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A highly regioselective, protecting group controlled, synthesis of bicyclic compounds via Pd-catalysed intramolecular cyclisations

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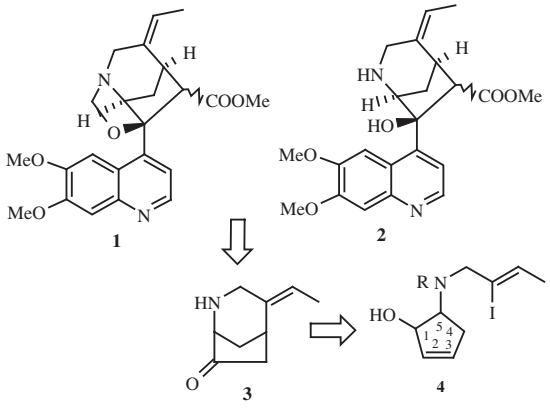
ABSTRACT

Intramolecular Pd-catalysed cyclisation reactions for the preparation of bicyclic compounds have been studied as a model system towards the synthesis of corialstonine and corialstonidine. Significant differences in reactivity have been observed for the cyclic allyl alcohols possessing O-protected and free OH functionalities. Cyclisation via the intramolecular Heck reaction, for both derivatives, proved to be highly regioselective and while the O-protected compound favoured the *exo* mode of cyclisation, the unprotected alcohol preferred the *endo* cyclisation pathway. Brief computational studies were carried out in order to obtain further insight into these processes.

Corialstonine (**1**) and corialstonidine (**2**) are quinine-like alkaloids isolated from *Alstonia coriacea*, and are shown to have moderate antimalarial activity against *Plasmodium falciparum*.[1] Although the stereochemistry of these natural products has not been fully established, their structural properties and biological profiles make them attractive synthetic targets. Our interest in developing a synthetic route for these alkaloids led us retrosynthetically to structure **3** which was expected to be accessible via intramolecular Heck reaction of the cyclopentene derived allyl alcohol **4**.

The success of this approach would rely on the potential to control the regioselectivity of the cyclisation step.[2] Only the C–C bond formation involving C(3) of cyclopentene derivative **4** (the *endo* mode of cyclisation related to the allyl alcohol functionality), upon β-elimination of palladium hydride and tautomerisation, would lead to the desired compound. An alternative pathway, via cyclisation onto C(2), would furnish an unwanted regioisomeric product (the *exo* mode of cyclisation related to the allyl alcohol functionality). The Heck reaction of allylic alcohols has been widely explored, but mainly as an intermolecular variant.[3] The reaction of these unsaturated alcohols usually affords products of C(3)-substitution.[3a] However, if the reaction conditions favour the ionic pathway, the regioselectivity may be reversed to yield the product of C(3)-substitution.[3b] Intramolecular processes leading to polycyclic



Scheme 1.

derivatives may afford products of both *exo* and *endo* cyclisations, which are often controlled by the ring size.[4] Some transformations employing cyclic allyl alcohols, for the synthesis of bicyclic compounds, yielded a mixture of products with the *exo* cyclisation pathway as the major one.[5] The variability of the results related to the regioselectivity issue, and lack of information associated with the synthesis of bicyclic compounds via the general approach outlined in Scheme 1 prompted the study presented herein.

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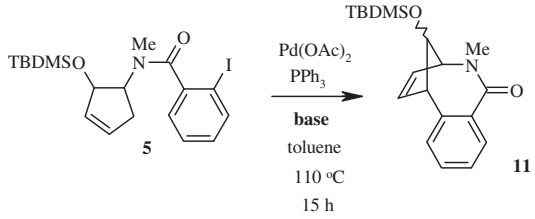
The readily accessible amide **5** was selected as a model compound to study the cyclisation leading to bicyclic compounds. Although the results employing **5** would not be directly transferable to the conversion **4**→**3** due to the formation of different rings (azabicyclo[4.2.1]nonane from **5** vs azabicyclo[3.2.1]octane from **4**), the study was however expected to provide insight into the elements controlling the regioselectivity. Compound **5** was prepared starting from crotonaldehyde using adapted literature procedures (Scheme 2).[6] The stereochemistry of the product was established following the preparation of compound **10**, and was elucidated by analysis of the H–H NOESY data which suggested that 10 was obtained as a 4.3:1 mixture of *cis* and *trans* isomers. Establishing the exact ratio of the diastereomers for compound **5** was problematic due to ^{1}H NMR complexity caused by restricted rotation around the amide bond, in addition to the existence of *cis*/*trans* isomers. Methylation of compound **10** to produce **5** was necessary since the attempts to cyclise **10** under various conditions used for Pd-catalysed processes failed.

The initial cyclisation experiment, carried out on O-protected derivative **5**, employed $Pd(OAc)_2/PPh_3$ as the catalytic system and Cs_2CO_3 as the base in refluxing toluene (Scheme 3; Table 1, entry a).[7]

Product **11** was isolated as a single regioisomer in 60% yield and was formed via the *exo* cyclisation mode, involving C(2). Inspection of the ^{1}H NMR spectrum of the crude reaction mixture did not show the presence of the regioisomeric product which would have arisen from the cyclisation reaction involving C(3). We briefly screened other bases and their effect on the yields (Table 1). In all cases, the only product isolated was the bicyclic compound **11**, while the use of Et_3N (Table 1, entry c) proved to be the most efficient furnishing the product in 73% yield. On the other hand, K_2CO_3 afforded a complex mixture which included only a small quantity of **11**, as judged by analysis of the ^{1}H NMR spectrum of the crude product.

Further studies of these processes were carried out on OH-derivative **12**, which was easily accessible via desilylation of **5** under standard conditions.[8] Similarly, as for compound **5**, unambiguous determination of the *cis*/*trans* ratio of **12** proved difficult due to the complexity of the ^{1}H NMR spectrum. The initial cyclisation reaction of compound **12** was carried out using similar conditions



Scheme 3.

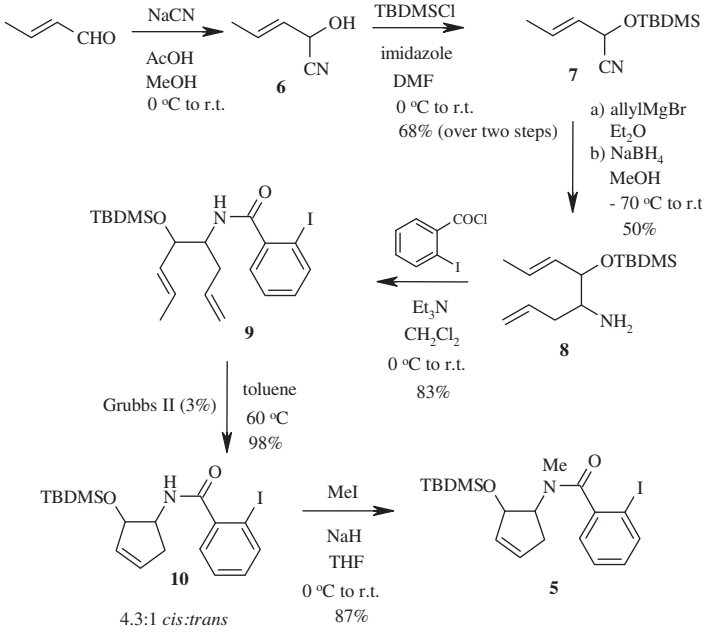
Table 1
Variation of the base in the cyclisation reaction of **5**[a]

Entry	Base	Product	Yield[b] (%)
a	Cs_2CO_3	**11**	60
b	Proton sponge[c]	**11**	51
c	Et_3N	**11**	73
d	K_2CO_3	—	—[d]

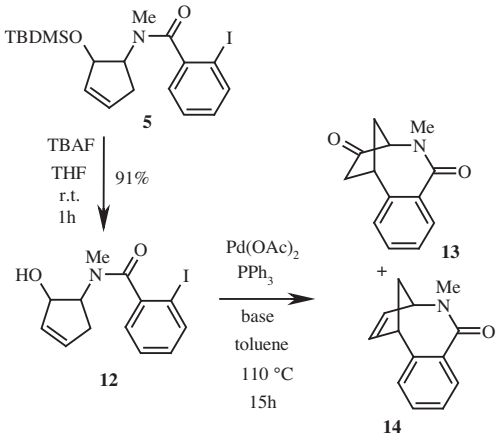
[a] Reaction conditions: **5** (0.066 mmol), $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %) base (0.132 mmol), toluene (6.5 mL), 110 °C, 15 h.
[b] Isolated yield.
[c] 1,8-Bis(dimethylamino)naphthalene.
[d] Complex mixture as suggested by analysis of the ^{1}H NMR spectrum.

with Et_3N as the base (Scheme 4; Table 2, entry a). The reaction was again highly regioselective furnishing two products via *endo* cyclisation, compounds **13** and **14**, in 75% yield and in the ratio 1.3:1.[9] Interestingly, the observed regioselectivity contrasted with that represented by the transformation **5**→**11**. Product **13** was formed via cyclisation at C(3) followed by palladium hydride elimination to generate the enol and then the final product via tautomerisation.

Analysis of mass spectral data for the by-product **14** suggested loss of oxygen (*m*/*z*: observed M^+ 199). Further examination, specifically of the H–H COSY and H–H NOESY spectra, supported the proposed structure. Particularly notable was the absence of any correlation between NC*H* and ArC*H* and correlation of both of these with the CH_2 and different olefinic protons. This product was likely formed via initial addition of ArPdI onto the double bond followed by β-elimination of the [Pd]OH species to afford **14**.[4d,10] Since com-



Scheme 2.



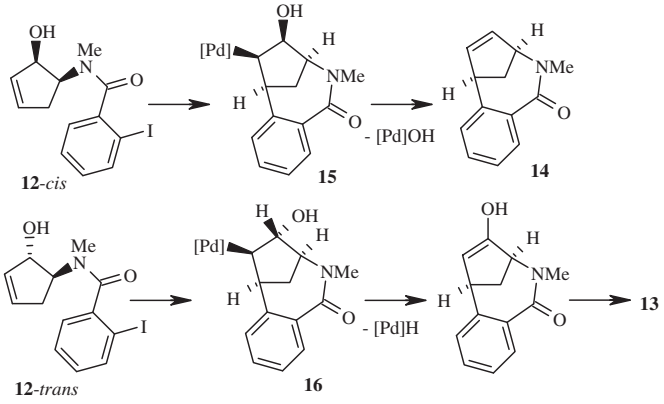
Scheme 4.

Table 2
Variation of the base in the cyclisation reaction of **12**[a]

Entry	Base	Product	Yield[b] (%)
a	Et_3N	**13/14**	75 (1.3:1)
b	Cs_2CO_3	**13**	38
c	Proton sponge[c]	—	—[d]

[a] Reaction conditions: **12** (0.303 mmol), $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), base (0.606 mmol), toluene (30 mL), 110 °C, 15 h.
[b] Isolated yield.
[c] 1,8-Bis(dimethylamino)naphthalene.
[d] Complex mixture as suggested by analysis of the ^1H NMR spectrum.

pound **12** was used as a mixture of *cis* and *trans* isomers it is likely that the by-product **14** was produced via the reaction involving *cis*-**12** (Scheme 5). Upon the *syn* addition of Ar[Pd]I to form the C(3)-Ar bond, intermediate **15** was generated which then furnished **14** via elimination of the *syn* positioned [Pd] and OH groups.[4d,10] The same transformation for *trans*-**12** produced the target compound **13** via intermediate **16**, in which [Pd] and H were *syn* positioned (Scheme 5). Although the mechanistic explanation seems reasonable, the ratio of **13**/**14** does not reflect the *cis*/*trans* ratio of **10**. This may suggest that the reaction conditions used for the sequence **10**→**5**→**12** altered the *cis*/*trans* ratio or that other processes interfere with the expected *syn* [Pd]X (X = OH or H) elimination, and this remains to be investigated further.[11] The cyclisation reaction was also carried out with two other bases (Table 2, entries b and c). When Cs_2CO_3 was used under the described conditions the expected product **13** was obtained in 38% yield, while only traces of



Scheme 5.

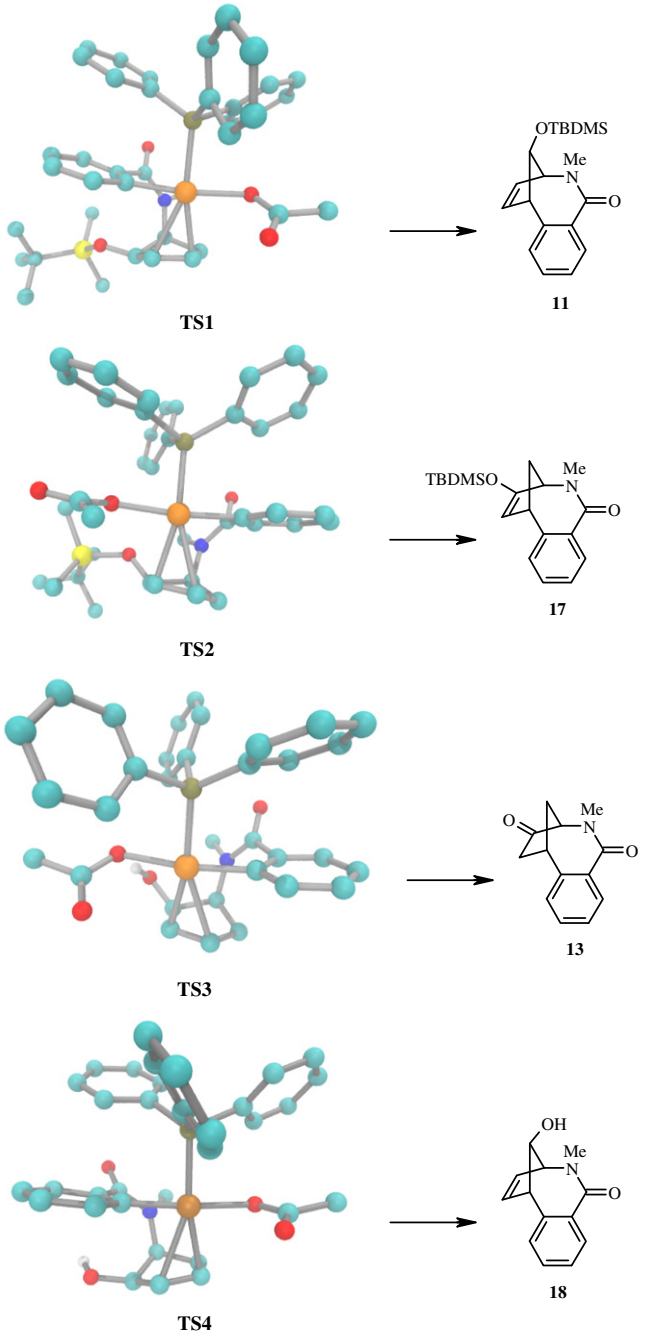


Figure 1. Transition states of the cyclisation reactions of **5** and **12**.

14 were observed. The use of proton sponge afforded a mixture of products in very low yields and with only partial conversion.

To gain a better insight into the origin of the highly regioselective cyclisation with O-protected **5** and the free alcohol **12**, we studied transition states leading to products **11** and **13** and their regioisomeric equivalents **17** and **18** by computational methods. All initial calculations were performed on derivatives *cis*-**5** and *cis*-**12**. The transition state searches were carried out using DFT with the B3LYP hybrid functional and def2-SVP basis set for all atoms, in vacuum, and the single point energies at the located transition states were recalculated using the same functional and def2-TZVP basis set for all atoms in vacuum.[12] The transition states were characterised by frequency analysis.[13] Although the aryl iodide initiated the oxidative addition in the studied reactions, the

calculations were performed on transition states having acetate as the Pd-ligand rather than iodide, since $Pd(OAc)_2$ was used as a source of Pd(0).[14] Compound *cis*-**5** afforded product **11** via transition state TS1 (Fig. 1) positioning the phenyl substituent *syn* to the OTBDMS moiety and leading to the *exo* cyclisation mode. Alternatively, the *endo* cyclisation is favoured by TS2 leading to the unobserved compound **17**. The calculated energy difference between TS1 and TS2 is 3.4 kcal/mol in favour of TS1, corroborating the observed results. Inspection of the molecular models did not reveal any obvious steric effects accountable for the high level of the experimentally observed regioselectivity. It is possible that the phenyl moiety, due to its planarity, is less involved in steric interactions with the large TBDMS group (TS1) than the acetate (TS2) possessing an sp^3 carbon. Additionally, the π–π interactions of the phenyls from the phosphine ligand and the aryl group involved in C–C bond formation may provide support in directing the reacting phenyl to minimise steric clashes in TS1. Compound *cis*-**12** showed completely opposite results. It favoured the *endo* mode of cyclisation furnishing exclusively product **13** via transition state TS3, while the regioisomeric product **18**, obtained via TS4, was not detected. The energy difference between TS3 leading to **13** and TS4 furnishing **18**, 13.6 kcal/mol, was higher than that calculated for TS1/TS2. This was somewhat surprising since the removal of TBDMS was expected to reduce steric interactions. The observed results were attributed to the additional stabilisation of TS3 due to potential H-bonding interactions between the *syn* positioned acetate and OH functionalities.

Computational studies were also carried out on *trans*-**5** and *trans*-**12** as well, and the results showed the same trend as described for related *cis*-**5** and *cis*-**12** (these results will be discussed in a full account of this work).

In conclusion, our brief study of the intramolecular Heck reaction on cyclic allyl alcohols has revealed the ability of the proximal OH-group to influence the regioselectivity of the cyclisation. Further study of these processes and their application in the synthesis of corialstonine and corialstonidine is currently underway.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.02.068.

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7. *General procedure for the preparation of compound **11***:
A mixture of compound **5** (30 mg, 0.066 mmol), $Pd(OAc)_2$ (1.5 mg, 0.0066 mmol), PPh_3 (3.5 mg, 0.0131 mmol), base (2 equiv, see Table 1) in toluene (6.5 mL) was refluxed under a nitrogen atmosphere for 15 h. The solvent was evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2 (20 mL), washed with H_2O (2 × 5 mL), dried (Na_2SO_4) and filtered. The solvent was then evaporated under reduced pressure and the residue purified by flash chromatography (SiO_2, 8:2 v/v petroleum ether/Et_2O) to afford the product **11** as a light yellow oil (see Table 1 for yields).
IR ν_{max} 2927, 2856, 1615, 1390, 776, 740. ^{1}H NMR (500 MHz, $CDCl_3$): δ −0.12, 0.03 (2s, 6H, Si*t*Bu*Me*$_2$), 0.63 (s, 9H, Si*t**Bu*Me$_2$), 3.25 (s, 3H, N-CH_3), 3.61 (dd, 1H, *J* = 6.5 Hz, *J* = 3.5 Hz, C*H*-C_6H_4), 3.97 (dd, 1H, *J* = 6.5 Hz, *J* = 3 Hz, NC*H*-CHOTBDMS), 4.55 (t, 1H, *J* = 6.5 Hz, C*H*OTBDMS), 5.83 (dd, 1H, *J* = 6 Hz, *J* = 3 Hz, CH(C_6H_4)CH=C*H*), 6.06 (dd, 1H, *J* = 6 Hz, *J* = 3.5 Hz, CH(C_6H_4)C*H*=CH), 7.10 (dd, 1H, *J* = 7.0 Hz, *J* = 1.5 Hz, ArH), 7.26–7.34 (m, 2H, ArH), 8.57 (dd, 1H, *J* = 8.0 Hz, *J* = 1.5 Hz, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ −5.0, −4.96, 17.6, 25.3, 40.0, 56.0, 66.5, 69.6, 126.5, 127.4, 129.21, 130.8, 133.9, 134.7,138.3, 139.5, 167.8. *m*/*z* (EI): 329.1 (M^+), 314.1, 272.1, 215.0, 198.1, 156. HRMS (ESI): calcd for $C_{19}H_{28}NO_2Si$ $(M+H)^+$ 330.18838, found 330.18711
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9. *General procedure for the preparation of compounds **13**/**14***: Cyclisation **12**→**13**/**14** was carried out according to the general procedure described for compound **11** (see Table 2 for yields).[7]
*Compound **13***
IR ν_{max} 1745, 1615, 1387, 1264, 1241, 703. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.34 (dd, 1H, *J* = 14.5 Hz, *J* = 3 Hz, C*H*$_2$CH-N), 2.52 (dd, 1H, *J* = 19 Hz, *J* = 3 Hz, CH_2C=O), 2.58–2.64 (m, 1H, C*H*$_2$CH-N), 2.78 (dd, 1H, *J* = 19 Hz, *J* = 8.5 Hz, CH_2C=O), 3.36 (s, 3H, N-CH_3), 3.76 (t, 1H, *J* = 7.5 Hz, C*H*-C_6H_4), 3.81 (d, 1H, *J* = 8 Hz, CH-N), 7.22 (dd, 1H, *J* = 7.5 Hz, *J* = 1.5 Hz, ArH), 7.24–7.42 (m, 2H, ArH), 8.57 (dd, 1H, *J* = 8.0 Hz, *J* = 1.5 Hz, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 33.8, 40.2, 42.4, 48.2, 63.3, 127.1, 129.0, 130.5, 131.7, 135.0, 143.9, 165.8, 212.0. *m*/*z* (EI): 215.1 (M^+), 197.1, 172.1, 158.1, 144.1, 131.1. HRMS (ESI): calcd for $C_{13}H_{14}NO_2$ $(M+H)^+$ 216.10191, found 216.10168.
*Compound **14***
IR ν_{max} 1610, 1593,1389, 1251, 761, 739. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.1 (d, 1H, *J* = 12.5 Hz, CH_2), 2.46 (dt, 1H, *J* = 12.5 Hz, CH_2), 3.27 (s, 3H, N-CH_3), 3.75 (dd, 1H, *J* = 6.5 Hz, *J* = 3 Hz, C*H*-C_6H_4), 4.31 (dd, 1H, *J* = 7.5 Hz, *J* = 2.5 Hz, CH-N), 5.88 (dd, 1H, *J* = 5.5 Hz, *J* = 2.5 Hz, =C*H*–CH–N), 6.05 (dd, 1H, *J* = 5.5 Hz, *J* = 3 Hz, C*H*=CH–CH–N), 7.22 (dd, 1H, *J* = 7.5 Hz, *J* = 1.5 Hz, ArH), 7.26–7.30 (m,1H, ArH), 7.32–7.35 (m, 1H, ArH), 8.6 (dd, 1H, *J* = 8.0 Hz, *J* = 1.5 Hz, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 37.1, 39.0, 51.4, 65.3, 126.5, 127.9, 128.11, 131.02, 132.0, 135.6, 138.13, 144.44, 166.4. *m*/*z* (EI): 199.1 (M^+), 184.0, 170.0, 141.0, 128.1, 115.0. HRMS (ESI): calcd for $C_{13}H_{14}NO$ $(M+H)^+$ 200.10699, found 200.10611.
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