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Domino Strategy for the Stereoselective Construction of Angularly Fused Tricyclic Ethers

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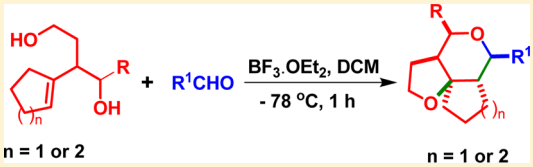
Supporting Information

ABSTRACT: A stereoselective synthesis of decahydrofuro[3,2-*d*]-isochromene derivatives has been achieved by the condensation of 2-cyclohexenylbutane-1,4-diol with aldehydes in the presence of a stochiometric amount of $BF_3{\cdot}OEt_2$ in dichloromethane at −78 °C. Similarly, the condensation of 2-cyclopentenylbutan-1,4-diol with aldehydes provides the corresponding octahydro-2*H*-cyclopenta[*c*]furo-[2,3-*d*]pyran derivatives in good yields with high diastereoselectivity. It is an elegant strategy for the quick construction of tricyclic architectures with four contiguous stereogenic centers in a single step. These tricyclic frameworks are the integral part of numerous natural products.



Polyheterocyclic frameworks are privileged scaffolds in medicinal chemistry. These structures are important synthetic targets for organic chemists due to their prevalence in numerous synthetic and naturally occurring molecules.[1] In particular, angularly fused polyheterocyles have become interesting targets among the synthetic community.[2] Moreover, oxygen-containing fused structures having the characteristic [6-6-5] tricyclic system comprise the core of various naturally occurring molecules that possess a variety of biological activities. For example, Phomactin A is a specific platelet activating factor (PAF) antagonist, which inhibits the PAF-induced platelet aggregation and Neovibsanins are found to display neurite outgrowth activity in PC12 cells (Figure 1).[3] As

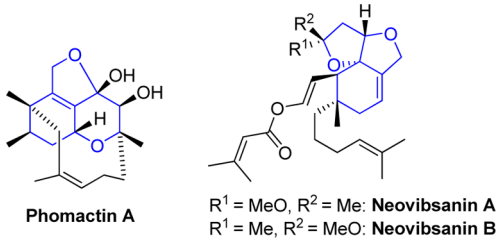


Figure 1. Natural products containing tricyclic structures.

a result, a few approaches have been described in the literature to construct the relevant scaffolds.[4] However, most of these approaches involve a multistep reaction sequence; therefore, it is highly desirable to pursue efficient approaches for the stereoselective construction of such skeletons.

The "Prins cyclization" is a direct and efficient route for the stereoselective construction of the tetrahydropyran ring system, which is a backbone of many natural products.[5] In particular, its intramolecular version has become very popular for the stereoselective synthesis of fused and bridged oxacycles.[6,7] Furthermore, it has been successfully applied in the total synthesis of biologically active natural products.[8]

Following our interests in domino cyclization,[9] we report a novel and efficient strategy for the stereoselective synthesis of decahydrofuro[3,2-*d*]isochromene and octahydro-2*H*-cyclopenta[*c*]furo[2,3-*d*]pyran derivatives. The required enediols (**3**) and (**4**) were prepared by the condensation of diethyl succinate with cyclic ketone under basic conditions. The resulting diesters[10] were reduced under LAH conditions to produce the corresponding enediols (**3**) and (**4**) (Scheme 1).

At the outset, we attempted the coupling of enediol (**4**) (1.0 equiv) with *p*-tolualdehyde (1.2 equiv) in the presence of $BF_3{\cdot}OEt_2$ (1.2 equiv). The reaction proceeded smoothly at −78 °C with high stereocontrol (entry a, Table 1). However, the reaction was found to be sluggish at 0 °C, resulting in the decomposition of starting material (entry b, Table 1). Other Lewis acids such as $SnCl_4$, $TiCl_4$, and $In(OTf)_3$ gave the product relatively in lower yields (entries c−e, Table 1), whereas TMSOTf gave the mixture of products (entry f, Table 1). Bronsted acids such as *p*-TSA and CSA failed to initiate the reaction even after a long reaction time at elevated temperature (entries g, h, Table 1). Though the reaction was successful with 1.2 equiv of TfOH, the required product was isolated in low yield (entry i, Table 1). We further performed the reaction in different solvents such as THF, benzene, and CH_3CN (entries j−l, Table 1). Among them, DCM gave the best results in terms of yield. The structure and relative stereochemistry of **6a** were established by 1D and 2D NMR experiments (Supporting Information).

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Scheme 1. Preparation of Starting Materials 3 and 4

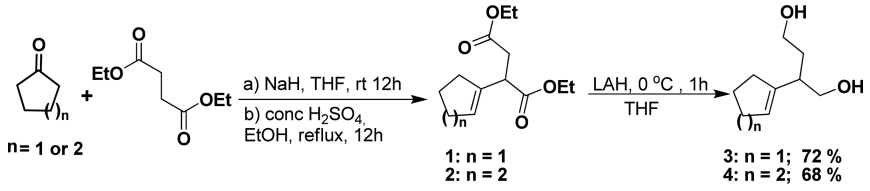
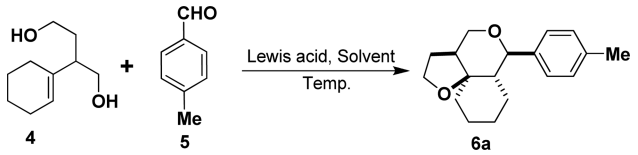


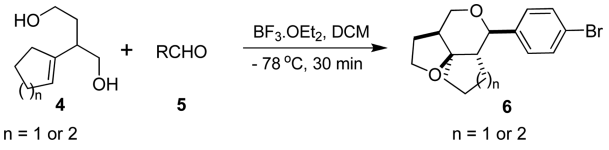
Table 1. Optimization of the Reaction Conditions

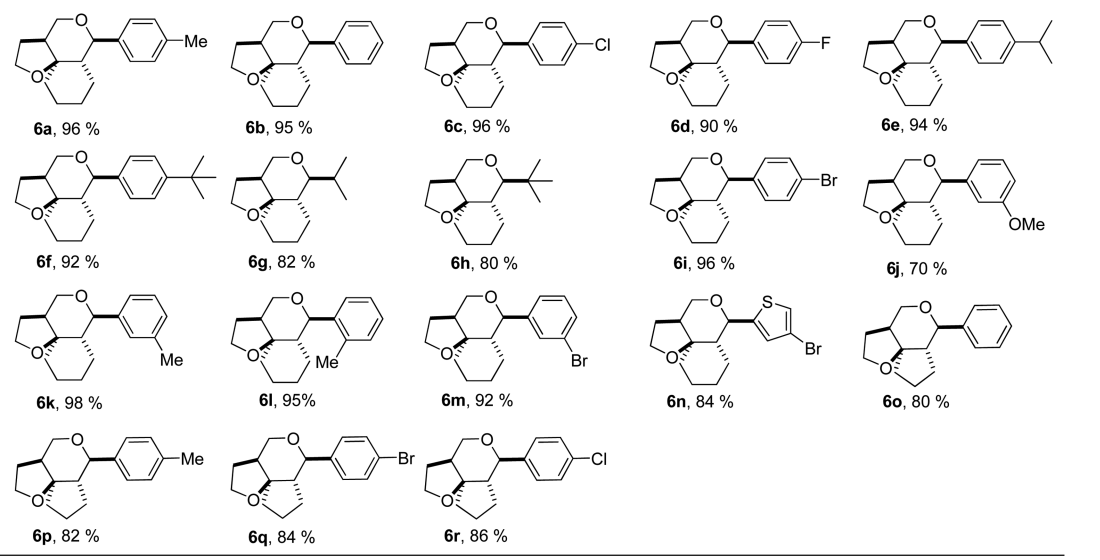


entry	Lewis/Bronsted acid	equiv	solvent	temp (°C)	time (h)	Yield (%)[a]
a	$BF_3{\cdot}OEt_2$	1.2	DCM	−78	1	95
b	$BF_3{\cdot}OEt_2$	1.2	DCM	0	1	50
c	$SnCl_4$	1.0	DCM	−78	1	70
d	$TiCl_4$	1.0	DCM	−78	1	60
e	$ln(OTf)_3$	1.0	DCM	25	1	50
f	TMSOTf	1.2	DCM	−78	1	mix
g	*p*-TSA	1.0	DCE	80	15	
h	CSA	1.0	DCE	80	16	
i	TfOH	1.2	DCM	−78	1	20
j	$BF_3{\cdot}OEt_2$	1.2	THF	−78 to 25	10	
k	$BF_3{\cdot}OEt_2$	1.2	benzene	−78 to 25	10	
l	$BF_3{\cdot}OEt_2$	1.2	CH_3CN	−78 to 25	10	

[a]Yield refers to pure products after column chromatography.

Table 2. Synthesis of Decahydrofuro[3,2-*d*]isochromene/Octahydro-2*H*-cyclopenta[*c*]furo[2,3-*d*]pyran Derivatives[a]





[a]Yields refer to the pure products after column chromatography.

The scope of the reaction is further exemplified with diverse aldehydes bearing different substitution patterns on the aromatic ring (Table 2). In all the cases, the products were obtained in good yields with high selectivity. It is noteworthy to mention that a wide range of functional groups are well tolerated under the reaction conditions. The functional groups

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Scheme 2. Preparation of Compounds 9a−e

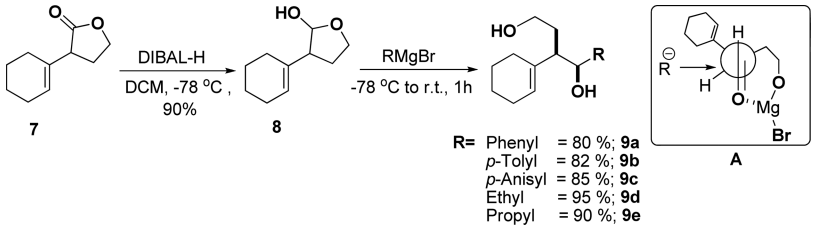
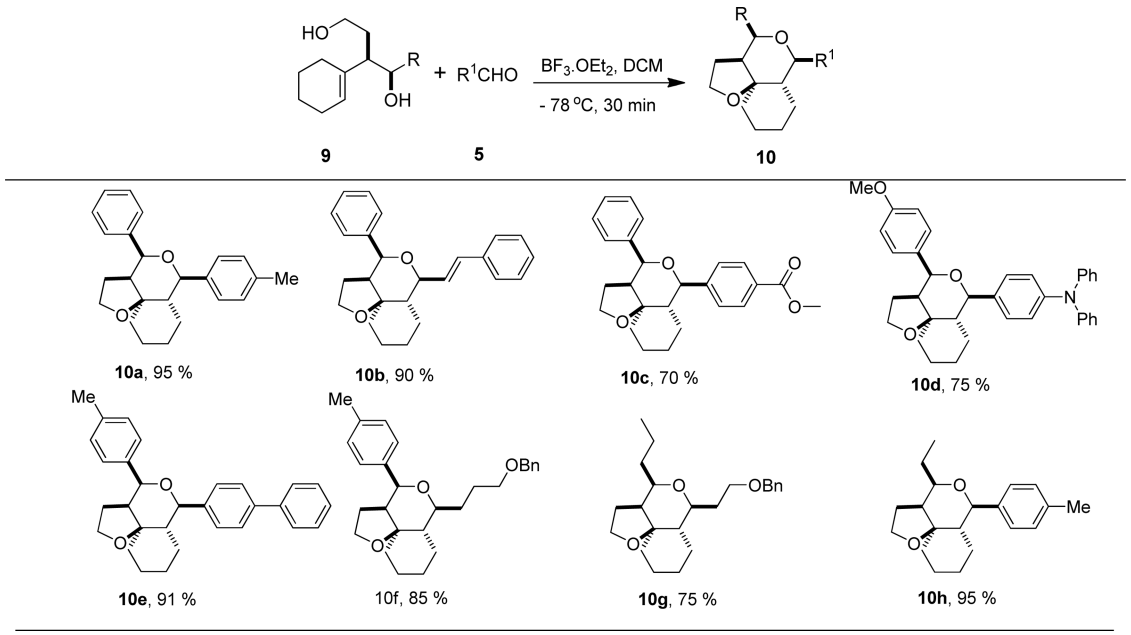


Table 3. Synthesis of Substituted Decahydrofuro[3,2-*d*]isochromene[a]



[a]Yields refer to the pure products after column chromatography.

present on the aromatic ring had shown some effect on the conversion. It was observed that alkyl substituted aromatic aldehydes gave the products relatively in higher yields than the corresponding halide or methoxy-substituted aldehydes. The reaction is further extended to aliphatic aldehydes (Table 2, **6g** and **6h**) and heterocyclic aldehyde (Table 2, **6n**). This method also works well with sterically hindered substrates such as *p*-*tert*-butylbenzaldehyde and pivalaldehyde (Table 2, **6f** and **6h**). Therefore, this method is successful with aromatic, aliphatic, and heteroaromatic aldehydes to generate the products with diverse substitution patterns. However, the reactions were not successful with ketones like cyclohexanone and acetone.

In order to broaden the scope of this methodology, we studied the effect of substituents on the enediol precursor. Accordingly, we prepared a series of substituted enediols adopting the synthetic sequence as outlined in Scheme 2. The intermediate, cyclohexenyl butyrolactone (**7**), was prepared by reacting cyclohexanone with γ-butyrolactone.[11] Reduction of lactone **7** with DIBAL-H afforded the lactol **8** in 90% yield, which was then treated with Grignard reagents to produce the substituted enediols **9** with good diastereoselectivity, which was confirmed by NMR. The relative stereochemistry of compound **9** was established as *syn* with respect to −OH and $-CH_2CH_2OH$ groups based on the stereochemistry of **10a**, which was confirmed by X-ray crystallography. The observed stereochemistry is consistent with a known method,[12] in which *anti*-Cram's stereoselection was explained based on a chelate model **A** (Scheme 2).

Treatment of various substituted enediols **9** with different aldehydes under optimized conditions gave the corresponding decahydrofuro[3,2-*d*]isochromene derivatives (**10**) in excellent yields (**10a−h**, Table 3). There was no effect of the substituents on the stereochemical outcome of the reaction, which was confirmed by a single-crystal X-ray diffraction of **10a** (Supporting Information). The reaction was quite successful with different aldehydes bearing olefin (**10b**, Table 3), ester (**10c**, Table 3), and *N*,*N*-diphenylamino functionalities (**10d**, Table 3). Furthermore, aliphatic aldehyde bearing a benzyloxy group also participated effectively (**10f** and **10g**, Table 3). However, the aliphatic aldehyde having an amide functionality (*N*-(3-oxopropyl)benzamide) failed to give the product under similar conditions.

On the basis of our previous observations,[9] we proposed a plausible reaction mechanism in Scheme 3. The reaction is expected to proceed through the formation of oxocarbenium ion **I** from the condensation of aldehyde with enediol under acidic conditions. The resulting oxocarbenium ion is trapped by an internal olefin, leading to the formation of a cyclic carbocation **II**, which is simultaneously neutralized by a tethered hydroxyl group to generate the tricyclic **III** ether, as depicted in Scheme 3. The exceptional diastereoselectivity observed in this process can be explained by a favorable trapping of the more stable carbocation from a less hindered

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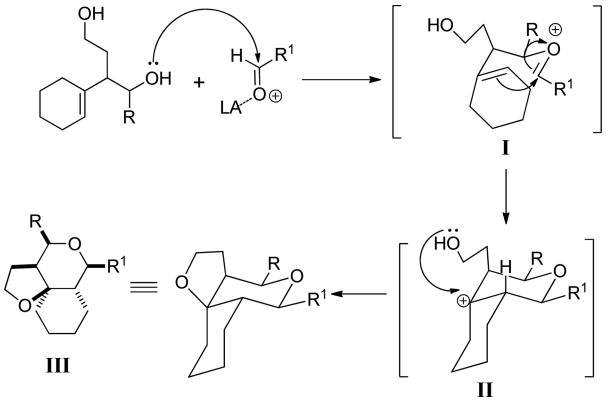
Scheme 3. A Plausible Reaction Pathway



equatorial side to overcome unfavorable 1,3-diaxial interactions.[13]

In conclusion, we have developed a novel strategy for the efficient synthesis of angularly fused tricyclic ethers from aldehydes and enediols using a stoichiometric amount of $BF_3 \cdot Et_2O$. It is an elegant approach for the stereoselective synthesis of decahydrofuro[3,2-*d*]isochromene and octahydro-2*H*-cyclopenta[*c*]furo[2,3-*d*]pyran derivatives. This method offers numerous advantages such as good yields, excellent diastereoselectivity, diverse functional group tolerance, and a wide substrate scope, which make it an attractive strategy for the synthesis of biologically relevant structural scaffolds with four contiguous stereogenic centers.

EXPERIMENTAL SECTION

General. All solvents were dried according to standard literature procedures. The reactions were performed in oven-dried round-bottom flasks, the flasks were fitted with rubber septa, and the reactions were conducted under a nitrogen atmosphere. Glass syringes were used to transfer solvents. Crude products were purified by column chromatography on silica gel of 60−120 or 100−200 mesh. Thin-layer chromatography plates were visualized by exposure to ultraviolet light and/or by exposure to iodine vapors and/or by exposure to methanolic acidic solution of *p*-anisaldehyde, followed by heating (<1 min) on a hot plate (~250 °C). Organic solutions were concentrated on a rotary evaporator at 35−40 °C. IR spectra were recorded on an FT-IR spectrometer. ^{1}H and ^{13}C NMR (proton-decoupled) spectra were recorded in $CDCl_3$ solvent on a 200, 300, 400, or 500 MHz NMR spectrometer. Chemical shifts (δ) were reported in parts per million (ppm) with respect to TMS as an internal standard. Coupling constants (J) are quoted in hertz (Hz). Mass spectra were recorded on a mass spectrometer by electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) technique.

X-ray Crystallography. X-ray data for the compounds were collected at room temperature using a Smart Apex CCD diffractometer with graphite monochromated Mo Kα radiation (λ = 0.71073 Å) with the ω-scan method. Preliminary lattice parameters and orientation matrices were obtained from four sets of frames.

Integration and scaling of intensity data was accomplished using the SAINT program.[14] The structure was solved by direct methods using SHELXS-2014,[15] and refinement was carried out by the full-matrix least-squares technique using SHELXL-2014.[15] Anisotropic displacement parameters were included for all non-hydrogen atoms. All H atoms were positioned geometrically and treated as riding on their parent C atoms [C−H = 0.93−0.97 Å and U_{iso}(H) = 1.5U_{eq}(C) for methyl H or 1.2U_{eq}(C) for other H atoms]. The methyl groups were allowed to rotate but not to tip.

Typical Procedure for Domino Cyclization. To a mixture of 2-cyclohexenylbutan-1,4-diol (0.5 mmol) and *p*-tolualdehyde (0.6 mmol) in anhydrous DCM (5 mL) was added $BF_3 \cdot OEt_2$ (1.2 equiv) at −78 °C. The resulting mixture was allowed to stir at the same temperature for 1 h. After completion, the reaction was quenched with sat. $NaHCO_3$ solution. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (2 × 5 mL). The organic phases were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting crude product was purified by silica gel column chromatography (100−200 mesh) using a ethyl acetate/hexane gradient mixture to afford the pure product **6a** (Table 2, entry a).

*6-p-Tolyldecahydrofuro[3,2-d]isochromene (**6a**).* Viscous liquid; Yield 130 mg, 96%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 7.9 Hz, 2H), 4.31 (d, J = 11.1 Hz, 1H), 4.08 (dd, J = 12.3, 0.9 Hz, 1H), 4.0 (td, J = 3.2, 8.6 Hz, 1H), 3.91 (q, J = 8.3 Hz, 1H), 3.85 (dd, J = 3.2, 12.2 Hz, 1H), 2.50−2.42 (m, 1H), 2.33 (s, 3H), 2.10−2.01 (m, 2H), 1.90 (dd, J = 5.1, 10.9 Hz, 1H), 1.77−1.71 (m, 1H), 1.69−1.52 (m, 3H), 1.42−1.36 (m, 1H), 1.34−1.24 (m, 2H), 1.05 (d, J = 14.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.8, 137.4, 129.0, 126.7, 80.8, 79.8, 66.4, 64.8, 45.3, 41.8, 32.2, 28.1, 23.0, 22.4, 21.1, 21.0; IR (KBr): υ 3019, 2925, 2855, 1216, 1110, 771, 667; HRMS (Orbitrap ESI) calcd for $C_{18}H_{25}O_2$ [M + H]$^+$: 273.1849. Found: 273.1844.

*6-Phenyldecahydrofuro[3,2-d]isochromene (**6b**).* Pale yellow liquid; Yield 122 mg, 95%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36−7.27 (m, 5H), 4.35 (d, J = 10.9 Hz, 1H), 4.10 (dd, J = 1.0, 12.3 Hz, 1H), 4.01 (td, J = 3.6, 8.6 Hz, 1H), 3.91 (q, J = 8.6 Hz, 1H), 3.87 (dd, J = 3.2, 12.2 Hz, 1H), 2.52−2.43 (m, 1H), 2.11−2.02 (m, 2H), 1.91 (dd, J = 5.1, 10.9 Hz, 1H), 1.78−1.73 (m, 1H), 1.69−1.53 (m, 3H), 1.43−1.38 (m, 1H), 1.35−1.27 (m, 2H), 1.04 (d, J = 14.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.8, 128.3, 127.8, 126.8, 81.0, 79.8, 66.4, 64.8, 45.3, 41.9, 32.2, 28.1, 23.0, 22.4, 21.0; IR (KBr): υ 3029, 2925, 2855, 1453, 1218, 1110, 1030, 771, 700; HRMS (Orbitrap ESI) calcd for $C_{17}H_{23}O_2$ [M + H]$^+$: 259.1692. Found: 259.1688.

*6-(4-Chlorophenyl)decahydrofuro[3,2-d]isochromene (**6c**).* Viscous liquid; Yield 141 mg, 96%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33−7.30 (m, 2H), 7.27−7.25 (m, 2H), 4.32 (d, J = 11.1 Hz, 1H), 4.09 (dd, J = 0.7, 12.3 Hz, 1H), 4.00 (td, J = 3.2, 9.0 Hz, 1H), 3.91 (q, J = 8.5 Hz, 1H), 3.85 (dd, J = 3.2, 12.2 Hz, 1H), 2.49−2.39 (m, 1H), 2.11−1.98 (m, 2H), 1.84 (dd, J = 5.0, 10.3 Hz, 1H), 1.78−1.72 (m, 1H), 1.70−1.52 (m, 3H), 1.44−1.38 (m, 1H), 1.31−1.21 (m, 2H), 1.01 (d, J = 14.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 139.4, 133.4, 128.5, 128.2, 80.2, 79.6, 66.6, 64.8, 45.2, 42.2, 32.2, 28.1, 22.9, 22.3, 21.0. IR (KBr): υ 3005, 2929, 2856, 1491, 1217, 1108, 1029, 771, 747, 665; HRMS (Orbitrap ESI) calcd for $C_{17}H_{22}ClO_2$ [M + H]$^+$: 293.1302. Found: 293.1297.

*6-(4-Fluorophenyl)decahydrofuro[3,2-d]isochromene (**6d**).* Viscous liquid; Yield 124 mg, 90%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31−7.25 (m, 2H), 7.06−7.00 (m, 2H), 4.33 (d, J = 10.9 Hz, 1H), 4.08 (dd, J = 0.9, 12.2 Hz, 1H), 4.00 (td, J = 3.2, 8.6 Hz, 1H), 3.91 (q, J = 8.6 Hz, 1H), 3.85 (dd, J = 3.2, 12.2 Hz, 1H), 2.49−2.40 (m, 1H), 2.11−1.99 (m, 2H), 1.86 (dd, J = 5.1, 10.9 Hz, 1H), 1.78−1.72 (m, 1H), 1.70−1.53 (m, 3H), 1.44−1.38 (m, 1H), 1.32−1.21 (m, 2H), 1.02 (d, J = 14.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 160.6, 136.6, 128.4, 128.3, 115.0, 114.5, 80.2, 79.6, 66.4, 64.8, 45.2, 42.1, 32.1, 28.0, 22.9, 22.3, 20.9; IR (KBr): υ 3019, 2933, 2857, 1512, 1215, 742, 667; HRMS (Orbitrap ESI) calcd for $C_{17}H_{22}FO_2$ [M + H]$^+$: 277.1598. Found: 277.1591.

*6-(4-Isopropylphenyl)decahydrofuro[3,2-d]isochromene (**6e**).* Pale yellow liquid; Yield 141 mg, 94%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24−7.18 (m, 4H), 4.32 (d, J = 10.9 Hz, 1H), 4.08 (dd, J = 1.0, 12.3 Hz, 1H), 4.01 (td, J = 3.2, 8.6 Hz, 1H), 3.91 (q, J = 8.5 Hz, 1H), 3.85 (dd, J = 3.2, 12.2 Hz, 1H), 2.89 (hep, J = 6.8 Hz, 1H), 2.52−2.42 (m, 1H), 2.10−2.01 (m, 2H), 1.93 (d, J = 5.3, 11.1 Hz, 1H), 1.77−1.71 (m, 1H), 1.70−1.52 (m, 3H), 1.43−1.36 (m, 1H), 1.35−1.25 (m, 2H), 1.23 (d, J = 7.0 Hz, 6H), 1.09 (d, J = 13.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.4, 138.1, 126.8, 126.4, 80.8, 79.8, 66.4, 64.8, 45.3, 41.7, 33.8, 32.2, 28.1, 24.0, 23.9, 23.0, 22.5, 21.0; IR (KBr): υ 3007, 2930, 2859, 1459, 1216, 1108, 771, 745, 665; HRMS (Orbitrap ESI) calcd for $C_{20}H_{29}O_2$ [M + H]$^+$: 301.2162. Found: 301.2155.

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6-(4-tert-Butylphenyl)decahydrofuro[3,2-d]isochromene (**6f**). Pale yellow liquid; Yield 144 mg, 92%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36−7.34 (m, 2H), 7.25−7.22 (m, 2H), 4.32 (d, J = 11.1 Hz, 1H), 4.08 (dd, J = 1.0, 12.2 Hz, 1H), 4.01 (td, J = 3.0, 8.6 Hz, 1H), 3.91 (q, J = 8.5 Hz, 1H), 3.85 (dd, J = 3.2, 12.2 Hz, 1H), 2.51−2.42 (m, 1H), 2.10−2.01 (m, 2H), 1.93 (dd, J = 5.1, 10.9 Hz, 1H), 1.77−1.71 (m, 1H), 1.69−1.52 (m, 3H), 1.43−1.37 (m, 1H), 1.35−1.25 (m, 2H), 1.10 (d, J = 14.0 Hz, 1H), 1.30 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.7, 137.7, 126.5, 125.2, 80.7, 79.8,, 66.3, 64.8, 45., 41.6, 34.5, 32.2, 31.3, 28.1, 23.0, 22.5, 21.1; IR (KBr): υ 3018, 2924, 2853, 1462, 1216, 771; HRMS (Orbitrap ESI) calcd for $C_{21}H_{31}O_2$ $[M + H]^+$: 315.2318. Found: 315.2310.

6-Isopropyldecahydrofuro[3,2-d]isochromene (**6g**). Pale yellow liquid; Yield 91 mg, 82%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.96−3.90 (m, 2H), 3.84 (q, J = 8.3 Hz, 1H), 3.63 (dd, J = 3.5, 12.0 Hz, 1H), 3.23 (dd, J = 2.7, 10.0 Hz, 1H), 2.24−2.15 (m, 1H), 2.00−1.86 (m, 3H), 1.74−1.53 (m, 6H), 1.47−1.40 (m, 2H), 1.23−1.11 (m, 1H), 1.00 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 81.1, 80.2, 66.1, 64.6, 44.9, 37.7, 32.3, 28.2, 28.1, 23.2, 22.4, 21.1, 20.5, 14.1; IR (KBr): υ 2926, 2855, 1456, 1369, 1222, 1079, 1031, 771, 668; HRMS (APCI) calcd for $C_{14}H_{25}O_2$ $[M + H]^+$: 225.1849. Found: 225.1848.

6-tert-Butyldecahydrofuro[3,2-d]isochromene (**6h**). Pale yellow liquid; Yield 95 mg, 80%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.90 (q, J = 7.7 Hz, 1H), 3.84−3.78 (m, 2H), 3.58 (dd, J = 4.7, 12.0 Hz, 1H), 2.82 (d, J = 6.4 Hz, 1H), 2.20−2.11 (m, 1H), 2.00−1.92 (m, 1H), 1.93−1.86 (m, 1H), 1.83−1.76 (m, 2H), 1.73−1.65 (m, 2H), 1.50−1.24 (m, 5H), 0.95 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 88.6, 81.8, 69.0, 64.9, 40.4, 39.3, 36.6, 34.9, 32.5, 30.6, 26.5, 24.5, 23.6; IR (KBr): υ 2927, 2855, 1453, 1362, 1218, 1076, 1029, 771, 669; HRMS (Orbitrap ESI) calcd for $C_{15}H_{27}O_2$ $[M + H]^+$: 239.2005. Found: 239.2001.

6-(4-Bromophenyl)decahydrofuro[3,2-d]isochromene (**6i**). Viscous liquid; Yield 161 mg, 96%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (d, J = 8.3 Hz, 2H), 7.19 (d, J = 8.3 Hz, 2H), 4.31 (d, J = 10.9 Hz, 1H), 4.08 (dd, J = 0.9, 12.2, 1H), 3.99 (td, J = 3.5, 8.8, 1H), 3.90 (q, J = 8.5 Hz, 1H), 3.85 (dd, J = 3.2, 12.2, 1H), 2.48−2.39 (m, 1H), 2.11−1.98 (m, 2H), 1.83 (dd, J = 5.1, 10.9 Hz, 1H), 1.78−1.72 (m, 1H), 1.70−1.53 (m, 3H), 1.44−1.38 (m, 1H), 1.30−1.23 (m, 2H), 1.01 (d, J = 14.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.8, 131.4, 128.5, 121.5, 80.2, 79.6, 66.4, 64.8, 45.1, 42.1, 32.1, 28.0, 22.9, 22.3, 21.0. IR (KBr): υ 2929, 2857, 1487, 1456, 1218, 1109, 1009, 771; HRMS (APCI) calcd for $C_{17}H_{22}BrO_2$ $[M + H]^+$: 337.0797. Found: 337.0784

6-(3-Methoxyphenyl)decahydrofuro[3,2-d]isochromene (**6j**). Pale yellow liquid; Yield 100 mg, 70%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27−7.25 (m, 1H), 6.90 (d, J = 7.4 Hz, 1H), 6.88−6.86 (m, 1H), 6.82 (ddd, J = 0.8, 2.5, 8.0 Hz, 1H), 4.31 (d, J = 10.9 Hz, 1H), 4.09 (dd, J = 1.0, 12.3 Hz, 1H), 4.00 (td, J = 3.2, 8.8 Hz, 1H), 3.91 (q, J = 8.6 Hz, 1H), 3.85 (dd, J = 3.2, 12.2 Hz, 1H), 3.81 (s, 3H), 2.50−2.41 (m, 1H), 2.10−2.00 (m, 2H), 1.89 (dd, J = 5.1, 10.9 Hz, 1H), 1.78−1.71 (m, 1H), 1.69−1.52 (m, 3H), 1.44−1.38 (m, 1H), 1.34−1.24 (m, 2H), 1.07 (d, J = 14.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.6, 142.3, 129.3, 119.3, 113.0, 112.6, 80.9, 79.7, 66.4, 64.8, 55.1, 45.2, 41.9, 32.2, 28.1, 23.0, 22.4, 21.0. IR (KBr): υ 2925, 2854, 1586, 1455, 1256, 1109, 1029, 772; HRMS (EI) calcd for $C_{18}H_{24}O_3$ $[M]^+$: 288.1725 Found: 288.1730

6-m-Tolyldecahydrofuro[3,2-d]isochromene (**6k**). Pale yellow liquid; Yield 133 mg, 98%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25−7.18 (m, 1H), 7.15−7.06 (m, 3H), 4.31 (d, J = 11.1 Hz, 1H), 4.09 (d, J = 12.2 Hz, 1H), 4.02 (td, J = 3.2, 9.0 Hz, 1H), 3.91 (q, J = 8.3 Hz, 1H), 3.85 (dd, J = 3.0, 12.4 Hz, 1H), 2.56−2.40 (m, 1H), 2.35 (s, 3H), 2.13−1.99 (m, 2H), 1.92 (dd, J = 5.0, 10.9 Hz, 1H), 1.80−1.50 (m, 4H), 1.45−1.23 (m, 3H), 1.06 (d, J = 13.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.6, 138.0, 128.6, 128.1, 127.3, 124.1, 81.1, 79.8, 66.4, 64.8, 45.3, 41.8, 32.2, 28.1, 23.0, 22.4, 21.4, 21.0; IR (KBr): υ 2924, 2854, 1456, 1219, 1111, 1031, 773; HRMS (Orbitrap ESI) calcd for $C_{18}H_{25}O_2$ $[M + H]^+$: 273.1849. Found: 273.1842.

6-o-Tolyldecahydrofuro[3,2-d]isochromene (**6l**). Pale yellow liquid; Yield 129 mg, 105−107 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (d, J = 7.3 Hz, 1H), 7.23−7.19 (m, 1H), 7.18−7.13 (m, 2H), 4.60 (d, J = 11.1 Hz, 1H), 4.08 (dd, J = 0.9, 12.2 Hz, 1H), 4.04 (td, J = 3.0, 8.8 Hz, 1H), 3.93 (q, J = 8.5 Hz, 1H), 3.85 (dd, J = 3.2, 12.3 Hz, 1H), 2.55−2.44 (m, 1H), 2.42 (s, 3H), 2.13−2.00 (m, 3H), 1.79−1.73 (m, 1H), 1.69−1.55 (m, 3H), 1.44 (d, J = 14.4 Hz, 1H), 1.32−1.19 (m, 2H), 1.06 (d, J = 14.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 135.9, 130.4, 127.5, 126.8, 126.3, 79.9, 66.5, 65.0, 45.5, 40.9, 32.6, 29.7, 28.2, 23.0, 22.5, 22.1, 19.7;. IR (KBr): υ 3006, 2932, 2859, 1458, 1217, 1107, 1029, 745, 666 ; HRMS (Orbitrap ESI) calcd for $C_{18}H_{25}O_2$ $[M + H]^+$: 273.1849. Found: 273.1844

6-(3-Bromophenyl)decahydrofuro[3,2-d]isochromene (**6m**). Pale yellow liquid; Yield 154 mg, 92%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49−7.47 (m, 1H), 7.44−7.40 (m, 1H), 7.24−7.19 (m, 2H), 4.31 (d, J = 10.9 Hz, 1H), 4.09 (dd, J = 1.0, 12.3 Hz, 1H), 4.01 (td, J = 3.2, 8.6 Hz, 1H), 3.91 (q, J = 8.5 Hz, 1H), 3.85 (dd, J = 3.3, 12.3 Hz, 1H), 2.49−2.40 (m, 1H), 2.11−1.98 (m, 2H), 1.85 (dd, J = 5.1, 10.9 Hz, 1H), 1.79−1.73 (m, 1H), 1.71−1.52 (m, 3H), 1.47−1.40 (m, 1H), 1.33−1.21 (m, 2H), 1.04 (d, J = 14.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.1, 130.9, 129.8, 125.7, 122.6, 79.6, 66.4, 64.9, 45.2, 42.0, 32.1, 28.0, 22.9, 22.3, 21.1. IR (KBr): υ 3015, 2931, 2858, 1569, 1216, 1109, 1216, 1109, 1028, 747, 667; HRMS (APCI) calcd for $C_{17}H_{22}BrO_2$ $[M + H]^+$: 337.0797. Found: 337.0788

6-(4-Bromothiophen-2-yl)decahydrofuro[3,2-d]isochromene (**6n**). Pale yellow liquid; Yield 143 mg, 84%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 (d, J = 1.3 Hz, 1H), 6.90 (d, J = 1.2 Hz, 1H), 4.60 (d, J = 10.9 Hz, 1H), 4.06 (dd, J = 1.5, 12.3 Hz, 1H), 3.99 (td, J = 3.2, 8.8 Hz, 1H), 3.89 (q, J = 8.6 Hz, 1H), 3.85 (dd, J = 3.3, 12.3 Hz, 1H), 2.41−2.31 (m, 1H), 2.09−2.01 (m, 1H), 1.96 (td, J = 5.1, 13.4 Hz, 1H), 1.85 (dd, J = 5.0, 10.9 Hz, 1H), 1.79−1.73 (m, 1H), 1.72−1.60 (m, 3H), 1.48−1.42 (m, 1H), 1.30−1.18 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.2, 127.6, 122.2, 108.8, 79.5, 75.8, 66.5, 64.9, 45.0, 42.8, 32.2, 28.0, 22.8, 22.6, 20.9. IR (KBr): υ 2920, 2851, 1458, 1219, 1106, 1029, 772, 600; HRMS(EI) calcd for $C_{15}H_{19}BrO_2S$ $[M]^+$: 342.0289. Found: 342.0280.

6-Phenyloctahydro-2H-cyclopenta[c]furo[2,3-d]pyran (**6o**). Pale yellow liquid; Yield 97 mg, 80%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36−7.26 (m, 5H), 4.13 (d, J = 12.2 Hz, 1H), 3.97−3.86 (m, 2H), 3.79−3.34 (m, 2H), 2.39−2.30 (m, 1H), 2.18−2.08 (m, 3H), 2.06−1.98 (m, 1H), 1.87−1.64 (m, 4H), 1.29−1.20 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.8, 128.3, 127.8, 127.3, 89.7, 83.4, 66.9, 64.9, 47.3, 40.1, 34.3, 29.4, 25.9, 21.7; IR (KBr): υ 2921, 2850, 1453, 1218, 1112, 1029, 771, 749, 605; HRMS(EI) calcd for $C_{16}H_{20}O_2$ $[M]^+$: 244.1463 Found: 244.1460.

6-p-Tolyloctahydro-2H-cyclopenta[c]furo[2,3-d]pyran (**6p**). Pale yellow liquid; Yield 105 mg, 82%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22 (d, J = 7.9 Hz, 2H), 7.14 (d, J = 7.7 Hz, 2H), 4.11 (d, J = 12.0 Hz, 1H), 3.96−3.86 (m, 2H), 3.75 (dd, J = 2.7, 12.2 Hz, 1H), 3.72 (d, J = 11.2 Hz, 1H), 2.40−2.28 (m, 1H), 2.33 (s, 3H), 2.17−2.07 (m, 3H), 2.05−1.97 (m, 1H), 1.87−1.68 (m, 3H), 1.27−1.19 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.9, 137.5, 129.0, 127.3, 89.8, 83.3, 66.9, 64.9, 47.1, 40.2, 34.4, 29.4, 26.0, 21.8, 21.0. IR (KBr): υ 2952, 2921, 1515, 1453, 1218, 1111, 1031, 809, 771 HRMS (Orbitrap ESI) calcd for $C_{17}H_{23}O_2$ $[M + H]^+$: 259.1692. Found: 259.1689.

6-(4-Bromophenyl)octahydro-2H-cyclopenta[c]furo[2,3-d]pyran (**6q**). Pale yellow liquid; Yield 135 mg, 84%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (d, J = 8.3 Hz, 2H), 7.21 (d, J = 8.3 Hz, 2H), 4.11 (d, J = 12.2 Hz, 1H), 3.95−3.86 (m, 2H), 3.74 (dd, J = 2.7, 12.3 Hz, 1H), 3.72 (d, J = 10.9 Hz, 1H), 2.36−2.26 (m, 1H), 2.18−2.08 (m, 2H), 2.05−1.95 (m, 2H), 1.87−1.68 (m, 4H), 1.22−1.15 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.0, 131.4, 129.0, 121.7, 89.5, 82.7, 66.9, 64.9, 47.2, 40.0, 34.3, 29.4, 25.6, 21.8. IR (KBr): υ 2952, 2870, 1591, 1488, 1218, 1112,1006, 815, 772; HRMS(EI) calcd for $C_{16}H_{19}BrO_2$ $[M]^+$: 322.05684 Found: 322.05680.

6-(4-Chlorophenyl)octahydro-2H-cyclopenta[c]furo[2,3-d]pyran (**6r**). Pale yellow liquid; Yield 118 mg, 86%; ^{1}H NMR (300 MHz, $CDCl_3$): δ7.33−7.30 (m, 2H), 7.28−7.25 (m, 2H), 4.11 (d, J = 12.2 Hz, 1H), 3.95−3.86 (m, 2H), 3.77−3.71 (m, 2H), 2.36−2.26 (m, 1H), 2.18−2.08 (m, 2H), 2.06−1.95 (m, 2H), 1.87−1.68 (m, 4H), 1.23−1.15 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.4, 133.5, 128.7, 128.4, 89.5, 82.6, 66.9, 64.9, 47.3, 40.0, 34.3, 29.4, 25.8, 21.9. IR (KBr): υ 2956, 2851, 1491, 1217, 1089, 1011, 819, 748; HRMS(EI) calcd for $C_{16}H_{19}ClO_2$ $[M]^+$: 278.1073 Found: 278.1070.

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*4-Phenyl-6-p-tolyldecahydrofuro[3,2-d]isochromene (**10a**).* White solid; mp 140−142 °C. Yield 165 mg, 95%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38−7.34 (m, 2H), 7.32−7.27 (m, 4H), 7.23−7.16 (m, 3H), 4.93 (d, *J* = 3.0 Hz, 1H), 4.56 (d, *J* = 11.1 Hz, 1H), 3.94 (td, *J* = 2.8, 9.4 Hz, 1H), 3.80 (dd, *J* = 8.5, 17.2 Hz, 1H), 2.35 (s, 3H), 2.27−2.17 (m, 2H), 2.07−2.01 (m, 1H), 1.93−1.88 (m, 1H), 1.78−1.57 (m, 4H), 1.51−1.31 (m, 3H), 1.13 (d, *J* = 13.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.6, 138.0, 137.3, 128.9, 128.0, 126.9, 126.7, 125.1, 80.7, 80.4, 76.3, 64.8, 50.8, 41.7, 32.4, 25.3, 23.1, 22.3, 21.1, 21.1; IR (neat): υ 2932, 2860, 1540, 1141, 1068, 1029, 814, 752, 700; HRMS(EI) calcd for $C_{24}H_{28}O_2$ $[M]^+$: 348.2089 Found: 348.2079.

*Crystal Data for **10a**.* $C_{24}H_{28}O_2$ (*M* = 348.46): monoclinic, space group $P2_1/c$ (No. 14), *a* = 18.4384(16) Å, *b* = 8.3568(7) Å, *c* = 13.1820(11) Å, β = 108.980(1)°, *V* = 1920.7(3) Å^3, *Z* = 4, *T* = 294.15 K, μ(Mo Kα) = 0.075 mm^{-1}, D_{calc} = 1.205 g/mm^3, 21 823 reflections measured (4.672 ≤ 2Θ ≤ 56.656), 4619 unique (R_{int} = 0.0244), which were used in all calculations. The final R_1 was 0.0532 ($I > 2\sigma(I)$) and wR_2 was 0.1466 (all data). CCDC 1423578 contains supplementary Crystallographic data for the structure. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44(0) 1223 336 033; email: deposit@ccdc.cam.ac.uk].

*4-Phenyl-6-styryldecahydrofuro[3,2-d]isochromene (**10b**).* White solid; mp 145−147 °C. Yield 162 mg, 90%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44−7.41 (m, 2H), 7.38−7.29 (m, 6H), 7.26−7.20 (m, 2H), 6.67 (d, *J* = 15.8 Hz, 1H), 6.25 (dd, *J* = 7.4 Hz, 15.8, 1H), 4.87 (d, *J* = 3.0 Hz, 1H), 4.25 (dd, *J* = 7.7, 9.9 Hz, 1H), 3.91 (td, *J* = 2.8, 9.4 Hz, 1H), 3.78 (dd, *J* = 8.5, 16.7 Hz, 1H), 2.18−2.08 (m, 2H), 2.02−1.96 (m, 1H), 1.82−1.06 (m, 6H), 1.53−1.40 (m, 2H), 1.34−1.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.5, 136.7, 132.5, 128.6, 128.4, 128.09, 127.6, 126.8, 126.5, 125.1, 80.0, 79.8, 76.0, 64.7, 50.7, 40.2, 32.5, 25.2, 23.0, 22.5, 20.9; IR (neat): υ 3026, 2930, 2860, 1494, 1449, 1214, 1138, 1066, 1028, 964, 843, 748, 694; HRMS(EI) calcd for $C_{25}H_{28}O_2$ $[M]^+$: 360.2089 Found: 360.2075.

*Methyl 4-(4-Phenyldecahydrofuro[3,2-d]isochromen-6-yl)-benzoate (**10c**).* White solid; mp 148−150 °C. Yield 137 mg, 70%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07−8.04 (m, 2H), 7.50−7.47 (m, 2H), 7.38−7.30 (m, 4H), 7.25−7.21 (m, 1H), 4.95 (d, *J* = 3.0 Hz, 1H), 4.66 (d, *J* = 10.9 Hz, 1H), 3.94 (td, *J* = 2.7, 9.3 Hz, 1H), 3.92 (s, 3H), 3.81 (dd, *J* = 8.6, 16.9 Hz, 1H), 2.29−2.17 (m, 2H), 2.10−2.04 (m, 1H), 1.89 (dd, *J* = 4.8, 10.8 Hz, 1H), 1.8−1.59 (m, 4H), 1.54−1.46 (m, 2H), 1.43−1.34 (m, 1H), 1.07 (d, *J* = 14.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 146.1, 141.2, 129.65, 128.1, 126.9, 125.0, 80.4, 80.2, 76.5, 64.9, 52.0, 50.8, 41.9, 32.4, 25.3, 23.0, 22.2, 21.1; IR (neat): υ 2931, 2861, 1719, 1611, 1437, 1275, 1107, 1069, 1028, 751, 704; HRMS(EI) calcd for $C_{25}H_{28}O_4$ $[M]^+$: 392.1987 Found: 392.1977.

*4-(4-(4-Methoxyphenyl)decahydrofuro[3,2-d]isochromen-6-yl)-N,N-diphenylaniline (**10d**).* Pale yellow solid; mp 220−222 °C. Yield 199 mg, 75%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31−7.21 (m, 8H), 7.12−7.04 (m, 6H), 7.03−6.97 (m, 2H), 6.88−6.83 (m, 2H), 4.88 (d, *J* = 2.93 Hz, 1H), 4.55 (d, *J* = 11.0 Hz, 1H), 3.94 (td, *J* = 2.4, 9.2 Hz, 1H), 3.80 (dd, *J* = 8.4, 14.9 Hz, 1H), 3.78 (s, 3H), 2.3−2.13 (m, 2H), 2.03−1.95 (m, 1H), 1.93−1.86 (m, 1H), 1.8−1.43 (m, 6H), 1.43−1.18 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.4, 147.7, 147.2, 135.3, 133.8, 129.1, 127.8, 126.34, 124.1, 123.9, 122.6, 113.4, 80.5, 80.4, 76.2, 64.8, 55.2, 51.0, 41.7, 32.4, 29.6, 25.4, 23.1, 22.4, 21.1; IR (neat): υ 2928, 2857, 1589, 1510, 1490, 1276, 1246, 1174, 1069, 1032, 832, 753, 696; HRMS(EI) calcd for $C_{36}H_{37}NO_3$ $[M]^+$: 531.2773 Found: 531.2770.

*6-(Biphenyl-4-yl)-4-p-tolyldecahydrofuro[3,2-d]isochromene (**10e**).* White solid; mp 155−157 °C. Yield 192 mg, 91%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64−7.56 (m, 4H), 7.50−7.40 (m, 4H), 7.38−7.33 (m, 1H), 7.30−7.24 (m, 2H), 7.16−7.10 (m, 2H), 4.93 (d, *J* = 2.4 Hz, 1H), 4.64 (d, *J* = 11.1 Hz, 1H), 3.96 (td, *J* = 2.6, 9.2 Hz, 1H), 3.82 (dd, *J* = 8.3, 16.8 Hz, 1H), 2.32 (s, 3H), 2.29−2.19 (m, 2H), 2.09−2.00 (m, 1H), 1.95 (dd, *J* = 4.3, 10.5 Hz, 1H), 1.81−1.33 (m, 7H), 1.20 (d, *J* = 13.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.9, 140.6, 140.1, 138.5, 136.32, 128.7, 128.7, 127.4, 127.1, 127.0, 125.0, 80.6, 80.4, 76.3, 64.8, 50.9, 41.8, 32.5, 25.4, 23.1, 22.4, 21.19, 21.0; IR (neat): υ 2930, 2860, 1514, 1486, 1451, 1140, 1099, 1070, 1032, 968, 833, 752, 696; HRMS(EI) calcd for $C_{30}H_{32}O_2$ $[M]^+$: 424.24023 Found: 424.24020.

*6-(3-(Benzyloxy)propyl)-4-p-tolyldecahydrofuro[3,2-d]isochromene (**10f**).* Pale yellow liquid; Yield 178 mg, 85%; ^{1}H NMR (500 MHz, $CDCl_3$): 7.36−7.31 (m, 4H), 7.3−7.26 (m, 1H), 7.22−7.18 (m, 2H), 7.14−7.10 (m, 2H), 4.67 (d, *J* = 2.2 Hz, 1H), 4.52 (ABq, *J* = 12.0 Hz, 2H), 3.85 (td, *J* = 3.0, 9.1 Hz, 1H), 3.74 (dd, *J* = 5.4, 13.7 Hz, 1H), 3.63−3.57 (m, 1H), 3.53 (t, *J* = 6.4 Hz, 2H), 2.33 (s, 3H), 2.1−1.71 (m, 7H), 1.70−1.60 (m, 4H), 1.60−1.51 (m, 2H), 1.47 (d, *J* = 13.2 Hz, 1H), 1.43−1.37 (m, 1H), 1.24−1.13 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 139.0, 138.6, 136.1, 128.7, 128.3, 127.6, 127.4, 124.9, 80.4, 76.5, 75.6, 72.8, 70.4, 64.7, 50.6, 39.8, 32.5, 29.4, 25.2, 25.2, 23.2, 22.3, 21.0, 20.9; IR (neat): υ 2929, 2858, 1514, 1451, 1095, 1067, 1028, 738, 696; HRMS(EI) calcd for $C_{28}H_{36}O_3$ $[M]^+$: 420.2664 Found: 420.2660.

*6-(2-(Benzyloxy)ethyl)-4-propyldecahydrofuro[3,2-d]isochromene (**10g**).* Pale yellow liquid; Yield 134 mg, 75%; ^{1}H NMR (500 MHz, $CDCl_3$): 7.35−7.32 (m, 4H), 7.31−7.27 (m, 1H), 4.56−4.47 (m, 2H), 3.91 (td, *J* = 3.0, 8.6 Hz, 1H), 3.83 (dd, *J* = 8.3, 16.7 Hz, 1H), 3.68−3.59 (m, 2H), 3.56−3.49 (m, 2H), 2.10−1.99 (m, 2H), 1.96−1.89 (m, 1H), 1.86−1.78 (m, 1H), 1.77−1.66 (m, 1H), 1.66−1.39 (m, 10H), 1.36−1.24 (m, 2H), 1.20−1.10 (m, 1H), 0.92 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 138.6, 128.2, 127.5, 127.3, 80.4, 74.5, 73.9, 72.9, 67.1, 64.8, 49.1, 40.9, 36.3, 33.2, 32.4, 24.6, 23.1, 22.4, 20.8, 19.2, 14.0; IR (neat): υ 2930, 2862, 1453, 1361, 1091, 1030, 737, 697; HRMS(EI) calcd for $C_{23}H_{34}O_3$ $[M]^+$: 358.2507 Found: 358.2500.

*4-Ethyl-6-p-tolyldecahydrofuro[3,2-d]isochromene (**10h**).* White solid; mp 92−94 °C. Yield 142 mg, 95%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21−7.17 (m, 2H), 7.16−7.12 (m, 2H), 4.33 (d, *J* = 10.9 Hz, 1H), 3.99 (td, *J* = 2.8, 8.8 Hz, 1H), 3.90 (dd, *J* = 8.3, 16.9 Hz, 1H), 3.61 (td, *J* = 2.7, 6.8 Hz, 1H), 2.33 (s, 3H), 2.31−2.25 (m, 1H), 2.04 (td, *J* = 5.1, 13.4 Hz, 1H), 1.95−1.88 (m, 1H), 1.80 (dd, *J* = 5.1, 10.9 Hz, 1H), 1.74−1.42 (m, 7H), 1.42−1.22 (m, 2H), 1.05 (d, *J* = 14.2 Hz, 1H), 0.92 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 138.2, 137.1, 128.9, 126.9, 80.5, 80.4, 77.3, 76.6, 64.9, 48.3, 41.7, 32.4, 27.2, 24.4, 23.0, 22.4, 21.0, 10.3; IR (neat): υ 2929, 2860, 1514, 1454, 1368, 1166, 1078, 1032, 996, 963, 863, 813; HRMS(EI) calcd for $C_{20}H_{28}O_2$ $[M]^+$: 300.20893 Found: 300.20890.

*Preparation of Compounds **3** and **4**.* To the ice-cooled solution of NaH (12 mmol) in 20 mL of THF was added a solution diethyl succinate (6 mmol) in THF, and the mixture was stirred for 10 min. One drop of EtOH was added to initiate the reaction. After 10 min, cyclohexanone or cyclopentanone (6 mmol) was added dropwise over 1 h, and the reaction mixture was stirred for 12 h at rt. The reaction was quenched with 4 M HCl and extracted with EtOAc (3 × 20 mL). Combined organic layers were dried over Na_2SO_4 and filtered, and the solvent was removed under vacuo. The resulting brown syrup was dissolved in EtOH (20 mL) and acidified with conc H_2SO_4 and stirred for 1 h at 0 °C. The reaction mixture was warmed up to rt and refluxed for 12 h. The reaction mixture was quenched with a saturated solution of $NaHCO_3$ and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. The crude solution of diester was added to the solution of LAH (24 mmol) at 0 °C. The reaction mixture was stirred at the same temp for 30 min. After consumption of starting material, the reaction was quenched with sat NH4Cl and filtered over Celite and washed with hot ethyl acetate. The filtrate was dried over Na_2SO_4 and evaporated under vacuum. The residue was purified using column chromatography.

*2-Cyclopentenylbutane-1,4-diol (**3**).* Pale yellow liquid; Yield 673 mg, 72%; ^{1}H NMR (500 MHz, $CDCl_3$): 5.55 (S, 1H), 3.75−3.70 (m, 1H), 3.67−3.55 (m, 3H), 2.62−2.55 (m, 1H), 2.36−2.31 (m, 2H), 2.29−2.23 (m, 2H), 1.91−1.84 (m, 2H), 1.75−1.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.32, 126.68, 64.6, 61.2, 41.5, 33.4, 32.3, 32.2, 23.1. IR (KBr): 3312, 2923, 2875, 2857, 1660, 1438, 1218,

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1046, 1026, 918, 771; HRMS (ESI-Orbitrap) calcd for $C_9H_{17}O_2$ $[M + H]^+$: 157.1223 Found: 157.1222.

*2-Cyclohexenylbutane-1,4-diol (**4**).* Pale yellow liquid; Yield 693 mg, 68%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.58 (S, 1H), 3.72−3.67 (m,1H), 3.65−3.59 (m, 1H), 3.57−3.48 (m, 2H), 2.32−2.26 (m, 1H), 2.06−2.01 (m, 2H), 1.98−1.88 (m, 2H), 1.69−1.58 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.2, 124.6, 64.5, 61.3, 47.4, 32.9, 25.2, 25.2, 22.8, 22.5; IR (neat): υ 3335, 2927, 2884, 2852, 1700, 1676, 1608, 1436, 1218, 1025, 770; HRMS (ESI Orbitrap) calcd for $C_{10}H_{18}O_2Na$ $[M + Na]^+$: 193.1190 Found: 193.1202.

*Preparation of Compounds **9a**−**e**.* To the solution of compound 7 (2 mmol) in DCM was added a 1.5 M solution of DIBAL-H (2 mL) at −78 °C, and the reaction mixture was stirred at the same temp for 1 h. After consumption of starting material, as evident by TLC, the reaction was quenched with 20 mL of a saturated solution of tartaric acid and stirred at rt for 30 min. The organic layer was separated, and the aq layer was extracted with DCM (3 × 10 mL). The organic layer was dried over Na_2SO_4 and evoparated under vacuum. Crude lactol was taken in 10 mL of dry THF, and to it was added 4 mmol of RMgBr (R = Ethyl, Propyl, Phenyl, *p*-Tolyl, *p*-Anisyl) at 0 °C. The reaction was stirred for 2 h. Then, the reaction was quenched with saturated NH_4Cl and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, and the crude material was purified by colum chromatography.

*2-Cyclohexenyl-1-phenylbutane-1,4-diol (**9a**).* Pale yellow liquid; Yield 393 mg, 80%; ^{1}H NMR (500 MHz, $CDCl_3$): δ7.32−7.21 (m, 5H), 5.37 (s, 1H), 4.60 (d, J = 7.6 Hz, 1H), 3.70−3.65 (m, 1H), 3.59−3.53 (m, 1H), 2.36−2.31 (m, 1H), 2.00−1.67 (m, 6H), 1.47−1.38 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.5, 137.4, 127.9, 127.3, 126.6, 124.5, 76.7, 61.8, 52.6, 32.5, 27.4, 25.2, 22.8, 22.3; IR (neat): υ 3328, 2922, 1661, 1450, 1346, 1012, 917, 756, 698; HRMS (ESI Orbitrap) calcd for $C_{16}H_{22}O_2Na$ $[M + Na]^+$: 269.1512 Found: 269.1514.

*2-Cyclohexenyl-1-p-tolylbutane-1,4-diol (**9b**).* Pale yellow liquid; Yield 426 mg, 82%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21−7.07 (m, 4H), 5.38 (s, 1H), 4.58 (d, J = 7.5 Hz, 1H), 3.73−3.63 (m, 1H), 3.61−3.51 (m, 1H), 2.33 (s, 3H), 2.03−1.63 (m, 7H), 1.51−1.37 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.3, 137.5, 136.7, 128.6, 126.3, 124.3, 76.4, 61.8, 52.4, 32.3, 27.3, 25.1, 22.8, 22.3, 21.1; IR (neat): υ 3328, 2922, 1450, 1346, 1012, 917, 756, 698; HRMS (ESI Orbitrap) calcd for $C_{17}H_{24}O_2Na$ $[M + Na]^+$: 283.1674 Found: 283.1671.

*2-Cyclohexenyl-1-(4-methoxyphenyl)butane-1,4-diol (**9c**).* Pale yellow liquid; Yield 469 mg, 85%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 5.36 (s, 1H), 4.56 (d, J = 7.8 Hz, 1H), 3.80 (s, 3H), 3.76−3.66 (m, 1H), 3.62−3.53 (m, 1H), 2.36−2.28 (m, 1H), 2.03−1.94 (m, 1H), 1.91−1.60 (m, 5H), 1.48−1.36 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7, 137.5, 135.5, 127.6, 124.4, 113.2, 76.3, 61.8, 55.1, 52.65, 32.7, 27.2, 25.1, 22.8, 22.3; IR (neat): υ 3336, 2923, 1611, 1511, 1440, 1242, 1174, 1030, 828, 752; HRMS (ESI Orbitrap) calcd for $C_{17}H_{25}O_3$ $[M + H]^+$: 277.1803 Found: 277.1809.

*3-Cyclohexenylhexane-1,4-diol (**9d**).* Pale yellow liquid; Yield 376 mg, 95%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.51−5.48 (m, 1H), 3.72−3.65 (m, 1H), 3.61−3.54 (m, 1H), 3.48−3.41 (m, 1H), 2.06−1.89 (m, 5H), 1.83−1.74 (m, 1H), 1.72−1.51 (m, 6H), 1.35−1.25 (m, 1H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.1, 123.7, 74.6, 61.7, 51.5, 32.7, 28.1, 25.9, 25.2, 22.9, 22.5, 10.0; IR (neat): υ 3310, 2922, 2876, 1443, 1042, 969, 800; HRMS (ESI Orbitrap) calcd for $C_{12}H_{23}O_2$ $[M + H]^+$: 199.1692 Found: 199.1694.

*3-Cyclohexenylheptane-1,4-diol (**9e**).* Pale yellow liquid; Yield 381 mg, 90%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.50 (s, 1H), 3.72−3.66 (m, 1H), 3.61−3.50 (m, 2H), 2.06−1.88 (m, 6H), 1.84−1.75 (m, 1H), 1.73−1.43 (m, 6H), 1.38−1.25 (m, 2H), 0.92 (t, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.0, 123.7, 73.0, 61.8, 51.6, 37.4, 32.1, 25.2, 25.0, 22.9, 22.5, 18.9, 14.0; IR (neat): υ 3329, 2926, 2871, 1447, 1216, 1123, 1049, 998, 918, 752; HRMS (ESI Orbitrap) calcd for $C_{13}H_{25}O_2$ $[M + H]^+$: 213.1849 Found: 213.1850.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02241.

Crystallographic data for **10a** (CIF)

NOESY and DQFCOSY study of **6a**, ORTEP diagram for compound **10a**, and copies of ^{1}H and ^{13}C NMR spectra of products (**6a−r**,**10a−h**, **3**, **4**, and **9a−e**) (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Soc. Rev.* **2014**, *43*, 3106. (b) Shakoori, A.; Bremner, J. B.; Willis, A. C.; Haritakun, R.; Keller, P. A. *J. Org. Chem.* **2013**, *78*, 7639. (c) Liu, T.; Wang, R.; Yang, H.; Fu, H. *Chem. - Eur. J.* **2011**, *17*, 6765. (d) Brimble, M. A.; Haym, I.; Sperry, J.; Furkert, D. P. *Org. Lett.* **2012**, *14*, 5820. (e) Caron, P. Y.; Deslongchamps, P. *Org. Lett.* **2010**, *12*, 508. (f) Blaszykowski, C.; Aktoudianakis, E.; Bressy, C.; Alberico, D.; Lautens, M. *Org. Lett.* **2006**, *8*, 2043.

(2) (a) Erguden, J. K.; Moore, H. W. *Org. Lett.* **1999**, *1*, 375. (b) Raffa, G.; Rusch, M.; Balme, G.; Monteiro, N. *Org. Lett.* **2009**, *11*, 5254. (c) An, J.; Lu, L.-Q.; Yang, Q.-Q.; Wang, T.; Xiao, W.-J. *Org. Lett.* **2013**, *15*, 542. (d) Gharpure, S. J.; Niranjana, P.; Porwal, S. K. *Org. Lett.* **2012**, *14*, 5476. (e) Lee, H. Y.; Jung, Y.; Yoon, Y.; Kim, B. G.; Kim, Y. *Org. Lett.* **2010**, *12*, 2672. (f) Brummond, K. M.; Chen, D.; Davis, M. M. *J. Org. Chem.* **2008**, *73*, 5064. (g) Patil, N. T.; Kavthe, R. D.; Raut, V. S.; Shinde, V. S.; Sridhar, B. *J. Org. Chem.* **2010**, *75*, 1277.

(3) (a) Imagawa, H.; Saijo, H.; Yamaguchi, H.; Maekawa, K.; Kurisaki, T.; Yamamoto, H.; Nishizawa, M.; Oda, M.; Kabura, M.; Nagahama, M.; Sakurai, J.; Kubo, M.; Nakai, M.; Makino, K.; Ogata, M.; Takahashi, H.; Fukuyama, Y. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2089. (b) Shi, H.; Fang, L.; Tan, C.; Shi, L.; Zhang, W.; Li, C.-c.; Luo, T.; Yang, Z. *J. Am. Chem. Soc.* **2011**, *133*, 14944. (c) Seth, P. P.; Totah, N. L. *Org. Lett.* **2000**, *2*, 2507. (d) King, T. J.; Farrell, I. W.; Halsall, T. G.; Thaller, V. *J. Chem. Soc., Chem. Commun.* **1977**, 727.

(4) (a) Hehn, J. P.; Herdtweck, E.; Bach, T. *Org. Lett.* **2011**, *13*, 1892. (b) Maity, S.; Matcha, K.; Ghosh, S. *J. Org. Chem.* **2010**, *75*, 4192. (c) Huang, S.; Du, G.; Lee, C. S. *J. Org. Chem.* **2011**, *76*, 6534. (d) Joo, J. M.; Yuan, Y.; Lee, C. *J. Am. Chem. Soc.* **2006**, *128*, 14818. (e) Foote, K. M.; Hayes, C. J.; John, M. P.; Pattenden, G. *Org. Biomol. Chem.* **2003**, *1*, 3917.

(5) Reviews on Prins reaction; see: (a) Olier, C.; Kaafarani, M.; Gastaldi, S. S.; Bertrand, M. P. *Tetrahedron* **2010**, *66*, 413. (b) Crane, E. A.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2010**, *49*, 8316. (c) Pastor, I. M.; Yus, M. *Curr. Org. Chem.* **2012**, *16*, 1277. (d) Han, X.; Peh, G. R.; Floreancig, P. E. *Eur. J. Org. Chem.* **2013**, *2013*, 1193.

(6) (a) Spivey, A. C.; Laraia, L.; Bayly, A. R.; Rzepa, H. S.; White, A. J. *Org. Lett.* **2010**, *12*, 900. (b) Chavre, S. N.; Ullapu, P. R.; Min, S. J.; Lee, J. K.; Pae, A. N.; Kim, Y.; Cho, Y. S. *Org. Lett.* **2009**, *11*, 3834. (c) Barbero, A.; Diez-Varga, A.; Pulido, F. J. *Org. Lett.* **2013**, *15*, 5234. (d) Elsworth, J. D.; Willis, C. L. *Chem. Commun.* **2008**, 1587.

(7) (a) Cho, Y. S.; Kim, H. Y.; Cha, J. H.; Pae, A. N.; Koh, H. Y.; Choi, J. H.; Chang, M. H. *Org. Lett.* **2002**, *4*, 2025. (b) Chen, Z. H.;

DOI: 10.1021/acs.joc.5b02241
J. Org. Chem. 2015, 80, 12580−12587

Tu, Y. Q.; Zhang, S. Y.; Zhang, F. M. *Org. Lett.* **2011**, *13*, 724. (c) Overman, L. E.; Velthuisen, E. J. *J. Org. Chem.* **2006**, *71*, 1581. (d) Bunt, A. J.; Bailey, C. D.; Cons, B. D.; Edwards, S. J.; Elsworth, J. D.; Pheko, T.; Willis, C. L. *Angew. Chem., Int. Ed.* **2012**, *51*, 3901.

(8) (a) Kwon, M. S.; Woo, S. K.; Na, S. W.; Lee, E. *Angew. Chem., Int. Ed.* **2008**, *47*, 1733. (b) Li, B.; Lai, Y. C.; Zhao, Y.; Wong, Y. H.; Shen, Z. L.; Loh, T. P. *Angew. Chem., Int. Ed.* **2012**, *51*, 10619. (c) Cons, B. D.; Bunt, A. J.; Bailey, C. D.; Willis, C. L. *Org. Lett.* **2013**, *15*, 2046. (d) Fenster, E.; Fehl, C.; Aube, J. *Org. Lett.* **2011**, *13*, 2614. (e) Lee, H. M.; Nieto-Oberhuber, C. N.; Shair, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 16864. (f) Gesinski, M. R.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2011**, *133*, 9727. (g) Manaviazar, S.; Hale, K. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 8786.

(9) (a) Reddy, B. V. S.; Prasad, D. M.; Sridhar, B.; Kiran, S. K. *J. Org. Chem.* **2014**, *79*, 2289. (b) Reddy, B. V. S.; Swathi, V.; Swain, M.; Bhadra, M. P.; Sridhar, B.; Satyanarayana, D.; Jagadeesh, B. *Org. Lett.* **2014**, *16*, 6267. (c) Reddy, B. V. S.; Medaboina, D.; Sridhar, B. *J. Org. Chem.* **2015**, *80*, 653.

(10) Lee, W.-W. W.; Gan, L.-M.; Loh, T.-P. *Synlett* **2005**, 2473.

(11) Schultz, A. G.; Sundararaman, P. *J. Org. Chem.* **1984**, *49*, 2455.

(12) Tomooka, K.; Okinaga, T.; Suzuki, K.; Tsuchihashi, G.-I. *Tetrahedron Lett.* **1989**, *30*, 1563.

(13) Diez-Varga, A.; Barbero, H.; Pulido, F. J.; Gonzalez-Ortega, A.; Barbero, A. *Chem. - Eur. J.* **2014**, *20*, 14112.

(14) *SAINT*, Version 6.28a; Bruker: Madison, WI, 2002 and *SMART*, Version 5.625; Bruker: Madison, WI, 2001.

(15) Sheldrick, G. M. *Acta Crystallogr.* **2015**, *C71*, 3.

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J. Org. Chem. 2015, 80, 12580−12587