Stereoselective Synthesis of (–)-Trachelanthamidine via Palladium-Catalysed Intramolecular Allylation

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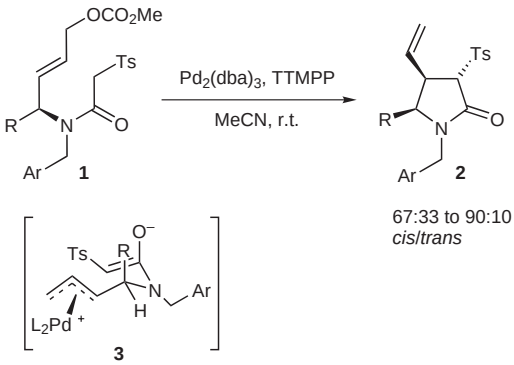
Abstract: A stereoselective synthesis of (–)-trachelanthamidine has been developed, employing a palladium-catalysed cyclisation as the key step.

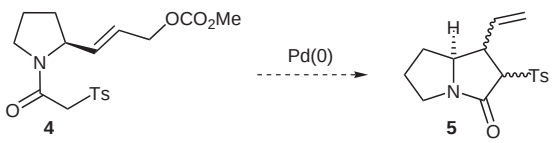
Key words: allyl complexes, cyclisations, lactams, palladium, stereoselective synthesis

We have previously shown that amino acid derived allylic carbonates **1** undergo facile palladium-catalysed cyclisation to yield 4,5-*cis*-disubstituted γ-lactams **2** in a diastereoselective manner (Scheme 1).[1]



Scheme 1

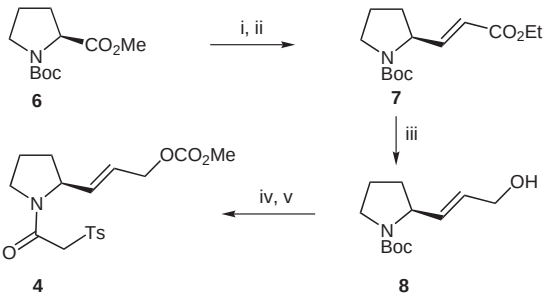
We were keen to extend this approach to include pyrrolizidines **5**. The pyrrolizidine moiety features in a large number of natural products and biologically significant compounds, and it was anticipated that this new approach would provide a useful addition to existing synthetic methods.[2] It appeared that these bicyclic products should be accessible from the allylic carbonate **4** (Scheme 2).



Scheme 2

The *S*-configuration of **4** indicated readily available L-proline as the source of chirality. In contrast with acyclic substrates **1**, covalent attachment of the R substituent to nitrogen as in **4** appeared to disfavour the Pd-allyl intermediate adopting a conformation equivalent to **3**, which had been proposed to explain the predominant *syn* relationship between the R and the vinyl groups in **2** (Scheme 1). Thus, the stereochemical outcome of the proposed **4** → **5** cyclisation reaction would provide further information concerning the validity of these simple reactive conformer models.

The assembly of the L-proline derived allylic carbonate **4** is depicted in Scheme 3. Reduction of Boc-protected L-proline methyl ester **6**[3] was carried out using DIBAL-H at low temperature. Wittig homologation of the resultant crude aldehyde provided the unsaturated ester **7**, which was reduced to the alcohol **8** with DIBAL-H in the presence of $BF_3{\cdot}OEt_2$.[4] N-Deprotection of **8** and coupling of the resulting crude amine with tosylacetic acid using PyBOP[5] gave a hydroxyamide, which was converted into carbonate **4** under standard conditions.



Scheme 3 *Reagents and conditions*: (i) DIBAL-H (1.2 equiv), PhMe, –78 °C, 3.5 h; (ii) Ph_3PCHCO_2Et (2 equiv), CH_2Cl_2, r.t., 12 h, 72% (2 steps); (iii) DIBAL-H (3 equiv), $BF_3{\cdot}OEt_2$ (1 equiv), CH_2Cl_2, –78 °C to 0 °C, 3 h, 72%; (iv) a. TFA (50 equiv), CH_2Cl_2, r.t., 30 min; b. $TsCH_2CO_2H$ (1 equiv), PyBOP (1 equiv), Hünigs base (5.5 equiv), CH_2Cl_2, r.t., 12 h; (v) methyl chloroformate (2 equiv), pyridine (2 equiv), DMAP (cat.), CH_2Cl_2, 12 h, 53% (3 steps).

Initial attempts to effect cyclisation of **4** were made using the method optimised previously ($Pd_2(dba)_3$ (5 mol%), TTMPP[6] (0.5 equiv, MeCN, r.t.).[1] Surprisingly, the cyclisation did not occur under these conditions; even after heating for 24 hours only traces of product were observed. In light of this result, it was considered that the extra strain inherent in the formation of a bicyclo[3.3.0] system indi-

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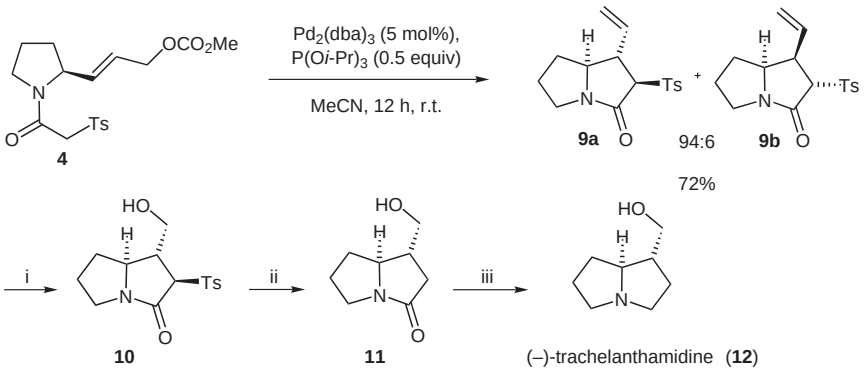
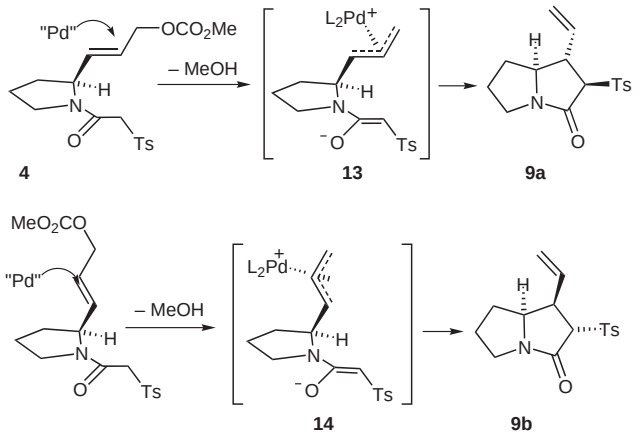


Scheme 4 *Reagents and conditions*: (i) a. O_3 (g), CH_2Cl_2, –78 °C, 1 h; b. DMS (4 equiv), r.t., 12 h; c. $NaBH_4$ (4 equiv), EtOH–H_2O, r.t., 1 h, 82%; (ii) 6% Na(Hg) (6 equiv), MeOH, –15 °C, 1 h, 75%; (iii) $LiAlH_4$ (2.1 equiv), THF, reflux, 12 h, 99%.

cated the need for a more reactive π-allyl complex, since TTMPP is a strong π-donor and as such reduces the reactivity of the π-allyl complex towards nucleophiles. In addition, TTMPP has a large cone angle (185°),[7] which may further attenuate the reactivity of complexes containing this ligand. Therefore, the cyclisation reaction was repeated employing triisopropyl phosphite; this ligand is very different from TTMPP in terms of both electronic factors and steric bulk (cone angle 130°).[8] With this modified ligand, the cyclisation proceeded at room temperature to give a 94:6 mixture of pyrrolizidines **9a** and **9b** (Scheme 4).

We attribute this striking reversal in selectivity compared with the acyclic systems **1** previously studied to the adoption by the allylic carbonate of conformation **13**, in which the allylic moiety is oriented in an 'outside' manner with respect to the pyrrolidine ring; this gives **9a** as the major product. This model is in keeping with the proposals of Houk (Scheme 5).[9] Conformation **14**, leading to **9b** is disfavoured, since it places the allylic moiety 'inside' with respect to the pyrrolidine ring, where it suffers steric buttressing against the ring atoms in the heterocycle. The acyclic nature of substrates **1** is such that the equivalent conformation **3** (Scheme 1) does not suffer from the equivalent steric interactions.[10]



Scheme 5

Encouraged by the excellent selectivity of the palladium-catalysed cyclisation of **4**, the conversion of the major pyrrolizidine product **9a** into the alkaloid (–)-trachelanthamidine **12** was undertaken (Scheme 4).[8] Ozonolysis of **4** with reductive work-up proceeded smoothly to give alcohol **10**. However, higher yields were obtained when the ozonolysis reaction was quenched with DMS and the isolated, crude aldehyde treated with $NaBH_4$ in a separate step. The relative and absolute stereochemistry of alcohol **10** was unambiguously assigned by X-ray crystallography (Figure 1).[11] It was decided to carry out desulfonylation prior to reduction of the lactam since it was anticipated that the presence of the electron-withdrawing amide group would facilitate reductive cleavage of the α-carbon–sulfur bond. In the event, detosylation with sodium amalgam[12] proceeded uneventfully to yield lactam **11**; reactions using sodium in liquid ammonia were also effective but slightly lower-yielding. Finally, reduction of the lactam with $LiAlH_4$ in THF under reflux proceeded quantitatively to give (–)-trachelanthamidine (**12**), which had spectroscopic and other physical data in agreement with those previously reported.[13]

In summary, the work described herein shows that an allylic carbonate derived from the cyclic aminoacid L-proline shows markedly different palladium-catalysed cyclisation behaviour from that of the acyclic congeners studied previously. These differences are explained in terms of a modification of steric effects, which stems from the cyclic nature of the substrate. Functional group

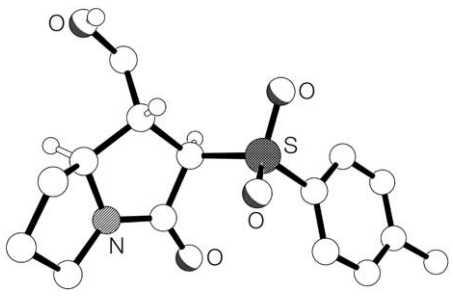


Figure 1 The molecular structure of **10**.

manipulations of the major cyclisation product have been used in a successful total synthesis of the pyrrolizidine natural product (–)-trachelanthamidine.[14,15]

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References and Notes

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(10) A referee has made the reasonable suggestion that in the cyclisations of **1**, the same conformation is adopted as for cyclisation of **4**, but that for **1** Pd approaches the π-bond from the opposite face due to the absence of the constraining ring and the consequent ability of the *N*-acyl moiety to rotate. This would necessitate a subsequent change in the conformation of the π-allyl complex to allow cyclisation to take place.
(11) We thank Dr. A. J. P. White (Imperial College) for the X-ray structure determination. Full details will be reported elsewhere.
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(14) Data for **4**: R_f = 0.51 (10% MeOH–CH_2Cl_2); $[\alpha]_D^{22}$ –104.6 (*c* 1.0, $CHCl_3$). IR (film): ν_{max} = 2956, 1747, 1649, 1439, 1269, 1269, 1153, 1086, 941, 793, 729 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.78–7.76 (2 H, m, *ortho* Ts), 7.38–7.28 (2 H, m, *meta* Ts), 5.83–5.61 (2 H, m, CH=CH), 4.78–4.62 (3 H, m, CHN and C*H*$_2$OCO$_2$Me), 4.28–3.47 (4 H, m, C*H*$_2$Ts and CH_2N), 3.81–3.80 (3 H, m, OMe), 2.45 (3 H, s, Me of Ts), 2.21–1.69 (4 H, m, C*H*$_2$C*H*$_2$CHN). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.4, 159.8, 155.6, 155.5, 145.3, 145.2, 136.2, 135.7, 134.3, 133.4, 129.8, 128.7, 125.3, 123.0, 67.7, 66.9, 61.7, 61.4, 59.1, 58.0, 55.0, 54.8, 48.1, 46.8, 32.6, 30.4, 23.7, 21.8. MS (CI): *m/z* = 382 $[M + H]^+$, 306, 228, 152. HRMS: *m/z* calcd for $C_{18}H_{23}NO_6S$ $[M + H]^+$: 382.1324; found $[M + H]^+$: 382.1328. Anal. Calcd for $C_{18}H_{23}NO_6S$ (%): C, 56.68; H, 6.08; N, 3.67. Found: C, 56.53; H, 6.08; N, 3.53.
(15) **Preparation of 9a,b.** To a solution of allylic carbonate **4** (59.0 mg, 0.156 mmol, 1.0 equiv) in MeCN (2 mL) was added $Pd_2(dba)_3$ (7.30 mg, 0.008 mmol, 0.05 equiv) and triisopropyl phosphite (20.0 μL, 0.078 mmol, 0.5 equiv) at r.t. After 12 h the reaction was concentrated under reduced pressure and the residue purified by chromatography (Et_2O) to yield an inseparable 94:6 mixture of the pyrrolizidinones **9a** and **9b** (34 mg, 72%) as a colourless oil; R_f = 0.2 (Et_2O). IR (film): ν_{max} = 2972, 1703, 1421, 1317, 1177, 1086, 910, 814, cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (major isomer) = 7.83 (2 H, d, *J* = 8.0 Hz), 7.34 (2 H, d, *J* = 8.0 Hz), 5.96 (1 H, ddd, *J* = 16.0, 10.0, 7.0 Hz), 5.26 (1 H, d, *J* = 17.0 Hz), 5.21 (1 H, d, *J* = 9.0 Hz), 4.16 (d, *J* = 9.0 Hz, 1 H), 3.64–3.55 (m, 2 H), 3.47 (q, *J* = 7.0 Hz, 1 H), 3.09–3.03 (m, 1 H), 2.44 (s, 3 H), 2.27–1.97 (m, 3 H), 1.56–1.46 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (major isomer) = 163.9, 145.1, 135.1, 136.0, 129.7, 129.4, 118.0, 73.5, 63.7, 45.5, 41.8, 30.6, 26.2, 21.7. MS (CI): *m/z* calcd for $C_{16}H_{19}NO_3S$ $[M + H]^+$: 306.1164; found $[M + H]^+$: 306.1174.