CONCISE SYNTHESIS OF 1,3-DIACETOXY-2-[2'-(2'',4''-DIFLUOROPHENYL)PROP-2'-EN-1'-YL]PROPANE: AN INTERMEDIATE FOR POSACONAZOLE

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GRAPHICAL ABSTRACT

Abstract A concise process of 1,3-diacetoxy-2-[2'-(2'',4''-difluorophenyl)prop-2'-en-1'-yl]propane has been developed. Diethyl malonate was C-alkylated with 2,3-dichloropropene and then the ester groups were reduced by LiAlH4, followed by acylation to provide 2-(2'chloroprop-2'-en-1'-yl)-1,3-diacetoxypropane. The chloropropene was finally coupled with 2,4-difluorophenylmagnesium bromide and catalyzed by Fe(acac)3 to afford the title compound in good total yield.

Keywords 2,3-Dichloropropene; 2,4-difluorobromobenzene; posaconazole; tris(acetylacetonato)iron(III)

INTRODUCTION

Posaconazole (1) has been marketed as a novel extended-spectrum triazole antifungal agent for the treatment and prevention of life-threatening invasive fungal infection induced by many yeasts and molds.1 Because of its complicated structure, exploration for a novel synthetic process still attracts the attention of synthetic organic chemists.

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Posaconazole (I)

The 2,2,4-trisubstituted tetrahydronfuran skeleton with two chiral centers (2 in Scheme 1) is a critical unit for posaconazole as well as other analogs.\cite{2-4} Previously these two chiral centers were built via asymmetric synthesis involving tedious procedures or expensive chiral auxiliary agents.\cite{5,6} Later a novel synthesis was developed with enzymatically catalyzed process as a key step for the conversion of 6 into 7 (Scheme 1).\cite{7,8}

Compared with the asymmetric synthetic methods reported, this enzymatic process undoubtedly prevailed in high efficiency and environmental friendliness. However, the preparation of precursor 5 still remained complicated and tedious as disclosed in the following four patents: (1) in the first patent, Friedel–Crafts reaction of 1,3-difluorobenzene and chloroacetyl acid chloride gave 2-chloro-2',4'-difluoroacetophenone. This ketone was treated with acetate sodium, reacted with a Wittig reagent, and finally hydrolyzed to afford 3, which could be converted into 5 as described in Scheme 1.\cite{5} (2) In the second patent, the preparation of the precursor 5 started from Friedel–Crafts reaction of 1,3-difluorobenzene and acetic anhydride and was followed by Wittig reaction, radical substitution reaction, and C-alkylation of diethyl malonate. A tough problem in the radical reaction was that it was difficult to separate several bromo-substituted by-products when scaled up.\cite{9} (3) In the third patent, a single step for preparing 5 was disclosed by condensation of 2,4-difluorobromobenzene, allene, and diethyl malonate catalyzed by Pd(PPh₃)₄ in the presence of sodium hydride.\cite{10} (4) In the last patent, the ene reaction of 2-chloro-2',4'-difluoroacetophenone with (trimethylsilyl)methylmagnesium chloride gave 2-(2,4-difluorophenyl)-3-chloroprop-1-ene, which was condensed with diethyl malonate to afford 5.\cite{11} However, all the reported methods are often involved in one or more

\begin{center}
Scheme 1. Chemoenzymatic route of literature to the intermediate (2) of posaconazole.
\end{center}
drawbacks at least, such as tedious steps, rare or expensive materials, and harsh conditions.

Herein we report a novel and straightforward synthesis of 1,3-diacetoxy-2-[2\'(2\'', 4\''-difluorophenyl)prop-2\'-en-1\'-yl]propane (12), which could be enzymatically resolved to yield chiral compound 7, a key intermediate to posaconazole (Scheme 2).

RESULTS AND DISCUSSION

In our initial approach diethyl malonate was C-alkylated in ethanol with inexpensive 2,3-dichloropropene (8) in the presence of sodium ethoxide, to give diethyl 2-(2\''-chloroprop-2\''-en-1\''-yl)-1,3-propandioate (9) in 89% yield.\(^{[12]}\) Further reduction of the ester groups of 9 with LiAlH\(_4\) in refluxing tetrahydrofuran (THF) afforded the diol 10 in 91% yield, which was further acylated with Ac\(_2\)O to quantitatively provide the diacetoxy 11.

The key step of 11 to 12 was involved in Kumada cross-coupling\(^{[13,14]}\) of a vinyl chloride with Grignard reagent of an aryl bromide. Usually, Kumada cross-coupling between aryl magnesium bromides and a vinyl chloride was performed with air-sensitive nickel(0) or palladium as a catalyst, both metals respectively with phosphine compounds as its ligand.\(^{[15–22]}\) In the past decade, iron(III) complexes have been successfully applied to catalyze the coupling and numerous functional groups are tolerated (alkyl and aryl bromides, amides, esters, and even ketones.\(^{[23–29]}\) Because of its ready availability, low cost, and environmental friendliness, iron complexes have been attracting the attention of chemists in the field of catalysts.

In our case, tris(acetylacetonato) iron(III) \([\text{Fe(acac)}_3]\) was applied to catalyze cross coupling of 11 with 2,4-difluorophenyl magnesium bromide in tetrahydrofuran (THF)–N-methylpyrrolidin-2-one (NMP) (3:2 v/v)\(^{[23,30]}\) to give the title product 12 in a moderate yield (76%).

CONCLUSION

A novel and concise synthesis of 1,3-diacetoxy-2-[2\'(2\'', 4\''-difluorophenyl)prop-2\'-en-1\'-yl]propane has been developed in four steps from 2,3-dichloropropene and diethyl malonate in an overall yield of 60%. The key cross coupling of 2,4-difluorophenylmagnesium bromide with 2-(2\''-chloroprop-2\''-en-1\''-yl)-1,3-diacetoxypropane was catalyzed by inexpensive and nonpoisonous \([\text{Fe(acac)}_3]\) to give
the title compound in an excellent yield. The trace by-products can be easily removed by extraction or vacuum distillation. This method may be a useful approach for the synthesis of its 2-(2-substituted prop-2-en-1-yl)-1,3-dioxypropene derivatives.

**EXPERIMENTAL**

All reactions were performed in oven-dried (120°C) glassware. THF was distilled from sodium under N₂. NMP and Et₃N (triethylamine) were distilled from CaH₂ under N₂. Absolute ethanol was distilled from magnesium under N₂. Melting points were determined with a Büchi 540 melting-point apparatus and were uncorrected. Thin-layer chromatography (TLC) was performed on glass plates (GF₂₅₄, 50 mm × 100 mm, Marine Chemical Company of Qingdao, China) and compounds were stained with aqueous solution of 0.05% KMnO₄ after development. NMR spectra were taken on Bruker Avance III (500 MHz) with tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded using Agilent 1100 Series LC/MSD Trap. Infrared (IR) spectra were recorded using Perkin–Elmer 1600 series FTIR. Elemental analyses were performed on a Leco CHNS-932 Elemental Analyzer, Leco Corporation (USA).

**Diethyl 2-(2’-Chloroprop-2’-en-1’-yl)-1,3-propandioate (9)**

A glass reactor was charged with diethyl malonate (1.15 kg, 7.19 mol) and potassium iodide (300 mg). Then a solution of sodium ethoxide (490.0 g, 7.21 mol) in alcohol (2.50 L) was added dropwise under stirring at room temperature. After the resulting solution had refluxed for 10 min, 2,3-dichloropropene (780.0 g, 7.03 mol) was added dropwise over a period of 2 h. The mixture was continued to reflux for 2 h and then cooled down to room temperature. The reaction mixture evaporated under reduced pressure via a rotavapor to leave an oily residue, to which water (3 L) was added. The mixture was extracted with ethyl acetate (2 × 2 L). The combined organic layers were washed with brine (2 L), dried over anhydrous Na₂SO₄ (0.1 kg) overnight, and filtered. The solvent was removed via a rotavapor and the residual oil was distilled under reduced pressure to give the compound 9 (1.47 kg, 89.1%) as a colorless oil, which could be used directly in the next step. Rf = 0.65 (petroleum ether–ethyl acetate = 5:1); (bp: 94–100°C/2–3 mbar); IR (KBr) ν/cm⁻¹ 2965, 1734, 1638, 1370, 1240, 632; ¹H NMR (500 MHz, CDCl₃) δ 5.23 (s, 1H), 5.20 (s, 1H), 4.22–4.15 (m, 4H), 3.73 (t, J = 7.5 Hz, 1H), 2.91 (d, J = 7.6 Hz, 2H), 1.25 (t, 6H); MS (ESI⁺) m/z: 235 [M + 1]⁺, 257 [M + Na]⁺.

**2-(2’-Chloroprop-2’-en-1’-yl)-1,3-propanediol (10)**

A glass reactor was charged with THF (3.65 L) and LiAlH₄ (365 g, 9.62 mol). A solution of 9 (1.50 kg, 6.40 mol) in THF (2.50 L) was added at 0°C over 2 h under stirring. After complete addition, the reactants were stirred for 10 min at this temperature and then allowed to reflux 8 h. After cooling by ice water, the reaction mixture was slowly poured with agitations into the dilute hydrochloric acid (10 L) [prepared by mixing concentrated hydrochloric acid (1.75 L) with ice water (8.50 L)]. The resulting mixture was extracted with CH₂Cl₂ (2 × 5 L). The combined organic layers were washed...
with saturated brine, dried over anhydrous Na₂SO₄ (1.5 kg) overnight, and filtered. The solvent was evaporated under reduced pressure to afford the crude compound \(10\) (880 g, 91.4%) as a pale yellow solid, which can be used without purification in the next step. \(R_f = 0.35\) (petroleum ether–acetone = 3:1); mp 32–38 °C; IR (KBr) \(\nu/cm^{-1}\) 3306, 2940, 1637, 1150, 1034, 895, 660; \(^1\)H NMR (500 MHz, MeOD-d₄): \(\delta\) 5.26 (d, 1H, \(J = 1.0\)), 5.22 (d, 1H, \(J = 1.1\)), 3.60 (d, 4H, \(J = 5.5\)), 2.42 (dd, 2H, \(J = 7.2, 0.6\)), 2.06–1.98 (m, 1H); MS (ESI\(^{+}\)) \(m/z\): 151 [M + H\(^+\)], 173 [M+Na\(^+\)]. Anal. calcd. for C₆H₁₁ClO₂ (150.60): C, 47.85; H, 7.36. Found: C, 47.74; H, 7.15.

2-(2'-Chloroprop-2'-en-1'-yl)-1,3-diacetoxypropane (11)

In a glass reactor was added a solution of \(10\) (1.00 kg, 6.64 mol) and Et₃N (2 L, 14.4 mol) in CH₂Cl₂ (8 L). Then Ac₂O (1.40 kg, 13.7 mol) was added dropwise under stirring during 1.5 h under ice-water cooling. The resulting mixture was stirred at room temperature for 4 h and then treated cautiously with saturated aqueous NaHCO₃ (15.0 L). The organic layer was separated, washed with brine (10 L), and dried over anhydrous Na₂SO₄ (1 kg). The solvent was removed under vacuum to give the compound \(11\) (1.51 kg, 96.8%) as a pale yellow oil. \(R_f = 0.69\) (petroleum ether–ethyl acetate = 5:1); IR (KBr) \(\nu/cm^{-1}\) 3110, 2960, 1745, 1637, 1435, 1368, 1232, 1158, 1043, 890, 635; \(^1\)H NMR (500 MHz, CDCl₃): \(\delta\) 5.24 (d, 1H, \(J = 1.3\)), 5.18 (d, 1H, \(J = 1.1\)), 4.10 (dd, 2H, \(J = 11.2, 4.6\)), 4.05 (dd, 2H, \(J = 11.2, 5.6\)), 2.46–2.40 (m, 3H), 2.05 (s, 6H); MS (ESI\(^{+}\)) \(m/z\): 235 [M + H\(^+\)], 257 [M+Na\(^+\)]. Anal. calcd. for C₁₀H₁₅ClO₄ (234.68): C, 51.18; H, 6.44. Found: C, 51.11; H, 6.27.

1,3-Diacetoxy-2-[2''-2',4''-difluorophenyl]prop-2'-en-1'-yl]propane (12)

In a 500-mL, three-necked flask a little of I₂ was added to the mixture of flame-dried magnesium turnings (5.82 g, 240 mmol) and 15 ml of absolute THF; several minutes later about 0.5 mL of 2,4-difluorobromobenzene was injected. After initiation of the reaction warmed by means of a heat gun, the rest of 2,4-difluorobromobenzene (44.4 g, 230 mmol) and THF (350 mL) were added slowly, and the reaction temperature was kept between 40 and 50 °C.

A 20-L glass reactor was charged with magnesium turnings (52.4 g, 2.16 mol), absolute THF (1 L), and the solution of the 2,4-difluorophenylmagnesium bromide. Then 2,4-difluorobromobenzene (400 g, 2.07 mol) and THF (2.3 L) were added during the reaction temperature between 40 and 50 °C, to give a solution of 2,4-difluorophenylmagnesium bromide. This solution of 2,4-difluorophenylmagnesium bromide was added dropwise to a solution of \(11\) (492 g, 2.10 mol) and tris(acetylacetonato) iron(III) [Fe(acac)₃] (22.0 g, 62.3 mmol, 3% equiv. referred to compound \(11\)) in a mixed solution of THF (3 L) and NMP (2 L) in a glass reaction vessel at −5 °C over 1.5 h. Stirring was continued for 30 min at this temperature, and then the reaction mixture was quenched with aqueous 1 M HCl (8 L). After the organic layer was isolated, the aqueous layer was extracted with CH₂Cl₂ (2 × 3 L). The combined organic layer was washed with saturated aqueous NaHCO₃ (6 L) and brine (2 × 6 L) and dried (MgSO₄). Solvents were removed via a rotavapor and the residue was distilled under
vacuum to afford the title compound 12 (498 g, 76.0% based on compound 11) as a light yellow oil. \( R_f = 0.46 \) (petroleum ether–ethyl acetate = 87:13) (bp 136–141 \( ^\circ \)C/1–2 mbar); IR (KBr) \( \nu / \text{cm}^{-1} \) 3081, 2961, 1741, 1616, 1504, 1368, 969, 851, 607; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.23 (td, 1H, \( J = 8.6, 6.5 \)), 6.87–6.82 (m, 1H), 6.79 (ddd, 1H, \( J = 11.2, 8.8, 2.5 \)), 5.24 (d, 1H, \( J = 1.1 \)), 5.21 (s, 1H), 4.05 (dd, 2H, \( J = 11.1, 5.0 \)), 4.00 (dd, 2H, \( J = 11.1, 6.3 \)), 2.57 (d, 2H, \( J = 7.4 \)), 2.04–1.95 (m, 7H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 170.93 (s), 162.37 (dd, \( J_{CF} = 249.5 \) Hz, \( J_{CF} = 11.3 \) Hz), 159.86 (dd, \( J_{CF} = 249.5 \) Hz, \( J_{CF} = 11.3 \) Hz), 141.00 (s), 130.82 (dd, \( J_{CF} = 9.4, 5.9 \) Hz), 124.84 (dd, \( J = 14.3, 3.9 \) Hz), 118.70 (s), 111.40 (dd, \( J_{CF} = 21.0, 3.6 \) Hz), 104.21 (t, \( J_{CF} = 26.5 \)), 63.66 (s), 35.59 (s), 35.23 (d, \( J_{CF} = 3.7 \) Hz), 20.78 (s). MS (ESI\(^+\)) \( m/z \): 335 [M + Na]\(^+\). Anal. calcd. for C\(_{16}\)H\(_{18}\)F\(_2\)O\(_4\):(312.31): C, 61.53; H, 5.81. Found: C, 61.33; H, 5.63.

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**SUPPLEMENTAL INFORMATION**

Supplemental data for this article can be accessed on the publisher’s website.

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