The Stereoselective Synthesis of 2-Alkyl γ-Keto Acid and Heterocyclic Ketomethylene Peptide Isostere Core Units Using Chiral Alkylation by 2-Triflyloxy Esters

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A simple and general protocol for the enantioselective preparation of γ-keto acids and heterocyclic γ-keto acids which have an alkyl group at C-2 is reported. The alkyl group is introduced by chiral alkylation using a scalemic 2-triflyloxy ester. The alkylation takes place with inversion of configuration and is compatible with a variety of alkyl groups. This methodology is thus well-suited for the preparation of a wide variety of ketomethylene peptide isosteres.

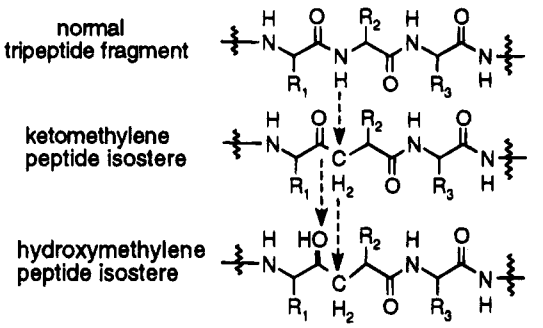
Introduction

The recognition that peptides and their analogs can be extremely attractive drug candidates has led to an explosion of interest in peptides and peptide mimetics.[1,2] Peptide mimetics (peptide isosteres), in which peptide bonds are replaced by other functions, can retain the binding properties of a peptide and thus bind strongly in the active site of a protease or enzyme, but they fail to undergo hydrolysis because they lack a scissile peptide bond and thus are not easily enzymatically degraded.[3] Two very common isosteric replacements are ketomethylene and hydroxymethylene groups (Chart 1).

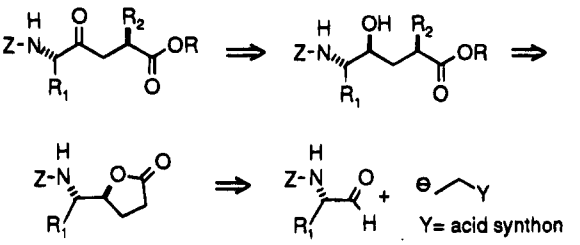
These peptide isosteres are characterized by a 1,4-disposition of an oxygenated functional group (ketone or hydroxy) and an acid derivative, and they have an alkyl group at C-2 which is a chiral center. Thus, they are functionally related to chiral 2-alkyl 4-keto esters. The majority of syntheses reported for these types of compounds have utilized construction of the 3,4-carbon–carbon bond by reaction of an amino aldehyde with a three-carbon nucleophilic species.[2,4] The resulting 4-hydroxy ester is lactonized and alkylated at C-2 with chiral induction to give hydroxymethylene peptide isosteres, which upon mild oxidation give ketomethylene peptide isosteres (Scheme 1).

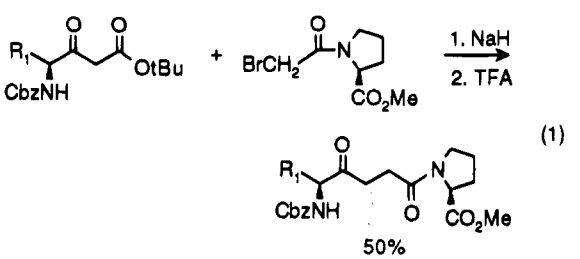
A much less common approach is to construct the 2,3-bond. We reported earlier that alkylation of *tert*-butyl 3-keto esters with ethyl bromoacetate followed by decarboxylation gave γ-keto esters, the core functionality of ketomethylene peptide isosteres.[5] Reduction of the ketone group gave hydroxymethylene analogs. By extension, 4-amino 3-keto esters were alkylated with bromoacetamides to give ketomethylene tripeptide isosteres in one step in very satisfactory yields (eq 1, for example).[5]

Chart 1



Scheme 1





(1)

Similar approaches have since been reported by others.[6,7] Alkyl groups at C-2 must still be installed by alkylation of a lactone enolate.[7]

To install an alkyl group at C-2 during the formation of the 2,3-bond would require a chiral alkylating agent. While bromoacetates are suitable alkylating agents for

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(4) Representative examples: (a) Baker, W. R.; Pratt, J. K. *Tetrahedron* **1993**, *49*, 8739–8756. (b) Diederich, A. M.; Ryckman, D. M. *Tetrahedron Lett.* **1993**, *34*, 6169. (c) Jones, D. M.; Nilsson, B.; Szelke, M. *J. Org. Chem.* **1993**, *58*, 2286. (d) D'Aniello, F.; Taddei, M. *J. Org. Chem.* **1992**, *57*, 5247. (e) Vara Prasad, J. V. N.; Rich, D. H. *Tetrahedron Lett.* **1991**, *32*, 5857 and references cited therein. (f) DeCamp, A. E.; Kawaguchi, A. T.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1991**, *32*, 1867.

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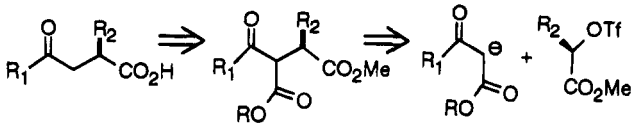
0022-3263/95/1960-5107$09.00/0

Scheme 2



enolates, we are aware of very few reports in which other α-bromo esters have been utilized successfully as alkylating agents for enolates.[8] On the other hand, it has been shown that optically pure α-triflyloxy esters can be prepared and that they react stereospecifically with a wide variety of nucleophiles to give substitution products with inverted configurations.[9] Although reactions of 2-triflyloxy esters with carbon-centered nucleophiles were not included in these studies, it has been reported that the enolate of di-*tert*-butyl malonate reacts with scalemic 2-nosyloxy esters to produce 2-alkylated malonate derivatives of high optical purity (>98% ee).[10] That report also stated that the nosylate leaving group was superior to other sulfonyloxy leaving groups, including the triflate group. We subsequently reported that optically pure 2-triflyloxy esters are excellent alkylating agents for β-keto ester enolates and the resulting 2-alkyl 4-keto esters are produced in good yields and high ee's.[11] This utilization of 2-triflyloxy esters as scalemic alkylating agents provides an excellent new method for the synthesis of 2-alkylated γ-keto acids, the core unit of 2-substituted ketomethylene peptide isosteres. We present the experimental details of this approach to 2-alkylated γ-keto acids as well as the extension of the methodology to the preparation of several heterocyclic ketomethylene peptide isosteres.

Results and Discussion

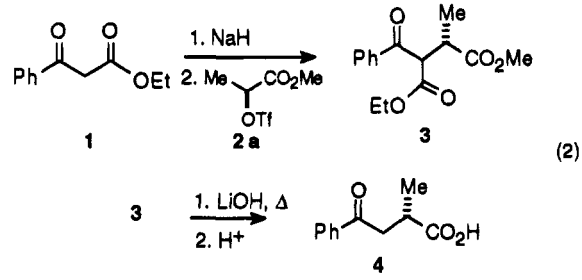
The synthesis of 2-alkylated γ-keto acids using scalemic α-triflyloxy esters as alkylating agents is based on the strategy shown in Scheme 2, the key step of which is the reaction between a β-keto ester enolate and the 2-triflyloxy ester. Although α-triflyloxy esters tend to be base sensitive, it was anticipated that the relatively low basicity of β-keto ester enolates would permit them to function as nucleophiles toward α-triflyloxy esters rather than as bases. This proved to be the case.

The reaction of β-keto ester **1** with methyl 2-(triflyloxy)-propionate, **2a**, produced tricarbonyl intermediate **3**. Basic saponification using lithium hydroxide in aqueous THF and thermal decarboxylation gave γ-keto acid **4** in 44% yield (eq 2). The absolute configuration of **4** is S since its optical rotation ($[\alpha]_D = -32$ (*c* 0.69, $CHCl_3$)) is in the same direction as that of a partially resolved sample of **4** ($[\alpha]_D = -31$ (*c* 1.0, EtOH)) whose configuration is known to be S.[12] This finding demonstrates that alkylation of **1** with 2-triflyloxy ester **2a** occurs with net inversion of configuration, as was also reported for the alkylation of di-*tert*-butyl malonate enolate with 2-nosyloxy esters.[10] The product configurations for the other alkylations reported here are assumed to result from inversion of configuration as well. Net inversion of configuration is consistent with direct C alkylation of the keto ester enolate by the 2-triflyloxy ester.

Table 1. Synthesis of 2-Substituted 4-Ketoalkanoic Acids 4 from the Reaction of *tert*-Butyl 3-Keto Esters with 2-Triflyloxy Esters 2

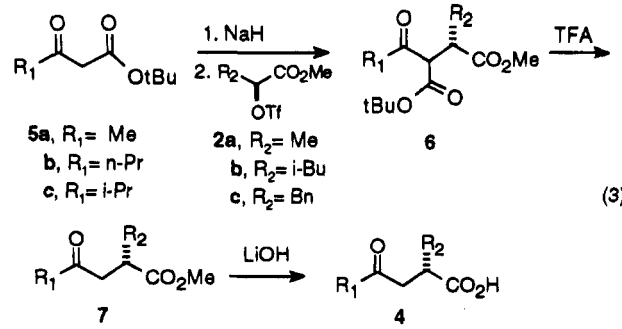
entry	reagents		product	yield (%)[a]	de (%)[b]	S:R[c]
1	**5a**	**2a**	**4aa**	54	98	99:1
2	**5a**	**2b**	**4ab**	54	88	94:6
3	**5a**	**2b**	**4ab**	45[d]	90	96:5
4	**5a**	**2c**	**4ac**	53	80	90:10
5	**5b**	**2a**	**4ba**	61[d]	93	96:4
6	**5c**	**2c**	**4cc**	72[d]	76	88:12
7	**11a**	**2a**	**9a**	51	52	76:24
8	**11b**	**2a**	**9b**	65	68	84:16
9	**11c**	**2a**	**9c**	46	56	78:22

[a] Yields are for isolated yields of pure **4** starting from **5** and **2**. [b] Diastereomeric excess determined from the coupling of acid **4** with (*S*)-(−)-α-methylbenzylamine. The diastereomeric excess corresponds to the enantiomeric excess of acid **4**. [c] Ratio of the S:R enantiomers of acid **4**. [d] Deesterification and decarboxylation: TFA at rt, 30 min, neutralization to pH 6, benzene reflux for 2 h.



(2)

While the alkylation of ethyl β-keto esters gave generally good chemical yields (44−90%), the optical yields were variable (28−94% ee).[11] This was due to the fact that decarboxylation under basic conditions required a long reflux period (10 h) to complete the decarboxylation.[13] As a consequence, significant improvement was realized by using *tert*-butyl β-keto esters as alkylation substrates since they could be hydrolyzed and decarboxylated under acidic conditions. Alkylation of *tert*-butyl β-keto esters **5a−c** with 2-triflyloxy esters **2a−c** followed by treatment of the crude alkylation product **6** with TFA (24 h) gave γ-keto esters **7** which were saponified with LiOH to produce γ-keto acids **4** (eq 3, Table 1, entries 1−6). Although this procedure entails an extra step



(3)

(8) (a) Compagne, R. S.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 1713. (b) Byk, G.; Gilon, C. *J. Org. Chem.* **1992**, *57*, 5687. (c) Beckett, R. P.; Brown, P. D.; Crimmin, M. J.; Galloway, W. A. Paper no. 147, Medicinal Chemistry. 204th National Meeting of the American Chemical Society, Denver, CO, 1993.

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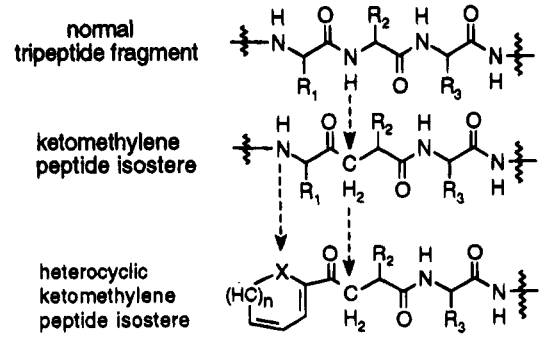
(saponification), the data in Table 1 illustrate that the overall yields are good (53–72%). Moreover, optical yields were also high (76–98% ee) as determined by coupling the keto acid to (*S*)-(−)-α-methylbenzylamine and measuring the diastereomeric excess. The reaction time can also be shortened considerably without loss of yield or optical purity by deesterifying with TFA (30 min), neutralizing to pH 6, and refluxing for 2 h in benzene.

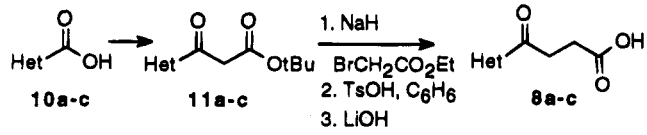
This chiral alkylation methodology allows for the preparation of 2-alkylated 4-keto esters and acids in good yields and high ee's. Not only are these compounds useful synthetic intermediates in their own right,[14] but they also constitute the core unit of ketomethylene peptide isosteres. Two additional structural features in ketomethylene peptide isosteres which are commonly found to be related to the protease inhibitor activity are (a) the electrophilicity of the ketone function and (b) heterocyclic groups attached to the inhibitor skeleton. The electrophilicity of the ketone group has a significant impact on the inhibitor activity. Structural changes which increase the electrophilicity of the ketone group tend to increase the protease inhibition by stabilizing the enzyme–inhibitor complex through addition of an active site serine hydroxyl or cysteine thiol group to the electrophilic carbonyl group or through hydration of the ketone which produces a tetrahedral transition state mimic.[3] For example, trifluoromethyl ketones have been found to be effective components of a variety of protease inhibitors,[15] as are pentafluoroethyl ketones.[16] Similarly, α,α-difluoroketomethylene peptide isosteres are often superior protease inhibitors relative to their non-fluorinated analogs.[15b,17] Other electron deficient carbonyl groups which have been used to enhance peptidase inhibitor activity include α-diketones,[18] α-keto esters,[19] tricarbonyl compounds,[20] and α-ketobenzoxazoles.[21]

A second structural feature commonly included in peptidase inhibitors is one or more heterocyclic rings which are moderately polar and serve to increase the water solubility and hence bioavailability of the inhibitor. A wide variety of heterocyclic rings have been utilized for this purpose, including pyridine, piperidine, pyrrolidine, indole, thiazole, and benzimidazole rings, in HIV protease inhibitors.[22] The morpholine ring has often been

Chart 2

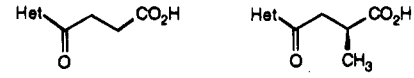


Scheme 3



employed for this purpose as well.[23] Besides solubility properties, heterocycles have also been used to enhance binding of the inhibitor to the protease. For instance, the oxygen atom of a conformationally restricted tetrahydrofuran ring has been used to mimic the carbonyl oxygen of an asparagine residue.[24] The thiophene ring has been incorporated into a peptidase inhibitor to bind to the zinc center of a metalloproteinase.[25]

With these considerations in mind, γ-keto acid fragments **8a–c** and **9a–c** were chosen as targets to demonstrate that the alkylation methodology under development could accommodate heterocyclic groups. Extension



8a, Het = 2-pyridyl)
8b, Het = 2-thienyl)
8c, Het = 2-furyl)

9a, Het = 2-pyridyl)
9b, Het = 2-thienyl)
9c, Het = 2-furyl)

of the peptide chain from the carboxyl group of the heterocyclic γ-keto acid units by coupling to amino acids would give peptide mimetics in which the heterocyclic ring could play a significant role (Chart 2).

Not only could the 2-pyridyl component in **8a** and **9a** (X = N, n = 1) serve as an isosteric replacement for an aromatic group in the substrate, but the electron-withdrawing ability of the pyridine ring would also increase the electrophilicity of the ketone carbonyl group in the active site. Thiophene derivatives **8b** and **9b** X = S, n = 0) provide a sulfur atom positioned for binding to the zinc center of a metalloproteinase. Furan derivatives **8c** and **9c** (X = O, n = 0) provides a heterocyclic oxygen mimic of the carbonyl group at the P_1 site of peptide substrate.[3]

Heterocyclic carboxylic acids **10a–c** were converted to the corresponding *tert*-butyl β-keto esters **11a–c** and then to achiral targets **8a–c** by the sequence shown in Scheme 3. For example, carbonyldiimidazole was used to condense pipecolic acid **10a** and the lithium enolate

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(23) For example: Jendralla, H.; Henning, R.; Seuring, B.; Herchen, J.; Kulitzscher, B.; Wunner, J. *Synlett* **1993**, 155.

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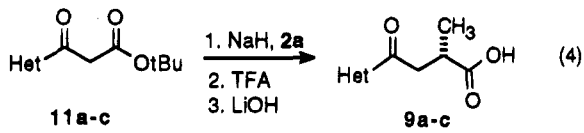
of *tert*-butyl acetate to give pyridyl β-keto ester **11a**.[26] Alkylation of **11a** with ethyl bromoacetate followed by removal of the *tert*-butyl group and decarboxylation by tosic acid in benzene and saponification with lithium hydroxide gave pyridyl keto acid **8a** in 42% overall yield.

Both 2-thiophenecarboxylic acid chloride and 2-furoyl chloride (prepared from acids **10b** and **10c**, respectively, with oxalyl chloride) were reacted with the lithium enolate of *tert*-butyl acetate to produce keto esters **11b** and **11c**, respectively.[27] The same alkylation, decarboxylation (TFA rather than tosic acid), and saponification sequence gave keto esters **8b** and **8c** in 42 and 57% overall yields, respectively.

These results establish that the reaction conditions are sufficiently mild to permit even the furan ring to survive the process unscathed. The intermediates need not be purified but are carried on immediately to the next step, and the overall yields of purified products for the three-step sequence are quite acceptable.

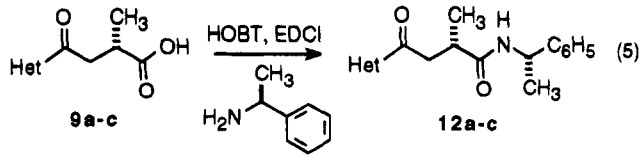
The stereoselective introduction of an alkyl substituent at C-2 was accomplished by the use of optically pure 2-triflyloxyesters for alkylation of the β-keto ester. β-Keto esters **11a–c** were alkylated with (*S*)-methyl 2-(triflyloxy)propionate[11] and then decarboxylated (TFA, CH_2Cl_2) and saponified to give keto acids **9a** (51%), **9b** (65%), and **9c** (46%) (eq 4, Table 1, entries 7–9). Again good



(4)

yields, mild conditions, and operational simplicity are the hallmarks of the procedure.

The stereochemical fidelity of the alkylated products was determined by coupling the keto acid unit to (*S*)-α-methylbenzylamine to give the diastereomeric amides **12a–c** (eq 5).[28] Examination of the crude products by



(5)

^{1}H NMR revealed that diastereomers were present to the extent of 50–68% de (Table 1).[29] The de values represent the loss in stereochemical integrity occurring during the three-step preparation of **9a–c** and are somewhat lower than the de values of 70–90% obtained for the chiral alkylation of nonheterocyclic β-keto esters by the same sequence. The reasons for this decrease are not clear, but the losses likely occur in the acidic decarboxylation step or the basic saponification step as noted previously.[11] Chromatographic purification of **12a–c** by either radial chromatography or preparative TLC gave single, optically pure amides (>97% de) as determined by NMR spectroscopy.

In summary, these results demonstrate a simple and general protocol for the preparation of γ-keto acids and heterocyclic γ-keto acids which have an alkyl group at C-2. The alkyl group is introduced enantioselectively by chiral alkylation with a scalemic 2-triflyloxy ester. The alkylation takes place with inversion of configuration and is compatible with a variety of alkyl groups. Selection of the chirality of the 2-triflyloxy ester dictates the chirality at C-2 of the alkylated product. Coupling the γ-keto acid fragment to chiral amines gives optically pure amides which can be obtained by routine chromatographic purification. This methodology is thus eminently suited for the preparation of a wide variety of ketomethylene peptide isosteres.

Experimental Section

Melting points are uncorrected. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. Thin-layer chromatography was performed on silica gel 60 F254 plates from EM reagents and visualized by UV irradiation or iodine. Analytical HPLC was performed with the indicated solvent systems and flow rates on 8 mm × 25 cm silica gel columns using UV detection (254 nm). Flash chromatography was performed using silica gel 60 (230–400 mesh). Radial chromatography was performed on 2 mm layer plates of silica gel 60 PF_{254} containing gypsum. Tetrahydrofuran was distilled from benzophenone ketyl. Other solvents were HPLC grade and were used without further purification. Starting materials were purchased from Aldrich and used as received. Heterocyclic β-keto ester **11a** was prepared by coupling pipecolic acid with the lithium enolate of *tert*-butyl acetate.[26] Heterocyclic β-keto esters **11b,c** were prepared by acylation of the lithium enolate of *tert*-butyl acetate with thienoyl chloride and furoyl chloride, respectively, by a standard procedure.[27]

(*S*)-2-Methyl-4-oxo-4-phenylbutanoic Acid (4). To a stirred, cold (0 °C) solution of (*S*)-methyl lactate (520 mg, 5.0 mmol) in dichloromethane (10 mL) under a nitrogen atmosphere was added triflic anhydride (0.92 mL, 5.4 mmol), followed by 2,6-lutidine (0.64 mL, 5.5 mmol). The resulting solution of 2-triflyloxy ester **2a** was stirred for 10 min and used in the next reaction without further purification.[30] Meanwhile, a solution of benzoylacetate **1** (1.92 g, 10 mmol) in THF (10 mL) was added dropwise to a stirred, cold (0 °C) suspension of NaH (530 mg of 50% in oil, 11 mol) in dry THF (50 mL) under a nitrogen atmosphere. After stirring for 10 min, the solution of 2-triflyloxy ester **2a** was diluted with an additional portion of dichloromethane (10 mL) and added dropwise to this gray suspension. The resulting mixture was stirred at room temperature for 24 h, treated with 1 N HCl solution (50 mL), and extracted with ethyl acetate (3 × 50 mL). The organic extracts were combined, washed with brine (100 mL), dried ($MgSO_4$), filtered through a short pad of silica gel, and concentrated by rotary evaporator (bath temperature = 30 °C) to provide a pale yellow oil.

The crude tricarbonyl compound **3** thus obtained was dissolved into 50% aqueous THF (80 mL), treated with $LiOH{\cdot}H_2O$ (2.5 g), and heated at reflux for 10 h. After the mixture was cooled to room temperature and ether (50 mL) and saturated $NaHCO_3$ (50 mL) were added, the aqueous phase was separated, acidified by 6 N HCl (pH 3), and extracted with ethyl acetate (3 × 80 mL). The combined organic extracts were washed with brine (100 mL), passed through a short pad of $MgSO_4$ and silica gel, and concentrated. (*S*)-2-Methyl-4-oxo-4-phenylbutanoic acid (**4**) was obtained as a white solid (392 mg, 44% based on methyl lactate) after purification by flash chromatography (hexane:ethyl acetate = 90:10 to 80:20 to 60:40): mp 119–120 °C; $[\alpha]^{25}_D$ −32.5 (*c* 0.69,

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(29) These values are only lower limits since it was not easy to determine the integrated areas of the NMR signals for the diastereomeric methyl groups in the crude product. The actual de's are most likely appreciably higher on the basis of the isolated yields of the pure diastereomer.

(30) Effenberger, F.; Burkhard, U.; Willfahrt, J. *Leibigs. Ann. Chem.* **1986**, 314.

$CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.32 (d, 3H, J = 7.0 Hz), 3.07 (dd, 1H, J = 4.6, 17.4 Hz), 3.15 (m, 1H), 3.44 (dd, 1H, J = 7.4, 17.4 Hz), 7.4–8.0 (m, 5H); FTIR ($CDCl_3$) 3600–2500 (br), 2907, 1715, 1690, 1372, 1297 cm^{-1}. Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.59; H, 6.36.

(*S*)-2-Isobutyl-4-oxopentanoic Acid (4ab). General Procedure. The following procedure for chiral alkylation using a *tert*-butyl β-keto ester as starting material, TFA deesterification/decarboxylation, and LiOH saponification is typical. To a stirred, cold (0 °C) solution of (*S*)-methyl 2-hydroxy-4-methylpentanoate (**2b**) (730 mg, 5.0 mmol) in dichloromethane (10 mL) was added triflic anhydride (0.92 mL, 5.4 mmol), followed by 2,6-lutidine (0.64 mL, 5.5 mmol) under an N_2 atmosphere. The mixture was stirred for 10 min, and the resulting solution of **2b** was used for the next reaction without further purification. Meanwhile, to a stirred, cold (0 °C) suspension of NaH (530 mg of 50% in oil, 11 mmol) in dry THF (50 mL) was added dropwise the solution of *tert*-butyl acetoacetate (1.58 g, 10 mmol) in THF (10 mL) under an N_2 atmosphere. After stirring for 10 min, the above triflate solution was diluted further with dichloromethane (10 mL) and added dropwise to this gray suspension of the β-keto ester enolate. The resulting mixture was stirred at room temperature for 24 h, quenched with 1 N HCl (50 mL), and extracted with ethyl acetate (3 × 50 mL). The organic extracts were combined, washed with brine (100 mL), dried ($MgSO_4$), passed through a short pad of silica gel, and concentrated by rotary evaporator (bath temperature = 30 °C) to provide a pale yellow oil. Without further purification, the above oil (**6ab**) was dissolved into dichloromethane (10 mL) and treated with TFA (3 mL) at room temperature for 24 h. After dilution with dichloromethane (100 mL), the resulting solution was washed with saturated $NaHCO_3$ (3 × 100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated by rotary evaporator (bath temperature = 30 °C) to provide (*S*)-methyl 2-isobutyl-4-oxopentanoate (**7ab**) as a yellow oil, which was used for the next reaction without further purification. A small amount of this crude product was purified for analysis by radial chromatography (hexane:ethyl acetate = 95:5) and Kugelrohr distillation (bath temperature = 100 °C/0.5 mmHg) to provide a colorless oil: $[\alpha]^{20}_D$ −12.0 (*c* 0.87, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.90 (two d, 6H, J = 6.4, 6.2 Hz), 2.2–2.7 (set of m, 3H), 2.16 (s, 3H), 2.69 (ABq, 2H), 2.92 (m, 1H), 3.68 (s, 3H); FTIR (neat) 2958, 1737, 1725, 1438, cm^{-1}. Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.23; H, 9.80.

The above crude methyl ester **7ab** was dissolved in THF and H_2O (30 mL/30 mL) and treated with $LiOH{\cdot}H_2O$ (450 mg, 10 mmol) at room temperature for 0.5 h. After dilution with ether (50 mL) and saturated $NaHCO_3$ (50 mL), the aqueous phase was separated, acidified by 6 N HCl (pH 3), and extracted with ethyl acetate (3 × 80 mL). The combined organic extracts were passed through a short pad of $MgSO_4$ and silica gel and concentrated to provide (*S*)-2-isobutyl-4-oxopentanoic acid (**4ab**) as a colorless oil (450 mg, 54% based on starting **2b**) after purification by radial chromatography (hexane:ethyl acetate = 95:5 to 80:20) and Kugelrohr distillation (bath temperature = 90–100 °C/ 0.5 mmHg): $[\alpha]^{25}_D$ −22.7 (*c* 0.33, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (two d, 6H, J = 6.2, 6.0 Hz), 2.2– 2.7 (set of m, 3H), 2.18 (s, 3H), 2.71 (m, 2H), 2.93 (m, 1H); FTIR (neat) 3500–2500 (br), 2959, 1708, 1369, 1170 cm^{-1}. Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.61; H, 9.13.

In a more rapid alternative method of deesterification/decarboxylation, the tricarbonyl intermediate **6ab** prepared as described above was treated with TFA (5 mL) at room temperature for 30 min and diluted with dichloromethane (50 mL). After the mixture was washed with saturated $NaHCO_3$ (80 mL), the organic layer was concentrated by rotary evaporation to provide an oil, which was then dissolved in benzene (80 mL) and heated at reflux for 2 h. After cooling to room temperature, the solution was concentrated by rotary evaporation (bath temperature = 30 °C) to provide crude **7ab** as an oil. Saponification to the 4-keto acid product was carried out as above to give (*S*)-2-isobutyl-4-oxopentanoic acid (**4ab**) in 45% yield (based on starting **2b**) after purification: $[\alpha]^{25}_D$ −22.7 (*c* 0.37, $CHCl_3$).

(*S*)-2-Methyl-4-oxopentanoic acid (4aa): yield 54% (based on **2a**) as a colorless oil after purification by radial chromatography (hexane:ethyl acetate = 95:5 to 80:20) and Kugelrohr distillation (bath temperature = 60–80 °C/0.5 mmHg); $[\alpha]^{25}_D$ −21.1 (*c* 0.8, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.22 (d, 3H, J = 6.6 Hz), 2.17 (s, 3H), 2.71 (m, 2H), 2.95 (m, 1H), 11.0 (br, 1H); FTIR (neat) 3600–2500 (br), 2957, 1755, 1716, 1362 cm^{-1}. Anal. Calcd for $C_6H_{10}O_3$: C, 55.37; H, 7.75. Found: C, 55.20; H, 7.58.

(*S*)-2-Benzyl-4-oxopentanoate (4ac). The reaction of **5a** with **2c** was carried out as described above, and (*S*)-methyl 2-benzyl-4-oxopentanoate (**7ac**) was obtained in 53% yield (based on **2c**) as a colorless oil after purification by radial chromatography (hexane:ethyl acetate = 95:5 to 80:20) and Kugelrohr distillation (bath temperature = 70–85 °C/0.5 mmHg): $[\alpha]^{25}_D$ −28.1 (*c* 0.85, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.10 (s, 3H), 2.4–3.3 (set of m, 5H), 3.66 (s, 3H, OCH_3), 7.26 (m, 5H); FTIR (neat) 3002, 2951, 1731, 1725, 1436 cm^{-1}. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.80; H, 7.37.

Methyl ester **7ac** was hydrolyzed with $LiOH{\cdot}H_2O$ in THF and H_2O by the same method as above and free carboxylic acid **4ac** coupled to (*S*)-(−)-α-methylbenzyl amine without further purification.

(*S*)-2-Methyl-4-oxoheptanoic acid (4ba): yield 61% (based on starting **2a**) as a colorless oil after purification by radial chromatography (hexane:ethyl acetate = 95:5 to 80:20); $[\alpha]^{25}_D$ −14.6 (*c* 0.48, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.91 (t, 3H, J = 7.2 Hz), 1.22 (d, 3H, J = 6.8 Hz), 1.61 (sextet, 2H, J = 7.2 Hz), 2.45 (t and dd, 3H, J = 7.6 Hz for triplet and J = 4.8, 20 Hz for dd), 2.94 (set of m, 2H); FTIR (neat) 3600–2500 (br), 2967, 1746, 1706, 1387 cm^{-1}. Anal. Calcd for $C_8H_{14}O_3$: C, 60.72; H, 8.92. Found: C, 60.55; H, 8.68.

(*S*)-2-Benzyl-5-methyl-4-oxohexanoic acid (4cc): yield 72% (based on starting **2c**) as a colorless oil after purification by radial chromatography (hexane:ethyl acetate = 95:5 to 80:20); $[\alpha]^{25}_D$ −8.3 (*c* 1.45, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.04 (two d, 6H, J = 7.6, 7.0 Hz), 2.3–3.4 (set of m, 6H), 7.1–7.4 (m, 5H), 10.3 (br, 1H); FTIR (neat) 3600–2500 (br), 2967, 1751, 1716, 1457 cm^{-1}. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.89; H, 7.54.

General Procedure for Amide Formation. Coupling of 4 to (*S*)-(−)-α-Methylbenzylamine (4aa). This procedure is typical. To a stirred, cold (0 °C) stirred solution of (*S*)-2-methyl-4-oxopentanoic acid (**4aa**) (220 mg, 1.7 mmol) in THF (40 mL) was added (*S*)-α-methylbenzylamine (0.41 mL, 3 mmol), followed by $HOBt{\cdot}H_2O$ (410 mg, 3 mmol) and EDCI (400 mg, 2 mmol). The resulting solution was stirred at 0 °C for 3 h and at room temperature overnight. After concentration by rotary evaporator, the white residue was taken up into ethyl acetate (80 mL) and 1 N HCl (80 mL). The organic phase was separated, washed with saturated $NaHCO_3$ (100 mL) and brine (100 mL), passed through a short pad of $MgSO_4$ and silica gel, and concentrated to provide the amide as a white solid (330 mg, 82%) after purification by radial chromatography (hexane:ethyl acetate = 95:5 to 80:20 to 60:40): mp 54–55 °C; $[\alpha]^{25}_D$ −98.6 (*c* 0.55, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.15 (d, 3H, J = 6.6 Hz), 1.46 (d, 3H, J = 6.8 Hz), 2.07 (s, 3H), 2.3–3.0 (set of m, 3H), 5.05 (m, 1H), 6.17 (brd, 1H), 7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 21.9, 30.2, 35.8, 47.3, 48.6, 126.0, 127.1, 128.5, 143.3, 174.5, 207.8; FTIR ($CHCl_3$) 3434, 3018, 1712, 1664, 1512, 1218 cm^{-1}; HPLC (2 mL/min, hexane:ethyl acetate = 50:50) t_R 3.61 (major), 4.39 (major); ratio was 99:1. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.19; H, 8.25; N, 5.88.

Coupling of 4ab to (*S*)-(−)-α-methylbenzylamine: yield 42% as a white solid after purification by radial chromatography (hexane:ethyl acetate = 95:5 to 80:20); mp 81–83 °C; $[\alpha]^{25}_D$ −100.3 (*c* 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.91 (two d, 6H, J = 6.8, 6.6 Hz), 2.2–2.7 (set of m, 3H), 1.47 (d, 3H, J = 6.8 Hz), 2.06 (s, 3H), 2.3–2.95 (set of m, 3H), 5.06 (m, 1H), 6.04 (brd, 1H), 7.31 (m, 5H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 21.9, 22.2, 23.0, 25.8, 30.1, 39.6, 41.5, 46.4, 48.7, 126.0, 127.1, 128.5, 143.2, 174.1, 207.9; FTIR ($CHCl_3$) 3434, 3018, 2960, 1712, 1664 cm^{-1}; HPLC (2 mL/min, hexane:ethyl acetate = 50:50) t_R 3.13 (minor), 3.35 (major); ratio 94:6. Anal. Calcd

for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 73.96; H, 9.06; N, 5.07.

Coupling of 4ac to (*S*)-(−)-α-methylbenzylamine: yield 70% as a glassy solid after purification by radial chromatography (hexane:ethyl acetate = 95:5 to 80:20 to 60:40); mp 89−91 °C; $[\alpha]^{25}_D$ −114.8 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.19 (d, 3H, *J* = 6.6 Hz), 2.05 (s, 3H), 2.5- 3.1 (set of m, 5H), 4.93 (m, 1H, *J* = 7.0 Hz), 5.76 (brs, 1H, *J* = 7.6 Hz), 7.25 (m, 10H), 1.39 (minor isomer, d, *J* = 7 Hz); ratio 10:1; ^{13}C NMR (400 MHz, $CDCl_3$) (minor isomer) δ 21.6 (21.7), 30.15 (33.9), 38.6 (40.2), 43.9, 45.4 (45.3), 48.5 (48.2), 125.9, 126.5, 127.0, 128.4, 128.5, 129.0, 139.1, 143.1, 172.9, 207.6; FTIR ($CDCl_3$) 3303, 3062, 2929, 1714, 1646 cm^{-1}; HPLC (3 mL/min, hexane:ethyl acetate = 1:1) t_R 3.10 (minor), 4.85 (major); ratio 90:10. Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.54; H, 7.36; N, 4.49.

Coupling of 4ba to (*S*)-(−)-α-methylbenzylamine: yield 93% as a white solid after recrystallization from hexane:ethyl acetate; mp 70−72 °C; $[\alpha]^{25}_D$ −78.1 (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.85 (t, 3H, *J* = 7.4 Hz), 1.15 and 1.13 (two d, 3H, *J* = 6.6, 6.8 Hz), 1.45 (d, 3H, *J* = 7.0 Hz), 1.51 (m, 2H), 2.30 (m, 3H), 2.80 (m, 2H), 5.05 (m, 1H), 6.31 (brd, 1H), 7.28 (m, 5H); FTIR ($CDCl_3$) 3326, 3057, 2977, 1715, 1646 cm^{-1}; HPLC (2 mL/min, hexane:ethyl acetate = 50:50) t_R 3.21 (minor), 3.62 (major); ratio 94:6. Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.65; H, 8.77; N, 5.53.

Coupling of 4cc to (S)-(−)-α-methylbenzylamine: yield 100% as a white solid after purification by radial chromatography (hexane:ethyl acetate = 95:5 to 80:20); mp 87−89 °C; $[\alpha]^{25}_D$ −78.1 (*c* 1.34, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.96−1.17 (set of m, 9H), 1.42 and 1.45 (two d, 3H, *J* = 7.0 Hz, ratio 9:1), 2.4−3.0 (set of m, 4H), 5.05 (m, 1H, *J* = 7.0 Hz), 6.25 (br d, 1H), 7.27 (m, 5H); ^{13}C NMR (400 MHz, $CDCl_3$) (minor isomer) δ 17.7 (17.8), 17.9, 18.1 (18.1), 21.9 (21.8), 35.5 (35.8), 40.9, 44.4 (44.3), 48.5 (48.5), 126.0, 127.0 (127.1), 128.4 (128.5), 143.4, 174.6, 213.9; ratio 88:12; FTIR ($CDCl_3$) 3316, 2977, 1716, 1656 cm^{-1}; HPLC (2 mL/min, hexane:ethyl acetate = 50:50) t_R 3.00 (minor), 3.29 (major); ratio 88:12. Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.39; H, 8.66; N, 5.32.

4-(2-Pyridyl)-4-oxobutanoic acid (8a) was prepared from **11a** by the following general procedure. A solution of **11a** (1.10 g, 5 mmol) in THF (20 mL) was added to a stirred suspension of NaH (400 mg, 50% in mineral oil, 10 mmol) in THF (60 mL) at 0 °C. After the mixture was stirred for 10 min, ethyl bromoacetate was added in one portion, and the mixture was stirred at 0 °C for 5 h. After addition of 1 N HCl (100 mL) and extraction with ethyl acetate (3 × 100 mL), the organic fraction was washed with brine (100 mL), dried ($MgSO_4$), passed through a 2 cm pad of silica gel, and concentrated to give a clear oil.

Without further purification, the above oil was dissolved in benzene (80 mL) and treated with tosic acid (400 mg) at reflux for 16 h. After cooling to room temperature, the solution was diluted with ethyl acetate (80 mL), washed with saturated $NaHCO_3$ (100 mL) and brine (100 mL), passed through a 2 cm pad of silica gel, and concentrated to give a brown oil.

Without further purification, the above oil was dissolved in 50% aqueous THF (80 mL) and treated with $LiOH{\cdot}H_2O$ (1 g) at room temperature for 1 h. After the reaction mixture was washed with ether (100 mL), the aqueous layer was acidified to pH 3 with 6 N HCl and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), and purified by radial chromatography (hexane:ethyl acetate = 95:5 to 80:20 to 60:40) to provide **8a** as a white solid (380 mg, 42%): mp 87−88 °C; NMR (200 MHz) δ 2.82 (t, 2H, *J* = 6.6 Hz), 3.57 (t, 2H, *J* = 6.6 Hz), 7.50 (m, 1H), 7.85 (m, 1H), 8.06 (m, 1H), 8.71 (m, 1H); IR (CH_2Cl_2) 3600−2500 (br), 3054, 1730, 1700 cm^{-1}. Anal. Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.27; H, 5.09; N, 7.70.

4-(2-Thienyl)-4-oxobutanoic acid (8b) was prepared as a white solid in 42% yield from **11b** by the same procedure: mp 119−120 °C; NMR (200 MHz) δ 2.81 (t, 2H, *J* = 6.6 Hz), 3.27 (t, 2H, *J* = 6.6 Hz), 7.15 (m, 1H), 7.67 (m, 1H), 7.79 (m, 1H); IR 3500−2500 (br), 3100, 1709, 1695, 1656 cm^{-1}. Anal. Calcd for $C_8H_8O_3S$: C, 52.16; H, 4.37. Found: C, 52.34; H, 4.02.

4-(2-Furyl)-4-oxobutanoic acid (8c) was prepared from **11c** as a white solid in 57% yield by the same procedure: mp 114−115 °C; ^1H NMR (200 MHz) δ 2.77 (t, 2H, *J* = 6.8 Hz), 3.19 (t, 2H, *J* = 6.8 Hz), 6.59 (m, 1H), 7.26 (d, 1H, *J* = 3.2 Hz), 7.65 (s, 1H). Anal. Calcd for $C_8H_8O_4$: C, 57.15; H, 4.79. Found: C, 56.91; H, 5.02.

(2*R*)-2-Methyl-4-(2-pyridyl)-4-oxobutanoic acid (9a) was prepared from keto ester **11a** by the following general procedure. A solution of keto ester **11a** (2.21 g, 10 mmol) in THF (20 mL) was added to a stirred suspension of NaH (530 mg, 50% in mineral oil, 11 mmol) in THF (50 mL) at 0 °C. After the mixture was stirred for 10 min, (2*S*)-methyl 2-(triflyloxy)-propionate (**2a**) (5 mmol, generated in solution from (*S*)-methyl lactate, triflic anhydride, and 2,6-lutidine[9a,30]) in CH_2Cl_2 (20 mL) was added. After the mixture was stirred at room temperature for 20 h, 1 N HCl (80 mL) was added and, the mixture was extracted with ethyl acetate (3 × 80 mL). The combined extracts were washed with brine (100 mL), filtered through a pad of $MgSO_4$ (1 cm) and silica gel (2 cm), and concentrated to give a clear oil.

Without purification, the above oil was dissolved in CH_2Cl_2 (15 mL), treated with TFA (5 mL), and refluxed for 24 h. The mixture was cooled, diluted with CH_2Cl_2 (150 mL), washed with saturated $NaHCO_3$ (3 × 100mL), filtered through a pad of $MgSO_4$ (1 cm) and silica gel (2 cm), and concentrated to provide a pale oil.

Without further purification, the above oil was dissolved in 50% aqueous THF (80 mL), treated with $LiOH{\cdot}H_2O$ (45 mg, 10 mmol), and stirred at room temperature for 30 min. The mixture was then washed with ether (50 mL), and the remaining aqueous solution was acidified to pH 3 with 6 N HCl and extracted with ethyl acetate (3 × 80 mL). These extracts were combined, dried ($MgSO_4$), and filtered through a 2 cm pad of silica gel. Evaporation gave an oil which was purified by radial chromatography to give **9a** as a clear oil (490 mg, 51%): $[\alpha]^{25}_D$ −31.3 (*c* 0.27, $CHCl_3$); ^1H NMR (200 MHz) δ 1.34 (d, 3H, *J* = 7.0 Hz), 3.15 (m, 1H), 3.52 (m, 2H), 7.50 (m, 1H), 7.86 (m, 1H), 8.05 (m, 1H), 8.70 (m, 1H); IR (neat) 3500−2500 (br), 3067, 1741, 1706 cm^{-1}. Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.73; N, 7.25. Found: C, 61.99; H, 5.81; N, 7.17.

(2*R*)-2-Methyl-4-(2-thienyl)-4-oxobutanoic acid (9b) was prepared from **11b** as a white solid in 65% yield by the same procedure: mp 83−87 °C; $[\alpha]^{25}_D$ −29.1 (*c* 0.69, $CHCl_3$); ^1H NMR (200 MHz) δ 1.31 (d, 3H, *J* = 7.0 Hz), 3.15 (m, 1H, *J* = 7.0 Hz), 3.21 (m, 2H), 7.14 (m, 1H), 7.65 (m, 1H), 7.76 (m, 1H). Anal. Calcd for $C_9H_{10}O_3S$: C, 54.53; H, 5.08. Found: C, 54.73; H, 5.26.

(2*R*)-2-Methyl-4-(2-furyl)-4-oxobutanoic acid (9c) was prepared from **11c** as a white solid in 46% yield by the same procedure: mp 72−73 °C; $[\alpha]^{25}_D$ −43.5 (*c* 0.7, $CHCl_3$); ^1H NMR (200 MHz) 1.29 (d, 3H, *J* = 7.0), 2.92 (dd, 1H, *J* = 5.4, 16.8 Hz), 3.14 (m, 1H), 3.33 (dd, 1H, *J* = 7.4, 16.8 Hz), 6.54 (m, 1H), 7.23 (d, 1H, *J* = 3.6 Hz), 7.60, (m, 1H); IR ($CDCl_3$) 3600−2500 (br), 3146, 1708, 1676 cm^{-1}. Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.16; H, 5.57.

2-Pyridyl 4-keto amide 12a was prepared by coupling 4-keto acid **9a** with (*S*)-α-methylbenzylamine by the following general procedure.[26] EDCI (380 mg, 2 mmol) was added to a stirred solution of **9a** (310 mg, 1.6 mmol), (*S*)-α-methylbenzylamine (0.3 mL), and HOBt (270 mg, 2 mmol) in THF (80 mL) at 0 °C. The mixture was stirred at 0 °C for 3 h and at room temperature overnight. After concentration, the residue was partitioned between ethyl acetate (100 mL) and 1 N HCl (50 mL). The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (50 mL). The organic extracts were combined, washed with saturated $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered through a 2 cm pad of silica gel, and concentrated. Analysis of the crude product by NMR showed doublets 1.48 δ (major) and 1.42 δ (minor) for the 2-methyl group corresponding to diastereomers in a ratio of 76:24 which was taken as the stereoselectivity of the alkylation step.

The residue was purified by radial chromatography (hexane: ethyl acetate = 95:5 to 80:20 to 60:40) to give a white solid (370 mg, 76%): mp 133–134 °C; $[\alpha]^{25}_D$ −95.3 (*c* 0.39, $CHCl_3$, sample was recrystallized from ethyl acetate/hexane); ^1H NMR (200 MHz) δ 1.28 (d, 3H, *J* = 7.0 Hz), 1.48 (d, 3H, *J* = 7.0 Hz), 2.95 (m, 1H), 3.21 (dd, 1H, *J* = 4.6, 18.6 Hz), 3.73 (dd, 1H, *J* = 8.8, 18.6 Hz), 5.10 (m, 1H, *J* = 7.4 Hz), 6.31 (br d, 1H, *J* = 7.4 Hz), 7.31 (m, 5H), 7.45 (m, 1H), 7.80 (m, 1H), 7.97 (m, 1H), 8.65 (m, 1H); ^{13}C NMR (100 MHz) δ 21.9, 36.1, 42.1, 48.6, 127.7, 126.1, 127.0, 127.2, 128.5, 136.8, 143.4, 148.9, 153.1, 174.7, 200.5; IR (KBr) 3306, 3076, 1693, 1659 cm^{-1}. Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 73.09; H, 7.00; N, 9.48.

2-Thienyl 4-keto amide 12b was prepared from 4-keto acid **9b** as a white solid in 80% yield by the same procedure: mp 84–85 °C; $[\alpha]^{25}_D$ −71.4 (*c* 1.1, $CHCl_3$); ^1H NMR (200 MHz) δ 1.26 (d, 3H, *J* = 6.8 Hz), 1.46 (d, 3H, *J* = 7.0 Hz), 2.9–3.5 (m, 3H), 5.04 (m, 1H, *J* = 6.8 Hz), 6.29 (br d, 1H, *J* = 7.2 Hz), 7.23 (m, 8H); ^{13}C NMR (100 MHz) δ 17.9, 22.0, 36.3, 43.2, 48.7, 126.1, 127.0, 128.2, 128.5, 132.4, 133.9, 143.4, 144.1, 174.4, 192.0. Anal. Calcd for $C_{17}H_{19}NO_2S$: C, 67.75; H, 6.35; N, 4.65. Found: C, 67.88; H, 6.19; N, 4.64.

The purified product was a single diastereomer. Examination of the crude product showed doublets at 1.46 and 1.41 δ corresponding to a ratio of diastereomers of 84:16 which was taken as the stereoselectivity of the alkylation step.

2-Furyl 4-keto amide 12c was prepared from 4-keto acid **9c** as a white solid in 76% yield by the same procedure: mp 94–95 °C; $[\alpha]^{25}_D$ −104.5 (*c* 0.56, $CHCl_3$); ^1H NMR (200 MHz) δ 1.23 (d, 3H, *J* = 6.8 Hz), 1.45 (d, 3H, *J* = 7.0 Hz), 2.80 (dd, 1H, *J* = 5.2, 16.8 Hz), 2.95 (m, 1H), 3.24 (dd, 1H, *J* = 9.0, 16.8 Hz), 5.05 (m, 1H, *J* = 7.0 Hz), 6.49 (m, 1H), 7.24 (m, 1H), 7.55 (m, 1H); IR 3300 (br), 3060, 1681 cm^{-1}. Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.77; H, 6.94; N, 4.95.

The purified product was a single diastereomer. Examination of the crude product showed doublets at 1.42 and 1.35 δ corresponding to a ratio of diastereomers of 78:22 which was taken as the stereoselectivity of the alkylation step.

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