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Titanocene(III) chloride mediated formal synthesis of magnofargesin and 7′-epimagnofargesin

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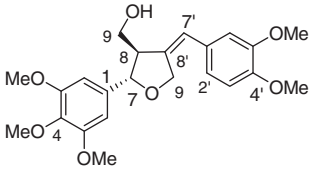
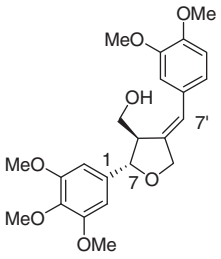
ABSTRACT

Formal synthesis of two bioactive lignans, magnofargesin and 7′-epimagnofargesin has been accomplished in both racemic and optically active forms through titanocene(III) chloride (Cp_2TiCl) mediated radical induced cyclization reaction. Ti(III) species was generated in situ from the commercially available titanocene dichloride (Cp_2TiCl_2) and activated zinc dust in dry THF.

Due to widespread occurrence in nature and broad range of biological activities lignans have attracted the attention of organic chemists in recent years. Magnofargesin (**1**) and its isomer 7′-epimagnofargesin (**2**) are two furano lignans. Magnofargesin was first isolated[1] from the flower buds of *Magnolia fargessi* also known as '*shin-i*', which has been used for many years in China and Japan as *materia medica*. It has been shown that (−)-magnofargesin is an antagonist of platelet-activating factor (PAF).[2] Antagonists of PAF have therapeutic potentiality for the treatment of asthma and protective activity against ischemic injury.[3]



Magnofargesin (**1**)



7′-epimagnofargesin (**2**)

Biotransformation study of (−) magnofargesin by *Spodoptera litura* larvae has been investigated thoroughly to obtain a useful *O*-demethylated[4] metabolite. (+)-Epimagnolin A,[1b] a growth inhibitory lignan against the larvae of *Drosophila melanogaster*, can also be easily synthesized from magnofargesin. In spite of such immense biological importance, to the best of our knowledge only one report by Wardrop and Fritz[5] has been documented in the literature for the synthesis of magnofargesin (**1**) in a multi-step process. In continuation of our ongoing research[6] on the total synthesis of natural products and related compounds through titanocene(III) chloride (Cp_2TiCl) mediated radical cyclization reactions, we describe herein the formal synthesis of magnofargesin (**1**) and 7′-epimagnofargesin (**2**) in a concise and efficient route by opening of epoxides using Cp_2TiCl as the radical initiator. Ti(III) species was generated in-situ from the readily available titanocene dichloride (Cp_2TiCl_2) and activated zinc dust in dry THF.[7]

The epoxy alcohol **7** was prepared from 3,4,5-trimethoxybenzaldehyde (**3**) as depicted in Scheme 1. Compound **3** on vinyl Grignard reaction afforded the allyl alcohol **4** (86%) which on epoxidation with *m*-CPBA afforded the epoxy alcohol **7** in only 25% yield as an inseparable mixture of two isomers in almost equal ratio (^{1}H NMR). The poor yield of the desired alcohol in this method prompted us to find out an alternative route to the epoxy alcohol **7** with an improved yield. Dihydroxylation[8] of the allyl alcohol **4** with OsO_4 and NMO in acetone–water (4:1) afforded the triol **5** in good yield as a mixture of two isomers in 1:1 ratio. Selective tosylation of the crude triol **5** with TsCl in pyridine furnished the tosylate **6** (44%). The treatment of the crude compound **6** with K_2CO_3 in MeOH at room temperature[9] afforded the terminal epoxide **7** in 92% yield as an inseparable mixture of two isomers in 1:1 ratio. The crude epoxide **7** was used for the synthesis of **1** and **2** without further purification. Thus, treatment of the epoxide **7** with sodium hydride and the easily accessible propargyl bromide **8** at low

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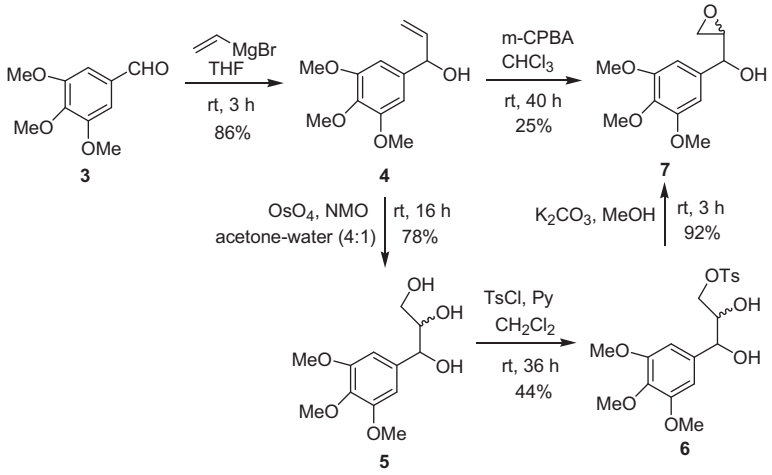
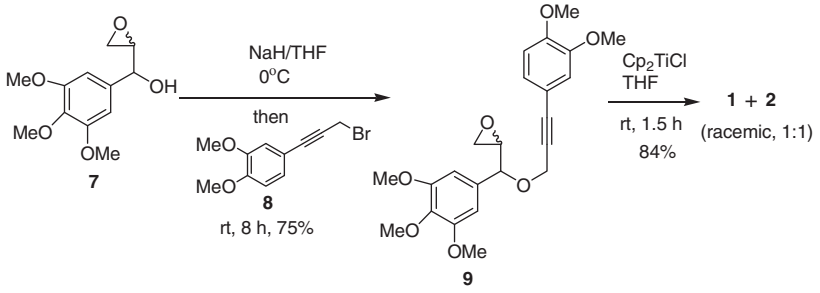


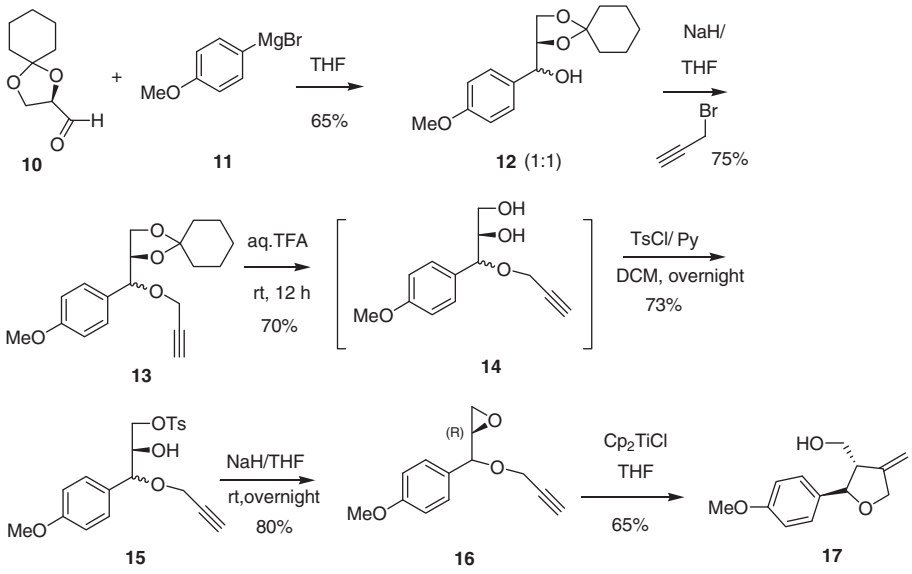
Scheme 1.



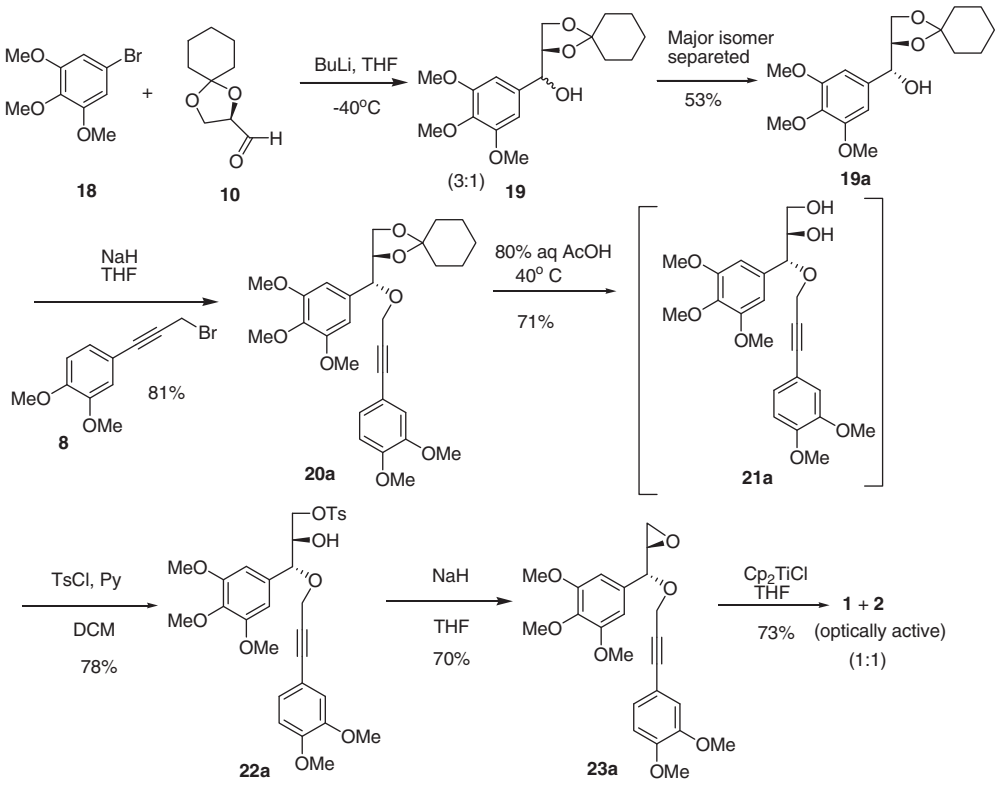
Scheme 2.

temperature afforded the epoxide **9** as a mixture of two isomers (1:1) in good yield (Scheme 2).

The radical cyclization of the crude epoxide **9** using titanocene(III) chloride (Cp_2TiCl) in THF at room temperature afforded a mixture of two isomers **1** and **2** in 1:1 ratio with 84% yield. The ratio of the two isomers was determined from the ^1H NMR spectrum of the crude cyclized product, where C-7 benzylic proton appeared as doublet at δ 4.86 ($J = 6.7$ Hz) for one isomer and at δ 5.08 ($J = 4$ Hz) for the other isomer. The ^1H NMR of the crude mixture was compared with the values reported in the literature by Wardrop[5] and it was found that both magnofargesin (**1**) and 7′-epimagnofargesin (**2**) were formed in equal ratio. Due to unavailability of the specific column used by Wardrop and Fritz,[5] our attempts to separate two isomers **1** and **2** by preparative TLC



Scheme 3.



Scheme 4.

and by HPLC [Column: 00G-4253-NO Luna 10u C 18(2); size-(250 × 10) mm 10u micr.; eluent: methanol–water (80:20)] with several solvent combinations were unsuccessful. So, we report here the formal synthesis of magnofargesin (**1**) and 7′-epimagnofargesin (**2**) in racemic forms using radical cyclization strategy.

After completion of the racemic synthesis of the mixture of **1** and **2**, we turned our attention toward enantioselective synthesis of the titled compounds starting from the easily accessible[10] (*R*)-2,3-*O*-cyclohexylideneglyceraldehyde (**10**). Initially, in a model study, (*R*)-2,3-*O*-cyclohexylideneglyceraldehyde (**10**) was converted into the epoxide **16** through a series of classical reactions as depicted in Scheme 3. Finally, the epoxide **16** was subjected to radical cyclization reaction using Cp_2TiCl in THF to produce the cyclized compound **17**.

Then, we undertook the synthesis of optically active magnofargesin (**1**) and its isomer 7′-epimagnofargesin (**2**) using the similar radical strategy. Thus, 3,4,5-trimethoxybromobenzene (**18**) was treated with *n*-BuLi in THF at −40 °C and then addition of the aldehyde **10** afforded the alcohol **19** as a mixture of two diastereomers[11] in a ratio of 3:1 (Scheme 4). The major isomer **19a** was separated by column chromatography and was subjected to *O*-alkylation with the bromo compound **8** in the presence of NaH in THF to afford the compound **20a**. Now, the deprotection of the cyclohexylidene group with aq. AcOH furnished the diol **21a**. Selective tosylation of the primary alcohol in **21a** afforded **22a** which on treatment with NaH in THF afforded the epoxide **23a**. Finally, the radical cyclization of the epoxide **23a** with Cp_2TiCl in THF afforded a mixture of two isomers in a ratio of 1:1.[12] The ratio of the two isomers was determined from the ^1H NMR spectrum of the crude cyclized product, where C-7 benzylic proton appeared as doublet at δ 4.86 (J = 6.7 Hz) for one isomer and at δ 5.08 (J = 3.9 Hz) for the other isomer. The ^1H NMR of the crude mixture was compared with the values reported in the literature by Wardrop[5] in their racemic synthesis and it was found that a mixture of magnofargesin (**1**) and 7′-epimagnofargesin (**2**) was formed in equal ratio. Two isomers **1** and **2** have already been separated by Wardrop and Fritz[5] in their racemic synthesis. Due to unavailability of the specific column used by Wardrop and Fritz, our attempts to separate the two isomers **1** and **2** by preparative TLC and by HPLC [Column: 00G-4253-NO Luna 10u C 18(2); size-(250 × 10) mm 10u micr.; eluent: methanol–water (80:20)] with several solvent combinations were unsuccessful. So, we report here the formal synthesis of magnofargesin (**1**) and 7′-epimagnofargesin (**2**) in optically active forms using radical cyclization strategy.

In conclusion, we have derived a new route for the formal synthesis of bioactive lignans, magnofargesin and 7′-epimagnofargesin in both racemic and optically active forms by radical cyclization of epoxides using titanocene(III) chloride as a radical source.

Acknowledgments

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12. *Typical radical cyclization procedure for the synthesis of **1** and **2***: a solution of titanocene dichloride (564 mg, 2.28 mmol) in dry THF (25 mL, not deoxygenated) was stirred with activated zinc dust (360 mg, 5.5 mmol) for 1 h under argon (activated zinc dust was prepared by washing 20 g of commercially available zinc dust with 60 mL of 4 M HCl and thorough washing with water and finally with dry acetone and then dried in vacuum). The resulting green solution was then added dropwise to a stirred solution of the epoxide **23a** (290 mg, 0.70 mmol) in dry THF (25 mL) at room temperature under argon during 1 h. The reaction mixture was stirred overnight and was decomposed with 10% H_2SO_4 (10 mL). Most of the solvent was removed under reduced pressure and the residue was extracted with diethyl ether (4 × 30 mL). The combined ether layer was washed with saturated $NaHCO_3$ (2 × 25 mL) and finally dried over Na_2SO_4. After removal of the solvent under reduced pressure the crude residue obtained was purified by column chromatography over silica gel (20% ethyl acetate in petroleum ether) to afford magnofargesin (**1**) and 7′-epimagnofargesin (**2**) as a mixture of two isomers in 1:1 ratio (213 mg, 73%). IR (neat): 3510, 3010, 2923, 2850, 1593, 1514, 1461 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$); 2.96–2.98 (m, ½H, C8-*H* for **1**), 3.40–3.49 (m, ½H, C8-*H* for **2**), 3.82–3.97 (m, 17 H, 5-OC*H*$_3$, C9-*H*), 4.58–4.69 (m, 1H, C9′-*H* for **2**), 4.73–4.77 (m, 1/2 H, C9′-*H* for **1**), 4.86 (d, *J* = 6.7, 1/2H, C7-*H* for **1**), 4.91–4.96 (m, 1/2H, C9′-*H* for **1**), 5.08 (d, *J* = 4 Hz, 1/2H, C7-*H* for **2**), 6.40 (s, 1/2H, C7′-*H* for **1**), 6.47 (s, 1/2H, C7′-*H* for **2**), 6.62 (s, 1H, C2-*H* and C6-*H*, for **2**), 6.64 (s, 1H, C2-*H* and C6-*H* for **1**), 6.71–6.74 (m, 1H, Ar*H*), 6.81–6.86 (m, 1H, Ar*H*), 6.89–6.93 (m, 1H, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.5, 153.4, 149.0, 148.4, 138.8, 137.8, 129.4, 122.1, 121.8, 120.6, 111.6, 111.3, 103.3, 103.1, 84.6, 82.4, 73.1, 61.8, 61.0, 56.2, 56.0, 52.0; HRMS Calcd. for $C_{23}H_{28}O_7$ (M^++Na): 439.1727; found 439.1733.