Cycloaddition of a Nitrone to 2-Aminobut-3-en-1-ol for Large-scale Preparation of 3-Aminopiperidin-4-ols: A New Asymmetric Synthesis of (2*R*,4*R*,5*S*)-Tetrahydropseudodistomin

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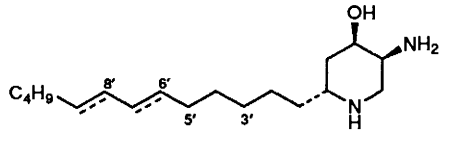
Cycloaddition of the nitrone, derived from tetradecanal, to 2-aminobut-3-en-1-ol provides a practical asymmetric synthesis of both (2*R*,4*R*,5*S*)-tetrahydropseudodistomin and all the stereoisomers of racemic tetrahydropseudodistomin.

Pseudodistomins A and B, isomeric piperidine alkaloids isolated from the Okinawan tunicate *Pseudodistoma kanoko*, have been shown to have *in vitro* antitumour activity against L1210 and L5178 leukaemia cells and to inhibit calmodulin-activated brain phosphodiesterase.[1] Their structures were initially deduced as **1** and **2a**, respectively, based on spectral evidence.[1] However, our recent synthesis of the triacetate of racemic **2a** brought into question the location of the diene in the side chain as first proposed.[2] Later, degradation studies of pseudodistomin B **2b** and the total synthesis of the racemic triacetate led to the revised structure as the 6',8'-diene.[3] However, because of the non-availability of the natural alkaloid, the structure of pseudodistomin A **1** remains to be confirmed. Because of the interest in pseudodistomins and in order to establish the relationship between structure and the biological activity, we have investigated the cycloaddition of the nitrone of tetradecanal to 2-aminobut-3-en-1-ol to give isoxazolidines which were converted into the corresponding 2-substituted 5-aminopiperidin-4-ols. By optimising the reaction conditions for the conversion, we have established a convenient procedure for the synthesis of pseudodistomins on a large scale; subsequently, (2*R*,4*R*,5*S*)-tetrahydropseudodistomin **3** was prepared in a new asymmetric eight-step synthesis from D-methionine ester.



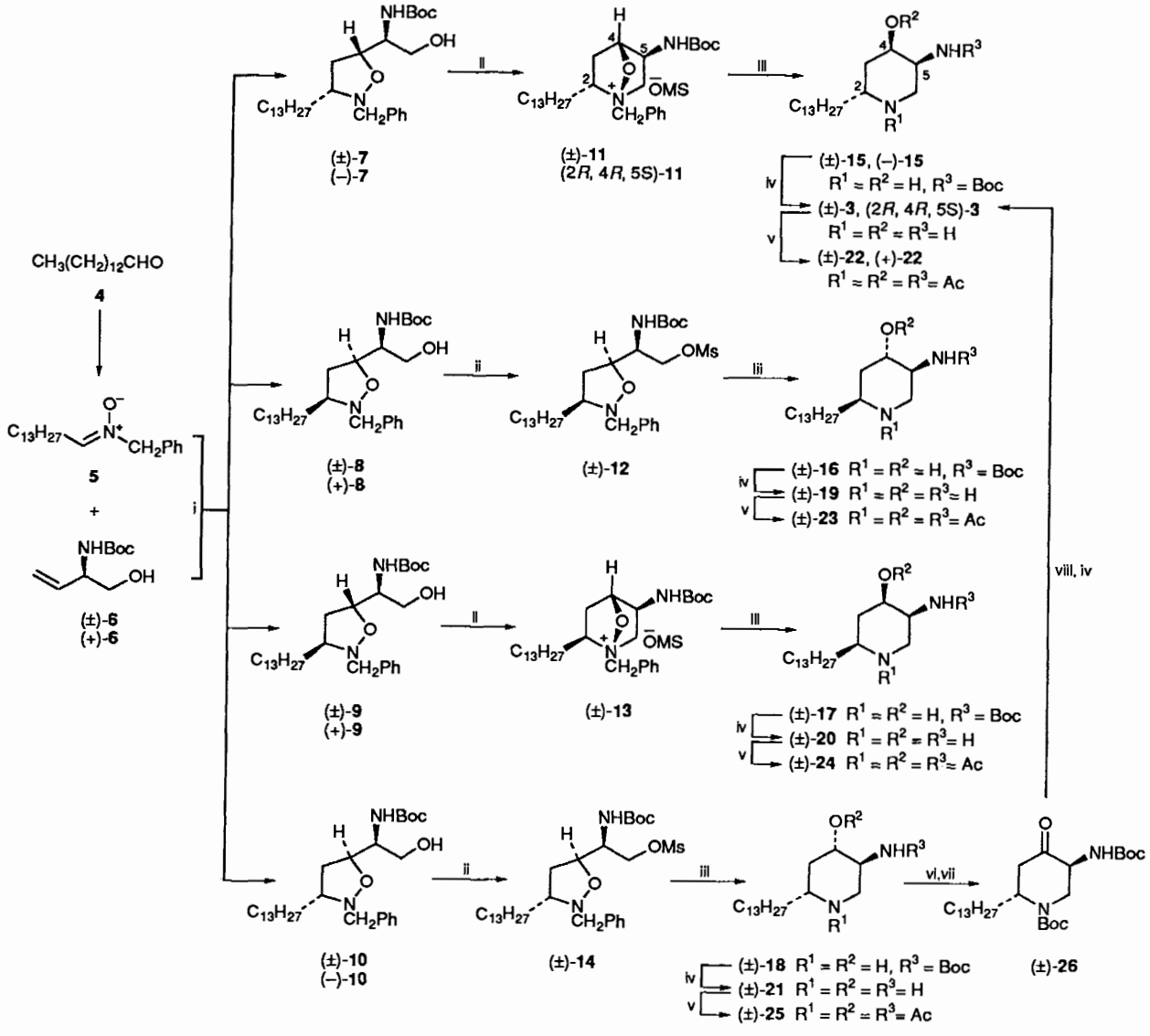
1 Pseudodistomin A: 3'-*trans*,5'-*cis*-diene (?)
2a Pseudodistomin B: initial: 3'-*trans*,5'-*trans*
2b Pseudodistomin B, revised: 6'-*trans*,8'-*trans*
3 Tetrahydropseudodistomin: 6',8'-saturated

Nitrone cycloaddition is useful for the construction of 1,3-amino alcohol systems widely found in natural products.[4] Initially, we investigated the cycloaddition of the nitrone derived from tetradecanal to the (±)-2-aminobut-3-en-1-ol **6**.[5] Tetradecanal **4** was condensed with *N*-benzylhydroxylamine[6] to give the nitrone **5** which upon cycloaddition to (±)-2-(*N*-*tert*-butoxycarbonylamino)but-3-en-1-ol **6** afforded a 2:3:3:5 mixture of four adducts (±)-**7**–(±)-**10** (81%) which was readily separated by chromatography. The stereostructures of (±)-**7**–(±)-**10** were unambiguously confirmed by the following ring transformation of the isoxazolidines to the readily assignable piperidine derivatives. Upon treatment with methanesulfonyl chloride–pyridine, the adducts (±)-**8** and (±)-**10** gave the corresponding mesylates (±)-**12** and (±)-**14** while the most nonpolar adduct (±)-**7** and the third one (±)-**9** gave the bicyclic compounds (±)-**11** and (±)-**13**, respectively, as a result of concomitant ring formation. Upon treatment of the two mesylates (±)-**12** and (±)-**14** with hydrogen in the presence of Pearlman catalyst the following smooth three-step sequence took place: cleavage of N–O bond, debenzylation, and *N*-alkylation to give the piperidinols (±)-**16** and (±)-**18** (62–70%). Similarly, the two quaternary salts (±)-**11** and (±)-**13** were converted into the piperidinols (±)-**15** and (±)-**17** (67–68%). Deprotection of the *N*-Boc group in the piperidinols (±)-**15**–(±)-**18** gave the amino alcohols (±)-**3** and (±)-**19**–(±)-**21**, respectively, in quantitative yields which were characterised as their corresponding triacetates (±)-**22**–(±)-**25**, of which (±)-**22** was identical with the authentic triacetate[1,2,7,8] upon comparisons of their spectral data. Careful spectral analyses of (±)-**23**–(±)-**25** involving comparisons with the known triacetate (±)-**22** firmly established the stereostructures of three other isomers as shown. The piperidinol (±)-**18**, prepared from the major adduct (±)-**10** was effectively converted into (±)-tetrahydropseudodistomin **3** by *N*-protection with $(Boc)_2O$, oxidation with chromium trioxide–pyridine to the ketone (±)-**26**, reduction with K-selectride,[7] and deprotection with trifluoroacetic acid (TFA) in 66% overall yield.

This method was successfully applied to the asymmetric synthesis of (2*R*,4*R*,5*S*)-tetrahydropseudodistomin **3** as follows. Cycloaddition of the nitrone **5** to the (+)-2-aminobut-3-en-1-ol **6** gave four optically active adducts **7**–**10** in 79% combined yields, of which the most nonpolar adduct (−)-**7** was subjected to mesylation, catalytic hydrogenolysis, and deprotection to afford the desired (2*R*,4*R*,5*S*)-tetrahydropseudodistomin **3** in 67% overall yield. Acetylation of the piperidinol (2*R*,4*R*,5*S*)-**3** with acetic anhydride–pyridine gave the triacetate (+)-**22**, m.p. 82–84 °C (Et_2O), $[\alpha]_D$ +70.3 (*c* 0.64, MeOH) {lit.,[1] $[\alpha]_D$ +33 (*c* 1, MeOH); lit.[8] $[\alpha]_D$ +36.9 (*c* 0.8, MeOH)} which was identical (IR, ^1H and ^{13}C NMR) with an authentic sample. Our asymmetric synthesis, providing fully characterised crystalline (+)-triacetyltetrahydropseudodistomin **22**, is an attractive alternative to the 24-step asymmetric synthesis reported recently by Knapp's group.[8]

Experimental

Cycloaddition of the Nitrone **5** *to* (+)-2-[N-(tert-*Butoxycarbonyl*)*amino*]*but*-3-*en*-1-*ol* **6**.—Tetradecanal **4** (2.23 g, 18.1 mmol) was added to a stirred mixture of *N*-benzylhydroxylamine (4.82 g, 22.7 mmol) and molecular sieves 4 Å (4.8 g) in toluene (40 cm^3). After being stirred at room temperature for 3 h, the reaction mixture was filtered. A solution of (+)-2-aminobut-3-en-1-ol **6** (2.6 g, 13.9 mmol) in toluene (50 cm^3) was added to the filtrate, and the mixture was refluxed for 94 h. After evaporation of the solvent, the residue was subjected to



Scheme 1 *Reagents and Conditions:* i, toluene, reflux; ii, $MeSO_2Cl$, pyridine, 0 °C; iii, 10% $Pd(OH)_2$-C, H_2, MeOH, 25 °C; iv, TFA, CH_2Cl_2, 25 °C; v, Ac_2O, pyridine, 25 °C; vi, $(Boc)_2O$, $NaHCO_3$, H_2O, MeOH, reflux; vii, CrO_3, pyridine, 25 °C; viii, K-Selectride, THF, −70 °C

flash column chromatography on silica gel (AcOEt–hexane = 1:2) to give the adducts (−)-**7** (0.98 g, 14%), (+)-**8** (1.30 g, 19%), (+)-**9** (1.35 g, 19%) and (−)-**10** (1.86 g, 27%).

(3R,5R)-2-*Benzyl*-5-[(1S)-1-tert-*butoxycarbonylamino*-2-*hydroxyethyl*]-3-*tridecylisoxazolidine* **7**: crystals, m.p. 60–62 °C (from hexane); $[\alpha]_D$ −52.2 (*c* 0.67, MeOH); δ_H(500 MHz; $CDCl_3$) 5.33 (1 H, br d, *J* 8, NH), 4.33 (1 H, br dt, *J* 8, 4.5, 5-H), 3.90 (1 H, br d, *J* 11, CH_2OH), 3.53–3.44 (2 H, m, $CHCH_2OH$), 2.79 (1 H, qd, *J* 8, 4, 3-H), 2.58 (1 H, dt, *J* 12.5, 8, 4-H) and 1.86 (1 H, ddd, *J* 12.5, 8, 5, 4-H) (Found: M^+, 504.3931. Calc. for $C_{30}H_{52}N_2O_4$: *M*, 504.3925).

(3S,5S)-2-*Benzyl*-5-[(1S)-1-tert-*butoxycarbonylamino*-2-*hydroxyethyl*]-3-*tridecylisoxazolidine* **8**: needles, m.p. 49–51 °C (from hexane); $[\alpha]_D$ +21.3 (*c* 0.90, MeOH); δ_H(500 MHz; $CDCl_3$) 5.54 (1 H, br d, *J* 8, NH), 4.36 (1 H, ddd, *J* 8, 6, 2, 5-H), 3.79–3.64 (2 H, m, CH_2OH), 3.60 (1 H, m, $CHCH_2OH$), 2.85 (1 H, br q, *J* 8, 3-H), 2.55 (1 H, dt, *J* 12, 8, 4-H) and 1.87 (1 H, br dt, *J* 12, 7, 4-H) (Found: M^+, 504.3929. Calc. for $C_{30}H_{52}N_2O_4$: *M*, 504.3925).

(3S,5R)-2-*Benzyl*-5-[(1S)-1-tert-*butoxycarbonylamino*-2-*hydroxyethyl*]-3-*tridecylisoxazolidine* **9**: crystals, m.p. 59–60 °C (from hexane); $[\alpha]_D$ +42.0 (*c* 0.79, MeOH); δ_H(200 MHz; $CDCl_3$) 5.04 (1 H, br d, *J* 7, NH), 4.09 (1 H, m, 5-H), 3.83–3.54 (3 H, m, $CHCH_2OH$), 2.87 (1 H, br, 3-H), 2.32 (1 H, dt, *J* 12, 7, 4-H) and 2.08 (1 H, dt, *J* 12, 7, 4-H) (Found: M^+, 504.3929. Calc. for $C_{30}H_{52}N_2O_4$: *M*, 504.3925).

(3R,5S)-2-*Benzyl*-5-[(1S)-1-tert-*butoxycarbonylamino*-2-*hydroxyethyl*]-3-*tridecylisoxazolidine* **10**: oil; $[\alpha]_D$ −60.8 (*c* 1.02, MeOH); δ_H(200 MHz; $CDCl_3$) 4.98 (1 H, br d, *J* 8, NH), 4.22 (1 H, br t, *J* 6.5, 5-H), 3.75–3.56 (3 H, m, $CHCH_2OH$), 2.74 (1 H, br, 3-H), 2.24 (1 H, dt, *J* 12, 7, 4-H) and 2.00 (1 H, br dt, *J* 12, 7, 4-H) (Found: M^+, 504.3933. Calc. for $C_{30}H_{52}N_2O_4$: *M*, 504.3925).

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