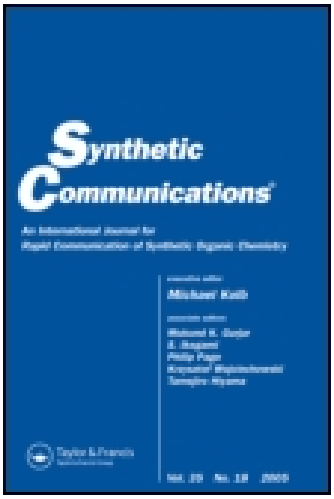

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 27 Dec 2013.

To cite this article: Ramakrishna Samala, Venkateshwarlu Gurram, Balaram Patro, Narender Pottabathini & K. Mukkanti (2014) Concise Total Synthesis of (-)-Erinapyrone B from D-(+)-Malic Acid, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 44:4, 500-506, DOI: 10.1080/00397911.2013.817017

To link to this article: http://dx.doi.org/10.1080/00397911.2013.817017

Synthetic Communications®, 44: 500–506, 2014

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2013.817017

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CONCISE TOTAL SYNTHESIS OF (−)-ERINAPYRONE B FROM D-(+)-MALIC ACID

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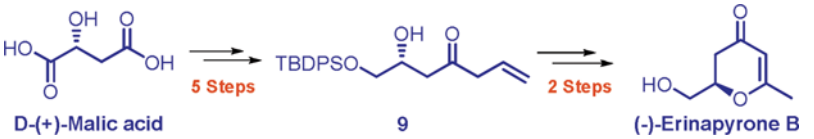
GRAPHICAL ABSTRACT



Abstract *A convenient and facile enantioselective synthesis of (−)-erinapyrone B from commercially available D-(+)-malic acid has been achieved in seven steps. One of the key steps in this synthesis was the one-pot reaction of palladium(II)-mediated Wacker-type oxidative cyclization in the presence of a catalytic amount of* p-*toluenesulphonic acid (*p-*TsOH) which has been found to be effective for the preparation of enantiopure 2,3-dihydro-4*H*-pyran-4-one from the corresponding enantiopure* β*-hydroxyenone via enantio-enriched diketohydroxy intermediate.*

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resource(s): Full experimental and spectral details.]*

Keywords 2,3-Dihydro-4*H*-pyran-4-one; β-hydroxyenone; oxidative cyclization; Pd-catalyzed; *p*-TsOH

INTRODUCTION

2,6-Disubstituted dihydropyrones are seemingly present in many natural products. These compounds are also important synthetic intermediates in the syntheses of biologically active molecules.[1] Their syntheses have been well established in the literature. For example, hetero-Diels–Alder reactions have been used to synthesize this type of compound.[2] New strategies that have been recently developed include the tandem aldol reaction / conjugate addition[3]and the oxidative cyclization of β-hydroxyenenoneswith palladium(II).[4] Erinapyrone A (**1**) and erinapyrone B (**2**)

Received April 5, 2013.

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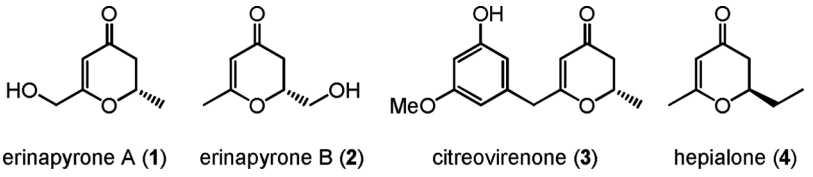
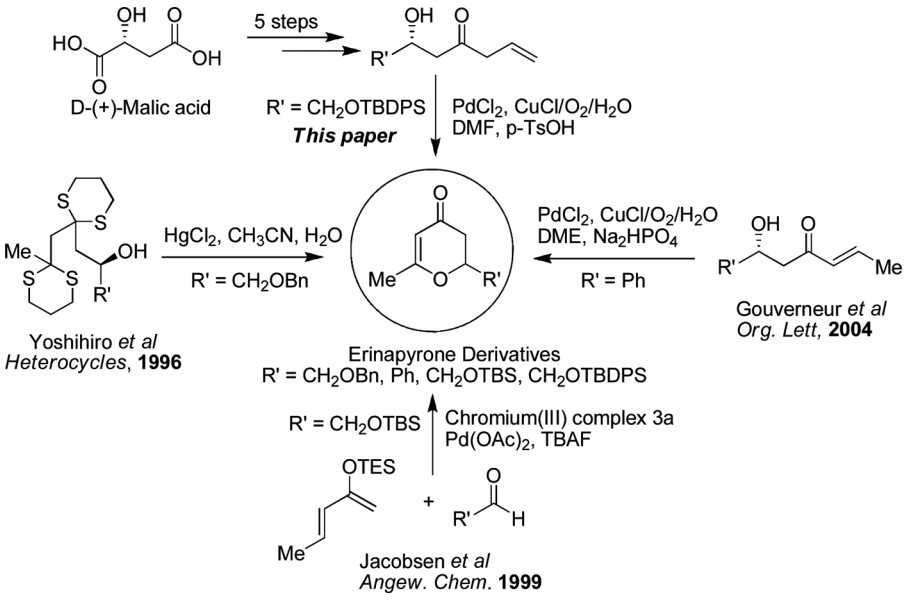


Figure 1. Natural products from *Hericium erinaceummycelia.*

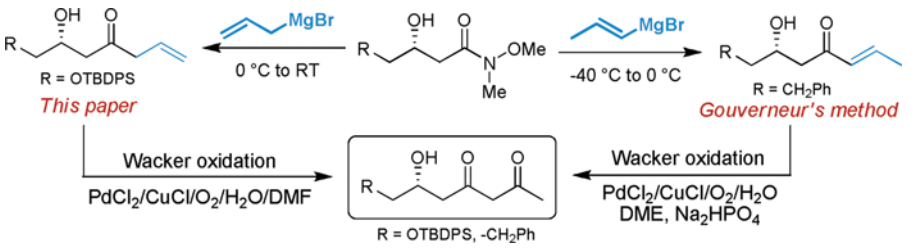
belong to the class of 2,6-dihydroxy dihydropyrones isolated from the culture broth of *Hericium erinaceum*mycelia (Fig. 1) reported by Kawagishi et al., which possess cytotoxicity toward HeLa cells.[5] The first total syntheses of optically active (−)-**1** and (−)-**2** were reported by Noda et al.[6] in a short route from bis-2-(1,3-dithianyl)methane, (*S*)-propylene oxide, (*R*)-benzyl glycidyl ether, and $HgCl_2$.[7,8]

In early 1999, Jacobsen et al. developed a palladium-mediated route for structurally diverse 2,3-dihydro-4*H*-pyran-4-ones using a concerted or stepwise hetero-Diels–Alder (HAD) reaction of aldehydes with Danishefsky'sdienes catalyzed by various Lewis acids that led to β-hydroxyenenones. These are common precursors for the preparation of 2,3-dihydro-4*H*-pyran-4-ones via Wacker-type oxidative palladium(II)-mediated cyclization.[9] See Scheme 1.

Based on these strategies, Reiter et al. reported the synthesis of 2,3-dihydro-4-*H*-pyran-4-ones using the common precursor of β-hydroxyenenones from the corresponding Grignard reagent and Weinreb amide.[4] The crotyl-β-hydroxyenenones were converted to the corresponding 2,3-dihydro-4*H*-pyran-4-ones via Wacker-type oxidative palladium(II)-mediated cyclization. We are interested in a facile synthesis of stereospecific (−)-erynopyrone B (**2**).We outline in this communication a versatile



Scheme 1. Methods available for the synthesis of dihydro-4*H*-pyran-4-ones.



Scheme 2. Approaches toward the synthesis of β-hydroxyenenone via Grignard reactions. (Figure is provided in color online.)

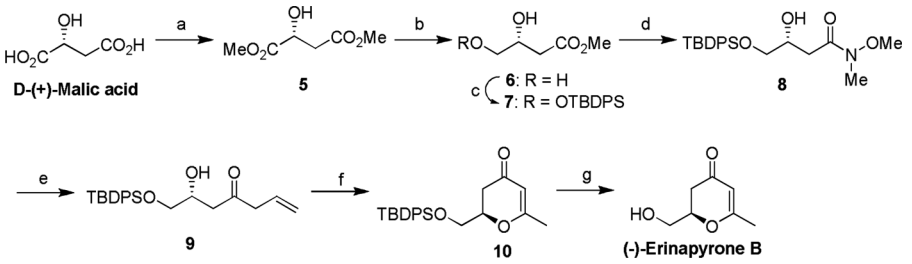
synthetic route of chiral erinapyrone B in seven steps from commercially available D-(+)-malic acid. Our approach is inspired by Reiter's method using the formation of β-hydroxyenenone as a key intermediate (Scheme 2). In Scheme 2, Gouverneur and colleagues[4] reported the synthesis of crotyl-b-hydroxyenenones using crotylmagnesium bromide as the Grignard reagent and performed the reactions at $-40°C$ to $0°C$ and then achieved the 6-hydroxyheptane-2,4-diones with an ee $> 97\%$ by Wacker oxidation using $PdCl_2/CuCl$ under oxygen atmosphere in a DME solvent. Based on the above information, we tried to use commercially available allylmagnesium bromide as the cost effective Grignard reagent than the crotylmagnesium bromide, performed the various reactions at ambient temperatures and optimized the reaction conditions successfully to achieve the allyl-b-hydroxyenenones in 69% yield with an ee of 99%, which proceeded for Wacker oxidation using $PdCl_2/CuCl$ under oxygen atmosphere in a DMF solvent. The reaction was carried out overnight and afforded the 6-hydroxyheptane-2,4-dione (**11**) and was confirmed by ^1H NMR and mass spectrum analysis.

Our aim is to cyclize the 6-hydroxyheptane-2,4-dione (**11**) to the corresponding dihydropyranone (**10**) without isolation of hydroxydiketones. We carried out the reaction mixture to next cyclisation with the addition of p-TsOH(cat.) and continued the reaction at room temperature for 3 h. After workup, silica gel column chromatography afforded the erinapyrone B with an ee of 99%.

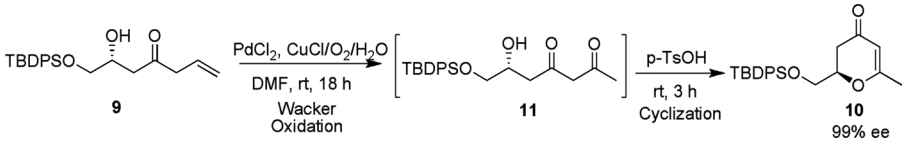
RESULTS AND DISCUSSIONS

We began with the esterification of D-(+)-malic acid by treatment of thionyl chloride in methanol. This resulted its dimethyl ester **5** in 90% yield.[10] The selective reduction of **5** in presence of $BH_3 \cdot Me_2S$ and sodium borohydride in tetrahydrofuran (THF) at rt for 3 h afforded **6** in excellent yield (90%).[11] The selective protection of **6** happened by the treatment of 1 equiv of *tert*-butyldiphenylsilylchloride and imidazole in dimethylformanide (DMF) resulting in ester **7** in 90% yield.[12] Reaction of **7** with *N,O*-dimethylhydroxylamine hydrochloride in the presence of trimethylaluminum provided the crystalline *N*-methoxy-*N*-methylamide **8** (70%), which on treatment with exposure to allyl magnesium bromide provided the novel enone **9** in 85% yield[13] (Scheme 3).

One-pot conversion from **9** to **10** happened by oxidation of eneone **9** using palladium(II) chloride / copper(I) chloride/oxygen in aqueous DMF[14] followed by the treatment with *p*-toluenesulfonic acid (*p*-TsOH)[8] at room temperature for



Scheme 3. Synthesis of (−)-erinapyrone B. Reagents and conditions: (a) $SOCl_2$, MeOH, rt, 18 h (95%); (b) $BH_3 \cdot Me_2S$, $NaBH_4$, THF, rt, 3 h (90%); (c) TBDPSCl, imidazole, DMF, rt, 18 h (90%); (d) (MeO)-MeNH · HCl, $Al(CH_3)_3$,CH_2Cl_2, reflux, 18 h (75%); (e) CH_2=CH-CH_2MgBr, THF, 0 °C, 2 h (85%); (f) $PdCl_2$, CuCl, O_2, DMF/H_2O, rt, 18 h; *p*-TsOH, rt, 3 h (60%); and (g) TBAF, THF, rt, 3 h (80%).



Scheme 4. One-pot reaction of β-hydroxyenone (9) to 2,3-dihydro-4*H*-pyran-4-one (**10**).

3 h affords dihydropyranone **10** in 60% yield with an enantiomeric excess of 99% (Scheme 4).

Deprotection of the TBDPS group[15] of **10** with tetrabutylammonium fluoride (TBAF) furnished (−)-erinapyrone B in 80% yield. ^{1}H, and ^{13}C NMR spectra of (−)-erinapyrone B matched with the literature reported values.[5]

CONCLUSION

In conclusion, we have developed a convenient, operationally simple, and efficient synthesis of erinapyrone B from commercially available D-(+)-malic acid in seven steps with 82% overall yield. The efforts to expand this work to the synthesis of other heterocyclic compounds are under way in our laboratory.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity instrument at rt at 400 MHz. Chemical shifts are reported in δ parts per million (ppm) downfield from tetramethylsilane (TMS) with reference to internal solvent and coupling constants in hertz. Infrared (IR) spectra were recorded on a Perkin-Elmer FT-IR spectrometer. Mass spectra were obtained on a high resolution Micromass QuattroMicro™ API-autospectrometer using electraspray ionization techniques (ESI). High-resolution mass spectrometry (HRMS) TOF ES mass spectra were recorded on a Waters-Alliance 2695 Separation Module/Q-TOF Micromass. Optical rotations were obtained on an automated Jasco P-1030 Polari meter. Chiral high-performance

liquid chromatography (HPLC) analysis was performed by Chiralcel OJH (4.6 × 250 mm), 5 μm, and Chiralpak-IC (250 × 4.6 mm), 5 μm, columns.

General Procedure for the Synthesis of (*R*)-7-(*tert*-Butyldiphenylsilyloxy)-6-hydroxyhept-1-en-4-one (9)

A solution of Weinreb amide **8** (1.0 g, 3.61 mmol) in 20 mL of THF was added dropwise to a solution of ally magnesium bromide (1 M solution in THF; 9.1 mL, 9.11 mmol) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for 2 h at room temperature, then added to aqueous 20% NH_4Cl solution (10 mL) at 0 °C, and extracted with ether (2 × 25 mL). The combined organic layer was washed with brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel (20% EtOAc in hexanes) to afford the title compound.

General Procedure for the Synthesis of (R)-7-(*tert*-Butyldiphenylsilyloxy)-6-hydroxyheptane-2,4-dione (11)

A 25-mL, three-necked, round-bottomed flask was charged with a mixture of palladium (II) chloride (35 mg, 0.2 mmol), cuprous chloride (99 mg, 1 mmol), and aqueous DMF (DMF/H2O = 7:1, 23 mL), and the reaction mixture was purged with oxygen for 10 min. The reaction was continued under oxygen for 1 h and then substrate **9** (0.38 g, 1 mmol) was added in DMF (2 mL) to the reaction mixture at the same temperature. The resulting reaction mixture was stirred at room temperature for 18 h under an oxygen atmosphere, which was used for next step without isolation. For the confirmation of compound **11**, 0.2 mL of this reaction mixture was concentrated and purified by preparative thin-layer chromatography (TLC) using 15% EtOAc in hexanes as an eluent to afford the title compound, which was confirmed by ^{1}H NMR and MS.

General Procedure for the Synthesis of (*R*)-2-((*tert*-Butyldiphenylsilyloxy)methyl)-6-methyl-2H-Pyran-4(3H)-one(10)

To this reaction mixture, *p*-TsOH (18 mg, 10% mol) was added and stirring was continued at room temperature for 3 h. The reaction mixture was diluted with water (10 mL) and extracted with ether (3 × 25 mL). The combined organic layer was washed with brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel (15% EtOAc in hexanes) to afford the title compound.

Spectral Data for New Compounds

(*R*)-7-(*tert*-Butyldiphenylsilyloxy)-6-hydroxyhept-1-en-4-one (9). Yield 0.79 g (85%), light yellow oil; R_f 0.5 (30% EtOAc/hexanes); IR (DCM film) 3445, 3304, 2956, 2929, 2857, 1714, 1463, 1427, 1393, 1260, 1187, 1112, 923, 823, 741, 703 cm^{-1}; $[\alpha]_D^{27}$ +10.91° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (m, 4H), 7.38 (m, 6H), 5.83 (m, 1H), 5.28 (m, 2H), 4.31 (s, 1H), 3.62 (d, 2H);

3.23 (d, 2H), 2.84 (s, 1H), 2.64 (d, 2H); 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.2, 135.4, 133.0, 133.0, 130.0, 129.8, 127.7, 119.1, 68.1, 66.9, 48.4, 45.0, 26.8, 19.2;MS (ESI) m/z 406.12 $(M + Na)^+$. HRMS calculated for $C_{23}H_{31}O_3Si$ $[M + Na]^+$ 405.1862; found 408.1877.

(R)-7-(*tert*-Butyldiphenylsilyloxy)-6-hydroxyheptane-2,4-dione (11). Gummy liquid; R_f 0.6 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (m, 4H), 7.45 (m, 6H), 4.43 (m, 1H), 3.96 (m, 2H), 2.68 (m,1H), 2.41 (m, 1H), 2.01 (s, 3H), 1.09 (s, 9H); MS (ESI) m/z 397.26 $(M + H)^+$.

(*R*)-2-((*tert*-Butyldiphenylsilyloxy)methyl)-6-methyl-2h-pyran-4(3H)-one (10). Yield 0.22 g (60%), light yellow oil; R_f 0.35 (20% EtOAc/hexanes); IR (DCM film) 3464, 3071, 2957, 2858, 1896, 1667, 1613, 1461, 1427, 1397, 1335, 1240, 1112, 1041, 903, 822, 703 cm^{-1}; $[\alpha]_D^{25}$ −91.22° (*c* 1.02, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (m, 4H), 7.38 (m, 6H), 5.36 (s, 1H), 4.46 (m, 1H), 3.93 (m, 2H), 2.62 (m,1H); 2.36 (m, 1H), 1.95 (s, 3H); 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.7, 174.1, 135.5, 132.5, 132.9, 129.8, 127.7, 127.7, 116.0, 104.6, 79.2, 64.9, 37.1, 29.6, 26.7, 20.9, 19.2; MS (ESI) m/z 381.4 $(M + H)^+$. HRMS calculated for $C_{23}H_{29}O_3Si$ $[M + H]^+$ 381.1886; found 381.1891.

Supporting Information

Full experimental details, ^{1}H and ^{13}C NMR spectra, and chiral HPLC chromatograms of all the important compounds associated with this article can be found via the Supplementary Content section of this article's Web page.

ACKNOWLEDGMENTS

The authors are grateful to GVK Biosciences Pvt. Ltd. for the financial support and encouragement. We thank Subhabrata Sen for his immense assistance.

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