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60, N; 7.03%). IR: (film) ν_{max}/ cm^{-1} 2730br. w (C–H), 1715s (C=O), 1555s (NO_2), 1380s (NO_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ1.00 (s, 3H, 2-CH_3), 1.03 (s, 3H, 2-CH_3), 1.62–1.71 (m, 3H, 3-C*H*H, 3-CH*H*, 4-C*H*H), 1.80–1.93 (m, 2H, 4-CH*H*, 5-C*H*H), 2.00–2.06 (m, 1H, 5-CH*H*), 2.12 (ddd, *J* 13.1, 9.8 and 5.8 Hz, 1H, 1"-C*H*H), 2.51 (ddd, *J* 13.7, 10.4 and 5.8 Hz, 1H, 1"-C*H*H), 4.19 (ddd, *J* 13.1, 10.4 and 5.5 Hz, 1H, 2"-C*H*H), 4.36 (ddd, *J* 13.1, 10.4 and 5.8 Hz, 1H, 2"-CH*H*), 9.62 (d, *J* 0.9 Hz, 1H, C*H*O). EIMS: *m/z* 198.1 (M^+ – 1). Calc. for $C_{10}H_{17}NO_3$: 199.12.

ii) (*R*)-Isomer: In the same manner as described above, (*R*)-**8'** was converted to impure (*R*)-**9'** (5.20 g). This was employed in the next step without further purification. An analytical sample was obtained by deprotection of the purified acetal (*R*)-**10'**. Properties of (*R*)-**9'**; n_D^{25} = 1.4830, $[\alpha]_D^{22}$ = +2.3 (*c* = 0.30, $CHCl_3$). Elemental analysis: (Found: C, 60.27; H, 8.48; N, 6.91. Calc. for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03%). Its IR and ^{1}H NMR spectra are indistinguishable from those of the (*S*)-Isomer. EIMS: *m/z* 198.00 (M^+ – 1). Calc. for $C_{10}H_{17}NO_3$: 199.12.

2-[2',2'-Dimethyl-1'-(2''-nitroethyl)cyclopentyl]-1,3-dioxolane **(10)** – i) (*S*)-Isomer**:** To a stirred mixture of impure (*S*)-**9** (6.18 g) and ethylene glycol (60 cm^3, 1.08 mmol), triethyl orthoformate (40 cm^3, 0.241 mmol) and *p*-toluenesulfonic acid monohydrate (*ca*. 10 mg) were added. The reaction mixture was stirred for 18 h at room temperature. This was then diluted with a saturated aqueous sodium hydrogen carbonate solution, and extracted with diethyl ether. The organic phase was dried with K_2CO_3, and concentrated in vacuo. The residue was chromatographed on silica gel (200 g, hexane/ethyl acetate, 30:1, with 0.1–0.2% of triethylamine) to give 7.78 g, (78% based on **7**, 3 steps) of **10** as a pale yellow oil. An analytical sample was further purified by distillation, b.p. 100°C/8 Torr, n_D^{21} = 1.4905, $[\alpha]_D^{26}$ = –11 (*c* = 0.28, $CHCl_3$). Elemental analysis: (Found: C, 59.11; H, 8.98; N, 5.84. Calc. for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76%). IR: ν_{max}/cm^{-1} 1550s (N=O), 1100m, 1075s, 1025m (film). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00 (s, 3H, 2'-CH_3), 1.01 (s, 3H, 2'-CH_3), 1.52–1.73 (m, 5H, 3',4'-H, 5'-C*H*H), 1.87–1.90 (m, 1H, 5'-CH*H*), 1.91 (ddd, *J* 13.8, 11.1 and 5.0 Hz, 1H, 1''-C*H*H), 2.38 (ddd, *J* 13.8, 11.4 and 5.9 Hz, 1H, 1''-CH*H*), 3.72–3.77 (m, 1H, 4-C*H*H), 3.84–3.90 (m, 2H, 4-CH*H*, 5-C*H*H), 3.99–4.03 (m, 1H, 5-CH*H*), 4.42 (ddd, *J* 12.8, 11.4 and 5.0 Hz, 2''-C*H*H), 4.63 (ddd, *J* 12.8, 11.1 and 5.9 Hz, 2''-CH*H*), 4.66 (s, 1H, 2-H).

ii) (*R*)-Isomer: In the same manner as described above, impure (*R*)-**9'** (4.89 g) was converted to (*R*)-**10'** (5.66 g, 73% based on **7**, 3 steps) as a pale yellow oil. An analytical sample was further purified by distillation; b.p. 100°C/8 Torr, n_D^{26} = 1.4882, $[\alpha]_D^{32}$ = +8.9 (*c* = 0.28, $CHCl_3$). Elemental analysis: (Found: C, 59.09; H, 8.53; N, 5.98. Calc. for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76%). Its IR and ^{1}H NMR spectra are indistinguishable from those of the (*S*)-Isomer.

Polyzonimine [6,6-Dimethyl-2-azaspiro[4.4]non-1-ene] **(1)** – i) (*S*)-Isomer**:** A solution of (*S*)-**10** (2.55 g, 10.5 mmol) in THF (10 cm^3) was added dropwise to a stirred and cooled suspension of $LiAlH_4$ (800 mg, 21.1 mmol) in THF (50 cm^3) at 0°C, and the reaction mixture was stirred for 3 h at room temperature. The excess $LiAlH_4$ was destroyed by the careful addition of water (0.8 cm^3), 15% aq. NaOH (0.8 cm^3) and water (2.4 cm^3) at 0°C. After having been stirred for 10 min, the mixture was filtered through Celite, and the filtrate was concentrated in vacuo to give crude (*S*)-**11** as a pale yellow oil. This was employed in the next step without further purification. IR: ν_{max}/cm^{-1} 3180br. w, 1660br. m, 1585br. m (N–H), 1100br. s (C–O–C), 965s (film). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.98 (s, 3H, 2'-CH_3), 0.99 (s, 3H, 2'-CH_3), 1.38–1.90 (m, 8H, 3',4',5',1''-H), 2.70 (dt, *J* 11.6, 11.6 and 5.2 Hz, 1H, 2''-C*H*H), 3.73–4.00 (m, 4H, 4,5-H), 4.72 (s, 1H, 2-H). A solution of the above described residue containing (*S*)-**11** in THF (20 cm^3) was acidified with 2 mol L^{-1} HCl aq. (5 cm^3), and the reaction mixture was stirred at room temperature overnight. It was then poured into 15% NaOH aq. and extracted with diethyl ether. The extract was dried with K_2CO_3, and concentrated under atmospheric pressure. The residue was distilled to give 860 mg (54% based on **10**, 2 steps) of (+)-**1** as a colorless oil, b.p. 81°C/10 Torr, n_D^{30} = 1.4768. $[\alpha]_D^{20}$ = +1.3 (*c* = 0.25, $CHCl_3$, 71% ee). IR: ν_{max}/cm^{-1} 2955s (C–H), 2870s (C–H), 1620s (C=N), 1465m, 1385m, 1370m, 1080w, 960w, 920w (film). ^{1}H NMR (500 MHz, $CDCl_3$) δ0.89 (s, 3H, 6-CH_3), 0.92 (s, 3H, 6-CH_3), 1.50–1.92 (m, 8H, 4,7,8,9-H), 3.74–3.86 (m, 2H, 3-H), 7.41 (t, *J* 2.5 Hz, 1H, 1-H). (300 MHz, $CDCl_3$) δ 0.89 (s, 3H, 6-CH_3), 0.91 (s, 3H, 6-CH_3), 1.48–1.93 (m, 8H, 4,7,8,9-H), 3.71–3.88 (m, 2H, 3-H), 7.40 (t, *J* 2.4 Hz, 1H, 1-H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 20.4 (8-C), 23.8 (6-CH_3), 24.6 (6-CH_3), 30.5 (4-C), 35.4 (9-C), 40.0 (7-C), 43.5 (6-C), 60.6 (3-C), 66.2 (5-C), 173.0 (1-C). (75 MHz, $CDCl_3$) δ 20.4 (8-C), 23.8 (6-CH_3), 24.5 (6-CH_3), 30.5 (4-C), 35.3 (9-C), 39.9 (7-C), 43.5 (6-C), 60.6 (3-C), 66.2 (5-C), 173.1 (1-C). HRFABMS (M + H^+) Found: 152.1447. Calc. for $C_{10}H_{17}N$: 152.1439. EIMS: *m/z* 151.0 (M^+). Calc. for $C_{10}H_{17}N$: 151.1. GLC (column: Chirasil – DEX CB®, 0.25 mm x 25 m, 1 min at 110°C +0.5°C/min; carrier gas: He, pressure 110 kPa): t_R = 20.38 min [87.7%, (+)-**1**], t_R = 21.80 min [12.3%, (–)-**1'**]. The enantiomeric purity of (+)-**1** was estimated to be 75.4% ee.

ii) (*R*)-Isomer: In the same manner as described above, (*R*)-**10'** (9.95 g, 40.9 mmol) was converted to (–)-**1'** (1.96 g, 32% based on **10'**, 2 steps) as a colorless oil; b.p. 81°C/10 Torr, n_D^{25} = 1.4791. $[\alpha]_D^{20}$ = –1.7 (*c* = 0.29, $CHCl_3$, 73% e.e.). Its IR and ^{1}H NMR spectra are indistinguishable from those of the (*S*)-Isomer. HRFABMS (M + H^+) Found: 152.1432. Calc. for $C_{10}H_{17}N$: 152.1439. EIMS: *m/z* 151.1 (M^+). Calc. for $C_{10}H_{17}N$: 151.1. GLC (column: Chirasil – DEX CB®, 0.25 mm x 25 m, 1 min at 110°C +0.5°C/min; carrier gas: He, pressure 110 kPa): t_R = 17.62 min [14.0%, (+)-**1**], t_R = 18.32 min [86.0%, (–)-**1'**]. The enantiomeric purity of (–)-**1'** was estimated to be 72% ee.

Enantiomer Enrichment of (+)-Polyzonimine (75.9% ee); A solution of crude (*S*)-(+)-**1** (2.31 g, 15.3 mmol, 75.9% ee), and D-tartaric acid (2.30 g, 15.3 mmol) in ethyl alcohol (40 cm^3) was stirred at 70°C for 10 min. After cooling overnight, the crystals were collected by filtration and washed with cooled hexane. The resulting crystals were dried under reduced pressure for 3–4 h at room temperature. This recrystallization was repeated for three times. Finally, the pure white needles of **12** (1.04 g, 23%) were obtained, m.p. 136–139°C, $[\alpha]_D^{25}$ = –11 (*c* = 0.22, MeOH). Elemental analysis: (Found: C, 55.84; H, 7.59; N, 4.67. Calc. for $C_{14}H_{23}NO_6$: C, 55.80; H, 7.69; N, 4.65%). IR: ν_{max}/cm^{-1} 3320br. s, 2960br. s, 1880br. m, 1725br. m, 1660w, 1585br.

m, 1410 br. s, 1335w, 1305m, 1265m, 1215m, 1135m, 1070s, 905m, 880w, 840m, 790m, 755 m, 680s, 620m (KBr). Then 0.27 g of pure salt **12** was treated with saturated aqueous K_2CO_3 solution. The aqueous solution was extracted with diethyl ether. The extract was dried with K_2CO_3, and concentrated under atmospheric pressure. The residue was distilled to give 58.2 mg (43%) of (+)-**1** as a colorless oil; b.p. 81°C/10 Torr, $[\alpha]_D^{22}$ = +3.3 (*c* = 0.26, $CHCl_3$). – HRFABMS (M + H^+) Found: 152.0384. Calc. for $C_{10}H_{17}N$: 152.1439. GLC (column: Chirasil – DEX CB®, 0.25 mm x 25 m, 1 min at 110°C +0.5°C/min; carrier gas: He, pressure 110 kPa): t_R = 17.00 min [~ 100 %, (+)-**1**]. The enantiomeric purity of (+)-**1** was estimated to be ~ 100% ee.

Enantiomer Enrichment of (–)-Polyzonimine (71.9% ee); A solution of crude (*R*)-(–)-**1'** (1.96 g, 13.0 mmol, 71.9 % ee), and L-tartaric acid (1.95 g, 13.0 mmol) in ethyl alcohol (45 cm^3) was manipulated in the same manner as described above for enantiomer enrichment of (+)-**1** to give 0.93 g of the pure white needles of **12'** (0.93 g, 24%), m.p. 130–135°C, $[\alpha]_D^{24}$ = +8.4 (*c* = 0.21, MeOH). Elemental analysis: (Found: C, 55.74; H, 7.52; N, 4.74. Calc. for $C_{14}H_{23}NO_6$: C, 55.80; H, 7.69; N, 4.65%). The pure salt **12'** (0.30 g) was treated with saturated aqueous K_2CO_3 solution. The aqueous solution was extracted with diethyl ether. The extract was dried with K_2CO_3, and concentrated under atmospheric pressure. The residue was distilled to give 22.5 mg (15%) of (–)-**1'** as a colorless oil; b.p. 81°C/10 Torr, $[\alpha]_D^{23}$ = –3.3 (*c* = 0.25, $CHCl_3$). Its IR spectrum is indistinguishable from that of the (*S*)-Isomer. HRFABMS (M + H^+) Found: 152.1448. Calc. for $C_{10}H_{17}N$: 152.1439. GLC (column: Chirasil – DEX CB®, 0.25 mm x 25 m, 1 min at 110°C +0.5°C/min; carrier gas: He, pressure 110 kPa): t_R = 17.88 min [~ 100%, (–)-**1'**]. The enantiomeric purity of (–)-**1'** was estimated to be ~ 100% ee.

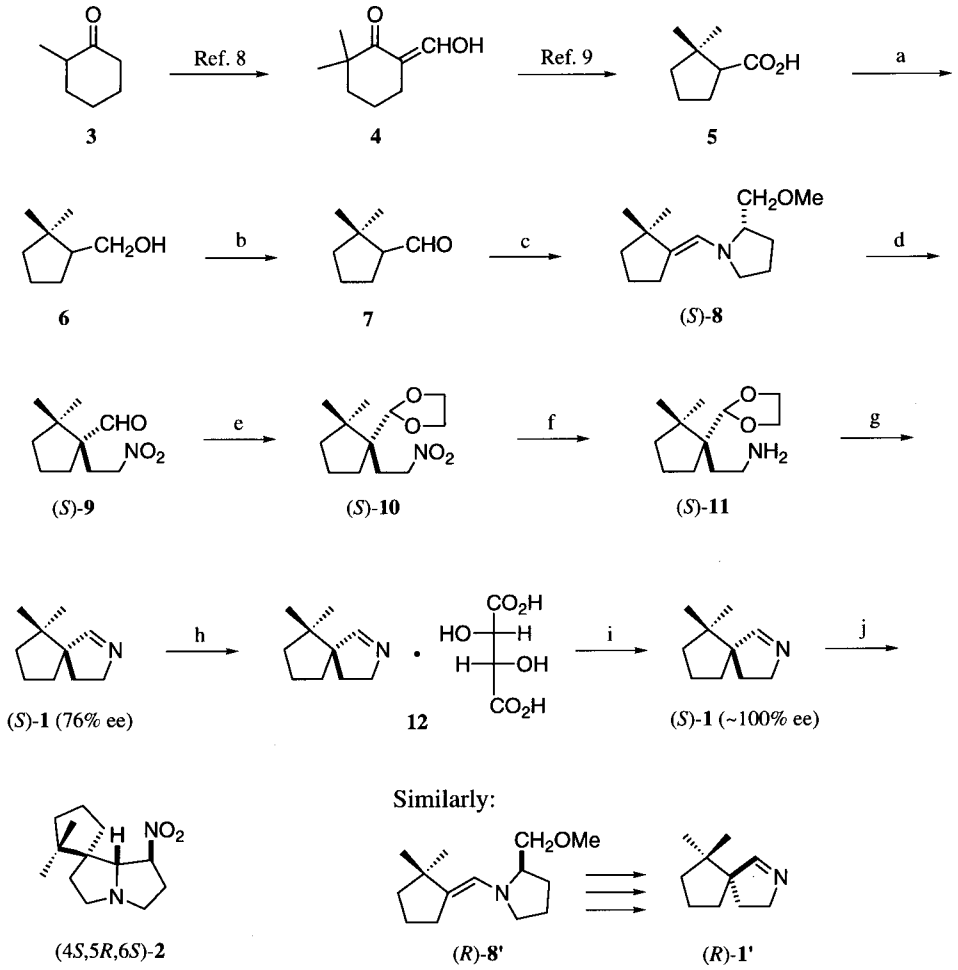
Nitropolyzonamine [2',2'-dimethyl-6-nitrospiro{1-azabicyclo[3.3.0]octane-4,1'-cyclopentane}] (**2**) - i) (4*S*,5*R*,6*S*)-Isomer: Neat iodonitropropane (1.14 g, 5.30 mmol) was added to (*S*)-**1** (0.10 g, 0.66 mmol) of 100% ee, and the mixture was heated at 60°C for 20 min. The flask was cooled and the reaction mixture was washed with diethyl ether and the diethyl ether was decanted from the solid. Pyridine (7 cm^3) was added to the solid material and the resulting solution was heated to reflux for 3 h. The reaction was allowed to cool, diluted with EtOAc and water. The aqueous layer was extracted with EtOAc and the combined organic extracts were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (20 g, ethyl acetate / methyl alcohol, 20:1) to give (4*S*,5*R*,6*S*)-**2** (106 mg, 67%) as a yellow oil. An analytical sample was further purified by recrystallization from hexane to give (4*S*,5*R*,6*S*)-**2** (53.3 mg, 34%) as colorless crystals, m.p. 69.5-70.5°C, $[\alpha]_D^{24}$ = +6.1 (*c* = 1.0, $CHCl_3$); ref. 3: m.p. 65.5-66.5°C, $[\alpha]_D^{20}$ = +12 ($CHCl_3$). The synthetic (+)-**2** showed higher mp and smaller $[\alpha]_D$ values than the natural product. IR: ν_{max}/cm^{-1} 2950br. s, 2670w, 1540 s, 1490s, 1430s, 1365s, 1350s, 1310s, 1270s, 1225s, 1195s, 1180s, 1150s, 1115s, 1080s, 1065s, 1025m, 1000m, 980m, 970m, 950m, 930m, 910m, 885s, 850s, 820s, 710s, 670s. (film) ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (s, 3H, 2'-CH_3), 0.96 (s, 3H, 2'-CH_3), 1.37–1.53 (m, 4H, 3',4'-H), 1.62–1.78 (m, 3H, 5'-H,3-C*H*H), 1.97 (ddd, *J* 11.9, 11.9 and 7.0 Hz, 1H, 3-CH*H*), 2.15-2.23 (m, 1H, 7-C*H*H), 2.38-2.48 (m, 2H, 7-CH*H*, 2-C*H*H), 2.85 (ddd, *J* 11.6, 7.3 and 4.0 Hz, 1H, 8-C*H*H), 3.06 (ddd, *J* 11.0, 8.9 and 2.2 Hz, 1H, 2-CH*H*), 3.25 (ddd, *J* 11.6, 8.9 and 6.7 Hz, 1H, 8-CH*H*), 3.74 (d, *J* 4.0 Hz, 1H, 5-H), 4.80 (td, *J* 7.3, 4.0 and 4.0 Hz, 1H, 6-H). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (s, 3H, 2'-CH_3), 0.96 (s, 3H, 2'-CH_3), 1.36–1.51 (m, 4H, 3',4'-H), 1.62–1.80 (m, 3H, 5'-H,3-C*H*H), 1.98 (ddd, *J* 12.0, 12.0 and 6.9Hz, 1H, 3-CH*H*), 2.13-2.26 (m, 1H, 7-C*H*H), 2.36-2.50 (m, 2H, 7-CH*H*, 2-C*H*H), 2.85 (ddd, *J* 11.7, 7.5 and 4.2 Hz, 1H, 8-C*H*H), 3.06 (ddd, *J* 11.1, 9.0 and 2.1 Hz, 1H, 2-CH*H*), 3.25 (ddd, *J* 11.7, 9.0 and 6.6 Hz, 1H, 8-CH*H*), 3.74 (d, *J* 4.2 Hz, 1H, 5-H), 4.80 (td, *J* 7.5, 3.9 and 3.9 Hz, 1H, 6-H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 19.5, 23.4, 24.8, 31.9, 32.3, 35.2, 39.2, 42.7, 52.3, 53.2, 56.6, 73.6, 88.2. ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5, 23.4, 24.8, 31.9, 32.3, 35.1, 39.1, 42.7, 52.3, 53.3, 56.6, 73.5, 88.1. HRFABMS (M + H^+) Found: 239.1754. EIMS: *m/z* 238.06 (M^+). Calc. for $C_{13}H_{22}N_2O_2$: 238.17.

ii) (4*R*,5*S*,6*R*)-Isomer: In the same manner as described above, (*R*)-**1'** (39.8 mg, 0.26 mmol) was converted to (4*R*,5*S*,6*R*)-**2'** (36.8 mg, 59%) as colorless crystals; m.p. 69.5-70.5°C, $[\alpha]_D^{25}$ = –6.2 (*c* = 0.9, $CHCl_3$). Its IR and ^{1}H NMR spectra are indistinguishable from those of the (*S*)-isomer. HRFABMS (M + H^+) Found: 239.1766. EIMS: *m/z* 237.87 (M^+): Calc. for $C_{13}H_{22}N_2O_2$: 238.17.

Results and Discussion

Our synthesis of polyzonimine (**1**) and nitropolyzonamine (**2**) are summarized in Scheme 1. We envisaged that asymmetric Michael addition of enamine **8** or its analogues to nitroethylene must be successful, if a proper chiral auxiliary is chosen. Nevertheless, we were not too optimistic to expect 100% asymmetric yield in that step, and therefore the enantiomeric purity of the product must be enriched later *via* an appropriate crystalline derivative.

2,2-Dimethylcyclopentanecarboxaldehyde (**7**), the known starting material, was synthesized by a route different from the previous ones.[2,5] Commercially available 2-methylcyclohexanone (**3**) was converted to **4** according to Kawanobe et al.[8]. Oxidation of **4** with



Scheme 1. Synthesis of polyzonimine (**1**) and nitropolyzonamine (**2**). Reagents: (a) $LiAlH_4$, Et_2O (87%). – (b) DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N (88%). – (c) (*S*)-prolinol methyl ether, MS 4A, C_6H_6. – (d) i) $AcOCH_2CH_2NO_2$, *N*-ethylmorpholine, MeCN; ii) chromatog. – (e) $HO(CH_2)_2OH$, TsOH, $HC(OEt)_3$ (78% based on **7** *via* **8**). – (f) $LiAlH_4$, THF. – (g) 2 mol L^{-1} HCl, THF (54% based on **10**). – (h) D-(–)-Tartaric acid (1 eq.), recrystallization from EtOH (23%). – (i) K_2CO_3, H_2O; extraction; distillation (44%). – (j) $I(CH_2)_3NO_2$, then C_5H_5N (34%).

hydrogen peroxide afforded **5**[9], which was reduced with lithium aluminum hydride to give alcohol **6**. Swern oxidation of **6** furnished the desired aldehyde **7**.

For the preparation of chiral enamine such as **8**, three chiral amines derived from (*S*)-proline were examined: (i) (*S*)-proline *tert*-butyl ester as employed by Yamada's group[10], (ii) (*S*)-prolinol methyl ether as used by Seebach's group[11], and (iii) (*S*)-1-amino-2-(1-methoxy-1-ethylpropyl)pyrrolidine as developed by Enders's group[12]. The aldehyde **7** could be converted to the corresponding enamines, when it was treated with the former two amines in the presence of MS 4A[13]. The third one which was prepared according to Enders et al.[14], however, did not afford the corresponding enamine, presumably due to the presence of the two bulky ethyl groups on the side-chain.

The next step was the crucial asymmetric Michael addition of the enamine **8** as well as its analogue prepared from (*S*)-proline *tert*-butyl ester to nitroethylene generated from 2-nitroethyl acetate[15] and *N*-ethylmorpholine in acetonitrile[16]. Chromatographic purification of the product over silica gel gave crude **9** with concomitant removal of the chiral auxiliary. Because neither determination of its absolute configuration nor estimation of its enantiomeric purity was possible, the crude product **9** was further processed to give **1** eventually. The absolute configuration of **9** as depicted in the formula became clear only after its conversion to (4*S*,5*R*,6*S*)-(+)-**2**.

Prior to the reduction of the nitro groups of **9**, its formyl group was protected as ethyleneacetal to give **10**. Reduction of the nitro compound **10** to amine **11** was best accomplished with lithium aluminum hydride. Catalytic hydrogenation of **10** with various catalysts was very sluggish in our hands. Treatment of **11** with hydrochloric acid gave (+)-polyzonimine (**1**), whose enantiomeric purity could be estimated by GC analysis on Chirasil-DEX-CB®. The enamine (*S*)-**8** turned out

to be the superior one in the asymmetric Michael reaction to give (+)-**1** of 75-76% ee, while the enamine derived from **7** and (*S*)-proline *tert*-butyl ester furnished (+)-**1** of only 4% ee. It thus became clear that the use of (*S*)-**8** gave predominantly the product **9** leading to the naturally occurring (+)-enantiomer of polyzonimine (**1**). The overall yield of (+)-**1** *via* (*S*)-**8** was 42% based on **7** (5 steps).

In order to prepare enantiomerically pure (+)-polyzonimine (**1**), a variety of optically active carboxylic acids were screened to examine the ease of their salt formation with (+)-**1**. After some experimentation, (+)-**1** was found to give a crystalline salt **12** with an equimolar amount of D-(–)-tartaric acid. The salt **12** was recrystallized several times from ethanol to furnish a pure sample, whose alkaline decomposition with potassium carbonate gave back pure (+)-polyzonimine (**1**) of 100% ee. Its IR, ^{1}H- and ^{13}C-NMR spectra were in good accord with the published data of (+)- and (±)-**1**[2,5,6]. In addition, the specific rotation, $[\alpha]_D^{22}$ = +3.3 ($CHCl_3$), of our synthetic (+)-**1** was also in good accord with the value, $[\alpha]_D^{20}$ = +3.26 ($CHCl_3$), reported for the natural product[2].

For establishment of the absolute configuration of (+)-**1**, it was converted to nitropolyzonamine (**2**) by treatment with 3-iodo-1-nitropropane in pyridine[3,5]. The resulting crystalline product was dextrorotatory, $[\alpha]_D^{24}$ = +6.1 ($CHCl_3$), and it was therefore (4*S*,5*R*,6*S*)-(+)-nitropolyzonamine (**2**). Our synthetic (+)-**2** showed the spectral data (IR, ^{1}H- and ^{13}C-NMR) identical with those reported for (+)- and (±)-**2**[3,5]. Accordingly, (+)-polyzonimine (**1**) possesses *S* configuration at its spiro center.

In a similar manner, the opposite enantiomer (–)-**1'** of polyzonimine, $[\alpha]_D^{23}$ = –3.3 ($CHCl_3$), was synthesized *via* enamine **8'** derived from **7** and (*R*)-prolinol methyl ether. Conversion of (–)-**1'** to (–)-**2'** was also achieved. The enantiomers of polyzonimine (**1** and **1'**) were bioassayed to compare their insect repellent activity. The test was executed under the standard conditions employed in Sumitomo Chemical Co. and was not designed to estimate their activity as a topical irritant. Neither of them showed insect repellent activity when tested on the German cockroach (*Blattella germanica*). Both of them, however, showed oviposition deterrant activity against the webbing clothes moth (*Tineola bisselliella*).

Conclusion

Enantiomerically pure (+)-polyzonimine (**1**), (–)-polyzonimine (**1'**), (+)-nitropolyzonamine (**2**) and (–)-nitropolyzonamine (**2'**) were synthesized, and the absolute configuration of (+)-**1** was established as *S*.

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