Antibiotics

Total Synthesis of Caprazol, a Core Structure of the Caprazamycin Antituberculosis Antibiotics**

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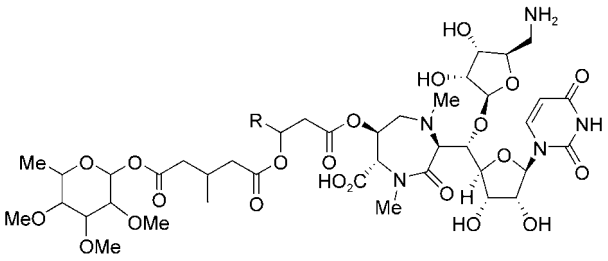
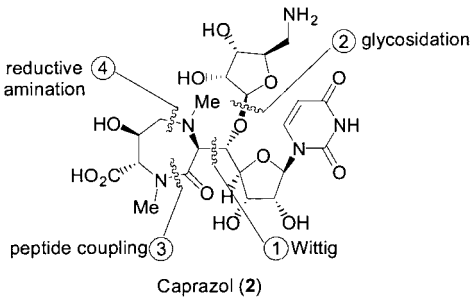
Tuberculosis (TB) is a disease, primarily of the respiratory system, from which two million people die each year. With resistant strains continuing to emerge, the development of new anti-TB agents with new mechanisms of action is of critical importance. The caprazamycins (CPZs; **1**, Scheme 1),[1] which were isolated from a culture broth of the Actinomycete strain *Streptomyces* sp. MK730-62F2 in



Scheme 1. Structures of the caprazamycins.

2003, have shown excellent antimycobacterial activity in vitro against drug-susceptible and multidrug-resistant *Mycobacterium tuberculosis* strains and exhibit no significant toxicity in mice. Caprazol (**2**, Scheme 2), the deacylated CPZ whose stereochemical structure (5′*S*,6′*S*,2‴*S*,3‴*S*) was recently revealed through X-ray crystal analysis,[2] consists of a uridine, an aminoribose, and a characteristic diazepanone. Liposido-



Scheme 2. Structure of caprazol (**2**) and the synthetic strategy.

mycins (LPSs), which are related nucleoside antibiotics, are also known to exhibit antibacterial activity similar to that of CPZs.[3] LPSs prevent the formation of one of the components of bacterial cell walls, peptidoglycan, by inhibiting Mra Y, a key enzyme for peptidoglycan biosynthesis.[4] It has been suggested that CPZs might follow the same mode of action as LPSs because of their complex structural and biological similarities. Consequently, they have become intriguing, challenging synthetic targets.[5] We report herein the first synthesis of caprazol (**2**).

One of the major difficulties posed by the synthesis is the introduction of the 5-aminoribose moiety found in **2** after construction of the uridyldiazepanone moiety, because the tertiary amines contained in the diazepanone structure inhibit the usual ribosylation promoted by Lewis acid,[6] and the 5′-hydroxy group is presumed to be in a highly sterically hindered position.[7] Furthermore, compound **2**, which contains a β-heterosubstituted carboxyl moiety, would be sensitive to basic conditions.[3c] Although a general method exists for the construction of β-glycosides through neighboring-group participation by using a glycosyl donor protected with a 2-*O*-acyl group, which is then usually deprotected under basic conditions, we planned to introduce the aminoribose protected with an acid-labile protecting group at an early stage of the synthesis. In so doing, we hoped to control the β-selective introduction by steric hindrance of a group installed on the α face of the ribofuranoside.[8]

Oxidation of 2′,3′-*O*-isopropylideneuridine (**3**) with IBX[9] followed by a two-carbon elongation with $Ph_3P{=}CHCO_2Me$ and BOM protection of the NH group at position 3 of the uracil moiety provided **4** (*trans*/*cis* = 37:1) over three steps (Scheme 3). Sharpless aminohydroxylation[10] of **4** with $(DHQD)_2AQN$ as a chiral ligand afforded **5**[11] with a 5′*S*,6′*S*/5′*R*,6′*R* ratio of 86:14. In the absence of the chiral ligand, the diastereoselectivity was reversed to give **5** in a ratio of 40:60 with a decrease in yield.

When the ribosyl fluoride **6a**[12] protected with an isopropylidene group was activated with $BF_3{\cdot}Et_2O$[13] at −30 °C, the corresponding ribosides were obtained in 79% yield and the stereoselectivity at the anomeric position was 27:73 (α/β). The use of AgOTf and Cp_2HfCl_2[14] (OTf = tri-

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Supporting information for this article (experimental details and characterization data for **3**–**16** and synthetic **2**) is available on the WWW under http://www.angewandte.org or from the author.

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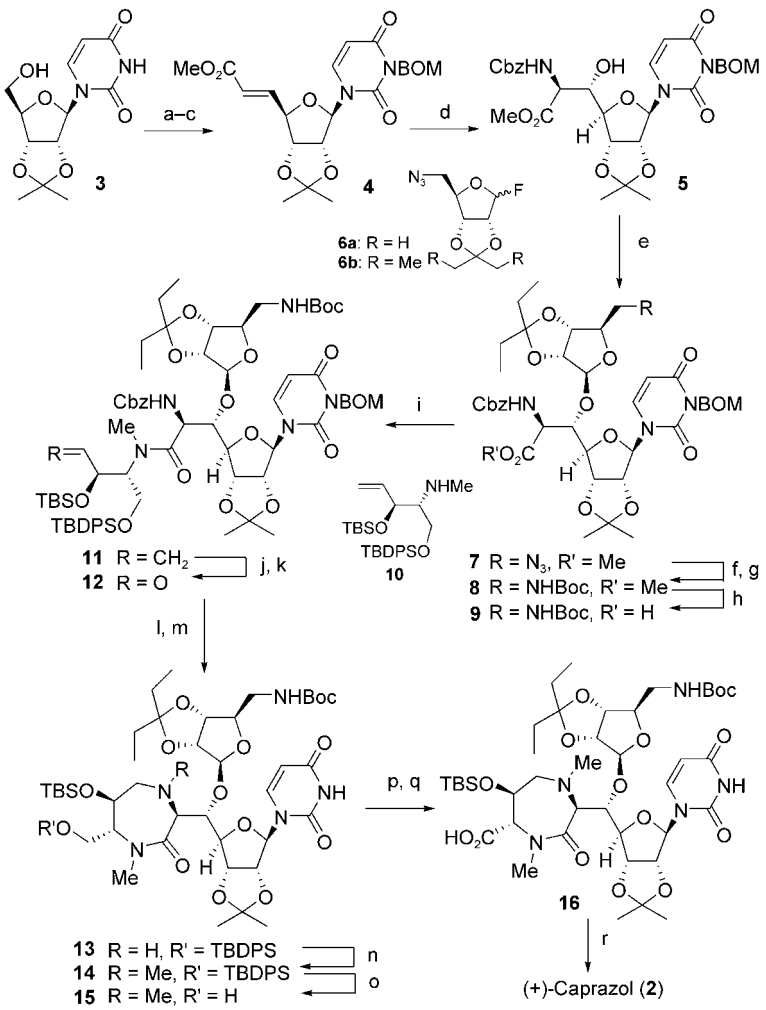

Scheme 3. Total synthesis of caprazol (**2**). Reagents and conditions: a) IBX, MeCN, 80 °C; b) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, −30 °C; c) BOMCl, Na_2CO_3, Bu_4NI, CH_2Cl_2/H_2O, room temperature, 70% over 3 steps; d) $CbzNH_2$, $K_2OsO_2(OH)_4$, $(DHQD)_2AQN$, NaOH, *t*BuOCl, *n*PrOH/H_2O, 5 °C→RT, 61%; e) **6**, $BF_3{\cdot}OEt_2$, MS4A, CH_2Cl_2, −30 °C, 80%; f) Ph_3P, H_2O, benzene/THF, 50 °C; g) $(Boc)_2O$, 95% over 2 steps; h) $Ba(OH)_2$, THF/H_2O, room temperature, 50%; i) **10**, DEPBT, $NaHCO_3$, THF, 0 °C→RT, 81%; j) OsO_4, NMO, *t*BuOH, acetone/H_2O, room temperature; k) $NaIO_4$, acetone/H_2O, room temperature, 61% over 2 steps; l) H_2, Pd/C, *i*PrOH, room temperature; m) $NaBH(OAc)_3$, AcOH, AcOEt, room temperature, 34% of **13** and 24% of **14** over 2 steps; n) $(CH_2O)_n$, $NaBH(OAc)_3$, AcOH, AcOEt, room temperature, 65%; o) NH_4F, MeOH, room temperature, 60%; p) Dess–Martin periodinane, CH_2Cl_2, room temperature; q) NaClO, NaH_2PO_4, *t*BuOH/H_2O, 56% over 2 steps); r) HF, THF/H_2O, 50%. Boc = *tert*-butoxycarbonyl, BOM = benzyloxymethyl, Cbz = benzyloxycarbonyl, DEPBT = 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one, $(DHQD)_2AQN$ = 1,4-bis(dihydroquinidinyl)anthraquinone, IBX = 1-hydroxy-1,2-benziodoxol-3-(1*H*)-one 1-oxide, MS4A = molecular sieves (4 Å), NMO = 4-methylmorpholine *N*-oxide, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl, THF = tetrahydrofuran.

fluoromethanesulfonate, Cp = cyclopentyl) as Lewis acids at −40 °C resulted in a loss of stereoselectivity. Further exploration with the ribosyl fluoride **6b**,[12] which possesses a more sterically hindered 3-pentylidene group, afforded the desired **7**[15] with good β selectivity (α/β = 4:96) when activation was conducted with $BF_3{\cdot}Et_2O$ at −30 °C. Notably, a decrease in β selectivity was again observed in the presence of a trifluoromethanesulfonate ion (that is, with AgOTf and Cp_2HfCl_2, when α/β = 11:89). Presumably, the β-*O*-trifluoromethanesulfonyl riboside intermediate[16] might be formed, and subsequent S_N2 attack of the alcohol would give the undesired α-riboside. Our simple and effective method can be considered an alternative for the construction of β-ribosides without neighboring-group participation.

The azide group in **7** was reduced to the corresponding amine, which was protected with a Boc group to give **8**. Basic hydrolysis of the methyl ester in **8** was troublesome[17] and the desired carboxylic acid **9** was obtained only when **8** was treated with $Ba(OH)_2$ in aqueous THF. Thus, treatment with base should be avoided in the synthesis to prevent β elimination followed by decomposition. Coupling of **9** with the secondary amine **10** by using DEPBT[18] gave the amide **11**. Compound **11** was treated with OsO_4, and the resulting mixture of the diastereomeric diols was oxidatively cleaved to provide the aldehyde **12**.

The next step involved the construction of the characteristic seven-membered diazepanone system, the system on which most of the synthetic studies for LPSs have focused.[5] Initial attempts to construct the diazepanone by deprotection of the Cbz group in **12** and reductive amination of the aldehyde, both promoted by catalytic hydrogenation with Pd/C, were unsuccessful because of the difficulty in hydrogenating the cyclic imine to give **13**. Additional forcing conditions under medium pressure gave the 5,6-dihydrouridine derivative owing to overreduction. After extensive efforts to overcome this problem, reductive amination was abandoned in favor of hydride reduction with $NaBH(OAc)_3$, and the desired diazepanone **13** was obtained along with its *N*-methylated compound **14**.[19] Compound **13** was methylated by using $(CH_2O)_n$ and $NaBH(OAc)_3$ to give **14**. Treatment of **14** with NH_4F in MeOH resulted in selective cleavage of the TBDPS protecting group at the primary hydroxy group to form **15**, which was then transformed into carboxylic acid **16** by a two-step sequence with Dess–Martin periodinane[20] and NaOCl[21] oxidation. Finally, global deprotection of **16** with aqueous HF provided (+)-**2** ($[\alpha]_D^{25} = +23.8$ (c = 0.24, dimethyl sulfoxide); literature value:[2] $[\alpha]_D^{19} = +28°$ (c = 0.5, dimethyl sulfoxide)), the properties of which were identical in all respects with those reported for the natural material.[2]

In conclusion, the first total synthesis of (+)-**2** in a highly concise manner over 18 steps, with uridine as the starting material, is reported. This work confirms the stereochemical assignments for the LPS core structure that were suggested by earlier synthetic studies.

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