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Tetrahedron Letters 46 (2005) 8579–8581
Tetrahedron Letters

Total synthesis of beauveriolide I

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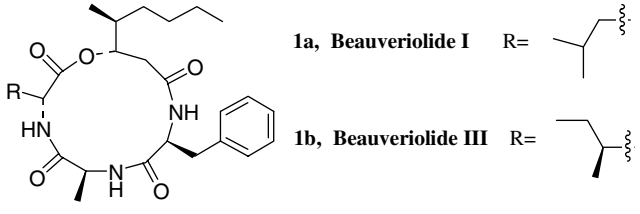
Received 18 July 2005; revised 29 September 2005; accepted 30 September 2005
Available online 14 October 2005

Abstract—The first total synthesis of beauveriolide I (**1a**), a selective ACAT inhibitor, is described. The key steps in this synthesis involved a diastereoselective aldol condensation sequence and a macrocyclization.

Beauveriolide I (**1a**) was first isolated in 1975 from the mycelium of the strain *Beauveria* sp.[1] Its structure was elucidated as *cyclo*-[(3*S*,4*S*)-3-hydroxy-4-methyl-octanoyl-L-phenylalanyl]-D-leu-Cine, a member of the cyclodepsipeptide family,[2] by spectral analyses and chemical degradation.

Recent studies show beauveriolide I (**1a**) and III (**1b**) can cause a reduction in both number and size of cytosolic lipid droplets in macrophages without any cytotoxic effect on macrophages.[3,4] Among these beauveriolides, beauveriolide I (**1a**) and III (**1b**) are the most potent inhibitors of lipid droplets formation in mouse macrophages. They inhibit Acyl-CoA: cholesterol acyltransferase (ACAT) activity specifically, resulting in the blockage of cholesterol ester (CE) synthesis, leading to a reduction of lipid droplets in macrophages.[5]



Intrigued by beauveriolides' bioactivity and interested in their SAR studies, we began the synthetic study and achieved the first total synthesis of beauveriolide I (**1a**). The retrosynthetic analysis is shown in Figure 1.

As the macrocyclization can be achieved by either amide bond or ester bond formation, the major endeavor is the synthesis of the fragment **2** [(3*S*,4*S*)-3-hydroxy-4-methyloctanic acid], which is a common intermediate in beauveriolide I (**1a**), III (**1b**) and other beauveriolides.[6]

Diastereoselective aldol condensation has been utilized for the synthesis of compound (**2**). Reaction of 3-benzyloxypropionaldehyde[7] and chiral imide (**5**)[8] under Crimmins' condition[9] furnished *syn* aldol (**6a**)[10] in excellent yield and diastereoselectivity. Installation of TBDMS protecting group followed by reduction with $LiBH_4$ gave alcohol (**7**)[11]. Alcohol (**7**) was oxidized under Swern

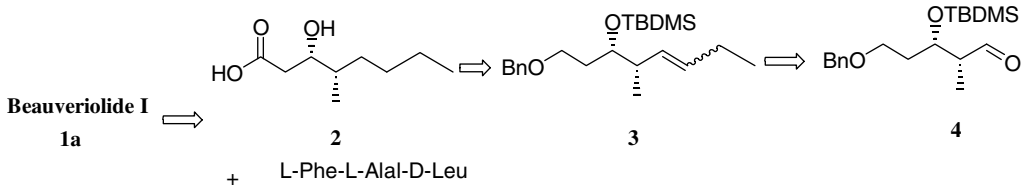


Figure 1. Retrosynthetic analysis of beauveriolide I.

Keywords: ACAT inhibitor; Beauveriolide I; Total synthesis.
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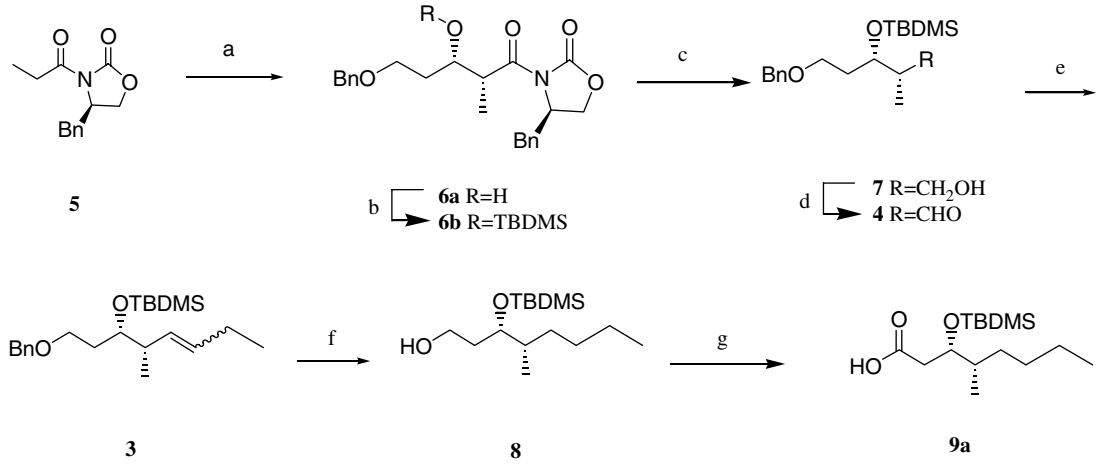
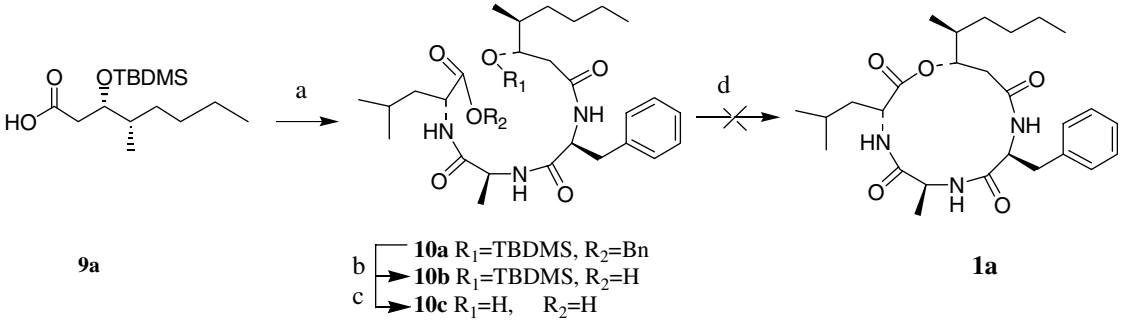
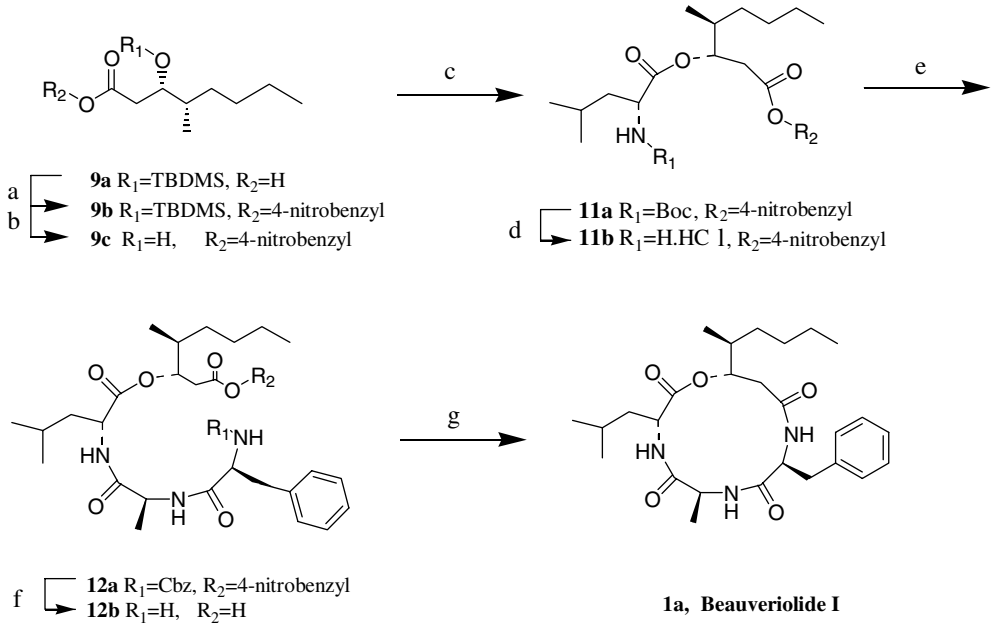
doi:10.1016/j.tetlet.2005.09.188



Scheme 1. Reagents and conditions: (a) 3-benzyloxypropionaldehyde, $TiCl_4$, DIPEA, NMP, CH_2Cl_2, −5 °C to rt, 3.5 h, 97%; (b) TBDMSCl, imidazole, DMF, rt, 30 h, 79%; (c) 2 M $LiBH_4$, H_2O, Et_2O, 0 °C to rt, 73%; (d) 1. $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 2. NEt_3, −78 °C to rt, 90%; (e) $[Ph_3PCH_2CH_2CH_3]Br$, 1.6 M *n*-BuLi, THF, rt, 2 h, 91%; (f) H_2, 10% Pd–C, EtOH, rt, 82%; (g) $NaIO_4$, $RuCl_3$(cat.), $CCl_4/CH_3CN/H_2O$ (v/v/v = 2/2/3), rt, 2 h, 78%.



Scheme 2. Reagents and conditions: (a) L-Phe-L-Ala-D-Leu-OBn, DCC, CH_2Cl_2, 0 °C to rt, 6 h; (b) H_2, 10% Pd–C, THF; (c) HOAc, heating; (d) 2-methyl-6-nitrobenzoic anhydride, DMAP, toluene.



Scheme 3. Reagents and conditions: (a) 4-nitrobenzyl bromide, DIPEA, DMF, rt, 7 h, 66%; (b) 65–75% HF-Py, THF, rt, 20 h, 70%; (c) DCC, DMAP(cat.), CH_2Cl_2, rt; (d) HCl/EtOAc, 4 h, 0 °C to rt; (e) *N*-Cbz-L-Phe-L-Ala, EDCI, DIPEA, HOSu(cat.), DMF, 0 °C to rt; (f) H_2, 10% Pd–C, THF/isopropanol (v/v = 1/2.5), rt; (g) BOP, DMAP, CH_3CN, rt, 68%.

condition,[12] and the resulting aldehyde (**4**) was allowed to react with propyltriphenylphosphonium bromide in the presence of *n*-BuLi to afford the corresponding olefinic isomers (**3**). Hydrogenation of the olefinic bond and removal of the benzyl protecting group were accomplished in one step over a catalytic amount of 10% Pd/C. Oxidation with $NaIO_4$ in the presence of $RuCl_3$[13] gave the desired acid (**9a**) in 89% yield (Scheme 1).

With the acid (**9a**) in hand, we tried to perform the macrocyclization by ester bond formation as shown in Scheme 2, where the suitably protected liner precursor **10a** was synthesized by coupling **9a** with L-Phe-L-Ala-D-Leu-OBn in the presence of DCC and DMPA, followed by hydrolysis to remove the TBDMS group. However, unfortunately, the desired compound **1a** could not be obtained under various conditions.[14]

We therefore selected the macrocyclization through amide bond formation. The synthetic sequence of compound **12a** was shown in Scheme 3. Protection of **9a** using 4-nitrobenzyl bromide in the presence of DIPEA in DMF yielded ester **9b**. Removal of the TBDMS protecting group by treating with HF-pyridine afforded compound **9c**,[15] which was coupled with *N*-Boc-D-Leu[16] by using DCC and catalytic amount of DMAP to give diester (**11a**). After removing the Boc group the corresponding protected tetradepsipeptide (**12a**) could be obtained by coupling with the *N*-Cbz-L-Phe-L-Ala[17] by using EDCI in the catalysis of HOSu. Subsequent reductive removal of the 4-nitrobenzyl group and the Cbz group gave the deprotected tetradepsipeptide (**12b**). The macrocyclization was performed successfully using BOP in acetonitrile under highly dilute conditions (5.3×10^{-3} mol/L)[18] to furnish beauveriolide I (**1a**)[19] in 68% yield. The structure of the product (**1a**) was confirmed by NMR and mass analysis for its structural data and rotation value matching well with the natural product.[2,20]

In conclusion, the first total synthesis of beauveriolide I (**1a**), an antibiotic from the culture broth of fungal *Beauveria* sp. FO-6979 was achieved. The synthesis is flexible and amenable to other analogues for SAR studies.

References and notes

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10. Analytical data of compound **6a**: pale-yellow oil, $[\alpha]_D^{25}$ −44.3 (*c* 0.3, $CHCl_3$). IR (film): 1778, 1695, 1387, 1209, 1109 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.24–1.28 (m, 2H), 1.29 (d, 3H, $J = 4.5$ Hz), 1.71–1.79 (m, 1H), 1.83–1.93 (m, 1H), 2.77 (dd, 1H, $J = 13.2$, 9.6 Hz), 3.25 (dd, 1H, $J = 13.2$, 3.3 Hz), 3.62–3.70 (m, 2H), 3.78–3.86 (m, 1H), 4.09–4.22 (complex, 3H), 4.52 (s, 2H), 4.64–4.72 (m, 1H), 7.19–7.38 (complex, 10H). FABMS: 398 ($M+H^+$), HR-FABMS: calcd for $C_{23}H_{28}NO_5$: ($M+H^+$), 398.1967, found: 398.1979.
11. Analytical data of compound **7**: $[\alpha]_D^{25}$ −8.5 (*c* 1.3, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 0.054 (s, 3H), 0.096 (s, 3H), 0.81 (d, 3H, $J = 7$ Hz), 0.88 (s, 9H), 1.78–1.84 (m, 2H), 1.98 (br, 1H), 3.50–3.56 (m, 3H), 3.69 (t, 1H, $J = 9.5$ Hz), 3.71–3.96 (m, 1H), 4.49 (q, 2H, $J = 11.5$ Hz), 7.26–7.36 (complex, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.8, −4.5, 12.4, 17.9, 25.8, 32.2, 39.9, 65.8, 67.1, 72.8, 73.0, 127.6, 127.7, 128.4, 138.4.
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15. Analytical data of compound **9c**: pale-yellow oil, ^1H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, 3H, $J = 6.4$ Hz), 0.92 (d, 3H, $J = 6.4$ Hz), 1.11–1.54 (m, 7H), 2.13 (br, 1H), 2.51–2.57 (complex, 2H), 3.98 (dt, 1H, $J = 4.4$, 8.4 Hz), 5.25 (s, 2H), 7.52 (d, 2H, $J = 8.4$ Hz), 8.23 (d, 2H, $J = 8.4$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.2, 22.9, 29.4, 32.4, 38.1, 38.8, 64.9, 71.3, 123.8, 128.4, 142.9, 147.7, 172.8. FABMS: 310.2 ($M+H^+$), HR-FABMS: calcd for $C_{16}H_{24}NO_5$: ($M+H^+$), 310.1654, found: 310.1664.
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19. Analytical data of compound **1a**: colorless needles, mp 242–244 °C (from MeOH); $[\alpha]_D^{25}$ −23.7 [*c* 0.7, $CHCl_3$–MeOH (4:1)]; IR (KBr): 3309, 1726, 1684, 1643, 1537 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$–CD_3OD = 4:1): δ 0.79 (t, 3H, $J = 6.5$ Hz), 0.80 (d, 3H, $J = 6.5$ Hz), 0.83 (d, 3H, $J = 6.0$ Hz), 0.85 (d, 3H, $J = 5.5$ Hz), 0.93–1.00 (m, 1H), 1.07–1.15 (m, 1H), 1.18 (d, 3H, $J = 7.0$ Hz, overlapped with 2H signal), 1.20–1.28 (m, 1H), 1.30–1.36 (m, 1H), 1.41–1.50 (m, 3H), 2.01–2.04 (m, 1H), 2.36 (dd, 1H, $J = 14.0$, 9.5 Hz), 2.42 (dd, 1H, $J = 14.0$, 5.5 Hz); 2.90 (dd, 1H, $J = 13.5$, 8.0 Hz), 2.99 (dd, 1H, $J = 13.5$, 8.5 Hz), 3.81 (dd, 1H, $J = 14.0$, 7.0 Hz), 4.16 (t, 1H, $J = 8.0$ Hz), 4.53–4.56 (m, 1H), 4.84–4.88 (m, 1H), 6.87–7.24 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$–CD_3OD = 4:1) δ 13.4, 14.5, 15.0, 21.7, 22.5, 24.5, 29.0, 30.3, 35.1, 35.3, 35.5, 40.8, 49.0, 52.3, 56.6, 76.0, 126.5, 128.1, 128.6, 136.0, 169.4, 171.0, 171.3, 171.8. FABMS: 488.3 ($M+H^+$), HR-FABMS: calcd for $C_{27}H_{42}N_3O_5$: ($M+H^+$), 488.3124, found 488.3147.
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