Efficient Syntheses of Biologically Important (S)-2-Amino-8-oxodecanoic Acid (Aoda) and Homologues

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Abstract: The efficient and practical asymmetric syntheses of the biologically important (S)-2-amino-8-oxodecanoic ester and its homologues have been achieved employing the Schöllkopf chiral auxiliary. Carbon-carbon bond formation between the appropriate alkyl bromide and the LDA generated anion of the Schöllkopf auxiliary, followed by hydrolysis provided the desired methyl ester of a long-chained keto amino acid in high yield with high selectivity.

Key words: alkylation, amino acids, asymmetric synthesis, chiral auxiliaries, diastereoselectivity

The unusual keto amino acid, (S)-2-amino-8-oxodecanoic acid (Aoda, 1), is a biologically important constituent of the naturally occurring cyclic tetrapeptides, such as apicidins1 (2 and 3) and 9,10-deepoxy-chlamydocin4 (Figure 1). Apicidins and structurally related cyclic tetrapeptides are known to be potent inhibitors of histone deacetylases.3,4 Integral nuclear isoforms that regulate gene transcription by deacetylating the ε-N-acetyl lysine residues of histones.3 Structural similarities between the Aoda moiety of apicidins and N-acetylated lysine residues of histone (5, Figure 1) suggest that Aoda is a reactive isostere of N-acetyl lysine and a key pharmacophoric element of these cyclic tetrapeptides.6,8 Consequently, extensive chemical modifications of the Aoda residue of apicidin were studied, which led to the discovery of a semi-synthetic, mechanism-based histone deacetylase inhibitors with an increased potency.4,6–8

Therefore, there has been considerable interest in the development of a methodology for the efficient preparation of this unusual keto amino acid. Initially, the asymmetric synthesis of the N- and C-protected Aoda was achieved by Viallefont in 1985.9 He employed the reaction of the appropriate organocuprates with a halogen derivative of L-homoserin. Very recently, three independent synthetic approaches of Aoda derivatives were reported for the synthesis of apicidins. Kitahara synthesized the 2-amino-8-protected hydroxydecanoic acid, using the appropriate Grignard reagent and 2-amino-γ-lactone.10 Singh accomplished the synthesis of the N- and C-protected Aoda under photolytic conditions in the presence of n-Bu3SnH, using L-glutamic acid.11 Murray et al. prepared N-Boc-L-Aoda from the Garner aldehyde in a six step process.12

As part of an ongoing program, aimed at the search for a non-cyclic tetrapeptide histone deacetylase inhibitors, we needed to synthesize both the enantiomers of Aoda and their related analogues in large quantities. In this paper, we wish to report the practical and versatile synthesis of the long-chained keto amino acids in an enantiomerically pure form.

There are a number of methodologies in the literature concerning the synthesis of amino acids containing long alkyl side chains.12,13 Most synthetic methods have employed the homologation of natural amino acids, with the appro-
priet reagents. However, we felt that these approaches were not suitable to the preparation of a series of ketone-containing amino acid derivatives. Consequently, a new enantioselective general synthesis of 6 was designed utilizing the reaction of alkyl bromides 9 with the Schöllkopf chiral auxiliary 8 with modest diastereoselectivity (producing trans product). Using established synthetic protocols of Li. Treatment of cy-

clic tertiary alcohols 10a-c with bromine and potassium bicarbonate provided the corresponding fragmentation products 9a-c in high yields (70%, 80%, and 65%, respectively). When the o-bromoketone 9b was treated with chiral lithiated bislactim ether 11, the tertiary alcohol 12 was produced with high diastereoface selection in 77% yield (Scheme 2). In this case, the addition of the lithiated bislactim ether 11 to the carbonyl group of 9b was much faster than to the primary alkyl bromide functional group. Therefore, the protection of the carbonyl group of the o-bromoketone 9 was necessary to obtain the desired product. Using p-TsOH as a catalyst, the keto group of 9 was protected by converting it into the ketal group giving compound 13 in high yield (80–95%) (Scheme 2).

The requisite o-bromoketones 9 could be conveniently prepared by a retro-Barbier fragmentation, according to established synthetic protocols of Li. Treatment of cy-

clic tertiary alcohols 10a-c with bromine and potassium bicarbonate provided the corresponding fragmentation products 9a-c in high yields (70%, 80%, and 65%, respectively). When the o-bromoketone 9b was treated with chiral lithiated bislactim ether 11, the tertiary alcohol 12 was produced with high diastereoface selection in 77% yield (Scheme 2). In this case, the addition of the lithiated bislactim ether 11 to the carbonyl group of 9b was much faster than to the primary alkyl bromide functional group. Therefore, the protection of the carbonyl group of the o-bromoketone 9 was necessary to obtain the desired product. Using p-TsOH as a catalyst, the keto group of 9 was protected by converting it into the ketal group giving compound 13 in high yield (80–95%) (Scheme 2).

Carbon-carbon bond formation between these alkyl bromides and the anion of the Schöllkopf chiral auxiliary was investigated (Scheme 3). Initially, the alkylation of 13b with the lithiated bislactim ether 11, generated in situ from 8 and n-BuLi in THF at –78 °C, was carried out at 0 °C, producing 14b in 84% yield along with its 5-epimer 15b with modest diastereoselectivity (trans/cis 6.6:1).

An attempt to improve the diastereoselectivity of the alkylation was executed by changing the reaction conditions. As illustrated in Table 1, when the process was carried out at a lower temperature (–40 °C), the selectivity was slightly improved (trans/cis 8.0:1). The alkylation of 13b with the recently described higher order bislactim ether lithium cyanocuprate furnished similar diastereoselectivity (trans/cis 7.8:1), but with a lower yield (68%). However, when the hard base LDA was employed instead of the soft base n-BuLi, the alkylation process at –50 °C provided the best trans-diastereoselectivity (trans/cis 12.3:1) in 82% isolated yield of 14b.

Separation of the major trans-isomer could easily be achieved by flash chromatography with diastereomeric excess higher than 98%. Treatment of the purified bislac-

tim ether product 14b with 0.1 N HCl in THF effected both the hydrolysis of the Schöllkopf chiral auxiliary and the removal of the ketal protecting group to give the desired methyl ester of Aoda 6b in 98% ee and 87% yield (Scheme 3).

The syntheses of the methyl ester of Aoda homologues (6a and 6c) was carried out by the same route starting from the corresponding alkyl bromides 13, and the route is amenable to scale-up to multigram level. Again, high diastereoselectivities of the alkylation process and high overall chemical yields were obtained, as summarized in Table 1 and Scheme 3.
4.33–4.40 (m, 1 H), 5.11 (s, 2 H), 5.25 (d, 1.37 (m, 4 H), 1.50–1.83 (m, 4 H), 2.35–2.44 (m, 4 H), 3.74 (s, 3 H),

4-Bromo-heptan-3-one (9a)
Yield: 70%; colorless oil.

IR (neat): 2940, 1460, 1072 cm–1.

1H NMR (300 MHz, CDCl3): δ = 1.04 (t, J = 7.5 Hz, 3 H), 1.66–1.77 (m, 2 H), 1.80–1.90 (m, 2 H), 2.41 (m, 4 H), 3.39 (t, J = 6.6 Hz, 2 H).

13C NMR and IR data are in agreement with published values.15 

6-Benzyloxycarbonylamino-8-oxo-decanoic Acid Methyl Ester

Yield: 95%; colorless oil.

IR (neat): 3270, 2928, 1744, 1671 cm–1.

1H NMR (300 MHz, CDCl3): δ = 1.05 (t, J = 7.2 Hz, 3 H), 1.37–1.48 (m, 2 H), 1.55–1.65 (m, 2 H), 1.82–1.91 (m, 2 H), 2.43 (m, 4 H), 3.40 (t, J = 6.6 Hz, 2 H).

13C NMR and IR data are in agreement with published values.17 

Preparation of 9a–c; General Procedure
To a stirred solution of cyclic tertiary alcohol 10 (3.5 mmol) in CHCl3 (10 mL) was added powdered K2CO3 (2.90 g, 21 mmol) at 0 °C (for 9a and 9b) or –40 °C (for 9c). The mixture was stirred for 10 min, and bromine (0.90 mL, 17.5 mmol) was added then was added dropwise. The reaction mixture was stirred at 0 °C (for 9a and 9b) or –40 °C (for 9c) for 10 h. The mixture was quenched with sat. Na2S2O3 solution (10 mL) and extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with brine, dried (MgSO4) and concentrated. The resultant residue was purified by flash chromatography (silica gel; hexanes–EtOAc, 10:1) to yield 9.

Yield: 70%; colorless oil.

IR (neat): 2940, 1460, 1072 cm–1.

Preparation of 13a–c; General Procedure
To a stirred solution of co-bromoketone 9 (1.1 mmol) in benzene (5 mL) was added ethylene glycol (0.15 mL, 2.75 mmol) and p-TsOH (10 mol%, 21 mg). The mixture was heated to reflux in a Dean–Stark apparatus for 12 h. After being cooled to r.t., the reaction mixture was poured into sat. NaHCO3 solution, and extracted with Et2O (2 × 10 mL). The combined organic layers were washed with brine, dried (MgSO4) and concentrated. The resultant residue was purified by flash chromatography (silica gel; petroleum ether–EtOAc, 15:1) to yield 13.

Yield: 80%; colorless oil.

IR (neat): 2947, 2879, 1460, 1070 cm–1.

Yield: 82%; colorless oil.

IR (neat): 2947, 2879, 1460, 1070 cm–1.

Yield: 80%; colorless oil.

IR (neat): 2944, 2880, 1462, 1073 cm–1.

Yield: 65%; colorless oil.

IR (neat): 2936, 2859, 1715, 1458, 1111 cm–1.

IR (neat): 2940, 1460, 1072 cm–1.

IR (neat): 2940, 1460, 1072 cm–1.

IR (neat): 2940, 1460, 1072 cm–1.
Preparation of 14a–c; General Procedure
A solution of LDA (2.2 mL, 0.5 M in THF, 1.1 mmol) was added to a stirred solution of the bislactim ether 8 (1.0 mmol) in THF (3 mL) at –78 °C, which was stirred for 20 min. Then, a solution of alkyl bromide 13 (300 mg, 1.1 mmol) in THF (2 mL) was added dropwise. The reaction mixture was warmed to –50 °C and stirred for 16 h. The solution was quenched with phosphate buffer solution (pH 7). The crude reaction mixture was warmed to r.t., and the solvent was removed in vacuo. The resulting material was diluted with water and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine, dried (MgSO₄) and concentrated. The residue was purified by flash chromatography (silica gel; hexanes–EtOAc, 10:1) to give pure 14.

Yield: 83%; colorless oil.

IR (neat): 2946, 2874, 1696, 1662, 1547, 1462, 1437, 1238, 1196, 1142, 1076, 1011 cm⁻¹.

HRMS (EI): m/z (rel. int.): 354 (M⁺, 23), 339 (15), 311 (22), 267 (43), 183 (73), 141 (42), 101 (50), 57 (13).

HRMS (Cl): m/z calc for C₁₉H₂₄N₂O₄ [M+H⁺], 354.1756; found, 354.1756.

2-Amino-7-oxo-nonanoic acid methyl ester (6a)
Yield: 92%; colorless oil; [α]D¹⁸ +15.4 (c 0.98, MeOH).

IR (neat): 2932, 2361, 1740, 1200 cm⁻¹.

HRMS (CI): m/z (rel. int.): 216 [M⁺+1], 215 [M⁺+1], 170 (100), 169 (100), 125 (24), 57 (100).

HRMS (Cl): m/z calc for C₁₉H₂₄N₂O₄ [M+H⁺], 354.1756; found, 354.1756.

2-Amino-8-oxodecanoic Acid
Yield: 87%; colorless oil; [α]D¹⁷ +16.3 (c 1.01, MeOH).

IR (neat): 3384, 2940, 2861, 1736, 1715 cm⁻¹.

HRMS (Cl): m/z calc for C₁₉H₂₄N₂O₄ [M+H⁺], 354.1756; found, 354.1756.

2-Amino-8-oxodecanic acid methyl ester (6b)
Yield: 98%; colorless oil; [α]D¹⁹ +17.8 (c 1.00, MeOH).

IR (neat): 3380, 2936, 2859, 1738, 1715 cm⁻¹.

HRMS (Cl): m/z calc for C₁₉H₂₄N₂O₄ [M+H⁺], 354.1756; found, 354.1756.

2-Amino-8-oxoundecanoic acid methyl ester (6c)
Yield: 98%; colorless oil; [α]D¹⁹ +17.8 (c 1.00, MeOH).

IR (neat): 3380, 2936, 2859, 1738, 1715 cm⁻¹.
Acknowledgment

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References

(2) Tani, H.; Fujii, Y.; Nakajima, H. Phytochemistry 2001, 58, 305.
(16) Both enantiomers of 8 are commercially available.
(18) Analysis by $^1$H NMR spectroscopy of the crude product indicated that two diastereoisomers of 12 was present in a 1:1 ratio and the desired alkylated bislactim ether 7b was not produced at all.
(19) Conversion of each pure diastereoisomers (14b and 15b) to the thermodynamic mixture was studied. In 0.5 M NaOMe–MeOH solution the two diastereoisomers slowly interconvert at r.t. eventually reaching thermodynamic equilibrium within about 1 week to give a 2.9:1 mixture of 14b and 15b.
(21) For a previous example employing LDA as a base see: Ohba, M.; Nishimura, Y.; Kato, M.; Fujii, T. Tetrahedron 1999, 55, 4999.
(22) The methyl ester of (S)-Aoda was transformed into the known N-Cbz and C-OMe protected Aoda. The structural assignment of 6b was strongly supported by comparing the spectral data of our synthesized N- and C-protected Aoda with those reported by Singh.11