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An organocatalytic route to the synthesis of lactone moiety of compactin and mevinolin

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ABSTRACT

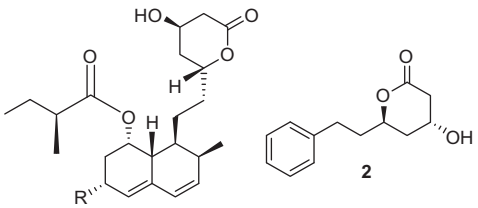
An efficient synthesis of lactone moiety of compactin has been achieved. The stereogenic centers were generated by means of iterative proline-catalyzed sequential α-aminoxylation and Horner–Wadsworth–Emmons (HWE) olefination of aldehydes.

Compactin (**1a**) and mevinolin (**1b**) (Fig. 1) are potent competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the enzyme involved in the rate-limiting step of cholesterol biosynthesis in humans.[1] Their ability to lower blood cholesterol levels, especially plasma low-density lipoprotein (LDL)[2] cholesterol in human beings, is important for the mitigation of arteriosclerosis. The unique structural features of this class of compounds called 'mevinic acids', and their potential applications as hypocholesterolemic agents have aroused a great interest among synthetic organic chemists, resulting in an onslaught of activity directed at the synthesis of these challenging target molecules.

Synthetic studies in mevinic acids can be grouped into three primary sections: (1) total synthesis, (2) synthesis of the decalin units, and (3) synthesis of β-hydroxy-δ-lactone moiety. The key structural feature of these molecule is chiral β-hydroxy-δ-lactone moiety which in its open acid form closely mimics mevalonic acid, a crucial intermediate in the biosynthesis of cholesterol,[3] hence several research groups worldwide have focused much attention on the stereocontrolled synthesis of the δ-lactone moiety (**2**).[4]

In recent years, the area of organocatalysis has emerged as a promising strategy and as an alternative to expensive protein catalysis and toxic metal catalysis,[5] thus becoming a fundamental tool in the catalysis toolbox available for asymmetric synthesis.[6] Recently, we developed an iterative approach to the enantiopure synthesis of *syn*/*anti*-1,3-polyols, which are based on proline-catalyzed sequential α-aminoxylation and Horner–Wadsworth–Emmons (HWE) olefination of aldehydes.[7]

As a part of our research programme aimed at developing enantioselective synthesis of biologically active natural products,[8] we became interested in devising a simple and concise route to lactone moiety (**2**) of compactin/mevinolin via our recently developed methodology[7] for enantiopure *syn*/*anti*-1,3-polyols using organocatalysis. Herein we report our successful endeavors toward the total synthesis of **2** employing proline-catalyzed sequential α-aminoxylation and Horner–Wadsworth–Emmons (HWE) olefination of aldehyde as the key step. As shown in Scheme 1, the synthesis of target compound **2** began with the aldehyde **3**, which was subjected to sequential α-aminoxylation using L-proline as a catalyst followed by HWE-olefination reaction



(+)-Compactin (**1a** R = H)
(+)-Mevinolin (**1b** R = Me)

Figure 1. Structures of (+)-compactin (1a), (+)-mevinolin (**1b**) and β-hydroxy-δ-lactone moiety (**2**).

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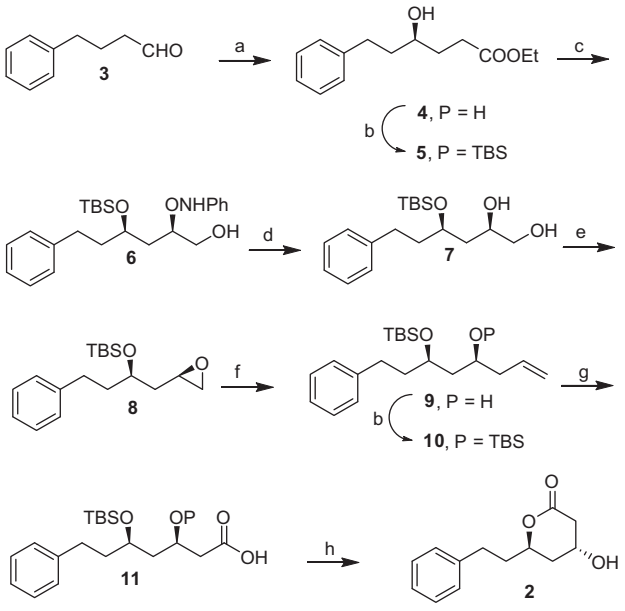

Scheme 1. Reagents and conditions: (a) (i) nitrosobenzene, L-proline, DMSO; $(EtO)2P(O)CH_2COOEt$, DBU, LiCl, CH_3CN; (ii) H_2/Pd–C, EtOAc, 8 h, 65%; (b) TBSCl, imidazole, DMF, overnight, 91%; (c) (i) DIBAL-*H*, DCM, −78 °C; (ii) L-proline, nitrosobenzene, DMSO; (iii) $NaBH_4$, MeOH, 0.5 h, 70% (over three steps); (d) H_2/Pd–C, EtOAc, 8 h, 92%; (e) (i) TsCl, Bu_2SnO, Et_3N, 2 h; (ii) K_2CO_3, MeOH, rt, 1 h, 82% (over two steps); (f) vinylmagnesium bromide, 1 h, 81%; (g) TBSCl, imidazole, DMF, overnight, 88%; (h) $RuCl_3{\cdot}3H_2O$, $NaIO_4$, CCl_4–H_2O–CH_3CN = 4:1:1, 5 h, 44%, (i) cat. HCl, MeOH, overnight, 79%.

to furnish *O*-amino-substituted allylic alcohol which was directly subjected to hydrogenation conditions using catalytic amounts of Pd/C to furnish the γ-hydroxy ester **4**[9] in good yield and in >97% ee.[10]

The free hydroxy group of γ-hydroxy ester **4** was protected as TBS ether to furnish compound **5** in 91% yield. The Dibal-H reduction of ester **5** at −78 °C furnished aldehyde which was subjected to α-aminoxylation catalyzed by L-proline, followed by in situ reduction using $NaBH_4$ to furnish the *O*-amino-substituted diol **6** in overall 70% yield and 92% de (determined from the ^1H and ^{13}C NMR spectral analysis). Compound **6** was subjected to reductive hydrogenation conditions to afford the diol **7**[11] in 92% yield, which on selective monotosylation and base treatment furnished epoxide **8** in 82% yield. Epoxide **8** was opened with vinylmagnesium bromide to get the homoallylic alcohol **9** in 81% yield, which on protection of free hydroxy as TBS ether afforded compound **10** in 88% yield. Olefinic oxidation of **10** using $RuCl_3{\cdot}3H_2O$ and $NaIO_4$ furnished the acid **11**, which was cyclized under acidic conditions (catalytic amount of HCl in MeOH) to give the lactone **2** in good yield. Mp: 106–107 °C; lit.[4e] mp: 108 °C, $[\alpha]_D^{25}$ +68.69 (*c* 2.0, $CHCl_3$); lit.[4h] $[\alpha]_D^{25}$ +68.88 (*c* 2.29, $CHCl_3$). The physical and spectroscopic data of **2** were in full agreement with the literature data.[4h,e]

In conclusion a short and efficient asymmetric synthesis of lactone moiety of compactin has been achieved by using a practical and efficient organocatalytic strategy amenable to both *syn* and *anti*-1,3-diol with high degree of enantio- and diastereoselectivities. The desired stereocenters can simply be achieved by changing the catalyst. Further application of this methodology to the syntheses of biologically active compounds containing 1,3-polyols is currently underway in our laboratory.

Acknowledgments

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References and notes

1. (a) Endo, A. *J. Med. Chem.* **1985**, *28*, 401–405; (b) Vega, L.; Crundy, S. *J. Am. Med. Assoc.* **1987**, *257*, 33–38. and references cited therein.
2. Goldstein, J. L.; Brown, M. S. *Annu. Rev. Biochem.* **1977**, *46*, 897–930.
3. (a) Stokker, G. E.; Hoffman, W. F.; Alberts, A. W.; Cragoe, E. J., Jr.; Deana, A. A.; Gilfilan, J. L.; Huff, J. W.; Novello, F. C.; Prugh, J. D.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* **1985**, *28*, 347–358; (b) Hoffman, W. F.; Alberts, A. W.; Cragoe, E. J., Jr.; Deana, A. A.; Evans, B. E.; Gilfilan, J. L.; Gould, N. P.; Huff, J. W.; Novello, F. C.; Prugh, J. D.; Rittle, K. E.; Smith, R. L.; Stokker, G. E.; Willard, A. K. *J. Med. Chem.* **1986**, *29*, 170–181; (c) Yadav, V. K.; Kapoor, K. K. *Ind. J. Chem.* **1996**, *35B*, 1125–1143.
4. For the synthesis of arylethyl or (*E*)-arylethenyl substituted β-hydroxy-δ-lactone, see: (a) Sabitha, G.; Sudhakar, K.; Srinivas, C.; Yadav, J. S. *Synthesis* **2007**, 705–708; (b) Bouzbouz, S.; Cossy, J. *Tetrahedron Lett.* **2000**, *41*, 3363–3366; (c) Kiyooka, S.-I.; Yamaguchi, T.; Maeda, H.; Kira, H.; Hena, M. A.; Horiike, M. *Tetrahedron Lett.* **1997**, *38*, 3553–3556; (d) Honda, T.; Ono, S.; Mizutani, H.; Hallinan, K. O. *Tetrahedron: Asymmetry* **1997**, *8*, 181–184; (e) Solladie, G.; Bauder, C.; Rossi, L. *J. Org. Chem.* **1995**, *60*, 7774–7777; (f) Minami, T.; Takahashi, K.; Hiyama, T. *Tetrahedron Lett.* **1993**, *34*, 513–516; (g) Bonini, C.; Pucci, P.; Viggiani, L. *J. Org. Chem.* **1991**, *56*, 4050–4052; (h) Roth, B. D.; Roark, W. H. *Tetrahedron Lett.* **1988**, *29*, 1255–1258; (i) Lynch, J. E.; Volante, R. P.; Wattley, R. V.; Shinkai, I. *Tetrahedron Lett.* **1987**, *28*, 1385–1387; (j) Guindon, Y.; Yoakim, C.; Bernstein, M. A.; Morton, H. E. *Tetrahedron Lett.* **1985**, *26*, 1185–1188; (k) Prasad, K.; Repic, O. *Tetrahedron Lett.* **1984**, *25*, 2435–2438; (l) Majewski, M.; Clive, D. L. J.; Anderson, P. C. *Tetrahedron Lett.* **1984**, *25*, 2101–2104.
5. Dalko, P. I. *Enantioselective Organocatalysis: Reactions and Experimental Procedures*; Wiley-VCH: Weinheim, 2007.
6. MacMillian, D. W. C. *Nature* **2008**, *455*, 304–308.
7. Kondekar, N. B.; Kumar, P. *Org. Lett.* **2009**, *11*, 2611–2614.
8. (a) Kumar, P.; Naidu, S. V.; Gupta, P. *J. Org. Chem.* **2005**, *70*, 2843–2846; (b) Kumar, P.; Naidu, S. V. *J. Org. Chem.* **2005**, *70*, 4207–4210; (c) Gupta, P.; Naidu, S. V.; Kumar, P. *Tetrahedron Lett.* **2005**, *46*, 6571–6573; (d) Kumar, P.; Gupta, P.; Naidu, S. V. *Chem. Eur. J.* **2006**, *12*, 1397–1402; (e) Kumar, P.; Naidu, S. V. *J. Org. Chem.* **2006**, *71*, 3935–3941; (f) Gupta, P.; Kumar, P. *Eur. J. Org. Chem.* **2008**, 1195–1202; (g) Pandey, S. K.; Pandey, M.; Kumar, P. *Tetrahedron Lett.* **2008**, *49*, 3297–3299; (h) Chowdhury, P. S.; Gupta, P.; Kumar, P. *Tetrahedron Lett.* **2009**, *50*, 7018–7020.
9. Spectral data of **4**: $[\alpha]_D^{25}$ −12.25 (*c* 1, $CHCl_3$). IR (neat, cm−1): ν_{max} 3486, 1730, 1602, 1491, 1023, 931. ^1H NMR (200 MHz, $CDCl_3$): δ 1.32 (t, *J* = 7.2 Hz, 3H), 1.86–1.71 (m, 2H), 1.87–2.00 (m, 2H), 2. 52 (t, *J* = 7.1 Hz, 2H), 2.67–2.95 (m, 2H), 3.66–3.76 (m, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 7.40–7.23 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): 14.1, 27.9, 30.8, 32.2, 39.1, 60.5, 70.6, 125.8, 128.4, 128.5, 141.9, 174.2. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.20; H, 8.46.
10. The enantiomeric excess was determined by converting the alcohol **4** into the Mosher ester and analyzing the ^{19}F spectrum.
11. Spectral data of **7**: $[\alpha]_D^{25}$ −20.8 (*c* 0.14, $CHCl_3$). IR ($CHCl_3$, cm^{-1}): ν_{max} 3412, 3018, 2938, 1612, 1513, 1248, 1215. ^1H NMR (200 MHz, $CDCl_3$): δ 0.10 (s, 6H), 0.91 (s, 9H), 1.25–1.28 (m, 2H), 1.54–1.62 (m, 1H), 1.67–1.71 (m, 1H), 1.78–1.89 (m, 2H), 2.58–2.68 (m, 2H), 3.47 (dd, *J* = 4.9, 11.1 Hz, 1H), 3.61 (dd, *J* = 7.5, 11.1 Hz, 1H), 3.85–4.08 (m, 2H), 7.09–7.31 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ −4.7, −4.1, 17.9, 25.8, 31.1, 38.9, 39.5, 67.0, 71.1, 72.0, 122.8, 125.9, 128.2, 128.4, 141.9. Anal. Calcd for $C_{18}H_{32}O_3Si$: C, 66.62; H, 9.94. Found: C, 66.56; H, 9.88.