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Stereoselective Synthesis of a Terpyrrolidine Unit, a Potential Building Block for Anion Recognition

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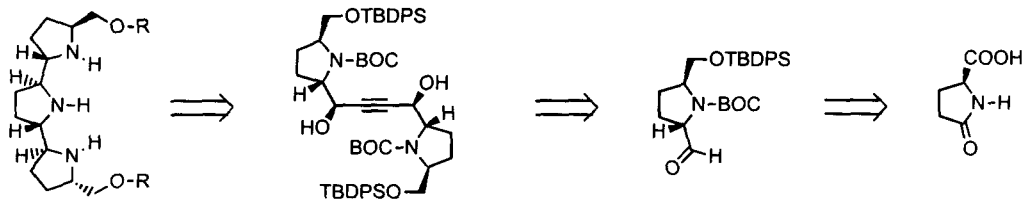
Abstract: The first stereoselective synthesis of a *trans-threo-trans-threo-trans* terpyrrolidine was achieved. A bidirectional strategy involving double acetylide coupling of two *trans*-N-BOC-pyrrolidine-aldehydes **3**, epimerisation-free hydrogenation and ring closure via a seven-membered cyclic sulfate gives access to the terpyrrolidine scaffold. © 1997 Elsevier Science Ltd.

Molecular recognition of anions plays a vital role on many biochemical pathways. Several attempts have been made to model anion binding on the molecular level.[1] Towards a project involving anion recognition, we envisioned a stereodefined terpyrrolidine core **1** as a key unit.[2] By means of medium and the degree of protonation (pH), one should influence the conformation of **1** and control its binding properties.



1 **2** **3** **4**

Scheme 1

A retrosynthetic analysis is shown in scheme 1: Cutting down the complexity of the polyamine skeleton bearing six stereogenic centres, we were intrigued by a bidirectional acetylide coupling of two *trans*-pyrrolidine aldehydes **3**, leading to diol **2**.[2] Cram addition (non-chelation control) in the formation of **2** could provide the desired *erythro*-stereochemistry.[4] Aldehyde **3** should be accessible from S-pyroglutamic acid **4**.

The synthesis of aldehyde **3** (scheme 2) commenced with the esterification of **4** followed by reduction of the resulting methyl ester to the amidoalcohol **5**.[5] After O-TBDPS- and N-BOC-protection, lactam **6** could easily be purified by recrystallisation. Reduction with $NaBH_4$ then furnished the labile lactamol, which was directly converted to the stable N,O-acetal **7** with 2,2-dimethoxy-propane.[6]

Transforming the N,O-acetal **7** into the *trans*-nitrile **8** was addressed next. When we checked various conditions to generate and trap an acyl-iminium ion from **7** with TMSCN, no profound effect was observed of

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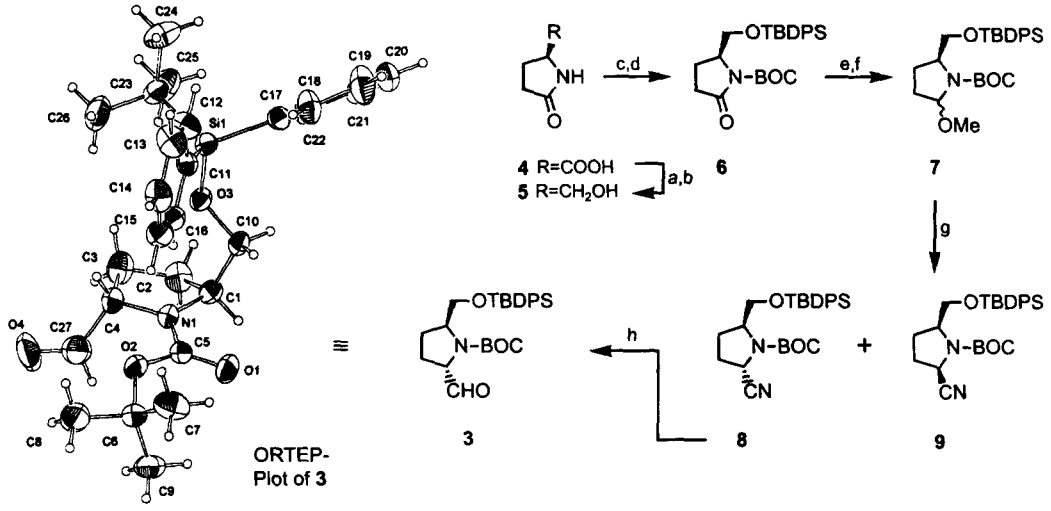
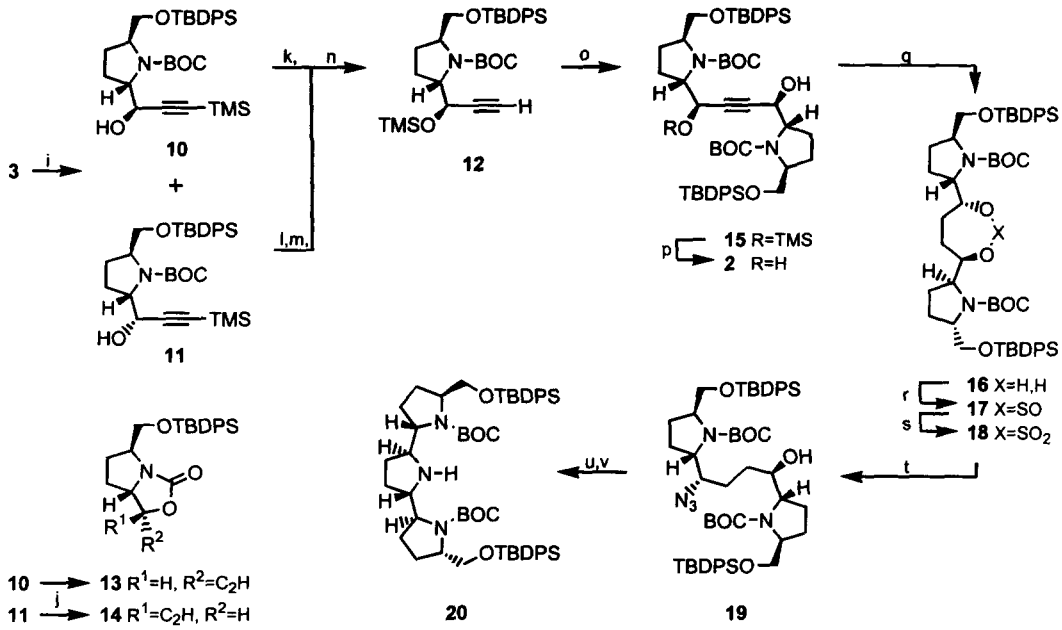


Scheme 2: a) DMP/MeOH, HCl (pH 1.3), 50°C, 6h, 94%. b) $NaBH_4$, THF/MeOH, 5°C, 1h, 99%. c) TBDPSCl, Im, DMF, 3h, 93%. d) BOC_2O, Py, 10% DMAP, CH_2Cl_2, 18h, 92%. e) $NaBH_4$, CH_2Cl_2/MeOH, -10°C, 2.5h, 99%. f) DMP, CH_2Cl_2, 1% CSA, 10min, 95%. g) TMSCN, 1% TMSOTf, CH_2Cl_2, -35°C, 5min, 95%. h) DIBAH, toluene/PE, -70°C, 1.5h, then tartrate buffer, 3h, 70%.

neither the Lewis acid ($SnCl_4$, $TiCl_4$, $ZnBr_2$, $BF_3{\cdot}OEt_2$, TMSOTf) nor the solvent (toluene, Et_2O, CH_2Cl_2) on the stereochemical outcome of the reaction (*trans*:*cis*=2-3:1). Best results were obtained using catalytic amounts of TMSOTf at -35°C, providing the easily separable nitriles **8** and **9** (76:24) in 95% combined yield.[7] Reducing the nitrile **8** to the aldehyde **3** turned out to be complicated by severe epimerisation and overreduction. Optimised conditions were found when applying toluene/PE 2:1 as solvent for the DIBAH-reduction. Careful workup using a neutral tartrate buffer (Rochelle's salt, NH_4Cl, tartaric acid, pH 6.5-7) allowed the isolation of **3** in good yield with no epimerisation (NMR).[8] X-ray structure analysis confirmed its relative and absolute configuration.[9] As expected, the larger CH_2-group (C10) was found axially oriented, due to $A^{1,3}$-strain exerted by the planarised N-carbamate (N1-C5).[10]

The addition of an acetylide anion was investigated next (scheme 3). Li- and Mg-reagents of TMS acetylene in THF or Et_2O could only be applied at very low temperatures (*erythro*:*threo*=60:40), as above -90°C remarkable enolisation of **3** occurred. The Zn-[11a] and $(^iPrO)_3Ti$-[11b] reagents did not react at all, whereas the metal fragment $(^iPrO)_2TiCl$-[11c] gave the propargylic alcohols **10** and **11** (3:1) in 88% yield, but the sensitive aldehyde **3** epimerised moderately (8%) during the reaction. HMPT applied as cosolvent [3] gave a 3:1 mixture in favour of **10**, however, TMS migration and a lowered yield overruled its beneficial effect. Finally the non-basic cerium compound [11d] proved best in terms of total yield (95%) and reliability.

Fortunately **10** and **11** were separable by chromatography. To overcome the neglible Cram selectivity (55:45), **11** was subjected to a Mitsunobu reaction.[12] Then simultaneous cleavage of the ester- and silyl-groups followed by TMS protection of the combined propargylic alcohols delivered the acetylene **12** in 70-75% total yield from **3**. The relative configurations of **10** (*erythro*) and **11** (*threo*) could be unambiguously determined after basic cyclisation of the N-BOC amino alcohols: Their cyclic carbamates **13** and **14** had vicinal coupling constants of 7.9 Hz (*cis*) and 3.1 Hz (*trans*), respectively.[13]



Scheme 3: i) Cl_2Ce-C≡C-TMS, THF, -85°C, 10min, 95%. j) NaH, THF, 45°C, 1.5h, 40%. k) K_2CO_3, MeOH, 2.5h, 94%. l) PPh_3, pNBA, DEAD, THF, 18h, 63%. m) NaOH, THF, 0°C, 3h, 96%. n) TMSCl, NEt_3, CH_2Cl_2, 0°C, 1h, 94%. o) BuLi, THF, HMPT, -90°C, **3**, 1h, 91%. p) 5% CSA, THF/MeOH, 0°C, 10min, 83%. q) H_2, Pt (5% on C), MeOH, 12h, 89%. r) $SOCl_2$, NEt_3, CH_2Cl_2, -10°C, 15min, 98%. s) 1% $RuCl_3$, $NaIO_4$, $CCl_4/CH_3CN/H_2O$, 0°C, 20min, quant. t) LiN_3, HMPT, 1h, then THF, pH 2 (H_2SO_4), 2.5h, 63%. u) MsCl, NEt_3, CH_2Cl_2, -30°C to 0°C, 2h, 97%. v) H_2, Pd (10% on C), MeOH, 0°C, 45min, then add $NaHCO_3$, RT, 18h, 68%.

All experiments of coupling **12** with **3** resembled the observations made previously, but HMPT could be used without side reactions (*erythro*:*threo*=2:1). After flash chromatographic separation, **15** was desilylated to the C_2-symmetrical diol **2**. Attempts to hydrogenate the triple bond with Pd/H_2 lead to deoxygenated and epimerised products due to the slow reduction of the hindered bis-allylic intermediate. But with Pt (5% on C) as hydrogenation catalyst, stereochemically pure (>99%) diol **16** could be isolated in high yield.[8]

With **16** at hand, the final ring closure was investigated in a variety of ways. Unfortunately protocols relying on the substitution of bis-sulfonates (Ts, Ms, Tf)[14] with primary amines entirely failed. Under basic reaction conditions elimination and intramolecular cyclisation of the BOC-group [15] always occurred faster than the sterically hindered intermolecular substitution. Non-basic conditions in the substitution and leaving-group attachment steps seemed more promising and thus the cyclic sulfate **18** was prepared.[16] Slow addition (0.1eq/min) of $SOCl_2$ to a cold (-10°C) dilute solution of **16** delivered the stable cyclic sulfite **17**. After its chromatographic purification, the RuO_4 oxidation to the capricious sulfate **18** performed excellent (98%, 2 steps). Ring opening with LiN_3 in HMPT succeeded at RT, and the resulting azido alcohol **19** was mesylated, followed by reduction of the azide to the amine. The *in-situ* cyclisation took place despite of sterical hindrance, and protected terpyrrolidine **20** could be isolated in a gratifying 68% yield. The NMR spectra of **20**·H^+ showed a half-set of well resolved signals reflecting its C_2-symmetry, while the resonances of the parent amine **20** were found broadened and the spectra complicated by conformational equilibra.[8]

In summary, we have disclosed the first synthesis of an enantiomerically pure terpyrrolidine. Readily cleaved O-TBDPS and N-BOC groups offer synthetical bandwidth towards various modifications. Studies are currently underway incorporating this novel chiral unit into elaborate receptors as well as investigating its complexing ability towards anions itself.

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6. $NaBH_4$ reduction of lactam **6** delivered the *cis*-lactamol only, while N-O-acetal **7** was found to be a 7:3 *trans/cis*-mixture.
7. *cis*-Nitrile **9** was recycled via epimerisation (20% $KO^tBu/^tBuOH$ in toluene, 0°C, 1.5h, 97%, **8**:**9**=56:44).
8. All new compounds gave analytical data in accordance with their proposed structures. Aldehyde **3** had: Mp 70.1°C (PE); $[\alpha]_D^{25}$ -60.1° (c=1.14, $CHCl_3$); ν_{max} (KBr) 2808, 2720, 1738, 1697; ^1H NMR δ (300 MHz, $CDCl_3$) 9.53/9.60 (55:45, d each, *J* = 2.6 Hz, 1H), 7.61-7.66 (m, 4H), 7.36-7.46 (m, 6H), 4.18/4.30 (45:55, d each, *J* = 9.0 Hz, 1H), 4.04/4.15 (45:55, m each, 1H), 3.87 (dd, *J* = 16.0, 4.5 Hz, 0.55H), 3.66 (m, 0.9H), 3.59 (dd, *J* = 16.8, 6.4 Hz, 0.55H), 2.20-2.40 (m, 1H), 1.88-2.18 (m, 3H), 1.34/1.43 (s each, 45:55, 9H), 1.06 (s, 9H); ^{13}C NMR δ (75 MHz, $CDCl_3$) 200.6, 154.3/153.4, 135.5, 133.5, 129.8, 129.7, 127.7, 80.9/80.8, 66.0/65.7, 64.3/63.9, 59.4/59.2, 28.3, 27.1, 26.9, 25.0, 19.2; Analysis $C_{27}H_{37}NO_4Si$ requires C 69.34, H 7.97, N 2.99, found C 69.09, H 7.78, N 3.09. Diol **16** had: $[\alpha]_D^{20}$ -40.2° (c=0.56, $CHCl_3$); ^1H NMR δ (600 MHz, $CDCl_3$) 7.60-7.66 (m, 8H), 7.32-7.44 (m, 12H), 4.41/4.62 (bs each, 2H), 3.90-4.05 (m, 4H), 3.82 (m, 2H), 3.68 (m, 2H), 3.53 (m, 2H), 1.87-2.20 (m, 6H), 1.70 (m, 2H), 1.51 (m, 2H), 1.46 (m, 2H), 1.28/1.45 (s each, 86:14, 18H), 1.04 (s, 18H); ^{13}C NMR δ (150 MHz, $CDCl_3$) 155.6/153.8, 135.5, 133.5, 129.7, 127.7, 80.2/80.0, 74.4/73.2, 64.1, 63.8/63.7, 60.2/59.5, 30.0, 28.6/28.3, 27.1, 25.9, 19.2; HRMS (FAB^+) $C_{56}H_{80}N_2O_8Si_2$ requires 965.5531 found 965.5537. Terpyrrolidine **20** had: $[\alpha]_D^{20}$ -32.0° (c=0.47, $CHCl_3$); ν_{max} (film) 3353, 1691; LRMS (EI) $[M+H^+]$, $C_{56}H_{80}N_3O_6Si_2$ requires 946.55 found 946.5-6. **20·TFA** had: ^1H NMR δ (600 MHz, CD_3OD) 7.69-7.73 (m, 8H), 7.50-7.53 (m, 4H), 7.47-7.50 (m, 8H), 4.17 (t, *J* = 9.0 Hz, 2H), 4.00 (m, 2H), 3.90 (dd, *J* = 9.0, 2.7 Hz, 2H), 3.77-3.87 (m, 4H), 2.37-2.45 (m, 2H), 2.31 (m, 2H), 2.15-2.28 (m, 4H), 1.88 (dd, *J* = 12.6, 6.6 Hz, 2H), 1.76-1.85 (m, 2H), 1.38 (s, 18H), 1.13 (s, 18H); ^{13}C NMR δ (150 MHz, CD_3OD) 157.5, 136.7, 134.5, 134.4, 131.1, 128.9, 83.7, 71.6, 67.1, 65.1, 61.2, 29.8, 28.7, 28.0, 27.7, 27.2, 20.0.
9. Crystal data for **3**: Monoclinic, $P2_1$, a=11.116(2)Å, b=8.1111(10)Å, c=15.558(2)Å, β=104.946(11)°, V=1355.3(3)Å^3, Z=2. 3763 independent reflections within 2.6°<2θ<22.97°, structural refinement by full-matrix least-squares on F^2 using the SHELXL 93 package to R=0.037, wR^2=0.095 and abs. struc. param. -0.07(14). The atomic coordinates are available on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.
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