# Total Synthesis of (+)-Polyzonimine

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(+)-Polyzonimine (**1**), a terpenoid insect repellent produced by a millipede, was synthesized by a reaction sequence which utilizes the asymmetric [2,3] sigmatropic rearrangement of the ammonium ylide formed from the salt (**10**) to generate the chiral intermediate (**2**).

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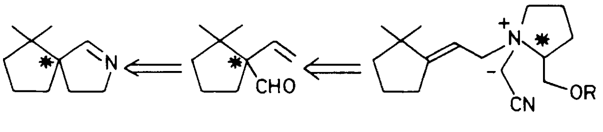
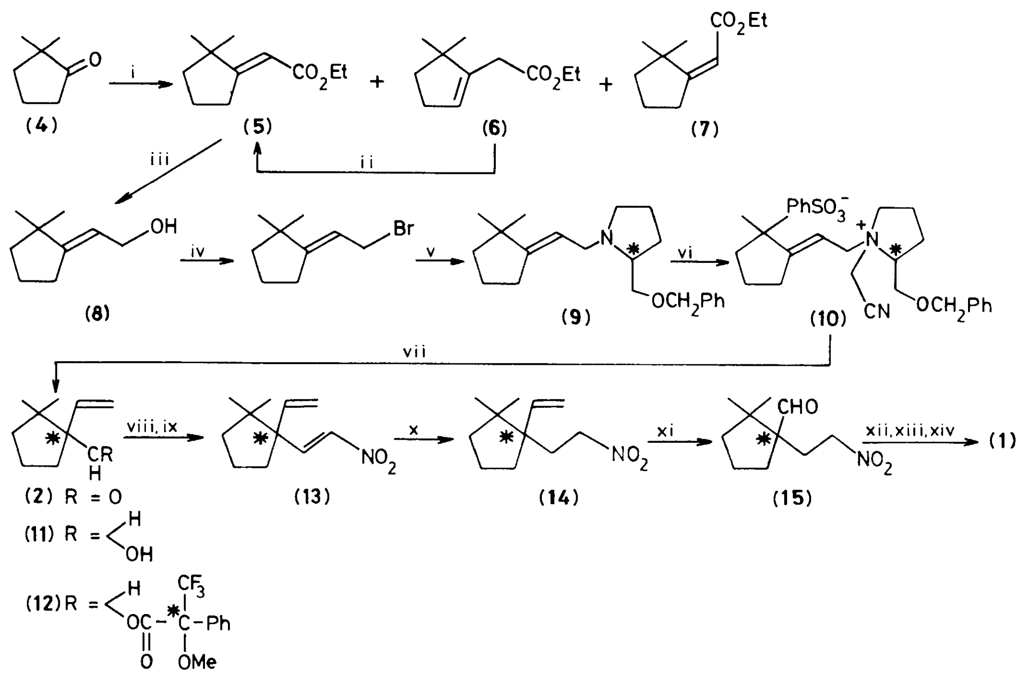
In 1975 Smolanoff *et al.*[1] reported the isolation of a novel nitrogenous monoterpenoid, the insect repellent (+)-6,6-dimethyl-2-azaspiro[4.4]non-1-ene [(+)-polyzonimine] (**1**) from the millipede *Polyzonium rosalbum*. Assignment of structure (**1**) for this natural product was based on the spectral analysis and the synthesis of (±)-polyzonimine.



(1) (2) (3)

We report here the total synthesis of (+)-polyzonimine (**1**) in which the key synthetic transformation leading to (**1**) is the asymmetric [2,3] sigmatropic rearrangement[2] of the ammonium ylide (**3**) to give the chiral intermediate (**2**). The first step in the synthesis (Scheme 1) was the Horner–Emmons reaction of the ketone (**4**)[3] with triethyl phosphonoacetate and NaH in refluxing dimethoxyethane (DME) to give a mixture of (**5**) and (**6**) (ratio 3:2, 85%) together with the *Z*-isomer (**7**)



**Scheme 1.** *Reagents and conditions:* i, NaH (1.6 equiv.), $(EtO)_2POCH_2CO_2Et$ (1.8 equiv.), DME, reflux, 15 h; ii, PPA (1 equiv.) on silica gel, $CH_2Cl_2$ (100%); iii, $LiAlH_4$ (1.2 equiv.), $AlCl_3$ (0.4 equiv.), $Et_2O$, 0°C, 1 h (94%); iv, $PBr_3$, pyridine, $Et_2O$, 0—25°C, 12 h; v, L-benzyloxyprolinol (1.1 equiv.), $K_2CO_3$, DMSO, 25°C, 15 h [60% from (**8**)]; vi, $PhSO_3CH_2CN$ (3 equiv.), acetonitrile, 25—60°C, 24 h; vii, (a) Bu$^t$OK, THF, DMSO, −78°C, 24 h, (b) $CuSO_4.5H_2O$, EtOH, 10 min [61% from (**9**)]; viii, nitromethane, KOH, MeOH, 25°C, 1 h; ix, methanesulphonyl chloride (6 equiv.), triethylamine, 25°C, 1.5 h [72% from (**11**)]; x, $NaBH_4$, MeOH, 0—25°C (87%); xi, (a) $O_3$, $CH_2Cl_2$, Pr$^i$OH, −78 °C, (b) $Me_2S$, −78 °C (88.2%); xii, ethylene glycol, triethyl orthoformate, *p*-$MeC_6H_4SO_2OH$, 25 °C, 0.5 h; xiii, $H_2$, $PtO_2$ (cat.), EtOH, 25°C, 5 h; xiv, 10% HCl, THF, 25°C, 10 h [50% from (**15**)].

(9%).† The mixture of (**5**) and (**6**) was treated with polyphosphoric acid (PPA) on silica gel in refluxing $CH_2Cl_2$ for 24 h to give the desired *exo*-ester (**5**) exclusively by isomerization of (**6**).

Reduction of the *exo*-ester (**5**) with $LiAlH_4$ and $AlCl_3$ in $Et_2O$ at 0°C provided (**8**). Bromination of the allylic alcohol (**8**) with $PBr_3$ and pyridine in $Et_2O$ followed by amination with L-benzyloxyprolinol and $K_2CO_3$ in dimethyl sulphoxide (DMSO) afforded, after alumina column chromatography, (**9**) in 60% overall yield. The pyrrolidine derivative (**9**) was converted into the quaternary salt (**10**) with cyanomethyl benzenesulphonate[4] in acetonitrile. Treatment of (**10**) with KOBu$^t$ in tetrahydrofuran (THF)–DMSO at −78 °C followed by hydrolysis with $CuSO_4 \cdot 5H_2O$ in refluxing EtOH for 10 min afforded the optically active olefin-aldehyde (**2**) $\{[\alpha]_D -7.06° (CHCl_3)\}$ in 61% overall yield.

The optical purity of (**2**) was determined by applying the methoxy(trifluoromethyl)phenylacetyl (MTPA) method.[5] Thus, reduction of (**2**) with $NaBH_4$ in MeOH followed by treatment with (+)-MTPA chloride in $CCl_4$, pyridine, and 4-*N*,*N*-dimethylaminopyridine (4-DMAP) gave the corresponding (+)-MTPA ester (**12**). The optical purity of (**12**) was estimated to be 68% enantiomeric excess from $^1H$ and $^{19}F$ n.m.r. spectra (300 MHz).

Condensation of (**2**) with nitromethane and KOH in MeOH followed by treatment with methanesulphonyl chloride and triethylamine in $Et_2O$ afforded (**13**) in 72% overall yield. Reduction of the α,β-unsaturated nitro compound (**13**) with $NaBH_4$ in MeOH gave (**14**). Ozonolysis of the olefinic function of (**14**) by $O_3$ in $CH_2Cl_2$–Pr$^i$OH at −78°C followed by treatment with $Me_2S$ at −78 to 25°C provided (**15**). Protection of the formyl group of (**15**) as the acetal (ethylene glycol and triethyl orthoformate) followed by reduction of the nitro group with $H_2$ and $PtO_2$ in EtOH gave the corresponding amino acetal which was immediately treated with 10% HCl in THF at 25 °C to give (**1**) by means of preparative g.c.

The synthetic polyzonimine (**1**) exhibited i.r. and n.m.r. spectra identical with those of the reported natural product.[1] The optical rotation observed for synthetic polyzonimine (**1**) was + 1.95° $(CHCl_3)$ $\{$lit.,[1] $[\alpha]_D$ + 3.26° $(CHCl_3)\}$.

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† All new compounds were fully characterized by spectroscopic methods ($^1H$ n.m.r., i.r., mass). Representative spectral properties of the key compounds are as follows: compound (**5**), i.r. $\nu_{max}$ (neat) 1720, 1650 cm$^{-1}$; $^1H$ n.m.r. δ $(CDCl_3)$ 1.1 (s, 6H, $CH_3 \times 2$), 1.29 (t, *J* 7.6 Hz, 3H, $-CO_2CH_2CH_3$), 2.97 (tt, *J* 2.6 and 7.2 Hz, 2H, ring $CH_2$), 4.20 (q, *J* 7.6 Hz, 2H, $-CO_2CH_2CH_3$, 5.72 (t, *J* 2.6 Hz, 1H, olefinic H); *m/z* 182 ($M^+$), 167, 137, 109. Compound (**9**), $^1H$ n.m.r. δ $(CDCl_3)$ 1.00 (s, 6H, $CH_3 \times 2$), 4.49 (s, 2H, $-OCH_2Ar$), 5.30 (tt, *J* 2.6 and 6.8 Hz, 1H, olefinic H), 7.26 (s, 5H, ArH); *m/z* 313.2402 ($C_{21}H_{31}NO$ requires 313.2404). Compound (**2**), i.r. $\nu_{max}$ (neat) 1708, 1630 cm$^{-1}$; $^1H$ n.m.r. δ $(CDCl_3)$ 0.97 (s, 3H, $CH_3$), 1.07 (s, 3H, $CH_3$), 5.01 (dd, *J* 1.6 and 17.4 Hz, 1H, olefinic H), 5.25 (dd, *J* 1.6 and 11 Hz, 1H, olefinic H), 6.10 (dd, *J* 11 and 17.4 Hz, 1H, olefinic H), 9.65 (s, 1H, CHO); *m/z* 152.1208 ($C_{10}H_{16}O$ requires 152.1200). Compound (**15**), i.r. $\nu_{max}$ (neat) 1705, 1550 cm$^{-1}$; $^1H$ n.m.r. δ $(CDCl_3)$ 1.0 (br. s, 6H, $CH_3 \times 2$), 4.30 (m, 2H, $-CH_2NO_2$), 9.62 (s, 1H, CHO); *m/z* (field desorption) 199 ($M^+$). Compound (**1**), i.r. $\nu_{max}$ (neat) 1620 cm$^{-1}$; $^1H$ n.m.r. δ $(CDCl_3)$ 0.88 (s, 3H, $CH_3$), 0.91 (s, 3H, $CH_3$), 1.70 (m, 8H), 3.79 (br. t, *J* 6.5 Hz, 2H, $-CH_2N=$), 7.37 (br. s, 1H, $-CH=N-$); *m/z* 151.1333 ($C_{10}H_{17}N$ requires 151.1360).