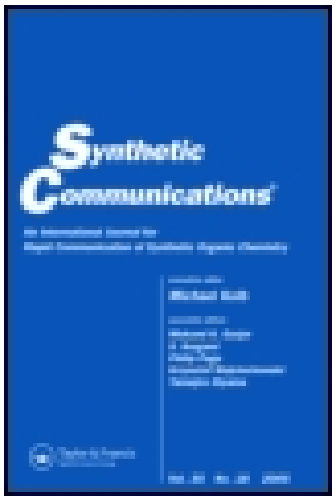

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A 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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Accepted author version posted online: 10 Sep 2014.

A 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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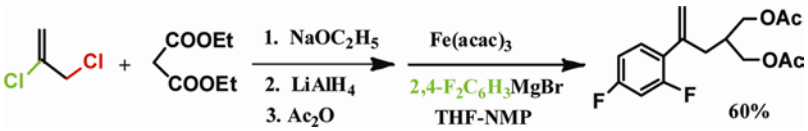
Abstract

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 $LiAlH_4$, 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 catalyzed by $Fe(acac)_3$ to afford the title compound in good total yield.



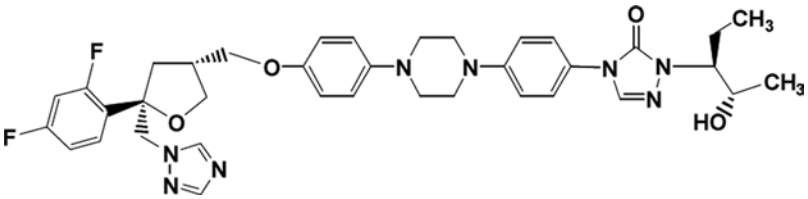
KEYWORDS: 2,3-Dichloropropene; 2,4-Difluorobromobenzene; Tris(acetylacetonato)iron(III); Posaconazole

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 moulds.[1] Due to its complicated structure, exploration for its novel synthetic process still attracted the attention of the synthetic organic chemists.

POSACONAZOLE (1)



The 2,2,4-trisubstituted tetrahydronfuran skeleton with two chiral centers (**2** in the Scmeme 1) is a critical unit for posaconazole as well as other analogs.[2-4] Early these two chiral centers were built via asymmetric synthesis involving tedious procedures or expensive chiral auxiliary agents.[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).[7-8]

Compared with the asymmetric synthetic methods reported, this enzymatic process undoubtedly prevailed in highly efficiency and environment-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 convert into **5** as described in Scheme 1;[5] (2) in the second patent, the preparation of the precursor **5** started from Friedel-Cratfs reaction

of 1,3-diflurobenzene and acetic anhydride and was followed by Wittig reaction, radical substitution reaction and final C-alkylation of diethyl malonate. A tough problem in the radical reaction was that it was difficult to separate several bromo-substituted byproducts when scaled up;[9] (3) in the third patent, a single step for preparing **5** was disclosed by condensation of 2,4-diflurobromobenzene, allene and diethyl malonate catalyzed by $Pd(PPh_3)_4$ in the presence of sodium hydride;[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**.[11] However, all the reported methods are often involved in one or more 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 THF afforded the diol **10** in 91% yield, which was further acylated with Ac_2O 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] Due to its ready availability, low cost, and environmental friendliness, iron complexes have been attracting attention of chemists in the field of catalysts.

In our case, tris(acetylacetonato) iron(III) [$Fe(acac)_3$] was applied to catalyze cross-coupling of **11** with 2,4-difluorophenyl magnesium bromide in THF-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 $Fe(acac)_3$ to give the title compound in an excellent yield. The trace byproducts 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-diactoxypropane derivatives.

EXPERIMENTAL SECTION

All reactions were performed in oven-dried (120 °C) glassware. Tetrahydrofuran (THF) was distilled from sodium under N_2. NMP (N-methylpyrrolidin-2-one) and Et_3N (triethylamine) were distilled from CaH_2 under N_2. Absolute ethanol was distilled from magnesium under N_2. Melting points were determined with a Büchi 540 Melting Point apparatus and were uncorrected. TLC was performed on glass plates (GF_{254}, 50 mm × 100 mm, Marine Chemical Company of Qingdao, China) and compounds were stained with aqueous solution of 0.05% $KMnO_4$ after developed. NMR spectra were taken on Bruker AVANCE III (500M Hz) with TMS as an internal standard. Mass spectra were recorded using Agilent 1100 Series LC/MSD Trap. IR spectra were recorded using Perkin–Elmer 1600 series FTIR. Elemental analyses were performed on Leco CHNS-932 Elemental Analyzer, Leco Corporation (USA).

4.2 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 two hours. The mixture was continued to reflux for two hours and then cooled down to room temperature. The reaction mixture evaporated under reduced pressure via a rotavapor to leave 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 Na_2SO_4 (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 colorless oil, which could be used directly in the next step. R_f = 0.65 (petroleum ether-ethyl acetate = 5:1); (bp：94-100 ºC/2-3 mbar); IR (KBr) ν/cm^{-1} 2965, 1734, 1638, 1370, 1240, 632; ^{1}H NMR (500 MHz, $CDCl_3$) 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 $[M+Na]^+$.

4.3 2-(2´-Chloroprop-2´-En-1´-Yl)-1,3-Propanediol (10)

A glass reactor was charged with THF (3.65 L) and $LiAlH_4$ (365 g, 9.62 mol). A solution of **9** (1.50 kg, 6.40 mol) in THF (2.50 L) was added at 0 ºC over 2 h under stirring. After complete addition, the reactants were stirred for 10 min at this temperature and then allowed to reflux 8 hours. After cooled down by ice-water, the reaction mixture was slowly poured with agitations into the dilute hydrochloric acid (10 L) [prepared by mixing conc. hydrochloric acid (1.75 L) with ice water (8.50 L)]. The resulting mixture was extracted with CH_2Cl_2 (2 × 5 L). The combined organic layers were washed with saturated brine, dried over anhydrous Na_2SO_4 (1.5 kg) overnight, and filtered. The solvent was evaporated under reduced pressure to afford the crude compound **10** (880 g, 91.4%) as 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 ºC; IR (KBr) ν/cm^{-1} 3306, 2940, 1637, 1150, 1034, 895, 660; ^{1}H NMR (500 MHz, MeOD-d_4): δ 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 $[M+1]^+$, 173 $[M+Na]^+$. Anal. Calcd for $C_6H_{11}ClO_2$ (150.60): C 47.85, H 7.36; Found: C 47.74, H 7.15.

4.4 2-(2´-Chloroprop-2´-En-1´-Yl)-1,3-Diacetoxypropane (11)

In a glass reactor was added a solution of **10** (1.00 kg, 6.64mol) and Et_3N (2 L, 14.4 mol) in CH_2Cl_2 (8 L). Then Ac_2O (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 sat. aq. $NaHCO_3$ (15.0 L). The organic layer was separated and washed with brine (10 L) and dried over anhydrous Na_2SO_4 (1 kg). The solvent was removed under vacuum to give the compound **11** (1.51 kg, 96.8%) as pale-yellow oil. R_f = 0.69 (petroleum ether-ethyl acetate = 5:1); IR (KBr) ν/cm^{-1} 3110, 2960, 1745, 1637, 1435, 1368,1232, 1158, 1043, 890, 635; ^{1}H NMR (500 MHz, $CDCl_3$) δ 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 $[M+1]^+$, 257 $[M+Na]^+$. Anal. Calcd for $C_{10}H_{15}ClO_4$ (234.68): C 51.18, H 6.44; Found: C 51.11, H 6.27.

4.5 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 I_2 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) was added slowly, and the reaction temperature was kept between 40-50 °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 above 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 40-50 °C, to give a solution of 2,4-difluorophenylmagnesium bromide.

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 was added the above solution of 2,4-difluorophenylmagnesium bromide dropwise at -5 ºC over 1.5 h. Stirring was continued for 30 min at this temperature, and then the reaction mixture was quenched with aq. 1 M HCl (8 L). After the organic layer was isolated, the aqueous layer was extracted with CH_2Cl_2 (2 × 3 L). The combined organic layer was washed with sat. aq. $NaHCO_3$ (6 L) and brine (2 × 6 L), and dried ($MgSO_4$). 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 light yellow oil. R_f = 0.46 (petroleum ether-ethyl acetate = 87:13); (bp: 136-141°C/ 1-2 mbar); IR (KBr) ν/cm^{-1} 3081, 2961, 1741, 1616, 1504, 1368, 969, 851, 607; ^{1}H NMR (500 MHz, $CDCl_3$): δ 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, $CDCl_3$) δ 170.93 (s), 162.37 (dd, $^1J_{CF}$ = 249.5 Hz, $^3J_{CF}$ = 11.3 Hz), 159.86 (dd, $^1J_{CF}$ = 249.5 Hz, $^3J_{CF}$ = 11.3 Hz), 141.00 (s), 130.82 (dd, $^2J_{CF}$ = 9.4, 5.9 Hz), 124.84 (dd, J = 14.3, 3.9 Hz), 118.70 (s), 111.40 (dd, $^2J_{CF}$ = 21.0, $^4J_{CF}$ = 3.6 Hz), 104.21 (t, $^3J_{CF}$ = 26.5), 63.66 (s), 35.59 (s), 35.23 (d, $^4J_{CF}$ = 3.7 Hz), 20.78 (s). MS (ESI^+) *m/z*: 335 $[M+Na]^+$. Anal. Calcd for $C_{16}H_{18}F_2O_4$ (312.31): C 61.53, H 5.81; Found: C 61.33, H 5.63.

FUNDING

We would like to thank Scientific Founds of Fujian Province (2011J01095) for the support of this work.

SUPPLEMENTAL INFORMATION

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

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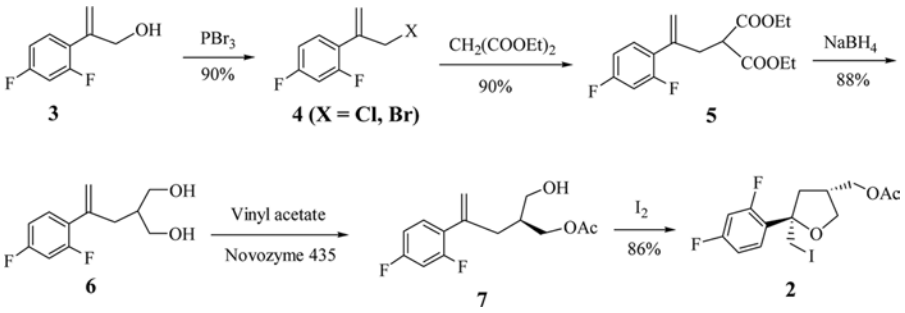
Djate, F.; Henin, J.; Laronze, J. Y.; Levy, J.; Noe, E.; Seraphin, D.; Zhang, Q.; Noe, E. *Tetrahedron Letters.* **1996**, *37*, 5701–5704.

Scheme 1. The chemoenzymatic route of literatures to the intermediate (2) of posaconazole



Scheme 2. New synthetic route of compound 12