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ARTICLE

Base promoted regioselective aromatization for the preparation of substituted 3-hydroxybenzene dicarboxylate

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Abstract

A new convenient base promoted aromatization process has been developed to prepare substituted 3-hydroxybenzene dicarboxylate using commercially available materials. In particular, regioselectivity will occur for substrates with mono-substitution at 5- or 6-position. This new process provides less reaction steps and moderate yields, and can be used extensively in the synthesis of other substrates to functionalize phenol esters.

Phenolic acid is naturally found in different plants, mainly including gallic acid, phloroglucinol compounds, Salvia miltiorrhiza, chlorogenic acid, quinic acid derivatives, tea polyphenol compounds, ellagic acid enamel, polyflavanol polyphenols, and phenylpropanoids. Phenolic acids have strong pharmacological effects in anti-oxidation, antibacterial, anti-inflammatory, and hypolipidemic effects, and have attracted many medicinal chemists to participate in their total synthesis, structure activity relationship (SAR), and pharmacology research. However, there is little literature to describe the synthesis of polyphenoic acids.[1–3]

Tilivalline is a metabolite from Klebsiella oxytoca that has been shown to be a cytotoxin and is a key event causing antibiotic-associated hemorrhagic colitis. Tilivalline shows cytotoxic to mouse leukemia L1210 cells owing to its unique structure of pyrrolo[1,4]benzodiazepine and indole framework.[4]

In 1998, Nagasaka et al first developed a new route for the synthesis of tilivalline, which was obtained from

commercial available diethyl acetylenedicarboxylate and diethyl furan-3, 4-dicarboxylate.[5] As a key building block, 2, 3-dicarboxylate phenol plays an important role in this overall synthesis. This scaffold can be easily prepared from cycloaddition product (D-A cycloaddition) by Lewis acid BF_3 promoted rearrangement in a yield of up to 81% (Scheme 1).

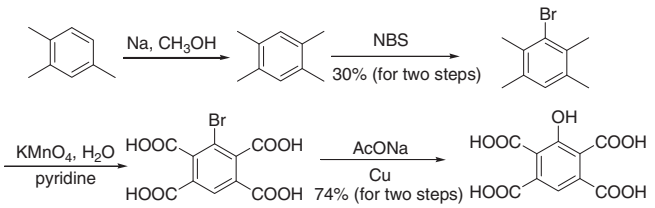
In order to expand the product pipeline of these compounds, more tilivalline analogs are needed for the high throughput screening (HTS). In the synthesis of these derivatives, substituted 3-hydroxybenzene dicarboxylate (**1**) (Figure 1) is highly desirable as an important building block. In this article, we described a convenient method to the synthesis of phenolic esters from the commercial available material.

1 | RESULTS AND DISCUSSION

In 2016, Kenta Kanosue et al developed a four-step synthesis route for the preparation of 3-hydroxypyromellitic acid from 1,2,4-trimethylbenzene[6] (Scheme 2). After methylation in Na/CH_3OH and bromination with NBS, bromodurene was obtained smoothly in a low yield (30%). In the following, bromodurene was oxidized with potassium permanganate in water to give 3-bromopyromellitic acid, which was finally treated with catalytic copper powder under the condition of sodium hydrate and sodium acetate in water to afford 3-hydroxypyromellitic acid in a yield of 74% for the last two steps. However, the tedious reaction steps, low yields (22% in total) and harsh reaction conditions limit their further use in industrial production.

Based on of this study, a same synthetic strategy can also be employed for the substituted 2, 3-dicarboxylic phenol (**1**), inspired by the successful synthesis of 2, 3-dicarboxylic phenol. We envisioned that Diels-Alder cycloaddition reaction of diethyl but-2-ynedioate and diethyl furan-3, 4-dicarboxylate (**2**) and continuous aromatization reaction promoted by Lewis acid could also give the title compound. The proposed synthetic route is shown in Scheme 3:

We then first attempt to synthesize tetraethyl norcantharidinate **3a** ($R_1 = R_2 = CO_2Et$) from diethyl but-2-ynedioate and diethyl furan-3, 4-dicarboxylate (**2a**, $R_1 = R_2 = CO_2Et$) by D-A [4 + 2] cycloaddition reaction.[7–9] Several solvents, temperature, and times have been optimized. The optimum reaction results showed that the reaction was carried out at 124°C for 20 hours in a sealed tube using toluene as solvent, and the optimum reaction yield is 51.4% (Table 1).



SCHEME 2 Original route to synthesis of phenolic acid

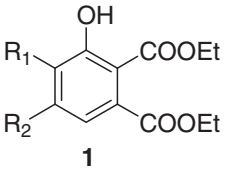
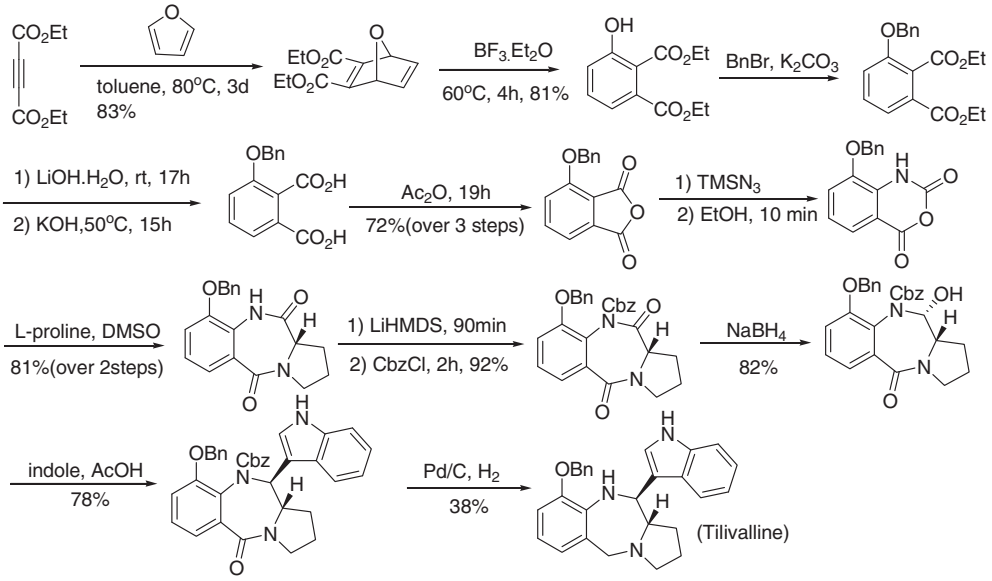


FIGURE 1 Chemical structure of the building block **1**



SCHEME 1 Total synthesis of tilivalline

SCHEME 3 Synthetic strategy of phenolic acid

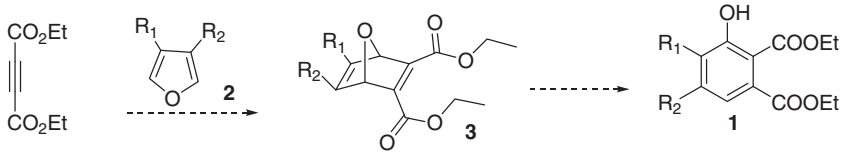
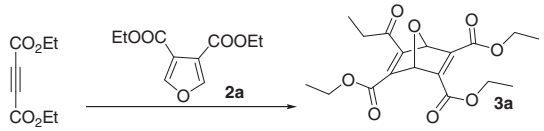
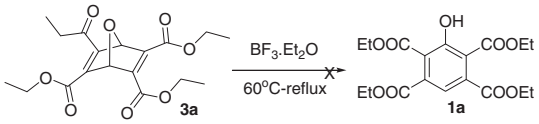


TABLE 1 Optimization of Diels-Alder reaction



Entry	Solvent	T/°C	Time (h)	Yield/%
1	**DCM**	**RT**	**24**	**Trace**
2	DCM	Reflux	24	<5%
3	Toluene	RT	24	Trace
4	Toluene	Reflux	24	28.9
5	Toluene	Sealed tube, 100	24	41.6
6	Toluene	Sealed tube, 124	20	51.4

TABLE 2 Aromatization rearrangement under acid condition

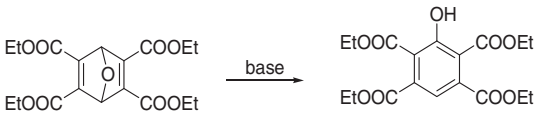


Condition	Solvent	T/°C	Time/h	Yield
$BF_3.Et_2O$	DCM	RT	48	No reaction
$BF_3.Et_2O$	DCM	Reflux	48	No reaction
TFA	DCM	Reflux	24	No reaction
HCl (36%)	H_2O	RT	24	No product
HCl (36%)	H_2O	Reflux	24	Decomposed

With the intermediate **3a** in hand, we then proceed to the Lewis acid-catalyzed aromatization reaction.[2,10,11] Unfortunately, no reaction occurred when the intermediate **3a** was treated with $BF_3.Et_2O$ under reflux condition (Table 2). Other acids, such as TFA and HCl have been tried, but no desired product (**1a**) was obtained.

Considering the presence of epoxide moiety in the structure which could undergo a ring opening reaction not only in the acid but also under the base condition, we therefore intend to use a base to promote the aromatization. Thus, different bases, solvents and temperature conditions have been tried for this step. To our surprise, the aromatization reaction proceeds well under all basic conditions and the desired compound can be obtained smoothly in a moderate yield. In particular, when NaOH was used as the base and EtOH as solvent, the yield of aromatization can be as high as 58.7%. The detailed optimization results were shown in Table 3:

TABLE 3 Condition optimization for base promoted aromatization reaction



Condition	Solvent	T/°C	Time/h	Yield
LiOH	C_2H_5OH	RT	48	39.3
LiOH	H_2O	RT	48	Destroyed
LiOH	C_2H_5OH	40	48	40.7
NaOH	C_2H_5OH	RT	24	45.3
NaOH	**C_2H_5OH**	**40**	**24**	**58.7**
NaOH	C_2H_5OH	Reflux	24	Destroyed
K_2CO_3	C_2H_5OH	RT	48	40.6
K_2CO_3	C_2H_5OH	40	48	38.9

The same methodology was further explored to synthesize phenol derivatives containing different functional group **1a-d** in a moderate to good yield (Table 4). However, only 2-furancarboxylic acid gives no desired product **1e** in the same condition.

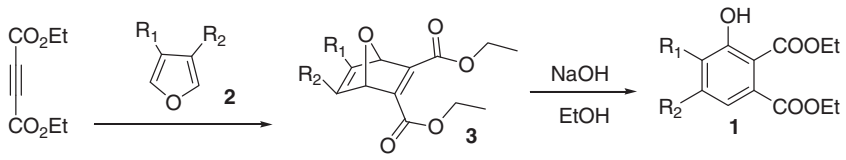
The formation of **3** from **1** is most likely via a SN2′ mechanism (Scheme 4). Thus, the ring opening is taking place by the attack the OH group to form an oxygen anion. Oxygen anion will rapidly capture proton to form hydroxyl group. Finally, H_2O was lost to complete the aromatization.

In particular, when only one position was occupied in 5- or 6-position, regioisomers will theoretically occur. However, for this rearrangement reaction, only one regioisomer was obtained (Scheme 5). According to ^1H NMR spectrum of compound **1c** (Figure 2), the coupling constants of the two protons in 7.68 (d, $J = 8.1$ Hz, 1H) and 6.84 (d, $J = 8.1$ Hz, 1H) clearly indicate that the two protons are in the ortho position instead of the meta position.

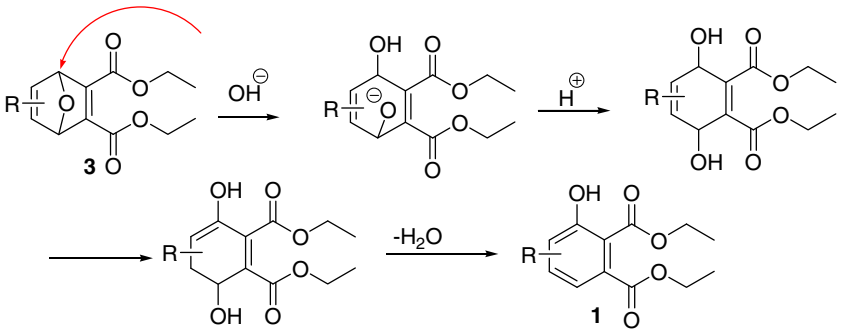
2 | SUMMARY

We developed a new convenient base promoted aromatization protocol to prepare different phenol derivatives

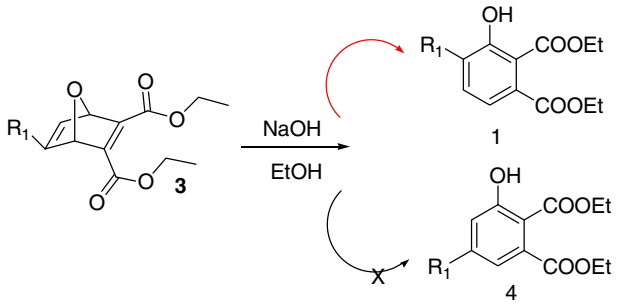
TABLE 4 Data for base promoted aromatization reaction



Entry	R_1	R_2	Yield (3)	Yield (1)
1	CO_2Et	CO_2Et	51.4% (**3a**)	58.7% (**1a**)
2	H	H	84% (**3b**)	90% (**1b**)
3	Br	H	66% (**3c**)	82% (**1c**)
4	CH_2OH	H	44.7% (**3d**)	50% (**1d**)
5	CO_2H	H	46% (**3e**)	— (**1e**)



SCHEME 4 Proposed aromatization mechanism



SCHEME 5 Regioselectivity in aromatization reaction

using the commercial available material. In particular, this new process provides a less reaction step and a better yield verse the original synthetic approach and will be extend to other substrate for the functional phenol ester.

3 | EXPERIMENTAL SECTION

Melting points were determined by a Mettler Toledo FP62 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 400 MHz on a Varian Unity nova 400 NMR spectrometer using tetramethylsilane (TMS) as an internal standard, and ^{13}C NMR spectra were recorded at 100 MHz respectively. Mass spectra were run on a Waters UPLC-MS instrument. TLC plates (GF 254) were bought from Branch Qingdao Haiyang Chemical Plant.

3.1 | A typical synthesis for tetraethyl 7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3,5,6-tetracarboxylate (3a)

A suspension of diethyl acetylenedicarboxylate (15.0 g, 14.1 mL, 88 mmol), Diethyl furan-3, 4-dicarboxylate (6.84 g, 7.3 mL, 100 mmol, 1.2 eq) and 50 mL dry toluene was charged in a sealed tube. The light-yellow reaction mixture was heated to 120°C for 4 hours. After being cooled to the room temperature, the solvent was removed completely under vacuum and the crude product was purified by column chromatography, eluting with PE: EA = 10:1 to give the title compound (17.4 g, 51.4%) as a white solid. M.p. 114.8°C-115.6°C; R_f = 0.26 (PE: EA = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.91 (d, J = 1.1 Hz, 2H), 4.31-4.25 (m, 9H), 1.31 (t, J = 7.1 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.71, 151.27, 87.15, 61.74, 14.02.

Compound **3b**[5] (84%) as a yellow liquid, R_f = 0.32 (PE: EA = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.16 (s, 2H), 5.62 (s, 2H), 4.21 (q, J = 7.1 Hz, 4H), 1.26 (t,

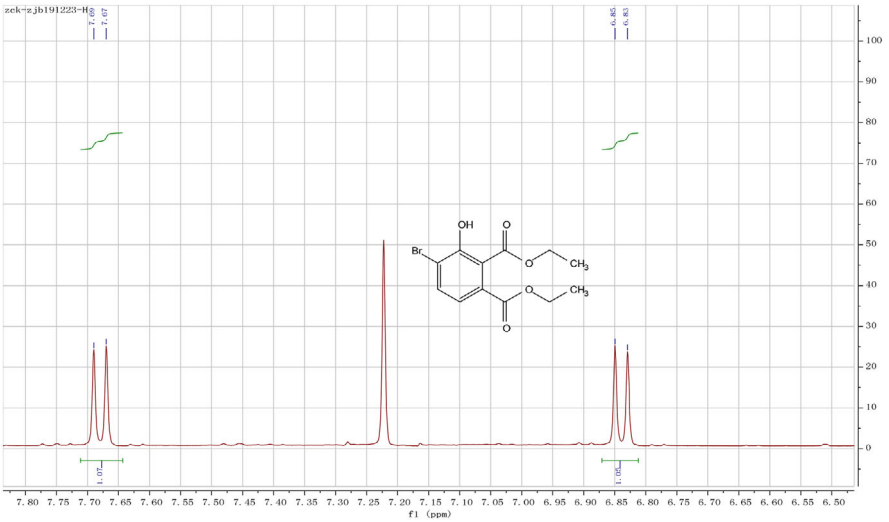


FIGURE 2 ^{1}H NMR spectrum for compound **1c**

J = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.01, 152.62, 143.17, 109.99, 85.01, 61.39, 14.05.

Compound **3c** (66%) as a yellow oil, R_f = 0.52(PE: EA = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.09 (s, 1H), 5.63 (s, 1H), 5.47 (s, 1H), 4.31-4.25 (m, 4H), 1.31 (t, J = 6.9 Hz, 6H).^{13}C NMR (100 MHz, $CDCl_3$) δ =162.57, 162.11, 152.25, 151.19, 139.02, 137.05, 89.60, 87.00, 62.99, 61.65, 14.07.

Compound **3d** (44.7%) as a clear oil. R_f = 0.26 (PE: EA = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.24 (s, 1H), 4.55-4.28 (m, 2H), 4.28-4.18 (m, 2H), 4.13-4.05 (m, 2H), 3.73 (dt, J = 14.2, 7.4 Hz, 1H), 3.52 (dd, J = 14.6, 7.3 Hz, 1H), 1.29 (t, J = 6.9 Hz, 3H), 1.23 (t, J = 5.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.12, 162.63, 158.38, 152.49, 152.18, 135.74, 86.09, 85.44, 61.81, 61.49, 59.33, 14.07.

Compound **3e** (46%) as a white solid, R_f = 0.61 (PE: EA = 3:1); m.p. 95.6.2°C-96.8°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.91 (s,1H), 4.48-4.06 (m,3H), 1.30 (t, J = 7.1 Hz,3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.69, 151.25, 87.13, 61.72, 14.01.

3.2 | A typical synthesis for tetraethyl 2,3,5,6-tetracarboxylate phenol (1a)

To a 25 mL round flask, a mixture of compound **3a** (200 mg, 0.52 mmol) and NaOH (102 mg, 4.24 mmol) in ethanol (10 mL) was added in sequence. The reaction mixture was stirred and heated at 40°C. After the consumption of starting material (by TLC), the reaction was then cooled to room temperature. After removal of the solvent, the residue was diluted in DCM and neutralized with 1 N HCl. The organic layer was separated and the aqueous layer was extracted with DCM (20 mL × 2). The combined organic layers were dried over $MgSO_4$. The solvent was distilled completely under reduced pressure, and the residue was purified by column chromatography using CH_2Cl_2: CH_3OH = 5:1 as eluent to afford the title compound (117.5 mg, 58.7%) as a red solid. m.p.124.6°C-126.4°C. R_f = 6.4 (CH_2Cl_2: CH_3OH = 10:1). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 6.61 (s, 1H), 3.97 (dtt, J = 8.3, 5.2, 1.3 Hz, 8H), 1.22-1.07 (m, 12H). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 167.58, 165.33, 120.18, 119.76, 112.24, 59.03, 58.18, 14.95, 14.58. IR (KBr) ν (cm^{-1}) = 3414, 3237, 2971, 2934, 2848, 1634, 1618, 1505, 1417, 1379, 1360, 1232, 1176, 1119, 1026, 941, 820.

Compound **1b**[5] (90%) as a yellow liquid, R_f = 0.47 (PE: EA = 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.72 (s, 1H), 7.40 (t, J = 7.9 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 7.4 Hz, 1H), 4.33 (dt, J = 17.7, 7.2 Hz, 4H), 1.33 (t, J = 7.2 Hz, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.78, 161.08, 161.05, 139.68, 134.30, 134.21, 119.39, 118.73, 62.01, 61.44, 13.94, 13.68.

Compound **1c** (82%) as a yellow liquid, R_f = 0.47 (PE: EA = 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 11.16 (s, 1H), 7.68 (d, J = 8.1 Hz, 1H), 6.84 (d, J = 8.1 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 4.33-4.27 (m, 2H), 1.32 (dt, J = 7.1, 3.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.61, 167.96, 157.41, 148.49, 137.43, 134.79, 119.61, 113.64, 62.77, 61.81, 14.08, 13.78.

Compound **1d** (50%) as a yellow liquid, R_f = 0.47 (PE: EA = 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.74 (s, 1H), 7.16 (s, 1H), 6.83, 6.96 (s, 1H), 5.21 (s, 1H), 4.60 (s, 1H), 4.26 (dd, J = 17.2, 7.7 Hz, 2H), 4.17 (t, J = 6.7 Hz, 2H), 1.26 (t, J = 7.3 Hz, 3H), 1.22 (t, J = 5.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.63, 161.60, 145.72, 144.60, 142.13, 116.68, 111.09, 87.88, 83.40, 71.34, 61.60, 29.67, 14.11.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Changkuo Zhao designed the study. Weihang Guo prepared the sample together. Xianheng Wang was responsible for the test in vitro. Yuhe Wang collected and analyzed the data. All authors gave the approval for the final submission.

DATA AVAILABILITY STATEMENT

Data are available as part of the electronic supplementary material.

ETHICS STATEMENT

No need for the animal ethics permission from local agent. Since no animal was used in this project.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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