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PAPER

Michael addition/pericyclization/rearrangement – a multicomponent strategy for the synthesis of substituted resorcinols†

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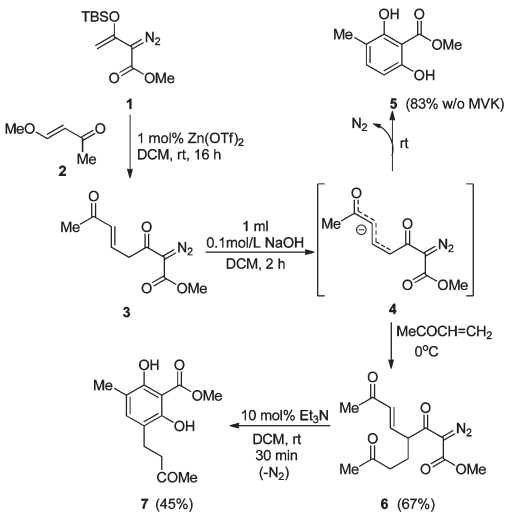
The combination of methyl 3,7-dioxo-2-diazo-4-octenoate from the zinc triflate catalyzed Mukaiyama–Michael reaction of methyl 3-*tert*-butylsilyloxy-2-diazobutenoate and 4-methoxy-3-buten-2-one with Michael acceptors (methyl vinyl ketone, *N*-phenylmaleimide, β-nitrovinylarenes) in the presence of a catalytic amount of base provides convenient access to highly substituted resorcinol derivatives. This transformation is achieved in an efficient one-pot multi-component transformation by the sequential addition of the reagents.

Introduction

Resorcinol and its derivatives are building blocks in organic synthesis that can be recognized in many natural products,[1,2] some of which exhibit biological activity.[3–6] Efficient methods for the synthesis of functionalized resorcinols are important, but the primary route available to them is from resorcinol, especially by electrophilic substitution, whose limitations include the directional selectivity of its hydroxyl groups.[1] A limited number of other methods that include ketene and diketene reactions are available, but their general applicability is lacking.[7,8] Using 3-*tert*-butylsilyloxy-substituted vinyl diazoacetates in Mukaiyama type addition reactions to assemble complex molecules,[9,10] we have recently reported a new methodology that provides access to 6-methyl-2-carboalkoxyresorcinols by a novel base-catalyzed pericyclization/rearrangement reaction of an enedione-diazoester, prepared from methyl 3-*tert*-butylsilyloxy-2-diazobut-3-enoate (**1**) with 4-methoxy-3-buten-2-one (**2**).[11] The product of the Mukaiyama–Michael reaction undergoes elimination of *tert*-butyldimethylsilyl methyl ether to form **3** that in the presence of a catalytic amount of base forms resorcinol derivative **5** through pericyclic ring closure that occurs with the loss of dinitrogen (Scheme 1). In that communication we provided evidence that the enedione-diazoester **3** underwent, in competition with formation of 6-methyl-2-carboalkoxyresorcinol (**5**), base catalyzed Michael addition with methyl vinyl ketone and subsequent conversion to the corresponding resorcinol compounds (**7**).[11] Encouraged by these results, we have explored this transformation by evaluating the suitability of other nucleophiles for the production of multi-substituted resorcinol derivatives. We now report examples that suggest the scope and limitations of the double Michael addition/pericyclization/rearrangement process that produces 4-substituted-6-methyl-2-carboalkoxyresorcinol derivatives, and we demonstrate that this complex process can be performed conveniently as a one-pot synthesis.



Scheme 1 Synthesis of 4-substituted-6-methyl-2-carboalkoxyresorcinols from methyl vinyl ketone.[11]

Results and discussion

In our previous report, methyl vinyl ketone was shown to be able to intercept enolate intermediate **4** to form the corresponding Michael addition product (**6**) and subsequently converted to

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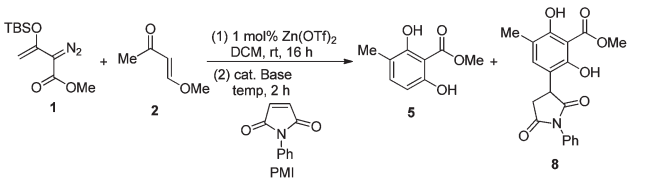
†Electronic supplementary information (ESI) available: NMR spectra, HMBC experiment for structural elucidation of **13c**, attempted reactions with **20**. See DOI: 10.1039/c2ob25776a

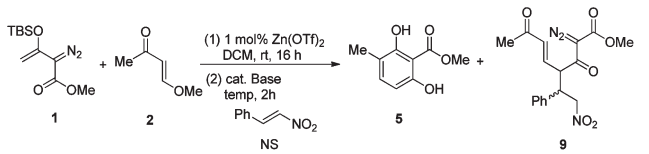
Table 1 One-pot reactions of **3**, formed from **1** + **2** catalyzed by zinc triflate, with *N*-phenylmaleimide under various conditions[a]



Entry	Base	Equiv. PMI	Temp.	Yield of **5** + **8** (%)	**5** : **8**
1	0.1 eq NaOH (aq)	1	rt	83	75 : 25
2	0.1 eq NaOH (aq)	2	rt	82	52 : 48
3	0.1 eq NaOH (aq)	4	rt	53	49 : 51
4	0.1 eq NaOH (aq)	2	0 °C	78	50 : 50
5	0.1 eq NaOH (aq)	2	40 °C	54	57 : 43
6	0.2 eq NaOH (aq)	2	rt	27	32 : 68
7	5 mol% Et_3N	2	rt	26[b]	—

[a] Yields and product ratios were determined by proton NMR spectroscopy based on internal standard. [b] Yield of product **8**, product **5** was not observed.

Table 2 One-pot reactions of **3**, formed from **1** + **2** catalyzed by zinc triflate, with β-nitrostyrene under various conditions[a]



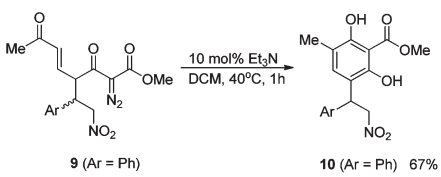
Entry	Base	Equiv. NS	Temp.	Yield **5** + **9** (%)	**5** : **9**
1	0.1 eq NaOH (aq)	2	rt	80	67 : 33
2	0.1 eq NaOH (aq)	4	rt	81	54 : 46
3	0.1 eq NaOH (aq)	8	rt	47	55 : 45
4	0.1 eq NaOH (aq)	4	0 °C	73	52 : 48
5	0.1 eq NaOH (aq)	4	40 °C	70	55 : 45
6	0.2 eq NaOH (aq)	4	rt	50	24 : 76
7	5 mol% Et_3N	2	rt	61	<4 : >96

[a] Yields and product ratios are determined based on internal standard in the reaction mixture.

resorcinol **7**. By lowering the reaction temperature from ambient to 0 °C and using six equivalents of methyl vinyl ketone, the competing intramolecular reaction that forms resorcinol **5** could be prevented, and Michael adduct **6** became the sole product of this transformation (67% isolated yield). In our efforts to extend this chemistry with other Michael acceptors, *N*-phenylmaleimide (PMI) was employed in reactions with enedione-diazoacetate **3** based on its reactivity as an electrophile in conjugate addition reactions.[12,13] The intended reaction occurs but, unlike reactions with methyl vinyl ketone in which the Michael addition product (**6**) is stable under the reaction conditions, the Michael addition product is not observed and, instead, resorcinol **8** is directly produced under the reaction conditions. The major competing reaction is pericyclization/rearrangement of **3** that forms **5**. Yields and product ratios (**8** : **5**) as a function of different reaction conditions with PMI are reported in Table 1. The yield of **8** and the relative ratio of **8** : **5** increase significantly when two equivalents of *N*-phenylmaleimide are employed (entries 1 and 2). However, a further increase in the relative amount of *N*-phenylmaleimide did not improve the product ratio and led to a decrease in product yield (entry 3), possibly because of anionic polymerization of PMI.[14] Unlike reactions in which methyl vinyl ketone was employed, where a lower temperature increased the ratio of the Michael addition/pericyclization/rearrangement product (**7**) relative to **5**, with *N*-phenylmaleimide a lower reaction temperature did not increase the **8** : **5** ratio (entry 4). Also, heating the reaction mixture at 40 °C in an oil bath did not alter the product ratio, and the yields of both **5** and **8** decreased with increasing temperature (entry 5). Increasing the amount and concentration of aqueous sodium hydroxide had a detrimental effect on the reaction by decreasing the yield of **8** although providing an increase in the **8** : **5** ratio (entry 6). The use of a catalytic amount of triethylamine instead of aqueous sodium hydroxide was also evaluated, but only a small amount of the intended product (**8**) was observed under these conditions (entry 7). These results suggest that, although *N*-phenylmaleimide is sufficiently reactive to capture enolate intermediate **4**, it is not reactive enough to completely overcome the competing intramolecular pericyclization of **4** to **5**.

β-Nitrostyrenes (NS) are widely applied as electrophiles in Michael addition reactions.[15] Due to the strong electron-withdrawing nature of the nitro group, β-nitrostyrene has shown higher reactivity compared to α,β-unsaturated carbonyl compounds.[16] With β-nitrostyrene as the electrophile in reactions with α-diazo-β-ketoester **3**, Michael adduct **9** is observed with resorcinol **5** formed as by-product. To overcome the competition, use of four equivalents of β-nitrostyrene was shown to be optimum (Table 2, entry 2), but in this case temperature had little influence on the product ratio (entries 4 and 5). An increase in the amount and concentration of sodium hydroxide solution does not provide a higher yield of the intended product, albeit the ratio of **9** : **5** does improve (entry 6). However, in contrast to the reactions with *N*-phenylmaleimide, switching from the heterogeneous reaction conditions that employ aqueous sodium hydroxide to homogeneous conditions that use triethylamine improves the result significantly: the resorcinol by-product is no longer observed in the reaction mixture, and the desired product is obtained in 61% isolated yield. Furthermore, the amount of β-nitrostyrene required could be reduced to two equivalents with triethylamine as the catalyst (entry 7).

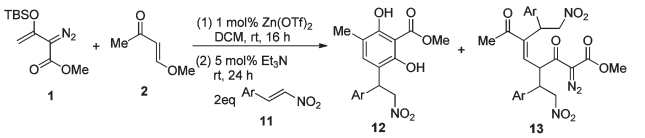
Efforts were made to convert compound **9** to the correspondent resorcinol by treating compound **9** with a catalytic amount of triethylamine. The reaction was sluggish at room temperature with 10 mol% of triethylamine and could not reach full conversion. Performing the reaction at 40 °C, however, allowed the production of resorcinol **10** in good isolated yield (eqn (1)).



9 (Ar = Ph) **10** (Ar = Ph) 67% (1)

To evaluate substrate scope with nitrostyrenes, we varied the aryl group (Table 3). These reactions were performed in one pot

Table 3 Synthesis of 4-(1′-aryl-2′-nitroethyl)resorcinols



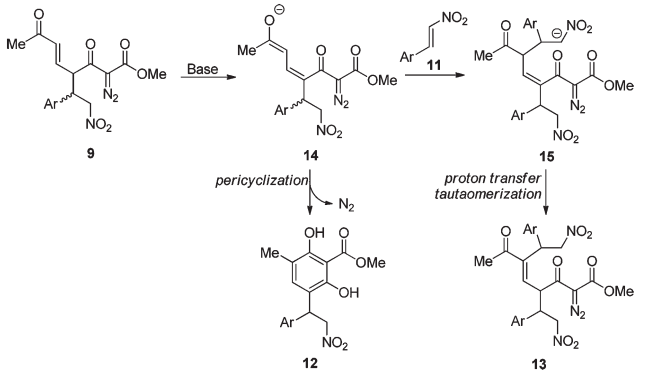
Compound	Ar	Yield of **12** + **13**[a] (%)	**12** : **13**
a	4-MeOC$_6$H$_4$	64	88 : 12
b	C$_6$H$_5$	61[b]	82 : 18
c	4-FC$_6$H$_4$	72	78 : 22
d	4-CF$_3$C$_6$H$_4$	74	77 : 23
e	1-Furyl	89	71 : 29[c]

[a] Isolated yield after purification. [b] Yield of compound **10** (= **12b**); for **13b** see ESI. [c] Structure **13** was obtained as a complicated mixture of several isomers.

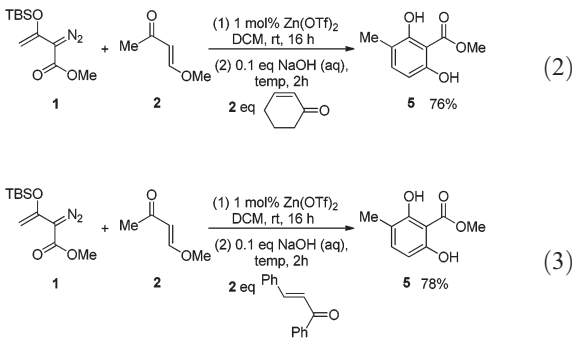
by combining vinyl ether and enone overnight followed by addition of the β-nitrostyrene and a catalytic amount of triethylamine. Interestingly, in all cases the initial Michael adducts **9** were partially converted to the corresponding resorcinols **12** in 2 h, and with an extended reaction time of 24 h, the intermediate Michael addition products (**9**) were fully consumed and resorcinols **12** became the major products of these reactions. A by-product resulting from a second addition of the nitrostyrene was also identified in these cases, and its structure was determined to be that of **13** by 1D and 2D NMR experiments.[17] At this point, we reexamined the reaction with β-nitrostyrene, and we found that compound **9** could also be completely converted to resorcinol **10** at room temperature given a longer reaction time. The one pot reaction provides better yield than the stepwise approach (50% yield compared to 41% combined yield in two steps). The nitrostyrene with an electron-withdrawing *para*-trifluoromethyl substituent seems to favor by-product **13** more than those with electron-donating groups, and a trend can be noticed when switching from 4-methoxylphenyl (**11a**) to 4-trifluoromethyl group (**11d**). However the difference in the **12** : **13** product ratio is rather small. A nitrovinyl compound with a heterocyclic ring (**11e**) also worked under these conditions.

From a mechanistic perspective, once the first addition product (**9**) is formed, deprotonation gives enolate **14** that can undergo pericyclization and rearrangement to resorcinol **12**, but it is also able to react with a second nitrostyrene at the position α to the carbonyl group, which is sterically favored compared to the γ position. Tautomerization of the double bond would lead to **13** (Scheme 2). The formation of **13** is an indication of the high reactivity of nitrostyrenes in comparison with other electrophiles since this second addition is not observed in reactions with other electrophiles in this system.

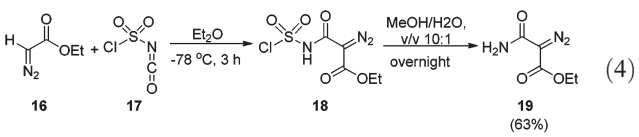
Commonly used enones such as cyclohexenone and chalcone failed to provide the corresponding adducts, and resorcinol **5** was the only product observed (*e.g.*, eqn (2) and (3)). Apparently these enones were not sufficiently reactive, due to electronic or steric factors, to capture the transient enolate intermediate (**5**) and thus could not compete with the pericyclization reaction.



Scheme 2 Proposed pathway from **9** to resorcinols **12** and the bis-Michael addition products **13**.

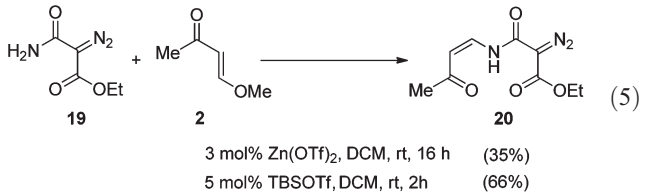


Replacing the CH_2 group in **1** with an NH group could potentially lead to formation of poly-substituted pyridines if the pericyclization/rearrangement transformation is possible with this compound. In order to explore this transformation, ethyl carbamoyl diazoacetate (**19**) was synthesized (eqn (4)).[18]



We subjected **19** and 4-methoxy-3-buten-2-one (**2**) to the conditions developed for the Mukaiyama–Michael addition reaction. The enone substrate **2** was fully consumed; however, the desired adduct **20** was obtained only in 35% yield (eqn (5)). Using an alternative procedure in which trialkylsilyl triflate was used to promote an aza-Michael addition of a primary amide and α,β-unsaturated ketones,[19] we were able to synthesize diazoester **20** in 66% yield (eqn (5)). In contrast to enedione-diazoester **3**, ethyl 2-(3-oxobut-1-enylcarbamoyl) diazoacetate (**20**) is sufficiently stable to undergo silica gel purification. In addition, the ^{1}H NMR spectrum of compound **20** shows a coupling constant of 8 Hz between the two vinyl protons indicating a *cis* geometry of the alkene double bond. By contrast, a 16 Hz coupling constant between the vinyl protons was observed in the ^{1}H NMR spectrum of compound **3** which indicates the *trans* geometry of the alkene. One possible explanation for this difference is that compound **20** takes a *cis* geometry so it can benefit from an intramolecular hydrogen bond while formation of a hydrogen bond is not an option in the structure of **3**. However, ethyl 2-(3-oxobut-1-enylcarbamoyl)diazoacetate (**20**) was unable to

undergo the desired cyclization/rearrangement reaction under a wide variety of reaction conditions.†



(5)

Conclusions

We report a straightforward synthesis of complex resorcinol derivatives through a novel multi-component strategy that begins with an efficient Lewis acid catalyzed Michael addition of enone **2** to enol diazoacetate **1** and continues with a base catalyzed Michael addition of a vinyl ketone, a maleimide, or a β-nitrostyrene and pericyclization/rearrangement. The second Michael addition and pericyclization/rearrangement are highly sensitive to base strength. The overall process can be achieved with the three components added in sequence in a one-pot manner, which is highly efficient and raises interest for further elaboration.

Experimental section

Materials and methods

Reactions were performed in oven-dried (140 °C) or flame-dried glassware. Dichloromethane (DCM) was passed through a solvent column prior to use and was not distilled. Thin layer chromatography (TLC) was carried out using EM Science silica gel 60 F254 plates. The developed chromatogram was visualized by UV lamp (254 nm) or ethanolate phosphomolybdic acid (PMA). Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated system on silica gel (230–400 mesh). NMR spectra were measured on a 400 MHz spectrometer (^{1}H at 400 MHz, ^{13}C at 100 MHz); chemical shifts are reported in ppm with the solvent signals as reference, and coupling constants (*J*) are given in hertz. Peak information is described as: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, hept = heptet, m = multiplet, comp = composite. High Resolution Mass Spectra (HRMS) were recorded by a ESI-TOF instrument in positive mode. 3-*tert*-Butyldimethylsilanyloxy-2-diazobut-3-enoate (**1**) was prepared by the method described by Ueda and Davies.[20] Zinc triflate, 4-methoxy-3-buten-2-one (**2**) and β-nitrostyrenes were purchased from Aldrich and used as received. The characterization of compound **19** has been reported.[19]

Synthesis of methyl 2,6-dihydroxy-3-methyl-5-(2,5-dioxo-1-phenylpyrrolidin-3-yl)benzoate (8). To a 4 dram vial was added zinc triflate (4 mg, 0.01 mmol), followed by *trans*-4-methoxy-3-buten-2-one (**2**) (103 mg, 0.930 mmol) and 4.0 mL of dry DCM. The mixture was stirred at room temperature. Methyl 3-*tert*-butyldimethylsilanyloxy-2-diazobut-3-enoate (**1**) (307 mg, 1.20 mmol) was added *via* syringe all at once. After 16 h the reaction mixture was concentrated under reduced pressure. To the resulting concentrated reaction mixture in a 4 dram vial was then added 2.0 mmol *N*-phenylmaleimide and 2 mL DCM, followed by 1.0 mL of 0.1 mol L^{-1} aqueous NaOH (0.1 mmol). After rapid stirring for 2 h, the stirrer was discontinued whereupon a deep red aqueous phase separated from a yellow organic phase. The organic phase was then removed by pipet and run through a short silica plug to remove the small amount of water. The resulting solution was concentrated under reduced pressure. The crude reaction mixture was purified by silica gel chromatography, eluting with 1 : 2 EtOAc–hexane to give 129 mg (0.363 mmol) yellow solid (39%). **8**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (br, 2H), 7.49 (t, J = 8.0 Hz, 2H), 7.40 (t, J = 8.0 Hz, 1H), 7.36 (d, J = 4.0 Hz, 2H), 7.20 (s, 1H), 4.09 (s, 3H), 3.98 (dd, J = 4.0, 12.0 Hz, 1H), 3.23 (dd, J = 8.0, 12.0 Hz, 1H), 2.97 (dd, J = 4.0, 16.0 Hz, 1H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 175.7, 170.0, 139.3, 132.4, 137.4, 129.1, 128.5, 126.6, 117.0, 115.1, 100.0, 77.2, 53.1, 43.6, 36.1, 15.1; IR (neat): 3369, 3068 (br), 2926, 2854, 1706, 1667, 1625 1600 cm^{-1}; HRMS (ESI) for $C_{19}H_{18}NO_6$ $[M + H]^+$ calcd 356.1135; found 356.1111.

Synthesis of methyl 3,7-dioxo-4-(1-phenyl-2-nitroethyl)-2-diazo-(*E*)-oct-5-enoate (9). The mixture of zinc triflate and **2** identical to that used for the synthesis of **8** was stirred at room temperature, then methyl 3-*tert*-butyldimethylsilanyloxy-2-diazobut-3-enoate (**1**) (281 mg, 1.10 mmol) was added all at once. After 16 h 2 equiv. of solid β-nitrostyrene (298 mg, 2.00 mmol) was added to the reaction solution. When the yellow solid (β-nitrostyrene) was fully dissolved 5.0 mol% of triethylamine (5 mg, 0.05 mmol) was added causing the color of the solution to turn from yellow to deep red. The reaction was stirred at room temperature for 2 h during which the color of the solution became darker. Product isolation was performed as previously described, and the product was isolated as a yellow syrup in 204 mg (0.567 mmol, 61%) as a mixture of two diastereomers that could not be separated by chromatography. NMR analysis showed a 2 : 1 diastereomeric ratio. **9**, major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.18 (comp, 5H), 6.69 (dd, J = 8.0, 16.0 Hz, 1H), 6.35 (d, J = 16.0 Hz, 1H), 5.14 (t, J = 8.0 Hz, 1H), 4.68–4.57 (comp, 2H), 4.20–4.05 (m, 1H), 3.79 (s, 3H); 2.27 (s, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 197.4, 188.7, 160.8, 140.2, 136.6, 135.8, 128.9, 128.3, 128.0, 78.3, 52.8, 52.4, 45.0, 27.3; **9**, minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.40 (dd, J = 8.0 Hz, 16.0 Hz, 1H), 5.98 (d, J = 16.0 Hz, 1H), 4.94 (t, J = 8.0 Hz, 1H), 4.76 (dd, J = 8.0 Hz, 12.0 Hz, 1H), 4.68–4.57 (m, 1H), 4.20–4.05 (m, 1H), 3.85 (s, 3H); 2.04 (s, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 197.5, 189.6, 161.0, 141.1, 136.0, 134.5, 129.0, 128.8, 128.1, 77.8, 52.6, 52.2, 45.6, 26.8; IR (neat): 2955, 2924, 2856, 2361, 2336, 2143, 1717, 1677, 1651 cm^{-1}; HRMS (ESI) for $C_{17}H_{18}N_3O_6$ $[M + H]^+$ calcd 360.1195; found: 360.1197.

Synthesis of methyl 2,6-dihydroxy-3-methyl-5-(1-phenyl-2-nitroethyl)benzoate (10). To a 4 dram vial was added 33 mg of methyl-3,7-dioxo-4-(1-phenyl-2-nitroethyl)-2-diazo-(*E*)-oct-5-enoate **9a** (0.10 mmol) and 0.5 mL DCM, then 1 mg of triethylamine (0.01 mmol). The reaction mixture was heated with stirring at 40 °C in an oil bath for 1 h. The resulting solution was concentrated under reduced pressure. The crude reaction mixture was purified with a short silica plug, eluting with DCM to give

20 mg (0.067 mmol, 67%) of a yellow oil. **10**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (br, 2H), 7.34–7.22 (comp, 5H), 7.03 (s, 1H), 5.16 (*t*, *J* = 8.0 Hz, 1H), 5.06 (dd, *J* = 8.0, 12.0 Hz, 1H), 4.96 (dd, *J* = 8.0, 12.0 Hz, 1H), 4.05 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 158.0, 155.9, 138.9, 136.9, 128.8, 127.8, 127.3, 116.8, 116.7, 99.7, 77.7, 53.0, 43.1, 15.4; IR (neat): 3427, 3121, 3026, 2959, 2921, 2849, 2358, 2329, 1673, 1624, 1549 cm^{-1}; HRMS (ESI) for $C_{17}H_{18}NO_6$ $[M + H]^+$ calcd 332.1134; found 332.1128.

Synthesis of methyl 2,6-dihydroxy-3-methyl-5-(1-phenyl-2-nitroethyl)benzoate (10) (one-pot method). To a 4 dram vial was added zinc triflate (2 mg, 0.005 mmol), followed by enone **2** (50 mg, 0.45 mmol) and 2 mL of dry DCM. The mixture was stirred at room temperature. Enol diazoacetate **1** (180 mg, 0.70 mmol) was added all at once. The yellow solution was allowed to react overnight. After 16 h, 2 equiv. of β-nitrostyrene (150 mg, 1.00 mmol) was added to the solution, followed by triethylamine (3 mg, 0.03 mmol, 5 mol%) after β-nitrostyrene was fully dissolved. The color of the solution turned from yellow to deep red upon addition of the base. The reaction was stirred at room temperature for 24 h during which time the solution became cloudy, and the red color became darker. The resulting solution was concentrated under reduced pressure, and the residue was purified by silica gel chromatography, eluting with 1 : 6 EtOAc–hexane, to give 76 mg (0.23 mmol, 50%) of a pale yellow syrup as methyl 2,6-dihydroxy-3-methyl-5-(1-phenyl-2-nitroethyl)benzoate (**10** or **12b**). Switching the eluent to 1 : 2 EtOAc–hexane allowed the isolation of 25 mg (0.049 mmol, 11%) of the double addition by-product (**13b**) as a mixture of multiple isomers that could not be separated by chromatography.†

Synthesis of methyl 2,6-dihydroxy-3-methyl-5-[1-(4-methoxyphenyl)-2-nitroethyl]benzoate (12a) and methyl 3,7-dioxo-4,6-[1-(4-methoxyphenyl)-2-nitroethyl]-2-diazooct-5-enoate (13a). To a 4 dram vial was added zinc triflate (2 mg, 0.005 mmol), followed by enone **2** (50 mg, 0.45 mmol) and 2 mL of dry DCM. The mixture was stirred at room temperature. Enol diazoacetate **1** (180 mg, 0.70 mmol) was added all at once. The resulting yellow solution was allowed to react overnight. After 16 h, 2.0 equiv. of 4-methoxy-β-nitrostyrene (179 mg, 1.0 mmol) was added to the solution, followed by triethylamine (3 mg, 0.03 mmol, 5 mol%) when 4-methoxy-β-nitrostyrene was fully dissolved. The color of the solution turned from yellow to deep red upon addition of the base. The reaction mixture was stirred at room temperature for 24 h during which time the solution became cloudy and the color became darker. The resulting solution was concentrated under reduced pressure, and the residue was purified by silica gel chromatography, eluting with 1 : 4 EtOAc–hexane, to give 90 mg (0.25 mmol, 56%) of a pale yellow solid identified as methyl 2,6-dihydroxy-3-methyl-5-[1-(4-methoxyphenyl)-2-nitroethyl]benzoate (**12a**). Switching the eluent to 1 : 2 EtOAc–hexane allowed the isolation of 21 mg (0.036 mmol, 8%) of a yellow syrup of methyl 3,7-dioxo-4,6-[1-(4-methoxyphenyl)-2-nitroethyl]-2-diazooct-5-enoate (**13a**) as a 6 : 1 mixture of two diastereomers that could not be separated by chromatography.

Methyl 2,6-dihydroxy-3-methyl-5-[1-(4-methoxyphenyl)-2-nitroethyl]benzoate (12a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (br, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.01 (s, 1H), 6.84 (d, *J* = 8.0 Hz, 2H), 5.10 (t, *J* = 8.0 Hz, 1H), 5.02 (dd, *J* = 8.0 Hz, 12.0 Hz, 1H), 4.90 (dd, *J* = 8.0 Hz, 12.0 Hz, 1H), 4.04 (s, 3H), 3.76 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 170.2, 158.8, 157.9, 155.8, 136.8, 130.8, 128.9, 117.1, 117.0, 116.7, 114.2, 77.9, 55.2, 53.0, 42.4, 15.4; IR (neat): 3381, 3167, 2957, 2838, 1676, 1613, 1549, 1436 cm^{-1}; HRMS (ESI) for $C_{18}H_{20}NO_7$ $[M + H]^+$ calcd 362.1240; found 362.1224.

Methyl 3,7-dioxo-4,6-[1-(4-methoxyphenyl)-2-nitroethyl]-2-diazooct-5-enoate (13a). Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.94 (d, *J* = 8.0 Hz, 2H), 6.79 (d, *J* = 8.0 Hz, 2H), 6.62 (d, *J* = 8.0 Hz, 1H), 5.51 (t, *J* = 12.0 Hz, 1H), 5.26 (dd, *J* = 8.0 Hz, 12.0 Hz, 1H), 4.87 (dd, *J* = 4.0 Hz, 8.0 Hz, 1H), 4.74 (dd, *J* = 4.0 Hz, 12.0 Hz, 1H), 3.95 (comp, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.76 (s, 3H), 3.74 (comp, 1H), 3.52 (dd, *J* = 8.0 Hz, 12.0 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.5, 189.0, 161.2, 159.6, 159.3, 144.4, 140.6, 130.8, 129.7, 129.1, 127.9, 114.8, 114.4, 77.6, 77.5, 55.4, 55.2, 52.6, 48.9, 45.6, 43.0, 27.6; IR (neat): 2957, 2923, 2145, 1711, 1673, 1649, 1610, 1549, 1512, 1437 cm^{-1}; HRMS (ESI) for $C_{27}H_{29}N_4O_{10}$ $[M + H]^+$ calcd 569.1874; found 569.1874.

Synthesis of methyl 2,6-dihydroxy-3-methyl-5-[1-(4-fluorophenyl)-2-nitroethyl]benzoate (12c) and methyl 3,7-dioxo-4,6-(1-(4-fluorophenyl)-2-nitroethyl)-2-diazooct-5-enoate (13c). To a 4 dram vial was added zinc triflate (2 mg, 0.005 mmol), followed by enone **2** (50 mg, 0.45 mmol) and 2 mL of dry DCM. The resulting mixture was stirred at room temperature. Enol diazoacetate **1** (180 mg, 0.70 mmol) was added all at once. The yellow solution was allowed to react overnight. After 16 h, 2.0 equiv. of solid 4-fluoro-β-nitrostyrene (167 mg, 1.00 mmol) was added to the solution followed by triethylamine (3 mg, 0.03 mmol, 5 mol%) when 4-fluoro-β-nitrostyrene was fully dissolved. Reaction was performed as for the synthesis of **12a** and **13a**. The resulting solution was concentrated under reduced pressure, and the residue was purified by silica gel chromatography, eluting with 1 : 6 EtOAc–hexane, to give 88 mg (0.25 mmol, 56%) of **12c** as pale yellow liquid then 40 mg (0.072 mmol, 16%) of **13c** as a yellow syrup which is a 2 : 1 mixture of two diastereomers that could not be separated by chromatography.

Methyl 2,6-dihydroxy-3-methyl-5-[1-(4-fluorophenyl)-2-nitroethyl]benzoate (12c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99 (br, 1H), 9.86 (br, 1H), 7.26 (t, *J* = 8.0 Hz, 2H), 7.00 (t, *J* = 8.0 Hz, 2H), 7.00 (s, 1H), 5.12 (t, *J* = 8.0 Hz, 1H) 5.05 (dd, *J* = 8.0 Hz, 16.0 Hz, 1H), 4.92 (dd, *J* = 8.0 Hz, 16.0 Hz, 1H), 4.06 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 161.9 (d, J_{CF} = 240 Hz), 158.0, 158.9, 136.7, 134.6, 129.4 (d, J_{CF} = 10 Hz), 116.9, 116.5, 115.8 (d, J_{CF} = 20 Hz), 99.8, 77.7, 53.0, 42.6, 15.4; IR (neat): 3432, 3117, 2962, 1673, 1625, 1551, 1510, 1437 cm^{-1}; HRMS (ESI) for $C_{17}H_{16}FNO_6$ $[M + H]^+$ calcd 350.1040; found 350.1019.

Methyl 3,7-dioxo-4,6-[1-(4-fluorophenyl)-2-nitroethyl]-2-diazooct-5-enoate (13c). Major isomer: ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.45 (dd, J = 4.0 Hz, 8.0 Hz, 2H), 7.14–7.10 (comp, 2H), 7.02–6.94 (comp, 4H), 6.65 (d, J = 8.0 Hz, 1H), 5.53 (t, J = 8.0 Hz, 1H), 5.22 (dd, J = 8.0 Hz, 12.0 Hz, 1H), 4.91(dd, J = 4.0 Hz, 12.0 Hz, 1H), 4.76 (dd, J = 4.0 Hz, 8.0 Hz, 1H), 4.04 (ddd, J = 4.0 Hz, 8.0 Hz, 12.0 Hz, 1H), 3.86 (s, 3 H), 3.83 (dd, J = 4.0 Hz, 12.0 Hz, 1H) 3.66 (dd, J = 8.0 Hz, 12.0 Hz, 1H); 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 188.9, 162.4 (d, J_{CF} = 200 Hz), 162.4 (d, J_{CF} = 190 Hz), 161.3, 144.0, 140.8, 134.4 (d, J_{CF} = 0.3 Hz), 131.8 (d, J_{CF} = 0.3 Hz), 130.2 (d, J_{CF} = 10 Hz), 129.8 (d, J_{CF} = 10 Hz), 116.4 (d, J_{CF} = 20 Hz), 116.0 (d, J_{CF} = 20 Hz), 77.5, 77.2, 52.7, 48.9, 45.5, 42.9, 27.5; visible signals of the minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (dd, J = 4.0 Hz, 8.0 Hz, 2H), 7.12–7.10 (comp, 4H), 7.07 (dd, J = 4.0 Hz, 8.0 Hz, 2H), 6.84 (d, J = 8.0 Hz, 1H), 5.52 (comp, 1H), 4.99 (dd, J = 4.0 Hz, 12.0 Hz, 1H), 4.56 (dd, J = 8.0 Hz, 12.0 Hz, 1H), 4.48 (dd, J = 4.0 Hz, 8.0 Hz, 1H), 4.15–4.09 (comp, 1H), 3.86–3.81 (1H), 3.63–3.68 (1H), 2.37 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.1, 188.9, 161.5, 160.6, 143.4, 141.0, 131.8 (d, J_{CF} = 0.3 Hz), 130.0 (d, J_{CF} = 7 Hz), 129.0 (d, J_{CF} = 7 Hz), 115.8 (d, J_{CF} = 17 Hz), 115.5 (d, J_{CF} = 17 Hz), 77.5, 77.3, 52.4, 49.0, 46.3, 41.6, 27.1; IR (neat): 2148, 1711, 1675, 1649, 1550, 1510, 1437 cm^{-1}; HRMS (ESI) for $C_{25}H_{23}F_2N_4O_8$ $[M + H]^+$ calcd 545.1484; found 545.1492.

Synthesis of methyl 2,6-dihydroxy-3-methyl-5-[1-(4-trifluoromethylphenyl]-2-nitroethyl)benzoate (12d) and methyl 3,7-dioxo-4,6-[1-(4-trifluoromethylphenyl)-2-nitroethyl]-2-diazooct-5-enoate (13d). To a 4 dram vial was added zinc triflate (2 mg, 0.005 mmol), followed by enone **2** (50 mg, 0.45 mmol) and 2 mL of dry DCM. The mixture was stirred at room temperature. Enol diazoacetate **1** (180 mg, 0.70 mmol) was added all at once. The yellow solution was allowed to react overnight. After 16 h, 2.0 equiv. of solid 4-trifluoromethyl-β-nitrostyrene (216 mg, 1.00 mmol) was added to the solution followed by triethylamine (3 mg, 0.03 mmol, 5 mol%) when the 4-trifluoromethyl-β-nitrostyrene was fully dissolved. Reaction was performed as for the synthesis of **12a** and **13a**. The resulting solution was concentrated under reduced pressure, and the residue was purified by silica gel chromatography, eluting with 1 : 6 EtOAc–hexane, to give 87 mg (0.26 mmol, 57%) of **12d** as pale yellow oil then 48 mg (0.075 mmol, 17%) and **13d** as a yellow syrup which is a 3 : 1 mixture of two diastereomers that could not be separated by chromatography.

Methyl 2,6-dihydroxy-3-methyl-5-[1-(4-trifluoromethylphenyl)-2-nitroethyl]benzoate (12d). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.02 (br, 1H), 9.87 (br, 1H), 7.57 (d, J = 8.0 Hz), 7.42 (d, J = 8.0 Hz), 7.02 (s, 1H), 5.19 (t, J = 8.0 Hz) 5.09 (dd, J = 8.0 Hz, 12.0 Hz), 5.02 (dd, J = 8.0 Hz, 12.0 Hz), 4.07 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 158.3, 155.9, 143.1, 136.7, 134.6, 129.6 (d, J_{CF} = 30 Hz), 129.4, 128.2, 125.7(d, J_{CF} = 3 Hz), 124.0 (q, J_{CF} = 270 Hz), 99.8, 77.2, 53.1, 43.2, 15.3; IR (neat): 3435, 3110, 2965, 2924, 1674, 1621, 1553, 1439 cm^{-1}; HRMS (ESI) for $C_{18}H_{17}F_3NO_6$ $[M + H]^+$ calcd 400.1008; found. 400.1014.

Methyl 3,7-dioxo-4,6-[1-(4-trifluorophenyl)-2-nitroethyl]-2-diazooct-5-enoate (13d). Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 6.89 (d, J = 8.0 Hz, 1H), 5.60 (t, J = 8.0 Hz, 1H), 5.23 (dd, J = 8.0 Hz, 12.0 Hz, 1H), 5.07 (dd, J = 4.0 Hz, 12.0 Hz, 1H), 5.06 (comp, 1H), 4.65 (dd, J = 8.0 Hz, 12.0 Hz, 1H), 4.56 (dd, J = 4.0 Hz, 12.0 Hz, 1H), 4.27 (ddd, J = 4.0 Hz, 8.0 Hz, 12.0 Hz, 1H), 3.56 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 198.7, 188.4, 160.6, 143.0, 142.3, 141.6, 139.9, 137.4, 137.1, 128.7, 127.5, 126.3, 126.0 (d, J_{CF} = 3 Hz), 125.6 (d, J_{CF} = 3 Hz), 123.7 (q, J_{CF} = 270 Hz), 77.1, 77.1, 52.5, 49.0, 46.4, 42.07, 27.1; visible signals of the minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 5.76 (t, J = 8.0 Hz, 1H), 4.12 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 129.9, 127.3, 125.2 (d, J_{CF} = 3 Hz), 125.1(d, J_{CF} = 3 Hz), 53.1, 48.7, 44.1, 40.8; IR (neat): 2960, 2923, 2853, 2154, 1714, 1679, 1651, 1621, 1554, 1439 cm^{-1}; HRMS (ESI) for $C_{27}H_{22}F_6N_4O_8$ $[M + H]^+$ calcd 645.1419; found 645.1425.

Synthesis of methyl 2,6-dihydroxy-3-methyl-5-[1-(1-furyl)-2-nitroethyl]benzoate (12e). To a 4 dram vial was added zinc triflate (2 mg, 0.005 mmol), followed by enone **2** (50 mg, 0.45 mmol) and 2 mL of dry DCM. With stirring at room temperature enol diazoacetate **1** (180 mg, 0.70 mmol) was added all at once, and the yellow solution was allowed to react overnight. After 16 h, 2.0 equiv. of 2-(2-nitrovinyl)furan (150 mg, 1.00 mmol) was added, followed by 5 mol% triethylamine (3 mg, 0.03 mmol) when 2-(2-nitrovinyl)furan was fully dissolved. The color of the solution turned from yellow to deep red upon addition of the base. The reaction solution was stirred at room temperature for 24 h during which time the color of the solution became darker. The resulting solution was concentrated under reduced pressure, and the crude residue was purified by silica gel chromatography, eluting with 1 : 6 EtOAc–hexane, to give 90 mg (0.28 mmol, 63%) of a yellow solid as major product **12e**. In addition, 58 mg (0.12 mmol, 26%) double addition by-product was obtained as a mixture of multiple isomers which could not be separated by chromatography. **12e**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.94 (br, 2H), 7.37 (s, 1H), 7.02 (s, 1H), 6.32 (d, J = 4.0 Hz), 6.18 (J = 4.0 Hz), 5.25 (t, J = 8.0 Hz), 4.91 (hept, J = 8.0 Hz), 4.07 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 158.4, 155.7, 142.4, 137.1, 117.0, 114.4, 110.5, 107.3, 99.6, 76.3, 53.0, 37.2, 15.3; IR (neat): 3392, 3125, 2967, 2923, 1669, 1626, 1545, 1437 cm^{-1}; HRMS (ESI) for $C_{15}H_{16}NO_7$ $[M + H]^+$ calcd 322.0927; found 322.0906.

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