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Chiron approach towards optically pure γ³-valerolactone from alanine

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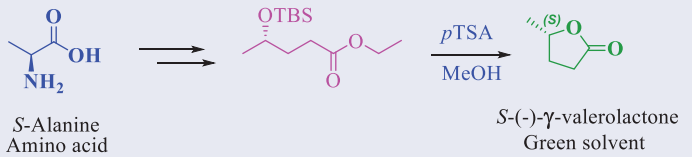
ABSTRACT

A concise synthesis of both enantiomers of γ-valerolactone has been developed from commercially available Alanine. The key steps in the synthesis of these γ-Lactones are DIBAL-H reduction of ester (**9**) followed by *in situ* Wittig reaction with $EtO_2CCH=PPh_3$ ylide (**13**) (Z/E = 1: 3.5) and one pot lactonization triggered by deprotection of O-TBS ether (**14**).

GRAPHICAL ABSTRACT



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KEYWORDS
Alanine; diazotization; lactonization; macrolides; γ-valerolactone

Introduction

γ-Lactones are important structural motifs and valuable building blocks in the synthesis of natural products and biologically active molecules such as pheromones, polyketides, and prostaglandins.[1] The enantiopure γ-valerolactone is used as a promising chiral starting material for the synthesis of fine chemicals, valuable intermediates & natural products. Few examples of intermediates are chiral pentane-1,4-diol, 5-methyl-3-methyl-enedihydrofuran-2(3*H*)-one and its derivatives while Phoracantholide-I (Pheromone) and Patulolide-C (Antifungal) being some of the examples of natural products[2] (Fig. 1).

Considering the high stereoselectivity during Wittig reaction of the corresponding lactol of optically pure γ-valerolactone, the latter becomes a very good chiral synthon in the synthesis of natural products.[2b,c,3] A variety of methods are in practice for the synthesis of optically pure γ-lactones starting from γ-keto esters that either use stoichiometric or catalytic chiral reagent systems[4] or enzymes as part of a greener approach for the asymmetric hydrogenation[5] of keto function. With a lot of progress being made in

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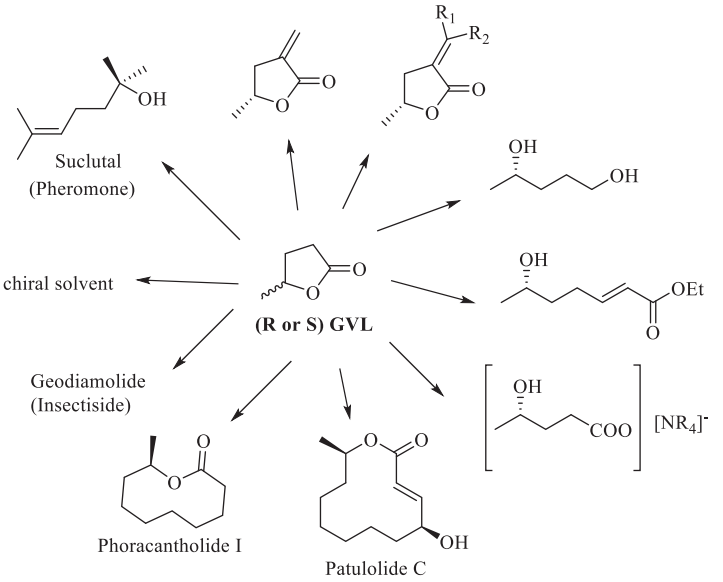


Figure 1. Selected application of optically pure γ-valerolactones.

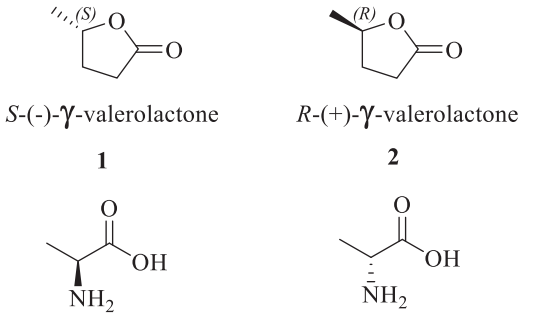
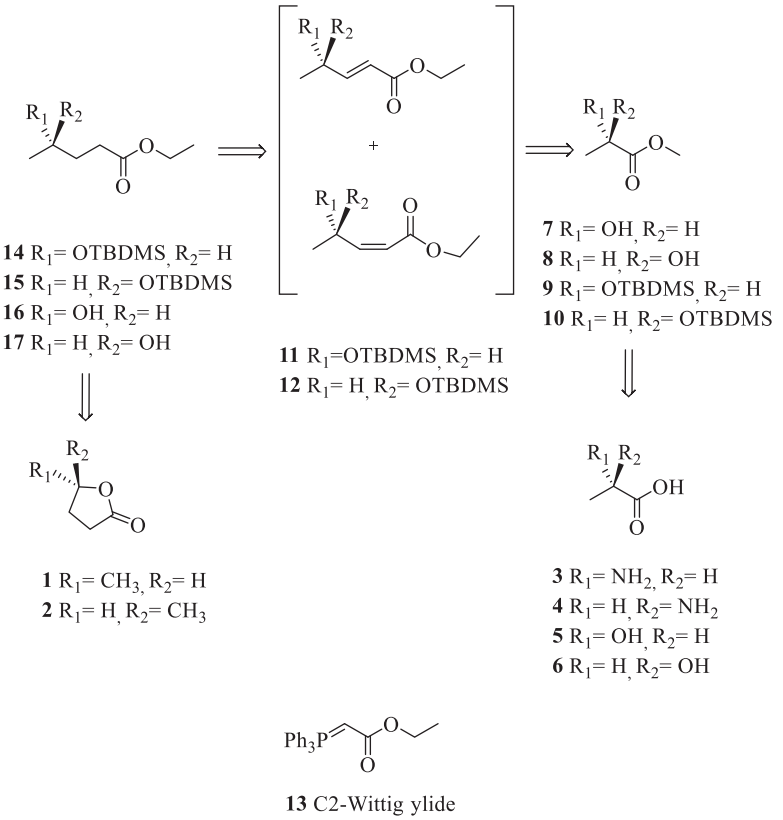


Figure 2. Chiral synthons.

the field of asymmetric reduction of γ-keto esters using enzymes[6] it has now become quite facile to obtain the chiral alcohols that afford chirally pure γ-valerolactones in large quantities starting from commercially viable chiral synthons. (Fig. 2).

Though various protocols reported in the literature for the stereoselective synthesis of *S*-(-)-γ-valerolactone **(1)** & *R*-(+)-γ-valerolactone (**2**),[7] our approach involves the synthesis of chiral γ-lactone from readily available chiral intermediate Alanine (**3**) or Methyl lactate (**7**) in a linear and high yielding approach. The retrosynthetic approach for the stereoselective synthesis of *S*- (-)-γ-valerolactone **(1)** & *R*-(+)-γ-valerolactone (**2**) is outlined in Scheme 1.

S-(-)-γ-valerolactone **(1)** is synthesized by one-pot lactonization of hydroxy ester (**16**) under acidic conditions that lead to deprotection of *O*-TBS ether (**14**). *O*-TBS ether (**14**) could be obtained from the hydrogenation of *E* &*Z* mixture of α,β-ethyl ester (**11**). The *E* &*Z* mixture of α,β-unsaturated ethyl ester **11** could be traced to two carbon

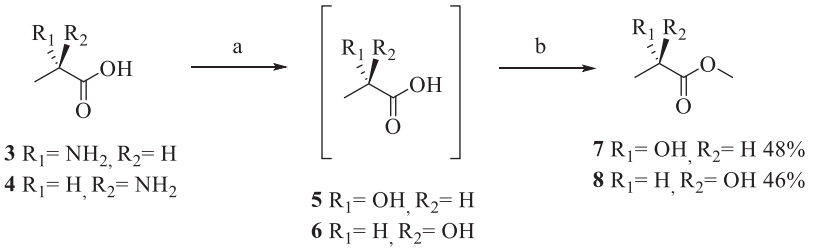


Scheme 1. Retrosynthetic approach for *S*-(-)-γ-Valerolactone (1) & *R*-(+)-γ-Valerolactone (2).

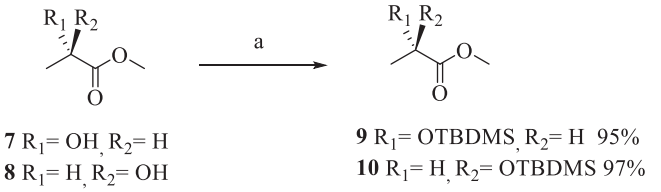
homologation of a transient aldehyde with Wittig ylide (**13**) while the aldehyde is obtained after DIBAL-H reduction of chirally pure TBS protected methyl lactate (**9**). The compound **9** was traced from corresponding chirally pure L-Alanine (**3**). Diazotization of L-Alanine **3** followed by hydration affords chirally pure lactic acid (**5**). Esterification of **5** lead to methyl lactate (**7**). Silylation of the secondary alcohol affords compound (**9**). Similarly, the antipode *R*-(+)-γ-valerolactone (**2**) was traced from D-Alanine (**4**).

Results and discussion

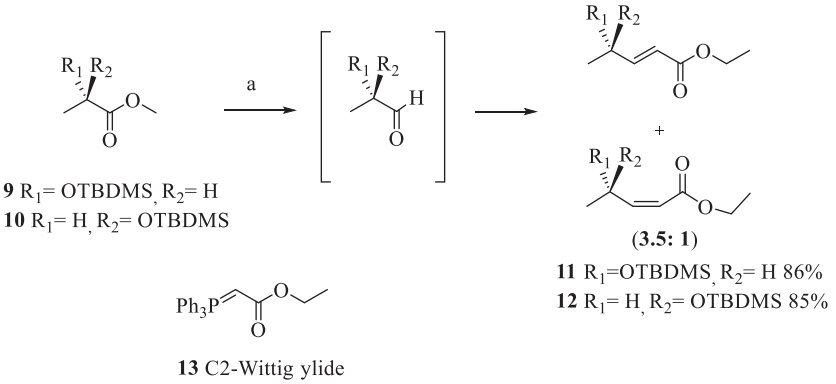
The synthesis of *S*-(-)-γ-valerolactone **(1)** & *R*-(+)-γ-valerolactone (**2**) began using commercially available L-Alanine (**3**) and its antipode (**4**). The L-Alanine (**3**) was subjected to diazotization as per published report[8] to yield the corresponding chirally pure lactic acid (**5**). Esterification in methanol of compound **5** afforded methyl lactate (**7**) as mentioned in Scheme 2. The secondary hydroxyl group of chirally pure methyl lactate **(7)** was protected as silyl ether using TBDMSCl and imidazole in DCM at room temperature.[9] (Scheme 3). The silyl protected Methyl lactate **(9)** obtained in the previous step was then subjected to reduction with DIBAL-H in DCM at -78 °C to yield a transient aldehyde which was then *in situ* converted to α,β-unsaturated ethyl ester (**11**) on treatment with two carbon ylide $EtO_2CCH=PPh_3$ (**13**) in DCM at room temperature by using Wittig protcol.[10] The α,β-unsaturated ethyl ester (**11**) was obtained in 86% yield



Scheme 2. Reagents and conditions: (a) $NaNO_2$, H_2SO_4; (b) MeOH, H_2SO_4, rt, 24 h.



Scheme 3. Reagents and conditions: (a) TBDMSCl/Imidazole, DCM, rt, 24 h.

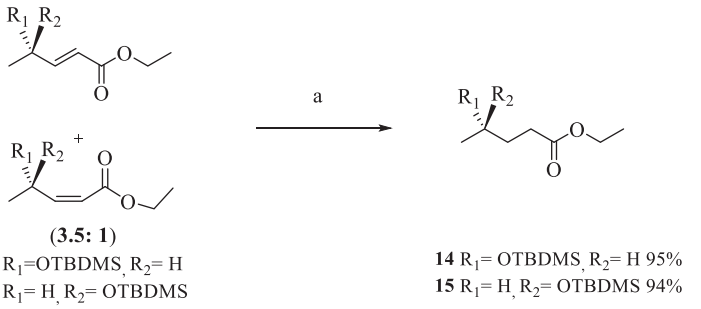


Scheme 4. Reagents and conditions: (a) (i) DIBAL-H, DCM, −78 °C, 2 h; (ii) $EtO_2CCH=PPh_3$ (13), rt, 24 h.

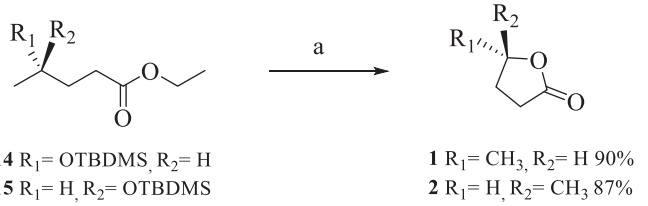
with *E* & *Z* ratio (3.5: 1) as indicated by proton NMR which was found to be in line with the literature[11] (Scheme 4). The *cis* and *trans* mixture of *α,β*-unsaturated ethyl esters (**11**) was subjected to hydrogenation on 10% Pd/C in ethyl acetate to afford saturated ethyl ester (**14**) in good yield (Scheme 5).

Finally, the lactonization to afford the title compound *S*-(-)-*γ*-valerolactone (**1**) was affected by one pot deprotection of silyl ether of saturated ethyl ester (**14**) with *p*TSA in MeOH at rt for 24 h. Similarly, the antipode *R*-(+)-*γ*-valerolactone (**2**) was traced from D-Alanine (4) following the same synthetic sequence (Scheme 6). An equilibrium between lactone (**1**) and *γ*-hydroxy ester intermediate (**16**) was observed in methanol under acidic conditions. It shifts towards lactone (**1**) by removal of methanol (Fig. 3).

Further, we have compared the enantiomeric excess of *S*-(-)-*γ*-valerolactone **(1)** & *R*-(+)-*γ*-valerolactone (**2**) synthesized starting with ethyl levulinate (**18**) as shown in



Scheme 5. Reagents and conditions: (a) H_2, 40 psi, Pd/C, Ethyl acetate, rt, 2 h.



Scheme 6. Reagents and conditions: (a) *p*TSA/MeOH, 24 h, rt.

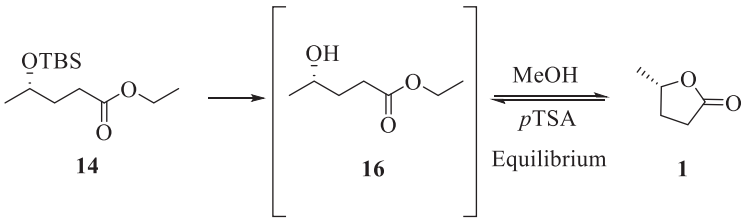
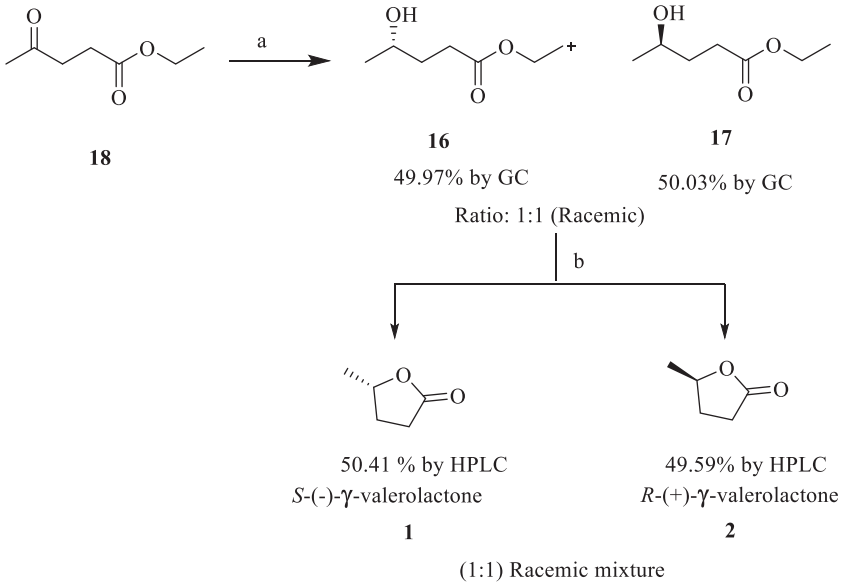


Figure 3. Lactonization triggered by pTSA in methanol.

Scheme 7. Thus ethyl levulinate (**18**) on reduction with $NaBH_4$ gave a racemic mixture of γ-hydroxyl esters (**16**) & (**17**) in ratio (1:1) (*Chromatographic conditions* [**GC conditions:** Column Betadex (30 m, 0.25 mm, 0.25 µm); Temp program: 100 °C (5 min Hold) to 200 °C then Ramp 5 °C min^{-1}; Injector temp: 200 °C, Detector temp: 210 °C, Carrier gas: Helium 2.0 mL (constant flow); Injection volume: 1.0 µL, Split ratio: 50:1; Diluent: DCM.]). This mixture was then further lactonized to corresponding racemic γ-valerolactone (**1**) & (**2**) in ratio (1:1). The corresponding *S*-(-)-γ-valerolactone **(1)** & *R*-(+)-γ-Valerolactone (**2**) synthesized was analyzed in comparison with the racemate and found to have ***ee*** > 99.62% (*S*-Isomer) & 99.66% (*R*-Isomer), respectively (*Chromatographic conditions* [HPLC Column condition: Chiralpak AD-H 250 × 4.6 mm ×5 µm; Mobile phase: *n*-Hexane: EtOH: TFA (950:50:0.5) % v/v; Flow rate: 0.8 mL min^{-1}, inj. vol: 10 µL, Run time: 35 min, Column temp: 10 °C, wavelength: 210 nm and diluent: Mobile Phase.])



Scheme 7. Reagents and conditions: (a) $NaBH_4$, THF/MeOH, 0–5 °C, 2 h, 98% Yield; (b) *p*TSA/MeOH, 24 h, rt, 90% Yield.

Conclusions

In conclusion, a concise and highly stereoselective synthesis of *S*-(-)-γ-valerolactone **(1)** & *R*-(+)-γ-valerolactone (**2**) with high ***ee*** has been developed from readily accessible starting materials in good yields. The route of synthesis developed for these γ-Lactones utilize fairly inexpensive reagents and operationally friendly processes. These γ-Lactones can be utilized for the stereoselective synthesis of macrolides. The application of this methodology for the synthesis of biologically active and complex macrolides is currently underway.

Experimental

All reagents were used as received from commercial sources without further purification or prepared as described in the literature. Reactions were stirred using Teflon-coated magnetic stirring bars. TLC plates were visualized by ultraviolet light or by treatment with a spray of $KMNO_4$, Chromatographic purification of products was carried out by flash column chromatography on silica gel (60–120 mesh, 100–200 mesh, and 230–400 mesh). Reactions were conducted under N_2 in anhydrous solvents such as DCM, THF, Toluene, and EtOAc. All reactions were monitored by TLC (silica-coated plates and visualized under UV light, in case of non UV-active intermediates used suitable charring solution). Yields refer to the isolation of compounds after chromatography and spectroscopic (^{1}H and ^{13}C NMR) analysis of the homogeneous material. Air-sensitive reagents were transferred by syringe or a double-ended needle. Evaporation of the solvents was performed at reduced pressure on a Buchi rotary evaporator. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Varian Gemini 200 and Brucker Avance 300 spectrometers. Chemical shifts (δ) are reported relative to TMS ($\delta = 0.0$) as

an internal standard. Mass spectra were obtained on GC-Ms, HRMS mass spectrometers of Agilent Technologies 1100 Series. Column chromatography was performed on silica gel (60–120 mesh) supplied by Acme Chemical, India. TLC was performed on Merck 60 F-254 silica gel plates. IR (FT-IR) spectra were recorded either on KBr pellets or neat as a thin film or in $CHCl_3$. Optical rotations were recorded on a JASCO DIP–360 digital polarimeter.

Synthesis of (ethyl (S)-4-((tert-butyldimethylsilyl)oxy)pentanoate (14)

To a solution of 11 (13 g, 0.050 mole) in ethyl acetate (130 mL) was added 10% Pd/C (50% wet) and hydrogenated for 2 h at rt with 40 *p*si, after completion of reaction as indicated by TLC, the catalyst was separated by filtration and solvent was evaporated to afford (14). Output: 12.35 g, Yield: 95%. Similarly, compound (15) was synthesized by using above procedure from antipode (12), Output: 12.22 g, Yield: 94%.

Colorless oil; *S*-Isomer (**14**): $[\alpha]_D^{25} = +19.63^\circ$ (c 2.0, $CHCl_3$); *R*-Isomer (**15**): $[\alpha]_D^{25} = -19.93^\circ$ (c 2.0, $CHCl_3$); IR (Neat): 2957, 2934, 2859, 2894, 1738, 836, 776 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.09 (q, $J = 6.9$ & 14.2 Hz, 2H), 3.81 (m, 1H), 2.32–2.38 (m, 2H), 1.67–1.76 (m, 2H), 1.23 (t, $J = 6.9$ Hz, 3H), 1.12 (d, $J = 5.9$ Hz, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta - 4.45$, -4.89, 14.19, 18.00, 23.64, 25.81, 30.39, 34.35, 60.15, 67.40, 173.84. HRMS: Calcd. for $C_{13}H_{29}O_3Si + H$: 261.1886, found: 261.1888.

Synthesis of S-(-)-γ–valerolactone (1)

The (ethyl (S)-4-((tert-butyldimethylsilyl) oxy)pentanoate (14) (10 g, 0.038 mole) was treated with *p*TSA (0.1g) in anhydrous methanol (100 mL) at rt for 24 h, solvent was evaporated and codistilled with MTBE (50 mL). The crude residue obtained was diluted with MTBE (100 mL) and washed with sat. $NaHCO_3$ (240 mL), the solvent was removed under reduced pressure and crude residue was further purified by fractional distillation to afford *S*-(-)-γ–Valerolactone (1) Output: 3.45 g yield: 90%. Similarly, *R*-(+)-γ–Valerolactone (2) was synthesized by using above procedure, Output: 3.34 g, Yield: 87%.

Colorless oil; *S*-Isomer (**1**): $[\alpha]_D^{22} = -37.79^\circ$ (c 1.0, MeOH); *R*-Isomer (**2**): $[\alpha]_D^{22} = +37.05^\circ$ (c 1.0, MeOH); IR (Neat): 2980, 2937, 1770, 1386, 1344, 1174, 1056, 942, 896 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.41$ (d, $J = 6.4$ Hz, 3H), 1.78-1.88 (m, 1H), 2.09 − 2.40 (m, 1H), 2.53 − 2.57 (m, 2H), 4.62 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.79$, 28.85, 29.44, 77.09, 177.14 ppm; GC-Ms: (100, M+).

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