



Total Synthesis of (–)-Caprazamycin A**

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Abstract: Caprazamycin A has significant antibacterial activity against *Mycobacterium tuberculosis* (TB). The first total synthesis is herein reported and features a) the scalable preparation of the syn-β-hydroxy amino acid with a thiourea-catalyzed diastereoselective aldol reaction, b) construction of a diazepanone with an unstable fatty-acid side chain, and c) global deprotection with hydrogenation. This report provides a route for the synthesis of related liponucleoside antibiotics with fatty-acid side chains.

Caprazamycin A (**1**) was isolated from *Streptomyces* sp. MK730-62F2 and is a liponucleoside characterized by a seven-membered diazepanone core with an amino ribose, a uridine, and a fatty-acid side chain (Figure 1).^[1] Several analogues

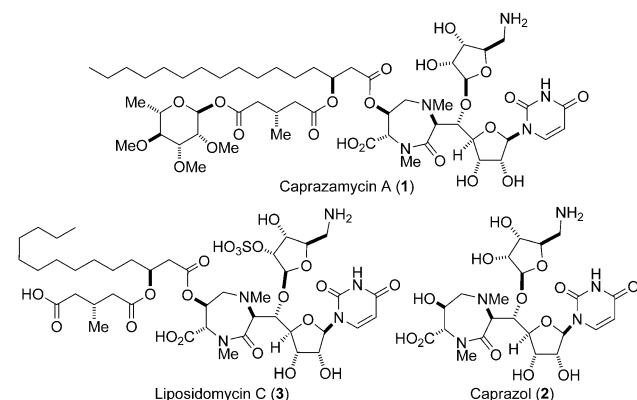


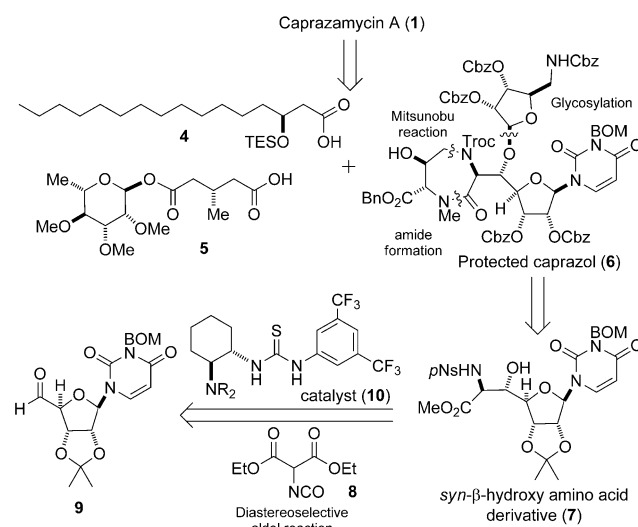
Figure 1. Caprazamycin A (**1**), caprazol (**2**), and liposidomycin C (**3**).

isolated by Igarashi et al. in 2003 share these features. Caprazamycins have antibacterial activity against *Mycobacterium tuberculosis* (TB), including multidrug-resistant TB (MDR-TB). Biological studies showed that it is an inhibitor of the peptidoglycan biosynthetic enzyme MraY.^[2] MraY is

essential for bacterial cell growth and is biosynthetically located upstream of an enzyme targeted by β-lactam and glycopeptide antibiotics (e.g. vancomycin). New antimicrobial agents targeting MraY are expected to be active against vancomycin- and methicillin-resistant *Staphylococcus aureus* (VRSA and MRSA).^[3] Recently, CPZEN-45, which exhibits more potent activity against TB, including extensively multi-drug-resistant TB (XDR-TB), has been developed based on caprazamycins.^[2b,4]

The complex structure and significant biological activities of caprazamycins have drawn much attention from synthetic chemists.^[5,6] Matsuda, Ichikawa, and co-workers accomplished the first total synthesis of palmitoyl caprazol and caprazol (**2**), which do not possess a fatty-acid side chain.^[7] Shibasaki, Watanabe, and co-workers recently reported the synthesis of **2** and the fatty-acid side chain.^[8] However, a total synthesis of the caprazamycins has not yet been reported because of the difficulty in introducing an unstable fatty-acid side chain. This difficulty has also hampered the total synthesis of related liponucleoside antibiotics, such as liposidomycin C (**3**).^[9] Therefore, we initiated a caprazamycin A (**1**) synthetic project, which would also be applicable to related natural products.

It is challenging to introduce a side chain containing unstable structures. To access caprazamycin A (**1**), it was envisioned that the unstable side chains **4** and **5** could be introduced to the protected caprazol **6** as the final step (Scheme 1). This would be followed by global deprotection without adversely affecting any functional groups. Benzyl



Scheme 1. Retrosynthesis of caprazamycin A (**1**). Cbz = benzyloxycarbonyl, BOM = benzyloxymethyl, TES = triethylsilyl.

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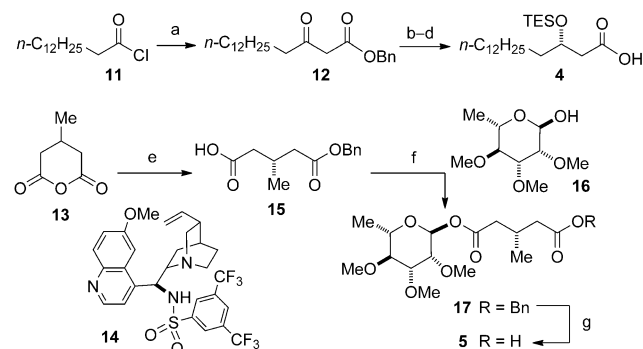
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(Bn), carboxybenzyl (Cbz), and benzyloxymethyl (BOM) protecting groups were selected and are readily removed by palladium-catalyzed hydrogenation. The protected **6** was prepared using a) the Mitsunobu reaction to construct the seven-membered diazepanone, and b) a diastereoselective aldol reaction of the isocyanate **8** and aldehyde **9** with the thiourea catalyst **10** to obtain the *syn*- β -hydroxy amino acid derivative **7**.^[10]

The fatty-acid side chains **4** and **5** were first prepared. The β -siloxy carboxylic acid **4** was synthesized from the acid chloride **11** by a modified Noyori asymmetric reduction^[11] of the β -ketoester **12**^[12] (Scheme 2). Enantioselective desym-



Scheme 2. Synthesis of the fatty-acid side chains **5** and **6**. Reagents and conditions: a) BnOAc, LDA, THF, -78°C ; b) H_2 , (*S*)-BINAP-RuBr₂ (4.0 mol %), MeOH, 50°C , 48%, 94% *ee* for two steps; c) TESOTf, 2,6-lutidine, CH_2Cl_2 , 0°C , 94%; d) H_2 , 10% Pd/C, EtOAc, 25°C , 92%; e) BnOH, catalyst **14** (10 mol %), CPME, 86%, 92% *ee*; f) Ghosez reagent, CH_2Cl_2 , 0°C ; then *n*BuLi, THF, 48%; g) H_2 , 10% Pd/C, EtOAc, 25°C , 92%. BINAP = 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl, CPME = cyclopentyl methyl ether, Ghosez reagent = 1-chloro-*N,N*,2-trimethylpropenylamine, LDA = lithium diisopropylamide, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran.

metrization of 3-methyl glutaric anhydride (**13**) using the cinchona alkaloid catalyst **14** and the procedure reported by Song and co-workers^[13] gave the carboxylic acid **15** with high enantioselectivity (92% *ee*). Condensation of **15** with the *L*-rhamnose derivative **16**,^[14] followed by removal of the benzyl group from ester **17** by hydrogenolysis, gave **5**.

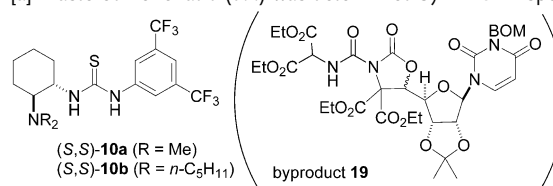
Construction of the *syn*- β -hydroxy amino acid moiety with an *S* configuration at C5' was then investigated. Several strategies have been employed for this in the past,^[5d,e,6g,i-k,7a,8a] two of which were used for the total synthesis of caprazol. One is a Sharpless asymmetric aminohydroxylation of the α,β -unsaturated ester^[7a] and the other is the diastereoselective isocyanoacetate aldol reaction.^[8a] We anticipated that the stereochemistry at C5' could be controlled with a novel diastereoselective aldol reaction using the isocyanate **8** in the presence of an organocatalyst.^[10]

Initially, **9**^[15] was treated with **8** and Et₃N (10 mol %) in toluene to give a mixture of the aldol adducts **18a** and **18b** in 50% yield with poor diastereoselectivity (1:1.8; Table 1, entry 1). In contrast, treatment with the (*S,S*)-thiourea catalyst **10a** (10 mol %) in toluene gave the desired aldol adduct **18a** as the major product in 64% yield (3.1:1), along with a small amount of byproduct (**19**; entry 2). The

Table 1: Optimization of diastereoselective aldol reaction.

Entry	Catalyst	Yield [%] ^[a]	Yield [%] (19)
1	Et ₃ N (10 mol %)	50 (d.r. = 1:1.8)	10
2	(<i>S,S</i>)- 10a (10 mol %)	64 (d.r. = 3.1:1)	7
3	(<i>S,S</i>)- 10b (10 mol %)	77 (d.r. = 6.5:1)	9
4	(<i>S,S</i>)- 10b (7 mol %)	80 (d.r. = 5.0:1)	0
5	(<i>R,R</i>)- 10b (10 mol %)	80 (d.r. > 1:20)	10

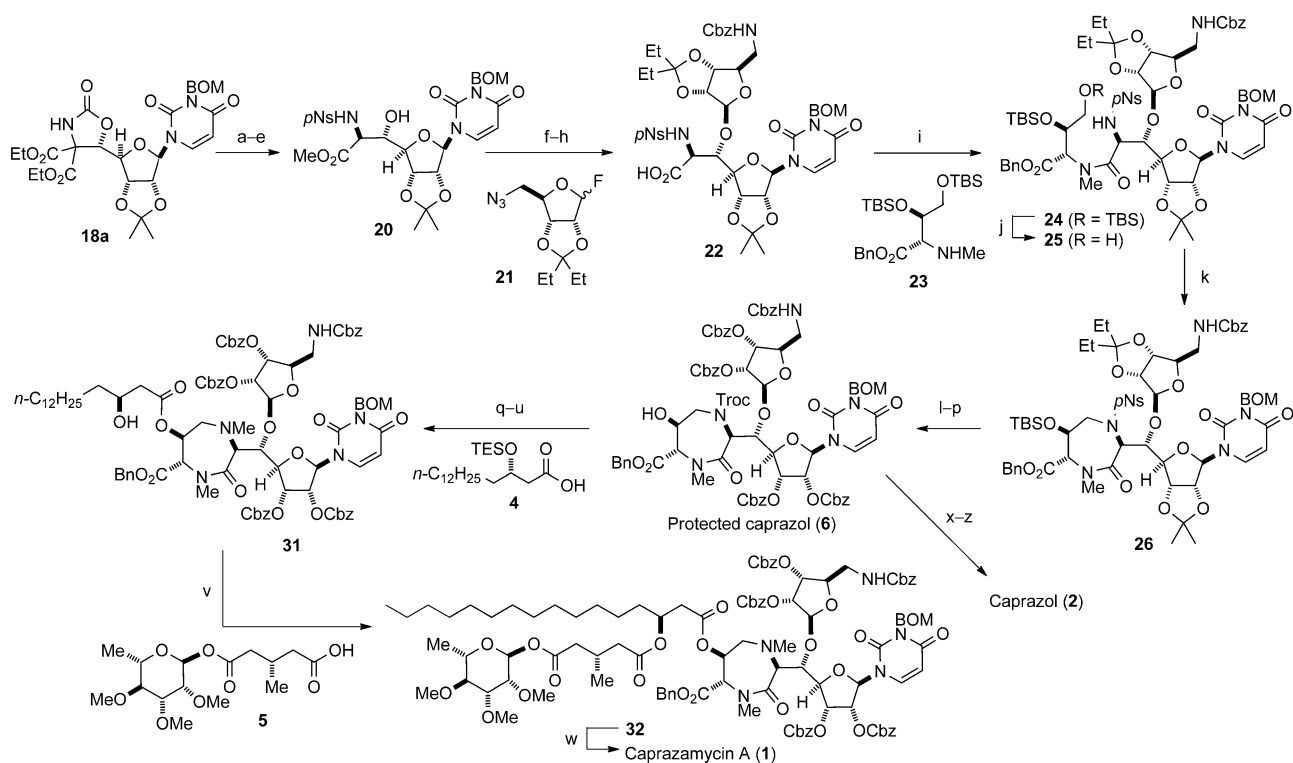
[a] Diastereomeric ratio (d.r.) was determined by ¹H NMR spectroscopy.



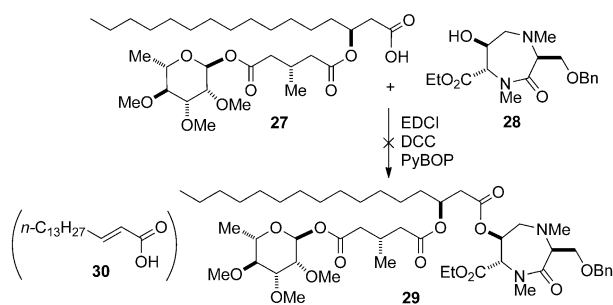
selectivity was improved to 6.5:1 by changing to the thiourea catalyst (*S,S*)-**10b** (10 mol %; entry 3). Formation of byproduct **19** was suppressed by reducing the amount of catalyst (7 mol %; entry 4). Use of the thiourea catalyst (*R,R*)-**10b** (10 mol %) gave the undesired diastereomer **18b** in 80% yield with high selectivity (> 20:1; entry 5). This protocol was also applied to the large-scale synthesis of **18a**.

The aldol adduct **18a** was converted into *syn*- β -hydroxy amino acid derivative **7** in good yield by regioselective decarboxylation and transesterification of the resultant thermodynamically stable *trans*-oxazolidinone in the presence of the zinc cluster Zn₄(OCOCF₃)₆O (Scheme 3).^[16] The minor isomer was removed during these transformations. Following the procedure of Matsuda, Ichikawa, and co-workers,^[7] the fluoride **21** underwent β -selective glycosylation, reduction of the azido group, Cbz protection, and hydrolysis under basic conditions to give **22**. The carboxylic acid **22** was treated with the Ghosez reagent^[17] and coupled with the *anti*- β -hydroxy amino acid derivative **23**.^[18] The TBS group was selectively removed and construction of the diazepanone core was extensively investigated. The Mitsunobu reaction of **25** using PPh₃ and di-*tert*-butyl azodicarboxylate (DBAD) proceeded to give the seven-membered ring without epimerization or other side reactions. Finally, protecting group manipulation of **26** gave the protected caprazol **6** and the structure was confirmed through conversion into caprazol (**2**).^[1,7a,8a]

With the side-chain fragments **4** and **5** and protected caprazol **6** in hand, we focused on the introduction of the fatty-acid side chain. This side chain readily decomposes through β -elimination of the β -acyloxy carbonyl under basic conditions and cleavage of the *O*-acylglycoside under acidic conditions. In fact, attempts to introduce the fatty-acid side chain **27**^[19] to model diazepanone **28** using EDCI caused β -elimination to give unsaturated carboxylic acid **30** instead of the desired **29** (Scheme 4). DCC and PyBOP were also



Scheme 3. Total synthesis of caprazamycin A (**1**). Reagents and conditions: a) aq. KOH, THF, 0 to 25 °C; b) DBU, THF, 70 °C, 86 % (2 steps); c) $\text{Zn}_4(\text{OCOCH}_3)_6\text{O}$ (3.2 mol %), MeOH, 50 °C, quant.; d) NaH, *p*NsCl, DMF, 0 to 25 °C; e) NaOMe, MeOH, 65 % (2 steps); f) **21**, $\text{BF}_3 \cdot \text{Et}_2\text{O}$, 4 Å M.S., CH_2Cl_2 , -30 °C, 71 %; g) PPh_3 , THF/PhH 1:1; then CbzCl, aq. NaHCO_3 , 0 to 25 °C; h) $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$, THF/ H_2O 4:1, 0 to 25 °C; i) Ghosez reagent, CH_2Cl_2 , 0 °C then **23**, aq. NaHCO_3 , 0 °C, 46 % (3 steps); j) CSA, MeOH/ CH_2Cl_2 1:1, 0 °C, 68 % (17 % for recovered **24**, b.r.s.m. 82 %); k) PPh_3 , DBAD, toluene, 0 °C, 75 %; l) K_2CO_3 , PhSH, MeCN, 0 to 25 °C, 73 %; m) TrocCl, DMAP, pyridine, CH_2Cl_2 , 0 to 25 °C, 79 %; n) TsOH· H_2O , MeOH, 60 °C, 41 % and diol having penthyldene acetal (21 %); o) CbzCl, DMAP, CH_2Cl_2 , 0 to 25 °C; p) *p*TsOH· H_2O , MeOH, 25 to 60 °C, 71 % (2 steps); q) **4**, EDCI, DMAP, CH_2Cl_2 , 0 to 25 °C; r) Zn, AcOH/THF, 25 °C; s) AcOH, $\text{ClCH}_2\text{CH}_2\text{Cl}$, 25 °C; t) $(\text{CH}_2\text{O})_m$, NaBH(OAc)₃, AcOH/ $\text{ClCH}_2\text{CH}_2\text{Cl}$, 25 °C; u) HF·py, THF, 0 °C to 25 °C, 43 % (5 steps); v) **5**, 2,4,6-trichlorobenzoyl chloride, DMAP, Et_3N , 0 to 25 °C, 64 %; w) Pd black, EtOH/ HCO_2H 20:1, 25 °C, 98 %; x) Zn, AcOH/THF, 25 to 50 °C; y) $(\text{CH}_2\text{O})_m$, NaBH(OAc)₃, AcOH/ CH_2Cl_2 , 25 °C, quant. (2 steps); z) Pd black, EtOH/ HCO_2H 10:1, 25 °C, 46 %. CSA = 10-camphor sulfonic acid, DBAD = di-*tert*-butyl azodicarboxylate, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMAP = *N,N*-dimethyl-4-aminopyridine, DMF = *N,N*-dimethylformamide, EDCI = 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide, M.S. = molecular sieves, *p*Ns = *p*-nitrobenzenesulfonyl, TrocCl = 2,2,2-trichloroethyl chloroformate, *p*Ts = *p*-toluenesulfonyl.



Scheme 4. Initial attempts to introduce fatty acid side chain (**27**).

ineffective. The β -hydroxy ester of diazepanone may also decompose through β -elimination and a retro-aldol reaction. Thus, **4** and **5** were introduced in a stepwise manner.

The final stage of this synthesis began with coupling **4** with the protected caprazol **6** without epimerization (Scheme 3). The Troc group was removed under mild reaction conditions without touching the unstable β -acyloxy moiety. This deprotection was followed by reductive amination. After removal

of the TES group, **5** was introduced to the resultant alcohol **31** using Yamaguchi conditions to give protected caprazamycin A (**32**).^[8b] Finally, global deprotection with hydrogenation in the presence of palladium black was successful without side-chain decomposition. This step completed the first total synthesis of caprazamycin A (**1**). The ^1H and ^{13}C NMR spectra, as well as IR and HRMS data for the synthetic **1** matched those of the natural product.^[20]

In summary, we have accomplished the first total synthesis of caprazamycin A in 23 steps (longest linear sequence from aldehyde **9**). The key points are a) scalable synthesis of the *syn*- β -hydroxy amino acid moiety with a thiourea-catalyzed diastereoselective aldol reaction, 2) maintaining the structural integrity of the diazepanone core during introduction of the fatty-acid side chain, and 3) global deprotection with hydrogenation. This is the first report detailing the introduction of the unstable fatty-acid side chain. This strategy should allow the synthesis of related liponucleoside antibiotics.

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- [15] The aldehyde **9** was prepared from commercially available uridine in three steps. See the Supporting Information.
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- [18] The amine **23** was synthesized from L-(+)-diethyl tartrate in ten steps. See the Supporting Information.
- [19] The carboxylic acid **27** was prepared from the precursor of **4** and **5** as described by Shibasaki and Watanabe et al. See Ref. [8b].
- [20] The NMR spectrum of caprazamycin A was dependent on concentration and pK_a. Thus, the NMR spectra was determined using [D₆]DMSO/D₂O/DCO₂D (20:1:1) for comparison. Also see the Supporting Information.