RESEARCH ARTICLE

De Novo Asymmetric Approach to Aspergillide-C: Synthesis of 4-epi-seco-Aspergillide-C

Yalan Xing[b] and George A. O'Doherty*[a]

[a] Dr. G. A. O'Doherty
Department of Chemistry and Chemical Biology
Northeastern University
360 Huntington Avenue, Boston 02115, USA
E-mail: g.odoherty@neu.edu

[b] Dr. Y. Xing
Department of Chemistry
William Paterson University
Wayne, New Jersey 07470, USA

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

Abstract: An asymmetric approach toward the synthesis of the marine natural product aspergillide-C has been developed. The convergent asymmetric synthesis uses two asymmetric Noyori transfer hydrogenations to enantioselectively prepare the two key fragments, a *C*-1 to *C*-7 pyranone fragment and a *C*-8 to *C*-14 β-keto-sulfone fragment. The absolute stereochemistry of the pyranone fragment was established by a Noyori reduction of β-furylketoester to form a furyl alcohol. An Achmatowicz rearrangement was used to stereoselectively convert the furyl alcohol in to the key pyranone fragment. The absolute stereochemistry of the β-keto-sulfone fragment was established by a Noyori reduction of an ynone to form a propargyl alcohol. An alkyne zipper isomerization was used to stereospecifically convert the propargyl alcohol in to the β-keto-sulfone fragment. Finally, a Pd-catalyzed *C*-glycosylation was used to diastereoselectively couple the two fragments, which when combined with a reduction and Julia-Kocienski type elimination formed a protected variant of the 4-*epi*-seco-acid of aspergillide-C.

Introduction

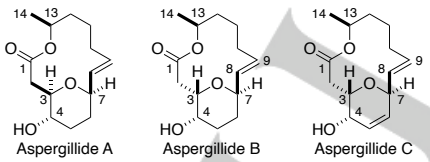
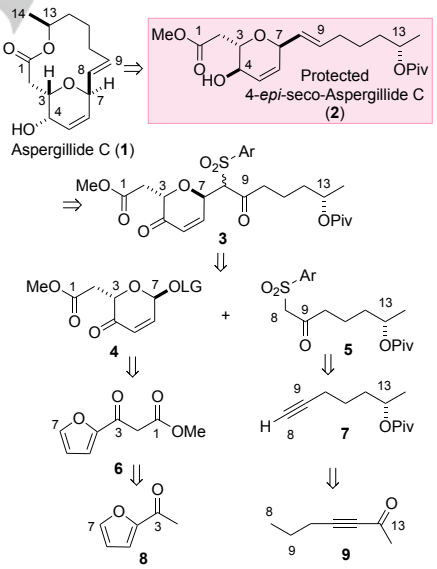


Figure 1. The aspergillides A, B and C

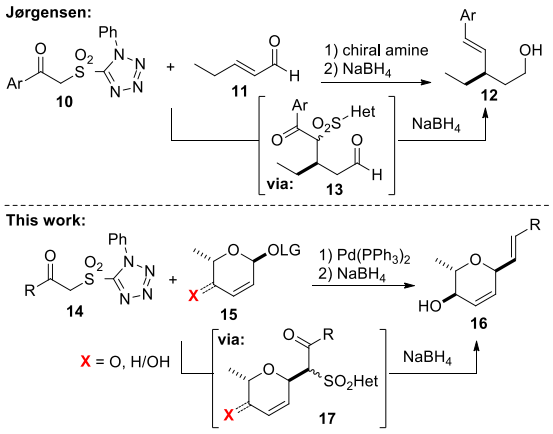
The aspergillides A, B, and C are a class of 14-membered macrolides isolated by Kusumi in 2007 from the marine-derived fungus *Aspergillus ostianus* strain 01F313 (Figure 1).[1] The structures and absolute configurations of aspergillides were determined by analyses of NMR spectra and modified Mosher's method. In addition to the 14-membered lactone, all three aspergillides share a 2,3,5-tri-substituted pyran and a *C*-8/9 trans-alkene. Of the three aspergillides, aspergillide-A and aspergillide-B are *C*-3 epimer, with aspergillide-A being a 1,3-cis-fused pyran and aspergillide-B being a 1,3-trans-fused pyran. Aspergillide-C shares the stereochemical features with aspergillide-B but differs in that it has extra unsaturation in the pyran at *C*-5/6. Despite these differences, all three aspergillides possess significant cytotoxicity against the mouse lymphocytic leukemia cell line (L1210) (LD_{50} = 2.1 for aspergillide-A, 71.0 for aspergillide-B, and 2.0 g/mL for aspergillide-C). Because of a combination of structural uniqueness and biological activity of the aspergillides, the synthesis of aspergillides has attracted much attention in synthetic community.[2,3,4,5,6,7] Herein we disclose our efforts at the *de novo* asymmetric synthesis of a *C*-4 epimer of the seco-acid of aspergillide-C. The synthetic approach that we envisioned was one ultimately aimed at the synthesis of aspergilide-C (Scheme 1).



Scheme 1. Proposed retrosynthetic approach to aspergillide-C

There have been three syntheses of aspergillide-A,[3,4] six syntheses of aspergillide-B[3,5] and five syntheses of aspergillide-C.[6] The effort we envision hues most closely to the synthesis accomplished by Srihari,[5a] where they prepared a protected seco-acid like **2** via a Lewis acid catalyzed alkylation of a pyranone (*e.g.*, **4**). More specifically, we were interested in the synthesis of pyranone **4**, which could serve as a Pd-glycosyl donor in a *C*-glycosylation reaction with β-keto-sulfone **5** to form **3**, a protected precursor to seco-acid of aspergillide-C. Key to this approach is the recognition that β-keto-sulfone **5** could function as a vinyl anion equivalent for Pd-π-allyl electrophiles. The

inspiration of this transformation builds upon the discovery of Jørgensen et al.[8] that keto-sulfones similar to **5** functioned as vinyl anion equivalents in Michael addition reactions. The synthesis of **4** in turn would result from a Noyori/Achmatowicz/acylation approach from β-ketoester **6**. Finally, β-ketoester **6** could be formed from 2-acetylfuran **8** by a one-step carboxymethylation. Herein we describe our efforts to develop a convergent asymmetric synthesis of aspergillide-C from achiral acylfuran **8** and ynone **9**. This synthetic approach is part of a larger effort aimed at exploring the stereochemical structure activity relationship (S-SAR) study of pyran containing polyketide natural products.[9]

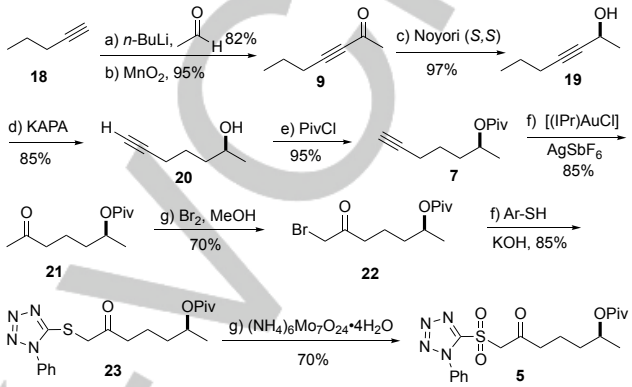


Scheme 2. Jørgensen asymmetric Michael/Julia-Kocienski and a variation

In the course of this effort, Jørgensen reported a novel use of the Julia-Kocienski type β-keto-sulfone **10** as vinyl anion equivalent in the chiral amine catalyzed asymmetric Michael addition to α/β-unsaturated enals, like **11** (Scheme 2). To complete the transformation the Michael addition product, the mixture of diastereomers, was treated with excess $NaBH_4$ to reduce the two carbonyl functionalities and subsequently induce a Julia-Kocienski type elimination to form alkene **12**. In this context, we similarly hypothesized that β-keto-sulfones could function as a vinyl anion equivalent to Pd-π-allyl cations. Specifically, β-keto-sulfones, like **14**, should couple with pyranone **15** via a Pd-π-allyl intermediate to form **17**, which upon reduction with excess $NaBH_4$ should produce **16** via a Julia-Kocienski type elimination. In the case of *C*-4 ketone oxidation state, the ketone would also be reduced by the excess $NaBH_4$.

Results and Discussion

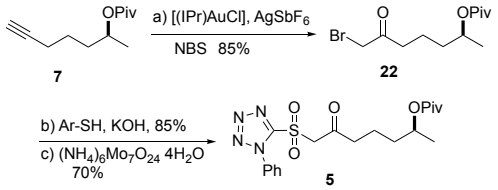
Our approach to aspergillide-C began with the asymmetric synthesis of the β-keto-sulfone fragment **5** (Scheme 3). Key to installing the asymmetry was the ability of the Noyori reduction in combination with the alkyne zipper isomerization to convert achiral ynone **9** into enantiomerically enriched ynol **19**.[10] This effort began with a practical and scalable synthesis of ynone **9**, via the lithium acetylide addition to acetaldehyde of the anion from alkyne **18** to give racemic **19**. A MnO_2 oxidation of (*rac*)-**19** gave ynone **9** in excellent overall yield. Exposure of **9** to the Noyori hydrogen transfer asymmetric reduction gave propargyl alcohol **19** in excellent yield (97%) and high enantiopurity.[11] Treatment of **19** to the alkyne-zipper reagent KAPA pioneered by Brown[12] gave excellent yield of **20** with no erosion of enantiomeric purity. The secondary alcohol of **20** was protected as a pivalate (PivCl, pyridine) to form **7** in excellent yield (95%) and then the alkyne in **7** was hydrated via gold catalysis (IPrAuCl in aqueous MeOH, 85%) to give ketone **21**. Next the methylketone in **21** was mono-brominated (Br_2, MeOH) to give **22**, which was then displaced with a thiolate anion to give β-keto-sulfide **23**. A per-oxidation of the sulfide in **23** with ammonium molybdate gave the desired β-keto-sulfone **5** in good yield (70%).



Reagents and conditions: (a) *n*-BuLi, acetaldehyde, –78 °C - 0 °C, 82%; (b) MnO_2, THF, rt, 95%; (c) HCOONa, cetyl trimethylammonium bromide, Noyori (*S,S*), rt, 97%; (d) KH, $H_2N(CH_2)_3NH_2$, 15 °C to rt, 85%; (e) PivCl, pyridine, rt, 95%; (f) [(IPr)AuCl], $AgSbF_6$, MeOH, rt, 85%; (g) Br_2, MeOH, rt, 70%; (h) ArSH, KOH, MeOH, rt, 85%; (i)$(NH_4)_6Mo_7O_{24}$ $4H_2O$, H_2O_2, EtOH, rt, 70%. PivCl = 2,2 Dimethylpropanoyl chloride, ArSH = 1-pheny-1*H*-tetrazole-5-thiol [(IPr)AuCl] = Chloro[1,3-bis(2,6 diisopropylphenyl)imidazol-2 ylidene]gold(I)

Scheme 3. Alkyne zipper approach to the synthesis of β-ketosulfone **5**

We next looked to improve the efficiency of the synthesis of **5** via an oxidative hydration of **7** (Scheme 4). This began with the exposure of **7** to a variant of the conditions developed by Hammond.[13] Specifically, exposure of **7** to the same gold catalyst system in the presence of NBS gave bromoketone **22**. The bromo-ketone produced under these conditions reacted similar to the potassium thioate to give **23** and then oxidized with ammonium molybdate to give β-keto-sulfone **5**.

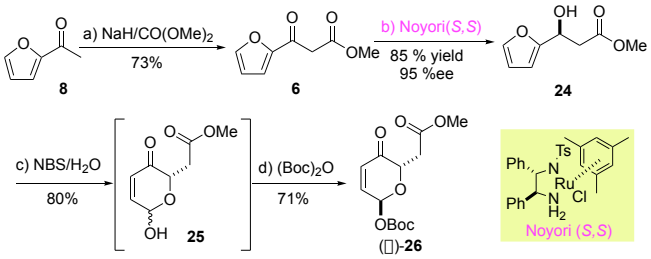


Reagents and conditions: (a) [(IPr)AuCl], $AgSbF_6$, NBS, MeOH, 65 °C, 85%; (b) ArSH, KOH, MeOH, rt, 85%; (c) $(NH_4)_6Mo_7O_{24}$ $4H_2O$, H_2O_2, EtOH, rt, 70%. PivCl = 2,2-Dimethylpropanoyl chloride, ArSH = 1-pheny-1*H*-tetrazole-5-thiol [(IPr)AuCl] = Chloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]gold(I)

Scheme 4. Improved synthesis of β-ketosulfone **5**

Recently we reported an efficient asymmetric synthesis of α-enone **26** from commercially available **8** via a Noyori/Achmatowicz sequence (Scheme 5).[14,15] The synthesis began with the base promoted conversion of acetylfuran **8** into β-

ketoester **6**. We have explored many different ways to achieve this transformation[16] but have found this is most practically accomplished on scale with the use of NaH as base in the presence of excess dimethylcarbonate. Under these conditions ($NaH/CO(OMe)_2$ in THF) β-ketoester **6** can be prepared in very good yield (73%). Exposure of furylketone **6** to the asymmetric Noyori hydrogen transfer reduction (HCOONa, (*S,S*)-Noyori) converted it into a furan alcohol **24** in excellent yield (85%) and enantiomeric excess (>95% ee).[17] The furan alcohol **24** was oxidatively hydrated under the Achmatowicz conditions (NBS in buffered THF/H_2O) to give pyranone **25** as a mixture of anomers. Finally, the pyranone **25** as a crude mixture of anomers was diastereoselectively converted into the Boc-protected (α)-pyranone **26** in 71% yield.[18]

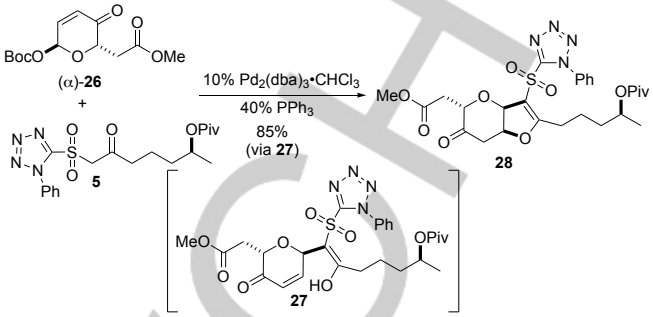


Reagents and conditions: (a) NaH, $CO(OMe)_2$, THF, 50 °C, 73%; (b) HCOONa, cetyltrimethylammonium bromide, Noyori *(S,S)*, rt, 85%; (c) NBS,$NaHCO_3$, $NaOAc{\bullet}3H_2O$, THF/H_2O, 0 °C, 80%; (d) DMAP, $(Boc)_2O$, CH_2Cl_2, –78 °C, 71%. DMAP = 4-Dimethylaminopyridine, $(Boc)_2O$ = Di-*t*-butyl dicarbonate

Scheme 5. Synthesis of Pd-pyranone donor α-enone **26**

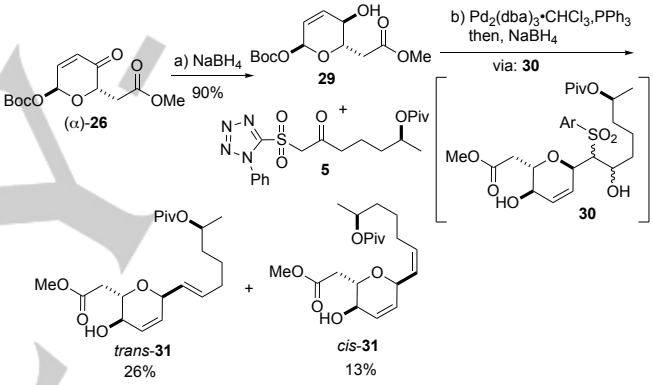
We next looked to explore the fragment coupling of **5** and α-enone **26** via a catalytic Pd-π-allyl intermediate (Scheme 6). Our previous experiences with the Pd-catalyzed glycosylation of pyranones involved mostly oxygen[19] and nitrogen nucleophiles.[20] These catalytic Pd-glycosylation require a Pd-π-allyl intermediate that can be generated form pyranones like **26** by its exposure to a catalytic amount of $Pd(PPh_3)_2$ mixture created from a 1:2 ratio of a Pd to phosphine mixture of 10% $Pd_2(dba)_3{\bullet}CHCl_3$ and 40% PPh_3.[19,20] When a 1:1 mixture of **5** and **26** was exposed to our usually "$Pd(PPh_3)_2$" catalyst system, an excellent yield of a bicyclic coupling product **28** was formed, which lacked the vinyl protons in the ^1H NMR that one would associate with the desired product **27**. Presumably the dihydrofuran ring in **28** was formed from a base catalyzed 1,4-addition of the enol in **27**. Unfortunately, despite our best efforts to carefully monitor the reaction, we could not find any conditions that produced **27**. Similarly, we did not detect the formation of **27** via β-elimination upon the treatment of **28** with various bases.

We next looked to prevent the unwanted 1,4-addition by removing the α-enone in **26** (Scheme 7). This was most easily accomplished by reducing the ketone in **26** under the Luche conditions ($NaBH_4/CeCl_3$, 90% yield) to give allylic alcohol **29** as a single diastereomer. When a 1:1 mixture of pyran **29** and β-keto-sulfone **5** was exposed to the same Pd(0) conditions as before gave a coupling product, presumably compound **30**, that was difficult to isolate. When the crude product was exposed to $NaBH_4$/MeOH, a 2:1 mixture of alkene stereoisomers was isolated in a 39% yield. The trans-alkene isomer *trans*-**31**, which is a protected 4-*epi*-seco-aspergillide-C, could be isolated from this mixture by silica chromatography in a 26% yield. The alkene stereochemistry of *trans*-**31** was confirmed by ^1H NMR with a coupling constant between the hydrogens at *C*-8 and *C*-9 (15.6 Hz). A similar coupling constant analysis of the ^1H NMR for the minor isomer *cis*-**31** revealed values consistent with a *cis*-alkene (10.4 Hz).



Reagents and conditions: $Pd_2(dba)_3{\bullet}CHCl_3$ (10 mol%), PPh_3 (40 mol%), CH_2Cl_2, 0 °C, 85%. dba = dibenzylideneacetone

Scheme 6. Pd-catalyzed fragment coupling/annulation



Reagents and conditions: (a) $NaBH_4$, $CeCl_3$, CH_2Cl_2, –78 °C, 90%; (b) $Pd_2(dba)_3{\bullet}CHCl_3$ (10 mol%), PPh_3 (40 mol%), CH_2Cl_2, 0°C, then $NaBH_4$, MeOH, –78 °C. *trans*-**31** 26%, *cis*-**31** 13%. dba = dibenzylideneacetone

Scheme 7. Synthesis of a protected 4-*epi*-seco-aspergillide-C, *trans*-**31**

Conclusion

In conclusion, a convergent asymmetric synthesis of a protected seco-4-*epi*-aspergillide-C *trans*-**31** has been achieved in twelve total steps (7 longest linear steps) from achiral starting materials, furan **6** and ynone **9**. The route featured a novel use of β-keto-sulfone **5** as formal "alkene anion" Pd-π-allyl-nucleophile in a convergent coupling reaction that brings together the two key fragments for seco-aspergillide-C. The asymmetry of the two fragments was introduced with a Noyori hydrogen transfer reaction of achiral acetylfuran **6** and ynone **9**. Further efforts to develop this chemistry for complete total synthesis are ongoing and will be reported in due course.

Supporting information summary

General methods, experimental procedures, and $^1H/^{13}C$ NMR spectra can be found in supporting information.

Acknowledgements

This research was funded by NIH (AI142040 and AI154860) and NSF (CHE-2102649). Acknowledgment is made to the Donors of the American Chemical Society Petroleum Research Fund (PRF#58838-UNI1) for support of this research.

Keywords: aspergillide-C •β-ketosulfone reductive elimination • *C*-glycosylation • De novo asymmetric synthesis • Noyori reduction • Pd-catalyzed allylation

[1] K. Kito; R. Ookura, S. Yoshida, M. Namikoshi, T. Ooi, T. Kusumi, *Org. Lett.* **2008**, *10*, 225–228

[2] For a review of the syntheses of Aspergillide A/B/C, see: (a) T. Nagasawa, S. Kuwahara, *Heterocycles*., **2012**, *85*, 587-613.

[3] For a synthesis of Aspergillide A/B, see: (a) F. Haruhiko, H. Yamaguchi, M. Sasaki, *Org. Lett.*, **2010**, *12*, 1848-1851. (b) M. Kanematsu, M. Yoshida, K. Shishido, *Angew. Chem. Int. Ed*. **2011**, *50*, 2618 –2620.

[4] For a synthesis of Aspergillide A, see: J. B. Mateus-Ruiz, A. Cordero-Vargas, *J. Org. Chem*. **2019**, *84*, 11848−11855.

[5] For a synthesis of Aspergillide B, see: a) J. Liu, K. Xu, J. He, L. Zhang, X. Pan, X. She, *J. Org. Chem*. **2009**, *74*, 5063–5066. b) Y. Sridhar, P. Srihari, *Eur. J. Org. Chem*. **2013**, 578–587. c) B. M. Trost, M. J. Bartlett, *Org. Lett.*, **2012**, *14*, 1322-1325. d) S. M. Hande, J. Uenishi, *Tetrahedron Lett*. **2009**, *50*, 189–192

[6] For a synthesis of Aspergillide C, see: a) P. Srihari, N. H. Krishna, Y. Sridhar, A. Kamal Beilstein, *J. Org. Chem*. **2014**, *10*, 3122–3126. b) P. Srihari, Y. Sridhar, *Eur. J. Org. Chem*. **2011**, 6690–6697. c) J. D. Panarese, S. P. Waters, *Org. Lett*., **2009**, *11*, 5086-5088. d) T. Nagasawa, S. Kuwahara, *Org. Lett*., **2009**, *11*, 761-764. e) H. Kobayashi, M. Kanematsu, M. Yoshida, K. Shishido, *Chem. Commun*., **2011**, *47*, 7440–7442. f) M. Kanematsu, M. Yoshida, K. Shishido, *Tetrahedron Lett*. **2011**, *52*, 1372–1374.

[7] For an approach to Aspergillide B, see: (a) K. Bhavani, E. GyanChander, S. Das, J. S. Yadav, *ChemistrySelect* **2018**, *3*, 3391-3393.

[8] M. Nielsen, C. B. Jacobsen, M.W. Paixao, N. Holub, K. Jorgensen, *J. Am. Chem. Soc*. **2009**, *131*, 10581-10586

[9] a) H.-Y. L. Wang, B. Wu, Q. Zhang, Y. Rojanasakul, G. A. O'Doherty, *ACS Med. Chem. Lett.* **2011**, 2, 259-263. b) H.-Y. L. Wang, Y. Rojanasakul, G. A. O'Doherty, *ACS Med. Chem. Lett*. **2011**, 2, 264-269. c) A. Iyer, M. Zhou, N. Azad, H. Elbaz, L. Wang, D. K. Rogalsky, Y. Rojanasakul, G. A. O'Doherty, J. M. Langenhan, *ACS Med. Chem. Lett*. **2010**, *1*, 326-330. d) H.-Y. L. Wang, W. Xin, M. Zhou, T. A. Stueckle, Y. Rojanasakul, G. A. O'Doherty, *ACS Med. Chem. Lett*. **2011**, *2*, 73-78. e) C. M. Goins, T. D. Sudasinghe, X. Liu, Y. Wang, G. A. O'Doherty, D. R. Ronning, *Biochemistry*, **2018**, *57*, 2383-2393. f) X. Liu, Y. Wang, R. I. Duclos, G. A. O'Doherty, *ACS Med. Chem. Lett*. **2018**, *9*, 274-278. g) X. Liu, Y. Wang, G. A. O'Doherty, *Asian J. O. C*. **2015**, *4*, 994-1009. h) M. Mulzer, B. Tiegs, Y. Wang, G. W. Coates, G. A. O'Doherty, *J. Am. Chem. Soc*. **2014**, *136*, 10814-10820.

[10] a) K. F. Avocetien, J. J. Li, X. Liu, Y. Wang, Y. Xing, G. A. O'Doherty, *Org. Lett.* **2016**, *18*, 4970–4973. b) Y. Xing, J. H. Penn and G. A. O'Doherty, *Synthesis*, **2009**, 2847-2854. c) Y. Xing and G. A. O'Doherty, *Org. Lett*. **2009**, *11*, 1107–1110. d) M. Li and G. A. O'Doherty, *Org. Lett*. **2006**, *8*, 6087-6090. e) K. Avocetien, Y. Li, G. A. O'Doherty, in *Modern Alkyne Chemistry – Catalytic and Atom-Economic Transformations*, (Eds.: B. M. Trost, C.-J. Li) Wiley-VCH Verlag GmbH & Co. KG, Weinheim, **2014**, pp. 365-393.

[11] The enantiomeric purity of ynols **19** and **20** were made by comparison of optical rotation data (ref. 5e) and by the observation of a single diastereomer in the coupling of downstream product **5** with both (α)-**26** and **29**.

[12] C. A. Brown, A. Yamashita. *J. Am. Chem. Soc*. **1975**, *97*, 4, 891-892

[13] W. Wang, J. Jasinski, G. B. Hammond, B. Xu. *Angew. Chem. Int. Ed*. **2010**, *49*, 7247 –7252

[14] a) R. Noyori and T. Ohkuma, *Angew. Chem. Int. Ed*., **2001**, *40*, 40-73. b) R. Noyori, M. Yamakawa and S. Hashiguchi, *J. Org. Chem*., **2001**, *66*, 7931-7944. c) Li, M., Scott, J. G., O'Doherty, G. A. *Tetrahedron Lett*. **2004**, 45, 1005-1009.

[15] An Achmatowicz reaction is the oxidative rearrangement of furfuryl alcohols to 2-substituted 6-hydroxy-2H-pyran-3(6H)-ones, see: (a) O. Achmatowicz, R. Bielski, C*arbohydr. Res*. **1977**, *55*, 165-176. For its use in carbohydrate synthesis see: (b) D. Balachari, G. A. O'Doherty, *Org. Lett*. **2000**, *2*, 863-866. (c) D. Balachari, G. A. O'Doherty, *Org. Lett*. **2000**, *2*, 4033-4036.

[16] K. R. Francisco, Y. Li, B. Lindquist-Kleissler, J. Zheng, Y. Xing, G. A. O'Doherty, *J. CO2 Utilization*. **2021**, *54*, 101774.

[17] M. Li, J. G. Scott, G. A. O'Doherty, *Tetrahedron Lett*. **2004**, 45, 1005-1009.

[18] S. O. Bajaj, J. R. Farnsworth, G. A. O'Doherty, *Org. Synth.* **2014**, *91*, 338-355.

[19] a) S. O. Bajaj, E. U. Sharif, N. G. Akhmedov, G. A. O'Doherty, *Chem. Sci.* **2014**, *5*, 2230-2234. b) H. Guo and G. A. O'Doherty, *Angew. Chem. Int. Ed*. **2007**, *46*, 5206-5208. c) W. Liu, Q. Chen, J. Liang, Z. Du, K. Zhang, X, Zheng, G. A. O'Doherty, *Synlett*, **2015**, *26*, 1683-1686. d) M. Zhou and G. A. O'Doherty, *Org. Lett*. **2006**, *8*, 4339-4342. e) R. S. Babu and G. A. O'Doherty, *J. Carb. Chem*. **2005**, *24*, 169-177. f) R. S. Babu, M. Zhou and G. A. O'Doherty, *J. Am. Chem. Soc*. **2004**, *126*, 3428 - 3429. g) R. S. Babu, G. A. O'Doherty, *J. Am. Chem. Soc*. **2003**, *125*, 12406-12407. h) R. S. Babu, Q. Chen, S.-W. Kang, M. Zhou, M., G. A. O'Doherty, *J. Am. Chem. Soc*. **2012**, *134*, 11952-11955.

[20] S. R. Guppi, M. Zhou and G. A. O'Doherty, *Org. Lett*. **2006**, *8*, 293-296.

A Table of Contents entry:

A convergent de novo asymmetric synthesis of a protected seco-acid precursor to the marine natural product aspergillide-C has been developed. A Pd-catalyzed *C*-glycosylation was used to diastereoselectivley couple the two key chiral fragments. The two fragments were prepared asymmetrically by two distinct asymmetric Noyori transfer hydrogenation of an achiral acylfuran and ynone.