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Total Synthesis of Phaseolinic Acid by Enyne Cyclization

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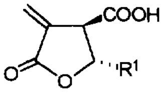
Abstract: Enantiopure phaseolinic acid was synthesized from (*R*)-4'-chloro-1'-*n*-pentyl-2'-butenyl 3-trimethylsilyl-2-propynoate by palladium (II) catalyzed cyclization reaction as the key step. Copyright © 1996 Published by Elsevier Science Ltd

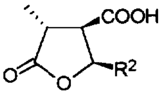
INTRODUCTION

Optically active polysubstituted γ-butyrolactones are a class of compounds of great significance not only because of their occurence in a large variety of biologically active natural products but also because of their possible utilization as building blocks for the synthesis of natural products[1]. In naturally occurring γ-lactones, the main characteristics is the different stereochemical relations between the substituted groups, e.g. ***trans***-β,γ-substituents for (-) -methylenolactocin and protolichesterinic acid, while *cis*-β,γ-substituents for phaseolinic acid and nephromopsinic acid. Although several groups[2] developed different routes to synthesize β,γ-***trans***-substituted γ-lactones in the past years, no report provided a route to the synthesis of β,γ-*cis*- substituted γ-lactones. In the palladium(II) catalyzed enyne cyclization reactions of 4'-halo-1'-alkyl-2'-butenyl 2-alkynoates,



$R^1=C_5H_{11}$ (-)-Methylenolactocin

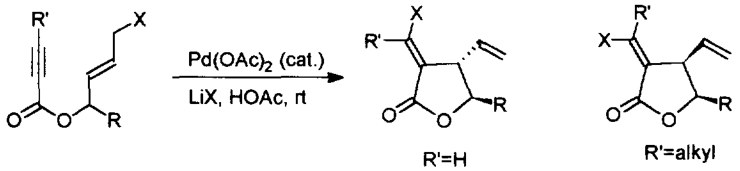
$R^1=C_{13}H_{27}$ Protolichesterinic acid



$R^2=C_5H_{11}$ Phaseolinic acid

$R^2=C_{13}H_{27}$ Nephromopsinic acid

we found that the diastereoselectivity of β,γ-substituents could be controlled by the substituents on the triple bond of the alkynoates[3]: When R'=H, β,γ-*trans*-substituted cyclization product is obtained; while when R'=alkyl, β,γ- *cis*-substituted cyclization product is obtained (Scheme I). Based on this discovery, we have synthesized (-)-methylenolactocin in enantiomerically pure form from corresponding alkynoate[2b]. Thus the problem of synthesizing enantiomerically pure phaseolinic acid, in which the β,γ-substituents are in *cis*-form, becomes just how to choose a proper R' group in the starting material. The R' group should induce the β,γ-*cis*- selectivity and could be easily removed after the cyclization. The trimethylsilyl group was chosen as the substituent group in our synthetic strategy.

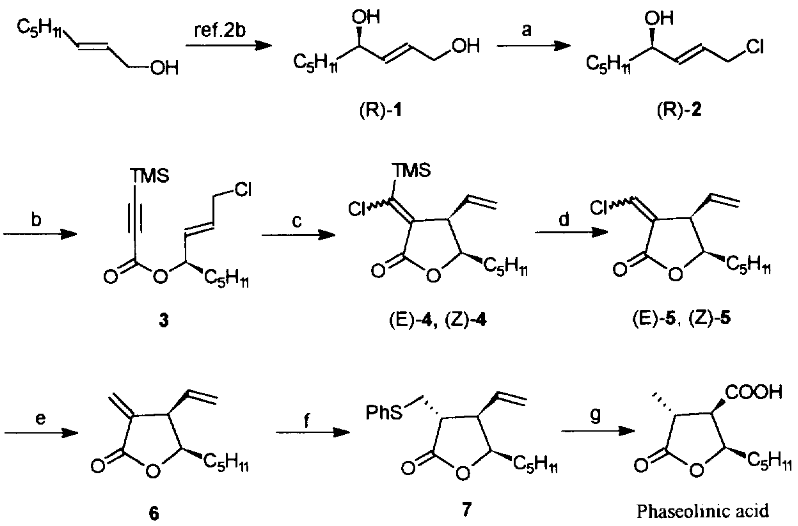


Scheme I

RESULTS AND DISCUSSION

Optically active allylic alcohol **2** was synthesized according to the literature procedure[2b]. Esterification of **2** (Scheme II) with 3-trimethylsilyl-2-propiolic acid in the presence of DCC and a catalytic amount of DMAP in CH_2Cl_2 gave the allylic trimethylsilyl propynoate **3**. Cyclization reaction took place in the presence of $Pd(OAc)_2$ (0.05 eq) and LiCl (4 eq) in acetic acid at room temperature giving the cyclic products (*E*)-**4** and (*Z*)-**4**, which could be easily separated by column chromatography on silic gel, both with 100% β,γ-*cis*- diastereoselectivity. The stereochemistry was determined by the coupling constant[4] from ^1H NMR spectra and 2D NOESY spectroscopy. With compounds (*E*)-**4** and (*Z*)-**4** at hand, we wished to reduce the double bond directly. It is noted that the α- and β- substituents in the target molecule should be *trans-*. Catalytic hydrogenation would give *cis*- product[5]. Reduction with active metals, e.g., magnesium in *t*-butyl alcohol, did reduce the double bond and remove the chlorine atom at the double bond, however, it gave low yields and α,β substituents were also *cis-*. Attempting to react the double bond with thiophenol by Michael addition reaction, resulted an addition-elimination reaction.

Then the desilylation reaction was carried out according to Buynak's procedure[6] in the presence of 2 eq of TBAF and 2 eq of HOAc in THF to produce (*E*)-**5** and (*Z*)-**5** in high yield. The chlorine atom in (*E*)-**5** and (*Z*)-**5** was removed with Zn-Ag couple under Heathcock's condition[7] to afford **6**.



Scheme II *reagents and conditions*: a, $MeSO_2Cl$, *s*-collidine, LiCl, DMF, -50~-30°C; b, TMS—≡—COOH, DCC, DMAP, CH_2Cl_2, -20~0°C; c, $Pd(OAc)_2$, LiCl, HOAc, rt; d, TBAF-HOAc, THF, 0°C~rt; e, Zn-Ag, MeOH, reflux; f, PhSH, Et_3N, THF, rt; g, (i) $NaIO_4$, $RuCl_3{\cdot}H_2O$, CCl_4-MeCN-H_2O, rt; (ii)Na-Hg, NaH_2PO_4, MeOH, -20°C.

Compound **6** reacted with PhSH in the presence of Et_3N in THF, as a fact, only the thermodynamically favored diastereomer **7** was obtained, the stereochemistry of which was also confirmed by 2D NOESY spectroscopy. Compound **7** underwent oxidation by $NaIO_4$ and catalytic $RuCl_3{\cdot}H_2O$ in CCl_4-MeCN-H_2O, followed by desulfonylation with Na-Hg in the presence of NaH_2PO_4 in absolute methanol, phaseolinic acid {$[\alpha]_D^{25}$ =-142 (c=0.22, $CHCl_3$), m.p. 138-140°C; Lit[8]: $[\alpha]_D$=-150 (c=0.2, $CHCl_3$), m.p. 139-140°C} was obtained.

In summary, the success of the total synthesis of phaseolinic acid indicates again that our palladium(II) catalyzed enyne cyclization reaction is highly stereoselective and efficient for the synthesis of both β,γ- *cis*- and β, γ- *trans*-[2b] substituted γ-butyrolactones in optically pure form.

EXPERIMENTAL

Infrared spectra were obtained with a Shimadzu IR-440 instrument. Proton magnetic resonance spectra were recorded with a Varian EM-390 or Bruker AM-300 spectrometer and were reported in ppm downfield of internal tetramethylsilane (δ units). Mass spectral data were taken on a Finnigan 4021 spectrometer. Optical rotations were measured on a Perkin-Elmer 241 MC instrument. Elemental analyses were run on a Carlo-Erba 1106 instrument.

***(R)-2-(E)-Nonen-1,4-diol,* (*R*)-1** was prepared according to literature procedure[2b] from 2-(*E*)-octenol with >97% ee as determined on the basis of the NMR spectra of the Mosher ester.

***(R)-1-Chloro-2-(E)-nonen-4-ol,* (*R*)-2**. To a solution of **(*R*)-1** (6.32g, 40 mmol), lithium chloride (2.60g ,60 mmol) and *s*-collidine (4.90g ,42 mmol) in DMF (80 mL) at -50^0 C under vigorous stirring, was added slowly a solution of methane sulfonyl chloride(4.60g, 40 mmol) in DMF(20 mL). After addition, the mixture was kept at -50^{0}C for 2h, -30^{0}C for 4h, then 30 mL of water was added and the resulting solution was extracted with ethyl acetate (100 mL×4), washed sequentially with water, 10% hydrochloric acid (10 mL×2), brine (10 mL), and dried (Na_2SO_4). Column chromatography on silica gel (eluent: petroleum ether : ethyl acetate=10:1) gave **(*R*)-2** (5.1g, 73%). $[\alpha]_D^{25}$ = -6.0 (c=2.4, $CHCl_3$). ^{1}H NMR (90 MHz, CCl_4): 5.8~5.6 (m, 2H), 4.1~3,9 (m, 3H), 1.6~0.7(m, 11H) ppm. IR (neat): 3350, 2910, 2850, 1480, 983, 794 cm^{-1}. MS (m/e): 175 (M$^+$+1, 0.21), 141 (4.1), 123 (11.7), 107 (36.5), 105 (base), 99 (59.8), 69 (50.7). Anal. calcd. for $C_9H_{17}ClO$: C, 60.83, H, 10.19, Found: C, 60.75, H, 9.87.

***(R)-4'-Chloro-1'-n-pentyl-2'(E)-butenyl 3-trimethylsilyl propynoate,* 3**. To a solution of 3-trimethylsilyl propionic acid (4.26g, 30 mmol) and **(*R*)-2** (4.9g, 28 mmol) in CH_2Cl_2 (100 mL) at -20^{0}C, was added dropwise with a solution of DCC (7.9g , 30 mmol) and DMAP (20 mg) in CH_2Cl_2 (50 mL). The resulting mixture was kept at -20^{0}C for 10h, then filtered, and then washed with CH_2Cl_2. The solvent was removed, chromatography on silica gel (eluent: petroleum ether : ethyl acetate=100:1) gave **3** (5.5g, 66%). $[\alpha]_D^{25}$ = -9.3 (c=1.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): 5.87 (dd, 1H, *J*=15.3, 7.6 Hz), 5.77 (ddd, 1H, *J*=15.3, 8.7, 6.6 Hz), 5.32 (m, 1H), 4.04 (m, 2H), 1.72~1.27 (m, 8H), 0.88 (t, 3H, *J*= 6.8 Hz), 0.24 (s, 9H) ppm. IR (neat): 2920, 2880, 2170, 1710, 1460, 1220, 982, 848, 790 cm^{-1}. MS (m/e): 265 (M$^+$ -Cl, 27.2), 193 (1.5), 175 (3.4), 145 (8.8), 125 (base), 97 (20.0), 72 (14.2). Anal. calcd. for $C_{15}H_{25}ClO_2Si$: C, 59.88, H, 8.37. Found: C, 59.85, H, 8.56.

***(4R,5R)-3-[(E)/(Z)]--Trimethylsilyl chloromethylene-4-vinyl-5-n-pentyl-γ-butyrolactone,* (*E*)-4 / (*Z*)-4**. A solution of **3** (1.20g, 4 mmol), LiCl (0.69g, 16 mmol) and $Pd(OAc)_2$ (45mg, 0.2 mmol) of in HOAc (20 mL) was stirred at rt until **3** was consumed . The resulting mixture was extracted with Et_2O (250 mL), then washed with water (15 mL×4), brine (15 mL) and dried (Na_2SO_4). Chromatography on silic gel (eluent: petroleum ether :ethyl acetate=50:1) afforded **(*E*)-4** (0.54g, 45%) and **(*Z*)-4** (0.33g, 28%). **(*E*)-4** : $[\alpha]_D^{25}$ = +53.5 (c=1.0, $CHCl_3$). ^{1}H NMR (300MHz, $CDCl_3$): 5.67 (ddd, 1H, *J*=17.0, 9.8, 8.3 Hz), 5.27 (d, 1H, *J*=9.8 Hz), 5.18 (dd, 1H, *J*=17.0, 1.0 Hz), 4.44 (ddd, 1H, *J*=8.3, 8.2, 6.0 Hz), 3.88 (dd, 1H, *J*=8.3, 6.0 Hz), 1.73~1.29 (m, 8H), 0.89 (t, 3H, *J*=6.8 Hz), 0.33 (s, 9H) ppm. IR (neat): 2930, 2870, 1760, 1610, 1240, 850, 775 cm^{-1}. MS (m/e): 301 (M$^+$+1, 0.02), 285 (59.8), 267 (13.9), 229 (23.5), 217 (30.4), 203 (36.9), 185 (base), 93 (59.0), 73 (62.8). Anal. calcd. for $C_{15}H_{25}ClO_2Si$: C, 59.88, H, 8.37. Found: C, 59.84, H, 8.57. **(*Z*)-4**: $[\alpha]_D^{25}$ = +59.0 (c=1.0, $CHCl_3$). ^{1}H NMR (300MHz, $CDCl_3$): 5.82 (ddd, 1H, *J*=17.3, 10.5, 6.0 Hz), 5.31 (d, 1H, *J*=10.5 Hz), 5.12 (dd, 1H, *J*=17.3, 0.7 Hz), 4.33 (m, 1H), 3.76 (t, 1H, *J*=6.0 Hz), 1.70~1.32 (m, 8H), 0.90 (t, 3H, *J*=6.8 Hz), 0.29 (s, 9H) ppm. IR (neat): 2940, 2880, 1770, 1605, 1250, 1200, 850, 780 cm^{-1}. MS (m/e): 301(M$^+$+1, 0.4), 285 (0.4), 187(45.6), 185 (base), 157 (18.0), 93 (18.3), 73 (45.2). Anal. calcd. for $C_{15}H_{25}ClO_2Si$: C, 59.88, H, 8.37. Found: C, 59.89, H, 8.47.

(4R,5R)-3-(E)-Chloromethylene-4-vinyl-5-n-pentyl γ-butyrolactone, **(*E*)-5**. To a solution of **(*E*)-4** (420 mg, 1.4 mmol) and HOAc (1.9 mL, 2.8 mmol) in THF (10 mL) was added 1M solution of TBAF in THF (2.8 mL) at rt with stirring. After the reaction was completed, the mixture was diluted with 50 mL of Et_2O, washed with H_2O (5 mL), brine (5 mL) and dried (Na_2SO_4). Chromatography on silic gel (eluent: petroleum ether : ethyl acetate=10:1) gave **(*E*)-5** (268 mg, 84%). $[\alpha]_D^{25}$ = +84.3 (c=2.3, $CHCl_3$). ^{1}H NMR (300 MHz, 7.32 (d, 1H, *J*=2.0 Hz), 5.65 (ddd, 1H, *J*=16.1, 9.9, 8.6 Hz), 5.29 (d, 1H, *J*=9.9 Hz), 5.22 (dd, 1H, *J*=16.1, 1.0 Hz), 4.46 (ddd, 1H, *J*=8.8, 8.6, 6.5 Hz), 3.82 (m, 1H), 1.71~1.32 (m, 8H), 0.90 (t, 3H, 6.8 Hz) ppm. IR (neat): 2960, 2880, 1768, 1644, 1200, 930, 795 cm^{-1}. MS (m/e): 229 (M$^+$+1, 5.8), 175 (1.2), 157 (4.8), 128 (74.5), 93 (base), 65 (48.9). Anal. calcd. for $C_{12}H_{17}ClO_2$: C, 63.02, H, 7.49. Found: C, 62.78, H, 7.56.

(4R,5R)-3-(Z)-Chloromethylene-4-vinyl-5-n-pentyl γ-butyrolactone, **(*Z*)-5**. **(*Z*)-4** (300 mg) was treated similarly to give **(*Z*)-5** (193 mg, 85%). $[\alpha]_D^{25}$ = +102.0 (c=2.5, $CHCl_3$). ^{1}H NMR (300MHz, $CDCl_3$): 6.48 (d, 1H, *J*=2.3 Hz), 5.73 (ddd, 1H, *J*=17.0, 9.5, 8.1 Hz), 5.31 (d, 1H, *J*=9.5 Hz), 5.26 (d, 1H, *J*=17.0 Hz), 4.50 (m, 1H), 3.76 (m, 1H), 1.55~1.31 (m, 8H), 0.90 (t, 3H, *J*=6.7 Hz) ppm. IR (neat): 2960, 2880, 1770, 1642, 1190, 940, 796 cm^{-1}. MS (m/e): 229 (M$^+$+1, 12.1), 193 (3.0), 175 (2.6), 157 (3.7), 128 (69.3), 93 (base), 65 (52.8). Anal. calcd. for $C_{12}H_{17}ClO_2$: C, 63.02, H, 7.49. Found C, 63.11, H, 7.53.

(4R,5R)-3-Methylene-4-vinyl-5-n-pentyl γ-butyrolactone, **6**. To a newly prepared Zn-Ag (0.65 g) couple was added a mixture of **(*E*)-5** and **(*Z*)-5** (228 mg, 1 mmol) in MeOH (3 mL) at reflux. After work up by chromatography (silic gel, eluent: petroleum ether : ethyl acetate=10:1) gave the product **6** (175 mg, 90%). $[\alpha]_D^{25}$ = +52.0 (c=1.4, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): 6.27 (d, 1H, *J*=2.7 Hz), 5.72 (m, 1H), 5.51 (d, 1H, *J*=2.7Hz), 5.28 (dd, 1H, *J*=10.2, 1.5 Hz), 5.22 (d, 1H, *J*=17.1 Hz), 4.56~4.50 (m, 1H), 3.75~3.65 (m, 1H), 1.65~1.25 (m, 8H), 0.89 (t, 3H, *J*=6.7 Hz) ppm. IR (neat): 2950, 2880, 1775, 1670, 1640, 1270, 1120, 1000, 930 cm^{-1}. MS (m/e): 195 (M$^+$+1, 0.3), 194 (0.03), 165 (0.07), 151 (0.07), 137 (0.16), 123 (1.89), 94 (base), 66 (57.6). Anal calcd. for $C_{12}H_{18}O_2$: C, 74,23, H, 9.27. Found: C, 74.52, H, 9.25.

(3S,4R,5R)-3-Phenylthiomethyl-4-vinyl-5-n-pentyl γ-butyrolactone, 7. A solution of **6** (97 mg, 0.5 mmol), thiophenol (75 mg, 0.7 mmol) and Et_3N (80 mg, 0.7 mmol) in THF (5 mL) was kept at rt under stirring. After the reaction was completed, work up by chromatography on silic gel (eluent: petroleum ether : ethyl acetate=100:10) to give the product 7 (134 mg, 88%). $[\alpha]_D^{25}$ = +16.0 (c=1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): 5.71 (ddd, 1H, *J*=17.0, 10.2, 7.0 Hz), 5.16 (d, 1H, *J*=10.2 Hz), 5.06 (d, 1H, *J*=17.0 Hz), 4.53~4.42 (m, 1H), 3.32 (dd, 1H, *J*=13.7, 4.4 Hz), 3.25~3.07 (m, 2H), 2.78~2.67 (m, 1H), 1.63~1.27 (8H), 0.88 (t, 3H, *J*=6.7 Hz) ppm. IR (neat): 2920, 2860, 1776, 1610, 1190, 1010, 920 cm^{-1}. MS (m/e): 306 (M$^+$+2, 2.64), 304 (M^+, 30.6), 289 (1.6), 275 (5.5), 261 (2.4), 247 (1.8), 227 (12.1), 180 (base), 137 (49.4), 135 (50.5), 123 (52.6), 94 (32.1) 67 (60.9). Anal. calcd. for $C_{18}H_{24}O_2S$: C, 70.62, H, 7.90. Found: C, 70.83, H, 7.67.

Phaseolinc Acid. A solution of 7 (20 mg, 0.066 mmol), $NaIO_4$ (80 mg, 0.37 mmol) and $RuCl_3 \cdot H_2O$ (2 mg) in a mixture solvent (CCl_4 : MeCN : H_2O=1.5:1.5:1.0 mL) was kept at rt under stirring. After the reaction was completed, MeOH (20 mL) was added, the mixture was filtered through a pad of celite. The filtrate was concentrated to dryness, aqueous saturated $NaHCO_3$ solution (2 mL) was added. The aqueous solution was washed with Et_2O, then acidified with 20% HCl. The acidic aqueous solution was extracted with EtOAc (10 mL×6), and the EtOAc solution was dried (Na_2SO_4) and evaporated. MeOH (5 mL) and anhydrous NaH_2PO_4 (500 mg, 42 mmol) were added, 6% Na-Hg (200 mg, 5 mmol) was then added at -20^0C. Chromatography on silic gel (eluent: petroleum ether : ethyl acetate=1:1) afforded Phaseolinic Acid (8.0 mg, 57%), $[\alpha]_D^{25}$=-142 (c=0.22, $CHCl_3$), m.p. 138-140^{0}C {Lit[8]: $[\alpha]_D$=-150 (c=0.2, $CHCl_3$), m.p. 139-140^{0}C} with identical spectroscopic data with those reported[8].

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