Stereocontrolled Synthesis of the Quinaldic Acid Macrocyclic System of Thiostrepton**

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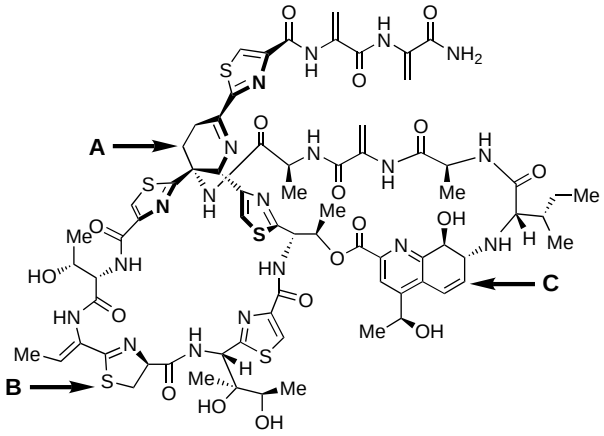
Dedicated to Professor Ralph F. Hirschmann on the occasion of his 80th birthday

Thiostrepton (**1**)[1] is the most complex and best characterized member of the thiopeptide antibiotics whose structure has been secured by X-ray crystallographic,[2] degradative,[3]



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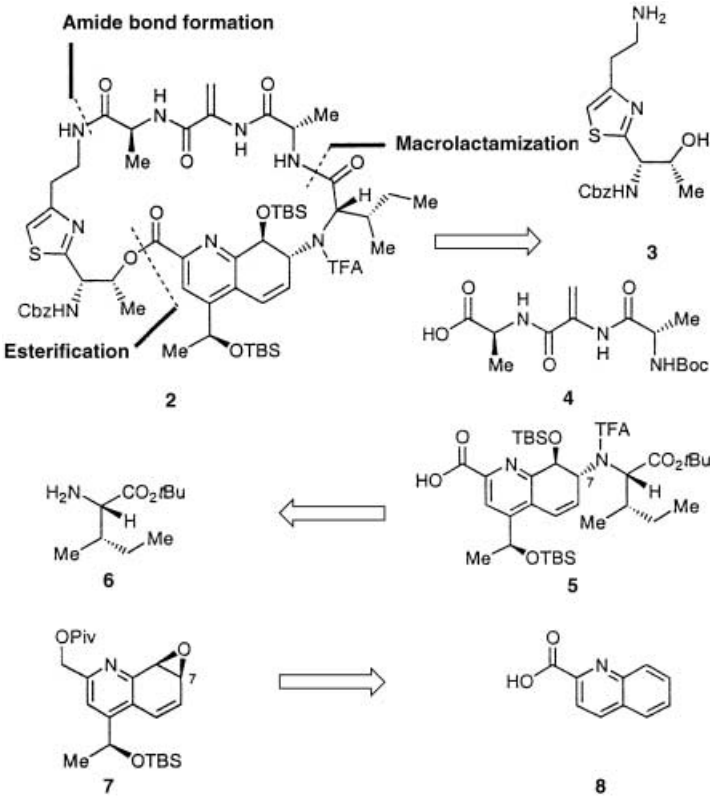
and spectroscopic techniques.[4] Produced by *Streptomyces azureus* ATCC 14921, *S. hawaiiensis* ATCC 12236, and *S. laurentii* ATCC 31255, this natural product is used as a topical antibiotic in veterinary medicine.[5] Its low solubility in water and poor bioavailability are the main obstacles that prevent its use in humans. This agent is widely used in recombinant DNA research.[6] Thiostrepton (**1**) is active against gram-positive bacteria, and exerts its biological action by binding to the 23S region of ribosomal RNA and ribosomal protein L11, thereby blocking the GTPase-dependent activities of the 50S ribosomal subunit.[7] Furthermore, **1** exhibits antimalarial activity against *Plasmodium falciparum*, which is the parasite responsible for causing over 85% of human malarial infections.[8] Isolated in 1955, thiostrepton itself still remains elusive to total synthesis, although the construction of its dehydropiperidine moiety has recently been reported;[9] simpler members of the thiopeptide family have also been prepared.[10] From a synthetic perspective, thiostrepton presents a considerable challenge, not only because of its highly complex molecular architecture, but also because of several sensitive functionalities. The most impressive features of this target molecule reside within three domains: a) region A includes the dehydropiperidine ring system that bears a quaternary center composed of three carbon atoms and a nitrogen atom and serves as the fulcrum for the molecule's two macrocycles; b) region B includes a thiazoline ring known for its sensitivity towards both acidic and basic conditions; and c) region C carries the novel quinaldic acid moiety with three asymmetric centers. Other notable features of this novel natural product include a contiguous dehydroamino acid tail (a motif which is relatively conserved throughout the thiopeptide family), three dehydroalanine moieties, one dehydrothreonine unit, a dihydroxyisoleucine side chain, and four thiazole rings. Herein we report a stereocontrolled synthesis of a model system **2** (Scheme 1) for the highly functionalized quinaldic acid macrocycle of **1**.



Scheme 1. Retrosynthetic analysis of the thiostrepton quinaldic acid macrocycle **2**.

Retrosynthetic analysis of the targeted quinaldic acid macrocycle model system **2** at two of the three indicated bonds (two amides, one ester) leads to the dehydroalanine tripeptide acid **4**, the simplified dehydropiperidine thiazole equivalent **3**, and the quinaldic acid system **5**. Further discon-

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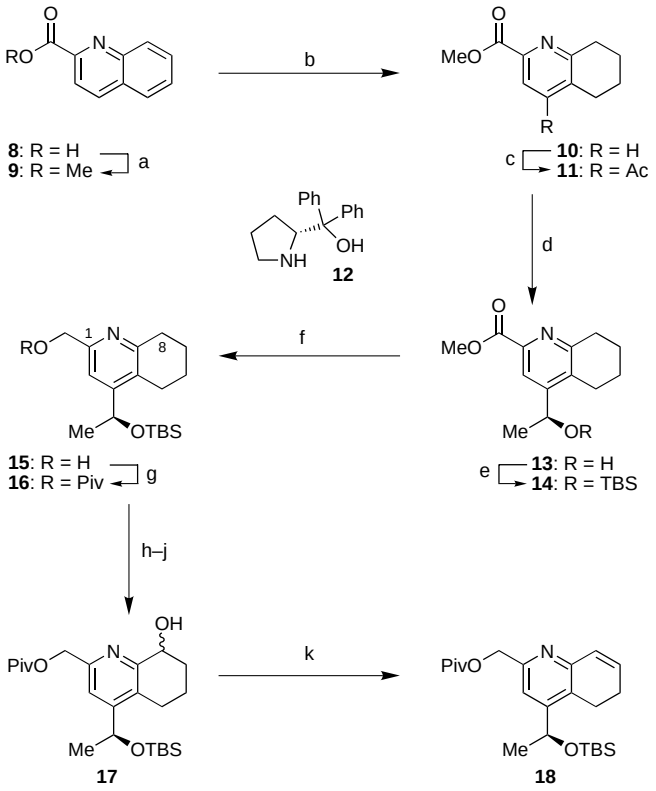
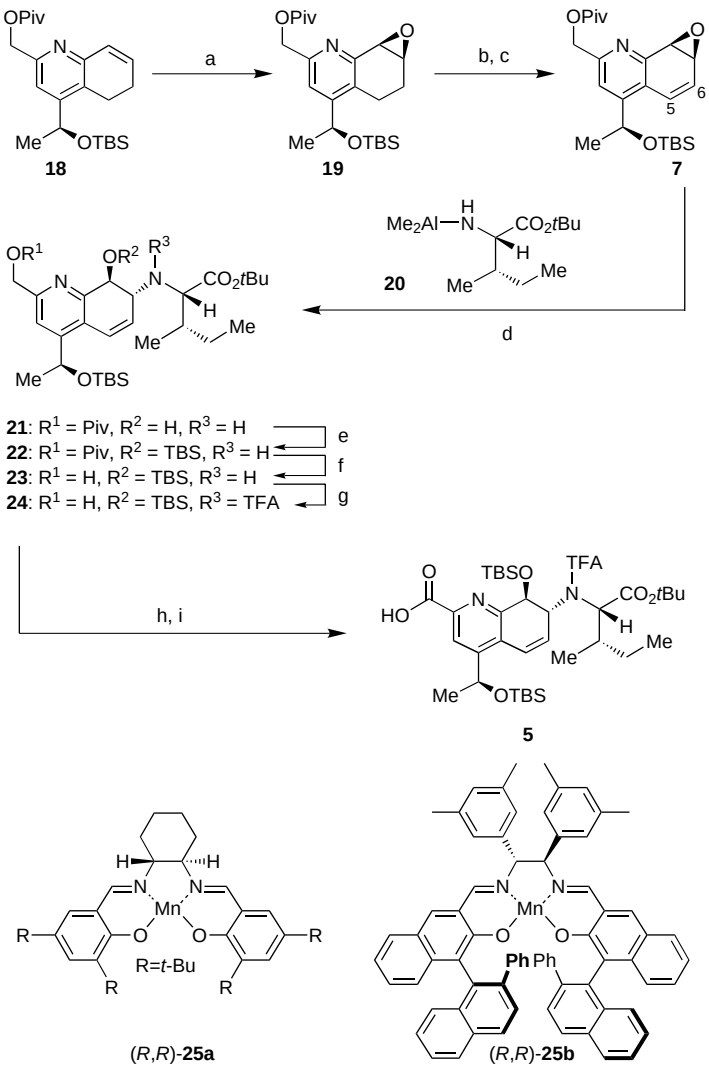
nection of the quinaldic acid fragment **5** reveals isoleucine derivative **6** and vinyl epoxide **7**. Intermediate **7** was traced to the commercially available 2-quinoline carboxylic acid (**8**). Significantly, it was envisioned that the three stereocenters of **5** could arise from an asymmetric reduction of the corresponding methyl ketone and a regioselective nucleophilic opening of the corresponding vinyl epoxide at C7 by using **6**.

Esterification of the commercially available 2-quinolinecarboxylic acid (**8**, Scheme 2) gave **9**. Selective reduction of the quinoline system **9** under catalytic hydrogenation conditions[11] afforded 5,6,7,8-tetrahydro derivative **10**. Nucleophilic addition of an acetyl radical species[12] *para* to the protonated pyridine nitrogen atom proceeded in nearly quantitative yield to generate the prochiral acetyl derivative **11**. To reduce the pyridine-containing methyl ketone **11** asymmetrically, a modified CBS[13] procedure, which required the in situ preparation of *B*-methoxyoxazaborolidine catalyst, was employed.[14] Methyl ketone **11** was reduced by using chiral ligand **12** (4 mol%) and a stoichiometric amount of $BH_3 \cdot SMe_2$ to provide alcohol **13** (95%, 90% *ee*). Following TBS protection (TBSOTf, 2,6-lutidine, 90%), the resulting ester **14** was reduced with $LiAlH_4$ to the primary alcohol **15** (88%) and subsequently protected (PivCl, pyridine, 82%) as pivaloate ester **16**. Pivaloate **16** was oxygenated at C8 by means of a Boekelheide-type cascade sequence (Scheme 2, steps h–j): 1) *m*CPBA-induced oxidation; 2) trifluoroacetylation (TFAA) of the resulting *N*-oxide; and 3) rearrangement and $NaHCO_3$-induced trifluoroacetate cleavage to give a mixture of C8 alcohols **17**[15] in 54% overall yield. Finally, elimination of triflic acid from the triflate of **17** (Tf_2O, 2,6-*t*Bu-4-Me-py) led to the desired olefin **18** in 81% yield.

Epoxidation of olefin **18** was then studied under a variety of conditions (Scheme 3), aiming for optimum diastereoselec-



Scheme 2. Synthesis of **18**. Reagents and conditions: a) MeOH, $SOCl_2$ (3.0 equiv), 60°C, 6 h, 99%; b) PtO_2/H_2, CF_3CO_2H, 25°C, 4 h, 60%; c) MeCHO, H_2O_2 (2.0 equiv), $FeSO_4$ (0.1 equiv), CF_3CO_2H (1.0 equiv), 25°C, 2 h, 99%; d) **12** (4 mol%), $B(OMe)_3$ (0.12 equiv), $BH_3 \cdot SMe_2$ (1.0 equiv), THF, 25°C, 4 h, 95%, 90% *ee*; e) TBSOTf (2.0 equiv), 2,6-lutidine (2.0 equiv), CH_2Cl_2, 0°C, 4 h, 90%; f) $LiAlH_4$ (1.1 equiv), THF, 0°C, 0.5 h, 88%; g) PivCl (3.0 equiv), pyridine (3.0 equiv), CH_2Cl_2, 25°C, 24 h, 82%; h) *m*CPBA (1.0 equiv), CH_2Cl_2, 25°C, 12 h, 99%; i) TFAA (3.0 equiv), CH_2Cl_2, 25°C, 12 h, 73%; j) aqueous $NaHCO_3$ (2M), CH_2Cl_2, 25°C, 8 h, 75%; k) Tf_2O (1.0 equiv), 2,6-*t*Bu-4-Me-pyridine (2.0 equiv), CH_2Cl_2, 25°C, 1 h, 81%. TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate; *m*CPBA = *m*-chloroperoxybenzoic acid; TFAA = trifluoroacetic anhydride; Tf_2O = trifluoromethanesulfonic anhydride; 2,6-lutidine = 2,6-dimethylpyridine; Piv = pivaloate = trimethylacetate.



Scheme 3. Synthesis of **5**. Reagents and conditions: a) **25b** (1 mol%), 4-phenylpyridine *N*-oxide, NaOCl, pH 11.5, phosphate buffer, CH_2Cl_2, 25°C, 1 h, 74%, 80% *de*; b) NBS (1.1 equiv), AIBN (10 mol%), CCl_4, 80°C, 1 h, 63%; c) DBU (1.0 equiv), PhMe, 60°C, 2 h, 86%; d) **20** (9.0 equiv), PhMe, 25°C, 36 h, 56%; e) TBSOTf (3.0 equiv), Hünig's base (5.0 equiv), CH_2Cl_2, 0°C, 4 h, 88%; f) K_2CO_3 (1.0 equiv), MeOH, 25°C, 10 h, 99%; g) TFAA (4.0 equiv), pyridine (20 equiv), CH_2Cl_2; then K_2CO_3 (1.0 equiv), MeOH, 25°C, 10 h, 84% over two steps; h) IBX (1.1 equiv), DMSO, 25°C, 4 h, 98%; i) $NaClO_2$ (2.0 equiv), NaH_2PO_4 (4.0 equiv), 2-methyl-2-butene (6.0 equiv), H_2O, *t*BuOH, 25°C, 1 h, 95%. NBS = *N*-bromosuccinimide; AIBN = 2,2′-azobisisobutyronitrile; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; IBX = *o*-iodylbenzoic acid; DMSO = dimethyl sulfoxide; Hünig's base = *N*,*N*-diisopropylethylamine.

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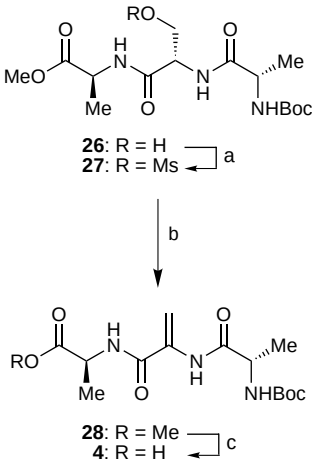
tivity. Attempts to epoxidize **18** selectively with the commercially available Jacobsen–Katsuki catalyst **25a**[16] with either NaOCl or *m*CPBA/4-methylmorpholine *N*-oxide[17] as oxidants led to low yields, poor stereoselectivity, and significant C–H oxidation, with subsequent aromatization. In contrast to these results, the more recently disclosed Katsuki catalyst **25b**[18] (1 mol %) in conjunction with NaOCl allowed selective epoxidation of **18** (74 %, 80 % *de*). Introduction of the desired double bond in **19** was then effected by selective benzylic bromination (NBS/AIBN, 63 %), followed by elimination of HBr under basic conditions in toluene at 60 °C to give epoxide **7** (86 %).[19]

The highly sensitive nature of epoxide **7** did not allow introduction of nucleophiles through Brønsted or Lewis acid activation. It was, therefore, necessary to activate the isoleucine nucleophile as its dimethylaluminum derivative **20** through the addition of stoichiometric amounts of $AlMe_3$ before the opening of **7**, which led to amino alcohol **21** regioselectively in 56 % yield.[20] Accompanying the desired product **21** was the corresponding phenol (19 %). Neither the regioisomer of **21** nor its isomer from 1,4 addition to the vinyl epoxide moiety were observed in this reaction. Interestingly, the same nucleophile **20** led to the exclusive opening of the *saturated* (C5/C6) epoxide in the opposite regiochemical sense (at C8). Amino alcohol **21** was then selectively protected as its TBS derivative **22** (TBSOTf, 2,6-lutidine, 88 %), from which the pivaloate group was smoothly removed with K_2CO_3 in MeOH (99 %) to afford intermediate **23**. To trifluoacetylate the secondary amino group, **23** was treated with TFAA in pyridine, and then K_2CO_3 in MeOH was used to cleave the trifluoroacetate selectively from the primary alcohol trifluoroacetate (84 % over two steps). The resulting product **24** was oxidized in a two-step process (IBX; $NaClO_2$) to the desired quinaldic acid fragment **5** in 93 % yield.

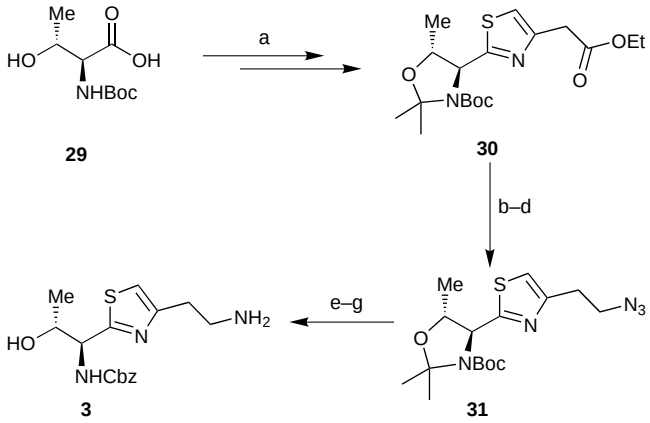
Dehydroalanine tripeptide segment **4** was synthesized from the individual component amino acid derivatives to afford **26** by following standard peptide-coupling protocols (Scheme 4).



Scheme 4. Synthesis of **4**. Reagents and conditions: a) MsCl (1.1 equiv), Et_3N (1.1 equiv), CH_2Cl_2, 0 °C, 13 h, 79 %; b) DBU (1.1 equiv), CH_2Cl_2, 0 °C, 16 h, 81 %; c) LiOH (2.0 equiv), THF, 25 °C, 2 h, 92 %. Ms = methanesulfonyl.

A mesylation/elimination sequence led to dehydroalanine tripeptide ester **28** via mesylate **27**, and, finally, LiOH-induced ester hydrolysis furnished the tripeptide carboxylic acid **4** in 92 % yield.

The required thiazole fragment **3** was derived from L-threonine **29** (Scheme 5). Standard acetonide formation and thiazole generation according to the Hantzsch protocol[21] led to derivative **30**. Reduction of the ester group ($LiBH_4$/LiCl, 88 %) in **30**, iodide formation (PPh_3, I_2, imidazole, 92 %), and displacement with NaN_3 (96 %) led to azide **31**. Acid-induced acetonide cleavage (TFA, 84 %) followed by Cbz protection (83 %) of the resulting amino group and Staudinger reduction (PPh_3/H_2O, 87 %) of the azide moiety then led to the desired thiazole **3**.



Scheme 5. Synthesis of **3**. Reagents and conditions: a) ref. [21]; b) $LiBH_4$ (3.0 equiv), LiCl (3.0 equiv), THF, 25 °C, 24 h, 88 %; c) PPh_3 (1.3 equiv), imidazole (1.4 equiv), I_2 (1.5 equiv), 25 °C, 1.5 h, 92 %; d) NaN_3 (1.0 equiv), DMF, 25 °C, 14 h, 96 %; e) TFA, CH_2Cl_2, 0 °C, 6 h, 84 %; f) CbzCl (1.0 equiv), $NaHCO_3$, THF/H_2O (1:1), 25 °C, 4 h, 83 %; g) PPh_3 (1.0 equiv), THF, H_2O, 50 °C, 6 h, 87 %. DMF = *N*,*N*-dimethylformamide; TFA = trifluoroacetic acid; Cbz = benzyloxy carbonyl.

The assembly of the quinaldic acid macrocycle **2** began with the coupling of carboxylic acid fragment **4** with amino thiazole derivative **3** under EDC/HOBt conditions, which led to secondary alcohol **32** in 71 % yield (Scheme 6). Quinaldic acid derivative **5** was appended onto fragment **32** by means of a Yamaguchi esterification[22] to furnish advanced intermediate **33** in 71 % yield. The Boc and *t*Bu groups were then removed from **33** by TFA in the presence of triisopropylsilane (to prevent degradation of the dehydroalanine moiety) to afford amino acid **34** (86 %). Ring closure of **34** led to macrocycle **2** in an unoptimized yield of 30 %.

The described chemistry offers methods for the construction of the quinaldic acid system[24] of thiostrepton (**1**) and its incorporation into the macrocycle of the natural product. The following communication describes the construction of the dehydropiperidine domain of this target molecule.[23]

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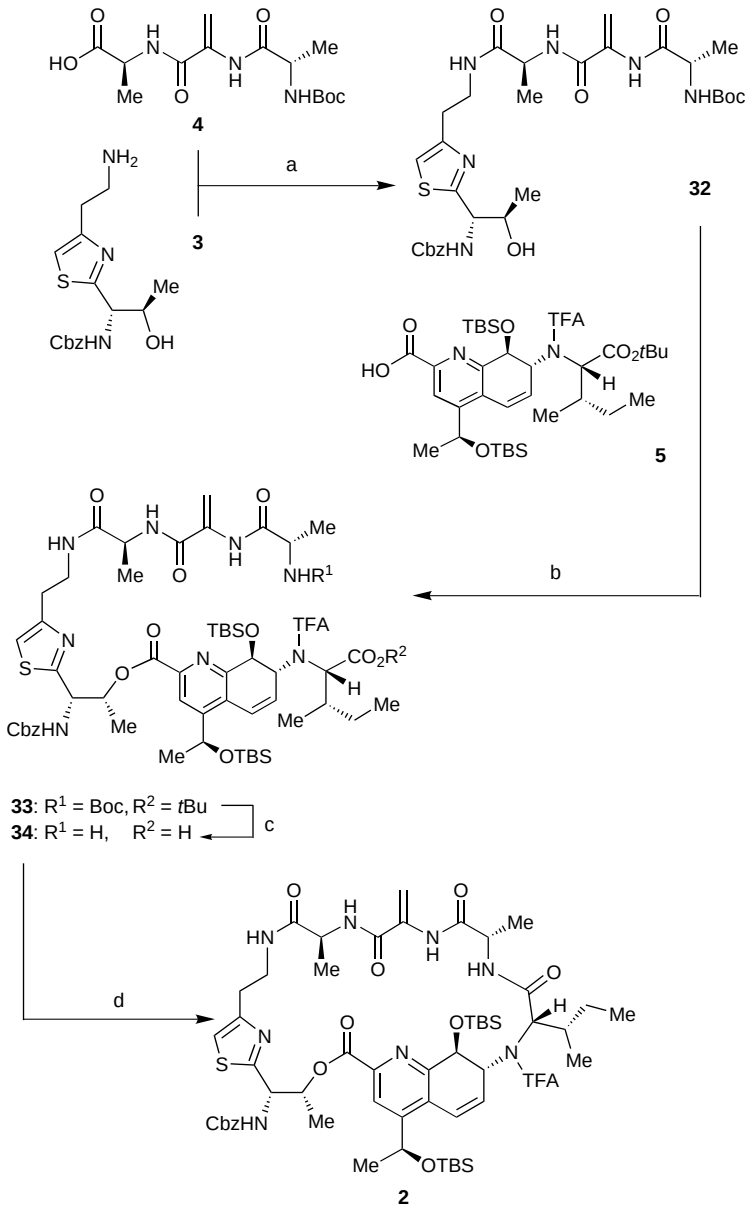

Scheme 6. Synthesis of **2**. Reagents and conditions: a) EDC (1.1 equiv), HOBt (1.1 equiv), DMF, 0°C, 16 h, 72%; b) 2,4,6-trichlorobenzoyl chloride (1.5 equiv), Et_3N (7.0 equiv), PhMe; then 4-DMAP (2.5 equiv), **5** (1.3 equiv), THF, 25°C, 71%; c) TFA/CH_2Cl_2 (3:1), triisopropylsilane (19 equiv), 25°C, 2.5 h, 86%; d) HATU (3.0 equiv), 2,4,6-collidine (9.0 equiv), MeCN, 0°C, 24 h, 30%. EDC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; HOBt = 1-hydroxybenzotriazole hydrate; 4-DMAP = 4-dimethylaminopyridine; HATU = *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate; 2,4,6-collidine = 2,4,6-trimethylpyridine.

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[24] Note added in proof: For an alterntive approach to a quinaldic acid system, see: S. Higashibayashi, T. Mori, K. Shinko, K. Hashimoto, M. Nakata, *Heterocycles* **2002**, *57*, 111 – 122.

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