Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 4865–4870

Regioselective Baeyer–Villiger lactonization of 2-substituted pyrrolidin-4-one. Synthesis of statine

Meng-Yang Chang,[a,*] Yung-Hua Kung[a] and Shui-Tein Chen[b]

[a]*Department of Applied Chemistry, National University of Kaohsiung, Kaohsiung 811, Taiwan*
[b]*Institute of Biological Chemistry, Academia Sinica, Nankang, Taipei 115, Taiwan*

Received 22 March 2006; revised 28 April 2006; accepted 8 May 2006
Available online 30 May 2006

Abstract—Nine 2-substituted pyrrolidin-4-ones **4a**–**i** were obtained via a series of functional group transformation of known prolinol **5** by facile six kinds of methodologies. The target structure of 1,3-amino alcohols **2a**–**i** was constructed in the regioselective Baeyer–Villiger lactonization of ketones **4a**–**i** and reduction of the resulting 4-substituted tetrahydro-1,3-oxazin-6-ones **3a**–**i**. A new and straightforward synthesis of (3*S*,4*S*)-statine (**6**) has been established starting from *trans*-(2*S*,4*R*)-4-hydroxyproline (**1**).

1. Introduction

Based on the structural framework of *trans*-(2*S*,4*R*)-4-hydroxyproline, it possesses three functional groups that can be easily modified, and these are 1-amino, 2-carboxylate and 4-hydroxy groups.[1] The skeleton represents the significant feature for producing a series of different carbon framework such as monocycles (pyrrole,[2a] pyrrolidine,[2b,c,l] piperidine,[2d] and azanucleoside[2e]), fused or bridged bicycles (pyrrolizidine[2f] or azabicycles[2g,h,m]), polycycles,[2i–k,n] macrocycle,[2o] etc. using a facile and efficient modification technique.

Recently we have introduced a new and straightforward approach to the bicyclic 7-azabicyclo[2.2.1]heptane,[2m] hexahydro-1*H*-indol-3-one[2n] and pyrrolophane[2o] skeleton via an intramolecular basic alkylation, acidic aldol condensation, and a ring-closing metathesis reaction of the 2-substituted pyrrolidin-4-one framework employing *trans*-(2*S*,4*R*)-4-hydroxyproline as the starting material. To explore a novel synthetic application of *trans*-4-(2*S*,4*R*)-hydroxyproline (**1**), synthetic studies toward 1,3-amino alcohols and (3*S*,4*S*)-statine were further investigated.

Amino alcohols are an important class of compounds. In addition to their use as auxiliaries and ligands, the biological activities associated with this functional group have attracted intense interests among synthetic and medicinal chemists in these compounds.[3] Accordingly, several useful synthetic strategies have been developed for the synthesis of amino alcohols with the stereo- and regiochemical controls.[3] Here we want to use the key regiospecific Baeyer–Villiger lactonization reaction in the preparation of various 1,3-aminoalcohols. By the key reaction, synthesis of (3*S*,4*S*)-statine has been established.

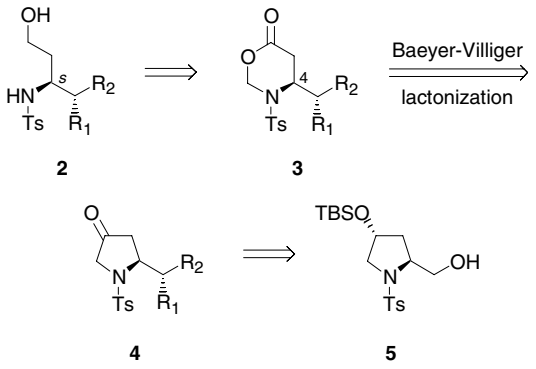
2. Results and discussion

The retrosynthetic analysis of various 1,3-aminoalcohols **2** was shown in Scheme 1. We want to examine the synthesis of 4-substituted tetrahydro-1,3-oxazin-6-ones **3** employing the key regiospecific Baeyer–Villiger lactonization of 2-substituted pyrrolidin-4-one framework **4** and apply the route to the synthesis of 1,3-amino alcohols **2**. Thus, different 2-substituents on the pyrrolidin-4-one framework **4** could be synthesized by a series of functional group transformations of prolinol **5**.

We reported the approach toward prolinol **5** from *trans*-(2*S*,4*R*)-4-hydroxyproline (**1**) via the following four-step reactions: (i) esterification with thionyl chloride and methanol, (ii) tosylation with *p*-toluenesulfonyl chloride and triethylamine, (iii) silylation with *t*-butyldimethylsilyl

Keywords: *trans*-(2*S*,4*R*)-4-Hydroxyproline; Prolinol; 1,3-Amino alcohol; Regioselectivity; Baeyer–Villiger lactonization; Tetrahydro-1,3-oxazin-6-one; Statine.
* Corresponding author. Tel.: +886 7 591 9464; fax: +886 7 591 9348; e-mail: mychang@nuk.edu.tw

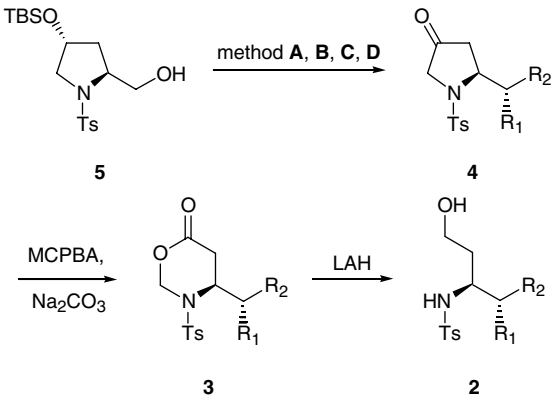
0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.05.027



Scheme 1.

chloride and imidazole, and (iv) reduction of the resulting ester with sodium borohydride in the presence of lithium chloride. Thus prolinol **5** was obtained in 90% overall yield with only once purification.[2m,n,o]

As shown in Scheme 2, synthesis of nine 2-substituted pyrrolidin-4-ones **4a–i** involving four straightforward synthetic strategies A–D was described as follows: (method A) compound **4a** was provided via benzylation of compound **5** with benzyl bromide and sodium hydride in tetrahydrofuran at rt, desilylation with tetrabutylammonium fluoride in tetrahydrofuran and followed by subsequent oxidation of the corresponding secondary alcohol with pyridinium chlorochromate and Celite in dichloromethane at rt; (method B) compounds **4b–d** were provided via Swern oxidation of compound **5** with oxalyl chloride and dimethylsulfoxide in dichloromethane at −78 °C, Grignard addition with three different arylmagnesium bromide reagents (C_6H_5, 2-$MeOC_6H_4$, and 3,4-$CH_2O_2C_6H_3$) in tetrahydrofuran at −78 °C, acid-mediated dehydroxylation and desilylation with boron trifluoride etherate and triethylsilane in dichloromethane at 0 °C, and pyridinium chlorochromate mediated oxidation; (method C) compounds **4e–f** were provided via oxidation of compound **5** with ruthenium trichloride and sodium periodate in co-solvent (water/acetonitrile/carbon tetrachloride = 2/2/3) at rt, double Grignard addition of the resulting acid with two arylmagnesium bromide reagents (C_6H_5 and 3,4-$CH_2O_2C_6H_3$), dehydroxylation and desilylation, and oxidation; (method D) compounds **4g–i** were provided via the above similar methodologies employing Swern oxidation, Grignard addition with aryl or alkylmagnesium bromide reagents (phenyl, *n*-propyl, and allyl), benzylation, desilylation and followed by subsequent oxidation. Thus, nine compounds **4a–i** were provided by six standard protocols from prolinol **5** in modest yields (see Table 1).



method A
(1) NaH, BnBr; (2) TBAF then PCC
(**a**) R_1=H, R_2=OBn
method B
(1) Swern ox.; (2) R_2MgBr; (3) Et_3SiH, BF_3-OEt_2; (4) PCC
(**b**) R_1=H, R_2=C_6H_5 (**c**) R_1=H, R_2=2-$CH_3OC_6H_4$
(**d**) R_1=H, R_2=3,4-$CH_2O_2C_6H_3$
method C
(1) $RuCl_3$, $NaIO_4$; 2) R_2MgBr; 3) Et_3SiH, BF_3-OEt_2; 4) PCC
(**e**) R_1=R_2=C_6H_5 (**f**) R_1=R_2=3,4-$CH_2O_2C_6H_3$
method D
(1) Swern ox.; (2) R_2MgBr; (3) NaH, BnBr; (4) TBAF then PCC
(**g**) R_1=OBn, R_2=C_6H_5 (**h**) R_1=OBn, R_2=$CH_2CH_2CH_3$
(**i**) R_1=OBn, R_2=CH_2CH=CH_2

Scheme 2.

For the diastereoselective Grignard addition of aldehyde (from Swern oxidation of prolinol **5**) in the methods B and D, we found that sole secondary alcohols were generated by the arylmagnesium bromide reagents. When the aldehyde was treated with alkylmagnesium bromide reagents, two stereoisomers were provided in 2:1 and 3:1 ratios. The difference between aryl and alkylmagnesium bromide reagents was not further investigated. The relative configurations on the structure of ketones **4g–i** with two contiguous stereocenters are based upon the ^1H NMR spectral data from the literature.[4] As shown in Diagram 1, the stereochemical structure of ketone **4i** was determined by single-crystal X-ray analysis.[5]

With the above results and enough amounts of ketones **4a–i**, Baeyer–Villiger lactonization reaction was next examined. While poring over the related literature of regioselective Baeyer–Villiger reaction, we found that Young and co-workers had developed the copper(II) acetate-mediated ring expansion of 4-ketoprolines with *m*-chloroperoxybenzoic acid in 1,2-dichloroethane and followed by acidic hydrolysis in acetone to afford the single stereoisomers of aspartic acid analogs with no racemization in modest yield.[6] How is the regioselective Beayer–Villiger process initiated? According to literature reports, the most likely explanation would be that

Table 1. The yields of compounds **2a–i**, **3a–i** and **4a–i**

Entry	**4**, yield (%)[a,b]	**3**, yield (%)[a,c]	**2**, yield (%)[a,d]
1	**4a**, 76	**3a**, 89	**2a**, 89
2	**4b**, 52	**3b**, 83	**2b**, 83
3	**4c**, 51	**3c**, 80	**2c**, 80
4	**4d**, 48	**3d**, 83	**2d**, 85
5	**4e**, 45	**3e**, 80	**2e**, 85
6	**4f**, 40	**3f**, 82	**2f**, 86
7	**4g**, 42	**3g**, 73	**2g**, 82
8	**4h**, 20	**3h**, 75	**2h**, 84
9	**4i**, 24	**3i**, 78	**2i**, 86

[a] The product was adjusted based on isolated products.
[b] All yields were based on compound **5** confirmed.
[c] All yields were based on compounds **4a–i** confirmed.
[d] All yields were based on compounds **3a–i** confirmed.

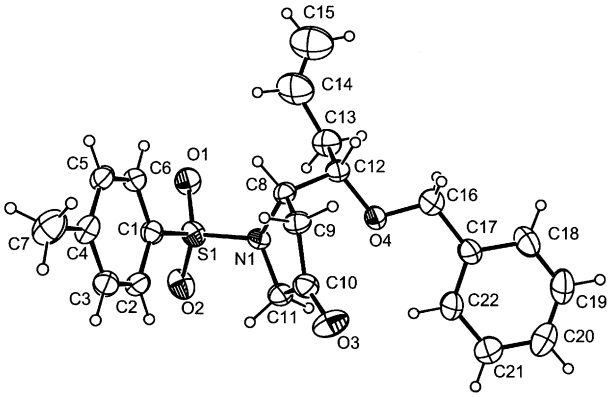


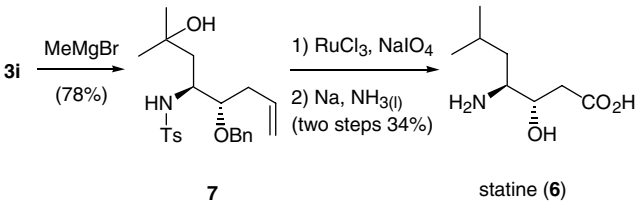
Diagram 1. X-ray crystallography of compound **4i**.

it is controlled by involvement of the nitrogen lone pair on substituted pyrrolidin-4-ones.[6]

According to the unique synthetic reports, model substrate **4a** was first treated with the combination of copper(II) acetate and *m*-chloroperoxybenzoic acid. The resulting product **3a** was provided in moderate (53%) yield. In order to increase higher yields, other commercial available reagents and reaction conditions were tested. When the reaction was treated with the combination of sodium carbonate and *m*-chloroperoxybenzoic acid, the yield of compound **3a** was increased to 89% yield without other regioisomers. For the synthetic efficiency of 4-substituted tetrahydro-1,3-oxazin-6-ones **3a**–**i**,[7] sodium carbonate is better than copper(II) acetate in our cases during the overall regiospecific Baeyer–Villiger ring expansion process. The difference between sodium carbonate and copper(II) acetate was not clear. This combination could provide an easy and straightforward standard operation protocol with better yields than the literature reports. Although the synthetic applications of regioselective Beayer–Villiger process have been developed by Young's group, the present work is complementary to existing methodology.

Among the NMR data of nine oxazinones **3a**–**i** at room temperature, compounds **3a** and **3c** exhibited a mixture of rotamers in nearly 1:1 ratio. This phenomenon is usually expected in the related acylproline derivatives and so it was not surprising that it occurred with the related oxzainone analogs.[6,8] Reduction of compounds **3a**–**i** with lithium aluminum hydride in tetrahydrofuran was yielded different substituents 1,3-aminoalcohols **2a**–**i** in 80–89 % yields.[9] These experimental results are summarized in Table 1.

To deserve to be mentioned, compound **2h** was an analog of C2-homo-dihydroceramide with apoptotic activities in HL-60 human leukemia cells.[10a,b] Therefore, the present methodology provided a new approach to the preparation of sphingolipid family derivatives.[10d,e] Based on the experimental simplicity, the preparation of compound **3i** was also conducted in a multigram scale (10 mmol) with 65% yield from ketone **4i**. With these results in hand, the next focus was to examine the synthesis of (3*S*,4*S*)-statine (**6**).



Scheme 3.

Statine, [(3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid], a naturally occurring amino acid of nonproteogenic origin, is a key component in the pepstain family of aspartic protease inhibitors.[11] Statine and its structurally modified analogs have been widely used in the design of peptide mimics as potential inhibitors of rennin and other aspartic proteases.[12] Statine has attached a lot interest because of its potential use in the treatment of hypertension and congestive heart failure. Considerable efforts have been devoted to the total synthesis of (3*S*,4*S*)-statine and its analogs.[13]

As shown in Scheme 3, treatment of compound **3i** with excess methylmagnesium bromide was obtained tertiary alcohol **7**. Oxidation of alcohol **7** with ruthenium oxide was yielded benzyl acid as major product accompanied with a trace amount of benzoyl acid isomer. Finally, statine (**6**) was accomplished by subsequent reduction with sodium and liquid ammonia under the Birch process (desulfonation, debenzylation/debenzoylation and dehydroxylation).[13k,14]

3. Conclusion

In summary, we develop a straightforward approach to the 4-substituted tetrahydro-1,3-oxazin-6-one skeleton based on the regiospecific Baeyer–Villiger ring expansion reaction as the key step and apply this route to synthesize statine. For the application and investigation of *trans*-4-(2*S*,4*R*)-hydroxyproline, synthetic study toward acyclic aminoalcohol framework has not been explored. We are currently studying the scope of this process as well as additional applications of this approach to the synthesis of various potential biological activities compounds using *trans*-4-(2*S*,4*R*)-hydroxyproline as the starting material.

Acknowledgements

The authors would like to thank the National Science Council (NSC 94-2113-M-390-001) of the Republic of China for financial support. We also thank Professor Michael Y. Chiang (National Sun Yat-Sen University) for structural determination of compound **4i** by X-ray diffraction analysis.

References and notes

1. For a review, see Remuzon, P. *Tetrahedron* **1996**, *52*, 13803.

2. For related references, see (a) Azizian, J.; Karimi, A. R.; Kazemizadeh, Z.; Mohammadi, A. A.; Mohammadizadeh, M. R. *J. Org. Chem.* **2005**, *70*, 1471; (b) Del Valle, J. R.; Goodman, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 1600; (c) Gonzalez, T.; Abad, O.; Santano, M. C.; Minguillon, C. *Synthesis* **2004**, 1171; (d) Honda, T.; Takahashi, R.; Namiki, H. *J. Org. Chem.* **2005**, *70*, 499; (e) Qiu, X.-L.; Qing, F.-L. *Bioorg. Med. Chem.* **2005**, *13*, 277; (f) Pandey, G.; Lakshmaiah, G. *Synlett* **1994**, 277; (g) Han, G.; LaPorte, M. G.; Folmer, J. J.; Werner, K. M.; Weinreb, S. M. *J. Org. Chem.* **2000**, *65*, 6293; (h) Houghton, P. G.; Humphrey, G. R.; Kennedy, D. J.; Roberts, D. C.; Wright, S. H. B. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1421; (i) Tamura, O.; Yanagimachi, T.; Ishibashi, H. *Tetrahedron: Asymmetry* **2003**, *14*, 3033; (j) Hu, H.; Zhai, H. *Synlett* **2003**, 2129; (k) Breslin, H. J.; Kukla, M. J.; Ludovici, D. W.; Mohrbaeher, R.; Ho, W.; Miranda, M.; Rodgers, J. D.; Hitchens, T. K.; Leo, G.; Gauthier, D. A.; Chih, Y. H.; Scott, M. K.; De Clercq, E.; Pauwels, R.; Andries, K.; Janssen, M. A. C.; Janssen, P. A. J. *J. Med. Chem.* **1995**, *38*, 771; (l) Chang, M. Y.; Chen, S. T.; Chang, N. C. *Heterocycles* **2003**, *60*, 1203; (m) Chang, M. Y.; Chen, H. P. *Heterocycles* **2005**, *65*, 1705; (n) Chang, M. Y.; Chen, H. P.; Lin, C. Y.; Pai, C. L. *Heterocycles* **2005**, *60*, 1999; (o) Chang, M. Y.; Pai, C. L.; Chen, H. P. *Tetrahedron Lett.* **2005**, *46*, 7705.

3. (a) Ager, D.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835; (b) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, *25*, 117; (c) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517; (d) Juaristi, E. *Enantioselective Synthesis of β-amino Acids*; Wiley-VCH: New York, 1997; (e) Bodmann, K.; Bug, T.; Steinbeisser, S.; Kreuder, R.; Reiser, O. *Tetrahedron Lett.* **2006**, *47*, 2061; (f) Huguenot, F.; Brigaud, T. *J. Org. Chem.* **2006**, *71*, 2159; (g) Fustero, S.; Jimenez, D.; Sanz-Cervera, J. F.; Sanchez-Rosello, M.; Esteban, E.; Simon-Fuentes, A. *Org. Lett.* **2005**, *7*, 3433.

4. (a) Ohtake, N.; Jona, H.; Okada, S.; Okamoto, O.; Imai, Y.; Ushijima, R.; Nakagawa, S. *Tetrahedron: Asymmetry* **1997**, *8*, 2939; (b) Dinh, T. Q.; Smith, C. D.; Armstrong, R. W. *J. Org. Chem.* **1997**, *62*, 790; (c) Dinh, T. Q.; Du, X.; Smith, C. D.; Armstrong, R. W. *J. Org. Chem.* **1997**, *62*, 6773; (d) Na, H. S.; Choi, J.; Yu, J.; Shin, K. J.; Yoo, K. H.; Kim, D. J.; Park, S. W. *Heterocycles* **1998**, *48*, 2365; (e) Armstrong, J. D.; Keller, J. L.; Lynch, J.; Liu, T.; Hartner, F. W.; Ohtake, N.; Okada, S.; Imai, Y.; Okamoto, O.; Ushijima, R.; Nakagawa, S. *Tetrahedron Lett.* **1997**, *38*, 3203.

5. Single-crystal X-ray diagram: crystal of compound **4i** was grown by slow diffusion of ethyl acetate into a solution of compound **4i** in dichloromethane to yield colorless prism. The compound crystallizes in the orthorhombic crystal system. space group P 212121(# 19), $a = 96.0657(12)$ Å, $b = 8.0954(16)$ Å, $c = 42.812(9)$ Å, $V = 2102.2(7)$ Å^3, $Z = 8$, $d_{calcd} = 2.524$ mg/m^3, absorption coefficient 0.362 mm^{-1}, $F(000) = 1696$, 2θ range (1.90–26.00°).

6. (a) Burtin, G.; Corringer, P. J.; Hitchcock, P. B.; Young, D. W. *Tetrahedron Lett.* **1999**, *40*, 4275; (b) Burtin, G.; Corringer, P. J.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3451.

7. A representative procedure of tetrahydro-1,3-oxazin-6-ones **3a**–**i** is as follows: a solution of ketones **4a**–**i** (0.3 mmol) in dichloromethane (2 mL) was added to a stirred solution of *m*-chloroperoxybenzoic acid (120 mg, 75%, 0.52 mmol) and sodium bicarbonate (85 mg, 0.8 mmol) in dichloromethane (10 mL). The reaction mixture was stirred at rt for 4 h. Saturated sodium carbonate solution (5 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/ethyl acetate = 3/1–1/1) afforded compounds **3a**–**i**. Representative data for compound **3e**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, $J = 8.0$ Hz, 2H), 7.37–7.24 (m, 12H), 5.67 (d, $J = 12.0$ Hz, 1H), 4.76 (dd, $J = 8.0$, 15.0 Hz, 1H), 4.69 (d, $J = 12.0$ Hz, 1H), 4.49 (d, $J = 8.0$ Hz, 1H), 2.62 (dd, $J = 7.0$, 17.0 Hz, 1H), 2.46 (dd, $J = 7.0$, 17.0 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.47, 145.02, 139.37, 138.70, 135.01, 130.19 (2×), 129.43 (2×), 129.03 (2×), 128.74 (2×), 127.96 (2×), 127.86 (2×), 127.76, 127.17, 74.49, 55.15, 53.64, 32.14, 21.64; HRMS (ESI) *m*/*z* calcd for $C_{24}H_{24}NO_4S$ (M^++1) 422.1426, found 422.1428. For compound **3g**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, $J = 8.5$ Hz, 2H), 7.43–7.39 (m, 10H), 7.31 (d, $J = 8.0$ Hz, 2H), 5.86 (dd, $J = 0.5$, 12.0 Hz, 1H), 5.37 (d, $J = 12.0$ Hz, 1H), 5.14 (d, $J = 2.0$ Hz, 1H), 4.66 (d, $J = 11.0$ Hz, 1H), 4.52 (d, $J = 11.0$ Hz, 1H), 3.79 (ddd, $J = 2.0$, 7.0, 10.0 Hz, 1H), 3.10 (dd, $J = 11.0$, 16.5 Hz, 1H), 2.40 (s, 3H), 2.11 (dd, $J = 7.0$, 16.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.92, 144.91, 137.54, 136.92, 134.66, 130.14 (2×), 128.97 (2×), 128.58 (2×), 128.44, 128.02, 127.86 (2×), 127.70 (2×), 126.07 (2×), 83.29, 75.85, 72.20, 56.84, 27.45, 21.60; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{26}NO_5S$ (M^++1) 452.1532, found 452.1533. For compound **3i**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, $J = 8.5$ Hz, 2H), 7.38–7.28 (m, 7H), 5.97–5.89 (m, 1H), 5.80 (d, $J = 11.5$ Hz, 1H), 5.37 (d, $J = 11.5$ Hz, 1H), 5.23 (d, $J = 17.5$ Hz, 1H), 5.16 (dd, $J = 1.0$, 10.0 Hz, 1H), 4.71 (d, $J = 11.5$ Hz, 1H), 4.44 (d, $J = 11.5$ Hz, 1H), 3.94 (td, $J = 3.5$, 8.0 Hz, 1H), 3.63 (td, $J = 3.5$, 6.0 Hz, 1H), 2.59–2.49 (m, 2H), 2.45 (dd, $J = 8.0$, 17.0 Hz, 1H), 2.43 (s, 3H), 2.31 (dd, $J = 8.0$, 17.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.96, 145.03, 137.21, 134.97, 133.84, 130.18 (2×), 128.62 (2×), 128.18 (3×), 127.88 (2×), 118.40, 80.95, 76.44, 72.82, 52.87, 33.77, 30.52, 21.65; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{26}NO_5S$ (M^++1) 416.1532, found 416.1533.

8. (a) Hanessian, S.; Sumi, K.; Vanasse, V. *Synlett* **1992**, 33; (b) Hondrelis, J.; Lonergan, G.; Voliotis, S.; Matsoukas, J. *Tetrahedron* **1990**, *46*, 565.

9. A representative procedure of compounds **2a**–**i** is as follows: Excess lithium aluminum hydride (38 mg, 1.0 mmol) was added to a solution of compounds **3a**–**i** (0.1 mmol) in tetrahydrofuran (10 mL). The reaction mixture was stirred at rt for 10 h. Saturated sodium bicarbonate solution (1 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/ethyl acetate = 1/1) afforded compounds **2a**–**i**. Representative data for compound **2a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, $J = 8.5$ Hz, 2H), 7.34–7.30 (m, 3H), 7.27–7.20 (m, 4H), 4.98 (d, $J = 8.5$ Hz, 1H), 4.40 (d, $J = 12.0$ Hz, 1H), 4.31 (d, $J = 12.0$ Hz, 1H), 3.88–3.83 (m, 1H), 3.68–3.64 (m, 1H), 3.60 (br s, 1H), 3.58–3.55 (m, 1H), 3.29 (dd, $J = 1.8$, 9.5 Hz, 1H), 3.13 (dd, $J = 4.5$, 9.5 Hz, 1H), 2.42 (s, 3H), 1.75–1.68 (m, 1H), 0.90–0.85 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.43, 137.42, 136.70, 129.68 (2×), 128.50 (2×), 127.96, 127.72 (2×), 126.98 (2×), 73.25, 71.26, 58.62, 50.52, 35.11, 21.54; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{24}NO_4S$ (M^++1) 350.1426, found 350.1428. For compound **2b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, $J = 8.5$ Hz, 2H), 7.31–7.23 (m, 3H), 7.18 (d, $J = 7.0$ Hz, 2H), 6.95 (d, $J = 7.0$ Hz, 2H), 4.84 (d, $J = 8.0$ Hz, 1H), 3.83 (td, $J = 3.0$, 11.5 Hz, 1H),

3.70–3.64 (m, 1H), 3.62–3.58 (m, 1H), 2.66 (dd, $J = 5.5$, 13.0 Hz, 1H), 2.60 (dd, $J = 7.0$, 14.0 Hz, 1H), 2.43 (s, 3H), 2.10 (br s, 1H), 1.80–1.74 (m, 1H), 1.48–1.41 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.38, 137.45, 136.74, 129.73 (2×), 129.41 (2×), 128.53 (2×), 126.93 (2×), 126.64, 58.91, 52.38, 41.60, 36.61, 21.52; HRMS (ESI) m/z calcd for $C_{17}H_{22}NO_3S$ (M^++1) 320.1320, found 320.1322. For compound **2d**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, $J = 8.0$ Hz, 2H), 7.25 (d, $J = 8.0$ Hz, 2H), 6.59 (d, $J = 7.5$ Hz, 1H), 6.39 (d, $J = 7.5$ Hz, 1H), 6.38 (s, 1H), 5.90 (d, $J = 5.0$ Hz, 2H), 4.85 (br s, 1H), 3.85 (td, $J = 3.0$, 11.5 Hz, 1H), 3.68–3.58 (m, 2H), 2.55–2.51 (m, 2H), 2.43 (s, 3H), 2.07 (br s, 1H), 1.82–1.76 (m, 1H), 1.49–1.43 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.55, 146.18, 143.33, 137.38, 130.53, 129.58 (2×), 126.91 (2×), 122.36, 109.52, 108.21, 100.86, 58.82, 52.63, 41.38, 37.03, 21.49; HRMS (ESI) m/z calcd for $C_{18}H_{22}NO_5S$ (M^++1) 364.1219, found 364.1221. For compound **2e**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, $J = 8.0$ Hz, 2H), 7.28–7.04 (m, 12H), 4.56 ($J = 8.5$ Hz, 1H), 4.34 (ddd, $J = 3.0$, 8.5, 17.0 Hz, 1H), 3.90 (d, $J = 8.5$ Hz, 1H), 3.87 (td, $J = 4.5$, 9.5 Hz, 1H), 3.67 (dt, $J = 4.5$, 9.5 Hz, 1H), 2.42 (s, 3H), 2.05–1.98 (m, 1H), 1.65 (br s, 1H), 1.50–1.44 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.16, 140.81, 140.34, 137.45, 129.63 (2×), 128.81 (2×), 128.78 (2×), 128.55 (2×), 128.05 (2×), 127.05, 126.87 (2×), 126.58, 58.70, 56.08, 54.16, 35.52, 21.52; HRMS (ESI) m/z calcd for $C_{23}H_{26}NO_3S$ (M^++1) 396.1633, found 396.1635. For compound **2f**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, $J = 8.0$ Hz, 2H), 7.19 (d, $J = 8.0$ Hz, 2H), 6.69 (d, $J = 8.0$ Hz, 1H), 6.60 (s, 2H), 6.59 (d, $J = 8.0$ Hz, 1H), 6.50 (s, 2H), 6.40 (s, 1H), 5.92 (s, 2H), 5.85 (dd, $J = 0.5$, 18.5 Hz, 2H), 4.58 ($J = 8.0$ Hz, 1H), 4.13 (ddd, $J = 3.0$, 8.5, 17.0 Hz, 1H), 3.89 (m, 1H), 3.70 (d, $J = 9.0$ Hz, 1H), 2.42 (s, 3H), 2.06–1.99 (m, 1H), 1.61 (br s, 1H), 1.49–1.42 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.93, 147.58, 146.52, 146.23, 143.15, 137.35, 134.94, 134.39, 129.41 (2×), 126.79 (2×), 121.59, 121.19, 108.63, 108.44, 108.12, 108.06, 101.08, 100.89, 58.62, 55.73, 54.54, 35.94, 21.52; HRMS (ESI) m/z calcd for $C_{25}H_{26}NO_7S$ (M^++1) 484.1433, found 484.1436. For compound **2g**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, $J = 8.0$ Hz, 2H), 7.44–7.38 (m, 2H), 7.33–7.23 (m, 8H), 7.00 (d, $J = 7.0$ Hz, 2H), 4.90 (d, $J = 9.5$ Hz, 1H), 4.53 (d, $J = 11.5$ Hz, 1H), 4.01 (d, $J = 11.5$ Hz, 1H), 4.00 (d, $J = 3.0$ Hz, 1H), 3.82 (td, $J = 4.0$, 12.0 Hz, 1H), 3.61–3.56 (m, 1H), 3.54–3.48 (m, 1H), 2.44 (s, 3H), 1.63–1.50 (m, 2H), 1.55 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.52, 137.56, 137.27, 137.14, 129.74 (2×), 128.74 (2×), 128.64 (2×), 128.16, 128.05, 128.02 (2×), 127.12 (2×), 126.62 (2×), 81.64, 70.91, 58.24, 55.39, 30.13, 21.59; HRMS (ESI) m/z calcd for $C_{24}H_{28}NO_4S$ (M^++1) 426.1739, found 426.1738. For compound **2h**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, $J = 8.5$ Hz, 2H), 7.38–7.24 (m, 7H), 4.95 (d, $J = 9.0$ Hz, 1H), 4.51 (d, $J = 11.0$ Hz, 1H), 4.39 (d, $J = 11.0$ Hz, 1H), 3.82 (td, $J = 3.5$, 9.0, 12.0 Hz, 1H), 3.60 (dt, $J = 4.5$, 12.0 Hz, 1H), 3.57–3.53 (m, 1H), 3.25 (td, $J = 1.5$, 6.5 Hz, 1H), 2.42 (s, 3H), 2.05 (br s, 1H), 1.78–1.65 (m, 2H), 1.27–1.11 (m, 2H), 1.03–0.89 (m, 2H), 0.63 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.40, 138.04, 137.80, 129.61 (2×), 128.41 (2×), 127.90 (3×), 127.00 (2×), 80.79, 72.53, 58.67, 52.62, 36.01, 32.62, 21.45, 18.97, 13.83; HRMS (ESI) m/z calcd for $C_{21}H_{30}NO_4S$ (M^++1) 392.1896, found 392.1897. For compound **2i**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, $J = 8.5$ Hz, 2H), 7.35–7.25 (m, 7H), 5.59–5.51 (m, 1H), 4.98 (d, $J = 10.0$ Hz, 1H), 4.88–4.84 (m, 2H), 4.57 (d, $J = 11.5$ Hz, 1H), 4.40 (d, $J = 11.5$ Hz, 1H), 3.80–3.74 (m, 1H), 3.60–3.54 (m, 2H), 3.35 (td, $J = 2.0$, 7.5 Hz, 1H), 2.42 (s, 3H), 2.34 (dd, $J = 5.0$, 7.0 Hz, 1H), 2.17–2.11 (m, 1H), 1.92–1.86 (m, 1H), 1.78–1.71 (m, 1H), 1.69–1.62 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.48, 138.10, 137.63, 133.92, 129.64 (2×), 128.46 (2×), 127.99, 127.95 (2×), 127.04 (2×), 117.90, 80.26, 72.53, 58.72, 52.80, 35.97, 35.06, 21.52; HRMS (ESI) m/z calcd for $C_{21}H_{28}NO_4S$ (M^++1) 390.1739, found 390.1742.

10. (a) Shikata, K.; Niiro, H.; Azuma, H.; Tachibana, T.; Ogino, K. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 613; (b) Shikata, K.; Niiro, H.; Azuma, H.; Ogino, K.; Tachibana, T. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2723; (c) de Jonge, S.; Lamote, I.; Venkataraman, K.; Boldin, S. A.; Hillaert, U.; Rozenski, J.; Hendrix, C.; Busson, R.; de Keukeleire, D.; van Calenbergh, S.; Futerman, A. H.; Herdewijn, P. *J. Org. Chem.* **2002**, *67*, 988; (d) Liao, J.; Tao, J.; Lin, G.; Liu, D. *Tetrahedron* **2005**, *61*, 4715; (e) Howell, A. R.; So, R. C.; Richardson, S. K. *Tetrahedron* **2004**, *60*, 11327.
11. (a) Umezawa, U.; Aoyagi, T.; Morishima, H.; Matzusaki, M.; Hamada, H.; Takeuchi, T. *J. Antibiot.* **1970**, *23*, 259; (b) Rich, D. H. *J. Med. Chem.* **1985**, *28*, 263; For a review, see: (c) Rich, D. H. In *Proteinase Inhibitors*; Barrett, A. J., Salvesen, G., Eds.; Elsevier: New York, 1986; p 179.
12. (a) Takemoto, Y.; Matsumoto, T.; Ito, Y.; Terashima, S. *Chem. Pharm. Bull.* **1991**, *39*, 2425; (b) Holladay, M. W.; Salituro, F. G.; Rich, D. H. *J. Med. Chem.* **1987**, *30*, 374; (c) Schaschke, N. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 855.
13. For recent synthetic studied for statine, see: (a) Ko, S. Y. *J. Org. Chem.* **2002**, *67*, 2689; (b) Yoo, D.; Oh, J. S.; Kim, Y. G. *Org. Lett.* **2002**, *4*, 1213; (c) Kwon, S. J.; Ko, S. Y. *Tetrahedron Lett.* **2002**, *43*, 639; (d) Pesenti, C.; Bravo, P.; Corradi, E.; Frigerio, M.; Meille, S. V.; Panzeri, W.; Viani, F.; Zanda, M. *J. Org. Chem.* **2001**, *66*, 5637, and cited references therein; (e) Andres, J. M.; Pedrosa, R.; Perez, A.; Perez-Encabo, A. *Tetrahedron* **2001**, *57*, 8521; (f) Alemany, C.; Bach, J.; Farras, J.; Garcia, J. *Org. Lett.* **1999**, *1*, 1831; (g) Reddy, G. V.; Rao, G. V.; Iyengar, D. S. *Tetrahedron Lett.* **1999**, *40*, 775; (h) Sengupta, S.; Sarma, D. S. *Tetrahedron: Asymmetry* **1999**, *10*, 4633; (i) Lee, K. Y.; Kim, Y. H.; Park, M. S.; Oh, C. Y.; Ham, W. H. *J. Org. Chem.* **1999**, *64*, 9450; (j) Kazmaier, U.; Krebs, A. *Tetrahedron Lett.* **1999**, *40*, 479; (k) Aoyagi, Y.; Williams, R. M. *Tetrahedron* **1998**, *54*, 10419; (l) Hoffman, R. V.; Tao, J. *J. Org. Chem.* **1997**, *62*, 2292, and cited references therein; (m) Gennari, C.; Moresca, D.; Vulpetti, A.; Pain, G. *Tetrahedron* **1997**, *53*, 5593; (n) Nebois, P.; Greene, A. E. *J. Org. Chem.* **1996**, *61*, 5210; (o) Ma, D.; Ma, J.; Ding, W.; Dai, L. *Tetrahedron: Asymmetry* **1996**, *7*, 2365; (p) Gennari, C.; Pain, G.; Moresca, D. *J. Org. Chem.* **1995**, *60*, 6248; (q) Williams, R. M.; Colson, P.-J.; Zhai, W. *Tetrahedron Lett.* **1994**, *35*, 9371; (r) d'Aniello, F.; Mann, A.; Matii, D.; Taddei, M. *J. Org. Chem.* **1994**, *59*, 3762; (s) Lu, Y.; Miet, C.; Kunesch, N.; Poisson, J. E. *Tetrahedron: Asymmetry* **1993**, *4*, 893; (t) Kessler, H.; Schudok, M. *Synthesis* **1990**, 457; (u) Ohta, T.; Shiokawa, S.; Sakamoto, R.; Nozoe, S. *Tetrahedron Lett.* **1990**, *31*, 7329; (v) Misiti, D.; Zappia, G. *Tetrahedron Lett.* **1990**, *31*, 7359; (w) Reetz, M. T.; Drewes, M. W.; Matthews, B. R.; Lennick, K. *J. Chem. Soc., Chem. Commun.* **1989**, 1474; (x) Midland, M. M.; Afonso, M. M. *J. Am. Chem. Soc.* **1989**, *111*, 4368; (y) Kunieda, T.; Ishizuka, T.; Higuchi, T.; Hirobe, M. *J. Org. Chem.* **1988**, *53*, 3381; (z) Nishi, T.; Kitamura, M.; Ohkuma, T.; Noyori, R. *Tetrahedron Lett.* **1988**, *29*, 6327.
14. A representative procedure of statine (**6**) is as follows: Compound **7** (42 mg, 0.1 mmol) was dissolved in carbon tetrachloride (2 mL), acetonitrile (2 mL) and water (3 mL) with vigorous stirring. Then sodium periodate (105 mg, 0.5 mmol) and ruthenium(III) chloride hydrate (5 mg) were added. The reaction was stopped after 6 h, diluting with dichloromethane (20 mL) and the organic layer was

separated. The aqueous layer was then extracted with dichloromethane (2×10 mL) and the organic layers were filtered on a Celite pad, collected and evaporated to afford the crude products under reduced pressure. Without further purification, sodium (20 mg, 0.9 mmol) was added to a solution of the resulting mixture products in liquid ammonia (5 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h then it was warmed to −30 °C for 1 h. Water (5 mL) was poured into the reaction mixture and evaporated to afford the residue under reduced pressure. Water (10 mL) was poured into the residue and extracted with diethyl ether (3×20 mL). Aqueous hydrochloric acid solution (37%, 1 mL) was added to the water layer at rt. Then the water was evaporated under reduced pressure to give the crude hydrochloride salt. The crude salt was purified by ion exchange chromatography (Dowex 50WX-100, eluted with 0.1 N ammonium water to give the corresponding statine (**6**) (34%, 7.5 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.03 (dt, $J = 5.0$, 7.5 Hz, 1H), 3.30 (dt, $J = 6.0$, 8.0 Hz, 1H), 2.57 (dd, $J = 5.0$, 15.5 Hz, 1H), 2.43 (dd, $J = 7.5$, 15.5 Hz, 1H), 1.76–1.67 (m, 1H), 1.57–1.48 (m, 2H), 0.95 (d, $J = 7.0$ Hz, 3H), 0.94 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.63, 68.04, 53.63, 41.20, 38.16, 23.63, 21.85, 20.65. The NMR spectral data of statine (**6**) were in accordance with those reported in the literature.[13a]