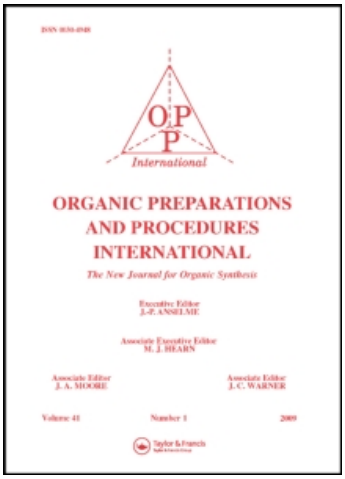

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SYNTHESIS OF CONAGENIN AND α-METHYLSERINE. A REVIEW

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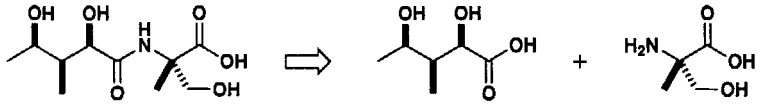
INTRODUCTION

Conagenin is a low molecular weight immunomodulator isolated from the culture broth of the soil bacterium *Streptomyces roseosporus* MI696-AF3 by Ishizuka and co-workers in 1991.[1] Conagenin stimulates activated T cells to induce lymphokine,[1] a type of cytokine, which is only one example among a wide range of biological activities of conagenin.[2] Proliferation of T cells and generation of antitumor cells were enhanced by conagenin. In addition, conagenin improves the efficiency of antitumor agents such as cyclophosphamide, mitomycin C and adriamycin. Since conagenin itself does not show cytotoxicity to higher organisms, it may be a potential agent for cancer chemotherapy.

The structure of conagenin, including absolute configuration, was determined by X-ray structural analysis as shown in structure **1**.[1] The single crystal obtained from aqueous methanol was determined as monoclinic space group $P2_1$. The absolute configuration was elucidated by the anomalous dispersion effect of C, N, and O atoms for Cu $K\alpha$ radiation. Conagenin consists of two simple but densely functionalized fragments, a (2*R*,3*S*,4*R*)-2,4-dihydroxy-3-methylpentanoic acid moiety (**2**) and an (*S*)-α-methylserine unit (**3**). The pentanoic acid fragment (**2**) contains three-(2*R*,3*S*,4*R*)-contiguous stereogenic centers, and the carboxylic group in **2** is linked to the stereochemically congested α-amino group in the quaternary stereocenter of the α-methylserine (**3**). Since an adjacent stereogenic center often disturbs the construction of a new stereogenic center, well-designed methodology is required for the stereoselective synthesis of the contiguous stereogenic centers in **2**. Stereoselective construction of quaternary stereogenic centers substituted with nitrogen is one of the most difficult task in organic synthesis. These challenging structural features coupled with significant biological activity make this molecule as an attractive target for synthetic chemists.

The first synthesis of conagenin was reported by Hatakeyama in 1996.[3] Following this work, a formal synthesis by Enders (1999),[4] total syntheses by Nagao (2001)[5] and by Ichikawa



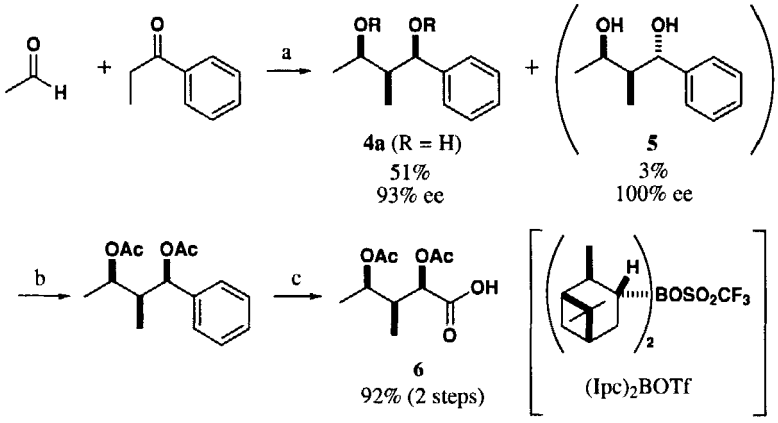
(+)-conagenin (**1**) | 2,4-dihydroxy-3-methylpentanoic acid (**2**) | α-methylserine (**3**)

(2005)[6] have been described. During the preparation of this manuscript, two total syntheses appeared.[7,8] This review will focus on three topics: the stereoselective synthesis of the 2,4-dihydroxy-3-methylpentanoic acid (**2**), the enantioselective synthesis of the α-methylserine (**3**), and the coupling of these two fragments **2** and **3**.

I. STEREOSELECTIVE SYNTHESIS OF 2,4-DIHYDROXY-3-METHYLPENTANOIC ACID

1. Asymmetric Aldol Reaction of Chiral Boron Enolate

The three consecutive stereocenters in pentanoic acid **6** were constructed by asymmetric aldol reactions followed by diastereoselective reductions (*Scheme 1*).[3] The enolate, which was derived by treatment of propiophenone with (–)-$(Ipc)_2BOTf$[9] and diisopropylethylamine (DIPEA) in CH_2Cl_2, was allowed to react with acetaldehyde. The resulting boron aldolate was reduced directly with $NaBH_4$ in the presence of methanol. The desired diol **4a** and its epimer **5** were isolated in 51% yield with 93% ee, and 3% yield with 100% ee, respectively.



4a (R = H) 51% 93% ee | **5** 3% 100% ee | **6** 92% (2 steps) | $(Ipc)_2BOTf$

(a) (–)-$(Ipc)_2BOTf$, DIPEA, CH_2Cl_2, –78 to –23 °C, then $NaBH_4$, MeOH, –23 °C;
(b) Ac_2O, Et_3N, DMAP (cat), CH_2Cl_2; (c) $RuCl_3$ (cat), HIO_4, $CH_3CN/CCl_4/H_2O$ (5:5:8).

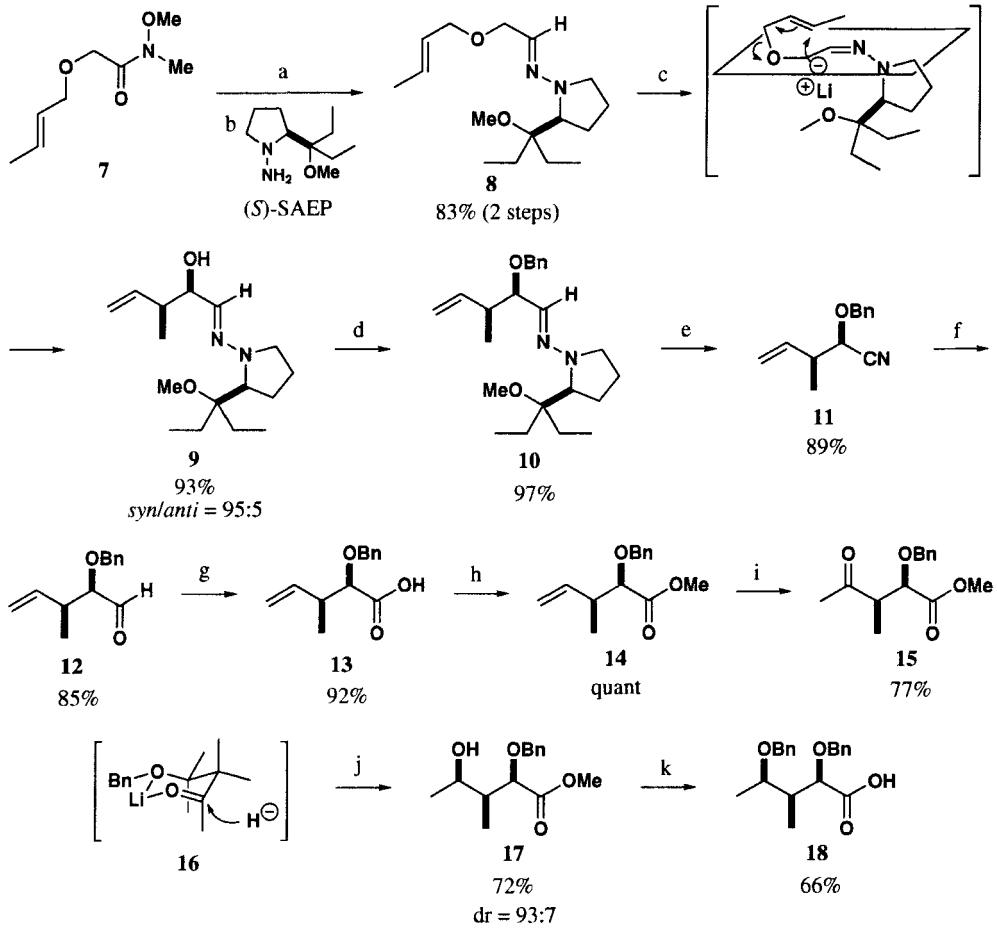
Scheme 1

No other isomers having 2,3-*anti* configuration were detected. Methanol was crucial for the stereoselective reduction. When the aldolate was reduced in the absence of methanol, no diastereoselectivity was observed. After protection of two hydroxy groups in **4a** by the reaction with acetic anhydride in the presence of triethylamine and *N*,*N*-dimethylaminopyridine

(DMAP) in CH_2Cl_2, oxidative cleavage of the phenyl ring in **4b** with RuO_4 provided carboxylic acid **6** in 92% yield. It should be noted that periodic acid is superior to sodium periodate in RuO_4 oxidations of aromatic compounds.[10]

2. Asymmetric [2,3] Wittig Rearrangement

Enders described the diastereo- and enantioselective synthesis of protected β-substituted γ,δ-unsaturated α-hydroxyaldehyde (**12**) by asymmetric [2,3] Wittig rearrangement of (*S*)-1-amino-2-(1-ethyl-1-methoxypropyl)pyrrolidine (SAEP) hydrazones (*Scheme 2*); **12** was successfully employed for the synthesis of protected 2,4-dihydroxy-3-methylpentanoic acid.[4]



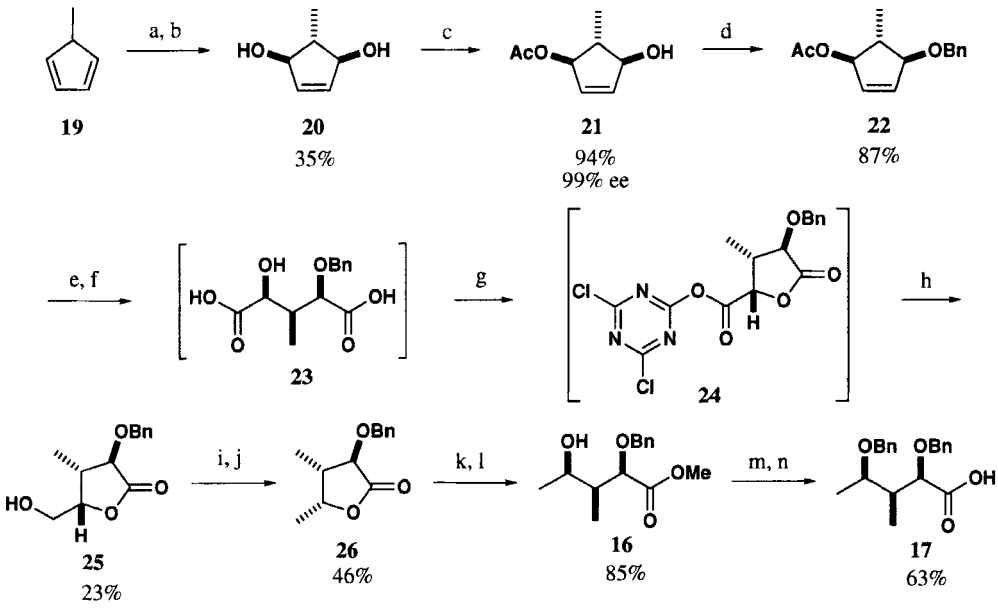
(a) $LiAlH_4$, THF, 0 °C; (b) SAEP, 0 °C to rt; (c) LDA, THF/DMPU (5:1), –78 °C, 22 h; (d) BnBr, 18-crown-6, KH, THF, 0 °C, 2 h; (e) MMPP, MeOH, 0 °C, 1 h; (f) DIBAL-H, pentane, –78 °C, 2 h, then MeOH, –78 to 0 °C, 2 h, then 1 M H_2SO_4, 0 °C, 1 h; (g) PDC, DMF, rt, 12 h; (h) CH_2N_2, ether, rt; (i) $PdCl_2$, CuCl, O_2 (5 bar), H_2O/acetone (1:6), 70 °C, 4 h; (j) LiI, $LiBH_4$, ether, –100 °C, 2 h; (k) $BnOCNHCCl_3$, BF_3•OEt_2, cyclohexane, rt, 0.5 h, then 1.1 M K_2CO_3, MeOH, rt, 12 h, and 1 M HCl.

Scheme 2

The Weinreb amide **7** was reduced by $LiAlH_4$ followed by the reaction with SAEP to give hydrazone **8** in 83% yield. The hydrazone **8** was deprotonated by treatment with lithium diisopropylamide (LDA) in THF/*N*,*N*-dimethyl propyleneurea (DMPU) at –78 °C. The resulting 1-azaallyl anion spontaneously rearranged to afford homoallyl alcohol **9** in 93% yield with the *syn*/*anti* ratio 95:5.[11] The desired diastereomer *syn*-**9** could be enriched to ≥99:1 dr by chromatographic separation. The hydroxy group in compound **9** was protected as a benzyl ether by using KH/18-crown-6/BnBr system without epimerization. The auxiliary, SAEP, was oxidatively removed with magnesium monoperoxyphthalate (MMPP) to give nitrile **11**. Attempts to hydrolyze **11** to acid **13** or methyl ester **14** were unsuccessful under both acidic and basic conditions. Accordingly, the nitrile group was reduced with diisobutylaluminium hydride (DIBAL) in pentane. Use of CH_2Cl_2 as solvent in this reduction resulted in a partial epimerization at the α-center (20%). The resultant aldehyde **12** was oxidized with pyridinium dichromate (PDC), and esterification of **13** with diazomethane furnished the methyl ester **14**. Since the Wacker oxidation of the terminal olefin of **14** using a DMF/H_2O system as solvent as reported by Tsuji[12] led to up to 20% epimerization, modified reaction conditions using an acetone/water solvent mixture were devised to alleviate this problem. Reduction of ketone **15** with $LiBH_4$ (10 eq) in the presence of excess LiI (10 eq) in ether at –100 °C proceeded in a *syn*-selective manner in 72% yield.[13] The selectivity in this reduction is rationalized by assuming the formation of six-membered chelate complex **16**, which would be attacked by the hydride anion from the least hindered face. Finally, the hydroxy group in **17** was protected as benzyl ether with *O*-benzyltrichloroacetimidate in the presence of a catalytic amount of BF_3•OEt_3[14] to afford **18** in 66% yield.

3. Enzymatic De-symmetrization of 5-Methyl-2-cyclopentene-1,4-diol

Chemo-enzymatic methodology was utilized for the synthesis of the pentanoic acid moiety **17** of conagenin. The synthesis started with 5-methylcyclopentadiene (**19**) which was converted into diol **20** by the one-pot sequence involving photo-sensitized oxidation followed by reduction with thiourea (*Scheme 3*).[5] Enzymatic acetylation of the σ-symmetric prochiral diol **20** with lipase AK (Amano Pharmaceutical Co. Ltd) in the presence of vinyl acetate gave the monoester **21** in 94% yield with 99% ee, and the remaining hydroxy group was protected as the benzyl ether with benzyl bromide in the presence of Ag_2O in 87% yield. Oxidative cleavage of the double bond in cyclopentene **22**, followed by alkaline hydrolysis of the acetate, gave hydroxy dicarboxylic acid **23**. Lactonization of **23** with cyanuric chloride followed by chemoselective reduction of **24** by $NaBH_4$ afforded the hydroxymethyl γ-lactone **25** (23% yield from **22**). The hydroxymethyl group in **25** was reduced to a methyl group by Barton's radical-induced deoxygenation procedure[15] to produce lactone **26** in 46% yield. Ring-opening of the lactone with aqueous NaOH in MeOH followed by treatment with methyl iodide gave corresponding methyl ester **16** in 85% yield. Following similar procedures reported by Enders, **16** was converted into **17** in 63% overall yield.

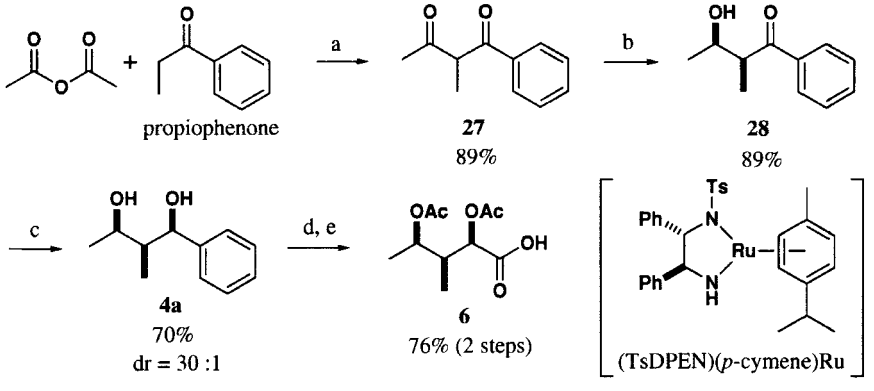


(a) O_2, hv, rose bengal, AcONa, MeOH, –78 °C, 80 min; (b) $(NH_2)_2CS$, MeOH, rt, 13 h; (c) lipase AK, CH_2=CHOAc, THF, rt, 7 h; (d) Ag_2O, BnBr, KI, toluene, rt, 15.5 h; (e) $NaIO_4$, $KMnO_4$, Na_2CO_3, acetone/water (5:6), rt, 1 h; (f) 1 M NaOH, MeOH, rt, 1 h; (g) cyanuric chloride, NMM, DME, rt, 3 h; (h) $NaBH_4$, 0 °C, 10 min; (i) PhOCSCl, DMAP, CH_2Cl, rt, 4 h; (j) AIBN, *n*-Bu_3SnH, toluene, 75 °C, 1 h; (k) 1 M NaOH, MeOH, rt, 1 h; (l) K_2CO_3, MeI, acetone, rt, 3.5 h; (m) $BnOCNHCCl_3$, BF_3•OEt_2, cyclopentane, rt, 2 h; (n) 1 M K_2CO_3, MeOH, reflux, 2 h.

Scheme 3

4. Dynamic Kinetic Resolution (DKR) by Transfer Hydrogenation of a β-Diketone

The three consecutive stereogenic centers in Hatakeyama's key intermediate **4a** were constructed in three steps starting from propiophenones *via* dynamic kinetic resolution (DKR) based on transfer hydrogenation and chelation-controlled reduction (*Scheme 4*).[6] Lewis



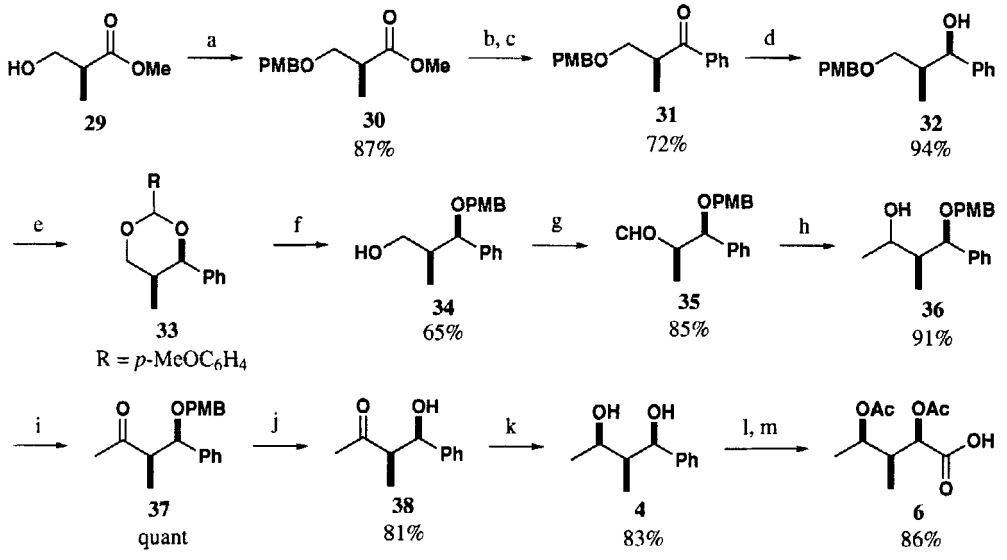
(a) TsOH, $2BF_3$•3AcOH; (b) (TsDPEN)(*p*-cymene)Ru, HCOOH, Et_3N, CH_2Cl_2, 40 °C, 3 h; (c) $Zn(BH_4)_2$, ether, 0 °C, 30 min; (d) Ac_2O, DMAP, pyridine, rt, 30 min; (e) $RuCl_3$•*n*H_2O, H_5IO_6, $CCl_4/CH_3CN/H_2O$ (2:2:3), rt, 18 h.

Scheme 4

acid-catalyzed acylation of propiophenone with acetic anhydride afforded 1,3-diketone **27** in 89% yield. Diketone **27** was subjected to transfer hydrogenation catalyzed by chiral ruthenium complex, (TsDPEN)(*p*-cymene)Ru, as reported by Cossy[16] to give β-hydroxyketone **28**. During the course of this reaction, the stereogenic center in the substrate **27** spontaneously racemized, and the transfer hydrogenation proceeded in an enantiomer-selective and diastereoface-selective manner, resulting in the *syn*-diastereomer **28** in 89% yield. The chelation-controlled diastereoselective reduction of **28** by zinc borohydride [$Zn(BH_4)_2$][17] gave the 1,3-*syn*-diol **4a** with high selectivity (30:1). After purification by chromatography and recrystallization, acetylation of the two hydroxy groups in **4a** followed by oxidative cleavage of the phenyl group afforded the pentanoic acid moiety **6** in 76% yield.

5. Chelation-controlled Reduction of Methyl 3-Hydroxy-2-methylpropanoate

Commercially available methyl (*S*)-3-hydroxy-2-methylpropanoate (**29**) was used for synthesis of pentanoic acid moiety (*Scheme 5*) and α-methylserine fragment (*Scheme 21*).[7]



(a) 2-PMBoxy-3-nitropyridine, PPTS, CH_2Cl_2, reflux, overnight; (b) LiOH, H_2O, rt, 4 h; (c) PhLi, ether, 0 °C, 30 min; (d) $Zn(BH_4)_2$, ether, 0 °C, 30 min; (e) DDQ, MS 3 Å, CH_2Cl_2, rt., 1 h; (f) DIBAL-H, CH_2Cl_2, –80 °C, 1 h; (g) Dess-Martin periodinate, CH_2Cl_2, rt., 30 min; (h) MeLi, ether, –80 °C, 30 min; (i) Dess-Martin periodinate, CH_2Cl_2, rt., 30 min; (j) DDQ, CH_2Cl_2, rt., 1 h; (k) $Zn(BH_4)_2$, ether, 0 °C, 30 min; (l) Ac_2O, pyridine, DMAP, rt., 30 min; (m) $RuCl_3$ (cat), H_5IO_6, CH_3CN-CCl_4-H_2O, rt., 18 h.

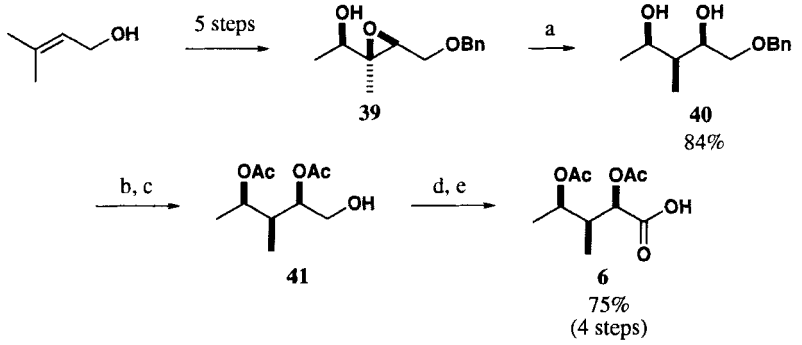
Scheme 5

Protection of the hydroxy group in **29** with *p*-methoxybenzyloxy-3-nitropyridine[18] and pyridinium *p*-toluenesulfonate (PPTS) gave *p*-methoxybenzyl (PMB) ether **30** in 87% yield. Saponification with lithium hydroxide followed by treatment of the resultant carboxylic acid with two equivalent of phenyllithium afforded phenyl ketone **31** in 72% yield. Chelation-controlled reduc-

tion of ketone **31** was carried out by using $Zn(BH_4)_2$ to give alcohol **32** in 94% yield with high diastereoselectivity (19:1). The PMB group in **32** was transformed into benzylidene acetal **33** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in the presence of molecular sieves (3 Å) in CH_2Cl_2. Reductive cleavage of the benzylidene acetal group with diisobutylaluminium hydride afforded the primary alcohol **34** in 65% yield. Oxidation of **34** with Dess-Martin periodinate gave aldehyde **35**, which was treated with methyllithium in ether at –80 °C to afford a 4:1 mixture of two diastereomers of secondary alcohol **36** in 77% overall yield for two steps. Oxidation of **36** with Dess-Martin periodinate gave ketone **37**, which was then reduced with $Zn(BH_4)_2$ to afford a low level of diastereoselectivity; however, removal of PMB group in **37** with DDQ followed by reduction of the resulting β-hydroxy ketone **38** with $Zn(BH_4)_2$ in ether at 0 °C furnished the *syn*-1,3-diol **4** with high diastereoselectivity (>50:1) in 83% yield. Diol **4** was transformed into **6** in 86% yield by the procedure reported by Hatakeyama.[3]

6. Ti(III)-mediated Ring Opening of Chiral 2,3-Epoxy Alcohol

The synthesis started with 3-methyl-2-buten-1-ol, which was transformed into chiral epoxy alcohol **39** in five steps: i) protection of the hydroxy group as a benzyl ether, ii) allylic oxidation with SeO_2, iii) addition of methylmagnesium iodide to the resulting aldehyde, iv) kinetic resolution of the allylic alcohol by the Sharpless epoxidation, and v) diastereoselective epoxidation with *m*CPBA. Reductive ring-opening of the epoxide with Cp_2TiCl[19] (generated from three equivalents of Cp_2TiCl_2 and six equivalents of Zn in the presence of three equivalents of $ZnCl_2$) was carried out in THF to afford the diol **40** exclusively in 84% yield with trace amounts of the *anti,anti* diastereomer. After removal of the minor diastereomer by silica gel chromatography, acetylation of the two hydroxy groups and removal of the benzyl group by palladium-catalyzed hydrogenolysis afforded primary alcohol **41**, which was oxidized to carboxylic acid by a two-step process involving SO_3-pyridine and sodium chlorite oxidation to furnish **6** in 75% yield over 4 steps.

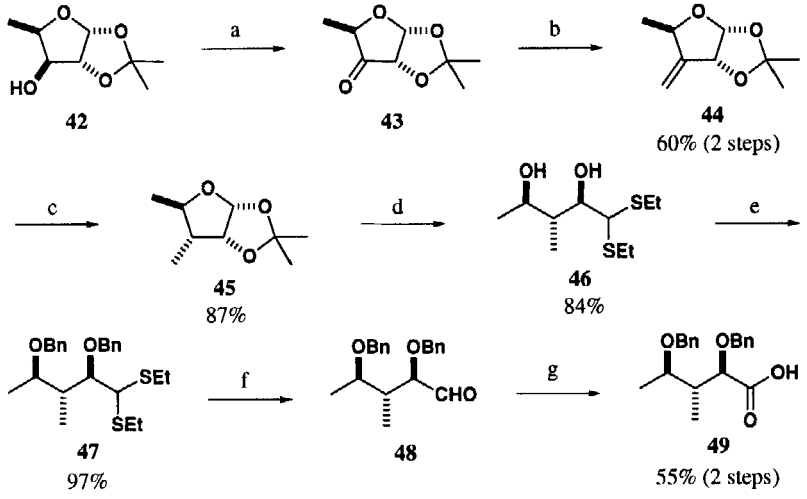


(a) Cp_2TiCl_2, Zn, $ZnCl_2$, THF, –20 °C to rt., 6 h; (b) Ac_2O, Et_3N, DMAP, CH_2Cl_2; (c) H_2, 10% Pd/C, EtOAc, rt., 1 h; (d) SO_3-Py, Et_3N, DMSO, CH_2Cl_2, 0 °C; (e) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, rt.

Scheme 6

7. Chiron Approaches Using D-Xylose and Poly-[(R)-3-hydroxybutyric] Acid from Sugar Cane

The epimer at C-3 position of 2,3-dihydroxy-3-methylpentanoic acid moiety of conagenin was synthesized by Herczegh and co-workers[20] starting from 5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (**42**) (*Scheme 7*), which was prepared from D-xylose in four steps.[21] The secondary hydroxy group in **42** was oxidized with chromium trioxide-pyridine complex to the

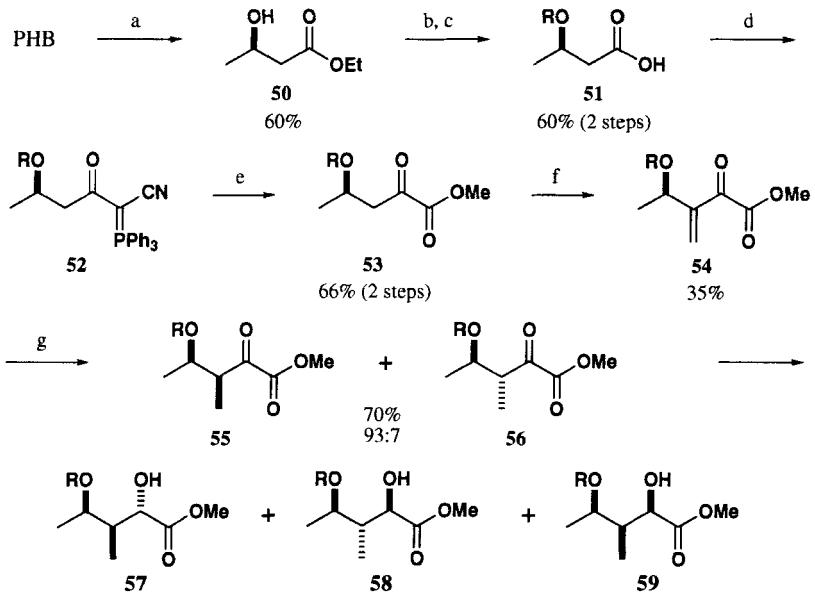


(a) CrO_3•2Py, Ac_2O, CH_2Cl_2; (b) Ph_3PCH_3Br, *n*-BuLi, THF; (c) H_2, 10% Pd/C, EtOAc; (d) EtSH, conc. HCl, THF, 0 °C; (e) BnBr, NaH, TBAI, THF; (f) $HgCl_2$, $CdCO_3$, acetone/water; (g) PDC, DMF.

Scheme 7

ketone, which was readily converted to the exo-methylene compound **44** by the Wittig reaction in 60% from **42**. Catalytic hydrogenation of **44** using 10% Pd on charcoal in ethyl acetate gave **45** as a single diastereomer in 87% yield. Treatment of **45** with ethanethiol in a mixture of hydrochloric acid and THF gave dihydroxy dithioacetal **46** in 84% yield. After protection of the two hydroxy groups with benzyl bromide and sodium hydride, dithioacetal **47** was treated with $HgCl_2$ to give the aldehyde **48**, which was subsequently oxidized with PDC to give carboxylic acid **49** in 55% yield from **47**.

Poly-[(*R*)-3-hydroxybutyric] acid (PHB) is a readily accessible chiral synthon prepared from sugar cane.[22] Starting from PHB, the pentanoic acid moiety of conagenin and its diastereomer were synthesized (*Scheme 8*).[23] Acid-catalyzed depolymerization of PHB in the presence of ethanol gave ethyl ester **50** in enantiomerically pure form in 60% yield. After protection of the hydroxy group with *tert*-butyldimethylsilyl (TBDMS) chloride, saponification of ethyl ester (LiOH/aq. MeOH) gave carboxylic acid **51** in 60% yield in two steps. Conversion of **51** to 2-oxo ester **53** was achieved in 66% yield; treatment of **51** with (cyanomethylene)triphenylphosphorane in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI) and 4-dimethylaminopyridine (DMAP) afforded the β-ketocyanophosphorane **52**, which was oxidized with



condition	yield, %	57/58/59
Bu_4NBH_4, MeOH, –78 °C	67	85:6:9
$LiBH_4$, Et_2O, –90 °C	53	54:5:41

(a) H_2SO_4 (cat), 1,2-dichloroethane, EtOH, 2 days; (b) TBDMSCl, imidazole, DMF; (c) LiOH, MeOH, H_2O/HCl; (d) Ph_3PCHCN, EDCI, DMAP, CH_2Cl_2; (e) O_3, MeOH, CH_2Cl_2, –78 °C; (f) $(CH_2O)_n$, morpholine, AcOH, 70 °C; (g) H_2, Pd/C, EtOAc.

Scheme 8

ozone as reported by Wasserman and Ho[24] to provide 2-oxo ester **53**. Mannich methylenation of **53** with excess paraformaldehyde and a catalytic amount of morpholine in acetic acid afforded α-keto-β-methylene ester **54** in 35% yield. Hydrogenation of **54** on 5% palladium on charcoal gave a 93:7 mixture of diastereomers **55** and **56** in 70% yield.

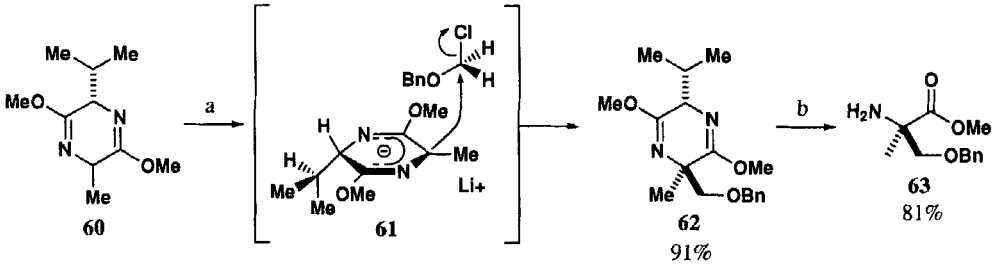
This mixture was subjected to reduction with tetrabutylammonium borohydride in methanol to give a 85:6:9 mixture of α-hydroxy esters **57**, **58** and **59** in 67% yield. The desired diastereomer **59**, which has same configuration as the pentanoic acid moiety of conagenin, was obtained in only 6%. The reduction using lithium borohydride in ether improved the yield of **59** to 22%.

II. STEREOSELECTIVE SYNTHESIS OF α-METHYLSERINE

1. Schöllkopf's bis(Lactim) Ether Method

The enantioselective synthesis of α-methylserine was achieved by Schöllkopf and co-workers (*Scheme 9*).[25] Mixed *bis*(lactim) ether **60** which contains L-valine as chiral auxiliary was metallated with *n*-butyllithium to give the lithium compound **61**, which reacted with chloromethyl benzyl ether to afford the (3*R*)-adduct **62** as a single diastereomer in 91% yield.[26]

Hydrolysis of **62** with 0.25 M HCl at room temperature afforded (*R*)-*O*-benzyl-α-methylserine methyl ester (**63**) in 81% yield. The chiral auxiliary of L-valine was recovered in enantiomerically pure form.

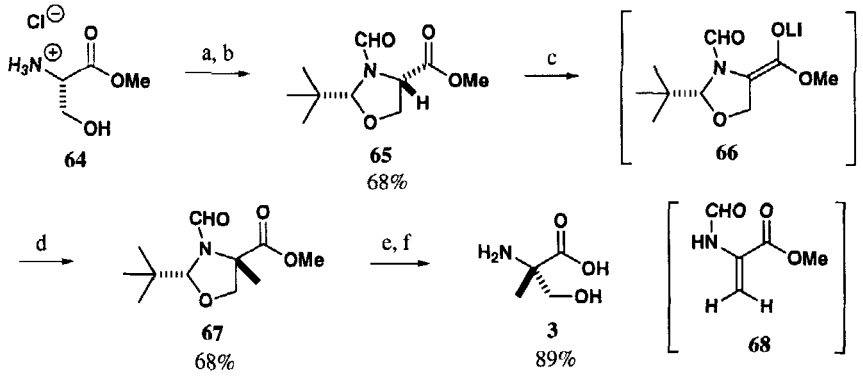


(a) BuLi, THF, –78 °C, 10 min, then $BnOCH_2Cl$, –70 °C, 4 h; (b) 0.25 M HCl, rt. 5 days.

Scheme 9

2. Seebach's α-Alkylation of Serine with Self-reproduction of the Chiral Center

Seebach reported a new method for the alkylation of serine using *N*-formyl substituted heterocycles such as **65** (*Scheme 10*).[27] A mixture of serine methyl ester hydrochloride, Et_3N, pivalaldehyde and pentane was heated at reflux with continuous removal of water to afford a 1:1 diastereomeric oily mixture of N,O-acetal in 81% yield which was treated with acetic formic anhydride in ether to furnish N-formyloxazolidine **65** as crystals in 84% yield. Treatment of **65** with lithium diisopropylamide (LDA) in THF at –78 °C gave an orange solution of the enolate **66**, which reacted with iodomethane in the presence of HMPA to afford **67** in 68% yield. It should be noted that enolate **66** slowly decomposes to α-aminoacrylate **68** with β-elimination and that only a poor yield (46%) of the alkyation was realized without co-solvent such as HMPA or DMPU. The hydrolysis of oxazolidine **67** was effected by refluxing in 6 M HCl to give (*S*)-α-methylserine (**3**) in 89% yield after purification through ion exchange column.

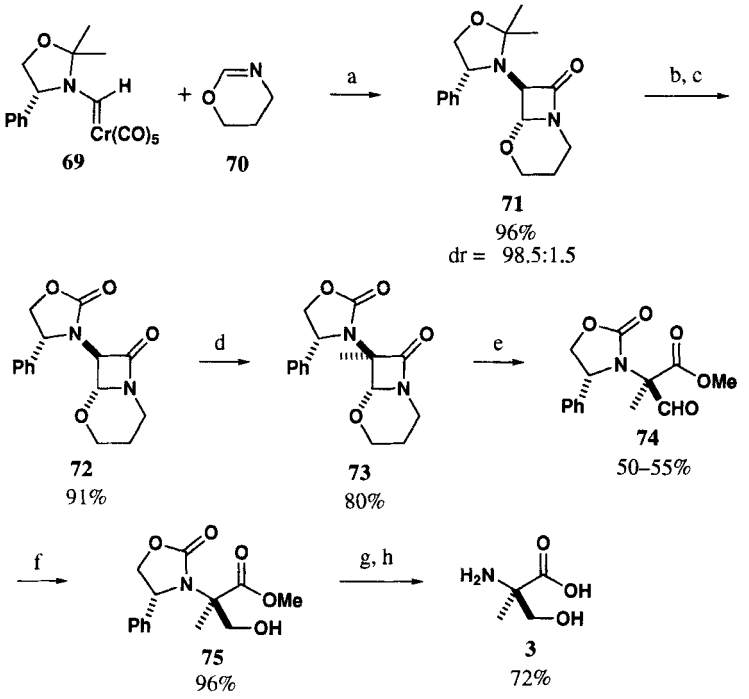


(a) pivalaldehyde, triethylamine, pentane, reflux, Dean-Stark trap; (b) acetic formic anhydride; (c) LDA, THF, –78 °C; (d) MeI, THF, HMPA; (e) 6 M HCl, reflux; (f) ion exchange column.

Scheme 10

3. *Hegedus' Synthesis of α-Alkylated α-Amino Acid from Chromium-carbene Complex-derived β-Lactam*

The synthesis by Hegedus starts with the optically active β-lactam **71** prepared by photochemical reaction of chromium aminocarbene complexes **69** (*Scheme 11*).[28] Irradiation of an ethereal solution of aminocarbenechromium complex **69**[29] and 5,6-dihydro-4*H*-1,3-oxazine **70**



(a) CO (60 psi), hv (med. press 450-W Hg lamp), ether, 24 h; (b) 0.2 M HCl, THF, 25 °C, 45 min; (c) triphosgene, DIEA, CH_2Cl_2, 0 °C, 45 min; (d) KHMDS, THF, –78 °C, 1 h, then CH_3I, DMF, –78 °C, 15 min; (e) HCl in MeOH, 25 °C, 24 h, then 1 M HCl/THF (1:1), 25 °C, 48 h; (f) $NaBH_4$, CH_3OH, 0 °C, 45 min; (g) 1 M KOH/dioxane (1:1), 25 °C, 16 h; (h) Li, NH_3, *t*-BuOH, THF, –78 °C, 10 min; 2 M KOH, 70 °C, 2 h, ion exchange.

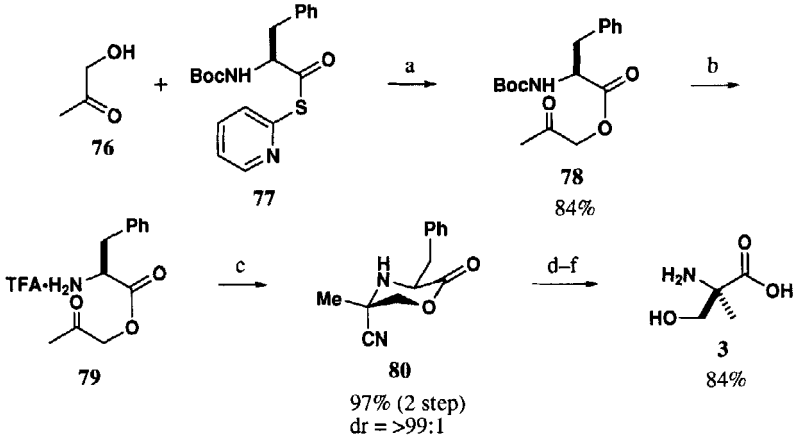
Scheme 11

using medium pressure Hg lamp for 24 hours under the pressure of CO (60 psi) produced β-lactam **71** in 95% yield with an excellent diastereomer ratio (>98.5:1.5). Because of the steric hindrance of the dimethyl group in oxazolidine **71**, alkylation on the β-lactam ring under a wide variety of conditions failed, either resulting in recovered starting material or decomposition. The oxazolidine group was converted to oxazolidinone **72** by simple hydrolysis of the acetonide under acidic condition followed by recyclization with triphosgene. Deprotonation of **72** with potassium hexamethyldisilazide (KHMDS) followed by alkylation with methyl iodide gave **73** with clean retention of stereochemistry in 73% yield over three steps from **71**. Use of lithium bases, such as *tert*-butyllithium or LDA, in the presence or absence of HMPA or TMEDA, resulted in lower yields of **73**. The β-lactam ring in **73** was readily cleaved by HCl in methanol, and the remaining aminal was cleaved by using 1 M HCl in THF to form the corresponding alde-

hyde **74**, which was treated with $NaBH_4$ in methanol to afford **75** in 96% yield. Hydrolysis of the methyl ester with aq. KOH in dioxane followed by cleavage of the oxazolidinone ring with lithium in liquid ammonia and *t*-BuOH afforded (R)-α-methylserine in 72% yield.

4. Ohfune's Asymmetric Strecker Synthesis

Ohfune's synthesis is based on an intramolecular Strecker-type reaction using phenylalanine as chiral auxiliary (*Scheme 12*).[30] Condensation of hydroxyacetone (**76**) with *N*-Boc-L-phenylalanine 2-pyridyl thiol ester (**77**) in toluene at room temperature gave ester **78** in 84% yield. After removal of Boc group with trifluoroacetic acid (TFA), the resulting TFA salt **79** was treated with two equiv of NaCN in 2-propanol to afford the cyclic amino nitrile **80** in 97% yield with excellent stereoselectivity (~98% diastereomerc excess). The phenylalanine moiety in **80** was removed by treatment with *tert*-butyl hypochlorite and triethylamine followed by hydrolysis of the resultant mixture of enamine and imine with concentrated HCl to provide (*R*)-α-methylserine in 84% yield after purification.

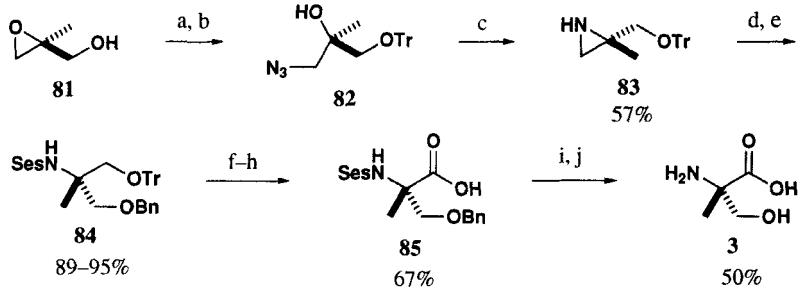


(a) toluene, rt, 5 days; (b) TFA/CH_2Cl_2 (1:1), 0 °C, 1.5 h; (c) 2 equiv NaCN, 2-propanol, rt, 2 h; (d) 2 equiv *t*-BuOCl, ether, 0 °C, 30 min, rt, 2 h, then Et_3N, rt, 8 h; (e) conc. HCl, 0 °C, 4 h, rt, 48 h, then 80 °C, 24 h; (f) Dowex 50W x 4 (elution with 1 N NH_3), then recrystallized from H_2O/EtOH/Et_2O.

Scheme 12

5. Nucleophilic Ring Opening of N-Sulfonylaziridine

The synthesis of α-methylserine was accomplished using aziridine **83** as an intermediate, which was prepared from commercially available (*S*)-(–)-2-methylglycidol (**81**) (93% ee) as shown in *Scheme 13*.[31] After protection of the hydroxy group in **81** as its trityl ether, epoxy ring opening was carried out using sodium azide in the presence of ammonium chloride in methanol to afford azidoalcohol **82**, which was treated with triphenylphosphine in hot acetonitrile. The aziridine **83** was isolated in 57% yield with no loss of stereochemistry (>92% ee).[32] *N*-Protection of **83** with β-trimethylsilylethanesulfonyl chloride (Ses–Cl) followed by nucleophilic ring-opening of the resultant activated aziridine with sodium benzyl alkoxide afforded aminodiol



Ses = $-SO_2CH_2CH_2SiMe_3$

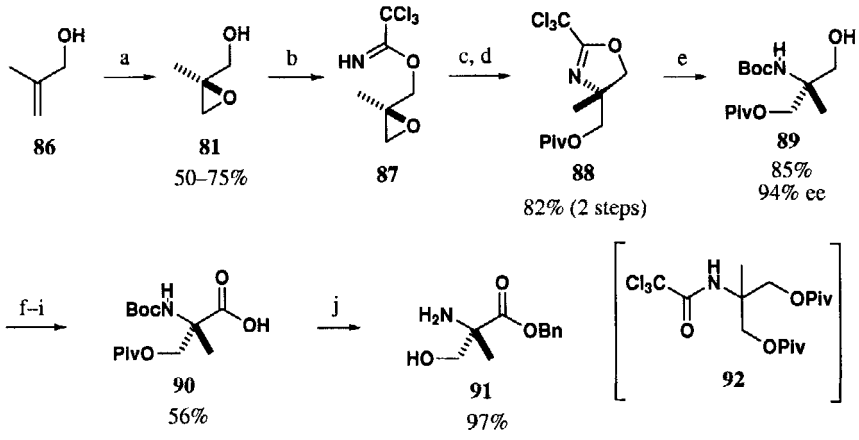
(a) TrCl, Et_3N, DMAP, CH_2Cl_2, rt, 48 h; (b) NaN_3, NH_4Cl, MeOH, 64 °C, 3 h; (c) Ph_3P, CH_3CN, 83 °C, 30 min; (d) $Me_3SiCH_2CH_2SO_2Cl$, Et_3N, CH_2Cl_2, 0 °C, 1 h; (e) BnONa, dioxane, 90 °C, 3 h; (f) $TsOH•H_2O$, MeOH, rt, 15 h; (g) $Py•SO_3$, Et_3N, $DMSO/CH_2Cl_2$ (3:1), rt, 30 min; (h) $NaClO_2$, *iso*-butene, NaH_2PO_4, THF/H_2O (3:1), 2 h; (i) TBAF, dioxane, 110 °C, 12 h; (j) H_2, $Pd(OH)_2$, CH_3OH, HCOOH, 1 h.

Scheme 13

derivative **84** in 89–95% yield. Removal of the trityl group in **84** with *p*-toluenesulfonic acid in methanol, followed by a two-step oxidation of the resulting primary hydroxy group employing sulfur trioxide pyridine complex and sodium chlorite gave **85** in 67% yield. Removal of the Ses and benzyl groups with TBAF and catalytic hydrogenolysis afforded α-methylserine in 50% yield after ion-exchange chromatography.

6. Et_2AlCl-catalyzed Cyclization of a Chiral Epoxytrichloroacetimidate

Hatakeyama developed a new synthetic route to α-methylserine employing Lewis acid-catalyzed cyclization of an epoxytrichloroacetimidate (*Scheme 14*).[3] The Katsuki-Sharpless catalytic asymmetric epoxydation of methallyl alcohol **86** with TBHP using a catalytic amount of diisopropyl L-tartarate and titanium tetraisopropoxide afforded (*S*)-2-methylglycidol (**81**) in 94% ee. Treatment of **81** with trichloroacetonitrile in the presence of a catalytic amount of DBU gave the trichloroacetimidate **87**, which was subjected to 0.5 equivalent of diethylaluminium chloride (Et_2AlCl) in CH_2Cl_2; cyclization occurred at room temperature with complete regio- and stereoselectivity to afford the oxazoline **88** in 82% yield after pivaloylation.[33] When $BF_3•OEt_2$ was used as Lewis acid instead of Et_2AlCl, a 1:2 mixture of **88** and achiral dipivalate **92** was isolated in 82% yield. A one-pot sequence involving hydrolysis of the oxazoline with HCl and *N*-protection with Boc_2O afforded alcohol **89** in 85% yield with 94% ee, which showed no racemization occurred during the sequence from **81** to **89**. Recrystallization from hexane led to an enhancement of optical purity of **89**. Transformation of the hydroxy group of **89** into a carboxylic acid group was achieved by Swern oxidation followed by sodium chlorite oxidation to yield **90** in 56% yield. Saponification of pivalate **90** with ethanolic NaOH followed by esterification with benzyl bromide and K_2CO_3, and removal of the Boc group with trifluoroacetic acid furnished **91** in 97% yield. Recently, synthesis of α-methylserine employing this Hatakeyama route was reported by Chakruborty.[8]

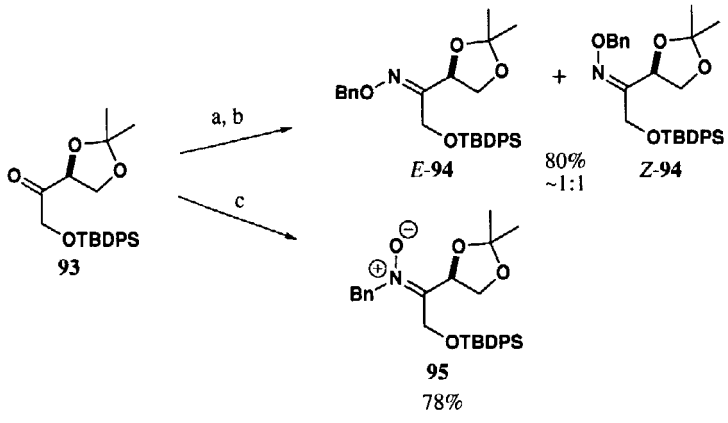


(a) L-DIPT (0.06 eq), $Ti(O\text{-}i\text{-}Pr)_4$ (0.05 eq), *t*-BuOOH (2 eq), CH_2Cl_2, –20 °C; (b) CCl_3CN, DBU (0.1 eq), CH_2Cl_2, –20 °C; (c) Et_2AlCl (0.5 eq), CH_2Cl_2; (d) *t*-BuCOCl, Et_3N, DMAP (cat), CH_2Cl_2; (e) 1 M HCl, THF, then $NaHCO_3$, Boc_2O; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –60 °C to 25 °C; (g) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O (4:1); (h) 2 M NaOH/EtOH (1:5); (i) BnBr, K_2CO_3, DMF; (j) CF_3CO_2H, CH_2Cl_2.

Scheme 14

7. Diastereoselective Addition of Organometallic Reagent to Oxime Ether and Nitrone Derived from L-Erythrulose

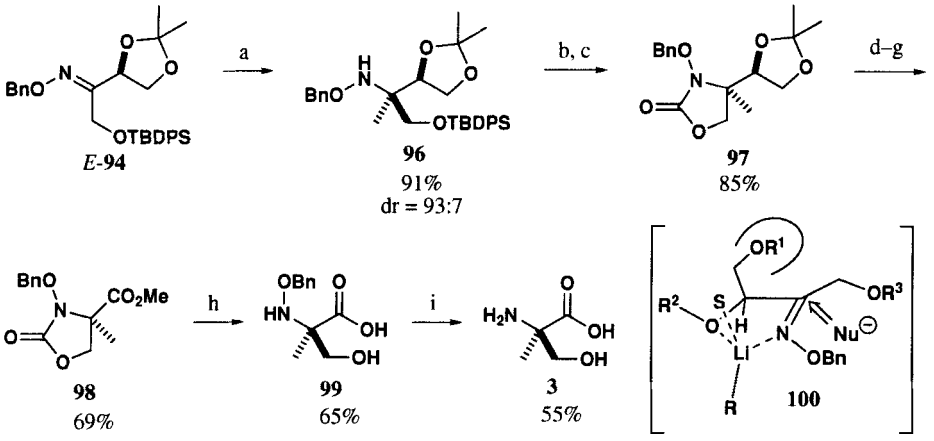
Marco and Carda reported the synthesis of (*R*)-α-methylserine utilizing stereoselective addition of organometallic reagents to a chiral oxime ether and nitrone prepared from L-erythrulose derivative **93**.[34] Oxime ether **94** and nitrone **95** were synthesized by the reaction of protected L-erythrulose **93** with *O*-benzylhydroxylamine hydrochloride and *N*-benzylhydroxylamine hydrochloride, respectively (*Scheme 15*).



(a) $BnONH_2$, Py, MeOH; (b) chromatographic separation; (c) BnNHOH, $MgSO_4$, CH_2Cl_2, rt, 48 h.

Scheme 15

Scheme 16 illustrates the synthetic route to α-methylserine from *O*-benzyl oxime **94**.[34a,b] *E*- and *Z*-isomers of **94** were separated from the crude mixture by column chromatography. The reaction of *E*-oxime **94** with methyllithium in ether occurred at 0 °C to afford *O*-benzylhydroxylamine **96** in 91% yield with a high 93:7 diastereoselectivity. The configuration of the product can be explained by assuming a five-membered α-chelate and a preferred approach of methyllithium from the less hindered *Si* side of the C=N bond (*Structure **100***). In the case of the *Z*-isomer, both yield (62%) and diastereoselectivity (25:75) were poor. After removal of silyl

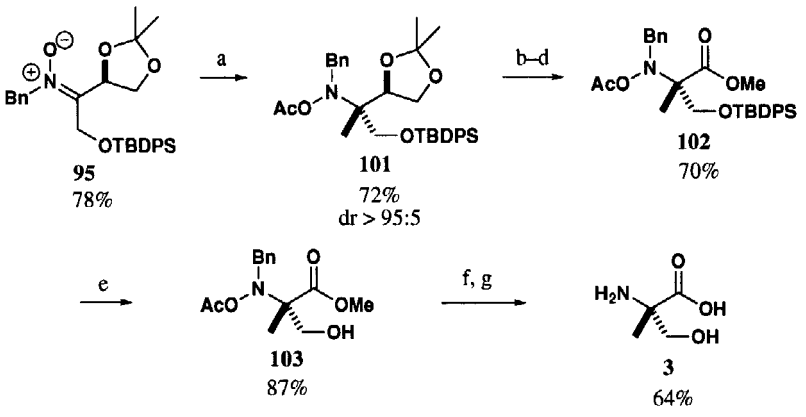


(a) MeLi, ether, 0 °C, 1 h; (b) TBAF, THF, rt; (c) CDI, benzene, reflux, 4 h; (d) PPTS, MeOH/H_2O (9:1), reflux, 12 h; (e) $NaIO_4$ (2.0 eq), THF, rt, 2 h; (f) $NaClO_2$, aq. NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, rt, 12 h; (g) CH_2N_2, ether; (h) NaOH, EtOH/H_2O (1:1), rt, 12 h; (i) H_2, Pd/C, MeOH, rt, 48 h.

Scheme 16

group in **96** with TBAF, the resulting amino alcohol was transformed into oxazolidinone **97** by reaction with carbonyldiimidazole (CDI). The minor isomer arising from addition of MeLi (**94** to **96**) was removed by column chromatography at this stage. Removal of the acetonide group in **97** with pyridinium *p*-toluenesulfonate (PPTS) in aqueous methanol gave the diol, which was transformed into methyl ester **98** in 69% overall yield by a three-step sequence involving (i) cleavage of the diol with sodium periodate, (ii) sodium chlorite oxidation, and (iii) esterification with diazomethane. After hydrolysis of both methyl ester and oxazolidinone ring in **98** with NaOH in aqueous EtOH, reductive cleavage of the N–O bond in oxime ether **99** afforded α-methylserine **3** in 36% yield over two steps.

An alternative route from erythrulose derivative **93** was developed using a nitrone intermediate (*Scheme 17*).[34c] Reaction of nitrone **95** with a five-fold excess of methylmagnesium chloride in the presence of one equivalent of zinc bromide in THF at –78 °C followed by quenching with acetic anhydride gave N-acetoxy derivative **101** in 72% yield with >95:5 dr. When methyllithium was used in Et_2O, the unwanted diastereomer was obtained as a major product (10:90 dr). Treatment of **101** with periodic acid gave the aldehyde, which was subjected to sodium chlorite oxidation. The resulting carboxylic acid was esterified with diazomethane to



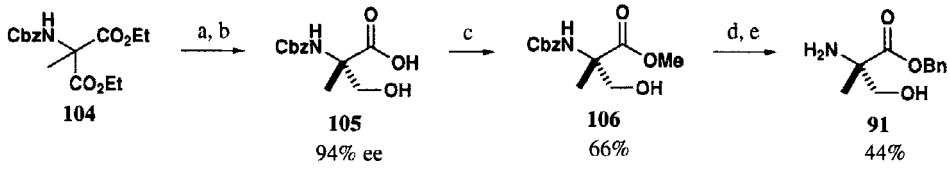
(a) MeMgCl (5 eq), $ZnBr_2$ (1 eq), –78 °C, 5 h; (b) H_5IO_6 (2.3 eq), ether, rt, 4 h; (c) $NaClO_2$, H_2O_2, CH_3CN-phosphate buffer, <10 °C, 4 h; (d) CH_2N_2; (e) TBAF, THF, rt, 1 h; (f) H_2 (70 psi), $Pd(OH)_2$, MeOH, rt, 5 days; (g) NaOH, EtOH/H_2O (1:1), rt, 1 h.

Scheme 17

afford methyl ester **102** in 70% yield from **101**. After desilylation of **102** with TBAF in THF, hydrogenolysis of **103** in the presence of Pearlman's catalyst (H_2, 70 psi) resulted in the removal of the benzyl group and cleavage of the N–O bond. Finally, saponification of the ester group with NaOH in aqueous ethanol yielded (*S*)-α-methylserine (**3**) in 56% yield from **102**. Since D-erythrulose can be prepared from D-isoascorbic acid,[35] the synthetic routes using L-erythrulose as a starting material (*Schemes 15–17*) can be applied to the synthesis of (*R*)-α-methylserine.

8. Nagao's Enzymatic De-symmetrization of Prochiral α-Aminomalonate

Nagao *et al.* reported the chemo-enzymatic approach for the synthesis of (*S*)-methylserine benzyl ester **91** starting from σ-symmetric prochiral diethyl α-aminomalonate **104** (*Scheme 18*).[5] De-symmetrization was achieved by enzymatic hydrolysis using porcine liver esterase followed by reduction with $LiBH_4$ in ether/THF mixture to afford *N*-Cbz-α-methylserine (**105**) in 94% ee. Esterification of **105** with (trimethylsilyl)diazomethane gave the methyl ester **106** in 66% yield. After removal of the Cbz group in **106** by hydrogenolysis, transesterification of methyl ester was carried out by the reaction with benzyl alcohol and triethylamine (10:1) at 60 °C for two days to afford benzyl ester **91** in 44% yield.

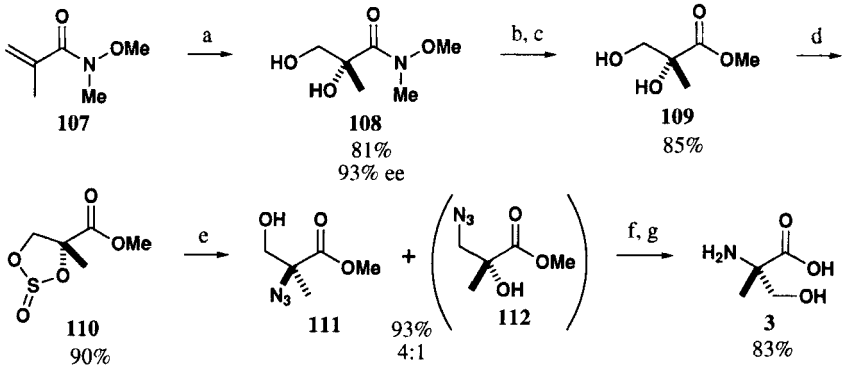


(a) porcine liver esterase, 15 M phosphate buffer (pH 7.0)/MeCN (10:1), rt, 12 h; (b) $LiBH_4$, Et_2O/THF (3:1), reflux, 1.5 h; (c) $TMSCHN_2$, MeOH/benzene (2:7), rt, 4 h; (d) H_2, 10% Pd/C, MeOH, rt, 12 h; (e) BnOH/Et_3N (10:1), 60 °C, 2 days.

Scheme 18

9. Ring-opening Reaction of Cyclic Sulfite with Sodium Azide

Avenoza and Peregrina found that the Sharpless asymmetric aminohydroxylation (AA) of α-methylacrylic acid derivatives gave the unwanted regioisomers as the major products with poor enantioselectivities. This observation led them to utilize Sharpless asymmetric dihydroxylation (AD) followed by nucleophilic substitution with sodium azide *via* the cyclic sulfite (*Scheme 19*).[36] AD of methyl and benzyl esters of α-methylacrylic acid using AD-mixα suffered from poor ee; however, Weinreb's amide **107** gave the *R*-diol **108** in 81% yield with 93% ee. The amide group of **108** was converted into the methyl ester by saponification with



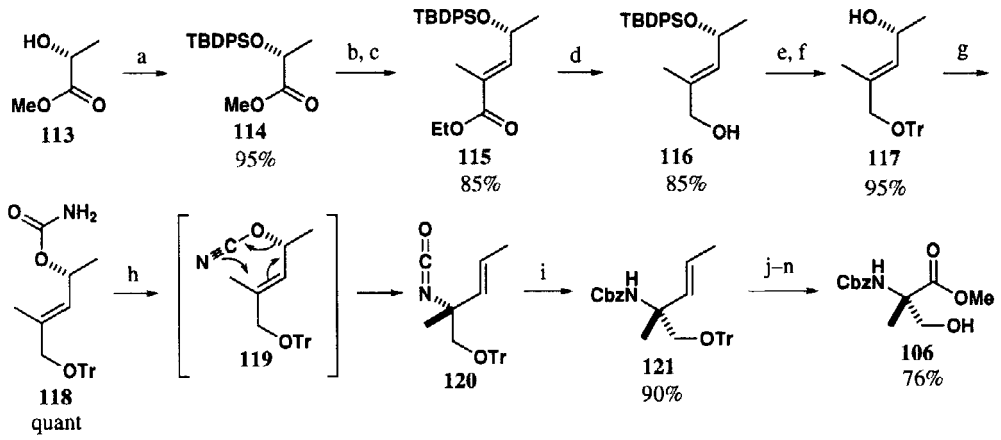
(a) AD-mix α, $MeSO_2NH_2$, *t*-BuOH/H_2O (1:1), 0 °C, 12 h; (b) LiOH•H_2O, H_2O/CH_3OH (1:3), rt, 2 h; (c) AcCl, CH_3OH, reflux, 12 h; (d) $SOCl_2$, CCl_4, reflux, 4 h; (e) NaN_3, DMF, 50 °C, 2 days; (f) 6 M HCl, reflux, 12 h; (g) H_2, Pd/C, CH_3OH, rt, 24 h.

Scheme 19

LiOH in aqueous methanol followed by esterification with acetyl chloride in refluxing methanol in 85% yield. The *vic*-diol group of **109** was transformed into cyclic sulfite **110** in 90% yield. Nucleophilic displacement of **110** with sodium azide in DMF at 50 °C for two days gave a 4:1 mixture of azido ester **111** and **112** in 93% yield.[37] Similar results could also be obtained *via* a cyclic sulfate using a three-step sequence: (i) oxidation with $NaIO_4$, (ii) ring opening reaction with sodium azide, and (iii) hydrolysis of the resulting sulfate with 20% sulfuric acid to afford a mixture of **111** and **112** with higher regioselectivity (9:1) in 65% overall yield from **110**. Since the yields of the desired **111** in these two routes were comparable, it is clearly unnecessary to carry out the three-step pathway. After chromatographic separation, the azide methyl ester **111** was subjected to acidic hydrolysis and palladium-catalyzed hydrogenation to afford α-methylserine **3** in 83% yield. When the hydrogenation was carried out prior to hydrolysis, the yield of α-methylserine decreased to 59%.

10. [3.3] Sigmatropic Rearrangement of an Allyl Cyanate

Starting from commercially available methyl D-lactate (**113**), chirality was transferred to the quaternary stereocenter of α-methylserine by [3.3] sigmatropic rearrangement (*Scheme 20*).[6] After protection of the hydroxy group of **113** as *tert*-butyldiphenylsilyl (TBDPS) ether, methyl



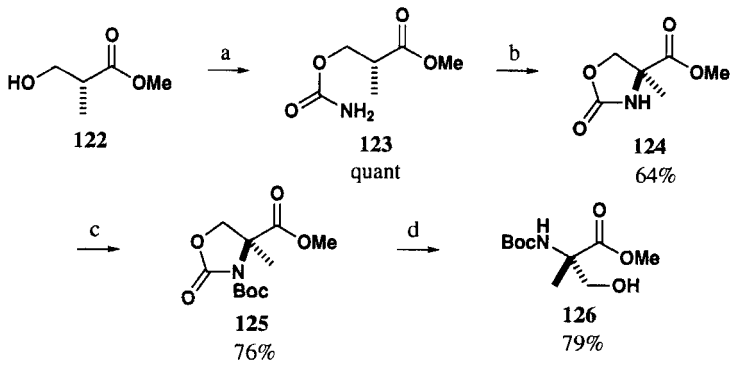
(a) TBDPSCl, imidazole, DMF, rt, 48 h; (b) DIBAL-H, CH_2Cl_2, –78 °C, 30 min; (c) $Ph_3PC(CH_3)COOEt$, CH_2Cl_2, rt, 30 min; (d) DIBAL-H, CH_2Cl_2, –78 °C, 30 min; (e) TrCl, Py, 70 °C, 5 h; (f) TBAF, CH_3CN, 60 °C, 7 h; (g) CCl_3CONCO, CH_2Cl_2, 0 °C, 30 min, then aq K_2CO_3/MeOH, rt, 2 h; (h) PPh_3, CBr_4, Et_3N, CH_2Cl_2, –10 °C, 30 min; (i) $PhCH_2ONa$, MS4A, THF, rt, 1 h; (j) OsO_4, NMO, acetone/H_2O, rt, 3 h; (k) $NaIO_4$, THF/H_2O (5:1), rt, 2 h; (l) $NaClO_2$, 2-methyl-2-butene, KH_2PO_4, *t*-BuOH/H_2O (4:1), rt, 30 min; (m) MeI, K_2CO_3, DMF, rt, 4 h; (n) TFA, CH_2Cl_2, rt, 10 min.

Scheme 20

ester **114** was reduced with diisobutylaluminium hydride (DIBAL) and the resulting aldehyde was transformed into α,β-unsaturated ester **115** by the reaction with ethyl-2-(triphenylphosphoranylidene) propionate to afford **115** in 85% yield over two steps. The α,β-unsaturated ester **115** was reduced with DIBAL to give allyl alcohol **116** in 85% yield. Protection of the hydroxy group in **116** as its trityl ether and removal of the TBDPS group with tetrabutylammonium fluoride provided allyl alcohol **117** in 95% yield. Treatment of **117** with trichloroacetyl isocyanate, followed by hydrolysis of the resultant *N*-trichloroacetyl carbamate gave allyl carbamate **118**, which was then subjected to dehydration by the modified Appel conditions[38] to generate allyl cyanate **119**, which spontaneously rearranged into allyl isocyanate **120**. After careful work-up, the resulting isocyanate **120** was treated with sodium benzyl alkoxide in THF to afford benzyl carbamate **121** in 90% yield from **118**. The enantiomeric excess of **121** was determined to be 97%, which shows that the chirality transfer using [3.3] sigmatropic rearrangement of allyl cyanate was achieved with excellent selectivity. The double bond in **121** was transformed to a methoxycarbonyl group by a four-step sequence: (i) osmium-catalyzed dihydroxylation with *N*-methylmorpholine *N*-oxide, (ii) diol cleavage with sodium periodate, (iii) oxidation of resulting aldehyde to the carboxylic acid with $NaClO_2$, and (iv) esterification with methyl iodide in the presence of potassium carbonate. Finally, the trityl group was removed with trifluoroacetic acid in CH_2Cl_2 to furnish the protected α-methylserine **106**, a segment for conagenin synthesis.

11. Dirhodium(II)-catalyzed Intramolecular C–H Amination Reaction

Yakura reported[7] the synthesis of α-methylserine based on the stereospecific dirhodium(II)-catalyzed C–H amination reaction reported by DuBois[39] (*Scheme 21*).



(a) $CCl_3CON{=}C{=}O$, CH_2Cl_2, rt, 1 h, then, neutral Al_2O_3; (b) $PhI(OAc)_2$ (4.2 eq), MgO (6.9 eq), $Rh_2(OAc)_4$ (10 mol%), reflux, 40 h; (c) Boc_2O, Et_3N, DMF, rt, 12 h; (d) Cs_2CO_3, MeOH, rt, 1 h.

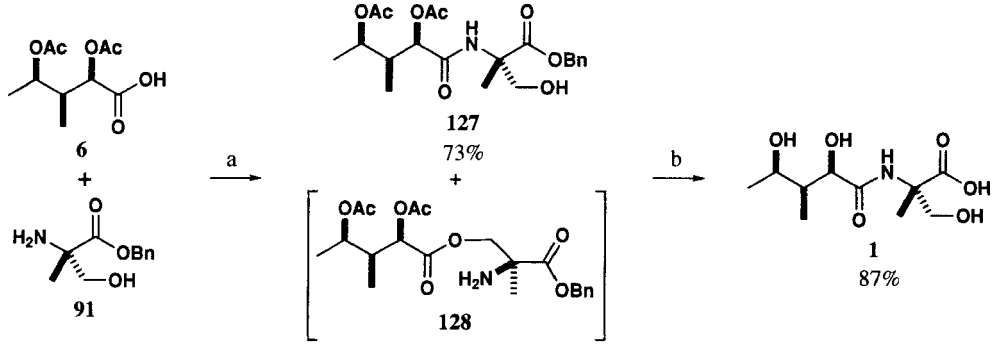
Scheme 21

The precursor of intramolecular C–H amination was prepared from commercially available methyl (*R*)-3-hydroxy-2-methylpropanoate (**122**) by the reaction with trichloroacetyl isocyanate in CH_2Cl_2 followed by treatment with neutral alumina to afford **123** quantitatively. Carbamate **123** underwent C–H amination using 10 mol% dirhodium tetraacetate, 4.2 equivalents of (diacetoxyiodo)benzene, and 6.9 equivalents of magnesium oxide in CH_2Cl_2 under reflux for 40 hours to afford oxazolidinone **124** in 64% yield based on the consumed **123** (53% of starting material **123** recovered). After N-Boc carboxylation of **124**, the oxazolidinone ring in **125** was opened by treatment with cesium carbonate in methanol[40] to yield *N*-Boc-α-methylserine methyl ester **126**.

III. ASSEMBLY OF PENTANOIC ACID AND α-METHYLSERINE

1. First Successful Example (Hatakeyama)

The first synthesis of conagenin was achieved by Hatakeyama as shown in *Scheme 22*.[3] Pentanoic acid moiety **6** was condensed with α-methylserine benzyl ester (**91**) with

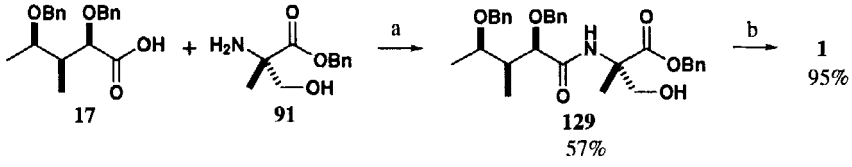


(a) $EtN{=}C{=}N(CH_2)_3NMe_2{\cdot}HCl$, HOBt, NMM, DMF; (b) 1 M K_2CO_3/MeOH (1:3)

Scheme 22

1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCl) as a dehydrating reagent in the presence of 1-hydroxybenzotriazole (HOBt) and *N*-methylmorpholine in DMF to afford the amide (**127**) in 73% yield. When this reaction was carried out in CH_2Cl_2, the products were a mixture of **127** (40%) and ester **128** (30%). However, treatment of the *O*-acylated amine **128** with 1 M $NaHCO_3$ in THF at room temperature resulted in its quantitative isomerization to **127**. Removal of the protecting groups of **127** with 1 M K_2CO_3 in methanol furnished (+)-conagenin (**1**) in 87% yield.

In the synthesis of Nagao (*Scheme 23*),[5] condensation of benzyl-protected pentanoic acid **17** with **91** was carried out by procedures similar to those employed in *Scheme 22*. Catalytic hydrogenolysis of benzyl ethers and ester in **129** completed the synthesis of (+)-conagenin in 95% yield.

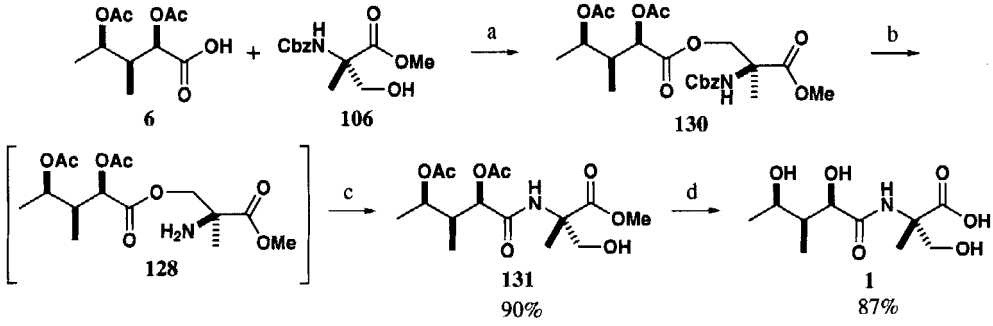


(a) EDCl, HOBt, NMM, DMF, rt, 6 h; (b) H_2, 10% Pd-C, MeOH, rt, 5 days.

Scheme 23

2. Intramolecular Ester-to-amide Exchange Strategy (Ichikawa, Yakura)

Following the observation of Hatakeyama with respect to the transformation of **128** into **127**, a new strategy to assemble two fragments **6** and **106** was developed to take advantage of an intramolecular acyl-transfer reaction (*Scheme 24*).[6] Pentanoic acid **6** was coupled with α-methylserine methylester **106** by employing dicyclohexylcarbodiimide in the presence of



(a) DCC, DMAP, HOBt, CH_2Cl_2; (b) H_2, 10% Pd-C, THF; (c) aq $NaHCO_3$; (d) 1 M K_2CO_3, MeOH.

Scheme 24

DMAP and 1-hydroxybenzotriazole (HOBt) to provide the ester **130**. Upon removal of the Cbz group in **130** by hydrogenolysis, the resulting amino ester was subsequently treated with aqueous sodium bicarbonate. Intramolecular O→N acyl-transfer reaction occurred smoothly to furnish

the amide **131** in 90% yield over three steps from **6**. Treatment of **131** with 1 M K_2CO_3 in methanol resulted in the hydrolysis of two acetates and methyl ester group to afford conagenin (**1**) in 87% yield. Yakura[6] employed a similar strategy with modification of protecting groups.

IV. CONCLUSIONS

In this review, an attempt has been made to highlight features of the three synthetic problems with conagenin; construction of an array of the three consecutive stereocenters in the left portion of the pentanoic acid, asymmetric synthesis of the quaternary stereogenic center bearing a nitrogen substituent in the right fragment of α-methylserine, and the difficult formation of the amide bond between the α-alkyl carboxylic acid and the sterically congested amine of α-methylserine. Among this triad, the synthesis of α-methylserine is particularly interesting which shows the development of generally useful synthetic methods to effectively install a quaternary stereocenter containing a nitrogen substituent.

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