

Total Synthesis of the Post-translationally Modified Polyazole Peptide Antibiotic Goadsporin

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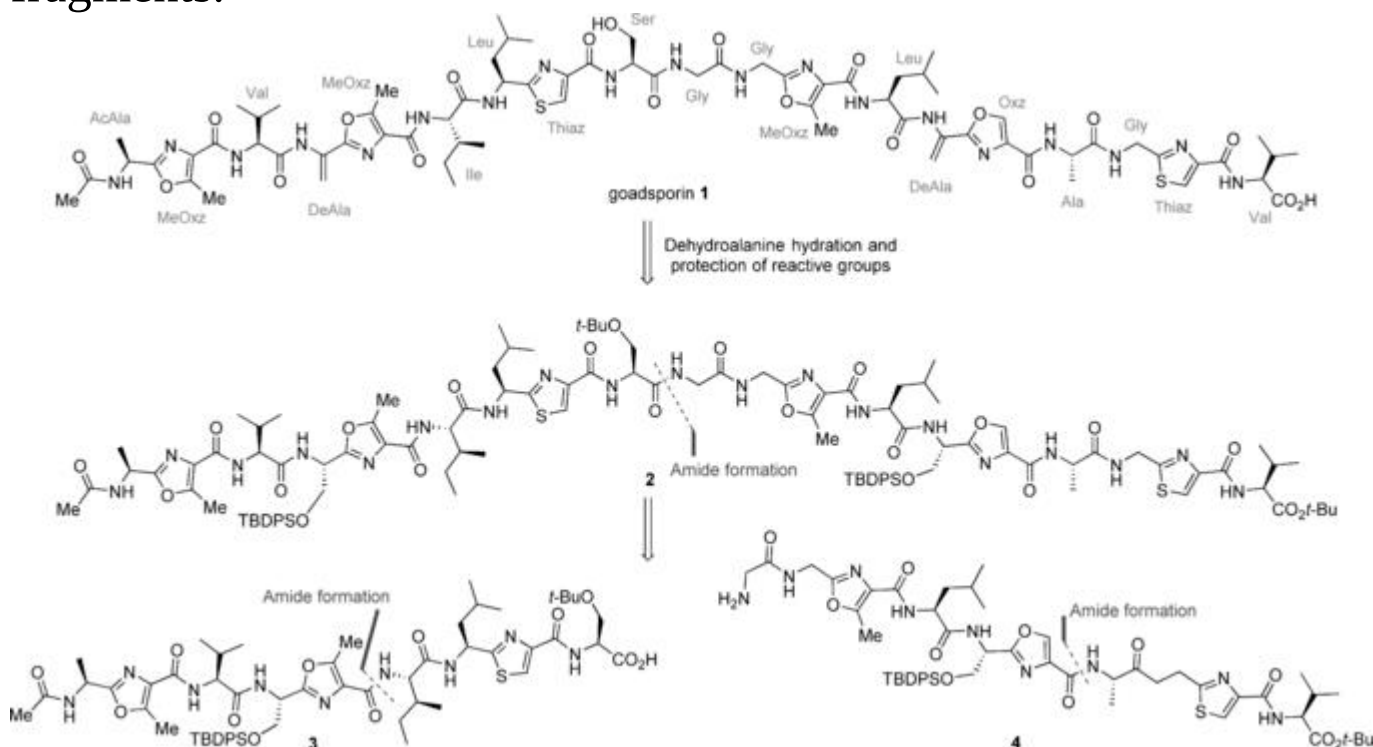
Abstract

The structurally unique polyazole antibiotic goadsporin contains six heteroaromatic oxazole and thiazole rings integrated into a linear array of amino acids that also contains two dehydroalanine residues. An efficient total synthesis of goadsporin is reported in which the key steps are the use of rhodium(II)-catalyzed reactions of diazocarbonyl compounds to generate the four oxazole rings, which demonstrates the power of rhodium carbene chemistry in organic chemical synthesis.

Goadsporin (**1**) is a secondary metabolite of *Streptomyces* sp. TP-A0584, a soil-derived actinomycete bacterium, and was first isolated and characterized by detailed NMR spectroscopic studies in 2001 by Onaka et al.[\[1\]](#) The natural product contains four oxazole and two thiazole rings incorporated within a linear array of amino acids that interestingly also contains two dehydroalanine residues and N-terminal acetylation. Belonging to the class of ribosomally synthesized and post-translationally modified peptides (RiPPs), goadsporin can further be classed as a thiazole/oxazole-modified microcin (TOMM), within

which it is specifically classified as a linear azol(in)e-containing peptide (LAP).[2] The biosynthesis of goadsporin has been fully elucidated; it originates from a sequence of 19 _L-amino acids (ATVSTILCSGGTLSSAGCV), with each of the aromatic heterocycles resulting from the condensation of two amino acids.[3] The two dehydroalanine residues have recently been proposed to be formed through the glutamylation of serine, followed by glutamate elimination.[4] Goadsporin has been reported as a potential antibiotic, showing growth inhibition against *Streptomyces* strains when present at high concentrations,[1a] including against *S. scabies* (MIC=0.2 $\mu\text{g mL}^{-1}$), the causative organism of potato scab, which is an economically important agricultural disease. It also induces sporulation and the production of secondary metabolites in a range of other *Streptomyces* strains,[1a] and although the mechanism of action is unknown, the reasons for immunity in the producing strain have been investigated.[1c] In continuation of our interest in the synthesis and properties of post-translationally modified peptide antibiotics such as the amythiamicins,[5] telomestatin,[6] and plantazolicin,[7] we embarked upon a total synthesis of goadsporin. We herein report the first synthesis of this complex polyazole antibiotic in which the four five-membered oxazole rings of the natural product are formed from simple precursors, such as carboxamides or nitriles, as facilitated by metallocarbene chemistry. Our synthetic strategy involves protection of the serine side chain alcohol and the C-terminal valine carboxylic acid with a *tert*-butyl ether and ester, respectively, orthogonal to silyl protection of the two serine residues

that will serve as precursors to the dehydroalanine functionalities. Disconnection at a central amide bond in the protected compound **2** leads to the two fragments **3** and **4**, adorned with suitable protecting groups, which can both be broken down further at an amide bond (Scheme 1) to give four approximately equally sized fragments.



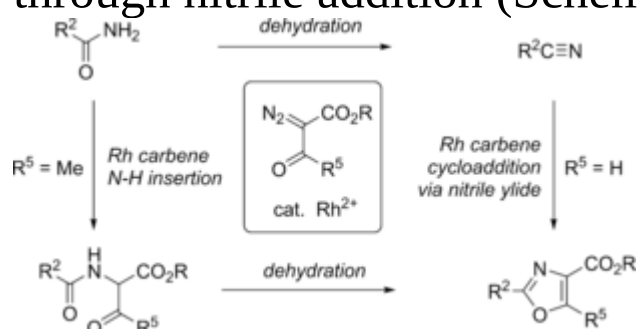
Scheme 1.

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Retrosynthetic analysis of goadsporin **1** via protected form **2**, which is split into the left- and right-hand fragments **3** and **4**. TBDPS=*tert*-butyldiphenylsilyl.

Although some of the building blocks required for the synthesis of goadsporin are readily available proteinogenic L-amino acids, the heterocyclic components need to be accessed. Whilst the two thiazoles should be approachable through the well-established Hantzsch reaction, we elected to synthesize the four oxazoles by using rhodium carbene chemistry, a mild and versatile

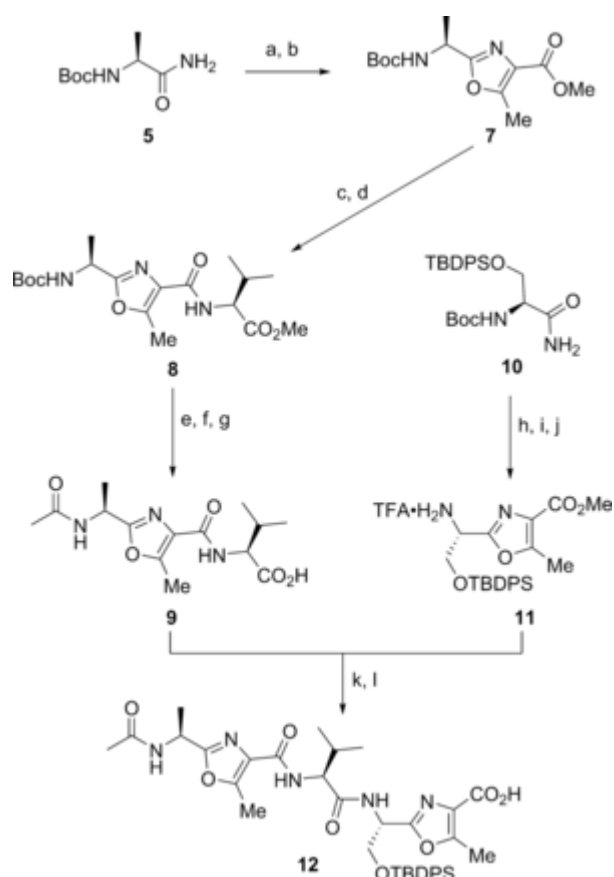
method used previously in the synthesis of azole-containing natural products.[5-7] Reaction of diazocarbonyl compounds with catalytic amounts of rhodium(II) complexes forms an intermediate metallocarbene, which can undergo an N–H insertion reaction into a carboxamide, followed by cyclodehydration to give the heteroaromatic oxazole. Alternatively, the steps can be reversed, with the carboxamide dehydrated to a nitrile that reacts to give substituted oxazoles directly (Scheme 2).[8] Both methods are used in the present study, with oxazoles 7, 11, and 20 produced through N–H insertion (Scheme 3 and Scheme 5), and oxazole 21 produced through nitrile addition (Scheme 5).



Scheme 2.

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Construction of oxazole rings from carboxamides or nitriles using rhodium carbene chemistry.



Scheme 3.

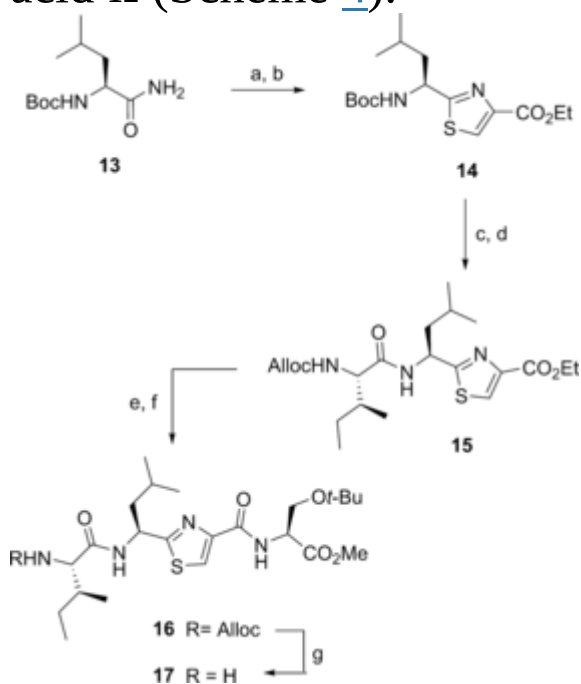
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Synthesis of bis-oxazole 12. Reagents and conditions: a) $\text{Rh}_2(\text{OAc})_4$, methyl 2-diazo-3-oxobutanoate 6, CHCl_3 , 80 °C, 16 h, 56 %; b) NEt_3 , PPh_3 , I_2 , CH_2Cl_2 , 16 h, 73 %; c) LiOH , $\text{MeOH}/\text{H}_2\text{O}$, 1 h, quantitative; d) valine methyl ester hydrochloride, DIPEA, HATU, DMF, 16 h, 82 %; e) HCl in dioxane, 4 h, 91 %; f) DIPEA, Ac_2O , CH_2Cl_2 , 56 h, 93 %; g) LiOH , $\text{MeOH}/\text{H}_2\text{O}$, 4 h, 96 %; h) $\text{Rh}_2(\text{OAc})_4$, 6, CHCl_3 , 80 °C, 16 h, 73 %; i) NEt_3 , PPh_3 , I_2 , CH_2Cl_2 , 16 h, 74 %; j) $\text{TFA}/\text{CH}_2\text{Cl}_2$ (95:5), 0 °C, 20 min, 90 %; k) 2,6-di-*tert*-Bu-4-Me-pyridine, HBTU, HOAt, CH_2Cl_2 , 16 h, 75 %; l) Me_3SnOH , DCE, 80 °C, 16 h, quantitative.

DIPEA=diisopropylethylamine, HATU=1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate, HBTU=*N,N,N',N'*-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate, HOAt=1-hydroxy-7-azabenzotriazole, DCE=1,2-dichloroethane.

The synthesis started with the N-terminal bis-oxazole fragment 12. Reaction of Boc-protected alaninamide 5 with diazo- β -ketoester 6 in chloroform with 2 mol % of rhodium(II) acetate dimer, followed by dehydration using iodine, triphenylphosphine, and triethylamine[9] in dichloromethane gave the 5-methyloxazole 7. Ester hydrolysis and amide coupling with valine methyl ester hydrochloride gave compound 8. At this point the acetyl group was introduced through Boc-deprotection, followed by acetylation (structure confirmed by X-ray crystallography; see the Supporting Information). Subsequent ester hydrolysis of the acetylated product gave acid 9 (Scheme 3). The second oxazole was synthesized analogously: rhodium(II) acetate catalyzed the reaction of the serine carboxamide 10, which is readily obtained in two steps from the Boc-serine methyl ester, to give the desired oxazole after cyclodehydration, which was then Boc-deprotected with trifluoroacetic acid to give oxazole 11. Amide coupling between 9 and 11 under standard conditions (HATU, HOAt, DIPEA, and DMF) gave high levels of racemization of the valine residue,[10] with a d.r. of 1.0:0.9 as observed by HPLC. After optimization, which led to the use of a different base and coupling agent (2,6-di-*t*-Bu-4-Me-pyridine, HBTU, and HOAt in dichloromethane), the bis-oxazole was successfully synthesized in good yield with a d.r. of 1.0:0.05. Cleavage of the ester using the known mild hydrolysis reagent trimethyltin hydroxide in 1,2-dichloroethane[11] gave the bis-oxazole carboxylic acid 12 (Scheme 3). Synthesis of the second quarter began with the conversion of Boc-protected leucinamide amide 13 into the

corresponding thioamide with Lawesson's reagent in dichloromethane, followed by Hantzsch reaction with ethyl bromopyruvate under modified conditions[[12](#)] to give thiazole **14**. Boc-deprotection and amide coupling with *N*-Alloc-isoleucine gave thiazole **15** in good yield, the structure of which was confirmed by X-ray crystallography (see the Supporting Information). Hydrolysis and coupling to the commercially available serine (*O*-*tert*-Bu) methyl ester hydrochloride gave **16**, which underwent deprotection using palladium(0) tetrakis(triphenylphosphine) with diethylamine in dichloromethane to give the free amine **17**, ready for subsequent coupling with the bis-oxazole acid **12** (Scheme [4](#)).

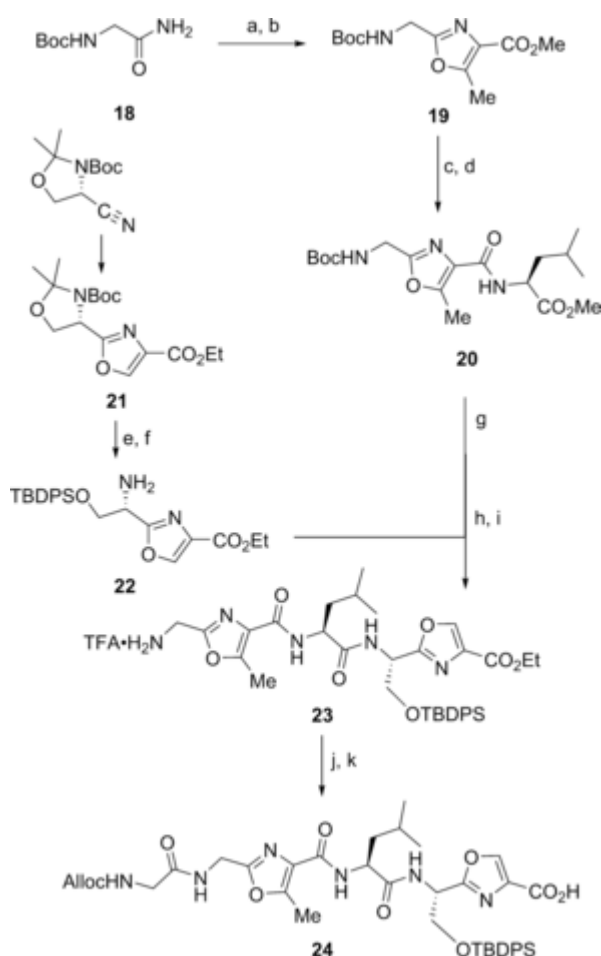


Scheme 4.

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Synthesis of thiazole fragment **17**. Reagents and conditions: a) Lawesson's reagent, CH₂Cl₂, 16 h, quantitative; b) i. KHCO₃, ethyl bromopyruvate, DME, −40 °C—RT, 16 h, ii. TFAA, 2,6-lutidine, DME, −10 °C, 1 h, 76 %; c) HCl in dioxane, 1 h, 99 %; d) *N*-Alloc-isoleucine, DIPEA, HATU, DMF, 16 h, 64 %; e) LiOH,

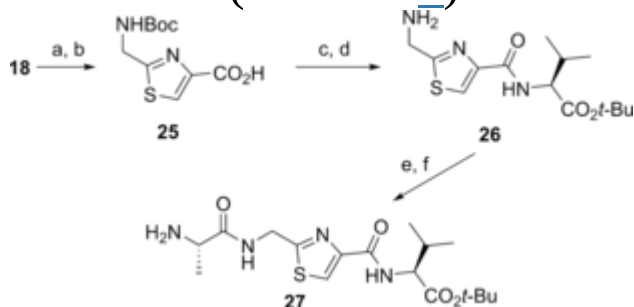
MeOH/H₂O, 2.5 h, 100 %; f) serine(*O*-*tert*-Bu) methyl ester hydrochloride, DIPEA, HATU, DMF, 16 h, 94 %; g) HNEt₂, Pd(PPh₃)₄, CH₂Cl₂, 4 h, quantitative. DME=1,2-dimethoxyethane, TFAA=trifluoroacetic anhydride, Alloc=allyloxycarbonyl. In another rhodium carbene mediated step, oxazole 19 was formed from *N*-Boc-glycinamide 18(Scheme 5). Ester hydrolysis and coupling to leucine methyl ester hydrochloride gave oxazole 20. Oxazole 21 was prepared as previously described from *N*-Boc-serine methyl ester through rhodium carbene mediated nitrile cycloaddition,[6, 7] and after deprotection with TFA, was O-protected with *tert*-butyldiphenylsilyl chloride to give oxazole 22. Amine 22 was then coupled with the acid derived from hydrolysis of ester 20 to give bis-oxazole 23 after removal of the Boc group, with no evidence for any racemization at the leucine α -CH. Finally, coupling with *N*-Alloc-glycine, and cleavage of the terminal ethyl ester delivered bis-oxazole carboxylic acid 24 (Scheme 5).



Scheme 5.

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- Synthesis of bis-oxazole **24**. Reagents and conditions: a) $\text{Rh}_2(\text{OAc})_4$, **6**, CHCl_3 , 80°C , 16 h, 81 %; b) NEt_3 , PPh_3 , I_2 , CH_2Cl_2 , 16 h, 33 %; c) LiOH , $\text{MeOH}/\text{H}_2\text{O}$, 17 h, quantitative; d) leucine methyl ester hydrochloride, DIPEA, HATU, DMF, 16 h, 85 %; e) $\text{TFA}/\text{CH}_2\text{Cl}_2$ (9:1), 0°C to RT, 5 h, 96 %; f) TBDPSCl , NEt_3 , imidazole, CH_2Cl_2 , 16 h, 78 %; g) LiOH , $\text{MeOH}/\text{H}_2\text{O}$, 2 h, 93 %; h) DIPEA, HATU, DMF, 16 h, 71 %; i) $\text{TFA}/\text{CH}_2\text{Cl}_2$ (95:5), 0°C , 50 min, quantitative; j) *N*-Alloc-glycine, DIPEA, HATU, HOAt, DMF, 2 h, 78 %; k) Me_3SnOH , 1,2-DCE, 80°C , 8 h, quantitative.
- Synthesis of the C-terminal quarter began with the preparation of thiazole **25**. Conversion of *N*-Boc-glycinamide **18** into the corresponding thioamide was followed by Hantzsch reaction with bromopyruvic acid and calcium carbonate in methanol gave the desired

thiazole-4-carboxylic acid **25** in excellent yield. Amide coupling to commercially available valine *tert*-butyl ester ensued smoothly. Selective removal of the Boc group in the presence of the *tert*-butyl ester proceeded with methanesulfonic acid in a mixture of dichloromethane/*tert*-butyl acetate[[13](#)] to give the free amine, which was immediately coupled to *N*-Alloc-alanine in high yield. Finally, removal of the Alloc group gave the C-terminal thiazole **27** (Scheme [6](#)).



Scheme 6.

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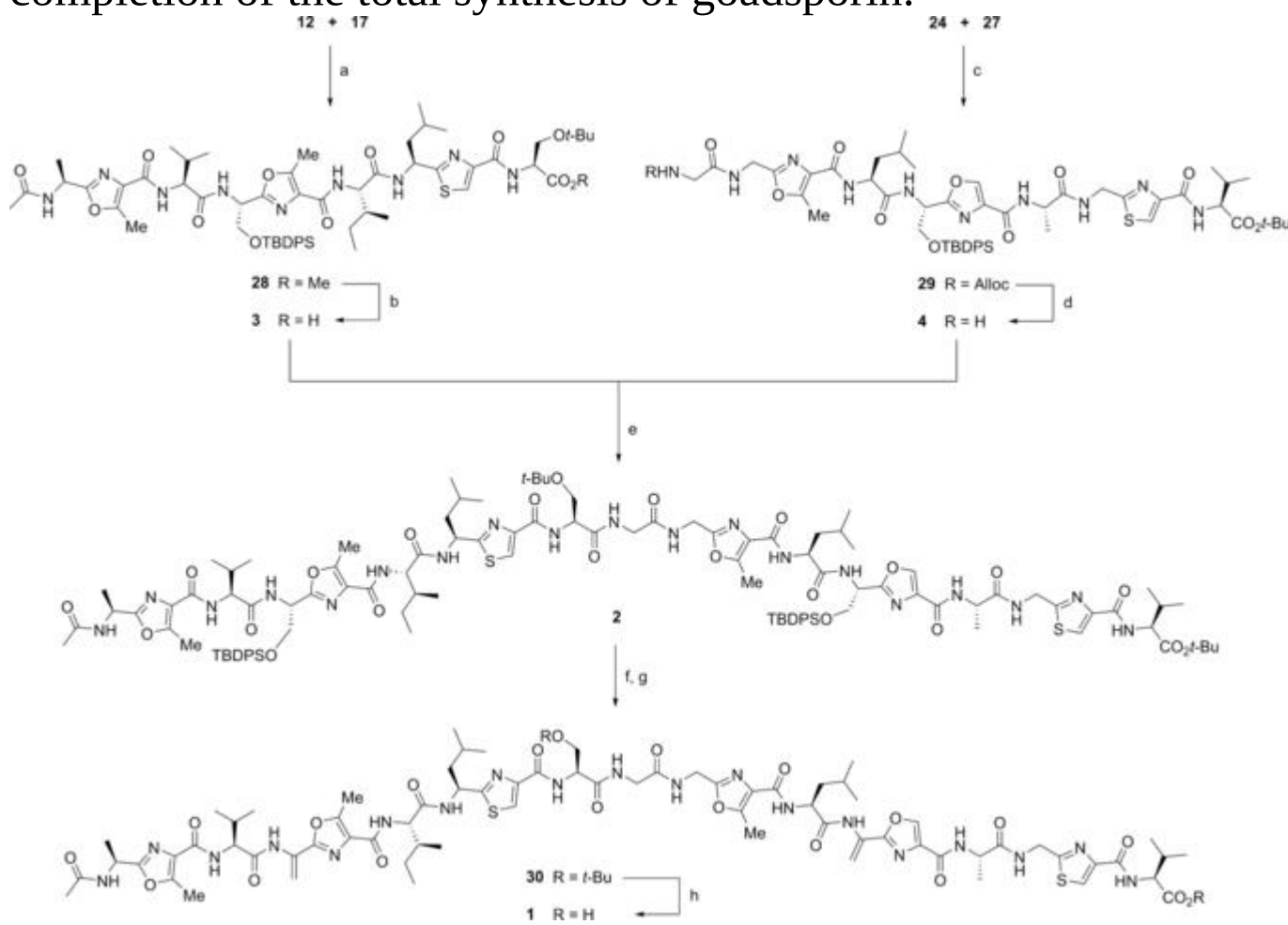
Synthesis of thiazole **27**. Reagents and conditions: a) Lawesson's reagent, CH₂Cl₂, 16 h, 84 %; b) CaCO₃, bromopyruvic acid, MeOH, 87 h, 98 %; c) valine *tert*-butyl ester hydrochloride, DIPEA, HATU, DMF/CH₂Cl₂ (1:1), 3 h, 93 %; d) methanesulfonic acid, *t*-BuOAc/CH₂Cl₂ (1:1), 7 h, quantitative; e) *N*-Alloc-alanine, DIPEA, HATU, DMF, 16 h, 78 %; f) HNEt₂, Pd(PPh₃)₄, CH₂Cl₂, 1.5 h, 80 %.

With all four fragments in hand, it remained to perform the relevant coupling reactions. Acid **12** and amine **17** were coupled under HATU conditions to give bis-oxazole-thiazole **28**, the hydrolysis of which delivered acid **3**.

Likewise, acid **24** and amine **27** were coupled together to give bis-oxazole-thiazole **29**, which was deprotected to give amine **4**. The union of the left- and right-hand fragments **3** and **4** was brought about through a further HATU-mediated reaction to give the complete linear

polyazole peptide 2 (Scheme 7). Double removal of the two silyl groups using TBAT in THF gave the corresponding diol, dehydration of which with methanesulfonyl chloride and triethylamine, followed by addition of DBU, installed the two dehydroalanine residues in the complete sequence 30. Finally, the *tert*-butyl ether and ester protecting groups were removed under mildly Lewis acidic conditions with zinc bromide in chloroform[14] to give goadsporin. Given the previously noted racemization of a valine α -CH, all of the the C-terminal valine intermediates (27, 29, 4, 2, and 30) were carefully checked by NMR to exclude the possibility of racemization, even though the valine residue is not directly involved in any of the coupling reactions. Following purification by column chromatography, our synthetic material co-eluted with natural goadsporin by HPLC as shown in the Supporting Information. The proton and carbon NMR spectra, obtained at 500 and 800 MHz, of the synthetic material were fully assigned using a range of experiments, including NOESY (see the Supporting Information), and were fully consistent with the structure. However, there was one difference in the proton NMR spectrum of the synthesized sample compared with the data reported for the natural product, namely the α -H of the C-terminal valine. This variation was echoed in the carbon NMR spectrum, in which signals for the thiazole and valine at the C terminus again varied slightly from the reported data. Having ruled out the possibility of any racemization of the C-terminal valine (see above), we ascribe this difference to the exchangeable nature of the C-terminal carboxylic acid of goadsporin. In light of this, a

slight differences in pH or would cause different rates of exchange of the carboxylic acid, thereby resulting in a different chemical shift of the signals at the C terminus.[15] However, the NMR spectra of a mixed co-sample of synthetic and natural material confirmed the presence of a single compound, thus confirming completion of the total synthesis of goadsporin.



Scheme 7.

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Completion of the synthesis of goadsporin (1). Reagents and conditions: a) DIPEA, HATU, HOAt, DMF, 5 h, 80 %; b) Me_3SnOH , DCE, 70 °C, 16 h, quantitative; c) DIPEA, HATU, HOAt, DMF, 16 h, 81 %; d) HNEt_2 , $\text{Pd}(\text{PPh}_3)_4$, CH_2Cl_2 , 4 h, 77 %; e) DIPEA, HATU, HOAt, DMF, 5 h, 66 %; f) TBAT, THF, 4 h, 61 %; g) MsCl , NEt_3 , THF, 0 °C, 3 h, then DBU, CHCl_3 , 0 °C, 4 h,

36 %; h) ZnBr₂, CHCl₃, RT, 16 h, then 35 °C, 2 h, 66 %.

TBAT=tetra-*n*-butylammonium triphenyldifluorosilicate,

DBU=1,8-diazabicyclo[5.4.0]undec-7-ene.

In conclusion, the rhodium carbene route described above not only forms the basis for the first total synthesis of the fascinating polyazole peptide antibiotic goadsporin, but also makes available a wide range fragment structures and intermediates that are not available through nature's biosynthetic machinery.

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Conflict of interest

The authors declare no conflict of interest.

Ancillary

Supporting Information

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