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ChemPubSoc Europe

Accepted Article

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To be cited as: Eur. J. Org. Chem. 10.1002/ejoc.201600994

Link to VoR: http://dx.doi.org/10.1002/ejoc.201600994

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Biomimetic synthesis of urukthapelstatin A by Aza-Wittig ring contraction**

Sebastian Schwenk, Cyril Ronco, Ansgar Oberheide, and Hans-Dieter Arndt*

[*] M. Sc. S. Schwenk, Dr. C. Ronco[+], B. Sc. A. Oberheide, Prof. Dr. H.-D. Arndt

Friedrich-Schiller-Universität, Institut für Organische Chemie und Makromolekulare Chemie

Humboldtstr. 10, 07743 Jena (Germany)

E-mail: *hd.arndt@uni-jena.de*

http://www.arndtgroup.uni-jena.de/

[+]New address:

Prof. Dr. C. Ronco, Université de Nice Sophia-Antipolis, Institut de Chimie, 28 Avenue Valrose, 06108 Nice Cedex 2 (France)

[**]This research was supported in part by the Alexander-von-Humboldt foundation (fellowship to C.R.) and the TMWWDG (grant No. 43-5572-321-12040-12). We thank Ms. Heidi Zdon for lab support and the NMR platform Jena (Dr. Peter Bellstedt) for excellent service.

Abstract

Marine bacteria produce highly cytotoxic polyheterocyclic cyclopeptide natural products by ribosomal peptide biosynthesis. Among them, urukthapelstatin A features a chain of five 2,4'-connected azole rings within an cyclooctapeptide framework. We report on a novel synthesis design that uses only α-amino acids as starting materials and has led to an efficient and stereoselective total synthesis of urukthapelstatin A. A kinetically favored macrothiolactonizations and a high-yielding Aza-Wittig heterocyclization for contracting the macrocyle were crucial for success. These investigations have additionally uncovered the unsuspected configurational lability of the embedded enamide substructure in solution.

Polyheterocyclic, macrocyclic natural products enjoy continued interest both in biosynthesis research as well as unique hit compounds for drug design.[1] Among them, purely amino acid derived polyazole cyclopeptides have been identified that are produced by *Actinomycetes* from marine environments. Three compounds, urukthapelstatin A (**1**, Figure 1),[2] mechercharstatin (**2**, also known as mechercharmycin or IB-01211),[3] and YM-216391 (**3**)[4] are derived from eight amino acids and share very similar structures with five contiguously catenated azoles linked via their 2 and 4'-positions, all closed by a lipophilic tripeptide section. They are produced by different species but show all high cytotoxicity in cancer cell line growth inhibition in the 10 nM range, potentially indicating a common ecological purpose or similar molecular target that remains unclear to date. The related but smaller marthiapeptide (**4**) contains four catenated thiazol(in)es and displays reduced cytotoxicity (sub-μM).[5] In contrast, telomestatin (**5**) features eight cyclocatenated azoles and is considerably less toxic (μM).[6] It however displays interesting selectivity that is attributed to high affinity of the almost planar polyazole **5** to G-quadruplex structures in telomeres and its resulting interference with telomere signaling in sensitive cell lines.[7]

The biosynthesis of polyazole cyclopeptides can be assumed to proceed by ribosomal peptide biosynthesis and posttranslational modification (RiPPs), as it was clearly shown in the case of YM-216391.[8] This pathway is shared by the structurally related bacteriocins, a large class of metabolites from marine cyanobacteria that is rich in cyclopeptide congeners containing azole rings.[9] Bacteriocins with directly connected azole rings have not (yet) been described, however.

Due to their remarkable bioactivity which seems to be linked to the polyazole fragments embedded in a ring structure, total syntheses have been pursued for urukthapelstatin A (**1**),[10] mechercharstatin (**2**),[11] YM-216391 (**3**),[12] telomestatin (**4**),[13] and marthiapeptide (**5**).[14] These reports differ conceptually in the methods employed for closing the macrocycle and for azole formation in late stage intermediates. However, most of these works report either a problematic macrocycle formation event or difficulties when creating the ultimate azole ring in the macrocycle.

These issues likely relate to the molecular structure of oxazole and thiazole-containing scaffolds (Figure 2). Gas phase measurements report opening angles of 146° for oxazole[15] and 134° for thiazole[16] for substituents attached on a 2,4-disubstituted azole **11**. While more elaborate analyses are certainly possible, simple geometry suggests that a ring of such azoles should suffer from angle strain when it is composed from less than ten oxazoles or less than eight thiazoles (**12**, average corner angle α for a decagon: 144°; octagon: 135°). Likewise, enthalpic and/or entropic strain may increase when an azole ring is constructed within a macrocycle already formed. Either a change in

angle occurs when side-chain functionalized peptides are employed (path A) or the chain length is shortened when the chain is formed via the heteroatom (path B). However, path B features a larger ring size than A, and hence could be more easily accessed by initial macrocyclization. In terms of this analysis an Aza-Wittig reaction should be suited very well for azole formation as it's precursor topology conforms to path B and azole formation will be induced under neutral conditions in an intramolecular fashion via an iminophosphorane intermediate.[17]

In order to probe this hypothesis we designed a novel synthesis of urukthapelstatin A based on the considerations above (Figure 1). As Aza-Wittig reactions perform especially well for thiazole formation, retrosynthetic dehydration (a) and Aza-Wittig disconnection (b) led us to the azido-macrothiolactone **6**, that should be easily prepared by thiolactonization (c) from ω-mercapto ester **7**. Precursor **7** features a turn-inducing DLL-configured tripeptide in its center procting two semi-rigid appendages that should facilitate ring closure.[18] It disconnects favorably into *bis*-azole fragment **8**, regular tripeptide **9**, and aminoalcohol **10** by peptide coupling (d) and condensing oxazole formation (e). *Bis*-azole **8** should be similarly accessed from a mono-thioazole acid (f). Overall, all building blocks can such be assembled from natural amino acid, leading to a biomimetic synthesis design.[1c]

The synthesis began with the construction of the azole building blocks (Scheme 1). Two charges of serine (**13**) were divergently protected as allyl ester **14** (85%) or by installing TBS- and Boc-protecting groups (→ **15**, 95%)[26] and then united to dipeptide **16** by using EDC (76% yield). Oxazole formation mediated by DAST[19a] followed by $BrCCl_3$/DBU oxidation[20] performed reproducibly to deliver oxazole **17** in 68% yield. Deprotection to amino alcohol **10** was then quantitatively achieved with aqueous TFA.

For the N-terminus cysteine derivative **18** was converted to azide **20** by azide transfer[17] and used to construct thiazole **21** by high yielding one-pot Tr-deprotection - thioesterification - Aza-Wittig - oxidation sequence employing acid **19** (4 steps, 87% yield). Its NHBoc group was swiftly exchanged for an azide group (→ **22**, 95%).[17] Attempts to hydrolyze methyl ester **22** were characterized by side reactions, notably STr-elimination and degradation. After considerable experimentation it was found that NaOH buffered with TFE created conditions that would cleanly deliver acid **23** (99% yield) and could circumvent the usage of toxic tin reagents.[21] Coupling to H-*β*-OH-Phe-Me (mixture of stereoisomers) then proceeded smoothly and gave dipeptide **24** in 85% yield. For oxazoline formation DOF was then favorably used,[19b] but the following oxidation had to be performed with limiting reagent and at low temperature to avoid overoxidation (36% over two steps). Methyl ester deprotection by using Me_3SnOH[22] then cleanly delivered acid **8**.

In order to assemble the backbone structure, manual peptide synthesis on Tr-resin was employed after loading with protected Thr (0.7 mmol/g, Scheme 2). Regular Fmoc/tBu chemistry and terminally Boc-protected D-*allo*-Ile delivered tripeptide acid **9** in 96% isolated yield overall. Coupling of acid **9** to amino alcohol **10** by using HBTU succeeded in > 90% yield. However, significant epimerization of the Thr residue in amide **26** occurred under these conditions (*d.r. 2:1). Careful optimization (PyAOP, EtN(*i*Pr)$_2$, -3 °C → 20 °C) reduced diastereomer formation (*d.r. > 9:1), at the expense of yield (50%). Anyhow, the minor *R*-isomer(*) was easily separated by chromatography and its solubility in EtOAc.[1] Hydroxymethyl peptide **26** was then transformed into *bis*-oxazole **27** by using DAST,[19] followed by oxidation with DBU and excess CCl_4[13] in a solvent mixture containing pyridine, which was crucial to minimize side product formation. After acid-mediated *t*Bu- and Boc-deprotection of *bis*-oxazole **27** *bis*-azole acid **8** was attached to give octapeptide precursor **7** (82% yield). Deallylation proceeded cleanly with morpholine as allyl scavenger,[23] and acid-mediated detritylation furnished cyclization precursor **28** (97% yield).

The crucial macrocyclization performed excellently by using PyBOP (88% yield, Scheme 3) when slow addition of the precursor to the reagent was employed (syringe pump).[24] Interestingly, macro-thiolactone **6** was stable to isolation and chromatography, suggesting low residual ring strain. Furthermore, ring contraction of azidothioester **6** by Aza-Wittig reaction in 2,6-lutidine as solvent[17] followed by oxidation delivered the penta-azole macrocycle **29** in gratifying 79% yield. *E*2-type *anti* elimination then proceeded cleanly via the stable mesylate that was eliminated smoothly by employing DBU to give Z-configured urukthapelstatin A (**1**, 61%). Analytical data (^{1}H, ^{13}C, HRMS, TLC) of the final product were identical to data reported for the natural product.[2,10] As a control, *syn* elimination conditions (CuCl/EDC)[25] gave an isomer distinct of **1** to which *E*-configuration was assigned by NOESY-NMR. The stereoisomeric purity was high in both cases (d.r. >95:5).

While performing these studies and in contrast to an earlier report,[10] we found the *Z*- and *E*-isomers of **1** to be distinct and separable by TLC and HPLC (Figure 3 and supporting info). To our surprise, apparent isomer "contaminations" appeared even after stringent separation by prep. HPLC. Closer inspection and monitoring revealed that isomers of **1** slowly interconvert between *Z* and *E* forms when dissolved in aqueous acetonitrile (pH 3) or SDS buffer (pH 7.4) (d.r. 95:5 → 75:25 during 96 h at 20°C, Figure 3). Hence, although the compound seems to be configurationally stable in the solid state and can be crystallized,[2] it is not fully stable in solution. This observation will be important for future biological testing and compound design.

[1] The minor isomer *R*-**26** was converted to the final product **1** as well by using the synthesis described and an interchange of final elimination conditions, thereby confirming independently the stereochemical assignments.

In summary, we report the first stereoselective synthesis of urukthapelstatin A (**1**) that proceeds reproducibly in satisfactory yield. Critical steps were optimized by judicious synthesis design, most notably the macrocyclization via a novel macrothiolactone and the azole formation via Aza-Wittig ring contraction. In extension, the chemistry developed here should allow for a permutation of individual building blocks, in order to prepare derivatives with improved stability for structural and biological investigations. Such studies are currently underway in our laboratory.

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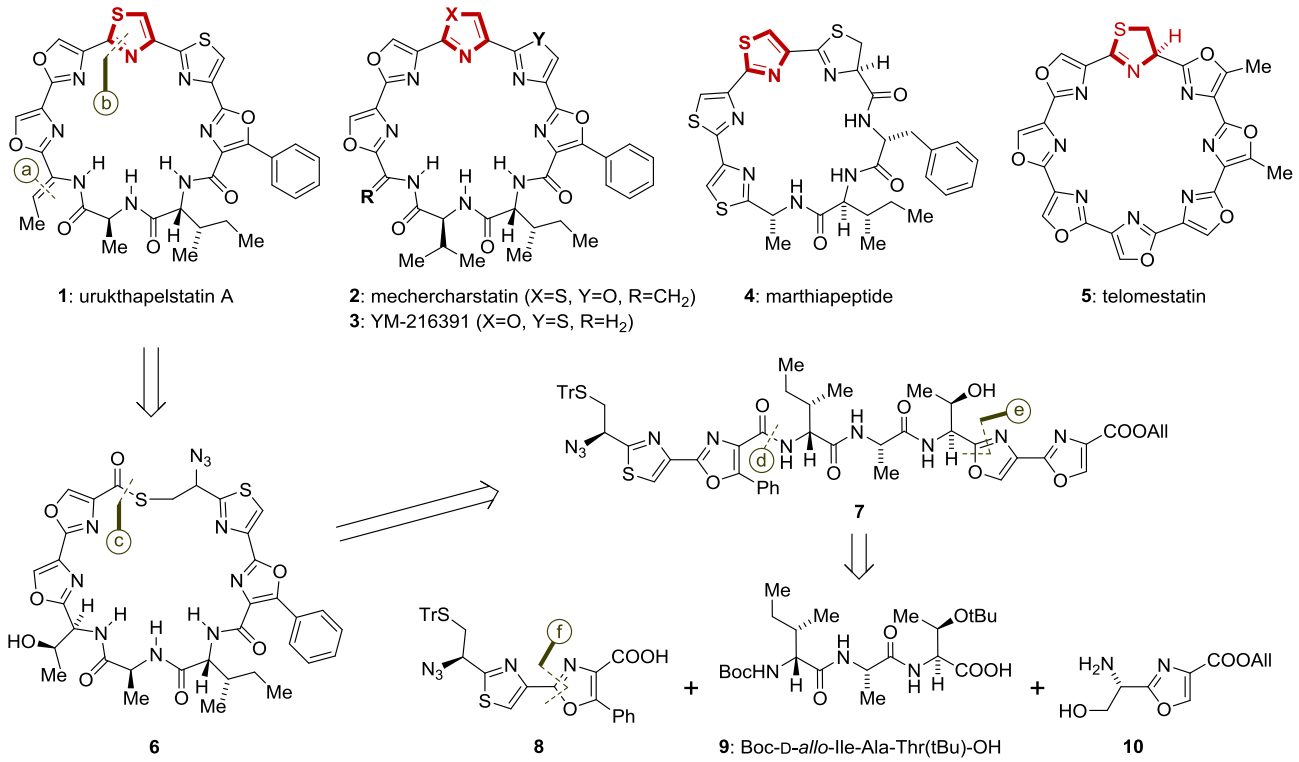


Figure 1. Polyazole cyclopeptide natural products originating from RiPPs and synthesis planning for urukthapelstatin A with crucial azole rings highlighted. Abbreviations: All = Allyl; Alloc = Allyloxycarbonyl; Boc = *tert*-Butyloxycarbonyl; DBU = 1,8-Diazabicyclo[5.4.0]undec-7-en; DAST = Diethylaminosulfur trifluoride; DMAP = 4-Dimethylaminopyridine; DOF = Bis(2-methoxyethyl)aminosulfur trifluoride ("Deoxo-Fluor"); HBTU = *O*-(Benzotriazol-1'-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; HOBt = 1-Hydroxybenzotriazole; PyBOP = (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate; Ms = Methylsulfonyl; TBS = *tert*-Butyldimethylsilyl; TFE = 2,2,2-Trifluoroethanol; Tr = Triphenylmethyl.

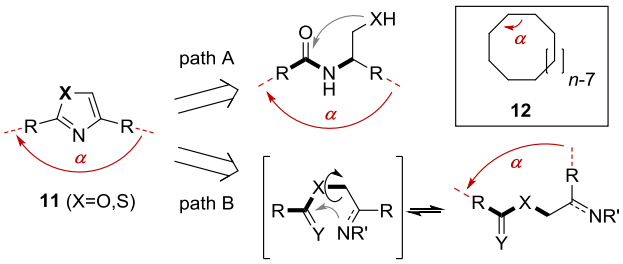
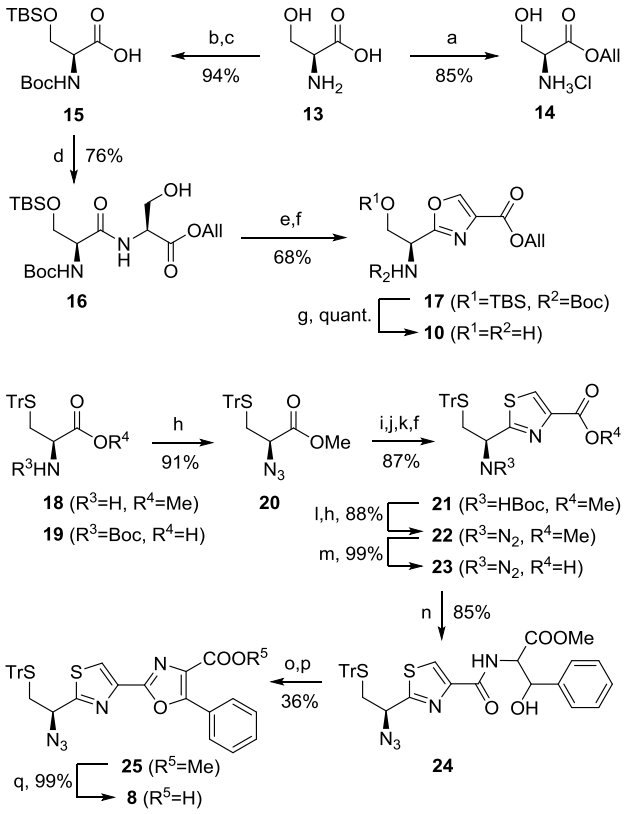
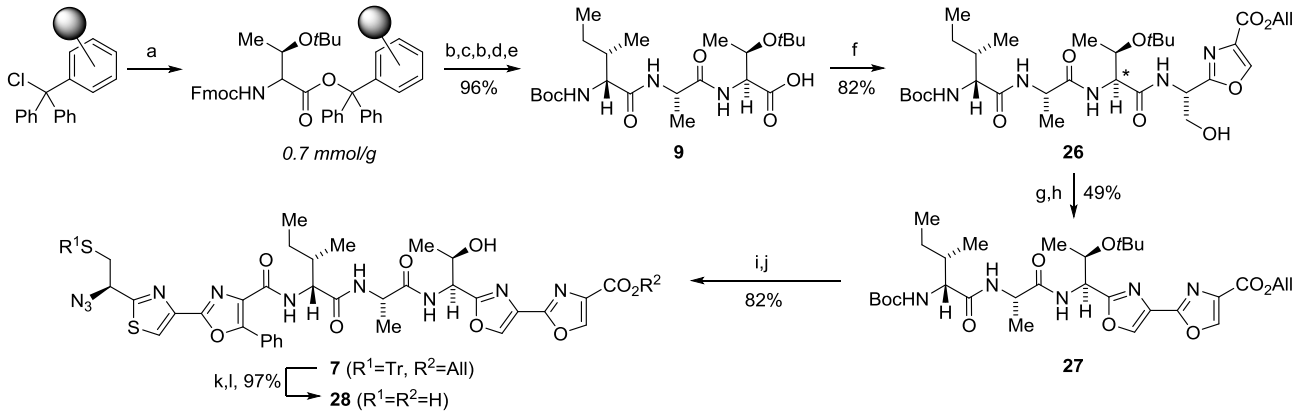


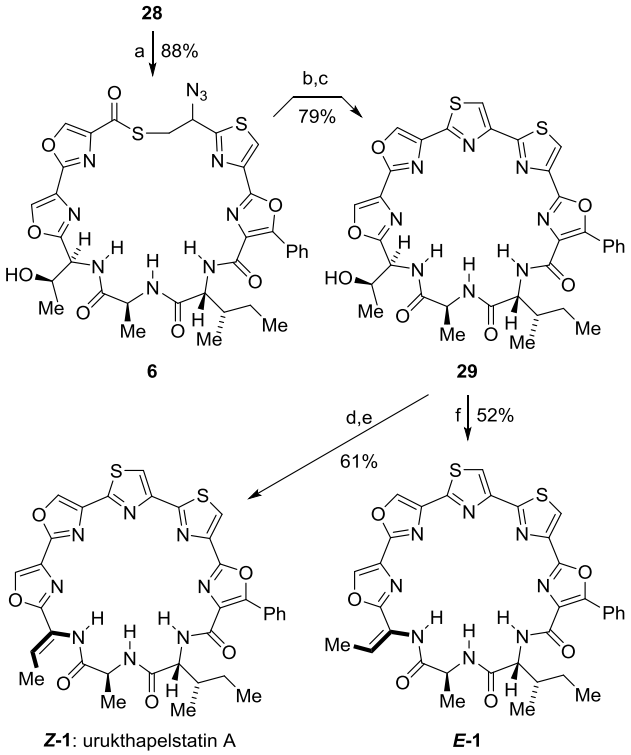
Figure 2. Considerations for azole-forming reactions within macrocycles.



Scheme 1. Synthesis of azole building blocks. Reagents and conditions: a) $SOCl_2$ (2.2 equiv.), allyl alcohol, 0 °C → 60 °C, 20 h; b) Boc_2O (1.2 equiv., 2.5 M in 1.4-dioxane), Na_2CO_3 (1 equiv.), sat. $NaHCO_3/H_2O$ (1:1), 0 °C → 20 °C, 24 h; c) TBSCl (1.3 equiv.), imidazole (3 equiv.), DMF, 0 °C → 20 °C, 14 h; d) **13** (1.2 equiv.), EDC (1.1 equiv.), HOBt (1.1 equiv.), NEt_3 (2 equiv.), CH_2Cl_2/DMF (50:1), 20 °C, 19 h; e) DAST (1.1 equiv.), K_2CO_3 (2.1 equiv.), CH_2Cl_2, -78 °C → 20 °C, 3.5 h; f) $BrCCl_3$ (1.4 equiv.), DBU (2.4 equiv.), CH_2Cl_2, -30 °C → 20 °C, 5 h; g) TFA/H_2O (17:2), 20 °C, 14 h; h) TFN_3 (3 equiv.), $ZnSO_4$ (0.05 equiv.), CH_2Cl_2/MeOH/H_2O (2:5:1), 0 °C → 20 °C, 2 h; i) TFA (5vol%), Et_3SiH (5vol%), CH_2Cl_2, 20 °C, 1 h; j) **19** (1.2 equiv.), EDC x HCl (1.2 equiv.), HOBt (1.1 equiv.), EtN(*i*Pr)$_2$ (1.3 equiv.), CH_2Cl_2/DMF (9:1), -10 °C → 20 °C, 15 min; k) PPh_3 (1.35 equiv.), CH_2Cl_2/DMF (10:1), -10 °C → 20 °C, 15 h; l) 4 M HCl in 1,4-dioxane, 20 °C , 20 h; m) 5 M NaOH/CH_2Cl_2/MeOH/TFE (0.1:2:1:1), 20 °C , 3 d; n) Ph-(CHOH)-($CHNH_2$)-COOMe (1.2 equiv.), HBTU (1.2 equiv.), EtN(*i*Pr)$_2$ (2 equiv.), CH_2Cl_2/DMF (1:1), 0 °C → 20 °C, 3.5 h; o) DOF (1.2 equiv.), pyridine (2 equiv.), THF, -65 °C → 20 °C, 4 h; p) $BrCCl_3$ (0.9 equiv.), DBU (1 equiv.), CH_2Cl_2, -50 °C → -25 °C, 30 h; q) Me_3SnOH (2 equiv.), 1,2-dichloroethane, 80 °C, 22 h.



Scheme 2. Peptide chain assembly and azole appendage. Reagents and conditions: a) trityl chloride resin, Fmoc-L-Thr(*t*Bu)-OH (1 equiv.), EtN(*i*Pr)$_2$ (3 equiv.), CH_2Cl_2/DMF (1:1), 20 °C, 5.5 h; resin loading 0.7 mmol/g; b) piperidine/DMF (1:4), 20 °C , 22 min; c) Fmoc-L-Ala-OH (4equiv.), HOBt (4 equiv.), HBTU (4equiv.), EtN(*i*Pr)$_2$ (8 equiv.), DMF, 20 °C, 7 h; d) Boc-D-*allo*-Ile-OH (1.5 equiv.), HOBt (1.5 equiv.), HBTU (1.5 equiv.), EtN(*i*Pr)$_2$ (2.5 equiv.), DMF, 20 °C, 6 h; e) HFIP/CH_2Cl_2 (3:7), 20 °C, 30 min; f) **10** (0.9 equiv.), PyAOP (1.1 equiv.), EtN(iPr)$_2$ (1.8 equiv.), CH_2Cl_2/DMF (1:1), -5 °C → 20 °C, 22 h; g) DAST (1.1 equiv.), K_2CO_3 (2 equiv.), CH_2Cl_2, -78 °C → 20 °C, 5.5 h; h) DBU (10 equiv.), CCl_4/pyridine/MeCN (2:3:3), -60 °C → 20 °C, 3 d; i) Anisole (2.3 equiv.), TFA/CH_2Cl_2 (1:1), 0 °C → 20 °C, 3 h; j) **8** (1.2 equiv.), HBTU (1.6 equiv.), EtN(*i*Pr)$_2$ (3 equiv.), CH_2Cl_2/DMF (1:1), 0 °C → 20 °C, 2 d; k) Pd(dba)$_2$ (0.2 equiv.), morpholine (20 equiv.), CH_2Cl_2, 20 °C, 4 h; l) Et_3SiH (5 vol%), TFA (3 vol%), CH_2Cl_2, 20 °C, 1 h.



Scheme 3. Macrocyclization and synthesis of urukthapelstatin A (**1**) and its *E*-isomer. Reagents and conditions: a) PyBOP (1.2 equiv.), $EtN(iPr)_2$ (2 equiv.), CH_2Cl_2/DMF (6:1), 20 °C, 24 h; b) PPh_3 (1.5 equiv.), 2,6-lutidine, 20 °C → 60 °C, 7 h; c) $BrCCl_3$ (1.2 equiv.), DBU (1.5 equiv.), CH_2Cl_2, -50 °C → 20 °C, 8 h; d) MsCl (2 equiv.), NEt_3 (3 equiv.), CH_2Cl_2, 20 °C, 2.5 h; e) DBU (3 equiv.), CH_2Cl_2, 20 °C, 1.5 h; f) CuCl (12.5 equiv.), EDC x HCl (3 equiv.), CH_2Cl_2/DMF (96:4), 20 °C, 30 h.

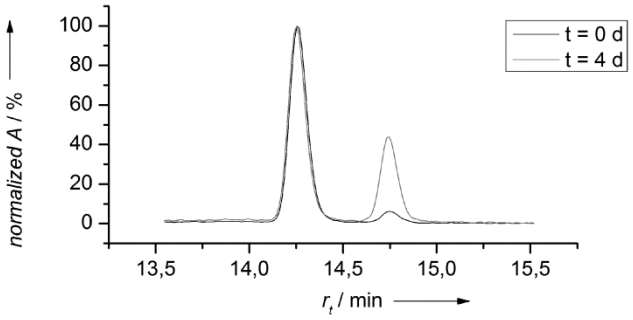
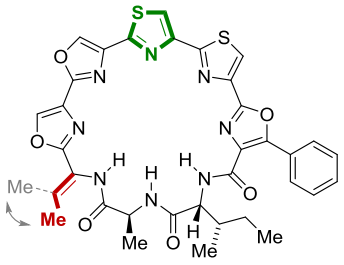


Figure 3. *E*/*Z*-Isomerization of the enamide **1** monitored by HPLC. *Z*-Isomer after isolation (black, *Z*/*E* = 95:5) and after 96 h (grey, *Z*/*E* = 72:28, normalized; see supp. info for details).

Graphical abstract for the table of contents



urukthapelstatin A

Text suggestion for the table of contents:

Constraining well dosed. The first stereoselective total synthesis of urukthapelstatin A is reported that employs a novel synthesis design. A kinetically favored macrothiolactonizations and a high-yielding Aza-Wittig heterocyclization for contracting the macrocyle were crucial for success. The embedded enamide substructure of the target molecules was found to slowly isomerize in solution.

Key topic:

Total synthesis