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AN ENANTIOSELECTIVE SYNTHESIS OF (*6R*)-LACTACYSTIN

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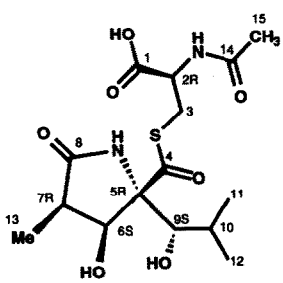
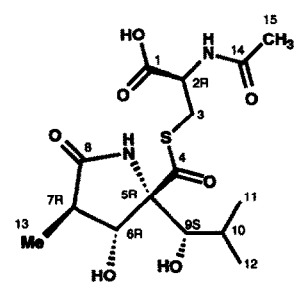
Summary: *The first enantiospecific, stereocontrolled total synthesis of (6R)-lactacystin, a potential neurotrophic agent, is described.*

Lactacystin (**1**), a microbial natural product discovered recently by Ōmura et al.[1,2] mimics the activity of nerve growth factor[3-6] to induce differentiation and neurite growth in a neuroblastoma cell line (Neuro 2A cells). The great therapeutic potential of small molecules with neurotrophic activity encouraged us to develop a total synthesis of **1**[7] and also to study the synthesis and bioassay of analogous structures. We report herein a short, effective and stereocontrolled synthesis of the (*6R*)-diastereomer of lactacystin (**2**), a compound of special interest for the optimization of biological activity as a function of stereochemistry. The pathway of synthesis, outlined in the accompanying scheme, starts with (*S*)-(+)-methyl-3-hydroxy-2-methylpropionate (**3**, Aldrich) and (*2R,3S*)-3-hydroxyleucine (**5**). A simple enantioselective synthesis of the latter from isobutyraldehyde and *t*-butyl bromoacetate has recently been reported from these laboratories.[8]

The 2-phenyl-1,3-oxazoline derivative **6**[9] was prepared from the methyl ester of **5** using methyl orthobenzoate in the presence of *p*-toluenesulfonic acid as catalyst. Aldol coupling of oxazoline **6** with the triethylsilyloxy aldehyde **4** was effected in good yield to form the required β-hydroxy ester **7** by the following process. Deprotonation of **6** with $KN(Me_3Si)_2$ in THF at -78 °C for 30 min afforded a yellow solution of the potassium enolate which was treated with 1.1 equiv of $ZnCl_2$ in ether at -78 °C for 20 min to form the corresponding zinc enolate. Then 1.3 equiv of the triethylsilyloxy aldehyde **4** in THF was added slowly at -78 °C and the reaction was allowed to proceed at that temperature for 1 h. Quenching at -78 °C with saturated ammonium chloride solution, extractive isolation and chromatography on silica gel provided stereoselectively the aldol product **7** (84%).[10] A parallel aldol coupling was carried out using the threonine analog of **6** (methyl



1



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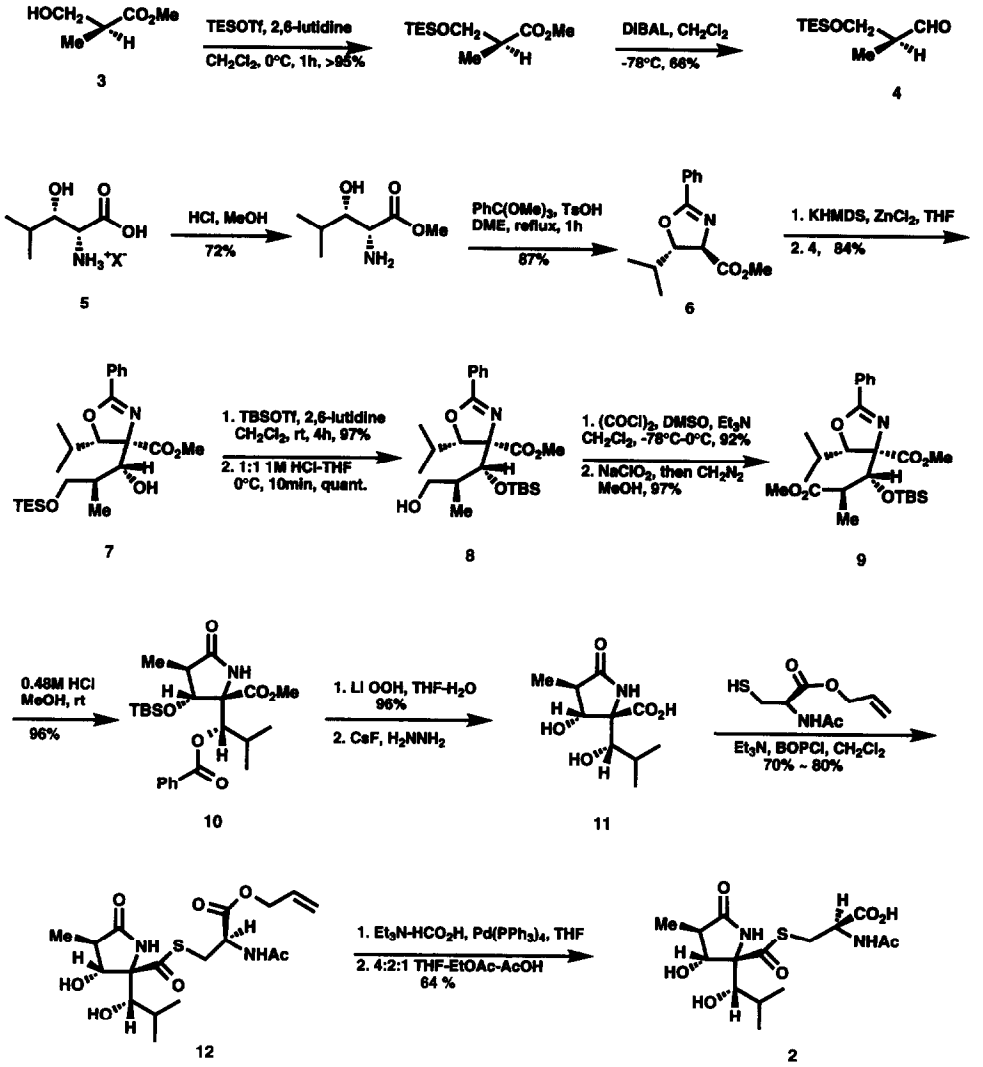
TESOTf, 2,6-lutidine
CH2Cl2, 0°C, 1h, >95%
DIBAL, CH2Cl2
-78°C, 66%
HCl, MeOH
72%
PhC(OMe)3, TsOH
DME, reflux, 1h
87%
1. KHMDS, ZnCl2, THF
2. 4, 84%
1. TBSOTf, 2,6-lutidine
CH2Cl2, rt, 4h, 97%
2. 1:1 1M HCl-THF
0°C, 10min, quant.
1. (COCl)2, DMSO, Et3N
CH2Cl2, -78°C-0°C, 92%
2. NaClO2, then CH2N2
MeOH, 97%
0.48M HCl
MeOH, rt
96%
1. LiOOH, THF-H2O
96%
2. CsF, H2NNH2
Et3N, BOPCl, CH2Cl2
70% ~ 80%
1. Et3N-HCO2H, Pd(PPh3)4, THF
2. 4:2:1 THF-EtOAc-AcOH
64 %
3
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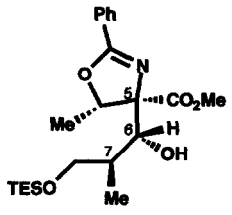
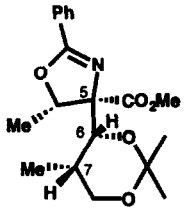
12
2

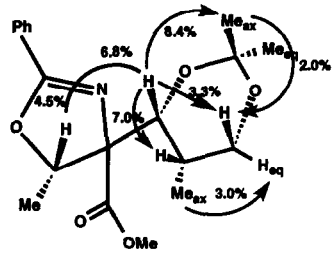
replacing isopropyl) and aldehyde **4** to form stereoselectively the analog of **7** having methyl instead of isopropyl (**13**). The stereochemistry of (**13**) was demonstrated after desilylation (HF–THF–H_2O, 23 °C, 2.5 h) and conversion to acetonide **14** by ^1H NMR analysis including NOE data, as shown. In the aldol reaction to form **13** the face selectivity at C(5) is clearly determined by the steric screening of methyl at the vicinal stereocenter on the oxazoline ring whereas the stereochemistry at C(6) in **13** is probably controlled by a combination of preferred enolate and transition state geometries. If the preferred enolate has the *trans* arrangement of O^- and N substituents, a chair six-membered transition state would provide the observed C(6) stereochemistry. The enolate with *cis* O^- and N substituents would have to react preferentially via a boat six-membered transition state to produce the observed aldol **13**. In any event, the stereochemistry of the aldol product **7** follows by analogy with **13**.



13



14, $J_{6,7}$ = 2.4Hz



14

Silylation of **7** with *t*-butyldimethylsilyl triflate afforded a bis-silyl ether from which the triethylsilyl (TES) group could be removed selectively in quantitative yield to form the primary alcohol **8**. Conversion of CH_2OH of **8** to COOMe gave the dimethyl ester **9** which upon treatment with HCl in methanol underwent oxazoline cleavage and lactam formation to afford **10** in excellent yield.[11] The methyl ester function of **10** could be saponified using LiOH–H_2O_2–H_2O at 23 °C for 24 h. However, the benzoate ester was quite resistant to cleavage and this operation required special conditions since the product was destroyed by strong base. Treatment with CsF in H_2NNH_2 at 75 °C for 10 h caused both desilylation and debenzoylation to give the dihydroxy acid **11** which was used in the next step without purification. Reaction of **11** with bis(2-oxo-3-oxazolidinyl)phosphinic chloride–Et_3N and N-acetylcysteine allyl ester formed the thio ester **12** which was cleaved to **2**, as previously reported for the synthesis of **1**,[7] using triethylammonium formate (5 equiv) with $Pd(Ph_3P)_4$ as catalyst in THF at 23 °C for 12 h. The product was isolated by evaporation of solvent, addition of water, extraction of the aqueous layer with EtOAc to remove extractable impurities, and concentration of the aqueous layer to give crude **2**. Purification of **2** was effected by application of a concentrated methanolic solution to silica gel, elution with THF–EtOAc–HOAc, removal of solvent, and trituration of the colorless crystalline solid with EtOAc to remove any trace of EtOAc–soluble material.[12] The (*6R*)-lactacystin thus obtained was both chromatographically and spectroscopically homogeneous.[12] Care must be taken during the chromatographic purification, since (*6R*)-lactacystin was found to be considerably more susceptible to retroaldol cleavage of the 5,6 bond than is lactacystin.

The synthesis of (*6R*)-lactacystin described above is sufficiently short and efficient to allow the synthesis of any required amount of this substance. This route has also been used for the synthesis of the analog of **2** in which the isopropyl subunit is replaced by methyl using (*2R,3S*)-threonine as starting material. Sufficient amounts of these analogs of lactacystin are now available for biological evaluation.[13]

References and Notes

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9. New compounds were characterized by ^{1}H NMR (500 MHz), ^{13}C NMR, IR, and HRMS data.
10. Physical data for **7**: TLC Rf=0.67 (33% ethyl acetate in hexane). $[\alpha]_D^{20}$ = -63.3° (c 0.36, $CHCl_3$). LRMS (FAB, +, NaI) $C_{24}H_{39}NO_5Si$, m/z=450(MH^+), 472 ($M+Na^+$). HRMS (FAB, +, NaI) found 450.2689 (MH^+), calcd. 450.2676 (MH^+). IR (neat, cm^{-1}) 3303, 2957, 2880, 1731, 1644, 1453. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03-8.01, 7.51-7.39 (m, 5H), 4.80 (d, J=4.6Hz, 1H), 4.22 (dd, J=6.5, 1.3Hz, 1H), 3.76 (s, 3H), 3.66-3.59 (m, 2H), 2.60 (d, J=6.6Hz, 1H), 2.06 - 1.98 (m, 1H), 1.98 - 1.94 (m, 1H), 1.12 (d, J=7.0Hz, 3H), 1.10 (d, J=6.8Hz, 3H), 0.95 (t, J=8.0Hz, 3x3H), 0.87 (d, J=6.6Hz, 3H), 0.59 (q, J=8.0Hz, 3x2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 165.3, 131.6, 128.7, 128.3, 127.6, 89.5, 84.3, 76.4, 68.1, 52.2, 37.7, 29.8, 20.7, 16.8, 11.3, 6.8, 4.4.
11. Physical data for **10**: TLC Rf=0.25 (33% ethyl acetate in hexane). $[\alpha]_D^{20}$ = +50.5° (c 0.82, $CHCl_3$). LRMS (FAB, +, NaI) $C_{24}H_{37}NO_6Si$, m/z=464 (MH^+), 486 ($M+Na^+$). HRMS (FAB, +, NaI) found 486.2313 ($M+Na^+$), calcd. 486.2288 ($M+Na^+$). IR (neat, cm^{-1}) 3213, 3099, 2958, 2932, 2858, 1727, 1710, 1467. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.0 - 7.97, 7.6 - 7.43 (m, 5H), 6.81 (s, 1H), 5.70 (d, J=4.6Hz, 1H), 4.01 (d, J=8.4Hz, 1H), 3.84 (s, 3H), 2.41 (quint, J=7.5Hz, 1H), 1.97-1.88 (m, 1H), 1.10 (d, J=7.1Hz, 3H), 0.99 (d, J=6.8Hz, 3H), 0.96 (d, J=6.8Hz, 3H), 0.82 (s, 9H), 0.23 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.5, 171.9, 164.5, 133.1, 130.2, 129.7, 128.7, 81.7, 75.4, 70.0, 52.6, 44.1, 30.6, 25.8, 21.1, 18.2, 18.1, 14.3, -4.3, -5.3.
12. Physical data for **2**: mp 162-165 °C (dec.). TLC Rf = 0.65 (THF : EtOAc : AcOH = 4 : 2 : 1), $[\alpha]_D$ = + 65.7° (c 0.89, MeOH). LRMS (FAB, +, NaI) $C_{15}H_{24}N_2O_7S$, m/z=377 (MH^+), 399 ($M+Na^+$). HRMS (FAB, +, NaI) found 399.1206 ($M+Na^+$), calcd. 399.1202 ($M+Na^+$). IR (neat, cm^{-1}) 3270, 3079, 2965, 2931, 1703, 1698, 1692, 1661, 1549. ^{1}H NMR (500 MHz, pyridine-d_5) δ 9.89 (s, 1H, **NH**), 9.20 (d, J=8.3Hz, 1H, **NH**Ac), 5.39 - 5.35 (m, 1H, SCH_2**CH**NHAc), 4.95 (d, J=7.1Hz, 1H, Me_2CH**CH**OH), 4.67 (d, J=8.8Hz, 1H, MeCH**CH**OH), 3.99 (dd, J=13.5, 4.5Hz, 1H, SCH_2), 3.62 (dd, J=13.5, 8.7Hz, 1H, SCH_2), 3.33 (quint, J=8.3Hz, 1H, Me_2**CH**), 2.22 (dq, J=8.8, 6.8Hz, 1H, MeCHCON), 2.06 (s, 3H, NH**Ac**), 1.44 (d, J=7.2Hz, 3H, **Me**CH), 1.25 (d, J=6.6Hz, 3H, **Me**$_2$CH), 1.11 (d, J=6.8Hz, 3H, **Me**$_2$CH). ^{1}H NMR (500 MHz, D_2O) δ 4.28 (dd, J=8.7, 4.0Hz, 1H), 4.10 (d, J=6.7Hz, 1H), 3.88 (d, J=9.0Hz, 1H), 3.39 (dd, J=14.1, 4.1Hz, 1H), 3.03 (dd, J=14.0, 8.9Hz, 1H), 2.66 (quint, J=8.1Hz, 1H), 1.89 (s, 3H), 1.57 (oct, J=6.7Hz, 1H), 1.05 (d, J=7.2Hz, 3H), 0.85 (d, J=6.6Hz, 3H), 0.73 (d, J=6.8Hz, 3H). ^{13}C NMR (100 MHz, pyridine-d_5) δ 203.1, 178.5, 173.6, 170.3, 82.3, 77.4, 77.0, 52.6, 44.6, 31.7, 31.4, 23.0, 21.3, 19.7, 15.0.
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