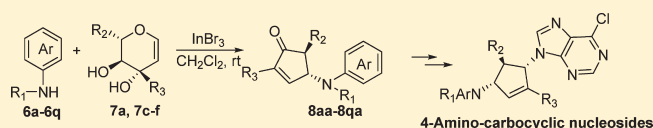


InBr₃-Catalyzed Glycosidation of Glycals with Arylamines: An Alternative Approach To Access 4-Aminocyclopent-2-enones

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S Supporting Information

ABSTRACT: To turn side products into major products, a novel strategy to access biologically active 4-aminocyclopent-2-enones was developed. These compounds were originally identified as side products but became major products when 3,5-dimethylpyran-3,4-diol **7a** was used as the substrate and 30% InBr₃ as the catalyst. Aryl- or heteroarylamines as well as variously substituted glycals can be used in this reaction, and the corresponding 4-aminocyclopent-2-enones were obtained in moderate to good yields. These compounds can be further used to prepare 4-aminocarbocyclic nucleosides.



INTRODUCTION

The cyclopentanone nucleus is the typical structural core of natural or synthetic prostaglandins possessing potent antiviral activity.^{1–7} The 2,3-unsaturated versions, cyclopent-2-enones, especially those with a 4-amino substituent (**A**, Figure 1) have also been reported with activity against a wide variety of DNA and RNA viruses. In early 1987, Masayoshi et al.⁸ patented a series of 4-aminocyclopent-2-enones, and similar compounds with more diversity were further claimed later by Santoro and his colleagues.^{5,9,10} In general, these 4-aminocyclopent-2-enones not only displayed antiviral activity on their own^{6,7} but also served as key intermediates to the synthesis of 4-amino carbocyclic nucleosides (**B**, Figure 1) as analogues of the antiviral drug Carbovir.¹¹

In spite of the interesting biological capacity of 4-aminocyclopent-2-enones, synthetic methods to approach this class of compounds have been less documented. In 1980, Scettri and colleagues¹² reported the first synthesis of 4-aminocyclopent-2-enones through a two-step process (Michael addition and aldol condensation). Later, two additional strategies were claimed^{5,10,12} including direct amination of 4-hydroxycyclopent-2-enone intermediates or Mo-catalyzed ring-opening of Diels–Alder cycloadducts followed by oxidation. These methods generally suffered from poor yields or substrate scope limitation.^{5,8} Therefore, new methods are needed to readily synthesize this class of compounds and to assist further evaluation of their pharmaceutical utility.¹³

RESULTS AND DISCUSSION

During our natural product-based drug discovery program, we^{14,15} recently found that glycosidation of aniline **1A** with glycal **2a** yielded two diastereomers **3Aa** and **4Aa** as the major products in 56% and 28% yields, respectively (Scheme 1). Interestingly, a side product was obtained when this reaction was conducted in

gram scales. Although the yield of this product was extremely poor (<5%), we managed to collect sufficient sample and fully characterize its structure as **5Aa** by all spectroscopic data including 2D NMR (HMBC, Scheme 1).

Similar side product **5Bb** was also obtained in 4% yield after a close re-examination of the reaction¹⁴ between aniline **1B** and glycal **2b** confirming the generality of such products in this reaction. Since compounds **5Aa** and **5Bb** belong to the 4-aminocyclopent-2-enone class, structurally distinct from our reported¹⁴ glycosidation products **3Aa**, **3Bb** and **4Aa**, **4Bb**, this indicated that a novel synthetic pathway for 4-aminocyclopent-2-enones might be developed. However, the paucity of the reaction yields (<5%) and substrate scope need to be fully addressed before this reaction can be experimentally useful.

In the synthesis of compounds **3Aa**, **3Bb** and **4Aa**, **4Bb**, we have elucidated¹⁴ the importance of the 3-OAc group in glycal **2a** or **2b** via coordination to InBr₃. Therefore, we envisioned that replacing such fast-moving acetate function in **2a** or **2b** with a free hydroxyl group (**7b**) would possibly slow down or even suppress the formation of products **3Aa**, **3Bb** and **4Aa**, **4Bb** and increase the formation of 4-aminocyclopent-2-enone **5Aa**, **5Bb**. In this regard, using *p*-chlorobenzeneamine **6a** as the model substrate, glycosidation with pyran-3,4-diol **7b** was conducted with 10% InBr₃ as the catalyst in CH₂Cl₂ at rt, a condition¹⁴ similar to that of preparation of compounds **3Aa**, **3Bb** and **4Aa**, **4Bb** (Scheme 2).

Unfortunately, this reaction led to a complex mixture containing several inseparable products. To further prevent the nucleophilic attack of aniline to the C-3 of glycal **7b**, sterically encumbered glycal **7a**¹⁶ bearing a C3-methyl group was employed, and we were pleased to find that the expected 4-aminocyclopent-2-enone **8aa**

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was obtained in 48% isolated yield and no cyclization products structurally similar to **3Aa**, **3Bb** or **4Aa**, **4Bb** were isolated at all. Compound **8aa** was also fully characterized by the spectroscopic data including 2D NMR (HMBC, $^1\text{H}-^1\text{H}$ COSY, Scheme 2), and the *trans* configuration between the 5-methyl and 4-amino groups was confirmed by the small couplings constant between H4 and H5 ($J_{\text{H4}-\text{H5}} = 2.7$ Hz) and the NOE interactions between H4 and 5-Me (see Supporting Information). This result indicated that 4-aminocyclopent-2-enone **8aa** could be prepared as the major product when a correct substrate, such as glycal **7a**, was employed. It must be noted that no Cotton effect was observed in the CD spectra of compounds **5Aa** and **8aa**, indicating that they were racemates.

To improve the reaction yield, we screened several Lewis acid catalysts through the model reaction of arylamine **6a** and glycal **7a** (see Table 1). It was found that 30 mol % of InBr_3 offered the best result leading to product **8aa** in 75% isolated yield. Other Lewis acids including InCl_3 , $\text{In}(\text{OTf})_3$, and FeCl_3 also promoted this reaction, but the yields were lower. Much poorer yield or decomposition was observed when TMSOTf or AgOTf was used as the catalyst.

With the optimized reaction conditions, we then set out to explore the substrate scope and limitation. First, a series of diversified arylamines (**6b–n**) bearing different substitution patterns were employed to react with glycal **7a** (Table 2). The reaction generally proceeded smoothly, affording 4-aminocyclopent-2-enones **8ba–na** in moderate to good yields. The location, size, and electronic properties of the substituents in arylamines did not play significant roles in the production of the corresponding products, except for unsubstituted aniline **6e**, *m*-toluidine **6g**, and 4-trifluoromethylbenzenamine **6j** giving somewhat lower yields (45–57%). Naphthalen-2-amine (**6i**) gave product **8ia** also in lower yield (57%), indicating that the steric effect in the substrate played a role in the reaction. This was further confirmed by the finding that naphthalen-1-amine did not react with glycal

7a at all (not shown in the Table 2). It is of note that secondary amines **6l** and **6n** also participated in this reaction and offered products **8la** and **8na** in 85% and 68% yields, respectively. However, heteroaryl amine **6m** reacted with **7a** more slowly, yielding 4-aminocyclopent-2-enone **8ma** in only 33% yield.

It has to be noted that in several cases further glycosidation of the second NH in anilines with glycal **7a** was observed as a negligible side reaction. However, such side reactions can be significantly enhanced when 2 equiv or more of glycal **7a** was used, especially in the case of anilines **6o** (*p*-MeO-C₆H₄NH₂), **6p** (*p*-AcNH-C₆H₄NH₂), and **6q** (*p*-morpholinoaniline) each bearing an electron-donating substituent. As illustrated in Figure 2, treating anilines **6o–q** with 2 equiv of glycal **7a** for 24 h afforded 4-aminocyclopent-2-enones **8oa**, **8pa**, and **8qa** in 49%, 41%, and

Table 1. Optimization of Reactions Conditions of **6a** and **7a**

entry	Lewis acid	time (h)	solvent	yield ^a (%)
1	InBr_3 (10 mol %)	2	CH_2Cl_2	48
2	InBr_3 (30 mol %)	4	CH_2Cl_2	75
3	InBr_3 (30 mol %)	12	CH_2Cl_2	75
4	InCl_3 (30 mol %)	12	CH_2Cl_2	12
5	$\text{In}(\text{OTf})_3$ (30 mol %)	12	CH_2Cl_2	36
6	FeCl_3 (1.0 equiv)	10	CH_2Cl_2	50
7	AuCl_3 (30 mol %)	12	CH_3CN	trace
8	TMSOTf (1.0 equiv)	12	CH_2Cl_2	dec
9	AgOTf (30 mol %)	12	CH_2Cl_2	8

^a Isolated yield of **8aa**.

Scheme 2. Reactions of Arylamine **6a** with Glycals **7a,b**

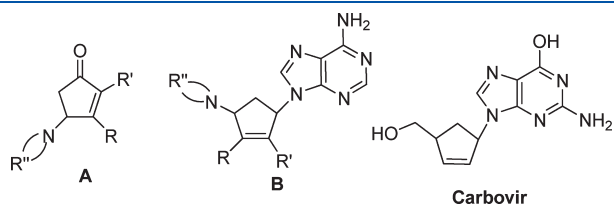
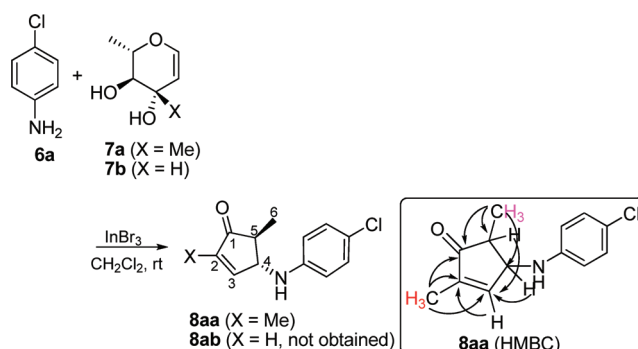
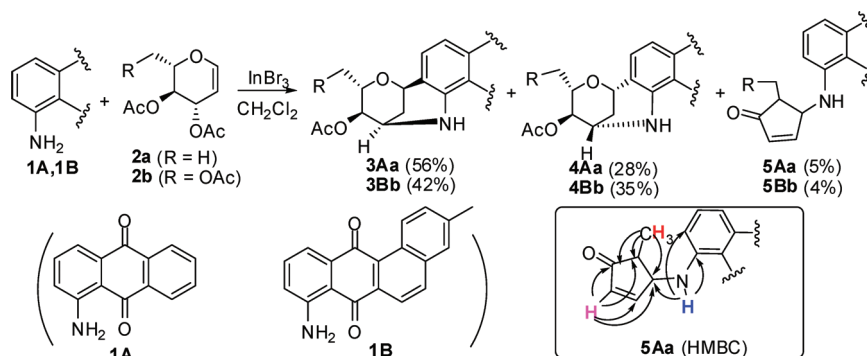


Figure 1. Reported strategies to access 4-aminocyclopent-2-enones.

Scheme 1. Glycosidation of Arylamines **1A,B** and Glycals **2a,b**



51% yields, respectively, along with the corresponding over-reacted products **80a'**, **8pa'**, and **8qa'** in 22%, 32%, and 18% yields.

To further explore the substrate scope, glycals **7a**, **7c**, **7d**, **7e**, and **7f** with variant substituents¹⁶ were subjected to the same reaction. As depicted in Table 3, the corresponding 4-aminocyclopent-2-enones were obtained in 49–78% isolated yields. It is noteworthy that CH₂OH-substituted glycals **7e** survived the reaction very well, leading to cyclopentenone **8ae** in 64% yield (entry 4), which could be used for further transformations.

Although InBr₃-catalyzed glycosidations of anilines and glycals have been reported previously by us^{14,15} and others,^{16,17} the distinguished different products in the current study indicated that a new reaction mechanism may exist that favors the formation of 4-aminocyclopent-2-enones. Therefore, to rationalize this process, a tentative reaction pathway was proposed according to Minehan's report^{17b} involving the formation of a common cationic intermediate **I** (Figure 3). Such indate species (**I**) can be formed from glycal **7a** through a Ferrier-type rearrangement.^{14,17b} Subsequent nucleophilic attack by aniline **6e** followed by ring-opening yielded species **III**, which was then converted to the racemic *trans*

product, 4-aminocyclopent-2-enone **8ea**, through intermediate **IV**^{18,19} by a 4π conrotatory electrocyclic procedure.

To explore the synthetic utility of this methodology, 4-amino carbocyclic nucleosides were prepared from the 4-aminocyclopent-2-enone

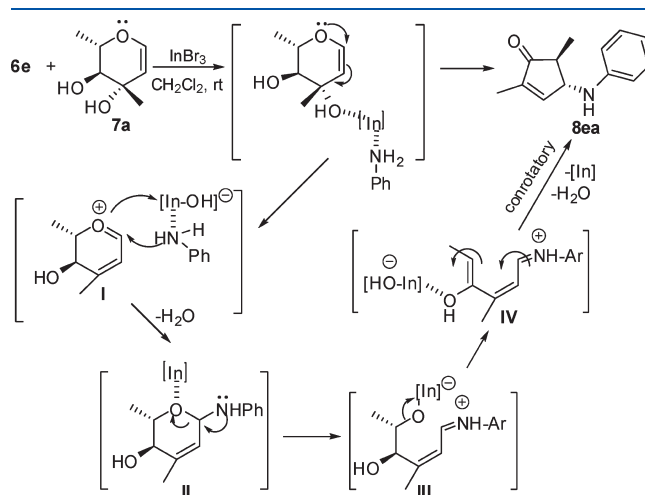


Figure 3. Possible reaction pathway.

Table 2. Substrate Scope Study: InBr₃-Catalyzed Glycosidation of Aryl Amines with Glycal **7a**^a

entry	arylamine	product	yield ^b (%)
1	<i>p</i> -Cl-C ₆ H ₄ NH ₂ (6a)	8aa	75
2	<i>m</i> -Cl-C ₆ H ₄ NH ₂ (6b)	8ba	65
3	<i>p</i> -Br-C ₆ H ₄ NH ₂ (6c)	8ca	70
4	<i>p</i> -F-C ₆ H ₄ NH ₂ (6d)	8da	73
5	C ₆ H ₅ NH ₂ (6e)	8ea	57
6	<i>p</i> -toluidine (6f)	8fa	78
7	<i>m</i> -toluidine (6g)	8ga	45
8	<i>m,p</i> -(MeO) ₂ -C ₆ H ₃ NH ₂ (6h)	8ha	68
9	naphthalen-2-amine (6i)	8ia	57
10	<i>p</i> -CF ₃ -C ₆ H ₄ NH ₂ (6j)	8ja	54
11	biphenyl-4-amine (6k)	8ka	78
12	<i>N</i> -methylaniline (6l)	8la	85
13	5-methylisoxazol-3-amine (6m)	8ma	33
14	1,2,3,4-tetrahydroquinoline (6n)	8na	68

^a The concentration was 0.05 M. ^b Isolated yield.

Table 3. Scope Study: Reactions of Arylamines with Different Glycals^a

entry	amine	glycals	product	yield ^b (%)
1	6a	7a (R ₁ = R ₂ = Me)	8aa	75
2	6a	7c (R ₁ = Me, R ₂ = H)	8ac	49
3	6a	7d (R ₁ = <i>n</i> -Bu, R ₂ = Me)	8ad	68
4	6a	7e (R ₁ = Me, R ₂ = OHCH ₂)	8ae	64
5	6a	7f (R ₁ = <i>n</i> -Hex, R ₂ = Me)	8af	63
6	6l	7a (R ₁ = R ₂ = Me)	8la	85
7	6l	7c (R ₁ = Me, R ₂ = H)	8lc	56
8	6l	7d (R ₁ = <i>n</i> -Bu, R ₂ = Me)	8ld	76
9	6k	7a (R ₁ = R ₂ = Me)	8ka	78
10	6k	7c (R ₁ = Me, R ₂ = H)	8kc	69

^a The concentration was 0.05 M. ^b Isolated yield.

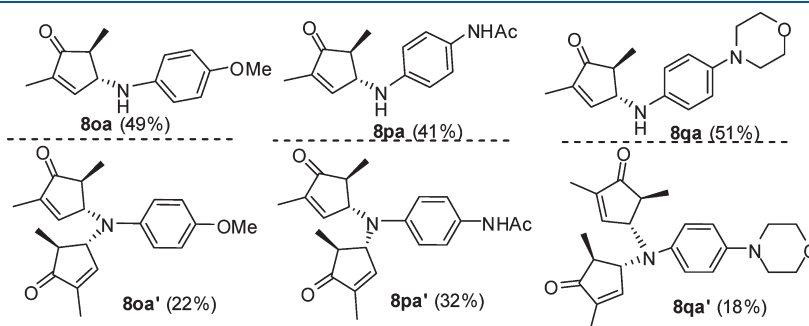
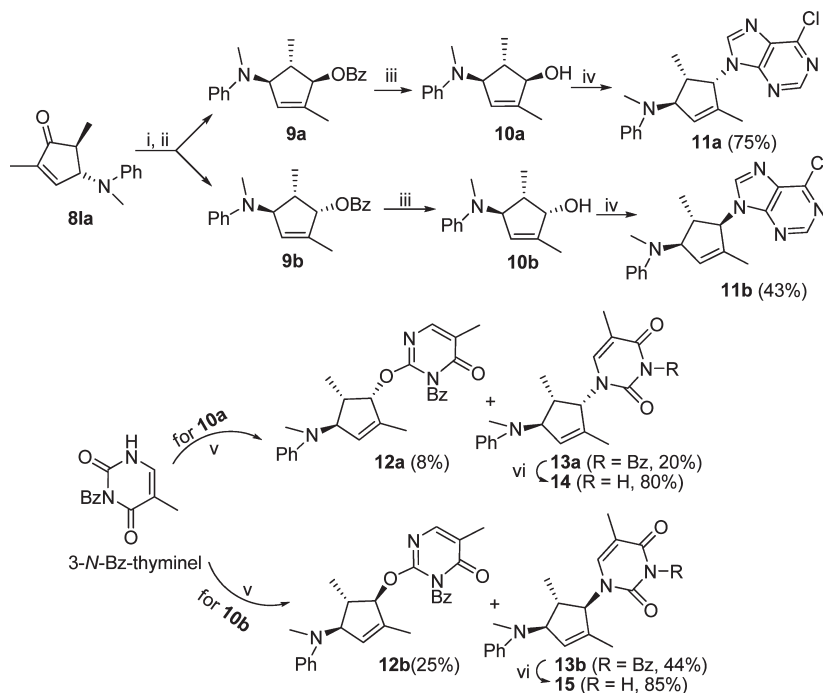


Figure 2. Reaction Products of Arylamines **6o–q** with Excessive Glycal **7a**

Scheme 3. Synthetic Utility Study^a

^a Reagents and conditions: (i) $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, NaBH_4 , MeOH, rt, 2 h, 99%, (2:1 *trans:cis*); (ii) $(\text{PhCO})_2\text{O}$, DMAP, Py, CH_2Cl_2 , rt, 6 h, isolation, 99%; (iii) $\text{LiOH} \cdot \text{H}_2\text{O}$, MeOH/THF/ H_2O = 5:3:2, rt, 5 h; (iv) 6-chloropurine, DEAD, PPh_3 , THF, rt, 1 h; (v) 3-*N*-benzoylthymine, DEAD, PPh_3 , THF, rt, overnight; (vi) NH_3 in MeOH, rt, overnight.

8a (Scheme 3). Luche reduction of ketone **8a** followed by a *cis/trans* separation process yielded *trans,trans*-**10a** and *trans,cis*-**10b**. Mitsunobu condensation of **10a** and **10b** with 6-chloropurine afforded the corresponding carbocyclic nucleosides **11a** and **11b** in 75% and 43% yield, respectively. These two compounds can be used as precursors to prepare diversified nucleosides **B** (Figure 1) through further functionalizing the purine 4'-Cl substituent. Similar condensation of **10a** or **10b** with *N*-benzoylthymine²⁰ proved to be sluggish, yielding the corresponding carbocyclic *N*-nucleosides **13a** and **13b** as the major products in moderate yields, along with corresponding carbocyclic *O*-nucleosides **12a** and **12b** as the minor products. Debenzoylation of **13a** and **13b** provided the corresponding carbocyclic *N*-nucleosides **14** and **15** in 80% and 85% yield, respectively. The relative *trans,trans*- and *trans,cis*-configurations between H1, H4, and H5 in these compounds were determined by the corresponding small coupling constants¹¹ in the ¹H NMR spectra and by the NOE effects of intermediates **9a,9b**.

CONCLUSION

A novel strategy to access biologically active 4-aminocyclopent-2-enones was developed. These compounds were originally identified as side products and then were turned into major products by using the appropriately substituted glycal substrate and 30% InBr_3 as the catalyst. A variety of aryl- or heteroaryl amines as well as diversified glycals were used in this reaction, and the corresponding 4-aminocyclopent-2-enones were obtained in moderate to good yields. The unique features of the products not only provide potential value for drug development but also provide the basis for further generation of diversified carbocyclic nucleosides.

EXPERIMENTAL SECTION

General Procedure for InBr_3 -Catalyzed Glycosidation of Glycals and Aryl Amines. InBr_3 (21.2 mg, 0.06 mmol) was placed in a dried reaction flask, which was heated in vacuo and filled with N_2 . A solution of an appropriate glycal (0.20 mmol) and a substituted or unsubstituted aniline (0.20 mmol) in anhydrous CH_2Cl_2 (4 mL) was added under N_2 . The mixture was stirred at 27 °C under N_2 for 12 h. After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with water and extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , concentrated in vacuo, and purified by column chromatography on silica gel to afford corresponding 4-aminocyclopent-2-enones **5Aa–8kc**.

4-Amino-5-methylcyclopent-2-enone (5Aa): red solid (obtained as side product in 5% yield); ¹H NMR (300 MHz, CDCl_3) δ 9.98 (d, J = 7.5 Hz, 1H), 8.23 (m, 2H), 7.69 (m, 5H), 7.17 (d, J = 8.1 Hz, 1H), 6.36 (m, 1H), 4.55 (m, 1H), 2.45 (m, 1H), 1.40 (d, J = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl_3) δ 207.8, 185.4, 183.4, 159.3, 150.5, 135.6, 134.9, 134.6 (2C), 134.1, 133.3, 132.8, 126.8, 126.7, 117.5, 116.6, 113.8, 60.5, 49.1, 14.2; MS (EI-LR) 317 (M^+); HRMS calcd for $\text{C}_{20}\text{H}_{15}\text{NO}_3$ (M^+) 317.1052, found 317.1046.

4-Amino-5-acetyloxymethylcyclopent-2-enone (5Bb): red solid (obtained as side product in 4% yield); ¹H NMR (300 MHz, CDCl_3) δ 9.86 (d, J = 8.7 Hz, 1H), 9.53 (d, J = 9.3 Hz, 1H), 8.29 (d, J = 8.7 Hz, 1H), 8.08 (d, J = 8.7 Hz, 1H), 7.73 (m, 1H), 7.62 (m, 4H), 7.18 (d, J = 7.8 Hz, 1H), 6.41 (m, 1H), 4.96 (d, J = 7.8 Hz, 1H), 4.54 (m, 2H), 2.72 (m, 1H), 2.55 (s, 3H), 2.01 (s, 3H); ¹³C NMR (100 MHz, CDCl_3) δ 203.8, 186.3, 185.9, 170.7, 160.8, 149.5, 138.8, 136.7, 136.5, 135.6 (2C), 134.9, 134.5, 132.1, 128.7, 128.3, 128.2, 127.6, 122.2, 116.9, 116.7, 113.2, 61.6, 55.9, 53.3, 21.5, 20.7; MS (EI-LR) 439 (M^+); HRMS calcd for $\text{C}_{27}\text{H}_{21}\text{NO}_5$ (M^+) 439.1420, found 439.1410.

2,5-Dimethyl-4-(4-chlorophenylamino)cyclopent-2-enone (8aa): colorless oil, 75% yield; ¹H NMR (300 MHz, CDCl_3) δ 7.19 (s,

1H), 7.15 (m, 2H), 6.60 (m, 2H), 4.17 (d, $J = 6.0$ Hz, 1H), 3.77 (br s, 1H), 2.19 (dq, $J = 2.7, 7.5$ Hz, 1H), 1.80 (s, 3H), 1.31 (d, $J = 7.5$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 208.8, 153.8, 145.4, 142.3, 129.3 (2C), 122.8, 114.6 (2C), 60.0, 48.9, 14.8, 10.2; MS (EI-LR) 235 (M^+); HRMS calcd for $\text{C}_{13}\text{H}_{14}\text{ClNO}$ (M^+) 235.0764, found 235.0757.

2,5-Dimethyl-4-(3-chlorophenylamino)cyclopent-2-enone (8ba): colorless oil, 65% yield; ^1H NMR (300 MHz, CDCl_3) δ 7.21 (s, 1H), 7.10 (t, $J = 8.1$ Hz, 1H), 6.71 (m, 1H), 6.65 (t, $J = 1.8$ Hz, 1H), 6.54 (dd, $J = 2.1, 8.1$ Hz, 1H), 4.19 (br s, 1H), 3.80 (br s, 1H), 2.19 (dq, $J = 2.4, 7.5$ Hz, 1H), 1.82 (s, 3H), 1.33 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 208.7, 153.6, 147.9, 142.4, 135.2, 130.4, 118.1, 113.1, 111.7, 59.7, 48.9, 14.8, 10.2; MS (EI-LR) 235 (M^+); HRMS calcd for $\text{C}_{13}\text{H}_{14}\text{ClNO}$ (M^+) 235.0764, found 235.0761.

4-(4-Bromophenylamino)-2,5-dimethylcyclopent-2-enone (8ca): yellow oil, 70% yield; ^1H NMR (300 MHz, CDCl_3) δ 7.27 (m, 3H), 6.54 (m, 2H), 4.17 (s, 1H), 3.73 (br s, 1H), 2.19 (m, 1H), 1.81 (s, 3H), 1.31 (d, $J = 7.5$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 208.8, 153.7, 145.8, 142.4, 132.2, 131.9, 116.7, 115.1, 109.9, 60.0, 48.9, 14.9, 10.2; MS (EI-LR) 279 (M^+); HRMS calcd for $\text{C}_{13}\text{H}_{14}\text{BrNO}$ (M^+) 279.0259, found 279.0252.

4-(4-Fluorophenylamino)-2,5-dimethylcyclopent-2-enone (8da): colorless oil, 73% yield; ^1H NMR (300 MHz, CDCl_3) δ 7.21 (s, 1H), 6.91 (m, 2H), 6.62 (m, 2H), 4.15 (s, 1H), 3.52 (br s, 1H), 2.19 (m, 1H), 1.80 (s, 3H), 1.30 (d, $J = 7.5$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 208.9, 156.2 (d, $J = 235.5$ Hz), 154.1, 143.0, 142.1, 116.0, 115.8, 114.7, 114.6, 60.7, 48.8, 14.8, 10.2; MS (EI-LR) 219 (M^+); HRMS calcd for $\text{C}_{13}\text{H}_{14}\text{FNO}$ (M^+) 219.1059, found 219.1047.

4-(Phenylamino)-2,5-dimethylcyclopent-2-enone (8ea): yellow oil, 57% yield; ^1H NMR (300 MHz, CDCl_3) δ 7.23 (m, 3H), 6.77 (t, $J = 7.2$ Hz, 1H), 6.68 (d, $J = 8.1$ Hz, 2H), 4.23 (d, $J = 2.1$ Hz, 1H), 3.68 (br s, 1H), 2.23 (dq, $J = 2.4$ Hz, $J = 7.5$ Hz, 1H), 1.81 (s, 3H), 1.31 (d, $J = 7.5$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 209.1, 154.3, 146.7, 142.0, 129.4 (2C), 118.3, 113.5 (2C), 60.0, 49.0, 14.8, 10.2; MS (EI-LR) 201 (M^+); HRMS calcd for $\text{C}_{13}\text{H}_{15}\text{NO}$ (M^+) 201.1154, found 201.1162.

4-(4-Methylphenylamino)-2,5-dimethylcyclopent-2-enone (8fa): colorless oil, 78% yield; ^1H NMR (300 MHz, CDCl_3) δ 7.23 (s, 1H), 7.02 (d, $J = 8.1$ Hz, 2H), 6.60 (d, $J = 8.4$ Hz, 2H), 4.20 (s, 1H), 3.48 (br s, 1H), 2.22 (m, 4H), 1.81 (s, 3H), 1.31 (d, $J = 7.5$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 209.2, 154.5, 144.4, 141.9, 129.9 (2C), 127.7, 113.8 (2C), 60.4, 49.0, 20.3, 14.8, 10.2; MS (EI-LR) 215 (M^+); HRMS calcd for $\text{C}_{14}\text{H}_{17}\text{NO}$ (M^+) 215.1310, found 215.1319.

2,5-Dimethyl-4-(3-tolylamino)cyclopent-2-enone (8ga): colorless oil, 45% yield; ^1H NMR (300 MHz, CDCl_3) δ 7.23 (s, 1H), 7.11 (m, 1H), 6.60 (d, $J = 6.9$ Hz, 1H), 6.50 (s, 2H), 4.22 (s, 1H), 3.67 (br s, 1H), 2.29 (s, 3H), 2.20 (m, 1H), 1.81 (s, 3H), 1.31 (d, $J = 7.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 209.1, 154.4, 146.7, 141.9, 139.2, 129.3, 119.2, 114.3, 110.6, 59.9, 49.0, 21.5, 14.8, 10.1; MS (EI-LR) 215 (M^+); HRMS calcd for $\text{C}_{14}\text{H}_{17}\text{NO}$ (M^+) 215.1310, found 215.1314.

4-(3,4-Dimethoxyphenylamino)-2,5-dimethylcyclopent-2-enone (8ha): yellow oil, 68% yield; ^1H NMR (300 MHz, CDCl_3) δ 7.23 (m, 1H), 6.76 (dd, $J = 1.5$ Hz, $J = 8.4$ Hz, 1H), 6.29 (s, 1H), 6.22 (m, 1H), 4.14 (s, 1H), 3.82 (m, 6H), 3.42 (br s, 1H), 2.19 (m, 1H), 1.80 (s, 3H), 1.30 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 209.2, 154.5, 150.0, 142.3, 142.0, 141.3, 113.0, 104.7, 99.9, 61.1, 56.5, 55.7, 48.9, 14.9, 10.2; MS (EI-LR) 261 (M^+); HRMS calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_3$ (M^+) 261.1365, found 261.1357.

2,5-Dimethyl-4-(naphthalene-2-ylamino)cyclopent-2-enone (8ia): yellow oil, 57% yield; ^1H NMR (300 MHz, CDCl_3) δ 7.65 (m, 3H), 7.39 (m, 1H), 7.31 (s, 1H), 7.24 (m, 1H), 6.91 (m, 2H), 4.37 (br s, 1H), 3.89 (br s, 1H), 2.27 (m, 1H), 1.84 (s, 3H), 1.38 (d, $J = 7.5$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 209.1, 154.1, 144.4, 142.2, 134.9, 129.3, 127.8, 127.6, 126.5, 125.9, 122.5, 118.1, 105.6, 59.9, 49.0, 14.9, 10.2; MS (EI-LR) 251 (M^+); HRMS calcd for $\text{C}_{17}\text{H}_{17}\text{NO}$ (M^+) 251.1310, found 251.1307.

2,5-Dimethyl-4-(4-(trifluoromethyl)phenylamino)cyclopent-2-enone (8ja): white solid, 54% yield; ^1H NMR (300 MHz, CDCl_3) δ 7.43 (d, $J = 8.7$ Hz, 2H), 7.20 (s, 1H), 6.68 (d, $J = 8.1$ Hz, 2H), 4.28 (m, 1H), 4.06 (m, 1H), 2.23 (dq, $J = 2.4$ Hz, $J = 7.5$ Hz, 1H), 1.83 (s, 3H), 1.34 (d, $J = 7.5$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 208.4, 153.2, 149.3, 142.7, 126.8 (2C), 112.5 (2C), 59.5, 49.0, 14.8, 10.2; MS (EI-LR) 269 (M^+); HRMS calcd for $\text{C}_{14}\text{H}_{14}\text{F}_3\text{NO}$ (M^+) 269.1027, found 269.1027.

4-(Biphenyl-4-ylamino)-2,5-dimethylcyclopent-2-enone (8ka): yellow solid, 78% yield; ^1H NMR (300 MHz, CDCl_3) δ 7.43 (m, 6H), 7.25 (m, 2H), 6.73 (d, $J = 8.4$ Hz, 2H), 4.25 (br s, 1H), 3.82 (br s, 1H), 2.25 (dq, $J = 2.4$ Hz, $J = 7.5$ Hz, 1H), 1.82 (s, 3H), 1.34 (d, $J = 7.5$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 209.0, 154.2, 146.1, 142.1, 140.8, 131.2, 128.6 (2C), 128.1 (2C), 126.2 (3C), 113.7 (2C), 59.9, 49.0, 14.8, 10.2; MS (EI-LR) 277 (M^+); HRMS calcd for $\text{C}_{19}\text{H}_{19}\text{NO}$ (M^+) 277.1467, found 277.1460.

2,5-Dimethyl-4-(methyl(phenyl)amino)cyclopent-2-enone (8la): yellow oil, 85% yield; ^1H NMR (300 MHz, CDCl_3) δ 7.25 (m, 2H), 7.13 (s, 1H), 6.87 (d, $J = 8.1$ Hz, 2H), 6.79 (m, 1H), 4.66 (d, $J = 2.1$ Hz, 1H), 2.69 (s, 3H), 2.35 (dq, $J = 2.7$ Hz, $J = 7.5$ Hz, 1H), 1.85 (m, 3H), 1.25 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 208.7, 155.7, 149.7, 142.9, 129.2 (2C), 117.9, 113.9 (2C), 65.9, 44.5, 32.4, 14.6, 10.2; MS (EI-LR) 215 (M^+); HRMS calcd for $\text{C}_{14}\text{H}_{17}\text{NO}$ (M^+) 215.1310, found 215.1309.

2,5-Dimethyl-4-(5-methylisoxazol-3-ylamino)cyclopent-2-enone (8ma): yellow oil, 33% yield; ^1H NMR (300 MHz, CDCl_3) δ 7.23 (s, 1H), 5.5 (s, 1H), 4.30 (m, 1H), 3.90 (d, $J = 9.0$ Hz, 1H), 2.30 (s, 3H), 2.21 (dq, $J = 2.7$ Hz, $J = 7.2$ Hz, 1H), 1.80 (s, 3H), 1.31 (d, $J = 7.5$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 208.8, 169.1, 163.7, 154.0, 142.2, 93.3, 60.1, 49.0, 14.4, 12.4, 10.1; MS (EI-LR) 206 (M^+); HRMS calcd for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_2$ (M^+) 206.1055, found 206.1061.

4-(3,4-Dihydroquinolin-1(2H)-yl)-2,5-dimethylcyclopent-2-enone (8na): yellow oil, 68% yield; ^1H NMR (300 MHz, CDCl_3) δ 7.14 (d, $J = 1.5$ Hz, 1H), 7.01 (m, 2H), 6.80 (d, $J = 8.4$ Hz, 1H), 6.64 (t, $J = 7.2$ Hz, 1H), 4.71 (s, 1H), 3.07 (m, 2H), 2.78 (t, $J = 6.3$ Hz, 2H), 2.45 (m, 1H), 1.88 (m, 5H), 1.33 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 209.0, 156.1, 145.1, 142.8, 129.6, 127.0, 123.3, 116.6, 111.2, 64.0, 44.4, 43.4, 28.1, 22.2, 15.0, 10.3; MS (EI-LR) 241 (M^+); HRMS calcd for $\text{C}_{16}\text{H}_{19}\text{NO}$ (M^+) 241.1467, found 241.1469.

4-(4-Methoxyphenylamino)-2,5-dimethylcyclopent-2-enone (8oa): yellow oil, 49% yield; ^1H NMR (300 MHz, CDCl_3) δ 7.23 (s, 1H), 6.80 (d, $J = 8.7$ Hz, 2H), 6.66 (d, $J = 8.7$ Hz, 2H), 4.14 (s, 1H), 3.75 (s, 3H), 2.18 (m, 1H), 1.80 (s, 3H), 1.29 (d, $J = 7.5$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 209.2, 154.6, 152.8, 141.9, 140.7, 115.4 (2C), 115.0 (2C), 61.2, 55.7, 48.9, 29.6, 14.8, 10.2; MS (EI-LR) 231 (M^+); HRMS calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_2$ (M^+) 231.1259, found 231.1260.

4,4'-(4-Methoxyphenylazanediyl)bis(2,5-dimethylcyclopent-2-enone) (8oa'): yellow oil, 22% yield; ^1H NMR (300 MHz, CDCl_3) δ 7.23 (s, 1H), 7.20 (s, 1H), 6.88 (dd, $J = 1.5$ Hz, $J = 8.7$ Hz, 2H), 6.74 (d, $J = 8.7$ Hz, 2H), 4.02 (m, 2H), 3.74 (s, 3H), 2.31 (m, 2H), 1.77 (s, 6H), 1.22 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 208.5, 208.4, 156.4, 156.2, 142.4, 142.3, 139.2, 138.9, 126.1, 126.0, 114.0 (2C), 67.3, 66.9, 55.3, 46.1, 46.0, 14.1 (2C), 10.3 (2C); MS (EI-LR) 339 (M^+); HRMS calcd for $\text{C}_{21}\text{H}_{25}\text{NO}_3$ (M^+) 339.1834, found 339.1842.

N-(4-(3,5-Dimethyl-4-oxocyclopent-2-enylamino)phenyl)acetamide (8pa): yellow oil, 41% yield; ^1H NMR (300 MHz, CDCl_3) δ 7.29 (d, $J = 9.0$ Hz, 2H), 7.20 (m, 2H), 6.63 (d, $J = 9.0$ Hz, 2H), 4.18 (br s, 1H), 2.21 (m, 4H), 1.80 (s, 3H), 1.32 (d, $J = 7.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 209.0, 168.1, 154.2, 143.9, 142.1, 129.0, 122.4 (2C), 113.9 (2C), 60.4, 48.9, 24.2, 14.8, 10.2; MS (EI-LR) 258 (M^+); HRMS calcd for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_2$ (M^+) 258.1368, found 258.1367.

N-(4-(Bis(3,5-dimethyl-4-oxocyclopent-2-enyl)amino)phenyl)acetamide (8pa'): yellow oil, 32% yield; ^1H NMR (300 MHz, CDCl_3) δ 7.59 (br s, 1H), 7.31 (dd, $J = 2.1$ Hz, $J = 8.7$ Hz, 2H), 7.20 (m,

2H), 6.83 (dd, $J = 2.1$ Hz, $J = 8.7$ Hz, 2H), 4.08 (br s, 2H), 2.39 (m, 2H), 2.11 (s, 3H), 1.83 (m, 6H), 1.22 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 208.2, 208.0, 168.3, 156.7 (2C), 143.2, 143.1, 142.8, 142.6, 121.7, 121.6, 121.0, 120.9, 66.4, 65.5, 46.0, 45.7, 24.2, 14.0, 13.9, 10.3, 10.2; MS (EI-LR) 366 (M^+); HRMS calcd for $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_3$ (M^+) 366.1943, found 366.1930.

2,5-Dimethyl-4-(4-morpholinophenylamino)cyclopent-2-enone (8qa): colorless oil, 51% yield; ^1H NMR (300 MHz, CDCl_3) δ 7.22 (s, 1H), 6.84 (d, $J = 8.4$ Hz, 2H), 6.66 (d, $J = 8.4$ Hz, 2H), 4.15 (br s, 1H), 3.83 (m, 4H), 3.43 (br s, 1H), 3.04 (m, 4H), 2.20 (dq, $J = 2.4$ Hz, $J = 7.5$ Hz, 1H), 1.80 (s, 3H), 1.29 (d, $J = 7.5$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 209.2, 154.6, 144.3, 141.9, 140.9, 118.2 (2C), 115.0 (2C), 67.0 (2C), 60.9, 50.9 (2C), 48.9, 14.8, 10.2; MS (EI-LR) 286 (M^+); HRMS calcd for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_2$ (M^+) 286.1681, found 286.1673.

4,4'-(4-Morpholinophenylazanediyl)bis(2,5-dimethylcyclopent-2-enone (8qa')): colorless oil, 18% yield; ^1H NMR (300 MHz, CDCl_3) δ 7.23 (m, 2H), 6.87 (m, 2H), 6.75 (d, $J = 8.7$ Hz, 2H), 4.03 (s, 2H), 3.84 (s, 4H), 3.08 (s, 4H), 2.34 (m, 2H), 1.78 (s, 6H), 1.25 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 208.4 (2C), 156.6, 156.4, 142.5, 142.3, 125.3, 125.2, 116.2 (2C), 67.3 (2C), 66.8 (2C), 49.5 (2C), 46.2, 46.1, 14.1 (2C), 10.3 (2C); MS (EI-LR) 394 (M^+); HRMS calcd for $\text{C}_{24}\text{H}_{30}\text{N}_2\text{O}_3$ (M^+) 394.2256, found 394.2253.

4-(4-Chlorophenylamino)-2-methylcyclopent-2-enone (8ac): yellow oil, 49% yield; ^1H NMR (300 MHz, CDCl_3) δ 7.25 (s, 1H), 7.15 (m, 2H), 6.57 (m, 2H), 4.58 (br s, 1H), 3.76 (br s, 1H), 2.89 (dd, $J = 6$ Hz, $J = 18.6$ Hz, 1H), 2.17 (dd, $J = 2.1$ Hz, $J = 18.6$ Hz, 1H), 1.83 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 206.6, 155.1, 145.1, 143.9, 129.3 (2C), 123.1, 114.5 (2C), 51.7, 42.9, 10.0; MS (EI-LR) 221 (M^+); HRMS calcd for $\text{C}_{12}\text{H}_{12}\text{ClNO}$ (M^+) 221.0607, found 221.0608.

2-Butyl-4-(4-chlorophenylamino)-5-methylcyclopent-2-enone (8ad): yellow oil, 68% yield; ^1H NMR (300 MHz, CDCl_3) δ 7.15 (m, 3H), 6.59 (d, $J = 8.7$ Hz, 2H), 4.17 (s, 1H), 3.75 (m, 1H), 2.19 (m, 3H), 1.47 (m, 2H), 1.29 (m, 5H), 0.90 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 208.5, 152.7, 146.8, 145.3, 129.2 (2C), 122.8, 114.5 (2C), 60.1, 49.2, 29.5, 24.4, 22.4, 14.7, 13.7; MS (EI-LR) 277 (M^+); HRMS calcd for $\text{C}_{16}\text{H}_{20}\text{ClNO}$ (M^+) 277.1233, found 277.1235.

4-(4-Chlorophenylamino)-5-(hydroxymethyl)-2-methylcyclopent-2-enone (8ae): yellow oil, 64% yield; ^1H NMR (300 MHz, CDCl_3) δ 7.30 (s, 1H), 7.13 (d, $J = 8.7$ Hz, 2H), 6.64 (d, $J = 8.7$ Hz, 2H), 4.58 (s, 1H), 4.08 (dd, $J = 4.2$ Hz, $J = 11.1$ Hz, 1H), 3.90 (dd, $J = 4.8$ Hz, $J = 11.1$ Hz, 1H), 3.80 (br s, 1H), 2.41 (br s, 1H), 2.35 (m, 1H), 1.81 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 207.6, 156.1, 145.1, 142.9, 129.3 (2C), 123.1, 114.7 (2C), 60.5, 56.0, 54.6, 10.0; MS (EI-LR) 251 (M^+); HRMS calcd for $\text{C}_{13}\text{H}_{14}\text{ClNO}_2$ (M^+) 251.0713, found 251.0713.

4-(4-Chlorophenylamino)-2-hexyl-5-methylcyclopent-2-enone (8af): yellow oil, 63% yield; ^1H NMR (300 MHz, CDCl_3) δ 7.14 (m, 3H), 6.59 (d, $J = 8.4$ Hz, 2H), 4.17 (s, 1H), 3.75 (br s, 1H), 2.18 (m, 3H), 1.45 (m, 2H), 1.28 (m, 9H), 0.87 (t, $J = 6.3$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 208.5, 152.6, 146.9, 145.3, 129.2 (2C), 122.8, 114.5 (2C), 60.1, 49.2, 31.4, 29.0, 27.3, 24.7, 22.4, 14.7, 14.0; MS (EI-LR) 305 (M^+); HRMS calcd for $\text{C}_{18}\text{H}_{24}\text{ClNO}$ (M^+) 305.1546, found 305.1547.

2-Methyl-4-(methyl(phenyl)amino)cyclopent-2-enone (8lc): yellow oil, 56% yield; ^1H NMR (300 MHz, CDCl_3) δ 7.25 (m, 3H), 6.84 (m, 3H), 5.04 (br s, 1H), 2.73 (m, 4H), 2.26 (dd, $J = 2.1$ Hz, $J = 18.6$ Hz, 1H), 1.87 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 206.9, 157.2, 149.6, 144.0, 129.3 (2C), 118.1, 114.0 (2C), 57.3, 388.2, 32.2, 10.0; MS (EI-LR) 201 (M^+); HRMS calcd for $\text{C}_{13}\text{H}_{15}\text{NO}$ (M^+) 201.1154, found 201.1161.

2-Butyl-5-methyl-4-(methyl(phenyl)amino)cyclopent-2-enone (8ld): yellow oil, 76% yield; ^1H NMR (300 MHz, CDCl_3) δ 7.27 (t, $J = 7.8$ Hz, 2H), 7.11 (s, 1H), 6.89 (d, $J = 8.4$ Hz, 2H), 6.79 (t, $J = 6.9$ Hz, 1H), 4.68 (s, 1H), 2.71 (s, 3H), 2.38 (dq, $J = 2.7$ Hz, $J = 7.5$ Hz,

1H), 2.26 (m, 2H), 1.52 (m, 2H), 1.38 (m, 2H), 1.26 (d, $J = 7.5$ Hz, 3H), 0.94 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 208.5, 154.6, 149.7, 147.5, 129.2 (2C), 117.8, 113.9 (2C), 65.9, 44.8, 32.3, 29.6, 24.4, 22.3, 14.6, 13.7; MS (EI-LR) 257 (M^+); HRMS calcd for $\text{C}_{17}\text{H}_{23}\text{NO}$ (M^+) 257.1780, found 257.1776.

4-(Biphenyl-4-ylamino)-2-methylcyclopent-2-enone (8kc): yellow oil, 69% yield; ^1H NMR (300 MHz, CDCl_3) δ 7.52 (m, 2H), 7.46 (d, $J = 8.7$ Hz, 2H), 7.41 (m, 2H), 7.27 (m, 2H), 6.72 (d, $J = 8.7$ Hz, 2H), 4.67 (d, $J = 3.0$ Hz, 1H), 3.84 (br s, 1H), 2.95 (dd, $J = 6.0$ Hz, $J = 18.6$ Hz, 1H), 2.30 (dd, $J = 2.1$ Hz, $J = 18.6$ Hz, 1H), 1.84 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 206.8, 155.5, 145.9, 143.7, 140.8, 131.4, 128.6 (2C), 128.1 (2C), 126.3 (3C), 113.7 (2C), 51.7, 43.1, 10.0; MS (EI-LR) 263 (M^+); HRMS calcd for $\text{C}_{18}\text{H}_{17}\text{NO}$ (M^+) 263.1310, found 263.1302.

Preparation of (1,5-trans,4,5-trans)-2,5-Dimethyl-4-(methyl(phenyl)amino)cyclopent-2-enyl benzoate (9a) and (1,5-cis,4,5-trans)-2,5-Dimethyl-4-(methyl(phenyl)amino)cyclopent-2-enyl Benzoate (9b). Compound **8la** (456 mg, 2.121 mmol) and $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (1.58 g, 4.242 mmol) were dissolved in MeOH (50 mL). To the solution was added NaBH_4 (160 mg, 4.242 mmol) portionwise. The reaction mixture was stirred at rt for 2 h. After being quenched with water (1 mL), the solution was concentrated in vacuo and extracted with CH_2Cl_2 . After being dried over Na_2SO_4 , the crude product was purified by silica gel chromatography to give the alcohol intermediate as a mixture of diastereomers (455 mg, 99%) as a yellow oil. To the above-prepared intermediate (455 mg, 2.097 mmol) in CH_2Cl_2 (20 mL) were added pyridine (497 mg, 13.192 mmol), 4-dimethylaminopyridine (25.6 mg, 0.209 mmol), and benzoic anhydride (947 mg, 4.194 mmol), and the reaction was stirred at rt for 6 h. The mixture was concentrated in vacuo and purified by silica gel chromatography (EtOAc/hexane 1:80) to give benzoate **9a** (443 mg, 1.378 mmol) and benzoate **9b** (222 mg, 0.691 mmol).

(1,5-trans,4,5-trans)-2,5-Dimethyl-4-(methyl(phenyl)amino)cyclopent-2-enyl benzoate (9a): ^1H NMR (400 MHz, CDCl_3) δ 8.05 (dd, $J = 1.2$ Hz, $J = 8$ Hz, 2H), 7.55 (dt, $J = 1.2$, 7.6 Hz, 1H), 7.44 (dt, $J = 1.6$, 7.0 Hz, 2H), 7.23 (dt, $J = 1.2$, 6.8 Hz, 2H), 6.86 (d, $J = 8$ Hz, 2H), 6.72 (t, $J = 7.2$ Hz, 1H), 5.63 (s, 1H), 5.46 (dd, $J = 0.4$, 4.0 Hz, 1H), 4.51 (t, $J = 1.6$ Hz, 1H), 2.79 (s, 3H), 2.25 (m, 1H), 1.82 (s, 3H), 1.31 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.4, 150.1, 140.7, 132.9, 131.0, 130.3, 129.5 (2C), 129.1 (2C), 128.4 (2C), 116.9, 113.5 (2C), 86.0, 69.6, 44.6, 32.1, 18.1, 14.1; MS (EI-LR) 321 (M^+); HRMS calcd for $\text{C}_{21}\text{H}_{23}\text{NO}_2$ (M^+) 321.1729, found 321.1731.

(1,5-cis,4,5-trans)-2,5-Dimethyl-4-(methyl(phenyl)amino)cyclopent-2-enyl benzoate (9b): ^1H NMR (400 MHz, CDCl_3) δ 8.05 (m, 2H), 7.55 (dt, $J = 1.2$, 7.6 Hz, 1H), 7.44 (t, $J = 7.6$ Hz, 2H), 7.21 (m, 2H), 6.85 (d, $J = 8.4$ Hz, 2H), 6.72 (t, $J = 7.2$ Hz, 1H), 5.95 (d, $J = 6.4$ Hz, 1H), 5.71 (s, 1H), 4.82 (m, 1H), 2.73 (s, 3H), 2.47 (m, 1H), 1.82 (s, 3H), 1.08 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.7, 150.4, 140.8, 133.1, 132.9, 130.2, 129.6 (2C), 129.1 (2C), 128.3 (2C), 116.8, 113.5 (2C), 81.8, 70.9, 40.5, 32.0, 14.7, 13.4; MS (EI-LR) 321 (M^+); HRMS calcd for $\text{C}_{21}\text{H}_{23}\text{NO}_2$ (M^+) 321.1729, found 321.1731.

Preparation of (1,5-trans,4,5-trans)-2,5-Dimethyl-4-(methyl(phenyl)amino)cyclopent-2-enol (10a) and (1,5-cis,4,5-trans)-2,5-Dimethyl-4-(methyl(phenyl)amino)cyclopent-2-enol (10b). Compound **9a** (443 mg, 1.380 mmol) and $\text{LiOH} \cdot \text{H}_2\text{O}$ (86.8 mg, 2.07 mmol) in MeOH/THF/ H_2O (5:2:1) (10 mL) were stirred at rt for 5 h. After evaporation of the solvents, the crude product was purified by silica gel chromatography to give **10a** (239 mg, 80%): ^1H NMR (600 MHz, CDCl_3) δ 7.23 (t, $J = 7.2$ Hz, 2H), 6.86 (d, $J = 8.4$ Hz, 2H), 6.70 (t, $J = 7.2$ Hz, 1H), 5.45 (s, 1H), 4.38 (d, $J = 1.8$ Hz, 1H), 4.02 (d, $J = 5.4$ Hz, 1H), 2.74 (s, 3H), 1.95 (m, 1H), 1.81 (s, 3H), 1.21 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 150.3, 143.6, 129.0 (2C), 128.5, 116.7, 113.4 (2C), 83.8, 68.4, 47.7, 32.1, 17.2, 13.6; MS (EI-LR) 217 (M^+); HRMS calcd for $\text{C}_{14}\text{H}_{19}\text{NO}$ (M^+) 217.1467, found 217.1469.

Compound **10b** (121 mg, 81%) was obtained following the same procedure as described above: ^1H NMR (600 MHz, CDCl_3) δ 7.22 (t, J = 7.8 Hz, 2H), 6.82 (d, J = 8.4 Hz, 2H), 6.70 (t, J = 7.2 Hz, 1H), 5.55 (s, 1H), 4.72 (m, 1H), 4.43 (d, J = 6.6 Hz, 1H), 2.68 (s, 3H), 2.21 (m, 1H), 1.86 (s, 3H), 1.13 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 150.4, 143.9, 130.8, 129.0 (2C), 116.5, 113.2 (2C), 79.5, 70.0, 41.5, 31.8, 14.5, 12.7; MS (EI-LR) 217 (M^+); HRMS calcd for $\text{C}_{14}\text{H}_{19}\text{NO}$ (M^+) 217.1467, found 217.1469.

General Procedure for the Mitsunobu Reaction to Prepare Compounds 11a, 11b, 12a, 12b, 13a, and 13b. To a suspension of **10a** or **10b** (54 mg, 0.249 mmol), PPh_3 (163 mg, 0.622 mmol), and 6-chloropurine or 3-*N*-benzoylthymine²⁰ (0.298 mmol) in dry THF (5 mL) at 0 °C was added dropwise a solution of DEAD (40% toluene solution, 0.27 mL, 0.622 mmol) in dry THF (2 mL). The mixture was stirred at rt for 1 h, diluted with water, and extracted with CH_2Cl_2 (2 \times 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , concentrated in vacuo, and purified by column chromatography on silica gel (EtOAc/hexane 1:5) to afford the corresponding condensation product.

4-Amino carbocyclic nucleoside 11a: yellow oil, 75% yield; ^1H NMR (300 MHz, CDCl_3) δ 8.75 (s, 1H), 7.97 (s, 1H), 7.21 (t, J = 7.8 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 6.72 (m, 1H), 6.01 (s, 1H), 5.61 (br s, 1H), 4.88 (br s, 1H), 2.79 (s, 3H), 2.73 (m, 1H), 1.75 (s, 3H), 0.65 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 152.2, 151.9, 151.0, 149.9, 143.7, 137.8, 135.9, 131.7, 129.0, 128.7, 117.3, 113.9, 113.5, 70.9, 64.9, 41.0, 32.1, 14.6, 13.0; MS (EI-LR) 353 (M^+); HRMS calcd for $\text{C}_{19}\text{H}_{20}\text{ClN}_5$ (M^+) 353.1407, found 353.1406.

4-Amino carbocyclic nucleoside 11b: yellow oil, 43% yield; ^1H NMR (300 MHz, CDCl_3) δ 8.74 (s, 1H), 8.06 (s, 1H), 7.24 (m, 2H), 6.88 (d, J = 8.7 Hz, 2H), 6.75 (t, J = 7.5 Hz, 1H), 5.86 (d, J = 1.2 Hz, 1H), 5.06 (d, J = 7.5 Hz, 1H), 4.65 (m, 1H), 2.90 (s, 3H), 2.55 (m, 1H), 1.60 (s, 3H), 1.26 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 151.9, 151.8, 151.1, 149.8, 144.0, 137.6, 132.8, 131.8, 129.1 (2C), 117.7, 114.1 (2C), 69.6, 68.6, 46.3, 32.9, 17.4, 13.9; MS (EI-LR) 353 (M^+); HRMS calcd for $\text{C}_{19}\text{H}_{20}\text{ClN}_5$ (M^+) 353.1407, found 353.1408.

4-Amino carbocyclic-O-nucleoside 12a: yellow oil, 8% yield; ^1H NMR (300 MHz, CDCl_3) δ 8.39 (s, 1H), 8.19 (d, J = 7.2 Hz, 2H), 7.67 (t, J = 7.5 Hz, 1H), 7.52 (t, J = 7.5 Hz, 2H), 7.23 (t, J = 7.8 Hz, 2H), 6.82 (d, J = 8.1 Hz, 2H), 6.69 (t, J = 7.2 Hz, 1H), 5.98 (d, J = 6.9 Hz, 1H), 5.66 (s, 1H), 4.82 (s, 1H), 2.71 (s, 3H), 2.49 (m, 1H), 2.15 (s, 3H), 1.84 (s, 3H), 1.05 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 165.2, 164.6, 163.1, 161.7, 150.4, 141.0, 134.2, 132.5, 130.4 (2C), 129.0 (2C), 128.7 (2C), 128.3, 116.6, 115.4, 113.3 (2C), 84.5, 70.5, 40.8, 32.0, 14.8, 13.4, 12.1; MS (EI-LR) 429 (M^+); HRMS calcd for $\text{C}_{26}\text{H}_{27}\text{N}_3\text{O}_3$ (M^+) 429.2052, found 429.2049.

4-Amino carbocyclic-N-nucleoside 13a: yellow oil, 20% yield; ^1H NMR (300 MHz, CDCl_3) δ 7.90 (m, 2H), 7.64 (t, J = 7.5 Hz, 1H), 7.49 (t, J = 7.5 Hz, 2H), 7.25 (t, J = 8.1 Hz, 2H), 6.85 (m, 3H), 6.77 (t, J = 7.5 Hz, 1H), 5.96 (s, 1H), 5.52 (d, J = 8.1 Hz, 1H), 4.73 (m, 1H), 2.74 (s, 3H), 2.61 (m, 1H), 2.00 (s, 3H), 1.79 (s, 3H), 1.02 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.9, 162.6, 150.8, 150.1, 138.3, 136.5, 136.0, 134.9, 131.5, 130.2 (2C), 129.2 (2C), 129.1 (2C), 117.5, 113.8 (2C), 110.7, 71.7, 65.6, 39.7, 32.1, 14.9, 13.6, 12.8; MS (EI-LR) 429 (M^+); HRMS calcd for $\text{C}_{26}\text{H}_{27}\text{N}_3\text{O}_3$ (M^+) 429.2052, found 429.2044.

4-Amino carbocyclic-O-nucleoside 12b: yellow oil, 25% yield; ^1H NMR (300 MHz, CDCl_3) δ 8.41 (s, 1H), 8.19 (d, J = 8.4 Hz, 2H), 7.68 (t, J = 7.5 Hz, 1H), 7.53 (t, J = 7.2 Hz, 2H), 7.21 (t, J = 7.5 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 6.69 (t, J = 7.2 Hz, 1H), 5.58 (s, 1H), 5.47 (d, J = 3.6 Hz, 1H), 4.49 (s, 1H), 2.76 (s, 3H), 2.28 (m, 1H), 2.16 (s, 3H), 1.83 (s, 3H), 1.30 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 165.1, 164.4, 163.1, 161.7, 150.2, 141.1, 134.2, 130.5, 130.4 (2C), 129.0 (2C), 128.7 (2C), 128.3, 116.6, 115.5, 113.3 (2C), 88.7, 69.4, 44.5, 32.1, 18.3, 14.3, 12.1; MS (EI-LR) 429 (M^+); HRMS calcd for $\text{C}_{26}\text{H}_{27}\text{N}_3\text{O}_3$ (M^+) 429.2052, found 429.2048.

4-Amino carbocyclic-N-nucleoside 13b: yellow oil, 44% yield; ^1H NMR (300 MHz, CDCl_3) δ 7.91 (m, 2H), 7.65 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 8.1 Hz, 2H), 7.26 (m, 2H), 6.91 (m, 3H), 6.80 (t, J = 7.2 Hz, 1H), 5.84 (s, 1H), 5.13 (s, 1H), 4.51 (s, 1H), 2.85 (s, 3H), 2.16 (m, 1H), 1.98 (s, 3H), 1.72 (s, 3H), 1.26 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.9, 162.5, 150.5, 149.8, 138.0, 136.1, 134.9, 133.9, 131.5, 130.3 (2C), 129.1 (4C), 118.1, 114.7 (2C), 111.6, 69.7, 67.6, 45.6, 33.4, 17.5, 14.1, 12.7; MS (EI-LR) 429 (M^+); HRMS calcd for $\text{C}_{26}\text{H}_{27}\text{N}_3\text{O}_3$ (M^+) 429.2052, found 429.2043.

Preparation of 4-Amino Carbocyclic-N-nucleosides 14 and 15. A mixture of **13a** or **13b** (36 mg, 0.087 mmol) and NH_3 (solution in methanol, 1.5 mL) was stirred at rt overnight. The solvent was evaporated in vacuo, and the crude was purified by column chromatography (EtOAc/hexane 2:3) to afford **14** or **15** as white solids.

4-Amino carbocyclic nucleoside 14: 80% yield; ^1H NMR (300 MHz, CDCl_3) δ 9.55 (s, 1H), 7.23 (t, J = 7.5 Hz, 2H), 6.83 (d, J = 8.1 Hz, 2H), 6.74 (m, 2H), 5.90 (s, 1H), 5.55 (d, J = 7.8 Hz, 1H), 4.69 (s, 1H), 2.74 (s, 3H), 2.61 (m, 1H), 1.96 (s, 3H), 1.73 (s, 3H), 0.93 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.9, 152.0, 150.1, 138.8, 136.3, 135.8, 129.1 (2C), 117.4, 113.8 (2C), 110.6, 71.8, 65.2, 39.6, 32.1, 14.7, 13.5, 12.7; MS (EI-LR) 325 (M^+); HRMS calcd for $\text{C}_{19}\text{H}_{23}\text{N}_3\text{O}_2$ (M^+) 325.1790, found 325.1793.

4-Amino carbocyclic nucleoside 15: 85% yield; ^1H NMR (300 MHz, CDCl_3) δ 9.39 (s, 1H), 7.25 (m, 2H), 6.89 (d, J = 8.1 Hz, 2H), 6.83 (s, 1H), 6.78 (t, J = 7.2 Hz, 1H), 5.79 (s, 1H), 5.14 (s, 1H), 4.52 (m, 1H), 2.83 (s, 3H), 2.11 (s, 1H), 1.94 (d, J = 0.9 Hz, 3H), 1.66 (s, 3H), 1.25 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.8, 151.6, 149.8, 138.3, 136.3, 133.3, 129.1, 117.9, 114.6, 111.6, 69.6, 67.3, 45.5, 33.2, 17.3, 14.0, 12.6; MS (EI-LR) 325 (M^+); HRMS calcd for $\text{C}_{19}\text{H}_{23}\text{N}_3\text{O}_2$ (M^+) 325.1790, found 325.1787.

■ ASSOCIATED CONTENT

S Supporting Information. General information and copies of ^1H and ^{13}C NMR spectra for the characterization of all final compounds are reported. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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