ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2015, **51**, 12867

Received 22nd June 2015,
Accepted 9th July 2015

DOI: 10.1039/c5cc05070g

www.rsc.org/chemcomm

Facile access to a heterocyclic, sp^3-rich chemical scaffold *via* a tandem condensation/intramolecular nitrone–alkene [3+2] cycloaddition strategy†

M. J. Rawling,[a] T. E. Storr,[a] W. A. Bawazir,[ab] S. J. Cully,[a] W. Lewis,[a] M. S. I. T. Makki,[b] I. R. Strutt,[c] G. Jones,[c] D. Hamza[c] and R. A. Stockman*[a]

A heterocyclic, sp^3-rich chemical scaffold was synthesised in just 6 steps *via* a highly regio- and diastereo-selective tandem nitrone formation/intramolecular nitrone–alkene [3+2] cycloaddition reaction. A library of 543 lead-like compounds based on the scaffold core has been produced.

Libraries of small molecules capable of exploring novel, three-dimensional chemical space are highly desired in early-stage probe- and drug-discovery screening programmes.[1] Multiple authors have suggested that molecules containing a high fraction of sp^3-hybridised carbon atoms (Fsp^3) and numerous stereocentres have a lower rate of attrition during each stage of the drug discovery and development process once a hit has been established, thus potentially providing higher-quality lead compounds.[2,3] However, the development of facile synthetic routes to libraries of stereochemically-rich molecules with a high Fsp^3 remains a formidable challenge for the chemical community.[4]

Over the past decade our group has been interested in the rapid synthesis of architecturally complex molecules from simple, symmetrical starting materials, through de-symmetrising tandem reactions.[5] This has led to the efficient synthesis of a number of natural products including xenovenine (4 steps),[6] alkaloid *cis*-223B (3 steps),[6,7] histrionicotoxin (9 steps),[8] anatoxin-a (10 steps),[9] hippodamine (8 steps) and epi-hippodamine (11 steps).[10] We have recently demonstrated that through tandem reactions involving key complexity-generating, ring-forming operations, such as [3+2] dipolar cycloadditions, densely-functionalised tricyclic cores containing a spirocyclic centre can be generated in a diastereoselective manner.[5,11,12]

A current focus within our research group is the exploitation of the knowledge gained throughout these investigations, in the efficient synthesis of sp^3-rich chemical scaffolds for drug discovery.[13] Polycyclic scaffolds containing a central spiro-ring fusion are desirable in drug discovery due to their structural rigidity resulting in a reduced conformational entropy penalty upon ligand–protein binding.[14] In addition, incorporation of a spiro-centre often provides greater structural novelty and enhanced physical properties over that of flat, (hetero)aromatic compounds.[2,3] To maximise its potential a quality chemical scaffold should: (i) contain multiple points of diversity, (ii) be 'lead-like',[15] with a sufficiently low molecular weight ($\leq$300 Da) and *c*Log *P* ($\leq$3) to allow derivatisation of the scaffold core into a library of compounds that largely adheres to Lipinski's Rule of Five,[16] and (iii) not contain any metabolically labile moieties or toxicophores. From a practical standpoint, the synthetic route to a scaffold should be concise, reliable, safe, and scalable to provide rapid access to large quantities of material.

Following these guiding principles, we report the facile and diastereoselective synthesis of a novel, heterocyclic chemical scaffold **1** (Fig. 1). The rigid, tricyclic core of scaffold **1** contains four contiguous stereocentres with one spirocyclic centre, and has a high degree of bond saturation,[2] with an Fsp^3 value of 0.9. The scaffold **1** has three points of diversity (R^1, R^2 and R^3) to allow exploration of chemical space along three distinct vectors. The low molecular weight (196 Da) and *c*Log *P* (−1.2) of the unsubstituted scaffold **1** (R^1, R^2, R^3 = H) provides an excellent platform for diversification into a library of drug-like molecules, for screening against various biological targets.

On the basis of previous work, we envisioned that the 3-hydroxy lactam unit of scaffold **1** could be derived from key intermediate isoxazolidine **2**, by N–O bond reduction followed by cyclisation (Fig. 1).[5,12] It was proposed that spirocyclic isoxazolidine **2** could be obtained diastereoselectively through a tandem nitrone formation/intramolecular nitrone–alkene [3+2] cycloaddition from piperidinone **3**, in a single complexity-generating step. Mono-alkylated piperidinone **3** should be readily accessible from a suitable *N*-protected piperidinone **4**.

N-Benzyl piperidinone **4a** was selected as the starting point in the synthesis of scaffold **1** due to its commercial availability and low cost. Piperidinone **4a** was alkylated *via* hydrazone **5a** to avoid the well-documented issues associated with the direct alkylation of

[a] *School of Chemistry, University of Nottingham, Nottingham, NG7 2RD, UK. E-mail: robert.stockman@nottingham.ac.uk; Fax: +44 (0)115 951356*
[b] *Department of Chemistry, Faculty of Science, King Abdul-Aziz University, P.O. Box 80203, Jeddah 21315, Saudi Arabia*
[c] *Sygnature Discovery Limited, BioCity, Pennyfoot Street, Nottingham, NG7 1GF, UK*

† Electronic supplementary information (ESI) available: Experimental procedures, characterisation data, ^{1}H and ^{13}C NMR spectra. CCDC 1045613 and 1045614. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5cc05070g

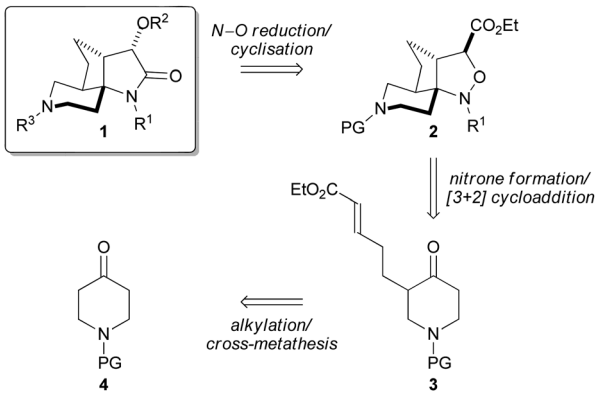
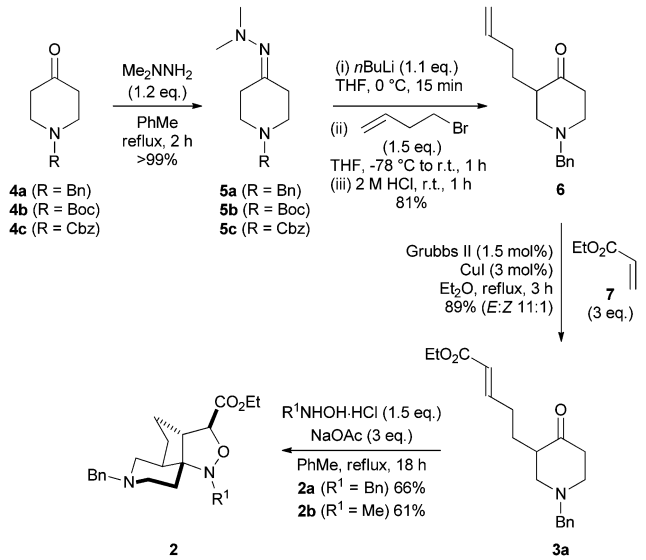


Fig. 1 Retrosynthetic analysis of scaffold **1**.

ketones (Scheme 1).[17] Treatment of piperidinone **4a** with a small excess of *N*,*N*-dimethylhydrazine (1.2 equiv.) under Dean–Stark conditions gave hydrazone **5a** in quantitative yield after 2 hours, with no need for purification.[18] α-Deprotonation of hydrazone **5a** with *n*BuLi (1.1 equiv.) then *C*-alkylation with 4-bromo-1-butene (1.5 equiv.) and *in situ* hydrolysis of the hydrazone moiety (2 M HCl), gave previously unreported homoallylated piperidinone **6** in excellent overall yield (81%). This one-pot procedure was typically performed on large scale, yielding up to 24 g of piperidinone **6** in a single batch. Unexpectedly, attempted alkylation of the carbamate-protected piperidinone analogues **4b** (*N*-Boc) and **4c** (*N*-Cbz) resulted in recovered starting material. Further investigation revealed that hydrazones **5b** and **5c** had formed without incident. However, α-deprotonation of hydrazones **5b** and **5c** using either LDA or *n*BuLi had not occurred, as quenching the reaction with D_2O revealed no deuterium incorporation by mass spectrometry or ^{1}H NMR spectroscopy. Common additives (LiCl, TMEDA and DMPU) for use with lithium bases were employed,[19] but failed to have any effect. The reason for the apparent lack of reactivity of *N*,*N*-dimethylhydrazones **5b** and **5c** to deprotonation is currently unknown, but was not explored further.[20]



Scheme 1 Synthesis of key intermediate isoxazolidine **2**.

The *trans*-α,β-unsaturated ester moiety was incorporated into *N*-benzyl piperidinone **3a** by cross-metathesis between ethyl acrylate **7** and the terminal olefin of **6**. Typical Grubbs cross-metathesis conditions (Grubbs II [10 mol%], ethyl acrylate **7** [8 equiv.], CH_2Cl_2, 20 °C)[21] gave α,β-unsaturated ester **3a** in a disappointing 32% yield (*E*:*Z* 9:1) after 4 days, which could not be improved by varying the catalyst, reagent stoichiometry, solvent or temperature. In an effort to improve both the yield and reaction rate, the 'Copper Iodide Effect' was utilised, as described by Lipshutz and co-workers.[22] Addition of copper iodide (3 mol%) as co-catalyst gave α,β-unsaturated ester **3a** (*E*:*Z* 11:1) in 89% isolated yield in only 3 hours on large scale (>10 g), representing a dramatic increase in conversion and reaction rate. Beneficially, the procedure also required considerably less Grubbs II catalyst (1.5 mol%) and ethyl acrylate **7** (3 equiv.) and was performed in ethereal solvent, rather than chlorinated media, deeming it more attractive from a financial, safety and environmental perspective.[23] The two geometric isomers of α,β-unsaturated ester **3a** were separated by silica gel column chromatography and the major (*E*)-isomer taken forward in the synthesis.

Treatment of piperidinone **3a** with *N*-benzylhydroxylamine hydrochloride (1.5 equiv.) in the presence of NaOAc (3.0 equiv.) in refluxing toluene afforded key intermediate tricyclic isoxazolidine **2a** in 66% isolated yield (Scheme 1). In a single complexity-generating operation, three new stereogenic centres and two new rings were formed, to generate a fused, tricyclic, spiro-isoxazolidine. Subjecting *N*-methylhydroxylamine hydrochloride to the same reaction conditions resulted in the analogous isoxazolidine **2b** in 61% isolated yield, showing that one point of diversity can be incorporated into the scaffold at this stage. Significantly, only a single regio- and diastereoisomer was observed by ^{1}H NMR spectroscopy in both cases.

The tandem reaction of piperidinone **3a** to isoxazolidine **2b** initially proceeds through condensation of **3a** with the mono *N*-substituted hydroxylamine to give nitrone **8** (Fig. 2). Subsequent intramolecular nitrone–alkene [3+2] cycloaddition gives two possible regioisomeric isoxazolidine products, **2b** or **9**. Computational analysis of isoxazolidines **2b** and **9** (Hartree–Fock 6-31G*) revealed a small energy difference between the two isomers, with the unobserved 6,6,5 ring system **9** being 4.62 kJ mol^{-1} lower in energy

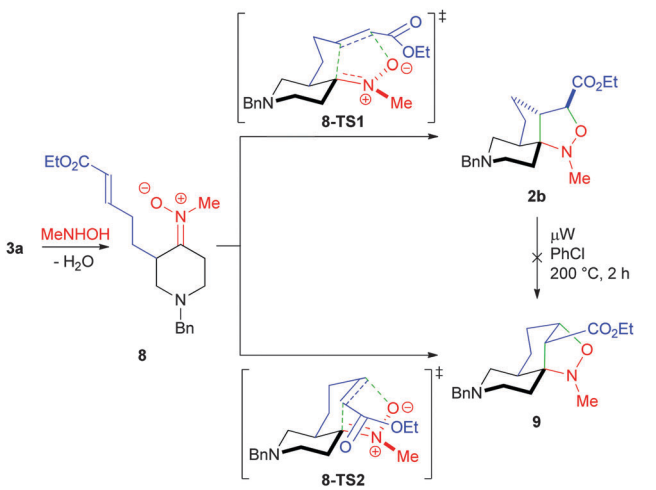


Fig. 2 Formation of regioisomeric isoxazolidines **2b** and **9**.

than the observed 6,5,5 ring system **2b**. However, the transition state **8-TS2** during formation of the lower energy 6,6,5 ring system **9** would experience substantial unfavourable steric interactions arising from the close proximity of the ester function to the developing congested spirocentre. Conversely, the transition state **8-TS1** in the formation of the 6,5,5 ring system **2b** has the ester moiety located away from the developing spirocentre, resulting in minimal steric interactions and therefore a more favourable reaction pathway. Attempted isomerisation of **2b** to the energetically favoured isoxazolidine **9** (μW, PhCl, 200 °C, 2 hours) resulted in a complex mixture of starting material **2b** and decomposition products.

Treatment of isoxazolidines **2a** and **2b** with activated zinc in aqueous acetic acid prompted smooth transformation to the corresponding 3-hydroxy lactams **11a** and **11b** in excellent yield (93% and 88% respectively) with no need for purification (Scheme 2). Mechanistically, reduction of the N–O bond in isoxazolidine **2**, followed by C–C bond rotation to **10**, allowed ring-closure to lactam **11**.

X-Ray crystallographic analysis of lactams **11a** and **11b** confirmed the atom connectivity and relative stereochemistry (Fig. 3). The X-ray images clearly show that the three points of diversification on scaffolds **11a** (atoms N1, N7 and O21, Fig. 3) and **11b** (atoms N1, N7 and O22, Fig. 3) will allow library synthesis in three defined and divergent trajectories, providing substantial exploration of three-dimensional chemical space.

With the scaffold core structure **11** in hand, it was important to demonstrate that the remaining two points of diversity on **1** (R^2 and R^3, Fig. 1) were capable of being functionalised without complication, prior to full library synthesis being undertaken. *O*-Alkylation of **11** was exemplified by deprotonation of the hydroxy function with sodium hydride, then treatment with stoichiometric iodomethane to give methyl ethers **12a** and **12b** in 65% and 61% isolated yield respectively (Scheme 3).

Deprotection of the piperidyl *N*-benzyl moiety of scaffolds **11a**, **11b**, **12a** and **12b** occurred cleanly using Pearlman's catalyst under an atmospheric pressure of hydrogen gas to give the secondary amines **13a–13d** in excellent yield (88–93%, Scheme 3). Interestingly, the lactam *N*-benzyl group of **11a** and **12a** was not cleaved under these conditions, presumably due to steric hindrance around the N–Bn bond imposed by the adjacent spirocentre. Remarkably, increasing the hydrogen pressure (50 atm, 4 days), addition of acid (AcOH or HCl) or employing typical transfer hydrogenation conditions (Pd/C, ammonium formate, MeOH, reflux, 24 h) also proved ineffective at lactam *N*-debenzylation in **11a** (R^1, Scheme 2).

The deprotected piperidyl nitrogen atom (N1, **11**, Fig. 3) represented the main library diversification point on scaffold **1**. Secondary amines can undergo an array of useful transformations for library synthesis, including (i) coupling with carboxylic acids to make amides,[24] (ii) reaction with isocyanates to form ureas, (iii) reductive amination with aldehydes or ketones to give tertiary amines,[25] and (iv) treatment with sulfonyl chlorides to make sulfonamides. A small, exemplary library of compounds was produced in good yield (30–72%) using typical reductive amination (conditions A), sulfonylation (conditions B) and amidation (conditions C) protocols (**11b**, **1a–e**, Fig. 4), proving that the final functional handle of scaffold **1** (R^3, Fig. 1) could be subjected to a variety of standard reactions without issue.

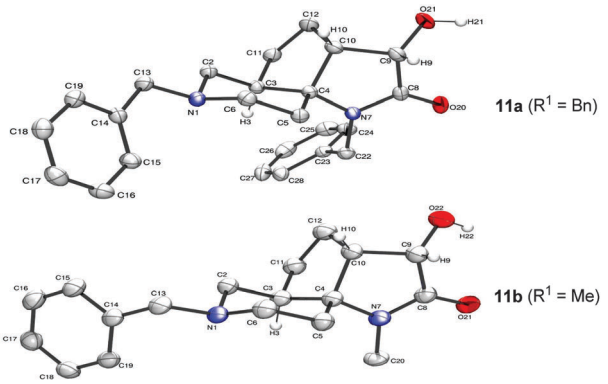
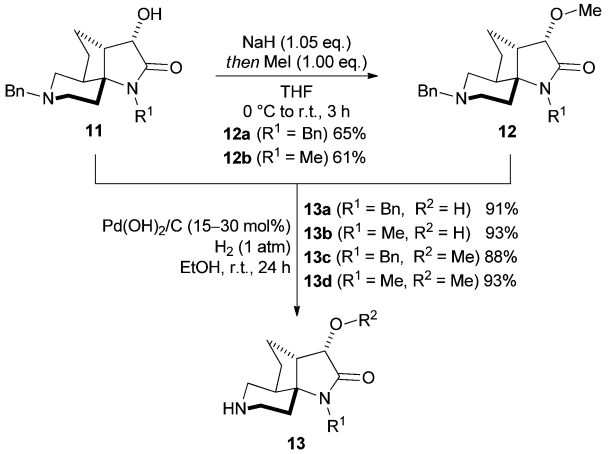


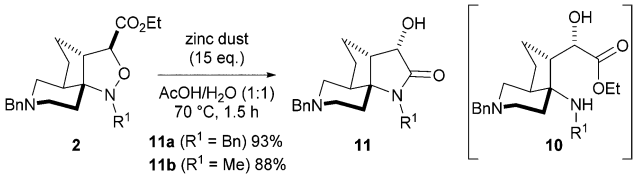
Fig. 3 X-ray crystallographic images of 3-hydroxy lactams **11a** and **11b**.



Scheme 3 *O*-Alkylation and *N*-debenzylation.

The synthetic route was scaled up to provide a total of 130 mmol of the scaffold core **11**. Derivatisation of R^1, R^2 and R^3 produced a library of 543 novel compounds (~0.1 mmol each) to be incorporated into the European Lead Factory's screening programme. Computational assessment of the library indicates that it is largely Lipinski's Rule of Five compliant, with an average molecular weight of 429 and *c*Log *P* of 1.6 (Fig. 5). The library also has a high degree of three-dimensionality and bond-saturation, with an average Fsp^3 of 0.54 (Fig. 5).

The development of efficient synthetic routes to libraries of small, sp^3-rich molecules for use in drug discovery remains a challenging but important goal. We have reported the facile synthesis and diversification of a novel, heterocyclic chemical scaffold **1**. The spirocyclic scaffold core **13** (R^1 = Bn or Me, R^2 = R^3 = H) was accessed in only six operationally simple synthetic steps from



Scheme 2 Reductive cyclisation of isoxazolidine **2** to 3-hydroxy lactam **11**.

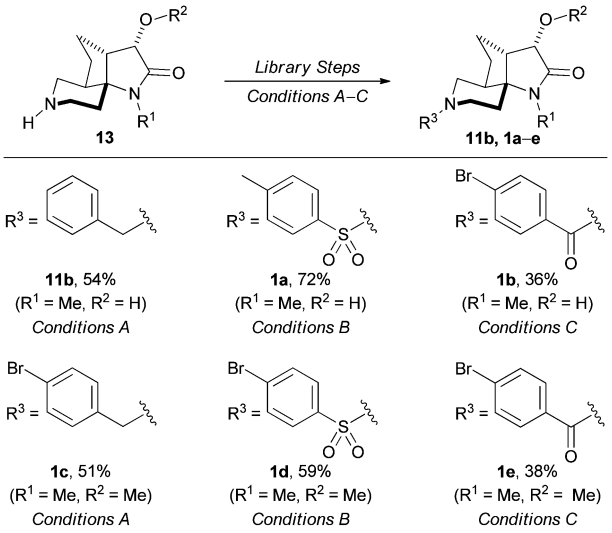


Fig. 4 Conditions A (*reductive amination*) – **13** (1.0 equiv.), ArCHO (1.5 equiv.), $NaBH(OAc)_3$ (1.2 equiv.), AcOH (2.5 equiv.), 1,2-DCE or NMP, 18 °C, 18 h; conditions B (*sulfonylation*) – **13** (1.0 equiv.), $ArSO_2Cl$ (1.3 equiv.), pyridine, 18 °C, 18 h; conditions C (*amidation*) – **13** (1.5 equiv.), $ArCO_2H$ (1.0 equiv.), HATU (2.0 equiv.), Hünig's base (3.0 equiv.), DMF, 18 °C, 18 h.

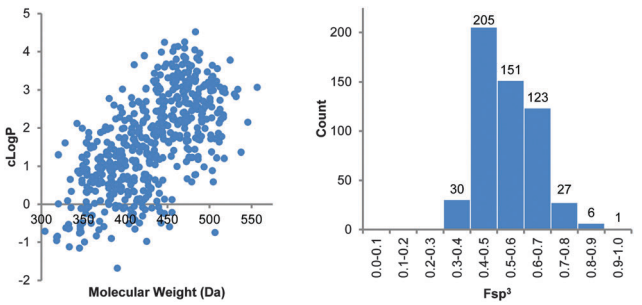


Fig. 5 Plot of cLog *P versus* MW (left) and Fsp^3 analysis (right) of the 543-compound library based on scaffold **1**.

commercially available *N*-benzyl piperidinone **4a**, in an overall yield of 41% (**13a**) or 36% (**13b**) (averaging 87% or 85% yield per step, respectively). The synthetic route to scaffold **13** required just one protecting group manipulation (*N*-debenzylation), and can be completed in less than five working days on a multi-gram scale. A highly regio- and diastereo-selective tandem condensation/intramolecular nitrone–alkene [3+2] cycloaddition reaction provided key intermediate isoxazolidine **2** in a single, complexity-generating operation, from α-functionalised piperidinone **3a**. Subsequent one-pot isoxazolidine N–O bond reduction and cyclisation gave the scaffold core structure **11**, which was confirmed by X-ray crystallographic analysis. Diversification of the scaffold core has provided a library of 543 drug-like molecules, which will be screened against various biological targets as part of the European Lead Factory. Work is ongoing within our laboratory to develop efficient routes to novel sp^3-rich chemical scaffolds for drug discovery.

This research was done within the European Lead Factory and has received support from the Innovative Medicines Initiative Joint Undertaking (grant no. 115489), with financial contribution from the European Union's Seventh Framework Programme (FP7/2007–2013) and EFPIA companies' in-kind contribution. The authors would like to thank Professor Christopher Moody and Tom McInally (University of Nottingham), in addition to Dr Iain Miller and Dr Geraint Jones (Sygnature Discovery Limited) for useful insight and discussion.

Notes and references

1 J.-L. Reymond and M. Awale, *ACS Chem. Neurosci.*, 2012, **3**, 649; A. W. Hung, A. Ramek, Y. Wang, T. Kaya, J. A. Wilson, P. A. Clemons and D. W. Young, *Proc. Natl. Acad. Sci. U. S. A.*, 2011, **108**, 6799; J.-L. Reymond, R. van Deursen, L. C. Blum and L. Ruddigkeit, *MedChemComm*, 2010, **1**, 30.
2 F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752.
3 M. Aldeghi, S. Malhotra, D. L. Selwood and A. W. E. Chan, *Chem. Biol. Drug Des.*, 2014, **83**, 450; F. Lovering, *MedChemComm*, 2013, **4**, 515; P. A. Clemons, J. A. Wilson, V. Dancik, S. Muller, H. A. Carrinski, B. K. Wagner, A. N. Koehler and S. L. Schreiber, *Proc. Natl. Acad. Sci. U. S. A.*, 2011, **108**, 6817; T. J. Ritchie and S. J. F. MacDonald, *Drug Discovery Today*, 2009, **14**, 1011; Y.-k. Kim, M. A. Arai, T. Arai, J. O. Lamenzo, E. F. Dean, III, N. Patterson, P. A. Clemons and S. L. Schreiber, *J. Am. Chem. Soc.*, 2004, **126**, 14740.
4 J. D. Sunderhaus and S. F. Martin, *Chem. – Eur. J.*, 2009, **15**, 1300; D. S. Tan, *Nat. Chem. Biol.*, 2005, **1**, 74; S. L. Schreiber, *Science*, 2000, **287**, 1964.
5 D. Robbins, A. F. Newton, C. Gignoux, J.-C. Legeay, A. Sinclair, M. Rejzek, C. A. Laxon, S. K. Yalamanchili, W. Lewis, M. A. O'Connell and R. A. Stockman, *Chem. Sci.*, 2011, **2**, 2232.
6 A. Barthelme, D. Richards, I. R. Mellor and R. A. Stockman, *Chem. Commun.*, 2013, **49**, 10507.
7 J.-C. Legeay, W. Lewis and R. A. Stockman, *Chem. Commun.*, 2009, 2207.
8 M. S. Karatholuvhu, A. Sinclair, A. F. Newton, M.-L. Alcaraz, R. A. Stockman and P. L. Fuchs, *J. Am. Chem. Soc.*, 2006, **128**, 12656; R. A. Stockman, *Tetrahedron Lett.*, 2000, **41**, 9163.
9 S. J. Roe, D. L. Hughes, P. Aggarwal and R. A. Stockman, *Synthesis*, 2009, 3775; S. J. Roe and R. A. Stockman, *Chem. Commun.*, 2008, 3432.
10 A. F. Newton, M. Rejzek, M.-L. Alcaraz and R. A. Stockman, *Beilstein J. Org. Chem.*, 2008, **4**, 4; M. Rejzek, R. A. Stockman and D. L. Hughes, *Org. Biomol. Chem.*, 2005, **3**, 73.
11 C. Gignoux, A. F. Newton, A. Barthelme, W. Lewis, M.-L. Alcaraz and R. A. Stockman, *Org. Biomol. Chem.*, 2012, **10**, 67; L. G. Arini, P. Szeto, D. L. Hughes and R. A. Stockman, *Tetrahedron Lett.*, 2004, **45**, 8371.
12 A. Sinclair, L. G. Arini, M. Rejzek, P. Szeto and R. A. Stockman, *Synlett*, 2006, 2321.
13 T. E. Storr, S. J. Cully, M. J. Rawling, W. Lewis, D. Hamza, G. Jones and R. A. Stockman, *Bioorg. Med. Chem.*, 2015, **23**, 2621–2628; M. C. McLeod, G. Singh, J. N. Plampin, III, D. Rane, J. L. Wang, V. W. Day and J. Aube, *Nat. Chem.*, 2014, **6**, 133; M. E. Welsch, S. A. Snyder and B. R. Stockwell, *Curr. Opin. Chem. Biol.*, 2010, **14**, 347.
14 Y. Zheng, C. M. Tice and S. B. Singh, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 3673; C. M. Marson, *Chem. Soc. Rev.*, 2011, **40**, 5514; J. H. Meyer and P. A. Bartlett, *J. Am. Chem. Soc.*, 1998, **120**, 4600; J. Ding, M. E. Fraser, J. H. Meyer, P. A. Bartlett and M. N. G. James, *J. Am. Chem. Soc.*, 1998, **120**, 4610; W. W. Smith and P. A. Bartlett, *J. Am. Chem. Soc.*, 1998, **120**, 4622.
15 H. Jhoti, G. Williams, D. C. Rees and C. W. Murray, *Nat. Rev. Drug Discovery*, 2013, **12**, 644; M. Congreve, R. Carr, C. Murray and H. Jhoti, *Drug Discovery Today*, 2003, **8**, 876.
16 C. A. Lipinski, F. Lombardo, B. W. Dominy and P. J. Feeney, *Adv. Drug Delivery Rev.*, 1997, **23**, 3.
17 R. Lazny and A. Nodzewska, *Chem. Rev.*, 2010, **110**, 1386.
18 M. G. Banwell, M. J. Coster, N. L. Hungerford, M. J. Garson, S. Su, A. C. Kotze and M. H. G. Munro, *Org. Biomol. Chem.*, 2012, **10**, 154.
19 D. B. Collum, *Acc. Chem. Res.*, 1992, **25**, 448.
20 H. Sun, K. M. Millar, J. Yang, K. Abboud and B. A. Horenstein, *Tetrahedron Lett.*, 2000, **41**, 2801.
21 S. J. Connon and S. Blechert, *Angew. Chem., Int. Ed.*, 2003, **42**, 1900.
22 K. Voigtritter, S. Ghorai and B. H. Lipshutz, *J. Org. Chem.*, 2011, **76**, 4697.
23 P. Anastas and N. Eghbali, *Chem. Soc. Rev.*, 2010, **39**, 301.
24 L. A. Carpino, *J. Am. Chem. Soc.*, 1993, **115**, 4397.
25 A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff and R. D. Shah, *J. Org. Chem.*, 1996, **61**, 3849.

