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Efficient synthesis of 4-hydroxycyclopentenones: dysprosium(III) triflate catalyzed Piancatelli rearrangement

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ABSTRACT

4-Hydroxycyclopentenones represent a privileged scaffold in chemical synthesis. A dysprosium(III) trifluoromethanesulfonate catalyzed rearrangement of furylcarbinols to 4-hydroxycyclopentenones via a 4π electrocyclization has been developed. The catalytic Piancatelli rearrangement affords a single trans-diastereomer from both aryl and alkyl substituted furylcarbinols.

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1. Introduction

The chemistry of 4-hydroxycyclopentenones was fueled in the 1980s by the synthesis of prostaglandins.[1] Over the years this core structure has become a privileged building block that has been used to access a wide array of natural products and biologically active molecules (Fig. 1).[2] Among the various methods available to access the 4-hydroxycyclopentenone core, the Piancatelli rearrangement discovered in 1976 remains one of the most direct.[3] The cascade rearrangement transforms a furylcarbinol into a substituted 4-hydroxycyclopentenone in one-step. The reaction is believed to proceed through a series of cascading events that terminates with

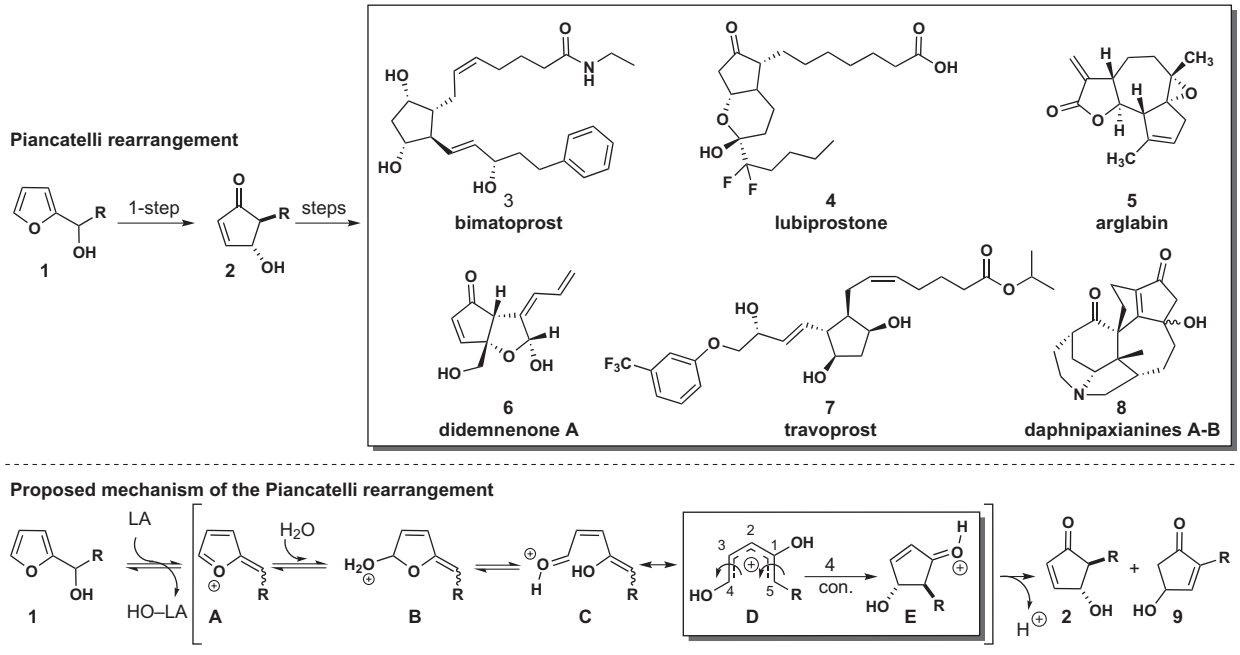

Fig. 1. Representative applications of the Piancatelli rearrangement for the synthesis of 4-hydroxycyclopentenones.

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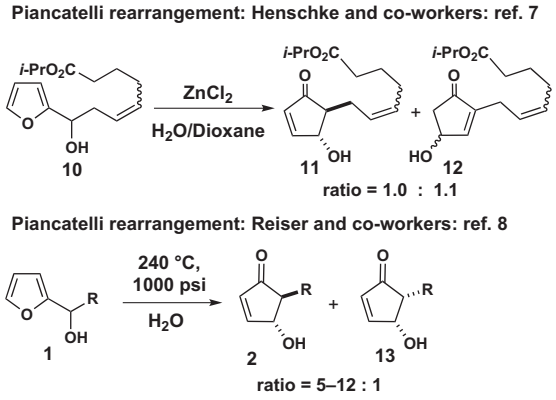
a 4π electrocyclic ring closure of a pentadienyl cation (**D**),[4] analogous to the Nazarov cyclization.[5] Some of the current drawbacks with the Piancatelli rearrangement are the use of stoichiometric quantities of Brønsted or Lewis acid, the product is often isolated in low yield (40–55%), and the acid catalyzed reaction can result in the formation of polymeric material that may be difficult to remove, especially on scale.[6] Moreover, the rearrangement often results in an inseparable mixture of 4-hydroxycyclopentenone isomers (**2** and **9**), which are typically processed through a second rearrangement step into the thermodynamically more stable isomer (**9**).

Despite these challenges, the Piancatelli rearrangement still remains a highly attractive method that is widely used in academia and industry. For example, Henschke and co-workers demonstrated the utility of the cascade rearrangement as an integral part in their strategy for the synthesis of a 4-hydroxycyclopentenone (**12**), a common intermediate from which several active pharmaceutical ingredients could be accessed.[7] The reaction was conducted on multi kilogram scale with superstoichiometric quantities of $ZnCl_2$ (16 equiv) and despite optimization the reaction resulted in a 1.0:1.1 mixture of cyclopentenone isomers that were converted to the thermodynamic isomer in 55% yield over two steps. Recently, Reiser and co-workers have demonstrated that the Piancatelli rearrangement can be accelerated at high temperature (240 °C) and pressure (1000 psi) using a microreactor.[8] Under these conditions higher yields and shorter reaction times were observed. Clearly, progress is being made in further improving the Piancatelli rearrangement however Scheme 1, more research is still required to reduce the catalyst loading, increase the efficiency and avoid the formation of cyclopentenone isomer mixtures.



Scheme 1. Recent examples of the Piancatelli rearrangement.

2. Results and discussion

In our efforts to develop new methods for the synthesis of substituted cyclopentenones, we recently demonstrated that dysprosium triflate ($Dy(OTf)_3$) was an excellent catalyst for the aza- and oxa-Piancatelli rearrangements.[9] These cascade rearrangements were shown to be compatible with aniline and alcohol nucleophiles using 5 mol % $Dy(OTf)_3$ as the catalyst. Given the number of strategies used for the synthesis of biologically active molecules that rely on the Piancatelli rearrangement and the current limitations, we directed our efforts toward developing a catalytic cascade rearrangement using $Dy(OTf)_3$. We envisioned that the milder catalytic conditions would be compatible with more functionalized substrates and would result in the exclusive formation of kinetic isomer **2**, which could be transformed into the thermodynamic isomer **9** under known conditions if desired. It's important to note that the initial inspiration for studying the catalytic activity of $Dy(OTf)_3$ came from a pioneering report by Batey and co-workers in 2007.[10] In this report they demonstrated the synthetic potential of rare earth Lewis acids, including $Dy(OTf)_3$, in a related rearrangement of furfural.

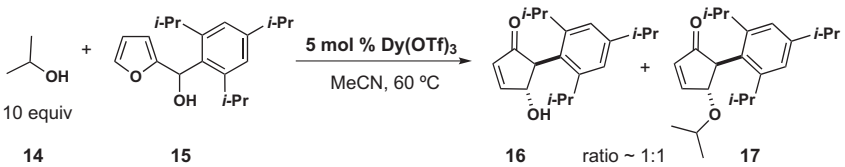
Our initial optimization studies evolved from an observation made while investigating the oxa-Piancatelli rearrangement.[9c,9d] During these studies 4-hydroxycyclopentenone **16** was observed in 52% yield when 10 equiv of *i*-PrOH was added to 2-furylcarbinol **15** in the presence of 5 mol % $Dy(OTf)_3$ and heated to 60 °C in acetonitrile (Scheme 2).

The preference for addition by water, generated in situ during the formation of oxocarbenium ion **A** (Fig. 1), in the presence of excess *i*-PrOH was surprising as in the aza-Piancatelli reaction water could be used as a co-solvent without observation of the 4-hydroxycyclopentenone product. Encouraged by the ability to use catalytic conditions and based on the importance of 4-hydroxycyclopentenones as intermediates in synthesis, we decided to explore the rearrangement with water in more detail. The results from these studies are described herein.

We elected to start by screening alcohol additives in the presence of water as a co-solvent (Table 1). In all cases examined the addition of an alcohol had a positive effect on the efficiency of the Piancatelli rearrangement. Even though the reaction benefited from the use of phenols, we decided to pursue the use of *i*-PrOH and *t*-BuOH. These alcohols are advantageous for synthesis due to their low cost and ease of purification. Further optimization revealed that 10 mol % $Dy(OTf)_3$ in a solvent mixture of *t*-BuOH/H_2O (5:1) at 80 °C gave the best results (**entry 8**). A side product originating from *i*-PrOH acting as a nucleophile was observed when a solvent system of *i*-PrOH/H_2O (5:1) was used. We never observed any side product originating from the addition of *t*-BuOH probably due to its steric bulk preventing nucleophilic attack. In the absence of an alcohol additive the reaction was more sluggish and lower yielding (entry 10).

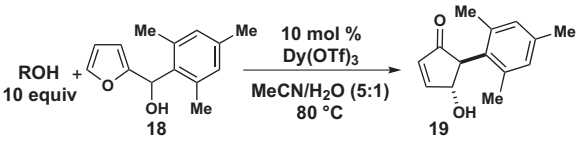
With the optimized reaction conditions in hand, we then investigated the substrate scope with furylcarbinols substituted with an aryl group at the 2-position (Scheme 3). Short reaction times and excellent yields were observed in all cases. Heteroaromatic groups, such as thiophene **23** were also well tolerated in the reaction. Importantly, the products were isolated exclusively as the trans-diastereomer, which is consistent with the proposed conrotatory 4π electrocyclization (Fig. 1).

After successfully demonstrating the generality of the $Dy(OTf)_3$ catalyzed Piancatelli reaction with furylcarbinols bearing aromatic side-chains, we turned our attention to investigate the reaction with aliphatic side-chains. Disappointingly, the rearrangement with *n*-butylfurylcarbinol was exceedingly sluggish and extensive decomposition was observed. Because prostaglandin analogues

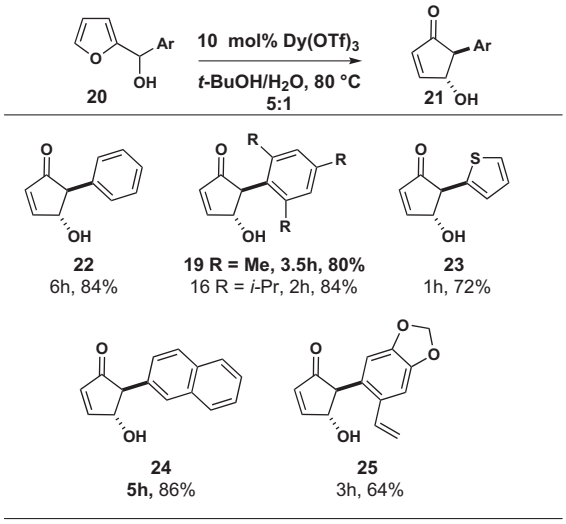


Scheme 2. Formation of 4-hydroxycyclopentenone via the oxa-Piancatelli rearrangement.

Table 1
Optimization studies with alcohol additives



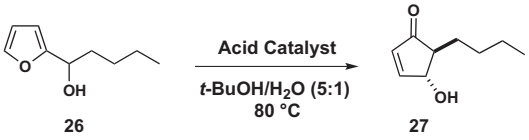
Entry	ROH	Time (h)	Yield (%)
1	MeOH	16	76
2	*i*-PrOH	4.5	80
3	*t*-BuOH	3.25	80
4	F_6*i*-PrOH	7	76
5	Phenol	4.5	80
6	*p*-Nitro phenol	4.5	80
7	*p*-Methoxy phenol	3.5	80
8	**5:1 t-BuOH/H2O**	**3.5**	**80**
9	5:1 *i*-PrOH/H_2O	3.5	64
10	—	19	70



Scheme 3. Substrate scope with aromatic groups at the 2-position of the furylcarbinol.

commonly feature lengthy alkyl side-chains, we sought to overcome this limitation by screening other Lewis and Brønsted acids in an attempt to improve both reactivity and efficiency (Table 2). The use of 10 mol % Dy(OTf)$_3$ gave the desired product in 60% yield,

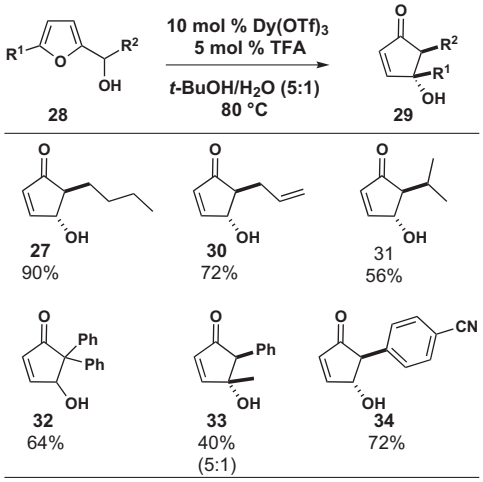
Table 2
Lewis and Brønsted acid screen



Entry	Acid	equiv	Time (h)	Yield (%)
1	Dy(OTf)$_3$	0.10	72	60
2	Dy(OTf)$_3$	0.30	—	Decomp.
3	Dy(Cl)$_3$	0.10	146	44
4	Dy(OAc)$_3$	0.10	>240	No reaction
5	Sc(OTf)$_3$	0.10	20	53
6	$ZnCl_2$	1.00	>240	Incomplete
7	TFA	0.05	96	Decomp.
8	TFA	0.20	18	24
9	*Dy(OTf)$_3$+TFA*	*0.10+0.05*	*16*	*90*
10	Dy(Cl)$_3$+TFA	0.10+0.05	24	48
11	Dy(OAc)$_3$+TFA	0.10+0.05	168	28

but 30 mol % resulted in decomposition. Switching to other sources of dysprosium, such as Dy(Cl)$_3$ and Dy(OAc)$_3$, proved unsuccessful (entries 3 and 4). The use of slightly more Lewis acidic Sc(OTf)$_3$ (10 mol %) resulted in 53% yield, but decomposition was still extensively observed. Unfortunately, under the *t*-BuOH/H_2O (5:1) solvent mixture stoichiometric $ZnCl_2$ proved ineffective and catalytic trifluoroacetic acid resulted in only modest success (Table 2, entries 6–8). To our gratification, we found that utilizing a combination of Dy(OTf)$_3$ (10 mol %) and TFA as co-catalysts (5 mol %) dramatically increased the yield and efficiency (entry 9). Yin and co-workers also observed that a combination of Lewis and Brønsted acid afforded optimal results for a related rearrangement.[11] A small Brønsted acid screen: potassium dihydrogen phosphate, acetic acid, phosphoric acid, trifluoromethanesulfonic acid, and hydrochloric acid, at 5 mol % in combination with 10 mol % Dy(OTf)$_3$ was performed, however, the combination of TFA with Dy(OTf)$_3$ proved optimal. It is interesting to note that the efficiency of the Dy(Cl)$_3$ and Dy(OAc)$_3$ catalyzed reaction was also improved by the addition of 5 mol % TFA, albeit to a smaller extent (compare entries 3 and 4 to 10 and 11). Further studies are currently underway to fully elucidate the beneficial effect of the TFA additive. With optimized reaction conditions (entry 9) in hand for the rearrangement of a furylcarbinol substituted with an *n*-butyl side-chain, the scope was extended to include other aliphatic derivatives.

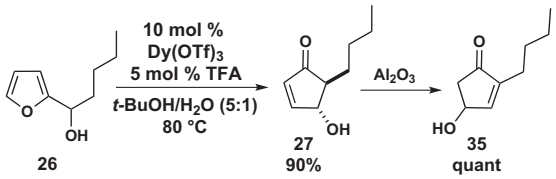
Pleasingly, the dual system proved general for a variety of substrates as illustrated in Scheme 4. Terminal alkenes and branched alkanes were well tolerated. Moreover, we discovered that the combination of Lewis and Brønsted acid catalysts was beneficial for substrates that had previously proved challenging or exceedingly sluggish under only Lewis acid catalysis. Cyclopentenones **32**–**34** were accessed from the corresponding substituted furylcarbinol in moderate to good yield (40–72% yield, Scheme 4).



Scheme 4. Substrate scope under the combination of Dy(OTf)$_3$ and TFA catalysis.

Having determined that our Lewis/Brønsted acid catalyst system can be used to access a range of desirable cyclopentenones, we wanted to address a key part of the overall strategy for the synthesis of prostaglandin analogues, in controlling the formation of cyclopentenone isomers. Interestingly, using our catalytic Dy(OTf)$_3$ conditions the more thermodynamically stable isomer was only observed for compounds **23** and **33** (5% and 6%, respectively). Presumably this is due to the activating group at the 5-position of the cyclopentenone, which helps facilitate the rearrangement. To promote the isomerization we chose to use conditions developed

by Piancatelli.[12] Subjection of **27** to basic alumina (Brockman Grade III) led to complete cyclopentenone isomerization (Scheme 5). This stepwise approach provides a high yielding and simple synthetic procedure to both isomers, thus increasing the versatility of the rearrangement.



Scheme 5. Efficient access to both cyclopentenone isomers.

3. Conclusion

We have developed an efficient, catalytic method for the rearrangement of furylcarbinols to 4-hydroxycyclopentenones. Catalytic $Dy(OTf)_3$ was determined to be optimal for the rearrangement of furylcarbinols bearing aromatic substituents at the 2-position, while the combination of TFA and $Dy(OTf)_3$ was required for the more challenging substrates, such as those with aliphatic side-chains. This process is mild, operationally simple, and compatible with a variety of substituted furylcarbinols. In addition, the mild reaction conditions developed allow for both cyclopentenone isomers to be accessed in high yield using a controlled stepwise approach.

4. Experimental

4.1. Materials and general experimental details

Unless stated otherwise, reactions were conducted in air dried glassware under an atmosphere of air using reagent grade solvents. Reaction temperatures were controlled using a Heidolph temperature modulator, and unless stated otherwise, reactions were performed at room temperature (rt, approximately 23 °C). Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F_{254} pre-coated plates (0.25 mm) and visualized by exposure to UV light (254 nm) or stained with anisaldehyde and potassium permanganate. Flash column chromatography was performed using normal phase silica gel (60 Å, 230–240 mesh, Merck KGA).

^{1}H NMR spectra were recorded on Varian spectrometers (at 400, 500 or 600 MHz) and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. ^{13}C NMR spectra were recorded on Varian spectrometers (125 or 150 MHz). Data for ^{13}C NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, and coupling constant (Hz). IR spectra were recorded on a Perkin Elmer Spectrum Two FT-IR spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the UC Santa Barbara Mass Spectrometry Facility on a (Waters Corp.) Micromass QTOF2 with an electrospray ionization source.

Furylcarbinols were prepared according to literature precedent by reacting furfural with the corresponding Grignard reagent.

4.2. General experimental procedure A: Scheme 3

Furylcarbinol was dissolved in a solution of *t*-BuOH/H_2O. To the reaction mixture at rt was added 10 mol % of $Dy(OTf)_3$. The reaction mixture was immediately fitted with a reflux condenser and placed in an oil bath pre-heated to 80 °C. The reaction was monitored by TLC. Upon completion, the reaction was then quenched with saturated aqueous sodium bicarbonate, diluted with H_2O, and extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered, and then concentrated in vacuo. The residue was purified by column chromatography.

*4.2.1. 4-Hydroxy-5-(2,4,6-triisopropylphenyl)cyclopent-2-en-1-one (**16**).* According to general procedure A $Dy(OTf)_3$ (5 mg, 0.008 mmol, 0.1 equiv) was added to furan-2-yl(2,4,6-triisopropyl) methanol (25 mg, 0.08 mmol, 1 equiv) in 1.5 mL of *t*-BuOH and 0.3 mL H_2O. The resulting reaction mixture was heated to 80 °C for 2 h. The reaction was then quenched with 1.5 mL of saturated aqueous sodium bicarbonate, diluted with 3 mL H_2O, and extracted with diethyl ether (3×7 mL). The combined organic layers were dried over $MgSO_4$, filtered, and then concentrated in vacuo. The residue was purified by column chromatography to afford cyclopentenone **16** (21 mg, 84%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, J=5.8, 1.9 Hz, 1H), 7.26 (s, 1H), 7.03 (d, J=1.8 Hz, 1H), 6.99 (d, J=1.9 Hz, 1H), 6.39 (dd, J=5.8, 1.3 Hz, 1H), 4.94 (dt, J=5.9, 1.8 Hz, 1H), 3.99 (d, J=3.1 Hz, 1H), 3.26–3.16 (m, 1H), 2.92–2.82 (m, 1H), 2.41 (d, J=5.9 Hz, 1H), 2.02–1.92 (m, 1H), 1.33 (d, J=6.6 Hz, 3H), 1.29–1.13 (m, 12H), 1.05 (d, J=6.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.1, 159.7, 148.4, 148.2, 147.5, 134.6, 128.3, 122.8, 121.3, 79.6, 57.4, 34.3, 30.9, 30.6, 25.2, 24.1, 24.1, 23.9, 23.5; IR (thin film, cm^{-1}) 3501, 3075, 2959, 2869, 1699, 1102, 765; HRMS (ESI) m/z 323.1973 (323.1987 calcd for $C_{20}H_{28}NaO_2^+[MNa]^+$).

*4.2.2. 4-Hydroxy-5-mesitylcyclopent-2-en-1-one (**19**).* According to general procedure A $Dy(OTf)_3$ (7 mg, 0.0115 mmol, 0.1 equiv) was added to furan-2-yl(mesityl)methanol (25 mg, 0.115 mmol, 1 equiv) in 1.5 mL of *t*-BuOH and 0.3 mL H_2O. The resulting reaction mixture was heated to 80 °C for 2 h. The reaction was then quenched with 1.5 mL of saturated aqueous sodium bicarbonate, diluted with 3 mL H_2O, and extracted with diethyl ether (3×7 mL). The combined organic layers were dried over $MgSO_4$, filtered, and then concentrated in vacuo. The residue was purified by column chromatography to afford cyclopentenone **19** (20 mg, 80%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, J=5.9, 2.0 Hz, 1H), 6.79 (m, 2H), 6.32 (m, 1H), 5.07–5.04 (m, 1H), 3.89 (d, J=3.1 Hz, 1H), 2.39 (s, 3H), 2.26 (s, 4H), 1.90 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.4, 160.3, 138.4, 137.0, 136.1, 134.4, 130.3, 130.1, 129.2, 78.2, 58.3, 21.2, 20.8, 20.3; IR (thin film, cm^{-1}) 3419, 3062, 2963, 2921, 1701, 852; HRMS (ESI) m/z 239.1055 (239.1055 calcd for $C_{14}H_{16}NaO_2^+[MNa]^+$).

*4.2.3. 4-Hydroxy-5-phenylcyclopent-2-en-1-one (**22**).* According to general procedure A $Dy(OTf)_3$ (8.7 mg, 0.014 mmol, 0.1 equiv) was added to furan-2-yl(phenyl)methanol (25 mg, 0.14 mmol, 1 equiv) in 1.5 mL of *t*-BuOH and 0.3 mL H_2O. The resulting reaction mixture was heated to 80 °C for 6.5 h. The reaction was then quenched with 1.5 mL of saturated aqueous sodium bicarbonate, diluted with 3 mL H_2O, and extracted with diethyl ether (3×7 mL). The combined organic layers were dried over $MgSO_4$, filtered, and then concentrated in vacuo. The residue was purified by column chromatography to afford cyclopentenone **22** (21 mg, 84%) as brown oil. Spectral data for **22** were consistent with those previously reported.[8a]

*4.2.4. 4-Hydroxy-5-(thiophen-2-yl)cyclopent-2-en-1-one (**23**).* According to general procedure **A** $Dy(OTf)_3$ (8.5 mg, 0.014 mmol, 0.1 equiv) was added to furan-2-yl(thiophen)methanol (25 mg, 0.14 mmol, 1 equiv) in 1.5 mL of *t*-BuOH and 0.3 mL H_2O. The resulting reaction mixture was heated to 80 °C for 1 h. The reaction was then quenched with 1.5 mL of saturated aqueous

sodium bicarbonate, diluted with 3 mL H_2O, and extracted with diethyl ether (3×7 mL). The combined organic layers were dried over $MgSO_4$, filtered, and then concentrated in vacuo. The residue was purified by column chromatography to afford cyclopentenone **23** (18 mg, 72%) as an orange oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (dd, J=5.9, 2.1 Hz, 1H), 7.25 (dd, J=5.2, 1.3 Hz, 1H), 7.03–7.00 (m, 1H), 7.00–6.97 (m, 1H), 6.31 (dd, J=5.9, 1.5 Hz, 1H), 5.09–5.03 (m, 1H), 3.74 (d, J=3.0 Hz, 1H), 2.63 (d, J=6.1 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.1, 161.3, 137.7, 133.8, 127.3, 126.1, 125.0, 79.0, 57.1; IR (thin film, cm^{-1}) 3397, 3106, 2889, 1696, 1027, 697; HRMS (ESI) m/z 203.0130 (203.0143 calcd for $C_9H_8NaO_2S^+$[MNa]$^+$).

*4.2.5. 4-Hydroxy-5-(naphthalen-2-yl)cyclopent-2-en-1-one (**24**).* According to general procedure **A** Dy(OTf)$_3$ (6.8 mg, 0.012 mmol, 0.1 equiv) was added to furan-2-yl(naphthalen) methanol (25 mg, 0.12 mmol, 1 equiv) in 1.5 mL of *t*-BuOH and 0.3 mL H_2O. The resulting reaction mixture was heated to 80 °C for 5 h. The reaction was then quenched with 1.5 mL of saturated aqueous sodium bicarbonate, diluted with 3 mL H_2O, and extracted with diethyl ether (3×7 mL). The combined organic layers were dried over $MgSO_4$, filtered, and then concentrated in vacuo. The residue was purified by column chromatography to afford cyclopentenone **24** (22 mg, 86%) as yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 (dd, J=9.0, 2.5 Hz, 2H), 7.79–7.76 (m, 1H), 7.64–7.61 (m, 1H), 7.60 (dd, J=5.8, 2.1 Hz, 1H), 7.48 (qd, J=7.0, 3.4 Hz, 2H), 7.14 (dd, J=8.4, 1.8 Hz, 1H), 6.33 (dd, J=5.8, 1.4 Hz, 1H), 5.01 (s, 1H), 3.57 (d, J=2.8 Hz, 1H), 2.66 (d, J=5.7 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.5, 162.0, 134.6, 134.2, 133.6, 132.7, 129.0, 127.8, 127.8, 126.5, 126.2, 125.8, 79.0, 62.4; IR (thin film, cm^{-1}) 3397, 3054, 2902, 1697, 1035, 745; HRMS (ESI) m/z 247.0724 (247.0735 calcd for $C_{15}H_{12}NaO_2^+$[MNa]$^+$).

*4.2.6. 4-Hydroxy-5-(6-vinylbenzo[d][1,3]dioxol-5-yl)cyclopent-2-en-1-one (**25**).* According to the general procedure **A** Dy(OTf)$_3$ (6 mg, 0.010 mmol, 0.1 equiv) was added to furan-2-yl(6-vinylbenzo[*d*][1,3]dioxol)methanol (25 mg, 0.102 mmol, 1 equiv) in 1.5 mL of *t*-BuOH and 0.3 mL H_2O. The resulting reaction mixture was heated to 80 °C for 3 h. The reaction was then quenched with 1.5 mL of saturated aqueous sodium bicarbonate, diluted with 3 mL H_2O, and extracted with diethyl ether (3×7 mL). The combined organic layers were dried over $MgSO_4$, filtered, and then concentrated in vacuo. The residue was purified by column chromatography to afford cyclopentenone **25** (16 mg, 64%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, J=5.8, 2.2 Hz, 1H), 7.00 (s, 1H), 6.73 (dd, J=17.1, 10.9 Hz, 1H), 6.39 (s, 1H), 6.37 (dd, J=5.87, 1.39, 1H), 5.94 (dd, J=6.84, 1.5, 2H), 5.54 (dd, J=17.4, 1.3 Hz, 1H), 5.24 (dd, J=10.9, 1.2 Hz, 1H), 4.99–4.86 (m, 1H), 3.69 (d, J=2.9 Hz, 1H), 2.43 (d, J=5.9 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.6, 161.4, 147.9, 147.5, 134.8, 134.1, 132.1, 128.2, 116.2, 108.6, 106.6, 101.4, 79.4, 59.6; IR (thin film, cm^{-1}) 3406, 3084, 2902, 1698, 1483, 1036, 733; HRMS (ESI) m/z 267.0615 (267.0633 calcd for $C_{14}H_{12}NaO_4^+$[MNa]$^+$).

4.3. General experimental procedure B: Scheme 4

Furylcarbinol was dissolved in a solution of *t*-BuOH/H_2O. To the reaction mixture at rt were added 10 mol % of Dy(OTf)$_3$ and 5 mol % TFA. The reaction mixture was immediately fitted with a reflux condenser and placed in an oil bath pre-heated to 80 °C. The reaction was monitored by TLC. Upon completion, the reaction was then quenched with saturated aqueous sodium bicarbonate, diluted with H_2O, and extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered, and then concentrated in vacuo. The residue was purified by column chromatography.

*4.3.1. 5-Butyl-4-hydroxycyclopent-2-en-1-one (**27**).* According to general procedure **B** Dy(OTf)$_3$ (10 mg, 0.016 mmol, 0.1 equiv) was added to (furan-2-yl)pentan-1-ol (25 mg, 0.16 mmol, 1 equiv) in 1.5 mL of *t*-BuOH and 0.3 mL H_2O. The resulting reaction mixture was treated with trifluoroacetic acid (0.6 μL, 0.008 mmol, 0.05 equiv) and heated to 80 °C for 16 h. The reaction was then quenched with 1.5 mL of saturated aqueous sodium bicarbonate, diluted with 3 mL H_2O, and extracted with diethyl ether (3×7 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography to afford cyclopentenone **27** (22 mg, 90%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, J=5.8, 2.2 Hz, 1H), 6.20 (d, J=5.7 Hz, 1H), 4.70 (t, J=2.7 Hz, 1H), 2.32–2.17 (m, 1H), 2.00 (s, 1H), 1.92–1.81 (m, 1H), 1.51–1.31 (m, 5H), 0.92 (t, J=7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.2, 161.6, 134.5, 76.8, 55.6, 29.6, 28.5, 22.9, 14.1; IR (thin film, cm^{-1}) 3407, 2957, 2860, 1694, 1098; HRMS (FI) m/z 154.0991 (154.0994 calcd for $C_9H_{14}NaO_2^+$[MNa]$^+$).

*4.3.2. 5-Allyl-4-hydroxycyclopent-2-en-1-one (**30**).* According to general procedure **B** Dy(OTf)$_3$ (11 mg, 0.018 mmol, 0.1 equiv) was added to (furan-2-yl)but-3-en-1-ol (25 mg, 0.18 mmol, 1 equiv) in 1.5 mL of *t*-BuOH and 0.3 mL H_2O. The resulting reaction mixture was treated with trifluoroacetic acid (0.7 μL, 0.009 mmol, 0.05 equiv) and heated to 80 °C for 15 h. The reaction was then quenched with 1.5 mL of saturated aqueous sodium bicarbonate, diluted with 3 mL H_2O, and extracted with diethyl ether (3×7 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography to afford cyclopentenone **30** (18 mg, 72%) as a brown oil. Spectral data for **30** were consistent with those previously reported.[13]

*4.3.3. 4-Hydroxy-5-isopropylcyclopent-2-en-1-one (**31**).* According to the general procedure **B** Dy(OTf)$_3$ (11 mg, 0.018 mmol, 0.1 equiv) was added to (furan-2-yl)-2-methyl-propanol (25 mg, 0.178 mmol, 1 equiv) in 1.5 mL of *t*-BuOH and 0.3 mL H_2O. The resulting reaction mixture was treated with trifluoroacetic acid (0.7 μL, 0.009 mmol, 0.05 equiv) and heated to 80 °C for 34 h. The reaction was then quenched with 1.5 mL of saturated aqueous sodium bicarbonate, diluted with 3 mL H_2O, and extracted with diethyl ether (3×7 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography to afford cyclopentenone **31** (14 mg, 56%) as an oil. Spectral data for **31** were consistent with those previously reported.[14]

*4.3.4. 4-Hydroxy-5,5-diphenylcyclopent-2-en-1-one (**32**).* According to general procedure **B** Dy(OTf)$_3$ (6 mg, 0.010 mmol, 0.1 equiv) was added to furan-2,2-yl(diphenyl)methanol (25 mg, 0.10 mmol, 1 equiv) in 1.5 mL of *t*-BuOH and 0.3 mL H_2O. The resulting reaction mixture was treated with trifluoroacetic acid (0.4 μL, 0.005 mmol, 0.05 equiv) and heated to 80 °C for 43 h. The reaction was then quenched with 1.5 mL of saturated aqueous sodium bicarbonate, diluted with 3 mL H_2O, and extracted with diethyl ether (3×7 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography to afford cyclopentenone **32** (16 mg, 64%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (dd, J=5.8, 2.5 Hz, 1H), 7.49–7.40 (m, 2H), 7.40–7.27 (m, 6H), 7.16–7.07 (m, 2H), 6.43 (dd, J=5.8, 1.3 Hz, 1H), 5.54 (dt, J=7.9, 1.9 Hz, 1H), 1.59 (d, J=8.5 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.9, 161.7, 140.5, 139.6, 134.7, 129.9, 128.8, 128.6, 128.5, 127.7, 127.5, 78.8, 65.7; IR (thin film, cm^{-1}) 3418, 3059, 2983, 1705, 1044, 697; HRMS (ESI) m/z 273.0881 (273.0891 calcd for $C_{17}H_{14}NaO_2^+$[MNa]$^+$).

*4.3.5. 4-Hydroxy-4-methyl-5-phenylcyclopent-2-en-1-one (**33**).* According to general procedure **B** Dy(OTf)$_3$ (8.1 mg,

0.013 mmol, 0.1 equiv) was added to 5-methylfuran-2-yl(phenyl) methanol (25 mg, 0.132 mmol, 1 equiv) in 1.5 mL of *t*-BuOH and 0.3 mL H_2O. The resulting reaction mixture was treated with trifluoroacetic acid (0.6 μL, 0.007 mmol, 0.05 equiv) and heated to 80 °C for 15.5 h. The reaction was then quenched with 1.5 mL of saturated aqueous sodium bicarbonate, diluted with 3 mL H_2O, and extracted with diethyl ether (3×7 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography to afford cyclopentenone **33** (10 mg, 40%) as an oil. Spectral data for **33** were consistent with those previously reported and was found to have a 5:1 ratio of diastereomers.[15]

*4.3.6. 4-(2-Hydroxy-5-oxocyclopent-3-en-1-yl)benzonitrile (**34**).* According to the general procedure **B** $Dy(OTf)_3$ (7.6 mg, 0.013 mmol, 0.1 equiv) was added to 4-(furan-2-yl(hydroxy) methyl)benzonitrile (25 mg, 0.125 mmol, 1 equiv) in 1.5 mL of *t*-BuOH and 0.3 mL H_2O. The resulting reaction mixture was treated with trifluoroacetic acid (0.5 μL, 0.006 mmol, 0.05 equiv) and heated to 80 °C for 18 h. The reaction was then quenched with 1.5 mL of saturated aqueous sodium bicarbonate, diluted with 3 mL H_2O and extracted with diethyl ether (3×7 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography to afford cyclopentenone **34** (18 mg, 72%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (dd, J=5.8, 2.1 Hz, 1H), 7.62 (d, J=8.2 Hz, 2H), 7.28 (d, J=8.2 Hz, 2H), 6.36 (dd, J=5.8, 1.3 Hz, 1H), 5.01 (s, 1H), 3.55 (d, J=3.0 Hz, 1H), 2.66 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ=203.5, 161.8, 142.2, 134.3, 132.6, 129.2, 128.1, 118.5, 111.3, 105.0, 61.8 IR (thin film, cm^{-1}) 3537, 3057, 2917, 2849, 2228, 1693, 1104; HRMS (ESI) m/z 222.0523 (222.0531 calcd for $C_{12}H_9NNaO_2^+$[MNa]$^+$).

4.4. 2-Butyl-4-hydroxycyclopent-2-en-1-one (35)

4-Hydroxy-5-butylcyclopent-2-enone (25 mg, 0.162 mmol) was adsorbed on alumina (850 mg, Brockman grade III) for 23 h and eluted with 4:1 benzene/diethyl ether, which was concentrated in vacuo to afford cyclopentenone **35** (25 mg, 100%) as an oil. Spectral data matched literature precedent.[16]

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