EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Enantioselective Synthesis of the C23-C33 Aetheramide A Fragment and Its C32-Epimer

Authors: Tibor Peňaška, Petr Koukal, and Martin Kotora

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201701416

Link to VoR: http://dx.doi.org/10.1002/ejoc.201701416

Supported by
ACES Asian Chemical Editorial Society

WILEY-VCH

10.1002/ejoc.201701416

WILEY-VCH

COMMUNICATION

Enantioselective Synthesis of the C23-C33 Aetheramide A Fragment and Its C32-Epimer

Tibor Peňaška[a,b] Petr Koukal,[a] and Martin Kotora*[a]

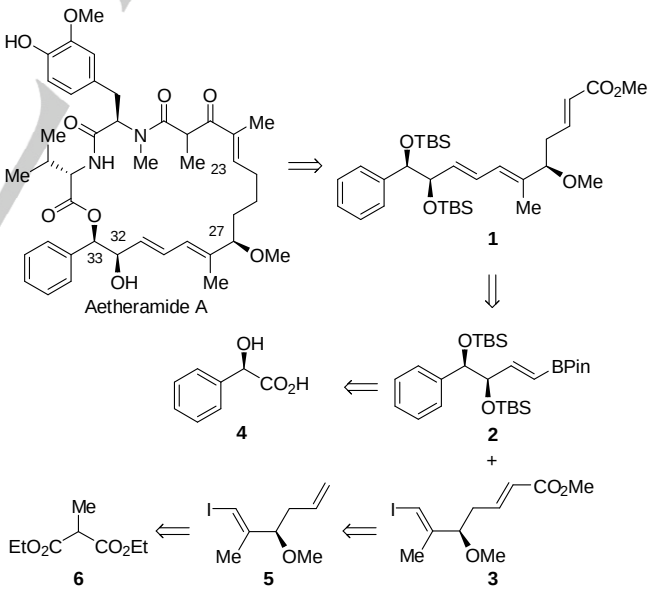
Dedication

Abstract: The key aetheramide A intermediate with natural (*R,R,R*) configuration along with the one having unnatural (*R,S,R*) configuration were synthesized. The syntheses of both stereoisomers were accomplished by using Suzuki coupling of two advanced chiral building blocks: (*R,R*)- and (*R,S*)-vinyl boronates and a (*R*)-iodoalkene. The former was prepared from (*R*)-mandelic acid and the latter by enantioselective allylation of 3-iodoacryl aldehyde.

The research in the area of natural products provides a large palette of novel compounds possessing versatile biological activity which drives development of new drugs. Aetheramides A (Scheme 1) and B are secondary metabolites of novel myxobacteria genus *Aetherobacter rufus* (*Aether* was a god of light in Greek mythology) isolated and characterized by Müller´s group in 2012.[1] Aetheramides are macrocyclic compounds possessing six stereogenic centers, comprising a polyketide moiety and two amino acids. These structurally interesting cyclic depsipeptides show potential anti-HIV activity (IC_{50} = ~15 nM), cytostatic activity against human colon tumor (IC_{50} = 110 nM), and also antifungal activity against *Candida albicans*,[2] which represents over 80% of all forms of human candidosis.[3]

Aetheramides have become an interesting synthetic target, due to their structure and bioactivity. An enantioselective synthesis of a MEM-protected aetheramide A derivative starting from ethyl cinnamate was published by Akasapu et al. in 2014.[4] The same year, a preparation of a polyketide precursor of aetheramides from a chiral furyl carbinol was reported by Prasad et al.[5] Enantioselective total syntheses of aetheramides A and B and other stereoisomers thereof were accomplished by He et al. from an achiral starting material in 15 steps and 5.3% overall yield for aetheramide A and 3.6% for aetheramide B.[6] Still in 2016 He et al. reported ~~a~~ preparation of aetheramides A and B by using a different strategy (15-steps, 4.7% overall yield).[7] Three different approaches were also tested in synthesis of the protected aetheramide by Prasad *et al.* in 2017.[8] The total synthesis of aetheramide A was also accomplished by Kalesse et al. in 2016 (18 steps, 0.24% overall yield). One of the key fragments along its synthesis was ester **1** (the C23-C33 fragment) possessing three stereogenic centers, Its preparation was accomplished in 9 steps starting from ethyl cinnamate.[9] It should be noted that in all syntheses the construction of stereocenters was based on the use of stoichiometric amounts of chiral auxiliaries. A related class of compounds possessing similar structural features like aetheramides are nannocystines.[10]

We envisioned that the key ester **1** could be synthesized from a readily available natural chiral starting material and by enantioselective allylation of an aldehyde (Scheme 1). Moreover, the convergent synthetic approach would also allow synthesis of various diastereoisomers. We presumed that the fragment **1** could be prepared by the Suzuki coupling of chiral building blocks **2** and **3**. The building block **2** was to be formed by diastereoselective ethynylation of (*R*)-mandelic aldehyde prepared from (*R*)-mandelic acid **4**. The second chiral building block **3** was expected to be prepared by cross-metathesis reaction of methyl acrylate and the product of enantioselective catalytic allylation of (*E*)-3-iodomethacryldehyde **5**, which can be prepared from methyl diethylmalonate **6**.[11]



Scheme 1. Retrosynthetic analysis of the C23-C33 Aetheramide A fragment **1**.

The synthesis of vinyl pinacol boronates (*R,R*)- and (*R,S*)-**2** (Scheme 2) started from commercially available (*R*)-mandelic acid **4**. Esterification of **4** with MeOH provided **7** in 88 % yield[12], which was followed by protection of hydroxyl with the TBS group giving rise to **8** in almost quantitative yield (99 %).[13] The next step, reduction of the ester to an aldehyde by using DIBAL[13] furnished

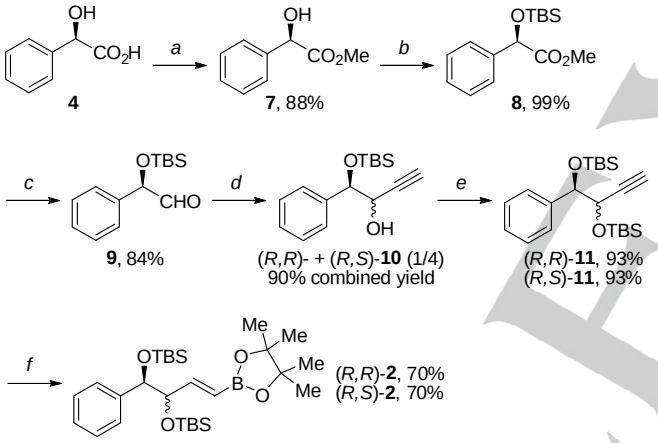
[a] T. Peňaška, P. Koukal, Prof. Dr. M. Kotora
Department of Organic Chemistry
Faculty of Science, Charles University
Hlavova 8, 128 43 Praha 2, Czech Republic
E-mail: kotora@natur.cuni.cz
http://orgchem.natur.cuni.cz/kotora/
[b] A visiting student from Department of Organic Chemistry
Faculty of Natural Sciences, Comenius University in Bratislava,
Mlynská dolina, Ilkovičova 6, SK-84215 Bratislava, Slovakia

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

10.1002/ejoc.201701416

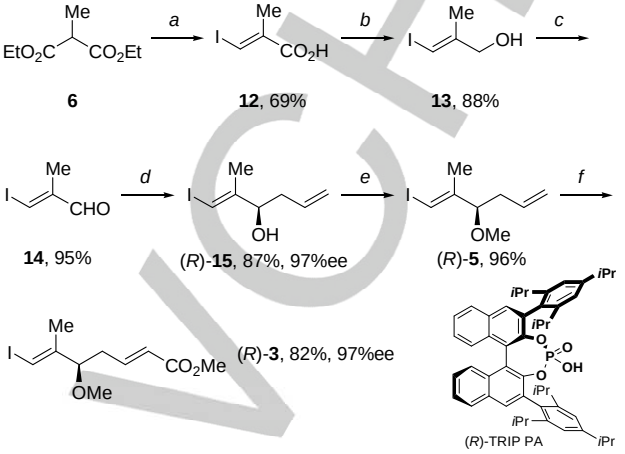
9 in 84% yield. The second stereocenter was generated through nucleophilic addition of ethynylmagnesium chloride to aldehyde **9** giving rise to a 1:4 mixture of (*R,R*)-*syn*- and (*R,S*)-*anti*-**10** in 90% isolated yield. The *syn* and *anti* diastereoisomers were readily separable by column chromatography on silica gel.[14] The preferential formation of (*R,S*)-**10** suggests that the addition was controlled by steric factors and not by chelatation of the magnesium atom to the oxygen atom.

Next, protection of both isomers, (*R,S*)- and (*R,R*)-**10**), with the TBS group furnished the respective alkynes (*R,S*)- and (*R,R*)-**11** in identical 93% isolated yields. Then hydroboration of both alkynes to yield **2** followed. Although this transformation was assumed to be a rather easy step, it proved otherwise. Initially, a simple hydroboration with HBPin was attempted, but, surprisingly, no reaction was observed and the alkyne was recovered intact. After some experimental work (see SI for details), it was found that hydroboration with HBPin catalyzed by $RhCl(CO)(PPh_3)_2$ (2 mol%)[15,16] under microwave irradiation at 100 °C for 1 h provided selectively the desired vinyl boronate **2** (*E/Z* = 99/1) in 70% isolated yield. Thus, vinyl boronates (*R,R*)- and (*R,S*)-**2** were prepared in 6 steps from **4** with the overall yields of 6 and 34%, respectively.



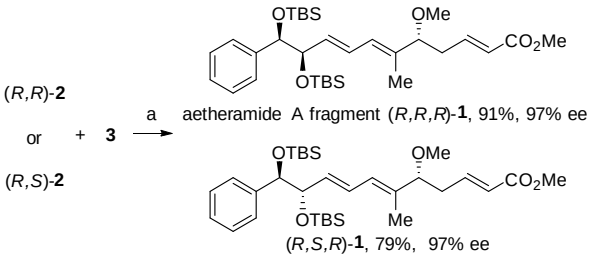
Scheme 2. Preparation of boronic acid esters (*R,R*)- and (*R,S*)-**2**. a) p-toulenesulfonic acid, MeOH, reflux, 12 h; b) TBSCl, imidazole, DMF, 20 °C, 12 h; c) DIBAL, Et_2O, -78 °C, 30 min; d) ethynylmagnesium chloride, THF, 0 °C, 1 h ((*R,R*)-**10** and (*R,S*)-**10** separated in 18 and 72% yields, respectively); e) TBSCl, imidazole, DMF, 20 °C, 12 h; f) HBPin, $Rh(PPh_3)_2(CO)Cl$ (2 mol-%), CH_2Cl_2, 100 °C, MWI, 1 h

The chiral iodoester **3** was also synthesized in six steps (Scheme 3). Methylmalonate **6** was converted in two consecutive steps to carboxylic acid **12** in 69% yield.[17] Reduction of acid **12** with $LiAlH_4$ yielded alcohol **13** in 88% yield.[18] Oxidation with MnO_2 followed and a solution of aldehyde **14** in toluene was obtained after simple filtration of MnO_2. The exact concentration of this stock solution was determined by using ^1H NMR. Then enantioselective allylation of aldehyde **14** with allyl pinacolboronate catalyzed by (*R*)-TRIP-PA was carried out providing iodoalcohol (*R*)-**15** in 87% isolated yield and excellent enantioselectivity of 97% ee.[11] The reaction sequence continued with methylation of the hydroxyl group to yield methyl ether (*R*)-**5** in 96% yield. The subsequent cross-metathesis of (*R*)-**5** with methyl acrylate catalyzed by Grubbs 2nd generation catalyst (2 mol-%) furnished (*R*)-**3** exclusively as *E*-isomer in 82 % yield and 97% ee.[19]



Scheme 3. Preparation of iodoester **3**. a) 1. NaH, Et_2O, reflux, 2 h; 2. CHI_3, Et_2O, 20 °C→reflux, overnight; 3. KOH, EtOH, H_2O, reflux, overnight; b) $LiAlH_4$, Et_2O, 20 °C, 3 h; c) MnO_2, toluene, 35 °C, 24 h; d) allylboronic pinacol ester, (*R*)-TRIP-PA (2.5 mol-%), toluene, -40 °C, 4 days; e) MeI, NaH, THF, 0°C→20 °C, 2 h; f) methylacrylate, Grubbs 2nd generation catalyst (2 mol-%), CuI, Et_2O, reflux, 3 h.

With both synthetic building blocks **2** and **3** in hand, we proceeded with the last step of the synthesis – the coupling affording **1**. Thus the coupling of (*R,R*)-**2** with (*R*)-**3** at 20 °C provided the desired key aetheramide precursor (*R,R,R*)-**1** within 1 hour in excellent 91% isolated yield and 97% ee (Scheme 4). The successful course of the reaction under these mild reaction conditions was enabled by the use of thallium(I) ethoxide as a base (TlOEt is converted to thallium(I) hydroxide by the reaction with water).[20,21] In an analogical manner proceeded coupling of (*R,S*)-**2** and (*R*)-**3** giving rise to the hitherto unknown diastereoisomer (*R,S,R*)-**1** in 79 % isolated yield and 97% ee.[22]



Scheme 4. Preparation of aetheramide A fragment **1**: a) $Pd(PPh_3)_4$ (20 mol-%) EtOTl (1.5 eq), THF/H_2O (3/1), 60 min, 20 °C.

In summary, we accomplished preparation of the key advanced precursor of aetheramide A - (*R,R,R*)-polyketide fragment. It was synthesized from two chiral building blocks that were prepared from simple starting materials in 6 steps, respectively. Its (*R,S,R*)-stereoisomer has also been prepared by

the same method. Since mandelic acid **4** is commercially available in both enantiomeric forms and enantioselective allylation of 2-iodomethacryldehyde catalyzed by chiral TRIP-PAs or *N,N'*-dioxides[10] can provide both enantiomers, the outlined method can, in principle, allow to access all possible enantiomers of **1**.

Experimental Section

For details see SI.

Acknowledgements

Authors gratefully acknowledge financial support from the Czech Science Foundation (P207/11/0587), Tibor Peňaška thanks the National Scholarship Programme of the Slovak Republic.

Keywords: aetheramide • catalysis • enantioselective allylation • hydroboration • Suzuki coupling

[1] R. Garcia, M. Stadler, K. Gemperlein, R. Müller, *Int. J. Syst. Evol. Microbiol.* **2016**, *66*, 928−938.

[2] A. Plaza, R. Garcia, G. Bifulco, J. P. Martinez, S. Hüttel, F. Sasse, A. Mayerhans, M. Stadler, R. Müller, *Org. Lett.* **2012**, *14*, 2854−2857.

[3] Williams, D. W.; Kuriyama, T.; Silva, S.; Malic, S.; Lewis, M. A. O. *Periodontology 2000,* **2011**, *55*, 250−265.

[4] A. K. Ghosh, K. V. Rao, S. Akasapu, *Tetrahedron Lett.* **2014**, *55*, 5191−5194.

[5] O. Revu, K. R. Prasad, *Synlett.* **2014**, *25*, 2887−2890.

[6] N. Qi, S. R. Allu, Z. Wang, Q. Liu, J. Guo, Y. He, *Org. Lett.* **2016**, *18*, 4718−4721.

[7] N. Qi, Z. Wang, S. R. Allu, Q. Liu, J. Guo, Y. He, *J. Org. Chem.* **2016**, *81*, 12466−12471.

[8] O. Revu, K. R. Prasad, *J. Org. Chem.* **2017**, *82*, 438−460.

[9] L. Gerstmann, M. Kalesse, *Chem. Eur. J.* **2016**, *22*, 11210−11212.

[10] For nannocystin characterisation, see: H. Hoffmann, H. Kogler, W. Heyse, H. Matter, M. Caspers, D. Schummer, C. Klemke-Jahn, A. Bauer, G. Penarier, L. Debussche, M. Brçnstrup, *Angew. Chem. Int. Ed.* **2015**, *54*, 10145–0148. Synthesis nannocystin Ax: Poock, C.; Kalesse, M. *Org. Lett.* **2017***, 19*, 4536-4539.

[11] P. Koukal, J. Ulč, D. Nečas, M. Kotora, *Eur. J. Org. Chem.* **2016**, *12*, 2110−2114. For another paper dealing with allylation of haloacryl aldehydes, see: E. Matoušová, P. Koukal, B. Formánek, M. Kotora, *Org. Lett.* **2016**, *18*, 5656−5659.

[12] V. Valerio, C. Madelaine, N. Maulide, *Chem. Eur. J.* **2011**, *17*, 4742−4745.

[13] Y. Kobayashi, Y. Takemoto, T. Kamijo, H. Harada, Y. Ito, S. Terashima, *Tetrahedron.* **1992**, *48*, 1853−1868.

[14] M. Kotora, E. Negishi, *Tetrahedron Lett.* **1996**, *37*, 9041−9042.

[15] S. Pereira, M. Srebnik, *Tetrahedron Lett.* **1996**, *19*, 3283−3286.

[16] For the recent example of catalytic hydroboration of alkynes, see: K. Wang, R. W. Bates, *Synthesis* **2017**, *49*, 2749-2752.

[17] D. Menche, J. Hassfeld, J. Li, K. Mayer, S. Rudolph, *J. Org. Chem.* **2009**, *74*, 7220−7229.

[18] D. R. Brandt, K. M. Pannone, J. J. Romano, E. G. Casillas, *Tetrahedron* **2013**, *69*, 9994−10002.

[19] K. Voigtritter, S. Ghorai, B. H. Lipshutz, *J. Org. Chem.* **2011**, *76*, 4697−4702.

[20] F. Glaus, K.-H. Altmann, *Angew. Chem. Int. Ed.* **2015**, *54*, 1937−1940.

[21] K. A. Scheidt, T. D. Bannister, A. Tasaka, M. D. Wendt, B. M. Savall, G. J. Fegley, W. R. Roush, *J. Am. Chem. Soc.* **2002**, *124*, 6981−6990.

[22] No racemization was observed during the course of the synthesis. Since (*R,R*)- and (*R,S*)-**2** were prepared from enantiomeric ally pure (*R*)-mantellic acid and no racemization was observed during the course of the reaction, the final enantiopurity of (*R,R,R*)- and (*R,S,R*)-**1** is reflected by enantiopurity of (*R*)-**2**.

10.1002/ejoc.201701416

WILEY-VCH

COMMUNICATION

*Tibor Peňaška, Petr Koukal, and Martin Kotora**

Page No. – Page No.

Enantioselective Synthesis of the C23-C33 Aetheramide A Fragment and Its C32-Epimer

C23-33 fragments of aetheramide A fragments with natural (*R*,*R*,*R*) and unnatural (*R*,*S*,*R*) configuration were synthesized from (*R*)-madelic acid and 3-iodomethacrylaldehyde with the use of catalytic enantioselective allylation.