Green Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/greenchem

Green Chemistry

COMMUNICATION

Synthesis of Biologically Active Natural Products, Aspergillides A and B, Entirely from Biomass Derived Platform Chemicals†

Received 00th April 2015,
Accepted 00th May 2015

DOI: 10.1039/x0xx00000x

www.rsc.org/greenchem

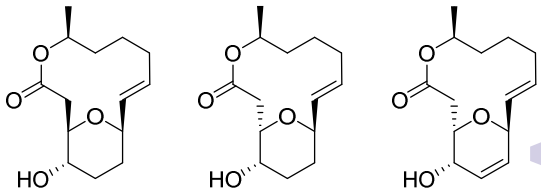
P. -F. Koh[b] and T. -P. Loh[a,b,c]

The depletion of finite fossil fuels drives the need to develop sustainable chemical feedstock such as biomass. The synthesis of biologically active natural products aspergillides A and B was achieved whereby all the carbon atoms present originated from biomass derived platform chemicals such as ethanol, levulinic acid and 5-hydroxymethylfurfural (HMF). The key steps in this synthesis include Noyori's asymmetric transfer hydrogenation, Achmatowicz rearrangement coupled with a triple reduction sequence, micellar Negishi coupling as well as an enzymatic kinetic resolution. Lipshutz's micellar Negishi coupling was also successfully applied on an advanced synthetic intermediate for the first time with good yield and excellent selectivity. This synthesis demonstrates the feasibility of constructing biologically active compounds using a sustainable chemical feedstock like biomass.

Biomass holds great promise to be a sustainable surrogate feedstock for both fuels and chemicals, in place of conventional fossil fuels, due to its renewability and abundance.[1] Biomass derived platform chemicals such as ethanol, levulinic acid and 5-hydroxymethylfurfural (HMF) are highlighted to be among the "top chemical opportunities from biorefinery carbohydrates".[2] Bioethanol is produced industrially while levulinic acid production from biomass has been commercialized and a pilot plant has been set up for HMF production in the form of HMF ether. In continuation of our group's efforts in biomass conversion,[3] we envisaged the synthesis of biologically active natural products entirely from biomass derived platform chemicals as synthesis in chemistry has traditionally employed chemicals derived from fossil fuels as starting materials and this mindset has to be reconsidered in view of sustainability and potential cost savings.

Aspergillides A, B and C are secondary metabolites isolated from marine fungus Aspergillus ostianus strain 01F313 by Kusumi's group in 2008 and exhibit potent cytotoxic activities towards mouse lymphocytic leukemia cell (L1210) with LD_{50} values of 2.1 μg/mL, 71.0 μg/mL and 2.0 μg/mL respectively (Figure 1).[4] A comprehensive review of prior syntheses of aspergillides A, B and C has been succinctly summarized up to 2011[5] and several recent syntheses have also been reported.[6]

Notably, Shishido's synthesis in 2011 provided a stereodivergent strategy to access both aspergillides A and B, and that the former could be isomerized to the latter.[7]



	aspergillide A	aspergillide B	aspergillide C
	1	**2**	**3**
LD_{50} values:	2.1 μg/mL	71.0 μg/mL	2.0 μg/mL

Fig. 1. Structures and biological activities of Aspergillides A, B and C.

We envisaged that aspergillide A, and hence aspergillide B, could be synthesized entirely from biomass derived platform chemicals, except for the protecting groups and reagents used, with the following disconnections (Figure 2). The macrocycle can be constructed using Yamaguchi macrolactonization,[8] while Negishi coupling[9] will connect fragments A and B where fragment A can be derived from levulinic acid **4** and fragment B can be derived from HMF **5** and ethanol through a series of transformations.

[a] *Hefei National Laboratory for Physical Sciences at the Microscale and Department of Chemistry, University of Science and Technology of China, Hefei, 230026 (P. R. China). Email: teckpeng@ntu.edu.sg*
[b] *Division of Chemistry & Biological Chemistry, Nanyang Technological University, 50 Nanyang Avenue, Singapore 639798.*
[c] *Collaborative Innovation Center of Chemistry for Energy Materials, P. R. China.*
† Electronic Supplementary Information (ESI) available: Characterization data for all new compounds, experimental procedures. CCDC 1047243]. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/x0xx00000x

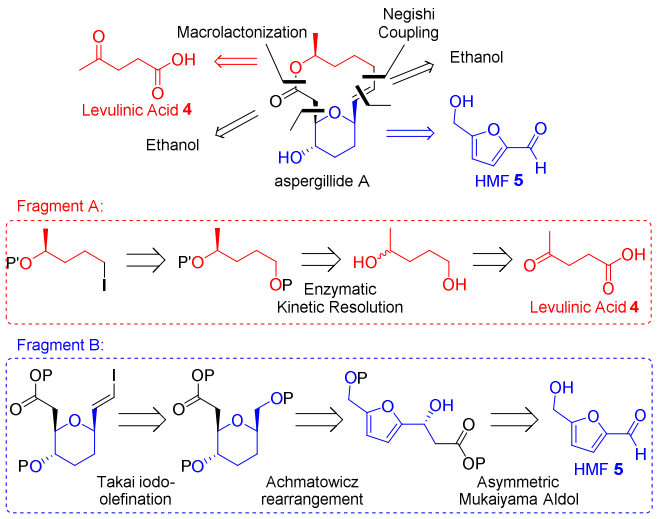
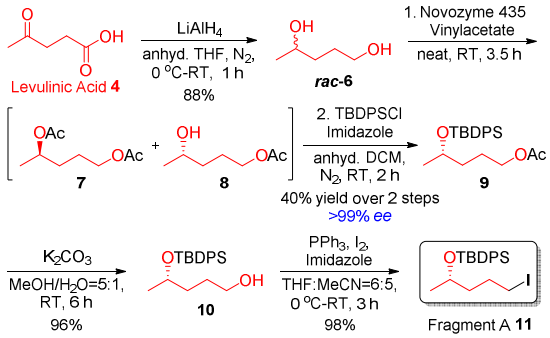


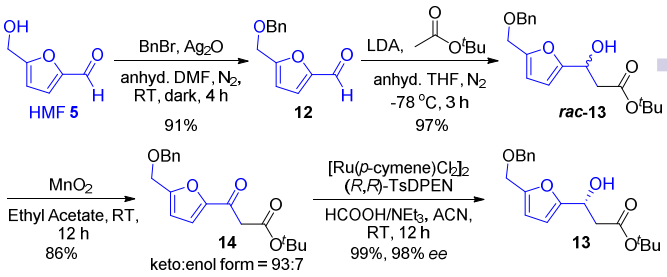
Fig. 2. Constructing aspergillide A from biomass derived platform chemicals.

Our synthesis began with the construction of enantioenriched fragment A from levulinic acid **4** (Scheme 1). **4** was completely reduced using $LiAlH_4$ to afford racemic diol **6** in 88% yield. Subsequently, **6** was subjected an enzymatic kinetic resolution[10] whereby the primary alcohol is acetylated first followed by enantioselective acetylation of one enantiomer of the secondary alcohol. After several optimizations,[11] the crude mixture of **7** and **8** could be directly protected as a silyl ether **9** in 40% yield over 2 steps out of the theoretical maximum of 50% and with excellent enantiomeric excess of >99%. The acetate group in **9** was selectively removed using K_2CO_3 to reveal primary alcohol **10** in 96% yield and then efficiently iodinated[12] to afford enantioenriched fragment A **11** in 98% yield.



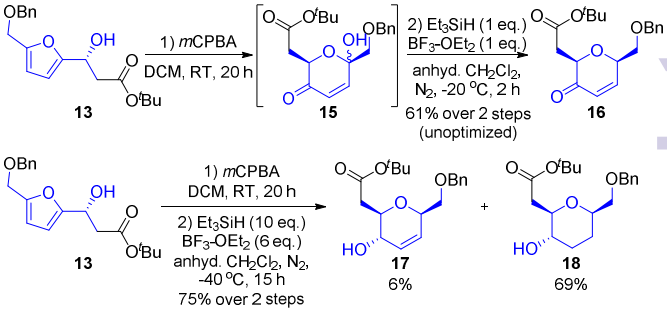
Scheme 1. Synthesis of enantioenriched fragment A from levulinic acid **4**.

Next, we focused on the synthesis of enantioenriched fragment B from HMF **5** (Scheme 2) by subjecting **5** to a benzylation reaction[13] to afford **12** in 91% yield. At this stage, we attempted several asymmetric Mukaiyama Aldol reactions[14] but no satisfactory results were obtained.[11] Instead, we decided to attempt dynamic enzymatic kinetic resolutions[15] on the racemic Aldol product ***rac*-13** but again no satisfactory results were obtained.[11] Fortunately, by oxidizing ***rac*-13** to **14** (keto:enol form = 93:7) and performing an asymmetric transfer hydrogenation,[16] enantioenriched *β*-hydroxyester **13** was synthesized in 99% yield with an excellent enantiomeric excess of 98%.



Scheme 2. Synthesis of enantioenriched fragment B from HMF **5**.

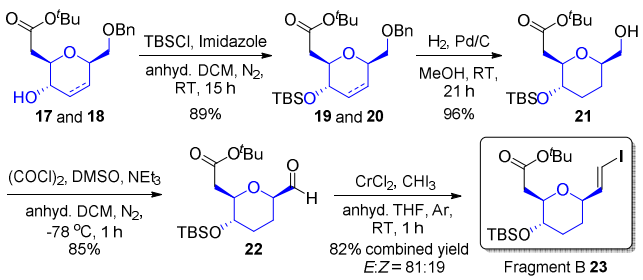
With the enantioenriched *β*-hydroxyester **13** in hand, we proceeded with the Achmatowicz rearrangement[11,18] using *m*CPBA to give the hemiacetal **15** in a diastereomeric ratio of 91:9 where the major isomer is presumed to be the one where the hydroxyl group is in axial position due to anomeric effect (Scheme 3). The crude mixture of **15** could be reduced[19] to give **16** with 61% unoptimized yield over 2 steps. Further optimizations[11] by temperature control and excess reagents allowed us to access the THP core of aspergillide A with the desired stereochemistry[20] by employing the Achmatowicz rearrangement followed by a triple reduction sequence where the formation of the desired *endo*-alcohol is rationalized to be due to the steric hindrance of the axial *α*-hydrogen atoms on the *exo* face. Pyrans **17** and **18** were synthesized with a combined yield of 75% over steps from **13**, where **17** is formed from the initial hemiacetal reduction of **15** to **16** followed by a 1,2-reduction while **18** is formed from a 1,4-reduction of **16** followed by a 1,2-reduction.



Scheme 3. Achmatowicz rearrangement and triple reduction sequence to access intermediates **17** and **18** with the desired stereochemistry.

Both **17** and **18** could be protected as the TBS ether to yield **19** and **20** as an inseparable mixture (Scheme 4). Removal of the benzyl protecting group in **19** and **20** as well as hydrogenation of the double bond provided a single product **21** in 96% yield. Swern oxidation[21] of the primary alcohol **21** to aldehyde **22** in 85% yield followed by Takai iodo-olefination[11,22] gave vinyliodide **23** as a separable mixture of *E* and *Z* isomers with a combined yield of 82%. The relative stereochemistry of the

THP core was confirmed using single crystal X-ray crystallography analysis[23] (Figure 3).



Scheme 4. Completing the synthesis of enantioenriched fragment B.

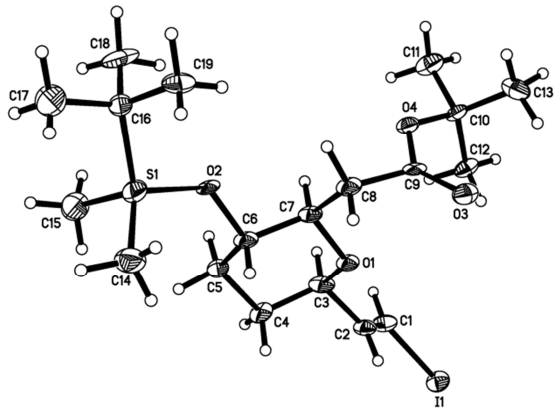
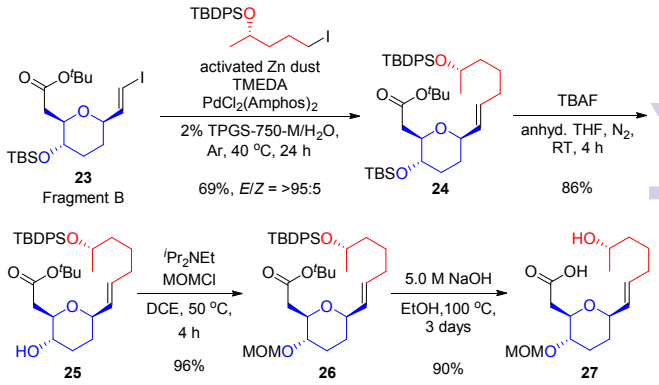
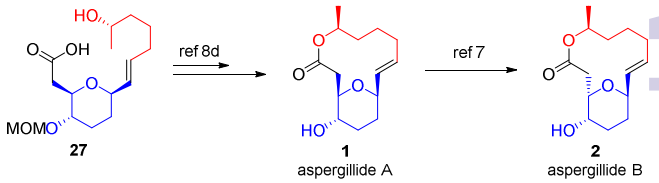


Fig. 3. ORTEP drawing of ***rac*-23**.

With the completion of both fragments A and B, we set out to attempt the Negishi coupling reaction by adopting the use of designer surfactants reported by Lipshutz's group in recent years.[9c,24] This variant of the Negishi coupling offers a variety of advantages such as the use of water as the reaction solvent and avoiding the prior preparation of organozinc coupling partner.[25] After several rounds of optimizations,[11] we were delighted to obtain the coupling product **24** in a good yield of 69% and excellent *E*/*Z* selectivity of greater than 95:5 (Scheme 5). This represents the first application of micellar Negishi coupling on an advanced intermediate in total synthesis. At this stage, the TBS group was deprotected using TBAF to give **25** and reprotected as MOM ether to give **26** in 83% yield over 2 steps. **26** was subsequently hydrolyzed under basic conditions to yield the seco acid **27**. As the macrolactonization of seco acid **27** followed by deprotection to afford aspergillide A **1** has been reported[8d] and the isomerization of aspergillide A **1** to aspergillide B **2** has been reported by Shishido's group[7], this completes the formal syntheses of aspergillides A and B (Scheme 6).



Scheme 5. Micellar Negishi coupling and synthesis of seco acid **27**.



Scheme 6. Completion of the synthesis of aspergillides A and B.

Conclusions

The synthesis of biologically active natural products aspergillides A and B was achieved with biomass derived platform chemicals. All the carbon atoms present in aspergillides A and B are derived entirely from biomass platform chemicals such as levulinic acid, HMF and ethanol. The key steps in this synthesis include Noyori's asymmetric transfer hydrogenation, Achmatowicz rearrangement coupled with a triple reduction sequence, the first application of Lipshutz's micellar Negishi coupling as well as an enzymatic kinetic resolution. This challenges the current perceptions of synthesis with fossil fuels derived chemicals and serves as a precedent for the use of biomass platform chemicals in the synthesis of complex biologically active natural products.

Acknowledgements

This research was supported financially by National Natural Science Foundation of China (21372210), the Nanyang Technological University, the Singapore Ministry of Education Academic Research Fund (MOE2014-T1-001-102, MOE2012-T1-001-107) and the National Environment Agency (NEA-ETRP Project Ref. No. 1002 111). The authors would like to thank Dr Ganguly (NTU) and Dr Li (NTU) for their assistance with the single-crystal X-ray crystallography.

Notes and references

1 a) M. Besson, P. Gallezot and C. Pinel, *Chem. Rev.,* 2014, **114**, 1827-1870; b) R. A. Sheldon, *Green Chem.,* 2014, **16**, 950-963; c) A. J. J. Straathof, *Chem. Rev.,* 2013, **114**, 1871-1908; d) H. Kobayashi and A.Fukuoka, *Green Chem.,* 2013, **15**, 1740-1763; e) A. Brandt, J. Grasvik, J. P. Hallett and T. Welton, *Green Chem.,* 2013, **15**, 550-583; f) M. He, Y. Sun and B. Han, *Angew. Chem. Int. Ed.,* 2013, **52**, 9620-9633; g) P. Gallezot, *Chem. Soc. Rev.,* 2012, **41**, 1538-1558; h) D. M. Alonso, S. G. Wettstein and J. A. Dumesic, *Chem. Soc. Rev.,* 2012, **41**, 8075-8098; i) S. Chu, A. Majumdar, *Nature,* 2012, **488**, 294-303; j) C.-H. Zhou, X. Xia, C.-X. Lin, D.-S. Tong and J. Beltramini, *Chem. Soc. Rev.,* 2011, **40**, 5588-5617; k) P. N. R. Vennestrøm, C. M. Osmundsen, C. H. Christensen and E. Taarning, *Angew. Chem. Int. Ed.,* 2011, **50**, 10502-10509; l) A.-L. Marshall and P. J. Alaimo, *Chem. Eur. J.,* 2010, **16**, 4970-4980; m) J. Zakzeski, P. C. A. Bruijnincx, A. L. Jongerius and B. M. Weckhuysen, *Chem. Rev.,* 2010, **110**, 3552-3599; n) A. Corma, S. Iborra and A. Velty, *Chem. Rev.,* 2007, **107**, 2411-2502; o) J. N. Chheda, G. W. Huber and J. A. Dumesic, *Angew. Chem. Int. Ed.,* 2007, **46**, 7164-7183; p) G. W. Huber, S. Iborra and A. Corma, *Chem. Rev.,* 2006, **106**, 4044-4098.

2 a) T. Werpy and G. Petersen, Top Value Added Chemicals from Biomass, Volume I, Results of Screening for Potential Candidates from Sugar and Synthesis Gas, U.S. Department of Energy DOE/GO-102004-1992, Washington, 2004; b) J. J.Bozell and G. R. Petersen, Green Chem., 2010, **12**, 539-554.

3 a) D. H. Lukamto, P. Wang and T.-P. Loh, *Asian J. Org. Chem.,* 2013, **2**, 947-951; b) PCT *Int. Appl.* WO 2014/003690, 2014; c) J. Zhang, Y. Liu, S. Chiba and T.-P. Loh, *Chem. Commun.,* 2013, **49**, 11439-11441; d) P.-F. Koh, P. Wang, J.-M. Huang and T.-P. Loh, *Chem. Commun.,* 2014, **50**, 8324-8327; e) PCT *Int. Appl.* WO 2014/142761, 2014.

4 Isolation and cytotoxicity: a) K. Kito, R. Ookura, S. Yoshida, M. Namikoshi, T. Ooi and T. Kusumi, *Org. Lett.,* 2008, **10**, 225-228; Correction in structures: b) S. M. Hande and J. i. Uenishi, *Tetrahedron Lett.,* 2009, **50**, 189-192; c) R. Ookura, K. Kito, Y. Saito, T. Kusumi and T. Ooi, *Chem. Lett.,* 2009, **38**, 384.

5 T. Nagasawa and S. Kuwahara, *Heterocycles,* 2012, **85**, 587-613.

6 a) T. R. Pradhan, P. P. Das and D. K. Mohapatra, *Synthesis,* 2014, **46**, 1177-1184; b) J. Zeng, J. Ma, S. Xiang, S. Cai and X.-W. Liu, *Angew. Chem. Int. Ed.,* 2013, **52**, 5134-5137; c) Y. Sridhar and P. Srihari, *Eur. J. Org. Chem.,* 2013, 578-587; d) G. V. M. Sharma and V. Manohar, *Tetrahedron: Asymmetry,* 2012, **23**, 252-263; e) B. M. Trost and M. Bartlett, J. *Org. Lett.,* 2012, **14**, 1322-1325.

7 a) M. Kanematsu, M. Yoshida and K. Shishido, *Angew. Chem. Int. Ed.,* 2011, **50**, 2618-2620; b) M. Kanematsu and K. Shishido, *J. Synth. Org. Chem. Jpn.,* 2012, **70**, 1196-1205.

8 a) J. Inanaga, K. Hirata, H. Saeki, T. Katsuki and M. Yamaguchi, *Bull. Chem. Soc. Jpn.,* 1979, **52**, 1989-1993; b) T. Nagasawa and S. Kuwahara, *Tetrahedron Lett.,* 2010, **51**, 875-877; c) T. Nagasawa, T. Nukada and S. Kuwahara, *Tetrahedron,* 2011, **67**, 2882-2888; d) H. Fuwa, H. Yamaguchi and M. Sasaki, *Org. Lett.,* 2010, **12**, 1848-1851; e) H. Fuwa, H. Yamaguchi and M. Sasaki, *Tetrahedron,* 2010, **66**, 7492-7503.

9 a) E.-i. Negishi, Q. Hu, Z. Huang, M. Qian and G. Wang, *Aldrichim. Acta,* 2005, **38**, 77-90; b) R. Jana, T. P. Pathak and M. S. Sigman, *Chem. Rev.,* 2011, **111**, 1417-1492; c) A. Krasovskiy, C. Duplais and B. H. Lipshutz, *Org. Lett.,* 2010, **12**, 4742-4744; d) B. H. Lipshutz, S. Ghorai, A. R. Abela, R. Moser, T. Nishikata, C. Duplais, A. Krasovskiy, R. D. Gaston and R. C. Gadwood, *J. Org. Chem.,* 2011, **76**, 4379-4391.

10 a) Review: A. Ghanem, *Tetrahedron,* 2007, **63**, 1721-1754; b) F. Felluga, C. Forzato, F. Ghelfi, P. Nitti, G. Pitacco, U. M. Pagnoni and F. Roncaglia, *Tetrahedron: Asymmetry,* 2007, **18**, 527-536.

11 Refer to Electronic Supplementary Information (ESI) for optimization conditions.

12 P. J. Garegg and B. Samuelsson, *J. Chem. Soc., Perkin Trans. 1,* 1980, 2866-2869.

13 L. Cottier, G. Descotes, L. Eymard and K. Rapp, *Synthesis,* 1995, 303-306.

14 a) F. Fu, Y.-C. Teo and T.-P. Loh, *Tetrahedron Lett.,* 2006, **47**, 4267-4269; b) J.-F. Zhao, B.-H. Tan and T.-P. Loh, *Chem. Sci.,* 2011, **2**, 349-352; c) T. Ollevier and B. Plancq, *Chem. Commun.,* 2012, **48**, 2289-2291; d) T. Kitanosono, T. Ollevier and S. Kobayashi, *Chem. Asian J.,* 2013, **8**, 3051-3062; e) D. A. Evans, J. A. Murry and M. C. Kozlowski, *J. Am. Chem. Soc.,* 1996, **118**, 5814-5815; f) S. E. Denmark, T. Wynn and G. L. Beutner, *J. Am. Chem. Soc.,* 2002, **124**, 13405-13407.

15 a) N. Kim, S.-B. Ko, M. S. Kwon, M.-J. Kim and J. Park, *Org. Lett.,* 2005, **7**, 4523-4526; b) J. Brem, A. Liljeblad, C. Paizs, M. I. Toşa, F.-D. Irimie and L. T. Kanerva, *Tetrahedron: Asymmetry,* 2011, **22**, 315-322; c) P. Hoyos, V. Pace and A. F. Alcántara, *Adv. Synth. Catal.,* 2012, **354**, 2585-2611; d) B. A. Persson, A. L. E. Larsson, M. Le Ray and J.-E. Bäckvall, *J. Am. Chem. Soc.,* 1999, **121**, 1645-1650.

16 a) A. Fujii, S. Hashiguchi, N. Uematsu, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.,* 1996, **118**, 2521-2522; b) R. Noyori and S. Hashiguchi, *Acc. Chem. Res.,* 1997, **30**, 97-102; c) Lutz F. Tietze, Y. Zhou and E. Töpken, *Eur. J. Org. Chem.,* 2000, 2247-2252; d) K. Everaere, A. Mortreux and J.-F. Carpentier, *Adv. Synth. Catal.,* 2003, **345**, 67-77; e) P. N. Liu, P. M. Gu, F. Wang and Y. Q. Tu, *Org. Lett.,* 2003, **6**, 169-172; f) S. Ishikawa, T. Hamada, K. Manabe and S. Kobayashi, *Synthesis,* 2005, 2176-2182; g) S. Gladiali and E. Alberico, *Chem. Soc. Rev.,* 2006, **35**, 226-236.

17 a) O. Achmatowicz Jr, P. Bukowski, B. Szechner, Z. Zwierzchowska and A. Zamojski, *Tetrahedron,* 1971, **27**, 1973-1996; b) Y. Lefebvre, *Tetrahedron Lett.,* 1972, **13**, 133-136; c) O. Achmatowicz Jr and R. Bielski, *Carbohydr. Res.,* 1977, **55**, 165-176; d) E. A. Couladouros and M. P. Georgiadis, *J. Org. Chem.,* 1986, **51**, 2725-2727; e) Review: M. P. Georgiadis, K. E. Albizati and T. M. Georgiadis, *Org. Prep. Proced. Int.,* 1992, **24**, 95-118; f) Application in Oligosaccharides synthesis: M. F. Cuccarese, G. A. O'Doherty in *Asymmetric Synthesis II: More Methods and Applications*, ed. M. Christmann and S. Bräse, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, pp. 249-259.

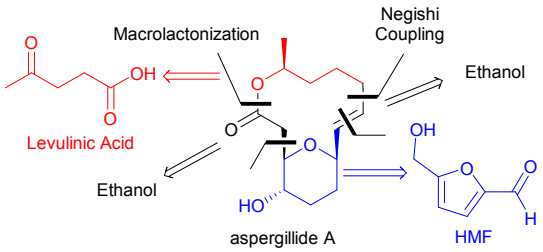
18 Recent examples of Achmatowicz rearrangement in total syntheses: a) Y. Sridhar and P. Srihari, *Org. Biomol. Chem.,* 2013, **11**, 4640-4645; b) A. K. Ghosh and Z.-H. Chen, *Org. Lett.,* 2013, **15**, 5088-5091; c) R. Bhuniya and S. Nanda, *Tetrahedron,* 2013, **69**, 1153-1165; d) H. Takamura, K. Tsuda, Y. Kawakubo, I. Kadota and D. Uemura, *Tetrahedron Lett.,* 2012, **53**, 4317-4319; e) P. Srihari and Y. Sridhar, *Eur. J. Org. Chem.,* 2011, 6690-6697; f) J. Robertson, C. North and J. E. R. Sadig, *Tetrahedron,* 2011, **67**, 5011-5023; g) A. T. Herrmann, S. R. Martinez and A. Zakarian, *Org. Lett.,* 2011, **13**, 3636-3639; h) J. A. Gazaille, J. A. Abramite and T. Sammakia, *Org. Lett.,* 2011, **14**, 178-181; i) K. C. Nicolaou, T. M. Baker and T. Nakamura, *J. Am. Chem. Soc.,* 2010, **133**, 220-226; j) A. K. Ghosh and J. Li, *Org. Lett.,* 2010, **13**, 66-69.

19 a) M. D. Lewis, J. K. Cha and Y. Kishi, *J. Am. Chem. Soc.,* 1982, **104**, 4976-4978; b) D. N. Kursanov, Z. N. Parnes and N. M. Loim, *Synthesis,* 1974, 633-651; c) J. M. Um, K. N. Houk and A. J. Phillips, *Org. Lett.,* 2008, **10**, 3769-3772.

20 NOESY analyses of products were not conclusive at this stage and the relative stereochemistry of the product was confirmed at a later stage with single crystal X-ray crystallography analysis.

21 a) A. J. Mancuso, S.-L. Huang and D. Swern, *J. Org. Chem.,* 1978, **43***,* 2480-2482; b) K. Omura and D. Swern, *Tetrahedron,* 1978, **34***,* 1651-1660; c) A. J. Mancuso, D. S. Brownfain and D. Swern, *J. Org. Chem.,* 1979, **44***,* 4148-4150.
22 a) K. Takai, K. Nitta and K. Utimoto, *J. Am. Chem. Soc.,* 1986, **108***,* 7408-7410; b) Selectivity optimization: D. A. Evans and W. C. Black, *J. Am. Chem. Soc.,* 1993, **115***,* 4497-4513.
23 The CIF file, ORTEP drawing and CCDC Deposition Number of the crystalline compound is provided in the Supplementary Materials.
24 a) 3rd generation surfactant "Nok": P. Klumphu and B. H. Lipshutz, *J. Org. Chem.,* 2014, **79***,* 888-900; b) B. H. Lipshutz, N. A. Isley, J. C. Fennewald and E. D. Slack, *Angew. Chem. Int. Ed.,* 2013, **52***,* 10952-10958.
25 Lipshutz's group used Zn dust stored in a glove box in his reports but in our study Zn dust (not stored in glove box) was activated immediately prior to use (without vacuum drying) in accordance to: S. Yamamura, M. Toda and Y. Hirata, *Org. Synth.,* 1973, **53***,* 86.

Colour graphic:



Text:

The synthesis of aspergillides A and B was achieved whereby all the carbon atoms originated from biomass derived platform chemicals.