Enantioselective Synthesis of (+)-Polyzonimine, Defensive Monoterpene Alkaloid Produced by a Milliped *Polyzonium rosalbum*, and Determination of Its S Absolute Configuration by Its Conversion to (4S,5R,6S)-(+)−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 (4S, 5R, 6S)-(+)−nitropolyzonamina, 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 (4S,5R,6S)-(+)−nitropolyzonamine, the hitherto uncertain absolute configuration of the former was established as S.

Keywords: alkaloids, asymmetric synthesis, insects, spirocyclic compounds

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**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, (+)-nitropolyzonimine \(2',2'\)-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 4S,5R,6S\(^4\). Because (+)-polyzonimine (1) co-occurs with (+)-nitropolyzonimine (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\(^7\).

**Figure 1.** Structures of polyzonimine and nitropolyzonamine.
Experimental

General

Boiling points and melting points: uncorrected values. – IR: Jasco 410 and Jasaco A-102. – ¹H NMR: Jeol JNM-LA500 (500 MHz) and Jeol JNM-AL300 (300 MHz) and Jeol JNMX 90A (90 MHz) (CHCl₃ at δ 7.26 as an internal standard). – Optical rotation: Jasco P-1020. – MS: Jeol JMS-AXS05HA and Jeol JMS-SX102A. – M.p.: Yanaco MP-33. – 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 (12.1 g, 85.2 mmol) in diethyl ether (36 cm³) was added dropwise to a stirred and cooled suspension of LiAlH₄ (6.50 g, 171 mmol) in diethyl ether (240 cm³) at 0°C, and the reaction mixture was stirred for 1.5 h at room temperature. The excess LiAlH₄ was destroyed by the careful addition of water (6.5 cm³), 15% aq. NaOH (6.5 cm³) and water (20 cm³) 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 chromatographed on silica gel (200 g, hexane/ethyl acetate, 50:1) to give 6.18 g of impure (5.94 g). This was used immediately in the next reaction without further purification. An analytical sample was obtained by deprotection of purified acetal (5.20 g). This was used in the next step without further purification. An analytical sample was obtained by deprotection of purified acetal (5.20 g, 171 mmol) and (R)-(-)-2-(methoxymethyl) pyrrolidine (4.40 g, 38.3 mmol) were converted to crude (R)-8 (8.36 g, quant.). IR: νmax/cm⁻¹ 1670s (C=O) (film), EIMS: m/z 223.10 (M⁺). Calc. for C₁₄H₂₅NO: 223.19.

i) (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: νmax/cm⁻¹ 1670s (C=O) (film), EIMS: m/z 223.10 (M⁺). Calc. for C₁₄H₂₅NO: 223.19.

2-Methoxymethyl-N-2″,2″-dimethylcyclopentylidenemethyl pyrrolidine (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 cm³) 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: νmax/cm⁻¹ 1660s (C=O) (film), EIMS: m/z 223.10 (M⁺). Calc. for C₁₄H₂₅NO: 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: νmax/cm⁻¹ 1670s (C=O) (film), EIMS: m/z 223.10 (M⁺). Calc. for C₁₄H₂₅NO: 223.19.

i-(2′-Nitroethyl)-2,2-dimethylcyclopentanecarboxaldehyde (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 cm³, 28.3 mmol) in acetonitrile (16 cm³) 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: nD₂₅ = 1.4830, [α]D₂₅ = −2.7 (c = 0.29, CHCl₃). Elemental analysis: (Found: C, 60.35; H, 8.41; N, 7.13. Calc. for C₁₀H₁₇NO₃: C, 60.28; H, 8.60, N; 7.03%). IR: νmax/cm⁻¹ 1670s (C=O) (film), EIMS: m/z 273.00 (M⁺). Calc. for C₁₀H₁₇NO₃: 273.00.
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 cm³; 1.08 mmol), triethyl orthoformate (40 cm³; 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 K₂CO₃, and concentrated in vacuo. The residue was chromatographed on silica gel (200 g, hexane/ethyl acetate, 10:1; v/v), and concentrated in vacuo. The residue of the above described residue containing (S)-11 in THF (20 cm³) was acidified with 2 mol L⁻¹ HCl aq. (5 cm³), 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 K₂CO₃, and concentrated under atmospheric pressure. The residue was distilled to give 860 mg (54% based on 10, 2 steps) of (+)-I as a colorless oil, b.p. 81°C/10 Torr, nD = 1.4768. [(α)D] = +1.3 (c = 0.25, CHCl₃, 71% ee). IR: νmax/cm⁻¹ 2955s (C–H), 2870s (C–H), 1620s (C=C), 1465m, 1435m, 1380m, 1290m, 1210m, 1080w, 960w, 920w (film). ¹H NMR (500 MHz, CDCl₃) δ0.89 (s, 3H, 6-CH₃), 0.92 (s, 3H, 6-CH₃), 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, CDCl₃) δ0.89 (s, 3H, 6-CH₃), 0.91 (s, 3H, 6-CH₃), 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). ¹³C-NMR (125 MHz, CDCl₃) δ 20.4 (8-C), 23.8 (6-CH₃), 24.6 (6-CH₃), 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, CDCl₃) δ 20.4 (8-C), 23.8 (6-CH₃), 24.5 (6-CH₃), 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 C₇H₁₁N⁺: 152.1439. EIMS: m/z 151.0 (M⁺). Calc. for C₇H₁₁N⁺: 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); fR = 20.38 min [87.7%, (+)-I], fR = 21.80 min [12.3%, (–)-I]. The enantiomeric purity of (+)-I was estimated to be 75.4% ee.

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, nD = 1.4905. [α]D = -11 (c = 0.28, CHCl₃). Elemental analysis: (Found: C, 59.11; H, 8.98; N, 5.84. Calc. for C₇H₁₁NO₄: C, 59.24; H, 8.70; N, 5.76%). IR: νmax/cm⁻¹ 1550s (N=O), 1100m, 1075s, 1025m (film). ¹H NMR (500 MHz, CDCl₃) δ 1.00 (s, 3H, 2'-CH₃), 1.01 (s, 3H, 2'-CH₃), 1.38–1.90 (m, 8H, 4,7,8,9-H), 1.91 (dd, J 13.8, 11.1 and 5.0 Hz, 1H, 1'-CH₂), 2.38 (dd, J 13.8, 11.4 and 5.9 Hz, 1H, 1'-CH₂), 3.72–3.77 (m, 1H, 4-CH₃), 3.84–3.90 (m, 2H, 4-CH₃, 5-CH₂), 3.99–4.03 (m, 1H, 5-CH₂), 4.42 (dd, J 12.8, 11.4 and 5.0 Hz, 2'-CH₂), 4.63 (dd, J 12.8, 11.1 and 5.9 Hz, 2'-CH₂), 4.66 (s, 1H, 2-H).
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 K₂CO₃ solution. The aqueous solution was extracted with diethyl ether. The extract was dried with K₂CO₃ 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, [α]D²⁴ = +3.3 (c = 0.26, CHCl₃) – HRFABMS (M + H⁺) Found: 239.1766. Calc. for C₁₃H₂₂N₂O₂: 238.175. EIMS: m/z 239.1764. 1H NMR (300 MHz, CDCl₃) δ 0.87 (s, 3H, 2'-CH₃), 0.96 (s, 3H, 2'-CH₃), 1.37–1.53 (m, 4H, 3',4'-H), 1.62–1.78 (m, 3H, 5'-H,3-C), 1.97 (ddd, J11, 9.9 and 7.0 Hz, 1H, 3'-CH), 2.15–2.23 (m, 3H, 5'-CH₂, 2'-CH₂), 2.36–2.50 (m, 2H, 2'-CH₂, 2-CH₂), 2.85 (ddd, J11, 7.7 and 4.2 Hz, 1H, 8-CH₂), 3.06 (ddd, J11, 1.1, 9.0 and 2.1 Hz, 1H, 1'-CH₂), 3.25 (ddd, J11, 11.7, 9.0 and 6.6 Hz, 1H, 8-CH₂), 3.74 (d, J = 4.2 Hz, 1H, 5'-H), 4.80 (td, J = 7.5, 3.9 and 3.9 Hz, 1H, 1'-H). 13C NMR (125 MHz, CDCl₃) 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. 13C NMR (75 MHz, CDCl₃) 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 239.1754. 

Results and Discussion

Our synthesis of polyzonimine (1) and nitropolyzonimine (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
hydrogen peroxide afforded 59, 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 group10, (ii) (S)-prolinol methyl ether as used by Seebach’s group11, and (iii) (S)-1-amino-2-(1-methoxy-1-ethylpropyl)pyrrolidine as developed by Enders’s group12. The aldehyde 7 could be converted to the corresponding enamines, when it was treated with the former two amines in the presence of MS 4A13. 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 acetate15 and N-ethylmorpholine in acetonitrile16. 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 (4S,5R,6S)-(+)--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 Chiral-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, 1H- and 13C-NMR spectra were in good accord with the published data of (+)- and (±)-1,5,6. In addition, the specific rotation, [α]D = +3.3 (CHCl3), of our synthetic (+)-1 was also in good accord with the value, [α]D = +3.26 (CHCl3), reported for the natural product 7.

For establishment of the absolute configuration of (+)-1, it was converted to nitropolyzonimine (2) by treatment with 3-iodo-1-nitropropane in pyridine 3,5. The resulting crystalline product was dextrorotatory, [α]D = +6.1 (CHCl3), and it was therefore (4S,5R,6S)-(+)-nitropolyzonimine (2). Our synthetic (+)-2 showed the spectral data (IR, 1H- and 13C-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, [α]D = –3.3 (CHCl3), 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 deterrent activity against the webbing clothes moth (Tineola bisselliella).

**Conclusion**

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

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**References**


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