Tetrahedron Letters, Vol.32, No.3, pp 401-404, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

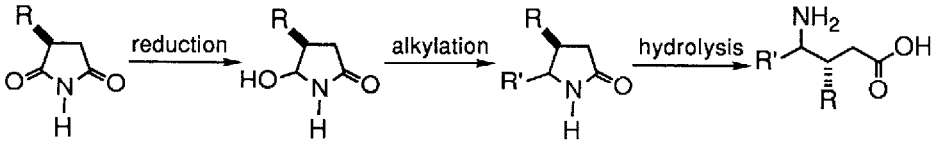
SYNTHESIS OF STATINE FROM (*S*)-MALIC ACID; STEREOCONTROL VIA RADICAL CYCLIZATION

Wim-Jan Koot, Roel van Ginkel, Mirko Kranenburg, Henk Hiemstra*,
Saskia Louwrier, Marinus J. Moolenaar, and W. Nico Speckamp*
Department of Organic Chemistry, University of Amsterdam,
Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands

Summary: Highly stereoselective syntheses of enantiomerically pure γ-amino acids statine and 4-*epi*-statine from (*S*)-malic acid are described by using, respectively, an intramolecular α-acylamino radical reaction and an intermolecular *N*-acyliminium allylsilane coupling.

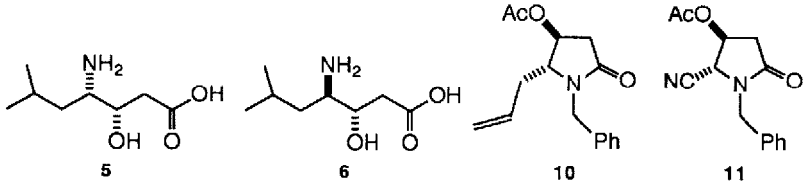
γ-Amino acids **4** can be synthesized from succinimides **1** (Scheme 1) in a general fashion through a sequence of reactions including reduction to hydroxylactam **2**, alkylation (via an *N*-acyliminium intermediate) to **3**, and hydrolytic ring opening.[1] The recent upsurge of interest in the synthesis of β-hydroxy-γ-amino acids, i.e. statine **5** and analogues,[2,3] prompted us to investigate the sequence of Scheme 1 for the case of R = OH. At the outset of this work we deemed two aspects of our approach particularly attractive, namely (1) the ready availability of enantiomerically pure **1** (R = OH)[4] from inexpensive (*S*)-malic acid and (2) the stereocontrolling effect of the 4-oxy substituent in **2** on the alkylation process at C-5.[5]

Scheme 1



1 **2** **3** **4**

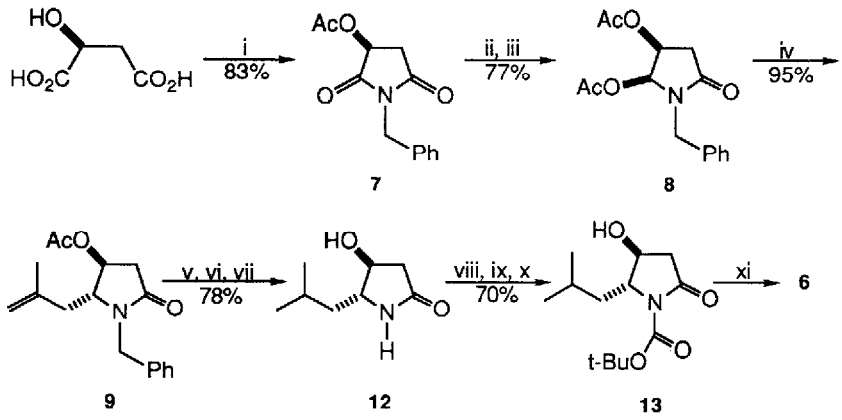
This communication reports our preliminary results, including highly stereoselective syntheses of statine **5** and 4-*epi*-statine **6** via, respectively, an intramolecular radical and an intermolecular cationic alkylation process **2** to **3** (Scheme 1). After completion of our present work a strategically related approach to statine analogues was published, albeit with racemic materials.[6]



5 **6** **10** **11**

Successive treatment of (*S*)-malic acid with acetyl chloride, benzylamine and acetyl chloride[4,7] (see Scheme 2) gave imide **7** as a crystalline solid [mp 58-60 °C, $[\alpha]^{20}_D$ -42° (*c* 1.18, MeOH)] with a benzyl protecting group on nitrogen. Early experiments with the *N*-unsubstituted imide (**1**, R = OAc) were thwarted by the water solubility of the subsequent intermediates. The optical purity of **7** was related to that of separately synthesized and well-known[8] 1-benzyl-3-hydroxysuccinimide and was found to be >95%. Regioselective reduction of **7**[4,7] gave a mixture of two stereoisomeric hydroxylactams from which the pure *cis*-product crystallized [mp 138.5-140.5 °C, $[\alpha]^{20}_D$ -79° (*c* 1.0, EtOH)] in 85% yield. Standard acetylation yielded key intermediate **8** [mp 92-93.5 °C, $[\alpha]^{20}_D$ -51° (*c* 1.0, $CHCl_3$)].

Scheme 2[a]

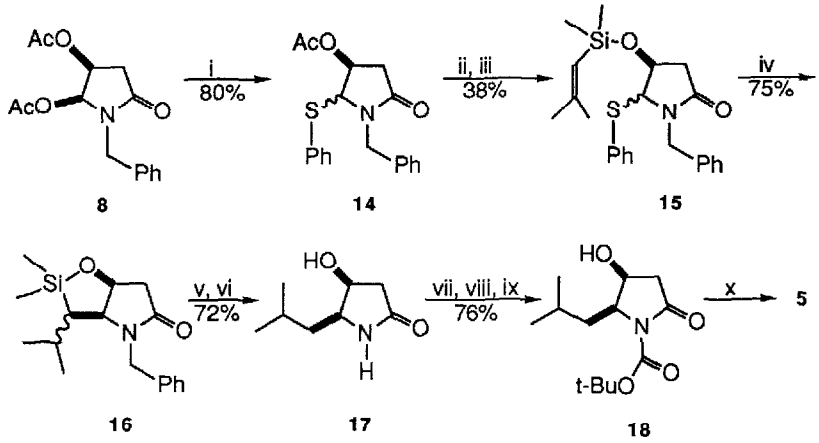


[a] Reagents, conditions: i, AcCl (excess), reflux, 2 h; $PhCH_2NH_2$, THF, 4 h; AcCl (excess), reflux, 18 h; ii, $NaBH_4$ (6 equiv), EtOH, -20 °C, 15 min; iii, Ac_2O, DMAP, py, 4 h; iv. $BF_3{\cdot}Et_2O$ (2 equiv), $CH_2{=}C(Me)CH_2SiMe_3$ (3 equiv), CH_2Cl_2, 18 h; v, MeOH, MeONa (cat), 2 h; vi, H_2, 5% Pd/C (cat), EtOH, 2 h; vii, Na, NH_3, -78 °C, 1.5 h; viii, TBDMSCl, imidazole, DMF, 18 h; ix, $(BOC)_2O$, Et_3N, DMAP, CH_2Cl_2, 18 h; x, KF, Bu_4NF, THF, 2 h; xi, ref 12.

We first investigated acid-induced alkylation at C-5 of diacetate **8**, proceeding via an *N*-acyliminium intermediate.[5,6,9] Thus, treatment of **8** with methallyltrimethylsilane[10] in the presence of $BF_3{\cdot}Et_2O$ yielded an 11:1 mixture of **9** and its *cis*-isomer. One recrystallization provided pure **9** in 85% yield as a crystalline solid [mp 78.5-79 °C, $[\alpha]^{20}_D$ +28° (*c* 0.79, $CHCl_3$)]. With $TiCl_4$ as Lewis acid a 9:1 *trans/cis* ratio was obtained also in near quantitative yield. Lower selectivity was found for less sterically-demanding electrophiles. Allyltrimethylsilane and trimethylsilyl cyanide gave upon reaction with **8** in the presence of $BF_3{\cdot}Et_2O$ ratio's of 71:29 and 67:33, respectively, the major products being **10** and **11**. The stereochemistry of the products followed from the ^1H NMR vicinal coupling constants between H-4 and H-5. These values were 5-6 Hz in the *cis*-series and <1 Hz in the *trans*-series.[5] Starting from **9**, deacetylation, hydrogenation and removal of the benzyl group gave lactam **12** as a crystalline solid. Despite several attempts **12** failed to give clean ring opening through acidic hydrolysis.[11] We therefore resorted to the preparation of **13**, which has been transformed to **6** by Johnson and coworkers.[12] Silylation,

introduction of the *tert*-butoxycarbonyl function and desilylation provided **13**, which showed properties [mp 117.5-118.5 °C, $[\alpha]^{20}_D$ -62° (*c* 1.56, MeOH)], very similar to the literature values [mp 118-120 °C, $[\alpha]^{20}_D$ -62.0° (*c* 1.49, MeOH)].[12]

Scheme 3[a]



[a] Reagents, conditions: i, PhSH (2 equiv), toluene, *p*-TsOH (cat), reflux, Dean Stark, 4 Å mol sieves, 18 h; ii, EtOH, EtONa (cat) 1.5 h; iii, $Me_2C{=}CHSi(Me)_2NMe_2$ (see text), THF, pentane, 4 h; iv, Bu_3SnH (1.5 equiv), AIBN (cat), benzene, reflux, 6 h; v, Bu_4NF (1.1 M in THF, 1 equiv.), CsF (2 equiv), THF, 18h; vi, Na, NH_3, -78 °C, 1.5 h; vii, TBDMSCl, imidazole, DMF, 18 h; viii, $(BOC)_2O$, Et_3N, DMAP, CH_2Cl_2, 18 h; ix, KF, Bu_4NF, THF, 2 h; x, ref. 12.

To access the corresponding *cis*-series we explored the radical cyclization methodology developed by Stork.[13,14] To this end bisacetate **8** was transformed to thioether **14**, in order to eventually generate a radical intermediate at C-5 (Scheme 3).[15] Deacetylation of **14** was followed by treatment of the resulting alcohol with the required aminosilane to give cyclization precursor **15**.[16] This aminosilane was readily prepared from $Me_2C{=}CHMgBr$ and chlorodimethyl(dimethylamino)silane. Radical cyclization readily took place under the usual conditions. A 3:2 mixture of isopropyl stereoisomers **16** was obtained as the only detectable products, indicating that the radical cyclization proceeded entirely 5-*exo* with respect to regiochemistry and completely *cis* as far as the ring junction is concerned. These assignments were confirmed by desilylation and debenzylation of **16** producing a single isomer **17**, clearly different from **12**. Because acidic hydrolysis was not possible, **17** was converted into **18**, which exhibited properties (mp 90.5-93 °C, $[\alpha]^{20}_D$ +60° (*c* 1.19, MeOH), similar to literature data (mp 92-94 °C, $[\alpha]^{20}_D$ +61.4° (*c* 1.77, MeOH). This completed a formal synthesis of natural statine.[12]

In conclusion we have shown, that (*S*)-malic acid is a useful starting material for the synthesis of statine and its C-4 epimer. The methodology used should be applicable to the synthesis of various statine analogues as well.

Acknowledgment: We thank C. Kruk and his staff for their help in obtaining and interpreting the NMR spectra. This investigation was supported by the Dutch Foundation for Chemical Research (SON) with financial support from the Dutch Organization for the Advancement of Pure Research (NWO).

References and Notes

1. H. Hiemstra, H. P. Fortgens, W. N. Speckamp, *Tetrahedron Lett.* **1984**, *25*, 3115; H. Hiemstra, W. J. Klaver, W. N. Speckamp, *J. Org. Chem.* **1984**, *49*, 1149; H. Hiemstra, W. J. Klaver, W. N. Speckamp, *Rec. Trav. Chim. Pays-Bas* **1986**, *105*, 299.
2. D. H. Rich, *J.Med.Chem.* **1985**, *28*, 263.
3. For recent syntheses of statine, see P. G. M. Wuts, S. R. Putt, *Synthesis* **1989**, 951; M. Sakaitani, Y. Ohfune, *J. Am. Chem. Soc.* **1990**, *112*, 1150; T. Nishi, Y. Morisawa, *Heterocycles* **1989**, *29*, 1835; M. M. Midland, M. M. Alfonso, *J. Am. Chem. Soc.* **1989**, *111*, 4368; M. T. Reetz, M. W. Drewes, B. R. Matthews, K. Lennick, *J. Chem. Soc., Chem. Commun.* **1989**, 1474; H. Yanagisawa, T. Kanazaki, T. Nishi, *Chem. Lett.* **1989**, 687; J. V. N. V. Prasad, D. H. Rich, *Tetrahedron Lett.* **1990**, *31*, 1803; Y. Takemoto, T. Matsumoto, Y. Ito, S. Terashima, *Tetrahedron Lett.* **1990**, *31*, 217; H. Takahata, K. Yamazaki, T. Takamatsu, T. Yamazaki, T. Momose, *J. Org. Chem.* **1990**, *55*, 3947; Y. Yamamoto, M. Schmid, *J. Chem. Soc., Chem. Commun.* **1989**, 1310; H. Kessler, M. Schudok, *Synthesis* **1990**, 457; G. Bringmann, G. Künkel, T. Geuder, *Synlett.* **1990**, 253.
4. A. R. Chamberlin, J. Y. L. Chung, *J. Am. Chem. Soc.* **1983**, *105*, 3653.
5. M. Thaning, L.-G. Wistrand, *Acta Chem. Scand.* **1989**, *43*, 290; *J. Org. Chem.* **1990**, *55*, 1406.
6. A. Bernardi, F. Micheli, D. Potenza, C. Scolastico, R. Villa, *Tetrahedron Lett.* **1990**, *31*, 4949.
7. For a similar procedure, see W. J. Klaver, H. Hiemstra, W. N. Speckamp, *J. Am. Chem. Soc.* **1989**, *111*, 2588.
8. O. Lutz, *J. Prakt. Chem.* **1904**, *70*, 1; K. L. Bhat, D. M. Flanagan, M. M. Joullié, *Synth. Commun.* **1985**, *15*, 587; K. Tamazawa, H. Arima, T. Kojima, Y. Isomura, M. Okada, S. Fujita, T. Furuya, T. Takenaka, O. Inagaki, M. Terai, *J. Med. Chem.* **1986**, *29*, 2504.
9. For an early example, see G. A. Kraus, K. Neuenschwander, *J. Chem. Soc., Chem. Commun.* **1982**, 134.
10. S. A. Carr, W. P. Weber, *J. Org. Chem.* **1985**, *50*, 2782.
11. T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3287.
12. R. G. Andrew, R. E. Conrow, J. D. Elliott, W. S. Johnson, S. Ramazani, *Tetrahedron Lett.* **1987**, *28*, 6535.
13. For a brief review, see G. Stork, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 149.
14. For recent applications, see G. Stork, R. Mah, *Tetrahedron Lett.* **1989**, *30*, 3609; K. Tamao, K. Maeda, T. Yamaguchi, Y. Ito, *J. Am. Chem. Soc.* **1989**, *111*, 4984; A. Kurek-Tyrlik, J. Wicha, A. Zarecki, G. Snatzke, *J. Org. Chem.* **1990**, *55*, 3484.
15. For this radical type, see J.-K. Choi, D. J. Hart, *Tetrahedron* **1985**, *41*, 3959; J. M. Dener, D. J. Hart, *Tetrahedron* **1988**, *44*, 7037; A. G. M. Barrett, D. Pilipauskas, *J. Org. Chem.* **1990**, *55*, 5194.
16. G. Stork, P. F. Keitz, *Tetrahedron Lett.* **1989**, *30*, 6981.

(Received in UK 25 October 1990)