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ARTIFICIAL INTELLIGENCE-DESIGNED STEREOSELECTIVE ONE-POT SYNTHESIS OF *trans*-*β*-LACTAMS AND ITS APPLICATION TO CHOLESTEROL ABSORPTION INHIBITOR SCH 47949 SYNTHESIS

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Abstract – Cholesterol absorption inhibitor drug SCH 47949 is synthesized stereoselectively using an artificial intelligence design proposed by SYNSUP. The key step involves a stereoselective one-pot preparation of the *trans*-*β*-lactam system through thermal electrocyclization. The *trans*-*β*-lactam intermediate is converted to SCH 47949 by a series of functional group transformations proposed by SYNSUP.

INTRODUCTION

Machine learning, which is a hub technology supporting advances in artificial intelligence (AI), has induced the third boom. AI is creating significant changes in society.[1] For example, AI using machine learning has beaten chess champions,[2] driven self-driving cars,[3] and aided with medical diagnoses.[4] In contrast to the recent AI boom, AI development in the field of synthetic organic chemistry began about 50 years ago and progress has been extremely slow. In 1969, Corey and Wipke reported the OCSS program,[4] which was the predecessor of LHASA.[5] At the same time, Berhson developed a completely different information-oriented system. This system was later named SYNSUP.[6] SYNSUP was the first automatic synthetic design system. In the 1970s, CYCLOPS[7] and EROS[8] were developed. These were logic-oriented systems. Since then, various types of AI programs have been reported. Figure 1 shows some examples. All of these early systems require the input of chemists at some point. Recently,

Grzybowski's group established a powerful expert system in this field.[9] In the current AI boom, a new approach that creates reaction rules without the assistance of chemistry experts has appeared. For an example, Waller's group has started to develop new syntheses using a Monte Carlo tree search and symbolic AI.[10]

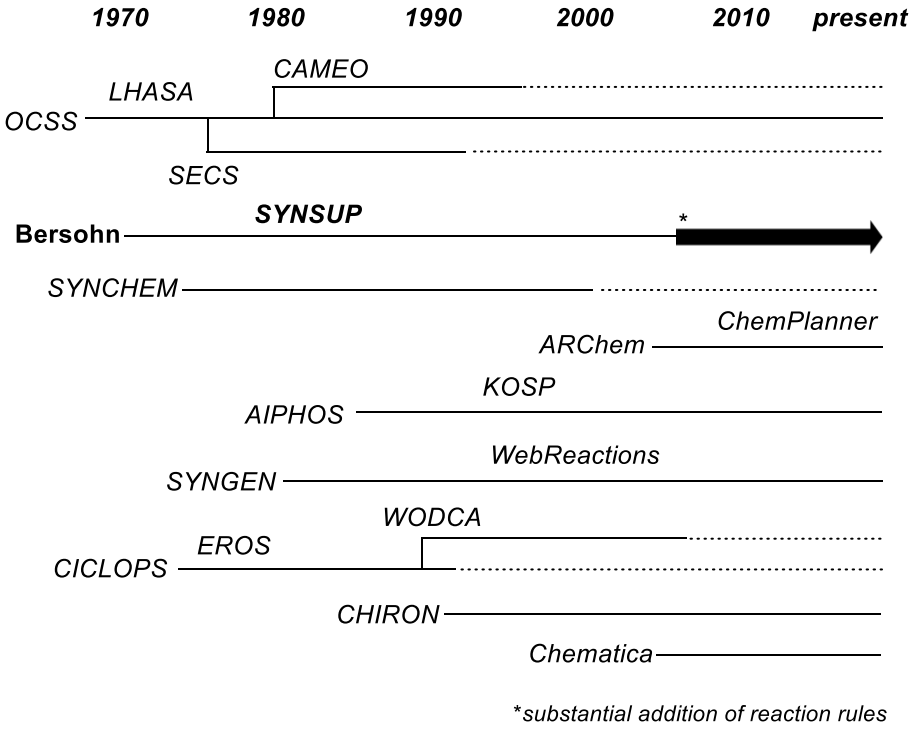
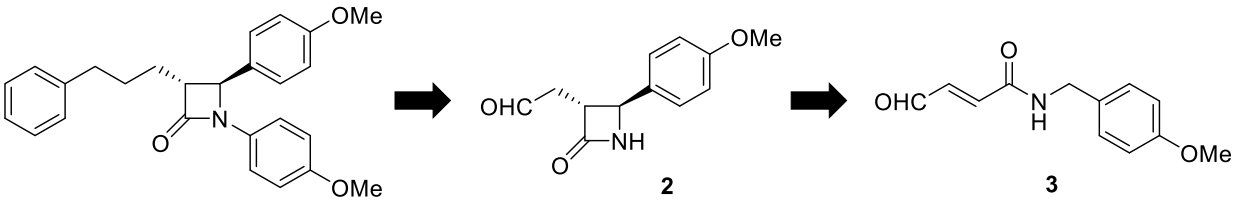


Figure 1. History of AI-designed synthetic programs

The knowledge bases in SYNSUP are comprised of reaction rules (~6,800) collected by experts and empirical rules to judge whether the reaction rules are applicable. Even now unrealistic synthetic routes are proposed together with creative synthetic routes. For SYNSUP to evolve, this issue must be resolved using feedback from experimental data. Herein, we report a new stereoselective synthesis of cholesterol absorption inhibitor SCH 47949 (**1**), which was proposed by SYNSUP (Scheme 1). SCH 47949 (**1**) shows Acyl-CoA cholesterol acyltransferase (ACAT) inhibition and cholesterol absorption inhibition activities.[11]



SCH 47949 (**1**)

Scheme 1. SYNSUP-designed retrosynthetic analysis of SCH 47949 (**1**)

RESULTS AND DISCUSSION

First, SYNSUP and an actual operation procedure are described. SYNSUP runs itself after inputting data, which includes the connection table of the target molecule and some constraints (options). The input data is generated using the original GUI software called CMBedit. In principle, the first run requires no options. The program runs following the directions of the preinstalled heuristics using the default values for basic options. The most elemental option is the step limit. The default is two steps. SYNSUP tries to complete routes within two steps. If it fails to build the specified number of routes, the step limit is increased to three and the search starts over. This process is repeated until the specified minimum number of routes is proposed. The default is 20. On the other hand, when the 100th route is proposed, the job is terminated since this is the default for the maximum number of proposed routes. Typical target molecules require more than three steps to synthesize from available starting materials. Consequently, the number of proposed routes can easily exceed 100, and the search is terminated halfway through an imaginary synthesis tree. Hence, constraints (options) are specified, and the job is resubmitted.

I. First Run

The implementation of this study is shown below. Target molecule **1** was drawn using CMBedit (Figure 2).

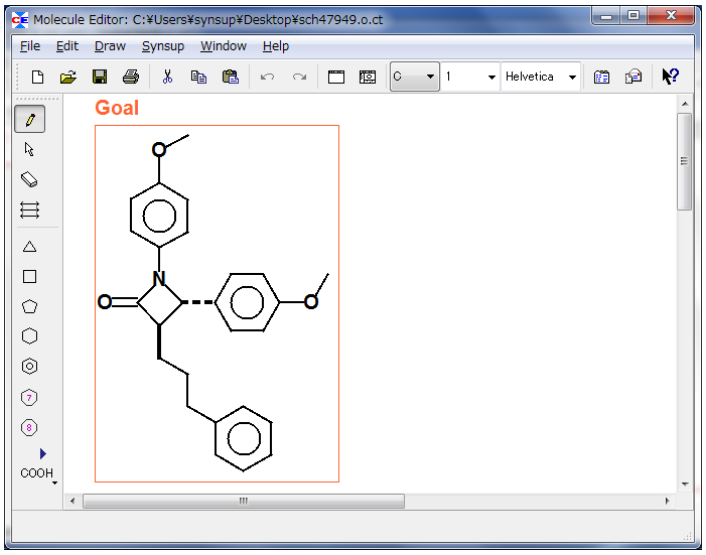


Figure 2. Molecule Editor of CMBedit

In 1.5 minutes, SYNSUP proposed 16 three-step routes for target molecule **1** starting from available compounds. Figures 3 and 4 show the tree-view and map-view modes, respectively. Figure 3 shows the search result in the tree-view mode. The left pane outlines the proposed routes in a synthesis tree-like manner. That is, the goal is placed in the top left and the predecessors are drawn on the right like a staircase. For example, Number 198, which is the serial number of the reaction rule, is currently selected in the number pane (left side), and the corresponding reaction is drawn in the figure pane (right side).

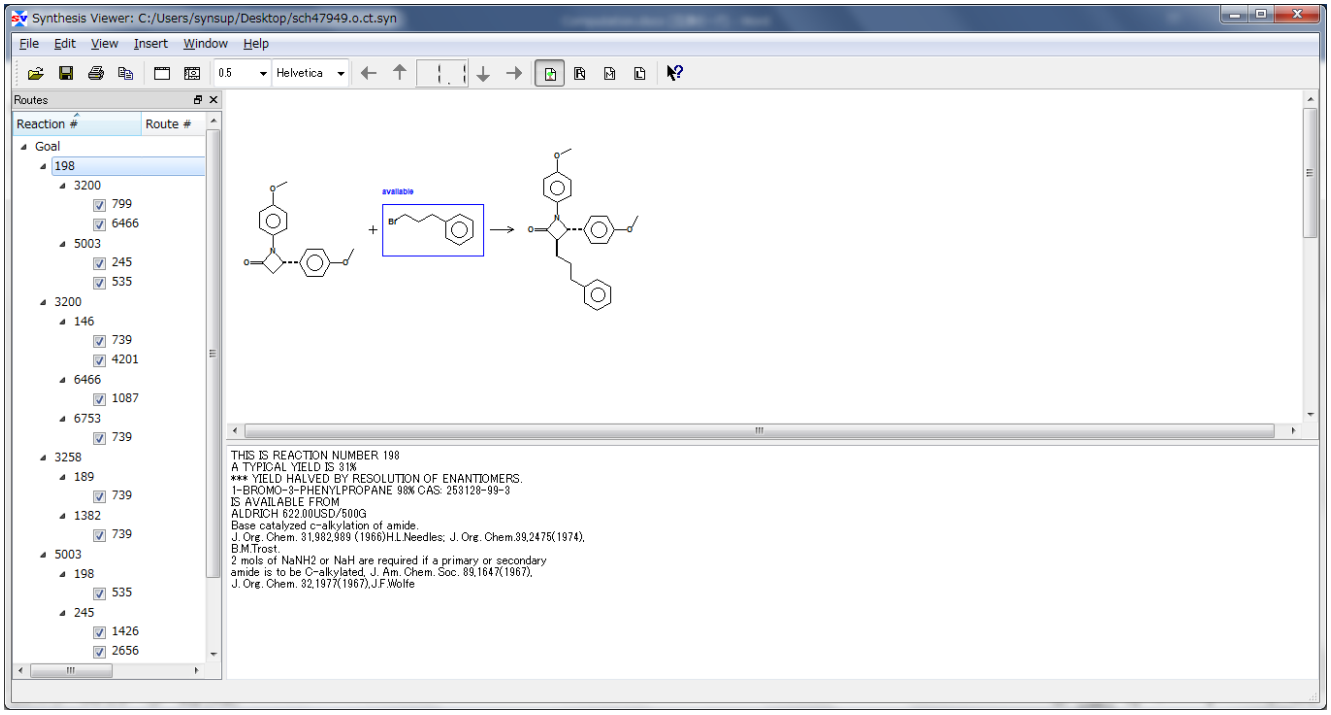


Figure 3. Synthesis viewer of CMBedit (three view mode)

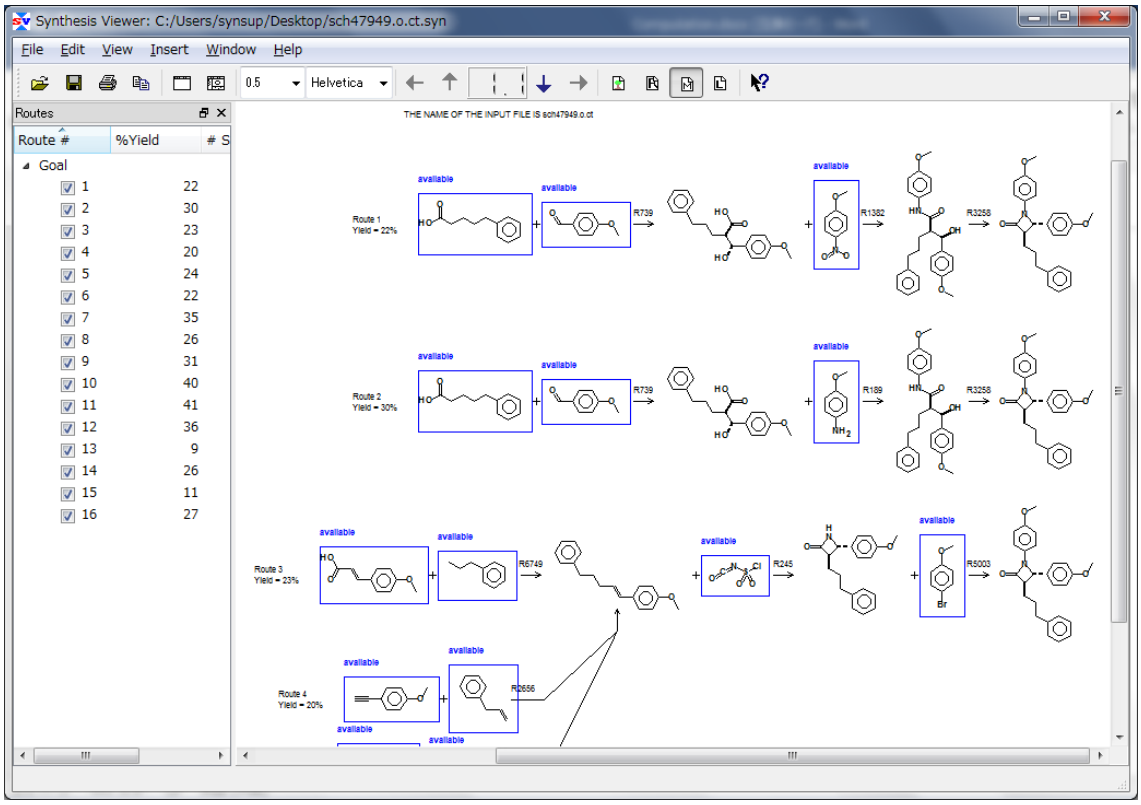


Figure 4. Synthesis viewer of CMBedit (map view mode)

Figure 4 displays the search result in the map-view mode. The first four routes are drawn in the figure pane. A blue box indicates a commercially available compound. Double-clicking the blue frame displays

the supplier and price in a separate window. Figure 5 shows three kinds of ring closing methods. Double-clicking a reaction arrow provides a brief description of the reaction and references in a separate window. In this case, a stereospecific intramolecular Mitsunobu reaction (Route 1), a [2+2] cycloaddition of an isocyanate and an alkene (Route 6), and an intramolecular amide formation (Route 15) are shown.

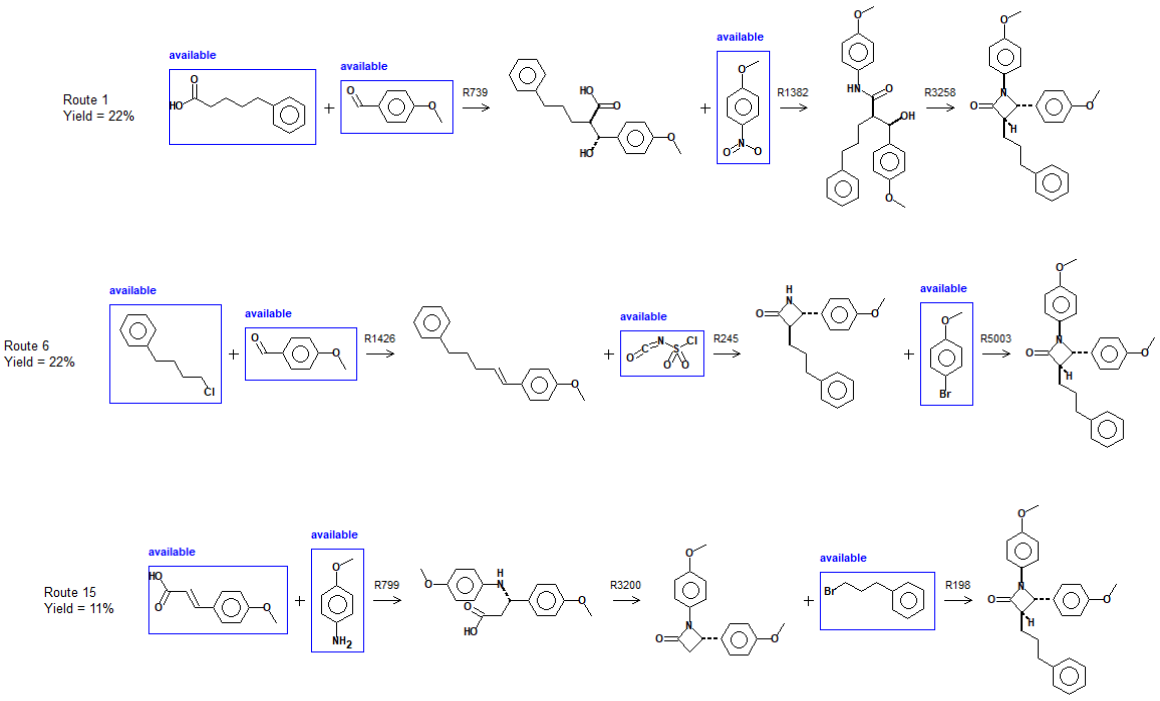


Figure 5. Three representative routes using different ring closing method

II. Second Run

Since the goal is to identify new methodologies for a *trans-β*-lactam synthesis, options for the route search by SYNSUP were specified to suppress amide formation and the [2+2] cycloaddition reaction. That is, the amide bond and the carbonyl-α carbon bond were specified as "start with" (highlighted with green) and ether formation was forbidden by "don't touch" (highlighted with a blue circle) (Figure 6). By suppressing the generation of unwanted routes, SYNSUP proposes new routes by pruning the previous run. In addition, "ring limit 0" and "step limit 6" are specified from the option menu. The latter is necessary to continue searching over the huge synthesis tree.

In about an hour, SYNSUP proposed 2,250 routes. Of these, 21 were four-step routes. Most used an intramolecular Mitsunobu reaction. The remainder employed the Ritter reaction and *N*-alkylation.

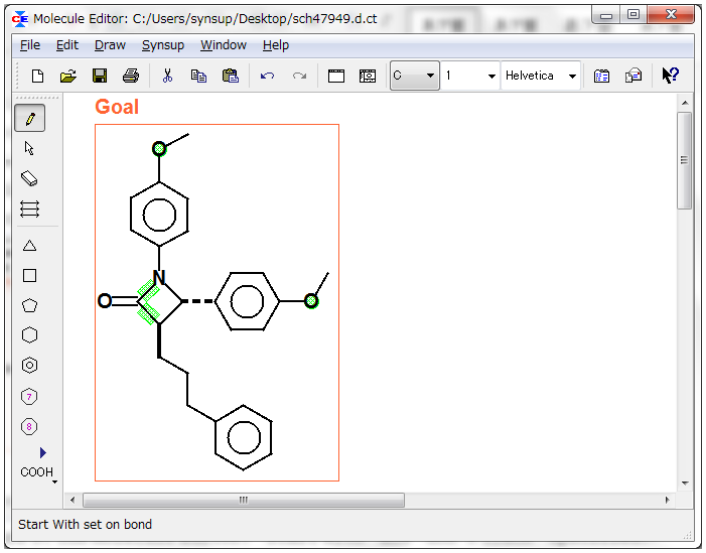


Figure 6. Molecule Editor

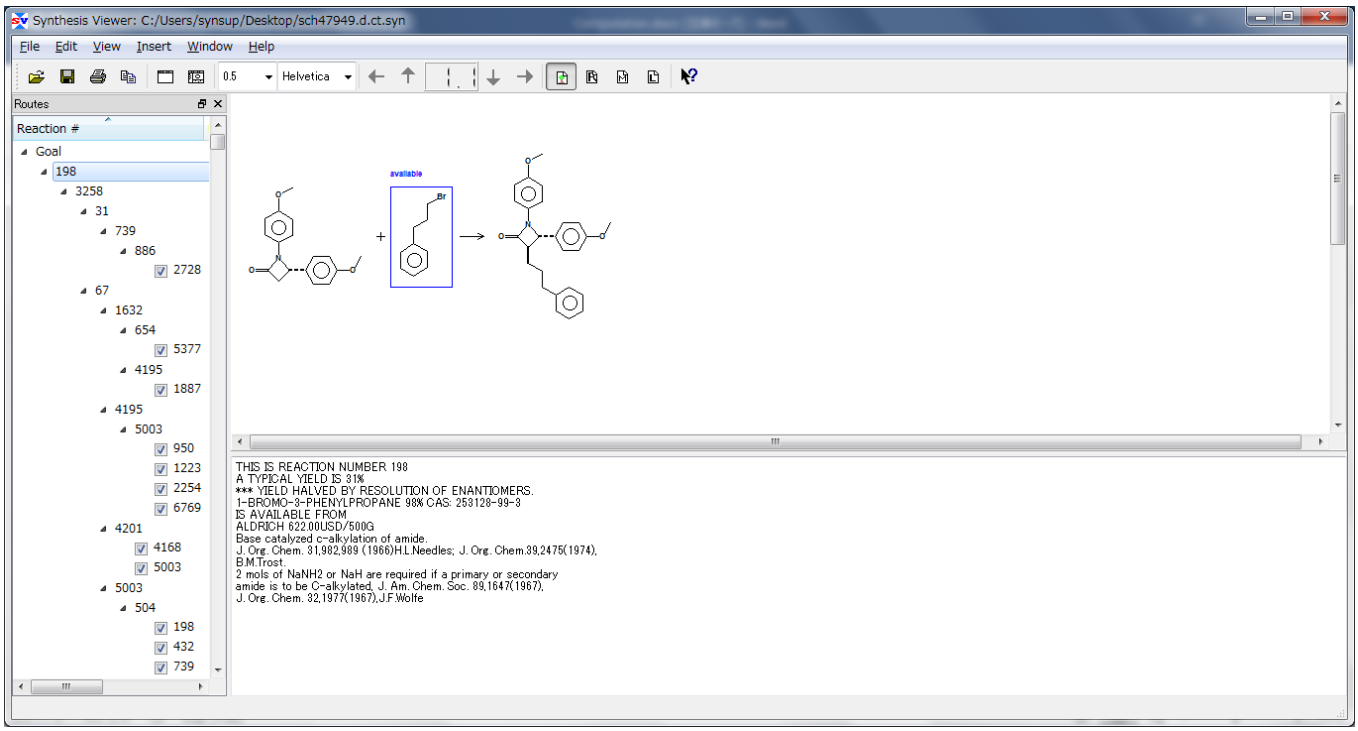


Figure 7a. Initial view

Additionally, 326 five-step routes and 1,903 six-step routes were proposed. Each route begins with commercially available compounds. Figure 7a (Initial view: when reaction number 198 is selected) shows the tree-view display. The proposed routes can be quickly reviewed. For uninteresting reactions, clicking the black triangle in front of the number turns it into a white triangle, and the subsequent “branches” are folded in and removed from view. Figure 7b shows the tree-view mode when folding in branches that follow reaction number 198.

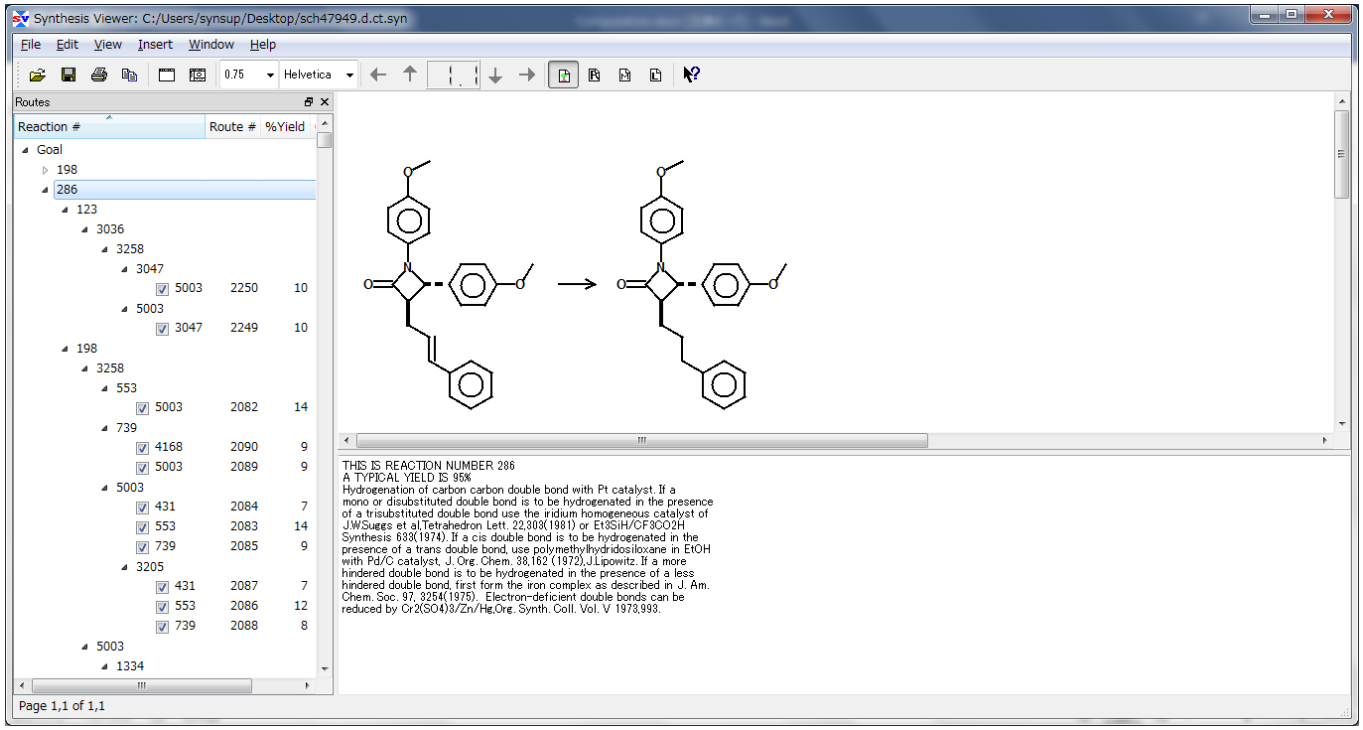


Figure 7b. Folded-in view

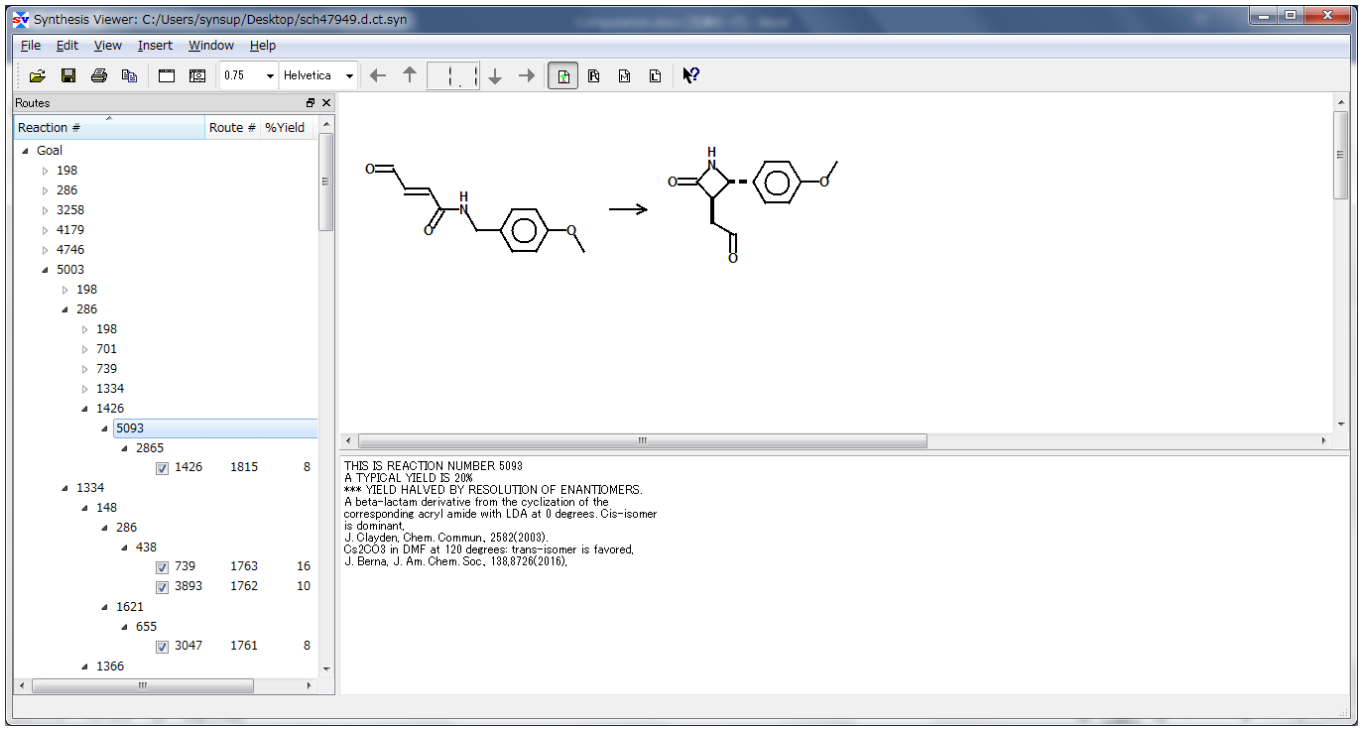


Figure 7c. Stereoselective approach to *trans-β*-lactam synthesis

This process revealed a new methodology. In the tree-view mode, clicking the black triangle in (a) turns it into a white triangle, and (b) subsequent "branches" are folded. Repeating this process for uninteresting reaction 11 times showed route number 1815, which involves a unique reaction number 5093 (Figure 7c).

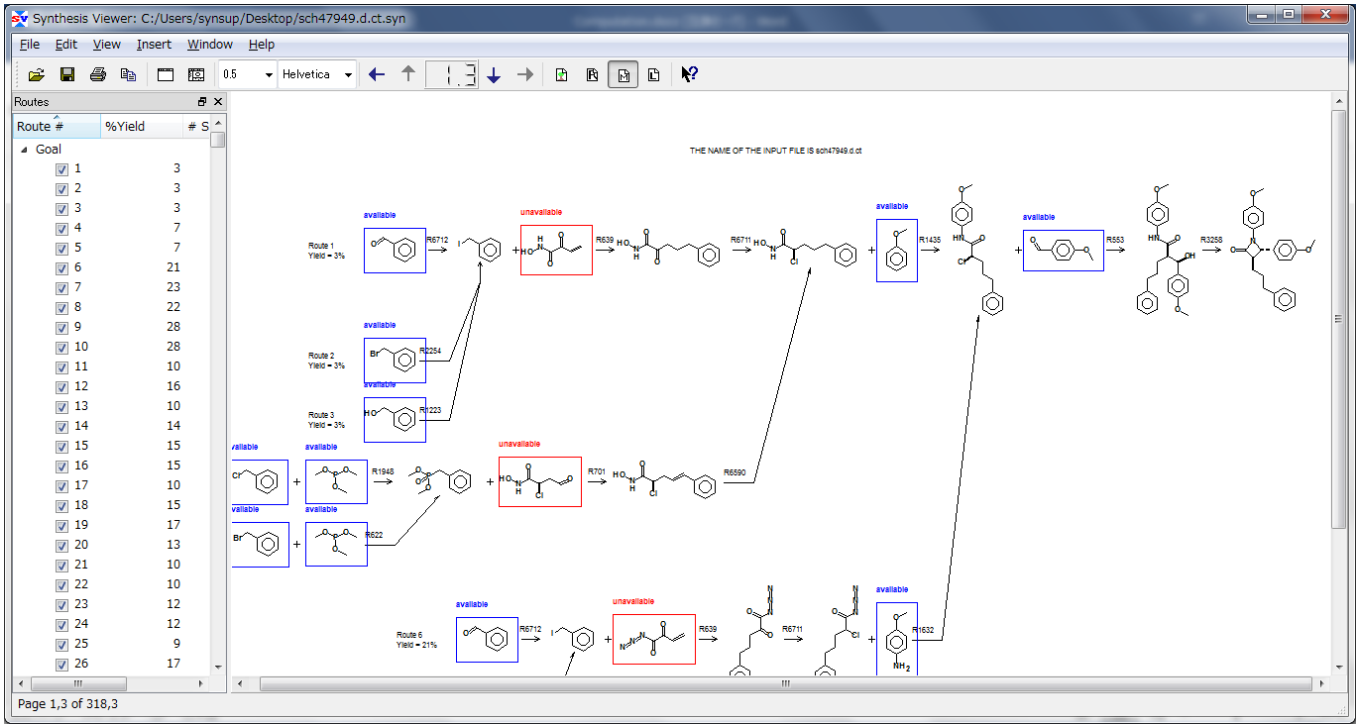


Figure 8. Map-view mode after hiding uninteresting route

This feature allows the huge synthesis tree to be easily reviewed to find routes of interest. The map-view mode has a similar feature to "hide" unwanted routes. Clicking the right button of the mouse on the arrow under that reaction number and selecting "Hide route(s)" in the menu removes trivial or susceptible routes from the display. Each route that passes the reaction at the same depth is removed from the pane. Repeating this process ten times reduced the routes (Figure 8). It should be mentioned that a red box in Figure 8 indicates a commercially unavailable compound.

After hiding uninteresting reactions ten times, route number 1815 appeared (Figure 9). Figure10 shows the entire transformation of route number 1815. As this is an inspiring new route, we selected it as our synthesis target.

Among the 2,250 proposed synthetic routes by SYNSUP, we were interested in a one-pot preparation of *trans-β*-lactam ring system **2** from unsaturated amide **3** (Scheme 1). The cited papers presented by the SYNSUP program for the transformation of **3** to **2** is an anionic *4-exo-trig* cyclization in the presence of a base (Scheme 2).[12]

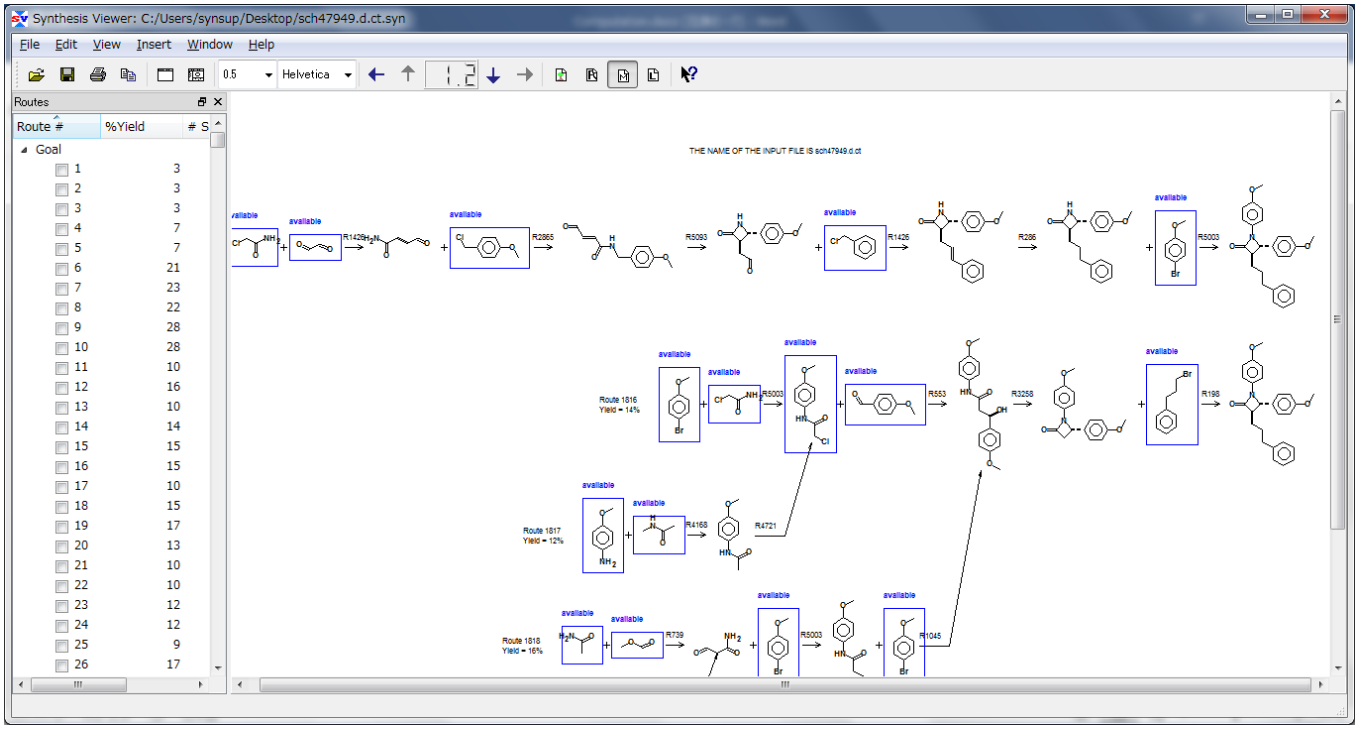


Figure 9. Map-view mode of route number 1815 indicates a novel synthetic route for SCH 47949 (**1**)

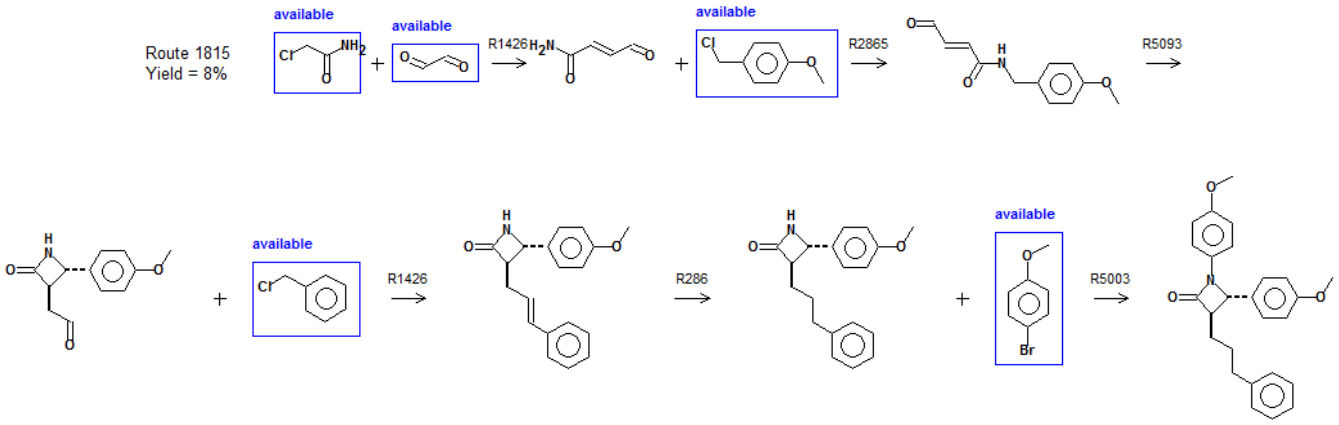
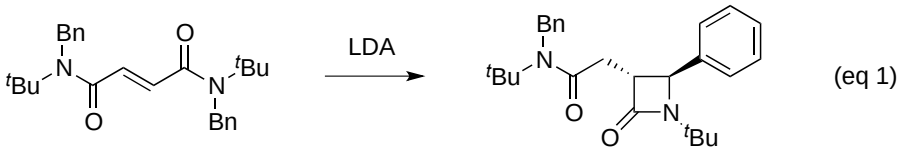


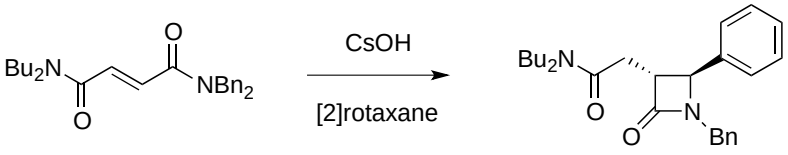
Figure 10

Clayden *et al*. (**2003**)



(eq 1)

Berna *et al*. (**2016**)

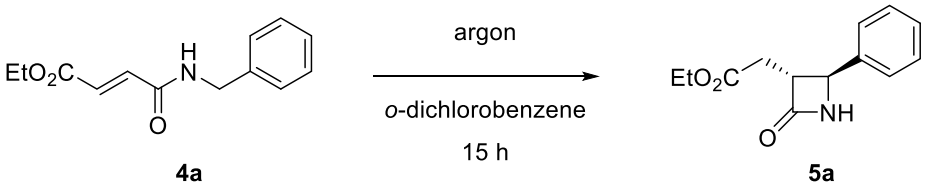


(eq 2)

Scheme 2. *β*-Lactam synthesis through anionic *4-exo-trig* cyclization

Based on the SYNSUP result and our knowledge of synthetic organic chemistry, we modified the reaction scheme to avoid side reactions by the reactive formyl group, to accommodate the electron withdrawing group, and to ease of substrate synthesis. Hence, we changed the group of **3** to ethyl ester moiety in model compound **4a** and set to realize a *4-exo-trig* cyclization of **4a**.

Table 1. Evaluation of the reaction conditions for cyclization



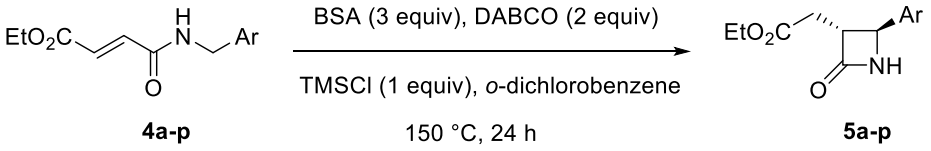
4a **5a**

entry[a]	base (equiv)	additive (equiv)	temperature (°C)	yield (%)
1[b]	LDA (2)	none	–78 to 0	0
2[c]	Cs_2CO_3 (10)	none	rt to 120	0
3[c]	BSA (2)	none	rt to 150	trace
4[c]	BSA (2) + Et_3N (2)	none	rt to 150	27
5[d]	BSA (2) + Et_3N (2)	TMSCl (1)	rt to 150	58
6[d]	Et_3N (2)	TMSOTf (2)	rt to 150	0
7[d]	Et_3N (2)	TMSCl (2)	rt to 150	0
8[d]	BSA (3) + DMAP (2)	TMSCl (1)	rt to 150	61
9[d]	BSA (3) + DABCO (2)	TMSCl (1)	rt to 150	75
10[d]	BSA (3) + $^iPr_2N$ (2)	TMSCl (1)	rt to 150	0

[a]All reactions were carried out in a screw-top test tube. [b]This reaction was run in THF solution. [c]0.1 M solution. [d]0.02 M solution.

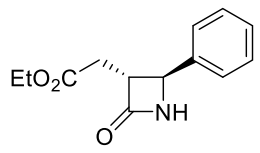
A variety of reaction conditions were examined to convert unsaturated amide ester **4a** into *β*-lactam **5a**. Desired product **5a** was not obtained when the cyclization was performed in the presence of organic acids (TsOH and CSA), inorganic acids (HCl and H_2SO_4), organic bases (DBN and DBU), or inorganic bases (KOH and K_2CO_3). Table 1 summarizes the results. Although LDA and Cs_2CO_3 proved to be ineffective (Table 1, entries 1 and 2), BSA (*N*,*O*-bis(trimethylsilyl)acetamide) provided a small amount of **5a** (Table 1, entry 3). In addition to acting as a base,[13] BSA is also used as a silylating agent.[14] Thus, a combination of BSA and base was examined. Cyclization using 3 equiv BSA and 2 equiv Et_3N provided *trans*-*β*-lactam **5a** as a single stereoisomer in 27% yield (Table 1, entry 4). The relative stereochemistry of **5a** was obviously *trans* according to the coupling constants ($J_{3,4}$ = 2.4 Hz) between the protons on C(3) and C(4).[15] It is noteworthy that the *cis* isomer was not detected in the crude reaction mixture in this research. The addition of 1 equiv TMSCl improved the chemical yield (Table 1, entry 5). Interestingly, the

cyclization did not proceed without BSA (Table 1, entries 6 and 7). DMAP could replace Et_3N (Table 1, entriy 8), but *N*,*N*-diisopropylethylamine was ineffective (Table 1, entry 10). The best result, 75% yield, was obtained when the transformation was conducted using 3 equiv BSA, 2 equiv DABCO, and 1 equiv TMSCl at 150 ˚C for 15 h (Table 1, entry 9).

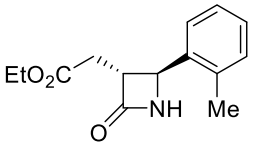


4a-p **5a-p**

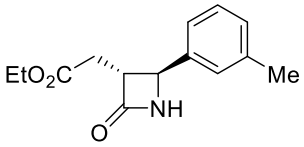
product and isolated yield



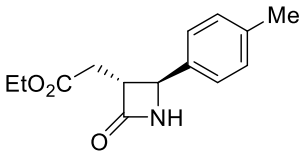
5a (75%)



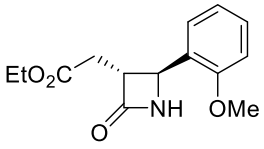
5b (67%)



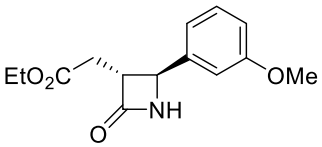
5c (63%)



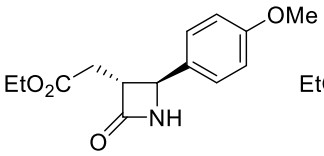
5d (66%)



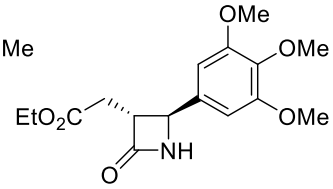
5e (62%)



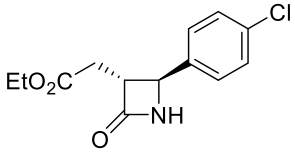
5f (63%)



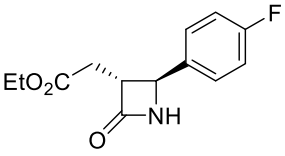
5g (64%)



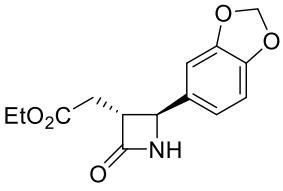
5h (52%)



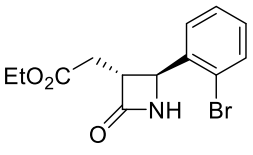
5i (73%)



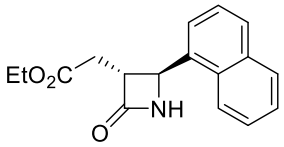
5j (77%)



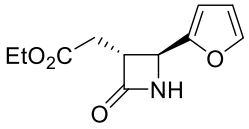
5k (60%)



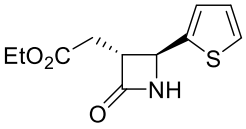
5l (65%)



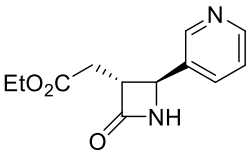
5m (61%)



5n (55%)



5o (66%)

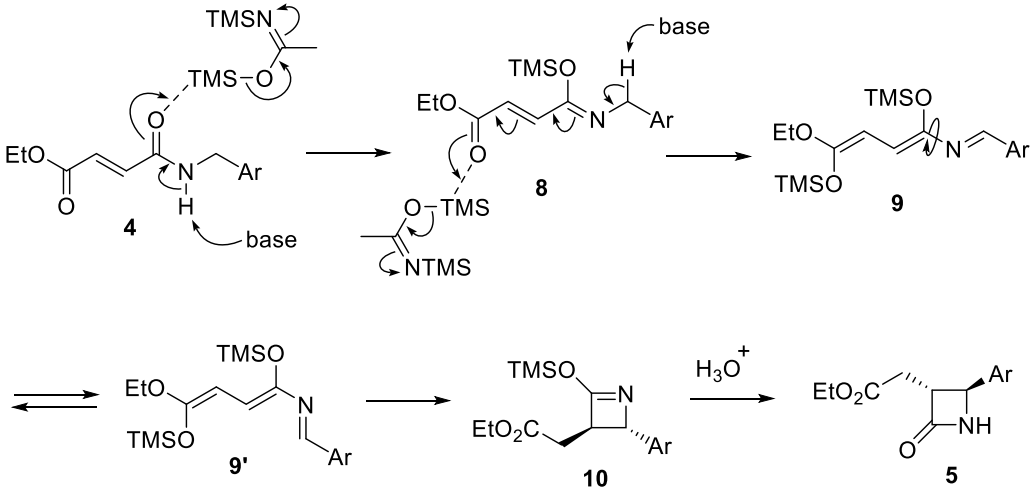


5p (55%)

Scheme 3. One-pot synthesis of *trans*-*β*-lactams

With the established reaction conditions for *trans*-*β*-lactam synthesis, the scope and limitation of this stereoselective cyclization were investigated using various unsaturated amide esters (Scheme 3). The

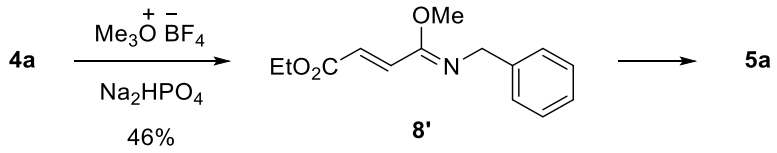
methyl substituent on the benzene ring of the reaction substrates **4b–d** had a negligible influence on chemical yields of products **5b–d**. Regarding the methoxy group on the benzene ring of the reaction substrate **4e–g**, the reactivity was the same as the case of the methyl group. However, the case of trimethoxy substrate **5h** decreased the yield. Substrates with an electron withdrawing halogen at the para position of the benzene ring such as **4i** and **4j** gave desired *trans*-*β*-lactams **5i** and **5j**, respectively, in good yields. The methylenedioxy group in **4k** survived under the reaction conditions to give **5k** in 60% yield. Substrates with a bromine or naphthyl substituent group on the benzene ring such as **4l** and **4m** provided cyclization products **5l** and **5m** in reasonable yields. Even substrates **4n–p** with heterocyclic ring moieties afforded desired products **5n–p** in moderate yields.



Scheme 4. Possible reaction mechanism

Scheme 4 depicts a possible reaction mechanism regarding this cyclization (**4** → **5**). Since only *trans*-*β*-lactams **5** were provided in this transformation, we believe that this cyclization proceeded via an electrocyclic reaction. Namely, after BSA activated the amide carbonyl group, a hydrogen on the nitrogen atom in **4** was removed by DABCO to give TMS-imidate intermediate **8**. Next, the ester carbonyl group in **8** was activated by BSA and a benzylic hydrogen of **8** was extracted by DABCO to afford the doubly conjugated TMS-imidate **9**. Once **9** adopted the s-*cis* conformation **9'**, a thermal electrocyclic ring closure process proceeded in a conrotatory fashion to provide cyclic TMS-imidate **10**.[16] After an acidic work-up, the desired *trans*-*β*-lactam **5** was obtained as a single stereoisomer.

To elucidate the proposed reaction mechanism, methylimidate **8'** was subjected to the present transformation. As expected, **5a** was isolated with the same chemical yield as the case involving **4a** (Scheme 5). This result is consistent with our proposed reaction mechanism.



Scheme 5. Experiment to elucidate the reaction mechanism

Manifest support for the *trans* relative configuration of the phenyl and acetate groups in **5j** was obtained by single-crystal X-ray analysis (Figure 11).

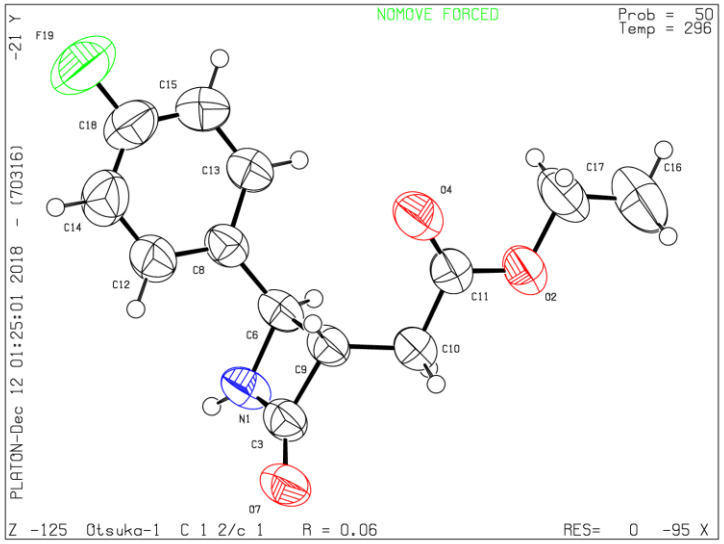
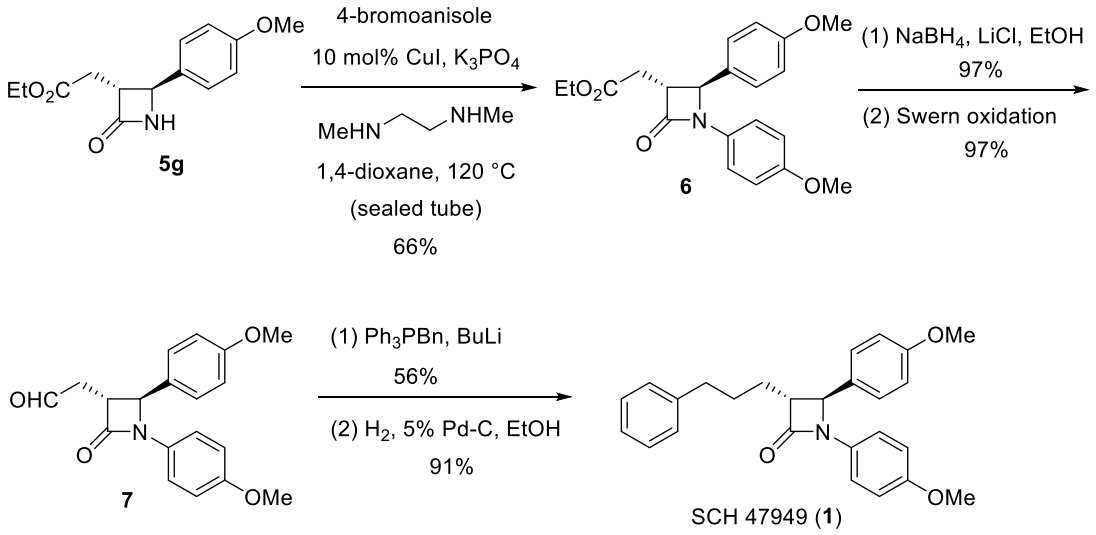


Figure 11. ORTEP drawing of the molecular structure of **5j**

After establishing a methodology to synthesize *trans*-*β*-lactam, the total synthesis of SCH 47949 (**1**) was examined according to the synthetic route proposed by SYNSUP. Namely, synthetic intermediate **5g** was subjected to a coupling reaction[17] with 4-bromoanisole in the presence of 10 mol% CuI to furnish coupling product **6** in 66% yield. The ester moiety of **6** was converted to the formyl group in **7** by $NaBH_4$ reduction[18] and a subsequent Swern oxidation. The side chain at C(3) position of SCH 47949 (**1**) was installed by a Wittig olefination and hydrogenation. Scheme 5 depicts the total synthesis of SCH 47949 (**1**). The spectroscopic properties of synthetic material **1** were identical with those reported for **1**.[11]

In conclusion, we demonstrate that AI (SYNSUP) basically designed a novel stereoselective synthesis of SCH 47949. This AI-designed methodology should also give access to a clinical drug (ezetimibe). Although the present synthetic route proposed by SYNSUP may not be as elegant as that developed by chemists, the present results should provide inspiration for synthetic chemists.



Scheme 5. Total synthesis of SCH 47949 (**1**)

EXPERIMENTAL

General. Unless otherwise noted, all reactions were performed in oven-dried glassware and sealed with a rubber septum under an atmosphere of argon. Anhydrous THF and CH_2Cl_2 were purchased from Kanto Chemical. Thionyl chloride was distilled prior to use. Et_3N, DBU, $^iPr_2NH$, TMSCl, pyridine, imidazole, and 1,4-dioxane were distilled from CaH_2 prior to use. DMF, *o*-dichlorobenzene, and DMSO were distilled from CaH_2 under reduced pressure. DABCO was recrystallized from EtOH/hexane prior to use. Unless otherwise stated, materials were obtained from commercial suppliers and used as received. Flash column chromatography was carried out using Cica Silica Gel 60 N (spherical/40-50 μm). Reactions and chromatography fractions were analyzed employing precoated silica gel 60 F_{254} plates (Merck). Compounds were visualized using an ultraviolet lamp (254 nm) and/or by staining with *p*-anisaldehyde (in EtOH) or potassium permanganate (in water containing NaOH and K_2CO_3). The IR spectra were measured on a SHIMADZU FT-IR 8300 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian 400 MR (400 MHz) spectrometer and the chemical shifts were reported relative to residual $CHCl_3$ (7.26 ppm). ^{13}C NMR spectra were recorded on a Varian 400 MR (100 MHz) spectrometer and the chemical shifts were reported relative to the solvent resonance ($CDCl_3$: δ 77.2 ppm). Mass spectra were recorded on a JEOL JMS-700 MStation or a JEOL JMS-T100 AccuTOF LC-plus. All melting points were determined on a Yanaco micro melting point apparatus and were uncorrected.

Ethyl (*E*)-4-(benzylamino)-4-oxobut-2-enoate (4a).[19] To a solution of fumaric acid monoethyl ester (1.32 g, 9.16 mmol) in THF (20.0 mL) were added $SOCl_2$ (1.33 mL, 18.3 mmol) and DMF (one drop) at 0 ˚C. The resulting mixture was stirred at room temperature for 2.5 h. The solvent was removed under reduced pressure to give the crude acid chloride as a pale yellowish syrup, which was used in the next step without further purification.

To a solution of the crude acid chloride in CH_2Cl_2 (20.0 mL) were added benzylamine (0.67 mL, 6.11 mmol) and Et_3N (3.40 mL, 24.4 mmol) at 0 ˚C, and the resulting mixture was stirred at room temperature for 15 h. The reaction mixture was quenched with water and extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography with hexane-EtOAc (2:1 v/v) as an eluent to afford amide **4a** (1.23 g, 86%) as white crystals. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.29 (t, *J* = 7.2 Hz, 3H), 4.22 (q, *J* = 7.2 Hz, 2H), 4.54 (d, *J* = 5.6 Hz, 2H), 6.21 (br s, 1H), 6.85 (d, *J* = 15.2 Hz, 1H), 6.93 (d, *J* = 15.2 Hz, 1H), and 7.26-7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 44.0, 61.2, 127.8, 128.0, 128.8, 130.5, 136.6, 137.6, 163.7, and 165.9.

Ethyl (*E*)-4-[(2-methylbenzyl)amino]-4-oxobut-2-enoate (4b). White crystals; mp 110-111 ˚C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (t, *J* = 7.2 Hz, 3H), 2.33 (s, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 4.54 (d, *J* = 5.2 Hz, 2H), 6.01 (br s, 1H), 6.84 (d, *J* = 15.6 Hz, 1H), 6.92 (d, *J* = 15.6 Hz, 1H), and 7.17-7.24 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 19.1, 42.4, 61.3, 126.4, 128.2, 129.0, 130.6, 130.8, 135.2, 136.4, 136.7, 163.5, and 165.9; IR ($CDCl_3$) 3303, 3079, 2916, 2848, 1711, 1631, 1540, 1302, and 1178 cm^{-1}; HRMS calcd for $C_{14}H_{18}O_3N$ $[M+H]^+$ 248.1287, found 248.1288.

Ethyl (*E*)-4-[(3-methylbenzyl)amino]-4-oxobut-2-enoate (4c). White crystals; mp 68.0-68.5 ˚C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (t, *J* = 7.2 Hz, 3H), 2.33 (s, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 4.48 (d, *J* = 5.6 Hz, 2H), 6.42 (br s, 1H), 6.84 (d, *J* = 15.2 Hz, 1H), 6.96 (d, *J* = 15.2 Hz, 1H), 7.01-7.10 (m, 3H), and 7.22 (dd, *J* = 7.8 Hz, 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 21.4, 44.0, 61.2, 125.0, 128.5, 128.7, 128.7, 130.4, 136.7, 137.5, 138.5, 163.6, and 165.9; IR ($CDCl_3$) 3303, 3079, 2916, 2848, 1711, 1664, 1631, 1540, 1302, and 1178 cm^{-1}; HRMS calcd for $C_{14}H_{18}O_3N$ $[M+H]^+$ 248.1287, found 248.1288.

Ethyl (*E*)-4-[(4-methylbenzyl)amino]-4-oxobut-2-enoate (4d). White crystals; mp 114-115 ˚C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (t, *J* = 7.2 Hz, 3H), 2.33 (s, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 4.49 (d, *J* = 5.6 Hz, 2H), 6.19 (br s, 1H), 6.84 (d, *J* = 15.6 Hz, 1H), 6.92 (d, *J* = 15.6 Hz, 1H), and 7.13-7.19 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 21.2, 43.9, 61.3, 128.1, 129.6, 130.6, 134.5, 136.5, 137.6, 163.6, and 165.9; IR ($CDCl_3$) 3284, 2916, 2848, 1712, 1665, 1631, 1426, and 1296 cm^{-1}; HRMS calcd for $C_{14}H_{18}O_3N$ $[M+H]^+$ 248.1287, found 248.1284.

Ethyl (*E*)-4-[(2-methoxybenzyl)amino]-4-oxobut-2-enoate (4e). White crystals; mp 83.5-84.0 ˚C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.29 (t, *J* = 7.2 Hz, 3H), 3.87 (s, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 4.53 (d, *J* = 6.0 Hz, 2H), 6.34 (br s, 1H), 6.78-6.94 (m, 4H), and 7.27-7.30 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 39.8, 55.4, 61.2, 110.4, 120.7, 125.5, 129.2, 130.0, 130.2, 136.7, 157.6, 163.4, and 165.8; IR ($CDCl_3$) 3272, 3070, 2982, 2982, 2916, 2837, 1723, 1603, 1541, 1494, 1297, 1160, and 1119 cm^{-1}; HRMS calcd for $C_{14}H_{18}O_4N$ $[M+H]^+$ 264.1236, found 264.1237.

Ethyl (*E*)-4-[(3-methoxybenzyl)amino]-4-oxobut-2-enoate (4f). White crystals; mp 89.0-89.5 ˚C; ^{1}H

NMR ($CDCl_3$, 400 MHz) δ 1.25 (t, *J* = 7.2 Hz, 3H), 3.76 (s, 1H), 4.11 (q, *J* = 7.2 Hz, 2H), 4.47 (d, *J* = 5.6 Hz, 2H), 6.76-6.85 (m, 5H), 7.00 (d, *J* = 15.2 Hz, 1H), and 7.22 (dd, *J* = 7.8 Hz, 7.8Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 44.0, 55.3, 61.3, 113.2, 113.6, 120.2, 129.9, 130.6, 136.5, 139.1, 160.0, 163.7, and 165.9; IR ($CDCl_3$) 3272, 3070, 2982, 2916, 2837, 1723, 1603, 1541, 1494, 1297, 1245, 1160, and 1119 cm^{-1}; HRMS calcd for $C_{14}H_{18}O_4N$ $[M+H]^+$ 264.1236, found 264.1237.

Ethyl (*E*)-4-[(4-methoxybenzyl)amino]-4-oxobut-2-enoate (4g). White crystals; mp 105-106 ˚C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.29 (t, *J* = 7.2 Hz, 3H), 3.80 (s, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 4.47 (d, *J* = 6.0 Hz, 2H), 6.01 (br s, 1H), 6.82-6.91 (m, 4H), and 7.22 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 43.6, 55.4, 61.3, 114.3, 129.5, 129.6, 130.7, 136.4, 159.3, 163.5, and 165.8; IR (neat) 3296, 2975, 1712, 1632, 1555, 1335, 1297, 1176, and 1166 cm^{-1}; HRMS calcd for $C_{14}H_{18}O_4N$ $[M+H]^+$ 264.1236, found 264.1240.

Ethyl (*E*)-4-oxo-4-[(3,4,5-trimethoxybenzyl)amino]but-2-enoate (4h). White crystals; mp 87.0-88.0 ˚C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.29 (t, *J* = 7.2 Hz, 3H), 3.81 (s, 3H), 3.82 (s, 6H), 4.21 (q, *J* = 7.2 Hz, 2H), 4.44 (d, *J* = 5.6 Hz, 2H), 6.39 (br s, 1H), 6.47 (s, 2H), 6.86 (d, *J* = 15.2 Hz, 1H), and 6.96 (d, *J* = 15.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 44.3, 56.0, 60.8, 61.2, 104.9, 130.4, 133.4, 136.6, 136.9, 153.2, 163.7, and 165.8; IR (neat) 3288, 2980, 2939, 1722, 1667, 1594, 1508, 1461, 1332, and 1300 cm^{-1}; HRMS calcd for $C_{16}H_{22}O_6N$ $[M+H]^+$ 324.1447, found 324.1445.

Ethyl (*E*)-4-[(4-chlorobenzyl)amino]-4-oxobut-2-enoate (4i). White crystals; mp 121.5-122 ˚C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.31 (t, *J* = 7.2 Hz, 3H), 4.24 (q, *J* = 7.2 Hz, 2H), 4.52 (d, *J* = 6.4 Hz, 2H), 6.03 (br s, 1H), 6.85 (d, *J* = 15.2 Hz, 1H), 6.90 (d, *J* = 15.2 Hz, 1H), and 7.22-7.33 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 43.3, 61.3, 129.0, 129.3, 130.7, 133.6, 136.2, 136.4, 163.8, and 165.9; IR (neat) 3309, 1708, 1631, 1545, 1491, 1306, 1182, 1176, 1000, and 559 cm^{-1}; HRMS calcd for $C_{13}H_{14}O_3NClNa$ $[M+Na]^+$ 290.05599, found 290.05708.

Ethyl (*E*)-4-[(4-fluorobenzyl)amino]-4-oxobut-2-enoate (4j). White crystals; mp 117.5-118 ˚C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.25 (t, *J* = 7.2 Hz, 3H), 4.11 (q, *J* = 7.2 Hz, 2H), 4.47 (d, *J* = 6.0 Hz, 2H), 6.75 (br s, 1H), 6.81 (d, *J* = 15.6 Hz, 1H), 6.97-7.01 (m, 3H), and 7.22-7.25 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 43.3, 61.3, 115.6, 115.8, 129.7, 129.8, 130.8, 133.4, 133.5, 136.3, 161.2, 163.6, 163.7, and 165.9; IR (neat) 3305, 1708, 1632, 1512, 1308, 1297, 1218, 1176, and 1158 cm^{-1}; HRMS calcd for $C_{13}H_{15}O_3NF$ $[M+H]^+$ 252.1036, found 252.1035.

Ethyl (*E*)-4-[(benzo[*d*][1,3]dioxol-5-ylmethyl)amino]-4-oxobut-2-enoate (4k). White crystals; mp 121-122 ˚C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.29 (t, *J* = 7.2 Hz, 3H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.43 (d, *J* = 5.6 Hz, 2H), 5.94 (s, 2H), 6.18 (br s, 1H), 6.75-6.78 (m, 3H), 6.83 (d, *J* = 15.2 Hz, 1H), and 6.91 (d, *J* = 15.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 43.8, 61.2, 101.1, 108.3, 108.5, 121.3, 130.3, 131.4, 136.6, 147.1, 147.9, 163.7, and 165.9; IR ($CDCl_3$) 3299, 2367, 1711, 1634, 1504, 1443, 1253, 1122, 1102,

and 616 cm^{-1}; HRMS calcd for $C_{14}H_{16}O_5N$ $[M+H]^+$ 278.1028, found 278.1023.

Ethyl (*E*)-4-[(2-bromobenzyl)amino]-4-oxobut-2-enoate (4l). White crystals; mp 106-107 ˚C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.27 (t, *J* = 7.2 Hz, 3H), 4.17 (q, *J* = 7.2 Hz, 2H), 4.59 (d, *J* = 6.0 Hz, 2H), 6.71 (br s, 1H), 6.81 (d, *J* = 15.2 Hz, 1H), 6.97 (d, *J* = 15.2 Hz, 1H), 7.14 (ddd, *J* = 7.6 Hz, 7.6 Hz, 1.6Hz, 1H), 7.26 (ddd, *J* = 7.6 Hz, 7,6 Hz, 1.2 Hz, 1H), 7.37 (dd, *J* = 7.6 Hz, 1.6 Hz, 1H), and 7.53 (dd, *J* = 7.6 Hz, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 44.3, 61.3, 123.9, 127.9, 129.6, 130.6, 130.8, 133.0, 136.2, 136.7, 163.7, and 165.7; IR (neat) 3281, 3084, 1712, 1667, 1636, 1469, 1423, 1303, 1181, 1040, 989, and 748 cm^{-1}; HRMS calcd for $C_{13}H_{14}O_3NBrNa$ $[M+Na]^+$ 334.00548, found 334.00686.

Ethyl (*E*)-4-[(naphthalen-1-ylmethyl)amino]-4-oxobut-2-enoate (4m). White crystals; mp 123 ˚C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.15 (t, *J* = 7.2 Hz, 3H), 3.88 (q, *J* = 7.2 Hz, 2H), 4.88 (d, *J* = 5.2 Hz, 2H), 6.78 (d, *J* = 15.6 Hz, 1H), 6.87 (br s, 1H), 6.96 (d, *J* = 15.6 Hz, 1H), 7.35-7.52 (m, 4H), 7.7 (d, *J* = 7.6 Hz, 1H), 7.81 (d, *J* = 7.6 Hz, 1H), and 7.93 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 42.2, 61.1, 123.5, 125.4, 126.1, 126.8, 127.1, 128.8, 128.9, 130.4, 131.5, 132.8, 133.9, 136.4, 163.5, and 165.9; IR (neat) 3301, 1713, 1664, 1631, 1541, 1299, 1175, 795, and 776 cm^{-1}; HRMS calcd for $C_{17}H_{17}O_3NNa$ $[M+Na]^+$ 306.11061, found 306.10981.

Ethyl (*E*)-4-[(furan-2-ylmethyl)amino]-4-oxobut-2-enoate (4n). White crystals; mp 58.5-59.0 ˚C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.25 (t, *J* = 7.2 Hz, 3H), 4.14 (q, *J* = 7.2 Hz, 2H), 4.48 (d, *J* = 5.6 Hz, 2H), 6.78 (d, *J* = 15.6 Hz, 1H), 6.21-6.27 (m, 2H), 6.79 (d, *J* = 15.6 Hz, 1H), 7.04 (d, *J* = 15.6 Hz, 1H), 7.21 (br s, 1H), and 7.30 (dd, *J* = 1.2 Hz, 0.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 36.8, 61.2, 107.9, 110.5, 130.5, 136.5, 142.4, 150.6, 163.7, and 165.9; IR (neat) 3288, 3075, 2983, 1723, 1666, 1643, 1549, 1506, 1368, 1301, 1271, 1173, 1032, 978, 741, and 600 cm^{-1}; HRMS calcd for $C_{11}H_{13}O_4NNa$ $[M+Na]^+$ 246.07423, found 246.07372.

Ethyl (*E*)-4-oxo-4-[(thiophen-2-ylmethyl)amino]but-2-enoate (4o). White crystals; mp 87.5-88.0 ˚C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.27 (t, *J* = 7.2 Hz, 3H), 4.14 (q, *J* = 7.2 Hz, 2H), 4.68 (d, *J* = 5.6 Hz, 2H), 6.74 (br s, 1H), 6.82 (d, *J* = 15.2 Hz, 1H), 6.92-7.00 (m, 3H), and 7.21 (dd, *J* = 5.2 Hz, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 38.7, 61.3, 125.6, 126.6, 127.1, 130.8, 136.2, 140.0, 163.5, and 165.8; IR (neat) 3311, 3076, 1709, 1663, 1633, 1544, 1365, 1299, 1176, 1005, 696, and 546 cm^{-1}; HRMS calcd for $C_{11}H_{14}O_3NS$ $[M+H]^+$ 240.06944, found 240.06871.

Ethyl (*E*)-4-oxo-4-[(pyridin-3-ylmethyl)amino]but-2-enoate (4p). White crystals; mp 85.0-86.0 ˚C; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.27 (t, *J* = 7.2 Hz, 3H), 4.17 (q, *J* = 7.2 Hz, 2H), 4.54 (d, *J* = 5.6 Hz, 2H), 6.83 (d, *J* = 15.6 Hz, 1H), 6.97 (d, *J* = 15.6 Hz, 1H), 7.08 (br s, 1H), 7.26 (dd, *J* = 8.0 Hz, 4.4 Hz, 1H), 7.65 (ddd, *J* = 8.0 Hz, 1.7 Hz, 1.7 Hz, 1H), and 8.47-8.50 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 41.4, 61.4, 123.9, 130.9, 133.6, 136.0, 136.1, 149.1, 149.3, 163.9, and 165.8; IR (neat) 3275, 3054, 2983, 1722, 1670, 1648, 1549, 1479, 1427, 1368, 1301, 1271, 1172, 1031, 977, and 713 cm^{-1}; HRMS calcd for

$C_{12}H_{15}O_3N_2$ $[M+H]^+$ 235.1083, found 235.1081.

Ethyl 2-((3*R,4*S**)-2-oxo-4-phenylazetidin-3-yl)acetate (5a).** To a solution of amide **4a** (51.0 mg, 0.219 mmol) in *o*-dichlorobenzene (11.0 mL) were added DABCO (49.0 mg, 0.437 mmol), TMSCl (0.027 mL, 0.219 mmol), and BSA (0.160 mL, 0.656 mmol) at room temperature. The resulting mixture was stirred at 150 ˚C for 24 h. The solvent was removed under reduced pressure. The reaction mixture was quenched with a 10% aqueous HCl solution and extracted three times with EtOAc. The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography with hexane-EtOAc (2:1, v/v) as an eluent to afford **5a** (38.3 mg, 75%) as white crystals; mp 66.0-67.0 ˚C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.21 (t, *J* = 7.2 Hz, 3H), 2.76 (dd, *J* = 16.8 Hz, 10.0 Hz, 1H), 2.88 (dd, *J* = 16.8 Hz, 4.8 Hz, 1H), 3.31 (ddd, *J* = 10.0 Hz, 4.8 Hz, 2.4 Hz, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 4.53 (d, *J* = 2.4 Hz, 1H), 6.54 (br s, 1H), and 7.30-7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 33.1, 56.9, 57.6, 61.1, 125.9, 128.3, 128.8, 139.5, 169.5, and 171.0; IR (neat) 3276, 2982, 1763, 1734, 1455, 1373, 1188, 1032, 699, 498, 460, 445, 435, and 405 cm^{-1}; HRMS calcd for $C_{13}H_{16}O_3N$ $[M+H]^+$ 234.1130, found 234.1130.

Ethyl 2-((3*R,4*S**)-2-oxo-4-(2-tolyl)azetidin-3-yl)acetate (5b).** White crystals; mp 91.0-92.0 ˚C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23 (t, *J* = 7.2 Hz, 3H), 2.33 (s, 3H), 2.85 (dd, *J* = 16.8 Hz, 8.0 Hz, 1H), 2.91 (dd, *J* = 16.8 Hz, 5.2 Hz, 1H), 3.34 (ddd, *J* = 8.0 Hz, 5.2 Hz, 2.4 Hz, 1H), 4.16 (dq, *J* = 7.2 Hz, 1.2 Hz, 2H), 4.81 (d, *J* = 2.4 Hz, 1H), 6.07 (br s, 1H), 7.16 (m, 3H), and 7.46 (dd, *J* = 7.6 Hz, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 19.4, 33.1, 54.1, 56.4, 61.1, 124.6, 126.7, 128.0, 130.7, 135.2, 137.5, 169.6, and 170.9; IR ($CDCl_3$) 3251, 1769, 1730, 1378, 1290, 1031, 752, and 616 cm^{-1}; HRMS calcd for $C_{14}H_{18}O_3N$ $[M+H]^+$ 248.1287, found 248.1291.

Ethyl 2-((3*R,4*S**)-2-oxo-4-(3-tolyl)azetidin-3-y)acetate (5c).** White crystals; mp 55.0-55.5 ˚C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22 (t, *J* = 7.2 Hz, 3H), 2.36 (s, 3H), 2.76 (dd, *J* = 16.8 Hz, 10.0 Hz, 1H), 2.89 (dd, *J* = 16.8 Hz, 4.8 Hz, 1H), 3.32 (ddd, *J* = 10.0 Hz, 4.8 Hz, 2.0 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 4.51 (d, *J* = 2.0 Hz, 1H), 6.31 (br s, 1H), 7.12-7.19 (m, 3H), and 7.26 (dd, *J* = 7.6 Hz, 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 21.5, 33.1, 57.0, 57.6, 61.1, 123.1, 126.5, 128.8, 129.2, 138.6, 139.5, 169.4, and 171.0; IR (neat) 3267, 2981, 1765, 1736, 1375, 1189, 1162, 1139, 1035, 788, 773, and 700 cm^{-1}; HRMS calcd for $C_{14}H_{18}O_3N$ $[M+H]^+$ 248.1287, found 248.1284.

Ethyl 2-((3*R,4*S**)-2-oxo-4-(4-tolyl)azetidin-3-yl)acetate (5d).** White crystals; mp 84.5-85.5 ˚C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.21 (t, *J* = 7.2 Hz, 3H), 2.34 (s, 3H), 2.75 (dd, *J* = 16.4 Hz, 10.0 Hz, 1H), 2.87 (dd, *J* = 16.4 Hz, 4.4 Hz, 1H), 3.29 (ddd, *J* = 10.0 Hz, 4.4 Hz, 2.4 Hz, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 4.50 (d, *J* = 2.4 Hz, 1H), 6.38 (br s, 1H), 7.17 (d, *J* = 8.0 Hz, 2H), and 7.27 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 21.2, 33.1, 57.0, 57.5, 61.1, 125.9, 129.5, 136.5, 138.2, 169.5, and 171.0; IR (neat) 3243, 1783,1728, 1401, 1306, 1296, 1281, 1218, 1191, 1179, and 804 cm^{-1}; HRMS calcd for

$C_{14}H_{18}O_3N$ $[M+H]^+$ 248.1287, found 248.1286.

Ethyl 2-((3*R,4*S**)-2-(2-methoxyphenyl)-4-oxoazetidin-3-yl)acetate (5e).** White crystals; mp 86.0-87.0 ˚C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23 (t, *J* = 7.2 Hz, 3H), 2.83 (dd, *J* = 16.8 Hz, 8.0 Hz, 1H), 2.91 (dd, *J* = 16.8 Hz, 5.4 Hz, 1H), 3.40 (ddd, *J* = 8.0 Hz, 5.4 Hz, 2.4 Hz, 1H), 3.81 (s, 3H), 4.15 (q, *J* = 7.2 Hz, 2H), 4.76 (d, *J* = 2.4 Hz, 1H), 6.43 (br s, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.97 (dd, *J* = 7.2 Hz, 7.2 Hz, 1H), 7.27 (ddd, *J* = 8.0 Hz, 7.2 Hz, 0.8 Hz, 1H), and 7.34 (dd, *J* = 7.2 Hz, 0.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 33.1, 53.1, 54.6, 55.3, 60.9, 110.2, 120.7, 125.9, 127.7, 129.1, 157.0, 169.9, and 171.1; IR (neat) 3237, 2980, 1760, 1737, 1494, 1465, 1291, 1246, 1182, 1161, 1029, and 756 cm^{-1}; HRMS calcd for $C_{14}H_{18}O_4N$ $[M+H]^+$ 264.1236, found 264.1237.

Ethyl 2-((3*R,4*S**)-2-(3-methoxyphenyl)-4-oxoazetidin-3-yl)acetate (5f).** White crystals; mp 35.0-36.0 ˚C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22 (t, *J* = 7.2 Hz, 3H), 2.75 (dd, *J* = 16.8 Hz, 10.0 Hz, 1H), 2.88 (dd, *J* = 16.8 Hz, 4.8 Hz, 1H), 3.32 (ddd, *J* = 10.0 Hz, 4.8 Hz, 2.4 Hz, 1H), 3.80 (s, 3H), 4.14 (q, *J* = 7.2 Hz, 2H), 4.51 (d, *J* = 2.4 Hz, 1H), 6.39 (br s, 1H), 6.84 (ddd, *J* = 8.0 Hz, 2.8 Hz, 0.4 Hz, 1H), 6.93-6.96 (m, 2H), and 7.27 (dd, *J* = 8.0 Hz, 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 33.1, 55.4, 56.9, 57.5, 61.1, 111.4, 113.7, 118.2, 130.0, 141.2, 160.1, 169.4, and 170.9; IR (neat) 3287, 2980, 1765, 1735, 1604, 1585, 1492, 1288, 1262, 1190, 1160, 1037, 787, and 695 cm^{-1}; HRMS calcd for $C_{14}H_{18}O_4N$ $[M+H]^+$ 264.1236, found 264.1240.

Ethyl 2-((3*R,4*S**)-2-(4-methoxyphenyl)-4-oxoazetidin-3-yl)acetate (5g).** White crystals; mp 64.0-65.0 ˚C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22 (t, *J* = 7.2 Hz, 3H), 2.75 (dd, *J* = 16.8 Hz, 10.0 Hz, 1H), 2.89 (dd, *J* = 16.8 Hz, 4.8 Hz, 1H), 3.30 (ddd, *J* = 10.0 Hz, 4.8 Hz, 2.4 Hz, 1H), 3.81 (s, 3H), 4.14 (q, *J* = 7.2 Hz, 2H), 4.50 (d, *J* = 2.4 Hz, 1H), 6.12 (br s, 1H), 6.90 (dd, *J* = 6.8 Hz, 2.0 Hz, 2H), and 7.31 (dd, *J* = 6.8 Hz, 2.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 33.1, 55.4, 57.0, 57.3, 61.1, 114.2, 127.2, 131.5, 159.7, 169.5, and 171.0; IR ($CDCl_3$) 3294, 2917, 1769, 1731, 1515, 1249, 1034, and 404 cm^{-1}; HRMS calcd for $C_{14}H_{18}O_4N$ $[M+H]^+$ 264.1236, found 264.1230.

Ethyl 2-((3*R,4*S**)-2-oxo-4-(3,4,5-trimethoxyphenyl)azetidin-3-yl)acetate (5h).** Colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23 (t, *J* = 7.2 Hz, 3H), 2.75 (dd, *J* = 16.8 Hz, 10.0 Hz, 1H), 2.88 (dd, *J* = 16.8 Hz, 4.8 Hz, 1H), 3.32 (ddd, *J* = 10.0 Hz, 4.8 Hz, 2.0 Hz, 1H), 3.82 (s, 3H), 3.85 (s, 6H), 4.15 (q, *J* = 7.2 Hz, 2H), 4.49 (d, *J* = 2.0 Hz, 1H), 6.29 (br s, 1H), and 6.60 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 33.0, 56.3, 57.0, 57.7, 61.0, 61.1, 102.7, 135.2, 137.9, 153.7, 169.3, and 171.0; IR (neat) 3311, 2941, 1766, 1735, 1593, 1463, 1238, 1126, and 1006 cm^{-1}; HRMS calcd for $C_{16}H_{21}O_6N$ $[M+H]^+$ 324.1447, found 324.1449.

Ethyl 2-((3*R,4*S**)-2-(4-chlorophenyl)-4-oxoazetidin-3-yl)acetate (5j).** White crystals; mp 58.5-59.0 ˚C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23 (t, *J* = 7.2 Hz, 3H), 2.76 (dd, *J* = 16.8 Hz, 10.4 Hz, 1H), 2.90 (dd, *J* = 16.8 Hz, 4.4 Hz, 1H), 3.28 (ddd, *J* = 10.4 Hz, 4.4 Hz, 2.4 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 4.53 (d, *J*

= 2.4 Hz, 1H), 6.38 (br s, 1H), and 7.34 (s, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 33.1, 57.1, 57.2, 61.2, 127.4, 129.1, 134.2, 138.1, 169.2, and 171.0; IR (neat) 3285, 2982, 1764, 1734, 1494, 1376, 1189, 1165, 1091, 1033, and 1015 cm^{-1}; HRMS calcd for $C_{13}H_{14}O_3NClNa$ $[M+Na]^+$ 292.05304, found 292.05161.

Ethyl 2-((3*R,4*S**)-2-(4-fluorophenyl)-4-oxoazetidin-3-yl)acetate (5k).** White crystals; mp 36.5-37.0 ˚C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22 (t, *J* = 7.2 Hz, 3H), 2.76 (dd, *J* = 16.8 Hz, 10.4 Hz, 1H), 2.90 (dd, *J* = 16.8 Hz, 4.4 Hz, 1H), 3.29 (ddd, *J* = 10.4 Hz, 4.4 Hz, 2.0 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 4.53 (d, *J* = 2.0 Hz, 1H), 6.37 (br s, 1H), 7.06 (dd, *J* = 8.4 Hz, 8.8 Hz, 2H), and 7.37 (dd, *J* = 8.4 Hz, 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 33.1, 57.1, 61.1, 115.7, 115.9, 127.6, 127.7, 135.3, 135.3, 161.5, 163.9, 169.4, and 171.0; IR (neat) 3273, 2983, 1766, 1733, 1604, 1511, 1376, 1226, 1190, 1159, 1034, and 836 cm^{-1}; HRMS calcd for $C_{13}H_{15}O_3NF$ $[M+H]^+$ 252.1036, found 252.1033.

Ethyl 2-((3*R,4*S**)-2-(benzo[*d*][1,3]dioxol-5-yl)-4-oxoazetidin-3-yl)acetate (5i).** White crystals; mp 121-122 ˚C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23 (t, *J* = 7.2 Hz, 3H), 2.74 (dd, *J* = 16.8 Hz, 10.0 Hz, 1H), 2.88 (dd, *J* = 16.8 Hz, 4.8 Hz, 1H), 3.29 (ddd, *J* = 10.0 Hz, 4.8 Hz, 2.4 Hz, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 4.47 (d, *J* = 2.4 Hz, 1H), 5.97 (s, 2H), 6.08 (br s, 1H), and 6.78-6.89 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 33.1, 57.2, 57.6, 61.2, 101.4, 106.2, 108.5, 119.5, 133.4, 147.8, 148.3, 169.2, and 171.0; IR (neat) 3284, 1764, 1732, 1504, 1491, 1245, 1038, and 744 cm^{-1}; HRMS calcd for $C_{16}H_{21}O_6N$ $[M+H]^+$ 278.1028, found 278.1024.

Ethyl 2-((3*R,4*S**)-2-(2-bromophenyl)-4-oxoazetidin-3-yl)acetate (5l).** White crystals; mp 72.0-72.5 ˚C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23 (t, *J* = 7.2 Hz, 3H), 2.96 (d, *J* = 2.8 Hz, 1H), 2.98 (d, *J* = 2.0 Hz, 1H), 3.34 (ddd, *J* = 10.4 Hz, 4.4 Hz, 2.4 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 4.96 (d, *J* = 2.4 Hz, 1H), 6.56 (br s, 1H), 7.17 (ddd, *J* = 7.6 Hz, 7.6 Hz, 1.6 Hz, 1H), 7.36 (ddd, *J* = 7.6 Hz, 7.6 Hz, 1.2 Hz, 1H), 7.52 (dd, *J* = 7.6 Hz, 1.6 Hz, 1H), and 7.55 (dd, *J* = 7.6 Hz, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 32.8, 56.1, 56.1, 61.1, 122.5, 126.6, 128.1, 129.6, 133.0, 138.8, 169.6, and 170.8; IR (neat) 3307, 1766, 1736, 1470, 1441, 1376, 1185, 1161, 1029, and 754 cm^{-1}; HRMS calcd for $C_{13}H_{14}O_3NBrNa$ $[M+Na]^+$ 336.00343, found 336.00181.

Ethyl 2-((3*R,4*S**)-2-(naphthalen-1-yl)-4-oxoazetidin-3-yl)acetate (5m).** White crystals; mp 122-123 ˚C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.16 (t, *J* = 7.2 Hz, 3H), 2.98-3.00 (m, 2H), 3.42 (ddd, *J* = 6.8 Hz, 2.4 Hz, 2.4 Hz, 1H), 4.06-4.20 (m, 2H), 5.38 (d, *J* = 2.4 Hz, 1H), 6.40 (br s, 1H), 7.48-7.57 (m, 3H), 7.66 (d, *J* = 7.2 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), and 7.88-7.92 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 33.1, 54.0, 56.4, 61.2, 122.2, 122.3, 125.6, 126.1, 126.6, 128.7, 129.2, 130.6, 133.8, 135.3, 169.5 and 170.8; IR (neat) 3249, 1763, 1733, 1511, 1377, 1192, 1172, 1031, 799, and 778 cm^{-1}; HRMS calcd for $C_{17}H_{18}O_3N$ $[M+H]^+$ 284.12867, found 284.12996.

Ethyl 2-((3*R,4*S**)-2-(furan-2-yl)-4-oxoazetidin-3-yl)acetate (5n).** White crystals; mp 46.0-47.0 ˚C; ^{1}H

NMR ($CDCl_3$, 400 MHz) δ 1.21 (t, *J* = 7.2 Hz, 3H), 2.73 (dd, *J* = 16.8 Hz, 10.0 Hz, 1H), 2.87 (dd, *J* = 16.8 Hz, 4.8 Hz, 1H), 3.65 (dddd, *J* = 10.0 Hz, 4.8 Hz, 2.4 Hz, 0.8 Hz, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 4.54 (d, *J* = 2.4 Hz, 1H), 6.34-63.5 (m, 3H), and 7.34 (dd, *J* = 1.2 Hz, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 32.6, 55.7, 53.9, 61.1, 108.0, 110.7, 142.9, 151.9, 169.0, and 170.8; IR (neat) 3273, 2982, 1769, 1734, 1376, 1300, 1260, 1192, 1151, 1034, and 744 cm^{-1}; HRMS calcd for $C_{11}H_{13}O_4NNa$ $[M+Na]^+$ 246.07423, found 246.07316.

Ethyl 2-((3*R,4*S**)-2-oxo-4-(thiophen-2-yl)azetidin-3-yl)acetate (5o).** Yellow crystals; mp 36.0-37.0 ˚C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22 (t, *J* = 7.2 Hz, 3H), 2.74 (dd, *J* = 16.8 Hz, 10.0 Hz, 1H), 2.88 (dd, *J* = 16.8 Hz, 4.8 Hz, 1H), 3.45 (ddd, *J* = 10.0 Hz, 4.8 Hz, 2.4 Hz, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 4.80 (d, *J* = 2.4 Hz, 1H), 6.54 (br s, 1H), 6.97 (dd, *J* = 5.2 Hz, 3.6 Hz, 1H), 7.07 (dd, *J* = 3.6 Hz, 1.2 Hz, 1H), and 7.26 (dd, *J* = 5.2 Hz, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 32.8, 53.5, 57.6, 61.2, 125.1, 125.3, 127.2, 143.6, 168.9, and 170.8; IR (neat) 3287, 2981, 1768, 1733, 1376, 1189, 1162, 1032, 852, and 706 cm^{-1}; HRMS calcd for $C_{11}H_{13}O_3NSNa$ $[M+Na]^+$ 262.05138, found 262.05067.

Ethyl 2-((3*R,4*S**)-2-oxo-4-(pyridin-3-yl)azetidin-3-yl)acetate (5p).** White crystals; mp 73.0-73.5 ˚C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.21 (t, *J* = 7.2 Hz, 3H), 2.79 (dd, *J* = 16.8 Hz, 10.4 Hz, 1H), 2.92 (dd, *J* = 16.8 Hz, 4.4 Hz, 1H), 3.45 (ddd, *J* = 10.4 Hz, 4.4 Hz, 2.0 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 4.59 (d, *J* = 2.0 Hz, 1H), 6.62 (br s, 1H), 7.32 (dd, *J* = 8.0 Hz, 4.8 Hz, 1H), 7.77 (ddd, *J* = 8.0 Hz, 0.8 Hz, 0.8 Hz, 1H), 8.56 (d, *J* = 4.8 Hz, 1H), and 8.63 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 33.0, 55.5, 57.1, 61.3, 123.8, 133.6, 135.2, 147.9, 149.8, 168.9, and 170.9; IR (neat) 3272, 2983, 1767, 1733, 1431, 1377, 1192, 1161, 1030, 913, 743, and 714 cm^{-1}; HRMS calcd for $C_{12}H_{15}O_3N_2$ $[M+H]^+$ 235.1083, found 235.1086.

Ethyl (2*E*,4*Z*)-4-(benzylimino)-4-methoxybut-2-enoate (8'). To a solution of amide **4a** (0.140 g, 0.600 mmol) in CH_2Cl_2 (12.0 mL) were added Na_2HPO_4 (0.425 g, 3.00 mmol) and trimethyloxonium tetrafluoroborate (0.443 g, 3.00 mmol) at 0 ˚C. The resulting mixture was stirred at room temperature for 24 h. The reaction mixture was quenched with an aqueous $NaHCO_3$ solution at 0 ˚C. The mixture was extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography with hexane-EtOAc (16:1 v/v) as an eluent to give **8'** (68.6 mg, 46%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25 (t, *J* = 7.2 Hz, 3H), 3.72 (s, 3H), 4.19 (q, *J* = 7.2 Hz, 2H), 4.64 (s, 2H), 6.53 (d, *J* = 15.6 Hz, 1H), and 7.15-7.29 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 52.0, 53.1, 61.2, 126.8, 127.3, 127.8, 128.2, 128.5, 140.4, 157.0, and 166.4; IR (neat) 2981, 2944, 1722, 1621, 1305, 1280, 1178, and 1035 cm^{-1}; HRMS: calcd for $C_{14}H_{17}O_3N$ $[M]^+$ 247.1208, found 247.1208.

Ethyl 2-((2*S,3*R**)-1,2-bis(4-methoxyphenyl)-4-oxoazetidin-3-yl)acetate (6).** A screw-top test tube was charged with **5g** (0.185 g, 0.703 mmol), CuI (13.3 mg, 0.0703 mmol), K_3PO_4 (0.298 g, 1.41 mmol), 4-bromoanisole (0.105 mL, 0.843 mmol), and *N,N'*-dimethylethylenediamine (0.0150 mL, 0.141 mmol)

in 1,4-dioxane (0.12 mL). The reaction mixture was stirred at 120 ˚C for 23 h. The resulting suspension was filtered through a pad of silica gel with EtOAc. The filtrate was concentrated. The residue was purified by column chromatography with hexane-EtOAc (2:1, v/v) as an eluent to afford **6** (0.171 g, 66%) as a pale brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.20 (t, *J* = 7.2 Hz, 3H), 2.79 (dd, *J* = 16.8 Hz, 10.0 Hz, 1H), 2.95 (dd, *J* = 16.8 Hz, 4.4 Hz, 1H), 3.35 (ddd, *J* = 10.0 Hz, 4.4 Hz, 2.4 Hz, 1H), 3.73 (s, 3H), 3.79 (s, 3H), 4.14 (q, *J* = 7.2 Hz, 2H), 4.75 (d, *J* = 2.4 Hz, 1H), 6.77 (dd, *J* = 6.8 Hz, 2.0 Hz, 2H), 6.89 (dd, *J* = 6.8 Hz, 2.0 Hz, 2H), 7.22 (dd, *J* = 6.8 Hz, 2.0 Hz, 2H), and 7.29 (dd, *J* = 6.8 Hz, 2.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 33.2, 55.4, 55.5, 56.0, 60.9, 61.1, 114.4, 114.5, 118.5, 127.5, 129.5, 131.3, 156.1, 159.8, 165.5, and 171.0; IR (neat) 2996, 2979, 2958, 2936, 2909, 2837, 1747, 1613, 1514, 1389, 1033, and 831 cm^{-1}; HRMS calcd for $C_{21}H_{23}O_5N$ $[M]^+$ 369.1576, found 369.1576.

2-((2*S,3*R**)-1,2-Bis(4-methoxyphenyl)-4-oxoazetidin-3-yl)acetaldehyde (7).** To a solution of **6** (26.0 mg, 0.0704 mmol) in EtOH (0.7 mL) were added LiBr (24.4 mg, 0.282 mmol) and $NaBH_4$ (11.9 mg, 0.317 mmol). The resulting mixture was stirred at room temperature for 3 h. The reaction mixture was quenched with water and extracted three times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography with hexane-EtOAc (1:2 v/v) as an eluent to afford the corresponding alcohol (22.3 mg, 97%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.09-2.14 (m, 2H), 2.70 (br s, 1H), 3.13 (ddd, *J* = 8.0 Hz, 8.0 Hz, 2.4 Hz, 1H), 3.73 (s, 3H), 3.80-3.82 (m, 5H), 4.67 (d, *J* = 2.4 Hz, 1H), 6.77 (dd, *J* = 6.8 Hz, 2.4 Hz, 2H), 6.89 (dd, *J* = 6.8 Hz, 2.4 Hz, 2H), 7.22 (dd, *J* = 6.8 Hz, 2.4 Hz, 2H), and 7.28 (dd, *J* = 6.8 Hz, 2.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.8, 55.4, 55.5, 59.0, 60.9, 61.3, 114.4, 114.6, 118.5, 127.4, 129.6, 131.2, 156.2, 159.8, and 167.8; IR (neat) 3438, 2934, 1739, 1513, 1249, 1032, and 830 cm^{-1}; HRMS calcd for $C_{19}H_{20}O_4N$ $[M-H]^-$ 326.1404, found 326.1392.

A solution of $(COCl)_2$ (0.0320 mL, 0.379 mmol) in CH_2Cl_2 (1.3 mL) was cooled to −70 ˚C, and DMSO (0.0400 mL, 0.569 mL) in CH_2Cl_2 (0.8 mL) was added. The resulting mixture was stirred for 5 min, and then the above alcohol (62.0 mg, 0.190 mmol) in CH_2Cl_2 (0.5 mL) was added slowly. After stirring at −70 ˚C for 1 h, Et_3N (0.158 mL, 1.14 mmol) was added. The resulting solution was stirred at the same temperature for an additional 2.5 h. The reaction mixture was quenched with an aqueous NH_4Cl solution. The resulting mixture was stirred at room temperature for 10 min. The mixture was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography with hexane-EtOAc (1:2 v/v) as an eluent to afford aldehyde **7** (59.9 mg, 97%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.95 (ddd, *J* = 18.4 Hz, 10.0 Hz, 0.8 Hz, 1H), 3.16 (dd, *J* = 18.4 Hz, 4.4 Hz, 1H), 3.40 (ddd, *J* = 10.0 Hz, 4.4 Hz, 2.4 Hz, 1H), 3.73 (s, 3H), 3.79 (s, 3H), 4.63 (d, *J* = 2.4 Hz, 1H), 6.77 (dd, *J* = 6.8 Hz, 2.4 Hz, 2H), 6.90 (dd, *J* = 6.8 Hz, 2.0 Hz, 2H), 7.21 (dd, *J* = 6.8 Hz, 2.4 Hz, 2H), 7.28 (dd, *J* = 6.8 Hz, 2.0 Hz, 2H), and 9.84 (s,

1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 42.6, 54.0, 55.4, 55.5, 61.0, 114.4, 114.6, 118.5, 127.5, 129.2, 131.2, 156.2, 159.9, 165.6, and 198.8; IR (neat) 2837, 1744, 1513, 1249, 1031, and 831 cm^{-1}; HRMS calcd for $C_{19}H_{20}O_4N$ $[M]^+$ 325.1323, found 325.1314.

(3*R,4*S**)-1,4-Bis(4-methoxyphenyl)-3-(3-phenylpropyl)azetidin-2-one (1).**[20] ^{n}BuLi (1.55 M solution, 0.0360 mL, 0.0558 mmol) was added to a solution of Ph_3PBrBn (26.6 mg, 0.0614 mmol) in THF (0.5 mL) at 0 ˚C. The resulting mixture was stirred at room temperature for 30 min. A solution of **7** (11.5 mg, 0.0353 mmol) in THF (0.24 mL) was added at 0 ˚C, and the resulting mixture was stirred at room temperature for 6.5 h. The reaction mixture was quenched with an aqueous NH_4Cl solution. The mixture was extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography with hexane-EtOAc (2:1 v/v) as an eluent to afford the corresponding olefin (7.9 mg, 56%, E:Z = 10:3) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.67-2.75 (m, 0.77H), 2.83-3.01 (m, 1.23H), 3.17 (ddd, *J* = 8.8 Hz, 5.6 Hz, 2.4 Hz, 0.23H), 3.24 (ddd, *J* = 9.6 Hz, 5.2 Hz, 2.4 Hz, 0.77H), 3.73-3.74 (m, 3H), 3.79 (s, 3H), 5.55 (d, *J* = 2.4 Hz, 0.23H), 4.66 (d, *J* = 2.4 Hz, 0.77H), 5.72 (ddd, *J* = 11.6 Hz, 7.2 Hz, 7.2 Hz, 0.23H), 6.25 (ddd, *J* = 15.6 Hz, 7.2 Hz, 6.4 Hz, 0.77H), 6.49 (d, *J* = 15.6 Hz, 0.77H), 6.59 (d, *J* = 11.6 Hz, 0.23H), 6.75-6.80 (m, 2H), 6.86-6.89 (m, 2H), and 7.18-7.38 (m, 9H); IR (neat) 3011, 2955, 2933, 2916, 2837, 1746, 1612, 1514, 1388, 1248, 1033, 830, and 754 cm^{-1}; HRMS calcd for $C_{26}H_{24}O_3N$ $[M-H]^-$ 398.1758, found 398.1756.

To a solution of the above compound (12.7 mg, 0.0318 mmol) in EtOH (0.42 mL) was added Pd/C 5% (1.20 mg). The mixture was stirred at room temperature under a H_2 atmosphere for 16 h. The reaction mixture was filtered and concentrated. The residue was purified by column chromatography with hexane-EtOAc (4:1 v/v) as an eluent to afford **1** (11.6 mg, 91%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.78-2.01 (m, 4H), 2.64 (t, *J* = 7.2 Hz, 2H), 3.05-3.09 (m, 1H), 3.73 (s, 3H), 3.80 (s, 3H), 4.55 (d, *J* = 2.0 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), and 7.14-7.29 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.6, 29.1, 35.9, 55.4, 55.6, 60.6, 61.0 114.4, 114.7, 118.4, 126.0, 127.3, 128.5, 128.6, 130.2, 131.5, 141.9, 156.0, 159.8, and 167.4.

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