Approaches to the stereoselective synthesis of (+)-lactacystin utilizing organocatalytic reactions

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Received 24 December 2013; accepted (revised) 5 June 2014

Efforts toward a stereoselective synthetic route to (+)-lactacystin based on organocatalytic transformations and intramolecular amino hydroxylation for creating the tetrasubstituted stereogenic center are described. Tethered aminohydroxylation of an allylic carbamate following Donohue's protocol affords a regioisomeric amino alcohol derivative, while Lewis acid promoted epoxide opening by a trichloroacetimidate yields a tetrahydrofuran derivative.

Keywords: Lactacystin, Baylis-Hillman reaction, organocatalytic, anti-aldol reaction, tethered aminohydroxylation

Lactacystin 1, Figure 1, was isolated by Omura and co-workers through screening of thousands of microbial cultures for the potential to induce differentiation of neuro 2A (neuroblastoma) cell line. The novel γ-lactam thio ester structure was elucidated via 1H and 13C NMR and single-crystal X-ray crystallography which revealed the absolute stereochemistry. Research with radio labelled lactacystin revealed that its biological activity was due to potent, highly selective and irreversible inhibition of proteasome mediated peptidase activity. Proteasomes are large proteins that help degrade ubiquitin conjugated proteins and mediate the turnover of various proteins including those involved in cell cycle progression and regulation of gene transcription. The β-lactone omuralide 2 derived from 1 in vivo is the actual biological agent that acts by acylation of the amino terminal threonine residue of the proteasome. Lactacystin has also been used in biology groups as it is useful for the study of protein biochemistry and cell biology.

The intriguing structural features and the host of biological activities have made lactacystin an attractive target for synthetic and medicinal chemists. Stereoselective construction of the tetrasubstituted carbon (C5 lactacystin numbering) is an essential step in any synthesis of 1. Many ingenious routes to this exciting target have been developed. An aldol reaction and its vinylogous variant has been employed for the creation of the C5 stereocenter with excellent stereocontrol by Corey, Smith, Adam, Panek, Donohue, Silverman and Baldwin. An Overman rearrangement has been employed by Chida and Gonda. Kang employed intramolecular amidomercuration, a dynamic diastereoselective Strecker reaction was employed by Ohfune and co-workers while Shibasaki developed an enantioselective Strecker reaction using gadolinium complex. Hayes and Wardrop utilized an intramolecular C-H insertion of an alkylidene carbene to introduce the tetrasubstituted carbon. Hatekeyama and Miyaoka used desymmetrization for the construction of C5 center and Jacobsen employed a catalytic enantio-and diastereoselective conjugate addition of α-aminocynoacetate to unsaturated silyl amide to create the C5 center. Lewis acid catalyzed epoxide opening by trichloroacetimidate was employed by Pattenden, and an Ugi reaction by Kobayashi. Herein, are reported the efforts toward the synthesis of (+)-lactacystin by taking advantage of organocatalytic transformations. Unlike many of the earlier reported routes that utilize aldol chemistry to set the key challenging tetrasubstituted C-5 stereocenter, our proposed route is characterized by tethered amino hydroxylation of an alkene.

Results and Discussion

As depicted in Scheme I, lactacystin can be obtained from ester 3, a known intermediate, which in turn was envisioned to be obtained by tethered amino hydroxylation of allylic carbamate 4 followed by selective deprotection of OP, oxidation of the primary hydroxy group and lactamization. The compound 4
was envisaged to be obtained from triol derivative 5 by adjustment of protecting groups. Compound 5 and 6 were envisaged by organocatalytic MacMillan anti-aldo and Baylis-Hillman reactions respectively. The synthesis commenced with the diastereo-selective Baylis-Hillman reaction using the chemistry developed by Leahy. Thus exposure of isobutyraldehyde 7 to chiral sulfonamide 8 in CH$_2$Cl$_2$ at 0°C for 18 hr in the presence of DABCO (50 mol %) resulted in ester 6 (76%, >99% ee) after acid catalyzed methanolysis. Protection of the hydroxy group by reaction with MOM-Cl in the presence of base yielded compound 9 (95% yield). Chemoselective reduction of the ester with DIBAL-H furnished allylic alcohol 10 that on Swern oxidation afforded aldehyde 11 cleanly (98% yield). Substrate controlled Mukaiyama aldol reaction of 11 with silyl ketene acetal 12 promoted by BF$_3$.Et$_2$O afforded hydroxy ester 13 as the sole product, (Scheme II). The structure of 13 was assigned by deprotection of MOM group and concomitant cyclization to yield the unsaturated lactone 14. While NOE was observed between C6 H and C7 H (lactacystin numbering), no NOE was observed between C6 H and C9 H, thus pointing to anti disposition of C7 Me and C6 OH and a syn disposition of the C6 OH and C9 OMOM in compound 13. The formation of 13 can be rationalized by the re-face attack of the silyl ketene acetal 12 to the less hindered re-face of the Lewis acid coordinated aldehyde that adopts the s-cis conformation relative to the double bond as depicted in transition state i. The si-face attack of the silyl ketene acetal would lead to unfavourable steric interactions between the Me group and the Lewis acid.

Since the stereocenters at C6 and C9 in lactacystin are anti disposed, a diastereoselective organocatalyzed anti-aldol reaction was explored using MacMillan’s protocol. Thus reaction of 11 with an excess of propionaldehyde 12 (5 eq) in the presence of D-proline (10 mol %) in 1,4-dioxane at +10°C furnished diol 5 after reduction of the β-hydroxy aldehyde with sodium borohydride. The structure of diol 5 was confirmed by $^1$H NMR and NOE studies on the acetonide 16, obtained by exposure of 5 to 2,2-DMP and catalytic CSA in CH$_2$Cl$_2$. Characteristically H$_4$ showed a diaxial coupling with H$_8$ ($J = 10.6$ Hz, $J_{b,c} = 11.3$ Hz) and revealed NOE with the axial methyl group of the acetinone and H$_4$ confirming the anti disposition of hydroxy and methyl groups in 5. Further selective benzylation of the primary hydroxy group in 5 using sodium hydride and benzyl bromide afforded carbinol 17. Deprotection of the MOM group furnished diol 18 that was transformed into 1,3-acetonide 19 under standard conditions. The configuration of the secondary carbinol relative to the
OMOM group in 5 was ascertained by $^1$H NMR and NOE studies on 19 (Scheme III). Characteristically, no NOE was observed between $H_a$ and $H_b$, and the $^{13}$C chemical shifts of the acetonide methyl groups ($\delta$ 24.1 and 23.7) suggested a half chair conformation for the acetonide as would be expected from anti 1,3-diol, Scheme III (Ref 13).

Having introduced three of the four stereogenic centers we turned our attention to the creation of the tetrasubstituted center. The diol 5 was converted into the dibenzyl ether 20 following standard conditions. Deprotection of the MOM group and reaction of the ensuing carbinol 21 with trichloroisocyanate followed by hydrolysis afforded the allylic carbamate 4.
Intramolecular aminohydroxylation following Donohue’s protocol\(^1\) afforded oxazinone \(23\) instead of the desired oxazolidinone \(22\) as evident from the recovery of starting material upon acetylation indicating the tertiary nature of the newly created carbinol, (Scheme IV). Thus the C-O quaternary center was created and not the desired C-N. A plausible explanation for the formation of \(23\) to the exclusion of \(22\) is due to the steric interactions between the Os atom and the C7 Me group in transition state \(\text{iii}\) leading to \(22\) which is minimized in transition \(\text{ii}\) leading to compound \(23\).

As an alternate route, after considerable experimentation we focused on BF\(_3\).Et\(_2\)O promoted epoxide opening by an imidate \(15\) to introduce the quaternary stereogenic center. The hydroxy group directed epoxidation of \(17\) with 100% m-CPBA\(^1\) under an inert atmosphere was added a solution of (2R)-bornane-10,2-sultam (6.27 g, 29 mmol, 1 eq) in toluene (30 mL) drop-wise. The reaction mixture was stirred at RT for 1 hr, and solid CuCl was added (272 mg, 2.7 mmol). A solution of acryloyl chloride (4.4 mL, 54 mmol) in toluene (60 mL) was added dropwise at \(0^\circ\text{C}\) and the stirring continued for an additional 30 min. The reaction mixture was diluted with EtOAc (200 mL) and quenched with ice pieces. The layers were separated and the organic layer was washed with \(\text{H}_2\text{O},\) brine, dried with anhyd. Na\(_2\)SO\(_4\) and filtered. The solvent was removed under reduced pressure and the residue was purified by flash chromatography over silica gel using 20% EtOAc/hexane (v/v) as the eluent and hydrolysis of the imidate probably during workup (Scheme V). Thus our efforts were frustrated once again. A successful route to lactacystin would require a non participating protecting group at C8.

**Experimental Section**

Compound 8: To a suspension of NaH (2.0 g, 60% in Nujol, 50 mmol, 1.7 eq) in anhydrous toluene (130 mL) cooled at \(0^\circ\text{C}\) maintained under \(\text{N}_2\) atmosphere was added a solution of (2R)-bornane-10,2-sultam (6.27 g, 29 mmol, 1 eq) in toluene (30 mL) drop-wise. The reaction mixture was stirred at RT for 1 hr, and solid CuCl was added (272 mg, 2.7 mmol). A solution of acryloyl chloride (4.4 mL, 54 mmol) in toluene (60 mL) was added dropwise at \(0^\circ\text{C}\) and the stirring continued for an additional 30 min. The reaction mixture was diluted with EtOAc (200 mL) and quenched with ice pieces. The layers were separated and the organic layer was washed with \(\text{H}_2\text{O},\) brine, dried with anhyd. Na\(_2\)SO\(_4\) and filtered. The solvent was removed under reduced pressure and the residue was purified by flash chromatography over silica gel using 20% EtOAc/hexane (v/v) as the eluent and hydrolysis of the imidate probably during workup (Scheme V). Thus our efforts were frustrated once again. A successful route to lactacystin would require a non participating protecting group at C8.
16.7, 10.3 Hz, 1H), 6.49 (dd, J = 16.7, 1.6 Hz, 1H), 5.85 (dd, J = 10.3, 1.6 Hz, 1H), 3.94 (dd, J = 13.8 Hz, 1H), 3.45 (d, J = 13.8 Hz, 1H), 2.19-2.09 (m, 2H), 1.96-1.88 (m, 3H), 1.48-1.34 (m, 2H), 1.18 (s, 3H), 0.98 (s, 3H); 13C NMR (75 MHz, CDCl3): δ 163.8, 131.3, 127.8, 65.1, 53.1, 48.6, 47.8, 44.7, 32.9, 26.5, 20.9, 19.9; IR (neat): 2962, 1678, 1333, 1310, 1131, 536 cm⁻¹; MS (ESI): m/z 270 [M+Na]+; HRMS (ESI): m/z [M+Na]+ Calcd for C13H20NO3S: 270.1158. Found: 270.1157.

Compound 6: To a stirred solution of acrylamide 8 (3.1 g, 11.5 mmol, 1 eq) in dichloromethane (16 mL) cooled at 0°C, isobutyrinaldehyde (15.8 mL, 172.5 mmol, 15 eq) followed by DABCO (645 mg, 5.75 mmol, 0.5 eq) were added. The solution was stirred at 0°C for 18 hr, then concentrated under reduced pressure to furnish the crude product which was purified by flash chromatography using 2% EtOAc/hexane (v/v) as the eluent to afford dioxinone as a colourless oil (1.8 g, 8.9 mmol) in 76% yield. TLC (SiO2): Rf = 0.4 (ethyl acetate:hexanes, 1:9); [α]D²⁵ = -13.1° (c = 0.38 in CHCl3); 1H NMR (300 MHz, CDCl3): δ 6.38 (d, J = 1.5 Hz, 1H), 5.76 (d, J = 1.5 Hz, 1H), 4.07 (d, J = 6.9 Hz, 1H), 3.78 (s, 3H), 2.93-2.82 (br, 1H), 1.95-1.85 (m, 1H), 0.97 (d, J = 6.9 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H); 13C NMR (75 MHz, CDCl3): δ 175.0, 149.7, 133.7, 131.0, 1131, 536 cm⁻¹; IR (neat): 3498, 2964, 1714, 1038 cm⁻¹; MS (ESI): m/z 159 [M+H]+; HRMS (ESI): m/z [M+H]+ Calcd for C8H15O3: 159.1016. Found 159.1019; HPLC conditions: Daicel Chiralcel OD, 2-propanol: hexane 1:2 (0.5 mL/min), tR = 16 min (R) and 18.5 min (S).

Compound 9: To a stirred solution of compound 6 (2.4 g, 15 mmol, 1 eq), TBAI (553.5 mg, 1.5 mmol,
10 mol%) in anhydrous dichloromethane (75 mL) cooled at 0°C, was added dropwise N,N-diisopropyl-ethylamine (5.2 mL, 30 mmol, 2 eq). The reaction mixture was stirred at 0°C for 10 min. MOM-Cl (1.4 mL, 18 mmol, 1.2 eq) was added and the mixture was stirred gradually allowing it to attain at RT and stirred further for a period of 4 hr. The reaction mixture was washed with water, dried over anhydrous Na₂SO₄ and filtered. The solvent was evaporated under reduced pressure to furnish the crude product which was purified by flash column chromatography using 2% EtOAc/hexane (v/v) as the eluent to afford 9 as a colourless oil (2.6 g, 12.74 mmol) in 85% yield. TLC (SiO₂): Rf = 0.7 (ethyl acetate:hexanes, 1:9); [α]D = −11.2° (c = 1.9, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ 6.27 (d, J = 1.5 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H); 13C NMR (75 MHz, CDCl₃): δ 166.5, 140.0, 126.0, 94.7, 79.0, 55.5, 51.5, 31.9, 16.8, 16.1; IR (neat): 3444, 2965, 1037 cm⁻¹; MS (ESI): m/z 225 [M+Na]+; HRMS (ESI): m/z [M+Na]+ Calcd for C₁₀H₁₈O₄Na: 225.1097. Found: 225.1100.

Compound 10: To a solution of compound 9 (10.5 g, 52 mmol, 1 eq) in anhydrous CH₂Cl₂ (175 mL) cooled at −78°C and maintained under nitrogen atmosphere was added DIBAL-H (81.7 mL, 114.4 mmol, 1.4 M in toluene, 2.2 eq) drop-wise during 30 min. The mixture was stirred further for a period of 30 min and quenched using saturated aqueous solution of sodium potassium tartarate. The reaction mixture was extracted with CH₂Cl₂ (150 mL × 3). The combined organic layers were washed with brine solution, dried over anhyd. Na₂SO₄ and filtered. Evaporation of the solvent under reduced pressure afforded the crude product which was purified by flash column chromatography using 20% EtOAc/hexane (v/v) as the eluent to afford allylic alcohol 10 as a colourless oil (8.6 g, 49.33 mmol) in 95% yield. TLC (SiO₂): Rf = 0.2 (ethyl acetate: hexanes, 2:8); [α]D = −5.25° (c = 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ 5.28 (s, 1H), 5.07 (s, 1H), 4.67 (d, J = 6.8 Hz, 1H), 4.47 (d, J = 6.8 Hz, 1H), 4.18 (d, J = 13.6 Hz, 1H), 4.04 (d, J = 13.6 Hz, 1H), 3.68 (d, J = 8.3 Hz, 1H), 3.37 (s, 3H), 1.89-1.79 (m, 1H), 1.05 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 146.2, 114.3, 93.9, 84.5, 62.2, 55.6, 30.7, 19.2, 19.0; IR (neat): 3444, 2965, 1037 cm⁻¹; MS (ESI): m/z 197 [M+Na]+.

Compound 11: To a solution of oxalyl chloride (0.75 mL, 8.6 mmol, 1.5 eq) in DCM (30 mL) cooled at −78°C under nitrogen atmosphere was added neat DMSO (1.3 mL, 18.3 mmol, 3.2 eq) dropwise and stirred for 5 min at the same temperature. To the above, a solution of the allylic alcohol 10 (1 g, 5.74 mmol, 1 eq) in DCM (6 mL) was added dropwise. The reaction mixture was stirred for 15 minutes at the same temperature, Et₃N (4.0 mL, 57.4 mmol, 5 eq) was added dropwise at −78°C. The reaction mixture was allowed to warm to RT, water (10 mL) was added and the organic layer was separated. The aqueous layer was extracted with CH₂Cl₂ (50 mL × 2). The combined organic layers were washed successively with 1 M HCl (10 mL), water, brine, dried over anhydrous Na₂SO₄ and filtered. Evaporation of the solvent under reduced pressure afforded the crude product which was purified by flash column chromatography using 10% EtOAc/hexane (v/v) as the eluent to afford aldehyde 11 (964 mg, 5.6 mmol) as a colourless liquid in 97% yield. TLC (SiO₂): Rf = 0.4 (ethyl acetate:hexane, 2:8); [α]D = −13.3° (c = 3.4, CHCl₃); ¹H NMR (500 MHz, CDCl₃): δ 9.56 (s, 1H), 6.39 (s, 1H), 6.15 (s, 1H), 4.50 (d, J = 6.4 Hz, 1H), 4.48 (d, J = 6.4 Hz, 1H), 4.30 (d, J = 6.4 Hz, 1H), 3.32 (s, 3H), 1.91-1.83 (m, 1H), 0.89 (d, J = 7.4 Hz, 3H), 0.85 (d, J = 7.4 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 193.6, 149.5, 135.3, 95.2, 55.8, 31.9, 19.1, 17.0; IR (neat): 2963, 1692, 1040 cm⁻¹; MS (ESI): m/z 195 [M+Na]+; HRMS (ESI): m/z [M+Na]+ Calcd for C₇H₁₀O₂Na: 195.0997. Found: 195.1021.

Compound 13: To a solution of compound 11 (344 mg, 2 mmol, 1 eq) in anhydrous CH₂Cl₂ (10 mL) cooled at −78°C, maintained under nitrogen atmosphere was added silylketene acetal 12 (384 mg, 2.4 mmol, 1.2 eq) dropwise followed by BF₃·OEt₂ (0.3 mL, 2 mmol, 1 eq) during 30 min and the mixture stirred further for a period of 20 min. The reaction mixture was quenched using saturated aqueous solution of ammonium chloride and extracted with CH₂Cl₂ (30 mL × 3). The combined organic layers were washed with brine solution, dried over anhyd. Na₂SO₄ and filtered. Evaporation of the solvent under reduced pressure afforded the crude product which was purified by flash column chromatography using 5% EtOAc/hexane (v/v) as the eluent to afford β-hydroxy ester 13 (411 mg, 1.5 mmol) as a colourless liquid in 75% yield. TLC (SiO₂): Rf = 0.5 (ethyl acetate: hexane, 2:8); ¹H NMR (300 MHz, CDCl₃): δ 5.28 (s, 1H), 5.16 (s, 1H), 4.60 (d, J = 6.8
Compound 14: To a solution of the compound 13 (108 mg, 0.62 mmol, 1 eq) in CH$_2$Cl$_2$ (0.1 mL) cooled at 0°C, was added TFA (0.95 mL) and stirred at RT for 12 hr. The reaction mixture was diluted with CH$_2$Cl$_2$ (3 mL) and the pH adjusted to 7 with saturated aq. sodium carbonate. The layers were separated and the organic layer was washed with saturated water, brine, dried over anhyd. Na$_2$SO$_4$ and filtered. The solvent was evaporated in vacuo and the residue was purified by column chromatography over silica gel using 2% EtOAc/hexane (v/v) as the eluent to furnish compound 14 as colourless oil (108 mg, 0.485 mmol) in 81% yield. TLC (SiO$_2$: R$_f$ = 0.8 (ethyl acetate:hexanes, 1.5:8.5)); HRMS (ESI): m/z 297 [M+Na]$^+$.

Compound 15: To a solution of the compound 14 (108 mg, 0.485 mmol, 1 eq) in 1,4-dioxane (0.6 mL) cooled at 0°C, was added TFA (0.95 mL) and stirred at RT for 1 hr. The reaction mixture was diluted with CH$_2$Cl$_2$ (10 mL), washed with water, brine, dried over anhydrous Na$_2$SO$_4$ and filtered. The solvent was removed in vacuo and the residue was purified by flash chromatography on silica gel using 3% EtOAc/hexane (v/v) as the eluent to furnish compound 15 as a colourless oil (196.3 mg, 0.72 mmol) in 90% yield. TLC (SiO$_2$: R$_f$ = 0.8 (ethyl acetate:hexanes, 3:7)); [α]$^2$$^5_D$ = −24° (c = 1.3, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$): δ 5.23 (d, J = 1.5 Hz, 1H), 5.16 (d, J = 1.5 Hz, 1H), 5.12 (d, J = 1.5 Hz, 1H), 4.51 (d, J = 1.5 Hz, 1H), 4.36 (d, J = 1.5 Hz, 1H), 3.91 (d, J = 1.5 Hz, 1H), 3.77 (d, J = 1.5 Hz, 1H), 3.71 (d, J = 1.5 Hz, 1H), 3.48 (t, J = 11.3 Hz, 1H), 3.34 (s, 3H), 2.05-1.80 (m, 2H), 1.41 (s, 3H), 1.30 (s, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H), 0.66 (d, J = 6.8 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 144.9, 117.0, 94.6, 93.9, 83.0, 74.7, 66.2, 55.8, 31.7, 31.0, 29.7, 19.9, 18.8, 17.7, 12.8; IR (neat): 2958, 2930, 1037 cm$^{-1}$; MS (ESI): m/z 295 [M+Na]$^+$; HRMS (ESI): m/z [M+Na]$^+$ Calcd for C$_{12}$H$_2$O$_5$Na: 295.1567. Found: 295.1569.

Compound 16: To a solution of compound 5 (186 mg, 0.80 mmol, 1 eq) in anhydrous CH$_2$Cl$_2$ (4 mL) cooled at 0°C, maintained under N$_2$ atmosphere was added neat 2,2-dimethoxy-propane (2.2-DMP) (147 µL, 1.2 mmol, 1.5 eq) followed by catalytic amounts of (-)-camphorsulphonic acid (19 mg, 0.08 mmol, 10 mol%). The reaction mixture was stirred at RT for 1 hr. The reaction mixture was diluted with CH$_2$Cl$_2$ (10 mL), washed with water, brine, dried over anhydrous Na$_2$SO$_4$ and filtered. The solvent was removed in vacuo and the residue was purified by column chromatography over silica gel using 3% EtOAc/hexane (v/v) as the eluent to furnish compound 16 as a colourless oil (196.3 mg, 0.72 mmol) in 90% yield. TLC (SiO$_2$: R$_f$ = 0.8 (ethyl acetate:hexanes, 3:7)); [α]$^2$$^5_D$ = −24° (c = 1.3, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$): δ 5.23 (d, J = 1.5 Hz, 1H), 5.16 (d, J = 1.5 Hz, 1H), 5.12 (d, J = 1.5 Hz, 1H), 4.51 (d, J = 1.5 Hz, 1H), 4.36 (d, J = 1.5 Hz, 1H), 3.91 (d, J = 1.5 Hz, 1H), 3.77 (d, J = 1.5 Hz, 1H), 3.71 (d, J = 1.5 Hz, 1H), 3.48 (t, J = 11.3 Hz, 1H), 3.34 (s, 3H), 2.05-1.80 (m, 2H), 1.41 (s, 3H), 1.30 (s, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H), 0.66 (d, J = 6.8 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 144.9, 117.0, 94.6, 93.9, 83.0, 74.7, 66.2, 55.8, 31.7, 31.0, 29.7, 19.9, 18.8, 17.7, 12.8; IR (neat): 2958, 2930, 1037 cm$^{-1}$; MS (ESI): m/z 295 [M+Na]$^+$; HRMS (ESI): m/z [M+Na]$^+$ Calcd for C$_{12}$H$_2$O$_5$Na: 295.1567. Found: 295.1569.

Compound 17: To a suspension of NaH (66.0 mg, 60% in Nujol, 1.65 mmol, 1.1 eq) in anhydrous THF (4 mL) cooled at 0°C, maintained under N$_2$ atmosphere was added a solution of compound 5 (346 mg, 1.5 mmol, 1 eq) in THF (1 mL) dropwise. The reaction mixture was stirred at RT for 15 min. Benzy1 bromide (183 µL, 1.5 mmol, 1 eq) was added dropwise at 0°C and the stirring continued for an additional 1 hr. The reaction mixture was diluted with EtOAc (20 mL) and quenched with ice pieces. The layers were separated and the organic layer was washed with H$_2$O, brine, dried with anhyd. Na$_2$SO$_4$ and filtered. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel using 10% EtOAc/hexane (v/v) as the eluent to afford compound 17 as a colourless oil (418.6 mg,
1.3 mmol) in 87% yield. TLC (SiO$_2$): $R_f = 0.5$ (ethyl acetate: hexanes, 2:8); $[\alpha]^{25}_D = -16^\circ$ ($c = 0.37$, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.40-7.21 (m, 5H), 5.24 (d, $J = 1.5$ Hz, 1H), 5.12 (d, $J = 1.5$ Hz, 1H), 4.56 (d, $J = 6.8$ Hz, 1H), 4.50 (s, 2H), 4.38 (d, $J = 6.8$ Hz, 1H), 3.97 (d, $J = 6.8$ Hz, 1H), 3.78 (d, $J = 6.8$ Hz, 1H), 2.66 (d, $J = 9.1$, 3.8 Hz, 1H), 1.98 (s, 1H), 1.94-1.78 (m, 1H), 1.35 (s, 3H), 1.28 (s, 3H). 0.94 (d, $J = 6.8$ Hz, 3H), 0.91 (d, $J = 6.6$ Hz, 3H), 0.80 (d, $J = 6.8$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 143.9, 138.9, 128.2, 127.5, 127.3, 112.0, 100.8, 80.3, 76.6, 73.1, 72.3, 37.7, 32.0, 24.1, 23.7, 19.3, 17.8, 14.6; IR (neat): 2927, 2871, 1026 cm$^{-1}$; MS (ESI): $m/z$ 341 [M+Na$^+$].

**Compound 19:** To a stirred solution of compound 18 (129 mg, 0.4 mmol, 1 eq) in anhydrous methanol (2 mL) cooled at 0°C pyridinium para-toluenesulfonate (10 mg, 0.04 mmol, 10 mol%) was added. The solution was stirred at RT for 6 hr, the reaction was quenched by the addition of triethylamine (0.2 mL). The solution was concentrated under reduced pressure to furnish the crude product which was purified by flash column chromatography using 15% EtOAc/hexane (v/v) as the eluent to afford 18 as a colourless oil (90 mg, 0.35 mmol) in 87% yield. TLC (SiO$_2$): $R_f = 0.4$ (ethyl acetate:hexanes, 3:7); $[\alpha]^{25}_D = -22.3^\circ$ ($c = 1.5$, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.44-7.24 (m, 5H), 5.14 (s, 2H), 4.50 (s, 2H), 4.11 (d, $J = 6.8$ Hz, 1H), 3.83 (d, $J = 7.6$ Hz, 1H), 3.64 (dd, $J = 9.1$, 3.8 Hz, 1H), 3.50 (dd, $J = 9.1$, 7.6 Hz, 1H), 2.25-2.14 (m, 1H), 1.98-1.84 (m, 1H), 0.98 (d, $J = 6.8$ Hz, 3H), 0.92 (d, $J = 7.6$ Hz, 3H), 0.89 (d, $J = 6.8$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 147.1, 137.6, 128.5, 127.9, 127.8, 116.1, 87.3, 76.6, 71.0, 66.4, 37.9, 31.7, 20.1, 17.0, 14.3; IR (neat): 3417, 2962, 2928, 2873, 1036 cm$^{-1}$; MS (ESI): $m/z$ [M+Na$^+$].

**Compound 20:** To a suspension of NaH (132.0 mg, 60% in Nujol, 3.2 mmol, 2.2 eq) in anhydrous THF (6 mL) cooled at 0°C maintained under N$_2$ atmosphere was added a solution of compound 5 (346 mg, 1.5 mmol, 1 eq) in THF (2 mL) dropwise. The reaction mixture was stirred at RT for 15 min. Benzylic bromide (366 µL, 3.0 mmol, 2 eq) was added dropwise at 0°C and the stirring continued for an additional 1 hr. The reaction mixture was diluted with EtOAc (20 mL) and quenched with ice pieces. The layers were separated and the organic layer was washed with H$_2$O, brine, dried with anhyd. Na$_2$SO$_4$ and filtered. The solvent was removed under reduced pressure and the residue was purified by flash chromatography over silica gel using 10% EtOAc/hexane (v/v) as the eluent to afford compound 20 as a colourless oil (418.6 mg, 1.3 mmol) in 87% yield. TLC (SiO$_2$): $R_f = 0.8$ (ethyl acetate:hexanes, 2:8); $[\alpha]^{25}_D = -16^\circ$ ($c = 0.37$, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.37-7.16 (m, 10H), 5.28 (d, $J = 1.5$ Hz, 1H), 5.25 (d, $J = 1.5$ Hz, 1H), 4.59 (d, $J = 7.0$ Hz, 1H), 4.48 (d, $J = 11.3$ Hz, 1H), 4.45-4.36 (m, 3H), 4.20 (d, $J = 11.3$ Hz, 1H), 3.93 (d, $J = 4.2$ Hz, 3H), 3.71 (d, $J = 8.0$ Hz, 1H), 3.55 (dd, $J = 8.7$, 3.2 Hz, 1H), 3.46 (dd, $J = 8.7$, 6.4 Hz, 1H), 3.36 (s, 3H), 2.11-1.92 (m, 2H), 1.00 (d, $J = 6.8$ Hz, 3H), 0.99 (d, $J = 6.8$ Hz, 3H), 0.91 (d, $J = 6.6$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 144.2, 138.9, 138.6, 128.3, 127.8, 127.6, 127.5, 117.3, 94.2, 83.9, 80.3, 73.2, 71.9, 70.1, 55.8, 36.4, 30.9, 20.9, 16.3, 15.2; IR (neat): 2929, 1364, 1027, 738 cm$^{-1}$; MS (ESI): $m/z$ 345 [M+Na$^+$]. HRMS (ESI): $m/z$ 341 [M+Na$^+$].

**Compound 21:** To a solution of the compound 20 (200 mg, 0.62 mmol, 1 eq) was added TFA (3 mL) and stirred at RT for 12 hr. The reaction mixture was diluted with chloroform (30 mL). The organic layer
was washed with saturated aq. sodium carbonate, H₂O, brine, dried over anhydrous Na₂SO₄ and filtered. The solvent was removed in vacuo and the residue was purified by column chromatography over silica gel using 5% EtOAc/hexane (v/v) as the eluent to furnish compound 58 as colourless oil (195 mg, 0.58 mmol) in 93% yield. TLC (SiO₂): Rf = 0.3 (ethyl acetate:hexanes, 1.5:8.5); [α]₂⁵D = −13° (c = 0.6, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ 7.28-7.09 (m, 10H), 5.16 (d, J = 1.5 Hz, 1H), 5.13 (d, J = 1.5 Hz, 1H), 4.45 (d, J = 11.5 Hz, 1H), 4.32 (d, J = 6.2 Hz, 2H), 4.14 (d, J = 11.5 Hz, 1H), 3.8-3.7 (m, 2H), 3.74 (t, J = 7.4 Hz, 1H), 3.33 (dd, J = 6.8 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 147.7, 138.4, 128.3, 127.8, 127.7, 127.5, 115.3, 83.1, 78.4, 73.1, 71.7, 71.2, 37.3, 31.9, 20.1, 17.8, 15.4; IR (neat): 3449, 2963, 2870, 1454, 1065, 1026, 698 cm⁻¹; MS (ESI): m/z 256 [M+ Na⁺]; HRMS (ESI): m/z [M+ Na⁺]⁺ Calcd for C₂₅H₂₃NO₂Na: 391.2249. Found 391.2234.

Compound 23: To a solution of the compound allyl carbamate 4 (41 mg, 0.1 mmol, 1 eq) in propanol (1.2 mL) was added a freshly prepared aqueous solution of sodium hydroxide (0.5 mL, 0.08M). The solution was stirred for 5 mins, freshly prepared tert-butyl hypochlorite (11 µL, 0.1 mmol, 1 eq) was added and the mixture was stirred for 5 min. To the above mixture was added disopropyl-ethylamine (1 µL, 5 mol%) and the mixture stirred for a further 5 min period. Sodium hydroxide solution (0.6 mL, 0.08M) followed by a solution of OsO₄ (0.25 mL, 4 mol%) were added and the mixture stirred overnight. The reaction was quenched by the addition of sodium sulfite (50 mg) and stirred for 30 min. The aqueous layer was extracted with EtOAc (10 mL x 3) and the organic layers were combined, washed with brine, dried over anhyd. Na₂SO₄ and filtered. The solvent was removed in vacuo and the residue was purified by column chromatography over silica gel using 25% EtOAc/hexane (v/v) as the eluent to furnish compound 23 as colourless oil (40 mg, 0.17 mmol) in 85% yield. TLC (SiO₂): Rf = 0.18 (ethyl acetate:hexanes, 3:7); [α]₂⁵D = −13° (c = 0.6, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ 7.56-7.20 (m, 10H), 4.98 (d, J = 3.8 Hz, 1H), 4.79-4.67 (m, 2H), 4.61 (d, J = 10.0 Hz, 1H), 4.51 (d, J = 10.0 Hz, 1H), 4.13 (d, J = 6.3 Hz, 1H), 3.91 (t, J = 8.8 Hz, 1H), 3.81 (t, J = 12.5 Hz, 1H), 3.72 (d, J = 12.5 Hz, 1H), 3.54 (t, J = 8.8 Hz, 1H), 2.52-2.43 (m, 1H), 2.17-2.07 (m, 1H), 1.08 (d, J = 6.3 Hz, 3H), 1.03 (d, J = 7.5 Hz, 3H), 0.95 (d, J = 7.5 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 156.8, 137.6, 128.4, 127.8, 127.5, 87.9, 82.7, 79.4, 73.9, 72.3, 45.5, 38.5, 28.8, 21.3, 16.9, 10.7; IR (neat): 3368, 2970, 2878, 1721, 1108, 1049 cm⁻¹; MS (ESI): m/z 356 [M+ Na⁺].

Compound 24: To a solution of the compound 17 (200 mg, 0.62 mmol, 1 eq) and solid NaHCO₃ (260 mg, 3.1 mmol, 5 eq) in anhydrous chloroform (3 mL) cooled at 0°C, maintained under N₂ atmosphere was added 100% m-CPBA (321 mg, 1.86 mmol, 3 eq) in diethyl ether (25 mL). The reaction mixture was stirred at RT for 1 hr. The reaction mixture was diluted with chloroform (30 mL) and quenched with saturated aq. sodium sulphite. The layers were separated and the organic layer was washed with saturated aqueous sodium hydrogen carbonate, H₂O, brine, dried over anhydrous Na₂SO₄ and filtered. The
solvent was removed in vacuo and the residue was purified by column chromatography over silica gel using 5% EtOAc/hexane (v/v) as the eluent to furnish compound 24 as colourless oil (195 mg, 0.58 mmol) in 93% yield. TLC (SiO\(_2\)): \( R_f = 0.3 \) (ethyl acetate:hexanes, 1.5:8.5); [\( \alpha \)]\(_D^{25}\) = \( -13^\circ \) (c = 0.6, CHCl\(_3\)); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta \) 7.30-7.14 (m, 5H), 4.57 (d, \( J = 6.8 \) Hz, 1H), 4.42 (s, 2H), 4.35 (d, \( J = 6.8 \) Hz, 1H), 3.50-3.38 (m, 4H), 3.27 (s, 3H), 2.74 (d, \( J = 5.3 \) Hz, 1H), 2.58 (d, \( J = 5.3 \) Hz, 1H), 2.17-1.96 (m, 2H), 0.96 (d, \( J = 7.5 \) Hz, 3H), 0.95 (d, \( J = 6.8 \) Hz, 3H), 0.85 (d, \( J = 6.8 \) Hz, 3H); \(^1\)C NMR (75 MHz, CDCl\(_3\)): \( \delta \) 137.7, 128.4, 127.8, 97.3, 80.3, 76.4, 74.0, 73.5, 59.2, 56.0, 47.7, 34.8, 30.1, 20.3, 17.2, 14.7; IR (neat): 3421, 2963, 2931, 1719, 1031 cm\(^{-1}\); MS (ESI): \( m/\varepsilon = 361 \) [M+ Na]\(^+\); HRMS (ESI): \( m/\varepsilon = 359.1086 \) [M+ Na]\(^+\) Caled for C\(_{19}\)H\(_{20}\)O\(_3\)Na: 361.1986. Found: 361.1995.

Compound 25: To an ice-cold solution of epoxy alcohol 24 (416 mg, 1.23 mmol, 1 eq) in anhydrous dichloromethane (2.5 mL) were added triethylamine doped silica gel using 2% EtOAc/hexane (v/v) as the eluent to afford title compound 25 as a brown colour oil (520 mg, 1.1 mmol) in 87% yield. TLC (SiO\(_2\)): \( R_f = 0.7 \) (ethyl acetate:hexanes, 1.5:8.5); [\( \alpha \)]\(_D^{25}\) = \( -14^\circ \) (c = 0.57, CHCl\(_3\)); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta \) 7.30-7.20 (m, 5H), 5.23 (d, \( J = 6.0 \) Hz, 1H), 4.68 (d, \( J = 7.0 \) Hz, 1H), 4.44 (d, \( J = 7.0 \) Hz, 2H), 4.42 (d, \( J = 7.0 \) Hz, 1H), 3.61 (dd, \( J = 9.0 \), 4.0 Hz, 1H), 3.41 (dd, \( J = 9.0 \), 4.0 Hz, 1H), 3.61 (d, \( J = 5.0 \) Hz, 1H), 3.34 (s, 3H), 2.89 (d, \( J = 5.0 \) Hz, 1H), 2.73 (d, \( J = 5.0 \) Hz, 1H), 2.52-2.43 (m, 1H), 2.21-2.12 (m, 1H), 1.18 (d, \( J = 7.0 \) Hz, 3H), 1.08 (dd, \( J = 7.0 \) Hz, 3H), 0.92 (d, \( J = 6.0 \) Hz, 3H); \(^1\)C NMR (75 MHz, CDCl\(_3\)): \( \delta \) 162.3, 137.9, 129.4, 128.3, 127.6, 97.3, 82.6, 80.0, 76.4, 74.3, 73.2, 59.1, 56.2, 47.9, 35.0, 30.4, 20.5, 17.4, 15.4; IR (neat): 3425, 2964, 2931, 1721, 1151 cm\(^{-1}\); MS (ESI): \( m/\varepsilon = 504 \) [M+ Na]\(^+\); HRMS (ESI): \( m/\varepsilon = 504 \) [M+ Na]\(^+\) Caled for C\(_{21}\)H\(_{30}\)NO\(_3\)Cl\(_3\)Na: 504.1082. Found: 504.1097.

Compound 27: To a stirred solution of epoxytrichloroacetimidate 25 (95 mg, 0.2 mmol, 1 eq) in anhydrous dichloromethane (1.6 mL) cooled at \(-23^\circ\)C was added BF\(_3\)Et\(_2\)O (120 \( \mu \)L, 1.0 mmol, 5 eq). After being stirred at \(-23^\circ\)C for 1 hr, the temperature was gradually allowed to rise to RT and stirred further for period of 1 hr. The reaction mixture was quenched with saturated aqueous NaHCO\(_3\). The reaction mixture was diluted with EtOAc, washed with water, dried over anhydrous Na\(_2\)SO\(_4\) and filtered. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel using 25% EtOAc/hexane (v/v) as the eluent to afford 27 as a brown colour oil (37 mg, 0.15 mmol) in 75% yield. TLC (SiO\(_2\)): \( R_f = 0.1 \) (ethyl acetate:hexanes, 3:7); [\( \alpha \)]\(_D^{25}\) = \( +12^\circ \) (c = 0.56, CHCl\(_3\)); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta \) 4.40 (d, \( J = 6.0 \) Hz, 1H), 4.05-3.90 (m, 2H), 3.76 (d, \( J = 11.5 \) Hz, 1H), 3.53 (dd, \( J = 11.5 \), 8.5 Hz, 1H), 3.30 (dd, \( J = 11.5 \), 5.2 Hz, 1H), 2.39-2.27 (m, 1H), 1.97-1.84 (m, 1H), 1.04 (d, \( J = 7.0 \) Hz, 3H), 1.01 (d, \( J = 6.8 \) Hz, 3H), 1.00 (d, \( J = 6.8 \) Hz, 3H); \(^1\)C NMR (75 MHz, CDCl\(_3\)): \( \delta \) 98.9, 90.1, 76.9, 72.7, 63.8, 56.3, 39.1, 29.8, 29.1, 22.3, 17.1, 9.4; IR (neat): 3421, 2963, 2931, 1719, 1031; MS (ESI): \( m/\varepsilon = 271 \) [M+ Na]\(^+\).

Conclusion

In summary, we have disclosed two routes explored by us to synthesize lactacystin. Aminohydroxylation using the allylic carbamate 4 yielded the regioemeric amino alcohol derivative while Lewis acid catalyzed opening of epoxide 25 furnished tetrahydrofuran derivative. Efforts are in progress to complete the synthesis of lactacystin and the results shall be reported in due course.

Acknowledgements

PKS is thankful to the CSIR, New Delhi, for a fellowship. SR acknowledges funding from CSIR, New Delhi (ORIGIN program CSC-0108 of XII Five year plan). The authors thank Dr B. Jagadeesh, Head NMR center, for acquiring the NMR spectra and Dr R. Srinivas, Head NCMS division, for acquiring the mass spectra.

References

In the absence of inert atmosphere benzoate was formed as a side product (20%).

The configuration at C5 in compound 27 is assigned based on precedent assuming S

The reduction of 9 with DIBAL-H (1.1 eq) in dichloromethane at –78 °C afforded aldehyde 11 in 73% yield along with alcohol 10 in 15% yield.

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