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Enantioselective synthesis of (2*S*,3′*R*,7′*Z*)-*N*-(3′-hydroxy-7′-tetradecenoyl)-homoserine lactone

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ABSTRACT

A concise enantioselective total synthesis of (2*S*,3′*R*,7′*Z*)-*N*-(3′-hydroxy-7′-tetradecenoyl)-homoserine lactone is described. Key feature of this protocol is a catalytic asymmetric hydrogenation and a prophenol–zinc-catalyzed diazo addition to imine reaction as genesis of chirality. Moreover, flexibility is built in the synthesis to generate enantioenriched analogs using catalytic amount of enantioenriched C_2-symmetric ligands.

The quorum-sensing chemical entity *N*-acyl-homoserine lactone (AHL) is found to be responsible for intercellular communication in Gram-negative bacteria.[1] This chemical motif also induces gene encoding enzymes involved in their own synthesis, hence often called as autoinducer.[2] Additionally, the AHL molecule displays an unusual property of growth inhibition of *Rhizobium bacteria* which harbor the conjugative sym plasmid pRL1JI.[3] Various acyl-homoserine lactones have been identified and remarkably all contain a common structural motif, which is homoserine lactone possessing absolute configuration *S* with varying pendant saturated and unsaturated carbon chains.[4] Among them, (2*S*,3′*R*,7′*Z*)-*N*-(3′hydroxy-7′-tetradecenoyl)-homoserine lactone **1** showed impressive inhibitory activity against the growth of *R. leguminosarum* RBL5523.[5] Recently, Yajima et al. not only achieved the unambiguous total synthesis of natural (2*S*,3′*R*,7′*Z*)-*N*-(3′-hydroxy-7′-tetradecenoyl)-homoserine lactone **1** but also confirmed the absolute configuration of the natural product as 2*S*,3′*R*. Along this vein, all possible stereoisomers have been synthesized and established stereochemistry-activity relationship of this quorum-sensing pheromone. Intriguingly, the two stereogenic centers were installed by employing chiral pool starting materials.[5]

With our continued interest in developing catalytic routes to bioactive small molecules,[6] herein, we report a concise flexible route for the synthesis of natural (2*S*,3′*R*,7′*Z*)-*N*-(3′-hydroxy-7′-tetradecenoyl)-homoserine lactone **1** based on two catalytic steps: (a) prophenol–zinc-catalyzed nucleophilic addition of α-diazoacetate to imine, and (b) catalytic asymmetric transfer hydrogenation (CATHy™) reaction. Our retro synthetic analysis is delineated in Scheme 1.

Initially, we envisioned that the stereogenic center of (*S*)-homoserine lactone hydrochloride **3** could be accessed through a prophenol–zinc-catalyzed nucleophilic addition of α-diazoacetate **9** to *N*-Boc-furylimine **8**. To this end, we have appraised the recently reported Trost-reaction[7] conditions for this transformation. Accordingly, the catalyst generated from 5 mol% of (*S*,*S*)-prophenol/10 mol% of $(Et)_2Zn$ in THF was treated with ethyl diazoacetate (EDA) **9** (1.0 equiv) and *N*-Boc-imine **8** (1 equiv) at 0 °C for 12 h. The anticipated product **10** was furnished with 62% yield.[8] An effort to resolve the racemic diazoamine **10** on the chiral stationery phase was not successful. Then, hydrogenation followed by reduction of **10** afforded **7** in 87% yield. Fortunately, compound **7** was resolved after derivatization with *S*-MTPA acid. The enantiomeric ratio of corresponding *S*-MTPA ester was established by HPLC on the chiral stationery phase and found to be 92:8.

Deprotection of Boc protecting group under acidic conditions followed by oxidative cleavage of the furyl moiety and subsequent purification over Dowex 50WX8-400 led to **11** in 62% yield.[9] The optical data of **11** were in full agreement with that reported in the literature $[\alpha]_D^{25} = -7.4$ ($c = 0.18$, H_2O) {lit.[10] $[\alpha]_D^{23} = -8.0$ ($c = 6$, H_2O)} thus, the absolute configuration of the stereogenic center was assigned as *S*. Finally, **11** was refluxed in aqueous HCl (6*N*) resulting in **3** 65% yield (Scheme 2).[11]

Having prepared (2*S*)-homoserine lactone hydrochloride **3**, we next proceeded to synthesize the ethyl-(*S*)-3′-hydroxy(7′*Z*)-tetradecenoate **2**. The reaction of triphenylphosphonium salt **6** and

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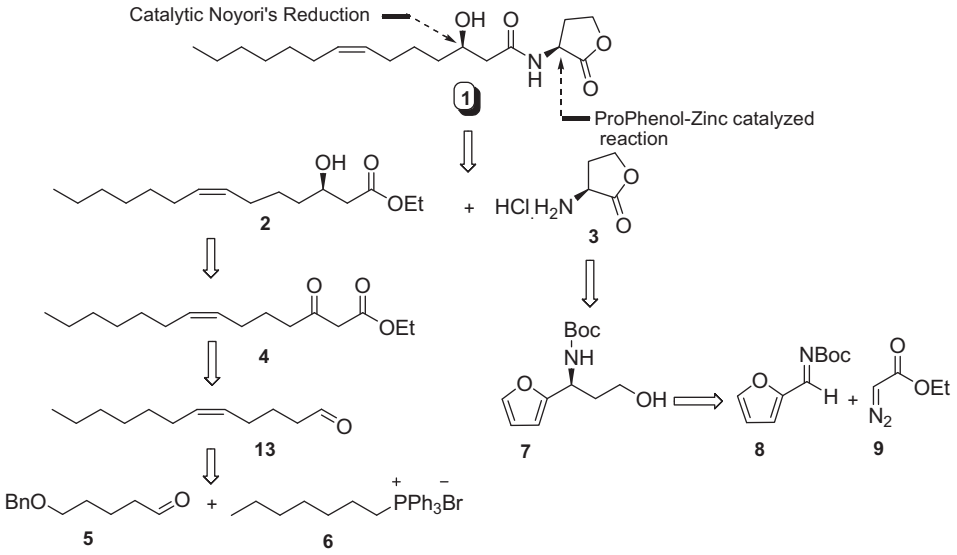
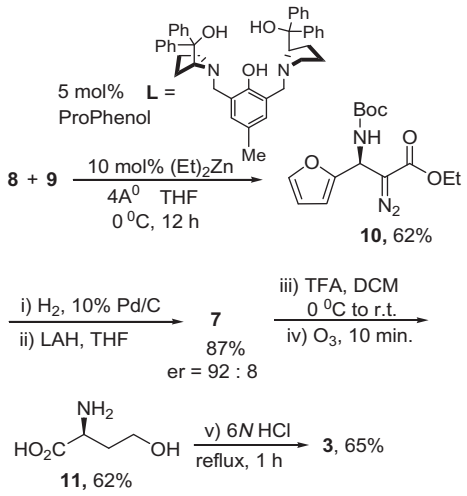
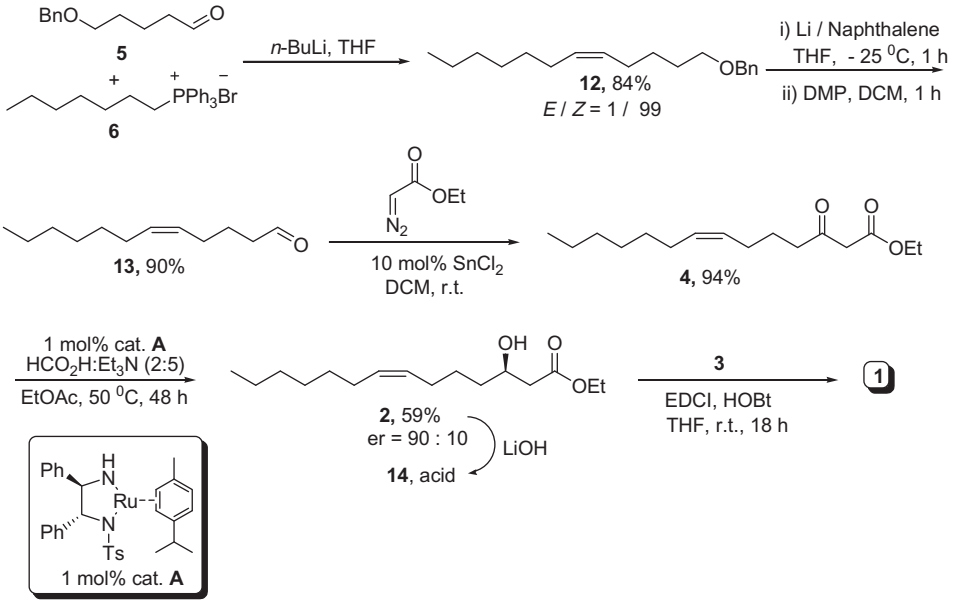


Scheme 1. Retro synthetic analysis.



Scheme 2. Homoserine lactone hydrochloride **3**.

benzyloxy pentanal **5** in THF:DMSO (2:1) with *n*-BuLi generated (*Z*)-olefin **12** (*Z*/*E* 99:1, judged by ^{13}C NMR) in 84% yield.[12] The compound **12** was subjected to reductive debenzylation (Li/naphthalene) followed by oxidation with Dess–Martin Periodinane furnished the aldehyde **13** in 90% yield. The aldehyde **13** was converted into β-ketoester **4** in 94% yield using ethyl diazoacetate in the presence of catalytic amount of $SnCl_2$.[13] Next, we focused on reduction of prochiral keto functionality of ester **2**. Initially, we had evaluated Noyori's catalytic asymmetric transfer hydrogenation in the presence of catalyst **A** and 2-propanol as the hydrogen donor.[14] The reduction of compound **2** by using 1 mol% of Ru-catalyst **A** and 7 mol% of KOH in 2-propanol at 80 °C for 6 h led to a low yield of desired product **2** (10%). However, the same substrate was exposed to formic acid:triethylamine (2:5) as a hydrogen source using 1 mol% of Ru-catalyst **A** in EtOAc at 50 °C for 48 h affording the alcohol **2** in 59% isolated yield with 90:10 enantiomeric ratio.[15,16] The optical purity and absolute configuration of new stereogenic center was assigned on the basis of sign of specific rotation with comparison of the literature data.[5] The hydroxy ester **2** was saponified to give corresponding acid **14** which then condensed with



Scheme 3. Synthesis of title compound **1**.

hydrochloride salt of **3** employing EDCI (1-ethyl-3-(3-dimethylaminopropyl) carbodiimide) with HOBt (1-hydroxy-benzotriazole) and Et_3N. The coupled product **1** was isolated in 72% yield. The spectral and analytical data of **1** were in full agreement with reported data $[\alpha]_D^{25} = -11.9$ ($c = 0.35$, $CHCl_3$). {lit.[5] $[\alpha]_D^{25} = -12.3$ ($c = 0.53$, $CHCl_3$)} (Scheme 3).

In conclusion, we have demonstrated a concise enantioselective total synthesis of (2*S*,3′*R*,7′*Z*)-*N*-(3′-hydroxy-7′-tetradecenoyl)-homoserine lactone, which was achieved using a catalytic asymmetric hydrogenation and a prophenol–zinc-catalyzed diazo addition to imine reaction as genesis of chirality. Further, this route will allow synthesizing all possible stereoisomers using an antipode of C_2-symmetric chiral template of corresponding ligands.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures, spectral data and copies of spectras for all compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.138.

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8. In place of ethyl diazoacetate, benzyl diazoacetate was employed. But, the resulting product showed inferior enantioselectivity (er 87:13 by chiral HPLC, Chiralpak AD–H column: 95/5 *n*-hexane/*i*-PrOH, flow rate 0.8 mL/min, $\lambda = 254$ nm, $\tau_{major} = 31.9$ min, $\tau_{major} = 34.7$ min).
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16. Experimental details for key steps, Compound **10**: To a solution of (*S*,*S*)-prophenol (378 mg, 0.512 mmol) in anhydrous THF (6 mL) was added a solution of diethylzinc (1.0 mL of a 1 M solution in hexane) at 0 °C. The reaction mixture was stirred at room temperature for 30 min. This solution was used as catalyst solution for the below reaction. An oven dried two-neck round bottomed flask was charged with activated 4 Å sieves, fitted with a septum, evacuated, flame dried, and purged with nitrogen. The flask was cooled to room temperature then furan-*N*-Boc-imine (2.0 g, 10.26 mmol) in THF (25 mL) and the catalyst solution (0.125 M) were added successively. The resulting reaction was cooled to 0 °C and ethyl diazoacetate (1.2 g, 10.26 mmol) was added dropwise. The resulting solution was stirred for 12 h; after which time, the reaction was then quenched with 0.5 M HCl (20 mL) and diluted with ethyl acetate (30 mL). The contents were extracted with ethyl acetate (3 × 15 mL). The combined organic phases were concentrated and the residue was purified over silica column eluting with hexane/EtOAc = 95:5) to afford 1.96 g (62%) of **10** as yellow oil. $[\alpha]_D^{25} = -8.5$ ($c = 0.45$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.33–7.36$ (m, 1*H*, furan), 6.30–6.33 (m, 1*H*, furan), 6.26 (d, $J = 3.1$ Hz, 1*H*, furan), 5.65 (d, $J = 7.5$ Hz, 1*H*, *CH*NH), 5.35 (br s, 1*H*, H–N), 4.22 (q, $J = 6.8$ Hz, 2*H*, $CO_2CH_2CH_3$), 1.46 (s, 9*H*, $C(CH_3)_3$), 1.28 (t, $J = 6.8$ Hz, 3*H*, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 154.6$, 151.0, 142.4, 110.5, 106.9, 61.0, 45.9, 28.2, 14.3 ppm. IR (KBr): $\upsilon = 3364$, 2092, 1685, 1521, 1163, 750, 632 cm^{-1}. MS (ESI) *m*/*z*: 332 $(M+Na)^+$. HRMS: calcd for $C_{14}H_{19}N_3O_5Na$ 332.1222; found 332.1232. Compound **2**: To a solution of **4** (500 mg, 1.86 mmol) in anhydrous EtOAc (5 mL) under argon was added HCOOH:Et_3N (2:5) mixture (0.25 mL) followed by the addition of Ru-catalyst **A** (0.011 g, 0.019 mmol, 1 mol %) which was predissolved in CH_2Cl_2 (2 × 1 mL). The resulting reaction mixture was heated to 50 °C for 48 h. After cooling the reaction mixture to room temperature, it was diluted with ethyl acetate (20 mL) and filtered through a pad of silica gel. The filtrate was concentrated in vacuo and the residue was subjected to silica gel flash column chromatography (5% EtOAc in hexane) to afford 298 mg (59%) of compound **2** as colorless oil. $[\alpha]_D^{25}$ −11.3 ($c = 0.25$, $CHCl_3$). {lit.[5] $[\alpha]_D^{22}$ −14.0 (c 0.85, $CHCl_3$)}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 5.25–5.38$ (m, 2*H*, =*CH*CH_2), 4.16 (q, $J = 6.8$ Hz, 2*H*, $CO_2CH_2CH_3$), 3.89–3.99 (m, 1*H*, *CH*OH), 2.91 (br s, 1*H*, OH), 2.45 (dd, $J = 2.9$, 16.6 Hz, 1*H*, 2-*CH*H), 2.35 (dd, $J = 2.9$, 16.6 Hz, 1*H*, 2-CH*H*), 1.96–2.08 (m, 4*H*, 2 × CH_2), 1.23–1.57 (m, 15*H*, 5 × CH_2 and CH_3), 0.89 (t, $J = 6.8$ Hz, 3*H*, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 173.1$, 130.5, 129.1, 67.9, 60.6, 41.3, 36.0, 31.7, 29.7, 29.0, 27.2, 26.9, 25.5, 22.6, 14.1, 14.0 ppm. IR (KBr): $\upsilon = 3466$, 2930, 2852, 2715, 1735, 1459, 1405, 1369, 1300, 1089, 1015, 725 cm^{-1}. MS (ESI) *m*/*z*: 293 $(M+Na)^+$. HRMS: Calcd for $C_{16}H_{30}O_3Na$ 293.2092; found 293.2093.