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Highly efficient and generalized asymmetric synthesis of quaternary stereogenic carbon-containing β-amino indanones/indanoles *via* Mannich-type additions between 1-indanones and *N-tert*-butanesulfinylketimines†

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Here we report that, unlike other ketones, 1-indanone and acetophenone derived enolates undergo Mannich-type addition reactions with *N-tert*-butanesulfinyl ketimines with excellent yields (up to 98%) and diastereoselectivity (>99/1). The resulting compounds represent a new type of biologically relevant β-aminoketone derivative bearing quaternary stereogenic carbon, which could be further converted into the corresponding β-amino ketones and β-amino alcohols, possessing three consecutive stereogenic centres.

Introduction

β-Amino carbonyl compounds are key intermediates in the production of numerous nitrogen-containing natural products and pharmaceuticals, in particular amino alcohols, amino acids, peptides and lactams.[1] Among numerous approaches for preparation of β-amino ketones,[2,3] the Mannich reaction has been proven to be the most generalized and reliable method.[4] In its classic version, the Mannich reaction involves a carbon–carbon bond formation *via* addition of an enolizable ketone to an *in situ* formed Schiff base. Since most of the Mannich reaction products contain a stereogenic carbon, the issue of stereocontrol in these reactions has received considerable attention.[3]

Nevertheless, in spite of the significant methodological developments in this area, preparation of β-amino carbonyl compounds possessing quaternary stereogenic centres still presents a formidable synthetic challenge.[4] From a conceptual standpoint, the Mannich-type reactions between enolizable ketones and (*S*)- or (*R*)-*N-tert*-butanesulfinyl ketimines would present an ideal approach for asymmetric synthesis of quaternary β-amino carbonyl compounds. However, quite surprisingly, this type of Mannich-type reaction has virtually not been studied.[5] Thus, there is only a handful of data on the additions of only ester enolates and not a single report dealing with the reactions of butanesulfinyl ketimines with ketone derived enolates.[5,6] Furthermore, there is only one example of the corresponding product possessing a quaternary stereogenic carbon next to another α-stereogenic carbon.[6e] One of the reasons that this chemistry of promising synthetic potential remains practically unexplored is the notably lower reactivity of *N-tert*-butanesulfinyl ketimines, as compared with the corresponding aldimines.[5,6] Additionally, *N-tert*-butanesulfinyl ketimines are configurationally unstable and undergo easy enaminolization; their reactivity and structural factors plague their synthetic applications.

Following our interest in the chemistry of *N-tert*-butanesulfinyl imines[7] and synthesis of biologically relevant β-trifluoromethyl-β-amino indanone derivatives,[8] we found that unlike other ketones, 1-indanone and acetophenone derived enolates undergo clean Mannich-type addition reactions with *N-tert*-butanesulfinyl ketimines with an excellent stereochemical outcome (up to 98% yields and 100/1 diastereoselectivity). The resulting products represent a new type of biologically relevant β-amino indanone derivative[9–11] containing amino group-

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†Electronic supplementary information (ESI) available: Experimental procedures, full spectroscopic data for compounds **3**, **4** and **5** and copies of ^{1}H NMR and ^{13}C NMR spectra. CCDC 951440. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ob00489b

bearing quaternary stereogenic carbon. The scope and limitations of these reactions, the mechanistic rationale for the observed stereochemical outcome and synthetic elaboration of the addition products into the corresponding free β-amino ketones and β-amino alcohols are also reported.

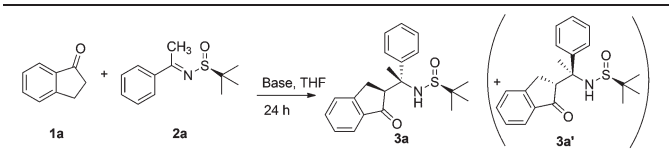
Results and discussion

Taking advantage of our previous experience in asymmetric Mannich-type additions of *N-tert*-butanesulfinyl imines with *C*-nucleophiles,[7,8,12] the preliminary scan of the reaction conditions was focused on the following factors: the stoichiometry of starting compounds, the nature of the base, the solvent and the reaction temperature. We found that the use of equimolar amounts of ketimine **2a** and 1-indanone **1a** is essential for the reaction outcome (Table 1). Quite successful result was obtained in the addition reaction conducted in THF in the presence of LDA at −78 °C. The reaction proceeded cleanly, affording the desired β-amino ketone **3a** in 88% yield and with 92 : 8 diastereoselectivity (entry 1, Table 1). It should be noted that with generation of two new stereogenic centres there could possibly be up to four stereoisomeric products. Detailed examination of the crude reaction mixtures by H-NMR allowed clear detection of only two diastereomers. Application of LiHMDS as the base (entry 2) led to a higher diastereoselectivity but also resulted in a lower yield. The use of stronger bases gave rather interesting results. Thus in the series of LiHMDS (entry 1), NaHMDS (entry 3) and KHMDS (entry 4) we observed a notably worsening outcome, possibly indicating the paramount importance of the coordinating/chelating properties of Li cations for the successful outcome of the reactions under study. Switching back to Li-derived strong bases, we also tried *n*-BuLi, which gave a rather disappointing yield and diastereoselectivity (entry 5). Furthermore, the stoichiometry between 1-indanone **1a** and the base (LiHMDS) was examined showing that the use of 1.5 equiv. of **1a** and 1.7 equiv. of LiHMDS allows for optimized yields without any effect on the diastereoselectivity (entry 6, Table 1).

Another important reaction factor was found to be the temperature. Elevating reaction temperature brought an increase in the yield (up to 90%), but caused a dramatic decrease in the diastereoselectivity (entries 7, 8). These results suggested an experiment in which ketimine **2a** was pre-cooled to −78 °C before being added to the reaction mixture. As shown in entry 9 this modification to the reaction procedure gave a much improved stereochemical outcome confirming the key role of the reaction temperature in the chemical yield and diastereoselectivity.

With the optimized reaction conditions in hand, our next goal was to explore the scope of these asymmetric Mannich-type reactions. First, we studied a series of substituted ketimines **2b–l** (Table 2). In general, all ketimines **2b–l** easily reacted with 1-indanone **1a** under standard conditions allowing preparation of the target products in good yields. In terms of diastereoselectivity, the results obtained were rather unexpected. Thus in the series of *para*-substituted derivatives **2b–h** (entries 2–8) we clearly observed some effect of the substituent steric bulk on the diastereoselectivity. For example, the highest level of selectivity (99 : 1) was observed in the series of *p*-halogen substituted derivatives **2d–f** (entries 4–6). By contrast, in the reactions of ketimines bearing bulkier substituents, such as **2b** (*p*-Me, entry 2), **2c** (*p*-MeO, entry 3), **2g** (*p*-NO_2, entry 7) and **2h** (*p*-CF_3, entry 8) the observed diastereoselectivity was in the range of 100 : 3 to 95 : 5. It should be emphasized that the electronic effect of the substituents was unnoticeable in terms of diastereoselectivity. For example, keti-

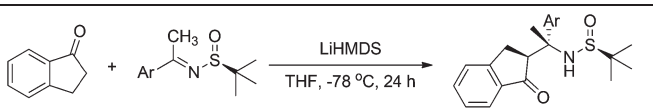
Table 1 Optimization of reaction conditions[a]



Entry	Base	Ratio (**1a**/**2a**/base)	Temp (°C)	Yield[a] (%)	dr[b]
1	LDA	1.0 : 1.0 : 1.0	−78	88	92 : 8
2	LiHMDS	1.0 : 1.0 : 1.0	−78	85	93 : 7
3	NaHMDS	1.0 : 1.0 : 1.0	−78	12	89 : 11
4	KHMDS	1.0 : 1.0 : 1.0	−78	<5	n.d.[c]
5	*n*-BuLi	1.0 : 1.0 : 1.0	−78	54	87 : 13
6	LiHMDS	1.5 : 1.0 : 1.7	−78	90	93 : 7
7	LDA	1.0 : 1.0 : 1.0	−40	93	85 : 15
8	LiHMDS	1.0 : 1.0 : 1.0	−40	91	88 : 12
9	LiHMDS	1.5 : 1.0 : 1.7	−78	92	98 : 2[d]

[a] Isolated yields. [b] The ratio determined by ^{1}H NMR on crude reaction mixtures. [c] Not determined. [d] Ketimine **2a** was pre-cooled to −78 °C, and then transferred *via* a cannula to the reaction mixture.

Table 2 Scope of *N-tert*-butanesulfinylketimines in the asymmetric additions[a]



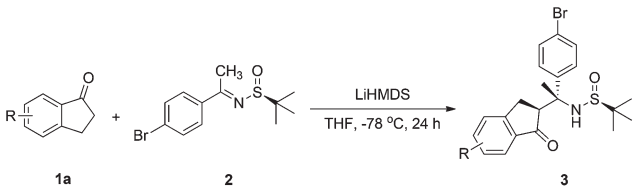
Entry	Ar	Product	Yield[b] (%)	dr[c]
1	C_6H_5	**3a**	92	98 : 2
2	4-MeC_6H_4	**3b**	89	97 : 3
3	4-MeOC_6H_4	**3c**	83	95 : 5
4	4-FC_6H_4	**3d**	94	99 : 1
5	4-ClC_6H_4	**3e**	93	99 : 1
6	4-BrC_6H_4	**3f**	94	99 : 1
7	4-$NO_2C_6H_4$	**3g**	98	97 : 3
8	4-$CF_3C_6H_4$	**3h**	95	96 : 4
9	3-ClC_6H_4	**3i**	81	91 : 9
10	3-BrC_6H_4	**3j**	76	90 : 10
11	2-Furyl	**3k**	83	93 : 7
12	2-Thienyl	**3l**	82	93 : 7

[a] Reaction conditions: 1-indanone **1a** (1.5 mmol), ketimine **2** (1.0 mmol), LiHMDS (1.7 mmol), THF (5 mL). [b] Isolated yields. [c] The isomer ratio determined by ^{1}H NMR integration of crude reaction mixtures.

mines **2c** (*p*-MeO, entry 3) and **2h** (*p*-CF_3, entry 8) showed virtually the same level of stereoselectivity. On the other hand, the electronic effect had a notable impact on the chemical yield. Thus, the lowest yield of 83% (entry 3) was obtained with ketimine **2c** (*p*-MeO) while the highest (98%, entry 7) was observed in the reaction of ketimine **2g** (*p*-NO_2). The position of the substituent on the aromatic ring of the acetophenone moiety in ketimines **2a–l** had an even more pronounced effect. As one can see from the entries 9 and 10, in the reactions of *m*-substituted imines **2i** (*m*-Cl) and **2j** (*m*-Br) the lowest diastereoselectivity of about 91 : 9 was observed. As discussed above, the same Cl- and Br-substituents but located in the *p*-position in the imines **2e** and **2f** gave the highest selectivity (99 : 1) (entry 5 *vs.* 9 and 6 *vs.* 10) in this study. Finally, we also conducted the addition reactions of ketimines **2k** (entry 11) and **2l** (entry 12) bearing 2-furyl and 2-thienyl rings, respectively. The results were rather satisfactory allowing preparation of adducts **2k,l** in reasonably good yields and diastereoselectivity. As one may agree, the data shown in Table 2 clearly suggest a rather high degree of the scope of this asymmetric Mannich-type reaction for preparation of β-amino indanones bearing various substituents in the α-position to the amino group.

Considering the unexpected and complex effect of the substituents in ketimines **2** on the stereochemical outcome of the reactions under study, it was quite logical to have some preliminary data on whether a similar effect can be observed using derivatives of starting 1-indanone **1**. As one can see from Table 3, in all cases studied (entries 2–7) an excellent level of diastereoselectivity (99 : 1) was observed and the target products were isolated with the yields exceeding 90%. The only exception was the addition of 6-Me substituted indanone (entry 1) resulting in a slightly lower yield and stereoselectivity. While the range and position of the substituents studied is somehow limited, these preliminary results suggest that the effect of substitution on the indanone component might not be as dramatic as it is on the ketimine part.

Table 3 Scope of 1-indanones in the asymmetric Mannich-type additions[a]



Entry	R	Product	Yield[b] (%)	dr[c]
1	6-Me	**3m**	86	97 : 3
2	6-F	**3n**	96	99 : 1
3	6-Cl	**3o**	91	99 : 1
4	6-Br	**3p**	94	99 : 1
5	5-F	**3q**	95	99 : 1
6	5-Cl	**3r**	90	99 : 1
7	5-Br	**3s**	93	99 : 1

[a] Reaction conditions: 1-indanone **1a** (1.5 mmol), ketimine **2** (1.0 mmol), LiHMDS (1.7 mmol), THF (5 mL). [b] Isolated yields. [c] The isomer ratio determined by ^{1}H NMR integration of crude reaction mixtures.

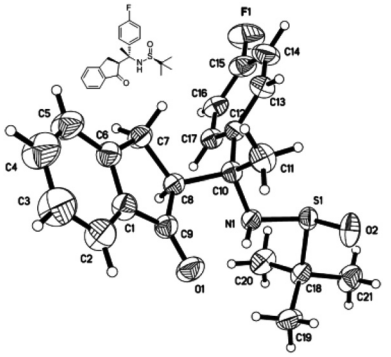


Fig. 1 OPTER diagram of compound **3d**.

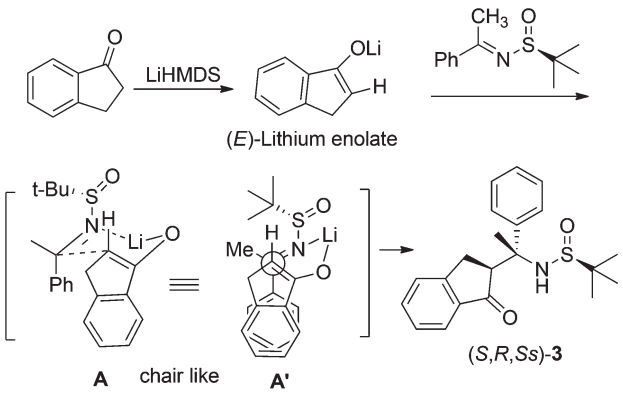
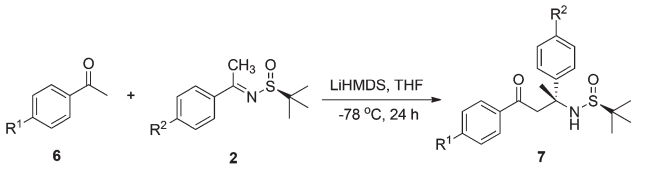


Fig. 2 Proposed mechanism for the Mannich addition.

To assign the absolute configuration of the two newly created stereogenic centres, we performed crystallographic analysis of compound **3d** (Fig. 1). As revealed by the X-ray study, the product **3d** has the (S,R,S_S) configuration. The absolute configurations of other products **3** were assigned as (S,R,S_S) by analogy, based on the similarity of their spectroscopic and chiroptical properties.

To account for the observed reactivity, the effect of the substituents and the absolute configuration of products **3**, we can propose transition state (TS) **A** as shown in Fig. 2. The following features were taken into consideration for construction of a plausible TS in the reactions under study: first, TS **A** is cyclic, chair-like,[13] and Li chelated, accounting for the poor reactivity in the case of Na- and K-cations; Second, the ketimines **2** react in the (*E*)-geometric configuration, as it is known that imines of this type exist as single stereoisomers.[14] Finally, as it is better seen from the Newman projection **A′**, the aromatic rings of both indanone **1** and ketimines **2** are over each other rendering TS **A** quite sensitive to the steric bulk and position of the substituents, in particular, on the ketimine phenyl. On the other hand, according to TS **A**, the substitution on the indanone aromatic ring, especially in the positions 5 and 6, might have much lesser effect on its stability. Another mechanistic

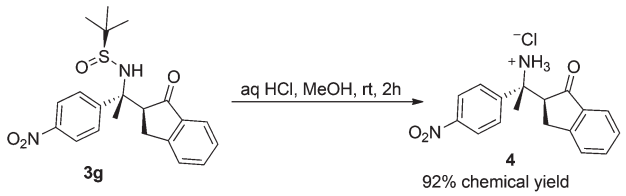
Table 4 Scope of acetophenone derivatives in the asymmetric Mannich-type additions[a]



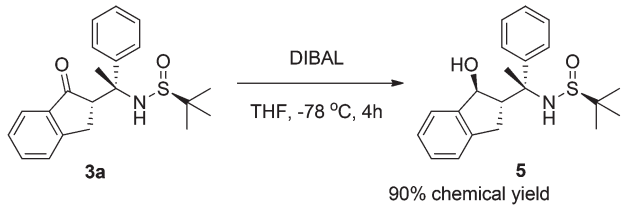
6 2 7

Entry	R^1	R^2	Product	Yield[b] (%)	dr[c]
1	H	H	**7a**	52	99 : 1
2	H	NO_2	**7b**	65	99 : 1
3	Br	Br	**7c**	73	99 : 1

[a] Reaction conditions: acetophenone derivatives **6** (1.5 mmol), ketimine **2** (1.0 mmol), LiHMDS (1.7 mmol), THF (5 mL). [b] Isolated yields. [c] The isomer ratio determined by ^{1}H NMR integration of crude reaction mixtures.



Scheme 1 Deprotection of **3g**.



Scheme 2 Reduction of **3a**.

conclusion one can draw based on these results is that the configurational homogeneity is of paramount importance to reduce the number of possible TSs[15] and obtain high stereochemical outcome. As in the present example, both reaction partners, indanones **1** and ketimines **2**, can react only in the corresponding (*E*)-configurations, which can account for generally high level of the observed diastereoselectivity.

In order to have some additional verification of the proposed mechanistic rationale, we decided to conduct experiments on the addition reactions between ketimines **2** and aceto- and propiophenones. As one may expect,[16] acetophenone can form only one homogeneous enolate, and therefore its reactions with imine **2a** should be highly diastereoselective. Quite agreeably, the addition of an acetophenone-derived enolate with **2a** afforded the product **7a** (Table 4) with excellent diastereoselectivity, although in a moderate chemical yield (entry 1). Encouraged by this result, we conducted additional experiments to briefly assess the generality of acetophenone-type substrates in these reactions. As an example of substituted imine reactions we studied the addition reaction of *p*-NO_2-imine **2** with acetophenone which gave the product **7b** in 65% yield and excellent (99 : 1) diastereoselectivity (entry 2). Finally, as an example of a substituted acetophenone reaction, the addition of *p*-Br-acetophenone with imine **2a** was conducted. The expected product **7c** was isolated in a good yield and, once again, with virtually complete stereoselectivity (entry 3). In sharp contrast, the reaction of propiophenone, which is expected to produce a mixture of (*E*)- and (*Z*)-enolates, virtually did not proceed (~5% yield of the mixture of products) under the standard conditions. This outcome clearly highlighted the anticipated sterically congested nature of the proposed TS **A** (Fig. 2) as well as the importance of enolate homogeneity.

As the final objective of this work, we believed that it might be important to demonstrate a preparation of free amino products as well as elaboration of compounds **3** to some more synthetically complex derivatives. To this end we conducted the deprotection of compound **3g** with gaseous HCl in methanol at room temperature (Scheme 1). Stirring the mixture for two hours gave rise to the corresponding hydrochloride **4**, which was isolated in 92% yield.

For the second objective, we demonstrate that DIBAL can be successfully used for highly stereoselective reduction of β-amino ketone **3a** to the corresponding β-amino alcohol **5**, isolated as a single product in 90% yield (Scheme 2). One may agree that the whole process including the described here Mannich-type addition reactions followed by DIBAL assisted reduction provides quite a simple and synthetically sound approach for preparation of enantiomerically pure β-amino alcohols possessing three consecutive stereogenic centres.

Conclusions

In summary, we have developed the first highly efficient asymmetric Mannich-type addition reactions between *N-tert*-butanesulfinylketimines and indanone enolates. Preliminary results also indicate that this type of asymmetric addition can be extended to acetophenone derivatives, rendering the reported results of greater synthetic potential. The compounds available by these reactions represent a new family of biologically relevant β-amino indanone derivatives bearing quaternary stereogenic carbon. The synthetic generality of this approach is demonstrated by using different substituents on aromatic rings of both 1-indanones and *N-tert*-butanesulfinylketimines. In all cases studied, practically useful levels of diastereoselectivity and chemical yields are obtained. It is suggested that the geometric homogeneity [(*E*)-configuration] of both ketimines and indanone enolates is a key feature providing for the excellent stereochemical outcome in these reactions. We also showed that the addition products could be further highly selectively converted into the corresponding free β-amino ketones and β-amino alcohols, possessing three consecutive stereogenic centres.

General information

All reagents were obtained from commercial suppliers and used without further purification. The reactions were conducted in a closed system in an atmosphere of N_2 and were monitored by TLC. Solvents were dried and distilled prior to use. Flash chromatography was performed using silica gel 60 (200–300 mesh). Thin layer chromatography was carried out on silica gel 60 F-254 TLC plates of 20 cm × 20 cm. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker AVANCE400M spectrometer. Melting points are uncorrected. Values of optical rotation were measured on a Rudolph Automatic Polarimeter A21101. Infrared spectra were obtained on a Bruker Vector 22 in KBr pellets. HRMS were conducted on an Agilent 6540Q-TOF LC/MS equipped with an electrospray ionization (ESI) probe operating in positive or negative ion mode.

Typical procedure for asymmetric addition of sulfinylimine

Into an oven-dried reaction vial flushed with N_2 was taken 1-indanone **1** (1.5 mmol) and anhydrous THF (5.0 mL). The reaction vial was cooled to −78 °C and LiHMDS (2 M in THF, 0.85 mL) was added dropwise with stirring. After 40 min at −78 °C, sulfinyl-imine **2** (1.0 mmol) dissolved in anhydrous THF (2 mL) was pre-cooled to −78 °C, and then added dropwise to the reaction mixture. Stirring was continued at −78 °C for 24 h, and then the reaction was quenched with saturated NH_4Cl (3.0 mL), followed by H_2O (5.0 mL) and the mixture was brought to room temperature. The organic layer was taken and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with water (1 × 30 mL) and brine solution (1 × 30 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated, and the crude mixture was charged onto silica gel and purified by flash chromatography to furnish the corresponding product **3**.

3a: White solid (327 mg, 92%). mp 199–200 °C. $[\alpha]_D^{25}$ = 89.0 (c = 0.58, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 7.7 Hz, 1H), 7.58 (td, J = 7.5, 1.1 Hz, 1H), 7.54–7.49 (m, 2H), 7.43–7.30 (m, 5H), 6.19 (s, 1H), 3.24 (dd, J = 8.2, 4.4 Hz, 1H), 2.76 (dd, J = 18.1, 8.2 Hz, 1H), 2.54 (dd, J = 18.0, 4.4 Hz, 1H), 1.68 (s, 3H), 1.28 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 208.3, 153.8, 142.9, 137.1, 135.5, 128.4, 127.7, 127.7, 127.4, 126.4, 124.0, 62.7, 57.1, 56.2, 30.0, 22.9, 21.6. IR (cm^{-1}): 3259, 2954, 2923, 2853, 1697, 1605, 1461, 1451, 1367, 1203, 1058, 780, 754, 706, 614. HRMS (ESI): $[M + Na]^+$ calcd for: $C_{21}H_{25}NO_2SNa$ 378.1504, Found: 378.1503.

3a′: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, J = 7.7 Hz, 1H), 7.54 (td, J = 7.5, 1.0 Hz, 1H), 7.37–7.31 (m, 2H), 7.22–7.12 (m, 5H), 6.37 (s, 1H), 3.52 (dd, J = 8.2, 5.0 Hz, 1H), 3.36 (dd, J = 17.2, 8.2 Hz, 1H), 3.02 (dd, J = 17.2, 5.0 Hz, 1H), 1.99 (s, 3H), 1.30 (s, 9H).

3b: White solid (329 mg, 89%). mp 136–137 °C. $[\alpha]_D^{25}$ = 68.3 (c = 0.76, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 7.7 Hz, 1H), 7.57 (td, J = 7.6, 1.0 Hz, 1H), 7.42–7.31 (m, 4H), 7.19 (d, J = 8.0 Hz, 2H), 6.14 (s, 1H), 3.22 (dd, J = 8.2, 4.4 Hz, 1H), 2.77 (dd, J = 18.0, 8.2 Hz, 1H), 2.53 (dd, J = 18.0, 4.4 Hz, 1H), 2.38 (s, 3H), 1.65 (s, 3H), 1.27 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 208.4, 153.9, 140.0, 137.4, 137.2, 135.4, 129.1, 127.7, 127.3, 126.4, 124.0, 62.5, 57.2, 56.2, 30.1, 22.9, 21.7, 21.1. IR (cm^{-1}): 3262, 2977, 2947, 2921, 2852, 1687, 1607, 1466, 1378, 1293, 1204, 1067, 1060, 851, 819, 754. HRMS (ESI): $[M + H^+]$ calcd for: $C_{22}H_{28}NO_2S$ 370.1841, Found: 370.1848.

3c: White solid (320 mg, 83%). mp 159–160 °C. $[\alpha]_D^{25}$ = 58.5 (c = 0.38, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 7.7 Hz, 1H), 7.58 (td, J = 7.6, 1.0 Hz, 1H), 7.45–7.32 (m, 4H), 6.94–6.88 (m, 2H), 6.14 (s, 1H), 3.84 (s, 3H), 3.22 (dd, J = 8.2, 4.4 Hz, 1H), 2.79 (dd, J = 18.0, 8.2 Hz, 1H), 2.53 (dd, J = 18.0, 4.4 Hz, 1H), 1.64 (s, 3H), 1.27 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 208.4, 159.0, 153.9, 137.2, 135.4, 135.0, 128.6, 127.7, 126.4, 124.0, 113.6, 62.4, 57.3, 56.1, 55.2, 30.1, 22.9, 21.7. IR (cm^{-1}): 3265, 2978, 2958, 2925, 2853, 1689, 1608, 1518, 1464, 1379, 1256, 1189, 1056, 1029, 844, 756, 740. HRMS (ESI): $[M + Na]^+$ calcd for: $C_{22}H_{27}NNaO_3S$ 408.1609, Found: 408.1610.

3d: White solid (351 mg, 94%). mp 112–113 °C. $[\alpha]_D^{25}$ = 98.6 (c = 1.05, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 7.7 Hz, 1H), 7.59 (td, J = 7.5, 1.1 Hz, 1H), 7.52–7.45 (m, 2H), 7.42–7.33 (m, 2H), 7.12–7.04 (m, 2H), 6.19 (s, 1H), 3.20 (dd, J = 8.2, 4.5 Hz, 1H), 2.78 (dd, J = 18.0, 8.2 Hz, 1H), 2.52 (dd, J = 18.0, 4.4 Hz, 1H), 1.66 (s, 3H), 1.27 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 208.0, 162.2 (d, J_{FC} = 247.3 Hz), 153.7, 138.8 (d, $^5J_{FC}$ = 3.2 Hz), 137.1, 135.5, 129.2 (d, $^4J_{FC}$ = 8.1 Hz), 127.8, 126.4, 124.1, 115.2 (d, $^3J_{FC}$ = 21.3 Hz), 62.4, 57.1, 56.3, 29.9, 22.9, 21.8. ^{19}F NMR (376 MHz, $CDCl_3$): δ −114.51. IR (cm^{-1}): 3665, 3256, 2981, 2961, 2925, 1686, 1606, 1512, 1467, 1379, 1286.9, 1226, 1206, 1169, 1066, 1060, 856, 754. HRMS (ESI): $[M + Na]^+$ calcd for: $C_{21}H_{24}FNO_2SNa$ 396.1409, Found: 396.1409.

3e: White solid (362 mg, 93%). mp 175–176 °C. $[\alpha]_D^{25}$ = 60.0 (c = 1.01, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 7.7 Hz, 1H), 7.59 (t, J = 7.4 Hz, 1H), 7.49–7.33 (m, 6H), 6.19 (s, 1H), 3.18 (dd, J = 8.1, 4.4 Hz, 1H), 2.78 (dd, J = 18.0, 8.2 Hz, 1H), 2.52 (dd, J = 18.0, 4.3 Hz, 1H), 1.66 (s, 3H), 1.27 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 207.9, 153.6, 141.7, 137.1, 135.6, 133.7, 128.9, 128.6, 127.9, 126.4, 124.1, 62.4, 56.9, 56.3, 29.9, 22.9, 21.6. IR (cm^{-1}): 3257, 2978, 2924, 1685, 1606, 1465, 1293, 1207, 1093, 1068, 1061, 1012, 854, 753, 618. HRMS (ESI): $[M + Na]^+$ calcd for: $C_{21}H_{24}ClNO_2SNa$ 412.1114, Found: 412.1114.

3f: White solid (407 mg, 94%). mp 178–179 °C. $[\alpha]_D^{25}$ = 42.3 (c = 1.01, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 7.7 Hz, 1H), 7.59 (td, J = 7.6, 1.0 Hz, 1H), 7.55–7.50 (m, 2H), 7.42–7.33 (m, 4H), 6.19 (s, 1H), 3.17 (dd, J = 8.2, 4.4 Hz, 1H), 2.78 (dd, J = 18.0, 8.2 Hz, 1H), 2.51 (dd, J = 18.0, 4.4 Hz, 1H), 1.65 (s, 3H), 1.27 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 207.9, 153.6, 142.2, 137.1, 135.6, 131.6, 129.2, 127.9, 126.4, 124.1, 121.9, 62.5, 56.9, 56.3, 29.9, 22.9, 21.5. IR (cm^{-1}): 3258, 2959, 2923, 1686, 1605, 1465, 1400, 1293, 1207, 1077, 1067, 1060, 1007, 851, 755, 615. HRMS (ESI): $[M + Na]^+$ calcd for: $C_{21}H_{24}BrNO_2SNa$ 456.0609, Found: 456.0607.

3g: Pale yellow solid (392 mg, 98%). mp 97–98 °C. $[\alpha]_D^{25}$ = 27.1 (c = 1.02, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, J = 8.9 Hz, 2H), 7.79 (d, J = 7.7 Hz, 1H), 7.72 (d, J = 8.9 Hz, 2H),

7.62 (td, J = 7.6, 0.9 Hz, 1H), 7.45–7.35 (m, 2H), 6.33 (s, 1H), 3.22 (dd, J = 8.2, 4.5 Hz, 1H), 2.77 (dd, J = 17.8, 8.3 Hz, 1H), 2.52 (dd, J = 17.8, 4.5 Hz, 1H), 1.74 (s, 3H), 1.29 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 207.3, 153.3, 150.4, 147.4, 136.8, 135.8, 128.5, 128.1, 126.5, 124.2, 123.6, 62.7, 56.7, 56.5, 29.7, 22.8, 21.6. IR (cm^{-1}): 3244, 2954, 2922, 1698, 1605, 1517, 1470, 1346, 1066, 874, 856, 758, 703. HRMS (ESI): $[M + Na]^+$ calcd for: $C_{21}H_{24}N_2O_4SNa$ 423.1354, Found: 423.1356.

3h: White solid (402 mg, 95%). mp 134–135 °C. $[\alpha]_D^{25}$ = 75.1 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 7.7 Hz, 1H), 7.70–7.57 (m, 5H), 7.44–7.33 (m, 2H), 6.26 (s, 1H), 3.21 (dd, J = 8.1, 4.5 Hz, 1H), 2.76 (dd, J = 17.9, 8.2 Hz, 1H), 2.51 (dd, J = 17.9, 4.4 Hz, 1H), 1.71 (s, 3H), 1.28 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 207.7, 153.5, 147.1, 137.0, 135.7, 130.0 (q, $^3J_{FC}$ = 32.6 Hz), 128.0, 127.9, 126.4, 125.4 (q, $^4J_{FC}$ = 3.8 Hz), 124.2, 124.0 (q, J_{FC} = 273.1 Hz), 62.7, 56.8, 56.5, 29.8, 22.9, 21.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.54. IR (cm^{-1}): 3257, 2978, 2925, 1686, 1608, 1467, 1414, 1380, 1325, 1289, 1208, 1167, 1124, 1074, 1069, 1058, 1015, 861, 840, 759, 750, 620. HRMS (ESI): $[M + Na]^+$ calcd for: $C_{22}H_{24}F_3NO_2SNa$ 446.1378, Found: 446.1378.

3i: White solid (315 mg, 81%). mp 146–147 °C. $[\alpha]_D^{25}$ = 24.8 (c = 0.36, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 7.7 Hz, 1H), 7.63–7.57 (m, 1H), 7.51 (s, 1H), 7.43–7.28 (m, 5H), 6.24 (s, 1H), 3.18 (dd, J = 8.1, 4.4 Hz, 1H), 2.80 (dd, J = 18.0, 8.2 Hz, 1H), 2.54 (dd, J = 18.0, 4.4 Hz, 1H), 1.66 (s, 3H), 1.29 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 207.9, 153.7, 145.3, 137.0, 135.6, 134.5, 129.7, 128.0, 127.9, 127.9, 126.5, 125.6, 124.1, 62.6, 56.8, 56.4, 29.8, 22.9, 21.5. IR (cm^{-1}): 3248, 2956, 2917, 2850, 1695.3, 1606, 1473, 1419, 1379, 1290, 1206, 1060, 789. HRMS (ESI): $[M + Na]^+$ calcd for: $C_{21}H_{24}ClNO_2SNa$ 412.1114, Found: 412.1114.

3j: White solid (329 mg, 76%). mp 119–120 °C. $[\alpha]_D^{25}$ = 89.5 (c = 1,01, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 7.7 Hz, 1H), 7.67 (t, J = 1.8 Hz, 1H), 7.60 (td, J = 7.6, 1.0 Hz, 1H), 7.49–7.34 (m, 4H), 7.27 (t, J = 7.9 Hz, 1H), 6.22 (s, 1H), 3.17 (dd, J = 8.2, 4.5 Hz, 1H), 2.80 (dd, J = 18.0, 8.2 Hz, 1H), 2.55 (dd, J = 18.0, 4.4 Hz, 1H), 1.65 (s, 3H), 1.28 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 207.8, 153.6, 145.6, 137.0, 135.6, 130.9, 130.9, 129.9, 127.9, 126.5, 126.0, 124.1, 122.7, 62.6, 56.9, 56.4, 29.9, 22.9, 21.5. IR (cm^{-1}): 3273, 2973, 2958, 2924, 1694, 1567, 1474, 1463, 1368, 1291, 1204, 1064, 1024, 856. HRMS (ESI): $[M + H]^+$ calcd for: $C_{21}H_{25}BrNO_2S$ 434.0789, Found: 434.0790.

3k: Yellow solid (286 mg, 83%). mp 147–148 °C. $[\alpha]_D^{25}$ = 51.5 (c = 1.03, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 7.7 Hz, 1H), 7.63–7.57 (m, 1H), 7.45–7.35 (m, 3H), 5.81 (s, 1H), 3.46 (dd, J = 8.3, 4.4 Hz, 1H), 3.02 (dd, J = 17.9, 8.3 Hz, 1H), 2.63 (dd, J = 17.9, 4.4 Hz, 1H), 1.59 (s, 3H), 1.24 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 207.8, 155.0, 153.6, 142.6, 137.1, 135.5, 127.7, 126.4, 123.9, 110.1, 109.4, 59.7, 55.8, 54.3, 29.6, 22.7, 21.2. IR (cm^{-1}): 3258, 2923, 1696, 1605, 1463, 1387, 1367, 1293, 1204, 1059, 1012, 865. HRMS (ESI): $[M + Na]^+$ calcd for: $C_{19}H_{23}NO_3SNa$ 368.1296, Found: 368.1297.

3l: Pale yellow solid (296 mg, 82%). mp 193–194 °C. $[\alpha]_D^{25}$ = 78.8 (c = 0.95, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 7.8 Hz, 1H), 7.59 (t, J = 7.4 Hz, 1H), 7.42–7.33 (m, 3H), 7.08–7.04 (m, 1H), 6.97 (dd, J = 4.8, 3.9 Hz, 1H), 6.24 (s, 1H), 3.21 (dd, J = 8.2, 4.4 Hz, 1H), 2.98 (dd, J = 18.0, 8.3 Hz, 1H), 2.68 (dd, J = 18.0, 4.4 Hz, 1H), 1.71 (s, 3H), 1.29 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 207.2, 153.7, 149.0, 137.0, 135.6, 127.8, 126.5, 126.5, 126.2, 126.1, 124.1, 61.8, 58.5, 56.4, 30.1, 23.0, 22.8. IR (cm^{-1}): 3241, 2923, 1686, 1607, 1465, 1385, 1291, 1240, 1188, 1062, 971. HRMS (ESI): $[M + Na]^+$ calcd for: $C_{19}H_{23}NO_2S_2Na$ 384.1068, Found: 384.1066.

3m: White solid (384 mg, 86%). mp 145–146 °C. $[\alpha]_D^{25}$ = 29.6 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57–7.48 (m, 3H), 7.43–7.35 (m, 3H), 7.28–7.20 (m, 1H), 6.21 (s, 1H), 3.16 (dd, J = 7.8, 4.1 Hz, 1H), 2.72 (dd, J = 17.8, 8.1 Hz, 1H), 2.50–2.35 (m, 4H), 1.63 (s, 3H), 1.27 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 207.9, 151.1, 142.3, 137.9, 137.2, 136.9, 131.5, 129.3, 126.1, 123.9, 121.9, 62.5, 57.2, 56.3, 29.5, 22.9, 21.5, 21.1. IR (cm^{-1}): 3255, 2977, 1686, 1493, 1399, 1284, 1163, 1068, 850. HRMS (ESI): $[M + H]^+$ calcd for: $C_{22}H_{27}BrNO_2S$ 448.0946, Found: 448.0950.

3n: White solid (433 mg, 96%). mp 158–159 °C. $[\alpha]_D^{25}$ = 43.2 (c = 0.66, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, J = 8.5 Hz, 2H), 7.42–7.35 (m, 3H), 7.34–7.29 (m, 2H), 6.05 (s, 1H), 3.23 (dd, J = 8.0, 4.3 Hz, 1H), 2.75 (dd, J = 17.8, 8.1 Hz, 1H), 2.48 (dd, J = 17.7, 3.7 Hz, 1H), 1.65 (s, 3H), 1.27 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 207.0 (d, $^5J_{FC}$ = 2.9 Hz), 162.4 (d, J_{FC} = 249.2 Hz), 149.1 (d, $^5J_{FC}$ = 2.0 Hz), 141.9, 138.6 (d, $^4J_{FC}$ = 7.3 Hz), 131.6, 129.2, 127.9 (d, $^4J_{FC}$ = 8.0 Hz), 123.4 (d, $^3J_{FC}$ = 23.8 Hz), 122.0, 109.8 (d, $^3J_{FC}$ = 21.8 Hz), 62.5, 57.8, 56.4, 29.4, 22.8, 21.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ −113.26. IR (cm^{-1}): 3262, 2978, 2961, 1690, 1488, 1442, 1400, 1266, 1076, 852. HRMS (ESI): $[M + Na]^+$ calcd for: $C_{21}H_{23}BrFNO_2SNa$ 474.0515, Found: 474.0514.

3o: White solid (425 mg, 91%). mp 137–138 °C. $[\alpha]_D^{25}$ = 23.5 (c = 0.68, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (s, 1H), 7.57–7.49 (m, 3H), 7.37 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.1 Hz, 1H), 6.03 (s, 1H), 3.22 (dd, J = 7.9, 4.2 Hz, 1H), 2.75 (dd, J = 18.0, 8.1 Hz, 1H), 2.48 (dd, J = 18.1, 4.0 Hz, 1H), 1.64 (s, 3H), 1.27 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 206.5, 151.6, 141.9, 138.5, 135.6, 134.3, 131.6, 129.2, 127.7, 123.8, 122.1, 62.5, 57.5, 56.4, 29.6, 22.9, 21.6. IR (cm^{-1}): 3262, 2978, 2961, 2926, 1692, 1468.3, 1399, 1240, 1196, 1078, 1060, 1007, 850, 837, 719. HRMS (ESI): $[M + Na]^+$ calcd for: $C_{21}H_{23}BrClNO_2SNa$ 490.0219, Found: 490.0222.

3p: White solid (482 mg, 94%). mp 170–171 °C. $[\alpha]_D^{25}$ = 9.8 (c = 0.69, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, J = 1.4 Hz, 1H), 7.69 (dd, J = 8.1, 1.7 Hz, 1H), 7.52 (d, J = 8.6 Hz, 2H), 7.37 (d, J = 8.6 Hz, 2H), 7.26 (d, J = 7.0 Hz, 1H), 6.02 (s, 1H), 3.21 (dd, J = 8.1, 4.4 Hz, 1H), 2.73 (dd, J = 18.1, 8.2 Hz, 1H), 2.45 (dd, J = 18.1, 4.3 Hz, 1H), 1.64 (s, 3H), 1.26 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 206.3, 152.1, 141.9, 138.8, 138.3, 131.6, 129.2, 128.0, 127.0, 126.8, 122.1, 62.5, 57.4, 56.4, 29.6, 22.9, 21.6. IR (cm^{-1}): 3261, 2977, 2961, 2924, 1694, 1466, 1399, 1374, 1239, 1195, 1077, 1060, 1007, 849, 835, 717. HRMS (ESI): $[M + Na]^+$ calcd for: $C_{21}H_{23}Br_2NO_2SNa$ 535.9693, Found: 535.9695.

3q: White solid (428 mg, 95%). mp 187–188 °C. $[\alpha]_D^{25}$ = 49.0 (c = 0.99, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (dd, J = 8.5, 5.3 Hz, 1H), 7.52 (d, J = 8.5 Hz, 2H), 7.38 (d, J = 8.6 Hz, 2H), 7.09 (td, J = 8.6, 1.9 Hz, 1H), 7.01 (d, J = 8.3 Hz, 1H), 6.13 (s, 1H), 3.20 (dd, J = 8.2, 4.4 Hz, 1H), 2.77 (dd, J = 18.2, 8.3 Hz, 1H), 2.50 (dd, J = 18.2, 4.3 Hz, 1H), 1.65 (s, 3H), 1.27 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 205.8, 167.6 (d, J_{FC} = 258.2 Hz), 156.5 (d, $^4J_{FC}$ = 10.3 Hz), 142.0, 133.5 (d, $^5J_{FC}$ = 1.6 Hz), 131.6, 129.2, 126.5 (d, $^4J_{FC}$ = 10.7 Hz), 122.1, 116.4 (d, $^3J_{FC}$ = 24.0 Hz), 113.1 (d, $^3J_{FC}$ = 22.4 Hz), 62.4, 57.1, 56.4, 29.8 (d, $^5J_{FC}$ = 1.9 Hz), 22.9, 21.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ −100.78. IR (cm^{-1}): 3263, 2976, 2965, 2928, 1689, 1613, 1590, 1481, 1400, 1271, 1244, 1084, 1057, 1007, 936, 852, 825, 794. HRMS (ESI): $[M + Na]^+$ calcd for: $C_{21}H_{23}BrFNO_2SNa$ 474.0515, Found: 474.0515.

3r: White solid (420 mg, 90%). mp 188–189 °C. $[\alpha]_D^{25}$ = 28.4 (c = 1.01, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, J = 8.1 Hz, 1H), 7.52 (d, J = 8.3 Hz, 2H), 7.41–7.32 (m, 4H), 6.08 (s, 1H), 3.19 (dd, J = 7.8, 4.2 Hz, 1H), 2.76 (dd, J = 18.1, 8.2 Hz, 1H), 2.49 (dd, J = 18.2, 3.8 Hz, 1H), 1.64 (s, 3H), 1.26 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 206.3, 155.0, 142.3, 142.0, 135.5, 131.6, 129.2, 128.8, 126.7, 125.2, 122.1, 62.5, 57.0, 56.4, 29.7, 22.9, 21.6. IR (cm^{-1}): 3256, 2983, 1701, 1597, 1399, 1323, 1201, 1067, 1053, 1008, 881, 833, 827, 789. HRMS (ESI): $[M + Na]^+$ calcd for: $C_{21}H_{23}BrClNO_2SNa$ 490.0219, Found: 490.0220.

3s: White solid (477 mg, 93%). mp 201–203 °C. $[\alpha]_D^{25}$ = 19.7 (c = 0.99, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, J = 8.4 Hz, 1H), 7.55–7.50 (m, 4H), 7.37 (d, J = 8.3 Hz, 2H), 6.07 (s, 1H), 3.18 (dd, J = 7.6, 4.1 Hz, 1H), 2.76 (dd, J = 18.2, 8.2 Hz, 1H), 2.50 (dd, J = 18.2, 3.8 Hz, 1H), 1.64 (s, 3H), 1.26 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 206.5, 155.1, 142.0, 135.9, 131.6, 131.2, 129.8, 129.2, 126.8, 125.3, 122.1, 62.5, 56.9, 56.4, 29.6, 22.9, 21.6. IR (cm^{-1}): 3259, 2983, 2965, 1698, 1594, 1575, 1399, 1321, 1200, 1052, 1007, 870, 830, 826, 787. HRMS (ESI): $[M + Na]^+$ calcd for: $C_{21}H_{23}Br_2NO_2SNa$ 535.9693, Found: 535.9692.

7a: Colourless oil (178 mg, 52%). $[\alpha]_D^{25}$ = −3.5 (c = 0.47, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, J = 4.0 Hz, 2H), 7.52 (t, J = 8.0 Hz, 1H), 7.40 (t, J = 7.2 Hz, 4H), 7.29 (t, J = 8.0 Hz, 2H), 7.20 (t, J = 7.2 Hz, 1H), 5.73 (s, 1H), 3.91 (d, J = 16.0 Hz, 1H), 3.79 (d, J = 16.0 Hz, 1H), 1.78 (s, 3H), 1.30 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 199.4, 146.7, 137.2, 133.5, 128.6, 128.5, 128.1, 127.0, 125.1, 59.5, 56.0, 49.4, 29.4, 23.0.IR (cm^{-1}): 3279, 2976, 2961, 2925, 1677, 1447, 1377, 1348, 1223, 1059, 761, 699, 690. HRMS (ESI): $[M + Na]^+$ calcd for: 366.1504, Found: 366.1502.

7b: Yellow oil (252 mg, 65%). $[\alpha]_D^{25}$ = −35.8 (c = 0.91, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ8.15 (d, J = 8.0 Hz, 2H), 7.89 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 8.0 Hz, 3H), 7.43 (t, J = 8.0 Hz, 2H), 5.62 (s, 1H), 4.00 (d, J = 18.4 Hz, 1H), 3.95 (d, J = 18.4 Hz, 1H), 1.78 (s, 3H), 1.31 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 199.0, 154.6, 146.7, 136.6, 133.9, 128.8, 128.1, 126.0, 123.8, 59.5, 56.3, 49.3, 29.3, 22.9. IR (cm^{-1}): 3278, 2976, 2926, 1676, 1597, 1519, 1449, 1347, 1225, 1058, 856, 757, 700, 689. HRMS (ESI): $[M + Na]^+$ calcd for: 411.1354, Found: 411.1352.

7c: White solid (364 mg, 73%). Mp 59–60 °C. $[\alpha]_D^{25}$ = −41.3 (c = 0.77, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ7.76 (d, J = 8.0 Hz, 2H), 7.59 (d, J = 12.0 Hz, 2H), 7.57 (d, J = 8.0 Hz, 3H), 7.43 (t, J = 8.0 Hz,2H), 5.62 (s, 1H), 4.00 (d, J = 18.4 Hz, 1H), 3.95 (d, J = 18.4 Hz, 1H), 1.78 (s, 3H), 1.31 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 199.0, 154.6, 146.7, 136.6, 133.9, 128.8, 128.1, 126.0, 123.8, 59.5, 56.3, 49.3, 29.3, 22.9. IR (cm^{-1}): 3277, 2975, 2961, 2924, 1677, 1584, 1486, 1397, 1382, 1219, 1070, 1055, 1004, 907, 823, 639. HRMS (ESI): $[M + Na]^+$ calcd for: 521.9714, Found: 521.9711.

General procedure for deprotection

0.5 mmol **3g** and 5 mL MeOH were placed in a 25 mL round-bottom flask and then 1 mL aqueous HCl (36%) was added dropwise with stirring at room temperature. Then a white solid was produced and the reaction process was monitored by TLC. After 2 h, the reaction was complete and the hydrochloride solid **4** was filtered. The crude product was washed with MeOH three times for purification.

4: White solid (153 mg, 92%). mp 192–193 °C. $[\alpha]_D^{25}$ = 101.1 (c = 0.68, MeOH). ^{1}H NMR (400 MHz, DMSO): δ 9.01 (s, 3H), 7.71–7.60 (m, 4H), 7.53–7.32 (m, 4H), 3.72–3.65 (m, 1H), 3.07–2.97 (m, 1H), 2.83 (dd, J = 17.8, 4.4 Hz, 1H), 1.74 (s, 3H).^{13}C NMR (101 MHz, DMSO): δ 204.7, 153.1, 139.6, 136.2, 135.6, 128.6, 128.3, 127.8, 126.8, 126.0, 123.3, 59.6, 53.6, 29.4, 20.8. IR (cm^{-1}): 3069, 2923, 2861, 2813, 2745, 1703.9, 1603, 1575, 1504, 1288, 762, 701. HRMS (ESI): $[M + Na]^+$ calcd for: $C_{17}H_{17}ClN_2O_3Na$ 355.0825, Found: 355.1276.

Reduction procedure

A solution of **3a** (710 mg, 0.2 mmol) in 3 mL of anhydrous THF was cooled to −78 °C. Then, DIBAL (1.0 M in toluene, 0.6 mL, 0.6 mmol) was added dropwise and the mixture was stirred at this temperature for 4 h. After completion of the reaction, several drops of saturated ammonium chloride solution were added and the mixture was allowed to come to room temperature. The solvents were removed, and the residue was dissolved in dichloromethane and extracted with brine. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*, and the crude mixture was charged onto silica gel and purified by flash chromatography to furnish the corresponding product **5** in 90% yield.

5: White solid (64 mg, 90%). mp 225–226 °C. $[\alpha]_D^{25}$ = 64.6 (c = 0.13, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61–7.56 (m, 2H), 7.42–7.35 (m, 2H), 7.32–7.20 (m, 4H), 7.14 (t, J = 7.1 Hz, 1H), 6.13 (s, 1H), 4.77 (t, J = 5.1 Hz, 1H), 3.66 (dd, J = 16.1, 9.8 Hz, 1H), 2.97 (dd, J = 16.1, 7.6 Hz, 1H), 2.76 (ddd, J = 9.7, 7.6, 5.3 Hz, 1H), 2.54 (d, J = 5.3 Hz, 1H), 1.80 (s, 3H), 1.29 (s, 9H).^{13}C NMR (101 MHz, $CDCl_3$): δ 147.8, 143.8, 143.8, 128.8, 128.3, 126.7, 126.7, 125.7, 125.4, 124.1, 62.8, 56.2, 54.8, 31.8, 29.7, 26.9, 23.2. IR (cm^{-1}): 3227, 2981, 2957, 2914, 1466, 1390, 1180, 1025, 1012, 960, 753, 734, 697. HRMS (ESI): $[M + Na]^+$ calcd for: $C_{21}H_{27}NO_2SNa$ 380.1660, Found: 380.1657.

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