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Synthetic studies on thiostrepton family of peptide antibiotics: synthesis of the dihydroquinoline portion of thiostrepton, the siomycins, and the thiopeptins

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Abstract—Synthesis of the dihydroquinoline portion of thiostrepton, the siomycins, and the thiopeptins, members of the thiostrepton family of peptide antibiotics, has been achieved featuring the one-pot olefination via the Matsumura–Boekelheide rearrangement ''using trifluoromethanesulfonic anhydride and triethylamine'' and the stereoselective addition reaction controlled by the stereocenter of the peri-position.

We have recently reported the synthesis of the dehydropiperidine,[1] dihydroquinoline,[2] and pentapeptide[3] segments (**1**, **2**, and **3**, respectively) of the thiostrepton family of peptide antibiotics (Fig. 1).[4–6] Compound **2** having the hydroxymethyl group is, however, the dihydroquinoline portion of only siomycin D_1. In this letter, we report the synthesis of the hydroxyethyl-bearing dihydroquinoline segment **4** of the more popular thiostrepton family of peptide antibiotics (e.g., thiostrepton, siomycins A and C, and thiopeptin A_{1b}, Fig. 1) via two different synthetic routes for the construction of the asymmetric center attached by the methyl group: the stereoselective addition of the methyl group to the aldehyde function and the stereoselective reduction of the methyl ketone function. In addition, we developed a one-pot procedure using trifluoromethanesulfonic anhydride (Tf_2O) and triethylamine to introduce the olefin function into the C7–C8 position of the 5,6,7,8-tetrahydroquinoline derivative via the Matsumura–Boekelheide rearrangement. In the following letter,[7] we report the synthesis of the siomycin cyclic core portion containing the dehydropiperidine, dihydroquinoline (i.e., **4**), L-valine, and masked dehydroalanine (i.e., β-phenylselenoalanine) segments.

We have previously synthesized the dihydroquinoline segment **2** of siomycin D_1 from 5,6,7,8-tetrahydroquinoline (**5**) featuring the modified Reissert–Henze reaction (**5**→**6**), the radical heteroaromatic substitution reaction (**6**→**7**), the Boekelheide rearrangement (**7**→**8**), and the Jacobsen asymmetric epoxidation (**8**→**9**) as the key steps (Scheme 1).[2] The intermediate aldehyde **9** (91% ee) was the starting substance for our first route. After a variety of unsuccessful experiments, the best conditions so far to introduce the methyl group to aldehyde **9** were as follows (Scheme 2). MeMgBr/Et_2O (1.1 equiv, 3 M) was added at −78 °C to a solution of **9** (1.0 equiv) and HMPA (1.1 equiv) in toluene. After 0.5 h at −78 °C, the desired addition product **10** was obtained in 48% yield together with the undesired stereoisomer **11** (15%) and the recovered **9** (20%). The configuration of the newly formed chiral center in **10** was determined by the transformation of **10** into the quinoline derivative **12**,[8] which was identical to the degradation product derived from thiostrepton[9] and siomycin A.[10] The configuration at the C5 position in **9** plays a key role in the

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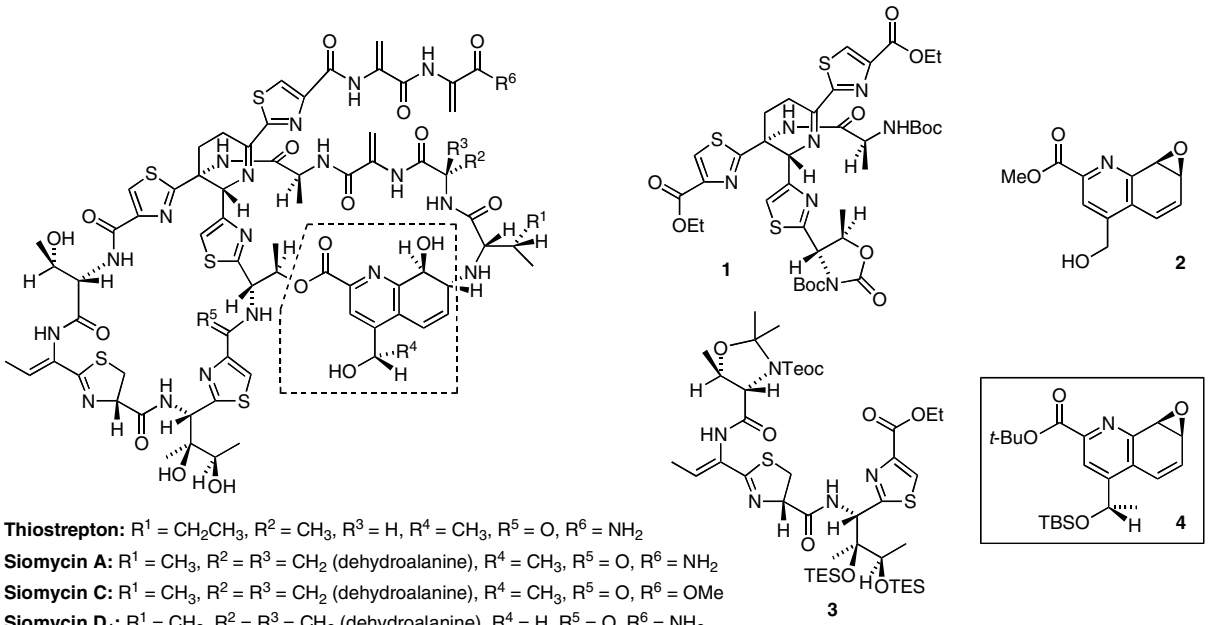


Thiostrepton: $R^1 = CH_2CH_3$, $R^2 = CH_3$, $R^3 = H$, $R^4 = CH_3$, $R^5 = O$, $R^6 = NH_2$

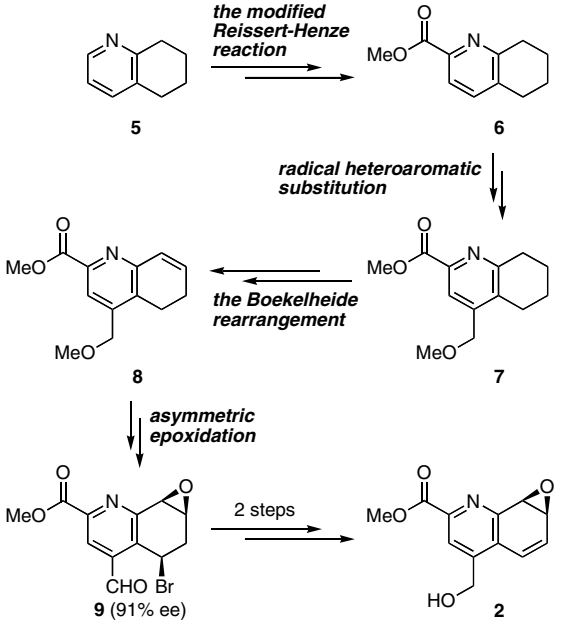
Siomycin A: $R^1 = CH_3$, $R^2 = R^3 = CH_2$ (dehydroalanine), $R^4 = CH_3$, $R^5 = O$, $R^6 = NH_2$

Siomycin C: $R^1 = CH_3$, $R^2 = R^3 = CH_2$ (dehydroalanine), $R^4 = CH_3$, $R^5 = O$, $R^6 = OMe$

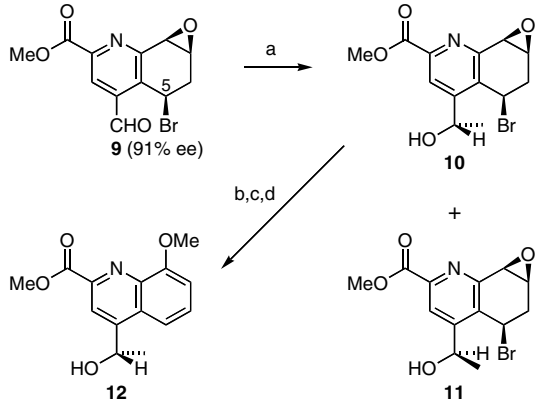
Siomycin D_1: $R^1 = CH_3$, $R^2 = R^3 = CH_2$ (dehydroalanine), $R^4 = H$, $R^5 = O$, $R^6 = NH_2$

Thiopeptin A_{1b}: $R^1 = CH_3$, $R^2 = CH_3$, $R^3 = H$, $R^4 = CH_3$, $R^5 = S$, $R^6 = OMe$

Figure 1.



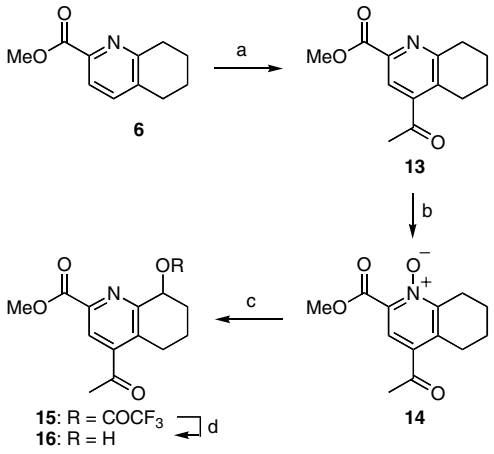
Scheme 1. Synthesis of the dihydroquinoline segment **2** of siomycin D_1.



Scheme 2. Synthesis of **10**. Reagents and conditions: (a) 3 M MeMgBr/Et_2O (1.1 equiv), HMPA (1.1 equiv), toluene, −78 °C, 0.5 h, 48% of **10**, 15% of **11**, 20% of **9**; (b) DBU (3.0 equiv), THF, rt, 1 h; (c) 1 M aq HCl, rt, 6 h; (d) CH_2N_2, MeOH, rt, 1 h, 83% (three steps). HMPA = hexamethylphosphoric triamide, DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene.

stereoselectivity of this reaction, the details of which will be discussed later. Although the hydroxyethyl-bearing dihydroquinoline substructure was secured at this stage, the synthetic route from **5** to **10** was lengthy and the total yield was not satisfactory. Therefore, we investigated a new route including the stereoselective reduction of the methyl ketone function.

Instead of hydroxymethylation (**6**→**7**, Scheme 1), methyl ester **6** was acetylated under the radical heteroaromatic substitution conditions[11] to afford **13** in 84% yield (Scheme 3), which was oxidized to *N*-oxide **14** with MCPBA in 88% yield. According to our reported procedure,[2] *N*-oxide **14** was next subjected to the Boekelheide rearrangement[12] with trifluoroacetic anhydride (TFAA) followed by hydrolysis of the resulting trifluoroacetate **15** in one pot with sodium methoxide to afford **16** in 52% yield. We expected that under the non-protic conditions, the olefin function would be directly introduced into the C7–C8 position. It was found that the one-pot treatment of **15** with DBU (3 equiv) at rt for 20 min afforded the elimination product **17** albeit in low yield (22%, see the figure of Table 1). Therefore, we anticipated that using Tf_2O instead of TFAA in the Matsumura–Boekelheide rearrangement would more efficiently afford the elimination product **17**.[13,14] The relevant



Scheme 3. Synthesis of **16**. Reagents and conditions: (a) MeCHO, H_2O, TFA (1.0 equiv), $FeSO_4{\cdot}7H_2O$ (0.1 equiv), aq H_2O_2 (2.0 equiv), 0 °C to rt, 3 h, 84%; (b) MCPBA (2.0 equiv), CH_2Cl_2, 0 °C to rt, 6 h, 88%; (c) TFAA (1.2 equiv), THF, rt, 40 min; (d) NaOMe (2.0 equiv), MeOH, rt, 20 min, 52% (two steps). MCPBA = 3-chloroperoxybenzoic acid.

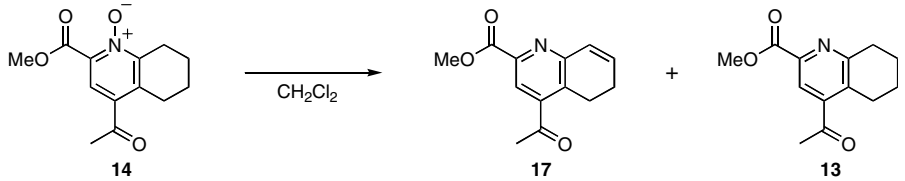
experimental data along this line are shown in Table 1. The treatment of **14** in CH_2Cl_2 with Tf_2O and the consecutive addition of 2,6-lutidine or diisopropylethylamine (DIPEA) expectedly afforded the elimination product **17** (entries 1 and 2). Interestingly but unexpectedly, deoxygenation of *N*-oxide **14** to **13** accompanied this reaction. Fortunately, we found that dilution of DIPEA in CH_2Cl_2 raised the ratio of **17**:**13** from 3.8:1 to 5.6:1 (entries 2 and 3). Triethylamine was found to be a more suitable base; the ratio was improved to 10:1 (entry 4). Finally, the best result was obtained by the slow addition of a 0.45 M CH_2Cl_2 solution of triethylamine to a solution of **14** and Tf_2O in CH_2Cl_2, giving only **17** in 98% yield (entry 6). To the best of our knowledge, this is the first example using Tf_2O in the Matsumura–Boekelheide rearrangement.[15]

Although the reaction mechanism for the accompanied deoxygenation remains to be solved,[16] that for the olefination using Tf_2O and a base via the Matsumura–Boekelheide rearrangement seems to be probable as depicted in Scheme 4. In the case of the Boekelheide rearrangement using TFAA,[12] the first step is the trifluoroacetylation of *N*-oxide **A** (=**14**) to give **B**. The trifluoroacetate anion abstracts the proton to give the unstable intermediate **C**, which undergoes rearrangement to give **D** (=**15**); then the base hydrolysis of **D** finally affords alcohol **E** (=**16**). For the Tf_2O case, *N*-oxide **A** is sulfonylated to give **F**, which is a stable trifluoromethanesulfonyloxy salt.[14] The base abstracts the proton to give the unstable intermediate **G**, which undergoes rearrangement to give **H**; finally, the β-elimination of **H** affords olefin **I** (=**17**).

Asymmetric epoxidation of **17** with Jacobsen's reagent **18**[17] afforded epoxide **19** (75% ee)[18] in 54% yield together with an 18% yield of the quinoline derivative **20** (Scheme 5). The absolute configuration of **19** was determined in the next stage. Bromination of **19** with NBS in CCl_4 afforded **21** in 56% yield together with a 6% yield of its diastereomer. The absolute configuration of **21** (and hence **19**) was confirmed by X-ray crystallographic analysis (Fig. 2).[19] After many unsuccessful reduction experiments using DIBAL, $LiBH(s\text{-}Bu)_3$, and $BH_3{\cdot}THF$, we found that the treatment of **21** with $NaBH_4$ in MeOH at −78 °C for 19 h afforded the desired reduction product **10** and its stereoisomer **11** in 81% and 11% yields, respectively.

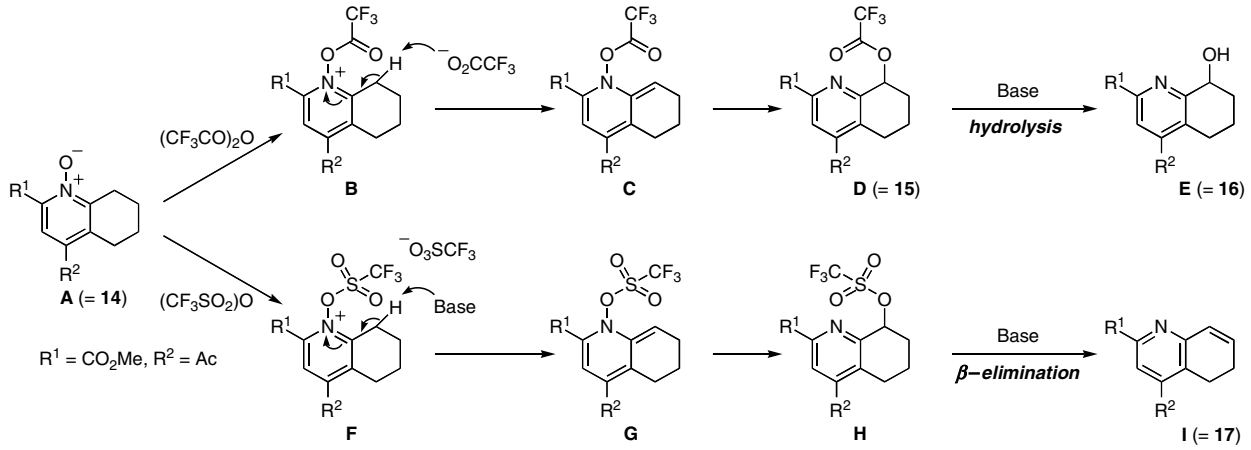
The stereoselectivity observed in the addition reactions to aldehyde **9** and methyl ketone **21** may be interpreted as follows (Scheme 6). Aldehyde **9**, coordinated with the

Table 1. One-pot olefination of **14** via the Matsumura–Boekelheide rearrangement

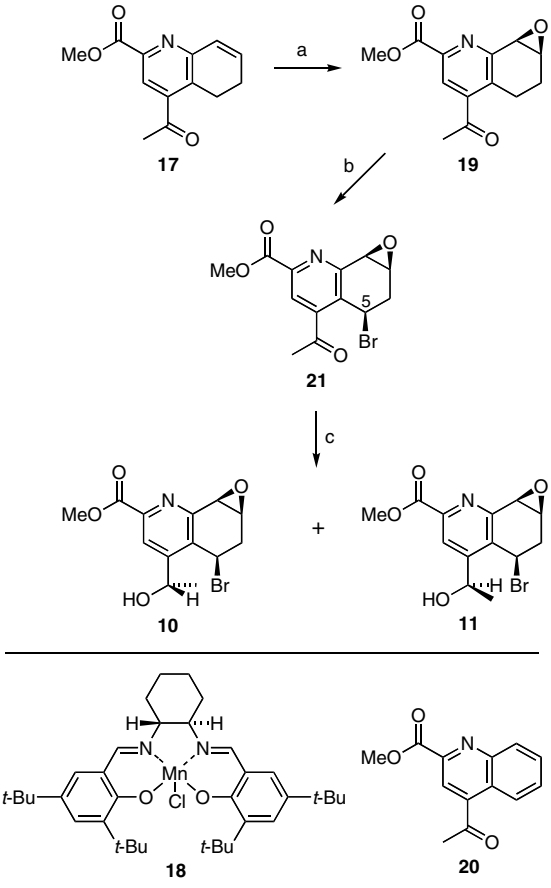


Entry	Conditions	Yield (%)[a] of **17**+**13**	Ratio[b] of **17**:**13**
1	Tf_2O (1.2 equiv) was added at 0 °C, then 2,6-lutidine (5.0 equiv) was added at 0 °C, then rt, 4 h	63	2.8:1
2	Tf_2O (1.2 equiv) was added at 0 °C, then DIPEA (5.0 equiv) was added at 0 °C, then rt, 4 h	54	3.8:1
3	Tf_2O (1.2 equiv) was added at 0 °C, then 2 M DIPEA (5.0 equiv)/CH_2Cl_2 was added at 0 °C during 10 min, then rt, 5 h	66	5.6:1
4	Tf_2O (1.2 equiv) was added at 0 °C, then 2 M Et_3N (5.0 equiv)/CH_2Cl_2 was added at 0 °C during 10 min, then rt, 5 h	58	10:1
5	Tf_2O (1.2 equiv) was added at 0 °C, then 0.45 M Et_3N (5.0 equiv)/CH_2Cl_2 was added at 0 °C during 0.5 h, then rt, 5 h	74	**17** only
6	Tf_2O (1.2 equiv) was added at 0 °C, then 0.45 M Et_3N (5.0 equiv)/CH_2Cl_2 was added at 0 °C during 1 h, then rt, 5 h	98	**17** only

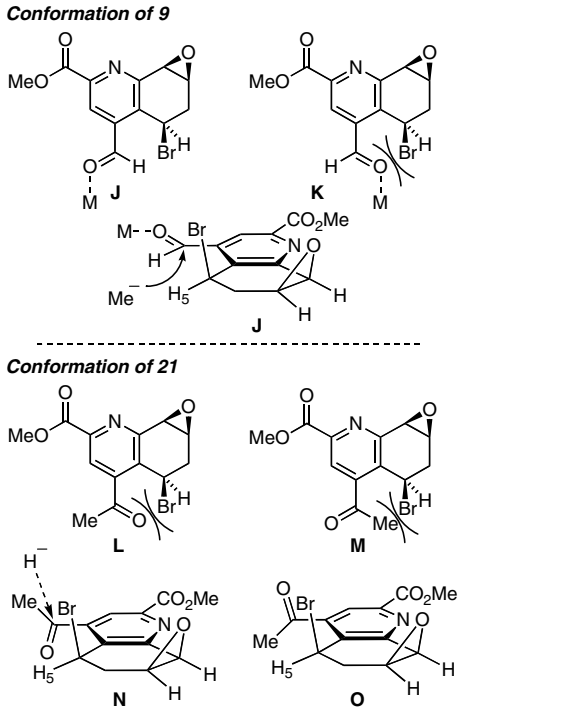
[a] Isolated yield (**17**+**13**) after silica-gel column chromatography.
[b] The ratio of **17**:**13** was based on ^1H NMR analysis of the isolated products.



Scheme 4. Mechanisms for the Boekelheide rearrangement and one-pot olefination via the Matsumura–Boekelheide rearrangement.



Scheme 5. New synthesis of **10**. Reagents and conditions: (a) **18** (0.05 equiv), 4-phenylpyridine *N*-oxide (0.5 equiv), PhIO (2.0 equiv), CH_3CN, −10 °C, 12 h, 54% of **19** (75% ee), 18% of **20**; (b) NBS (1.1 equiv), AIBN (0.1 equiv), CCl_4, 140 W sun lamp, 60 °C, 4 h, 56%, 6% of the diastereomer of **21**; (c) $NaBH_4$ (4.0 molar amounts), MeOH, −78 °C, 19 h, 81% of **10**, 11% of **11**. NBS = *N*-bromosuccinimide, AIBN = 2,2′-azobisisobutyronitrile.



Scheme 6. Plausible explanation for stereoselectivity in the reactions of **9** with MeMgBr and **21** with $NaBH_4$.

metal species under the stated reaction conditions, seems to prefer the conformation depicted as **J** rather than the conformation **K** because of steric crowding. The attack of a methyl anion seems to occur from the si-face of the aldehyde plane to avoid the bromine atom, affording the major isomer **10**.[20] In contrast, the carbonyl and pyridine planes of methyl ketone **21** seem to be twisted to avoid the steric repulsion found in the conformations **L** and **M**. Among the two conformations **N** and **O**, the former would be preferable to the latter from the view point of dipole–dipole interaction.[21] The hydride attack seems to occur from the re-face of the carbonyl plane, affording the major isomer **10**.

Comparing these two routes aimed at the preparation of **10**, the first one consists of the 15 steps from **5** to **10** in a 1.8% overall yield and the second one in 10 steps in a 14% overall yield. Therefore, through the second route,

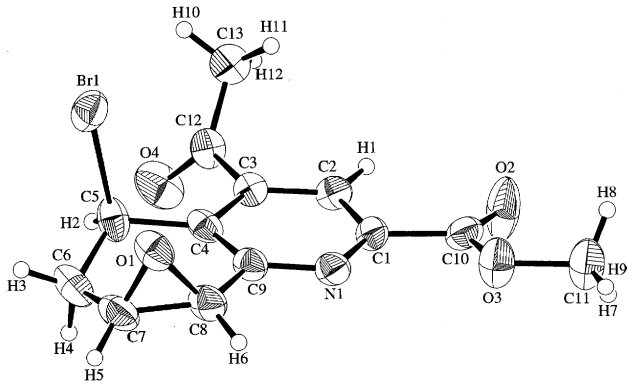
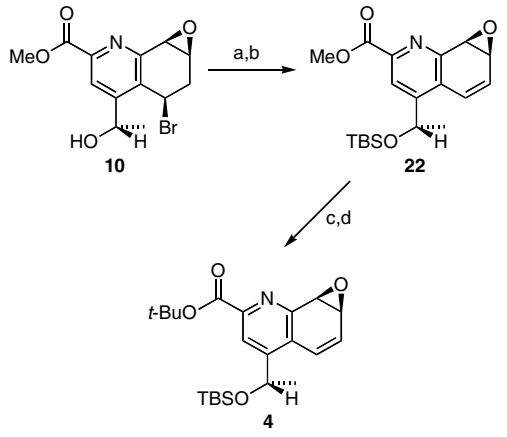


Figure 2. X-ray crystal structure of **21**.



Scheme 7. Synthesis of the dihydroquinoline segment **4**. Reagents and conditions: (a) TBSOTf (1.2 equiv), 2,6-lutidine (2.0 equiv), CH_2Cl_2, 0 °C, 0.5 h, 82%; (b) DBU (3.5 equiv), THF, rt, 1h, 95%; (c) TMSOK (1.0 equiv), Et_2O, 0 °C, 0.5 h; (d) Boc_2O (2.0 equiv), DMAP (0.3 equiv), *t*-BuOH, rt, 3 h, 86% (two steps). TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl, Boc = *tert*-butoxycarbonyl, DMAP = 4-(dimethylamino)pyridine.

we could obtain sufficient amounts of the hydroxyethyl-bearing dihydroquinoline substructure.

After silylation (82%) of **10**, the resulting silyl ether was subjected to dehydrobromination with DBU to afford **22** in 95% yield (Scheme 7). Methyl ester **22** was transformed into the desired dihydroquinoline segment **4** by deprotection with TMSOK[22] followed by re-esterification with Boc_2O[23] in 86% yield.

In summary, we have synthesized the dihydroquinoline segment **4** of thiostrepton, the siomycins, and the thiopeptins. The key reactions are the one-pot olefination via the Matsumura–Boekelheide rearrangement using Tf_2O and triethylamine and the stereoselective addition reaction controlled by the stereocenter of the peri-position. In the following letter,[7] we will describe the synthesis of the siomycin cyclic core portion containing the dehydropiperidine, dihydroquinoline (i.e., **4**), L-valine, and masked dehydroalanine (i.e., β-phenylselenoalanine) segments.

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18. The enantiomeric excess was not optimized. It was determined by chiral HPLC analysis (Daicel Chiralcel OD column, 4.6×250 mm, 90:10 hexane–IPA; 1 mL/min, 254 nm, $t = 20.6$ min; enantiomer of **19**, $t = 30.8$ min).
19. Recrystallization of **21** from 1:3 dioxane–hexane twice afforded crystals suitable for X-ray crystallographic analysis. Crystallographic data for **21** have been deposited with the Cambridge Crystallographic Data Centre with number 279853.
20. The fact that the compound **10** derived from **9** was identical with that derived from methyl ketone **21** confirmed the structure of **9** which had not been determined.
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