EurJOC
European Journal of Organic Chemistry

Communication
doi.org/10.1002/ejoc.202001046

Polyketide Synthesis | *Very Important Paper* |

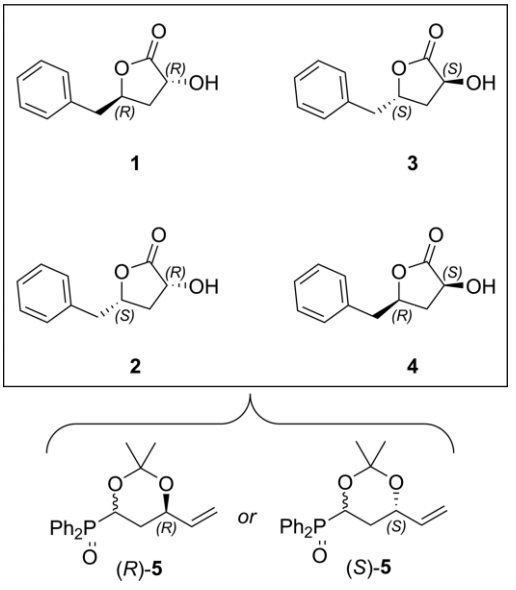
Stereocontrolled Synthesis of Harzialactone A and Its Three Stereoisomers by Use of Standardized Polyketide Building Blocks

Frederic Ballaschk,[a] Yasemin Özkaya,[a] and Stefan F. Kirsch*[a]

Abstract: In this paper, we present a short and convenient synthesis of the natural product Harzialactone A and its three stereoisomers. In a three-step synthesis starting from cheap and commercially available benzaldehyde, we created the small polyketidic compound with full control over its two stereogenic centers. To this end, we employed a chiral building block previously described by us, introducing the first stereogenic center through a Horner–Wittig reaction. The second stereogenic center was installed via stereocontrolled *syn*- or *anti*-reduction with the corresponding β-hydroxy ketone intermediates. Upon ozonolysis followed by oxidation the natural product and its stereovariants were produced with excellent enantio- and diastereopurities.

The term "polyketides" encompasses a wide range of naturally occurring compounds with a broad structural diversity that ranges from very simple molecules, such as 6-methyl salicylic acid[1] or Harzialactone A[2] (**1**, Scheme 1), to the highly complex structures of, for example, Butyrolactol A[3] or Discodermolide.[4] With their striking array of biological properties, polyketides are prime synthetic targets for chemists, and the 1,3-polyol motif is a distinguishing structural feature for many of them. Nature creates this characteristic unit via iterative polyketide synthases that linearly assemble polyketide intermediates from smaller malonyl-CoA or methylmalonyl-CoA units, involving subsequent chain alterations.[1,5]

Mimicking the biosynthetic pathway toward natural polyketides is a challenging but sublime task for synthetic chemists since nature's pure efficacy in forming carbon–carbon bonds and performing stereoselective carbonyl reductions and regioselective dehydratizations is simply unmatched. In the course of time, a multitude of elegant but individual solutions were developed to accomplish the formation of specific molecules with 1,3-polyols,[6,7] utilizing chiral ligands or catalysts,[8] or by starting with enantiomerically pure building blocks (i.e., chiral pool).[9] General strategies that adopt nature's iterative assembly of simple building blocks in natural product synthesis are less frequent. This shortcoming is even more surprising since



Scheme 1. Structure of (+)-Harzialactone A (**1**) and its stereoisomers (**2**–**4**).

most natural polyketides consist of molecules with an inherent modularity, and thus they may be efficiently synthesized by the repeated succession of similar reaction sequences.[7,10]

A classic in the bioinspired iterative synthesis of 1,3-polyol arrays is the repetitive allylation of aldehydes (consisting of only three steps including stereoselective allylation with chiral reagents, protection and oxidative aldehyde regeneration).[11] Particularly, the use of catalytic allylation methods is attractive,[12] and the arguably most advanced sequence is the one developed by Krische and co-workers[13] where Iridium-catalyzed carbonyl allylation was accomplished from both the alcohol or aldehyde oxidation level.[14] Other powerful concepts include the iterative stereoselective alkylation of cyanohydrin aceton-

[a] *F. Ballaschk, Y. Özkaya, Prof. Dr. S. F. Kirsch*
Organic Chemistry, Bergische Universität Wuppertal
Gaußstraße 20, 42119 Wuppertal, Germany
E-mail: sfkirsch@uni-wuppertal.de
https://www.oc.uni-wuppertal.de/prof-dr-stefan-f-kirsch.html
Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.202001046.

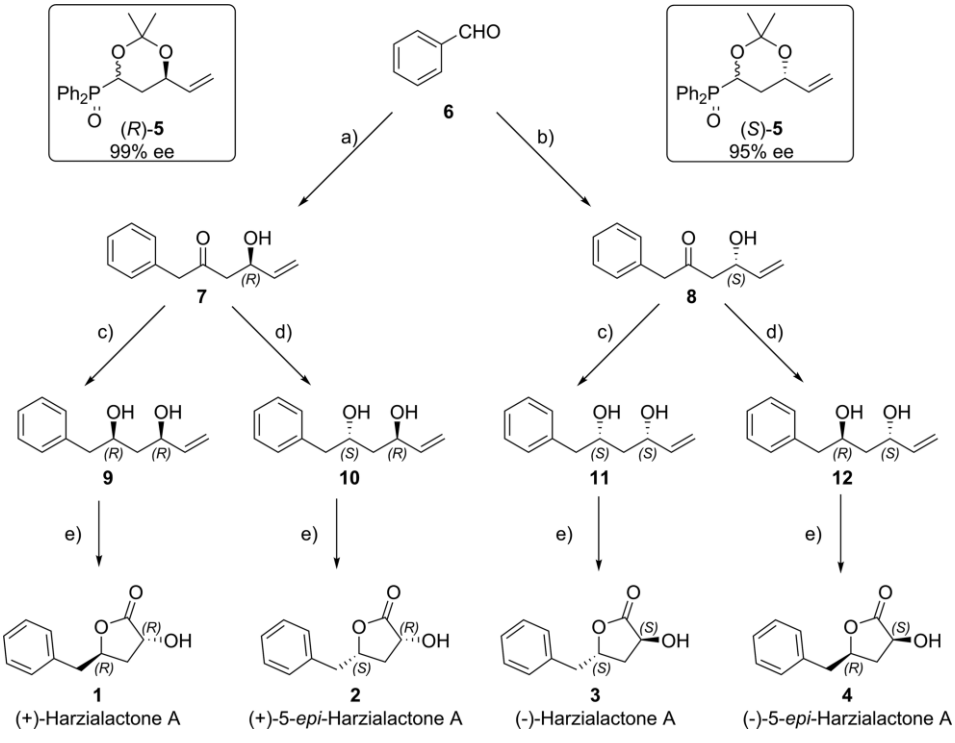
Communication
doi.org/10.1002/ejoc.202001046

ides,[15] or rely on the repetitive use of Aldol chemistry.[16] Moreover, iterative syntheses based on asymmetric epoxidations and subsequent reductive epoxide-openings were successfully utilized.[17]

We became involved in the field when embedding the asymmetric Overman rearrangement[18] as key step of a iterative sequence toward 1,3-polyols, which we then applied for several polyketide syntheses.[19] However, the multistep character of our repetitive sequence rendered this concept unattractive for the synthesis of more complex structures. Therefore, we then focused on the development of a chiral building block that is easily attached onto a growing carbon chain. In order to become effective as a standardized polyketide building block, its defining feature shall be that it possesses a pre-installed stereogenic secondary alcohol prone for stereocontrolled follow-up chemistry, and no challenging enantioselective reaction will be involved in the build-up of the polyketidic chain. To this end, we developed the acetonide **5** shown in Scheme 1, a reagent that is readily available in both enantiomeric forms[20] and thus became the ideal building block, in our hands: we already demonstrated its simple use in a short four step iteration sequence (consisting of Horner–Wittig reaction, reduction, protection and ozonolysis).[21] We now present the total synthesis of the polyketidic Harzialactone A and its three diastereomers using this standardized 1,3-diol precursor. The target compounds were obtained in high overall yields, in only three synthetic steps when starting with enantiomerically pure **5**.

Harzialactone A was first isolated by Numata and co-workers from a strain of *Trichoderma harzianum* OUPS-N1115, among several other secondary metabolites and lactones in 1998.[2] It was found to have potential antitumor and cytotoxic activity against cultured P388 cells[2] as well as leishmanicidal activity against *Leishmania amazonensis*.[22] Due to the biological properties, Harzialactone A (and its stereoisomers and derivatives) became an interesting target compound for synthetic endeavors. Numerous groups reported synthetic approaches toward racemic product mixtures[23] or enantioenriched material, starting from readily available carbohydrates[24] and enantiomerically pure epoxides,[25] or by using asymmetric catalysis[26] or kinetic resolution.[27]

We began the synthesis with the connection between building block **5**, the manufacturing of which was described elsewhere,[20] and inexpensive benzaldehyde (**6**), thus installing the first of the two stereogenic centers (Scheme 2). The Horner–Wittig reaction[28] proceeded in good yields without loss of enantiomeric excess: β-hydroxy ketone **7** having the *R*-configuration was obtained with the *R*-configured building block **5** in 71 % yield, upon acidic work-up. Its enantiomer **8** was produced in 83 % yield. The second stereogenic center was created by use of standard methods for the directed reduction: (1) The Narasaka–Prasad reaction[29] gave the corresponding *syn*-1,3-diols **9** and **11** when using diethylmethoxyborane and sodium borohydride. This conversion was successful with excellent diastereomeric ratios of > 99:1 and high yields (98 % for **7** → **9**



Scheme 2. Synthetic pathway for all four stereoisomers. a) i) DIPA (2 equiv.), *n*BuLi (2 equiv.), –78 °C, 15 min; ii) (*R*)-**5** (1 equiv.), –78 °C, 60 min; iii) **6** (3 equiv.), –78 °C to r.t., 90 min; iv) KO*t*Bu (1.3 equiv.), (THF), r.t., 60 min, 71 % b) i) DIPA (1 equiv.), *n*BuLi (1 equiv.), –78 °C, 15 min; ii) (*S*)-**5** (1 equiv.), –78 °C, 60 min; iii) **6** (1.3 equiv.), –78 °C to r.t., 90 min; iv) KO*t*Bu (1.3 equiv.), (THF), r.t., 60 min, 83 % c) i) Et_2BOMe (1.2 equiv.), –78 °C, 20 min; ii) $NaBH_4$ (1.1 equiv.), –78 °C, 2 h; iii) 2 N NaOH (13 equiv.), H_2O_2 (40 equiv.), (THF/methanol), r.t., 60 min; 98 %, *d.r.* > 99:1 (**9**); 93 %, *d.r.* > 99:1 (**11**); d) $Me_4N^+HB(OAc)_3^-$ (5 equiv.), –20 °C, 16 h, (MeCN/AcOH); 92 %, *d.r.* 95:5 (**10**); 92 %, *d.r.* 95:5 (**12**); e) i) O_3, NEt_3 (1 equiv.), (DCM/MeOH), –78 °C, 10 min then Me_2S (7.8 equiv.), –78 °C to r.t., 1.5 h; ii) Ag_2CO_3/Celite (1.2 equiv. or 5 equiv.), (benzene/DMF), reflux, 1 h; 56 % (**1**), 68 % (**2**), 57 % (**3**), 51 % (**4**).

and 93 % for **8** → **11**). (2) The creation of the *anti*-1,3-diols **10** and **12** was realized with the established Evans–Saksena reaction.[30] With tetramethylammonium triacetoxyborohydride at –20 °C, the reduction yielded a high diastereomeric ratio of 95:5 and a good yield of 92 % for **10** (from **7**). In a similar manner, the (*S*)-enantiomer **8** was converted under these conditions to provide the respective *anti*-diol **12** in 92 % yield and 95:5 diastereomeric ratio. The synthesis of all four stereovariants was thus completed. Finally, we chose to generate the lactone through a two-step sequence consisting of a lactol-forming ozonolysis followed by a selective oxidation to produce the desired target compounds **1**–**4**. While the ozonolysis of diols **9**–**12** was unproblematic in all cases, isolation of the corresponding lactols that formed upon cyclization of the primarily generated aldehydes proved difficult and low-yielding. As a result, we decided to directly convert the crude mixtures of olefin ozonolysis into the lactones through oxidation with Fétizon's reagent.[31] Of note, protection of the secondary alcohol was not required under those conditions. Gratifyingly, we were then able to produce the desired natural substance **1** and its three stereoisomers **2**–**4** in yields ranging from 51 % to 68 % over the two steps. Based on spectroscopic data,[2] the synthetic material was identical to natural Harzialactone A, and the optical rotation confirmed the absolute configuration we expected from our synthetic route.

In conclusion, we produced all four stereoisomers of Harzialactone A starting from benzaldehyde in a short three-step synthesis. The creation of all stereogenic centers was fully controlled, by using our standardized chiral building blocks for 1,3-polyol syntheses in combination with established *syn*- or *anti*-reduction protocols. The synthetic route is protective group-free, and only two intermediates were isolated by chromatography on the route from (**6** + **5**) to **1**(or **2,3,4**). We will continue to use building block **5**, and variants thereof, for the synthesis of more complex polyketidic structures.

Acknowledgments

Open access funding enabled and organized by Projekt DEAL.

Keywords: Harzialactone A · 1,3-Polyols · Polyketides · Natural products · Stereoselective synthesis

[1] J. Staunton, K. J. Weissman, *Nat. Prod. Rep.* **2001**, *18*, 380–416.
[2] T. Amagata, Y. Usami, K. Minoura, T. Ito, A. Numata, *J. Antibiot.* **1998**, *51*, 33–40.
[3] C. Kotake, T. Yamasaki, T. Moriyama, M. Shinoda, N. Komiyama, T. Furumai, M. Konishi, T. Oki, *J. Antibiot.* **1992**, *45*, 1442–1450.
[4] S. P. Gunasekera, M. Gunasekera, R. E. Longley, G. K. Schulte, *J. Org. Chem.* **1990**, *55*, 4912–4915.
[5] a) B. Shen, *Curr. Opin. Chem. Biol.* **2003**, *7*, 285–295; b) H. Chen, L. Du, *Appl. Microbiol. Biotechnol.* **2016**, *100*, 541–557; c) M. Cummings, R. Breitling, E. Takano, *FEMS Microbiol. Lett.* **2014**, *351*, 116–125.
[6] a) C. Sperandio, J. Rodriguez, A. Quintard, *Org. Biomol. Chem.* **2020**, *18*, 1025–1035; b) S. E. Bode, M. Wolberg, M. Müller, *Synthesis* **2006**, *2006*, 557–588.
[7] K. Zheng, C. Xie, R. Hong, *Front. Chem.* **2015**, *3*, 32.
[8] a) N. S. Chowdari, D. B. Ramachary, A. Córdova, C. F. Barbas, *Tetrahedron Lett.* **2002**, *43*, 9591–9595; b) A. Córdova, I. Ibrahem, J. Casas, H. Sundén, M. Engqvist, E. Reyes, *Chem. Eur. J.* **2005**, *11*, 4772–4784; c) L. Lin, K. Yamamoto, H. Mitsunuma, Y. Kanzaki, S. Matsunaga, M. Kanai, *J. Am. Chem. Soc.* **2015**, *137*, 15418–15421; d) Y. Shimoda, S. Kotani, M. Sugiura, M. Nakajima, *Chem. Eur. J.* **2011**, *17*, 7992–7995; e) A. Genoni, M. Benaglia, S. Rossi, G. Celentano, *Chirality* **2013**, *25*, 643–647; f) F. Maier, O. Trapp, *Angew. Chem. Int. Ed.* **2014**, *53*, 8756–8760; *Angew. Chem.* **2014**, *126*, 8901.
[9] a) A. B. Smith, S. M. Pitram, A. M. Boldi, M. J. Gaunt, C. Sfouggatakis, W. H. Moser, *J. Am. Chem. Soc.* **2003**, *125*, 14435–14445; b) A. B. Smith, S. M. Pitram, M. J. Fuertes, *Org. Lett.* **2003**, *5*, 2751–2754; c) Y. Mori, Y. Kohchi, M. Suzuki, H. Furukawa, *Chem. Pharm. Bull.* **1992**, *40*, 1934–1936.
[10] D. Mohapatra, P. Krishnarao, E. Bhimireddy, J. Yadav, *Synthesis* **2014**, *46*, 1639–1647.
[11] a) J. García-Fortanet, J. Murga, M. Carda, J. A. Marco, *Org. Lett.* **2003**, *5*, 1447–1449; b) S. BouzBouz, J. Cossy, *Org. Lett.* **2003**, *5*, 1995–1997.
[12] Z. Zhang, S. Aubry, Y. Kishi, *Org. Lett.* **2008**, *10*, 3077–3080.
[13] a) S. B. Han, A. Hassan, I. S. Kim, M. J. Krische, *J. Am. Chem. Soc.* **2010**, *132*, 15559–15561; b) I. S. Kim, M.-Y. Ngai, M. J. Krische, *J. Am. Chem. Soc.* **2008**, *130*, 6340–6341.
[14] A. Hassan, Y. Lu, M. J. Krische, *Org. Lett.* **2009**, *11*, 3112–3115.
[15] S. D. Rychnovsky, G. Griesgraber, *J. Org. Chem.* **1992**, *57*, 1559–1563.
[16] a) B. J. Albert, H. Yamamoto, *Angew. Chem. Int. Ed.* **2010**, *49*, 2747–2749; *Angew. Chem.* **2010**, *122*, 2807; b) B. J. Albert, Y. Yamaoka, H. Yamamoto, *Angew. Chem. Int. Ed.* **2011**, *50*, 2610–2612; *Angew. Chem.* **2011**, *123*, 2658.
[17] a) T. Katsuki, Lee, A. W. M., P. Ma, V. S. Martin, S. Masamune, K. B. Sharpless, D. Tuddenham, F. J. Walker, *J. Org. Chem.* **1982**, *47*, 1373–1378; b) K. C. Nicolaou, R. A. Daines, T. K. Chakraborty, Y. Ogawa, *J. Am. Chem. Soc.* **1987**, *109*, 2821–2822; c) S.-y. Tosaki, Y. Horiuchi, T. Nemoto, T. Ohshima, M. Shibasaki, *Chem. Eur. J.* **2004**, *10*, 1527–1544.
[18] a) S. F. Kirsch, L. E. Overman, N. S. White, *Org. Lett.* **2007**, *9*, 911–913; b) S. F. Kirsch, L. E. Overman, *J. Am. Chem. Soc.* **2005**, *127*, 2866–2867; c) J. S. Cannon, S. F. Kirsch, L. E. Overman, H. F. Sneddon, *J. Am. Chem. Soc.* **2010**, *132*, 15192–15203.
[19] a) S. Kirsch, P. Klahn, H. Menz, *Synthesis* **2011**, *2011*, 3592–3603; b) J. T. Binder, S. F. Kirsch, *Chem. Commun.* **2007**, 4164–4166; c) H. Menz, S. F. Kirsch, *Org. Lett.* **2009**, *11*, 5634–5637.
[20] A. Bredenkamp, Z.-B. Zhu, S. F. Kirsch, *Eur. J. Org. Chem.* **2016**, *2016*, 252–254.
[21] A. Bredenkamp, M. Wegener, S. Hummel, A. P. Häring, S. F. Kirsch, *Chem. Commun.* **2016**, *52*, 1875–1878.
[22] G. H. Braun, H. P. Ramos, C. Candido, B. B. Ana, C. Pedroso, N. Rita, K. A. Siqueira, M. A. Soares, G. M. Dias, L. G. Magalhães, S. R. Ambrósio, A. H. Januário, et al., *Nat. Prod. Res.* **2019**, 1–4.
[23] M. Sá, M. Peterle, M. Marques, *J. Braz. Chem. Soc.* **2019**, *30*, 1779–1787.
[24] a) H. B. Mereyala, M. Joe, R. R. Gadikota, *Tetrahedron: Asymmetry* **2000**, *11*, 4071–4081; b) V. U. Pawar, S. Ghosh, B. A. Chopade, V. S. Shinde, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7243–7245.
[25] a) G. Sabitha, R. Srinivas, S. K. Das, J. S. Yadav, *Beilstein J. Org. Chem.* **2010**, *6*, 8; b) L. He, S. Zhang, Y. Wu, Y. Li, *Chin. J. Chem.* **2011**, *29*, 2664–2668; c) S. Yamaguchi, T. Matsuo, K. Motokura, A. Miyaji, T. Baba, *Chem. Asian J.* **2016**, *11*, 1731–1737.
[26] a) S. P. Kotkar, G. S. Suryavanshi, A. Sudalai, *Tetrahedron: Asymmetry* **2007**, *18*, 1795–1798; b) D. Kumar, C. Reddy, B. Das, *Synthesis* **2011**, *2011*, 3190–3194.
[27] B. Chen, H.-F. Yin, Z.-S. Wang, J.-H. Xu, *Tetrahedron: Asymmetry* **2010**, *21*, 237–240.
[28] L. Horner, H. Hoffmann, H. G. Wippel, *Chem. Ber.* **1958**, *91*, 61–63.
[29] a) K.-M. Chen, K. G. Gunderson, G. E. Hardtmann, K. Prasad, O. Repic, M. J. Shapiro, *Chem. Lett.* **1987**, *16*, 1923–1926; b) K.-M. Chen, G. E. Hardtmann, K. Prasad, O. Repič, M. J. Shapiro, *Tetrahedron Lett.* **1987**, *28*, 155–158; c) K. Narasaka, H. C. Pai, *Chem. Lett.* **1980**, *9*, 1415–1418; d) K. Narasaka, F.-C. Pai, *Tetrahedron* **1984**, *40*, 2233–2238.
[30] a) D. A. Evans, K. T. Chapman, E. M. Carreira, *J. Am. Chem. Soc.* **1988**, *110*, 3560–3578; b) A. K. Saksena, P. Mangiaracina, *Tetrahedron Lett.* **1983**, *24*, 273–276.
[31] M. Fetizon, V. Balogh, M. Golfier, *J. Org. Chem.* **1971**, *36*, 1339–1341.

Received: July 31, 2020