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A Tandem Michael–S_N2-Mediated General Route to Six-Membered Heterocycles and Carbocycles

Ananta Kumar Atta[a] and Tanmaya Pathak*[a]

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A powerful, flexible, and stereoselective general strategy for the construction of chirally pure six-membered heterocycles and carbocycles by utilizing a tandem Michael–S_N2 sequence is described. The strategy avoids the tedious synthesis of separate starting materials prior to cyclization. The expedient and general strategy, which is virtually untapped until now, will enrich the arsenal of synthetic chemists for the preparation of cyclic compounds.

Introduction

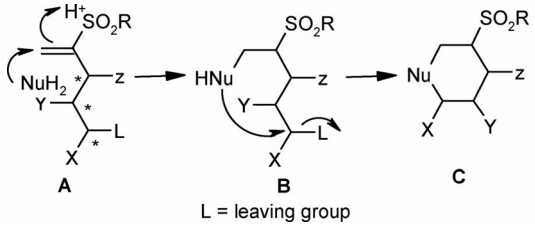
The importance of six-membered densely functionalized heterocycles[1,2] and carbocycles[3] in natural products and pharmaceuticals has led to outstanding developments in the synthetic strategies for achieving these structures. In particular, polyhydroxylated piperidines, as well as alkyl- and/or hydroxy-substituted carbocycles, are a common structural component in a large number of naturally occurring and biologically active molecules.[1–3]

Tandem reactions allow several new bonds to be generated in a one-pot fashion thereby avoiding the isolation of intermediates, minimizing the number of synthetic steps, and eliminating the need for stepwise purification processes.[4] The application of such strategies is therefore highly desirable in synthetic chemistry especially for accessing heterocycles and carbocycles.[4,5]

Concomitant alkylation and Michael addition may be considered an efficient tandem strategy for the construction of ring structures.[6,7] However, virtually all acyclic substrates used so far for such tandem reactions[6,7] have been devoid of asymmetric centers or functional groups on the carbon atoms connecting the Michael acceptor and the leaving group of a substrate. It should be noted that there have been several reports[6] on reactions involving first an S_N2 reaction followed by a Michael addition whereas the reverse reaction pattern, that is, Michael addition followed by S_N2 reactions have rarely been reported.[7]

Results and Discussion

Because carbon and other heteroatomic nucleophiles react efficiently at the electrophilic β position of vinylic sulfones,[8] we opined that the vinyl sulfone group of an acyclic vinyl sulfone with a properly positioned leaving group – as in **A**, Scheme 1 – would react efficiently with externally delivered nucleophiles. The intermediate **B** thus formed would displace the leaving group in an S_N2 fashion to afford six-membered heterocycles and carbocycles represented by the general structure **C**.



Scheme 1. General strategy for the synthesis of six-membered heterocycles and carbocycles.

However, only the isolation of appropriate intermediates would establish the sequence of reactions delineated in Scheme 1. We also argued that if the vinyl sulfones (like **A**) are derived from inexpensive chiral pools like carbohydrates, the sequence of reactions (Scheme 1) would generate compounds with well-defined chiral centers inherited from the carbohydrates used for the synthesis of the acyclic vinyl sulfone **A**. Moreover, it was necessary to design a concise route for the synthesis of vinyl sulfones represented by the general structure **A** in Scheme 1.

We planned to access highly functionalized and chiral Michael acceptors having a leaving group at the δ position from pentose and hexose sugars for tandem Michael–S_N2 reactions. Thus, the known *ribo*-tosyl derivative **1**[9] was regioselectively displaced at C2 with thiocresol to provide **2** (Scheme 2). The 3,4-isopropylidine group of **2** was deprotected to obtain **3**. Benzyl protection of **3** afforded **4**, which was ring-opened under acidic conditions. The product thus generated was reduced to the corresponding diol **5** by using

[a] Department of Chemistry, Indian Institute of Technology Kharagpur,
Kharagpur 721302, India
E-mail: tpathak@chem.iitkgp.ernet.in

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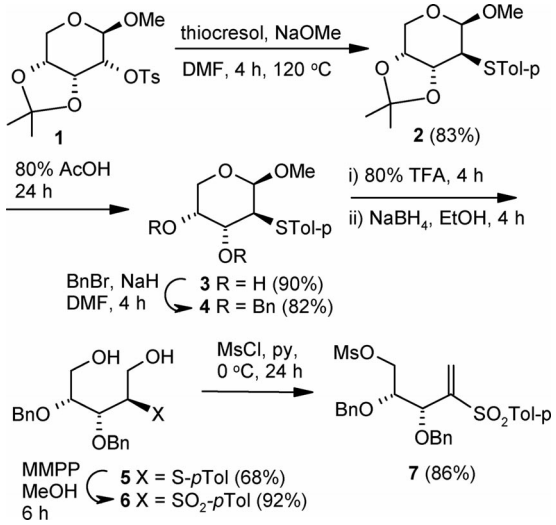
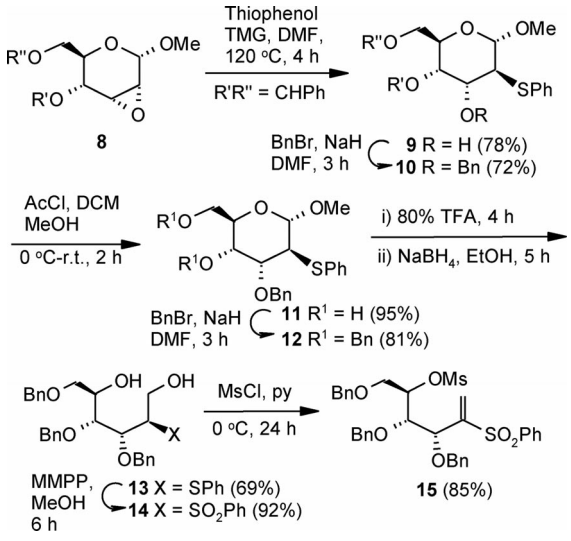
$NaBH_4$ in EtOH. The diol **5** was oxidized with magnesium monoperoxyphthalate hexahydrate (MMPP) to generate the sulfone derivative **6** in high yield. Mesylation of **6** and concomitant elimination of one mesyl group in pyridine afforded the required acyclic vinyl sulfone **7** (Scheme 2) in good yield.



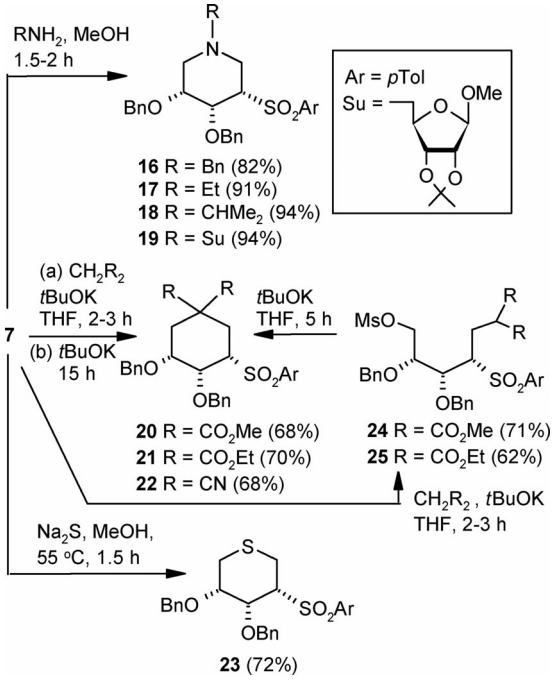
Scheme 2. Synthesis of pentosyl acyclic vinyl sulfone modified carbohydrates.

To synthesize the higher homologue of **7**, the glucopyranosyl epoxide **8**[10] was treated with thiophenol in a regioselective fashion to give **9** (Scheme 3). The free hydroxy group of **9** was benzylated to yield **10**. Compound **10** was deprotected under acidic conditions to generate **11**. Compound **11** was converted into the vinyl sulfone **15** via intermediates **12**–**14** following the procedure described for the synthesis of **7**.



Scheme 3. Synthesis of hexosyl acyclic vinyl sulfone modified carbohydrates.

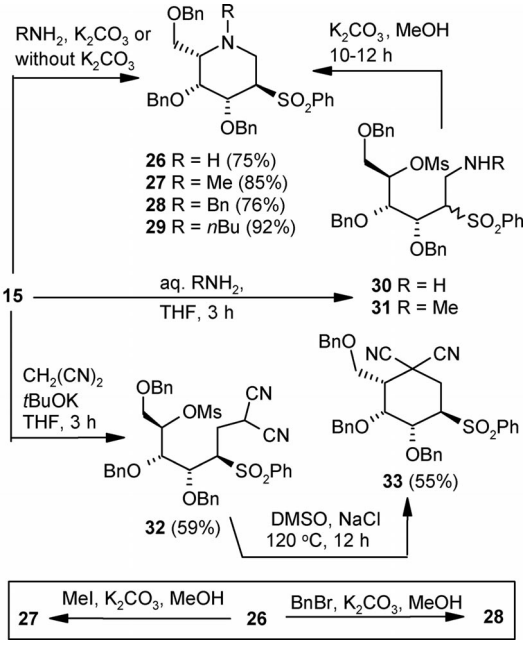
Acyclic vinyl sulfone **7** was treated with benzylamine, ethylamine, isopropylamine, and an amino sugar in MeOH to produce piperidine derivatives **16**–**19**, respectively, in good yields (Scheme 4). Carbon nucleophiles generated from active methylene compounds such as dimethyl or diethyl malonate using *t*BuOK in THF efficiently reacted with **7** in a Michael fashion and subsequent treatment with an additional amount of *t*BuOK in the same flask yielded cyclic products **20** and **21**. In addition, the potassium salt of malononitrile efficiently reacted with **7** to afford the carbocycle **22** (Scheme 4). Compound **7** also readily reacted with Na_2S in MeOH at 55 °C to afford the cyclic sulfide **23**.



Scheme 4. Synthesis of six-membered heterocycles and carbocycles.

The THF solution of hexosyl acyclic vinyl sulfone **15** having a leaving group at the δ position was treated with a 30% aq. ammonia solution and a 40% aq. methylamine solution to generate cyclic derivatives **26** and **27**, respectively, after K_2CO_3 treatment in a one-pot fashion (Scheme 5). In addition, **15** efficiently reacted with neat benzylamine and *n*-butylamine to generate the corresponding cyclic derivatives **28** and **29**, respectively. The potassium salt of malononitrile added to compound **15** in a Michael fashion to produce the mesyl derivative **32**, which was subsequently converted into the carbocyclic derivative **33** by using DMSO/NaCl (Scheme 5).

It should be noted for **16**–**23** that the SO_2Ar substituent is the only new chiral center to be generated during the reactions, whereas for compounds **26**–**29** and **33**, the SO_2Ar substituent and the ring carbon connected to CH_2OBn are the two new chiral centers generated after ring closure. However, the configuration of the ring carbon connected to CH_2OBn was easily assigned because of the S_N2 nature of the intramolecular cyclization reaction.



Scheme 5. Synthesis of six-membered heterocycles and carbocycles.

The structure of **18** was unambiguously established on the basis of an X-ray analysis of its single crystal (Figure 1). The ^{1}H NMR spectral patterns of **16**, **17**, and **19** are comparable to that of **18**, proving thereby the structural similarities of these compounds. The configuration of **20** was confirmed by COSY and NOESY experiments. The configurations of the sulfone-bearing carbon atom of **21** and **22** were confirmed on the basis of the ^{1}H NMR spectra, which are comparable to that of **20**. Compound **23** was formed in the same way and therefore was assigned the same configuration. Compound **26** was treated with methyl iodide or benzyl bromide separately to afford *N*-methylated **27** and *N*-benzylated **28**, respectively (Scheme 5). Because the configuration of the sulfone-bearing C atom of **27** had been confirmed by COSY–NOESY experiments, the configurations of compounds **26** and **28** were automatically confirmed. The spectral pattern of **29** is comparable to that of **28**, proving the structural similarities of the two compounds.

To establish the sequence of reactions in the tandem cyclization delineated in Schemes 4 and 5, we isolated compounds **24**, **25**, and **30**–**32**. All of these compounds after isolation and treatment with basic reagents also afforded cyclic products. The presence of the mesyl group in **24**, **25**, and **30**–**32** unambiguously confirmed that the Michael addition was indeed the first step in the sequence of reactions and that ring closure occurred by intramolecular nucleophilic displacement reactions.

The synthetic utility of many of these compounds was established by converting the sulfonylated piperidine derivatives **16**–**19**, **27**, and **28** into functionalized olefinic piperidines **34**–**39**, respectively, in moderate yields (Scheme 6).[1b,11]

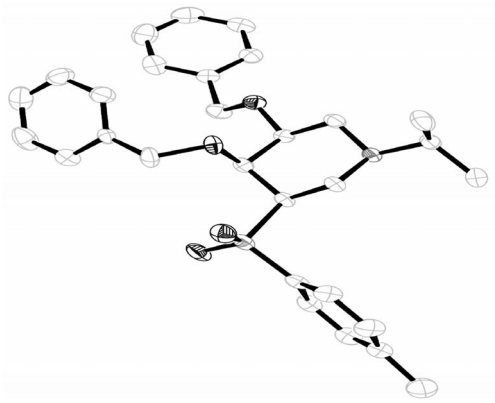
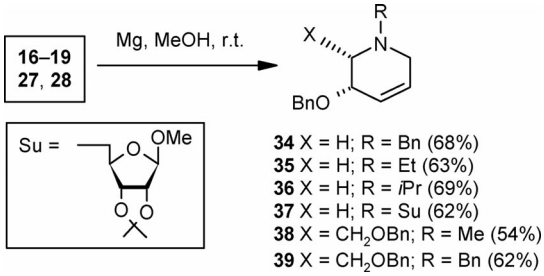
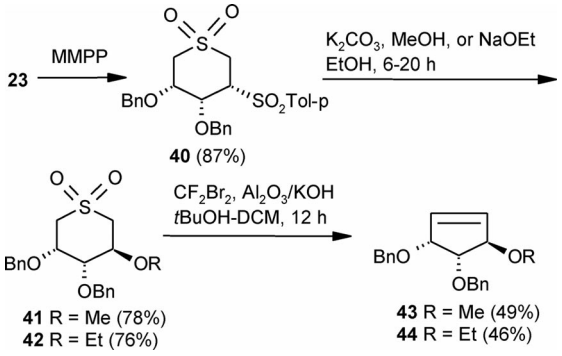


Figure 1. ORTEP diagram of compound **18**.



Scheme 6. Formation of olefinic piperidines from selected piperidine derivatives.

On the other hand, cyclic sulfide derivative **23** was oxidized to the corresponding sulfone **40** by using MMPP in MeOH (Scheme 7). The cyclic sulfone **40** on treatment with K_2CO_3/MeOH or NaOEt/EtOH underwent elimination–addition reactions to produce **41** and **42**, respectively. Sulfones **41** and **42** afforded cyclopentenols **43** and **44**, respectively, under modified Ramberg–Baecklund conditions (Scheme 7).[12] The configuration of **41** was confirmed by X-ray analysis of its single crystal (Figure 2). The ^{1}H NMR spectral pattern of **42** was comparable to that of **41**, proving thereby the structural similarities of the two compounds (Scheme 7). The isomers of **43** or **44** can be used for the synthesis of several natural products and biologically active compounds.[13]



Scheme 7. Cyclopentenol derivatives from cyclic sulfide **23**.

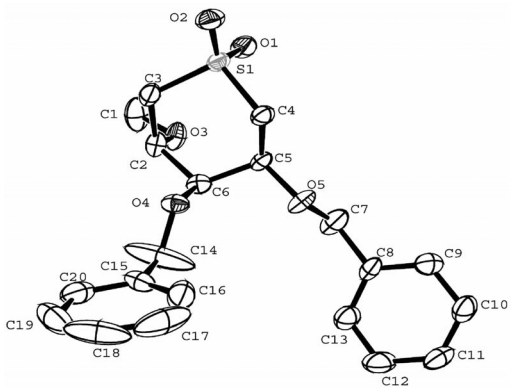


Figure 2. ORTEP diagram of compound **41**.

Conclusions

We have described a powerful, flexible, and stereoselective general strategy for the construction of chirally pure six-membered carbocycles and heterocycles from readily available acyclic vinyl sulfone-modified carbohydrates by utilizing a tandem Michael–S_N2 sequence. It should be re-emphasized that the synthesis of separate starting materials, a common practice in the preparation of heterocycles and carbocycles, is completely avoided in our approach. This diversity-oriented synthetic method generates N- or S-containing heterocycles as well as carbocycles by simply reacting easily accessible starting materials **7** or **15** with inexpensive reagents like carbon nucleophiles, amines, or Na_2S.

Experimental Section

Compound 2: *p*-Thiocresol (8.66 g, 69.85 mmol) was added to a well-stirred solution of NaOMe (2.26 g, 41.91 mmol) in DMF (40 mL) and the mixture was stirred for 0.5 h. A solution of **1** (5.0 g, 13.97 mmol) in DMF (20 mL) was added and the reaction mixture was heated at 120 °C. After 4 h, the mixture was cooled to room temperature and poured into an aq. saturated solution of NH_4Cl and the product was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried with anhyd. Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to leave a residue. The residue was purified over silica gel to afford **2** (3.59 g, 83%) as a yellow oil. $[\alpha]_D^{26}$ = –138.9 (*c* = 0.4, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.38 (s, 3 H), 1.45 (s, 3 H), 2.34 (s, 3 H), 3.23 (dd, *J* = 2.8, 3.2 Hz, 1 H), 3.41 (s, 3 H), 3.98–4.02 (m, 2 H), 4.16–4.17 (m, 1 H), 4.27–4.31 (m, 1 H), 4.72 (d, *J* = 3.2 Hz, 1 H), 7.11 (d, *J* = 8.0 Hz, 2 H), 7.45 (d, *J* = 8.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0, 26.2, 28.2, 53.1, 55.8, 58.6 (CH_2), 72.8, 74.4, 100.2, 108.8, 129.5, 130.9, 133.3, 137.6 ppm. HRMS (ES^+): calcd. for $C_{16}H_{22}O_4SNa$ $[M + Na]^+$ 333.1136; found 333.1136.

Compound 3: A solution of compound **2** (4.0 g, 12.90 mmol) in 80% aq. AcOH (30 mL) was stirred at room temperature. After 24 h, the acid was evaporated to dryness under reduced pressure to leave a residue. The residue was purified over silica gel to afford **3** (3.13 g, 90%) as a white solid. $[\alpha]_D^{26}$ = –228.7 (*c* = 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.35 (s, 3 H), 2.57–2.62 (m, 1 H), 2.76–2.80 (m, 1 H), 3.42 (s, 3 H), 3.44–3.47 (m, 1 H), 3.83 (q, *J* = 12.4, 36.8 Hz, 2 H), 3.96–4.00 (m, 2 H), 4.88 (d, *J* = 2.8 Hz, 1 H), 7.13 (d, *J* = 8.0 Hz, 2 H), 7.40 (d, *J* = 8.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0, 52.9, 55.6, 62.3 (CH_2), 68.4, 68.7, 100.7, 129.8, 131.1, 132.2, 137.4 ppm. HRMS (ES^+): calcd. for $C_{13}H_{18}O_4SNa$ $[M + Na]^+$ 293.0824; found 293.0818.

Compound 4: Compound **3** (3.0 g, 11.11 mmol) was stirred at 0 °C with NaH (1.09 g, 22.80 mmol) and benzyl bromide (3.8 mL, 52.20 mmol) in DMF (40 mL). The mixture was stirred at room temperature under N_2. After 4 h, the reaction mixture was poured into an aq. saturated solution of NH_4Cl and the product was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried with anhyd. Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to leave a residue. The residue was purified over silica gel to afford **4** (4.10 g, 82%) as a white semi-solid. $[\alpha]_D^{26}$ = –77.0 (*c* = 0.34, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.32 (s, 3 H), 3.39 (s, 3 H), 3.68–3.76 (m, 3 H), 3.84 (s, 2 H), 4.61–4.71 (m, 4 H), 4.80 (s, 1 H), 7.05 (d, *J* = 7.6 Hz, 2 H), 7.26–7.35 (m, 10 H), 7.41 (d, *J* = 8.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0, 51.0, 55.7, 61.1, 71.8 (CH_2), 72.4 (CH_2), 72.9, 77.4, 100.8, 127.4, 127.5, 127.7, 127.8, 128.2, 128.3, 129.5, 131.7, 132.1, 136.5, 138.2, 138.4 ppm. HRMS (ES^+): calcd. for $C_{27}H_{30}O_4SNa$ $[M + Na]^+$ 473.1757; found 473.1764.

Compound 5: A mixture of compound **4** (3.5 g, 7.78 mmol) and 80% aq. trifluoroacetic acid (20 mL) was stirred at room temperature. After 4–5 h, the reaction mixture was poured into an aq. saturated solution of $NaHCO_3$ and the product was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried with anhyd. Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to leave a residue. The residue was dissolved in EtOH (40 mL) and sodium borohydride (1.16 g, 31.12 mmol) was added at 0 °C. After being stirred for 4 h at room temperature, the reaction mixture was concentrated under reduced pressure to leave a residue. The residue was poured into saturated solution of $NaHCO_3$ and the product was extracted with EtOAC (3 × 30 mL). The combined organic layers were dried with anhyd. Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to leave a residue. The residue was purified over silica gel to afford compound **5** (2.31 g, 68%) as a white gum. $[\alpha]_D^{26}$ = –22.5 (*c* = 2.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.21 (br. s, 2 H), 2.33 (s, 3 H), 3.59–3.63 (m, 1 H), 3.73–3.86 (m, 3 H), 3.97–4.02 (m, 2 H), 4.12–4.14 (m, 1 H), 4.36 (d, *J* = 11.2 Hz, 1 H), 4.58 (d, *J* = 11.2 Hz, 1 H), 4.75 (q, *J* = 11.6, 24.8 Hz, 2 H), 7.07 (d, *J* = 8.0 Hz, 2 H), 7.20–7.22 (m, 2 H), 7.28–7.38 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0, 54.7, 59.6 (CH_2), 63.1 (CH_2), 71.9 (CH_2), 74.4 (CH_2), 76.6, 79.6, 127.8, 127.9 (2 C), 128.1, 128.4 (2 C), 129.8, 131.5, 131.9, 136.9, 137.6, 137.9 ppm.

Compound 6: Magnesium monoperoxyphthalate hexahydrate (11.85 g, 23.97 mmol) was added to a well-stirred solution of acyclic sulfide **5** (3.5 g, 7.99 mmol) in dry MeOH (40 mL) and the mixture was stirred at room temperature under N_2. After 6 h, the MeOH was evaporated to dryness under reduced pressure and the residue was poured into an aq. saturated solution of $NaHCO_3$ and the product was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried with anhyd. Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to leave a residue. The residue was purified over silica gel to afford sulfone **6** (3.46 g, 92%) as a white semi-solid. $[\alpha]_D^{26}$ = +20.6 (*c* = 0.2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.12 (br. s, 1 H), 2.37 (s, 3 H), 2.88 (br. s, 1 H), 3.65–3.68 (m, 1 H), 3.78 (s, 1 H), 3.85–3.87 (m, 1 H), 3.93–4.03 (m, 2 H), 4.12–4.15 (m, 1 H), 4.26–4.29 (m, 1 H), 4.51 (d, *J* = 11.2 Hz, 1 H), 4.64–4.72 (m, 3 H), 7.09–7.15 (m, 4 H), 7.25–7.36 (m, 8 H), 7.64 (d, *J* = 8.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 59.5 (CH_2), 60.1 (CH_2), 67.6, 72.1 (CH_2), 74.2 (CH_2), 75.6, 79.5, 127.7, 127.9, 128.0 (2 C), 128.2, 128.5, 129.4,

136.9, 137.4, 137.7, 144.4 ppm. HRMS (ES^+): calcd. for $C_{26}H_{30}O_6SNa$ $[M + Na]^+$ 493.1661; found 493.1652.

Compound 7: Methanesulfonyl chloride (2.5 mL, 31.9 mmol) in pyridine (10 mL) was added dropwise to a well-stirred solution of acyclic sulfone **6** (3.0 g, 6.38 mmol) in pyridine (20 mL) at 0 °C under N_2. After completion of the addition, the reaction mixture was kept at +4 °C. After 24 h (TLC), the reaction mixture was poured into an aq. saturated solution of $NaHCO_3$ and the product was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried with anhyd. Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to leave a residue. The residue was purified over silica gel to afford the required vinyl sulfone **7** (2.90 g, 86%) as a white solid; m.p. 92 °C, $[\alpha]_D^{26}$ = +39.0 (c = 0.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.41 (s, 3 H), 2.87 (s, 3 H), 3.97 (d, J = 11.6 Hz, 1 H), 4.07–4.10 (m, 1 H), 4.18 (d, J = 11.6 Hz, 1 H), 4.31–4.35 (m, 2 H), 4.39–4.42 (m, 1 H), 4.49–4.56 (m, 2 H), 6.15 (s, 1 H), 6.62 (s, 1 H), 7.01–7.03 (m, 2 H), 7.24–7.35 (m, 10 H), 7.69 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 37.4, 68.1 (CH_2), 71.1 (CH_2), 72.7 (CH_2), 75.2, 78.2, 127.8, 127.9, 128.1, 128.3, 128.4, 128.5 (CH_2), 129.9, 135.8, 136.5, 137.3, 144.9, 148.3 ppm. HRMS (ES^+): calcd. for $C_{27}H_{30}O_7S_2Na$ $[M + Na]^+$ 553.1325; found 553.1403.

Compound 9: Thiophenol (12.87 mL, 125.0 mmol) and tetramethylguanidine (9.4 mL, 75.0 mmol) were added to a well-stirred solution of epoxide **8** (6.60 g, 25.0 mmol) in DMF (40 mL) . The mixture was heated at 90–120 °C with stirring under N_2. After 4–5 h, the reaction mixture was poured into an aq. saturated solution of $NaHCO_3$ and the product was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried with anhyd. Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to leave a residue. The residue was purified over silica gel to afford the sulfide **9** (7.29 g, 78%) as a colorless oil. $[\alpha]_D^{26}$ = +51.6 (c = 4, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 3.14 (d, J = 7.2 Hz, 1 H), 3.43 (s, 3 H), 3.66 (d, J = 2.4 Hz, 1 H), 3.88 (t, J = 10.0 Hz, 1 H), 4.12 (dd, J = 2.8, 10.0 Hz, 1 H), 4.26–4.28 (m, 2 H), 4.34–4.38 (m, 1 H), 4.89 (s, 1 H), 4.68 (s, 1 H), 7.26–7.38 (m, 6 H), 7.44–7.52 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.6, 55.7, 58.6, 68.8, 69.1 (CH_2), 76.3, 101.3, 102.2, 126.2, 127.7, 128.2, 129.1, 129.4, 131.2, 133.8, 137.2 ppm. HRMS (ES^+): calcd. for $C_{20}H_{22}O_5SNa$ $[M + Na]^+$ 397.1086; found 397.1084.

Compound 10: Compound **9** (2.60 g, 6.95 mmol) was stirred at 0 °C with NaH (0.40 g, 8.34 mmol) and benzyl bromide (1.23 mL, 10.42 mmol) in DMF (30 mL). The mixture was stirred at room temperature under N_2. After 3 h, the reaction mixture was poured into an aq. saturated solution of NH_4Cl and the product was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried with anhyd. Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to leave a residue. The residue was purified over silica gel to afford **10** (2.31 g, 72%) as a yellow solid; m.p. 118 °C, $[\alpha]_D^{26}$ = +4.6 (c = 0.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 3.42 (s, 3 H), 3.62 (d, J = 2.0 Hz, 1 H), 3.81 (t, J = 10.4 Hz, 1 H), 4.01 (s, 1 H), 4.15 (dd, J = 2.4, 9.6 Hz, 1 H), 4.32–4.36 (m, 1 H), 4.43–4.50 (m, 1 H), 4.72 (q, J = 12.8, 28.8 Hz, 2 H), 4.84 (s, 1 H), 5.60 (s, 1 H), 7.23–7.29 (m, 10 H), 7.37–7.38 (m, 3 H), 7.49–7.51 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 50.8, 55.8, 58.6, 69.3 (CH_2), 72.6 (CH_2), 74.3, 76.8, 101.2, 102.2, 126.3, 127.3, 127.4, 127.8, 128.2 (2 C), 129.0, 129.3, 130.8, 134.2, 137.7, 138.4 ppm. HRMS (ES^+): calcd. for $C_{27}H_{28}O_5SNa$ $[M + Na]^+$ 487.1555; found 487.1564.

Compound 11: Acetyl chloride (0.67 mL, 9.43 mmol) was added dropwise to a well-stirred solution of compound **10** (2.92 g, 6.29 mmol) in a mixture of dry MeOH (20 mL) and a minimum amount of DCM at 0 °C under N_2 atmosphere over a period of 0.5 h. The resulting solution was stirred at room temperature. After 2 h, the solution was evaporated to dryness under reduced pressure and the residual liquid was co-evaporated twice with pyridine to yield a syrupy compound. The resulting syrupy compound was poured into a saturated solution of $NaHCO_3$ (150 mL) and the product was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried with anhyd. Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to leave a residue. The residue was purified over silica gel to afford compound **11** (2.25 g, 95%) as a yellow oil; $[\alpha]_D^{26}$ = +193.0 (c = 0.25, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.43–2.46 (m, 1 H), 3.39 (s, 3 H), 3.69 (s, 1 H), 3.79–3.99 (m, 5 H), 4.30 (d, J = 11.6 Hz, 1 H), 4.69 (d, J = 11.6 Hz, 1 H), 4.87 (s, 1 H), 7.19–7.21 (m, 2 H), 7.29–7.33 (m, 6 H), 7.38–7.43 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 48.5, 55.5, 63.0 (CH_2), 64.3, 68.7, 71.2 (CH_2), 76.3, 100.4, 127.8, 128.0, 128.1, 128.5, 129.3, 131.9, 134.0, 137.3 ppm. HRMS (ES^+): calcd. for $C_{20}H_{24}O_5SNa$ $[M + Na]^+$ 399.1242; found 399.1262.

Compound 12: Compound **11** (2.86 g, 7.60 mmol) was converted into **12** (3.42 g, 81%) following the procedure described for the preparation of **10**. White gum, $[\alpha]_D^{26}$ = +45.1 (c = 0.29, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 3.39 (s, 3 H), 3.62 (d, J = 2.8 Hz, 1 H), 3.76–3.80 (m, 2 H), 3.85 (d, J = 2.8 Hz, 1 H), 4.00–4.04 (m, 1 H), 4.32–4.46 (m, 4 H), 4.54–4.71 (m, 3 H), 4.89 (s, 1 H), 7.18–7.37 (m, 20 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 49.7, 55.6, 67.5, 69.7 (CH_2), 71.4 (CH_2), 71.5 (CH_2), 71.9, 73.6 (CH_2), 73.9, 101.1, 127.0, 127.5, 127.6, 127.8, 128.0, 128.2, 128.4, 128.6, 129.3, 131.8, 134.6, 138.2, 138.6 ppm. HRMS (ES^+): calcd. for $C_{34}H_{36}O_5SNa$ $[M + Na]^+$ 579.2181; found 579.2184.

Compound 13: Compound **12** (3 g, 5.40 mmol) was converted into **13** (2.02 g, 69%) following the procedure described for the preparation of **5**. White semi-solid, $[\alpha]_D^{26}$ = +21.2 (c = 0.4, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.51–2.54 (m, 1 H), 2.90 (d, J = 3.6 Hz, 1 H), 3.61–3.71 (m, 3 H), 3.74–3.81 (m, 1 H), 3.84–3.89 (m, 1 H), 4.02–4.05 (m, 1 H), 4.08–4.11 (m, 1 H), 4.22 (br. s, 1 H), 4.53–4.56 (m, 3 H), 4.63–4.69 (m, 3 H), 7.17–7.37 (m, 18 H), 7.41 (d, J = 7.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 54.1, 62.8, 71.1, 71.2 (CH_2), 73.4 (CH_2), 73.6 (CH_2), 74.0 (CH_2), 78.8, 79.9, 126.8, 127.7 (2 C), 127.8, 127.9, 128.0, 128.3, 128.4 (2 C), 129.0, 131.2, 135.4, 137.8, 137.9, 138.0 ppm. HRMS (ES^+): calcd. for $C_{33}H_{36}O_5SNa$ $[M + Na]^+$ 567.2181; found 567.2183.

Compound 14: Compound **13** (2 g, 3.68 mmol) was converted into **14** (1.95 g, 92%) following the procedure described for the preparation of **6**. White semi-solid, $[\alpha]_D^{26}$ = +33.9 (c = 0.6, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.66 (d, J = 4.8 Hz, 1 H), 2.95 (q, J = 5.6, 8.0 Hz, 1 H), 3.50 (dd, J = 6.0, 9.6 Hz, 1 H), 3.65 (dd, J = 2.8, 9.6 Hz, 1 H), 3.90–3.94 (m, 2 H), 4.07–4.17 (m, 2 H), 4.31–4.32 (m, 1 H), 4.44–4.53 (m, 3 H), 4.59–4.62 (m, 2 H), 4.72 (d, J = 11.6 Hz, 1 H), 4.83 (d, J = 11.2 Hz, 1 H), 7.10–7.12 (m, 2 H), 7.23–7.37 (m, 15 H), 7.47 (t, J = 7.6 Hz, 1 H), 7.76–7.78 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 58.6 (CH_2), 68.5, 70.0, 71.3, 73.0 (CH_2), 73.3 (CH_2), 73.5 (CH_2), 76.2, 79.8, 127.3, 127.5, 127.6, 127.8 (2 C), 127.9, 128.0, 128.1, 128.4 (2 C), 128.7, 133.0, 137.6, 137.7, 137.8, 141.0 ppm. HRMS (ES^+): calcd. for $C_{33}H_{36}O_7SNa$ $[M + Na]^+$ 599.2079; found 599.2070.

Compound 15: Compound **14** (2.50 g, 4.34 mmol) was converted into **15** (2.40 g, 85%) following the procedure described for the preparation of **7**. Colorless oil, $[\alpha]_D^{26}$ = +63.7 (c = 0.6, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.95 (s, 3 H), 3.60–3.72 (m, 2 H), 3.97 (d, J = 12.0 Hz, 1 H), 4.03 (dd, J = 1.6, 6.8 Hz, 1 H), 4.15 (d, J = 11.6 Hz, 1 H), 4.32 (d, J = 7.2 Hz, 1 H), 4.38–4.40 (m, 3 H), 4.49 (d, J = 11.2 Hz, 1 H), 5.12–5.13 (m, 1 H), 6.09 (s, 1 H), 6.60

(s, 1 H), 7.06–7.08 (m, 2 H), 7.16–7.18 (m, 2 H), 7.25–7.35 (m, 11 H), 7.40 (t, J = 7.6 Hz, 2 H), 7.54 (t, J = 7.6 Hz, 1 H), 7.83 (d, J = 7.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.7, 68.8 (CH_2), 70.8 (CH_2), 73.1 (CH_2), 73.4 (CH_2), 75.7, 80.3, 81.7, 127.7, 127.8, 127.9 (2 C), 128.0, 128.3, 128.4 (2 C), 128.7, 128.9, 129.1, 133.6, 136.5, 137.0, 137.6, 139.1, 149.0 ppm. HRMS (ES$^+$): calcd. for $C_{34}H_{36}O_8S_2Na$ [M + Na]$^+$ 659.1749; found 659.1729.

General Procedure for the Synthesis of 16–19: The appropriate amine (30 equiv./mmol) was added to a well-stirred solution of compound **7** (1 mmol) in MeOH (5 mL/mmol) . After 1.5–2 h, the MeOH was evaporated under reduced pressure and the residue was partitioned between an aq. saturated solution of NH_4Cl and EtOAc (3 × 15 mL). The combined organic layers were dried with anhyd. Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to leave a residue. The residue was purified over silica gel to afford **16**–**19**.

Compound 16: Compound **7** (0.30 g, 0.57 mmol) was converted into **16** (0.25 g, 82%) in 2 h following the general procedure. White solid, m.p. 105 °C, $[\alpha]_D^{26}$ = 15.2 (c = 0.55, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.35 (s, 3 H), 2.46 (t, J = 10.8 Hz, 1 H), 2.58 (t, J = 11.2 Hz, 1 H), 2.79 (dd, J = 4.4, 10.8 Hz, 1 H), 2.85 (dd, J = 3.6, 10.4 Hz, 1 H), 3.18–3.21 (m, 1 H), 3.46–3.50 (m, 2 H), 3.57 (d, J = 12.8 Hz, 1 H), 4.55 (q, J = 12.0, 27.2 Hz, 2 H), 4.65 (s, 1 H), 4.74 (d, J = 11.2 Hz, 1 H), 5.04 (d, J = 10.8 Hz, 1 H),7.11 (d, J = 8.0 Hz, 2 H), 7.18 (d, J = 6.4 Hz, 2 H), 7.26–7.34 (m, 13 H), 7.61 (d, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 47.8 (CH_2), 50.8 (CH_2), 62.0 (CH_2), 65.1, 71.1 (CH_2), 71.6, 73.9 (CH_2), 78.0, 127.1, 127.2, 127.3, 127.6, 127.7, 128.0, 128.3, 128.4, 128.6, 128.8, 129.4, 136.0, 137.5, 137.9, 138.6, 144.4 ppm. HRMS (ES$^+$): calcd. for $C_{33}H_{35}NO_4SNa$ [M + Na]$^+$ 564.2185; found 564.2185.

Compound 17: Compound **7** (0.15 g, 0.28 mmol) was converted into **17** (0.12 g, 91%) in 2 h following the general procedure. White solid, m.p. 97 °C, $[\alpha]_D^{26}$ = +37.0 (c = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 (t, J = 7.2 Hz, 3 H), 2.36 (s, 3 H), 2.43–2.50 (m, 3 H), 2.55 (t, J = 11.6 Hz, 1 H), 2.85 (dd, J = 4.0, 10.4 Hz, 2 H), 3.17–3.20 (m, 1 H), 3.51–3.54 (m, 1 H), 4.58–4.68 (m, 3 H), 4.78 (d, J = 11.2 Hz, 1 H), 5.06 (d, J = 10.8 Hz, 1 H), 7.16 (d, J = 8.4 Hz, 2 H), 7.24–7.37 (m, 10 H), 7.68 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.0, 21.5, 47.3 (CH_2), 50.7 (CH_2), 51.6 (CH_2), 65.0, 71.1 (CH_2), 71.5, 74.0 (CH_2), 78.1, 127.1, 127.4, 127.6, 127.7, 128.0, 128.4, 128.5, 129.5, 136.1, 137.9, 138.6, 144.4 ppm. HRMS (ES$^+$): calcd. for $C_{28}H_{34}NO_4S$ [M + H]$^+$ 480.2203; found 480.2224.

Compound 18: Compound **7** (0.28 g, 0.53 mmol) was converted into **18** (0.24 g, 94%) in 1.5 h following the general procedure. White solid, m.p. 96 °C, $[\alpha]_D^{26}$ = +31.0 (c = 2.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99 (t, J = 6.8 Hz, 6 H), 2.39 (s, 3 H), 2.62 (t, J = 10.4 Hz, 1 H), 2.76–2.80 (m, 4 H), 3.14–3.18 (m, 1 H), 3.47–3.52 (m, 1 H), 4.58–4.68 (m, 3 H), 4.79 (d, J = 11.2 Hz, 1 H), 5.06 (d, J = 10.8 Hz, 1 H), 7.19 (d, J = 8.0 Hz, 2 H), 7.27–7.38 (m, 10 H), 7.70 (d, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.9, 18.8, 21.5, 43.7, 46.4, 54.4, 65.3, 71.1, 71.7, 74.0, 78.7, 127.1, 127.3, 127.6, 127.7, 128.0, 128.2, 128.4, 128.5, 129.5, 136.2, 138.0, 138.7, 144.4 ppm. HRMS (ES$^+$): calcd. for $C_{29}H_{36}NO_4S$ [M + H]$^+$ 494.2359; found 494.2356.

Compound 19: Compound **7** (0.10 g, 0.19 mmol) was converted into **19** (0.12 g, 94%) in 2 h following the general procedure. Colorless oil, $[\alpha]_D^{26}$ = –2.3 (c = 0.38, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (s, 3 H), 1.46 (s, 3 H), 2.35 (s, 3 H), 2.44–2.56 (m, 2 H), 2.58–2.65 (m, 2 H), 2.82–2.90 (m, 2 H), 3.20 (s, 4 H), 3.52–3.56 (m, 1 H), 4.16 (t, J = 7.2 Hz, 1 H), 4.49–4.66 (m, 5 H), 4.75 (d, J = 11.2 Hz, 1 H), 4.91 (s, 1 H), 5.05 (d, J = 11.2 Hz, 1 H), 7.14 (d, J = 8.4 Hz, 2 H), 7.25–7.37 (m, 10 H), 7.66 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 24.9, 26.4, 47.9 (CH_2), 51.9 (CH_2), 54.7, 60.9 (CH_2), 64.9, 71.1 (CH_2), 71.4, 74.0 (CH_2), 77.8, 83.1, 84.2, 85.0, 109.3, 112.3, 127.2, 127.3, 127.6, 128.0, 128.4, 128.6, 129.5, 135.9, 137.9, 138.5, 144.4 ppm. HRMS (ES$^+$): calcd. for $C_{35}H_{44}NO_8S$ [M + H]$^+$ 638.2813; found 638.2780.

General Procedure for the Synthesis of 20 and 21: Dimethyl or diethyl malonate (5 equiv./mmol) was added to a well-stirred solution of tBuOK (3 equiv./mmol) in dry THF (20 mL) and the mixture was stirred for 0.5 h. A solution of **7** (1 mmol) in THF (10 mL) was then added and the reaction mixture was stirred at room temperature. After 2–3 h, tBuOK (2 equiv/mmol) was added to the same flask and the mixture was stirred for an additional 15 h. Then THF was evaporated under reduced pressure and the residue was partitioned between an aq. saturated solution of NH_4Cl and EtOAc (3 × 15 mL). The combined organic layers were dried with anhyd. Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to leave a residue. The residue was purified over silica gel to afford **20** and **21**, respectively.

Compound 20: Compound **7** (0.10 g, 0.19 mmol) was converted into **20** (0.073 g, 68%) in 18 h following the general procedure. White gum, $[\alpha]_D^{26}$ = +173.5 (c = 0.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.25–2.35 (m, 3 H), 2.38 (s, 3 H), 2.43–2.47 (m, 1 H), 3.14–3.18 (m, 1 H), 3.37–3.39 (m, 1 H), 3.57 (s, 3 H), 3.69 (s, 3 H), 4.61–4.66 (m, 3 H), 4.78 (d, J = 11.2 Hz, 1 H), 5.03 (d, J = 10.8 Hz, 1 H), 7.20 (d, J = 8.4 Hz, 2 H), 7.23–7.37 (m, 10 H), 7.71 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 25.9 (CH_2), 30.1 (CH_2), 52.9, 53.1, 53.9, 63.0, 70.6 (CH_2), 71.9, 74.1 (CH_2), 76.9, 127.2, 127.4, 127.7, 128.0, 128.3, 128.4, 128.6, 129.6, 135.4, 137.8, 138.4, 144.5, 170.2, 170.5 ppm. HRMS (ES$^+$): calcd. for $C_{31}H_{34}O_8SNa$ [M + Na]$^+$ 589.1866; found 589.1874.

Compound 21: Compound **7** (0.07 g, 0.13 mmol) was converted into **21** (0.055 g, 70%) in 18 h following the general procedure. White gum, $[\alpha]_D^{26}$ = +22.0 (c = 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (t, J = 7.2 Hz, 3 H), 1.21 (t, J = 7.2 Hz, 3 H), 2.24–2.35 (m, 3 H), 2.37 (s, 3 H), 2.44 (dd, J = 3.6, 13.2 Hz, 1 H), 3.13 (dd, J = 4.4, 12.0 Hz, 1 H), 3.45 (dd, J = 1.6, 10.0 Hz, 1 H), 3.99–4.07 (m, 2 H), 4.12–4.17 (m, 2 H), 4.61 (s, 2 H), 4.67 (s, 1 H), 4.78 (d, J = 10.8 Hz, 1 H), 5.04 (d, J = 10.8 Hz, 1 H), 7.20 (d, J = 7.6 Hz, 2 H), 7.23–7.37 (m, 10 H), 7.71 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7, 13.9, 21.5, 25.9 (CH_2), 30.1 (CH_2), 53.9, 61.7 (CH_2), 61.9 (CH_2), 63.2, 70.7 (CH_2), 72.0, 74.1 (CH_2), 77.1, 127.1, 127.3, 127.6, 128.0, 128.4, 128.6, 129.6, 135.6, 137.9, 138.4, 144.4, 169.8, 170.0 ppm. HRMS (ES$^+$): calcd. for $C_{33}H_{38}O_8SNa$ [M + Na]$^+$ 617.2179; found 617.2164.

Compound 22: Malononitrile (0.03 mL, 0.47 mmol) was added to a well-stirred solution of tBuOK (0.03 g, 0. 28 mmol) in THF (15 mL) and the mixture was stirred for 0.5 h. A solution of **7** (0.05 g, 0.094 mmol) in THF (5 mL) was added and the reaction mixture was stirred at room temperature. After 3 h, the THF was evaporated under reduced pressure and the residue was partitioned between an aq. saturated solution of NH_4Cl and EtOAc (3 × 15 mL). The combined organic layers were dried with anhyd. Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to leave a residue. The residue was purified over silica gel to afford **22** (0.032 g, 68%). White gum, $[\alpha]_D^{26}$ = +37.7 (c = 0.75, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.30–2.33 (m, 1 H), 2.38–2.43 (m, 4 H), 2.49 (t, J = 12.0 Hz, 1 H), 2.58 (t, J = 13.2 Hz, 1 H), 3.14–3.17 (m, 1 H), 3.62–3.66 (m, 1 H), 4.64 (m, 2 H), 4.75 (s, 1 H), 4.83 (d, J = 10.4 Hz, 1 H), 4.99 (d, J = 10.4 Hz, 1 H), 7.26–7.41 (m, 12 H), 7.71 (d, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR

(100 MHz, $CDCl_3$): δ = 21.6, 29.2 (CH_2), 30.9, 32.9 (CH_2), 62.0, 71.0, 71.7 (CH_2), 74.7 (CH_2), 75.8, 114.0, 114.1, 127.5, 127.8, 128.0, 128.2, 128.3, 128.6, 128.7, 130.2, 134.4, 136.7, 137.5, 145.7 ppm. HRMS (ES^+): calcd. for $C_{29}H_{28}N_2O_4SNa$ $[M + Na]^+$ 523.1661; found 523.1624.

Compound 23: Na_2S (0.27 g, 3.42 mmol) was added to a well-stirred solution of compound **7** (0.30 g, 0.57 mmol) in MeOH (20 mL). The mixture was heated at 55 °C with stirring under N_2. After 1.5 h, the MeOH was evaporated to dryness under reduced pressure and the residue was partitioned between an aq. saturated solution of $NaHCO_3$ and EtOAc (3 × 20 mL). The combined organic layers were dried with anhyd. Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to leave a residue. The residue was purified over silica gel to afford **23** (0.19 g, 72%) as a colorless oil. $[\alpha]_D^{26}$ = +99.6 (c = 0.75, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.36 (s, 3 H), 2.44–2.50 (m, 2 H), 3.07–3.14 (m, 2 H), 3.29–3.32 (m, 1 H), 3.62–3.64 (m, 1 H), 4.62–4.68 (m, 2 H), 4.73–4.78 (m, 2 H), 5.07 (d, J = 11.2 Hz, 1 H), 7.18 (d, J = 7.6 Hz, 2 H), 7.26–7.39 (m, 10 H), 7.69 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 21.9 (CH_2), 25.7 (CH_2), 68.8, 70.9 (CH_2), 72.5, 74.1 (CH_2), 81.1, 127.3 (2 C), 127.5, 127.8, 128.0, 128.5, 128.7, 129.7, 135.2, 137.8, 138.3, 144.8 ppm.

General Procedure for the Synthesis of 24 and 25: Dimethyl or diethyl malonate (5 equiv./mmol) was added to a well-stirred solution of *t*BuOK (3 equiv./mmol) in dry THF (20 mL) and the mixture was stirred for 0.5 h. A solution of **7** (1 mmol) in THF (10 mL) was added and the reaction mixture was stirred at room temperature. After 2–3 h, the THF was evaporated under reduced pressure and the residue was partitioned between an aq. saturated solution of NH_4Cl and EtOAc (3 × 15 mL). The combined organic layers were dried with anhyd. Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to leave a residue. The residue was purified over silica gel to afford **24** and **25**.

Compound 24: Compound **7** (0.10 g, 0.20 mmol) was converted into **24** (0.09 g, 71%) following the general procedure. Colorless oil, $[\alpha]_D^{26}$ = +35.0 (c = 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.38 (s, 3 H), 2.45–2.51 (m, 2 H), 2.79 (s, 3 H), 3.61 (s, 6 H), 3.72–3.75 (m, 2 H), 3.93–3.97 (m, 1 H), 4.17–4.19 (m, 1 H), 4.29 (dd, J = 3.2, 12.0 Hz, 1 H), 4.51 (dd, J = 10.8, 24.4 Hz, 2 H), 4.63–4.71 (m, 2 H), 4.87 (d, J = 10.8 Hz, 1 H), 7.19 (d, J = 8.0 Hz, 2 H), 7.26–7.36 (m, 10 H), 7.67 (d, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 23.4 (CH_2), 37.6, 49.1, 52.6, 62.0 (CH_2), 66.9, 72.1 (CH_2), 73.7, 74.3 (CH_2), 77.7, 128.0, 128.2 (2 C), 128.4, 128.6, 129.8, 134.9, 137.1, 144.8, 169.1, 169.4 ppm.

Compound 25: Compound **7** (0.20 g, 0.094 mmol) was converted into **25** (0.17 g, 62%) following the general procedure. Colorless oil, $[\alpha]_D^{26}$ = +31.1 (c = 1.7, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.16–1.20 (m, 6 H), 2.37 (s, 3 H), 2.41–2.55 (m, 2 H), 2.79 (s, 3 H), 3.72–3.77 (m, 2 H), 3.87–3.91 (m, 1 H), 3.98–4.45 (m, 4 H), 4.18 (d, J = 8.4 Hz, 1 H), 4.28–4.32 (m, 1 H), 4.51 (dd, J = 10.4, 25.6 Hz, 2 H), 4.65–4.71 (m, 2 H), 4.88 (d, J = 10.8 Hz, 1 H), 7.18 (d, J = 8.0 Hz, 2 H), 7.29–7.38 (m, 10 H), 7.67 (d, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (2 C), 21.5, 23.4 (CH_2), 37.7, 49.4, 61.5 (CH_2), 61.6 (CH_2), 62.1, 67.0 (CH_2), 72.1 (CH_2), 73.7, 74.3 (CH_2), 77.8, 127.9, 128.0, 128.2, 128.3, 128.6, 129.8, 135.1, 137.1, 137.2, 144.7, 168.7, 169.0 ppm.

General Procedure for the Synthesis of 26 and 27: A 30% aq. NH_3 solution (5 mL) or a 40% aq. methylamine solution was added to a well-stirred solution of compound **15** (1 equiv./mmol) in THF (30 mL) . After 2–3 h, 3 equiv./mmol of K_2CO_3 was added to the same flask. After 20 h, the THF was evaporated under reduced pressure, an aq. saturated $NaHCO_3$ solution was added, and the product was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried with anhyd. Na_2SO_4 and concentrated under reduced pressure to leave a residue. The residue was purified over silica gel to afford **26** or **27**, respectively.

Compound 26: Compound **15** (0.20 g, 0.308 mmol) was converted into **26** (0.131 g, 75%) following the general procedure. White semi-solid, $[\alpha]_D^{26}$ = –39.8 (c = 0.2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.80 (t, J = 7.2 Hz, 1 H), 2.88–2.95 (m, 1 H), 3.33 (t, J = 8.4 Hz, 1 H), 3.43–3.50 (m, 2 H), 3.76–3.83 (m, 1 H), 3.96–3.98 (m, 2 H), 4.37 (d, J = 10.8 Hz, 1 H), 4.45 (q, J = 11.6, 25.6 Hz, 2 H), 4.56 (d, J = 11.6 Hz, 1 H), 4.72 (t, J = 9.6 Hz, 2 H), 7.08–7.13 (m, 4 H), 7.24–7.36 (m, 13 H), 7.47 (t, J = 7.2 Hz, 1 H), 7.78 (d, J = 7.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.0 (CH_2), 58.2, 62.7, 69.5 (CH_2), 71.2 (CH_2), 72.4, 73.4 (CH_2), 74.6 (CH_2), 80.3, 127.3, 127.5, 127.7 (2 C), 127.8, 127.9, 128.0, 128.2 (2 C), 128.4, 128.7, 132.9, 137.2, 137.7, 138.3, 141.1 ppm. HRMS (ES^+): calcd. for $C_{33}H_{35}NO_5SNa$ $[M + Na]^+$ 580.2150; found 580.2143.

Compound 27. Method A: Compound **7** (0.20 g, 0.307 mmol) was converted into **27** (0.15 g, 85%) following the general procedure. Colorless oil, $[\alpha]_D^{26}$ = +112.0 (c = 0.35, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.28 (br. s, 4 H), 2.46 (t, J = 12.0 Hz, 1 H), 3.29 (dd, J = 8.8 Hz, 1 H), 3.59–3.62 (m, 1 H), 3.89 (dd, J = 2.4, 10.8 Hz, 1 H), 4.04–4.10 (m, 2 H), 4.37 (s, 2 H), 4.41 (d, J = 11.2 Hz, 1 H), 4.60 (d, J = 11.6 Hz, 1 H), 4.37 (t, J = 9.6 Hz, 2 H), 7.08–7.13 (m, 4 H), 7.18–7.36 (m, 13 H), 7.49 (t, J = 7.6 Hz, 1 H), 7.77 (d, J = 7.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 42.6, 53.6 (CH_2), 61.0, 64.7, 69.4 (CH_2), 71.7 (CH_2), 73.3 (CH_2), 73.5, 75.1 (CH_2), 80.4, 127.4, 127.5, 127.6, 127.7, 127.8, 128.1, 128.2, 128.3, 128.4, 128.7, 132.9, 137.1, 137.7, 138.3, 141.0 ppm. HRMS (ES^+): calcd. for $C_{34}H_{38}NO_5S$ $[M + H]^+$ 572.2471; found 572.2468.

Method B: Compound **26** was stirred at 0 °C with K_2CO_3 and MeI in MeOH. The mixture was stirred at room temperature under N_2. After 7 h, the reaction mixture was poured into an aq. saturated solution of NH_4Cl and the product was extracted with EtOAc. The combined organic layers were dried with anhyd. Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to leave a residue. The residue was purified over silica gel to afford **27**.

General Procedure for the Synthesis of 28 and 29: A mixture of compound **15** and the neat amine (20 equiv./mmol) was stirred at ambient temperature. After 1–1.5 h, the residue was partitioned between an aq. saturated solution of NH_4Cl and EtOAc (3 × 15 mL). The combined organic layers were dried with anhyd. Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to leave a residue. The residue was purified over silica gel to afford **28** or **29**.

Compound 28. Method A: Compound **15** (0.15 g, 0.23 mmol) was converted into **28** (0.12 g, 76%) in 1 h following the general procedure. Colorless oil, $[\alpha]_D^{26}$ = +112.0 (c = 0.35, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.60 (t, J = 10.8 Hz, 1 H), 2.89 (br. s, 1 H), 3.16–3.20 (m, 1 H), 3.59–3.68 (m, 2 H), 3.74–3.84 (m, 3 H), 3.95–3.97 (m, 1 H), 4.12 (s, 1 H), 4.40–4.44 (m, 3 H), 4.57 (d, J = 11.2 Hz, 1 H), 4.66–4.75 (m, 2 H), 7.12–7.37 (m, 20 H), 7.46 (t, J = 7.2 Hz, 1 H), 7.69 (d, J = 8.0 Hz, 2 H) ppm. HRMS (ES^+): calcd. for $C_{40}H_{42}NO_5S$ $[M + H]^+$ 648.2784; found 648.2750.

Method B: Compound **26** was stirred at 0 °C with K_2CO_3 and BnBr in MeOH. The mixture was stirred at room temperature under N_2. After 7 h, the reaction mixture was poured into an aq. saturated solution of NH_4Cl and the product was extracted with EtOAc. The combined organic layers were dried with anhyd. Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to leave a residue. The residue was purified over silica gel to afford **28**.

Compound 29: Compound **15** (0.15 g, 0.23 mmol) was converted into **29** (0.13 g, 92%) in 1.5 h following the general procedure. Colorless oil, $[\alpha]_D^{26}$ = –14.2 (*c* = 0.25, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.2 Hz, 3 H), 1.15–1.24 (m, 2 H), 1.34–1.38 (m, 2 H), 2.48–2.74 (m, 4 H), 3.37 (dd, *J* = 3.6, 12.0 Hz, 1 H), 3.47 (t, *J* = 8.8 Hz, 1 H), 3.59–3.62 (m, 1 H), 3.86–3.89 (m, 1 H), 3.94–3.99 (m, 1 H), 4.07 (s, 1 H), 4.35–4.42 (m, 3 H), 4.55 (d, *J* = 11.6 Hz, 1 H), 4.70 (t, *J* = 10.8 Hz, 2 H), 7.04–7.06 (m, 2 H), 7.12–7.14 (m, 2 H), 7.21–7.35 (m, 13 H), 7.48 (t, *J* = 7.6 Hz, 1 H), 7.77 (d, *J* = 8.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 20.5 (CH_2), 26.4 (CH_2), 48.9 (CH_2), 52.7 (CH_2), 61.0, 61.4, 68.8 (CH_2), 71.5 (CH_2), 73.2 (CH_2), 73.9, 74.8 (CH_2), 80.2, 127.3, 127.4, 127.7, 128.0 (2 C), 128.1, 128.3, 128.6, 132.8, 137.2, 37.8, 138.5, 141.1 ppm. HRMS (ES^+): calcd. for $C_{37}H_{44}NO_5S$ $[M + H]^+$ 614.2940; found 614.2934.

General Procedure for the Synthesis of 30 and 31: A 30% aq. NH_3 solution (excess) and a 40% aq. $MeNH_2$ solution (excess) were separately added a well-stirred solution of compound **15** (1 mmol) in THF (30 mL) . After 2–3 h, the THF was evaporated under reduced pressure, an aq. saturated $NaHCO_3$ solution was added, and the product was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried with anhyd. Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to leave a residue. The residue was purified over silica gel to afford **30** and **31**, respectively.

Compound 30: Compound **15** was converted into **30** as a mixture of isomers following the general procedure. ^1H NMR (400 MHz, $CDCl_3$): see the spectrum in the Supporting Information.

Compound 31: Compound **15** was converted into **31** as a single compound following the general procedure. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.09 (s, 3 H), 2.91–3.00 (m, 4 H), 3.08–3.18 (m, 1 H), 3.50 (dd, *J* = 3.4, 11.2 Hz, 1 H), 3.63–3.72 (m, 2 H), 3.91–3.96 (m, 1 H), 4.27–4.28 (m, 1 H), 4.31–4.55 (m, 4 H), 4.77 (dd, *J* = 11.0, 24.8 Hz, 2 H), 5.10–5.14 (m, 1 H), 7.23–7.30 (m, 15 H), 7.36–7.43 (m, 2 H), 7.51–7.55 (m, 1 H), 7.76–7.77 (m, 2 H) ppm.

Compound 32: Compound **15** (0.10 g, 0.153 mmol) was converted into **32** (0.064 g, 59%) following the procedure described for the preparation of **24**. Colorless oil, $[\alpha]_D^{26}$ = +20.2 (*c* = 1.75, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.47–2.53 (m, 1 H), 2.63–2.68 (m, 1 H), 2.97 (s, 2 H), 3.37 (dd, *J* = 4.8, 10.4 Hz, 1 H), 3.59–3.64 (m, 1 H), 3.75 (t, *J* = 6.4 Hz, 1 H), 3.79–3.81 (m, 1 H), 4.21 (d, *J* = 4.8 Hz, 1 H), 4.38–4.51 (m, 5 H), 4.69 (t, *J* = 10.0 Hz, 2 H), 4.95–4.99 (m, 1 H), 7.25–7.26 (m, 7 H), 7.32–7.36 (m, 8 H), 7.43 (t, *J* = 7.6 Hz, 2 H), 7.61 (t, *J* = 7.2 Hz, 1 H), 7.78 (d, *J* = 7.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4, 26.2 (CH_2), 38.5, 61.8 (CH_2), 68.1, 73.5 (CH_2), 73.6 (CH_2), 73.7 (CH_2), 78.4, 79.1, 112.2, 112.3, 127.9, 128.2, 128.3, 128.4, 128.6 (2 C), 128.7, 128.8, 129.6, 134.5, 136.0, 136.3 (2 C), 137.0 ppm.

Compound 33: A well-stirred solution of compound **32** (0.06 g, 0.085 mmol) in DMSO (10 mL) was heated at 120–130 °C with H_2O (1 mL) and NaCl (0.025 g, 0.425 mmol). After 12 h, an aq. saturated solution of $NaHCO_3$ was added and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried with anhyd Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to leave a residue. The residue was purified over silica gel to afford **33** (0.028 g, 55%) as a colorless oil. $[\alpha]_D^{26}$ = 90.2 (*c* = 0.08, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.28 (dd, *J* = 3.2, 13.6 Hz, 1 H), 2.71 (t, *J* = 13.2 Hz, 1 H), 2.89 (t, *J* = 5.6 Hz, 1 H), 3.17 (dd, *J* = 8.4 Hz, 1 H), 3.45–3.50 (m, 1 H), 3.69–3.71 (m, 1 H), 4.02 (d, *J* = 11.6 Hz, 1 H), 4.28 (d, *J* = 11.6 Hz, 1 H), 4.48 (d, *J* = 11.2 Hz, 1 H), 4.57–4.67 (m, 3 H), 4.80 (q, *J* = 10.4, 28.0 Hz, 2 H), 7.21–7.31 (m, 12 H), 7.34–7.41 (m, 3 H), 7.53 (t, *J* = 7.6 Hz, 2 H), 7.68 (t, *J* = 7.6 Hz, 1 H), 7.84 (d, *J* = 7.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.8 (CH_2), 34.1, 44.8, 61.6, 65.5 (CH_2), 71.6 (CH_2), 71.9, 73.2 (CH_2), 75.2 (CH_2), 76.0, 113.3, 114.4, 126.9, 127.6 (2 C), 127.8 (2 C), 128.1, 128.2, 128.3 (2 C), 128.5 (2 C), 128.7, 129.6, 134.4, 136.4, 137.1, 137.2, 137.6 ppm. HRMS (ES^+): calcd. for $C_{36}H_{34}N_2O_5SNa$ $[M + Na]^+$ 629.2086; found 629.2090.

General Procedure for Desulfonylation: Mg turnings (15 mmol) were added to a well-stirred solution of compound **16**–**19**, **27** or **28** in dry MeOH (15 mL). After 3–4 h, another portion of Mg turnings (15 mmol) and dry MeOH (5 mL) were added. The mixture was stirred for an additional 10 h and the reaction mixture was filtered through Celite. The residue was washed thoroughly with MeOH. The combined organic layers were dried with anhyd Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to leave a residue. The residue was purified over silica gel to afford **34**–**39**, respectively.

Compound 34: Compound **16** (0.20 g, 0.369 mmol) was converted into **34** (0.07 g, 68%) following the general procedure. Yellow oil, $[\alpha]_D^{26}$ = +57.5 (*c* = 0.2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.60 (dd, *J* = 6.0, 11.2 Hz, 1 H), 2.79 (dd, *J* = 4.4, 11.2 Hz, 1 H), 2.99 (q, *J* = 16.0, 25.6 Hz, 2 H), 3.63 (dd, *J* = 13.2, 35.2 Hz, 2 H), 4.08–4.10 (m, 1 H), 4.56 (s, 2 H), 5.85–5.91 (m, 2 H), 7.26–7.42 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.6 (CH_2), 54.2 (CH_2), 62.3 (CH_2), 70.4 (CH_2), 71.9, 126.0, 127.1, 127.4, 127.7, 128.2, 128.3, 128.9, 129.0, 137.9, 138.6 ppm. HRMS (ES^+): calcd. for $C_{19}H_{22}NO$ $[M + H]^+$ 280.1719; found 280.1698.

Compound 35: Compound **17** (0.15 g, 0.313 mmol) was converted into **35** (0.042 g, 63%) following the general procedure. Colorless oil, $[\alpha]_D^{26}$ = +74.4 (*c* = 0.75, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.11 (t, *J* = 7.2 Hz, 3 H), 2.46–2.56 (m, 3 H), 2.81 (dd, *J* = 4.8, 11.2 Hz, 1 H), 2.91–2.96 (m, 2 H), 4.10 (br. s, 1 H), 4.62 (s, 2 H), 5.87–5.90 (m, 2 H), 7.26–7.37 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.9, 51.8 (CH_2), 52.1 (CH_2), 54.5 (CH_2), 70.5 (CH_2), 71.9, 126.0, 127.4, 127.7, 128.3, 128.7, 138.7 ppm. HRMS (ES^+): calcd. for $C_{14}H_{20}NO$ $[M + H]^+$ 218.1563; found 218.1539.

Compound 36: Compound **18** (0.20 g, 0.406 mmol) was converted into **36** (0.065 g, 69%) following the general procedure. Brown oil, $[\alpha]_D^{26}$ = 42.7 (*c* = 0.25, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.05–1.08 (m, 6 H), 2.48–2.53 (m, 1 H), 2.78–2.89 (m, 2 H), 3.00–3.10 (m, 2 H), 4.10 (br. s, 1 H), 4.59–4.65 (m, 2 H), 5.83–5.91 (m, 2 H), 7.25–7.38 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.9, 18.2, 48.1 (CH_2), 50.2 (CH_2), 53.8, 70.5 (CH_2), 72.6, 126.1, 127.4, 127.7, 128.3, 129.2, 138.7 ppm. HRMS (ES^+): calcd. for $C_{15}H_{22}NO$ $[M + H]^+$ 232.1719; found 232.1691.

Compound 37: Compound **19** (0.26 g, 0.408 mmol) was converted into **37** (0.095 g, 62%) following the general procedure. Yellow oil, $[\alpha]_D^{26}$ = –14.9 (*c* = 0.24, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.31 (s, 3 H), 1.48 (s, 3 H), 2.60 (d, *J* = 7.2 Hz, 2 H), 2.68–2.72 (m, 1 H), 2.79–2.83 (m, 1 H), 3.04 (q, *J* = 10.4, 38.0 Hz, 2 H), 3.83 (s, 3 H), 4.10 (br. s, 1 H), 4.36 (t, *J* = 7.2 Hz, 1 H), 4.58–4.64 (m, 3 H), 4.73 (d, *J* = 6.0 Hz, 1 H), 4.96 (s, 1 H), 5.85 (s, 2 H), 7.26–7.37 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.0, 26.4, 52.6 (CH_2), 54.8, 55.2 (CH_2), 60.9 (CH_2), 70.4 (CH_2), 71.7, 83.0, 84.3, 85.2, 109.5, 112.2, 126.0, 127.4, 127.6, 128.2, 128.5, 138.7 ppm. HRMS (ES^+): calcd. for $C_{21}H_{30}NO_5$ $[M + H]^+$ 376.2109; found 376.2119.

Compound 38: Compound **27** (0.09 g, 0.158 mmol) was converted into **38** (0.028 g, 54%) following the general procedure. Colorless oil, $[\alpha]_D^{26}$ = +57.0 (*c* = 0.09, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.49 (s, 3 H), 2.95 (d, *J* = 17.2 Hz, 1 H), 3.04 (q, *J* = 2.0,

4.4 Hz, 1 H), 3.18 (d, J = 17.6 Hz, 1 H), 3.68–3.78 (m, 2 H), 4.11–4.12 (m, 1 H), 4.48–4.52 (m, 2 H), 4.60 (s, 2 H), 5.79 (s, 2 H), 7.27–7.35 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 43.0, 52.5 (CH_2), 61.4, 67.4 (CH_2), 71.0 (CH_2), 72.8, 73.3 (CH_2), 125.6, 127.5, 127.7, 127.9, 128.2, 128.3 (2 C), 138.5, 138.7 ppm. HRMS (ES^+): calcd. for $C_{21}H_{26}NO_2$ $[M + H]^+$ 324.1964; found 324.1978.

Compound 39: Compound **28** (0.08 g, 0.124 mmol) was converted into **39** (0.03 g, 62%) following the general procedure. Yellow oil, $[\alpha]_D^{26}$ = +60.2 (c = 0.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.07 (s, 2 H), 3.52–3.56 (m, 1 H), 3.69 (dd, J = 3.6, 10.4 Hz, 1 H), 3.82–3.92 (m, 2 H), 4.03 (d, J = 13.6 Hz, 1 H), 4.31–4.32 (m, 1 H), 4.49–4.57 (m, 3 H), 4.61 (d, J = 11.6 Hz, 1 H), 5.68–5.74 (m, 2 H), 7.23–7.37 (m, 15 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 47.9 (CH_2), 58.1, 59.7 (CH_2), 65.9 (CH_2), 70.7 (CH_2), 73.4 (CH_2), 74.1, 126.6, 126.8, 127.2, 127.5, 127.6 (2 C), 127.7, 128.2, 128.4, 128.7, 138.5, 138.7, 139.7 ppm. HRMS (ES^+): calcd. for $C_{27}H_{30}NO_2$ $[M + H]^+$ 400.2277; found 400.2260.

Compound 40: Magnesium monoperoxyphthalate hexahydrate (0.40 g, 0.96 mmol) was added to a well-stirred solution of sulfide **23** (0.15 g, 0.32 mmol) in dry MeOH (20 mL) and the mixture was stirred at room temperature under N_2. After 6 h, the MeOH was evaporated to dryness under reduced pressure and the residue was dissolved in an aq. saturated solution of $NaHCO_3$ and DCM (3 × 15 mL). The combined organic layers were dried with anhyd. Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to leave a residue. The residue was purified over silica gel to afford the sulfone **40** (0.14 g, 87%) as a white solid; m.p. 206 °C, $[\alpha]_D^{26}$ = +46.0 (c = 0.04, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.43 (s, 3 H), 2.99 (d, J = 13.6 Hz, 1 H), 3.18–3.21 (m, 1 H), 3.41 (d, J = 13.2 Hz, 1 H), 3.51–3.65 (m, 2 H), 3.92–3.94 (m, 1 H), 4.61–4.68 (m, 2 H), 4.86–4.89 (m, 2 H), 5.00 (d, J = 10.8 Hz, 1 H), 7.26–7.41 (m, 12 H), 7.71 (d, J = 8.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 46.3 (CH_2), 50.7 (CH_2), 61.4, 71.2, 71.8 (CH_2), 75.0 (CH_2), 76.8, 127.6, 127.8, 128.0, 128.2, 128.3, 128.6, 128.7, 130.2, 134.2, 136.6, 137.3, 145.9 ppm. HRMS (ES^+): calcd. for $C_{26}H_{28}O_6S_2Na$ $[M + Na]^+$ 523.1219; found 523.1230.

Compound 41: Potassium carbonate (0.05 g, 0.36 mmol) was added to a well-stirred solution of **40** (0.06 g, 0.12 mmol) in dry MeOH (20 mL) and the mixture was stirred at room temperature under N_2. After 20 h, the MeOH was evaporated to dryness under reduced pressure and the residue was partitioned between an aq. saturated solution of $NaHCO_3$ and EtOAc (3 × 15 mL). The combined organic layers were dried with anhyd. Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to leave a residue. The residue was purified over silica gel to afford sulfone **41** (0.045 g, 78%) as a white solid; m.p. 138 °C, $[\alpha]_D^{26}$ = –36.8 (c = 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.17–3.31 (m, 3 H), 3.34 (s, 3 H), 3.58 (t, J = 12.0 Hz, 1 H), 3.77–3.79 (m, 1 H), 4.00–4.01 (m, 1 H), 4.28–4.32 (m, 1 H), 4.56–4.67 (m, 3 H), 4.88 (d, J = 12.0 Hz, 1 H), 7.30–7.39 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 48.0 (CH_2), 51.7 (CH_2), 57.2, 72.0 (CH_2), 73.6, 73.8 (CH_2), 74.9, 127.6, 127.8, 128.0 (2 C), 128.5 (2 C), 137.4, 137.6 ppm. HRMS (ES^+): calcd. for $C_{20}H_{24}O_5SNa$ $[M + Na]^+$ 399.1236; found 399.1294.

Compound 42: NaOEt (0.025 g, 0.36 mmol) was added to a well-stirred solution of **40** (0.06 g, 0.12 mmol) in dry EtOH (20 mL) and the mixture was stirred at room temperature under N_2. After 6 h, EtOH was evaporated to dryness under reduced pressure and the residue was partitioned between an aq. saturated solution of $NaHCO_3$ and EtOAc (3 × 15 mL). The combined organic layers were dried with anhyd. Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to leave a residue. The residue was purified over silica gel to afford compound **42** (0.036 g, 76%) as a white semi-solid. $[\alpha]_D^{26}$ = –42.2 (c = 1.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16 (t, J = 6.8 Hz, 3 H), 3.13–3.19 (m, 1 H), 3.24–3.37 (m, 3 H), 3.54–3.63 (m, 2 H), 3.86–3.89 (m, 1 H), 3.96–3.97 (m, 1 H), 4.32–4.36 (m, 1 H), 4.57–4.67 (m, 3 H), 4.78 (d, J = 12.0 Hz, 1 H), 7.30–7.37 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.0, 48.6 (CH_2), 51.7 (CH_2), 65.0 (CH_2), 71.9 (CH_2), 72.9, 73.7 (CH_2), 73.8, 74.3, 127.6, 127.8, 128.0 (2 C), 128.5 (2 C), 137.4, 137.7 ppm. HRMS (ES^+): calcd. for $C_{21}H_{26}O_5SNa$ $[M + Na]^+$ 413.1393; found 413.1355.

Compound 43: CBr_2F_2 (1 mL) was added dropwise to a vigorously stirred mixture of the sulfone **41** (0.055 g, 0.146 mmol), alumina-supported KOH (0.30 g), tBuOH (6 mL), and DCM (5 mL) kept at 5–10 °C. The reaction mixture was stirred at room temperature for an additional 12 h after which the solid catalyst was removed by filtration through a Celite bed. The filtrate was evaporated to dryness under reduced pressure. The filter cake was washed thoroughly with DCM and the washes were combined with the residue from the first filtrate. The combined organic layers were dried with anhyd. Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure to leave a residue. The residue was purified over silica gel to afford **43** (0.022 g, 49%) as a colorless oil. $[\alpha]_D^{26}$ = –306.9 (c = 0.05, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.44 (s, 3 H), 3.85–3.88 (m, 1 H), 4.54–4.64 (m, 5 H), 4.74 (d, J = 11.6 Hz, 1 H), 6.01–6.03 (m, 1 H), 6.09–6.11 (m, 1 H), 7.27–7.40 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 57.4, 70.8 (CH_2), 72.0 (CH_2), 78.6, 83.8, 88.0, 127.5, 127.6, 127.9, 128.3 (2 C), 131.8, 135.6, 138.1, 138.5 ppm. HRMS (ES^+): calcd. for $C_{20}H_{22}O_3Na$ $[M + Na]^+$ 333.1467; found 333.1451.

Compound 44: Compound **42** (0.07 g, 0.179 mmol) was converted into **44** (0.027 g, 46%) following the procedure described for the preparation of **43**. Colorless oil, $[\alpha]_D^{26}$ = –85.8 (c = 0.05, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (t, J = 6.8 Hz, 3 H), 3.62–3.66 (m, 2 H), 3.87 (t, J = 5.2 Hz, 1 H), 4.54 (d, J = 5.6 Hz, 1 H), 4.58 (s, 2 H), 4.62 (d, J = 12.0 Hz, 1 H), 4.68–4.69 (m, 1 H), 4.75 (d, J = 11.6 Hz, 1 H), 6.00–6.01 (m, 1 H), 6.07–6.09 (m, 1 H), 7.27–7.39 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.6, 65.4 (CH_2), 70.9 (CH_2), 72.1 (CH_2), 78.7, 84.2, 86.5, 127.6 (2 C), 128.0 (2 C), 128.3 (2 C), 131.6, 136.3, 138.3, 138.6 ppm. HRMS (ES^+): calcd. for $C_{21}H_{24}O_3Na$ $[M + Na]^+$ 347.1623; found 347.1607.

CCDC-752657 (for **18**) and -752658 (for **41**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see also the footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra for new compounds and NOESY–COSY data for **14** and **19**.

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