Blackham, E. E., & Booker-Milburn, K. (2017). A Short Synthesis of (±)-3-Demethoxyerythratidinone by Ligand Controlled Selective Heck Cyclization of Equilibrating Enamines. *Angewandte Chemie - International Edition*, 56(23), 6613-6616. https://doi.org/10.1002/anie.201701775
A Short Synthesis of (±)-3-Demethoxyerythratidinone by Ligand-Controlled Selective Heck Cyclization of Equilibrating Enamines

Emma E. Blackham and Kevin I. Booker-Milburn*

Abstract: A short, 5-step total synthesis of (±)-3-demethoxyerythratidinone from a simple pyrrole derivative is described. Features include the formation of gram quantities of a key tricyclic aziridine from a challenging photochemical cascade reaction through the use of flow photochemistry. The final step involved a highly unusual Heck cyclization whereby ligand control enabled efficient formation of the natural product in 69% yield from the minor isomer present in an equilibrating mixture of labile enamines.

The alkaloid (±)-3-demethoxyerythratidinone 1 is one of over 100 natural products produced by the Erythrina genus of flowering plants.[1] The Erythrina alkaloids display a broad range of pharmacological activities including hypotensive, sedative, neuromuscular blocking, CNS depressing and curare-like activities. The key structural feature of this family is the tetracyclic tetrahydroisoquinoline core. Since the first total synthesis of 1 by Tsuda in 1984,[2] this tetracyclic alkaloid has been used by others in order to demonstrate the utility of various synthetic methodologies.[3] A very elegant synthesis was recently reported by Reisman, where chiral sulfanyl imine chemistry was used to control the stereocchemistry of the key quaternary center,[3d] giving (±)-3-demethoxyerythratidinone in just six steps overall (Figure 1).

Individually both photochemical and Pd-catalyzed cross-coupling methodologies have been shown to be powerful techniques in organic synthesis as well as valuable tools in the synthesis of complex molecular architectures.[4] We have previously reported the photochemical transformation of simple N-butyl-substituted pyrroles into complex tricyclic aziridines 2.[5] We recently demonstrated that these strained photochemical products undergo a range of thermal and Pd-catalyzed ring-opening/annulation reactions to produce a broad range of fused polyheterocycles, in just two steps from simple pyrroles (Scheme 1).[6] We were therefore keen to exploit the functionality and inherent strain in these aziridines as part of an alkaloid synthesis, in particular the aziridine carboxylates 3. Herein we report a short total synthesis of (±)-1 utilizing a highly unusual and selective, ligand controlled intramolecular Heck-reaction onto one of a pair of equilibrating enamine intermediates.

Our initial strategy to 1 (Scheme 1) involved aryl cyclization onto the iminium ion 4 which itself would be generated by in situ decarboxylation of the amino acid 5.[7] Although iminium ion cyclizations are one of the most frequently used approaches to such alkaloids,[8] these have usually involved the intermediary of N-acyliminium ions.[9] The requisite amino-acid 5 should be obtained by Pd0-catalyzed acetate ring-opening of the aziridine 3 followed by N-alkylation with the iodide 6.

Irradiation of pyrrole 7 (254 nm) gave the aziridine (±)-8 in a 39% yield (Scheme 2). As before, we found that this two-
These are not the final page numbers!
Table 1: Optimization of an intramolecular Heck reaction via equilibrating enamine isomers and the effect of phosphorous ligands.

| Entry | Catalyst | Ligand | Solvent | (±)-17 [%] | (±)-1 [%]|[a] |
|-------|----------|--------|---------|------------|---------|-----|
| 1[b]  | Pd(dba)3 | PPh3   | DMF     | 65         | 0       |     |
| 2     | Pd(OAc)2 | PPh3   | PhMe    | 56         | 28      |     |
| 3     | Pd(OAc)2 | P(OPh)1| PhMe    | 62         | 4       |     |
| 4     | Pd(OAc)2 | P(4-MeOC6H4)2 | PhMe | 13 | 53 |     |
| 5     | Pd(OAc)2 | (Cy)2  | PhMe    | <10        | 69      |     |
| 6     | Pd(OAc)2 | P(4Bu)3 | PhMe    | 8          | 3       |     |
| 7     | Pd(OAc)2 | (−)-DIOP| PhMe    | 55         | 40[e]   |     |
| 8     | Pd(OAc)2 | (R)-Pr-PHOX | PhMe | 30 | 32[d] |     |

[a] 1 equiv of TBAI. [b] Isolated yields. [c] 25 % ee in favor of (−)-1. [d] 38% ee in favor of (+)-1.

isolated yield. Under these conditions it was likely that Heck cyclization of 19 to (±)-1 was occurring to a significant degree.

This raised the attractive prospect of modifying the reaction conditions such that (±)-1 could be produced as the sole product from the minor component (19) by in situ equilibration of this enamine mixture, thus considerably shortening the overall synthesis of this natural product. We postulated that varying the Pd ligand might affect reaction selectivity and so a brief survey was undertaken (Table 1).

Use of triphenylphosphite had the opposite effect giving 62% (±)-17 with only 4% (±)-1 (entry 3). Employing the more electron-rich tris(p-methoxyphenyl) phosphine as a ligand, however, favored formation of (±)-1 (53%) over (±)-17 (13%) (entry 4). The most consistent results were obtained with the alkyl phosphine ligand (Cy)3P which gave 69% isolated yield of 1 and just 10% of the isomer (±)-17 (entry 5) in a single telescoped sequence from the ester (±)-16. This optimized result concluded a 5-step synthesis of (±)-1 in 15% overall yield from pyrrole 7 (Scheme 2).

It is clear that electron-rich phosphines (entries 4 and 5) likely favor the formation of (±)-1 by cyclization of the organopalladium-enamine isomer 21. Conversely, comparatively electron poor ligands (entries 2 and 3) likely favor cyclization to (±)-17 via the isomer (±)-20. It is possible that L2HΠPd from β-hydride elimination may serve as a convenient catalyst for the isomerization of (±)-18 to 19 and different ligands will affect the reactivity of such a catalyst e.g. reductive elimination vs. enamine isomerization. Waldmann previously observed isomerized products from Heck cyclization onto dihydro-4-pyridones (enaminones) and attributed these to isomerization of initially formed organo-palladiono-enamine via α,ω-o-allyl rearrangement. In our case the same reaction conditions (Table 1, entry 1) lead only to (±)-17 and so it is likely that a pathway involving isomerization of (±)-18 and 19 is plausible.

As 19 is achiral then this opened up the possibility of effecting an asymmetric synthesis of (+)-1 directly from the mixture of enamines. After screening a range of chiral ligands it became clear that most resulted in a mixture of (±)-17 and 1 with little ee observed for the latter (see the Supporting Information). Use of (−)-DIOP gave 55% yield of (±)-17 and 40% of 1 with an ee of 25% in favor of (−)-1 (Table 1, entry 7). (R)-Pr-PHOX (Table 1, entry 8) gave a 32% isolated yield of 1 with an ee of 38% in favor of the natural enantiomer (+)-1. Attempts to increase this by use of additives (e.g. Ag salts) resulted in inferior results or inhibition of reaction.

In conclusion, we have developed a short 5-step sequence to (±)-3-demethoxyerythratidinone in 15% overall yield from the simple pyrrole carboxylate 7. Notable features include the use of a powerful two-photon cycloaddition–rearrangement reaction to provide a reactive aziridine 8, the key intermediate of the synthesis. This was produced in gram quantities using flow-photochemistry, which would have been very difficult to achieve in batch due to the high dilution and irradiation times required. This study also uncovered a highly unusual and selective, ligand-controlled intramolecular Heck reaction. By use of electron rich phosphines (±)-3-demethoxyerythratidinone (1) was formed as the major product from Heck cyclization onto the minor component of a pair of enamine isomers. Use of electron poor phosphate ligands gave an isomer of the natural product by cyclization onto the major enamine isomer in the mixture. The generality of such a switching process and the mechanistic understanding merits further investigation. Use of chiral ligands for the asymmetric synthesis of (+)-1 yielded mixed results; up to 38% ee was observed in favor of (+)-1 but at the expense of product selectivity.

Acknowledgements

We thank the EPSRC Bristol Chemical Synthesis Doctoral Training Centre (EP/G036764/1) and the University of Bristol for PhD studentship funding (E.E.B.) as well as Dr. John Bower for helpful discussion.

Conflict of interest

The authors declare no conflict of interest.
Keywords: cycloaddition · Heck reaction · ligands · photochemistry · total synthesis

[1] A. F. Parsons, M. J. Palframan in The Alkaloids: Chemistry and Biology, Vol. 68 (Ed.: A. C. Geoffrey), Academic Press, New York, 2010, pp. 39–81.

[2] Y. Tsuda, A. Nakai, K. Ito, F. Suzuki, M. Haruna, Heterocycles 1984, 22, 1817.

[3] a) F. Zhang, N. S. Simpkins, C. Wilson, Tetrahedron Lett. 2007, 48, 5942–5947; b) S. T. Heller, T. Kiho, A. R. H. Narayan, R. Sarpong, Angew. Chem. Int. Ed. 2013, 52, 11129; Angew. Chem. 2013, 125, 11335; c) H. T. Luu, S. Wiesler, G. Frey, J. Streiff, Org. Lett. 2015, 17, 2478; d) K. V. Chung, R. Navarro, S. E. Reisman, Chem. Sci. 2011, 2, 1086; e) R. Xu, Q. Gu, W. Wu, Z. Zhao, S. You, J. Am. Chem. Soc. 2014, 136, 15469; f) J. M. Joo, R. A. David, Y. Yuan, C. Lee, Org. Lett. 2010, 12, 5704; g) M. Paladino, J. Zaitman, M. A. Ciufofini, Org. Lett. 2015, 17, 3422.

[4] a) T. Bach, J. P. Hehna, Angew. Chem. Int. Ed. 2011, 50, 1000; Angew. Chem. 2011, 123, 1032; b) K. C. Nicolaou, P. G. Bulger, D. Sarlah, Angew. Chem. Int. Ed. 2005, 44, 4442; Angew. Chem. 2005, 117, 4516; c) M. D. Karkas, J. A. Porco, C. R. J. Stephenson, Chem. Rev. 2016, 116, 9683; d) G. Zeni, R. C. Larock, Chem. Rev. 2006, 106, 4644; e) J. Y. Lee, Y. S. Lee, B. Y. Chung, H. Park, J. Am. Chem. Soc. 2006, 128, 11611; f) K. V. Chung, R. Navarro, S. E. Reisman, J. Am. Chem. Soc. 2011, 133, 13087.

[5] K. G. Maskill, J. P. Knowles, L. D. Elliott, R. W. Alder, K. I. Booker-Milburn, Angew. Chem. Int. Ed. 2013, 52, 1499; Angew. Chem. 2013, 125, 1539.

[6] a) E. E. Blackham, J. P. Knowles, J. Burgess, K. I. Booker-Milburn, Chem. Sci. 2016, 7, 2302; b) J. P. Knowles, K. I. Booker-Milburn, Chem. Eur. J. 2016, 22, 11429.

[7] R. T. Dean, H. C. Padgett, H. Rapoport, J. Am. Chem. Soc. 1976, 98, 7448.

[8] a) A. Padwa, Q. Wang, J. Org. Chem. 2006, 71, 7391; b) Q. Wang, A. Padwa, Org. Lett. 2006, 8, 601; c) S. Gao, Y. Q. Tu, X. Hu, S. Wang, R. Hua, Y. Jiang, Y. Zhao, X. Fan, S. Zhang, Org. Lett. 2006, 8, 2373; d) Y. Tsuda, Y. Sakai, A. Nakai, M. Kaneko, Y. Ishiguro, K. Isobe, J. Taga, T. Sano, Chem. Pharm. Bull. 1990, 38, 1462; e) H. Ishibashi, T. Sato, M. Takahashi, M. Hayashi, K. Ishikawa, M. Ikeda, Chem. Pharm. Bull. 1990, 38, 907; f) J. Cassayre, B. Quiel-Sire, B. J. Sauenier, S. Z. Zard, Tetrahedron Lett. 1998, 39, 8995; g) S. Chikaoaka, A. Toyao, O. Ogasawara, O. Tamura, H. Ishibashi, J. Org. Chem. 2003, 68, 312; h) F. Zhang, N. S. Simpkins, C. Wilson, Tetrahedron Lett. 2007, 48, 5942; i) J. Y. Lee, Y. S. Lee, B. Y. Chung, H. Park, Tetrahedron 1997, 53, 2449.

[9] H. H. Wasserman, R. M. Amici, J. Org. Chem. 1989, 54, 5843.

[10] L. D. Elliott, J. P. Knowles, P. J. Koovits, K. G. Maskill, M. J. Ralph, G. Lejeune, M. Eberle, M. B. Berry, K. I. Booker-Milburn, Chem. Eur. J. 2014, 20, 15226.

[11] B. M. Trost, T. R. Verhoeven, J. Org. Chem. 1976, 41, 3215.

[12] S. F. Martin, Acc. Chem. Res. 2002, 35, 895.

[13] B. Belleau, Can. J. Chem. 1957, 35, 651.

[14] A Heck-type cyclization has previously been employed in a low yielding synthesis of 17, a non-natural isomer of 1.

[15] An examine-Heck approach to (±)-2-epi-erythrinitol was reported: a) J. H. Rigby, C. Deur, M. J. Heeg, Tetrahedron Lett. 1999, 40, 6887; b) J. H. Rigby, R. C. Hughes, M. J. Heeg, J. Am. Chem. Soc. 1995, 117, 7834.

[16] S. Kirschbaum, H. Waldmann, Tetrahedron Lett. 1997, 38, 2829.

[17] Y. Onozaki, N. Kurono, H. Senboku, M. Tokuda, K. Orito, J. Org. Chem. 2009, 74, 5486.

[18] C. H. Tolman, J. Am. Chem. Soc. 1970, 92, 2953.

[19] a) D. Gauthier, A. T. Lindhardt, E. P. J. Olsen, J. Overgaard, T. Skrydstrup, J. Am. Chem. Soc. 2010, 132, 7998; b) E. Larionov, H. Li, C. Mazet, G. K. Le Anh Tuan, Bull. Korean Chem. Soc. 2010, 31, 1800.

[20] An examine-Heck approach to (±)-2-epi-erythrinitol was reported: a) J. H. Rigby, C. Deur, M. J. Heeg, Tetrahedron Lett. 1999, 40, 6887; b) J. H. Rigby, R. C. Hughes, M. J. Heeg, J. Am. Chem. Soc. 1995, 117, 7834.
A Short Synthesis of (±)-3-Demethoxyerythratidinone by Ligand-Controlled Selective Heck Cyclization of Equilibrating Enamines

Five steps to success: A short total synthesis of (±)-3-demethoxyerythratidinone (1) has been completed using a combination of photochemistry and Pd-catalyzed Heck cyclization. A key feature was the ability to control the outcome of the Heck cyclization onto an equilibrating mixture of labile enamines by ligand choice.