A Novel Synthetic Route to (±)-Perhydrogephyrotoxin

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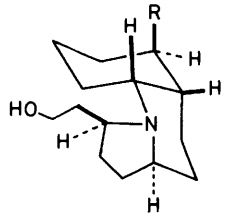
Total synthesis of (±)-perhydrogephyrotoxin (**3**) starting from 1,3-bis(trimethylsiloxy)buta-1,3-diene is presented; an efficient new decarboxylative reduction of γ-carbamoyloxy-α,β-enoate (**14**) by lithium dibutylcuprate is also presented.

The structures of gephyrotoxin (**1**) and dihydrogephyrotoxin (**2**), isolated from the skin extract of the Neotropical poison dart frog *Dendrobates histrionicus*, have been elucidated by Daly, Tokuyama, and co-workers.[1] The scarcity of natural gephyrotoxin (15 mg of gephyrotoxin from 3200 frogs)[2] together with its unusual perhydropyrrolo[1,2-*a*]quinoline structure and interesting muscarine antagonistic activity have made the alkaloids gephyrotoxin (**1**)[3] and perhydrogephyrotoxin (**3**)[4] attractive targets for total synthesis. Furthermore, structure–activity correlations for gephyrotoxin class alkaloids have not fully been delineated because of the limited supplies available from natural sources.[5] It is especially important to develop a stereoselective synthetic route to these bases. In this communication we present a total synthesis of (±)-perhydrogephyrotoxin (**3**).

The requisite thiolactam (**8**) was stereoselectively synthesised as shown in Scheme 1.† Thus, the Diels–Alder reaction of *trans*-1,3-bis(trimethylsiloxy)buta-1,3-diene[6] with ethyl *trans*-oct-2-enoate‡ in xylene at 175 °C in a sealed glass tube gave a cycloadduct (**4**) (95%, b.p. 150—153 °C/1 Torr). Reaction of (**4**) with ethylene glycol in the presence of a catalytic amount of toluene-*p*-sulphonic acid in refluxing benzene gave an acetal (**5**) [84%, b.p. 140 °C/1 Torr, i.r. ($CHCl_3$): 1705 and 1644 cm^{-1}] which was converted into an amide (**6**) by the successive treatments shown in Scheme 1 {iii (95%, b.p. 150 °C/3 Torr), iv (100%), v [78%, i.r. ($CHCl_3$): 2250 cm^{-1}], and vi [90%, i.r. ($CHCl_3$): 3485, 3405, and 1680 cm^{-1}]}.



(**1**) R = $CH_2CH{=}^{Z}CHC{\equiv}CH$

(**2**) R = $CH_2CH{=}CHCH{=}CH_2$

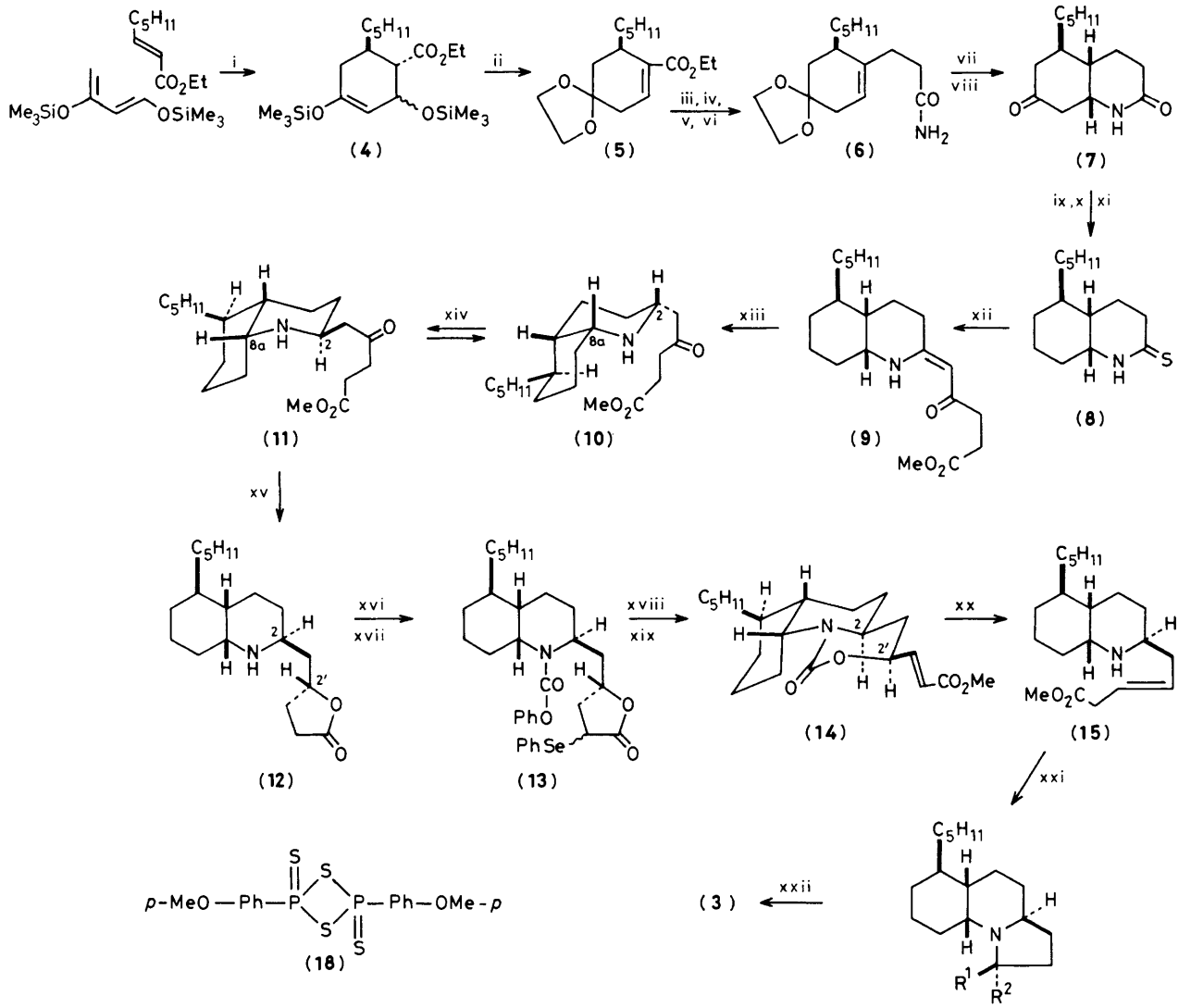
(**3**) R = $[CH_2]_4Me$

Deacetalization of (**6**) afforded a ketoamide [97%, i.r. ($CHCl_3$): 3500—3420, 1708, and 1680 cm^{-1}] which was treated with 5% NaOMe to give a keto-lactam (**7**) as the sole isolable product [61%, m.p. 162 °C, i.r. ($CHCl_3$): 3383—3200, 1714, and 1660 cm^{-1}]. We were unable to detect any stereoisomer of (**7**) in the present synthesis. Thioacetalisation of (**7**) followed by desulphurisation with Raney nickel gave a lactam [96%, m.p. 117 °C, i.r. ($CHCl_3$): 3380—3180 and 1645 cm^{-1}] which was transformed into a key intermediate (**8**) (94%, m.p. 134 °C) by treatment with Lawesson's reagent.[7]

The next step of the synthesis was the addition of the C_5 moiety to the thiolactam carbon of (**8**)[8] to give a vinylogous lactam (**9**) [81%, m.p. 52 °C, i.r. ($CHCl_3$): 3400—3180, 1730, and 1600 cm^{-1}]. The keto-ester (**10**) [non-steroid form, ^1H n.m.r. ($CDCl_3$) δ 2.90 (1H, m, $W_{\frac{1}{2}}$ 8 Hz, 8a-H), 3.05 (1H, doublets of double triplets, *J* 9.5, 6.5, and 3.5 Hz, 2-H)], obtained by reduction of (**9**) at pH 4 (indicator: bromocresol green) in 99% yield, was equilibrated (Et_3N–MeOH) with (**11**) [steroid form, ^1H n.m.r. ($CDCl_3$) δ 3.05 (1H, double

† All new compounds reported in this communication exhibited satisfactory spectroscopic and analytical and/or mass spectral data consistent with the structures.

‡ Prepared following the general procedure (W. S. Wadsworth, Jr., and W. D. Emmons, *J. Am. Chem. Soc.*, 1961, **83**, 1733) from triethyl phosphonoacetate, n-hexanal, and NaH in Et_2O at 0 °C (82%, b.p. 88—90 °C/8 Torr).



Scheme 1. *Reagents and conditions:* i, 175 °C, 48 h; ii, $(CH_2OH)_2$, *p*-$MeC_6H_4SO_2OH$, benzene, reflux, 10 h; iii, Bu^i_2AlH (2.3 equiv.), n-hexane–toluene (6 : 1), −73 °C, 3 h; iv, Bu^nLi, dry tetrahydrofuran–hexamethylphosphoric triamide (THF–HMPT) (2 : 1), −73 °C and then *p*-$MeC_6H_4SO_2Cl$ (1.2 equiv.), −73 → 0 °C; v, $CuCH_2CN$ (5 equiv.), THF, −73 → −30 °C; vi, 30% H_2O_2, 25% aq. KOH, room temp., 12 h; vii, 5% aq. HCl, Me_2CO, 56 °C, 30 min; viii, 5% NaOMe (8 equiv.), MeOH, 65 °C, 20 min; ix, $(CH_2SH)_2$ (1.86 equiv.), $BF_3{\cdot}Et_2O$ (1.08 equiv.), $CHCl_3$, room temp., 1 h; x, Raney W-2 Ni (53 equiv.), EtOH, 78 °C, 20 h; xi, (**18**) (1.0 equiv.), xylene, 140 °C, 1 h; xii, $BrCH_2COCH_2CH_2CO_2Me$ (1.4 equiv.), $CHCl_3$, room temp., 2 h, and then $PhP(CH_2CH_2NMe_2)_2$ (1.5 equiv.), 61 °C, 2 h; xiii, $NaBH_3CN$ (0.5 equiv.), 5% aq. HCl–MeOH (1 : 1), 1 h; xiv, Et_3N (4.55 equiv.), MeOH, 65 °C, 5 h; xv, $NaBH_4$ (1.1 equiv.), MeOH, −20 °C, 1 h, and then *p*-$MeC_6H_4SO_2OH$ (1.0 equiv.), benzene, reflux, 1 h; xvi, $ClCO_2Ph$ (10 equiv.), pyridine, catalytic amount of 4-dimethylaminopyridine, room temp., 2 days; xvii, lithium cyclohexylisopropylamide (10 equiv.), THF–HMPT, −73 → −40 °C, and then PhSeCl (2.4 equiv.), −73 °C, 10 min; xviii, LiOH (10 equiv.), MeOH–H_2O (16 : 1), reflux, 12 h, acidified with 5% aq. HCl, and then CH_2N_2 work-up; xix, 30% H_2O_2 (135 equiv.), pyridine–CH_2Cl_2 (1 : 5), 0 °C, 30 min; xx, $LiBu_2Cu$ (2.3 equiv.), THF, −73 °C, 5 min; xxi, 1% NaOMe (9 equiv.), MeOH, reflux, 1.5 h; xxii, Bu^i_2AlH (10 equiv.), n-hexane–toluene (1 : 1), −60 → −30 °C, 30 min.

triplets, *J* 11.7 and 3.7 Hz, 8a-H), 3.32 (1H, doublets of double triplets, *J* 9.5, 6.5, and 3.5 Hz, 2-H)] in a *ca.* 3 : 1 ratio.

Compound (**11**) was the desired intermediate for the synthesis, and although (**11**) was obtained as a minor product, the equilibrium was in essence satisfactory, since the major compound (**10**) could be recycled for the equilibration reaction. Reduction of (**11**) followed by refluxing in benzene in the presence of toluene-*p*-sulphonic acid afforded a lactone (**12**) as a single product [99%, i.r. ($CHCl_3$): 3500 and 1767 cm^{-1}]. Although the stereochemistry at the C-2′ carbon was not clarified at this stage, the β-configuration at the C-2′ in (**12**) was inferred from the nuclear Overhauser effect (*ca.* 9% enhancement) of the hydrogen at the C-2 position by irradiation of the hydrogen at the C-2′ position in (**14**) derived from (**12**).

Protection of the secondary amino group in (**12**), step xvi in Scheme 1 [99%, i.r. ($CHCl_3$): 1768 and 1695 cm^{-1}] followed by phenylselenylation by a standard procedure gave the

carbamate (**13**)(87%). Treatment of (**13**) with LiOH in 94% aq. MeOH, followed by methylation with CH_2N_2, gave a cyclic urethane derivative [80%, i.r. ($CHCl_3$): 1725 and 1677 cm^{-1}] which on reacting with 30% H_2O_2 gave the Overman intermediate (**14**)[4a] [100%, i.r. ($CHCl_3$): 1720 and 1678 cm^{-1}].

Although organocopper(I) reagents have usually been used for conjugate additions and substitution reactions in synthetic chemistry, the Gilman reagent lithium dibutylcuprate was effectively employed for the decarboxylative reduction of (**14**)[9] to give an amine (**15**) in quantitative yield. Treatment of (**15**) with 1% NaOMe gave the tricyclic compounds (**16**) (51%) and (**17**)(9%), and subsequent treatment of (**16**) with Bu^i_2AlH afforded (±)-perhydrogephyrotoxin (**3**) in 98% yield. The spectral data [i.r. ($CHCl_3$), ^1H and ^{13}C n.m.r.] of the synthesised compound (**3**) were identical with authentic spectra.[4]

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