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Der Pharma Chemica, 2011, 3 (5):341-347
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Synthesis of all the isomers of aliphatic side chain of Microcoline-B

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ABSTRACT

Synthesis of possible isomers of 2, 4-dimethyloctanoic acid, C_2-methyl centre was fixed by suing resolution method and C_4-methyl group was introduced by Evans asymmetric alkylation method.

Keyword: 2, 4-dimethyloctanoic acid, L-phenylalaninol, alkylation, D-phenylalaninol.

INTRODUCTION

The search for new immunosuppressive agents from natural sources has led to the discovery of structurally diverse and biologically operative compounds. Cyclosporine and FK-506 are the two examples of the natural products that have shown particular promise in the treatment of organ transplantation rejection through suppression of the immune response. Structure activity relationship (SAR) of these compounds lead to the discovery of novel intracellular targets for immunosuppression and new therapeutics devoid of the toxic side effects associated with our current drugs.

The absolute stereochemistry of the three asymmetric centres in the molecule was not assigned in the original isolation work. Comparison of ^{13}C and ^{1}H NMR chemical shifts with those of the corresponding majusculamide D compounds seemed to suggest that C_4-stereochemistry may also be S in the microcolins.

MATERIALS AND METHODS

General: - Melting points were determined in a sulfuric acid-bath and are uncorrected. IR spectra were recorded in KBr on a Shimadzu 435 spectrometer, ^{1}H NMR spectra on a Varian Gemini 200 MHz spectrometer with TMS as an internal standard and mass spectra on a Perkin Elmer Hitachi RDO-62 and MS-30 instrument.

i. General Procedure for the synthesis of (2S)-N-((S)-1-hydroxy-3-phenylpropan-2-yl)-2-methylpent-4-enamide (3a) and (2R)-N-((S)-1-hydroxy-3-phenylpropan-2-yl)-2-methylpent-4-enamide (3b):

To a stirred solution of racemic mixture, **(±)** 2- Methy1-4 pentenoic acid **(1)** (37 g, 325 mmol) in dry benzene (200 m1), thiony1 chloride (26 ml, 357 mmol) was added at room temperature. The reaction mixture was stirred for 8 h and concentrated to get crude acid chloride **(2)** (42 g).

The acid chloride **2** (42g, 316 mmol) in dry dioxane (100 ml) was added to a stirred solution of L-phenylalaninol (50g. 332 mmol) and trietylamine (69 ml, 632 mmol) in dry dioxane (330 ml) at 5-10^{0}C. After 2 h dioxane was removed under reduced pressure and the reaction mixture was neutralized with 1 N HC1. After usual workup, the mixture of amides **3a** and **3b** was subjected to column chromatography by eluting with 25-40% ethy1 acetate in hexane to obtain the faster moving amide **3a** (26 g, 32.5%) followed by slower moving amide **3b** (22.4 g, 28%).

For Amide-Faster (3a):

$[\alpha]_{D:}$ -13.1^0 (c=1.65 in $CHC1_3$).; Mp : 99-101 ºC; IR (KBr): 3570-3325 cm^{-1} (-NH, OH), 1660 cm^{-1} (C=O).; ^{1}H NMR ($CDCl_3$, 200MHZ): δ 7.40-7.14 (m, 5H, aromatic), 5.80-5.60 (m, 2H, -NH and –CH=CH_2), 5.10-4.95 (m, 2H, -CH= CH_2), 4.26-4.10 (m, 1H ,-$CHCH_2OH$), 3.72- 3.50 (m, 2H,-C$\underline{H_2}$ OH), 2.95-2.75 (m,2H,-CH_2Ph), 2.60 (bs, 1H, -OH, D_2O exchangeable), 2.40-2.00 (m, 3H, -$CHCH_3$ and allylic CH_2), 1.05 (d, J=7.25 Hz, 3H,-CHCH).

Amide-Slower (3b):

$[\alpha]_D$:-3.05^0 (c=1.38 in $CHC1_3$); mp: 104-106 ^{0}C.; ^{1}H NMR ($CDC1_3$, 200 MHz): δ 7.30-7.10 (m, 5H, aromatic), 5.70-5.45 (m, 2H, -NH and –CH=CH_2), 5.02-4.86 (m, 2H, -CH= CH_2), 4.20-4.10 (m,1H, $CHCH_2OH$), 3.70-3.50 (m, 2H, -CH_2OH), 2.90-2.75 (m,2H,-CH_2Ph), 2.32-2.00 (m, 3H, -$CHCH_3$ and allylic CH_2) 1.05 (d, J=6.12 Hz, 3H, -$CHCH_3$).

ii. (R)-3-((S)-4-((benzyloxy) methyl) pentanoyl)-4-benzyloxazolidin-2-one (5):

To a stirred solution of acid **4** (1.6 g, 7.2 mmol) and triethylamine (1.1 ml, 7.9 mmol) in dry THF (30 ml) at -78^{0}C was added trimethy1acety1 chloride (0.93 ml, 7.5 mmol). The resultant white suspension was stirred for 10 min at -78^{0}c and 45 min at 0^{0}C, it was re-cooled to -78^{0}C and a pre-cooled (-78^{0}C) solution of metallated oxazolidinone [prepared by the addition of 4 ml (2M) solution in hexane of n-BuLi to a solution of 1.4 g (7.9 mmol) of oxazolidinone) 43 in dry THF (10 ml) at -78^{0}c was added via cannula. The reaction mixture at -78^{0}C was stirred for 45min at 0^{0}C, and then quenched by the addition of saturated aqueous ammonium chloride solution. Volatiles were removed in vacuo and the residue was extracted with DCM (3x30 ml). the combined organic phase was washed with $NaHCO_3$ solution followed by water, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography using 2:8 mixture of ethy1 acetate-hexane to give compound **5** (1.33 g, 48%) as a thick syrup.

$[\alpha]_D$:-24.88^0 (c=1.05 in $CHC1_3$); ^{1}H NMR ($CDC1_3$, 200 MHz): 7.40-7.10 (m, 10H, aromatic), 4.65-4.50 (m, 1H, C_4-1H), 4.45 (s, 2H, OCH_2Ph), 4.05 (d, J=4.50 Hz, 2H, C_5-2H), 3.40-3.15 (m, 3H, -CH_2OBn and –CHPh), 3.05-2.85 (m, 2H,-CH_2CO-), 2.70-2.55 (dd, J=8.99 and 12.58 Hz, 1H,-CHHPh), 2.00-1.70 (m, 2H, C_3-1H), 1.65 1.45 (m, 1H, -$CHCH_3$), 0.95 (D, J=7.19 Hz, 3H, CH_3CH-)

iii. (R)-3-((R)-2-((S)-3-(benzyloxy)-2-methylpropyl)hex-4-enoyl)-4-benzyloxazolidin-2-one (6):
To a solution of compound **5** (1.24 g, 3.3 mmol) in dry THF (10 ml) at -40^{0}C lithium hexamethy1disilylazide (1M solution in THF, 3.6 ml, 3.6 mmol) was added and stirred at the same temperature for 45 min, ice cooled solution of croty1bromide (1.67 ml, 16.2 mmol) in dry THF (2 ml) was added to the reaction mixture via cannula and stirred for 2 h at the same temperature. Reaction mixture was quenched by the addition of saturated aqueous ammonium chloride solution and volatiles were removed under vacuum. The residue was dissolved in DCM (50 m1) washed with water, dried with Na_2SO_4 and concentrated to get pale yellow oil. This was purified by column chromatography using 15 % EtOAc-Hexane mixture as eluent to obtain compound 6 (0.83 g, 58%) as a colorless oil.

$[\alpha]_D$:-27.09^0 (c=0.62 in $CHC1_3$).; ^{1}H NMR ($CDC1_3$, 200 MHz): 7.40-7.10 (m, 10H, aromatic), 5.60-5.30 (m, 2H, Olefinic), 4.60-4.45 (m, 1H, C_4-1H), 4.40 (s, 2H,-OCH_2Ph), 4.10-3.78 (2xm, 3H, C_5-2H and -CH-CO-), 3.40-3.16 (m, 3H, -CH_2OBn and-CHHPh), 2.65-2.45 (m, 1H, -CHHPh), 2.40-1.20 (4xm, 8H, CH_3CH=CH-CH_2, C_1"-2H and –$CHCH_3$), 0.90 (d, J=7.5 Hz, 3H, CH_3CH-).

iv. (R)-2-((S)-3-(benzyloxy)-2-methylpropyl) hexan-1-ol (7):
To an ice cooled suspension of lithium borohydrirde (35 mg, 1.6 mmol) in ether was added compound **6** (0.63 g, 1.5 mmol) and H_2O (0.03ml, 1.6 mmol). Reaction mixture was stirred at the same temperature for 1h and quenched with 1 M aqueous NaOH solution. The mixture was stirred until both layers were clear and diluted with ether. Organic layer was separated, washed with brine dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography using 20% EtOAc-Hexane mixture as eluent to give alcohol **7** (0.24 g, 60%) as a syrup.

$[\alpha]_D$: 5.0^0 (c=0.72 in $CHC1_3$).; ^{1}H NMR ($CDC1_3$, 200 MHz): 7.30-7.10 (m, 5H, aromatic), 5.50-5.20 (m, 2H, Olefinic), 4.40 (s, 2H, -OCH_2Ph), 3.44 (d, J=4.55 Hz, 2H, -CH_2OH), 3.20 (d, J=6.36 Hz, 2H, - CH_2OBn), 2 .10-1.00 (4xm, 9H, C_2-1H, C_1-2H, C_2-1H, C_3-2H and C_6-3H), 0.86 (d, J-6.36 Hz, 3H, CH_3CH-).

v .(R)-2-((S)-3-(benzyloxy)-2-methylpropyl)hexyl 4-methylbenzenesulfonate (8):
Compound **7** (0.15 g, 0.57 mmol) dissolved in dry DCM (2ml) was cooled to ^{0}C. DMAP (0.091 g, 0.7 mmol), tosylchloride (0.120 g, 0.63 mmol) were added and this mixture was stirred at room temperature for 4h. The reaction mixture was diluted with DCM, washed with water dried (Na_2SO_4) and volatiles were removed under vacuum. Residue was purified by a silica gel column using 15 % EtOAc-hexane to give compound **8** (0.206 g, 86%) as a syrup.
$[\alpha]_D$:-2.20^0 (c=1 in $CHC1_3$).; ^{1}H NMR ($CDC1_3$, 200 MHz): 7.70 (D, J=7.23 Hz, 2H, aromatic), 7.30-7.10 (m, 7H, aromatic), 5.50-5.10 (m, 2H, Olefinic), 4.38 (s, 2H, -OCH_2Ph), 3.90-3.70 (m, 2H,-CH_2OTs), 3.12 (d, J=5.96 Hz, 2H, -CH_2OBn), 2.38 (s, 3H, CH_3 of Tosy1), 2.02-0.95 (5xm, 9H, C_2'-1H, C_1-2H, C_2-1H, C_3-2H and C_6-3H), 0.80 (d, J=6.80 Hz, 3H, CH_3CH-).

vi .1-(((2S,4R)-2,4-Dimethy1octyloxy)methy1)benzene (9):
To an ice cooled suspension of LAH (0.017 g, 0.46 mmol) in dry THF (2 ml) was added compound **8** (0.19 g, 0.46 mmol) in THF (1 ml). The reaction mixture was stirred at 50^{0}C for 3 h. Excess LAH was quenched with saturated aqueous Na_2SO_4 solution, filtered and washed with

THF (3x5 ml). The combined filtrates were concentrated under vacuum. Residue was dissolved in DCM, washed with water, dried (Na_2SO_4) and concentrated. The crude compound was purified by passing through silica gel column using 7% EtOAc-Hexane mixture as eluent to give compound **9** (76 mg, 68%) as a liquid.

$[\alpha]_D$: -8.480 (X=0.33 in$CHC1_3$).; ^{1}H NMR ($CDC1_3$, 200 MHz): 7.38-7.16 (m, 5H, aromatic), 5.50-5.25 (m, 2H, Olefinic), 4.45 (s, 2H, -OCH_2Ph), 3.30-3.15 (m, 2H, -CH_2OBn), 2.10-1.05 (4xm, 9H, C_2-H, C_3-2H, C_4-H, C_5-2H and C_8-3H), 0.95-0.80 (2xd, J=6.32 Hz, 6H, C_2-CH_3 and C_4-CH_3).

vii. (2S,4R)-2,4-Dimethyloctan-1-ol (10):
A mixture containing compound **9** (70 mg, 0.28 mmol) and 10% palladium on carbon (10 mg) in EtOAc (2 ml) was stirred under hydrogen atmosphere at room temperature for 4 h. the catalyst was filtered through a pad of celite and washed with ethy1 acetate. The filterate was concentrated to afford compound **10** (40 mg, 89%) as a syrupy liquid.

$[\alpha]_D$: 10.9^0 (c=0.22 in $CHC1_3$).; ^{1}H NMR ($CDC1_3$, 200 MHz): 3.50-3.30 (m, 2H, -CH_2-OH), 2.10-1.00 (bm, 10H, C_2-H, C_3-2H, C_4-H, C_5-2H, C_6-2H and C_7-2H), 0.95-0.75 (m, 9H, C_2-CH_3, C_4-CH_3 and C_8-3H).

viii. (2S, 4R)-2, 4- Dimethyloctanoic acid (11):
Oxidation of compound **10** (35 mg, 0.22 mmol) using Jones reagent was carried out by the procedure described earlier. Crude compound was purified by column chromatography using 1:1 ethy1 acetate-hexane to give acid **11** (27 mg, 71%) as a thick syrup.
$[\alpha]_D$: 6.00 (c=0.25 in MeOH), lit 6.50 (c=0.05 in MeOH).; ^{1}H NMR ($CDC1_3$, 200 MHz): 2.30-2.10 (m, 1H, C_2-H), 2.00-1.10 (bm, 12H, C_2-CH_3, C_3-2H, C_4-H, C5-2H, C_6-2H and C_7-2H), 0.90-0.72 (m, 6H, C4-CH_3 and C_8-3H).

ix. (S)-3-((R)-4-((benzyloxy) methyl) pentanoyl)-4-benzyloxazolidin-2-one (13):
Compound **13** was prepared by using the same procedure as described for compound **5** in 49% yield.
$[\alpha]_D$: 24.89^0 (c=0.45 in $CHC1_3$).; ^{1}H NMR ($CDC1_3$, 200 MHz): 7.40-7.10 (m, 10H, aromatic), 4.65-4.45 (m, 1H, C4-1H), 4.45 (s, 2H, OCH_2Ph), 4.15-3.95 (m, 2H, C5-2H), 3.40-3.20 (m, 3H,-CH_2OBn and-CHHPH), 3.00-2.80 (m, 2H, -CH_2CO), 2.68-2.50 (dd, J=9.09 and 11.36 Hz, 1H,-CHHPh), 1.90-1.70 (m, 2H, C_3-2H), 1.65-1.45 (m, 1H, -$CHCH_3$), 0.94 (d, J-6.81 Hz, 3H, CH_3CH-).

x. (S)-3-((S)-2-((R)-3-(benzyloxy)-2-methylpropyl) hex-4-enoyl)-4-benzyloxazolidin-2-one (14):
Compound **14** was prepared by using the same procedure as described for compound **6** in 58% yield.
$[\alpha]_D$: 31.11^0 (c=0.45 in $CHC1_3$).; ^{1}H NMR ($CDC1_3$, 200 MHz): 7.40-7.10 (m, 10H, aromatic), 5.60-5.40 (m, 2H, Olefinic), 4.60-4.45 (m,1H,C_4-1H), 4.42 (s, 2H, OCH_2Ph), 4.10-3.95 (m, 2H, C_5-2H), 3.95-3.80 (m, 1H, CHCO-), 3.40-3.20 (m, 3H, -CH_2OBn and –CHHPh), 2.65-2.50 (m, 1H, -CHHPh), 2.40-1.20 (4xm, 8H, C_2 -1H, C_3-2H,C_6-3H and C_1"-2H), 0.92 (d, J=6.81 Hz, 3H, CH_3CH-).

xi. (S)-2-((R)-3-(benzyloxy)-2-methylpropyl) hexan-1-ol (15):
Compound **15** was prepared by using the same procedure described for compound **7** in 61% yield.
$[\alpha]_D$:-4.7^0 (c=1.4 in $CHC1_3$).; ^{1}H NMR ($CDC1_3$, 200 MHz): 7.40-7.15 (m, 5H, aromatic), 5.55-5.25 (m, 2H,Olefinic), 4.42 (s, 2H, -OCH_2Ph), 3.50-3.40 (m, 2H,-CH_2OH), 3.20 (d, J=6.81 Hz, 2H, -CH_2OBn), 2.20-1.00 (4xm, 9H, C_2-1H, C_1'-2H, C_2-1H, C_3-2H and C_6-3H), 0.90 (d, J=6.81 Hz, 3H, CH_3CH-).

xii. (S)-2-((R)-3-(benzyloxy)-2-methylpropyl) hexyl 4-methylbenzenesulfonate (16):
Compound **16** was prepared by using the same procedure described for compound **8** in 88% yield.
$[\alpha]_D$: 7.92^0 (c=0.48 in $CHC1_3$).; ^{1}H NMR ($CDC1_3$, 200 MHz): 7.72 (d, J=8.64 Hz, 2H, aromatic), 7.35-7.18 (m, 7H, aromatic), 5.40-5.05 (m, 2H, Olefinic), 4.40 (s, 2H, -OCH_2Ph), 3.95-3.75 (m,2H, CH_2OTs), 3.18 (d, J=6.36 Hz, 2H, -CH_2OBn), 2.40 (s, 3H, CH_3 of Tosyl), 2.10-0.90 (5xm, 9H, C_2-1H, C_2-2H, C_2-1H, C_3-2H and C_6-3H), 0.85 (d, J=6.82 Hz, 3H, CH_3CH-).

xiii. 1-(((2R, 4S)-2,4-dimethyloctyloxy)methyl)benzene (17):
Compound **17** was prepared by using the same procedure described for compound **9** in 68% yield.
$[\alpha]_D$: 11.7^0 (c=0.62 in $CHC1_3$).; ^{1}H NMR ($CDC1_3$, 200 MHz): 7.32-7.14 (m, 5H,aromatic), 5.55-5.22 (m, 2H, Olefinic), 4.45 (s, 2H, -OCH_2Ph), 3.30-3.10 (m,2H,-CH_2OBn), 2.00-1.05 (3xm,9H,C_2-H,C_3-2H,C_4-H,C_5-2H and C_8-3H), 0.95-0.75 (2xd, J=6.82 Hz, 6H, C_2-CH_3 and C_4-CH_3).

xiv. (2R, 4S)-2, 4-Dimethyloctan-1-ol (18):
Compound **18** was prepared by using the same procedure described for compound **10** in 91% yield.
$[\alpha]_D$: 20.0^0 (c=0.32 in $CHC1_3$).; ^{1}H NMR ($CDC1_3$, 200MHz): 3.5-3.30 (m, 2H,-CH_2OH), 1.80-1.60 (m, 1H, C_2-H), 1.60-1.40 (m, 1H, C_4-H), 1.40-1.05 (m, 8H, C_3-2H, C_5-2H, C_6-2H and C_7-2H), 1.00-0.80 (m, 9H, C_2-CH_3, C_4-CH_3 and C_8-3H).

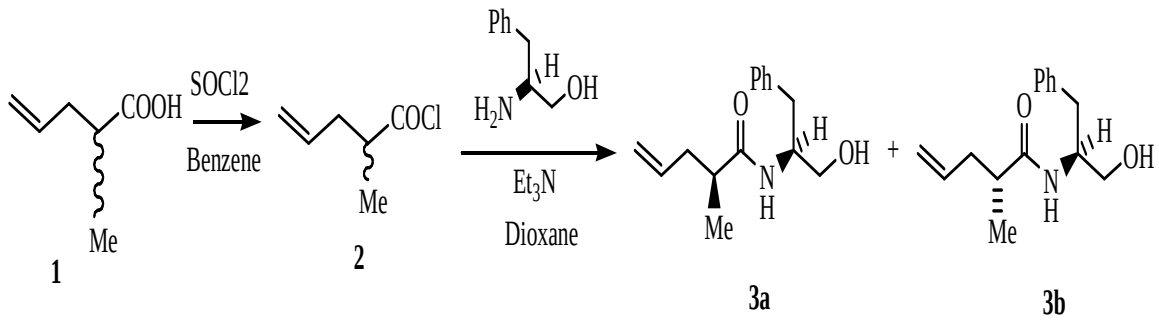
xv. (2R, 4S)-2, 4-Dimethyloctanoic acid (19):
Compound **19** was prepared by using the same procedure described for compound **11** in 71% yield.
$[\alpha]_D$: -5.95^0 (c=0.31 in MeOH). ; ^{1}H NMR ($CDC1_3$, 200 MHz): 9.00 (bs, 1H, -CO_2H), 2.65-2.45 (m, 1H, C_2-H), 1.80-1.10 (m, 12H, C_2-CH_3, C_3-2H, C_4-H, C_5-2H, C_6-2H, and C_7-2H), 1.05-0.80 (m, 6H, C_4-CH_3 and C_8-3H).

RESULTS AND DISCUSSION

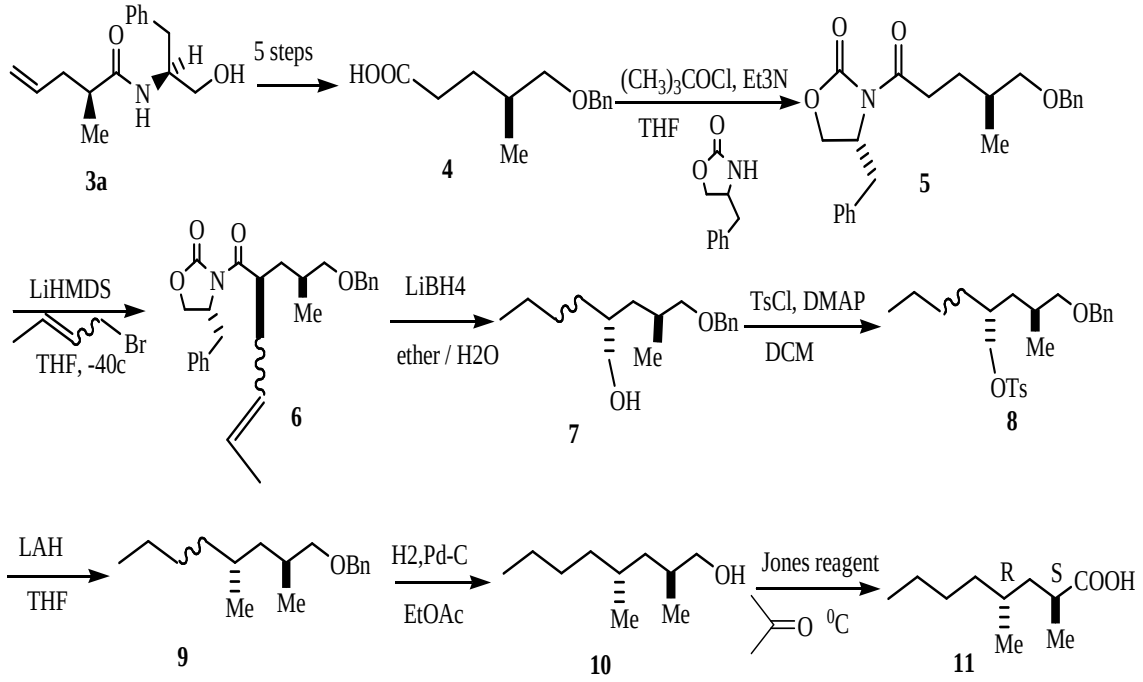
Synthesis of (2S)-N-((S)-1-hydroxy-3-phenylpropan-2-yl)-2-methylpent-4-enamide (3a) and (2R)-N-((S)-1-hydroxy-3-phenylpropan-2-yl)-2-methylpent-4-enamide (3b):
Quantitatively the racemic mixture of **(±)** 2- Methy1-4 pentenoic acid **(1)** in dry benzene, thiony1 chloride was added at room temperature. The reaction mixture was stirred for 8 h and concentrated to get crude acid chloride. The acid chloride **2** in dry dioxane was added to a stirred

solution of L-phenylalaninol and trietylamine in dry dioxane at 5-10 ^{0}C to give Synthesis of (2S)-N-((S)-1-hydroxy-3-phenylpropan-2-yl)-2-methylpent-4-enamide **(3a)** and (2R)-N-((S)-1-hydroxy-3-phenylpropan-2-yl)-2-methylpent-4-enamide **(3b)**:

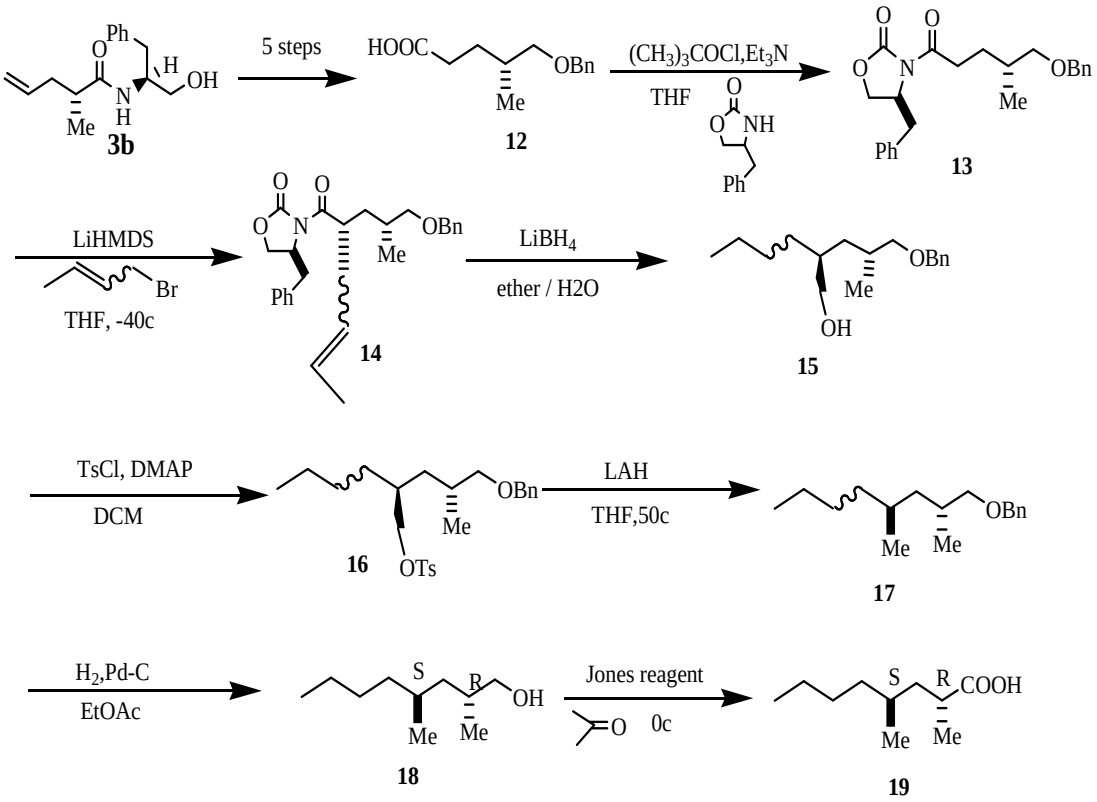
Scheme-1



Scheme-2



Scheme-3



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