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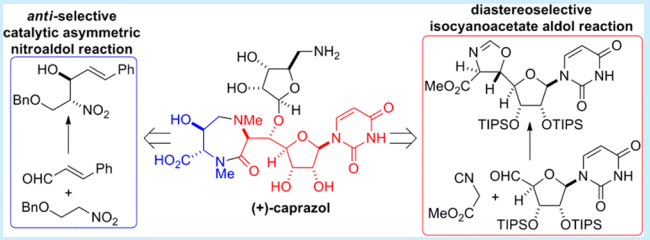
Catalytic Asymmetric Total Synthesis of (+)-Caprazol

Purushothaman Gopinath, Lu Wang, Hikaru Abe, Gandamala Ravi, Takashi Masuda, Takumi Watanabe,* and Masakatsu Shibasaki*

Institute of Microbial Chemistry (BIKAKEN), Tokyo, 3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141-0021, Japan

Supporting Information

ABSTRACT: Catalytic asymmetric total synthesis of caprazol, a lipo-nucleoside antibiotic, has been accomplished employing two of the stereoselective C−C bond forming reactions as key transformations. The stereochemistries of the β-hydroxy-α-aminoester moiety at the juncture of the uridine part and diazepanone part, and of the β-hydroxy-α-amino acid moiety embedded in the diazepanone system, were constructed using a diastereoselective isocyanoacetate aldol reaction (dr = 88:12) and an enantioselective *anti*-nitroaldol reaction catalyzed by a Nd/Na-chiral amide ligand (dr = 12:1, 95% ee), respectively.



Despite the large number of chemotherapies available, tuberculosis (TB) remains a serious infectious disease causing human mortality. Moreover, public health has become further endangered by the emergence of extensively multidrug-resistant TB (XDR-TB), for which most of the available clinical drugs are ineffective. In 2003, lipo-nucleoside antibiotics caprazamycins were reported as promising anti-TB natural products.[1] Caprazamycins comprise a mixture of seven constituents possessing aliphatic side chains of varying lengths and branched patterns. Among them, caprazamycin B (**3**) exhibits the most potent anti-TB activity, due mainly to the inhibition of MraY,[2] a key enzyme in the peptidoglycan biosynthesis pathway of the pathogens (Figure 1). Semisynthetic structure−activity relationship (SAR) studies starting from natural caprazamycins were thoroughly executed to identify CPZEN-45 (**2**)[3] an anti-XDR-TB agent. It is noteworthy that the mechanisms underlying the intriguing anti-XDR-TB activity is the inhibition of WecA,[2] an enzyme involved in the biosynthesis of mycolyl arabinogalactan, which is essential for *Mycobacterium tuberculosis*,[4] yet it has never been a molecular target of clinical anti-TB drugs.

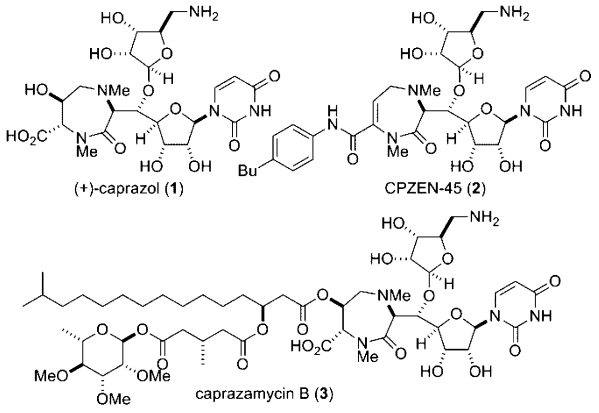


Figure 1. Structure of caprazol and related compounds.

(+)-Caprazol (**1**) is a core structure of caprazamycins and a minor component of caprazamycin production by fermentation. Although caprazol itself exhibits only weak anti-TB activity,[5] most of its molecular skeleton is shared by CPZEN-45; caprazol would be a reasonable starting point toward SAR studies of WecA inhibitors to combat XDR-TB by an unprecedented mode of action. Therefore, we attempted to establish an efficient synthetic route to caprazol and caprazamycins that is amenable to developing a structurally and stereochemically diverse library of compounds. This synthetic route is expected to accelerate SAR studies, which in turn will facilitate the discovery of more promising lead compounds and the identification of a pharmacophore of WecA inhibitors using chemical biology approaches.

Although tremendous effort by many research groups has focused on building the framework of caprazamycin-related natural products including liposidomycins[6] in an asymmetric manner, only one total synthesis of a natural product of this class, caprazol, has been completed to date by Matsuda and Ichikawa et al.[7] In these reports, two key stereochemical issues were addressed by taking advantage of Sharpless' asymmetric aminohydroxylation of the α,β-unsaturated ester and the chirality of D-serine. A subsequent series of comprehensive SAR studies[5,8] focused on antibacterial leads, including antimethicillin-resistant *Staphylococcus aureus* (MRSA) and antivancomycin-resistant enterococci (VRE) agents.[8c] Whereas other attempts relied on a number of C−H, C−O, and C−N bond formations and/or a chiral pool as starting material to furnish the requisite stereochemistry,[9] stereoselective C−C bond-forming reactions were scarcely adopted.[9j−l,10,11] Our approach centered on catalytic enantio- and diastereoselective aldol-type chemistry to

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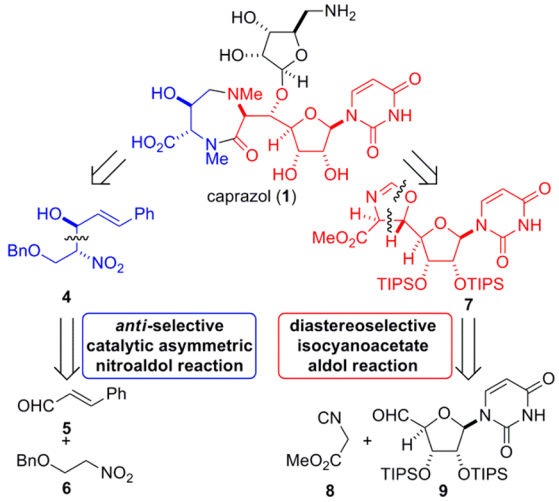
provide the stereocontrol required for the synthesis of caprazol and caprazamycin B, which enabled the construction of the molecular architecture and simultaneous installation of the correct configuration, making the entire synthetic process more efficient. Along this line, we previously reported the catalytic asymmetric synthesis of the side-chain portion (western zone) of caprazamycin B[12] utilizing a direct catalytic enantioselective thioamide aldol reaction.[13] It also included a newly developed catalytic enantioselective alcoholysis of 3-methylglutaric anhydride.[14]

Scheme 1 summarizes our approach to address the key stereochemical issues associated with β-hydroxy-α-amino acid

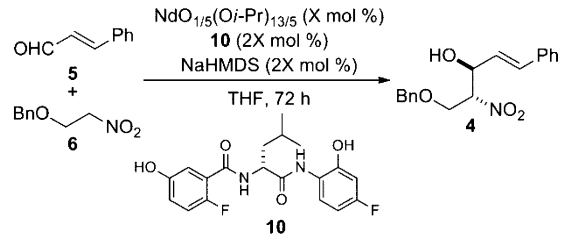
Scheme 1. Key Stereoselective Aldol-Type Processes in This Study



moieties located inside the diazepanone ring system and between the diazepanone and uridine units. The former would utilize a highly *anti*-selective nitroaldol reaction catalyzed by a heterogeneous heterobimetallic Nd/Na-chiral amide ligand complex that was recently developed in our laboratory.[15] Notably, single proton transfer during the C−C bond assemblage in this reaction realizes perfect atom economy. The latter should take advantage of substrate-controlled diastereoselective isocyanoacetate aldol reaction.

Table 1 shows the optimization of the *anti*-selective asymmetric nitroaldol reaction using cinnamaldehyde (**5**) and *O*-benzylnitroethanol (**6**)[16] as the substrates catalyzed by the Nd/Na-chiral amide ligand (**10**) complex to afford adduct **4**. All reactions were conducted at the concentration 0.25 M (based on **5** for entries 1−7 and **6** for entries 8−11). At first, a 5-fold amount of **6** toward **5** was used, and the reactions were performed for 72 h at −40 °C with varying catalyst loading (entries 1 to 3). Although less loading gave a better dr and ee, the selectivity of each was unsatisfactory. Upon lowering the temperature to −60 °C, both the dr and ee improved, although 9 mol % of catalyst was required to realize an acceptable reaction rate (entries 4 and 5). Use of an increased amount of **6** improved the yield but lowered the dr (entry 6). The carbon nanotube condition[17] was beneficial to *anti*-selectivity, although the reaction rate was slowed (entry 7). Switching the ratio of the substrates afforded similar results (entry 8 vs 6) and was advantageous toward saving commercially unavailable substrate **6**. Although a ratio of 2:1 still afforded a reasonable dr (7:1, entry 10) and an excellent ee, a 5:1 ratio is preferred (entry 9).

Table 1. Optimization of *anti*-Selective Catalytic Enantioselective Nitroaldol Reaction



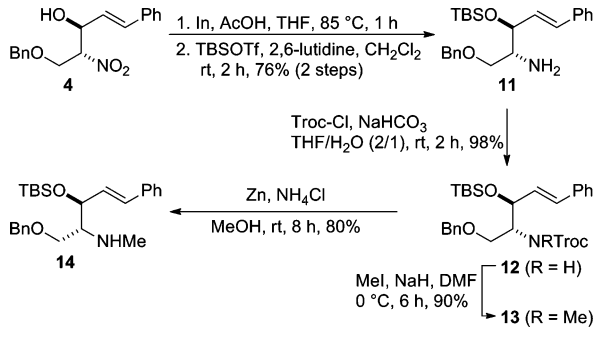
entry[a]	5:6	x	temp (°C)	yield[b] (%)	dr	ee[c] (%)
1	1:5	3	−40	52	8:1	85
2	1:5	6	−40	85	2.4:1	75
3	1:5	9	−40	97	1.2:1	74
4	1:5	6	−60	<3	nd	nd
5	1:5	9	−60	52	18:1	96
6	1:10	9	−60	87	9:1	95
7[d]	1:10	9	−60	45	15:1	95
8	10:1	9	−60	68	12:1	94
9	5:1	9	−60	66	15:1	95
10	2:1	9	−60	66	6:1	95
11[e]	5:1	9	−60	75	12:1	95

[a]All of the reactions were conducted in concentration of 0.25 M. [b]NMR yield using 1,1,2,2-tetrachloroethane as an internal standard. [c]Determined by HPLC methods using a chiral stationary phase. [d]A carbon nanotube-confined catalyst was used. [e]The reaction was performed for 120 h.

Prolonging the reaction time to 120 h improved the chemical yield up to 75% with a slight loss of dr (dr = 12:1, 95% ee, entry 11), which was set as the standard protocol in the present study. To clarify the factors affecting dr upon changing the ratio of the substrates, a more detailed study is needed and currently ongoing. It is noteworthy that the nitroaldol process using **5** and **6** as the substrates under conventional conditions (treatment of base) is troublesome, which gives not only *anti*- and *syn*-products but also double nitroaldol and Michael adducts to result in a complex mixture.

Next, the NO_2 group of **4** was reduced to a primary amine by an In-mediated process, followed by protection as TBS ether **11** (Scheme 2). The NH_2 functionality was then tentatively

Scheme 2. Synthesis of the Diazepanone Precursor 14



protected with Troc to give **12**, to which the Me group was introduced by a conventional procedure to afford a masked secondary amine **13**. Removal of the Troc gave **14** uneventfully.

Next, we examined the diastereoselective isocyanoacetate aldol reaction, the other key stereoselective transformation. A similar approach employing ribose-derived aldehyde was

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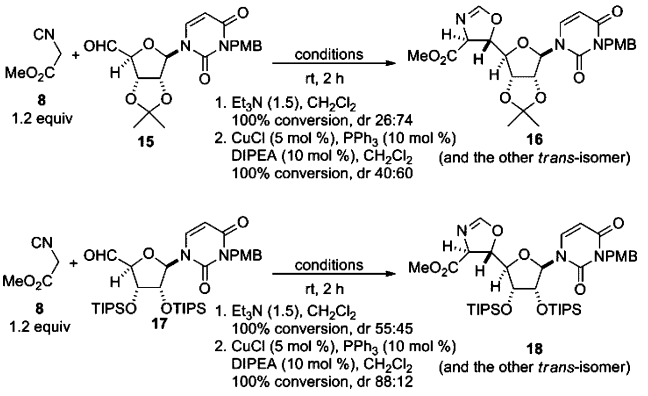
reported by Le Merrer,[11] where *trans*-oxazoline with an incorrect configuration was the major product (26:74). Our preliminary study using PMB-protected uridine-derived aldehyde is shown in Scheme 3. As presumed based on Le Merrer's results, the

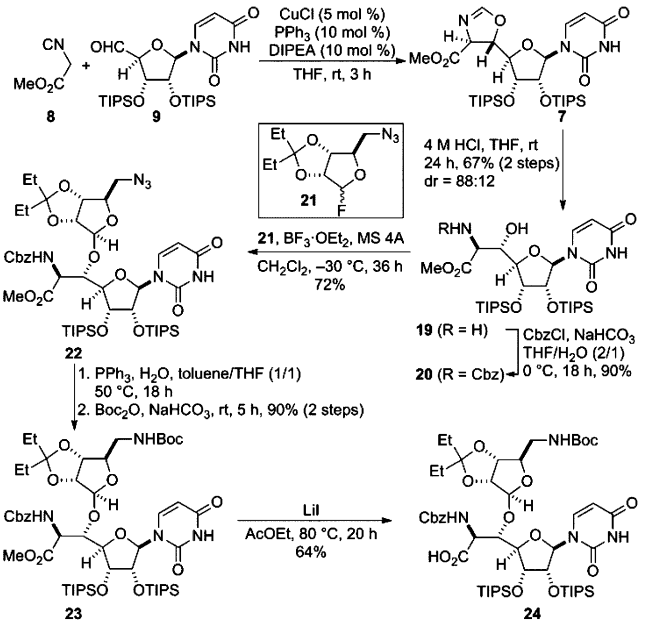
Scheme 3. Preliminary Study of Diastereoselective Isocyanoacetate Aldol Reaction



formation of an undesired diastereomer of *trans*-oxazoline predominated when Et_3N and **8** (1.2 equiv) were treated with the isopropylidene-protected aldehyde **15** in CH_2Cl_2. Changing the protective group from isopropylidene to TIPS (**17**) improved the selectivity, but the dr (ca. 1:1) remained unsatisfactory. The Cu(I)-catalyzed conditions reported by Kirchner[18] dramatically increased the dr to 88:12. Even with this method, the isopropylidene congener **15** gave a poor result (40:60), demonstrating that the correct choice of the protecting group for the ribose part is crucial.

Actually, protection of the NH was not needed in the synthetic pathway: the aldol process of **8** and **9** proceeded more cleanly with the same selectivity by changing the solvent from CH_2Cl_2 to THF (88:12) at the expense of a slightly longer reaction time (2 h vs 3 h; Scheme 4). At this step, the oxazoline product **7** could not be purified on silica gel because of its susceptibility to

Scheme 4. Synthesis of Uridine-Derived Carboxylic Acid 24

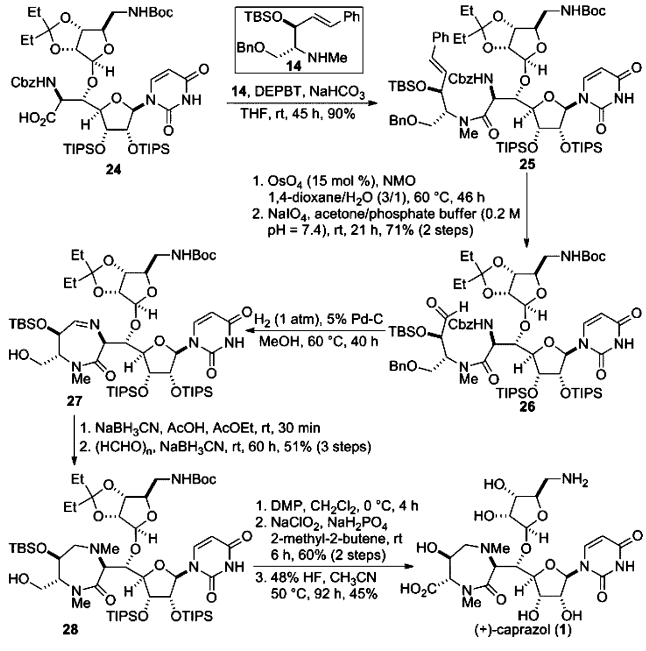


decomposition. Acid hydrolysis conducted with the crude material occurred uneventfully to obtain β-hydroxy-α-amino ester **19**. Satisfied with the successful key stereoselective C–C bond formation, we undertook further transformations toward caprazol inspired by Matsuda and Ichikawa's procedure.[5,7]

The NH_2 group was protected as a benzyl carbamate (**20**), with which an *O*-glycosylation procedure[7b] was applied with some modification. The acceptor **20** and donor **21** were coupled under Lewis acidic conditions with $BF_3{\cdot}OEt_2$ (36 h, −30 °C) to afford the desired β-anomer **22** in 72% yield. Successful interconversion of the functional groups (N_3 to BocNH) gave **23**, which was followed by the nucleophilic cleavage of the ester to give a carboxylic acid **24**.

This set the stage for the endgame of the synthesis including the diazepanone formation. The precedents generally required either reductive amination or lactamization for the cyclization other than some exceptions such as Takemoto's Pt-catalyzed 7-*endo* cyclization of an internal alkynyl amide.[19] In the present study, we adopted a reductive amination. Coupling of the two segments (**14** and **24**) was achieved using the DEPBT method[20] to give the amide intermediate **25** (Scheme 5). The benzylidene moiety of **25**, a hidden formyl functionality, was oxidatively cleaved to afford a cyclization precursor **26**.

Scheme 5. Construction of the Diazepanone System and Completion of the Total Synthesis



Hydrogenolysis using Pd-catalysts under a H_2 atmosphere with AcOH as an additive removed the Cbz and Bn groups with the utmost efficiency with concomitant intramolecular imine formation to result in **27**. An undesired reaction, hydrogenation of the double bond on uracil, however, also proceeded. Although Kurosu et al. recently reported that formic acid as an additive suppresses the intractable side reaction,[21] this new protocol did not work in the present system. Unfortunately, it was difficult to eliminate the side products associated with this over-reduction at any of the later steps of the synthesis. Eventually, hydrogenolysis upon gentle heating without acid was found to work satisfactorily: removal of the Cbz and Bn groups and instantaneous cyclization proceeded with 5% Pd–C under

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atmospheric H_2 in MeOH at 60 °C whereas no reaction took place at room temperature. The double bond of the imine within **27** was effectively reduced with $NaBH_3CN$, followed by methylation ($NaBH_3CN$, paraformaldehyde) to give **28**.

The unveiled primary alcohol was transformed into carboxylate by the standard two-step oxidation sequence. The final global deprotection was achieved by 48% HF in CH_3CN, thereby completing the catalytic asymmetric total synthesis of (+)-caprazol (**1**). In terms of the spectral data, and physicochemical properties, the synthetic sample was indistinguishable from the sample derived from natural caprazamycins.

In summary, catalytic enantioselective total synthesis of (+)-caprazol (**1**) was achieved, in which stereoselective C−C bond forming reactions furnished the two β-hydroxy-α-amino acid-derived substructures: an *anti*-selective nitroaldol reaction catalyzed by a heterogeneous heterobimetallic Nd/Na-chiral amide ligand complex, and a diastereoselective isocyanoacetate aldol reaction. Further synthetic studies toward the catalytic asymmetric total synthesis of caprazamycin B and SAR studies to obtain anti-XDR-TB leads and gain more mechanistic insight into WecA inhibition are underway.

■ ASSOCIATED CONTENT

Supporting Information

Characterization of new data, HPLC data, and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: twatanabe@bikaken.or.jp.
*E-mail: mshibasa@bikaken.or.jp.

Notes

The authors declare no competing financial interest.

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