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Syntheses of dipeptides containing (1*R*,5*S*)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxylic acid (4), (1*R*,5*S*)-spiro[3-azabicyclo[3.1.0]hexane-6,1′-cyclopropane]-2(*S*)-carboxylic acid (5) and (1*S*,5*R*)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2(*S*)-carboxylic acid (6)

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Abstract—Versatile syntheses of dipeptides that incorporate the 3-azabicyclo[3.1.0]hexane system are described.

Proline and its natural and unnatural synthetic substituted derivatives have played critical integral roles in the initiation, optimisation and ultimately therapeutic commercialisation of peptidomimetic substrates of enzymes. Most notably in the antiviral area, proline occupies the P1′ position of three of the identified cleavage sites of the HIV gene product presented to the viral aspartic protease, a process essential for particle maturation.[1] Further encouraged by the observation that mammalian endopeptidases do not readily cleave such proline containing peptide bonds and the prospect of reduced toxicity and improved bioavailability, chemists in academia and pharmaceutical companies have designed and constructed transition-state like dipeptide isostere mimics that were subsequently incorporated into efficacious therapeutic agents such as Saquinavir **1** (Fig. 1),[2] Indinavir[3] and Nelfinavir.[4]

More recently, using the 4B/5A cleavage site of the HCV gene product as a template,[5] workers at Boehringer-Ingelheim,[6] Schering-Plough,[7] Eli Lilly[8] and Vertex[9] have used the structural P2 proline ligand as a basis to impart desired conformations and optimise interactions between inhibitor and the virally encoded serine protease leading to recent clinical candidates such as BILN2061 **2** (Fig. 2).

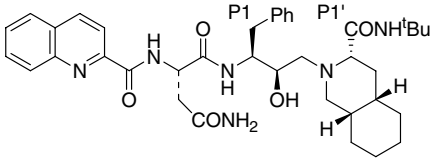

Figure 1. Saquinavir (**1**).

Towards a similar goal we wished to incorporate (1*R*,5*S*)-spiro[3-azabicyclo[3.1.0]hexane-6,1′-cyclopropane]-2(*S*)-carboxylic acid **4**[10] and the previously unknown spirocyclopropyl analogue **5** and the cis-isomer **6** into a series of potential enzyme inhibitors (Fig. 3).

Beginning with Garner aldehyde **7**,[11] our general approach to the pyrrolidines (**4**–**6**) is shown in Scheme 1.

When exposed to cyclopropyltriphenylphosphorane generated under salt free conditions, to prevent racemisation, aldehyde **7** provided alkene **8** in 79% yield.[11] The

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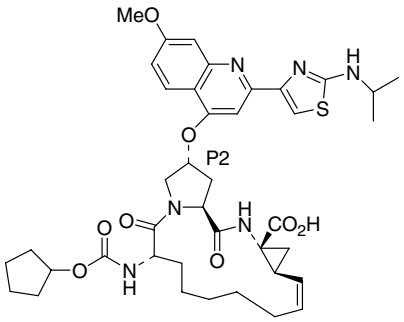


Figure 2. BILN2061 (**2**).

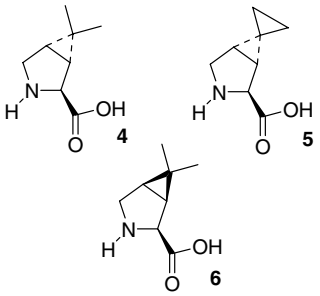
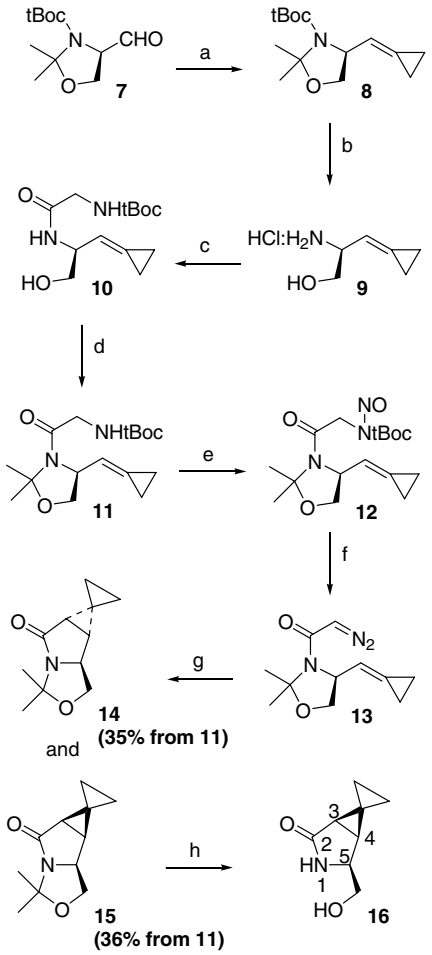


Figure 3. (1*R*,5*S*)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-(2*S*)-carboxylic acid (**4**), spirocyclopropyl analogue (**5**), and the cis-isomer (**6**).

N,*O*-dimethyl ketal and carbamate protecting groups were removed under aqueous acidic conditions and the resulting hydrochloride salt **9** was treated with an active ester of *t*-Boc-glycine in the presence of triethylamine to provide amide **10**. The ketal functionality was reintroduced using 2,2-dimethoxypropane under Lewis acid catalysis. The carbamate **11** was N-nitrosylated and rearranged in crude form in the presence of pyrrolidine to the α-diazoketone **13**.[12] Palladium acetate induced carbene formation generated, in equal proportions, two pyrrolidones **14** and **15** which were readily separated by silica gel column chromatography and identified by NMR spectroscopy (**14**; $J_{4,5} = 0$ Hz vs **15**; $J_{4,5} = 5.7$ Hz). The structure of the 'cis'-isomer **15** was later confirmed by single crystal X-ray analysis[13] of lactam **16** after removal of the *N*,*O*-dimethyl acetal (Fig. 4).

In contrast, carbamates **17a,b**, prepared according to Scheme 1, utilising the appropriate yield, generated the '*trans*'-cyclopropanes **18a,b**, respectively, as the only isolated products (Scheme 2), when subjected to the same reaction sequence.

The dramatic differences in the stereochemical outcomes of the aforementioned carbene insertion processes can be tentatively envisioned using the transition state conformations **19** and **20** (Fig. 5). It is reasonable to assume that the carbenes generated from **17a** and **b** exist in the *exo*-form **19** avoiding potential steric and electronic interactions that can be viewed from the *endo* conformation **20**, hence leading to the trans-cycloaddition products**18a** and **b**. Such repulsions are possibly avoided when utilising the cyclopropyl group, effectively reducing the size of the alkyl group and allowing free interconversion between *exo*-**19** and *endo*-**20** conformations



Scheme 1. Reagents and conditions: (a) Cyclopropyltriphenylphosphonium bromide, KHMDS, THF, reflux; (b) HCl, MeOH; (c) *t*-Boc-Gly-OSu, Et_3N, MeOH-THF; (d) 2,2-dimethoxypropane, BF_3/Et_2O, acetone; (e) $NOBF_4$, pyridine, CH_3CN; (f) pyrrolidine; (g) $Pd(OAc)_2$, benzene, reflux; (h) HCl, MeOH.

and hence the production of both *trans*-**14** and *cis*-**15** adducts.

Following reduction of lactam **16**, pyrrolidine **21** was condensed with commercially available *t*-Boc-L-*tert*-Leu-OH, providing amide **22** (Scheme 3). Catalytic

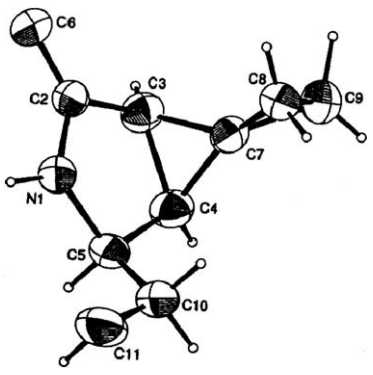
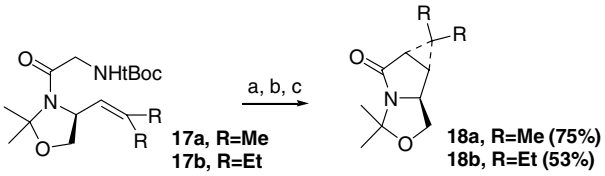


Figure 4. ORTEP diagram (40% probability ellipsoids) showing the crystallographic atom numbering scheme and solid-state conformation of lactam (**16**).



Scheme 2. Reagents and conditions: (a) $NOBF_4$, pyridine, CH_3CN; (b) pyrollidine; (c) $Pd(OAc)_2$, benzene, reflux.

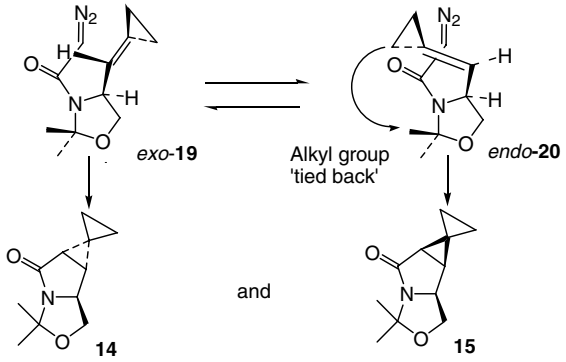
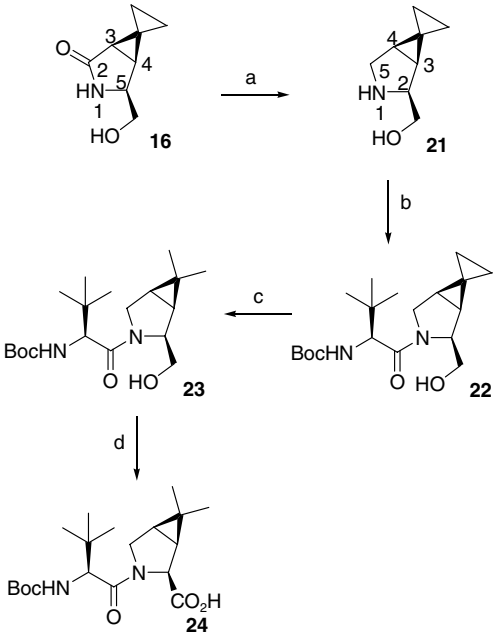


Figure 5. Putative transition state conformations **19** and **20** depicting the formation of both *trans*-**14** and *cis*-**15** cycloaddition adducts.

hydrogenolysis of the exposed cyclopropyl group provides the bicycle **23**. Finally, oxidation of the primary alcohol provided dipeptide **24** that incorporates the *cis*-3-azabicyclo[3.1.0] hexane system.[14]

In turn, the *N*,*O*-dimethyl ketals **14**, **18a** and **b** were smoothly transformed into dipeptides **25**[15] and **26a**,[16]**b** (Fig. 6).



Scheme 3. Reagents and conditions: (a) LAH, THF, reflux; (b) *t*-Boc-L-*tert*-Leu-OH, BOP reagent Et_3N, CH_2Cl_2; (c) PtO_2, AcOH/EtOAc, H_2; (d) Jones reagent.

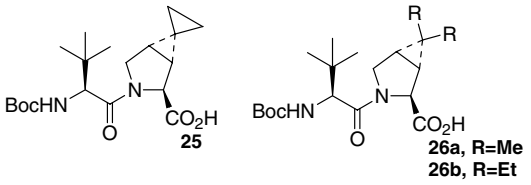


Figure 6. Dipeptides **25**, **26a** and **b** produced from intermediates **14**, **18a** and **b**, respectively.

In summary, we have described the syntheses of dipeptides that incorporate the *cis*- and *trans*-3-azabicyclo-[3.1.0] systems utilising a carbene insertion reaction as the key step. It is hoped that this work will expand the arsenal of proline analogues available to chemists, particularly those involved in the design of enzyme inhibitors.

Acknowledgements

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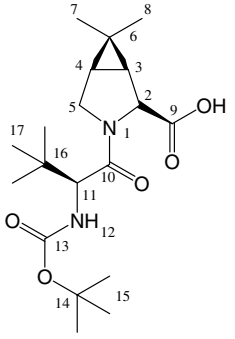
12. *Typical cycloaddition procedure*. Nitrosium tetrafluoroborate (6.63 g; 56.8 mmol) was added, in one portion, to a solution of carbamate **11** (8.81 g; 28.4 mmol) in anhydrous acetonitrile (45 ml) and pyridine (6.9 ml) at −40 °C, under an atmosphere of nitrogen. After 2 h, TLC indicated that no starting material was present and pyrrolidine (20 ml; 0.24 mol) was added. The reaction mixture was immediately removed from the cooling bath and stirred at room temperature for 1 h. The volatiles were removed under reduced pressure and the residue was subjected to silica gel column chromatography using EtOAc/hexanes (1:4) to provide the crude diazoacetamide **13**, a yellow oil, which was used immediately in the next step. To a solution of diazoacetamide **13** in anhydrous benzene (220 ml), $Pd(OAc)_2$ (0.317 g; 1.4 mmol) was added and the resulting orange solution was heated to 70 °C, under an atmosphere of nitrogen, for 1.5 h. After cooling, the benzene was removed under reduced pressure and the crude brown reaction product was purified by silica gel column chromatography using EtOAc/hexanes (1:5) as eluent providing the *exo*-type cycloadduct **14** (1.94 g; 35%), as a light-yellow solid followed by the *endo*-isomer **15** (1.97 g; 36%).
13. Crystallographic data for lactam 16 have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 607122. Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
14. NMR experiments were carried out on Varian Inova 500 MHz and 600 MHz spectrometers. Proton and carbon resonance assignments were accomplished based on the analysis of the 2D COSY, HSQC and HMBC experiments. Stereochemistry was defined based on the 2D NOESY experiments. Selected NMR data of compound **24**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.25 (1H, d, $J = 9.8$ Hz, H-12), 4.79 (1H, d, $J = 6.5$ Hz, H-2), 4.28 (1H, d, $J = 9.8$ Hz, H-11), 4.13 (1H, dd, $J = 6.3$, 10.3 Hz, H-5), 3.65 (1H, dd, $J = 1.2$, 10.3 Hz, H-5′), 1.81 (1H, dd, $J = 6.5$, 8.0 Hz, H-3), 1.55 (1H, m, $J = 1.2$, 6.3, 8.0 Hz, H-4), 1.44 (9H, s, H-15), 1.08 (3H, s, H-7), 1.06 (3H, s, H-8), 1.02 (9H, s, H-17); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.9 (C-10), 172.0 (C-9), 155.8 (C-13), 79.9 (C-14), 61.3 (C-2), 58.4 (C-11), 49.7 (C-5), 35.5 (C-16), 30.3 (C-3), 28.3 (C-15), 26.8 (C-4), 26.5 (C-7), 26.2 (C-17), 20.7 (C-6), 14.5 (C-8).



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15. Selected NMR data of compound **25**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.24 (1H, d, $J = 10.0$ Hz, H-12), 4.63 (1H, s, H-2), 4.27 (1H, d, $J = 10.0$ Hz, H-11), 4.04 (1H, d, $J = 9.8$ Hz, H-5), 3.76 (1H, dd, $J = 4.2$, 9.8 Hz, H-5′), 2.18 (1H, d, $J = 6.6$ Hz, H-3), 1.97 (1H, dd, $J = 4.2$, 6.6 Hz, H-4), 1.42 (9H, s, H-15), 1.01 (9H, s, H-17), 0.91 (2H, m, H-7, H-7′), 0.66 (1H, m, H-8), 0.50 (1H, m, H-8′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2 (C-10), 174.0 (C-9), 155.9 (C-13), 79.8 (C-14), 60.0 (C-2), 58.7 (C-11), 49.0 (C-5), 35.1 (C-16), 28.3 (C-15), 26.3 (C-17), 23.2 (C-3), 21.0 (C-4), 16.3 (C-6), 6.6 (C-7), 0.7 (C-8).
16. Selected NMR data of compound **26a**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.22 (1H, d, $J = 10.2$ Hz, H-12), 4.47 (1H, s, H-2), 4.24 (1H, d, $J = 10.3$ Hz, H-11), 4.04 (1H, d, $J = 10.5$ Hz, H-5), 3.85 (1H, dd, $J = 5.5$, 10.5 Hz, H-5′), 1.65 (1H, d, $J = 7.7$ Hz, H-3), 1.48 (1H, dd, $J = 5.5$, 7.7 Hz, H-4), 1.40 (9H, s, H-15), 1.05 (3H, s, H-7), 1.01 (9H, s, H-17), 0.90 (3H, s, H-8); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.1 (C-10), 172.3 (C-9), 156.0 (C-13), 79.8 (C-14), 59.5 (C-2), 58.7 (C-11), 48.1 (C-5), 35.0 (C-16), 29.7 (C-3), 28.2 (C-15), 27.3 (C-4), 26.22 (C-17), 26.19 (C-7), 19.3 (C-6), 12.4 (C-8).