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Asymmetric total synthesis of antiviral agents (+)-sattazolin and (+)-sattabacin

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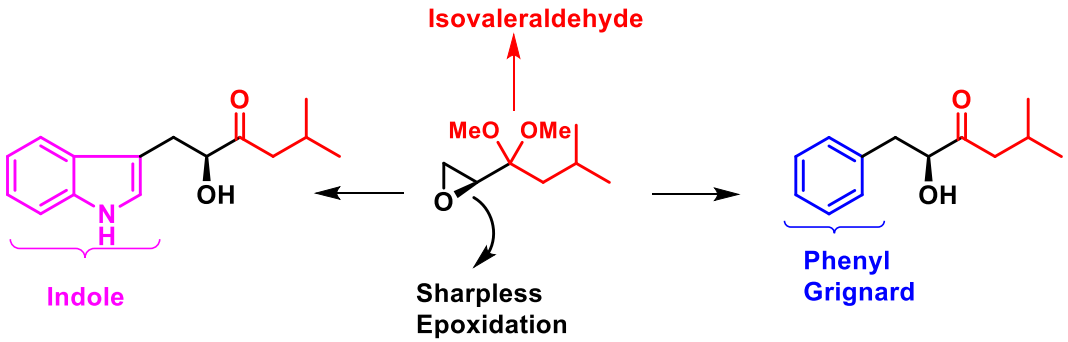
Abstract

The concise enantioselective total synthesis of antiviral agents (+)-sattazolin and (+)-sattabacin are described in six steps. This synthetic strategy started from commercially available isovaleraldehyde and the key reactions involved in this synthesis are Sharpless epoxidation, phenyl Grignard, Eu(III) catalyzed ring opening of chiral epoxide with indole.



Keywords: Sattazolin, sattabacin, natural products, antiviral, enantioselective

Introduction

The potent antiviral (herpes simplex virus) acyloin natural products namely sattazolin and sattabacin were isolated from soil bacteria *Bacillus sp*., by Satta *et al*. with ID_{50} values of 1.5 µg/mL and 3 µg/mL respectively[1]. The sattazolin selectively inhibits protein synthesis in Herpes virus-infected cells. The antiviral activity of sattabacin against VZV infections in human fibroblast cells, the median inhibitory concentrations (ID_{50}) of both acyclovir and penciclovir have showed to 3 and 4 µg/mL respectively. The ID_{50} value of sattabacin 12 µg/mL against VZV infections[2] indicates the sattabacin is more effective than other antiviral compounds.

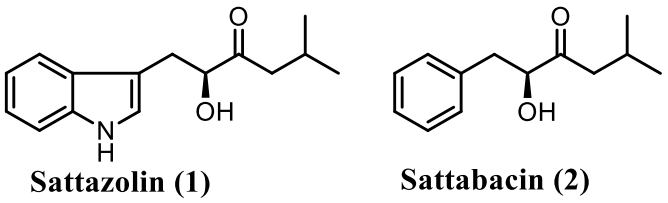


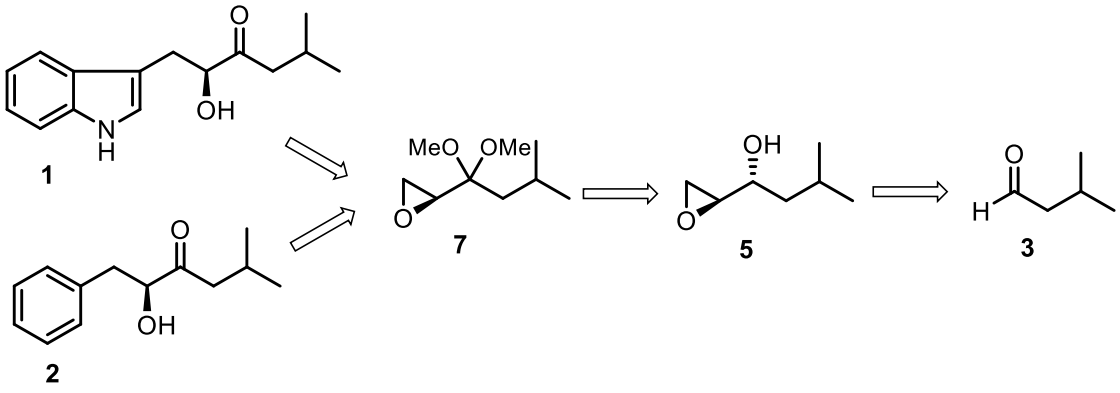
Figure 1

Miller *et al*. reported the first asymmetric total synthesis of the sattabacin and sattazolin in three and seven overall steps respectively.[3,4] Their structural similarity, no complexity and interesting biological activity of both the natural products drove us to their total synthesis.

As part of our regular research program on the synthesis of biologically active natural and synthetic compounds,[5-9] we herein report the total synthesis of antiviral agents of (+)-sattazolin and (+)-sattabacin (Figure-1).

Results and Discussion

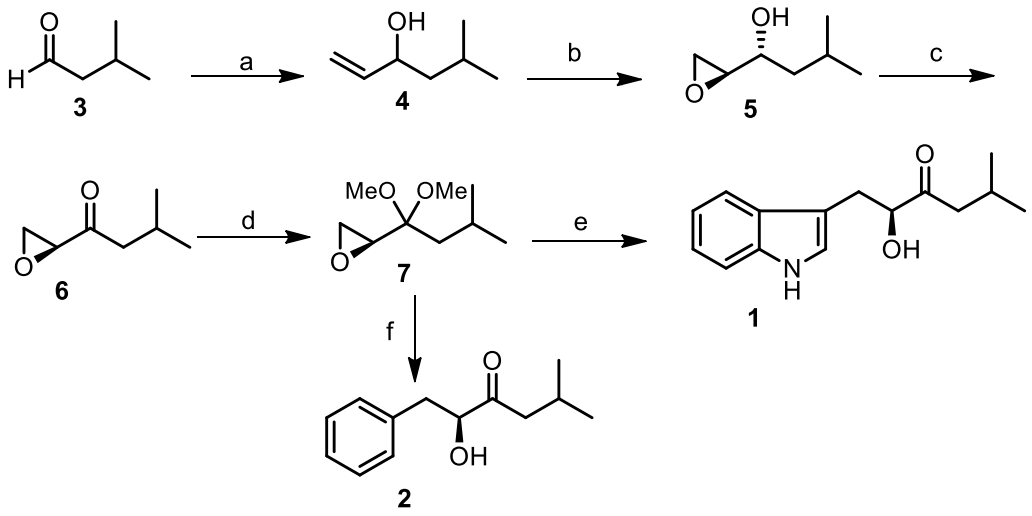
Retrosynthetic analysis is shown in scheme 1, the sattazolin (**1**) and sattabacin (**2**) could be obtained from common intermediate **7** *via* Eu (III) catalyzed ring opening with indole and regioselective ring opening with phenyl Grignard. The common intermediate **7** could be derived from compound **5** through oxidation followed by keto protection, compound **5** could be constructed from compound **3** by using vinyl Grignard and Sharpless epoxidation.



Scheme 1. Retrosynthesis of target compounds.

Total synthesis of sattazolin and sattabacin started from commercially available isovaleraldehyde (**3**), which was treated with vinyl magnesium bromide to give racemic allylic alcohol **4** in 88% yield.[10] The Sharpless epoxidation of allylic alcohol **4** was conducted at -20 °C in CH_2Cl_2 using $Ti(O^iPr)_4$, *t*-butyl hydroperoxide (TBHP) and diisopropyl-*D*-tartrate. After 4h, the chiral epoxide **5** with the desired epoxide configuration could be isolated in good yield[11,12] after separation from the remaining (S)-**4** alcohol resulting from the kinetic resolution which occurred.

The hydroxy group in compound **5** was oxidized with Dess-Martin periodinane (DMP) and $NaHCO_3$ in CH_2Cl_2 to afford compound **6** in 70% yield.[13,14] The keto group in compound **6** was protected as an acetal by the use of trimethylorthoformate[15] in benzene at reflux for 5 h to afford compound **7** in 73% yield. This protected compound **7** was used as common intermediate for both the target compounds.



Scheme 2. Synthesis of target compounds **1** and **2**. *Reagents and conditions:* (a) Vinyl magnesium bromide, THF, 0 °C to r.t, 1 h, 88%; (b) (-) DIPT, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, -20 °C, 5h, 88%; (c) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C to r.t, 1h, 70%; (d) $HC(OCH_3)_3$, PPTS (cat), benzene, reflux, 5h, 79%; (e) Indole, $Eu(OTf)_3$, DCE, reflux, 3h, 74%; (f) (i) Phenyl magnesium bromide, CuI (cat), THF, -78 °C to -30 °C, 1h, (ii) 4 N HCl, THF, r.t, 30 min, 76%.

It has already been reported[4] that the direct opening of epoxy ketone **6** with indole in presence of Lewis acid ($Yb(OTf)_3$) did not allow to furnish compound **1**. To overcome this we have protected the epoxy ketone as dimethylacetal **7**. Then, **7** was reacted with indole in refluxing DCE and in the presence of $Eu(OTf)_3$ as catalyst for 3h. We were then pleased to isolate the target compound sattazolin (**1)** in 74% yield.

Further we have synthesized sattabacin (**2**), from the common intermediate acetal **7.** The latter was treated with freshly prepared phenyl magnesium bromide[16,17] and CuI in THF at -78 °C to -30 °C for 1 h. The acetal deprotection was achieved after treatment with 4N HCl in THF at room temperature for 30 min to give sattabacin (**2**) in good yields[18,19] as shown in the Scheme 2. Compared to the earlier reports, we synthesized our target molecules in fewer steps with appreciable yields and resolved the difficulties in the synthesis of sattazolin to our best. We also confirmed the enantiomeric excess of sattabacin and sattazolin as 84.5% by performing chiral HPLC. The spectral data of our target compounds sattazolin and sattabacin were matched with spectral data and optical rotation of the natural products.

Conclusions

In summary, we have accomplished the enantioselective total synthesis of the antiviral agents sattazolin and sattabacin in 6 overall steps. The key features of the developed synthetic strategy are Sharpless epoxidation for fixing the chiral center via kinetic resolution of allylic alcohol, and the target compounds **1** and **2** were obtained from common intermediate **7** respectively by Eu(III) catalyzed ring opening with indole, regioselective ring opening with phenyl Grignard in high yields.

Experimental Section

General. All reagents were purchased from commercial sources and were used without additional purification. All reactions were performed under an inert atmosphere unless otherwise noted. THF was freshly distilled over Na/benzophenone ketyl. Hexane refers to the fraction boiling in the 60–80 °C range. Column chromatography was performed on silica gel (Acme grade 60–120 mesh). All reactions were monitored by TLC to completion; TLC plates (Merck precoated silica gel 60 F 254 plates) were made visible with UV light, in an I_2 chamber or with phosphomolybdic acid spray. Melting points were recorded using a Buchi M-560 melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer. ^{1}H NMR spectra were recorded on Bruker-400 MHz, spectrometer in $CDCl_3$ and using TMS as internal standard, ^{13}C NMR spectras were recorded on Bruker-100 MHz. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. Optical rotations were measured on Rudolph Autopol IV polarimeter at 25 °C.

5-Methylhex-1-en-3-ol (4). To a stirred solution of isovaleraldehyde (3.0 g, 34.89 mmol) in dry THF (30 mL) vinyl magnesium bromide (45 mL, 45.34 mmol, 1M, THF) was added at 0 ^{o}C and stirred for 1 h. After completion (TLC), the reaction was quenched with saturated NH_4Cl and extracted with EtOAc (3x20 mL). The combined organic layers were washed with brine and dried over Na_2SO_4 then concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel (60-120 mesh) by eluting with EtOAc-hexane (1:9) to give compound **4** as yellow oil. Yield: 3.5 g (88%). IR (neat): 3447, 2958, 2873, 1466, 1368, 1193, 1038 cm.$^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.94 - 5.80 (m, 1H), 5.23 (d, 1H, *J* 17.1 Hz), 5.09 (d, 1H, *J* 10.3 Hz), 4.23 - 4.12 (m, 1H), 1.83 - 1.64 (m, 1H), 1.51 - 1.41 (m, 1H), 1.39 - 1.22 (m, 1H), 0.94 (d, 3H, *J* 2.0 Hz), 0.92 (d, 3H, *J* 2.0 Hz).; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.6, 114.3, 71.4, 46.1, 24.4, 23.0, 22.3.; MS (ESI): *m*/*z* = 132 $[M+H_2O]^+$.

(*R*)-3-Methyl-1-[(*S*)-oxiran-2-yl]butan-1-ol (5). To a stirred solution of diisopropyl-*D*-tartrate (3.5 mL, 16.84 mmol) in dry CH_2Cl_2 (15 mL) cooled to -20 ^{o}C was added titanium tetraisopropoxide (4.1 mL, 14.0 mmol) and stirring was continued for 30 min. at this temperature. Racemic alcohol **4** (3.2 g, 28.0 mmol in dry CH_2Cl_2 (10 mL) was added stirred for 30 min at -20 ^{o}C and dry TBHP (tertiary butyl hydrogen peroxide) (14.9 mL, 56 mmol, 3.74 M, toluene) was added and the mixture allowed to stir at -20 ^{o}C for 5 h. After completion of reaction, monitored by TLC (50% conversion takes place), the reaction mixture was diluted with Et_2O (20 mL) and quenched with ferrous sulfate [8 g, dissolved in 10% aqueous tartaric acid, 25 mL], the mixture was then stirred for 1 h and extracted with CH_2Cl_2 (3x30 mL). The organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel (60-120 mesh) by eluting with EtOAc-hexane (1:9) mixture to afford, unreacted (*S*)-allylic alcohol **4** (1.5 g) and chiral epoxide **5** as a colorless liquid. Yield: 1.6 g (44%). Optical rotation $[\alpha]_D^{25}$ +10.2 (c 1, MeOH); [lit.[10] $[\alpha]_D^{25}$ +11 (c 1, MeOH)].; IR (neat): 3414, 2924, 2858, 1463, 1382, 1219, 1022 cm.$^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.97 - 3.88 (m, 1H), 3.05 - 2.97 (m, 1H), 2.82 (dd, 1H, *J* 5, 2.8 Hz), 2.73 (dd, 1H, *J* 5.6, 3.5 Hz), 1.93 - 1.85 (m, 1 H), 1.83

(brs, 1H), 1.26 - 1.48 (m, 2H), 1.01 - 0.92 (m, 6H).; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 66.5, 54.7, 43.2, 42.2, 24.4, 23.4, 21.9.; MS (ESI): *m/z* = 148 $[M+H_2O]^+$.

(*S*)-3-Methyl-1-(oxiran-2-yl)butan-1-one (6). To a stirred solution of alcohol **5** (1.3 g, 10.0 mmol) in dry CH_2Cl_2 (15 mL) was added Dess-Martin periodinane (5.5 g, 13.0 mmol) and $NaHCO_3$ (1.7 g, 20.0 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 1 h. After completion the reaction (monitored by TLC), was quenched with saturated $Na_2S_2O_3$ and extracted with CH_2Cl_2 (3x15 mL). The organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography using silica gel (60-120 mesh) by eluting with EtOAc-hexane (1:9) mixture to give chiral epoxy keto compound **6** as pale yellow oil. Yield: 0.9 g (70%). Optical rotation $[\alpha]_D^{25}$ +7.3 (c 0.9, $CHCl_3$). IR (neat): 2922, 2852, 1736, 1461, 1280, 1019 cm.$^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.41 (dd, 1H, *J* 4.7, 2.4 Hz), 2.98 (dd, 1H, *J* 5.8, 4.7 Hz), 2.85 (dd, 1H, *J* 5.8, 2.2 Hz), 2.39 - 2.26 (m, 1H), 2.24 - 2.10 (m, 2H), 0.94 (d,3H, *J* 6.6 Hz), 0.91 (d, 3H, *J* 6.4 Hz).; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.4, 59.2, 55.7, 40.1, 26.4, 22.7, 22.3.; MS (ESI): *m/z* = 129 $[M+H]^+$.

(*S*)-2-(1,1-Dimethoxy-3-methylbutyl)oxirane (7). To a stirred solution of compound **6** (0.7 g, 5.46 mmol) in dry benzene (5 mL) were added trimethylorthoformate (2.4 mL, 21.84 mmol) and catalytic amount of PPTS at 0 °C. The reaction mixture was stirred under reflux condition for 5 h and after the completion of the reaction (monitored by TLC), quenched with $NaHCO_3$ solution, the solvent was evaporated under reduced pressure and extracted with EtOAc (3x10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography using silica gel (60-120 mesh) by eluting with EtOAc-hexane (1:9) mixture to give keto protected compound **7** as colorless liquid. Yield: 0.75 g (79%). Optical rotation $[\alpha]_D^{25}$ +13.8 (c 1, $CHCl_3$).; IR (neat): 2924, 2854, 1629, 1216, 1122 cm.$^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.28 (s, 3H), 3.21 (s, 3H), 3.03 - 2.99 (m, 1H), 2.87 - 2.83 (m, 1H), 2.73 - 2.69 (m, 1H), 1.92 - 1.80 (m, 1H), 1.66 - 1.61 (m, 2H), 1.01 - 0.93 (m, 6H).; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 98.9, 53.7, 49.2, 48.5, 43.1, 42.9, 24.1, 23.8, 23.6.; MS (ESI): *m/z* = 175 $[M+H]^+$.

(*S*)-2-Hydroxy-1-(1*H*-indol-3-yl)-5-methylhexan-3-one (1). Indole (0.134 g, 1.1 mmol) and $Eu(OTf)_3$ (0.102 g, 0.17 mmol) were added to a stirred solution of keto protected compound **7** (100 mg, 0.57 mmol) in dry DCE (5 mL) at room temperature under nitrogen atmosphere. The reaction mixture was refluxed for 3 h, after completion of the reaction (monitored by TLC), quenched with $NaHCO_3$ solution (3 mL), and the reaction mixture extracted with CH_2Cl_2 (3x5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel (60-120 mesh) by eluting with EtOAc-hexane (2:8) mixture to afford compound **1** as orange oil. Yield: 104 mg (74%). Optical rotation $[\alpha]_D^{25}$ +55 (c 0.9, $CHCl_3$); [Lit.[1] $[\alpha]_D^{25}$ +58 (c 1.5, $CHCl_3$)].; IR (neat): 3415, 3320, 2922, 2853, 1707, 1461, 1096 cm.$^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (s, 1H), 7.63 (d, 1H, *J* 7.7 Hz), 7.39 - 7.32 (m, 1H), 7.25 - 7.01 (m, 3H), 4.51 - 4.41 (m, 1H), 3.56 - 3.40 (m, 1H), 3.30 (dd, 1H, *J* 15.1, 4.3 Hz), 3.06 (dd, 1H, *J* 15.1, 6.9 Hz), 2.39 (d, 2H, *J* 6.7 Hz), 2.21 - 2.08 (m, 1H), 0.90 (d, 3H, *J* 6.6 Hz), 0.87 (d, 3H, *J* 6.7 Hz).; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.7, 136.0, 127.4, 122.8, 122.1, 119.5, 118.6, 111.1, 110.6, 76.8, 47.2, 29.6, 24.4, 22.5.; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{20}O_2N$: 246.1488; found: 246.1491.

(*S*)-2-Hydroxy-5-methyl-1-phenylhexan-3-one (2). Freshly prepared phenyl magnesium bromide (0.68 mL, 0.68 mmol) was added to a stirred suspension of CuI (10 mg, 0.057 mmol) in dry THF (4 mL) at -78 °C, and the resulting mixture was stirred for 30 min at same temperature. A solution of keto protected compound **7** (100 mg, 0.57 mmol) in dry THF (2 mL) was added to the reaction mixture at -78 °C and stirred for 1 h at -30 °C. The reaction was quenched with a saturated solution of NH_4Cl after completion of the reaction (monitored by TLC), and concentrated, the residue was extracted with EtOAc (3x5 mL). The combined organic layers were concentrated under reduced pressure to obtain crude product. A solution of 4 N HCl (0.1 mL) was added to the obtained crude

product which was dissolved in the THF and the mixture was stirred at room temperature for 30 min. After completion of the reaction (monitored by TLC) quenched with $NaHCO_3$ solution, and the solvent was evaporated under reduced pressure. The residue was extracted with EtOAc (3x5 mL), the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel (60-120 mesh) by eluting with EtOAc-hexane (1:9) mixture to afford, target compound **2** as colorless liquid. Yield: 90 mg (76%). Optical rotation $[\alpha]_D^{25}$ +33.2 (c 1.5, $CHCl_3$); [Lit.[1] $[\alpha]_D^{25}$ +35 (c 0.7, $CHCl_3$)]. IR (neat): 3450, 2924, 2855, 1711, 1459, 1217, 1046 $cm.^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): 7.34 - 7.28 (m, 2H), 7.26 - 7.21 (m, 3H), 4.41 - 4.35 (m, 1H), 3.43 (d, 1H, *J* 5.3 Hz), 3.13 (dd, 1H, *J* 14, 4.5 Hz), 2.83 (dd, 1H, *J* 14.1, 7.5 Hz), 2.37 (d, 2H, *J* 6.9 Hz), 2.24 - 2.12 (m, 1H), 0.93 (s, 3H), 0.91 (s, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.1, 136.6, 129.2, 128.5, 126.8, 77.4, 47.3, 40.0, 24.5, 22.6, 22.5.; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{13}H_{19}O_2$: 207.1379; found: 207.1383.

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Supplementary Material

Copies of ^1H and ^{13}C NMR spectra of all compounds are available in the supplementary material associated with this manuscript.

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