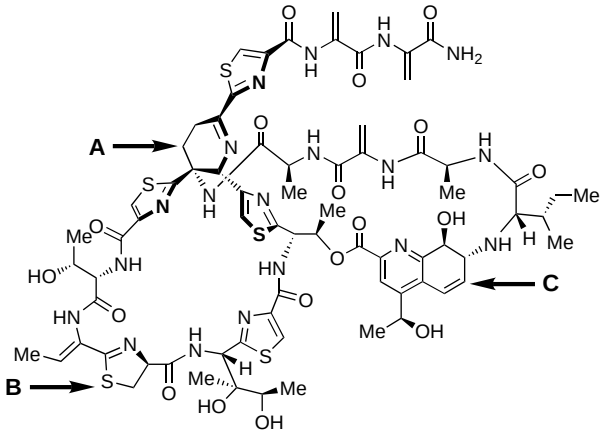
Stereocontrolled Synthesis of the Quinaldic Acid Macrocyclic System of Thiostrepton**

K. C. Nicolaou,* Brian S. Safina, Christian Funke, Mark Zak, and Frédéric J. Zécri

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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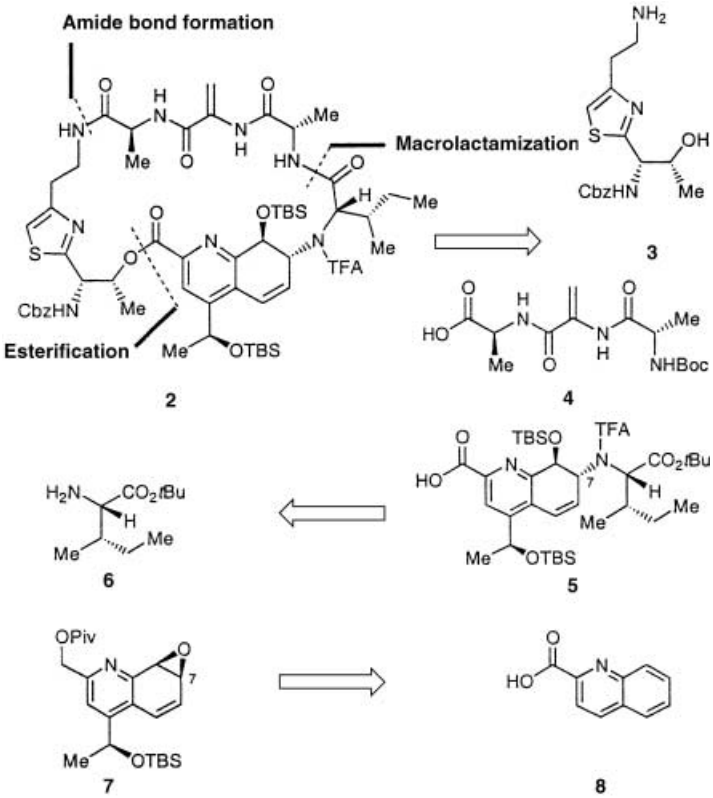
and spectroscopic techniques.[4] Produced by *Streptomyces azureus* ATCC 14921, *S. hawaiiensis* ATCC 12236, and *S. laurentii* ATCC 31255, this natural product is used as a topical antibiotic in veterinary medicine.[5] Its low solubility in water and poor bioavailability are the main obstacles that 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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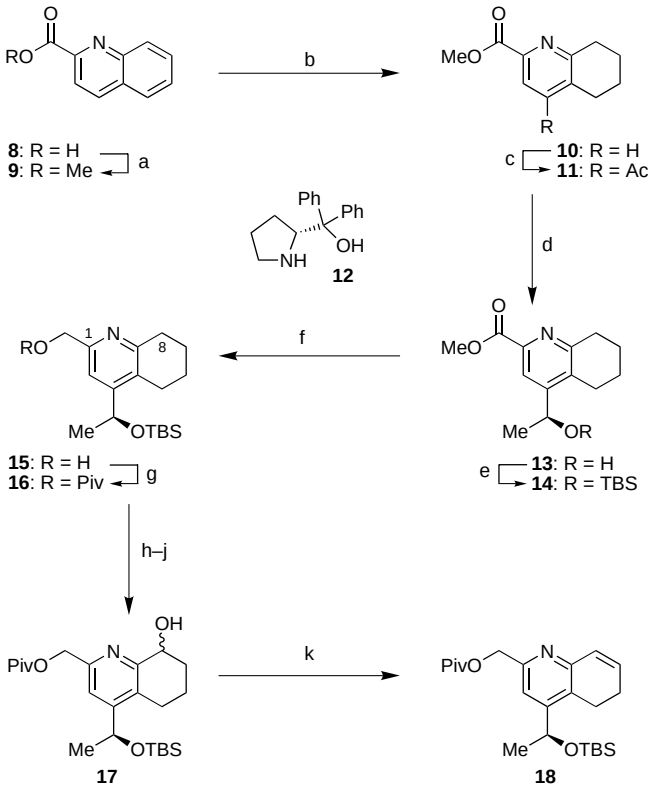
[**] We thank Drs. D. H. Huang and G. Suizdak for NMR spectroscopic and mass spectrometric assistance, respectively, as well as Mike Sertic (University of California, San Diego) for experimental assistance. Financial support for this work was provided by The Skaggs Institute for Chemical Biology, the National Institutes of Health (USA), fellowships from The Skaggs Institute for Research (to M.Z. and F.Z.), and grants from Abbott, Amgen, Array Biopharma, Boehringer-Ingelheim, Glaxo, Hoffmann-LaRoche, DuPont, Merck, Novartis, Pfizer, and Schering Plough.

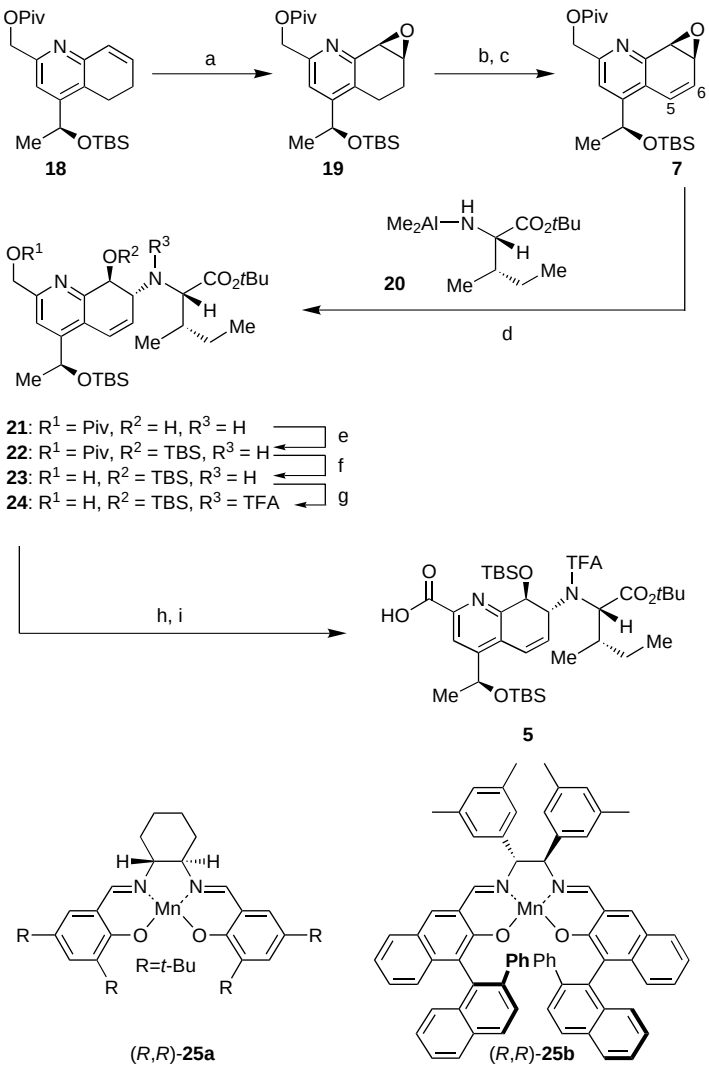
nection of the quinaldic acid fragment **5** reveals isoleucine derivative **6** and vinyl epoxide **7**. Intermediate **7** was traced to the commercially available 2-quinoline carboxylic acid (**8**). Significantly, it was envisioned that the three stereocenters of **5** could arise from an asymmetric 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.



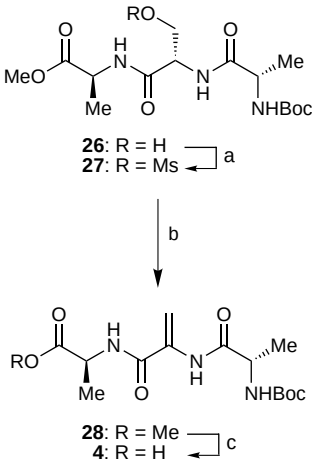
Scheme 3. Synthesis of **5**. Reagents and conditions: a) **25b** (1 mol%), 4-phenylpyridine *N*-oxide, NaOCl, pH 11.5, phosphate buffer, CH_2Cl_2, 25°C, 1 h, 74%, 80% *de*; b) NBS (1.1 equiv), AIBN (10 mol%), CCl_4, 80°C, 1 h, 63%; c) DBU (1.0 equiv), PhMe, 60°C, 2 h, 86%; d) **20** (9.0 equiv), PhMe, 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.

  0044-8249/02/11411-2018 $ 20.00+.50/0 *Angew. Chem.* **2002**, *114*, Nr. 11

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.

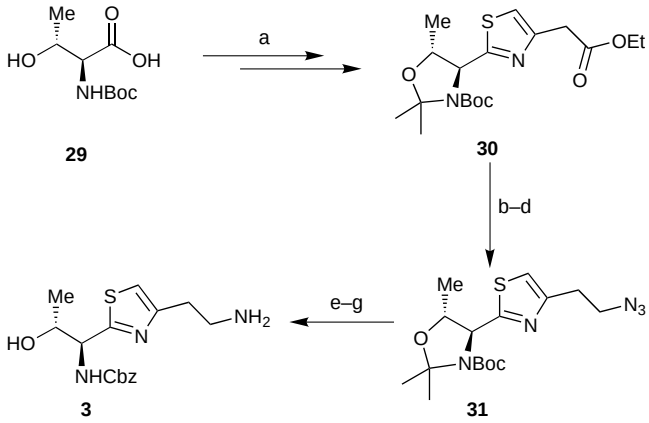
Dehydroalanine tripeptide segment **4** was synthesized from the individual component amino acid derivatives to afford **26** by following standard peptide-coupling protocols (Scheme 4).



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**.

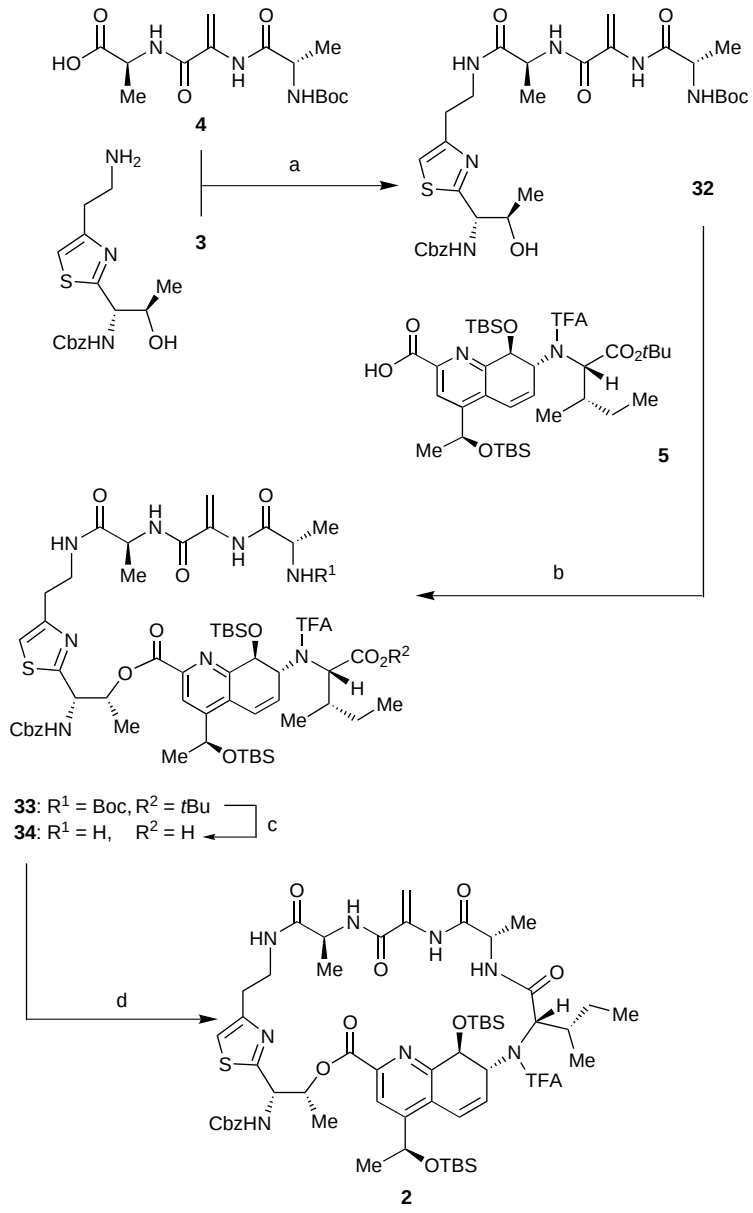


Scheme 5. Synthesis of **3**. Reagents and conditions: a) ref. [21]; b) $LiBH_4$ (3.0 equiv), LiCl (3.0 equiv), THF, 25 °C, 24 h, 88 %; c) PPh_3 (1.3 equiv), imidazole (1.4 equiv), I_2 (1.5 equiv), 25 °C, 1.5 h, 92 %; d) NaN_3 (1.0 equiv), DMF, 25 °C, 14 h, 96 %; e) TFA, CH_2Cl_2, 0 °C, 6 h, 84 %; f) 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]

Received: January 2, 2002 [Z 18462]



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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