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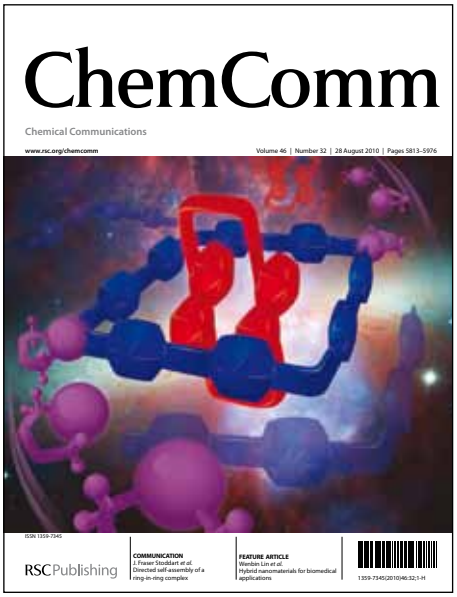

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ARTICLE TYPE

Discovery of a multi-bond forming, four-step tandem process: construction of drug-like polycyclic scaffolds†

Mark W. Grafton, Louis J. Farrugia, Hans Martin Senn and Andrew Sutherland*

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A one-pot tandem process involving an Overman rearrangement, ring closing enyne metathesis and a hydrogen bonding directed Diels-Alder reaction has been developed for the efficient diastereoselective synthesis of functionalised amino substituted tetralin and indene ring systems.

A significant challenge facing medicinal chemistry and chemical biology is the elucidation and development of lead-hit compounds and small-molecule probes that allow insight into fundamental and disease-associated biological phenomena. To meet this challenge, a recent trend has been to move away from more traditional sp^2-rich aromatic and heteroaromatic compounds and instead to focus on sp^3-rich compounds for screening.[1] Compounds with a higher level of saturation have improved solubility,[1b] while the three-dimensional nature and higher complexity of such fragments allows better exploration of chemical space.[1c,2] Within this context, saturated and partially saturated forms of amino substituted indene and tetralin scaffolds have found widespread application (Fig. 1). These ring systems are components of natural products such as the antitumour antibiotic (–)-ptilocaulin **1**,[3] as well as the antibacterial family of hapalindoles (e.g. hapalindole A **2**).[4] New derivatives of nitrogen substituted tetralin ring systems have also found use in medicinal chemistry.[5,6] For example, steroidal analogues such as **3** and **4** are potent antiproliferative agents.[6b]

While interesting and novel strategies have been developed for the synthesis of amino substituted indene and tetralin ring systems,[3-7] these approaches tend to rely on traditional single-step transformations. Single-step reactions require their own set of reagents, catalysts, solvents and conditions. At the end of the reaction, time-intensive and yield reducing isolation and purification of each intermediate is necessary, resulting in significant waste. In recent years, the limitations of one-step transformations for the preparation of polycyclic ring systems have been overcome using tandem or cascade processes that permit several chemical reactions and the creation of multiple bonds in a single-pot operation.[8,9] Utilising such processes negates the need of handling and isolating intermediates and results in a substantial reduction in waste generation.

We now report the discovery and development of a novel, four-step, multi-bond forming tandem process that allows the diastereoselective synthesis of amino substituted, partially saturated, indene and tetralin ring systems from readily available alkyne derived allylic alcohols.

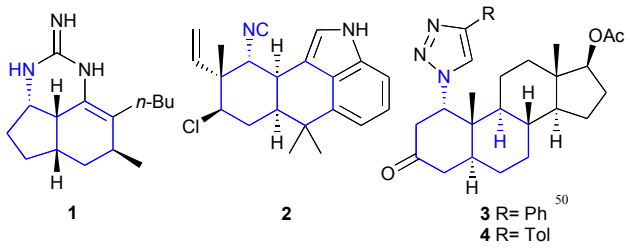
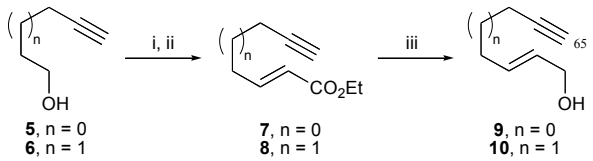


Fig. 1 Biologically active, nitrogen-substituted indene **1** and tetralin **2**-**4** containing compounds.

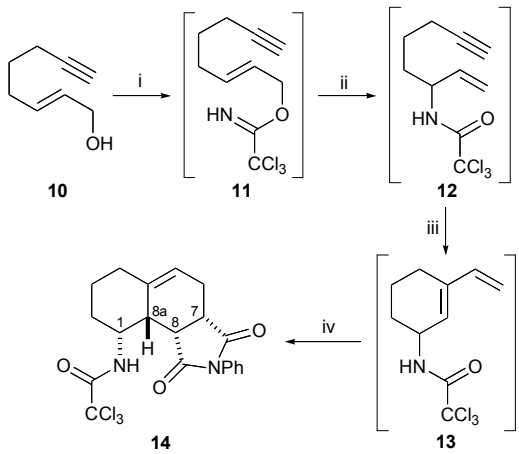
The alkyne derived allylic alcohol substrates required for the tandem process were easily prepared in three steps from commercially available 4-pentyn-1-ol (**5**) and 5-hexyn-1-ol (**6**) (Scheme 1). Use of a one-pot Swern oxidation and Horner-Wadsworth-Emmons reaction under Masamune-Roush conditions gave the corresponding (*E*)-α,β-unsaturated esters **7** and **8** in 95% and 99% yield, respectively.[10,11] Reduction of **7** and **8** with DIBAL-H then gave the desired allylic alcohol substrates **9** and **10** in excellent overall yield.



Scheme 1 *Reagents and conditions*: (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C; (ii) $(EtO)_2P(O)CH_2CO_2Et$, DBU, LiCl, MeCN, rt, **7** (95%), **8** (99%); (iii) DIBAL-H, Et_2O, –78 °C, **9** (93%), **10** (97%).

(2*E*)-Octa-2-en-7-yn-1-ol (**10**) was initially subjected to the four-step tandem process shown in Scheme 2. Conversion to allylic trichloroacetimidate **11** was followed by an Overman rearrangement[12] under thermal conditions (140 ºC) which gave allylic trichloroacetamide **12**. At this stage, Grubbs first generation catalyst[13] was added which effected the ring closing enyne metathesis reaction,[14] and this was followed by a Diels-Alder reaction with *N*-phenyl maleimide. After optimisation of each stage (variation of temperature and reaction time),[15] amido substituted tetralin derivative **14** was isolated as a single diastereomer in 72% yield over the four steps. The relative stereochemistry of **14** was confirmed by difference NOE

experiments which showed the *syn*-relationship of the hydrogen atoms at C-1, C-7, C-8 and C-8a.[16]



Scheme 2 *Reagents and conditions*: (i) Cl_3CCN, DBU, CH_2Cl_2, rt, 3 h; (ii) K_2CO_3, 140 ºC, toluene, 24 h; (iii) Grubbs I (10 mol%), 75 ºC, 48 h; (iv) *N*-phenyl maleimide, 111 ºC, 48 h, 72% from **10**.

Using these optimised conditions, the scope of the four-step tandem process was explored using allylic alcohols **9** and **10** and a range of dienophiles (Scheme 3). This produced a diverse series of amine substituted, partially saturated indene and tetralin scaffolds incorporating heteroatoms, quaternary centres as well as various functional groups in good yields over the four-steps. Interestingly, reaction of six-membered diene **13** with 1,4-naphthoquinone as part of the four-step tandem process gave oxidised Diels-Alder adduct **19**, while the analogous reaction with the cyclopentyl diene gave normal Diels-Alder adduct **21**.[17] Confirmation of the structure of **19** was achieved by X-ray crystallography (Fig. 2, see also supporting information†).[18] Diene **19** crystallises in the triclinic space group *P*–1 and the structure clearly shows the sp^2 nature of the C-7 and C-8 atoms.

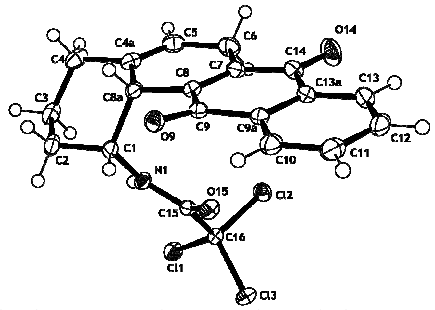
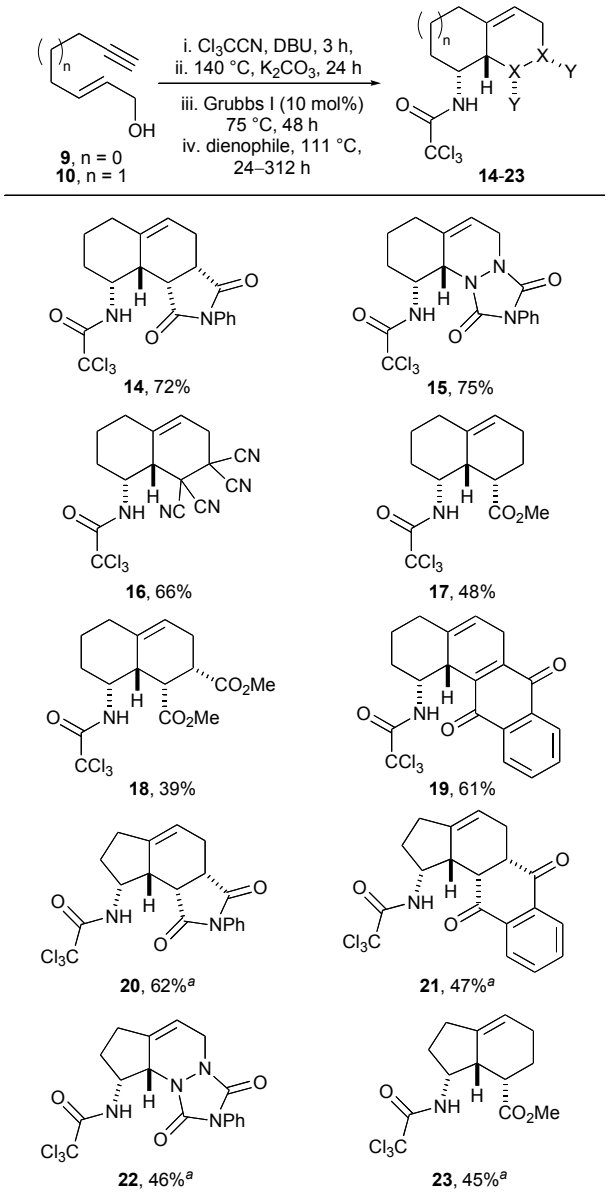


Fig. 2 Molecular structure of compound **19**. Displacement ellipsoids are drawn at 50% probability level and H-atoms are drawn with spheres of arbitrary radius.

More importantly, all the products from this four-step tandem process were isolated as single diastereomers, with some processes forming compounds with up to four contiguous stereogenic centres.[16] Moreover, the tandem processes involving the non-symmetrical dienophile, methyl acrylate gave only a single regioisomer (compounds **17** and **23**). We believe these results are due to the formation of a hydrogen bonding directed *endo* transition state between the trichloroacetamide hydrogen atom and the electron-rich atoms present in the side-chain of the dienophiles.[19] Evidence for such an effect was shown by repeating the Diels-Alder reaction of diene **13** with *N*-phenyl maleimide using methanol, rather than toluene as a solvent. In methanol, a hydrogen bonding directed Diels-Alder reaction is not possible due to competition with the solvent and as a consequence, a 1:1 mixture of the two *endo*-diastereomers were isolated in 87% yield.



Scheme 3 [a] The Diels-Alder reaction leading to the formation of compounds **20**–**23** was performed at 75 °C.

In order to further explore the cause for the selective formation of **14**, we embarked on a computational study using density-functional theory at the M06-2X/def2-TZVP level, including a polarisable continuum solvent model of toluene. The *endo* transition states for both the *syn* and *anti* attack of *N*-phenyl maleimide onto diene **13** were optimised (Fig. 3; *syn*/*anti* designates the approach of the dienophile with respect to the amide substituent of **13**).[20] The *syn*-TS is stabilised by a hydrogen bond of 2.10 Å length between the amide NH of **13** and an imide

oxygen of the dienophile (Fig. 3, bottom transition state). The calculated reaction Gibbs free energies are –93 (*syn*) and –85 (*anti*) kJ mol^{-1}. The *syn*-product **14** is favoured also on kinetic grounds; the calculated activation Gibbs free energies are 115 (*syn*) and 125 (*anti*) kJ mol^{-1}.[20] Assuming that the reaction is irreversible, and the ratio of *syn/anti*-product is entirely under kinetic control, the difference in activation energy translates into a *syn* selectivity of 23:1 at 384 K. This correlates well with what is observed experimentally for this Diels-Alder reaction. Analysis of the ^{1}H NMR spectrum of the crude material shows a *syn*/*anti* ratio of approximately 20:1.

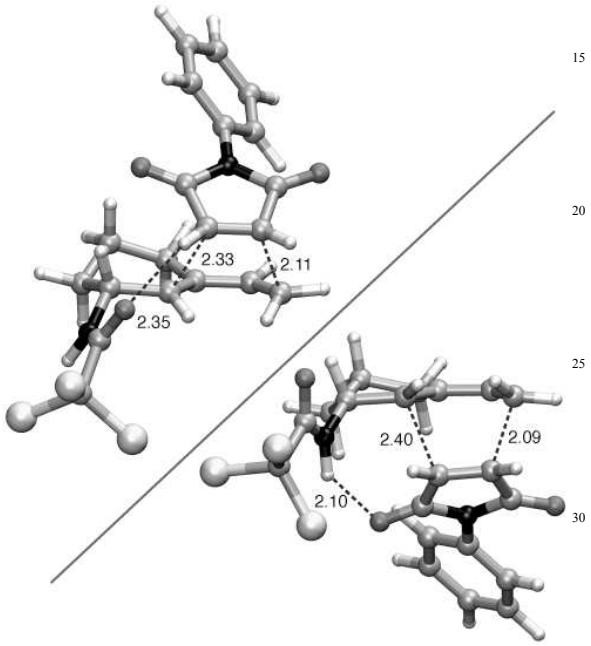


Fig. 3. DFT-optimised *anti* (top) and *syn* (bottom) transition states for the attack of *N*-phenyl maleimide onto **13**. Selected distances are given in Å.

In summary, a four-step tandem process that allows the rapid formation of multiple bonds and the generation of significant molecular complexity has been developed. The final step of the tandem process involving a Diels-Alder reaction was shown to proceed via a hydrogen bonding directed *endo* transition state forming compounds with up to four stereogenic centres in excellent diastereoselectivity. Current studies are underway to investigate the extension of this approach for the preparation of natural products and medicinally important agents.

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Notes and references

WestCHEM, School of Chemistry, The Joseph Black Building, University of Glasgow, Glasgow G12 8QQ, UK. Fax: +44 141 330 4888; Tel: +44 141 330 5936; E-mail: Andrew.Sutherland@glasgow.ac.uk

† Electronic Supplementary Information (ESI) available: Full experimental/computational procedures, spectroscopic data, NMR spectra for all compounds synthesised. CIF file for compound **19**. CCDC 876917. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b000000x/.

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20 For full details on computational modelling, see supplementary information†. ΔG values are calculated at 384 K, 100 kPa, relative to free reactants. Interestingly, the preference for *syn*-diastereomer **14** appears to be entropically favoured rather than enthalpic stabilisation (see Table S1).