RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2023, **13**, 29894

Synthesis of sulfonyl 2-aryl-5-methylenyltetrahydropyrans†

Meng-Yang Chang *[abc] and Kuan-Ting Chen[a]

Received 19th September 2023
Accepted 6th October 2023

DOI: 10.1039/d3ra06370d

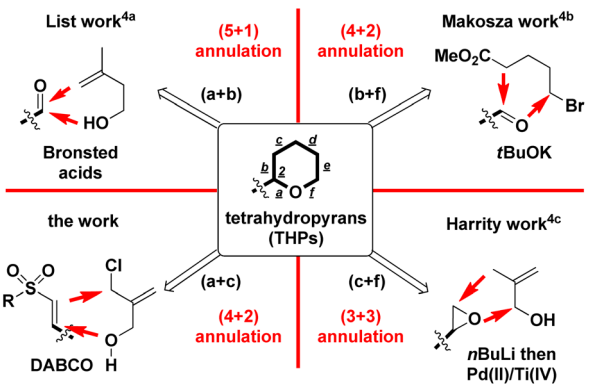
rsc.li/rsc-advances

In this study, the present research describes a high-yield method for the synthesis of sulfonyl 2-aryl-5-methylenetetrahydropyrans by one-pot straightforward DABCO-promoted intramolecular Michael addition of β-sulfonyl styrene with 2-chloromethyl-1-propenol followed by intramolecular alkylation. This Baylis–Hillman-type pathway provides a highly effective stereoselective annulation by forming one carbon–oxygen bond and one carbon–carbon bond.

Introduction

2-Substituted tetrahydropyrans (THPs) are an important class of scaffolds in a wide range of natural products, synthetic intermediates, and bioactive molecules.[1,2] Due to its potential applications, developing a new and more efficient one-pot synthetic route to the core framework of 2-functionalized THPs has attracted significant attention and general interest from organic chemists. Among the recent synthetic methods, employing Lewis acid-mediated or transition metal-promoted intramolecular Prins reaction, and Friedel–Crafts cyclization is a major route for synthesizing diversified 2-substituted THPs.[3] However, only some examples have been reported on synthesizing 2-substituted THPs by the intermolecular annulation pathway, as shown in Scheme 1. List *et al.* developed the synthesis of 2-aryl-4-methylene THPs *via* imino-imidodiphosphate Brønsted acids-catalyzed intermolecular Prins-type (5 + 1) cyclization of aldehydes with the homoallyl alcohol (for a + b bond formations).[4a] For the involvement of the 3-electron withdrawing group, Makosza and coworkers had documented the synthesis of 2-aryl-3-carboxylate THPs by employing the intermolecular (4 + 2) cyclization of *t*BuOK-mediated *in situ* formed δ-halocarbanions with aryl or alkylaldehydes (for b + f bond formations).[4b] Harrity and co-workers reported the intermolecular (3 + 3) annulation approach to construct 2-alkyl-3-methylenyl THPs *via* the addition of allylic carbanion (by *n*BuLi-mediated deprotonation) to monoalkyl epoxide and subsequent Pd(II)/Ti(IV)-promoted intramolecular cyclization (for c + f bond formations).[4c]

Therefore, further investigation of novel and efficient methods for generating 2-substituted THPs is still highly desired. Continuing our previous research on the recent synthesis of β-sulfonyl styrenes (prepared from Ac_2O-mediated reaction of arylacetaldehydes **1** with RSO_2Na),[5] we decided to prepare new 2-aryl-5-methylene THPs **5** containing a 3-sulfonyl substituent *via* the DABCO (*i.e.* 1,4-diazabicyclo [2.2.2]octane)-mediated intermolecular Michael addition of β-sulfonyl styrenes **2** with 2-chloromethyl-2-propen-1-ol (**3**). This was followed by sequential intramolecular ring-closure of the resulting **4** during Baylis–Hillman-type process (for a + c bond formations, Scheme 2)[6] Sulfone-bearing organic molecules usually exhibit unique and diverse behaviors including chemical, pharmaceutical, and material features. To the best of our knowledge, there have been no reports of DABCO-dependent routes toward the synthesis of sulfonyl 2-aryl-5-methylene THPs and the derivatives.[7]



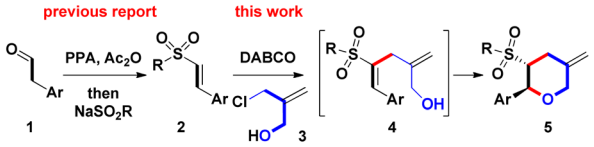
Scheme 1 Intermolecular annulation route toward substituted 2-aryltetrahydropyrans.

[a]*Department of Medicinal and Applied Chemistry, Kaohsiung Medical University, Kaohsiung 807, Taiwan. E-mail: mychang@kmu.edu.tw*

[b]*Department of Medical Research, Kaohsiung Medical University Hospital, Kaohsiung 807, Taiwan*

[c]*NPUST College of Professional Studies, National Pingtung University of Science and Technology, Pingtung 912, Taiwan*

† Electronic supplementary information (ESI) available: Scanned photocopies of NMR spectral data for all compounds and X-ray analysis data of **5m** and **5n** were supported. CCDC 2279054–2279055. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d3ra06370d

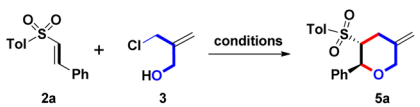


Scheme 2 Synthetic route toward 2-aryl-5-methylene THPs **5**.

Results and discussion

The initial study for examining the one-step formation of sulfonyl 2-phenyl-5-methylene THP **5a** commenced with the treatment of model β-sulfonyl styrene **2a** (Ar = Ph, R = Tol, 1 mmol), 2-chloromethyl-2-propen-1-ol (**3**, 1.0 equiv.), DABCO (20 mol%) in CCl_4 (15 mL) for 10 h at 25 °C as shown in Table 1, entry 1. Under the open-atmosphere condition, however, no observation of a reaction, and the starting **2a** was recovered as the major component. Prolonging the reaction time from 10 h to 30 and 90 h, only 25 °C yielded trace (8%) amounts of **5a** (entries 2 and 3). With the results in mind, the effect of reaction temperature was examined next. In entry 4, by controlling the reaction time as 10 h, the refluxing temperature (77 °C) produced a 78% yield of **5a**. The product yield could be increased by a refluxing condition. After adjusting the reaction time from 10 h to 20 h, and 30 h, we observed that 20 h and 30 h produced similar yields (89% and 88%) for forming **5a** (entries 5 and 6). Therefore, 77 °C and 20 h were chosen to screen the next reaction condition. Adjusting the catalytic amounts of DABCO from 20 mol% to 10 and 30 mol%, there was no observation of better yields (70% and 85%), as shown in entries 7 and 8. Furthermore, controlling catalytic amounts at 20 mol%, three organo diamines were screened (entries 9–11), including 4-DMAP, DBU, and urea. However, isolation of **5a** was still carried out at lower yields (21%, 65%, and 0%). Compared with a tertiary diamine (for DABCO), the results showed that three skeletons of pyridine (for 4-DMAP), amidine (for DBU), and lactam (for urea) were inappropriate to generate **5a**.[8] We chose DABCO to investigate the sequential reaction conditions from this phenomenon. By maintaining the combination of refluxing CCl_4 (77 °C) and 20 h, DME (dimethoxyethane), MeCN, and $(CH_2Cl)_2$ having similar boiling points (85 °C, 82 °C, and 84 °C) were selected as the solvents for screening optimal conditions. However, no better yields (48%, 15% and 53%) appeared (entries 12–14). Unexpectedly, entry 15 showed that DMF provided a complex mixture as the major component. Based on the results mentioned above, we realized that DABCO (20 mol%) base, CCl_4 solvent and reflux conditions were necessary for an optimal reaction condition (Table 1, entry 5) for the synthesis of **5a**. This expeditious synthetic route set up a *trans*-configuration between the 2-sulfonyl and 3-phenyl groups on **5a**, including the bond formations of 1 C–O bond and 1 C–C bond.

Table 1 Reaction conditions[a]



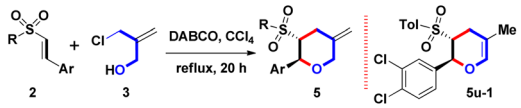
Entry	Base (mol%)	Solvent	Temp.	Time	%[b]
1	DABCO (20)	CCl_4	25	10	—[c]
2	DABCO (20)	CCl_4	25	30	—[c]
3	DABCO (20)	CCl_4	25	90	8
4	DABCO (20)	CCl_4	77	10	78
5	DABCO (20)	CCl_4	77	20	89
6	DABCO (20)	CCl_4	77	30	88
7	DABCO (10)	CCl_4	77	20	70
8	DABCO (30)	CCl_4	77	20	85
9	4-DMAP (20)	CCl_4	77	20	21
10	DBU (20)	CCl_4	77	20	65
11	Urea (20)	CCl_4	77	20	—[c]
12	DABCO (20)	DME	85	20	48
13	DABCO (20)	MeCN	82	20	15
14	DABCO (20)	$(CH_2Cl)_2$	84	20	63
15	DABCO (20)	DMF	154	20	—[d]

[a] The reactions were run on a 1 mmol scale with **2a** (257 mg), 2-chloromethyl-2-propen-1-ol (**3**, 106 mg, 1.0 equiv.), base (10–40 mol%), solvent (20 mL), temp. (25 °C, reflux), open-vessel conditions. [b] Isolated yields. [c] No reaction. [d] Unidentified and unknown mixture was isolated.

Diversified skeleton **5** was reacted under optimal reaction conditions (Table 1, entry 5) to study the substrate scope and limitations of this DABCO-mediated one-pot route, and give functionalized **5**, as shown in Table 2. For the Ar substituent on β-sulfonyl styrenes **2a–2w**, next the aromatic ring with diversified electron-neutral, electron-donating, or electron-withdrawing groups was examined, including Ph, 4-FC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$CF_3C_6H_4$, 4-$NO_2C_6H_4$, 4-PhC_6H_4, 2-naphthyl, 3,4-$(MeO)_2C_6H_3$, 3,4-$CH_2O_2C_6H_3$, 3,4-$Cl_2C_6H_3$, 3,4,5-$(MeO)_3C_6H_2$ and 2-thienyl groups (entries 1–23). However, many attempts to afford **5o** and **5p** failed due to the electron-withdrawing aryl groups (Ar = 4-$CF_3C_6H_4$ and 4-$NO_2C_6H_4$) on **2o** and **2p** could increase the electron-deficient density of the β-position such that DABCO-mediated Michael reaction pathway of **A** with **3** could be triggered to produce unidentified and unknown mixtures (entries 15 and 16). For the sulfonyl substituent (R) on β-sulfonyl styrenes **2a–2w**, the aromatic groups (R = Tol, Ph, 4-FC_6H_4, 4-$MeOC_6H_4$, 3-MeC_6H_4, 4-EtC_6H_4, 4-iPrC_6H_4, 4-*n*BuC_6H_4 and 4-*t*BuC_6H_4) and the aliphatic groups (R = Me and *n*Bu) were appropriate. The formation of **5a–5n**, **5q–5t**, and **5v–5w** obtained these yields in a range of moderate to good yields (70–90%) by the one-pot condition. Interestingly, only an 80% yield of **5u-1** with an *endo*-olefin was isolated *via* the double bond migration (entry 21). The determination of *trans*-stereochemical structures of **5m** and **5n** was done by single-crystal X-ray analysis.[9]

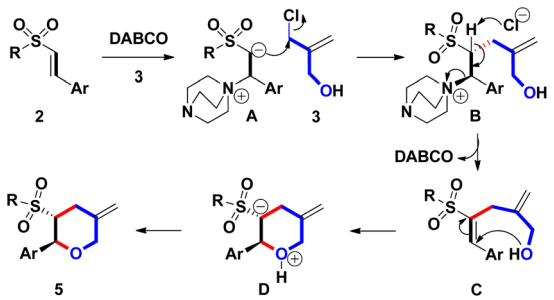
Based on the experimental results, a plausible mechanism for forming **5** was illustrated in Scheme 3. Initially, β-conjugation of **2** with DABCO provided a Baylis–Hillman adduct **A**. Subsequently, the spontaneous alkylation of the *in situ* formed α-carbanion of **A** with **3** led to the formation of **B**. After removing the α-proton of **B**, **C** was generated along with the recovery of DABCO. Under the reaction condition, intramolecular Michael annulation of **C** yielded **D**. Finally, proton exchange on **D**, the stereochemical synthesis of **5** was achieved. From the proposed mechanism, we found that catalytic amounts of DABCO seem to be workable for

Table 2 Synthesis of 5[a]



Entry	2, R═, Ar═	5, %[b]
1	**2a**, Tol, Ph	**5a**, 89
2	**2b**, Ph, Ph	**5b**, 85
3	**2c**, 4-FC_6H_4, Ph	**5c**, 80
4	**2d**, 4-$MeOC_6H_4$, Ph	**5d**, 84
5	**2e**, 3-MeC_6H_4, Ph	**5e**, 82
6	**2f**, 4-EtC_6H_4, Ph	**5f**, 83
7	**2g**, 4-$iPrC_6H_4$, Ph	**5g**, 82
8	**2h**, 4-*n*BuC_6H_4, Ph	**5h**, 84
9	**2i**, 4-*t*BuC_6H_4, Ph	**5i**, 82
10	**2j**, Me, Ph	**5j**, 80
11	**2k**, *n*Bu, Ph	**5k**, 78
12	**2l**, Tol, 4-FC_6H_4	**5l**, 70
13	**2m**, Tol, 4-MeC_6H_4	**5m**, 86
14	**2n**, Tol, 4-$MeOC_6H_4$	**5n**, 84
15	**2o**, Tol, 4-$CF_3C_6H_4$	**5o**, —[c]
16	**2p**, Tol, 4-$NO_2C_6H_4$	**5p**, —[c]
17	**2q**, Tol, 4-PhC_6H_4	**5q**, 80
18	**2r**, Tol, 2-naphthyl	**5r**, 82
19	**2s**, Tol, 3,4-$(MeO)_2C_6H_3$	**5s**, 87
20	**2t**, Tol, 3,4-$CH_2O_2C_6H_3$	**5t**, 86
21	**2u**, Tol, 3,4-$Cl_2C_6H_3$	**5u**, —[d]
22	**2v**, Tol, 3,4,5-$(MeO)_3C_6H_2$	**5v**, 90
23	**2w**, Tol, 2-thienyl	**5w**, 84

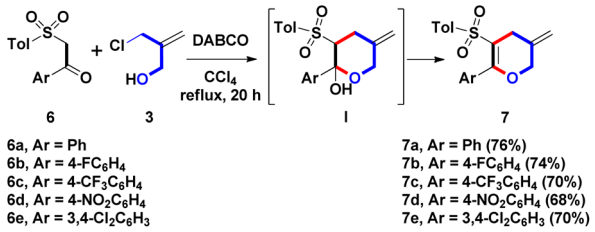
[a] The reactions were run on a 1 mmol scale with **2a–2v**, 2-chloromethyl-2-propen-1-ol (**3**, 106 mg, 1.0 equiv.), DABCO (23 mg, 20 mol%), CCl_4 (20 mL), 20 h, reflux (77 °C), open-vessel conditions. [b] Isolated yields. [c] Unidentified and unknown mixture. [d] **5u-1** (80%) was isolated.



Scheme 3 Plausible mechanism.

generating sulfonyl *trans*-THPs skeleton *via* a domino Baylis–Hillman-type process under open-vessel conditions.

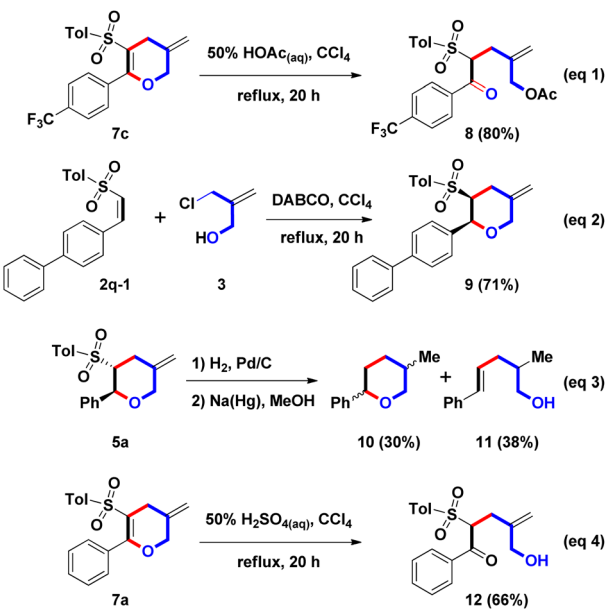
With the optimal reaction condition (DABCO/refluxing CCl_4), β-ketosulfone **6a** was selected as another starting materials to displace the previous β-sulfonyl styrene **2a** for investigating the synthesis of different sulfonyl skeletons (Scheme 4). Based on our previous work, the β-ketosulfones could be prepared easily from nucleophilic substitution of the commercial available α-bromo acetophenones with sulfonic sodium salts (RSO_2Na) in refluxing EtOH.[10] DABCO (20 mol%),



Scheme 4 Synthesis of 7a–7e.

treatment of **6a** with **3** produced sulfonyl dihydropyran (DHP) **7a** at a 76% yield *via* intermolecular α-allylation and intramolecular annulation. Compared with the conversion from β-sulfonyl styrene **2a** to sulfonyl THP **5a**, β-ketosulfone **6a** yielded sulfonyl DHP **7a** in the presence of DABCO (20 mol%). According to the optimal condition, two different starting materials possessed complementary methods in synthesizing the pyran family. Hemiacetal **I** was proposed as the possible intermediate during the one-pot formal (3 + 3) annulation process. After dehydration of **I**, a compound **7a** with a push–pull nature was generated. The DABCO-promoted route formed four DHPs **7b–7e** (Ar = 4-FC_6H_4, 4-$CF_3C_6H_4$, 4-$NO_2C_6H_4$, 3,4-$Cl_2C_6H_3$) in a range of 68–74% yields. In contrast to the unsuccessful result on the formation of **5o** and **5p**, especially, both electron-withdrawing 4-nirtophenyl and 4-trifluoromethylphenyl groups (for Ar) were well-suitable to provide **7c** and **7d** in modest yields. Conversely, the 3,4-dichlorophenyl group could yield **7e** with a terminal *exo*-olefin. However, no olefin migration behavior was observed compared with the generation **5u-1** with an *endo*-olefin.

Next, the ring-opening of DHP was examined (Scheme 5, eqn (1)). Under the boiling HOAc reaction condition, the hydrolysis of model substrate **7c** (Ar = 4-$CF_3C_6H_4$) was

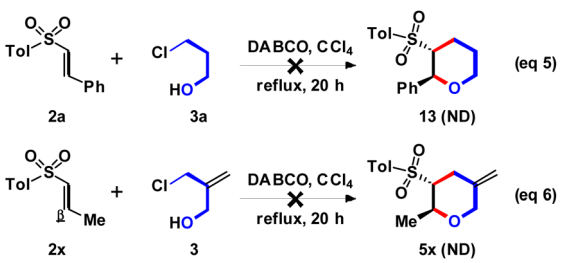


Scheme 5 Synthesis of 8–12.

preferred and allowed to proceed; then, acetylation of the resulting primary allylic alcohol afforded **8** in an 80% yield. On the other hand, DABCO-promoted annulation of (*Z*)-β-sulfonyl styrene and **3** were studied (eqn (2)). By the photo-initiated olefin isomerization of (*E*)-**2q** (Ar = 4-PhC$_6$H$_4$), model substrate (*Z*)-**2q-1** was generated.[11] Following similar reaction conditions, **9** was isolated in a 71% yield. Compared with the stereochemistry of **5q** with the *trans*-configurated structure (see ESI†), we envisioned that two adjacent stereochemical centers on **9** could be confirmed as *cis*-configuration. From the above results, we understood that olefinic isomerization of β-sulfonyl styrenes **2** could switch the stereochemistry of 3-sulfonyl-2-aryl THPs **5**.

The related Doremox surrogates were prepared (eqn (3)) to extend the synthetic application of this one-pot domino route. Cyclic ether **10** was a member of the rose oxide family, having perfumed properties.[12] After the hydrogenation and desulfonation reactions, **5a** was converted to **10** with a mixture of *cis* and *trans* isomers (ratio = 1 : 1) in a 30% yield *via* the two-step process. Unexpectedly, a primary alcohol **11** was generated in a 38% yield *via* the desulfonylative ring-opening process. Although the yield of **10** was low, a new synthetic route could be established. For the diversification of the two double bonds on **7a**, the oxidation reaction was chosen as the synthetic application. However, dihydroxylation of **7a** with the combination of OsO_4 and NMO provided complex and unknown mixture. And, *m*CPBA-mediated epoxidation of **7a** could not produce the desired epoxide product. With these results in hand, we understood that oxidation condition could not differentiate between *endo*- and *exo*-olefins. Therefore, we turned the focus to explore the hydrolysis of **7a**. By use of 50% $H_2SO_{4(aq)}$, ring-opening of **7a** (Ar = Ph) was achieved to **12** in a 66% yield. We found that the *endo*-enol olefin could convert into δ-hydroxy ketone *via* the ring-opening, and no influence for the *exo*-olefin. For the formation of two hydrated products **8** and **12**, we understood that mono-allylation of β-ketosulfone could be accomplished by the two-steps route, including DABCO-mediated stepwise (4 + 2) annulation followed by the acidic hydrolysis of the resulting sulfonyl DHP.

According to the above experimental results, the effect of π-bond role on **3** was studied next. However, the DABCO-catalyzed (4 + 2) annulation of **2a** with 3-chloro-1-propanol (**3a**) could not produce the expected **13**, and only **2a** was recovered as major component (Scheme 6, eqn (5)). The possible reason should be the reactivity of aliphatic chloride (for **3a**) was lower than allylic chloride (for **3**). On the other way, changing the β-aryl (for **2a–2w**, Ar) to β-aliphatic (for **2x**, Me) group was examined. However, the desired **5x** could not be observed, and the major starting material **2a** was recovered (eqn (6)). The results indicated that the β-aryl group could provided higher reactivity for the DABCO-catalyzed Michael addition than β-aliphatic group.



Scheme 6 Unsuccessful reactions.

Conclusion

In summary, in this study, a DABCO-promoted synthesis of *trans*-3-sulfonyl-2-aryl THPs **5** was developed. One-pot formal (4 + 2) annulation of β-sulfonyl styrenes **2** and **3** in CCl_4 solvent and reflux conditions furnished moderate to good yields. Moreover, DABCO-promoted synthesis of 3-sulfonyl-2-aryl DHPs **7** *via* one-pot formal (3 + 3) annulation of β-ketosulfones **6** and **3** was studied. Cyclic ether **10** with rose odorants could be synthesized. The related plausible mechanisms are also proposed. The one-pot open-vessel, atom-economic, convenient process provides a straightforward pathway for efficient formations of one C–O bond and one C–C bond. The structures of the key products were confirmed through X-ray crystallography. Further investigations regarding the synthetic application of β-sulfonyl styrene will be conducted and subsequently published in due course.

Experimental

General

All reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry air with magnetic stirring. Products in organic solvents were dried with anhydrous magnesium sulfate before concentration *in vacuo*. Melting points were determined with a SMP3 melting apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Varian INOVA-400 spectrometer operating at 400/600 and at 100/125 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (J) are given in Hertz. High resolution mass spectra (HRMS) were measured with a mass spectrometer Finnigan/Thermo Quest MAT 95XL. X-ray crystal structures were obtained with an Enraf-Nonius FR-590 diffractometer (CAD4, Kappa CCD).

A representative synthetic procedure of skeleton **5** is as follows: DABCO (1,4-diazabicyclo[2.2.2]octane, 23 mg, 20 mol%) was added to a solution of **2** (1.0 mmol) in CCl_4 (20 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 10 min. 2-Chloromethyl-2-propen-1-ol (**3**, 106 mg, 1.0 mmol) was added to the reaction mixture at 25 °C. The reaction mixture was stirred at reflux (77 °C) for 20 h. The reaction mixture was cooled to 25 °C and the solvent was concentrated. The residue was diluted with water (10 mL) and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexanes/EtOAc = 10/1 to 6/1) afforded **5**.

5-Methylene-2-phenyl-3-(toluene-4-sulfonyl)tetrahydropyran (5a)

Yield = 89% (292 mg); white solid; mp = 136–138 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{21}O_3S$ 329.1211, found 329.1218; ^1H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, J = 8.4 Hz, 2H), 7.16–7.08 (m, 5H), 7.01 (d, J = 8.4 Hz, 2H), 5.01 (s, 1H), 5.00 (s, 1H), 4.68 (d, J = 9.2 Hz, 1H), 4.27 (dd, J = 12.4, 1.2 Hz, 1H), 4.11 (d, J = 12.4 Hz, 1H), 3.62–3.56 (m, 1H), 3.05 (dd, J = 14.0, 3.6 Hz, 1H), 2.82 (dd, J = 13.6, 12.4 Hz, 1H), 2.33 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 143.8, 139.8, 137.5, 135.8, 129.2 (2×), 128.5 (2×), 128.3, 128.2 (2×), 128.0 (2×), 112.3, 79.9, 71.9, 65.5, 31.4, 21.5.

3-Benzenesulfonyl-5-methylene-2-phenyltetrahydropyran (5b)

Yield = 85% (267 mg); white solid; mp = 149–151 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{19}O_3S$ 315.1055, found 315.1059; ^1H NMR (600 MHz, $CDCl_3$): δ 7.41–7.36 (m, 3H), 7.23–7.20 (m, 2H), 7.15–7.12 (m, 3H), 7.09–7.07 (m, 2H), 5.03 (d, J = 0.6 Hz, 1H), 5.01 (d, J = 1.2 Hz, 1H), 4.69 (d, J = 9.0 Hz, 1H), 4.28 (dd, J = 12.6, 1.2 Hz, 1H), 4.13 (d, J = 12.6 Hz, 1H), 3.65–3.61 (m, 1H), 3.09 (ddd, J = 13.8, 4.2, 1.2 Hz, 1H), 2.84 (dt, J = 13.8, 1.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 139.7, 138.9, 137.2, 132.8, 128.8, 128.6 (2×), 128.3 (2×), 128.2 (2×), 127.9 (2×), 112.4, 80.0, 71.9, 65.4, 31.2.

3-(4-Fluorobenzenesulfonyl)-5-methylene-2-phenyltetrahydropyran (5c)

Yield = 80% (266 mg); white solid; mp = 132–134 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{18}FO_3S$ 333.0961, found 333.0952; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36–7.31 (m, 2H), 7.20–7.08 (m, 5H), 6.88–6.82 (m, 2H), 5.05 (s, 1H), 5.02 (s, 1H), 4.67 (d, J = 9.2 Hz, 1H), 4.28 (dd, J = 12.4, 0.8 Hz, 1H), 4.12 (d, J = 12.4 Hz, 1H), 3.63–3.56 (m, 1H), 3.13 (ddd, J = 13.6, 4.0, 1.2 Hz, 1H), 2.85 (dd, J = 13.6, 12.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.1 (d, J = 253.9 Hz), 139.6, 137.1, 135.0, 130.7 (d, J = 9.9 Hz, 2×), 128.9, 128.4 (2×), 128.2 (2×), 115.8 (d, J = 22.7 Hz, 2×), 112.7, 80.0, 72.0, 65.6, 31.1.

3-(4-Methoxybenzenesulfonyl)-5-methylene-2-phenyltetrahydropyran (5d)

Yield = 84% (289 mg); white solid; mp = 113–115 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{21}O_4S$ 345.1161, found 345.1155; ^1H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, J = 8.8 Hz, 2H), 7.14–7.11 (m, 5H), 6.67 (d, J = 9.2 Hz, 2H), 5.01 (s, 1H), 4.99 (d, J = 1.2 Hz, 1H), 4.68 (d, J = 9.2 Hz, 1H), 4.27 (dd, J = 12.4, 0.8 Hz, 1H), 4.12 (d, J = 12.4 Hz, 1H), 3.80 (s, 3H), 3.60–3.54 (m, 1H), 3.06 (dd, J = 14.0, 4.4 Hz, 1H), 2.81 (dd, J = 14.0, 12.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.1, 139.9, 137.5, 130.8, 130.2 (2×), 128.7, 128.4 (2×), 128.2 (2×), 113.9 (2×), 112.3, 80.0, 71.9, 65.6, 55.6, 31.4.

5-Methylene-2-phenyl-3-(toluene-3-sulfonyl)tetrahydropyran (5e)

Yield = 82% (269 mg); white solid; mp = 145–147 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{21}O_3S$ 329.1211, found 329.1216; ^1H NMR (400 MHz, $CDCl_3$): δ 7.26–7.23 (m, 1H), 7.19–7.05 (m, 8H), 5.04 (s, 1H), 5.01 (s, 1H), 4.67 (d, J = 9.2 Hz, 1H), 4.28 (d, J = 12.8 Hz, 1H), 4.13 (d, J = 12.4 Hz, 1H), 3.66–3.59 (m, 1H), 3.11 (dd, J = 13.6, 4.0 Hz, 1H), 2.84 (dd, J = 13.6, 12.8 Hz, 1H), 2.21 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 139.8, 138.7, 138.6, 137.2, 133.7, 128.7, 128.5, 128.4, 128.2 (2×), 128.1 (2×), 124.8, 112.4, 80.0, 72.0, 65.4, 31.2, 21.0.

3-(4-Ethylbenzenesulfonyl)-5-methylene-2-phenyltetrahydropyran (5f)

Yield = 83% (284 mg); white solid; mp = 106–108 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{23}O_3S$ 343.1368, found 343.1373; ^1H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, J = 8.4 Hz, 2H), 7.15–7.05 (m, 5H), 7.02 (d, J = 8.4 Hz, 2H), 5.03 (s, 1H), 5.00 (d, J = 0.8 Hz, 1H), 4.68 (d, J = 9.6 Hz, 1H), 4.27 (dd, J = 12.8, 1.2 Hz, 1H), 4.13 (d, J = 12.4 Hz, 1H), 3.64–3.57 (m, 1H), 3.09 (ddd, J = 14.0, 4.4, 1.2 Hz, 1H), 2.83 (t, J = 13.6 Hz, 1H), 2.61 (q, J = 7.6 Hz, 2H), 1.21 (t, J = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 149.8, 139.9, 137.4, 136.0, 128.7, 128.3 (2×), 128.2 (2×), 128.14 (2×), 128.09 (2×), 112.3, 80.0, 72.0, 65.4, 31.2, 28.8, 15.2.

3-(4-Isopropylbenzenesulfonyl)-5-methylene-2-phenyltetrahydropyran (5g)

Yield = 82% (292 mg); white solid; mp = 121–123 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{25}O_3S$ 357.1524, found 357.1529; ^1H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, J = 8.4 Hz, 2H), 7.13–7.01 (m, 7H), 5.04 (s, 1H), 5.01 (s, 1H), 4.67 (d, J = 9.6 Hz, 1H), 4.27 (d, J = 13.6 Hz, 1H), 4.13 (d, J = 12.8 Hz, 1H), 3.64–3.58 (m, 1H), 3.13 (dd, J = 14.4, 3.6 Hz, 1H), 2.89–2.81 (m, 2H), 1.21 (d, J = 6.8 Hz, 3H), 1.20 (d, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 154.3, 139.9, 137.2, 136.1, 128.7, 128.3 (2×), 128.2 (2×), 128.0 (2×), 126.7 (2×), 112.4, 80.1, 72.0, 65.3, 34.1, 31.1, 23.6, 23.4.

3-(4-*n*-Butylbenzenesulfonyl)-5-methylene-2-phenyltetrahydropyran (5h)

Yield = 84% (311 mg); white solid; mp = 100–102 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{27}O_3S$ 371.1681, found 371.1688; ^1H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, J = 8.4 Hz, 2H), 7.15–7.05 (m, 5H), 7.04 (d, J = 8.8 Hz, 2H), 5.03 (s, 1H), 5.00 (d, J = 1.2 Hz, 1H), 4.68 (d, J = 9.6 Hz, 1H), 4.27 (dd, J = 12.8, 1.2 Hz, 1H), 4.12 (d, J = 12.8 Hz, 1H), 3.64–3.57 (m, 1H), 3.10 (ddd, J = 14.0, 4.4, 1.2 Hz, 1H), 2.84 (dt, J = 13.6, 0.8 Hz, 1H), 2.56 (t, J = 7.6 Hz, 2H), 1.60–1.51 (m, 2H), 1.38–1.26 (m, 2H), 0.94 (t, J = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 148.5, 139.9, 137.3, 136.0, 128.6 (2×), 128.24 (2×), 128.17 (2×), 128.1, 127.9 (2×), 112.3, 80.0, 71.9, 65.4, 35.4, 33.1, 31.2, 22.2, 13.8.

3-(4-*t*-Butyl-benzenesulfonyl)-5-methylene-2-phenyltetrahydropyran (5i)

Yield = 82% (304 mg); white solid; mp = 102–104 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m/*

z: $[M + H]^+$ calcd for $C_{22}H_{27}O_3S$ 371.1681, found 371.1687; ^1H NMR (400 MHz, $CDCl_3$): δ 7.27–7.24 (m, 2H), 7.19–7.16 (m, 2H), 7.12–7.01 (m, 5H), 5.05 (s, 1H), 5.01 (d, J = 1.2 Hz, 1H), 4.67 (d, J = 9.6 Hz, 1H), 4.27 (dd, J = 12.4, 1.2 Hz, 1H), 4.13 (d, J = 12.4 Hz, 1H), 3.64–3.58 (m, 1H), 3.14 (dd, J = 14.0, 4.4 Hz, 1H), 2.85 (t, J = 13.6 Hz, 1H), 1.27 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 156.5, 139.9, 137.2, 135.7, 128.7, 128.3 (2×), 128.2 (2×), 127.7 (2×), 125.6 (2×), 112.4, 80.1, 72.0, 65.3, 35.0, 31.0, 30.9 (3×).

3-Methanesulfonyl-5-methylene-2-phenyltetrahydropyran (5j)

Yield = 80% (202 mg); colorless oil; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{13}H_{17}O_3S$ 253.0899, found 253.0904; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50–7.47 (m, 2H), 7.44–7.36 (m, 3H), 5.06 (d, J = 2.0 Hz, 1H), 5.05 (d, J = 1.6 Hz, 1H), 4.69 (d, J = 9.2 Hz, 1H), 4.33 (dd, J = 12.4, 1.2 Hz, 1H), 4.13 (d, J = 12.4 Hz, 1H), 3.33–3.26 (m, 1H), 3.09 (ddd, J = 15.2, 4.4, 1.2 Hz, 1H), 2.76 (dt, J = 12.4, 1.2 Hz, 1H), 2.00 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 139.4, 138.1, 129.5, 129.1 (2×), 128.1 (2×), 112.9, 79.8, 71.9, 66.0, 41.6, 29.7.

3-(*n*-Butane-1-sulfonyl)-5-methylene-2-phenyltetrahydropyran (5k)

Yield = 78% (229 mg); white solid; mp = 101–103 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{23}O_3S$ 295.1368, found 295.1374; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50–7.47 (m, 2H), 7.43–7.38 (m, 3H), 5.053 (d, J = 1.6 Hz, 1H), 5.047 (s, 1H), 4.67 (d, J = 9.2 Hz, 1H), 4.32 (dd, J = 12.4, 1.6 Hz, 1H), 4.13 (d, J = 12.4 Hz, 1H), 3.31–3.25 (m, 1H), 3.05 (ddd, J = 14.0, 4.4, 1.2 Hz, 1H), 2.76 (t, J = 13.6 Hz, 1H), 1.92–1.75 (m, 2H), 1.58–1.33 (m, 2H), 1.09–0.99 (m, 2H), 0.71 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 139.7, 138.3, 129.4, 128.9 (2×), 128.1 (2×), 112.7, 80.0, 72.1, 63.5, 53.0, 29.8, 23.5, 21.4, 13.2.

2-(4-Fluorophenyl)-5-methylene-3-(toluene-4-sulfonyl) tetrahydropyran (5l)

Yield = 70% (242 mg); white solid; mp = 171–173 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{20}FO_3S$ 347.1117, found 347.1124; ^1H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, J = 8.0 Hz, 2H), 7.14–7.10 (m, 2H), 7.07 (d, J = 8.0 Hz, 2H), 6.80–6.76 (m, 2H), 5.02 (s, 1H), 5.01 (s, 1H), 4.66 (d, J = 9.6 Hz, 1H), 4.27 (dd, J = 12.8, 1.2 Hz, 1H), 4.11 (d, J = 12.8 Hz, 1H), 3.56–3.50 (m, 1H), 3.03 (ddd, J = 14.0, 4.4, 1.2 Hz, 1H), 2.80 (dd, J = 13.6, 12.8 Hz, 1H), 2.36 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 162.9 (d, J = 245.6 Hz), 144.1, 139.6, 135.8, 133.4, 129.9 (d, J = 8.3 Hz, 2×), 129.3 (2×), 129.0 (2×), 115.1 (d, J = 21.3 Hz, 2×), 112.6, 79.2, 72.1, 65.7, 31.4, 21.5.

5-Methylene-3-(toluene-4-sulfonyl)-2-*p*-tolyltetrahydropyran (5m)

Yield = 86% (294 mg); white solid; mp = 169–171 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{23}O_3S$ 343.1368, found 343.1374; ^1H NMR (400 MHz, $CDCl_3$): δ 7.25 (d, J = 8.4 Hz, 2H), 7.01 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 7.6 Hz, 2H), 5.01 (s, 1H), 4.99 (d, J = 1.2 Hz, 1H), 4.62 (d, J = 9.6 Hz, 1H), 4.26 (dd, J = 12.8, 1.2 Hz, 1H), 4.10 (d, J = 12.8 Hz, 1H), 3.61–3.54 (m, 1H), 3.06 (ddd, J = 13.6, 4.4, 1.2 Hz, 1H), 2.81 (dd, J = 13.6, 12.8 Hz, 1H), 2.35 (s, 3H), 2.25 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 143.6, 139.9, 138.5, 135.9, 134.6, 129.1 (2×), 128.9 (2×), 128.1 (2×), 128.0 (2×), 112.3, 79.7, 71.9, 65.6, 31.3, 21.5, 21.1. Single-crystal X-ray diagram: crystal of compound **5m** was grown by slow diffusion of EtOAc into a solution of compound **5m** in THF to yield colorless prisms. The compound crystallizes in the orthorhombic crystal system, space group $P2_12_12_1$, a = 5.61670(10) Å, b = 15.9231(4) Å, c = 19.6051(4) Å, V = 1753.39(6) Å^3, Z = 4, d_{calcd} = 1.297 g cm^{-3}, $F(000)$ = 1728, 2θ range 2.078–27.006°, R indices (all data) R_1 = 0.0354, wR_2 = 0.0727.

2-(4-Methoxyphenyl)-5-methylene-3-(toluene-4-sulfonyl) tetrahydropyran (5n)

Yield = 84% (301 mg); white solid; mp = 168–170 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{23}O_4S$ 359.1317, found 359.1322; ^1H NMR (400 MHz, $CDCl_3$): δ 7.24 (d, J = 8.0 Hz, 2H), 7.02 (d, J = 8.4 Hz, 2H), 7.01 (d, J = 8.0 Hz, 2H), 6.58 (d, J = 8.4 Hz, 2H), 5.01 (s, 1H), 4.98 (s, 1H), 4.60 (d, J = 9.6 Hz, 1H), 4.25 (d, J = 12.8 Hz, 1H), 4.09 (d, J = 12.8 Hz, 1H), 3.72 (s, 3H), 3.59–3.53 (m, 1H), 3.06 (dd, J = 14.0, 3.6 Hz, 1H), 2.80 (t, J = 13.2 Hz, 1H), 2.32 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.8, 143.5, 139.9, 135.9, 129.4, 129.3 (2×), 129.1 (2×), 127.9 (2×), 113.5 (2×), 112.3, 79.4, 71.9, 65.6, 55.1, 31.3, 21.4. Single-crystal X-ray diagram: crystal of compound **5n** was grown by slow diffusion of EtOAc into a solution of compound **5n** in THF to yield colorless prisms. The compound crystallizes in the monoclinic crystal system, space group $P2_1/n$, a = 12.4097(3) Å, b = 9.8815(2) Å, c = 14.6434(3) Å, V = 1774.09(7) Å^3, Z = 4, d_{calcd} = 1.342 g cm^{-3}, $F(000)$ = 760.0, 2θ range 4.008–54.124°, R indices (all data) R_1 = 0.0395, wR_2 = 0.0890.

2-Biphenyl-4-yl-5-methylene-3-(toluene-4-sulfonyl) tetrahydropyran (5q)

Yield = 80% (323 mg); white solid; mp = 114–116 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{25}H_{25}O_3S$ 405.1524, found 405.1533; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49–7.42 (m, 4H), 7.38–7.34 (m, 1H), 7.30–7.25 (m, 4H), 7.19 (d, J = 8.0 Hz, 2H), 6.96 (d, J = 8.0 Hz, 2H), 5.07 (s, 1H), 5.03 (d, J = 0.8 Hz, 1H), 4.71 (d, J = 9.2 Hz, 1H), 4.30 (dd, J = 12.8, 1.2 Hz, 1H), 4.16 (d, J = 12.4 Hz, 1H), 3.69–3.62 (m, 1H), 3.16 (dd, J = 14.0, 4.0 Hz, 1H), 2.87 (t, J = 13.2 Hz, 1H), 2.21 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 143.6, 141.6, 140.5, 139.8, 136.1, 136.0, 129.1 (2×), 128.7 (2×), 128.6 (2×), 127.9 (2×), 127.4, 127.0 (2×), 126.9 (2×), 112.5, 79.8, 72.0, 65.5, 31.1, 21.4.

5-Methylene-2-naphthalen-2-yl-3-(toluene-4-sulfonyl) tetrahydropyran (5r)

Yield = 82% (310 mg); white solid; mp = 99–101 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{23}H_{23}O_3S$ 379.1368, found 379.1377; ^1H NMR (400 MHz, $CDCl_3$): δ 7.71–7.64 (m, 2H), 7.57 (s, 1H), 7.49 (d, J =

8.4 Hz, 1H), 7.46–7.42 (m, 2H), 7.16 (dd, J = 8.4, 1.6 Hz, 1H), 7.10 (d, J = 8.4 Hz, 2H), 6.58 (d, J = 8.4 Hz, 2H), 5.09 (s, 1H), 5.05 (d, J = 1.2 Hz, 1H), 4.81 (d, J = 9.6 Hz, 1H), 4.32 (dd, J = 12.8, 1.2 Hz, 1H), 4.19 (d, J = 12.8 Hz, 1H), 3.74–3.67 (m, 1H), 3.21 (dd, J = 14.0, 4.0 Hz, 1H), 2.90 (t, J = 13.2 Hz, 1H), 2.00 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 143.6, 139.9, 135.6, 134.3, 133.5, 132.9, 128.7 (2×), 128.2, 128.1, 128.0, 127.6 (2×), 127.3, 126.3, 126.0, 125.1, 112.5, 80.2, 72.1, 65.5, 30.9, 21.1.

2-(3,4-Dimethoxyphenyl)-5-methylene-3-(toluene-4-sulfonyl) tetrahydropyran (5s)

Yield = 87% (338 mg); white solid; mp = 120–122 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{25}O_5S$ 389.1423, found 389.1431; ^1H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, J = 8.0 Hz, 2H), 6.99 (d, J = 8.0 Hz, 2H), 6.72 (dd, J = 8.4, 2.0 Hz, 1H), 6.57 (d, J = 8.0 Hz, 1H), 6.45 (d, J = 2.0 Hz, 1H), 5.04 (s, 1H), 5.00 (s, 1H), 4.58 (d, J = 9.6 Hz, 1H), 4.26 (dd, J = 12.8, 1.2 Hz, 1H), 4.11 (d, J = 12.4 Hz, 1H), 3.80 (s, 3H), 3.66 (s, 3H), 3.59–3.52 (m, 1H), 3.14 (ddd, J = 14.0, 4.4, 1.2 Hz, 1H), 2.82 (t, J = 13.2 Hz, 1H), 2.32 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 149.3, 148.6, 143.7, 139.9, 136.1, 129.5, 128.9 (2×), 127.8 (2×), 121.2, 112.4, 110.5, 110.3, 80.0, 72.0, 65.6, 55.8, 55.4, 31.1, 21.4.

5-[5-Methylene-3-(toluene-4-sulfonyl)tetrahydropyran-2-yl] benzo[1,3]dioxole (5t)

Yield = 86% (320 mg); white solid; mp = 191–193 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{21}O_5S$ 373.1110, found 373.1115; ^1H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, J = 8.4 Hz, 2H), 7.07 (d, J = 8.4 Hz, 2H), 6.72 (dd, J = 8.0, 1.6 Hz, 1H), 6.57 (d, J = 8.0 Hz, 1H), 6.42 (d, J = 1.6 Hz, 1H), 5.85 (d, J = 1.2 Hz, 1H), 5.80 (d, J = 1.2 Hz, 1H), 5.02 (s, 1H), 5.00 (d, J = 1.2 Hz, 1H), 4.56 (d, J = 9.6 Hz, 1H), 4.25 (dd, J = 12.8, 1.6 Hz, 1H), 4.10 (d, J = 12.4 Hz, 1H), 3.54–3.47 (m, 1H), 3.09 (ddd, J = 14.0, 4.4, 1.2 Hz, 1H), 2.80 (t, J = 13.6 Hz, 1H), 2.36 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 147.8, 147.4, 143.7, 139.8, 136.0, 131.1, 129.1 (2×), 128.0 (2×), 122.6, 112.5, 107.9, 107.8, 101.0, 79.8, 72.0, 65.6, 21.1, 21.5.

2-(3,4-Dichlorophenyl)-5-methyl-3-(toluene-4-sulfonyl)-3,4-dihydro-2*H*-pyran (5u-1)

Yield = 80% (317 mg); colorless oil; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{19}Cl_2O_3S$ 397.0432, found 397.0441; ^1H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, J = 8.0 Hz, 2H), 7.42 (dd, J = 2.0, 0.4 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H), 7.28 (dd, J = 8.4, 0.8 Hz, 1H), 7.23 (d, J = 8.4 Hz, 2H), 6.25 (q, J = 1.2 Hz, 1H), 5.40 (d, J = 3.6 Hz, 1H), 3.83–3.78 (m, 1H), 2.63–2.57 (m, 1H), 2.42 (s, 3H), 2.28 (dd, J = 17.6, 6.4 Hz, 1H), 1.60 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 144.9, 138.1, 137.5, 136.0, 132.3, 132.2, 130.0, 129.5 (2×), 128.9, 128.5 (2×), 126.4, 106.6, 72.3, 61.9, 24.9, 21.6, 17.8.

5-Methylene-3-(toluene-4-sulfonyl)-2-(3,4,5-trimethoxyphenyl) tetrahydropyran (5v)

Yield = 90% (376 mg); white solid; mp = 141–143 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{27}O_6S$ 419.1528, found 419.1533; ^1H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.0 Hz, 2H), 6.25 (s, 2H), 5.05 (s, 1H), 5.00 (s, 1H), 4.54 (d, J = 9.6 Hz, 1H), 4.25 (dd, J = 12.8, 0.4 Hz, 1H), 4.10 (d, J = 12.8 Hz, 1H), 3.72 (s, 3H), 3.67 (s, 6H), 3.60–3.53 (m, 1H), 3.18 (dd, J = 14.0, 3.6 Hz, 1H), 2.82 (t, J = 13.6 Hz, 1H), 2.29 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 152.8 (2×), 143.8, 139.6, 138.0, 136.1, 132.2, 128.8 (2×), 127.7 (2×), 112.5, 105.1 (2×), 80.4, 72.0, 65.2, 60.5, 55.7 (2×), 30.7, 21.3.

5-Methylene-2-thiophen-2-yl-3-(toluene-4-sulfonyl) tetrahydropyran (5w)

Yield = 84% (281 mg); white solid; mp = 137–139 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{19}O_3S_2$ 335.0776, found 335.0782; ^1H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, J = 8.0 Hz, 2H), 7.12–7.10 (m, 3H), 6.97 (dd, J = 3.6, 1.2 Hz, 1H), 6.78 (dd, J = 5.2, 3.6 Hz, 1H), 5.07 (d, J = 8.8 Hz, 1H), 4.99 (s, 1H), 4.97 (s, 1H), 4.27 (d, J = 12.8 Hz, 1H), 4.10 (d, J = 12.8 Hz, 1H), 3.58–3.52 (m, 1H), 3.02 (dd, J = 14.0, 4.8 Hz, 1H), 2.81 (dt, J = 13.6, 2.0 Hz, 1H), 2.36 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 144.0, 140.5, 139.1, 135.7, 129.3 (2×), 128.2 (2×), 127.5, 126.6, 126.2, 112.5, 74.3, 71.3, 66.5, 31.1, 21.5.

A representative synthetic procedure of skeleton 7 is as follows: DABCO (1,4-diazabicyclo[2.2.2]octane, 23 mg, 20 mol%) was added to a solution of **6** (1.0 mmol) in CCl_4 (20 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 10 min. 2-Chloromethyl-2-propen-1-ol (**3**, 106 mg, 1.0 mmol) was added to the reaction mixture at 25 °C. The reaction mixture was stirred at reflux (77 °C) for 20 h. The reaction mixture was cooled to 25 °C and the solvent was concentrated. The residue was diluted with water (10 mL) and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexanes/EtOAc = 15/1 to 8/1) afforded 7.

3-Methylene-6-phenyl-5-(toluene-4-sulfonyl)-3,4-dihydro-2*H*-pyran (7a)

Yield = 76% (248 mg); white solid; mp = 158–159 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{19}O_3S$ 327.1055, found 327.1063; ^1H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, J = 8.4 Hz, 2H), 7.42–7.36 (m, 1H), 7.33–7.26 (m, 4H), 7.15 (d, J = 8.0 Hz, 2H), 5.22 (d, J = 1.2 Hz, 1H), 5.14 (d, J = 0.8 Hz, 1H), 4.49 (s, 2H), 3.30 (s, 2H), 2.37 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 162.2, 143.2, 138.8, 135.9, 133.7, 129.6, 129.4 (2×), 129.1 (2×), 127.4 (2×), 127.3 (2×), 113.7, 113.5, 71.1, 30.2, 21.4.

6-(4-Fluorophenyl)-3-methylene-5-(toluene-4-sulfonyl)-3,4-dihydro-2*H*-pyran (7b)

Yield = 74% (255 mg); white solid; mp = 162–164 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{18}FO_3S$ 345.0961, found 345.0970; ^1H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, J = 8.4 Hz, 2H), 7.30–7.25 (m, 2H), 7.17 (d, J = 8.0 Hz, 2H), 7.01–6.96 (m, 2H), 5.20 (d, J = 0.8 Hz,

1H), 5.13 (d, J = 0.8 Hz, 1H), 4.47 (s, 2H), 3.26 (br t, J = 1.6 Hz, 2H), 2.36 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.4 (d, J = 247.9 Hz), 161.1, 143.4, 138.6, 135.6, 131.5 (d, J = 8.4 Hz, 2×), 129.7 (d, J = 3.0 Hz), 129.2 (2×), 127.2 (2×), 114.4 (d, J = 22.0 Hz, 2×), 113.79, 113.77, 71.1, 30.2, 21.3.

3-Methylene-5-(toluene-4-sulfonyl)-6-(4-trifluoromethylphenyl)-3,4-dihydro-2*H*-pyran (7c)

Yield = 70% (276 mg); white solid; mp = 153–155 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{18}F_3O_3S$ 395.0929, found 395.0932; ^1H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 5.24 (d, J = 0.8 Hz, 1H), 5.18 (d, J = 0.8 Hz, 1H), 4.51 (s, 2H), 3.29 (s, 2H), 2.39 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 160.4, 143.8, 138.4, 137.4 (d, J = 1.5 Hz), 135.4, 131.5 (q, J = 32.6 Hz), 129.9 (2×), 129.4 (2×), 127.4 (2×), 124.5 (q, J = 3.8 Hz, 2×), 123.8 (q, J = 271.3 Hz), 114.6, 114.2, 71.4, 30.1, 21.5.

3-Methylene-6-(4-nitrophenyl)-5-(toluene-4-sulfonyl)-3,4-dihydro-2*H*-pyran (7d)

Yield = 68% (252 mg); white solid; mp = 138–140 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{18}NO_5S$ 372.0906, found 372.0902; ^1H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.8 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 5.24 (s, 1H), 5.18 (s, 1H), 4.51 (s, 2H), 3.23 (s, 2H), 2.41 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.4, 148.4, 144.1, 140.3, 138.1, 134.9, 130.5 (2×), 129.6 (2×), 127.4 (2×), 122.7 (2×), 114.7, 114.5, 71.4, 30.1, 21.5.

6-(3,4-Dichlorophenyl)-3-methylene-5-(toluene-4-sulfonyl)-3,4-dihydro-2*H*-pyran (7e)

Yield = 70% (276 mg); white solid; mp = 174–176 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{17}Cl_2O_3S$ 395.0276, found 395.0281; ^1H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.0 Hz, 1H), 7.24 (d, J = 2.0 Hz, 1H), 7.1–7.18 (m, 3H), 5.21 (s, 1H), 5.14 (s, 1H), 4.47 (s, 2H), 3.26 (s, 2H), 2.38 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.3, 143.8, 138.2, 135.2, 133.8, 133.5, 131.7, 131.0, 129.5, 129.3 (2×), 129.0, 127.2 (2×), 114.7, 114.2, 71.2, 30.0, 21.4.

Acetic acid 2-[3-oxo-2-(toluene-4-sulfonyl)-3-(4-trifluoromethylphenyl)propyl]allyl ester (8)

50% HOAc (10 mL) was added to a solution of **7c** (394 mg, 1.0 mmol) in CCl_4 (20 mL) at 25 °C. The reaction mixture was stirred at reflux (77 °C) for 20 h. The reaction mixture was cooled to 25 °C and the solvent was concentrated. The residue was diluted with water (10 mL) and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexanes/EtOAc = 10/1 to 6/1) afforded **8**. Yield = 80% (363 mg); colorless oil; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{22}F_3O_5S$ 455.1140, found 455.1148; ^1H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, J = 8.0 Hz, 2H), 7.71 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 5.36 (dd, J = 10.4, 3.6 Hz, 1H), 5.00 (s, 1H), 4.85 (s, 1H), 4.46 (d, J = 13.2 Hz, 1H), 4.40 (d, J = 13.2 Hz, 1H), 2.92–2.81 (s, 2H), 2.1 (s, 3H), 1.96 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 190.9, 170.4, 145.8, 139.6, 138.4, 134.9 (q, J = 32.6 Hz), 133.0, 129.68 (2×), 129.64 (2×), 129.3 (2×), 126.0 (q, J = 265.3 Hz), 125.7 (q, J = 3.8 Hz, 2×), 117.2, 68.5, 66.2, 31.3, 21.5, 20.6.

2-Biphenyl-4-yl-5-methylene-3-(toluene-4-sulfonyl) tetrahydropyran (9)

DABCO (1,4-diazabicyclo[2.2.2]octane, 23 mg, 20 mol%) was added to a solution of **2q-1** (334 mg, 1.0 mmol) in CCl_4 (20 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 10 min. 2-Chloromethyl-2-propen-1-ol (**3**, 106 mg, 1.0 mmol) was added to the reaction mixture at 25 °C. The reaction mixture was stirred at reflux (77 °C) for 20 h. The reaction mixture was cooled to 25 °C and the solvent was concentrated. The residue was diluted with water (10 mL) and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexanes/EtOAc = 10/1 to 6/1) afforded **9**. Yield = 73% (295 mg); White solid; mp = 167–169 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{25}O_3S$ 405.1524, found 405.1530; ^1H NMR (400 MHz, $CDCl_3$): δ 7.55–7.52 (m, 2H), 7.46–7.43 (m, 2H), 7.37–7.27 (m, 7H), 6.99 (d, J = 8.0 Hz, 2H), 5.07 (s, 2H), 5.06 (d, J = 2.8 Hz, 1H), 4.56 (d, J = 12.8 Hz, 1H), 4.23 (d, J = 12.8 Hz, 1H), 3.84–3.81 (m, 1H), 3.49 (dd, J = 14.8, 2.0 Hz, 1H), 2.85 (dd, J = 14.8, 2.0 Hz, 1H), 2.25 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 143.4, 140.7, 140.2, 137.7, 137.6, 136.3, 129.1 (2×), 128.7 (2×), 128.2 (2×), 127.3, 126.9 (2×), 126.6 (2×), 126.5 (2×), 113.0, 77.3, 72.3, 64.8, 31.9, 21.4.

5-Methyl-2-phenyltetrahydro-pyran (10) and 2-methyl-5-phenylpent-4-en-1-ol (11)

Pd/C (10%, 30 mg) was added to a solution of **5a** (164 mg, 0.5 mmol) in EtOAc (20 mL) at 25 °C. Hydrogen gas was installed to the reaction mixture at 25 °C. The reaction mixture was stirred at 25 °C for 20 h, filtered, and the solvent was concentrated. Without further purification, fleshly prepared sodium amalgam (6–8% Na/Hg, 300 mg) was added to a solution of the resulting crude product in MeOH (20 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 10 h, and the solvent was concentrated. The residue was diluted with water (10 mL) and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexanes/EtOAc = 15/1 to 8/1) afforded **10** and **11**. For compound **10**, ratio, *cis*/*trans* = 1 : 1; yield = 30% (26 mg); colorless liquid; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for

$C_{12}H_{17}O$ 177.1280, found 177.1286; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.13 (m, 5H), 4.32–4.22 (m, 1H), 4.05–3.98 (m, 1H), 3.32–3.20 (m, 1H), 2.05–1.31 (m, 5H), 1.08 (d, J = 6.8 Hz, 3/2H), 0.93 (d, J = 6.8 Hz, 3/2H). Compound **10** was known and their related analytical data (*e.g.*, HRMS and ^{1}H NMR) were identical with those in the reference **11b**. For compound **11**, yield = 38% (33 mg); colorless liquid; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{12}H_{17}O$ 177.1280, found 177.1288; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.28 (m, 4H), 7.23–7.18 (m, 1H), 6.42 (d, J = 15.6 Hz, 1H), 6.23 (dt, J = 15.6, 7.2 Hz, 1H), 3.57 (dd, J = 10.4, 6.0 Hz, 1H), 3.51 (dd, J = 10.4, 6.0 Hz, 1H), 2.38–2.31 (m, 1H), 2.15–2.07 (m, 1H), 1.87–1.79 (m, 1H), 1.47 (br s, 1H), 0.98 (d, J = 6.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 137.6, 131.4, 128.7, 128.5 (2×), 127.0, 126.0 (2×), 67.9, 36.9, 36.1, 14.5.

4-(Hydroxymethyl)-1-phenyl-2-tosylpent-4-en-1-one (12)

50% H_2SO_4 (10 mL) was added to a solution of **7a** (326 mg, 1.0 mmol) in CCl_4 (20 mL) at 25 °C. The reaction mixture was stirred at reflux (77 °C) for 20 h. The reaction mixture was cooled to 25 °C and the solvent was concentrated. The residue was diluted with water (10 mL) and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexanes/EtOAc = 8/1 to 2/1) afforded **12**. Yield = 66% (227 mg); colorless oil; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{21}O_4S$ 345.1161, found 345.1167; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97–7.94 (m, 2H), 7.63 (d, J = 8.4 Hz, 2H), 7.61–7.57 (m, 1H), 7.48–7.44 (m, 2H), 7.29 (d, J = 8.0 Hz, 2H), 5.46 (dd, J = 10.4, 4.0 Hz, 1H), 5.97 (s, 1H), 4.78 (d, J = 0.8 Hz, 1H), 4.02 (d, J = 13.6 Hz, 1H), 3.98 (d, J = 13.6 Hz, 1H), 2.93–2.83 (s, 2H), 2.43 (s, 3H), 1.66 (br s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 192.1, 145.5, 143.2, 137.1, 133.9, 133.2, 129.8 (2×), 129.6 (2×), 129.1 (2×), 128.7 (2×), 114.3, 68.6, 66.2, 31.5, 21.7.

Author contributions

Meng-Yang Chang: writing – review & editing, supervision. Kuan-Ting Chen: writing – original draft, conceptualization, methodology.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors would like to thank the Ministry of Science and Technology of the Republic of China (Taiwan) for its financial support (NSTC 112-2113-M-037-016-MY3).

Notes and references

1 Review articles on synthesis of THPs, see: (*a*) N. M. Nasir, K. Ermanis and P. A. Clarke, *Org. Biomol. Chem.*, 2014, **12**, 3323–3335; (*b*) A. B. III Smith, R. J. Fox and T. M. Razler, *Acc. Chem. Res.*, 2008, **41**, 675–687; (*c*) I. M. Pastor and M. Yus, *Curr. Org. Chem.*, 2007, **11**, 925–957.

2 Examples on synthesis of the biological active THPs, see: (*a*) S. Umamatheswari, B. Balaji, M. Ramanathan and S. Kabilan, *Eur. J. Med. Chem.*, 2011, **46**, 1415–1424; (*b*) P. Parthiban, G. Aridoss, P. Rathika, V. Ramkumar and S. Kabilan, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 2981–2985; (*c*) H. I. El-Subbagh, S. M. Abu-Zaid, M. A. Mahran, F. A. Badria and A. M. Alofaid, *J. Med. Chem.*, 2000, **43**, 2915–2921.

3 (*a*) A. P. Jadhav, J.-A. Oh, I.-S. Hwang, H. Yan and C. E. Song, *Org. Lett.*, 2018, **20**, 5319–5322; (*b*) H. Murayama, K. Nagao, H. Ohmiya and M. Sawamura, *Org. Lett.*, 2015, **17**, 2039–2041; (*c*) S. E. Ammann, G. T. Rice and M. C. White, *J. Am. Chem. Soc.*, 2014, **136**, 10834–10837; (*d*) H. Kim and C. Lee, *Org. Lett.*, 2011, **13**, 2050–2053; (*e*) A. Aponick and B. Biannic, *Org. Lett.*, 2011, **13**, 1330–1333; (*f*) A. Guérinot, A. Serra-Muns, C. Gnamm, C. Bensoussan, S. Reymond and J. Cossy, *Org. Lett.*, 2010, **12**, 1808–1811.

4 (*a*) L. Liu, P. S. J. Kaib, A. Tap and B. List, *J. Am. Chem. Soc.*, 2016, **138**, 10822–10825; (*b*) M. Barbasiewicz, A. Brud and M. Mąkosza, *Synthesis*, 2007, 1209–1213; (*c*) J. C. R. Brioche, K. M. Goodenough, D. J. Whatrup and J. P. A. Harrity, *Org. Lett.*, 2007, **9**, 3941–3943.

5 M.-Y. Chang, Y.-S. Wu and Y.-T. Hsiao, *Synthesis*, 2018, **50**, 4651–4658.

6 Examples on synthesis of methylene THPs, see: (*a*) C.-Y. Ho and L. He, *J. Org. Chem.*, 2014, **79**, 11873–11884; (*b*) K. Okuma, O. Sakai, T. Hayamo, K. Shioji and H. Matsuyama, *Bull. Chem. Soc. Jpn.*, 2005, **78**, 2209–2213; (*c*) J. van der Louw, G. J. J. Out, J. L. van der Baan, F. J. J. de Kanter, F. Bickelhaupt and G. W. Klumpp, *Tetrahedron Lett.*, 1989, **30**, 4863–4866; (*d*) J. van der Louw, J. L. van der Baan, G. J. J. Out, F. J. J. de Kanter, F. Bickelhaupt and G. W. Klumpp, *Tetrahedron*, 1992, **48**, 9901–9916; (*e*) Y. Huang and X. Lu, *Tetrahedron Lett.*, 1987, **28**, 6219–6220.

7 Review articles on Baylis–Hillman reactions, see: (*a*) D. Basavaiah and R. T. Naganaboina, *New J. Chem.*, 2018, **42**, 14036–14066; (*b*) Y. Wei and M. Shi, *Chem. Rev.*, 2013, **113**, 6659–6690; (*c*) D. Basavaiah and G. Veeraraghavaiah, *Chem. Soc. Rev.*, 2012, **41**, 68–78; (*d*) D. Basavaiah, A. J. Rao and T. Satyanarayana, *Chem. Rev.*, 2003, **103**, 811–892.

8 (*a*) J. Ammera, M. Baidyaa, S. Kobayashia and H. Mayr, *J. Phys. Org. Chem.*, 2010, **23**, 1029–1035; (*b*) M. Baidya and H. Mayr, *Chem. Commun.*, 2008, 1792–1794.

9 CCDC 2279054 (**5m**) and 2279055 (**5n**) contain the supplementary crystallographic data for this paper.†

10 (*a*) N.-C. Hsueh, M.-C. Tsai, M.-Y. Chang and H.-Y. Chen, *J. Org. Chem.*, 2019, **84**, 15915–15925; (*b*) M.-Y. Chang and Y.-S. Wu, *J. Org. Chem.*, 2019, **84**, 3638–3646; (*c*) N.-C. Hsueh, H.-Y. Chen and M.-Y. Chang, *J. Org. Chem.*, 2017, **82**, 13324–13332; (*d*) M.-Y. Chang, H.-Y. Chen and Y.-L. Tsai, *J. Org. Chem.*, 2019, **84**, 326–337.

11 Recent example on photoinduced olefin isomerization, see: Q. Zhou, X. Hong, H.-Z. Cui, Y. Sun, B. Zhan, A. Reheman and X.-F. Hou, *Tetrahedron Lett.*, 2020, 152396.

12 Synthesis of rose oxide, see:(*a*) H. Watkins, O. C. Liu and J. A. Krivda, *US Pat.*, US 5219836, 1993; (*b*) L. Coulombel, M. Weïwer and E. Duñach, *Eur. J. Org Chem.*, 2009, 5788–5795; (*c*) V. H. Rawal, S. P. Singh, C. Dufour and C. Michoud, *J. Org. Chem.*, 1991, **56**, 5245–5247; (*d*) V. H. Rawal, S. P. Singh, C. Dufour and C. Michoud, *J. Org. Chem.*, 1993, **58**, 7718–7727.