Pergamon

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Tetrahedron Letters 44 (2003) 8685–8687

TETRAHEDRON LETTERS

Synthesis of (−)-bestatin and the Taxotere® side-chain via nitroaldol reaction of (1*R*)-8-phenylmenthyl glyoxylate

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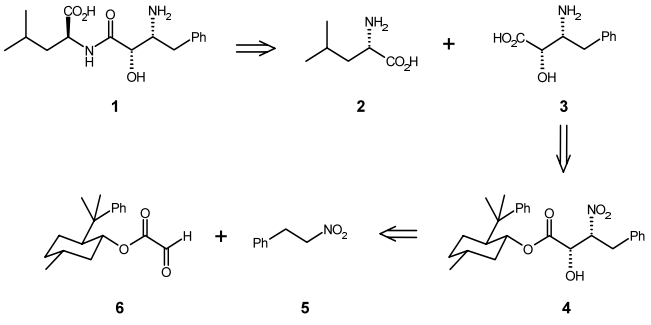
Received 8 July 2003; revised 9 September 2003; accepted 18 September 2003

Abstract—The nitroaldol reaction of (1*R*)-8-phenylmenthyl glyoxylate **6** with 1-nitro-2-phenylethane or with phenylnitromethane led stereoselectively to adducts **4** and **12**, which where then transformed into (−)-bestatin hydrochloride and the Taxotere® side-chain in overall yields of 31 and 52%.

In recent years, stereoselective synthesis of β-amino α-hydroxy acids has attracted much attention due to their presence in various medicinally important molecules.[1] Additionally, a number of their amide derivatives, isolated recently from bacterial cultures, displayed significant activity against aminopeptidases.[2] For this reason, several stereoselective synthetic methods for formation of β-amino α-hydroxy acids were recently presented, including aminohydroxylation,[3] reduction of α-ketoacid derivatives,[4] nucleophilic addition to chiral aldehydes,[5] amides[6] or imines,[7] cycloaddition reactions,[8] chiral epoxides[9] and β-lactam ring-opening procedures,[10] halocyclocarbamation of allylamines[11] and chiral α-amino or α-amino acid transformations.[12] Very recently, we have investigated nitroaldol reaction of chiral derivatives of glyoxylic acid bearing various auxiliaries, such as (1*R*)-8-phenylmenthol, (2*R*)-bornane-10,2-sultam, (4*R*)-methyl-(5*S*)-phenyloxazolidinone and 7,7-dimethylnorbornane-(1*S*,2*R*)-oxazolidinone with simple nitroalkanes.[13] In most cases the reaction proceeded with high stereoselectivity. The configuration of the major diastereoisomers formed in these reactions was established as (2*S*,3*R*)-like in most of the biologically important β-amino α-hydroxy carboxylic acid derivatives. Thus, the readily available nitroalcohols formed by this facile procedure appeared to be very convenient precursors for β-amino α-hydroxy acids. To illustrate this, we decided to synthesize (−)-bestatin **1**,[14] the potent inhibitor of leucine aminopeptidase and aminopeptidase B.[2b] The retrosynthetic analysis shown in Scheme 1 makes it clear that a chiral glyoxylate could serve as a starting material. On the basis of our model studies on diastereoselective nitroaldol additions, we chose (1*R*)-8-phenylmenthol as a convenient and efficient chiral auxiliary.

The reaction of (1*R*)-8-phenylmenthyl glyoxylate **6**[15] with 1-nitro-2-phenylethane **5**, catalyzed by activated aluminum oxide and carried out at −20°C, afforded a mixture (71:19:6:5) of diastereoisomeric nitroalcohols **4** in 89% yield (Scheme 2).

The major diastereoisomer **4**, which was isolated in 63% yield by column chromatography, was catalytically hydrogenated, followed by protection of the amino



Scheme 1.

Keywords: nitroalcohols; nitroaldol reactions; asymmetric induction; chiral auxiliary.

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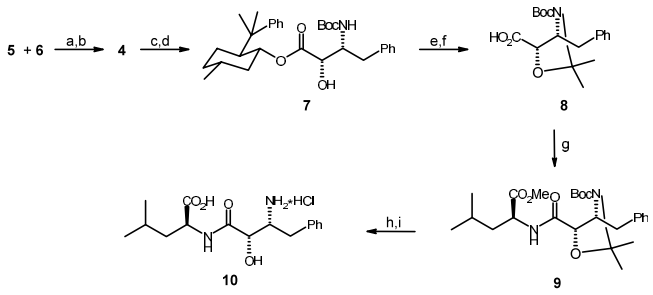
0040-4039/$ - see front matter © 2003 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2003.09.154



Scheme 2. *Reagents and conditions*: (a) activated Al_2O_3, dry THF, rt, 7 h; (b) column chromatography; (c) H_2, catalytic Raney-Ni, MeOH, rt, 16 h; (d) $(Boc)_2O$, satd aq. $NaHCO_3$, AcOEt, rt, 2 h; (e) DMP, catalytic TsOH, toluene, 50°C, 5 h; (f) MeONa, MeOH, rt, 24 h; (g) *N*-ethylmorpholine, isobutyl chloroformate, L-LeuOMe, THF (dry), −5°C→rt, 1 h; (h) catalytic TsOH, MeOH, rt, 24 h; (i) 1N HCl, rt, 16 h.

group using di-*tert*-butyl dicarbonate to afford product **7** in 95% overall yield. Compound **7** was then reacted with 2,2-dimethoxypropane (DMP) to give, after hydrolysis of the ester functionality, the acid **8** in 78% yield. The protected β-amino α-hydroxy acid **8** was coupled with the methyl ester of L-leucine using the mixed anhydride method, to afford dipeptide **9** (95% yield) which was finally deprotected in a two-step reaction sequence with 70% overall yield. (−)-Bestatin hydrochloride **10**, obtained in the eight-step sequence (31% overall yield), was shown to be identical in optical rotation ($[\alpha]_D = -14$) and ^1H and ^{13}C NMR data with the product reported in the literature.[14]

While carrying out the retrosynthetic analysis for (−)-bestatin we realized that the use of phenylnitromethane **11** instead of 1-nitro-2-phenylethane **5** opens a route to another biologically important synthetic target, namely (2*S*,3*R*)-3-*tert*-butoxycarbonylamino-2-hydroxy-3-phenylpropionic acid, a side-chain of Taxotere®.[16]

Condensation of glyoxalate **6** with phenylnitromethane **11**, catalyzed with activated aluminum oxide, carried out at 25°C, afforded an 87:13 mixture of two diastereoisomeric *syn*/*anti* nitroalcohols in 97% yield (Scheme 3).

The configuration of the major diastereoisomer (2*S*,3*R*)-**12** was established by X-ray analysis. Nitroalcohol **12**, isolated by column chromatography in 81% yield, was catalytically reduced and then protected with di-*tert*-butyl dicarbonate to give the appropriate *N*-Boc derivative in 93% overall yield. Subsequent acetylation (95% yield) and hydrolysis of the ester functionality (89% yield) furnished the amino acid **13**, which was esterified with diazomethane to afford the methyl ester **14** in 90% yield. Finally, the acetyl group was removed to give the ester **15** in 90% yield. Both compounds **14** and **15** had optical rotations and spectral properties identical to those reported in the literature.[16]

In conclusion, we have demonstrated that enantiomerically pure β-amino α-hydroxy acids can be readily synthesized by transformation of nitroalcohols obtained from (1*R*)-8-phenylmenthyl glyoxylate **6** via nitroaldol reactions. (−)-Bestatin and the Taxotere® side-chain were successfully synthesized in overall yields of 31 and 52%, respectively.

Acknowledgements

This work was supported by the State Committee for Scientific Research (Project PBZ 605/T09/1999).

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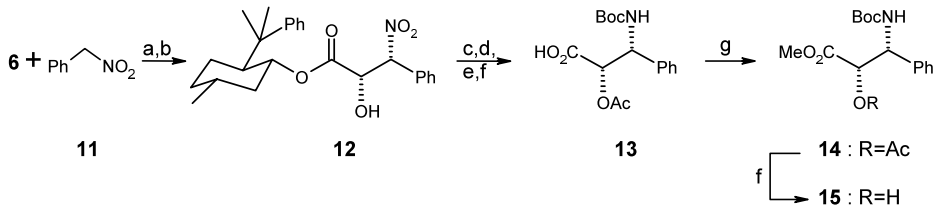

Scheme 3. *Reagents and conditions*: (a) activated Al_2O_3, dry THF, rt, 1 h; (b) column chromatography; (c) H_2, catalytic Raney-Ni, MeOH, rt, 12 h; (d) $(Boc)_2O$, satd aq. $NaHCO_3$, AcOEt, rt, 2 h; (e) Ac_2O, Et_3N, Et_2O, rt, 20 min; (f) MeONa (1 equiv.), MeOH, rt, 24 h; (g) CH_2N_2, Et_2O, rt, 16 h.

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