Total Synthesis of (+)-Polyzonimine

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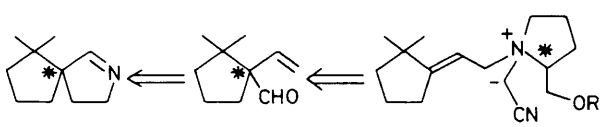
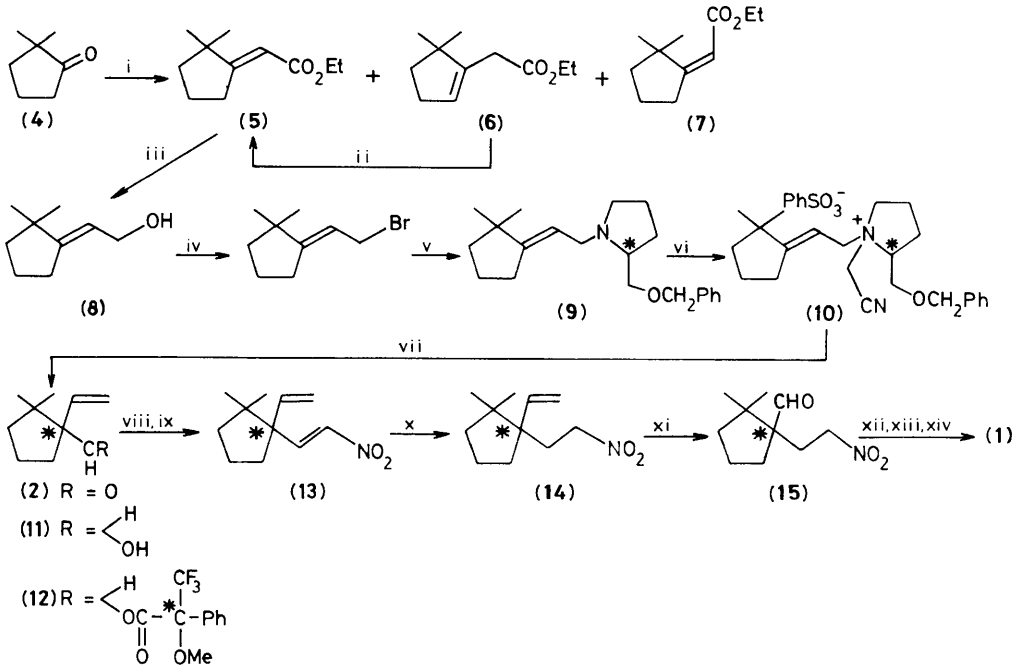
(+)-Polyzonimine (**1**), a terpenoid insect repellent produced by a millipede, was synthesized by a reaction sequence which utilizes the asymmetric [2,3] sigmatropic rearrangement of the ammonium ylide formed from the salt (**10**) to generate the chiral intermediate (**2**).

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^tOK, 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^iOH, −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^iOH 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° ($CHCl_3$)}.

Received, 17th November 1983; Com. 1506

† 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. ν_{max} (neat) 1720, 1650 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$) 1.1 (s, 6H, CH_3 × 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 × 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. ν_{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. ν_{max} (neat) 1705, 1550 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$) 1.0 (br. s, 6H, CH_3 × 2), 4.30 (m, 2H, $-CH_2NO_2$), 9.62 (s, 1H, CHO); *m/z* (field desorption) 199 (M^+). Compound (**1**), i.r. ν_{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).

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