Total Synthesis of (−)-Thiangazole, a Naturally-Occurring HIV-1 Inhibitor

Rodney L. Parsons, Jr., and Clayton H. Heathcock*

Department of Chemistry, University of California, Berkeley, California 94720

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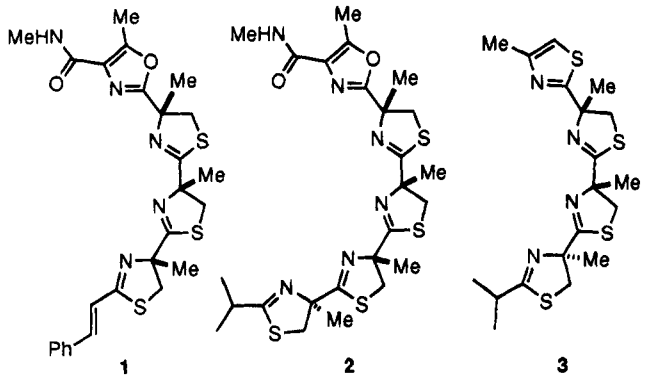
Summary: (−)-Thiangazole (**1**), a naturally-occurring inhibitor of HIV-1, has been prepared by total synthesis.

(−)-Thiangazole (**1**), isolated by Jansen and co-workers[1] from the gliding bacterium *Polyangium spec.*, is a structurally novel inhibitor of HIV-1. The compound is 100% effective against HIV-1 at 4.7 pM, shows no cell toxicity at 4.7 mM, and is highly selective for HIV-1 over HIV-2.[1a] It is related to a family of polythiazolines isolated from blue-green algae, of which tantazole B (**2**) and mirabazole B (**3**) are representative.[2,3] In this paper, we report a total synthesis of (−)-thiangazole (**1**).[4]



1 **2** **3**

As shown in Scheme 1, the previously-reported tripeptide **4**[4b] is deprotected by treatment with HBr in glacial acetic acid containing thioanisole[5] to obtain amine **5**, which is converted into amide **6** by treatment with dihydrocinnamoyl chloride in the presence of (*N,N*-dimethylamino)pyridine and Hünig's base in methylene chloride. After saponification of the methyl ester, acid **7** is coupled with the hydrochloride salt of *O*-benzylthreonine *N*-methylamide (**8**) by the method of Coste and coworkers.[6,7] Tetrapeptide **9** is reductively debenzylated, and the crude product is cyclized by treatment with $TiCl_4$ in CH_2Cl_2 to obtain the trithiazoline **10** in 68% yield, accompanied by 8% of a byproduct lacking the secondary alcohol. Compound **10** undergoes smooth oxidation to **11** upon treatment with the Dess–Martin reagent.[8] The oxazoline ring is closed by treatment of **11** with *p*-toluenesulfonic acid in refluxing benzene.[9] The synthesis is completed by dehydrogenation of the phenylethyl side chain with dichlorodicyanoquinone in benzene.[10]

The key to the synthesis was the development of an effective method for formation of the oxazole ring in the presence of the three thiazoline rings. The first method that we explored was cyclization of the threonine amide **10** to an oxazoline by treatment with Burgess' salt in refluxing THF according to the procedure of Wipf.[11] Although we did obtain the desired oxazoline by this method in 43% yield, oxidation to the oxazole failed.[12] Several other reagents (e.g., $SOCl_2$, $POCl_3$, $TiCl_4$) were not effective for the Robinson–Gabriel cyclodehydration of **11** to **12**. We were also unable to cyclize **11** by treatment with triphenylphosphine and iodine.[4d]

The synthetic (−)-thiangazole was identified by comparison of its ^1H NMR, ^{13}C NMR, IR, and UV spectra and optical rotation with those of an authentic sample.[1a] In summary, acid **7** is prepared in six steps in 34% overall yield starting from (*R*)-*N*-carbobenzyloxy-*S*-benzyl-2-methylcysteine and (*R*)-*S*-benzyl-2-methylcysteine methyl ester.[4b] Amide **8** is prepared in four steps in 89% overall yield starting from the commercially-available *t*-Boc derivative of *O*-benzylthreonine. Coupling of **7** with **8** and completion of the synthesis requires a total of five steps and proceeds in 23% overall yield. Thus, a total of 15 steps is required, with the longest linear sequence being 11 steps. The overall yield for the longest linear sequence is 8%.

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Supplementary Material Available: Experimental procedures and analytical data for all new compounds reported

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(7) Compound **8** is prepared from the commercially-available *t*-Boc derivative of *O*-benzylthreonine by a convenient four-step procedure (89% overall yield): 1. diazomethane in CH_2Cl_2; 2. methylamine in methanol; 3. trifluoroacetic acid in CH_2Cl_2 at 0 °C; 4. gaseous HCl in CH_2Cl_2.

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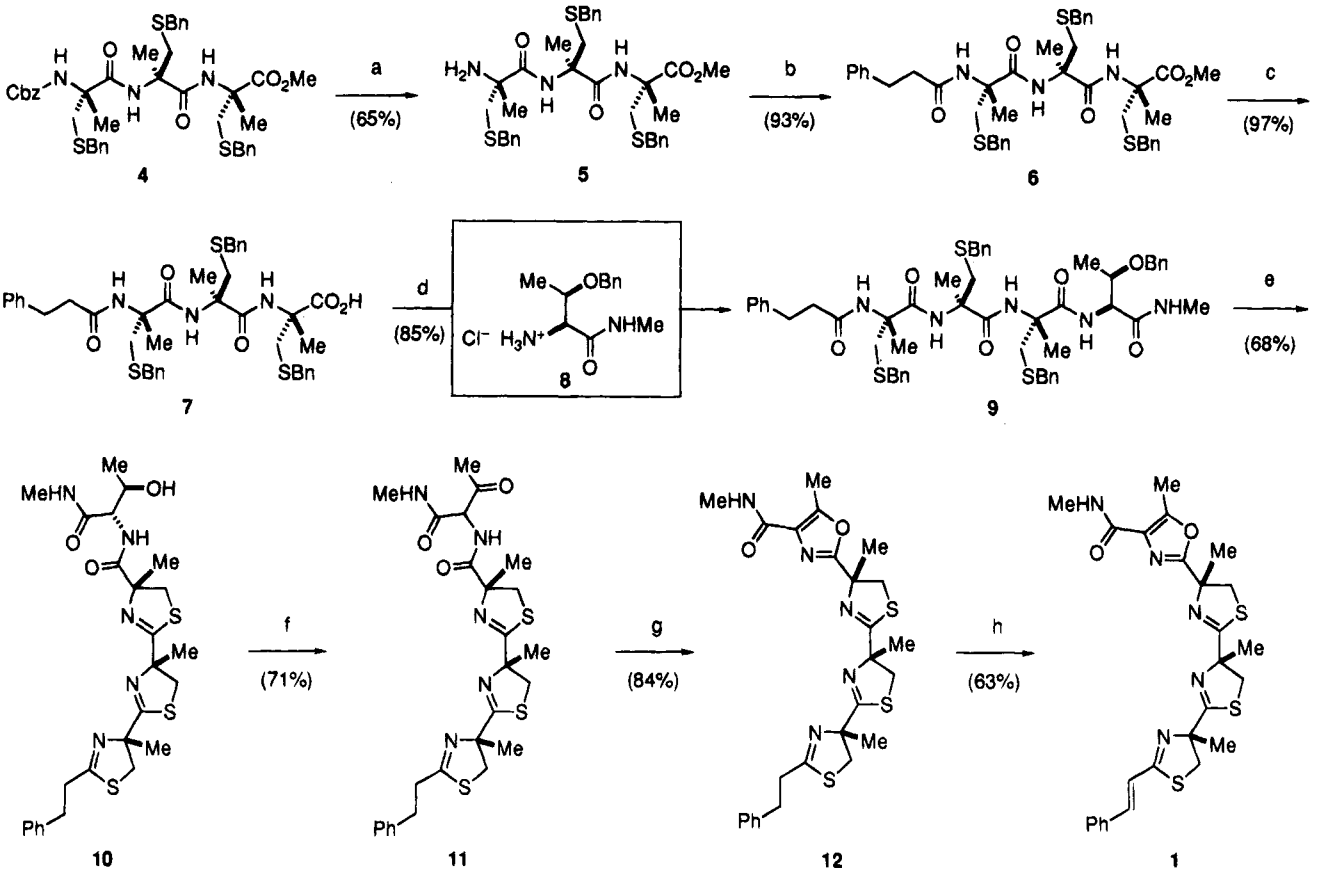
Scheme 1[a]



[a] (a) HBr, HOAc, thioanisole, CH_2Cl_2, rt; (b) $PhCH_2CH_2COCl$, DMAP, *i*-Pr_2EtN, −78 °C; (c) NaOH, DMF, rt; (d) PyBROP, DMAP, Hünig's base, CH_2Cl_2, rt; (e) (i) Na, NH_3, THF, −78 °C; (ii) NH_4Cl; (iii) $TiCl_4$, CH_2Cl_2; (f) Dess–Martin reagent, CH_2Cl_2, rt; (g) *p*-TsOH, benzene, reflux, 4-Å sieves; (h) DDQ, C_6H_6, reflux.

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