CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

Title: A Short Total Synthesis of (±)-Lycorane by a Sequential Intramolecular Acylal Cyclisation (IAC) and Intramolecular Heck Addition Reaction

Authors: Alessandra Monaco, Blanka R Szulc, Zenobia X Rao, Marta Barniol-Xicota, Moussa Sehailia, Bruno Borges, and Stephen Hilton

To be cited as: *Chem. Eur. J.* 10.1002/chem.201700143

Link to VoR: http://dx.doi.org/10.1002/chem.201700143

Supported by
ACES

WILEY-VCH

10.1002/chem.201700143

WILEY-VCH

COMMUNICATION

A Short Total Synthesis of (±)-γ-Lycorane by a Sequential Intramolecular Acylal Cyclisation (IAC) and Intramolecular Heck Addition Reaction

Alessandra Monaco,[a] Blanka R. Szulc,[a] Zenobia X. Rao,[a] Marta Barniol-Xicota,[b] Moussa Sehailia,[a] Bruno M. A. Borges[a] and Stephen T. Hilton*[a]

Abstract: An intramolecular acylal cyclisation (IAC) approach to the synthesis of a range of bicyclic heterocycles is reported. As an example of the utility of the IAC reaction, the methodology was applied in a protecting-group free five-step total synthesis of (±)-γ-lycorane, incorporating a novel intramolecular Heck addition reaction to generate the pentacyclic core structure of the natural product in good yield.

Heterocycles based on indole and substituted hydroindole derivatives are found in an array of natural products and have been heavily exploited in medicinal chemistry due to their potent and wide-ranging biological activities.[1] Examples of natural product alkaloids incorporating this bicyclic motif include the erythrina and lycorane alkaloid families which display potent and wide ranging biological activities.[1-3] Erythrina derived compounds **1-3**, display anxiolytic, anticonvulsant, sedative, antidepressive and antiepileptic effects,[4-6] whilst lycorane derivatives as exemplified by **4-10** display central nervous system effects, acethylcolinesterase inhibition, antimalarial, analgesic and anti-inflammatory activity.[7,8] Lycorane alkaloids have also been shown to display significant antiproliferative activity in various cancer cell lines including melanoma, multiple melanoma, leukaemia, carcinoma, lymphoma, glioblastoma and non-small cell lung cancer (Figure 1).[7,8]

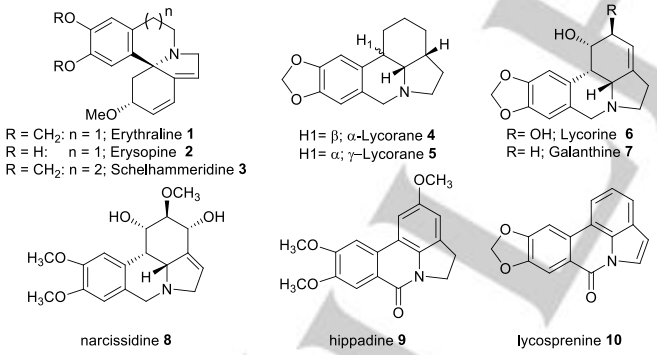


Figure 1. Natural products based on the erythratin **1-3** and lycorane cores **4-10**.

[a] Dr A. Monaco, Dr B. R. Szulc, Miss Z. X. Rao, Dr M. Sehailia, Mr B. M. A. Borges, Dr S. T. Hilton
UCL School of Pharmacy
University College London
29-39 Brunswick Square, London, WC1N 1AX, United Kingdom
E-mail: s.hilton@ucl.ac.uk

[b] Dr Marta Barniol-Xicota
Laboratori de Química Farmacèutica (Unitat Associada al CSIC), Facultat de Farmàcia, and Institute of Biomedicine (IBUB), Universitat de Barcelona, Av. Joan XXIII, s/n, Barcelona E-08028, Spain

Supporting information for this article is given via a link at the end of the document.

Due to their potent and wide ranging activities and their associated structural complexity, they have accordingly attracted significant efforts towards their syntheses,[9-15] including radical cyclisation, aminocyclisation, intramolecular addition reactions and several metal-catalyzed amidations amongst others.[9-16] Despite the structural diversity of both classes of compound and the wide array of synthetic methods used in their syntheses, many have focused on the synthesis of the dihydroindolenone core **11**, due to its ready elaboration to either of the core structures of erythrina (**1-3**) or lycorane alkaloids (**4-10**) (Figure 2).[10,16,17]

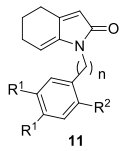
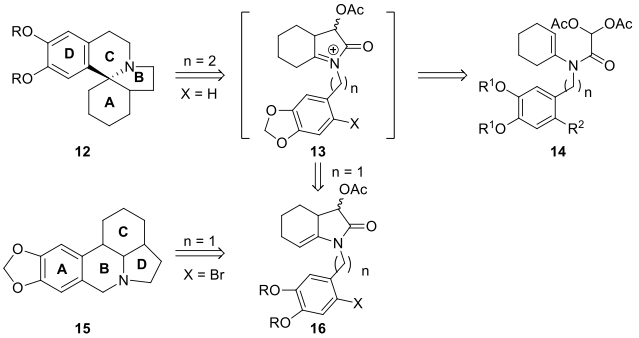


Figure 2. The hydroindolenone **11** intermediate used in the synthesis of both lycorane and erythratin.

As a result of the structural complexities and potent biological activities associated with each class of compound, we were interested in the development of novel methodology to access molecules related to the bicyclic core **11** as a route to both classes of compound.[18,19] We were also cognizant of the need to develop a flexible route which would facilitate the synthesis of a range of analogues for biological testing. In a previous approach to the erythratin core **12**, we had developed a facile two-step domino cyclisation process, which focused on a Lewis acid mediated intramolecular acylal cyclisation (IAC) via intermediate **13** (Scheme 1).[18-21] We were therefore interested in the possibility that in the case of an *N*-benzyl substituted analogue (n = 1), the intermediate iminium ion **13** would not undergo a further intramolecular addition reaction with the aryl moiety, but would instead undergo tautomerisation to the intermediate **16**, which with a suitably designed precursor could undergo radical cyclisation to generate the lycorane core **15** as per literature precedent and is outlined below (Scheme 1).[16]

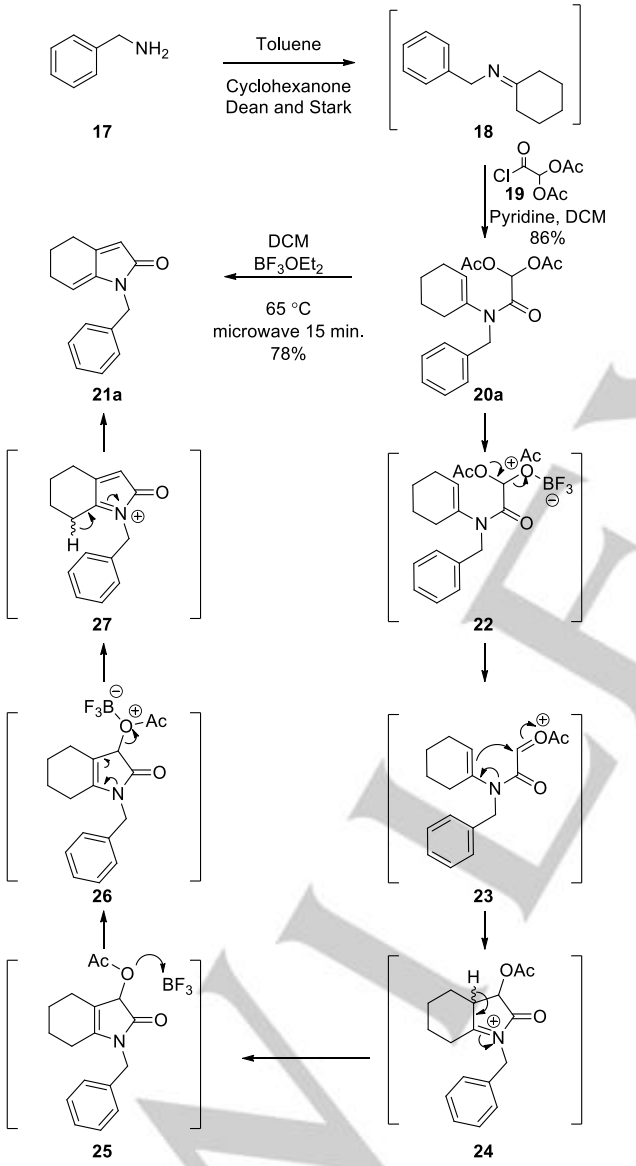


Scheme 1. Proposed synthetic route to both the erythratin **12** and lycorane **15** cores.

10.1002/chem.201700143

COMMUNICATION

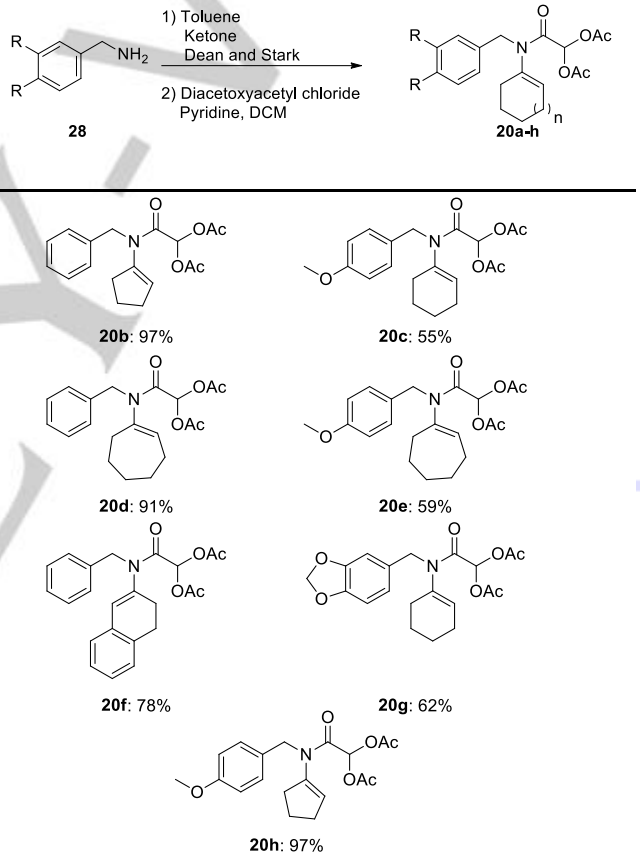
To investigate our hypothesis that both classes of compound could be accessed using this approach via simple variation of the *N*-substituent and to explore the synthesis of a range of bicyclic heterocycles related to compound **16**, we first reacted benzylamine **17** with cyclohexanone under Dean and Stark water removal conditions. Intermediate **18** was subsequently reacted with diacetoxyacetyl chloride **19**, in the presence of pyridine using our previously published methodology to give the intramolecular acylal cyclisation precursor **20a** in 86% yield.[18-21] On reaction with $BF_3.OEt_2$ (5 equiv.) and heating the reaction mixture in the microwave (Biotage Initiator) at 65 °C for 15 minutes, the reaction did not give the expected bicyclic heterocycle **16**, but instead led to formation of dihydroindolenone **21a** in good yield (78%) (Scheme 2).



Scheme 2. Cyclisation via an Intramolecular Acylal Cyclisation reaction to give the bicyclic core – **21a** and a proposed mechanism for formation.

Whilst obtention of the dihydroindolenone **21a** was unexpected as we had anticipated that product **16** would be predominant, it is likely that the intermediate bicyclic acetate - **24** (obtained after reaction of the nucleophilic enamine with the oxonium ion) is unstable and readily undergoes hydride loss to give **25**. Further activation via BF_3 and loss of acetate followed by tautomerisation provides a ready mechanistic route to the dihydroindolenone core **21a**.

Following the success in the formation of the bicyclic dihydroindolenone core **21a**, we next elected to explore the scope of this reaction in the synthesis of a range of closely related analogues through simple variation of the initial ketone component in order to explore the scope of the reaction with variation of ring size and incorporation of substituents on the aryl ring in order to develop an advanced intermediate towards the synthesis of the lycorane core **15**. The desired cyclisation precursors **20b**-**20h** were prepared in good yields (55-97%) as shown below (Scheme 3).

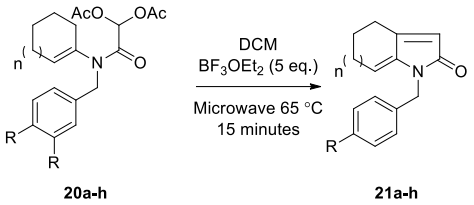


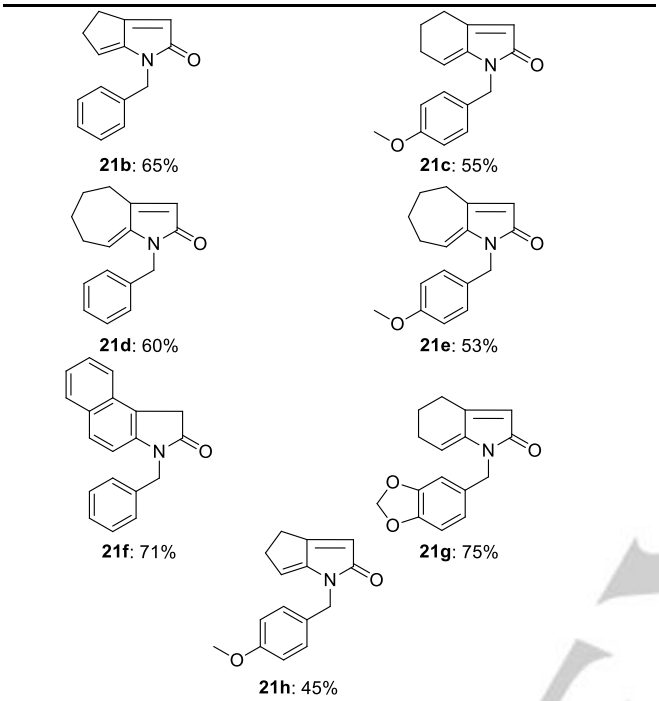
Scheme 3. Formation of bicyclic heterocycle cyclisation precursor analogues.

Compounds **20b** and **20d** were chosen to explore the effect of different ring sizes on the reaction outcome, whilst other cyclisation precursors were selected to explore the effects of electron-donating substituents on the aromatic ring as an approach towards the total synthesis of (±)-γ-Lycorane **5**. All reactions were heated in the microwave at 65 °C for 15 minutes as per the formation of the initial bicyclic dihydroindolenone **21a** and the results are shown below (Scheme 4).

10.1002/chem.201700143
WILEY-VCH

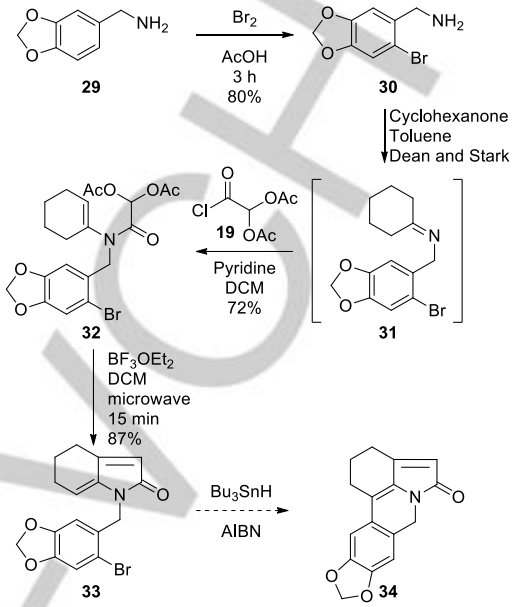
COMMUNICATION





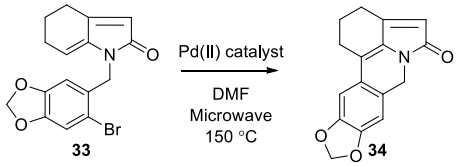
Scheme 4. Formation of bicyclic core analogues.

As can be seen above, all compounds gave good yields of the bicyclic core structures (**21b**-**21h**) following intramolecular acylal cyclisation. The formation of the bicyclic fused [3.3.0] and [5.3.0] ring systems in compounds **21b** and **21d** showed a reduction in yield (65% and 60% respectively) when compared with the initial cyclisation to give **21a**. The extended conjugated tricyclic compound was also obtained in good yield (71%), with the double bond undergoing a hydride shift to give the more thermodynamically stable compound **21f**.[22] Incorporation of an electron donating group on the *N*-benzyl substituent as exemplified by **21c** and others was also very well tolerated with good yields obtained in all cases 45-75%. Pleasingly, compound **21g** which is an advanced synthetic intermediate towards (±)-γ-lycorane **5**, was also obtained in excellent yield (75%). With the successful demonstration of the formation of the cyclized compounds which are suitable for elaboration to lycorane analogues, attention then focused on the total synthesis of (±)-γ-lycorane **5** to demonstrate the flexibility of our IAC approach. In order to access the core structure of lycorane and synthesize the B-ring of the tetracyclic core via our planned radical cyclisation mediated route, we required a halogen atom on the *N*-benzyl substituent. As such, piperonylamine **29** was reacted with bromine in acetic acid to give **30** in 80% yield. Generation of the free base, followed by condensation with cyclohexanone and diacetoxyacetyl chloride **19** gave the cyclisation precursor **32** in excellent yield (72%). Reaction with boron trifluoride diethyl etherate as per standard conditions gave the bicyclic dihydroindolenone **33** in 87% yield (Scheme 5).



Scheme 5. Synthesis of (±)-γ-lycorane cyclisation precursor **34**.

Attempts to synthesize lycorane from the bicyclic precursor **33** under previous analogous radical conditions led to degradation of the starting material in all cases.[16] We attributed this to the inherent stability of the conjugated double bond and therefore sought an alternative approach. We were therefore intrigued by a novel palladium-mediated intramolecular Heck reaction with the conjugated amidic carbonyl and as such, elected to explore a range of Heck coupling conditions with **33** (Scheme 6).[23]



Scheme 6. Synthesis of the pentacyclic (±)-γ-lycorane core **34** *via* an intramolecular Heck cyclisation.

Initial reaction of the cyclisation precursor **33** under Heck cyclisation conditions using palladium diacetate as catalyst in dioxane, gave the cyclized product **34** albeit in low yield (5%) (Table 1, Entry 1).[23] Optimization of the reaction conditions via use of triphenylphosphine palladium dichloride as catalyst and heating the reaction in the microwave at 150 °C for one hour afforded the Heck cyclisation product in good yield (74%) (Table 1, Entry 4).[23]

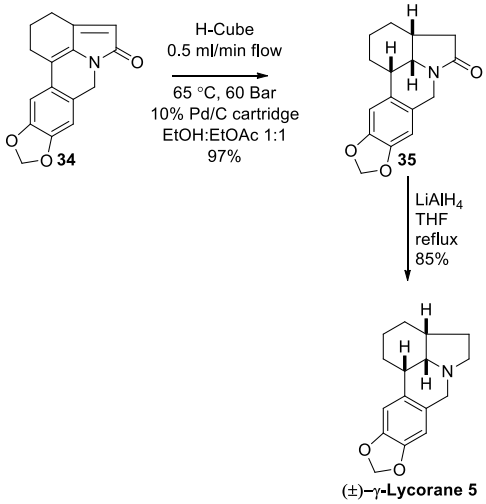
Table 1. Heck cross-coupling optimization.

Entry	Solvent	Time	Catalyst	Yield %
1	Dioxane	30 min.	$Pd(OAc)_2$	5
2	DMF	1h.	$Pd(OAc)_2$	20
3	DMF	1h.	$Pd(OAc)_2$	15
4	DMF	1h.	$(PPh_3)_2PdCl_2$	74

10.1002/chem.201700143

COMMUNICATION

Following efficient formation of the pentacyclic core of lycorane, we next sought to complete the total synthesis of (±)-γ-Lycorane **5**. Hydrogenation of the conjugated double bonds in **34** via use of an H-cube hydrogenation flow reactor using a mixture of ethanol and ethyl acetate as solvent to aid solubility, with a flow rate of 0.5 mL/ min and 10% palladium on charcoal as catalyst at 65 °C and 60 bar pressure gave the reduced product **35** in almost quantitative yield (97%). Reduction following literature precedent using lithium aluminium hydride completed the synthetic route to give the total synthesis of (±)-γ-Lycorane **5** in 85% yield (Scheme 7).[16e]



Scheme 7. Total synthesis of (±)-γ-lycorane 5.

In summary, we have developed a novel five-step route to the total synthesis of (±)-γ-Lycorane **5**, which is based on a novel sequential intramolecular acylal cyclisation/ Heck addition approach. In addition, we have shown that by variation of the starting ketone or the *N*-benzyl substituent of the precursor, we will be able to generate a number of substituted analogues as demonstrated by the efficient formation of the bicyclic core. Our approach is readily adaptable to incorporation of heteroatom substituents and further studies on these are under way in our laboratories and will be reported in due course.

Acknowledgements

This work was gratefully supported by an FNS visiting postdoctoral fellowship grant to A.M. [P2GEP2_151840] and a Leverhulme Trust project grant [F/01 232/A]. We thank the EPSRC UK National Mass Spectrometry Facility at Swansea University for spectroscopic services.

Keywords: *Erythrina* • Lewis acid • Lycorane • tandem cyclisation • Heck

[1] a) A. J. Clark, *Chem. Soc. Rev.* **2002**, *31*, 1-11; b) D. O'Hagan, *Nat. Prod. Rep.* **2000**, *17*, 435-446; c) M. d'Ischia, A. Napolitano and A. Pezzella, in *Comprehensive Heterocyclic Chemistry III*, eds. A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven and R. J. K. Taylor, Elsevier, Oxford, **2008**, 353-388.

[2] a) U. P. De Albuquerque, P. M. De Medeiros, A. L. S. De Almeida, J. M. Monteiro, E. M. D. F.L. Neto, J. G. De Melo, J. P. Dos Santos, *J. Ethnopharm.* **2007**, *114*, 325-354; b) Y. Tsuda, T. Sano in *The Alkaloids*, Vol 48 (Ed.: G. A. Cordell), Academic Press, New York, **1996**, 249-337.

[3] a) B. Deng, L. Ye, H. Yin, Y. Liu, S. Hu and B. Li, *J. Chromatogr. B* **2011**, *879*, 927-932; b) X. Li, H.-Y. Yu, Z.-Y. Wang, H.-F. Pi, P. Zhang and H.-L. Ruan, *Fitoterapia* **2013**, *88*, 82-90; c) W.-M. Wu, Y.-Y. Zhu, H.-R. Li, H.-Y. Yu, P. Zhang, H.-F. Pi and H.-L. Ruan, *J. Asian Nat. Prod. Res.* **2013**, *16*, 192-199; d) S.-D. Huang, Y. Zhang, H.-P. He, S.-F. Li, G.-H. Tang, D.-Z. Chen, M.-M. Cao, Y.-T. Di and X.-J. Hao, *Chin. J. Nat. Med.* **2013**, *11*, 406-410.

[4] G. M. Onusic, R. L. Nogueira, A. M. S. Pereira, M. B. Viana, *Braz. J. Med. Biol. Res.* **2002**, *35*, 473-477.

[5] S. M. M. Vasconcelos, N. M. Lima, G. T. M. Sales, G. M. A. Cunha, L. M. V. Aguiar, E. R. Silveira, A. C. P. Rodrigues, D. S. Macedo, M. M. F. Fonteles, F. C. F. Sousa, G. S. B. Viana, *J. Ethnopharmacol.* **2007**, *110*, 271-274.

[6] a) J. O. A. Flausino, A. M. Pereira, V. D. S. Bolzani, R. L. Nunes-de-Souza, *Biol. Pharm. Bull.* **2007**, *30*, 375-378; b) P. Setti-Perdigão, M. A. R. Serrano, O. A. Flausino, V. S. Bolzani, M. Z. P. Guimarães, N. G. Castro, *PloS ONE* **2013**, *8*, e82726; c) J. Sarris, E. McIntyre, D. Camfield, *CNS Drugs* **2013**, *27*, 207-219.

[7] a) Z.-M. Liu, X.-Y. Huang, M.-R. Cui, X.-D. Zhang, Z. Chen, B.-S. Yang and X.-K. Zhao, *Fitoterapia* **2015**, *101*, 188-193; b) B. Hao, S.-F. Shen and Q.-J. Zhao, *Molecules* **2013**, *18*, 2458-2468; c) J. McNulty, J. J. Nair, J. R. L. Little, J. D. Brennan, J. Bastida, *Bioorg. Med. Chem. Lett*. **2010**, *20*, 5290-5294; d) M. R. Herrera, A. K. Machocho, R. Brun, F. Viladomat, C. Codina, J. Bastida, *Planta Med.* **2001**, *67*, 191-193.

[8] a) D. Lamoral-Theys, A. Andolfi, G. Van Goietsenoven, A. Cimmino, B. Le Calvé, N. Wauthoz, V. Mégalizzi, T. Gras, C. Bruyère, J. Dubois, V. Mathieu, A. Kornienko, R. Kiss and A. Evidente, *J. Med. Chem.* **2009**, *52*, 6244-6256; b) W. E. Campbell, J. J. Nair, D. W. Gammon, C. Codina, J. Bastida, F. Viladomat, P. J. Smith and C. F. Albrecht, *Phytochemistry* **2000**, *53*, 587-591; c) X.-S. Liu, J. Jiang, X.-Y. Jiao, Y.-E. Wu, J.-H. Lin and Y.-M. Cai, *Cancer Lett.* **2009**, *274*, 16-24; d) P. Wang, H.-H. Yuan, X. Zhang, Y.-P. Li, L.-Q. Shang and Z. Yin, *Molecules* **2014**, *19*, 2469-2480; e) M. Jokhadze, L. Eristavi, J. Kutchukhidze, A. Chariot, L. Angenot, M. Tits, O. Jansen and M. Frédérich, *Phytother. Res.* **2007**, *21*, 622-6240; f) J. J. Nair, J. Staden, J. Bastida, *Curr. Med. Chem.* **2016**, *23*, 161-185; g) J. McNulty, J. J. Nair, M. Singhi, D. J. Crankshaw, A. C. Holloway, J. Bastida, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3233-3237; h) J. McNulty, J. J. Nair, J. Bastida, S. Pandey, C. Griffin, *Phytochemistry* **2009**, *70*, 913-919; i) Z. Jin, *Nat. Prod. Res*. **2005**, *22*, 111-126.

[9] For recent examples see: a) A. Padwa, H. I. Lee, P. Rashatasakhon, M. Rose, *J. Org. Chem.* **2004**, *69*, 8209-8218; b) M. A. Ledreau, D. Desmaele, F. Dumas, J. d'Angelo, *J. Org. Chem.* **1993**, *58*, 2933-2935; c) C. L'Homme, M. Ménard, *J. Org. Chem*. **2014**, *79*, 8481-8485; d) J. M. Joo, R. A. David, Y. Yuan, C. Lee, *Org. Lett*. **2010**, *12*, 5704-5707; d) J. X. Liang, J. B. Chen, J. P. Liu, L. Li, H. B. Zhang, *Chem. Commun*. **2010**, *46*, 3666-3668; e) T. Onoda, Y. Takikawa, T. Fujimoto, Y. Yasui, K. Suzuki, T. Matsumoto, *Synlett* **2009**, 1041-1046; f) Y. Yoshida, K. Mohri, K. Isobe, T. Itoh, K. Yamamoto, *J. Org. Chem*. **2009**, *74*, 6010-6015.

[10] For examples see: a) B. Juma, M. Adeel, A. Villinger, H. Reinke, A. Spannenberg, C. Fischer, P. Langer, *Adv. Synth. Catal.* **2009**, *351*, 1073-1079; b) P. C. Stanislawski, A. C. Willis, M. G. Banwell *Org. Lett*. **2006**, *8*, 2143-2146; c) G. Kim, J. H. Kim, K. Y. Lee, *J. Org. Chem.* **2006**, *71*, 2185-2187; d) Y. Yasui, K. Suzuki, T. Matsumoto, *Synlett* **2004**, 619-622; d) D. Kalaitzakis, T. Montagnon, E. Antonatou, G. Vassilikogiannakis, *Org. Lett*. **2013**, *15*, 3714-3717; e) S. Ogawa, N. Iida, E. Tokunaga, M. Shiro, N. Shibata, *Chem. Eur. J*. **2010**, *16*, 7090-7095; f) L. F. Tietze, N. Tolle, D. Kratzert, D. Stalke, *Org. Lett.* **2009**, *11*, 5230-5233; g) F. Z. Zhang, N. S. Simpkins, A. J. Blake, *Org. Biomol. Chem*. **2009**, *7*, 1963-1979; h) A. Padwa, Q. Wang, *J. Org, Chem*. **2006**, *71*, 7391-7402; i) H. Ishibashi, K. Sato, M. Ikeda, H. Maeda, S. Akai, Y. Tamura, *J. Chem. Soc. Perkin Trans. 1* **1985**, 605-609; j) Y.-M. Zhao, P. Gu, Y.-Q. Tu, H.-J. Zhang, Q.-W. Zhang, C.-A. Fan, *J. Org. Chem.* **2010**, *75*, 5289-5295.

[11] a) S. R. Angle, J. P. Boyce, *Tetrahedron Lett*. **1995**, *36*, 6185-6188; b) K. Nishimura, N. Fukuyama, T. Yashuhara, M. Yamashita, T. Sumiyoshi, Y. Yamamoto, K. –I Yamada, K. Tomioko, *Tetrahedron* **2015**, *71*, 7222-7226; c) Y. Wang, H. Lu, P. –F. Xu, *Acc. Chem. Res*. **2015**, *48*, 1832-1844; d) I. A. Andreev, N. K. Ratmanova, A. M. Novoselov, D. S. Belov, I. F. Seregina, A. V. Kurkin, *Chem. Eur. J*. **2016**, *22*, 7262-7267; e) Z. Sun, M. Zhou, X. Li, X. Meng, F. Peng, H. Zhang, Z. Shao, *Chem. Eur. J*. **2014**, *20*, 6112-6119; f) Y. –G. Jung, S. –C. Lee, H. –K. Cho, N. B. Darvatkar, J. –Y. Song, C. –G. Cho, *Org. Lett.* **2013**, *15*, 132-135; g) D. Liu, L. Ai, A. Zhao, J. Chen, H. Zhang, J. Liu, *Org. Biomol. Chem.* **2014**, *12*, 3191-3200; h) E. S. Conner, K. E. Crocker, R. G. Fernando, F. R. Fronczek, G. G. Stanley, J. R. Ragains, *Org. Lett*. **2013**, *15*, 5558-5561.

[12] a) G. Li, J. –H. Xie, J. Hou, S. –F. Zhu, Q. –L. Zhou, *Adv. Synth. Catal*. **2013**, *355*, 1597-1604; b) C. Liu, J. –H. Xie, Y. –L. Li, J. –Q. Chen, Q. –L. Zhou, *Angew. Chem. Int. Ed*. **2013**, *52*, 593-596; c) Y. Wang. Y. –C. Luo, H. –B. Zhang, P. –F. Xu, *Org. Biomol. Chem*. **2012**, *10*, 8211-8215; d) S. Rajkumar, K. Shankland, G. D. Brown, A. J. A. Cobb, *Chem. Sci*. **2012**, *3*, 584-588; e) R. J. Huntley, R. L. Funk, *Tetrahedron Lett*. **2011**, *52*, 6671-6674; f) B. D. Chapsal, I. Ojima, *Org. Lett.* **2006**, *8*, 1395-1398; g) K. Tomooka, M. Suzuki, K. Uehara, M. Shimada, T. Akiyama *Synlett* **2008**, 2518-2522; h) B. –C. Hong, R. Y. Nimje, M. –F. Wu, A. A. Sadani, *Eur. J. Org. Chem*. **2008**, 1449-1457; i) L. Dong, Y. –J. Xu, W. –C. Yuan, X. Cui, L. –F. Cun, L. –Z. Gong, *Eur. J. Org. Chem*. **2006**, 4093-4105.

[13] a) H. Fujioka, K. Murai, Y. Ohba, H. Hirose, Y. Kita, *Chem. Commun*. **2006**, 832-834; b) L. Dong, Y. –J. Xu, L. –F. Cun, X. Cui, A. –Q. Mi, Y. –Z. Jiang, L. –Z. Gong, *Org. Lett*. **2005**, *7*, 4285-4288; c) S. Gao, Y. Q. Tu, Z. Song, A. Wang, X. Fan, Y. Jiang, *J. Org. Chem*. **2005**, *70*, 6523-6525; d) T. Yasuhara, K. Nishimura, E. Osafune, O. Muraoka, K. Tomioka,, *Chem. Pharm. Bull*. **2004**, *52*, 1109-1113; e) T. Yasuhara, E. Osafune, K. Nishimura, M. Yamashita, K.-I. Yamada, O. Muraoka, K. Tomioka *Tetrahedron Lett*. **2004**, 3043-3045; f) A. Padwa, J. D. Ginn, S. K. Bur, C. K. Eidell, S. M. Lynch, *J. Org. Chem*. **2002**, *67*, 3412-3424; g) A. Padwa, M. A. Brodney, S. M. Lynch, *J. Org. Chem.* **2001**, *66*, 1716-1724; h) M. G. Banwell, J. E. Harvey, D. R. Hockless, *J. Org. Chem*. **2000**, *65*, 4241-4250.

[14] a) P. Magnus, J. M. Bailey, M. J. Porter, *Tetrahedron* **1999**, *55*, 13927-13936; b) H. Rudler, A. Parlier, M. Rudler, J. Vaissermann, *J. Organometallic Chem*. **1998**, *567*, 101-117; c) A. Padwa, M. A. Brodney, M. Dimitroff, *J. Org. Chem*. **1998**, *63*, 5304-5305; d) L. S. Beall, A. Padwa *Tetrhedron Lett*. **1998**, *39*, 4159-4162; e) J. H. Rigby, M. E. Mateo *Tetrahedron* **1996**, *52*, 10569-10582; f) M. G. Banwell, A. W. Wu, *J. Chem. Soc. Perkin Trans 1* **1994**, 2671-2672; g) H. Yoshizaki, H. Satoh, Y. Sato, S. Nukui, M. Shibasaki, M. Mori, *J. Org. Chem*. **1995**, *60*, 2016-2021; h) D. B. Grotjahn, K. P. C. Vollhardt, *Synthesis* **1993**, 579-605; i) V. K. Mishra, P. C. Ravikumar, M. E. Maier, *Tetrahedron* **2016**, *72*, 6499-6509; j) E. Ghiradi, R. Griera, M. Piccichè, E. Molins, I. Fernández, J. Bosch, M. Amat, *Org. Lett.* **2016**, *18*, 5836-5839.

[15] a) W. H. Pearson, J. M. Schkeryantz, *J. Org. Chem*. **1992**, *57*, 6783-6789; b) D. Pérez, E. Guitlán, L. Castedo, *Tetrahedron Lett*. **1992**, *33*, 2407-2408; c) C. –L. Wang, W. C. Ripka, P. N. Confalone, *Tetrahedron Lett.* **1984**, *25*, 4613-4616; d) J. –E. Bäckvall, P. G. Andersson, G. B. Stone, A. Gogoll, *J. Org. Chem.* **1991**, *56*, 2988-2993; e) H. Higashiyama, T. Honda, H. Otomasu, T. Kametani, *Planta Medica* **1983**, *48*, 268-271; f) H. Iida, Y. Yuasa, C. Kibayashi, J. *Am. Chem. Soc*. **1978**, *78*, 3598-3599; g) N. Ueda, T. Tokuyama, T. Sakan, *Bull. Chem. Soc. Jpn.* **1966**, *39*, 2012-2014; h) K. Kotera, *Tetrahedron* **1961**, *12*, 248-261.

[16] a) A. F. Parsons, D. A. J. Williams, *Tetrahedron* **2000**, *56*, 7217-7228; b) L. D. Miranda, S. Z. Zard, *Org. Lett*. **2002**, *4*, 1135-1138; c) M. Ikeda, S. Ohtani, T. Sato, H. Ishibashi, *Synthesis* **1998**, 1803-1806; d) J. Cossy, L. Tresnard, D. G. Pardo, *Eur. J. Org. Chem.* **1999**, 1925-1933; e) J. Cassayre, S. Z. Zard, *Synlett* **1999**, 501-503; f) S. A. A. E Bialy *Nat. Prod. Res*. **2008**, *22*, 1176-1188.

[17] a) H. Ishibashi, K. Kodama, M. Higuchi, O. Muraoka, G. Tanabe, Y. Takeda, *Tetrahedron* **2001**, *57*, 7629-7637; b) W. K. Goh, D. S. Black, N. Kumar, *Tetrahedron Lett*. **2007**, *48*, 9008-9011.

[18] A. Monaco, A. E. Aliev and S. T. Hilton, *Chem. Eur. J.* **2015**, *21*, 13909–13912.

[19] a) B. R. Szulc, B. C. Sil, A. Ruiz, S. T. Hilton, *Eur. J. Org. Chem*. **2015**, *34,* 7438-7442; b) B. R. Szulc, A. Ruiz, S. T. Hilton, **2014**, WO2014181101-A1.

[20] a) B. C. Sil, S.T. Hilton, Synlett **2013**, 2563-2566; b) A. E. Aliev, S. T. Hilton, W. B. Motherwell, D. L. Selwood, *Tetrahedron Lett.* **2006**, *47*, 2387-2390.

[21] K. M. Cook, S. T. Hilton, J. Mecinovic, W. B. Motherwell, W. D. Figg, C. J. Schofield, *J. Biol. Chem.* **2009**, *284*, 26831-26838.

[22] M. Ikeda, S. Ohtani, T. Yamamoto, T. Sato, H. Ishibashi, *J. Chem. Soc. Perkin Trans. 1*, **1998**, 1763-1768.

[23] a) Z. –H. Shao, H. –B. Zhang, Chin. J. Org. Chem. 2005, 25, 282-289; b) E. Coya, N. Sotomayor, E. Lete *Adv. Synth. Catal.* **2015**, *357*, 3206-3214; c) C. Blázquez-Barbadillo, E. Aranzamendi, E. Coya, E. Lete, N. Sotomayor, H. González-Díaz *RSC Adv*. **2016**, *6*, 38602-38610.

10.1002/chem.201700143

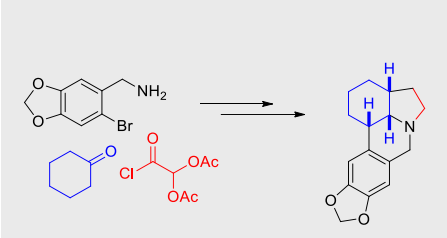
WILEY-VCH

COMMUNICATION

Entry for the Table of Contents (Please choose one layout)

Layout 2:

COMMUNICATION



A novel approach to the total synthesis of γ-lycorane: The pentacyclic structure of the natural product (±)-γ-lycorane was synthesized via a novel sequential Lewis acid mediated intramolecular acylal cyclisation (IAC)/ Heck coupling approach. Using this, methodology, a range of bicyclic heterocycles were also synthesised in good yields demonstrating the potential of the IAC reaction to access complex heterocycles.

Alessandra Monaco,[a] Blanka R. Szulc,[a] Zenobia X. Rao,[a] Marta Barniol-Xicota,[b] Moussa Sehailia,[a] Bruno M. A. Borges[a] and Stephen T. Hilton[a]*

Page No. – Page No.

A Short Total Synthesis of (±)-γ-Lycorane by a Sequential Intramolecular Acylal Cyclisation (IAC) and Intramolecular Heck Addition Reaction