Direct Synthesis of Bicyclic Acetals via Visible Light Catalysis

- Synergy of PC and HAT
- 39 examples, up to 90% yield
- 5/5, 5/6, 5/7, 6/6 bicyclic acetals
- Polysubstituted THF derivatives

HIGHLIGHTS
- Synergistic catalysis of photocatalyst and HAT reagent
- 5/5, 5/6, 5/7, 6/6 bicyclic acetals and polysubstituted THF formed in one step
- High stability of bicyclic acetal in SIF and SGF
Direct Synthesis of Bicyclic Acetals via Visible Light Catalysis

Fengjin Wu,1 Leifeng Wang,1,2 Ying Ji,3 Ge Zou,3 Hong Shen,3 David A. Nicewicz,1,2,* Jiean Chen,1,4,5,* and Yong Huang1,4,*

SUMMARY
Polysubstituted bicyclic acetals are a class of privileged pharmacophores with a unique 3D structure and an adjacent pair of hydrogen bond acceptors. The key, fused acetal functionality is often assembled, via intramolecular cyclization, from linear substrates that are not readily available. Herein, we report a formal cycloaddition between cinnamyl alcohols and cyclic enol ethers under ambient photoredox catalysis conditions. Polysubstituted bicyclic acetals can be prepared in one step from readily available building blocks. Employment of sugar-derived enol ethers allows easy access to a library of scaffolds with intriguing conformation and medicinal chemistry potential.

INTRODUCTION
Bicyclic acetals are prevalent structural motifs in natural products, pharmaceuticals, and agrochemicals (Pirrung et al., 1989; Brady et al., 2004; Alonso et al., 2005; Henry and Townsend, 2005; Zhou and Corey, 2005; Baird et al., 2009; Sastraruji et al., 2010; Mori et al., 2015; Ghosh et al., 2017; Karimov et al., 2018; Pan et al., 2018; Lenci et al., 2019; Bera et al., 2018). Compared with other privileged pharmacophores, such as biaryls, bicyclic acetals possess rigorous conformational rigidity, low molecular weight, and a pair of endogenous hydrogen bonding acceptors (King et al., 2004; Surleraux et al., 2005; Ghosh et al., 2009, 2011). They are strong binders to a number of important enzymes and do not carry the liability of instability at low pH environments like their acyclic counterparts (Evans et al., 1981; Coppola, 1984; Tufarillo and Winzenberg, 1986; Stern and Swenton, 1989; Roush and Sciotti, 1994). For instance, the bicyclic acetal interacts tightly with two neighboring amino acid residues in HIV-1 protease (Asp-29 and Asp-30), making them excellent candidates for antiviral agents (Figure 1) (King et al., 2004; Surleraux et al., 2005; Ghosh et al., 2009, 2011).

Considerable attention has been drawn to access bicyclic acetals. In general, two synthetic approaches are employed, both of which require linear synthesis of starting materials. The first approach uses gem-disubstituted alkenes bearing two terminal hydroxyl groups that can undergo Wacker-type oxidation, followed by ketalization to furnish the target skeleton (Figure 2A) (Alonso et al., 1998, 2003, 2011; Lorenzo et al., 2000a, 2000b; Roggenbuck et al., 2002; Messerle and Vuong, 2007; Velthuisen et al., 2013). The second option starts from α-halogenated monocyclic acetal. Halide atom abstraction generates an alkyl radical that is captured intramolecularly by a double or triple bond. This Ueno-Stork-type annulation has often been adopted to synthesize the bicyclic acetal core structures (Figure 2B) (Ueno et al., 1982; Stork et al., 1983; Cossey et al., 1994; Yanada et al., 2004; Hayashi et al., 2005; Fukuyama et al., 2016; Hwang et al., 2016; Kyne et al., 2018; Thapa et al., 2017; Venning et al., 2017). Both protocols feature intramolecular cyclization via pre-assembly start materials, which decreases structure versatility, especially when it comes to multisubstituted bicyclic acetals. We envisioned a formal cycloaddition, from readily available olefinic substrates, might present an alternative and modular approach to this type of structures. Herein, we report visible-light-mediated, formal [3 + 2] cycloadditions between commercially available allylic alcohols and cyclic enol ethers (Figure 2C). This transformation delivers the desired bicyclic acetals in a single step and polysubstituted analogs can be accessed.

In recent years, we developed a series of formal cycloaddition reactions involving styrenes catalyzed by strong photooxidants, acridinium salts (Riener and Nicewicz, 2013; Wang et al., 2017; Wu et al., 2018). Based on the work before, we envisioned that, if the styrene substrates bear a free hydroxy group, an
intramolecular event might occur to deliver cyclic acetals. If cyclic enol ethers are employed, the desired bicyclic acetal products might be obtained.

RESULT AND DISCUSSION

Our investigation began using cinnamyl alcohol and dihydropyran (DHP) as substrates. Preliminary trials, using PS-A and PhSSPh as catalysts, afforded the target bicyclic acetal (1) in 25% yield (Table 1, entry 1). The [5, 6] fused ring scaffold is in cis-configuration and moderate dr was observed for the pendant benzyl group (dr = 1.8:1). Side products of DHP were also observed concomitant with product formation. It appears that the addition of DHP to its radical cation \( \text{A} \) (Figure 2C) might be a competing major side reaction, giving rise to polymeric side products. Increasing the concentration of DHP effectively improves conversion, and high yields were obtained when 4 equiv. of DHP was used (entry 2). Additional acridinium salts were examined, and it was determined that the identity of both the counter ion and N-substituent are important for this reaction (entries 3 and 4). Transition metal-based photosensitizers are incompetent photoxidants, and no desired cycloadduct 1 was detected under these conditions (entries 5 and 6). A survey of additional solvents confirms 1,2-dichloroethane is the preferred reaction medium (entries 7–9). When either photocatalyst or light is omitted, the cycloadduct is not observed and PhSSPh is also essential to product formation.

The divergent aspect of this transformation was evaluated using various allylic alcohols and cyclic enol ethers (Figure 3). Cinnamyl alcohols show broad tolerance for substitution and electronic perturbation (products 1–4). Fused aryl substituents can be accommodated by the standard reaction conditions (products 5 and 6). Both \( \alpha \)- and \( \gamma \)-alkyl-substituted cinnamyl alcohols undergo smooth cycloaddition to yield bicyclic acetals bearing a vicinal stereogenic center (products 7 and 8). Heteroaryl analogs react with DHP in good efficiency (products 9–12). Besides DHP, cyclic enol ethers with different ring size show similar efficiency in forming the radical cation intermediate. The one-step protocol affords 5/5-7 fused cyclic acetals in moderate to good yield, some of which are undocumented scaffolds. In addition to cinnamyl alcohol, 2-aryl substituted allylic alcohols undergo formal \([4 + 2]\) cycloaddition reactions with DHP to give cyclic acetals with 6/6 ring juncture (products 15, 17). Alkyl allylic alcohols are also applicable to this formal cycloaddition reactions. However, we experienced isolation difficulties for certain substrates. For example, 2-ethylprop-2-en-1-ol reacted smoothly to give the corresponding [6,6] bicyclic acetal 16. On the other hand, the reaction using 3-methylbut-2-en-1-ol suffered from inseparable side products. NOE experiments confirmed formal cis-cycloaddition. Although the diastereoselectivity of the described reaction is moderate, it can be particularly valuable for drug screening, when biologically preferred stereochemistry is unknown. Alkynes can also be intercepted by the radical ring closure. Propargyl alcohols react with DHP to yield bicyclic acetals with an exocyclic double bond (products 18, 19, 20).

Further substitution of those bicyclic acetals can be accomplished using readily available enol ethers derived from monosaccharides (Figure 4). Natural product-like, polyoxy-substituted bicyclic acetals can
be prepared in moderate yield (Jiang et al., 2016). The stereochemistry of the substituents is predefined by the type of sugar starting materials used. Biological evaluation of this intriguing compound library is currently underway.

This cycloaddition can also be extended beyond cyclic enol ethers, as substituted vinyl ethers were also investigated against the standard reaction conditions (Figure 5). The reactions maintain comparable
efficiency and selectivity. Polysubstituted tetrahydrofuran (THF) analogs can be accessed in good yield. Ethyl vinyl ether (EVE) reacts smoothly with cinnamyl alcohols to give 2,4-substitued THFs (products 28 and 29). β-Substituted EVEs lead to 2,3,4-trisubstituted products (30–39). Interestingly, alkyl allylic alcohols are good substrate for β-phenyl EVEs. The relatively high redox potential of the unactivated double bond in these alcohols does not support single electron (SET) oxidation by the excited photosensitizer (Romero and Nicewicz, 2014). The olefin moiety of the enol ether is more prone to SET oxidation (for β-phenyl EVE, Ep/2 = +1.20 V versus SCE). As a consequence, β,β-disubstituted allylic alcohols can react with β-phenyl EVE to deliver a product bearing a quaternary carbon center (35) with complete anti-selectivity.

Isolated double bonds in substrates do not interfere with the photoredox process (37). A D-galactopyranose-derived allylic alcohol was also applied to the formal cycloaddition to give product with an additional sugar moiety (39).

The reaction between cinnamyl alcohol and DHP was monitored closely using GC. We found that acetal 40 was formed immediately upon mixing. It is intriguing that the concentration of 40 remained nearly consistent, at ca. 22%, for the first half of the reaction period, and bicyclic acetal product 1 was gradually formed (Figure 6).

Subjecting 40 alone to the standard reaction conditions failed to yield product 1 (Figure 6A), suggesting intramolecular cyclization is not operative. However, mixing 40 with DHP under the same conditions generates product 1 in 88% yield (GC, Figure 6B). This result indicates 40 might be a resting state, which helps prevent homodimerization of cinnamyl alcohols (Hamilton and Nicewicz, 2012; Grandjean and Nicewicz, 2013; Nicewicz and Nguyen, 2014; Perkowski et al., 2015; Margrey and Nicewicz, 2016). A competition experiment using 40 and substrate 41, was carried out (Figure 6C). Comparable yield of 1 and 3 was
obtained. These results suggest acetal 40 might also serve as a competitive nucleophile that reacts with DHP radical cation. It is also plausible that the combination of 40, DHP, and the acridinium salt generates catalytic amounts of acid that cause retro acetal formation to free up cinnamyl alcohol.

Unlike previous cycloaddition reactions involving styrene, DHP ($E_{1/2} = +1.51$ V vs. SCE) is more prone, than cinnamyl alcohol ($E_{1/2} = +1.77$ V vs. SCE), to single electron oxidation. Presumably, the acridinium salt is first excited to a highly oxidizing state ($\text{Mes-Acr}^+* E_{1/2} = +2.06$ V versus SCE) by blue LED irradiation. In contrast to nucleophilic addition to styrene-derived radical cation, which features exclusive anti-Markovnikov selectivity, the DHP radical cation reacts with the allylic alcohol at its $\alpha$-carbon, likely due to oxonium stabilization (Schmittel, 1994). DHP is oxidized by Mes-Acr$^+*$ to generate a key DHP radical cation (Roth et al., 2016). Subsequently, cinnamyl alcohol, or acetal intermediate 40 formed during the reaction, acts as a nucleophile to trap the DHP radical cation, which is followed by a Ueno-Stork-type annihilation (Alonso et al., 2011; Velthuisen et al., 2013; Ueno et al., 1982; Stork et al., 1983; Cossy et al., 1994; Yanada et al., 2004; Hayashi et al., 2005; Fukuyama et al., 2016; Hwang et al., 2016; Kyne et al., 2018). Subsequent HAT process, catalyzed by PhSSPh, closes the catalytic cycle.
Several cyclic acetals were evaluated for their preliminary metabolic stability. As shown in Table 2 (see also Tables S1–S6), all four products are stable after incubation with simulated intestinal fluid (SIF, pH 6.8) for 3 h. Stability after 1-h incubation with simulated gastric fluid (SGF, pH 1.2) varies, depending on structure. Bicyclic acetals 15, 1, and 27 are more stable than monocyclic product 35. The 6, 6-bicyclic product 15

**Figure 4. Structurally Sophisticated Bicyclic Acetals Derived from Saccharides**

Reaction conditions: photosensitizer (0.01 mmol, 5 mol%), PhSSPh (0.04 mmol, 20 mol%), allylic alcohol (0.2 mmol), monosaccharides (0.8 mmol) in 3 mL of DCE.

Several cyclic acetals were evaluated for their preliminary metabolic stability. As shown in Table 2 (see also Tables S1–S6), all four products are stable after incubation with simulated intestinal fluid (SIF, pH 6.8) for 3 h. Stability after 1-h incubation with simulated gastric fluid (SGF, pH 1.2) varies, depending on structure. Bicyclic acetals 15, 1, and 27 are more stable than monocyclic product 35. The 6, 6-bicyclic product 15

**Figure 4. Structurally Sophisticated Bicyclic Acetals Derived from Saccharides**

Reaction conditions: photosensitizer (0.01 mmol, 5 mol%), PhSSPh (0.04 mmol, 20 mol%), allylic alcohol (0.2 mmol), monosaccharides (0.8 mmol) in 3 mL of DCE.

Several cyclic acetals were evaluated for their preliminary metabolic stability. As shown in Table 2 (see also Tables S1–S6), all four products are stable after incubation with simulated intestinal fluid (SIF, pH 6.8) for 3 h. Stability after 1-h incubation with simulated gastric fluid (SGF, pH 1.2) varies, depending on structure. Bicyclic acetals 15, 1, and 27 are more stable than monocyclic product 35. The 6, 6-bicyclic product 15

**Figure 5. Synthesis of Polysubstituted THF Derivatives**

Reaction conditions: photosensitizer (0.01 mmol, 5 mol%), PhSSPh (0.04 mmol, 20 mol%), allylic alcohol (0.2 mmol), vinyl ether (0.8 mmol) in 3 mL of DCE.

Several cyclic acetals were evaluated for their preliminary metabolic stability. As shown in Table 2 (see also Tables S1–S6), all four products are stable after incubation with simulated intestinal fluid (SIF, pH 6.8) for 3 h. Stability after 1-h incubation with simulated gastric fluid (SGF, pH 1.2) varies, depending on structure. Bicyclic acetals 15, 1, and 27 are more stable than monocyclic product 35. The 6, 6-bicyclic product 15

**Figure 5. Synthesis of Polysubstituted THF Derivatives**

Reaction conditions: photosensitizer (0.01 mmol, 5 mol%), PhSSPh (0.04 mmol, 20 mol%), allylic alcohol (0.2 mmol), vinyl ether (0.8 mmol) in 3 mL of DCE.
is more stable than its corresponding 6, 5-bicyclic analog 1. Substituents on the six-membered ring have impacts on stability as tri-substitution of 1 leads to compound 27, which is the most stable scaffold tested. This exercise demonstrates that these bicyclic acetals are fairly stable in stimulated intestinal fluids, indicating degradation of these molecules might be very low at major human absorption sites. Furthermore, by modulating ring size and substitution pattern, bicyclic acetals can accomplish good stability in SGF.

**Figure 6. Control Experiments**

|   | 35 | 15 (Two Isomers) | 1 | 27 (Four Isomers) |
|---|----|------------------|---|------------------|
| SGF, 1 h |     |                  |   |                  |
| Degradation (%) | 99.4 | 4.4              | 12.4 | 1.3              |
| Classification  | Unstable | Fairly stable | Unstable | Fairly stable |
| SIF, 3 h |     |                  |   |                  |
| Degradation (%) | −2.6  | 0.1              | 0.1  | 0.5              |
| Classification  | Fairly stable | Fairly stable | Fairly stable | Fairly stable |

**Table 2. Stability of Cyclic Acetals in Simulated GI Fluids**
Conclusion
In summary, we developed an efficient strategy to prepare libraries of bicyclic acetals from allylic alcohols and cyclic enol ethers. This reaction pathway is distinct from reported [2 + 2], [4 + 2], and linear coupling involving styrenes. Under synergistic catalysis of an acridinium salt and PhSSPh, structurally intriguing scaffolds involving 5/5, 5/6, 5/7, and 6/6 bicyclic acetals are synthesized in one step. This approach can be applied to monosaccharide-derived substrates, gaining access to previously unattainable polysubstituted analogs. Additionally, use of acyclic vinyl ethers offers a straightforward entry to poly-substituted THF derivatives. Preliminary stability studies in simulated gastric fluids demonstrate bicyclic acetals are a promising class of chemical modality for medicinal chemistry.

Limitations of the Study
A transformation in diastereoselective version cannot be realized under the current reaction conditions.

Resource Availability
Lead Contact
Jiean Chen, chenja@pkusz.edu.cn.

Materials Availability
This study did not generate new unique reagents. All materials used in the work were sourced from public or commercial resources as described under Transparent Methods (see Supplemental Information).

Data and Code Availability
This study did not generate or use any new datasets or machine code.

METHODS
All methods can be found in the accompanying Transparent Methods supplemental file.

SUPPLEMENTAL INFORMATION
Supplemental Information can be found online at https://doi.org/10.1016/j.isci.2020.101395.

ACKNOWLEDGMENTS
This work was financially supported by the National Natural Science Foundation of China (21801011, 21825101, 21602007), China Postdoctoral Science Foundation (2018M630022), The International Postdoctoral Exchange Fellowship Program (20180033), Guangdong Basic and Applied Basic Research Foundation (2019A1515011641), and Shenzhen Basic Research Funds (JCYJ20170818085510474, JCYJ20170818085438996).

AUTHOR CONTRIBUTIONS
Methodology, F.W., D.A.N., J.C., and Y.H.; Investigation, F.W., L.W., Y.J., and G.Z.; Writing - Original Draft, F.W. and H.S.; Writing - Review & Editing, D.A.N., J.C., and Y.H.; Supervision, D.A.N., J.C., and Y.H.

DECLARATION OF INTERESTS
The authors declare no competing interests.

Received: May 25, 2020
Revised: June 26, 2020
Accepted: July 17, 2020
Published: August 21, 2020

REFERENCES
Alonso, F., Lorenzo, E., Melendez, J., and Yus, M. (2003). Straight and versatile synthesis of substituted perhydrofuro[2,3-b]pyrans from 2-chloromethyl-3-(2-methoxyethoxy)propene. Tetrahedron 59, 5199–5208.
Alonso, F., Lorenzo, E., and Yus, M. (1998). 2-chloromethyl-3-[2-methoxyethoxy]propene. Naphthalene-catalysed lithiation and reaction towards electrophiles. Tetrahedron Lett. 39, 3303–3306.
Alonso, F., Melendez, J., and Yus, M. (2005). A new 3-methylenedecane-1,5-dianion synthon: synthesis of perhydrofuro[2,3-b]pyrans and 1,7-dioxaspiro[4.5]decanes. Tetrahedron Lett. 46, 6519–6524.
Alonso, F., Rodriguez-Fernandez, M., Sanchez, D., and Yus, M. (2011). Synthesis of perhydrofuro[2,3-b]furans from isopentenyl alcohol through carboxylic-ene and Wacker-type reactions. Eur. J. Org. Chem. 2011, 6459–6469.

Baird, M.C., Pyne, S.G., Ung, A.T., Lie, W., Sastrarui, T., Jatsatienn, A., Jatipsatien, C., Dheeranupattana, S., Lowlam, J., and Boonchalermkit, S. (2009). Semisynthesis and biological activity of stemofoline alkaldoids. J. Nat. Prod. 72, 679–684.

Bera, S., Chatterjee, B., and Mondal, D. (2018). Advances in the asymmetric synthesis of bridged and fused bicyclic acetics. Eur. J. Org. Chem. 2018, 5337–5354.

Brady, T.P., Kim, S.H., Wen, K., and Theodorakis, E.A. (2004). Stereoselective total synthesis of (+)-norisolide. Angew. Chem. Int. Ed. 43, 739–742.

Coppola, G.M. (1984). Amberlyst-15, a superior acid catalyst for the cleavage of acetals. Synthesis 1984, 1021–1023.

Cossey, J., Ranaivosato, J.L., and Bellosta, V. (1994). Formation of radicals by irradiation of alkyl-halides in the presence of triethylamine. Tetrahedron Lett. 35, 8161–8162.

Evans, D.A., Tanis, S.P., and Hart, D.J. (1981). A general approach to catalytic anti-Markovnikov hydroetherification of alkenes. J. Org. Chem. 46, 169, 3967–3971.

Fukuyama, T., Fujita, Y., Rashid, M.A., and Ryu, I. (2018). Flow update for a cossy photocyclization. Org. Lett. 20(18), 5813–5821.

Lencì, E., Menchi, G., Saldivar-Gonzalez, F.I., Medina-Franco, J.L., and Trabocchi, A. (2019). Bicyclic acetics: biological relevance, scaffold analysis, and applications in diversity-oriented synthesis. Org. Biomol. Chem. 17, 1037–1052.

Lorenzo, E., Alonso, F., and Yus, M. (2000a). New trimethylmethanemethylene dianion syntheses: application to the preparation of substituted perhydroyfur3(3)-furanyl. Tetrahedron 56, 1745–1757.

Lorenzo, E., Alonso, F., and Yus, M. (2000b). Substituted perhydroyfurans: easy preparation from 2-chloromethyl-3-2-methoxysubstituted ethylidene-1,6-diols. Tetrahedron Lett. 41, 1661–1665.

Margeray, K.A., and Nicewicz, D.A. (2016). A general approach to catalytic alkenes anti-Markovnikov fluorohydrofunctionalization reactions via acridinium photoredox catalysis. Acc. Chem. Res. 49, 1997–2006.

Messerle, B.A., and Vuong, K.Q. (2007). Rhodium- and iridium-catalyzed double hydroalkoxylation of alkynes, an efficient method for the synthesis of O,O-acetals: catalytic and mechanistic studies. Organometallics 26, 3031–3040.

Mori, N., Kitahara, T., Mori, K., and Watanabe, H. (2015). Asymmetric formal synthesis of azadirachtin. Angew. Chem. Int. Ed. 54, 14920–14923.

Nicewicz, D.A., and Nguyen, T.M. (2014). Recent applications of organic dyes as photoredox catalysts in organic synthesis. ACS Catal. 4, 355–360.
Thapa, S., Basnet, P., and Giri, R. (2017). Copper-catalyzed dicarbofunctionalization of unactivated olefins by tandem cyclization/cross-coupling. J. Am. Chem. Soc. 139, 5700–5703.

Tufariello, J.J., and Winzenberg, K. (1986). A nitrone-based synthesis of the pyrrolizidine alkaloid croalbinecine. Tetrahedron Lett. 27, 1645–1648.

Ueno, Y., Chino, K., Watanabe, M., Moriya, O., and Okawara, M. (1982). Homolytic carbocyclization by use of heterogeneous supported organotin catalyst - a new synthetic route to 2-alkoxytetrahydrofurans and γ-butyrolactones. J. Am. Chem. Soc. 104, 5564–5566.

Velthuisen, E.J., Baughman, T.M., Johno, B.A., Temelkoff, D.P., and Weatherhead, J.G. (2013). Synthesis and pharmacokinetic profile of highly deuterated brecanavir analogs. Eur. J. Med. Chem. 63, 202–212.

Venning, A.R.O., Kwiatkowski, M.R., Peren, J.E.R., Lainhart, B.C., Gunuparan, A.A., and Alexanian, E.J. (2017). Palladium-catalyzed carbocyclizations of unactivated alkyl bromides with alkenes involving auto-tandem catalysis. J. Am. Chem. Soc. 139, 11595–11600.

Wang, L.F., Wu, F.J., Chen, J.A., Nicewicz, D.A., and Huang, Y. (2017). Visible-light-mediated [4+2] cycloaddition of styrenes: synthesis of tetralin derivatives. Angew. Chem. Int. Ed. 56, 6896–6900.

Wu, F.J., Wang, L.F., Chen, J.A., Nicewicz, D.A., and Huang, Y. (2018). Direct synthesis of polysubstituted aldehydes via visible-light catalysis. Angew. Chem. Int. Ed. 57, 2174–2178.

Yanada, R., Koh, Y., Nishimori, N., Matsumura, A., Obika, S., Mitsuwa, H., Fujii, N., and Takemoto, Y. (2004). Indium-mediated atom-transfer and reductive radical cyclizations of iodoalkynes: synthesis and biological evaluation of HIV-protease inhibitors. J. Org. Chem. 69, 2417–2422.

Zhou, G., and Corey, E.J. (2005). Short, enantioselective total synthesis of aflatoxin B2 using an asymmetric [3+2]-cycloaddition step. J. Am. Chem. Soc. 127, 11928–11929.
Supplemental Information

Direct Synthesis of Bicyclic Acetals via Visible Light Catalysis

Fengjin Wu, Leifeng Wang, Ying Ji, Ge Zou, Hong Shen, David A. Nicewicz, Jiean Chen, and Yong Huang
Supporting Information

I. Transparent Methods

General Information
All solvents were distilled according to general practice prior to use. Solvents for flash column chromatography were technical grade and distilled prior to use. ¹H NMR and ¹³C NMR data were recorded on Bruker 400 MHz (100 MHz for ¹³C) nuclear resonance spectrometers unless otherwise specified. ¹H and ¹³C NMR chemical shifts are given in ppm relative to SiMe₄, with the solvent resonance used as internal reference. Chemical shifts (δ) are given in parts per million and referenced to the residual solvent signal; and all coupling constants are reported in Hz. The following abbreviations were used to explain the multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Thin-layer chromatography (TLC) was conducted with 0.25 mm Yantai silica gel plates (60F-254) and visualized by exposure to UV light (254 nm) or stained with phosphomolybdic acid in EtOH. Flash column chromatography was performed using Tsingdao silica gel (60, particle size 0.040–0.063 mm). HRMS (ESI) analysis was performed by The Analytical Instrumentation Center at Peking University; Shenzhen Graduate School and (HRMS) data were reported with ion mass/charge (m/z) ratios as values in atomic mass units.
Preparation of acridinium photocatalysts

Photocatalysts (PS-A, PS-B, PS-C) used in this study were synthesized by the method of Fukuzumi et al. (Fukuzumi et al., 2004). Tetrafluoroboric acid (diethyl ether complex) was used for hydrolysis in PS-A and PS-C synthesis. HCl (4.0 M in 1, 4-dioxane) was used for hydrolysis in PS-B synthesis. Spectral data for these compounds matches the reported value in the literature.

9-mesityl-10-phenylacridin-10-i um tetrafluoroborate (PS-A):
Yellow solid. 1H NMR (500 MHz, Chloroform-d) δ 8.14 (s, 2H), 7.89 (dq, J = 14.2, 7.4, 6.8 Hz, 5H), 7.79 (t, J = 7.7 Hz, 2H), 7.75 – 7.69 (m, 2H), 7.60 (d, J = 9.1 Hz, 2H), 7.18 (s, 2H), 2.49 (s, 3H), 1.83 (s, 6H).

9-mesityl-10-phenylacridin-10-i um chloride (PS-B):
Yellow solid. 1H NMR (300 MHz, Chloroform-d) δ 8.23 (ddd, J = 8.9, 6.2, 1.8 Hz, 2H), 7.97 – 7.81 (m, 7H), 7.72 (d, J = 7.6 Hz, 2H), 7.59 (d, J = 9.0 Hz, 2H), 7.14 (s, 2H), 2.44 (s, 3H), 1.78 (s, 6H).

9-mesityl-10-methylacridin-10-i um tetrafluoroborate (PS-C):
Yellow solid. 1H NMR (300 MHz, Chloroform-d) δ 8.81 (d, J = 9.3 Hz, 2H), 8.41 (ddd, J = 9.3, 6.5, 1.8 Hz, 2H), 8.05 – 7.59 (m, 4H), 7.15 (s, 2H), 5.11 (s, 3H), 2.48 (s, 3H), 1.73 (s, 6H).
General procedure for acetals

PhSSPh (0.04 mmol, 8.7 mg), Mes-Acr-PhBF₄ (PS-A) (0.02 mmol, 4.6 mg) and (E)-3-phenylprop-2-en-1-ol (0.2 mmol, 26.8 mg) were weighed in an oven-dried 8 mL vial equipped with a magnetic stirring bar. The reaction vial was capped with a rubber septum and anhydrous DCE (3 mL) was added under an argon atmosphere. Then 3, 4-dihydro-2H-pyran (0.8 mmol, 73 μL) was added and the reaction vessel was fixed on a blue LED light reaction equipment (1 W, 452 nm). After TLC indicated a full conversion (usually 18 hours), the reaction was purified by flash silica gel column chromatography directly.
General procedure for substrates

Step 1:
To a stirred solution of aldehyde (10.3 mmol) in DCM (20 mL) at room temperature was added ethyl (triphenylphosphoranylidene)acetate (1.1 eq, 11.3 mmol). The reaction solution was stirred for 15 hours and then concentrated under vacuum condition. The residue was purified by flash silica gel column chromatography directly.

Step 2:
To a solution of corresponding ester (8.84 mmol) in DCM (70 mL) at $-78^\circ$C was added a 1.0 M solution of DIBAL-H (in hexane, 2.5 eq, 22 mmol) dropwise. After 3 hours, the reaction mixture was warmed to room temperature and quenched with 1N HCl (40 mL). The aqueous phase was separated and extracted with DCM. The combined organic extracts were washed with NaHCO$_3$, dried over Na$_2$SO$_4$. Then the solution was filtered and concentrated under vacuum condition. The residue was further purified by flash silica gel column chromatography.

To a solution of PhMgBr (25 mmol) in 30 ml of Et$_2$O was added Cul (0.29 g, 1.5 mmol). The mixture was stirred at room temperature for 0.5 hours. Then a solution of corresponding propargyl alcohol (10 mmol) in 10 mL Et$_2$O was added slowly. After the addition was completed, the reaction mixture was refluxed for 24 hours. After cooling to room temperature, an aqueous solution of NH$_4$Cl was added slowly. The organic layer was separated and aqueous layer was extracted with Et$_2$O. The combined organic extracts were dried over Na$_2$SO$_4$. Then the solution was filtered and concentrated under vacuum condition. The residue was purified by flash silica gel column chromatography (Duan et al., 2009).
Catalyst [Ru(N3P)(OAc)][BPh4] (0.005 mmol) was added to a solution of alkynol (17.6 mmol) in THF (15 mL). The resulting solution was stirred at 80 °C and monitored by TLC. When the maximum conversion was reached, the desired product was isolated by flash column chromatography on silica gel (Liu et al., 2010).

D-Galactal (730 mg, 5 mmol), which had been pre-dried under vacuum in a flame-dried flask for 1 h, was dissolved in anhydrous DMF (30 mL) under a N2 atmosphere. The reaction mixture was cooled to 0 °C, after which NaH (60% wt in mineral oil, 900 mg, 22.5 mmol) was added portionwise. When addition was completed the reaction was allowed to warm to room temperature. After being stirred at room temperature for 30 min, the solution was cooled to 0 °C and iodomethane (140 μL, 22.5 mmol) was added dropwise. The reaction mixture was then allowed to warm to room temperature and stirred for another 3 hours, and quenched with MeOH (0.5 mL). The solution was diluted with EtOAc (40 mL) and washed with water (3x 20 mL) and brine (20 mL), dried over Na2SO4 and concentrated in vacuum. Purification by column chromatography afforded target product as a pale yellow liquid (752 mg, 80%). Proton and carbon NMR were consistent with literature data (Balmond et al., 2014).

3, 4-O-Di-acetyl-L-rhamnal (520 mg, 2.43 mmol) was dissolved in a solution of MeOH (8 mL), H2O (1 mL) and Et3N (1 mL), and stirred for 18 hours. Then the solvent was removed to afford L-rhamnal as a solid. L-Rhamnal and imidazole (332 mg, 4.88 mmol) were dissolved in distilled pyridine (20 mL) under N2 atmosphere and the solution was cooled to 0 °C. 1,3-Dichloro-
1,1,3,3-tetraisopropyldisiloxane (1.2 mL, 3.75 mmol) was added dropwise and the solution was then allowed to warm to room temperature and stirred for 18 h. The reaction was quenched with H₂O (30 mL), extracted with EtOAc (50 mL). The organic layer was washed with brine (20 mL), dried over MgSO₄, filtered and concentrated in vacuum. Following purification by column chromatography afforded the desired product as a white solid (846 mg, 96%).

![Chemical Structure](https://example.com/structure.png)

3, 4-O-Di-acetyl-L-rhamnal (1.0 g, 4.67 mmol) was dissolved in a solution of MeOH (15 mL), H₂O (2 mL) and Et₃N (2 mL) and stirred for 18 hours. Then the solvents were removed and the residue was dissolved in EA, washed with H₂O and brine, and dried over Na₂SO₄. Following purification by column chromatography, L-rhamnal was obtained as a white solid (546 mg, 90% yield). L-rhamnal (546 mg, 4.2 mmol) was dissolved in anhydrous DMF (25 mL) under N₂ atmosphere. The reaction mixture was cooled to 0 °C, after which NaH (60%wt in mineral oil, 504 mg, 12.6 mmol) was added portionwise. When addition was completed the reaction was allowed to warm to room temperature. After being stirred at room temperature for 30 min, the solution was cooled to 0 °C and iodomethane (78 μL, 12.6 mmol) was added dropwise. The reaction mixture was then allowed to warm to room temperature and stirred for another 3 hours, and quenched with MeOH (0.5 mL). The solution was diluted with EtOAc (40 mL) and washed with water (3 x 20 mL) and brine (20 mL), dried over Na₂SO₄ and concentrated in vacuum. Purification by column chromatography afforded the target product as a pale yellow liquid (498 mg, 75%). Proton and carbon NMR were consistent with literature data.
II. Date S1: \(^1\text{H} \) NMR and \(^{13}\text{C} \) NMR spectra data of products (Related to Figure 3-5)

3-benzylhexahydro-4H-furo[2,3-b]pyran (1)

\[
\text{Eluent for purification: hexane: ethyl acetate = 10:1.}
\]

Colorless oil (35.3 mg, 81\% yield, dr = 1.8:1). Proton and carbon NMR were consistent with literature data. Cis-syn: \(^1\text{H} \) NMR (500 MHz, Chloroform-d) \(\delta\) 7.32 – 7.26 (m, 2H), 7.24 – 7.19 (m, 1H), 7.19 – 7.14 (m, 2H), 5.29 (d, \(J = 3.7 \) Hz, 1H), 3.92 – 3.85 (m, 1H), 3.82 – 3.74 (m, 2H), 3.65 (t, \(J = 8.1 \) Hz, 1H), 2.79 – 2.55 (m, 3H), 1.96 (m, 1H), 1.79 – 1.73 (m, 1H), 1.86 – 1.53 (m, 3H). Cis-anti: \(^1\text{H} \) NMR (500 MHz, Chloroform-d) \(\delta\) 7.32–7.26 (m, 2H), 7.24–7.19 (m, 1H), 7.19–7.14 (m, 2H), 5.04 (d, \(J = 3.6 \) Hz, 1H), 4.18 (t, \(J = 8.2 \) Hz, 1H), 3.92 – 3.85 (m, 1H), 3.65 (t, \(J = 8.1 \) Hz, 1H), 3.43 (td, \(J = 11.3, 2.4 \) Hz, 1H), 2.87 (dd, \(J = 13.3, 5.2 \) Hz, 1H), 2.79–2.55 (m, 2H), 1.86–1.53 (m, 4H), 1.38–1.32 (m, 1H). \(^{13}\text{C} \) NMR (trans & cis mixture) (101 MHz, Chloroform-d) \(\delta\) 140.12, 140.08, 128.51, 128.49, 128.36, 126.22, 126.18, 102.13, 101.96, 73.64, 69.87, 64.37, 60.98, 43.84, 42.52, 39.42, 38.73, 36.58, 33.38, 23.17, 22.45, 20.74, 19.57. HRMS calculated for C\(_{14}\)H\(_{18}\)O\(_2\) (M + Na\(^+\)): 241.1149, found: 241.1202.

3-(4-fluorobenzyl)hexahydro-4H-furo[2,3-b]pyran (2)

\[
\text{Eluent for purification: hexane: ethyl acetate = 10:1.}
\]

Colorless oil (30.7 mg, 65\% yield, dr = 1.3:1). Proton and carbon NMR were consistent with literature data (Yan et al., 2012). Cis-syn: \(^1\text{H} \) NMR (400 MHz, Chloroform-d) \(\delta\) 7.11 (m, 2H), 7.00 – 6.93 (m, 2H), 5.27 (d, \(J = 3.7 \) Hz, 1H), 3.90 – 3.83 (m, 1H), 3.81 – 3.71 (m, 2H), 3.67 – 3.58 (m, 1H), 2.77 – 2.47 (m, 3H), 2.00 – 1.90 (m, 1H), 1.78 – 1.71 (m, 1H), 1.88 – 1.44 (m, 3H). Cis-anti: \(^1\text{H} \) NMR (400 MHz, Chloroform-d) \(^1\text{H} \) NMR (400 MHz, Chloroform-d) \(\delta\) 7.11 (m, 2H), 7.00 – 6.93 (m, 2H), 5.02 (d, \(J = 3.4 \) Hz, 1H), 4.15 (t, \(J = 8.2 \) Hz, 1H), 3.90 – 3.83 (m, 1H), 3.67 – 3.58 (m, 1H), 3.46 – 3.37 (m, 1H), 2.82 (dd, \(J = 12.8, 4.6 \) Hz, 1H), 2.77 – 2.47 (m, 2H), 1.88 – 1.44 (m, 4H), 1.34 (m, \(J = 10.1, 5.4, 3.0 \) Hz, 1H). \(^{13}\text{C} \) NMR (trans & cis mixture) (101 MHz, Chloroform-d) \(\delta\) 162.66 (d, \(J = 245.3 \) Hz), 162.60 (d, \(J = 245.0 \) Hz), 135.72, 135.69,
129.88 (d, \( J = 8.0 \) Hz), 129.72 (d, \( J = 7.07 \) Hz), 115.41 (d, \( J = 21.2 \) Hz), 115.39 (d, \( J = 21.4 \) Hz), 102.11, 101.93, 73.52, 69.76, 64.38, 60.99, 43.79, 42.60, 39.53, 37.89, 36.52, 32.62, 23.11, 22.45, 20.69, 19.54. HRMS calculated for \( C_{14}H_{17}FO_2 \) (M + Na\(^+\)): 259.1105, found: 259.1105.

3-(4-phenoxyl benzyl)hexahydro-4H-furo[2,3-b]pyran (3)

Eluent for purification: hexane: ethyl acetate = 10:1. White solid (36.0 mg, 58% yield, \( \text{dr} = 1.4:1 \)). **Cis-syn:** \(^1\text{H NMR} (400 \text{ MHz, Chloroform-d}) \delta 7.37 – 7.29 (m, 2H), 7.16 – 7.05 (m, 3H), 7.07 – 6.98 (m, 2H), 6.98 – 6.88 (m, 2H), 5.30 (d, \( J = 3.7 \) Hz, 1H), 3.90 (t, \( J = 7.7 \) Hz, 1H), 3.85 – 3.74 (m, 2H), 3.72 – 3.58 (m, 1H), 2.80 – 2.51 (m, 3H), 1.98 (ddt, \( J = 12.1, 10.2, 5.0 \) Hz, 1H), 1.82 – 1.71 (m, 1H), 1.60 – 1.46 (m, 3H).

**Cis-trans:** \(^1\text{H NMR} (400 \text{ MHz, Chloroform-d}) \delta 7.36 – 7.30 (m, 2H), 7.15 – 7.06 (m, 3H), 7.03 – 6.97 (m, 2H), 6.97 – 6.91 (m, 2H), 5.05 (d, \( J = 3.5 \) Hz, 1H), 4.20 (t, \( J = 8.2 \) Hz, 1H), 3.89 (ddt, \( J = 11.7, 4.3, 2.4 \) Hz, 1H), 3.65 (dd, \( J = 8.4, 7.5 \) Hz, 1H), 3.49 – 3.38 (m, 1H), 2.84 (dd, \( J = 13.0, 4.7 \) Hz, 1H), 2.69 – 2.50 (m, 2H), 1.91 – 1.76 (m, 2H), 1.76 – 1.62 (m, 3H), 1.41 – 1.29 (m, 1H).

**Cis-syn:** \(^{13}\text{C NMR} (101 \text{ MHz, Chloroform-d}) \delta 157.35, 155.59, 134.97, 129.69, 129.54, 123.12, 119.00, 118.70, 101.97, 69.86, 60.99, 42.65, 36.58, 32.67, 23.16, 19.57.

**Cis-anti:** \(^{13}\text{C NMR} (101 \text{ MHz, Chloroform-d}) \delta 157.41, 155.52, 135.01, 129.72, 129.69, 123.07, 119.07, 118.60, 102.13, 73.61, 64.38, 43.78, 39.55, 37.95, 22.48, 20.75. HRMS calculated for \( C_{20}H_{22}O_3 \) (M + Na\(^+\)): 333.1461, found: 333.1459.

3-(3-fluoro-4-methoxybenzyl)hexahydro-4H-furo[2,3-b]pyran (4)

Eluent for purification: hexane: ethyl acetate = 10:1. Colorless oil (36.7 mg, 69% yield, \( \text{dr} = 1.1:1 \)). Isolated as an inseparable mixture of diastereomers. Spectral data for two diastereomers is given herein. **Cis-syn:** \(^1\text{H NMR} (400 \text{ MHz, Chloroform-d}) \delta 6.90 – 6.86 (m, 1H), 6.87 – 6.84 (m, 2H), 5.27 (d, \( J = 3.7 \) Hz, 1H), 3.86 (s, 4H), 3.75 (ddd, \( J = 12.8, 10.2, 7.9 \) Hz, 2H), 3.67 – 3.55 (m, 1H), 2.70 – 2.45 (m, 3H), 1.94 (dtd, \( J = 10.3, 6.3, 3.9 \) Hz, 1H), 1.85 – 1.70 (m, 2H), 1.67 – 1.51 (m, 3H).

**Cis-trans:** \(^1\text{H NMR} (400 \text{ MHz, Chloroform-d}) \delta 6.87 – 6.82 (m, 3H), 5.02 (d, \( J = 3.3 \) Hz, 1H), 4.16 (t, \( J = 8.2 \) Hz, 1H), 3.86 (s, 4H), 3.67 – 3.55 (m, 1H), 3.46 – 3.37 (m, 1H), 2.77 (dd, \( J = 13.3, 5.1 \) Hz, 1H), 2.70
2.45 (m, 2H), 1.85 – 1.70 (m, 2H), 1.67 – 1.51 (m, 2H), 1.33 (dq, \(J = 13.1, 2.9, 2.5\) Hz, 1H).

\(^{13}\)C NMR (trans & cis mixture) (101 MHz, Chloroform-\(d\)) \(\delta 153.49\) (d, \(J = 246.3\) Hz), 153.47 (d, \(J = 246.9\) Hz), 145.98 (d, \(J = 5.7\) Hz), 145.93 (d, \(J = 246.9\) Hz), 133.16, 133.11, 123.99 (d, \(J = 19.6\) Hz), 123.96 (d, \(J = 12.6\) Hz), 116.22 (d, \(J = 32.4\) Hz), 116.08 (d, \(J = 3.5\) Hz), 113.51 (d, \(J = 2.0\) Hz), 113.49 (d, \(J = 2.0\) Hz), 102.09, 101.92, 73.48, 69.73, 64.36, 60.99, 56.31, 56.30, 43.75, 42.45, 39.44, 37.77, 36.51, 32.47, 23.10, 22.46, 20.71, 19.53. HRMS calculated for \(\text{C}_{15}\text{H}_{19}\text{FO}_{3}(\text{M} + \text{Na}^+): 289.1210\), found: 289.1203.

3-(naphthalen-2-ylmethyl)hexahydro-4H-furo[2,3-b]pyran (5)

Eluent for purification: hexane: ethyl acetate = 10:1. Colorless oil (26.8 mg, 50% yield, \(dr = 1.1:1\)). Cis-syn: \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta 7.80\) (m, 3H), 7.62 (d, \(J = 1.7\) Hz, 1H), 7.53 – 7.43 (m, 2H), 7.32 (dd, \(J = 8.4, 1.8\) Hz, 1H), 5.31 (d, \(J = 3.7\) Hz, 1H), 3.96 – 3.87 (m, 1H), 3.88 – 3.75 (m, 2H), 3.66 (ddt, \(J = 11.3, 3.3, 1.7\) Hz, 1H), 2.91 (dd, \(J = 10.8, 5.7\) Hz, 1H), 2.87 – 2.75 (m, 2H), 2.05 – 1.95 (m, 1H), 1.82 (dq, \(J = 9.7, 2.2\) Hz, 1H), 1.68 – 1.58 (m, 3H). Cis-trans: \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta 7.88 – 7.73\) (m, 3H), 7.61 (d, \(J = 1.7\) Hz, 1H), 7.52 – 7.38 (m, 2H), 7.31 (dd, \(J = 8.5, 1.8\) Hz, 1H), 5.07 (d, \(J = 3.7\) Hz, 1H), 4.21 (t, \(J = 8.0\) Hz, 1H), 3.89 (dq, \(J = 11.7, 2.6\) Hz, 1H), 3.70 (dd, \(J = 8.4, 7.3\) Hz, 1H), 3.44 (ddd, \(J = 11.6, 10.6, 2.3\) Hz, 1H), 3.15 – 2.96 (m, 1H), 2.85 – 2.66 (m, 2H), 1.93 (dq, \(J = 9.0, 4.8, 4.0\) Hz, 1H), 1.85 – 1.64 (m, 3H), 1.42 – 1.29 (m, 1H). Cis-syn: \(^{13}\)C NMR (101 MHz, Chloroform-\(d\)) \(\delta 137.60, 133.55, 132.10, 128.18, 127.62, 127.40, 126.94, 126.56, 126.10, 125.40, 101.99, 69.93, 61.02, 42.35, 36.65, 33.60, 23.17, 19.61. Cis-trans: \(^{13}\)C NMR (101 MHz, Chloroform-\(d\)) \(\delta 137.61, 133.53, 132.12, 128.13, 127.62, 127.44, 127.08, 126.69, 126.09, 125.40, 102.15, 73.68, 64.37, 43.93, 39.34, 38.97, 22.55, 20.78. HRMS calculated for \(\text{C}_{18}\text{H}_{20}\text{O}_{2}(\text{M} + \text{Na}^+): 291.1356\), found: 291.1356.

3-((9H-fluoren-2-yl)methyl)hexahydro-4H-furo[2,3-b]pyran (6)

Eluent for purification: hexane: ethyl acetate = 10:1. White solid (34.9 mg, 57% yield, \(dr = 1.4:1\)). Cis-syn: \(^1\)H NMR (400 MHz, Chloroform-
$d$ δ 7.76 (d, $J = 7.6$ Hz, 1H), 7.70 (d, $J = 7.7$ Hz, 1H), 7.54 (dt, $J = 7.4$, 1.0 Hz, 1H), 7.41 – 7.34 (m, 2H), 7.33 – 7.27 (m, 1H), 7.18 (dd, $J = 7.7$, 1.5 Hz, 1H), 5.31 (d, $J = 3.7$ Hz, 1H), 3.90 (d, $J = 14.7$ Hz, 3H), 3.86 – 3.75 (m, 2H), 3.66 (ddq, $J = 11.0$, 3.1, 1.7 Hz, 1H), 2.92 – 2.58 (m, 3H), 2.00 (dt, $J = 10.8$, 2.9 Hz, 1H), 1.80 (dt, $J = 9.4$, 2.6 Hz, 1H), 1.66 – 1.58 (m, 3H). **Cis-trans:**

$^1$H NMR (400 MHz, Chloroform-δ) δ 7.77 (dt, $J = 7.5$, 0.9 Hz, 1H), 7.70 (d, $J = 7.8$ Hz, 1H), 7.54 (dq, $J = 7.4$, 1.0 Hz, 1H), 7.42 – 7.35 (m, 2H), 7.34 – 7.27 (m, 2H), 7.24 – 7.06 (m, 1H), 5.06 (d, $J = 3.6$ Hz, 1H), 4.22 (t, $J = 8.1$ Hz, 1H), 3.95 – 3.81 (m, 3H), 3.74 – 3.63 (m, 1H), 3.44 (ddd, $J = 11.6$, 10.7, 2.3 Hz, 1H), 2.96 – 2.84 (m, 1H), 2.77 – 2.58 (m, 2H), 1.98 – 1.85 (m, 1H), 1.83 – 1.65 (m, 3H), 1.43 – 1.30 (m, 1H). **Cis-syn:**

$^{13}$C NMR (101 MHz, Chloroform-δ) δ 143.69, 143.07, 141.49, 139.94, 138.79, 126.98, 126.73, 126.47, 125.02, 124.98, 119.83, 119.65, 101.99, 69.94, 61.00, 42.73, 36.82, 36.64, 33.55, 23.19, 19.61. **Cis-trans:**

$^{13}$C NMR (101 MHz, Chloroform-δ) δ 143.66, 143.10, 141.52, 139.95, 138.79, 127.14, 126.73, 126.47, 125.18, 125.00, 119.82, 119.67, 102.19, 73.71, 64.39, 43.89, 39.68, 38.92, 36.82, 22.52, 20.77. **HRMS** calculated for C$_{21}$H$_{22}$O$_2$ (M + Na$^+$): 329.1512, found: 329.1512.

3-(1-phenylethyl)hexahydro-4H-furo[2,3-b]pyran (7)

Eluent for purification: hexane: ethyl acetate = 10:1. Colorless oil (35.8 mg, 77% yield, dr = 2.4:1:1). Isolated as an inseparable mixture of diastereomers. Spectral data for the major diastereomer is given herein. **$^1$H NMR** (400 MHz, Chloroform-δ) δ 7.32 – 7.26 (m, 2H), 7.23 – 7.12 (m, 3H), 5.00 (d, $J = 3.4$ Hz, 1H), 4.01 (t, $J = 8.6$ Hz, 1H), 3.89 (ddt, $J = 11.7$, 3.9, 1.4 Hz, 1H), 3.54 (dd, $J = 8.8$, 6.7 Hz, 1H), 3.44 (ddd, $J = 11.5$, 10.4, 2.6 Hz, 1H), 2.75 (dq, $J = 8.7$, 6.9 Hz, 1H), 2.50 (qd, $J = 8.1$, 6.2 Hz, 1H), 1.97 – 1.37 (m, 4H), 1.25 (m, 1H), 1.31 (d, $J = 7.0$ Hz, 3H). **$^{13}$C NMR (three isomers)** (101 MHz, Chloroform-δ) δ 145.69, 145.25, 145.03, 128.56, 128.52, 128.44, 127.49, 127.12, 126.84, 126.50, 126.47, 126.37, 102.65, 102.38, 101.94, 72.69, 71.81, 68.92, 64.39, 64.14, 60.74, 48.01, 44.60, 44.42, 44.17, 43.30, 43.16, 42.25, 38.14, 35.77, 25.45, 24.06, 23.30, 22.57, 21.46, 21.08, 20.73, 20.56, 18.89. **HRMS** calculated for C$_{15}$H$_{20}$O$_2$ (M + Na$^+$): 255.1356, found: 255.1354.
3-benzyl-2-methylhexahydro-4H-furo[2,3-b]pyran (8)

Eluent for purification: hexane: ethyl acetate = 10:1. Colorless oil (21.3 mg, 46% yield, dr = 2.5:2.5:1.8:1). Isolated as an inseparable mixture of diastereomers. Spectral data for the major diastereomer is given herein.

$^1$H NMR (500 MHz, Chloroform-d) $\delta$ 7.30 (s, 2H), 7.21 (d, $J = 3.0$ Hz, 3H), 5.04 (d, $J = 3.6$ Hz, 1H), 4.57 (p, $J = 6.7$ Hz, 1H), 3.89 – 3.87 (m, 1H), 3.40 (dt, $J = 11.3$, 2.2 Hz, 1H), 2.89 – 2.82 (m, 1H), 2.70 (dd, $J = 7.7$, 3.2 Hz, 1H), 2.60 (dd, $J = 13.6$, 8.0 Hz, 1H), 1.94 (dd, $J = 6.5$, 3.1 Hz, 1H), 1.74 (s, 1H), 1.56 (dt, $J = 10.7$, 3.7 Hz, 3H), 1.10 (d, $J = 6.1$ Hz, 3H).

$^{13}$C NMR (four isomers) (126 MHz, Chloroform-d) $\delta$ 140.53, 140.37, 139.79, 128.94, 128.51, 128.47, 128.40, 126.27, 126.19, 126.08, 126.05, 101.56, 100.82, 100.51, 100.18, 82.11, 73.86, 64.44, 64.19, 61.06, 60.92, 50.43, 46.33, 45.08, 43.36, 42.58, 38.03, 37.59, 37.04, 34.62, 31.31, 30.98, 25.39, 23.56, 23.31, 22.63, 22.44, 22.19, 21.40, 20.82, 20.79, 20.72, 19.84, 18.85, 17.38.

HRMS calculated for C$_{15}$H$_{20}$O$_2$ (M + Na$^+$): 255.1356, found: 255.1355.

3-(benzofuran-5-ylmethyl)hexahydro-4H-furo[2,3-b]pyran (9)

Eluent for purification: hexane: ethyl acetate = 10:1. Colorless oil (35.6 mg, 69% yield, dr = 1.4:1). Cis-syn: $^1$H NMR (400 MHz, Chloroform-d) $\delta$ 7.61 (d, $J = 2.2$ Hz, 1H), 7.49 – 7.33 (m, 2H), 7.10 (dd, $J = 8.4$, 1.8 Hz, 1H), 6.72 (dd, $J = 2.2$, 1.0 Hz, 1H), 5.29 (d, $J = 3.7$ Hz, 1H), 3.89 (t, $J = 7.8$ Hz, 1H), 3.79 (ddd, $J = 10.1$, 8.6, 5.3 Hz, 2H), 3.66 (ddq, $J = 11.1$, 3.1, 1.8 Hz, 1H), 2.83 (dd, $J = 10.6$, 6.0 Hz, 1H), 2.78 – 2.67 (m, 2H), 2.03 – 1.90 (m, 1H), 1.80 (ddd, $J = 9.9$, 6.6, 4.4 Hz, 1H), 1.63 – 1.53 (m, 3H). Cis-trans: $^1$H NMR (400 MHz, Chloroform-d) $\delta$ 7.61 (d, $J = 2.2$ Hz, 1H), 7.45 – 7.34 (m, 2H), 7.09 (dd, $J = 8.4$, 1.8 Hz, 1H), 6.72 (dd, $J = 2.2$, 1.0 Hz, 1H), 5.05 (d, $J = 3.6$ Hz, 1H), 4.25 – 4.11 (m, 1H), 3.92 – 3.82 (m, 1H), 3.74 – 3.62 (m, 1H), 3.43 (ddd, $J = 11.6$, 10.7, 2.3 Hz, 1H), 3.07 – 2.88 (m, 1H), 2.74 – 2.59 (m, 2H), 1.88 (ddt, $J = 8.9$, 5.9, 2.9 Hz, 1H), 1.84 – 1.64 (m, 3H), 1.34 (m, 1H).

Cis-syn: $^{13}$C NMR (101 MHz, Chloroform-d) $\delta$ 153.67, 145.28, 134.55, 127.64, 124.72, 120.45, 111.25, 106.33, 101.99, 69.91, 60.99, 43.01, 36.60, 33.27, 23.17, 19.58. Cis-anti: $^{13}$C NMR
(101 MHz, Chloroform-d) δ 153.71, 145.26, 134.53, 127.62, 124.89, 120.63, 111.22, 106.36, 102.16, 73.65, 64.36, 43.80, 39.93, 38.64, 22.52, 20.77. HRMS calculated for C_{16}H_{18}O_{3} (M + Na^+): 281.1148, found: 281.1148.

3-(benzo[b]thiophen-2-ylmethyl)hexahydro-4H-furo[2,3-b]pyran (10)

Eluent for purification: hexane: ethyl acetate = 10:1.

Colorless oil (41.6 mg, 76% yield, dr = 1.4:1). Cis-syn: ¹H NMR (400 MHz, Chloroform-d) δ 7.82 – 7.71 (m, 1H), 7.68 (dd, J = 7.4, 1.3 Hz, 1H), 7.35 – 7.25 (m, 2H), 7.08 – 6.97 (m, 1H), 5.31 (d, J = 3.7 Hz, 1H), 4.03 (t, J = 8.1 Hz, 1H), 3.80 (ddd, J = 13.1, 6.7, 3.0 Hz, 2H), 3.72 – 3.60 (m, 1H), 3.05 (ddd, J = 14.9, 7.9, 1.0 Hz, 1H), 2.94 (ddd, J = 14.9, 7.6, 1.1 Hz, 1H), 2.87 – 2.73 (m, 1H), 2.09 (dq, J = 9.3, 2.7 Hz, 1H), 1.81 (ddd, J = 11.2, 6.4, 3.3 Hz, 1H), 1.63 – 1.56 (m, 3H).

Cis-trans: ¹H NMR (400 MHz, Chloroform-d) δ 7.77 (dd, J = 7.9, 1.2 Hz, 1H), 7.73 – 7.67 (m, 1H), 7.36 – 7.27 (m, 2H), 7.02 (d, J = 1.0 Hz, 1H), 5.07 (d, J = 3.6 Hz, 1H), 4.33 (t, J = 8.4 Hz, 1H), 3.95 – 3.85 (m, 1H), 3.72 (dd, J = 8.6, 7.4 Hz, 1H), 3.49 – 3.37 (m, 1H), 3.13 (ddd, J = 14.9, 5.5, 1.1 Hz, 1H), 2.89 (ddd, J = 14.9, 9.0, 1.0 Hz, 1H), 2.81 – 2.67 (m, 1H), 1.92 (dq, J = 9.1, 2.9 Hz, 1H), 1.89 – 1.65 (m, 3H), 1.42 – 1.31 (m, 1H).

Cis-syn: ¹³C NMR (101 MHz, Chloroform-d) δ 143.76, 139.93, 139.27, 124.26, 123.75, 122.84, 122.13, 121.19, 101.92, 69.77, 61.11, 42.36, 36.62, 28.80, 23.06, 19.52. Cis-trans: ¹³C NMR (101 MHz, Chloroform-d) δ 143.78, 139.94, 139.42, 124.25, 123.76, 122.88, 122.14, 121.39, 102.03, 73.48, 64.32, 43.93, 39.62, 33.94, 22.62, 20.77. HRMS calculated for C_{16}H_{18}O_{2}S (M + Na^+): 297.0920, found: 297.0920.

3-((hexahydro-4H-furo[2,3-b]pyran-3-yl)methyl)dibenzo[b,d]furan (11)

Eluent for purification: hexane: ethyl acetate = 10:1. White solid (46.2 mg, 75% yield, dr = 1.4:1). Isolated as an inseparable mixture of diastereomers. Spectral data for the two diastereomers is given herein. Cis-syn: ¹H NMR (400 MHz, Chloroform-d) δ 7.94 (dd, J = 7.7, 1.5 Hz, 1H), 7.73 (t, J = 2.1 Hz, 1H), 7.56 (d, J = 8.2 Hz, 1H), 7.50 – 7.41 (m, 2H), 7.34 (t, J = 7.5 Hz, 1H), 7.27 – 7.21 (m, 1H), 5.31 (d, J = 3.7 Hz,
1H), 3.93 – 3.84 (m, 1H), 3.84 – 3.77 (m, 2H), 3.73 – 3.63 (m, 1H), 2.94 – 2.85 (m, 1H), 2.82 – 2.66 (m, 2H), 1.99 (q, J = 4.8 Hz, 1H), 1.81 – 1.58 (m, 4H). **Cis-trans: 1H NMR** (400 MHz, Chloroform-d) δ 7.94 (dd, J = 7.7, 1.5 Hz, 1H), 7.73 (t, J = 2.1 Hz, 1H), 7.56 (d, J = 8.2 Hz, 1H), 7.50 – 7.41 (m, 2H), 7.34 (t, J = 7.5 Hz, 1H), 7.27 – 7.21 (m, 1H), 5.06 (d, J = 3.7 Hz, 1H), 4.21 (t, J = 8.0 Hz, 1H), 3.93 – 3.84 (m, 1H), 3.73 – 3.63 (m, 1H), 3.43 (td, J = 11.3, 2.4 Hz, 1H), 3.07 – 2.95 (m, 1H), 2.82 – 2.66 (m, 2H), 1.96 – 1.87 (m, 1H), 1.81 – 1.58 (m, 3H), 1.33 (m, 1H).

**13C NMR (trans & cis mixture)** (101 MHz, Chloroform-d) δ 156.51, 154.91, 154.86, 134.61, 127.64, 127.46, 127.17, 124.42, 124.40, 124.06, 122.66, 120.58, 120.56, 120.17, 120.06, 111.70, 111.54, 111.52, 102.19, 102.00, 73.64, 69.90, 64.37, 61.03, 43.87, 43.00, 39.95, 38.68, 36.66, 33.36, 23.18, 22.55, 20.78, 19.64. **HRMS calculated for C_{20}H_{20}O_{3} (M + Na^+):** 331.1305, found: 331.1302.

3-(thiophen-3-ylmethyl)hexahydro-4H-furo[2,3-b]pyran (12)

Eluent for purification: hexane: ethyl acetate = 10:1.

Colorless oil (30.0 mg, 67% yield, dr = 1.3:1). **Cis-syn: 1H NMR** (400 MHz, Chloroform-d) δ 7.28 – 7.25 (m, 1H), 6.97 – 6.86 (m, 2H), 5.29 (d, J = 3.7 Hz, 1H), 3.94 (t, J = 7.8 Hz, 1H), 3.77 (ddd, J = 12.8, 10.3, 7.7 Hz, 2H), 3.65 (ddt, J = 11.4, 3.3, 1.6 Hz, 1H), 2.83 – 2.57 (m, 3H), 1.99 (ddt, J = 12.1, 10.2, 4.9 Hz, 1H), 1.74 (m, 1H), 1.62 – 1.45 (m, 3H). **Cis-trans: 1H NMR** (400 MHz, Chloroform-d) δ 7.27 (d, J = 3.9 Hz, 1H), 6.96 – 6.88 (m, 2H), 5.03 (d, J = 3.3 Hz, 1H), 4.25 (t, J = 8.1 Hz, 1H), 3.89 (ddt, J = 11.7, 4.2, 2.5 Hz, 1H), 3.67 – 3.59 (m, 1H), 3.48 – 3.32 (m, 1H), 2.94 – 2.81 (m, 1H), 2.71 – 2.56 (m, 2H), 1.83 (m, 1H), 1.80 – 1.62 (m, 3H), 1.41 – 1.29 (m, 1H). **Cis-syn: 13C NMR** (101 MHz, Chloroform-d) δ 140.36, 127.90, 125.71, 120.59, 101.97, 69.98, 61.05, 41.85, 36.63, 27.98, 23.13, 19.47. **Cis-anti: 13C NMR** (101 MHz, Chloroform-d) δ 140.42, 128.03, 125.76, 120.75, 102.11, 73.75, 64.38, 43.89, 38.84, 33.14, 22.45, 20.75. **HRMS calculated for C_{12}H_{16}O_{3} (M + Na^+):** 247.0763, found: 247.0763.

3-(4-methoxybenzyl)hexahydrofuro[2,3-b]furan (13)
Eluent for purification: hexane: ethyl acetate = 10:1. Colorless oil (28.1 mg, 60% yield, dr = 1.9:1). Isolated as an inseparable mixture of diastereomers. Spectral data for the two diastereomer is given herein. **Cis-syn**: $^1$H NMR (400 MHz, Chloroform-d) δ 7.11 – 7.05 (m, 2H), 6.83 (dd, $J = 8.6$, 2.0 Hz, 2H), 5.71 (d, $J = 4.9$ Hz, 1H), 3.97 – 3.92 (m, 1H), 3.88 – 3.83 (m, 2H), 3.79 (s, 3H), 3.54 (dd, $J = 10.2$, 8.4 Hz, 1H), 2.77 (tt, $J = 10.9$, 5.2 Hz, 1H), 2.68 (dd, $J = 11.0$, 4.5 Hz, 1H), 2.62 (dd, $J = 8.2$, 3.3 Hz, 1H), 2.28 – 2.19 (m, 1H), 2.08 – 1.95 (m, 3H). **Cis-trans**: $^1$H NMR (400 MHz, Chloroform-d) δ 7.11 – 7.05 (m, 2H), 6.83 (dd, $J = 8.6$, 2.0 Hz, 2H), 5.74 (d, $J = 5.1$ Hz, 1H), 3.97 – 3.92 (m, 1H), 3.88 – 3.83 (m, 2H), 3.79 (s, 3H), 3.61 (dd, $J = 9.0$, 3.9 Hz, 1H), 2.62 (dd, $J = 8.2$, 3.3 Hz, 2H), 2.55 (ddt, $J = 8.5$, 5.5, 3.0 Hz, 1H), 2.28 – 2.19 (m, 1H), 2.08 – 1.95 (m, 1H), 1.89 – 1.83 (m, 1H), 1.66 – 1.57 (m, 1H). **$^{13}$C NMR (trans & cis mixture)** (101 MHz, Chloroform-d) δ 158.05, 158.03, 131.99, 131.96, 129.76, 129.21, 113.96, 113.90, 109.82, 109.17, 72.21, 72.19, 69.13, 67.76, 55.25, 48.36, 47.47, 45.43, 44.00, 38.69, 32.88, 31.91, 25.12. **HRMS** calculated for $C_{14}H_{18}O_3$ $(M + Na^+)$: 257.1148, found: 257.1150.

**3-benzyloctahydrofuro[2,3-b]oxepine (14)**

Eluent for purification: hexane: ethyl acetate = 10:1. Colorless oil (25.1 mg, 54% yield, dr = 2.1:1). Isolated as an inseparable mixture of diastereomers. Spectral data for the two diastereomer is given herein. **Cis-syn**: $^1$H NMR (400 MHz, Chloroform-d) δ 7.30 – 7.25 (m, 2H), 7.21 – 7.13 (m, 3H), 5.22 (d, $J = 5.5$ Hz, 1H), 4.05 (td, $J = 4.0$, 1.2 Hz, 1H), 4.02 (td, $J = 4.0$, 1.2 Hz, 1H), 3.77 (dd, $J = 8.5$, 6.1 Hz, 1H), 3.69 (dd, $J = 8.5$, 5.9 Hz, 1H), 2.60 (dd, $J = 13.4$, 10.5 Hz, 1H), 2.47 – 2.30 (m, 2H), 1.86 – 1.79 (m, 2H), 1.67 (ddt, $J = 8.8$, 5.8, 3.2 Hz, 2H), 1.44 – 1.33 (m, 3H). **Cis-trans**: $^1$H NMR (400 MHz, Chloroform-d) δ 7.30 – 7.25 (m, 2H), 7.21 – 7.13 (m, 3H), 5.16 (d, $J = 5.6$ Hz, 1H), 4.15 – 4.07 (m, 2H), 3.48 (t, $J = 8.5$ Hz, 1H), 3.38 (ddd, $J = 12.6$, 6.0, 2.6 Hz, 1H), 2.83 (dd, $J = 13.6$, 5.3 Hz, 1H), 2.55 – 2.40 (m, 2H), 2.47 – 2.30 (m, 2H), 2.04 – 1.97 (m, 1H), 1.86 – 1.79 (m, 2H), 1.67 (ddt, $J = 8.8$, 5.8, 3.2 Hz, 2H), 1.44 – 1.33 (m, 2H). **$^{13}$C NMR (trans & cis mixture)** (101 MHz, Chloroform-d) δ 140.92, 140.04, 128.65, 128.58, 128.43, 126.17, 125.96, 109.91, 109.53,
73.29, 71.96, 69.28, 68.91, 51.10, 48.49, 45.29, 42.83, 38.21, 34.07, 32.76, 32.33, 28.85, 26.70, 25.29, 24.72. **HRMS** calculated for C_{15}H_{20}O_{2} (M + Na^+): 255.1356, found: 255.1355.

3-phenylhexahydro-2H, 5H-pyrano[2,3-b]pyran (15)

Eluent for purification: hexane: ethyl acetate = 20:1. Colorless oil (24.0mg, 55% yield, dr = 3:1). Isolated as an inseparable mixture of diastereomers. Spectral data for the major diastereomer is given herein. **Cis-syn:** \(^{1}H\) NMR (400 MHz, Chloroform-d) \(\delta\) 7.35 – 7.29 (m, 2H), 7.26 – 7.21 (m, 3H), 4.88 (d, \(J = 2.2\) Hz, 1H), 4.19 – 4.06 (m, 1H), 3.99 – 3.85 (m, 1H), 3.79 – 3.66 (m, 1H), 3.65 – 3.52 (m, 1H), 3.15 – 3.02 (m, 1H), 1.94 - 1.92 (m, 1H), 1.92 – 1.75 (m, 2H), 1.75 – 1.70 (m, 2H), 1.70 – 1.59 (m, 1H), 1.59 – 1.51 (m, 1H). **Cis-anti:** \(^{1}H\) NMR (400 MHz, Chloroform-d) \(\delta\) 7.35 – 7.29 (m, 2H), 7.26 – 7.21 (m, 3H), 4.81 (d, \(J = 2.6\) Hz, 1H), 4.19 – 4.06 (m, 1H), 3.99 – 3.85 (m, 1H), 3.79 – 3.66 (m, 1H), 3.65 – 3.52 (m, 1H), 2.95 (tt, \(J = 11.9, 4.0\) Hz, 1H), 2.22 (q, \(J = 12.5\) Hz, 1H), 2.07 – 1.94 (m, 2H), 1.92 – 1.75 (m, 1H), 1.70 – 1.59 (m, 2H), 1.35 – 1.24 (m, 1H). \(^{13}C\) NMR (trans & cis mixture) (101 MHz, Chloroform-d) \(\delta\) 142.11, 141.55, 128.52, 127.42, 127.36, 126.71, 97.96, 97.23, 71.91, 67.52, 66.02, 61.68, 42.31, 36.97, 34.99, 34.81, 34.07, 29.40, 28.10, 25.03, 23.21, 20.54. **HRMS** calculated for C_{14}H_{18}O_{2} (M + Na^+): 241.1199, found: 241.1202.

3-methylhexahydro-2H, 5H-pyrano[2,3-b]pyran (16)

Eluent for purification: hexane: ethyl acetate = 20:1. Colorless oil (16.2 mg, 52% yield, dr = 3:1). Isolated as an inseparable mixture of diastereomers. Spectral data for the two diastereomer is given herein. **Cis-syn:** \(^{1}H\) NMR \(^{1}H\) NMR (400 MHz, Chloroform-d) \(\delta\) 4.69 (d, \(J = 2.6\) Hz, 1H), 3.92 (ddd, \(J = 11.4, 4.4, 2.5\) Hz, 1H), 3.89 – 3.81 (m, 1H), 3.62 (m, 1H), 3.10 (dd, \(J = 11.4, 10.3\) Hz, 1H), 1.83 – 1.70 (m, 3H), 1.62 – 1.50 (m, 3H), 1.48 – 1.43 (m, 1H), 1.34 – 1.25 (m, 1H), 0.78 (d, \(J = 6.7\) Hz, 3H). **Cis-anti:** \(^{1}H\) NMR (400 MHz, Chloroform-d) \(\delta\) 4.69 (d, \(J = 2.6\) Hz, 1H), 4.07 – 3.98 (m, 1H), 3.58 – 3.46 (m, 2H), 3.41 (t, \(J = 11.1\) Hz, 1H), 1.83 – 1.70 (m, 3H), 1.62 – 1.50 (m, 3H), 1.41 – 1.34 (m, 1H), 1.25 – 1.17 (m, 1H), 0.81 (d, \(J = 6.6\) Hz, 3H). \(^{13}C\) NMR (trans & cis mixture) (101 MHz, Chloroform-d) \(\delta\) 97.96, 97.30, 67.42,
67.06, 62.89, 34.59, 30.98, 30.67, 30.41, 28.12, 25.43, 20.48, 19.73, 17.27, 16.65. **HRMS** calculated for C₉H₁₆O₂ (M + H⁺): 157.1223, found: 157.1223.

4-methyl-3-phenylhexahydro-2H,5H-pyran[2,3-b]pyran (17)

Eluent for purification: hexane: ethyl acetate = 10:1. Colorless oil (37.6 mg, 81% yield, dr = 8.3:4.3:3.3:1). Isolated as an inseparable mixture of diastereomers. Spectral data for the major diastereomer is given herein. **¹H NMR** (500 MHz, Chloroform-d) δ 7.32 – 7.27 (m, 2H), 7.23 – 7.18 (m, 1H), 7.18 – 7.13 (m, 2H), 5.01 (d, J = 3.4 Hz, 1H), 4.01 (t, J = 8.6 Hz, 1H), 3.54 (td, J = 8.5, 1.9 Hz, 2H), 3.46 (ddd, J = 11.6, 10.5, 2.7 Hz, 1H), 2.54 – 2.47 (m, 1H), 1.94 (q, J = 3.3 Hz, 2H), 1.80 – 1.69 (m, 1H), 1.57 – 1.51 (m, 1H), 1.43 (m, 1H), 1.32 (m, 1H). **¹³C NMR** (four isomers) (101 MHz, Chloroform-d) δ 145.70, 145.25, 128.52, 128.44, 128.59, 128.49, 126.47, 126.37, 102.65, 102.38, 72.68, 71.81, 64.39, 64.13, 44.61, 44.16, 43.30, 43.16, 42.25, 24.06, 22.57, 21.08, 20.73, 20.55. **HRMS** calculated for C₁₅H₂₀O₂ (M + Na⁺): 255.1356, found: 255.1355.

3-(benzofuran-5-ylmethylene)hexahydro-4H-furo[2,3-b]pyran (18)

Eluent for purification: hexane: ethyl acetate = 20:1. Colorless oil (30.0 mg, 67% yield, E:Z = 4:1). Isolated as an inseparable mixture of diastereomers. Spectral data for the two isomers is given herein. **E-isomer:** **¹H NMR** (400 MHz, Chloroform-d) δ 7.62 (d, J = 2.2 Hz, 1H), 7.51 – 7.44 (m, 2H), 7.22 (dd, J = 8.6, 1.8 Hz, 1H), 6.76 (dd, J = 2.3, 1.0 Hz, 1H), 6.40 (dd, J = 10.3, 2.3 Hz, 1H), 5.26 (d, J = 3.9 Hz, 1H), 4.76 (dt, J = 12.9, 1.9 Hz, 1H), 4.46 (dd, J = 12.8, 1.8 Hz, 1H), 3.95 – 3.86 (m, 1H), 3.68 (ddt, J = 11.1, 4.0, 1.4 Hz, 1H), 3.05 – 2.95 (m, 1H), 1.99 (m, 1H), 1.71 – 1.58 (m, 1H), 1.57 – 1.54 (m, 2H). **Z-isomer:** **¹H NMR** (400 MHz, Chloroform-d) δ 7.62 (d, J = 2.2 Hz, 1H), 7.51 – 7.44 (m, 1H), 7.37 (d, J = 1.7 Hz, 1H), 7.12 (dd, J = 8.6, 1.9 Hz, 1H), 6.76 (dd, J = 2.3, 1.0 Hz, 1H), 6.40 (dd, J = 10.3, 2.3 Hz, 1H), 5.21 (d, J = 3.8 Hz, 1H), 4.93 (dt, J = 13.6, 2.5 Hz, 1H), 4.83 (dt, J = 13.6, 2.2 Hz, 1H), 3.95 – 3.86 (m, 1H), 3.51 (td, J = 11.2, 2.5 Hz, 1H), 2.85 (m, 1H), 2.18 (m, 1H), 1.71 – 1.58 (m, 1H), 1.57 – 1.54 (m, 1H), 1.29 (d, J = 3.8 Hz, 1H). **¹³C NMR (E & Z mixture)** (101 MHz, Chloroform-d) δ 153.95,
153.74, 145.53, 145.50, 140.70, 138.49, 132.14, 131.75, 127.76, 127.65, 124.80, 124.56, 121.64, 120.61, 120.24, 111.33, 111.26, 106.66, 106.62, 101.34, 100.62, 70.02, 70.00, 64.46, 61.56, 43.47, 38.33, 23.26, 23.03, 22.55, 20.62. **HRMS** calculated for C_{16}H_{16}O_{3} (M + Na^+): 279.0992, found: 279.0988.

3-benzylidenehexahydro-4H-furo[2,3-b]pyran (19)

![Structure](image)

Eluent for purification: hexane: ethyl acetate = 20:1. Colorless oil (22.5 mg, 52% yield, E:Z = 5.6:1). **E-isomer:** ¹H NMR (400 MHz, Chloroform-d) δ 7.38 – 7.32 (m, 2H), 7.28 (d, J = 12.3 Hz, 3H), 6.31 (q, J = 2.0 Hz, 1H), 5.26 (d, J = 3.9 Hz, 1H), 4.75 (dt, J = 13.1, 1.9 Hz, 1H), 4.45 (ddd, J = 13.1, 2.0, 0.6 Hz, 1H), 3.97 – 3.86 (m, 1H), 3.69 (dtd, J = 11.0, 3.8, 1.4 Hz, 1H), 3.02 – 2.95 (m, 1H), 2.05 – 1.94 (m, 1H), 1.72 – 1.63 (m, 1H), 1.61 – 1.54 (m, 2H). **Z-isomer:** ¹H NMR(400 MHz, Chloroform-d) δ 7.35 (t, J = 7.7 Hz, 2H), 7.25 – 7.19 (m, 1H), 7.19 – 7.11 (m, 2H), 6.29 (q, J = 2.6 Hz, 1H), 5.20 (d, J = 3.8 Hz, 1H), 4.90 (dt, J = 13.8, 2.5 Hz, 1H), 4.80 (dt, J = 13.9, 2.2 Hz, 1H), 3.93 – 3.81 (m, 1H), 3.50 (td, J = 11.3, 2.4 Hz, 1H), 2.84 (s, 1H), 2.21 – 2.07 (m, 1H), 2.08 – 1.92 (m, 1H), 1.72 – 1.63 (m, 1H), 1.36 (dq, J = 13.7, 3.4 Hz, 1H).

**E-isomer:** ¹³C NMR (101 MHz, Chloroform-d) δ 141.89, 136.74, 128.47, 127.85, 126.90, 121.51, 101.29, 69.85, 61.46, 38.30, 23.23, 22.58. **Z-isomer:** ¹³C NMR (101 MHz, Chloroform-d) δ 139.95, 136.99, 128.54, 127.91, 126.65, 120.49, 100.56, 70.01, 64.46, 43.56, 23.01, 20.59. **HRMS** calculated for C_{14}H_{16}O_{2} (M + H^+): 217.1123, found: 217.1124.

3-(4-methoxybenzylidene)hexahydro-4H-furo[2,3-b]pyran (20)

![Structure](image)

Eluent for purification: hexane: ethyl acetate = 20:1. Colorless oil (30.0 mg, 67% yield, E:Z = 4.6:1). **E-isomer:** ¹H NMR (500 MHz, Chloroform-d) δ 7.26 – 7.18 (m, 2H), 6.91 – 6.84 (m, 2H), 6.24 (q, J = 1.9 Hz, 1H), 5.25 (d, J = 3.9 Hz, 1H), 4.72 (dt, J = 12.8, 1.9 Hz, 1H), 4.42 (dd, J = 12.9, 1.8 Hz, 1H), 3.99 – 3.85 (m, 1H), 3.82 (s, 3H), 3.69 (dt, J = 11.0, 3.9, 1.6 Hz, 1H), 3.03 – 2.87 (m, 1H), 2.04 – 1.95 (m, 1H), 1.67 – 1.55 (m, 3H). **Z-isomer:** ¹H NMR (400 MHz, Chloroform-d) δ 7.15 – 7.02 (m, 2H), 6.94 – 6.85 (m, 2H), 6.23 (q, J = 2.6 Hz, 1H), 5.19 (d, J = 3.8 Hz, 1H), 4.88 (dt, J = 13.7, 2.5 Hz, 1H), 4.77 (dt, J = 13.7, 2.2 Hz, 1H),
3.88 (ddt, \( J = 9.7, 4.0, 1.6 \) Hz, 1H), 3.82 (s, 3H), 3.50 (ddd, \( J = 11.6, 10.9, 2.4 \) Hz, 1H), 2.87 – 2.72 (m, 1H), 2.20 – 2.07 (m, 1H), 1.99 (m, 1H), 1.68 – 1.61 (m, 1H), 1.36 (dt, \( J = 13.7, 3.5 \) Hz, 1H). E-isomer: \(^{13}\text{C NMR} \) (126 MHz, Chloroform-\( d \)) \( \delta \) 158.57, 139.84, 129.48, 129.09, 120.96, 113.96, 101.34, 69.91, 61.47, 55.30, 38.21, 23.22, 22.65. Z-isomer: \(^{13}\text{C NMR} \) (101 MHz, Chloroform-\( d \)) \( \delta \) 158.29, 137.45, 129.89, 129.14, 119.82, 113.99, 100.59, 70.01, 64.45, 55.28, 43.41, 23.00, 20.60. HRMS calculated for \( C_{18}H_{18}O_{3} \) (M + Na\(^{+} \)) : 269.1148, found: 269.1147.

3-benzyl-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)hexahydro-4H-furo[2,3-b]pyran (21)

Eluent for purification: hexane: ethyl acetate = 6:1. Colorless oil (47.3 mg, 43% yield, \( dr = 1.8:1.6:1:2:1 \)). Isolated as an inseparable mixture of diastereomers. Spectral data for the major diastereomer is given herein. \(^{1}\text{H NMR} \) (400 MHz, Chloroform-\( d \)) \( \delta \) 7.38 – 7.15 (m, 18H), 7.11 – 7.01 (m, 2H), 5.57 (d, \( J = 5.3 \) Hz, 1H), 4.69 – 4.50 (m, 5H), 4.44 (d, \( J = 11.0 \) Hz, 1H), 4.08 (dd, \( J = 8.9, 6.7 \) Hz, 1H), 3.83 (dt, \( J = 9.2, 3.1 \) Hz, 1H), 3.74 (dd, \( J = 10.6, 3.8 \) Hz, 1H), 3.70 – 3.62 (m, 2H), 3.58 (dd, \( J = 8.9, 4.3 \) Hz, 1H), 3.43 (t, \( J = 6.8 \) Hz, 1H), 2.65 (d, \( J = 7.8 \) Hz, 2H), 2.51 (dq, \( J = 11.2, 3.6 \) Hz, 1H), 2.27 – 2.14 (m, 1H). \(^{13}\text{C NMR (four isomers)} \) (101 MHz, Chloroform-\( d \)) \( \delta \) 140.10, 139.46, 138.43, 138.41, 138.12, 138.08, 138.01, 129.06, 128.89, 128.63, 128.55, 128.52, 128.49, 128.46, 128.42, 128.40, 128.36, 128.34, 128.32, 128.30, 127.98, 127.92, 127.89, 127.84, 127.78, 127.75, 127.72, 127.70, 127.58, 127.55, 127.43, 127.38, 126.36, 126.29, 126.17, 102.55, 102.33, 102.24, 101.15, 81.20, 80.88, 79.23, 79.07, 77.54, 77.25, 77.19, 75.69, 75.25, 74.91, 74.85, 74.50, 74.40, 74.12, 73.99, 73.93, 73.70, 73.62, 73.50, 73.46, 73.40, 73.31, 72.90, 72.00, 71.67, 71.55, 71.53, 70.83, 69.32, 69.22, 69.08, 68.47, 49.71, 47.73, 46.68, 46.36, 42.71, 42.54, 40.43, 40.39, 39.60, 38.88, 38.23, 34.87.

HRMS calculated for \( C_{36}H_{38}O_{5} \) (M + H\(^{+} \)) : 551.2792, found: 551.2789.

3-benzyl-4,5-dimethoxy-6-(methoxymethyl)hexahydro-4H-furo[2,3-b]pyran (22)

Eluent for purification: hexane: ethyl acetate = 6:1. Colorless oil (31.2 mg, 47%
yield, dr = 1.5:1.5:1.4:1). Isolated as an inseparable mixture of diastereomers. Spectral data for the major diastereomer is given herein. $^1$H NMR (400 MHz, Chloroform-d) $\delta$ 7.31 – 7.26 (m, 2H), 7.21 – 7.15 (m, 3H), 5.40 (d, $J = 4.3$ Hz, 1H), 3.81 (t, $J = 8.0$ Hz, 1H), 3.76 – 3.70 (m, 1H), 3.70 – 3.64 (m, 3H), 3.63 (s, 3H), 3.57 (s, 3H), 3.42 (s, 3H), 3.41 – 3.31 (m, 2H), 3.12 (dd, $J = 13.8, 4.9$ Hz, 1H), 2.72 (ddd, $J = 15.8, 10.6, 7.6, 5.1$ Hz, 1H), 2.48 (dd, $J = 13.8, 10.1$ Hz, 1H), 2.21 (ddd, $J = 9.4, 5.5, 4.2$ Hz, 1H).

$^{13}$C NMR (four isomers) (101 MHz, Chloroform-d) $\delta$ 141.44, 140.55, 140.23, 139.44, 129.03, 128.86, 128.61, 128.53, 128.52, 128.41, 128.39, 128.28, 126.40, 126.24, 126.13, 125.97, 102.56, 102.42, 102.25, 101.11, 83.16, 82.66, 80.54, 80.33, 79.07, 78.32, 77.40, 76.83, 74.11, 74.06, 73.88, 73.85, 71.93, 71.72, 71.61, 71.58, 71.13, 71.02, 70.73, 70.60, 60.42, 60.23, 59.91, 59.30, 59.18, 59.06, 58.95, 58.63, 58.59, 58.54, 57.54, 48.94, 47.17, 45.81, 45.65, 42.62, 42.33, 40.31, 40.25, 39.51, 38.81, 37.89, 34.35. HRMS calculated for C$_{18}$H$_{26}$O$_5$ (M + Na$^+$): 345.1672, found: 345.1672.

3-benzyl-5-methoxy-6-(methoxymethyl)hexahydro-4H-furo[2,3-b]pyran (23)

Eluent for purification: hexane: ethyl acetate = 6:1. Colorless oil (32.1 mg, 55% yield, dr = 1.3:1.2:1.2:1). Isolated as an inseparable mixture of diastereomers. Spectral data for the major diastereomer is given herein. $^1$H NMR (400 MHz, Chloroform-d) $\delta$ 7.32 – 7.26 (m, 2H), 7.24 – 7.13 (m, 3H), 5.47 (d, $J = 5.4$ Hz, 1H), 4.23 – 4.16 (m, 1H), 3.91 – 3.73 (m, 1H), 3.71 – 3.62 (m, 1H), 3.62 – 3.52 (m, 2H), 3.39 (s, 3H), 3.35 – 3.29 (m, 1H), 3.25 (s, 3H), 2.81 – 2.47 (m, 3H), 2.19 – 2.09 (m, 1H), 2.08 – 1.98 (m, 1H), 1.93 – 1.77 (m, 1H). $^{13}$C NMR (four isomers) (101 MHz, Chloroform-d) $\delta$ 140.27, 139.84, 139.80, 139.67, 128.89, 128.79, 128.59, 128.57, 128.53, 128.50, 128.38, 128.26, 126.33, 126.30, 126.26, 126.18, 103.10, 102.56, 101.96, 101.25, 75.06, 74.60, 73.77, 73.57, 73.31, 73.25, 72.36, 72.31, 72.23, 72.09, 71.61, 71.56, 71.52, 71.19, 69.88, 59.31, 59.26, 57.07, 56.59, 56.57, 56.40, 44.75, 44.64, 42.33, 42.09, 41.25, 40.25, 39.38, 38.55, 37.73, 36.85, 34.17, 33.11, 27.62, 27.56, 25.68, 22.13. HRMS calculated for C$_{18}$H$_{26}$O$_5$ (M + Na$^+$): 315.1567, found: 315.1566.

3-benzyl-6-(methoxymethyl)hexahydro-4H-furo[2,3-b]pyran (24)
Eluent for purification: hexane: ethyl acetate = 6:1. Colorless oil (34.1 mg, 65% yield, dr = 2.4:1.1:1:1). Isolated as an inseparable mixture of diastereomers. Spectral data for the major diastereomer is given herein. $^1$H NMR (400 MHz, Chloroform- $d$) $\delta$ 7.30 – 7.26 (m, 2H), 7.22 – 7.17 (m, 1H), 7.16 – 7.12 (m, 2H), 5.09 (d, $J = 3.2$ Hz, 1H), 4.19 (t, $J = 8.2$ Hz, 1H), 3.64 (t, $J = 8.3$ Hz, 1H), 3.58 – 3.49 (m, 1H), 3.47 – 3.41 (m, 1H), 3.39 (d, $J = 8.8$ Hz, 1H), 3.36 (s, 3H), 2.85 (dd, $J = 12.9$, 4.5 Hz, 1H), 2.67 – 2.52 (m, 2H), 1.84 (ddq, $J = 10.1$, 5.0, 2.3, 1.8 Hz, 2H), 1.76 (tt, $J = 12.1$, 3.2 Hz, 2H), 1.40 (m, 1H). $^{13}$C NMR (four isomers) (101 MHz, Chloroform- $d$) $\delta$ 140.85, 140.04, 139.97, 139.93, 128.75, 128.62, 128.52, 128.49, 128.30, 126.23, 126.20, 126.07, 102.99, 102.65, 102.62, 101.18, 75.60, 75.47, 75.39, 75.27, 74.09, 73.55, 72.39, 71.61, 70.53, 69.56, 69.02, 68.56, 59.24, 44.90, 44.02, 42.44, 39.44, 39.09, 38.78, 38.59, 36.15, 36.01, 33.12, 25.25, 24.34, 23.67, 22.68, 21.81, 19.45. HRMS calculated for C$_{16}$H$_{22}$O$_{3}$ (M + Na$^+$): 285.1461, found: 285.1465.

3-benzyl-4,5-dimethoxy-6-(methoxymethyl)hexahydro-4H-furo[2,3-b]pyran (25)

Eluent for purification: hexane: ethyl acetate = 10:1. Colorless oil (35.4 mg, 55% yield, dr = 6.7:6.5:7:1). Isolated as an inseparable mixture of diastereomers. Spectral data for the major diastereomer is given herein. $^1$H NMR (500 MHz, Chloroform- $d$) $\delta$ 7.30 – 7.27 (m, 2H), 7.24 – 7.18 (m, 3H), 5.42 (d, $J = 4.2$ Hz, 1H), 3.79 – 3.76 (m, 2H), 3.71 – 3.69 (m, 1H), 3.67 – 3.65 (m, 1H), 3.64 (s, 3H), 3.57 (s, 3H), 3.44 (dd, $J = 4.6$, 1.6 Hz, 2H), 3.41 (s, 3H), 3.35 – 3.32 (m, 1H), 3.11 (dd, $J = 9.8$, 2.5 Hz, 1H), 2.75 (ddd, $J = 7.5$, 5.9, 4.2 Hz, 1H), 2.64 – 2.59 (m, 1H), 2.21 – 2.17 (m, 1H). $^{13}$C NMR (four isomers) (126 MHz, Chloroform- $d$) $\delta$ 141.10, 140.50, 139.69, 128.91, 128.67, 128.51, 128.50, 128.37, 128.27, 126.29, 126.21, 125.90, 102.74, 102.31, 101.04, 80.87, 80.83, 80.67, 74.77, 74.20, 72.64, 71.93, 71.51, 71.30, 71.14, 70.97, 70.91, 70.39, 69.94, 69.63, 61.05, 60.83, 60.67, 59.19, 59.19, 59.16, 57.09, 57.03, 55.49, 48.16, 44.33, 42.48, 42.41, 40.95, 40.02, 39.80, 39.00, 35.26. HRMS calculated for C$_{16}$H$_{26}$O$_{5}$ (M + Na$^+$): 345.1672, found: 345.1672.
10-benzyl-2,2,4,4-tetraisopropyl-6-methylhexahydro-6H-furo[3',2':5,6]pyrano[3,4-f][1,3,5,2,4]trioxadisilepine (26)

Eluent for purification: hexane: ethyl acetate = 6:1. Colorless oil (44.6 mg, 44% yield, dr = 2.3:2:2:2:2:1). Isolated as an inseparable mixture of diastereomers. Spectral data for the major diastereomer is given herein. $^1$H NMR (400 MHz, Chloroform-d) $\delta$ 7.31 – 7.26 (m, 2H), 7.25 – 7.12 (m, 3H), 5.44 (d, $J = 4.5$ Hz, 1H), 4.19 – 3.99 (m, 1H), 3.82 – 3.67 (m, 2H), 3.40 (t, $J = 8.9$ Hz, 1H), 3.29 – 3.22 (m, 1H), 2.79 – 2.59 (m, 1H), 2.25 (dt, $J = 9.5, 5.0$ Hz, 1H), 1.98 (dd, $J = 9.0, 4.5$ Hz, 1H), 1.37 (d, $J = 6.2$ Hz, 1H), 1.15 – 1.00 (m, 31H).

$^{13}$C NMR (four isomers) (101 MHz, Chloroform-d) $\delta$ 140.77, 140.22, 139.51, 129.18, 128.78, 128.69, 128.56, 128.50, 128.47, 128.43, 128.21, 126.26, 126.09, 102.31, 101.86, 101.00, 77.91, 77.57, 77.21, 76.74, 76.33, 75.89, 74.01, 73.61, 73.52, 71.10, 71.06, 70.59, 70.54, 69.36, 68.63, 52.26, 49.36, 48.29, 43.41, 42.58, 41.05, 39.82, 39.00, 35.08, 18.14, 17.92, 17.90, 17.81, 17.75, 17.71, 17.67, 17.60, 17.53, 17.49, 17.44, 17.42, 17.38, 17.32, 17.30, 17.25, 17.23, 17.21, 16.99, 13.48, 12.98, 12.97, 12.92, 12.87, 12.78, 12.76, 12.73, 12.71, 12.34, 12.24, 12.20, 12.19.

HRMS calculated for C$_{27}$H$_{46}$O$_5$Si$_2$ (M + Na$^+$): 529.2776, found: 529.2768.

3-benzyl-4,5-dimethoxy-6-methylhexahydro-4H-furo[2,3-b]pyran (27)

Eluent for purification: hexane: ethyl acetate = 10:1. Colorless oil (36.7 mg, 77% yield, dr = 2.3:2:1.2:1). Isolated as an inseparable mixture of diastereomers. Spectral data for the major diastereomer is given herein. $^1$H NMR (400 MHz, Chloroform-d) $\delta$ 7.33 – 7.26 (m, 2H), 7.20 (t, $J = 6.9$ Hz, 3H), 5.44 (d, $J = 5.7$ Hz, 1H), 4.18 (dd, $J = 8.8, 6.6$ Hz, 1H), 3.70 – 3.63 (m, 1H), 3.63 (s, 3H), 3.37 (d, $J = 4.2$ Hz, 3H), 3.32 (t, $J = 9.2$ Hz, 1H), 3.05 – 2.95 (m, 2H), 2.83 (dd, $J = 8.9, 5.4$ Hz, 1H), 2.76 – 2.68 (m, 1H), 2.53 – 2.36 (m, 1H), 2.17 (dq, $J = 20.3, 5.3$ Hz, 1H), 1.29 (t, $J = 6.5$ Hz, 3H). $^{13}$C NMR (four isomers) (101 MHz, Chloroform-d) $\delta$ 141.41, 140.62, 140.28, 139.48, 129.03, 128.85, 128.56, 128.54, 128.51, 128.44, 128.41, 128.29,
HRMS calculated for $\text{C}_{17}\text{H}_{24}\text{O}_4$ (M + Na$^+$): 315.1567, found: 315.1565.

4-benzyl-2-ethoxytetrahydrofuran (28)

Colorless oil (33.4 mg, 81% yield, dr = 1.4:1). Isolated as an inseparable mixture of diastereomers. Spectral data for the two diastereomers is given herein. cis-isomer: $^1\text{H NMR}$ (500 MHz, Chloroform-$d$) $\delta$ 7.29 (dd, $J = 8.1$, 6.8 Hz, 3H), 7.23 – 7.15 (m, 2H), 5.19 – 5.09 (m, 1H), 3.91 (dd, $J = 8.4$, 7.1 Hz, 1H), 3.74 (ddq, $J = 27.0$, 9.6, 7.1 Hz, 1H), 3.65 – 3.55 (m, 1H), 3.44 (ddq, $J = 18.4$, 9.6, 7.1 Hz, 1H), 2.84 – 2.71 (m, 2H), 2.49 (ddd, $J = 15.9$, 8.7, 7.4 Hz, 1H), 2.21 (ddd, $J = 13.3$, 9.1, 5.6 Hz, 1H), 1.67 – 1.58 (m, 1H), 1.23 (t, $J = 7.1$ Hz, 3H).

trans-isomer: $^1\text{H NMR}$ (500 MHz, Chloroform-$d$) $\delta$ 7.29 (dd, $J = 8.1$, 6.8 Hz, 3H), 7.23 – 7.15 (m, 2H), 5.19 – 5.09 (m, 1H), 3.99 (dd, $J = 8.4$, 7.0 Hz, 1H), 3.74 (ddq, $J = 27.0$, 9.6, 7.1 Hz, 1H), 3.65 – 3.55 (m, 1H), 3.44 (ddq, $J = 18.4$, 9.6, 7.1 Hz, 1H), 2.74 – 2.64 (m, 3H), 2.00 (ddd, $J = 13.1$, 7.1, 1.3 Hz, 1H), 1.71 (ddd, $J = 13.2$, 7.9, 5.2 Hz, 1H), 1.18 (t, $J = 7.1$ Hz, 3H).

$^{13}\text{C NMR}$ (trans & cis mixture) (126 MHz, Chloroform-$d$) $\delta$ 140.86, 140.56, 128.69, 128.62, 128.44, 126.13, 126.05, 104.42, 103.95, 71.79, 71.72, 63.09, 62.69, 40.15, 39.93, 39.28, 39.16, 38.83, 15.37, 15.26.

HRMS calculated for $\text{C}_{18}\text{H}_{18}\text{O}_2$ (M + Na$^+$): 229.1199, found: 229.1197.

2-ethoxy-4-(naphthalen-2-ylmethyl)tetrahydrofuran (29)

Colorless oil (32.3 mg, 63% yield, dr = 1.1:1). Isolated as an inseparable mixture of diastereomers. Spectral data for the two diastereomers is given herein. cis-isomer: $^1\text{H NMR}$ (400 MHz, Chloroform-$d$) $\delta$ 7.83 – 7.75 (m, 3H), 7.64 – 7.59 (m, 1H), 7.45 (pd, $J = 6.9$, 1.6 Hz, 2H), 7.32 (dt, $J = 8.4$, 2.0 Hz, 1H), 5.20 – 5.13 (m, 1H), 3.94 (dd, $J = 8.3$, 7.2 Hz, 1H), 3.82 –
3.61 (m, 2H), 3.46 (ddq, \( J = 16.8, 9.7, 7.0 \text{ Hz}, 1\text{H} \)), 2.95 (dd, \( J = 7.8, 2.1 \text{ Hz}, 2\text{H} \)), 2.60 (ddd, \( J = 15.8, 8.6, 7.3 \text{ Hz}, 1\text{H} \)), 2.23 (ddd, \( J = 13.4, 9.1, 5.6 \text{ Hz}, 1\text{H} \)), 1.73 – 1.67 (m, 1H), 1.26 (t, \( J = 7.0 \text{ Hz}, 3\text{H} \)). **trans-isomer:** \(^1\text{H NMR} (400 \text{ MHz}, \text{Chloroform-d}) \) \( \delta \) 7.83 – 7.75 (m, 3H), 7.64 – 7.59 (m, 1H), 7.45 (pd, \( J = 6.9, 1.6 \text{ Hz}, 2\text{H} \)), 7.32 (dt, \( J = 8.4, 2.0 \text{ Hz}, 1\text{H} \)), 5.20 – 5.13 (m, 1H), 4.04 – 3.98 (m, 1H), 3.82 – 3.61 (m, 2H), 3.46 (ddq, \( J = 16.8, 9.7, 7.0 \text{ Hz}, 1\text{H} \)), 2.89 – 2.80 (m, 3H), 2.04 (ddd, \( J = 12.8, 6.2, 1.9 \text{ Hz}, 1\text{H} \)), 1.77 (ddd, \( J = 12.7, 7.5, 5.2 \text{ Hz}, 1\text{H} \)), 1.19 (t, \( J = 7.1 \text{ Hz}, 3\text{H} \)). \(^{13}\text{C NMR} (\text{trans & cis mixture}) (101 \text{ MHz}, \text{Chloroform-d}) \) \( \delta \) 138.35, 138.06, 133.59, 133.55, 128.04, 128.02, 127.61, 127.46, 127.31, 126.85, 126.77, 126.01, 125.98, 125.32, 125.28, 104.41, 103.95, 71.74, 63.10, 62.70, 40.10, 40.04, 39.45, 39.17, 38.82, 38.70, 15.38, 15.25. \( \text{HRMS calculated for } C_{17}H_{20}O_2 (M + Na^+) : 279.1356, \) found: 279.1355.

**4-benzyl-2-ethoxy-3-methyltetrahydrofuran (30)**

![4-benzyl-2-ethoxy-3-methyltetrahydrofuran (30)](image)

Eluent for purification: hexane: ethyl acetate = 100:1. Colorless oil (39.6 mg, 90% yield, \( dr = 2.4:2:1.7:1 \)). Isolated as an inseparable mixture of diastereomers. Spectral data for the major diastereomers is given herein. \(^1\text{H NMR} (400 \text{ MHz}, \text{Chloroform-d}) \) \( \delta \) 7.29 (m, 2H), 7.23 – 7.15 (m, 3H), 4.91 (d, \( J = 4.8 \text{ Hz}, 1\text{H} \)), 4.00 – 3.89 (m, 1H), 3.84 – 3.62 (m, 1H), 3.55 (t, \( J = 8.3 \text{ Hz}, 1\text{H} \)), 3.44 (m, 1H), 2.96 – 2.75 (m, 2H), 2.59 – 2.45 (m, 1H), 2.39 – 2.28 (m, 1H), 1.24 (td, \( J = 7.1, 0.9 \text{ Hz}, 3\text{H} \)), 1.03 – 0.99 (m, 3H). \(^{13}\text{C NMR (four isomers)} (101 \text{ MHz}, \text{Chloroform-d}) \) \( \delta \) 141.51, 140.77, 140.56, 140.47, 128.80, 128.59, 128.52, 128.44, 128.42, 128.39, 128.35, 126.06, 126.02, 125.80, 110.88 , 110.04, 105.52, 105.37, 72.47, 72.09, 71.36, 71.22, 63.42, 63.07, 62.79, 62.74, 48.15, 46.06, 44.73, 44.23, 42.03, 41.48, 41.47, 40.49, 38.87, 38.32, 35.53, 33.79, 16.94, 15.45, 15.36, 15.27, 15.24, 11.76, 11.68, 9.14. \( \text{HRMS calculated for } C_{14}H_{20}O_2 (M + Na^+) : 243.1356, \) found: 243.1354.

**2-ethoxy-4-(4-fluorobenzyl)-3-methyltetrahydrofuran (31)**

![2-ethoxy-4-(4-fluorobenzyl)-3-methyltetrahydrofuran (31)](image)

Eluent for purification: hexane: ethyl acetate = 100:1. Colorless oil (33.3mg, 70% yield, \( dr = 1.8:1.6:1.1:1 \)). Isolated as an inseparable mixture of diastereomers. Spectral data for the major diastereomers is given herein. \(^1\text{H NMR} (400 \text{ MHz}, \text{Chloroform-d}) \) \( \delta \) 7.16 –
7.06 (m, 2H), 6.95 (td, J = 8.7, 1.8 Hz, 2H), 4.70 (d, J = 3.1 Hz, 1H), 3.96 – 3.87 (m, 1H), 3.80 – 3.69 (m, 1H), 3.64 – 3.59 (m, 1H), 3.47 – 3.38 (m, 1H), 2.90 – 2.69 (m, 2H), 2.67 – 2.58 (m, 1H), 2.00 (tq, J = 8.7, 7.0 Hz, 1H), 1.23 – 1.20 (m, 3H), 0.98 (dd, J = 7.2 Hz, 3H). 13C NMR (four isomers) (101 MHz, Chloroform-d) δ 162.59, 162.58, 160.17, 160.15, 137.09 (d, J = 3.2 Hz), 136.19 (d, J = 3.2 Hz), 136.09 (d, J = 7.7 Hz), 129.95 (d, J = 7.7 Hz), 129.93 (d, J = 7.9 Hz), 129.76, 115.29 (d, J = 21.1 Hz), 115.27 (d, J = 21.2 Hz), 115.24 (d, J = 21.3 Hz), 115.18 (d, J = 21.1 Hz), 110.81, 110.00, 105.51, 105.32, 72.31, 71.94, 71.24, 71.06, 63.37, 63.07, 62.81, 62.75, 48.20, 45.89, 44.84, 44.17, 41.93, 41.57, 40.48, 38.04, 37.55, 34.74, 32.95, 17.01, 15.62, 15.33, 15.23, 15.20, 11.75, 11.61, 9.11. HRMS calculated for C14H19FO2 (M + Na+): 261.1621, found: 261.1620.

2-ethoxy-4-ethyl-3-phenyltetrahydrofuran (32)

Eluent for purification: hexane: ethyl acetate = 100:1. Colorless oil (35.7 mg, 81% yield, dr = 5:1). Isolated as an inseparable mixture of diastereomers. Spectral data for the two diastereomers is given herein. trans-trans-isomer: 1H NMR (500 MHz, Chloroform-d) δ 7.35 – 7.29 (m, 2H), 7.28 – 7.18 (m, 3H), 5.05 (d, J = 3.2 Hz, 1H), 4.23 (dt, J = 12.0, 8.1 Hz, 1H), 3.81 – 3.68 (m, 2H), 3.51 – 3.37 (m, 1H), 2.89 (dd, J = 8.2, 3.3 Hz, 1H), 2.28 – 2.18 (m, 1H), 1.65 – 1.57 (m, 1H), 1.50 – 1.41 (m, 1H), 1.20 (t, J = 7.1 Hz, 3H), 0.86 (t, J = 7.5 Hz, 3H). cis-trans-isomer: 1H NMR (500 MHz, Chloroform-d) δ 7.35 – 7.29 (m, 2H), 7.28 – 7.18 (m, 3H), 5.13 (s, 1H), 4.23 (dt, J = 12.0, 8.1 Hz, 1H), 3.81 – 3.68 (m, 1H), 3.65 (dd, J = 9.5, 8.3 Hz, 1H), 3.51 – 3.37 (m, 1H), 3.31 (d, J = 7.5 Hz, 1H), 2.75 (m, 1H), 1.73 – 1.68 (m, 1H), 1.23 (t, J = 7.1 Hz, 3H), 1.08 (dt, J = 13.8, 7.0 Hz, 1H), 0.82 (t, J = 7.2 Hz, 3H). 13C NMR (126 MHz, Chloroform-d) δ 142.21, 138.60, 128.62, 128.61, 128.05, 127.72, 126.57, 110.89, 108.97, 72.55, 72.18, 63.43, 62.64, 58.96, 54.58, 50.26, 43.25, 24.93, 21.74, 15.32, 15.30, 13.07, 12.81. HRMS calculated for C14H20O2 (M + Na+): 243.1356, found: 243.1356.

4-butyl-2-ethoxy-3-phenyltetrahydrofuran (33)

Eluent for purification: hexane: ethyl acetate = 100:1. Colorless oil
(44.7 mg, 90% yield, dr = 7.7:1). Isolated as an inseparable mixture of diastereomers. Spectral
data for the two diastereomers is given herein. **trans-trans-isomer: **$^1$H NMR (400 MHz,
Chloroform-$d$) $\delta$ 7.35 – 7.28 (m, 2H), 7.27 – 7.16 (m, 3H), 5.03 (d, $J = 3.3$ Hz, 1H), 4.25 – 4.16
(m, 1H), 3.78 – 3.67 (m, 2H), 3.41 (dq, $J = 9.6, 7.0$ Hz, 1H), 2.87 (dd, $J = 8.4, 3.3$ Hz, 1H), 2.27
(dtdd, $J = 9.9, 8.6, 7.2, 5.5$ Hz, 1H), 1.60 – 1.48 (m, 1H), 1.44 – 1.35 (m, 1H), 1.25 – 1.14 (m,
7H), 0.82 (t, $J = 7.0$ Hz, 3H). **cis-trans-isomer: **$^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 7.35 – 7.28
(m, 2H), 7.27 – 7.16 (m, 3H), 5.12 (s, 1H), 4.25 – 4.16 (m, 1H), 3.78 – 3.67 (m, 1H), 3.66 – 3.59
(m, 1H), 3.41 (dq, $J = 9.6, 7.0$ Hz, 1H), 3.28 (d, $J = 7.5$ Hz, 1H), 2.84 – 2.75 (m, 1H), 1.60 –
1.48 (m, 1H), 1.25 – 1.14 (m, 7H), 1.06 – 1.02 (m, 1H), 0.82 (t, $J = 7.0$ Hz, 3H). $^{13}$C NMR (101
MHz, Chloroform-$d$) $\delta$ 142.06, 138.57, 128.66, 128.56, 128.28, 127.70, 126.54, 126.51, 110.81,
108.86, 72.74, 72.31, 63.43, 61.85, 59.20, 54.65, 48.60, 41.25, 31.64, 30.59, 28.23, 22.80,
22.69, 15.29, 15.25, 13.91. **HRMS** calculated for C$_{16}$H$_{24}$O$_2$ (M + Na$^+$): 271.1669, found:
271.1671.

2-ethoxy-4-isopropyl-3-phenyltetrahydrofuran (34)

[Structural diagram]

Eluent for purification: hexane: ethyl acetate = 100:1. Colorless oil
(43.7 mg, 88% yield, dr = 2.8:1). Isolated as an inseparable mixture of diastereomers. Spectral
data for the two diastereomers is given herein. **trans-trans-isomer: **$^1$H NMR (400 MHz,
Chloroform-$d$) $\delta$ 7.34 – 7.18 (m, 5H), 4.95 (d, $J = 2.5$ Hz, 1H), 4.17 (t, $J = 8.0$ Hz, 1H), 3.82 –
3.64 (m, 2H), 3.49 – 3.34 (m, 1H), 3.01 (dd, $J = 7.4, 2.5$ Hz, 1H), 2.15 – 2.03 (m, 1H), 1.75 (dp,
$J = 8.8, 6.6$ Hz, 1H), 1.20 (dt, $J = 16.8, 7.1$ Hz, 3H), 0.87 – 0.82 (m, 6H). **cis-trans-isomer: **$^1$H
NMR (400 MHz, Chloroform-$d$) $\delta$ 7.34 – 7.18 (m, 5H), 5.01 (s, 1H), 4.22 (t, $J = 8.5$ Hz, 1H), 3.82 –
3.64 (m, 2H), 3.49 – 3.34 (m, 1H), 3.30 (d, $J = 7.2$ Hz, 1H), 2.53 (tdd, $J = 10.7, 8.6, 7.1$ Hz,
1H), 1.20 (dt, $J = 16.8, 7.1$ Hz, 3H), 1.08 (dq, $J = 10.9, 6.5$ Hz, 1H), 0.87 – 0.82 (m, 3H), 0.77
d(, $J = 6.6$ Hz, 3H). $^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 143.65, 138.72, 129.03, 128.53,
128.30, 127.74, 126.58, 126.32, 111.23, 109.49, 71.55, 71.03, 62.99, 62.50, 57.41, 55.58,
54.08, 49.24, 31.48, 27.41, 21.93, 21.85, 21.70, 21.04, 15.27. **HRMS** calculated for C$_{18}$H$_{22}$O$_2$
(M + Na$^+$): 257.1512, found: 257.1511.
2-ethoxy-4,4-dimethyl-3-phenyltetrahydrofuran (35)

Eluent for purification: hexane: ethyl acetate = 100:1. Colorless oil (22.0 mg, 50% yield). **1H NMR** (400 MHz, Chloroform-\(d\)) \(\delta\) 7.29 – 7.22 (m, 2H), 7.22 – 7.17 (m, 1H), 7.14 – 7.08 (m, 2H), 5.34 (d, \(J = 4.8\) Hz, 1H), 3.88 – 3.79 (m, 1H), 3.73 (dq, \(J = 9.5, 7.1\) Hz, 1H), 3.66 (d, \(J = 8.1\) Hz, 1H), 3.39 (dq, \(J = 9.5, 7.1\) Hz, 1H), 2.93 (d, \(J = 4.8\) Hz, 1H), 1.11 (t, \(J = 7.1\) Hz, 3H), 1.03 (s, 3H), 0.69 (s, 3H). **13C NMR** (101 MHz, Chloroform-\(d\)) \(\delta\) 137.38, 128.91, 128.17, 126.74, 109.17, 80.00, 64.00, 62.54, 43.39, 24.75, 22.86, 15.30. **HRMS** calculated for C\(_{14}\)H\(_{20}\)O\(_{2}\) (M + Na\(^{+}\)): 243.1356, found: 243.1355.

4-ethyl-2-methoxy-3-phenyltetrahydrofuran (36)

Eluent for purification: hexane: ethyl acetate = 100:1. Colorless oil (28.4 mg, 69% yield, dr = 5:1). Isolated as an inseparable mixture of diastereomers. Spectral data for the two diastereomers is given herein. **trans-trans-isomer:** **1H NMR** (400 MHz, Chloroform-\(d\)) \(\delta\) 7.27 – 7.21 (m, 2H), 7.18 – 7.09 (m, 3H), 4.86 (d, \(J = 3.1\) Hz, 1H), 4.20 – 4.11 (m, 1H), 3.59 (ddd, \(J = 12.6, 9.7, 8.4\) Hz, 1H), 3.27 (s, 3H), 2.79 (dd, \(J = 8.2, 3.1\) Hz, 1H), 2.15 (dttdd, \(J = 9.9, 8.3, 7.3, 5.7\) Hz, 1H), 1.51 (tdd, \(J = 15.0, 7.5, 5.7\) Hz, 1H), 1.45 – 1.29 (m, 1H), 0.77 (t, \(J = 7.4\) Hz, 3H). **cis-trans-isomer:** **1H NMR** (400 MHz, Chloroform-\(d\)) \(\delta\) 7.27 – 7.21 (m, 2H), 7.18 – 7.09 (m, 3H), 4.93 (s, 1H), 4.20 – 4.11 (m, 1H), 3.59 (ddd, \(J = 12.6, 9.7, 8.4\) Hz, 1H), 3.31 (s, 3H), 3.22 (d, \(J = 7.5\) Hz, 1H), 2.69 – 2.56 (m, 1H), 1.51 (dtt, \(J = 15.0, 7.5, 5.7\) Hz, 1H), 1.45 – 1.29 (m, 1H), 0.77 (t, \(J = 7.4\) Hz, 3H). **13C NMR** (trans & cis mixture) (126 MHz, Chloroform-\(d\)) \(\delta\) 205.16, 204.81, 157.10, 154.80, 128.78, 123.41, 123.38, 122.56, 120.34, 110.83, 110.80, 103.78, 103.73, 57.67, 57.54, 33.58, 33.35, 32.95, 31.89, 19.76, 17.95, 16.83, 16.45, 12.21, 12.09. **HRMS** calculated for C\(_{13}\)H\(_{18}\)O\(_{2}\) (M + H\(^{+}\)): 207.1380, found: 207.1370.

2-ethoxy-4-((E)-hept-4-en-1-yl)-3-phenyltetrahydrofuran (37)
Eluent for purification: hexane: ethyl acetate = 100:1. Colorless oil (30.6 mg, 53% yield, dr = 5:1). Isolated as an inseparable mixture of diastereomers. Spectral data for the two diastereomers is given herein. **trans-trans-isomer:**

$^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 7.34 – 7.27 (m, 2H), 7.26 – 7.20 (m, 3H), 5.38 – 5.23 (m, 2H), 5.02 (d, $J$ = 3.3 Hz, 1H), 4.24 – 4.16 (m, 1H), 3.80 – 3.65 (m, 2H), 3.49 – 3.35 (m, 1H), 2.87 (dd, $J$ = 8.4, 3.3 Hz, 1H), 2.27 (dtdd, $J$ = 10.0, 8.6, 7.3, 5.6 Hz, 1H), 1.99 – 1.87 (m, 4H), 1.54 (ddd, $J$ = 13.2, 10.7, 6.3 Hz, 1H), 1.40 (dtdd, $J$ = 13.2, 8.7, 6.5 Hz, 1H), 1.28 – 1.23 (m, 3H), 1.19 (t, $J$ = 7.2 Hz, 3H), 0.92 (t, $J$ = 7.2 Hz, 3H). **cis-trans-isomer:**

$^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 7.34 – 7.27 (m, 2H), 7.26 – 7.20 (m, 2H), 7.19 – 7.15 (m, 1H), 5.38 – 5.23 (m, 2H), 5.11 (s, 1H), 4.24 – 4.16 (m, 1H), 3.80 – 3.65 (m, 1H), 3.62 (dd, $J$ = 9.6, 8.2 Hz, 1H), 3.49 – 3.35 (m, 1H), 3.28 (d, $J$ = 7.5 Hz, 1H), 2.79 (dt, $J$ = 16.6, 8.3 Hz, 1H), 1.99 – 1.87 (m, 4H), 1.54 (ddd, $J$ = 13.2, 10.7, 6.3 Hz, 1H), 1.40 (dtdd, $J$ = 13.2, 8.7, 6.5 Hz, 1H), 1.28 – 1.23 (m, 3H), 1.19 (t, $J$ = 7.2 Hz, 3H), 0.92 (t, $J$ = 7.2 Hz, 3H). **13C NMR (trans & cis mixture) (101 MHz, Chloroform-$d$) $\delta$ 142.05, 141.99, 132.37, 131.93, 128.66, 128.56, 127.69, 126.55, 110.81, 108.86, 72.69, 72.69, 63.44, 63.42, 59.14, 54.59, 48.45, 41.19, 32.56, 32.38, 31.59, 31.35, 28.56, 28.33, 25.52, 20.45, 15.27, 14.30, 13.90. HRMS calculated for C$_{19}$H$_{28}$O$_2$ (M + Na$^+$): 311.1982, found: 311.1981.

**4-(2-((3r,5r,7r)-adamantan-1-yl)ethyl)-2-ethoxy-3-phenyltetrahydrofuran (38)**

Eluent for purification: hexane: ethyl acetate = 100:1. Colorless oil (51.0 mg, 72% yield, dr = 7.1:1). Isolated as an inseparable mixture of diastereomers. Spectral data for the two diastereomers is given herein. **trans-trans-isomer:**

$^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 7.35 – 7.29 (m, 2H), 7.27 – 7.16 (m, 3H), 5.02 (d, $J$ = 3.3 Hz, 1H), 4.19 (dd, $J$ = 8.2, 7.2 Hz, 1H), 3.81 – 3.57 (m, 2H), 3.43 (ddq, $J$ = 16.7, 9.7, 7.0 Hz, 1H), 2.87 (dd, $J$ = 8.2, 3.2 Hz, 1H), 2.18 (ddddd, $J$ = 13.1, 9.8, 8.7, 7.4 Hz, 1H), 1.95 – 1.87 (m, 3H), 1.71 – 1.47 (m, 8H), 1.39 (d, $J$ = 2.8 Hz, 6H), 1.18 (t, $J$ = 7.1 Hz, 3H), 1.02 – 0.85 (m, 2H). **cis-trans-isomer:**

$^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 7.35 – 7.28 (m, 2H), 7.27 – 7.16 (m,
3H), 5.10 (s, 1H), 4.19 (dd, J = 8.2, 7.2 Hz, 1H), 3.81 – 3.57 (m, 2H), 3.43 (ddq, J = 16.7, 9.7, 7.0 Hz, 1H), 3.28 (d, J = 7.5 Hz, 1H), 2.70 (qd, J = 9.0, 4.4 Hz, 1H), 1.95 – 1.87 (m, 2H), 1.87 – 1.80 (m, 1H), 1.71 – 1.47 (m, 8H), 1.37 – 1.30 (m, 6H), 1.18 (t, J = 7.1 Hz, 3H), 1.02 – 0.85 (m, 3H). 

$^{13}$C NMR (trans & cis mixture) (101 MHz, Chloroform-d) δ 142.20, 138.39, 128.75, 128.56, 128.24, 127.70, 126.53, 126.51, 110.83, 108.97, 72.78, 72.38, 63.38, 62.56, 59.24, 54.37, 49.09, 43.41, 43.06, 42.31, 42.19, 41.99, 37.20, 37.14, 37.10, 32.13, 32.05, 29.69, 28.83, 28.68, 28.63, 24.92, 20.97, 15.29, 15.27. 

HRMS calculated for C$_{24}$H$_{34}$O$_2$ (M + Na$^+$): 377.2451, found: 377.2453.

(3aS,5aR,8aR,8bS)-5-((5-ethoxy-4-phenyltetrahydrofuran-3-yl)methyl)-2,2,7,7-tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran (39)

Eluent for purification: hexane: ethyl acetate = 10:1. Colorless oil (Z: 42 mg, 78% yield, dr = 2.6:2:1; E: 42 mg, 69% yield, dr = 1.1:1). Isolated as an inseparable mixture of diastereomers. Spectral data for the major diastereomers is given herein. 

$^1$H NMR (400 MHz, Chloroform-d) δ 7.34 – 7.14 (m, 5H), 5.47 (dd, J = 5.2, 1.9 Hz, 1H), 5.01 (t, J = 3.2 Hz, 1H), 4.51 (m, 1H), 4.34 – 4.21 (m, 2H), 3.95 – 3.93 (m, 1H), 3.80 – 3.69 (m, 2H), 3.64 – 3.56 (m, 1H), 3.39 (m, 1H), 2.90 (dt, J = 8.7, 3.1 Hz, 1H), 2.62 – 2.52 (m, 1H), 1.79 – 1.76 (m, 1H), 1.63 – 1.49 (m, 1H), 1.50 (s, 3H), 1.44 – 1.37 (m, 9H), 1.17 (td, J = 7.1, 2.5 Hz, 3H). 

$^{13}$C NMR (trans & cis mixture) (101 MHz, Chloroform-d) δ 141.39, 141.35, 138.51, 128.68, 128.57, 128.44, 127.85, 127.77, 126.65, 126.62, 126.59, 110.81, 110.00, 109.07, 109.01, 108.98, 108.75, 108.24, 108.16, 96.52, 96.46, 96.41, 77.24, 73.12, 72.99, 72.85, 72.16, 71.77, 70.91, 70.89, 70.43, 70.38, 70.28, 67.47, 66.21, 65.69, 63.43, 63.34, 62.54, 59.30, 59.00, 47.27, 43.87, 36.95, 32.50, 32.21, 29.68, 29.20, 26.02, 25.98, 25.91, 24.86, 24.82, 24.44, 24.25, 15.29, 15.18. 

HRMS calculated for C$_{24}$H$_{34}$O$_7$ (M + Na$^+$): 457.2197, found: 457.2196

2-(cinnamyloxy)tetrahydro-2H-pyran (40)
Eluent for purification: hexane: ethyl acetate = 20:1.  

**¹H NMR** (400 MHz, Chloroform-$$d$$) δ 7.44 – 7.37 (m, 2H), 7.36 – 7.29 (m, 2H), 7.27 – 7.21 (m, 1H), 6.64 (dt, $$J = 15.9, 1.5$$ Hz, 1H), 6.33 (ddd, $$J = 15.9, 6.6, 5.6$$ Hz, 1H), 4.72 (dd, $$J = 4.2, 3.0$$ Hz, 1H), 4.42 (ddd, $$J = 12.9, 5.6, 1.6$$ Hz, 1H), 4.17 (ddd, $$J = 12.9, 6.6, 1.4$$ Hz, 1H), 3.93 (ddd, $$J = 11.3, 8.0, 3.4$$ Hz, 1H), 3.61 – 3.49 (m, 1H), 1.94 – 1.82 (m, 1H), 1.81 – 1.71 (m, 1H), 1.67 – 1.51 (m, 4H).

**¹³C NMR** (101 MHz, Chloroform-$$d$$) δ 136.81, 132.30, 128.50, 127.59, 126.48, 126.01, 97.86, 67.63, 62.24, 30.64, 25.48, 19.48. **HRMS** calculated for C$_{14}$$H_{18}$$O$_2$(M + Na$^+$): 241.1199, found: 241.1197.

5-(3-((tetrahydro-2H-pyran-2-yl)oxy)prop-1-yn-1-yl)benzofuran

Eluent for purification: hexane: ethyl acetate = 20:1. Colorless oil (6 mg, 23% yield).  

**¹H NMR** (500 MHz, Chloroform-$$d$$) δ 7.73 (d, $$J = 1.5$$ Hz, 1H), 7.64 (d, $$J = 2.2$$ Hz, 1H), 7.48 – 7.37 (m, 2H), 6.75 (d, $$J = 2.1$$ Hz, 1H), 4.94 (t, $$J = 3.5$$ Hz, 1H), 4.61 – 4.43 (m, 2H), 3.92 (ddd, $$J = 11.6, 9.0, 3.0$$ Hz, 1H), 3.59 (dtd, $$J = 11.0, 4.3, 1.6$$ Hz, 1H), 1.93 – 1.83 (m, 1H), 1.79 (tt, $$J = 10.2, 3.4$$ Hz, 1H), 1.72 – 1.57 (m, 4H).  

**¹³C NMR** (126 MHz, Chloroform-$$d$$) δ 154.65, 145.83, 128.28, 127.50, 125.09, 117.30, 111.47, 106.50, 96.89, 86.13, 83.70, 62.08, 54.90, 30.37, 25.45, 19.14. **HRMS** calculated for C$_{16}$$H$_{18}$$O$_3(M + Na$^+$): 279.0992, found: 279.0993.
(4)
cis-anti
cis-syn
cis-anti
(13)

![Diagram of chemical structures](image-url)
$^{1}H-H^1$ COSY and $^{1}H-H^1$ 2D-NOESY NMR spectrums of product 1
H$^1$-H$^1$ COSY and H$^1$-H$^1$ 2D-NOESY NMR spectrums of compound 18
$^1$H-$^1$H COSY and $^1$H-$^1$H 2D-NOESY NMR spectrums of compound 34
$^1$H-$^1$H COSY and $^1$H-$^1$H 2D-NOESY NMR spectrums of compound 35
III. Date S2: Stability of cyclic acetals in simulated GI fluids (Related to Table 2)

Instruments and Equipments:
Agilent 1260 HPLC with DAD and 6420 Triple Quad MS
Waters Xbridge C8 (4.6 mm× 150 mm × 3.5 μm) column
Waters CSH C18 (4.6 mm× 150 mm × 3.5 μm) column
Eppendorf ThermoMixer C
Eppendorf Multipette Xstream
Mettler Toledo Seven Excellence pH meter

Reagents and Materials:
Purified water, Milli-Q HPLC grade
Acetonitrile, Sigma-Aldrich HPLC grade
Ammonium Bicarbonate, Sigma-Aldrich
Simulated Gastric Fluid USP without enzymes (SGF, pH 1.2)
Simulated Intestinal Fluid USP without enzymes (SIF, pH 6.8)
Compounds 1, 15, 27, 35.

Experiment:
HPLC method

| Instrument | Agilent 1260 HPLC with DAD and 6420 Triple Quad MS |
|-----------|------------------------------------------------------|
| Column    | Waters Xbridge C8 (4.6 mm× 150 mm × 3.5 μm) column for Compound A, B, C, E  
Waters CSH C18 (4.6 mm× 150 mm × 3.5 μm) column for Compound D |
| Column temperature | 40 °C |
| Mobile phase | A: 10 mM NH4HCO3 in water  
B: ACN |
| Gradient program | Time (min) | A% | B%  
0.00 | 95 | 5  
15.00 | 5 | 95  
20.00 | 5 | 95  
20.10 | 95 | 5  
25.00 | 95 | 5 |
| Flow rate | 0.7 mL/min |
| Detector | UV 214nm for Compound A, B, C, D  
UV 224nm for Compound E |
| Injection volume | 10 μL |

The solution stability of four compounds were evaluated in SGF and SIF at 37 °C. Detailed information is shown in Table S1.
**Table S1** Stability testing plan, related to **Table 2**

| Conditions | Time point | Test media | Testing items          |
|------------|------------|------------|------------------------|
| 37 °C      | 1 hr       | SGF        | Final pH,              |
|            | 3 hr       | SIF        | % Purity,              |
|            |            |            | % Degradation.         |

**Testing media:**
Simulated Gastric Fluid USP without enzymes (SGF, pH 1.2)
Simulated Intestinal Fluid USP without enzymes (SIF, pH 6.8)

**Initial solution:**
Compound 35 was dissolved in ACN to make 2.5 mg/mL stock solutions. The solutions were diluted with ACN:water 1:1 to get 0.25 mg/mL initial solutions.
Compounds 15 was dissolved in ACN to make a 5 mg/mL stock solution. The solution was diluted with ACN:water 1:1 to get 0.5 mg/mL initial solution.
Compounds 1 and 27 were dissolved in ACN and methanol to make a 2.5 mg/mL stock solution. The solution was diluted with ACN:water 1:1 to get 0.25 mg/mL initial solutions.

**Sample solution:**
100 µL of each stock solutions were diluted with 900 µL of SGF and 900 µL of SIF.

**Testing procedure:**
All the sample solutions were placed in Thermomixer according to Table S1 conditions respectively. The final pH values were measured by pH meter. The purities and concentrations were determined by HPLC-MS. Significant degradation (> 5 percent) of a compound in this study could suggest potential instability.

**Table S2** Degradation studies in SIF and SGF at 37 °C (According to FDA: Waiver of In Vivo Bioavailability and Bioequivalence Studies), related to **Table 2**

| Classification | Degradation (%) after 1 h at 37 °C in SGF | Degradation (%) after 3 h at 37 °C in SIF |
|----------------|-------------------------------------------|-------------------------------------------|
| Fairly stable  | < 5%                                      | < 5%                                      |
| Unstable       | > 5%                                      | > 5%                                      |

**Results:**
The stability results of five intermediates and final pH values are listed in **Table S3 ~ S6** with stability classification remarks.

**Table S3** Stability results of compound 35 (λ = 214 nm), related to **Table 2**

| Condition | Test Media | Time (hr) | Purity (%) | Conc. (mg/mL) | Recovery (%) | Degradation (%) | Classification | Final pH |
|-----------|------------|-----------|------------|---------------|--------------|-----------------|----------------|----------|
| Initial   | ACN:water  | 0         | 95.74      | 0.25          |              |                 |                |          |
| Condition | Test Media | Time | Purity (%) | Conc. (mg/mL) | Recovery (%) | Degradation (%) | Classification | Final pH |
|-----------|------------|------|------------|---------------|--------------|----------------|----------------|---------|
| Initial   | ACN:water  | 0    | 93.70      | 0.5000        |              |                |                |         |
| 37 °C     | SGF        | 1hr  | 89.58      | 0.4585        | 91.71        | 4.3970         | Fairly stable  | 1.08    |
|           |            | 3hrs | 93.61      | 0.4848        | 96.97        | 0.0961         | Fairly stable  | 6.89    |

**Table S4** Stability results of compound 15 (λ = 214 nm), related to Table 2

| Condition | Test Media | Time | Purity (%) | Conc. (mg/mL) | Recovery (%) | Degradation (%) | Classification | Final pH |
|-----------|------------|------|------------|---------------|--------------|----------------|----------------|---------|
| Initial   | ACN:water  | 0    | 92.05      | 0.2500        |              |                |                |         |
| 37 °C     | SGF        | 1hr  | 80.65      | 0.2311        | 92.44        | 12.3846        | Unstable       | 1.09    |
|           |            | 3hrs | 91.95      | 0.2618        | 104.73       | 0.1086         | Fairly stable  | 6.88    |

**Table S5** Stability results of compound 1 (λ = 214 nm), related to Table 2

| Condition | Test Media | Time | Purity (%) | Conc. (mg/mL) | Recovery (%) | Degradation (%) | Classification | Final pH |
|-----------|------------|------|------------|---------------|--------------|----------------|----------------|---------|
| Initial   | ACN:water  | 0    | 99.78      | 0.2500        |              |                |                |         |
| 37 °C     | SGF        | 1hr  | 98.45      | 0.2598        | 103.90       | 1.3329         | Fairly stable  | 1.07    |
|           |            | 3hrs | 99.27      | 0.2663        | 106.54       | 0.5111         | Fairly stable  | 6.87    |
IV. Reference

Balmond, E. I., Benito-Alfonso, D., Coe, D. M., Alder, R. W., Mcgarrigle, E. M. and Galan, M. C. (2014). A 3,4-trans-fused cyclic protecting group facilitates α-selective catalytic synthesis of 2-deoxyglycosides. Angew. Chem. Int. Ed. 53, 8190-8194.

Duan, Z. C., Hu, X. P., Zhang, C., Wang, D. Y., Yu, S. B. and Zheng, Z. (2009). Highly enantioselective rh-catalyzed hydrogenation of beta,gamma-unsaturated phosphonates with chiral ferrocene-based monophosphoramidite ligands. J. Org. Chem. 74, 9191-9194.

Fukuzumi, S., Kotani, H., Ohkubo, K., Ogo, S., Tkachenko, N. V. and Lemmetyinen, H. (2004). Electron-transfer state of 9-mesityl-10-methylacridinium ion with a much longer lifetime and higher energy than that of the natural photosynthetic reaction center. J. Am. Chem. Soc. 126, 1600-1601.

Liu, P. N., Su, F. H., Wen, T. B., Sung, H. H. Y., Williams, I. D. and Jia, G. C. (2010). Selective and efficient cycloisomerization of alkynols catalyzed by a new ruthenium complex with a tetrade ntate nitrogen-phosphorus mixed ligand. Chem. Eur. J. 16, 7889-7897.

Yan, C. S., Peng, Y., Xu, X. B. and Wang, Y. W. (2012). Nickel-mediated inter- and intramolecular reductive cross-coupling of unactivated alkyl bromides and aryl iodides at room temperature. Chem. Eur. J. 18, 6039-6048.