A Highly Stereocontrolled, Four-Step Synthesis of (±)-Lasubine II

Jack D. Brown, Michael A. Foley, and Daniel L. Comins*

Contribution from the Department of Chemistry and Biochemistry, Utah State University, Logan, Utah 84322-0300. *Received March 17, 1988*

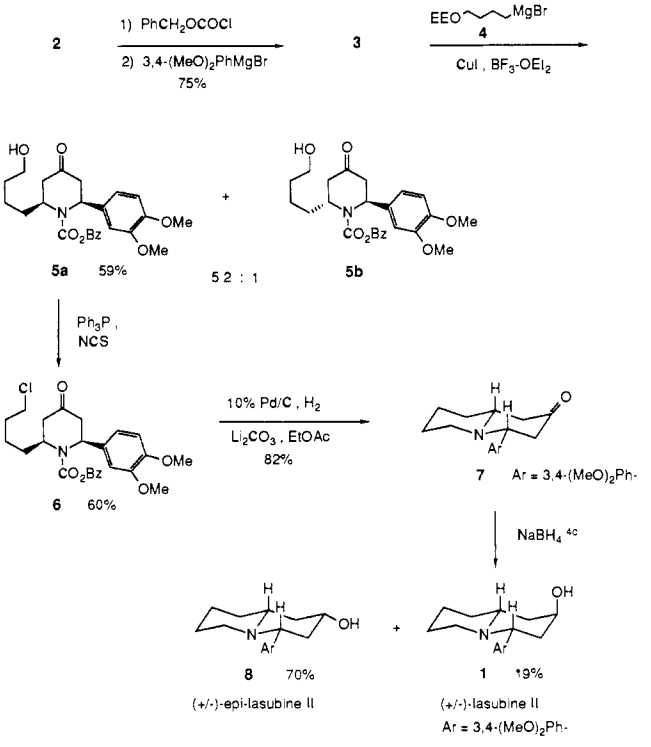
Abstract: A four-step synthesis of (±)-lasubine II (**1**) from 4-methoxypyridine is described. The addition of benzyl chloroformate to a mixture of (3,4-dimethoxyphenyl)magnesium bromide and 4-methoxypyridine gives the *N*-acyl-2,3-dihydro-4-pyridone **3** on workup with aqueous acid. Copper-mediated conjugate addition of (4-chlorobutyl)magnesium bromide to **3** affords *cis*-2,6-disubstituted piperidine **6**. Catalytic hydrogenolysis of **6** with palladium on carbon in the presence of lithium carbonate gives an 82% yield of quinolizidinone **7**. Reduction of **7** with lithium trisiamylborohydride provides (±)-lasubine II (**1**). The four-step total synthesis is carried out in 28% overall yield with excellent stereocontrol.

Since the first isolation of a Lythraceae alkaloid in 1962 by Ferris,[1] more than 40 alkaloids have been isolated from plants of the Lythraceae family. One of these alkaloids, lasubine II (**1**), was isolated in 1978 by Fuji and co-workers[2] from the leaves of *Lagerstroemia subcostata* koehne. Syntheses of racemic **1**, and related alkaloids, have been based on the use of Mannich reactions of pelletierine with substituted benzaldehydes[3] or on intermolecular nitrone cycloaddition.[4] These approaches are nonstereoselective and/or lengthy. A 10-step synthesis of (±)-lasubine II by Hoffmann and Endesfelder[5] utilized an intramolecular nitrone cycloaddition, which allowed for a higher degree of stereocontrol than the intermolecular cycloaddition approach. A drawback to their synthesis is a required inversion of the stereocenter at C-2. An unrelated synthesis of **1** by Narasaka and co-workers[6] from 2-(3,4-dimethoxyphenyl)-1,3-dithiane was carried out in 11 steps with a high degree of stereoselectivity. Although efficient and stereoselective routes to Lythraceae alkaloids bearing a trans C-4, C-10 hydrogen relationship, i.e., (±)-lasubine I, (±)-vertaline, and (±)-lythrancepine II, have been recently reported by Hart[7] and Speckamp,[8] a short and highly stereocontrolled synthesis of lasubine II has been lacking. We report here the synthesis of (±)-lasubine II (**1**) in four steps with a high degree of stereocontrol.

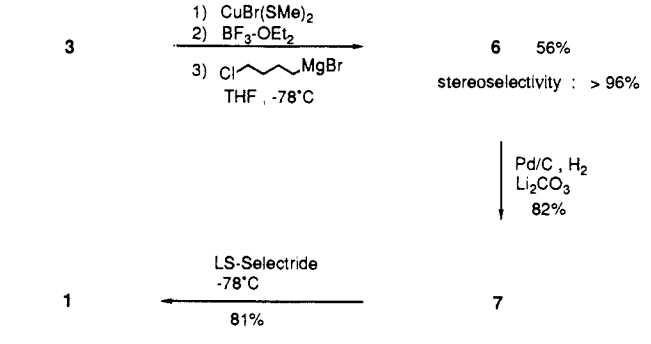
Results and Discussion

Our synthetic strategy followed the retrosynthetic analysis shown in Figure 1, which developed from our earlier model studies.[9] The desired *N*-acyl-2,3-dihydro-4-pyridone **3** was prepared in 75% yield by the addition of benzyl chloroformate to a mixture of 4-methoxypyridine and (3,4-dimethoxyphenyl)-magnesium bromide in tetrahydrofuran (THF) as shown in Scheme I. The copper-catalyzed addition of Grignard reagent **4** to **3** was examined under a variety of conditions. In all cases the stereoselectivity was low, less than 3:1. The stereoselectivity of the conjugate addition was improved to 5.2:1 (cis:trans) by utilizing an alkylcopper boron trifluoride complex[10] (−78 °C, THF, 3 h). In this manner, the cis alcohol **5a** could be isolated in 59% yield. The alcohol **5a** was converted to the chloride **6** in 60% yield by treatment with triphenylphosphine and *N*-chlorosuccinimide.[11]

Scheme I



Scheme II



This compound was cyclized by a one-pot procedure that involved catalytic hydrogenolysis of the benzyl carbamate group in the presence of lithium carbonate to give an 82% yield of quinolizidinone **7**. The preparation of **7** constitutes a six-step formal total synthesis of (±)-lasubine II (**1**), for treatment of **7** with sodium borohydride gives **1** and (±)-epilasubine II (**8**) in 19% and 70% yields, respectively.[4c]

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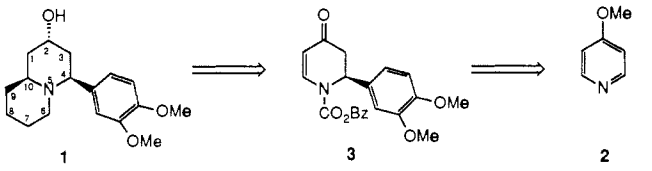

(+/-)-lasubine II

Figure 1.

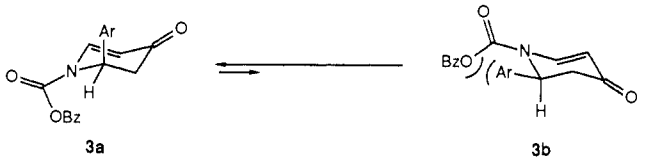

Figure 2.

An increase in the overall stereoselectivity, a decrease in the number of steps, and a higher overall yield were achieved by the following modifications depicted in Scheme II. An alkylcopper boron trifluoride complex prepared from (4-chlorobutyl)magnesium bromide[12] was treated with dihydropyridone **3** to give piperidone **6** directly with a very high degree of stereoselectivity (>96%). The use of copper(I) bromide–dimethyl sulfide complex was essential, for with copper(I) iodide the stereoselectivity had dropped to 0%. The high stereoselectivity of the $CuBr{\cdot}Me_2S$ reaction likely arises from a stereoelectronic effect. Due to a strong $A^{(1,3)}$ strain between the aryl group at C-2 and the *N*-acyl group of **3b** (see Figure 2), the aryl group will occupy the axial position via conformation **3a**.[13] Stereoelectronically preferred[14] axial attack by the organocuprate on the α,β-enone moiety of **3a** leads to the cis product. With a highly stereoselective two-step preparation of chloride **6** in hand, we concentrated on completing the synthesis of (±)-lasubine II. The last step in the synthesis involved a stereospecific reduction of the ketone carbonyl of quinolizidinone **7**. This was accomplished with lithium trisiamylborohydride[15] in THF at −78 °C to give (±)-lasubine II (**1**) and (±)-epilasubine II (**8**) in a ratio of 98:2.

We have described a highly stereoselective, four-step total synthesis of (±)-lasubine II starting from 4-methoxypyridine in 28% overall yield. The key step in the synthesis is a stereocontrolled, copper-mediated addition of (4-chlorobutyl)magnesium bromide to *N*-acyldihydropyridone **3**. The significant $A^{(1,3)}$ strain inherent in this ring system is presumed responsible for the high stereoselectivity observed in the conjugate addition step. This synthesis represents a new and efficient approach to Lythraceae alkaloids containing a cis C-4, C-10 hydrogen relationship, and the basic strategy should be amenable to the synthesis of a number of other quinolizidine and piperidine alkaloids.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Varian XL-300 spectrometer. Chemical shifts for ^1H NMR spectra are reported in ppm relative to Me_4Si (δ 0) and coupling constants are in hertz. ^{13}C NMR spectra are reported in ppm relative to the $CDCl_3$ absorption (77.0 ppm). Radial preparative-layer chromatography (radial PLC) was carried out by using a Chromatotron (Harrison Associates, Palo Alto, CA). Elemental analyses were carried out by M-H-W Laboratories, Phoenix, AZ.

***N*-[(Benzyloxy)carbonyl]-2-(3,4-dimethoxyphenyl)-4-oxo-1,2,3,4-tetrahydropyridine (3).** To a suspension of magnesium metal (0.73 g, 30 mmol) in THF (5 mL) under an atmosphere of nitrogen was added 1,2-dibromoethane (0.2 mL). The suspension was warmed by hand until a reaction commenced (bubbling and heating). When all the dibromoethane had reacted, THF (10 mL) was added. The solvent was removed by syringe and the magnesium was again washed with THF (10 mL). The solvent was again removed by syringe and THF (10 mL) was added. To this suspension was added 4-bromoveratrole (1.5 mL, 12 mmol). This mixture was stirred for 12 h at room temperature. The resulting Grignard reagent was then added slowly via a double-tipped needle to a solution of 4-methoxypyridine[9] (1.0 mL, 10 mmol) in THF (10 mL) at −23 °C. To this solution was added benzyl chloroformate (1.4 mL, 10 mmol) dropwise over a 10-min period. The solution was stirred at −23 °C for 4 h and then poured into stirred 10% HCl (25 mL). After stirring of the mixture for 10 min, the organic layer was separated. The aqueous layer was extracted with ether (2 × 50 mL). The combined organic extracts were washed with brine (25 mL) and dried over $MgSO_4$. The solution was filtered and concentrated to afford the crude product as a light-yellow solid. Recrystallization (acetone/hexanes) gave 2.8 g (75%) of **3** as white needles: mp 115 °C–117 °C; ^1H NMR ($CDCl_3$) δ 7.94 (d, J = 8.4 Hz, 1 H), 7.33 (m, 5 H), 6.8 (m, 3 H), 5.7 (d, J = 7.2 Hz, 1 H), 5.4 (d, J = 8.1 Hz, 1 H), 5.25 (m, 2 H), 3.84 (s, 3 H), 3.73 (s, 3 H), 3.13 (dd, J = 16.8 and 7.5 Hz, 1 H), 2.8 (d, J = 16.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 192, 153, 148, 149, 142, 135, 131, 128.6, 128.5, 128.3, 128.2, 118, 111, 109, 107, 69, 55.7, 55.5, 54.1; IR ($CDCl_3$) 3150, 2950, 1720, 1660, 1600, 950 cm^{-1}.

Anal. Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.87; H, 5.80; N, 3.82.

***cis*-*N*-[(Benzyloxy)carbonyl]-2-(3,4-dimethoxyphenyl)-6-(4-hydroxybutyl)piperidin-4-one (5a).** To a 25-mL round-bottomed flask equipped with a stir bar and purged with dry nitrogen were added magnesium metal (212 mg, 8.7 mmol) and THF (5 mL). To this suspension were added the 1-ethoxyethyl ether of 1-chloro-4-hydroxybutane (0.52 mL, 2.99 mmol) and ethylene dibromide (0.02 mL) as an entrainer. The suspension was warmed by hand until a reaction commenced (warming and cloudiness) and then heated to reflux for 4 h. The resulting Grignard reagent was added via a double-tipped needle to cuprous iodide (0.55 g, 2.9 mmol) in THF (5 mL) at −23 °C. The resulting heterogeneous mixture was stirred at −23 °C for 10 min and then cooled to −78 °C. To this mixture was added boron trifluoride etherate (0.18 mL, 1.44 mmol). The mixture stayed heterogeneous, and after 10 min, dihydropyridone **3** (530 mg, 1.44 mmol) in THF (5 mL) was added dropwise over a 10-min period. The mixture briefly became homogeneous. The mixture was stirred at −78 °C for 3 h and then poured into aqueous 20% NH_4Cl/NH_4OH (50:50) solution (50 mL). The aqueous layer was extracted with ether (2 × 50 mL), and the combined organic layers were washed with brine (50 mL) and dried over $MgSO_4$. The solution was filtered and concentrated to yield the crude product. No further purification was attempted. The compound was dissolved in THF (5 mL). Water (2 mL) and oxalic acid (182 mg, 1.44 mmol) were added, and the solution was stirred at room temperature for 4 h. The reaction was quenched by pouring the reaction mixture into 5% aqueous $NaHCO_3$ (25 mL). The aqueous layer was extracted with ether (2 × 50 mL), and the combined organic extracts were washed with brine (25 mL) and dried over $MgSO_4$. The solution was filtered and concentrated to give the crude product. Purification by radial PLC (SiO_2, 10% $MeOH/CH_2Cl_2$) gave 490 mg (73%) of a clear oil. The isolated product consists of two diastereomers (5.18:1 by ^1H NMR), which were separated by radial PLC (SiO_2, 80% ethyl acetate/0.5% ethanol/hexanes) to give 396 mg of the cis diastereomer **5a** and 84 mg of the trans diastereomer **5b**: ^1H NMR ($CDCl_3$) δ 7.4 (s, 5 H), 6.8 (m, 3 H), 5.9 (m, 1 H), 5.2 (s, 2 H), 4.7 (m, 1 H), 3.8 (s, 3 H), 3.7 (s, 3 H), 3.6 (m, 1 H), 3.4 (t, 2 H), 3.0 (dd, 1 H), 2.9–2.6 (m, 2 H), 2.3 (dd, 1 H), 1.8–0.9 (m, 6 H); IR (neat) 3530, 2975, 1700, 1620 cm^{-1}.

Anal. Calcd for $C_{25}H_{31}NO_6$: C, 68.01; H, 7.08; N, 3.16. Found: C, 67.90; H, 6.94; N, 3.14.

***N*-[(Benzyloxy)carbonyl]-6-(4-chlorobutyl)-2-(3,4-dimethoxyphenyl)-piperidin-4-one (6).** To a 25-mL round-bottomed flask equipped with a stir bar and purged with nitrogen were added Mg (0.12 g, 4.9 mmol) and diethyl ether (8 mL). To this suspension was added 1-bromo-4-chlorobutane (0.01 mL) at room temperature. The mixture was stirred at room temperature until a reaction commenced (warming, cloudiness) and then cooled to 0 °C. Additional 1-bromo-4-chlorobutane (0.5 mL, 4.3 mmol) was added and stirring was continued for 1 h at 0 °C. The solution was warmed to room temperature and transferred via a cannula to an addition funnel. To a separate 100-mL round-bottomed flask equipped with a stir bar and purged with nitrogen was added dihydropyridone **3** (0.5 g, 1.44 mmol) in THF (50 mL). To this solution was added $CuBr{\cdot}S(CH_3)_2$ (0.9

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g, 4.3 mmol), which formed a heterogeneous reaction mixture. The suspension was cooled to -78 °C and boron trifluoride etherate (0.26 mL, 22 mmol) was added. The preformed Grignard reagent was added dropwise over a 10-min period. The mixture became a golden yellow color and appeared to become homogeneous during the addition of the Grignard reagent. After the addition of the Grignard was complete, the reaction mixture returned to a heterogeneous state. The suspension was stirred for 4 h at -78 °C and poured into an aqueous 20% NH_4Cl/NH_4OH (50:50) solution (100 mL). After stirring the mixture 10 min, the organic layer was separated. The aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined organic extracts were washed with brine (50 mL) and dried over $MgSO_4$. The solution was filtered and concentrated to afford the crude product as a bright yellow oil. Purification by radial PLC (SiO_2, 30% EtOAc/hexanes) gave 380 mg (57%) of a light yellow oil. The isolated product consisted of two diastereomers (60:1 by ^1H NMR), which were separated by radial PLC (SiO_2, 20% acetone/hexanes) to give 370 mg (56%) of the cis isomer **6** and 5.2 mg of the trans isomer: ^1H NMR ($CDCl_3$) δ 7.5-7.3 (m, 5 H), 7.0-6.8 (m, 3 H), 6.1-5.8 (m, 1 H), 5.2 (s, 2 H), 4.8-4.6 (m, 1 H), 3.9 (m, 3 H), 3.7 (m, 3 H), 3.3 (br s, 2 H) 3.0 (m, 1 H), 2.8-2.6 (m, 2 H), 2.4 (m, 1 H), 1.6-1.0 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 206, 156, 150, 148, 136, 134, 128.8, 128.7, 128.5, 128.3, 119, 118, 112, 109, 68, 56, 54, 52, 45, 36, 32, 24; IR ($CDCl_3$) 2938, 2835, 1717, 1691, 1602, 1589, 1518, 1455, 1410, 1327, 1257, 1147, 1026 cm^{-1}.

Anal. Calcd for $C_{25}H_{30}ClNO_5$: C, 65.28; H, 6.57; N, 3.05. Found: C, 65.11; H, 6.28; N, 3.04.

Preparation of 6 from 5a. The piperidone **5a** (539 mg, 1.22 mmol) was dissolved in 10 mL of DMF under N_2. To this solution was added 326 mg (2.44 mmol) of *N*-chlorosuccinimide and the solution was cooled to 0 °C (ice bath). Triphenylphosphine (640 mg, 2.44 mmol) was added slowly, and after all the triphenylphosphine had been added, the solution was warmed to 50 °C and held there for 4 h. To this solution was then added 1 mL of methanol to consume the excess reagents. This reaction mixture was poured into water and extracted with ether. The combined ether extracts were washed twice with water and once with brine and dried over $MgSO_4$. Concentration of the organic phase gave the crude product, which was purified by radial PLC (1% MeOH/CH_2Cl_2) to give 336 mg (60%) of **6** as a clear oil. This material was identical with that prepared above.

4-(3,4-Dimethoxyphenyl)quinolizidin-2-one (7). To a 500-mL Parr bottle was added **6** (0.78 g, 1.7 mmol) in ethyl acetate (15 mL). To this solution were added lithium carbonate (0.12 g, 1.7 mmol) and 5% Pd/C (0.14 g). The mixture was shaken under 40 psi of hydrogen for 12 h, filtered through Celite, and concentrated to afford the crude product. Purification by radial PLC (SiO_2, 5% MeOH/CH_2Cl_2) gave 370 mg (75%) of **7** as a clear oil. Crystallization from methanol gave colorless crystals: mp 82-84 °C (lit.[4c] mp 83-84 °C); ^1H NMR ($CDCl_3$) δ 6.9 (s, 1 H), 6.8 (s, 2 H), 3.9 (s, 3 H), 3.8 (s, 3 H), 3.2 (dd, 1 H), 2.9-2.1 (m, 7 H), 1.9-1.1 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 207, 135, 119, 111, 109, 69, 62, 56, 53, 51, 48, 34, 26, 24; IR (neat) 2900, 2770, 2725, 1710 cm^{-1}.

(±)-Lasubine II (1). To a 5-mL round-bottomed flask equipped with a stir bar and purged with nitrogen was added 4-(3,4-dimethoxyphenyl)quinolizidin-2-one (**7**) (73 mg, 0.25 mmol) in THF (1 mL). This solution was cooled to -78 °C in preparation for its delivery to the reducing agent. To a separate 10-mL round-bottomed flask equipped with a stir bar and purged with nitrogen was added LS-Selectride (Aldrich Chemical Co.) (0.31 mL, 0.31 mmol) in THF (2 mL) cooled to -78 °C. The solution of quinolizidinone **7** was transferred via a cannula to the reducing agent and stirring was continued for 30 min. After 30 min, pH 7.0 phosphate buffer (1 mL) was added and the solution was warmed to room temperature. The reaction mixture was extracted with diethyl ether (2 × 25 mL), and the combined organic layers were washed with brine (25 mL). The solution was concentrated under reduced pressure to afford the crude boronate. The crude boronate was dissolved in ethanol, and 1 N NaOH (1 mL) was added. The mixture was refluxed for 1 h and then cooled to room temperature. The mixture was then poured into 5% aqueous $NaHCO_3$ (25 mL) and stirred for 10 min. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 × 25 mL). The combined organic extracts were washed with brine (25 mL) and dried over K_2CO_3. The solution was filtered and concentrated to afford the crude product. Purification by radial PLC (SiO_2, 5% $CHCl_3$/MeOH) gave 58 mg (81%) of (±)-lasubine II (**1**) as a viscous oil. The product was 98% pure containing only 2% of epilasubine II (**8**) as indicated by ^1H NMR: ^1H NMR ($CDCl_3$) δ 6.91 (s, 1 H), 6.86 (d, J = 7.2 Hz, 1 H), 6.79 (d, J = 8.2 Hz, 1 H), 4.15 (t, J = 2.6 Hz, 1 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 3.31 (dd, J = 11.5 and 3.2 Hz, 1 H), 2.69 (d, J = 11 Hz, 1 H), 2.35-2.41 (m, 1 H), 1.25-1.91 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ 148, 147, 137, 119, 111, 110, 64, 63, 56, 55.75, 55.7, 53.42, 40, 33, 25, 24; IR ($CDCl_3$) 3613, 3402, 3155, 3008, 2937, 2859, 2839, 2799, 2254, 1794, 1594, 1516, 1465, 1443, 1421, 1386, 1342, 1314, 1261, 1233, 1197, 1179, 1151, 1135, 1094, 1047, 1029, 908, 736 cm^{-1}. This is in agreement with reported spectra.[5]

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α-Amino Acids as Chiral Educts for Asymmetric Products. Alkylation of *N*-Phenylfluorenyl α-Amino Ketones. Synthesis of Optically Pure α-Alkyl Carboxylic Acids

William D. Lubell and Henry Rapoport*

Contribution from the Department of Chemistry, University of California, Berkeley, California 94720. *Received April 18, 1988*

Abstract: Regioselective enolization and alkylation of *N*-(9-phenylfluoren-9-yl)amino ketones provides diastereomeric mixtures of α′-alkyl branched α-amino ketones. Separation of the diastereomers provides >99% enantiomerically pure α′-alkyl branched α-amino ketones which can be epimerized at the α′-carbon with no loss of chiral integrity at the α-carbon. Deprotection and subsequent oxidative degradation of the diastereomerically pure alkylated products provide enantiomerically pure α-alkyl-substituted carboxylic acids. α-Methylpentanoic acid and α-phenylpropanoic acid are synthesized in >99% enantiomeric purity from this seven step process that utilizes L-alanine as a one-carbon chiral building block.

Because of their abundance in nature and their application in pharmaceuticals, much attention has been devoted to the preparation of enantiomerically pure α-amino carbonyl compounds.[1] Although several methods are available to stereoselectively introduce different electrophiles at the α-center of α-amino acid and α-amino amide derivatives,[1,2] no methodology existed for the regio- and stereoselective alkylation of α-amino ketones. Since α-amino ketones may possess two sites for possible carbon al-

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