Natural Product Synthesis | Hot Paper

DOI: 10.1002/anie.201411954

Total Synthesis of (−)-Caprazamycin A**

*Hugh Nakamura, Chihiro Tsukano, Motohiro Yasui, Shinsuke Yokouchi, Masayuki Igarashi, and Yoshiji Takemoto**

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

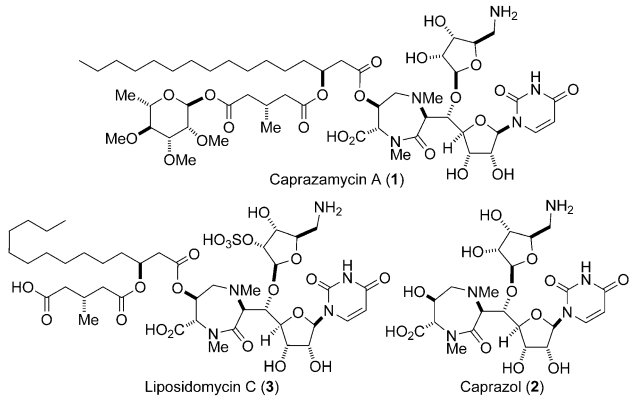
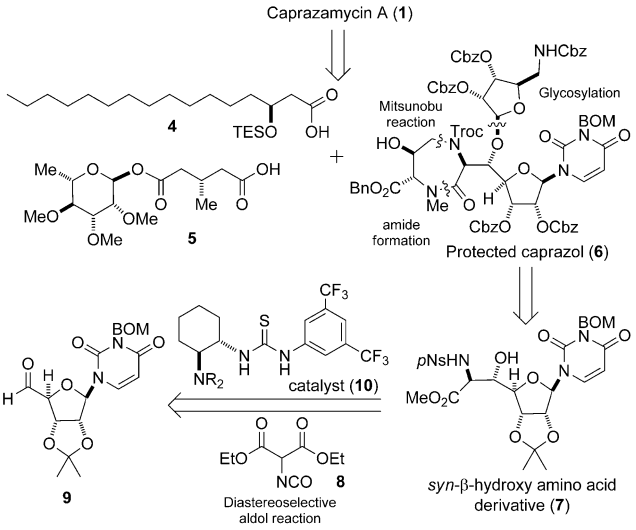


Figure 1. Caprazamycin A (**1**), caprazol (**2**), and liposidomycin C (**3**).

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 multidrug-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.

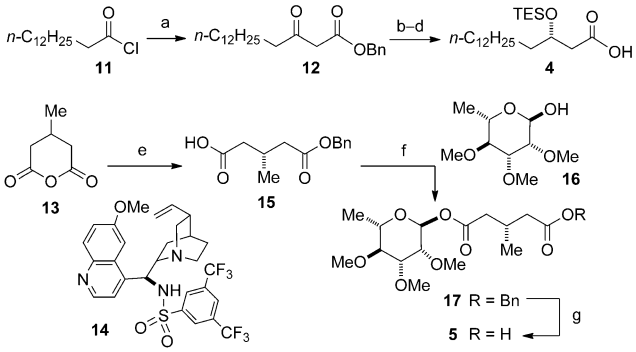
[*] H. Nakamura, Dr. C. Tsukano, M. Yasui, S. Yokouchi, Prof. Dr. Y. Takemoto
Graduate School of Pharmaceutical Sciences, Kyoto University
Yoshida, Sakyo-ku, Kyoto 606-8501 (Japan)
E-mail: takemoto@pharm.kyoto-u.ac.jp
Dr. M. Igarashi
Institute of Microbial Chemistry (BIKAKEN)
Kamiosaki, Shinagawa-ku, Tokyo 141-0021 (Japan)

[**] This work was supported by a Grant-in-Aid for Scientific Research (B) (JSPS KAKENHI no. 23390004, Y.T.), a Grant-in-Aid for JSPS fellows (H.N.) and Meiji Seika Pharma Award in Synthetic Organic Chemistry (Japan) (C.T.).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201411954.

(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-



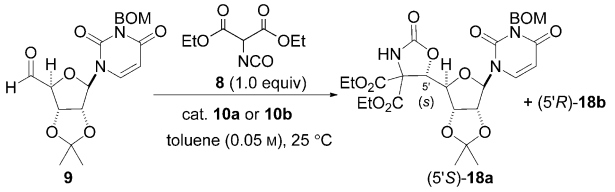
Scheme 2. Synthesis of the fatty-acid side chains **5** and **6**. Reagents and conditions: a) BnOAc, LDA, THF, −78 °C; b) H_2, (*S*)-BINAP-$RuBr_2$ (4.0 mol%), MeOH, 50 °C, 48%, 94% *ee* for two steps; c) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 94%; d) H_2, 10% Pd/C, EtOAc, 25 °C, 92%; e) BnOH, catalyst **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]

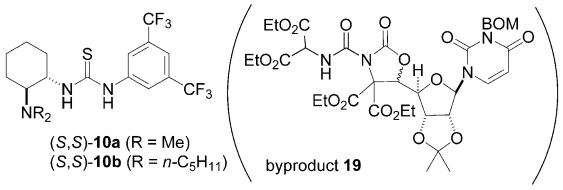
Initially, **9**[15] was treated with **8** and Et_3N (10 mol%) in toluene to give a mixture of the aldol adducts **18a** and **18b** in 50% yield with poor diastereoselectivity (1:1.8; Table 1, entry 1). In contrast, treatment with the (*S*,*S*)-thiourea catalyst **10a** (10 mol%) in toluene gave the 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_3N (10 mol%)	50 (d.r. = 1:1.8)	10
2	(*S*,*S*)-**10a** (10 mol%)	64 (d.r. = 3.1:1)	7
3	(*S*,*S*)-**10b** (10 mol%)	77 (d.r. = 6.5:1)	9
4	(*S*,*S*)-**10b** (7 mol%)	80 (d.r. = 5.0:1)	0
5	(*R*,*R*)-**10b** (10 mol%)	80 (d.r. > 1:20)	10

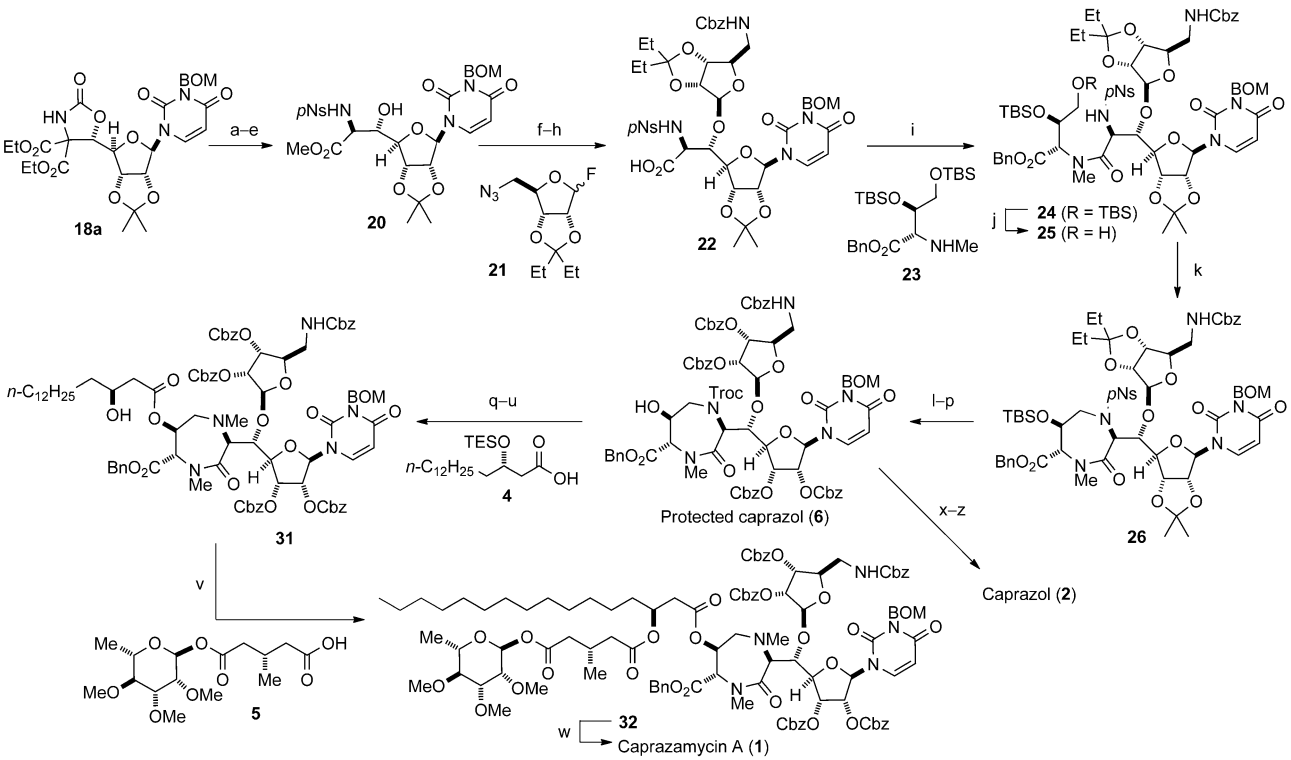
[a] Diastereomeric ratio (d.r.) was determined by ^1H NMR spectroscopy.



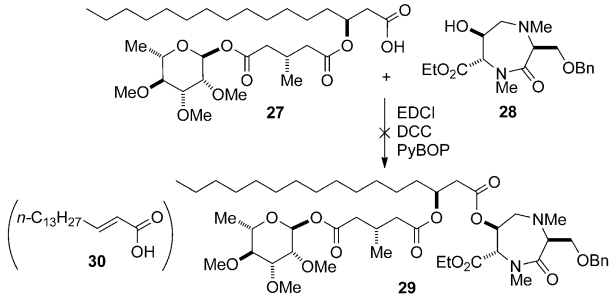
selectivity was improved to 6.5:1 by changing to the thiourea catalyst (*S*,*S*)-**10b** (10 mol%; entry 3). Formation of byproduct **19** was suppressed by reducing the amount of catalyst (7 mol%; entry 4). Use of the thiourea catalyst (*R*,*R*)-**10b** (10 mol%) gave the undesired diastereomer **18b** 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 $Zn_4(OCOCF_3)_6O$ (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 PPh_3 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) $Zn_4(OCOCF_3)_6O$ (3.2 mol%), MeOH, 50 °C, quant.; d) NaH, *p*NsCl, DMF, 0 to 25 °C; e) NaOMe, MeOH, 65% (2 steps); f) **21**, $BF_3{\cdot}Et_2O$, 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) $Ba(OH)_2{\cdot}8H_2O$, 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) $TsOH{\cdot}H_2O$, MeOH, 60 °C, 41% and diol having penthylidene acetal (21%); o) CbzCl, DMAP, CH_2Cl_2, 0 to 25 °C; p) $pTsOH{\cdot}H_2O$, 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, $ClCH_2CH_2Cl$, 25 °C; t) $(CH_2O)_n$, $NaBH(OAc)_3$, AcOH/$ClCH_2CH_2Cl$, 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) $(CH_2O)_n$, $NaBH(OAc)_3$, 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.

Received: December 12, 2014
Published online: ■■ ■■, ■■■■

Keywords: aldol reaction · antibiotics · natural products · organocatalysis · total synthesis

[1] a) M. Igarashi, N. Nakagawa, N. Doi, S. Hattori, H. Naganawa, M. Hamada, *J. Antibiot.* **2003**, *56*, 580; b) T. Takeuchi, M. Igarashi, H. Naganawa, JP P2003-12687A, **2003**; c) M. Igarashi, Y. Takahashi, T. Shitara, H. Nakamura, H. Naganawa, T. Miyake, Y. Akamatsu, *J. Antibiot.* **2005**, *58*, 327; d) C. Dini, *Curr. Top. Med. Chem.* **2005**, *5*, 1221; e) T. D. H. Bugg, A. J. Lloyd, D. I. Roper, *Infect. Disord.: Drug Targets* **2006**, *6*, 85.

[2] a) C. Dini, P. Collette, N. Drochon, J. C. Guillot, G. Lemoine, P. Mauvais, J. Aszodi, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1839; b) Y. Ishizaki, C. Hayashi, K. Inoue, M. Igarashi, Y. Takahashi, V. Pujari, D. C. Crick, P. J. Brennan, A. Nomoto, *J. Biol. Chem.* **2013**, *288*, 30309.

[3] K. Kimura, T. D. H. Bugg, *Nat. Prod. Rep.* **2003**, *20*, 252.

[4] a) Y. Takahashi, M. Igarashi, T. Miyake, H. Soutome, K. Ishikawa, Y. Komatsuki, Y. Koyama, N. Nakagawa, S. Hattori, K. Inoue, N. Doi, Y. Akamatsu, *J. Antibiot.* **2013**, *66*, 171; b) S. N. M. Hanif, A. J. Hickey, L. Garcia-Contreras, *J. Pharm. Biomed. Anal.* **2014**, *88*, 370.

[5] Synthetic studies toward caprazamycins: a) S. Hirano, S. Ichikawa, A. Matsuda, *Bioorg. Med. Chem.* **2008**, *16*, 5123; b) S. Ichikawa, *Chem. Pharm. Bull.* **2008**, *56*, 1059; c) K. Ii, S. Ichikawa, B. Al-Dabbagh, A. Bouhss, A. Matsuda, *J. Med. Chem.* **2010**, *53*, 3793; d) A. P. Spork, S. Koppermann, B. Dittrich, R. Herbst-Irmer, C. Ducho, *Tetrahedron: Asymmetry* **2010**, *21*, 763; e) F. Sarabia, C. Vivar-García, C. García-Ruiz, L. Martín-Ortiz, A. Romero-Carrasco, *J. Org. Chem.* **2012**, *77*, 1328; f) C. Tsukano, S. Yokouchi, A. L. Girard, T. Kuribayashi, S. Sakamoto, T. Enomoto, Y. Takemoto, *Org. Biomol. Chem.* **2012**, *10*, 6074; g) H. Miyaoka, J. Wada, E. Kawashima, *Heterocycles* **2014**, *88*, 719.

[6] Synthetic studies towards related liponucleoside antibiotics: a) M. R. Spada, M. Ubukata, K. Isono, *Heterocycles* **1992**, *34*, 1147; b) S. Knapp, S. Nandan, L. Resnick, *Tetrahedron Lett.* **1992**, *33*, 5485; c) K. S. Kim, I. H. Cho, Y. H. Ahn, J. I. Park, *J. Chem. Soc. Perkin Trans. 1* **1995**, 1783; d) W. J. Moore, F. A. Luzzio, *Tetrahedron Lett.* **1995**, *36*, 6599; e) K. S. Kim, C. S. Cheong, J. S. Hahn, J. I. Park, *Bull. Korean Chem. Soc.* **1997**, *18*, 465; f) Y. Le Merrer, C. Gravier-Pelletier, M. Gerrouache, J. C. Depezay, *Tetrahedron Lett.* **1998**, *39*, 385; g) K. S. Kim, Y. H. Ahn, *Tetrahedron: Asymmetry* **1998**, *9*, 3601; h) S. Knapp, G. J. Morriello, S. R. Nandan, T. J. Emge, G. A. Doss, R. T. Mosley, L. Chen, *J. Org. Chem.* **2001**, *66*, 5822; i) C. Gravier-Pelletier, M. Milla, Y. L. Merrer, J. C. Depezay, *Eur. J. Org. Chem.* **2001**, 3089; j) S. Knapp, G. J. Morriello, G. A. Doss, *Org. Lett.* **2002**, *4*, 603; k) B. Drouillat, O. Poupardin, Y. Bourdreux, C. Greck, *Tetrahedron Lett.* **2003**, *31*, 2781; l) A. Yamashita, E. B. Norton, R. T. Williamson, D. M. Ho, S. Sinishtaj, T. S. Mansour, *Org. Lett.* **2003**, *5*, 3305; m) F. Sarabia, L. Martin-Ortiz, F. J. Lopez-Herrera, *Org. Lett.* **2003**, *5*, 3927; n) N. Nakajima, T. Isobe, S. Irisa, M. Ubukata, *Heterocycles* **2003**, *59*, 107; o) S. Fukunishi, M. Ubukata, N. Nakajima, *Heterocycles* **2005**, *66*, 129; p) Y. Bourdreux, B. Drouillat, C. Greck, *Lett. Org. Chem.* **2006**, *3*, 368; q) S. Fukunishi, M. Ubukata, N. Nakajima, *Heterocycles* **2007**, *73*, 627; r) O. Monasson, M. Ginisty, G. Bertho, C. Gravier-Pelletier, Y. L. Merrer, *Tetrahedron Lett.* **2007**, *48*, 8149; s) X. H. Xu, A. E. Trunkfield, T. D. H. Bugg, F. L. Qing, *Org. Biomol. Chem.* **2008**, *6*, 157; t) O. Monasson, M. Ginisty, J. Mravljak, G. Bertho, C. Gravier-Pelletier, Y. L. Merrer, *Tetrahedron: Asymmetry* **2009**, *20*, 2320; u) M. J. Fer, P. Doan, T. Prangé, S. Calvet-Vitale, C. Gravier-Pelletier, *J. Org. Chem.* **2014**, *79*, 7758; v) A. P. Spork, M. Büschleb, O. Ries, D. Wiegmann, S. Boettcher, A. Mihalyi, T. D. H. Bugg, C. Ducho, *Chem. Eur. J.* **2014**, *20*, 15292.

[7] a) S. Hirano, S. Ichikawa, A. Matsuda, *Angew. Chem. Int. Ed.* **2005**, *44*, 1854; *Angew. Chem.* **2005**, *117*, 1888; b) S. Hirano, S. Ichikawa, A. Matsuda, *J. Org. Chem.* **2007**, *72*, 9936; c) S. Hirano, S. Ichikawa, A. Matsuda, *J. Org. Chem.* **2008**, *73*, 569.

[8] a) P. Gopinath, L. Wang, H. Abe, G. Ravi, T. Masuda, T. Watanabe, M. Shibasaki, *Org. Lett.* **2014**, *16*, 3364; b) P. Gopinath, T. Watanabe, M. Shibasaki, *J. Org. Chem.* **2012**, *77*, 9260.

[9] a) K. Isono, M. Uramoto, H. Kusakabe, K. Kimura, K. Izaki, C. C. Nelson, J. A. McCloskey, *J. Antibiot.* **1985**, *38*, 1617; b) K. Kimura, Y. Ikeda, S. Kagami, M. Yoshihama, K. Suzuki, H. Osada, K. Isono, *J. Antibiot.* **1998**, *51*, 1099; c) M. Ubukata, K. Kimura, K. Isono, C. C. Nelson, J. M. Gregson, J. A. McCloskey, *J. Org. Chem.* **1992**, *57*, 6392; d) K. Kimura, Y. Ikeda, S. Kagami, M. Yoshihama, M. Ubukata, Y. Esumi, H. Osada, K. Isono, *J. Antibiot.* **1998**, *51*, 647; e) K. Kimura, S. Kagami, Y. Ikeda, H. Takahashi, M. Yoshihama, H. Kusakabe, H. Osada, K. Isono, *J. Antibiot.* **1998**, *51*, 640.

[10] S. Sakamoto, N. Kazumi, Y. Kobayashi, C. Tsukano, Y. Takemoto, *Org. Lett.* **2014**, *16*, 4758.

[11] a) R. Noyori, H. Takaya, *Acc. Chem. Res.* **1990**, *23*, 345; b) V. Ratovelomanana-Vidal, C. Girard, R. Touati, J. P. Tranchier, B. Ben Hassine, J. P. Genêt, *Adv. Synth. Catal.* **2003**, *345*, 261.

[12] D. F. Taber, P. B. Deker, H. M. Fales, T. H. Jones, H. A. Lloyd, *J. Org. Chem.* **1988**, *53*, 2968.

[13] a) S. H. Oh, H. S. Rho, J. W. Lee, J. E. Lee, S. H. Youk, J. Chin, C. E. Song, *Angew. Chem. Int. Ed.* **2008**, *47*, 7872; *Angew. Chem.* **2008**, *120*, 7990; b) T. Honjo, T. Tsumura, S. Sano, Y. Nagao, K. Yamaguchi, Y. Sei, *Synlett* **2009**, 3279.

[14] a) M. S. Arias-Pérez, M. S. López, M. J. Santos, *J. Chem. Soc. Perkin Trans. 2* **2002**, 1549; b) D. A. Evans, W. C. Black, *J. Am. Chem. Soc.* **1993**, *115*, 4497.

[15] The aldehyde **9** was prepared from commercially available uridine in three steps. See the Supporting Information.

[16] T. Ohshima, T. Iwasaki, Y. Maegawa, A. Yoshiyama, K. Mashima, *J. Am. Chem. Soc.* **2008**, *130*, 2944.

[17] A. Devos, J. Remion, A.-M. Frisque-Hesbain, A. Colens, L. Ghosez, *J. Chem. Soc. Chem. Commun.* **1979**, 1180.

[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].

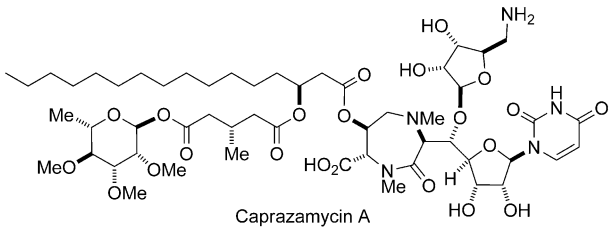
[20] The NMR spectrum of caprazamycin A was dependent on concentration and pK_a. Thus, the NMR spectra was determined using [D_6]DMSO/D_2O/DCO_2D (20:1:1) for comparison. Also see the Supporting Information.

Communications

Natural Product Synthesis

H. Nakamura, C. Tsukano, M. Yasui, S. Yokouchi, M. Igarashi, Y. Takemoto* _____ ■■■–■■■

Total Synthesis of (−)-Caprazamycin A



Caprazamycin A

Abra'capraza': Caprazamycin A has significant antibacterial activity against *Mycobacterium tuberculosis* (TB). The first total synthesis is herein reported and features the scalable preparation of the *syn*-β-hydroxy amino acid with a thiourea-catalyzed diastereoselective aldol reaction, construction of a diazepanone with an unstable fatty-acid side chain, and global deprotection with hydrogenation.