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Domino Michael–Michael and Aldol–Aldol Reactions: Diastereoselective Synthesis of Functionalized Cyclohexanone Derivatives Containing Quaternary Carbon Center

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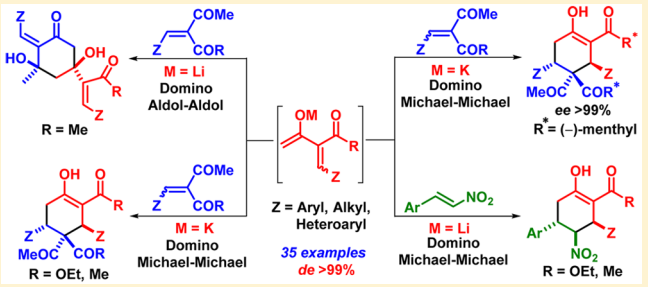
Supporting Information

ABSTRACT: A simple strategy for the synthesis of highly functionalized cyclohexanone derivatives containing an all-carbon quaternary center from α-(aryl/alkyl)methylidene-β-keto esters or β-diketones via a K-enolate mediated domino Michael–Michael reaction sequence with moderate to good yield and excellent diastereoselectivity (de > 99%) is described. Interestingly, Li-base mediated reaction of α-arylmethylidene-β-diketones affords functionalized 3,5-dihydroxy cyclohexane derivatives as the kinetically controlled products via a domino aldol–aldol reaction sequence with excellent diastereoselectivity. Li-enolates of the β-keto esters or β-diketones undergo facile domino Michael–Michael reaction with nitro-olefins to afford the corresponding nitrocyclohexane derivatives in good yields and excellent diastereoselectivity (de > 99%). The formation of the products and the observed stereoselectivity were explained by plausible mechanisms and supported by extensive computational study. An asymmetric version of the protocol was explored with (*L*)-menthol derived nonracemic substrates, and the corresponding nonracemic cyclohexanone derivatives containing an all-carbon quaternary center were obtained with excellent stereoselectivity (de, ee > 99%).



INTRODUCTION

Stereoselective creation of a quaternary carbon center is a demanding task and has drawn significant attention to the synthetic organic chemists over the decades.[1−3] Several attractive strategies have been introduced in the literature to achieve such quaternary carbon centers including metal and Lewis acid catalyzed reactions,[4] organocatalytic reactions,[5] enolate reactions,[6] rearrangement reactions,[7] etc. Cyclohexane skeletons containing a quaternary carbon center, especially an all-carbon quaternary center, are prevalent in many natural products as well as other biologically important compounds.[8] Considering structural diversity and stereoselectivity aspects, development of simple and efficient protocols for the construction of cyclohexane ring systems containing a quaternary carbon center is very desirable.[9] In this context, domino reactions made a significant contribution for the stereoselective construction of complex structural assemblies via single-pot multistep operations.[10]

In continuation of our research activities in enolate[11] and dianion[12] chemistry, recently, we have reported a simple strategy for the synthesis of highly functionalized 2,6-disubstituted piperidine ring systems via a one-pot two-step domino imino-aldol–aza-Michael reaction protocol using N-activated imines as the electrophiles.[13] We anticipated that, employing an activated olefin instead of an imine as the Michael acceptor, the strategy would lead to the formation of functionalized cyclohexanone derivatives via a domino inter- and intramolecular Michael reaction sequence. Applications of a domino Michael–Michael reaction sequence for the synthesis of carbacycles and heterocycles are known in the literature.[14] We have successfully developed a simple strategy for the synthesis of functionalized cyclohexanone derivatives containing an all-carbon quaternary center with structural diversity and excellent diastereoselectivity employing domino Michael–Michael/aldol–aldol reaction protocols. It is worth mentioning that the basic skeleton of such a type of substituted cyclohexanone derivative closely resembles to that of bilinderone, a natural product recently isolated from the root of *Lindera aggregate*.[15,16] Herein, we report our results in detail as an article.

RESULTS AND DISCUSSION

In order to study our proposed domino Michael–Michael reaction sequence, the precursor compounds α-arylmethylidene-β-keto esters (**1a–h**) were synthesized following a reported procedure.[17] Initially, for operational simplicity, another equivalent of the substrate itself was utilized as the electrophile. We expected that the substrate would react with its enolate to produce the desired cyclohexanone derivatives (Scheme 1). To study the viability of our approach, first, the enolate **2a**, generated from the compound **1a** by treatment with LDA at −50 °C, was allowed to react with one more equivalent

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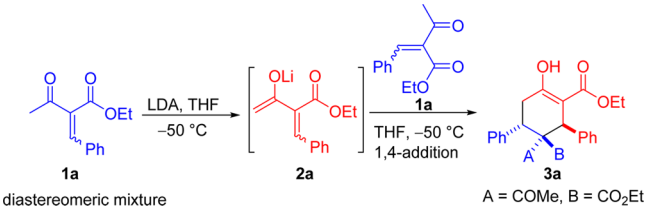
Scheme 1. Synthesis of Functionalized Cyclohexanone Derivatives



of **1a** at the same temperature. However, the progress of the reaction was found to be very slow.

To optimize the reaction conditions, a number of bases at different temperatures were screened.[18] Among the bases studied, KO*t*Bu was found to be the best in THF at 0 °C to produce the corresponding cyclohexanone derivative **3a** in 67% overall yield as a single diastereomer from **1a**. The generalization of the strategy was made by studying other substrates **1b−h** (Scheme 2).

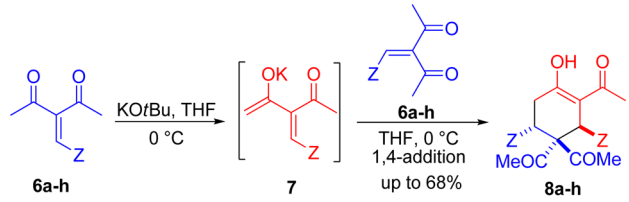
The cyclohexanone derivatives **3b−h** were obtained in good yields with excellent diastereoselectivity (de > 99%), as shown in Table 1. Compounds **3a−h** were found to exist in enol forms with 2,6-*trans* relative stereochemistry. The structures of **3a−h** were confirmed by the NMR and X-ray crystallographic data of **3a**,**e**,**h**.[19]

Next, the methodology was extended for *β*-diketone compounds **6**. When *α*-phenylmethylidene-*β*-diketone **6a** was treated with KO*t*Bu following identical reaction conditions as shown in Scheme 3, the corresponding cyclohexanone product **8a** was obtained in 65% yield as a single diastereomer.

For the generalization, other diketonic substrates **6b−h** were studied, and the results are shown in Table 2. The products **8** were found to exist in enol forms with 2,6-*trans* relative stereochemistry, as confirmed by the NMR and X-ray crystallographic data of **8a**,**c**,**g**.[19]

The proposed mechanism for the described reaction sequences (Schemes 2 and 3) is shown in Scheme 4. The enolate **2a**, generated from the starting substrate **1a**, undergoes 1,4-Michael addition with another molecule of **1a** to form two possible anionic intermediates **9a**,**b**, depending on the geometry of the double bond. Further intramolecular Michael addition of the intermediate **9a** from the *si*-face of the double bond produces the corresponding cyclohexanone derivative **3a** with 2,6-*trans*-stereochemistry exclusively through the transition state **10**. Formation of 2,6-diaxial *cis*-**3a** or 2,6-

Scheme 3. Cyclohexanone Derivatives from Diketonic Substrates



6a: Z = Ph; **6b**: Z = 4-MeC$_6$H$_4$; **6c**: Z = 4-OMeC$_6$H$_4$; **6d**: Z = 2-BrC$_6$H$_4$; **6e**: Z = 4-ClC$_6$H$_4$; **6f**: Z = 4-CNC$_6$H$_4$; **6g**: Z = Cyclohexyl; **6h**: Z = Naphthyl.

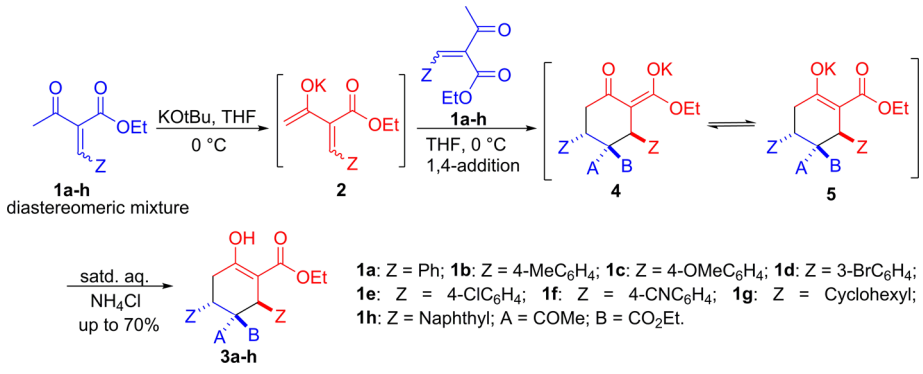
diequatorial *cis* isomer **12** via the transition state **11** was not observed at all. Probably due to 1,3-diaxial interaction in the case of *cis*-**3a** and allylic type of interaction in the case of **12**, these two products get destabilized and are not formed at all. Identical intramolecular Michael addition of the intermediate **9b** from the *re*-face of the double bond produces the same 2,6-*trans*-cyclohexanone **3a**.

Our mechanistic proposal was further supported by computational studies.[20] The *trans* products **3a** and **8a** were found to be more stable than the corresponding *cis* isomers by 7.87 and 7.88 kcal mol^{-1}, respectively.[20] To study the effect of the countercations of the bases on the reactivity of the substrates and the selectivity of the products when *β*-keto ester **1a** was treated with different bases (LDA, KO*t*Bu, NaH, and NaO*t*Bu), compound **3a** was produced as the only product in diastereomerically pure form in all the cases.

However, the scenario was entirely different for the *β*-diketone substrate **6a**. When **6a** was treated with LDA at −50 °C, along with the expected conjugate addition product **8a** (30%), another interesting product, 3,5-dihydroxy cyclohexanone **16a**, was also obtained in 35% yield (**8a**:**16a** ∼ 1:1) as a single diastereomer with 3,5-*cis* appendages, confirmed by the single-crystal X-ray studies (Scheme 5).[19]

Possible formation of **16a** could be explained by a one-pot four-step domino sequence involving enolization, intermolecular aldol reaction, followed by enolate isomerization,[21] and finally intramolecular aldol reaction.[22] The generalization of this domino aldol−aldol strategy was made by using other substrates **6b−d**, and the results are shown in Table 3. Compounds of the type **16** with a tertiary 3-hydroxy group and *cis*-3,5-dihydroxy derivatives are very important and found in the partial structure of natural products and bioactive molecules.[23]

Scheme 2. Domino Michael−Michael Reaction: Synthesis of Cyclohexanone Derivative Containing an All-Carbon Quaternary Center



1a: Z = Ph; **1b**: Z = 4-MeC$_6$H$_4$; **1c**: Z = 4-OMeC$_6$H$_4$; **1d**: Z = 3-BrC$_6$H$_4$; **1e**: Z = 4-ClC$_6$H$_4$; **1f**: Z = 4-CNC$_6$H$_4$; **1g**: Z = Cyclohexyl; **1h**: Z = Naphthyl; A = COMe; B = CO$_2$Et.

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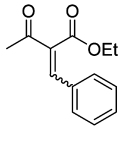
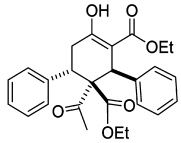
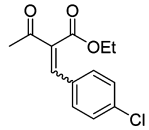
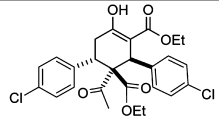
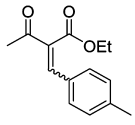
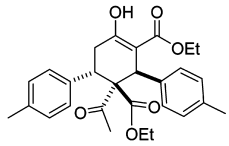
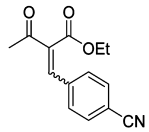
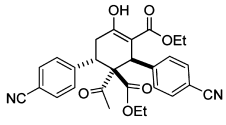
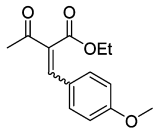
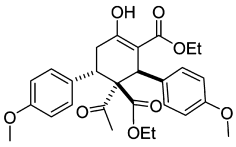
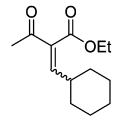
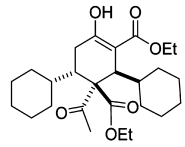
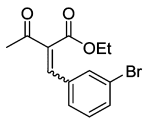
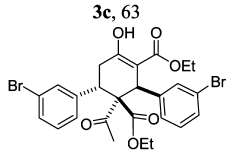
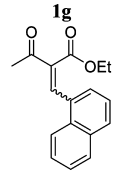
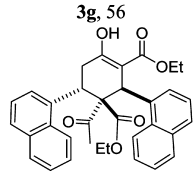
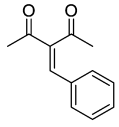
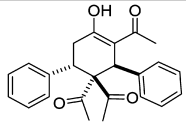
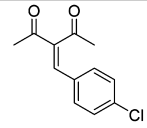
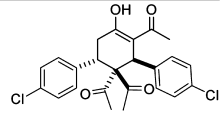
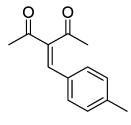
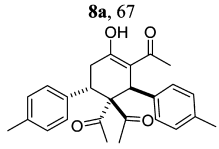
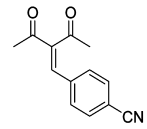
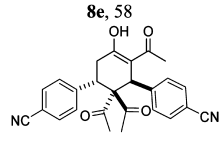
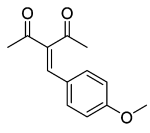
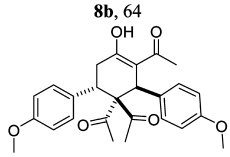
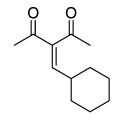
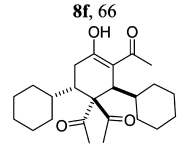
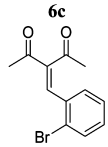
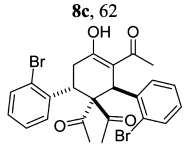
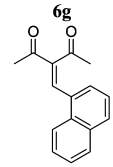
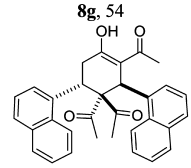
Table 1. Synthesis of Cyclohexanone Derivatives Containing an All-Carbon Quaternary Center via Domino Michael−Michael Reaction

β-Keto ester **1**	Cyclohexanone **3**[a], Yield (%)	β-Keto ester **1**	Cyclohexanone **3**[a], Yield (%)
			
1a	**3a**, 67	**1e**	**3e**, 64
			
1b	**3b**, 66	**1f**	**3f**, 65
			
1c	**3c**, 63	**1g**	**3g**, 56
			
1d	**3d**, 68	**1h**	**3h**, 70

[a]Product was obtained as a single diastereomer in all the cases.

Table 2. Synthesis of Cyclohexanone Derivatives Containing an All-Carbon Quaternary Center from Diketonic Substrates via Domino Michael−Michael Reaction

β-diketone **6**	Cyclohexanone **8**[a], Yield (%)	β-diketone **6**	Cyclohexanone **8**[a], Yield (%)
			
6a	**8a**, 67	**6e**	**8e**, 58
			
6b	**8b**, 64	**6f**	**8f**, 66
			
6c	**8c**, 62	**6g**	**8g**, 54
			
6d	**6d**, 68	**6h**	**8h**, 67

[a]Product was obtained as a single diastereomer in all the cases.

At this stage, we were perplexed to explain the formation of both the products (**8** and **16**) with a suitable mechanism. Computational studies revealed that the compound **8a** is more stable than the compound **16a** by 18.7 kcal mol^{-1} (Figure 1).

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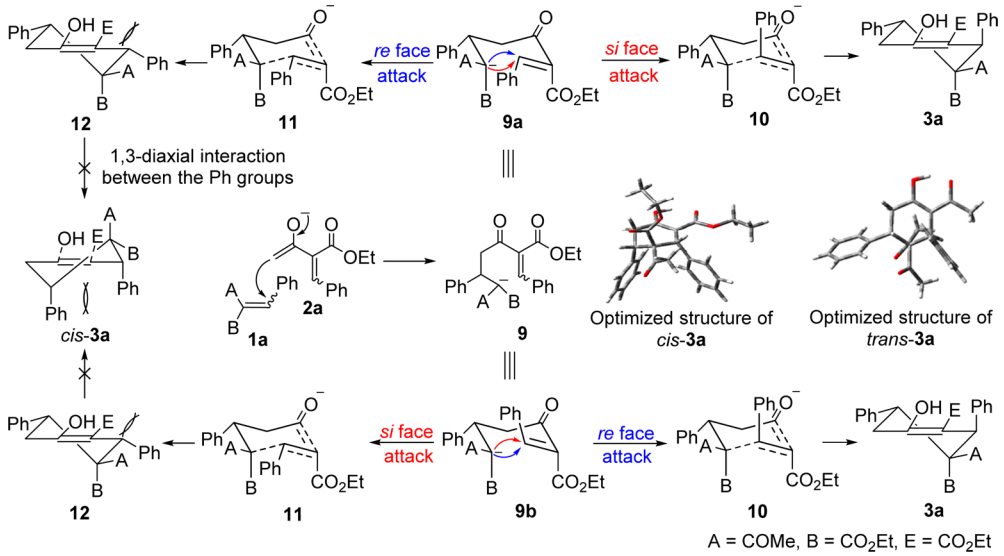
Scheme 4. Mechanism for Domino Michael–Michael Reactions



Scheme 5. Domino Michael–Michael and Aldol–Aldol Reactions

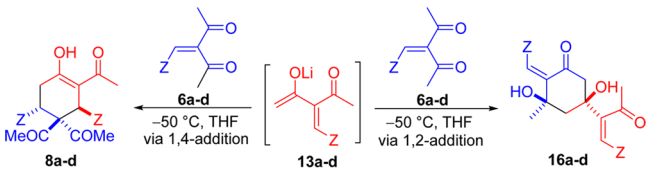
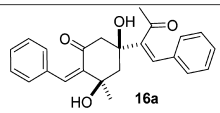
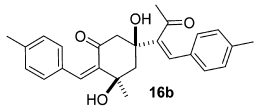
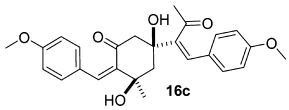
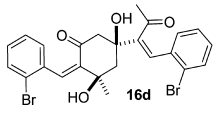


Table 3. Synthesis of *cis*-3,5-Dihydroxy Cyclohexanone Derivatives Containing Quaternary Carbon Centers

Entry	13	Time (h)	8[a]	Yield (%)	16[a]	Yield (%)
1	**13a**	18.0	**8a**	30	 **16a**	35
2	**13b**	22.0	**8b**	31	 **16b**	38
3	**13c**	24.0	**8c**	29	 **16c**	34
4	**13d**	24.0	**8d**	36	 **16d**	38

[a]Product was obtained as a single diastereomer in all the cases.

It is apparent from the computational result that the compound **16a** should be formed under kinetic conditions and **8a** must be formed under thermodynamic conditions. It is exactly the case here: when the temperature of the reaction was increased to room temperature, the compound **8a** was obtained as the only product under thermodynamic conditions. As expected, on lowering the temperature (to −78 °C from −50 °C), **16a** was formed in a relatively higher proportion (**16a:8a** = 1.5:1) under kinetic conditions (Figure 2).

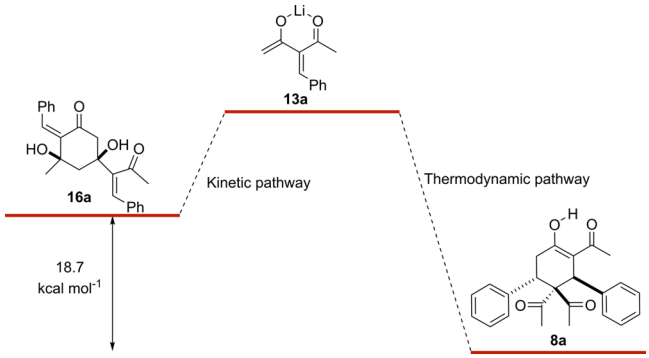


Figure 1. Energy profile for the thermodynamically and kinetically controlled products.

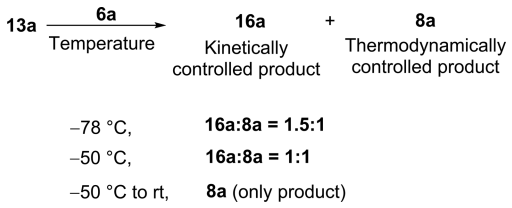


Figure 2. Kinetically vs thermodynamically controlled conditions.

The formation of a single diastereomer of the product **16a** was rationalized by a plausible mechanism, as shown in Scheme 6. At first, the Li-enolate **13a** was reacted with another molecule of **6a** in 1,2-fashion to obtain the intermediate **14**, which was converted to **15** via another enolization step. Finally, **15** underwent an intramolecular 1,2-addition from the *re*-face of the double bond to afford the end product **16a** as a single diastereomer with *cis* orientation of the −OH groups. The *cis* product was getting stabilized via an intramolecular hydrogen bonding. The other product *trans*-**16a** became unstable due to the absence of such a type of hydrogen bonding and was not observed at all. Further evidence in support of the relative stability of **16a** was provided by computational analysis, and the *cis* product **16a** was found to be more stable by 5.87 kcal mol^{-1} in comparison to the corresponding *trans* isomer (*trans*-**16a**).[20]

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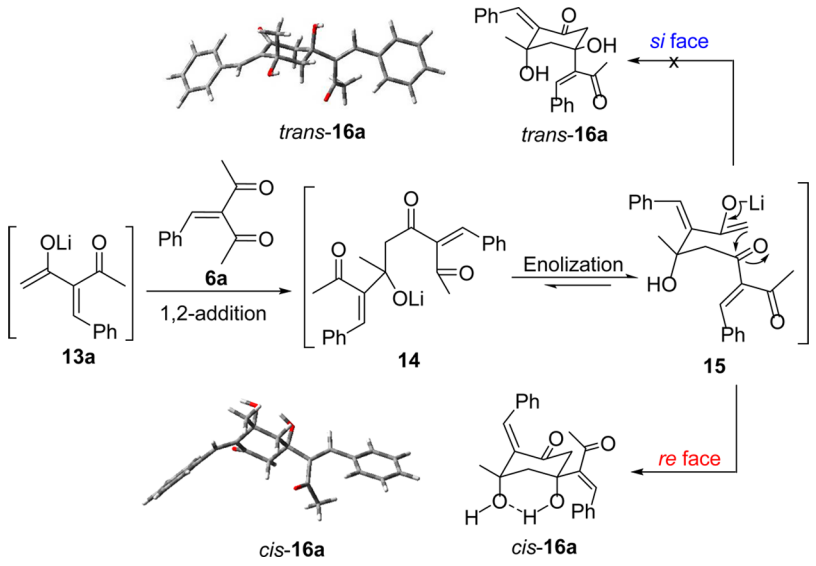
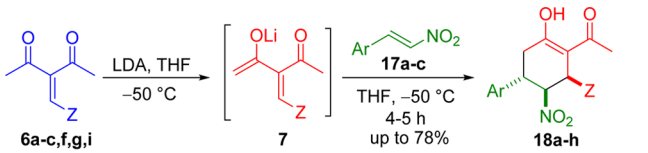
Scheme 6. Mechanism for Domino Aldol−Aldol Reaction



Scheme 7. Domino Michael−Michael Reaction with Nitro-olefins

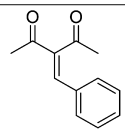
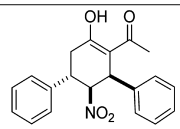
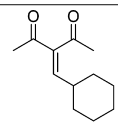
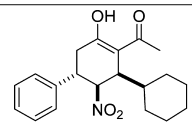
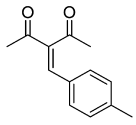
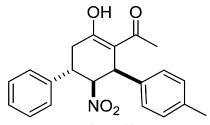
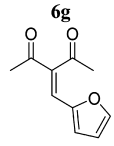
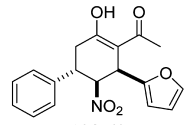
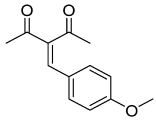
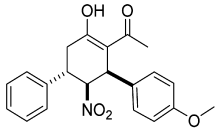
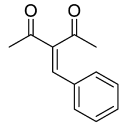
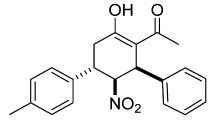
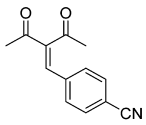
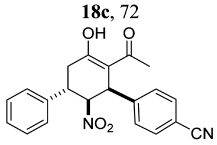
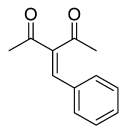
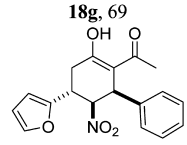


18a: Ar = Ph, Z = Ph; **18b**: Ar = Ph, Z = 4-MeC$_6$H$_4$; **18c**: Ar = Ph, Z = 4-OMeC$_6$H$_4$; **18d**: Ar = Ph, Z = 4-CNC$_6$H$_4$; **18e**: Ar = Ph, Z = cyclohexyl; **18f**: Ar = ph, Z = 2-furyl; **18g**: Ar = 4-MeC$_6$H$_4$, Z = Ph; **18h**: Ar = 2-furyl, Z = Ph.

To demonstrate the applicability of our protocol as a general methodology, the domino strategy was extended to other activated olefins (**17**) as the electrophiles. When the precursor compounds α-(aryl/alkyl)methylidene-β-diketones **6a−i** were treated with LDA as the base at −50 °C, followed by addition of the nitro-olefins **17a−c**, the functionalized nitrocyclohexanone derivatives **18a−h** were obtained with good yields as a single diastereomer (Scheme 7), and the results are shown in Table 4. Stereoselective synthesis of structurally similar nitrocyclohexanone compounds are known in the literature; however, they suffer from longer reaction times (up to 3 days in particular cases), costly catalysts, and sequential/stepwise addition/purification of the reagents/intermediates.[24]

The described methodology also works well with the other precursor compounds α-arylmethylidene-β-keto esters (**1a,c,d,i**) and furnished nitrocyclohexanone derivatives **19a−**

Table 4. Synthesis of Nitrocyclohexanone Derivatives via Domino Michael−Michael Reaction

β-diketone **6**	Nitrocyclohexanone **18**[a], Yield (%)	β-diketone **6**	Nitrocyclohexanone **18**[a], Yield (%)
 **6a**	 **18a**, 74	 **6g**	 **18e**, 75
 **6b**	 **18b**, 62	 **6i**	 **18f**, 68
 **6c**	 **18c**, 72	 **6a**	 **18g**, 69
 **6f**	 **18d**, 78	 **6a**	 **18h**, 74

[a]Product was obtained as a single diastereomer in all the cases.

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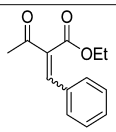
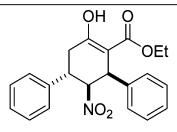
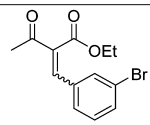
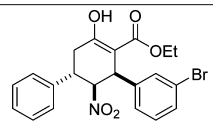
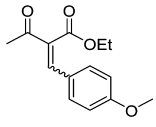
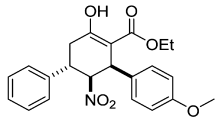
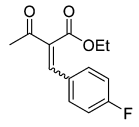
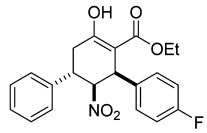
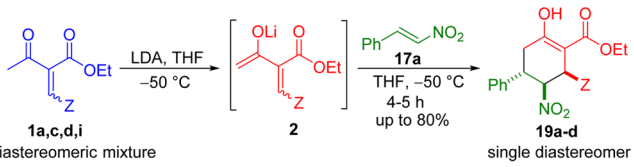
Table 5. Synthesis of Nitrocyclohexanone Derivatives via Domino Michael−Michael Reaction of α-Arylmethylidene-β-keto Esters and β-Nitrostyrene

β-Keto ester **1**	Nitrocyclohexanone **19**[a], Yield (%)[b]	β-Keto ester **1**	Nitrocyclohexanone **19**[a], Yield (%)[b]
 **1a**	 **19a**, 70	 **1d**	 **19c**, 73
 **1c**	 **19b**, 78	 **1i**	 **19d**, 80

[a]Product was obtained as a single diastereomer in all the cases.

Scheme 8. Domino Michael−Michael Reaction of β-Nitrostyrene with α-Arylmethylidene-β-keto Esters



19a: Z = Ph; **19b**: Z = 4-OMeC$_6$H$_4$; **19c**: Z = 3-BrC$_6$H$_4$; **19d**: Z = 4-FC$_6$H$_4$

d with good yields as a single diastereomer (Scheme 8, Table 5). The relative stereochemistry at the 4-, 5-, and 6-carbon centers of nitrocyclohexanone derivatives were unambiguously determined by single-crystal X-ray analysis.[19] Needless to say, such nitro-cylohexanes (**18** and **19**) are of immense synthetic utility.[25]

The synthetic potential of the strategy was further demonstrated by the synthesis of nonracemic cyclohexanone derivatives with an all-carbon quaternary center. For this purpose, the chiral precursor substrates **20a−c** were prepared from the corresponding enantiopure menthyl ester.[26] Next, the chiral substrate **20a** was reacted under our reaction conditions, and to our great pleasure, the corresponding chiral cyclohexanone derivative **22a** (Scheme 9, Table 6) was obtained in high yield with excellent diastereoselectivity (de > 99%). The strategy was generalized with other substrates **20b,c**, and the corresponding cyclohexanone derivatives **22b,c** were obtained in high yields, although they were found to exist as a mixture of rotamers in solution at room temperature. The structures of **22b,c** were confirmed by X-ray crystallographic analysis (Figure 3).[19] On the basis of low-temperature ^{1}H NMR studies (−40 to 40 °C), we could conclude that compounds **22b,c** indeed exist as a mixture of rotamers in solution.[27]

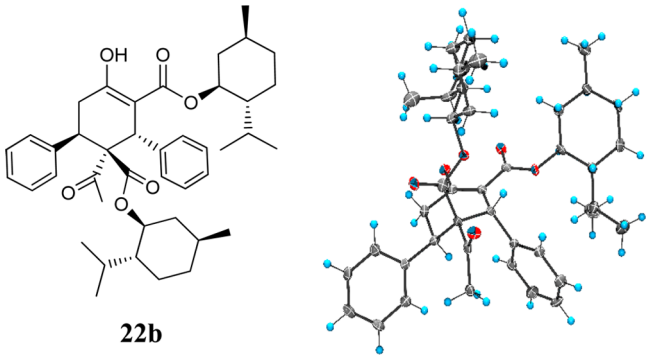
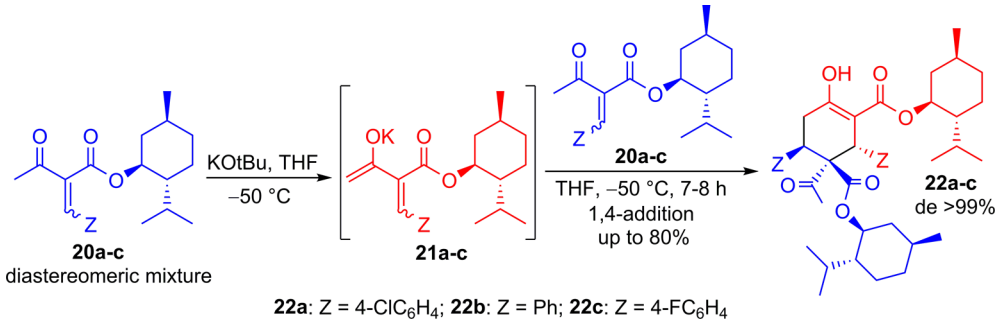


Figure 3. X-ray crystal structure of **22b** (50% ellipsoid contour percent probability).

CONCLUSION

In conclusion, we have developed a simple strategy for the construction of highly functionalized cyclohexanone derivatives containing an all-carbon quaternary center via domino Michael−Michael reaction protocols starting from α-(aryl/alkyl)methylidene-β-keto ester or β-diketone precursors in the presence of KO*t*Bu as the base. The similar reaction of α-arylmethylidene-β-diketones in the presence of LDA as the base produces another important class of functionalized 3,5-dihydroxy cyclohexane derivatives as the kinetically controlled

Scheme 9. Synthesis of Nonracemic Functionalized Cyclohexanone Derivatives



22a: Z = 4-ClC$_6$H$_4$; **22b**: Z = Ph; **22c**: Z = 4-FC$_6$H$_4$

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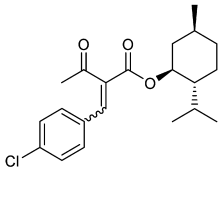
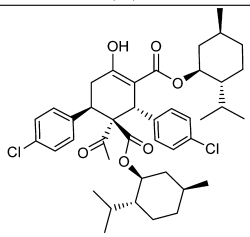
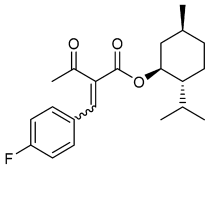
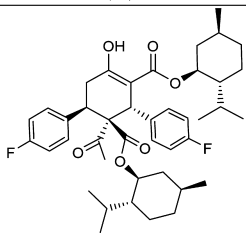
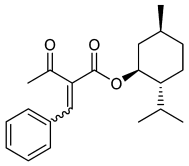
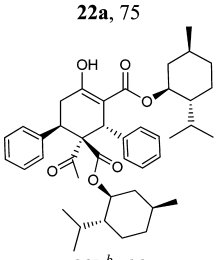
Table 6. Synthesis of Nonracemic Cyclohexanone Derivatives Containing an All-Carbon Quaternary Stereocenter via Domino Michael−Michael Reaction

β-Keto ester **20**	Cyclohexanone **22**[a], Yield (%)	β-Keto ester **20**	Cyclohexanone **22**[a], Yield (%)
 **20a**	 **22a**, 75	 **20c**	 **22c**[b], 80
 **20b**	 **22b**[b], 66		

[a]Product was obtained as a single diastereomer in all the cases. [b]Product exists as a mixture of rotamers in solution.

products via a domino aldol−aldol reaction sequence. This strategy has been generalized with a number of substrates with aromatic/aliphatic substituents and nonracemic substrates. In all the cases, the products were obtained as a single diastereomer. The structure and the relative stereochemistry of the products were confirmed by X-ray crystallographic data of a number of compounds. Thermodynamic and kinetic control of the reaction pathway and the formation of the products have been rationalized by plausible mechanisms and supported by computational studies. Further synthetic and mechanistic studies are in progress.

EXPERIMENTAL SECTION

General Experimental. Analytical thin-layer chromatography (TLC) was carried out using silica gel 60 F_{254} precoated plates. Visualization was accomplished with a UV lamp or I_2 stain. Silica gel 230−400 mesh size was used for flash column chromatography using the combination of ethyl acetate and petroleum ether as eluent. Unless noted, all reactions were carried out in oven-dried glassware under an atmosphere of nitrogen/argon using anhydrous solvents. Where appropriate, all reagents were purified prior to use following the guidelines of Perrin and Armerego.[28] All commercial reagents were used as received. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 400 MHz/500 MHz. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethyl silane (δ 0.00). ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), doublet of doublet (dd), triplet (t), quartet (q), multiplet (m). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 100 MHz/125 MHz. Mass spectra (MS) were obtained using an ESI mass spectrometer (TOF). IR spectra were recorded in KBr for solids. Melting points were determined using a hot stage apparatus and are uncorrected. Optical rotations were measured using a 2.0 mL cell with a 1.0 dm path length and are reported as $[\alpha]_D^{25}$ (c in g per 100 mL solvent) at 25 °C.

Experimental Procedures and Analytical Data. *General Procedure for the Synthesis of 2,6-Disubstituted Cyclohexene-3-carboxylates* ***3*** *(Table 1).* To a suspension of KO*t*Bu (33.8 mg, 0.3 mmol) in 1.0 mL of dry THF at 0 °C was slowly added compound **1a−h** (0.25 mmol) dissolved in 1.0 mL of dry THF, and the mixture was stirred for 3−4 h at the same temperature. After completion of the reaction, monitored by TLC (20% ethyl acetate in petroleum ether), it was quenched with saturated aqueous ammonium chloride solution. The aqueous layer was extracted with ethyl acetate (3 × 5.0 mL). The combined organic extract was washed with brine and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the crude reaction mixture was purified by flash column chromatography on silica gel (230−400 mesh) using 5% ethyl acetate in petroleum ether to afford the pure cyclohexanone products **3a−h**.

*Diethyl 1-Acetyl-4-hydroxy-2,6-diphenylcyclohex-3-ene-1,3-dicarboxylate (**3a**).* The general procedure described above was followed when **1a** (54.5 mg, 0.25 mmol) was reacted in the presence of 33.6 mg (0.3 mmol) of KO*t*Bu at 0 °C for 3.0 h to afford **3a** (36.5 mg, 67% yield) as a white solid, mp 124−126 °C; R_f 0.42 (30% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3428, 3030, 2987, 2924, 1714, 1661, 1494, 1453, 1411, 1371, 1352, 1328, 1311, 1292, 1264, 1217, 1099, 1070, 1047, 1016, 919, 831, 758, 736, 707; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (t, 3H, J = 7.4 Hz), 1.19 (t, 3H, J = 7.4 Hz), 1.69 (s, 3H), 2.83 (dd, 1H, J = 10.9, 18.9 Hz), 2.94 (dd, 1H, J = 6.3, 18.9 Hz), 3.93−4.06 (m, 3H), 4.07−4.15 (m, 1H), 4.25−4.33 (m, 1H), 4.69 (s, 1H), 7.16−7.29 (m, 10H), 12.37 (s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 13.8, 13.9, 29.8, 34.6, 39.6, 45.5, 60.6, 61.5, 67.6, 100.3, 127.1, 127.4, 127.7, 128.2, 129.7, 130.2, 139.9, 140.3, 170.7, 170.8, 171.4, 203.0; HRMS (ESI) calcd for $C_{26}H_{29}O_6$ (M + H$^+$): 437.1964, found: 437.1968.

*Diethyl 1-Acetyl-4-hydroxy-2,6-di-p-tolylcyclohex-3-ene-1,3-dicarboxylate (**3b**).* The general procedure described above was followed when **1b** (58.2 mg, 0.25 mmol) was reacted in the presence of 33.6 mg (0.3 mmol) of KO*t*Bu at 0 °C for 3.0 h to afford **3b** (38.4 mg, 66% yield) as a white solid, mp 125−127 °C; R_f 0.41 (30% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3425, 3025, 2977, 2924, 2857, 1709, 1662, 1624, 1515, 1505, 1444, 1352, 1367, 1356, 1327, 1310, 1291, 1260, 1219, 1193, 1176, 1117, 1094, 1068, 1052, 1020, 923, 866, 848, 829, 741, 722; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.0 (t, 3H, J = 7.1 Hz), 1.18 (t, 3H, J = 7.1 Hz), 1.71 (s, 3H), 2.25 (s, 3H), 2.29 (s, 3H), 2.75−2.88 (m, 2H), 3.89−3.94 (m, 1H), 3.97−4.02 (m, 2H), 4.06−4.14 (m, 1H), 4.24−4.32 (m, 1H), 4.61 (s, 1H), 6.98−7.06 (m, 6H), 7.13 (d, 2H, J = 8.0 Hz), 12.32 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 13.8, 21.0, 29.6, 34.6, 38.9, 45.1, 60.4, 61.3, 67.6, 100.3, 128.4, 128.9, 129.6, 129.9, 136.4, 136.7, 136.9, 137.0, 170.5, 170.8, 171.3, 202.9; HRMS (ESI) calcd for $C_{28}H_{33}O_6$ (M + H$^+$): 465.2277, found: 465.2279.

*Diethyl 1-Acetyl-4-hydroxy-2,6-bis(4-methoxyphenyl)cyclohex-3-ene-1,3-dicarboxylate (**3c**).* The general procedure described above

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was followed when **1c** (62.1 mg, 0.25 mmol) was reacted in the presence of 33.6 mg (0.3 mmol) of KO*t*Bu at 0 °C for 3.5 h to afford **3c** (39.1 mg, 63% yield) as a white solid, mp 102−105 °C; R_f 0.37 (30% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3420, 2980, 2937, 2840, 1710, 1658, 1610, 1513, 1466, 1423, 1400, 1364, 1296, 1251, 1220, 1180, 1114, 1096, 1065, 1032, 870, 828, 806; ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (t, 3H, J = 7.1 Hz), 1.21 (t, 3H, J = 7.1 Hz), 1.73 (s, 3H), 2.75−2.90 (m, 2H), 3.75 (s, 3H), 3.79 (s, 3H), 3.87−3.92 (m, 1H), 4.0−4.06 (m, 2H), 4.08−4.16 (m, 1H), 4.26−4.34 (m, 1H), 4.63 (s, 1H), 6.75 (d, 2H, J = 9.5 Hz), 6.80 (d, 2H, J = 8.8 Hz), 7.07 (d, 2H, J = 8.8 Hz) 7.20 (d, 2H, J = 8.8 Hz), 12.34 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 13.8, 29.7, 34.7, 38.7, 44.8, 55.1, 60.3, 60.5, 61.2, 61.4, 67.7, 100.5, 113.0, 113.5, 130.6, 131.3, 131.9, 132.3, 158.5, 158.8, 170.4, 170.9, 171.4, 203.1; HRMS (ESI) calcd for $C_{28}H_{33}O_8$ (M + H^+): 497.2175, found: 497.2174.

*Diethyl 1-Acetyl-2,6-bis(3-bromophenyl)-4-hydroxycyclohex-3-ene-1,3-dicarboxylate (**3d**).* The general procedure described above was followed when **1d** (74.5 mg, 0.25 mmol) was reacted in the presence of 33.6 mg (0.3 mmol) of KO*t*Bu at 0 °C for 3.0 h to afford **3d** (50.7 mg, 68% yield) as a white solid, mp 170−174 °C; R_f 0.4 (30% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3431, 3059, 2974, 2924, 1736, 1710, 1650, 1612, 1475, 1427, 1408, 1385, 1368, 1352, 1284, 1256, 1221, 1066, 1048, 1022, 997, 894, 825, 781, 718; ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (t, 3H, J = 7.1 Hz), 1.24 (t, 3H, J = 7.3 Hz), 1.84 (s, 3H), 2.75−2.91 (m, 2H), 3.82−3.88 (m, 1H), 3.98−4.10 (m, 2H), 4.12−4.21 (m, 1H), 4.27−4.37 (m, 1H), 4.61 (s, 1H), 7.06−7.24 (m, 4H), 7.28−7.33 (m, 3H), 7.37−7.45 (m, 3H), 12.36 (s, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 13.7, 13.8, 29.7, 33.8, 39.0, 44.9, 60.7, 61.8, 67.3, 99.5, 121.5, 122.2, 127.9, 129.1, 129.4, 129.6, 130.2, 130.6, 132.5, 133.2, 141.6, 142.6, 170.3, 170.4, 170.9, 201.6; HRMS (ESI) calcd for $C_{26}H_{27}Br_2O_6$ (M + H^+): 593.0174, found: 593.0170.

*Diethyl 1-Acetyl-2,6-bis(4-chlorophenyl)-4-hydroxycyclohex-3-ene-1,3-dicarboxylate (**3e**).* The general procedure described above was followed when **1e** (63.2 mg, 0.25 mmol) was reacted in the presence of 33.6 mg (0.6 mmol) of KO*t*Bu at 0 °C for 3.0 h to afford **3e** (40.4 mg, 64% yield) as a white solid, mp 182−184 °C; R_f 0.42 (30% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3450, 2984, 2925, 1727, 1703, 1657, 1492, 1444, 1400, 1358, 1326, 1287, 1261, 1228, 1198, 1173, 1090, 1065, 1049, 1014, 874, 841, 820, 734; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, 3H, J = 7.1 Hz), 1.15 (t, 3H, J = 7.6 Hz), 1.74 (s, 3H), 2.69−2.83(m, 2H), 3.75−3.79 (m, 1H), 3.93−4.0 (m, 2H), 4.01−4.11 (m, 1H), 4.20−4.30 (m, 1H), 4.58 (s, 1H), 7.01 (d, 2H, J = 8.6 Hz), 7.09−7.15 (m, 4H), 7.17−7.20 (m, 4H), 12.29 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 13.8, 29.8, 34.0, 38.9, 44.7, 60.7, 61.7, 67.5, 99.8, 127.8, 128.3, 130.8, 131.7, 132.9, 133.3, 137.8, 138.7, 170.4, 170.5, 171.0, 202.1; HRMS (ESI) calcd for $C_{26}H_{27}Cl_2O_6$ (M + H^+): 505.1184, found: 505.1187.

*Diethyl 1-Acetyl-2,6-bis(4-cyanophenyl)-4-hydroxycyclohex-3-ene-1,3-dicarboxylate (**3f**).* The general procedure described above was followed when **1f** (60.8 mg, 0.25 mmol) was reacted in the presence of 33.6 mg (0.3 mmol) of KO*t*Bu at 0 °C for 3.0 h to afford **3f** (39.5 mg, 65% yield) as a white solid, mp 250−252 °C; R_f 0.39 (30% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3450, 2924, 2853, 2227, 1704, 1658, 1625, 1504, 1463, 1399, 1292, 1262, 1226, 1195, 1172, 1096, 1066, 1050, 1019, 841; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, 3H, J = 6.8 Hz), 1.17 (t, 3H, J = 7.1 Hz), 1.82 (s, 3H), 2.81 (d, 2H, J = 8.8 Hz), 3.78 (t, 1H, J = 8.8 Hz), 3.93−4.02 (m, 2H), 4.06−4.15 (m, 1H), 4.23−4.32 (m, 1H), 4.67 (s, 1H), 7.18−7.21 (m, 2H), 7. 31 (d, 2H, J = 8.5 Hz), 7.44 (d, 2H, J = 8.6 Hz), 7.53 (d, 2H, J = 8.3 Hz), 12.34 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 13.8, 29.8, 33.5, 39.7, 45.3, 60.9, 62.1, 67.6, 99.1, 111.2, 111.6, 118.4, 118.5, 130.2, 131.3, 131.9, 144.3, 145.7, 170.0, 170.6, 170.7, 201.4; HRMS (ESI) calcd for $C_{28}H_{27}N_2O_6$ (M + H^+): 487.1869, found: 487.1866.

*Diethyl 1-Acetyl-2,6-dicyclohexyl-4-hydroxycyclohex-3-ene-1,3-dicarboxylate (**3g**).* The general procedure described above was followed when **1g** (56.1 mg, 0.25 mmol) was reacted in the presence of 33.6 mg (0.3 mmol) of KO*t*Bu at 0 °C for 4.0 h to afford **3g** (31.4 mg, 56% yield) as a white solid, mp 101−106 °C; R_f 0.44 (30% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3441, 2929, 2852, 1729, 1707, 1655, 1619, 1449, 1424, 1406, 1356, 1299, 1275, 1248, 1224, 1177, 1097, 1060, 1042, 1017, 917, 893, 841; ^1H NMR (400 MHz, $CDCl_3$) δ 0.70−0.74 (m, 1H), 0.92−1.17 (m, 9H), 1.24 (t, 3H, J = 7.1 Hz), 1.35 (t, 3H, J = 7.3 Hz), 1.62−1.73 (m, 12H), 2.10−2.22 (m, 1H), 2.24 (s, 3H), 2.26−2.31 (m, 1H), 3.12−3.14 (m, 1H), 4.03−4.12 (m, 1H), 4.14−4.25 (m, 2H), 4.30−4.38 (m, 2H), 12.26 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 14.1, 14.7, 26.5, 26.9, 27.3, 27.4, 27.8, 29.4, 31.1, 32.1, 35.7, 35.9, 38.6, 38.7, 40.9, 43.7, 44.1, 60.7, 61.4, 67.8, 99.3, 171.5, 172.2, 172.5, 204.1; HRMS (ESI) calcd for $C_{26}H_{41}O_6$ (M + H^+): 449.2907, found: 449.2903.

*Diethyl 1-Acetyl-4-hydroxy-2,6-di(naphthalen-1-yl)cyclohex-3-ene-1,3-dicarboxylate (**3h**).* The general procedure described above was followed when **1h** (67.1 mg, 0.25 mmol) was reacted in the presence of 33.6 mg (0.3 mmol) of KO*t*Bu at 0 °C for 3.0 h to afford **3h** (46.9 mg, 70% yield) as a white solid, mp 142−144 °C; R_f 0.36 (30% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3440, 3047, 2978, 2934, 1727, 1696, 1656, 1614, 1511, 1465, 1443, 1422, 1398, 1377, 1355, 1333, 1313, 1270, 1246, 1214, 1177, 1136, 1105, 1060, 1047, 1005, 909, 862, 841; ^1H NMR (400 MHz, $CDCl_3$) δ 0.67 (t, 3H, J = 7.1 Hz), 1.19 (t, 3H, J = 7.1 Hz), 1.56 (s, 3H), 3.03 (dd, 1H, J = 10.5, 19.0 Hz), 3.31 (dd, 1H, J = 6.1, 19.0 Hz), 3.78−3.87 (m, 1H), 3.90−3.98 (m, 1H), 4.22−4.30 (m, 1H), 4.33−4.41 (m, 1H), 4.99−5.04 (m, 1H), 6.22 (s, 1H), 7.32−7.36 (m, 1H), 7.43−7.50 (m, 2H), 7.53−7.59 (m, 3H), 7.63−7.70 (m, 2H), 7.74−7.83 (m, 4H), 8.08 (d, 1H, J = 8.8 Hz), 8.39 (d, 1H, J = 8.5 Hz), 12.39 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 13.4, 13.9, 28.0, 34.7, 35.4, 40.3, 60.4, 61.7, 68.6, 101.5, 122.3, 123.4, 124.9, 125.3, 125.4, 125.8, 126.0, 126.4, 127.2, 127.7, 128.3, 128.7, 129.3, 131.7, 133.1, 133.6, 133.9, 135.7, 137.2, 171.1, 171.3, 171.8, 205.5; HRMS (ESI) calcd for $C_{34}H_{33}O_6$ (M + H^+): 537.2277, found: 537.2277.

*General Procedure for the Synthesis of 2,6-Disubstituted-3-ene-triethanones **8** (Table 2).* To a suspension of KO*t*Bu (33.6 mg, 0.3 mmol) in 1.0 mL of dry THF at 0 °C was slowly added compound **6a−h** (0.25 mmol) dissolved in 1.0 mL of dry THF, and the mixture was stirred for 3−4 h at the same temperature. After completion of the reaction, monitored by TLC (20% ethyl acetate in petroleum ether), it was quenched with saturated aqueous ammonium chloride solution. The aqueous layer was extracted with ethyl acetate (3 × 5.0 mL). The combined organic extract was washed with brine and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the crude reaction mixture was purified by flash column chromatography on silica gel (230−400 mesh) using 5% ethyl acetate in petroleum ether to afford the pure cyclohexanone products **8a−h** as a white solid.

*1,1′,1″-(4-Hydroxy-2,6-diphenylcyclohex-3-ene-1,1,3-triyl)triethanone (**8a**).* The general procedure described above was followed when **6a** (47.0 mg, 0.25 mmol) was reacted in the presence of 33.6 mg (0.3 mmol) of KO*t*Bu at 0 °C for 3.5 h to afford **8a** (31.0 mg, 65% yield) as a white solid, mp. 120−125 °C; R_f 0.45 (25% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3430, 3060, 3030, 2923, 2853, 1724, 1686, 1610, 1495, 1454, 1415, 1351, 1266, 1238, 1188, 1172, 1082, 1030, 1003, 950, 767; ^1H NMR (400 MHz, $CDCl_3$) δ 1.14 (s, 3H), 1.96 (s, 3H), 2.44 (s, 3H), 2.98−3.01 (m, 2H), 3.85−3.90 (m, 1H), 4.68 (s, 1H), 7.16−7.27 (m, 7H), 7.30−7.40 (m, 3H); ^{13}C NMR$\{^1H\}$ (100 MHz, $CDCl_3$) δ 25.6, 30.1, 30.3, 36.9, 39.2, 43.3, 71.8, 108.6, 127.0, 128.2, 128.4, 129.0, 129.2, 130.0, 139.0, 140.2, 180.3, 200.3, 205.8, 208.8; HRMS (ESI-TOF) calcd for $C_{24}H_{25}O_4$ (M + H^+): 377.1752, found: 377.1754.

*1,1′,1″-(4-Hydroxy-2,6-di-p-tolylcyclohex-3-ene-1,1,3-triyl)triethanone (**8b**).* The general procedure described above was followed when **6b** (50.6 mg, 0.25 mmol) was reacted in the presence of 33.6 mg (0.3 mmol) of KO*t*Bu at 0 °C for 3.5 h to afford **8b** (32.4 mg, 64% yield) as a white solid, mp 140 °C; R_f 0.43 (25% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 2997, 2834, 1714, 1692, 1609, 1513, 1462, 1413, 1354, 1296, 1250, 1224, 1179, 1126, 1031, 950, 870, 836, 814, 790; ^1H NMR (400 MHz, $CDCl_3$) δ 1.19 (s, 3H), 1.95 (s, 3H), 2.27 (s, 3H), 2.35 (s, 3H), 2.42 (s, 3H), 2.95 (d, 2H, J = 9.0 Hz), 3.81−3.85 (m, 1H), 4.61 (s, 1H), 7.01−7.11 (m, 6H), 7.16 (d, 2H, J = 8.0 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 20.9, 21.0, 25.5, 30.1,

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30.4, 37.2, 38.9, 48.0, 72.1, 108.9, 129.0, 129.2, 129.6, 129.9, 136.0, 136.6, 137.3, 137.9, 180.3, 200.2, 205.9, 208.8; HRMS (ESI-TOF) calcd for $C_{26}H_{28}O_4$ (M + Na^+): 427.1885, found: 427.1886.

*1,1′,1″-(4-Hydroxy-2,6-bis(4-methoxyphenyl)cyclohex-3-ene-1,1,3-triyl)triethanone (**8c**).* The general procedure described above was followed when **6c** (54.6 mg, 0.25 mmol) was reacted in the presence of 33.6 mg (0.3 mmol) of KO*t*Bu at 0 °C for 3.5 h to afford **8c** (34.0 mg, 62% yield) as a white solid, mp 130−135 °C; R_f 0.35 (30% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 2997, 2953, 2834, 1714, 1692, 1609, 1512, 1462, 1413, 1354, 1296, 1251, 1224, 1179, 1126, 1117, 1031, 950, 870, 836, 814; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 3H), 1.95 (s, 3H), 2.40 (s, 3H), 2.90−2.95 (m, 2H), 3.76 (s, 3H), 3.81 (s, 3H), 4.61 (s, 1H), 5.30 (s, 1H), 6.74−6.77 (m, 2H), 6.88−6.90 (m, 2H), 7.10−7.14 (m, 4H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 25.6, 30.2, 30.4, 37.0, 38.4, 47.5, 55.1, 55.3, 72.1, 108.9, 113.6, 114.3, 130.5, 130.8, 131.0, 132.1, 158.4, 159.3, 179.8, 200.6, 206.1, 209.0; HRMS (ESI-TOF) calcd for $C_{26}H_{29}O_6$ (M + H^+): 437.1964, found: 437.1965.

*1,1′,1″-(2,6-Bis(2-bromophenyl)-4-hydroxycyclohex-3-ene-1,1,3-triyl)triethanone (**8d**).* The general procedure described above was followed when **6d** (66.8 mg, 0.25 mmol) was reacted in the presence of 33.6 mg (0.3 mmol) of KO*t*Bu at 0 °C for 3.5 h to afford **8d** (45.4 mg, 68% yield) as a white solid, mp 135−140 °C; R_f 0.40 (30% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3072, 2911, 1715, 1691, 1615, 1583, 1464, 1433, 1412, 1354, 1276, 1255, 1238, 1221, 1182, 1100, 1071, 1021, 942, 865, 833, 826; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (s, 3H), 1.97 (s, 3H), 2.60 (s, 3H), 2.98−3.15 (m, 2H), 4.30−4.36 (m, 1H), 5.40 (s, 1H), 7.03−7.07 (m, 1H), 7.16−7.20 (m, 1H), 7.24−7.30 (m, 1H), 7.45−7.52 (m, 4H), 7.65 (d, 1H, J = 8.0 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 25.3, 27.6, 28.9, 34.1, 38.5, 45.3, 71.9, 108.4, 125.7, 126.7, 128.4, 128.8, 130.1, 130.9, 132.5, 133.0, 133.3, 138.3, 181.6, 200.5, 206.6; HRMS (ESI-TOF) calcd for $C_{24}H_{22}Br_2O_4Na$ (M + Na^+): 554.9782, found: 554.9788.

*1,1′,1″-(2,6-Bis(4-chlorophenyl)-4-hydroxycyclohex-3-ene-1,1,3-triyl)triethanone (**8e**).* The general procedure described above was followed when **6e** (55.6 mg, 0.25 mmol) was reacted in the presence of 33.6 mg (0.3 mmol) of KO*t*Bu at 0 °C for 3.5 h to afford **8e** (32.2 mg, 58% yield) as a white solid, mp 125−130 °C; R_f 0.42 (30% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3399, 2924, 1695, 1617, 1492, 1416, 1358, 1241, 1197, 1151, 1110, 1092, 1015, 948, 871, 831, 772; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (s, 3H), 1.93 (s, 3H), 2.42 (s, 3H), 2.95 (d, 2H, J = 9.0 Hz), 3.72−3.77 (m, 1H), 4.66 (s, 1H), 6.99−7.24 (m, 6H), 7.37 (d, 2H, J = 8.3 Hz); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 25.5, 29.8, 30.5, 36.7, 38.9, 47.5, 72.2, 108.4, 128.6, 129.2, 130.9, 131.2, 133.1, 134.4, 137.6, 138.4, 180.1, 199.9, 205.3, 207.2; HRMS (ESI-TOF) calcd for $C_{24}H_{22}Cl_2O_4Na$ (M + Na^+): 467.0793, found: 467.0798.

*1,1′,1″-(2,6-Bis(4-cyanophenyl)-4-hydroxycyclohex-3-ene-1,1,3-triyl)triethanone (**8f**).* The general procedure described above was followed when **6f** (53.3 mg, 0.25 mmol) was reacted in the presence of 33.6 mg (0.3 mmol) of KO*t*Bu at 0 °C for 3.5 h to afford **8f** (35.2 mg, 66% yield) as a white solid, mp 165−170 °C; R_f 0.36 (30% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3407, 2926, 2356, 2228, 1696, 1606, 1504, 1415, 1359, 1240, 1169, 1117, 1044, 1019, 948, 872, 836; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.95 (s, 3H), 2.44 (s, 3H), 2.98−3.01 (m, 2H), 3.74−3.80 (m, 1H), 4.74 (s, 1H), 7.30−7.37 (m, 4H), 7.54 (d, 2H, J = 8.0 Hz), 7.70 (d, 2H, J = 8.1 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 25.5, 29.5, 30.5, 35.9, 39.8, 47.5, 72.3, 107.7, 111.4, 112.5, 117.9, 118.3, 130.5, 132.1, 132.6, 144.5, 144.7, 180.1, 199.6, 204.8, 205.3; HRMS (ESI-TOF) calcd for $C_{26}H_{22}N_2O_4Na$ (M + Na^+): 449.1477, found: 449.1471.

*1,1′,1″-(2,6-Dicyclohexyl-4-hydroxycyclohex-3-ene-1,1,3-triyl)triethanone (**8g**).* The general procedure described above was followed when **6g** (48.6 mg, 0.25 mmol) was reacted in the presence of 33.6 mg (0.3 mmol) of KO*t*Bu at 0 °C for 4.5 h to afford **8g** (26.2 mg, 54% yield) as a white solid, mp 105−110 °C; R_f 0.43 (30% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3419, 2932, 2849, 1703, 1612, 1448, 1419, 1356, 1275, 1246, 1186, 938; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.67−0.76 (m, 1H), 0.88−1.33 (m, 13H), 1.41−1.54 (m, 3H), 1.61−1.70 (m, 5H), 2.19 (s, 3H), 2.20 (s, 3H), 2.23−2.33 (m, 4H), 2.41−2.56 (m, 2H), 2.95−2.97 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 24.5, 25.1, 25.9, 26.4, 26.8, 27.1, 27.3, 29.6, 29.7, 30.3, 30.4, 31.6, 32.0, 32.3, 32.6, 35.1, 36.2, 38.6, 39.9, 40.4, 45.1, 73.1, 108.3, 149.8, 185.7, 194.5, 204.9, 208.4; HRMS (ESI-TOF) calcd for $C_{24}H_{36}O_4Na$ (M + Na^+): 411.2513, found: 411.2517.

*1,1′,1″-(4-Hydroxy-2,6-di(naphthalen-1-yl)cyclohex-3-ene-1,1,3-triyl)triethanone (**8h**).* The general procedure described above was followed when **6h** (59.6 mg, 0.25 mmol) was reacted in the presence of 33.6 mg (0.3 mmol) of KO*t*Bu at 0 °C for 4.0 h to afford **8h** (40.0 mg, 67% yield) as a white solid mp 185−190 °C; R_f 0.39 (30% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3406, 3063, 3009, 2925, 1710, 1687, 1616, 1598, 1509, 1413, 1352, 1276, 1248, 1226, 1181, 1084, 1034, 1020, 969, 950, 908, 879, 859, 801; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.31 (s, 3H), 1.89 (s, 3H), 2.75 (s, 3H), 3.16 (dd, 1H, J = 11.2, 19.8 Hz), 3.31 (dd, 1H, J = 6.6, 19.8 Hz), 4.87−4.92 (m, 1H), 5.93 (s, 1H), 7.29 (d, 1H, J = 8.0 Hz), 7.36 (d, 2H, J = 7.3 Hz), 7.43−7.48 (m, 1H), 7.52−7.59 (m, 2H), 7.62−7.71 (m, 4H), 7.82 (d, 1H, J = 8.1 Hz), 7.87−7.91 (m, 2H), 8.01 (d, 1H, J = 8.8 Hz) ; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 25.7, 28.4, 29.7, 34.8, 35.7, 41.4, 71.9, 109.4, 121.9, 122.0, 125.5, 125.8, 126.5, 126.6, 126.8, 127.8, 128.0, 128.7, 129.5, 129.6, 129.7, 131.5, 132.6, 133.8, 134.1, 135.4, 135.6, 181.3, 201.0, 206.5, 210.0; HRMS (ESI-TOF) calcd for $C_{32}H_{29}O_4$ (M + H^+): 477.2066, found: 477.2065.

*General Procedure for the Synthesis of cis-3,5-Dihydroxy Cyclohexanone Derivatives **16** (Table 3).* To a solution of diisopropylamine (0.09 mL, 0.64 mmol) in 2.0 mL of dry THF was added 2.0 (M) ^{n}BuLi (0.32 mL, 0.64 mmol) at 0 °C, and the mixture was stirred for 30 min under an argon atmosphere. The color of the solution changed to yellow. Then, the temperature was dropped down to −50 °C and compound **6a−d** (100.0 mg, 0.53 mmol) dissolved in 1.0 mL of dry THF was added slowly, and the mixture was stirred for 18−24 h. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with saturated aqueous ammonium chloride solution. The organic and aqueous layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 5.0 mL). The combined organic extract was washed with brine and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the crude reaction mixture was purified by flash column chromatography on silica gel (230−400 mesh) using 10% ethyl acetate in petroleum ether to afford the pure 3,5-dihydroxy cyclohexanones **16a−d** along with 2,6-disubstituted cyclohexanones **8a−d**.

*2-Benzylidene-3,5-dihydroxy-3-methyl-5-(3-oxo-1-phenylbut-1-en-2-yl)cyclohexanone (**16a**).* The general procedure described above was followed when **6a** (100.0 mg, 0.53 mmol) was reacted in the presence of LDA at −50 °C for 18.0 h to afford **16a** (35.0 mg, 35% yield) (and **8a**, 30.0 mg, 30% yield) as a white solid, mp 90−92 °C; R_f 0.43 (30% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3390, 3059, 2924, 2853, 1687, 1600, 1493, 1451, 1412, 1358, 1261, 1192, 1073, 1029, 926, 882, 812; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.62 (s, 3H), 2.04 (s, 3H), 2.36−2.40 (m, 1H), 2.48−2.52 (m, 1H), 2.87−2.92 (m, 1H), 3.25−3.28 (m, 1H), 3.70 (s, 1H), 5.32 (s, 1H), 6.65 (s, 1H), 7.07 (s, 1H), 7.23−7.36 (m, 10H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 27.5, 32.9, 47.4, 55.4, 76.8, 128.4, 128.6, 128.7, 129.0, 129.4, 134.5, 135.4, 144.0, 146.8, 204.1, 208.9; HRMS (ESI-TOF) calcd for $C_{24}H_{24}O_4Na$ (M + Na^+): 399.1572, found: 399.1578.

*3,5-Dihydroxy-3-methyl-2-(4-methylbenzylidene)-5-(3-oxo-1-p-tolylbut-1-en-2-yl)cyclohexanone (**16b**).* The general procedure described above was followed when **6b** (100.0 mg, 0.49 mmol) was reacted in the presence of LDA at −50 °C for 22.0 h to afford **16b** (38.0 mg, 38% yield) (and **8b**, 31.0 mg, 31% yield) as a white solid, mp 109−110 °C; R_f 0.42 (30% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3405, 3028, 2921, 1691, 1640, 1510, 1415, 1381, 1357, 1274, 1206, 1169, 1141, 889, 809; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61 (s, 3H), 2.06 (s, 3H), 2.33 (s, 3H), 2.35 (s, 3H), 2.39 (dd, 2H, J = 2.7, 14.7 Hz), 2.45−2.51 (m, 1H), 2.88 (dd, 1H, J = 2.7, 13.6 Hz), 3.51 (s, 1H), 5.22 (s, 1H), 6.63 (s, 1H), 7.02 (s, 1H), 7.10−7.15 (m, 6H), 7.19 (d, 2H, J = 8.3 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.3, 27.6, 32.7, 47.4, 55.2, 76.8, 128.6, 129.0, 129.3, 129.5, 131.6, 132.4, 138.7, 143.1, 145.9, 203.5, 208.9; HRMS (ESI-TOF) calcd for $C_{26}H_{28}O_4Na$ (M + Na^+): 427.1885, found: 427.1880.

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*3,5-Dihydroxy-2-(4-methoxybenzylidene)-5-(1-(4-methoxyphenyl)-3-oxobut-1-en-2-yl)-3-methylcyclohexanone (**16c**).* The general procedure described above was followed when **6c** (100.0 mg, 0.46 mmol) was reacted in the presence of LDA at −50 °C for 24.0 h to afford **16c** (34.0 mg, 34% yield) (and **8c**, 29.0 mg, 29% yield) as a white solid, mp 140−141 °C; R_f 0.37 (30% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3402, 3329, 2973, 2935, 1691, 1637, 1575, 1512, 1462, 1419, 1356, 1304, 1253, 1172, 1140, 1029, 912, 885, 831, 768; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.60 (s, 3H), 2.06 (s, 3H), 2.38 (dd, 1H, J = 2.0, 14.3 Hz), 2.45−2.48 (m, 1H), 2.87 (dd, 1H, J = 2.3, 14.0 Hz), 3.18−3.20 (m, 1H), 3.41 (s, 1H), 3.79 (s, 3H), 3.81 (s, 3H), 5.20 (s, 1H), 6.61 (s, 1H), 6.80−6.86 (m, 4H), 7.0 (s, 1H), 7.15 (d, 2H, J = 8.3 Hz), 7.30 (d, 2H, J = 8.3 Hz); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 27.5, 32.7, 47.4, 55.2, 55.3, 76.8, 113.7, 114.1, 126.8, 127.7, 129.2, 129.5, 130.2, 130.8, 141.7, 145.0, 159.9, 203.8, 209.2; HRMS (ESI-TOF) calcd for $C_{26}H_{28}O_6Na$ (M + Na^+): 459.1784, found: 459.1788.

*2-(2-Bromobenzylidene)-5-(1-(2-bromophenyl)-3-oxobut-1-en-2-yl)-3,5-dihydroxy-3-methylcyclohexanone (**16d**).* The general procedure described above was followed when **6d** (100.0 mg, 0.37 mmol) was reacted in the presence of LDA at −50 °C for 24.0 h to afford **16d** (36.0 mg, 36% yield) (and **8d**, 28.0 mg, 28% yield) as a light yellow solid, mp 130−132 °C; R_f 0.39 (30% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}) 3422, 3312, 2919, 1688, 1668, 1465, 1414, 1376, 1352, 1269, 1232, 1200, 1178, 1143, 1070, 1044, 1025, 939, 912, 879, 858, 835; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.69 (s, 3H), 1.93 (s, 3H), 2.47−2.56 (m, 2H), 2.90 (dd, 1H, J = 2.2, 14.4 Hz), 3.14−3.17 (m, 1H), 3.33 (s, 1H), 5.0 (s, 1H), 6.87 (s, 1H), 7.09−7.16 (m, 2H), 7.19−7.31 (m, 5H), 7.54 (d, 1H, J = 8.0 Hz), 7.62 (d, 1H, J = 7.8 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 27.9, 29.7, 32.4, 47.2, 54.6, 75.9, 123.6, 127.1, 127.7, 129.5, 130.2, 130.5, 132.4, 132.9, 135.6, 135.9, 145.3, 148.0, 200.7, 207.4; HRMS (ESI-TOF) calcd for $C_{24}H_{22}Br_2O_4Na$ (M + Na^+): 554.9782, found: 554.9783.

*General Procedure for the Synthesis of 4-Nitrocyclohexanone Derivatives **18** from β-Diketo Substrates (Table 4).* To a solution of diisopropylamine (0.09 mL, 0.64 mmol) in 2.0 mL of dry THF was added 2.0 (M) ^{n}BuLi (0.32 mL, 0.64 mmol) at 0 °C, and the mixture was stirred for 30 min under an argon atmosphere. The color of the solution changed to yellow. Then, the temperature was dropped down to −50 °C and compound **6** (100.0 mg, 0.53 mmol) dissolved in 1.0 mL of dry THF was added slowly, and the resulting mixture was stirred for another 45 min to allow the formation of the enolate. Then, β-nitro-styrene **17** (0.58 mmol) dissolved in 1.5 mL of dry THF was added, and the mixture was stirred for an additional 4 h at the same temperature. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with saturated aqueous ammonium chloride solution. The organic and aqueous layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 5.0 mL). The combined organic extract was washed with brine and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the crude reaction mixture was purified by flash column chromatography on silica gel (230−400 mesh) using 10% ethyl acetate in petroleum ether to afford the pure 3,5-disubstituted 4-nitrocyclohexanones **18a−h**.

*1-(2-Hydroxy-5-nitro-4,6-diphenylcyclohex-1-enyl)ethanone (**18a**).* The general procedure described above was followed when the enolate of **6a** (100 mg, 0.53 mmol) was reacted with 87 mg of **17a** (0.58 mmol) in the presence of LDA at −50 °C for 5 h to afford **18a** (132.4 mg, 74% yield) as a white solid, mp 154−156 °C; R_f 0.39 (30% ethyl acetate in petroleum ether); IR υ_{max} (KBr, cm^{-1}): 3429, 3063, 3027, 2922, 1625, 1552, 1454, 1369, 1286, 1226, 933, 765, 698, 600, 571, 541; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.95 (s, 3H), 2.70 (dd, 1H, J = 19.6, 11.6 Hz), 3.03 (dd, 1H, J = 19.6, 6.8 Hz), 3.57 (td, 1H, J_1 = 9.3, 5.4 Hz), 4.59 (d, 1H, J = 5.6 Hz), 5.34 (dd, 1H, J = 12.2, 5.5 Hz), 7.12−7.17 (m, 4H), 7.21−7.30 (m, 3H), 7.35−7.37 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 25.8, 36.8, 38.3, 45.2, 89.4, 107.3, 127.2, 127.8, 128.8, 129.1, 136.9, 139.4, 177.5, 201.3; HRMS (ESI-TOF) calcd for $C_{20}H_{18}NO_4$ (M − H^+): 336.1236, Found: 336.1239.

*1-(2-Hydroxy-5-nitro-4-phenyl-6-p-tolylcyclohex-1-enyl)-ethanone (**18b**).* The general procedure described above was followed when the enolate of **6b** (100 mg, 0.49 mmol) was reacted with 75 mg of **17a** (0.54 mmol) in the presence of LDA at −50 °C for 4.5 h to afford **18b** (107.7 mg, 62% yield) as a white solid, mp 178−180 °C; R_f 0.42 (30% ethyl acetate in petroleum ether); IR υ_{max} (KBr, cm^{-1}): 3425, 2921, 1625, 1575, 1548, 1415, 1368, 1287, 1238, 916, 725, 584, 512; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.95 (s, 3H), 2.35(s, 3H), 2.67 (dd, 1H, J = 13.7, 10.7 Hz), 3.01 (dd, 1H, J = 16.1, 6.8 Hz), 3.55 (m, 1H), 4.55 (d, 1H, J = 5.4), 5.32 (dd, 1H, J = 9.5, 5.4 Hz), 7.00 (d, 2H, J = 8.1 Hz), 7.16 (m, 4H), 7.22 (m, 1H), 7.25−7.30 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 21.2, 25.9, 29.8, 36.8, 38.3, 44.8, 89.4, 107.5, 127.2, 127.8, 128.6, 129.1, 129.8, 133.9, 138.6, 139.5, 177.3, 201.4; HRMS (ESI-TOF) calcd for $C_{21}H_{20}NO_4$ (M − H^+): 350.1392, Found: 350.1394.

*1-(2-Hydroxy-6-(4-methoxyphenyl)-5-nitro-4-phenylcyclohex-1-enyl)ethanone (**18c**).* The general procedure described above was followed when the enolate of **6c** (100 mg, 0.46 mmol) was reacted with 75 mg of **17a** (0.50 mmol) in the presence of LDA at −50 °C for 5.0 h to afford **18c** (121.2 mg, 72% yield) as a white solid, mp 160−162 °C; R_f 0.37 (30% ethyl acetate in petroleum ether); IR ν_{max} (KBr, cm^{-1}): 3500, 2914, 2879, 2841, 1612, 1556, 1511, 1444, 1417, 1367, 1283, 1261, 976, 961, 934, 841, 824, 749, 700, 630, 522, 488; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.95 (s, 3H), 2.67 (dd, 1H, J = 19.8, 11.5 Hz), 2.99 (dd, 1H, J = 19.8, 6.9 Hz), 3.50−3.57 (m, 1H), 3.80 (s, 3H), 4.54 (d, 1H, J = 5.5 Hz), 5.30 (dd, 1H, J = 12.3, 5.5 Hz), 6.87 (d, 2H, J = 8.6 Hz), 7.03 (d, 2H, J = 8.6 Hz), 7.15−7.29 (m, 5H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 25.9, 36.8, 38.2, 44.5, 55.3, 89.4, 107.5, 114.4, 127.2, 127.8, 128.3, 128.7, 129.1, 129.8, 139.5, 189.8, 177.1, 201.5; HRMS (ESI-TOF) calcd for $C_{21}H_{20}NO_5$ (M − H^+): 366.1341, Found: 366.1345.

*4-(2-Acetyl-3-hydroxy-6-nitro-5-phenylcyclohex-2-enyl)benzonitrile (**18d**).* The general procedure described above was followed when the enolate of **6f** (100 mg, 0.47 mmol) was reacted with 78 mg of **17a** (0.52 mmol) in the presence of LDA at −50 °C for 4.0 h to afford **18d** (132.6 mg, 78% yield) as a white solid, mp 164−166 °C; R_f 0.36 (30% ethyl acetate in petroleum ether); IR υ_{max} (KBr, cm^{-1}): 3419, 2982, 2912, 1640, 1560, 1548, 1520, 1438, 1372, 1290, 1274, 1110, 980, 908, 744, 632, 547; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.92 (s, 3H), 2.73 (dd, 1H, J = 19.8, 11.5 Hz), 3.05 (dd, 1H, J = 19.8, 6.8 Hz), 3.42−3.48 (m, 1H), 4.65 (d, 1H, J = 5.6 Hz), 5.38 (dd, 1H, J = 12.5, 5.6 Hz), 7.14−7.30 (m, 7H), 7.68−7.70 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 25.8, 36.9, 38.2, 45.0, 89.1, 106.3, 113.0, 118.2, 127.1, 128.1, 129.3, 129.5, 132.8, 133.5, 138.7, 142.6, 178.3, 200.6; HRMS (ESI-TOF) calcd for $C_{21}H_{17}N_2O_4$ (M − H^+): 361.1188, Found: 361.1185.

*1-(6-Cyclohexyl-2-hydroxy-5-nitro-4-phenylcyclohex-1-enyl)-ethanone (**18e**).* The general procedure described above was followed when the enolate of **6g** (100 mg, 0.51 mmol) was reacted with 84 mg of **17a** (0.56 mmol) in the presence of LDA at −50 °C for 4.5 h to afford **18e** (132.6 mg, 75% yield) as a thick liquid, R_f 0.40 (30% ethyl acetate in petroleum ether); IR υ_{max} (neat, cm^{-1}): 3032, 2927, 2853, 1703, 1601, 1550, 1497, 1450, 1416, 1365, 1271, 1032, 961, 763, 723, 701, 573, 500; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 0.83−0.88 (m, 1H), 1.03−1.34 (m, 4H), 1.54−1.78 (m, 6H), 2.24 (s, 3H), 2.52 (dd, 1H, J = 19.8, 8.6 Hz), 3.01 (dd, 1H, J = 19.8, 8.9 Hz), 3.30 (t, 1H, J = 4.6 Hz), 3.83−3.87 (m, 1H), 5.03 (dd, 1H, J = 12.0, 4.6 Hz), 7.21−7.34 (m, 5H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 24.9, 26.0, 26.9, 29.8, 32.1, 35.4, 37.7, 38.8, 39.3, 44.3, 89.7, 107.9, 127.2, 127.8, 129.2, 141.0, 183.2, 195.6; HRMS (ESI-TOF) calcd for $C_{20}H_{29}N_2O_4$ (M + NH_4^+): 361.2127, Found: 361.2120.

*1-(6-(Furan-2-yl)-2-hydroxy-5-nitro-4-phenylcyclohex-1-enyl)-ethanone (**18f**).* The general procedure described above was followed when the enolate of **6i** (100 mg, 0.56 mmol) was reacted with 92 mg of **17a** (0.62 mmol) in the presence of LDA at −50 °C for 4.0 h to afford **18f** (124.9 mg, 68% yield) as a white solid, mp 154−156 °C; R_f 0.38 (30% ethyl acetate in petroleum ether); IR υ_{max} (KBr, cm^{-1}): 3032, 2924, 1621, 1556, 1498, 1456, 1416, 1363, 1325, 1264, 1246, 1174, 1145, 1075, 1013, 962, 925, 886, 812, 765, 744, 701, 599, 573; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.06 (s, 3H), 2.64 (dd, 1H, J =

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19.5, 11.5 Hz), 2.99 (dd, 1H, J = 19.5, 7.1 Hz), 3.72 (td, 1H, J = 11.7, 6.8 Hz), 4.71 (d, 1H, J = 5.1 Hz), 5.24 (dd, 1H, J = 12.2, 5.1 Hz), 6.23 (d, 1H, J = 3.2 Hz), 6.37 (dd, 1H, J = 3.2, 2.0 Hz), 7.19−7.32 (m, 5H), 7.41 (d, 1H, J = 2.4 Hz); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) 25.3, 37.9, 38.2, 39.5, 88.1, 105.5, 110.5, 110.9, 127.2, 127.9, 129.2, 139.4, 143.8, 150.4, 178.2, 200.6; HRMS (ESI-TOF) calcd for $C_{18}H_{18}NO_5$ (M + H^+): 328.1185, Found: 328.1186.

*1-(2-Hydroxy-5-nitro-6-phenyl-4-p-tolylcyclohex-1-enyl)-ethanone (**18g**).* The general procedure described above was followed when the enolate of **6a** (100 mg, 0.53 mmol) was reacted with 95 mg of **17b** (0.58 mmol) in the presence of LDA at −50 °C for 5 h to afford **18g** (118.5 mg, 69% yield) as a white solid, mp 178−180 °C; R_f 0.42 (30% ethyl acetate in petroleum ether); IR υ_{max} (KBr, cm^{-1}): 3425, 2921, 1625, 1575, 1548, 1415, 1368, 1287, 1238, 916, 725, 584, 512; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.94 (s, 3H), 2.27 (s, 3H), 2.67 (dd, 1H, J = 19.5, 11.3 Hz), 3.00 (dd, 1H, J = 19.8, 7.0 Hz), 3.50−3.56 (m, 1H), 4.57 (d, 1H, J = 5.5 Hz), 5.30 (dd, 1H, J = 12.2, 5.5 Hz), 7.03−7.08 (m, 4H), 7.10−7.15 (m, 2H), 7.28−7.37 (m, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) 22.1, 27.2, 28.9, 37.4, 39.6, 44.0, 89.8, 108.5, 127.2, 127.6, 129.1, 129.8, 133.8, 138.1, 140.0, 177.3, 201.8; HRMS (ESI-TOF) calcd for $C_{21}H_{20}NO_4$ (M − H^+): 350.1392, Found: 350.1394.

*1-(4-(Furan-2-yl)-2-hydroxy-5-nitro-6-phenylcyclohex-1-enyl)-ethanone (**18h**).* The general procedure described above was followed when the enolate of **6a** (100 mg, 0.53 mmol) was reacted with 81 mg of **17c** (0.58 mmol) in the presence of LDA at −50 °C for 4.5 h to afford **18h** (135.2 mg, 74% yield) as a white solid, mp 152−154 °C; R_f 0.39 (30% ethyl acetate in petroleum ether); IR υ_{max} (KBr, cm^{-1}): 3032, 2924, 1621, 1556, 1498, 1456, 1416, 1363, 1325, 1264, 1246, 1174, 1145, 1075, 1013, 962, 925, 886, 812, 765, 744, 701, 599, 573; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.94 (s, 3H), 2.86 (dd, 1H, J = 19.8, 7.4 Hz), 3.02 (dd, 1H, J = 19.8, 7.1 Hz), 3.71−3.81 (m, 1H), 4.52−4.56 (m, 1H), 4.79−4.83 (m, 1H), 6.09 (d, 1H, J = 3.4 Hz), 6.24−6.26 (m, 1H), 7.09−7.12 (m, 2H), 7.26−7.37 (m, 4H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) 21.9, 37.8, 38.5, 42.2, 88.0, 103.8, 108.5, 111.2, 126.2, 127.2, 128.4, 138.5, 144.5, 149.7, 179.6, 201.1; HRMS (ESI-TOF) calcd for $C_{18}H_{18}NO_5$ (M + H^+): 328.1185, Found: 328.1188.

*General Procedure for the Synthesis of 4-Nitrocyclohexanone Derivatives **19** from β-Ketoester Substrates (Table 5).* To a solution of diisopropylamine (0.08 mL, 0.55 mmol) in 2.0 mL of dry THF was added 2.0 (M) ^{n}BuLi (0.28 mL, 0.55 mmol) at 0 °C, and the mixture was stirred for 30 min under an argon atmosphere. The color of the solution changed to yellow. Then, the temperature was dropped down to −50 °C and compound **1a,c,i,j** (100.0 mg, 0.46 mmol) dissolved in 1.0 mL of dry THF was added slowly, and the resulting mixture was stirred for another 45 min to allow the formation of the enolate. Then, β-nitro-styrene **17a** (0.51 mmol) dissolved in 1.5 mL of dry THF was added, and the mixture was stirred for an additional 4 h at the same temperature. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with saturated aqueous ammonium chloride solution. The organic and aqueous layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 5.0 mL). The combined organic extract was washed with brine and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the crude reaction mixture was purified by flash column chromatography on silica gel (230−400 mesh) using 10% ethyl acetate in petroleum ether to afford the pure 3,5-disubstituted 4-nitro-cyclohexanonecarboxylates **19a−d**.

*Ethyl 2-Hydroxy-5-nitro-4,6-diphenylcyclohex-1-enecarboxylate (**19a**).* The general procedure described above was followed when the enolate of **1a** (100 mg, 0.46 mmol) was reacted with 75 mg of **17a** (0.51 mmol) in the presence of LDA at −50 °C for 5.0 h to afford **19a** (117.8 mg, 70% yield) as a white solid, mp 119−121 °C; R_f 0.38 (20% ethyl acetate in petroleum ether); IR υ_{max} (KBr, cm^{-1}): 3028, 2994, 2962, 2918, 1660, 1624, 1557, 1495, 1471, 1455, 1412, 1369, 1354, 1315, 1285, 1256, 1225, 1217, 1158, 1105, 1069, 1049, 1029, 1013, 949, 911, 868, 830, 797, 773, 760, 725, 631, 605, 575; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 0.99 (t, 3H, J = 7.1 Hz), 2.63 (dd, 1H, J = 19.3, 11.2 Hz), 2.96 (dd, 1H, J = 19.3, 6.8 Hz), 3.58−3.65 (m, 1H), 3.99−4.08 (m, 2H), 4.62 (d, 1H, J = 5.6 Hz), 5.26−5.31 (m, 1H), 7.10−7.21 (m, 5H), 7.23−7.37 (m, 5H), 12.47 (s, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) 13.9, 37.1, 37.2, 43.6, 61.0, 89.2, 98.4, 127.3, 127.8, 128.1, 128.4, 128.5, 129.1, 137.7, 139.7, 170.1, 171.0; HMRS (ESI-TOF) Calcd for $C_{21}H_{21}NO_5Na$ (M + Na^+): 390.1317, Found: 390.1317.

*Ethyl 2-Hydroxy-6-(4-methoxyphenyl)-5-nitro-4-phenylcyclohex-1-enecarboxylate (**19b**).* The general procedure described above was followed when the enolate of **1c** (100 mg, 0.40 mmol) was reacted with 66 mg of **17a** (0.44 mmol) in the presence of LDA at −50 °C for 5.0 h to afford **19b** (124.8 mg, 78% yield) as a white solid, mp 158−160 °C; R_f 0.38 (20% ethyl acetate in petroleum ether); IR υ_{max} (KBr, cm^{-1}): 3425, 2934, 2838, 1656, 1611, 1584, 1553, 1511, 1457, 1406, 1368, 1281, 1249, 1218, 1176, 1064, 1032, 830, 763, 700, 626, 582; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.03 (t, 3H, J = 7.4 Hz), 2.61 (dd, 1H, J = 19.2, 11.2 Hz), 2.94 (dd, 1H, J = 19.5, 7.1 Hz), 3.55−3.62 (m, 1H), 3.78 (s, 3H), 4.01−4.07 (m, 2H), 4.58 (d, 1H, J = 5.5 Hz), 5.22−5.27 (m, 1H), 6.81−6.83 (m, 2H), 7.00−7.03 (m, 2H), 7.16−7.28 (m, 5H), 12.44 (s, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) 13.9, 37.0, 37.1, 42.9, 55.3, 61.0, 89.2, 98.6, 113.9, 127.3, 127.7, 129.1, 129.5, 139.8, 159.4, 169.9, 171.0; HMRS (ESI-TOF) Calcd for $C_{22}H_{23}NO_6Na$ (M + Na^+): 420.1423, Found: 420.1425.

*Ethyl 6-(3-Bromophenyl)-2-hydroxy-5-nitro-4-phenylcyclohex-1-enecarboxylate (**19c**).* The general procedure described above was followed when the enolate of **1j** (100 mg, 0.34 mmol) was reacted with 55 mg of **17a** (0.37 mmol) in the presence of LDA at −50 °C for 4.0 h to afford **19c** (109.6 mg, 73% yield) as a white solid, mp 164−168 °C; R_f 0.36 (20% ethyl acetate in petroleum ether); IR υ_{max} (KBr, cm^{-1}): 3431, 2922, 2830, 1657, 1630, 1596, 1554, 1474, 1442, 1412, 1370, 1289, 1246, 1212, 1170, 1132, 1065, 1031, 917, 876, 822, 782, 743, 715, 700, 641, 624, 583, 514; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.02 (t, 3H, J = 7.3 Hz), 2.64 (dd, 1H, J = 19.5, 11.5 Hz), 2.98 (dd, 1H, J = 19.5, 6.9 Hz), 3.53−3.60 (m, 1H), 4.04−4.09 (m, 2H), 4.57 (d, 1H, J = 5.7 Hz), 5.27 (dd, 1H, J = 12.4, 5.7 Hz), 6.98−7.48 (m, 9H), 12.47 (s, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) 13.8, 36.9, 37.1, 43.1, 61.1, 88.9, 97.8, 122.7, 127.2, 127.3, 127.9, 129.1, 130.1, 131.2, 131.4, 139.3, 140.2, 170.4, 170.7; HRMS (ESI-TOF) calcd for $C_{21}H_{21}BrNO_5$ (M + H^+): 446.0603, found 446.0607.

*Ethyl 6-(4-Fluorophenyl)-2-hydroxy-5-nitro-4-phenylcyclohex-1-enecarboxylate (**19d**).* The general procedure described above was followed when the enolate of **1i** (100 mg, 0.42 mmol) was reacted with 69 mg of **17a** (0.46 mmol) in the presence of LDA at −50 °C for 4.5 h to afford **19d** (130.5 mg, 80% yield) as a white solid, mp 150−152 °C; R_f 0.30 (20% ethyl acetate in petroleum ether); IR υ_{max} (KBr, cm^{-1}): 3437, 2992, 1659, 1622, 1604, 1555, 1506, 1472, 1458, 1421, 1368, 1354, 1283, 1257, 1226, 1161, 1107, 1068, 1047, 1011, 875, 830, 770, 732, 717, 702, 625, 582, 521; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.02 (t, 3H, J = 7.4 Hz), 2.64 (dd, 1H, J = 19.2, 11.3 Hz), 2.96 (dd, 1H, J = 19.2, 7.0 Hz), 3.54−3.60 (m, 1H), 4.03−4.09 (m, 2H), 4.61 (d, 1H, J = 5.8 Hz), 5.28 (q, 1H, J = 5.8 Hz), 6.98−7.02 (m, 2H), 7.08−7.11 (m, 2H), 7.16−7.30 (m, 5H), 12.47 (s, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) 13.9, 37.0, 37.1, 42.8, 61.1, 89.1, 98.3, 115.5, 115.6, 127.2, 127.9, 129.1, 129.9, 130.0, 133.5, 139.4, 161.7, 163.6, 170.2, 170.8; HMRS (ESI-TOF) Calcd for $C_{21}H_{21}FNO_5$ (M + H^+): 386.1404, Found: 386.1402.

*General Procedure for the Synthesis of 2,6-Disubstituted Nonracemic Cyclohexanone Derivatives **22** (Table 6).* To a suspension of KOtBu (33.8 mg, 0.3 mmol) in 1.0 mL of dry THF at −50 °C was slowly added compound **20a−c** (0.25 mmol) dissolved in 1.0 mL of dry THF, and the mixture was stirred for 7−8 h at the same temperature. After completion of the reaction, monitored by TLC (10% ethyl acetate in petroleum ether), it was quenched with saturated aqueous ammonium chloride solution. The aqueous layer was extracted with ethyl acetate (3 × 5.0 mL). The combined organic extract was washed with brine and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the crude reaction mixture was purified by flash column chromatography on silica gel (230−400 mesh) using 1% ethyl acetate in petroleum ether to afford the pure nonracemic cyclohexanone products **22a−c**.

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*(1S,2S,6R)-Bis((1S,2R,5S)-2-isopropyl-5-methylcyclohexyl) 1-Acetyl-2,6-bis(4-chlorophenyl)-4-hydroxycyclohex-3-ene-1,3-dicarboxylate (**22a**, Table 5).* The general procedure described above was followed when **20a** (100 mg, 0.28 mmol) was reacted in the presence of 34.8 mg (0.31 mmol) of KO*t*Bu at −50 °C for 7.5 h to afford **22a** (75.2 mg, 75% yield) as a white solid, mp 154−156 °C; R_f 0.58 (10% ethyl acetate in petroleum ether); $[\alpha]_D^{25}$ = −53.7 (*c* 0.11, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ ^1H NMR (500 MHz, $CDCl_3$) δ 0.35 (d, 1H, *J* = 6.9 Hz), 0.48 (d, 1H, *J* = 6.9 Hz), 0.72−0.94 (m, 22H), 1.25−1.42 (m, 4H), 1.63 (s, 3H), 2.82−2.95 (m, 2H), 3.74−3.77 (m, 1H), 4.59 (td, 1H, *J* = 10.9, 4.6 Hz), 4.72 (s, 1H), 4.86 (td, 1H, *J* = 10.9, 4.0 Hz), 7.08 (d, 2H, *J* = 8.6 Hz), 7.18 (d, 2H, *J* = 8.6 Hz), 7.25−7.29 (m, 4H), 12.42 (s, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 15.7, 16.8, 21.0, 21.1, 21.9, 22.1, 22.9, 23.5, 26.2, 26.6, 30.2, 31.1, 31.5, 34.0, 34.1, 34.8, 39.6, 39.9, 40.5, 45.8, 46.9, 47.0, 68.2, 74.9, 76.6, 100.7, 128.1, 128.3, 131.1, 131.7, 132.9, 133.3, 138.0, 139.2, 170.2, 170.8, 171.0, 203.6; HRMS (ESI) calcd for $C_{42}H_{55}Cl_2O_6$ (M + H^+): 725.3376, found: 725.3370.

*(1S,2S,6R)-Bis((1S,2R,5S)-2-isopropyl-5-methylcyclohexyl) 1-Acetyl-4-hydroxy-2,6-diphenylcyclohex-3-ene-1,3-dicarboxylate (**22b**, Table 5).* The general procedure described above was followed when **20b** (100 mg, 0.30 mmol) was reacted in the presence of 37.0 mg (0.33 mmol) of KO*t*Bu at −50 °C for 7.0 h to afford **22b** (66.0 mg, 66% yield) as a rotameric mixture in white solid, mp 162−164 °C; R_f 0.58 (10% ethyl acetate in petroleum ether); $[\alpha]_D^{25}$ = −2.8.1 (*c* 0.19, CH_2Cl_2); IR ν_{max} (KBr, cm^{-1}) 3421, 2957, 2871, 1726, 1651, 1619, 1497, 1455, 1421, 1395, 1355, 1288, 1265, 1220, 1140, 1103, 1044, 959, 934, 829, 760, 701; ^1H NMR (500 MHz, $CDCl_3$) δ 0.29 (d, 1H, *J* = 5.8 Hz), 0.39 (d, 1H, *J* = 6.4 Hz), 0.65−1.42 (m, 28H), 1.61 (s, 3H), 1.69−1.72 (m, 2H), 1.87−1.92 (m, 2H), 2.02−2.04 (m, 2H), 2.83−2.94 (m, 2H), 3.89−3.92 (m, 1H), 4.55−4.58 (m, 1H), 4.79 (s, 1H), 4.85−4.89 (m, 1H), 7.14−7.30 (m, 8H), 7.34−7.36 (m, 2H), 12.42 (s, 0.6H), 12.(s, 0.4H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 15.1, 15.4, 15.8, 16.8, 21.0, 21.1, 21.3, 21.8, 22.1, 22.4, 22.7, 23.0, 23.5, 24.4, 25.7, 26.1, 26.5, 29.9, 31.1, 31.5, 31.6, 34.0, 34.1, 34.2, 34.3, 35.2, 35.4, 39.1, 39.7, 40.0, 40.5, 41.2, 46.3, 46.7, 46.8, 47.0, 68.4, 74.5, 74.6, 76.2, 76.4, 101.0, 126.8, 126.9, 127.3, 127.5, 127.7, 128.0, 128.2, 128.3, 129.7, 129.9, 130.0, 130.5, 140.1, 140.6, 170.3, 170.7, 171.1, 204.9; HRMS (ESI) calcd for $C_{42}H_{57}O_6$ (M + H^+): 657.4155, found: 657.4151.

*(1S,2S,6R)-Bis((1S,2R,5S)-2-isopropyl-5-methylcyclohexyl) 1-Acetyl-2,6-bis(4-fluorophenyl)-4-hydroxycyclohex-3-ene-1,3-dicarboxylate (**22c**, Table 5).* The general procedure described above was followed when **20c** (100 mg, 0.29 mmol) was reacted in the presence of 39.1 mg (0.32 mmol) of KO*t*Bu at −50 °C for 8.0 h to afford **22c** (80.1 mg, 80% yield) as a rotameric mixture in white solid, mp 136−138 °C; R_f 0.52 (10% ethyl acetate in petroleum ether); $[\alpha]_D^{25}$ = −29.6 (*c* 0.14, CH_2Cl_2); IR ν_{max} (KBr, cm^{-1}) 3434, 2957, 2928, 2871, 1710, 1651, 1605, 1510, 1456, 1420, 1392, 1356, 1289, 1262, 1229, 1179, 1162, 1101, 1043, 1015, 981, 955, 913, 838, 543; ^1H NMR (400 MHz, $CDCl_3$) 0.33−0.96 (m, 21H), 0.99−1.42 (m, 8H), 1.56 (s, 3H), 1.59−1.77 (m, 4H), 1.86−2.03 (m, 3H), 2.80−2.96 (m, 2H), 3.77−3.81 (m, 1H), 4.55−4.62 (m, 1H), 4.74 (s, 1H), 4.83−4.89 (m, 1H), 6.86−6.91 (m, 2H), 6.97−7.01 (m, 2H), 7.09−7.13 (m, 2H), 7.30−7.34 (m, 2H), 12.41 (s, 0.9H), 12.55 (0.1H); ^{13}C NMR$\{^1H\}$ (125 MHz, $CDCl_3$) δ 15.1, 15.3, 15.7, 16.8, 21.0, 21.1, 21.3, 21.9, 22.0, 22.1, 22.4, 22.6, 23.0, 23.4, 24.6, 25.8, 26.1, 26.6, 29.9, 30.1, 31.1, 31.5, 31.6, 34.0, 34.2, 34.3, 34.8, 35.1, 38.4, 39.4, 40.0, 40.5, 41.2, 45.2, 45.7, 46.8, 46.9, 47.0, 47.1, 68.3, 68.7, 74.6, 74.8, 76.4, 76.6, 100.7, 100.9, 114.3, 114.4, 114.7, 114.8, 114.9, 115.0, 115.1, 115.2, 131.0, 131.1, 131.2, 131.9, 132.0, 132.4, 132.5, 135.3, 136.4, 160.8, 161.2, 162.8, 163.1, 170.4, 170.9, 171.0, 202.9, 204.0; HRMS (ESI-TOF) calcd for $C_{42}H_{55}F_2O_6$ (M + H^+): 693.3967, found: 693.3974.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01768.

Copies of ^1H and $^{13}C\{^1H\}$ NMR spectra of the compounds **3a−h**, **8a−h**, **16a−d**, **18a−h**, **19a−d**, **22a−c**; expansion of ^1H NMR spectra for the low-temperature experiment on **22b**; crystal structures; X-ray crystallographic data; and computational studies (PDF)

Crystallographic data (CIF)

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Notes

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■ DEDICATION

Dedicated to Prof. Michael Schmittel on the occasion of his 59th Birthday.

■ REFERENCES

(1) (a) Cristoffers, J., Baro, A., Eds. *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; Wiley-VCH: Weinheim, 2005. (b) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363.

(2) For reviews on the construction of a quaternary carbon, see: (a) Martin, S. F. *Tetrahedron* **1980**, *36*, 419. (b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037. (c) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (d) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591. (e) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105. (f) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (g) Das, J. P.; Marek, I. *Chem. Commun.* **2011**, *47*, 4593. (h) Wright, P. M.; Myers, A. G. *Tetrahedron* **2011**, *67*, 9853.

(3) For the synthesis of aza-heterocycles containing a quaternary carbon center, see: (a) Denolf, B.; Mangelinckx, S.; Törnroos, K. W.; De Kimpe, N. *Org. Lett.* **2007**, *9*, 187. (b) Vervisch, K.; D'hooghe, M.; Törnroos, K. W.; De Kimpe, N. *J. Org. Chem.* **2010**, *75*, 7734.

(4) (a) Trost, B. M.; Radinov, R.; Grenzer, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 7879. (b) Patil, N. T.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 6478. (c) Aggarwal, V. K.; Patin, A.; Tisserand, S. *Org. Lett.* **2005**, *7*, 2555. (d) Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 62. (e) Lee, A.-L.; Malcolmson, S. J.; Puglisi, A.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 5153. (f) Zhang, A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2006**, *128*, 5620. (g) Matsumoto, Y.; Yamada, K.; Tomioka, K. *J. Org. Chem.* **2008**, *73*, 4578. (h) Shibata, T.; Tahara, Y.-K.; Tamura, K.; Endo, K. *J. Am. Chem. Soc.* **2008**, *130*, 3451. (i) Han, Y.; Zhu, L.; Gao, Y.; Lee, C.-S. *Org. Lett.* **2011**, *13*, 588. (j) Kikushima, K.; Holder, J. C.; Gatti, M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2011**, *133*, 6902. (k) Lin, M.; Li, F.; Jiao, L.; Yu, Z.-X. *J. Am. Chem. Soc.* **2011**, *133*, 1690. (l) Shirakawa, S.; Koga, K.; Tokuda, T.; Yamamoto, K.; Maruoka, K. *Angew. Chem., Int. Ed.* **2014**, *53*, 6220. (m) Feng, J.; Garza, V. J.; Krische, M. J. *J. Am. Chem. Soc.* **2014**, *136*, 8911 and references cited therein. (n) Hong, Y.-C.; Gandeepan, P.; Mannathan, S.; Lee, W.-T.; Cheng, C.-H. *Org. Lett.* **2014**, *16*, 2806. (o) Fujii, T.; Orimoto, K.; Nakada, M. *Tetrahedron Lett.* **2014**, *55*, 1100.

(5) (a) Carlone, A.; Cabrera, S.; Marigo, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 1101. (b) Quintard, A.; Lefranc, A.; Alexakis, A. *Org. Lett.* **2011**, *13*, 1540. (c) Sanchez Duque, M. d. M.; Baslé, O.; Isambert, N.; Gaudel-Siri, A.; Génisson, Y.; Plaquevent, J.-C.;

DOI: 10.1021/acs.joc.5b01768
J. Org. Chem. 2015, 80, 9700−9712

Rodriguez, J.; Constantieux, T. *Org. Lett.* **2011**, *13*, 3296. (d) Kang, J. Y.; Carter, R. G. *Org. Lett.* **2012**, *14*, 3178. (e) Nugent, T. C.; Sadiq, A.; Bibi, A.; Heine, T.; Zeonjuk, L. L.; Vankova, N.; Bassil, B. S. *Chem.—Eur. J.* **2012**, *18*, 4088 and references cited therein. (f) Wu, B.; Chen, J.; Li, M.-Q.; Zhang, J.-X.; Xu, X.-P.; Ji, S.-J.; Wang, X.-W. *Eur. J. Org. Chem.* **2012**, *2012*, 1318 and references cited therein.

(6) (a) Kazmaier, U. *J. Org. Chem.* **1996**, *61*, 3694. (b) Spino, C.; Beaulieu, C. *Angew. Chem., Int. Ed.* **2000**, *39*, 1930. (c) Burke, E. D.; Gleason, J. L. *Org. Lett.* **2004**, *6*, 405. (d) Mermerian, A. H.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 5604. (e) DeGraffenreid, M. R.; Bennett, S.; Caille, S.; de Turiso, F. G.-L.; Hungate, R. W.; Julian, L. D.; Kaizerman, J. A.; McMinn, D. L.; Rew, Y.; Sun, D.; Yan, X.; Powers, J. P. *J. Org. Chem.* **2007**, *72*, 7455. (f) Kummer, D. A.; Chain, W. J.; Morales, M. R.; Quiroga, O.; Myers, A. G. *J. Am. Chem. Soc.* **2008**, *130*, 13231. (g) Hashimoto, T.; Sakata, K.; Maruoka, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 5014. (h) Linclau, B.; Cini, E.; Oakes, C. S.; Josse, S.; Light, M.; Ironmonger, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 1232. (i) Lim, H. J.; RajanBabu, T. V. *Org. Lett.* **2011**, *13*, 6596.

(7) (a) Hladezuk, I.; Olesker, A.; Tchertanov, L.; Cléophax, J. *Carbohydr. Res.* **2001**, *330*, 257. (b) Calad, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 2046. (c) Hashimoto, T.; Naganawa, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2009**, *131*, 6614. (d) Li, H.; Zhang, F.-M.; Tu, Y.-Q.; Zhang, Q.-W.; Chen, Z.-M.; Chen, Z.-H.; Li, J. *Chem. Sci.* **2011**, *2*, 1839. (e) Tan, J.; Cheon, C.-H.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 8264. (f) Tambutet, G.; Becerril-Jiménez, F.; Dostie, S.; Simard, R.; Prévost, M.; Mochirian, P.; Guindon, Y. *Org. Lett.* **2014**, *16*, 5698.

(8) (a) Takemoto, T.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1993**, *115*, 8477. (b) Zhai, H.; Luo, S.; Ye, C.; Ma, Y. *J. Org. Chem.* **2003**, *68*, 8268. (c) Min, S.-J.; Jones, G. O.; Houk, K. N.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 10078. (d) White, D. E.; Stewart, I. C.; Grubbs, R. H.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 810. (e) Ghosh, A. K.; Xi, K. *J. Org. Chem.* **2009**, *74*, 1163. (f) Nakajima, R.; Ogino, T.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc.* **2010**, *132*, 1236. (g) Boonsompat, J.; Padwa, A. *J. Org. Chem.* **2011**, *76*, 2753.

(9) (a) Ruhemann, S. *J. Chem. Soc., Trans.* **1909**, *95*, 109. (b) Nechepurenko, I. V.; Shul'ts, E. E.; Tolstikov, G. A. *Russ. J. Org. Chem.* **2003**, *39*, 1436. (c) Görlitzer, K.; Fabian, J.; Trittmacher, J. *Pharmazie* **2005**, *60*, 571. (d) Holan, M.; Pohl, R.; Císařová, I.; Jahn, U. *Eur. J. Org. Chem.* **2012**, *2012*, 3459.

(10) (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2006. (c) Barriault, L.; Denissova, I. *Org. Lett.* **2002**, *4*, 1371. (d) Ramachary, D. B.; Anebouselvy, K.; Chowdari, N. S.; Barbas, C. F., III *J. Org. Chem.* **2004**, *69*, 5838. (e) Rueping, M.; Kuenkel, A.; Fröhlich, R. *Chem.—Eur. J.* **2010**, *16*, 4173. (f) Duttwyler, S.; Lu, C.; Rheingold, A. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2012**, *134*, 4064.

(11) (a) Ghorai, M. K.; Das, K.; Kumar, A.; Das, A. *Tetrahedron Lett.* **2006**, *47*, 5393. (b) Ghorai, M. K.; Ghosh, K.; Yadav, A. K. *Tetrahedron Lett.* **2009**, *50*, 476. (c) Ghorai, M. K.; Ghosh, K.; Yadav, A. K.; Nanaji, Y.; Halder, S.; Sayyad, M. *J. Org. Chem.* **2013**, *78*, 2311. (d) Ghorai, M. K.; Das, S.; Das, K.; Kumar, A. *Org. Biomol. Chem.* **2015**, *13*, 9042.

(12) (a) Ghorai, M. K.; Kumar, A.; Halder, S. *Tetrahedron* **2007**, *63*, 4779. (b) Ghorai, M. K.; Halder, S.; Samanta, S. *Aust. J. Chem.* **2012**, *65*, 1262.

(13) Ghorai, M. K.; Halder, S.; Das, R. K. *J. Org. Chem.* **2010**, *75*, 7061.

(14) (a) Jung, M. E.; Ho, D. G. *Org. Lett.* **2007**, *9*, 375. (b) Hong, B.-C.; Nimje, R. Y.; Wu, M.-F.; Sadani, A. A. *Eur. J. Org. Chem.* **2008**, *2008*, 1449. (c) Tan, B.; Shi, Z.; Chua, P. J.; Zhong, G. *Org. Lett.* **2008**, *10*, 3425. (d) Liu, S.-W.; Hsu, H.-C.; Chang, C.-H.; Tsai, H.-H. G.; Hou, D.-R. *Eur. J. Org. Chem.* **2010**, *2010*, 4771. (e) Wu, B.; Liu, G.-G.; Li, M.-Q.; Zhang, Y.; Zhang, S.-Y.; Qiu, J.-R.; Xu, X.-P.; Ji, S.-J.; Wang, X.-W. *Chem. Commun.* **2011**, *47*, 3992.

(15) (a) Hill, R. A.; Sutherland, A. *Nat. Prod. Rep.* **2010**, *27*, 1110. (b) Wang, F.; Gao, Y.; Zhang, L.; Liu, J.-K. *Org. Lett.* **2010**, *12*, 2354.

(16) The relative stereochemistry at the 2- and 6-positions of the cyclohexanone ring in our case is trans compared to the cis relationship found in bi-linderone.

(17) Benfatti, F.; Bottoni, A.; Cardillo, G.; Gentilucci, L.; Monari, M.; Mosconi, E.; Stenta, M.; Tolomelli, A. *Eur. J. Org. Chem.* **2008**, *2008*, 6119.

(18) For optimization of the domino Michael−Michael reaction, see the Supporting Information, Table 1.

(19) For X-ray crystallographic data of **3a**,**e**,**h**; **8a**,**c**,**g**; **16a**,**b**; **18a**; and **22b**,**c**, see the Supporting Information.

(20) For the details of computational studies, see the Supporting Information.

(21) The enolate isomerization probably took place via an intramolecular 1,5-H shift or intermolecular H-transfer mechanism.

(22) 3,5-Diaxial *cis* product **16a** gets stabilized by an intramolecular hydrogen bonding, as observed in its single-crystal X-ray structure. Computational studies revealed that *cis* product **16a** is energetically more stable than the corresponding *trans* isomer by 5.87 kcal mol^{-1}. For details, see the Supporting Information.

(23) (a) Kesenheimer, C.; Groth, U. *Org. Lett.* **2006**, *8*, 2507. (b) Sicinski, R. R.; DeLuca, H. F. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 899. (c) Zanello, L. P.; Norman, A. W. *J. Biol. Chem.* **1997**, *272*, 22617.

(24) (a) Hoashi, Y.; Yabuta, T.; Yuan, P.; Miyabe, H.; Takemoto, Y. *Tetrahedron* **2006**, *62*, 365. (b) He, P.; Liu, X.; Shi, J.; Lin, L.; Feng, X. *Org. Lett.* **2011**, *13*, 936. (c) Ayyagari, N.; Namboothiri, I. N. N. *Tetrahedron: Asymmetry* **2012**, *23*, 605 and references cited therein.

(25) (a) Angle, S. R.; Wada, T. *Tetrahedron Lett.* **1997**, *38*, 7955. (b) Yasuhara, T.; Nishimura, K.; Yamashita, M.; Fukuyama, N.; Yamada, K.-I.; Muraoka, O.; Tomioka, K. *Org. Lett.* **2003**, *5*, 1123. (c) Hoashi, Y.; Yabuta, T.; Takemoto, Y. *Tetrahedron Lett.* **2004**, *45*, 9185. (d) Yamashita, M.; Yamada, K.-I.; Tomioka, K. *J. Am. Chem. Soc.* **2004**, *126*, 1954.

(26) Chavan, S. P.; Kale, R. R.; Shivasankar, S.; Chandake, S. I.; Benjamin, S. B. *Synthesis* **2003**, *17*, 2695.

(27) For low-temperature NMR studies of **22b**, see the Supporting Information.

(28) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: Oxford, 1988.

DOI: 10.1021/acs.joc.5b01768
J. Org. Chem. 2015, 80, 9700−9712